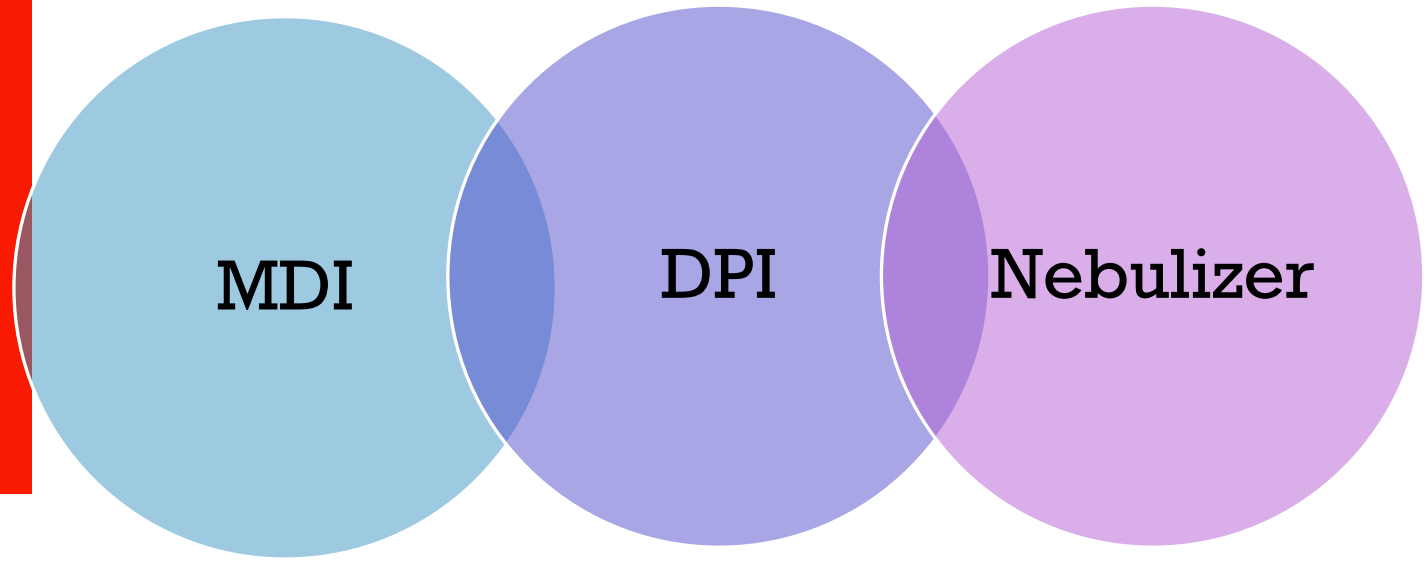
Nebulizer therapy

Presented by : Dr. N. Alizadeh

Clinical pharmacist, TUMS

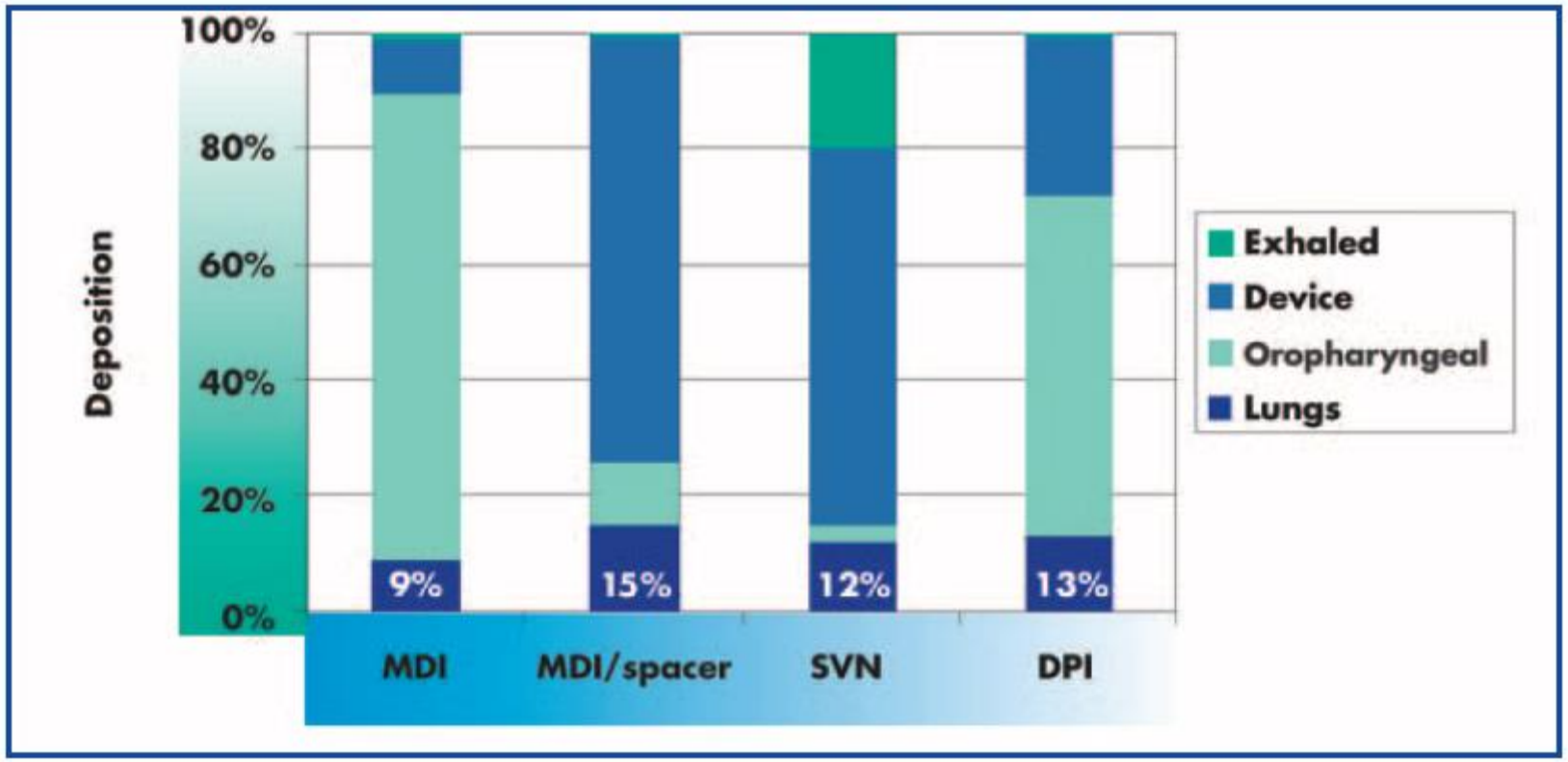
Type Of Inhaled Drug Delivery



selection of an aerosol delivery device

- Patient
- Convenience of the clinician and patient
- The ability of the patient to use the device correctly
- The durability of the device
- The cost of therapy

The available evidence from systematic reviews and meta-analyses suggests equivalence among nebulizers, pMDIs, and DPIs for delivery of beta agonists and glucocorticoids when **used correctly**



Drug disposition with 3 common aerosol inhaler devices, including an MDI with a spacer attached, showing similar lung deposition with varying amounts of loss in the oropharynx, device, and exhaled breath. MDI – metereddose inhaler; SVN – small volume nebulizer; DPI – dry powder inhaler.

(from Respir Care 2005; 50(3):367-382).

History of Nebulizers

- Although the term **“aerosol”** was not coined until around 1920, inhaled therapy for medicinal purposes dates back at least **4,000** years.
- The origins of inhalation therapy for lung complaints may have arisen in the traditional therapies of **Ayurvedic medicine** in India around 2000 BC.
- The compounds smoked included herbal preparations, most notably **datura** species, which contain potent alkaloids with **anticholinergic bronchodilating properties.**

  The datura roots were powdered together with other materials such as ginger and pepper, made into a paste for smearing on a reed that could be dried and smoked through a pipe.

simple pot with a reed in the lid

Fig. 1. Arica inhaler from coastal regions of northern Chile and southern Peru, dating from about 1500 AD. A tobacco-like mixture was prepared on the decorated wooden receptacle and inhaled through the hollow wooden mouthpiece. (Courtesy of Mark Sanders, Inhalatorium.com.)

History of Nebulizers

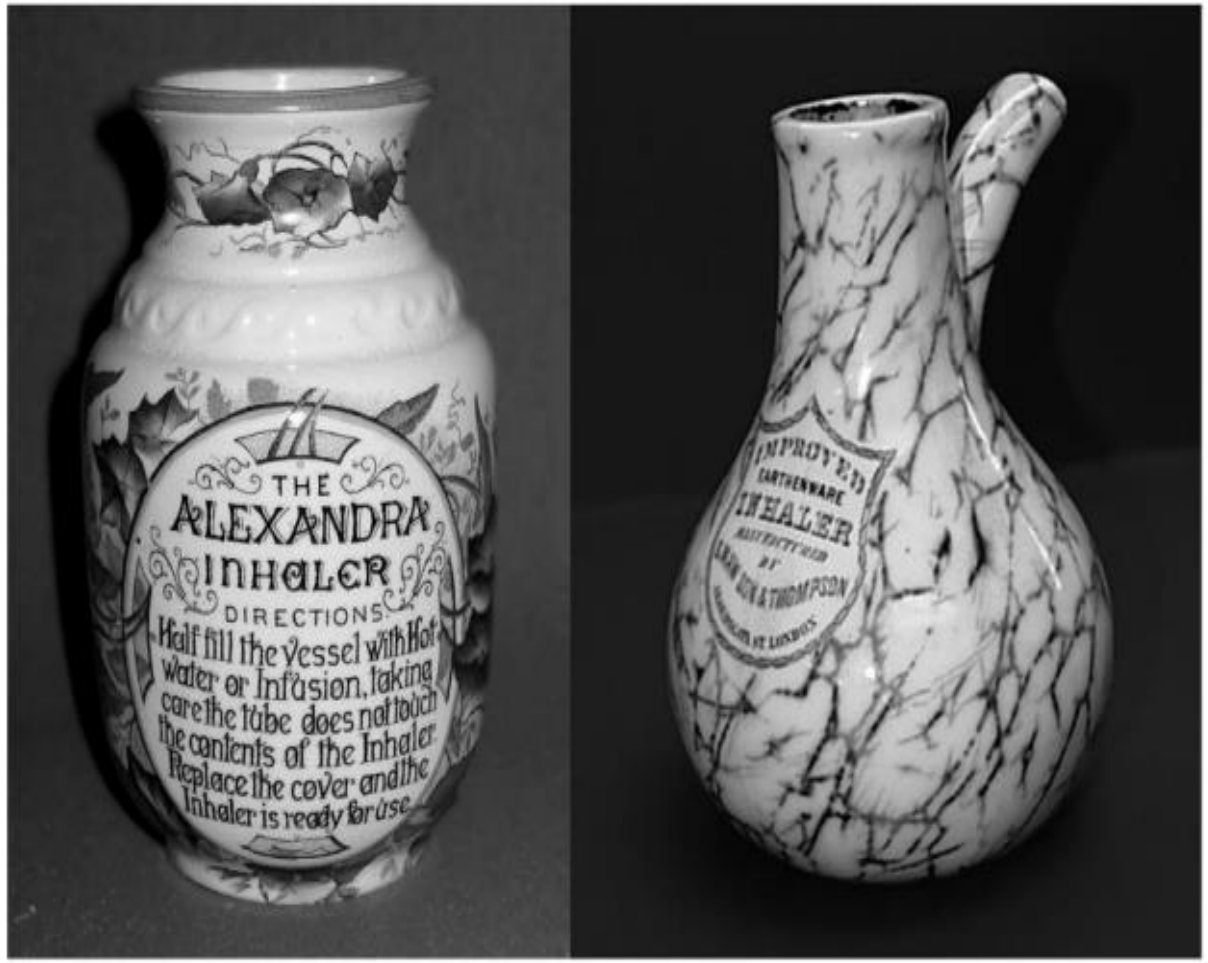
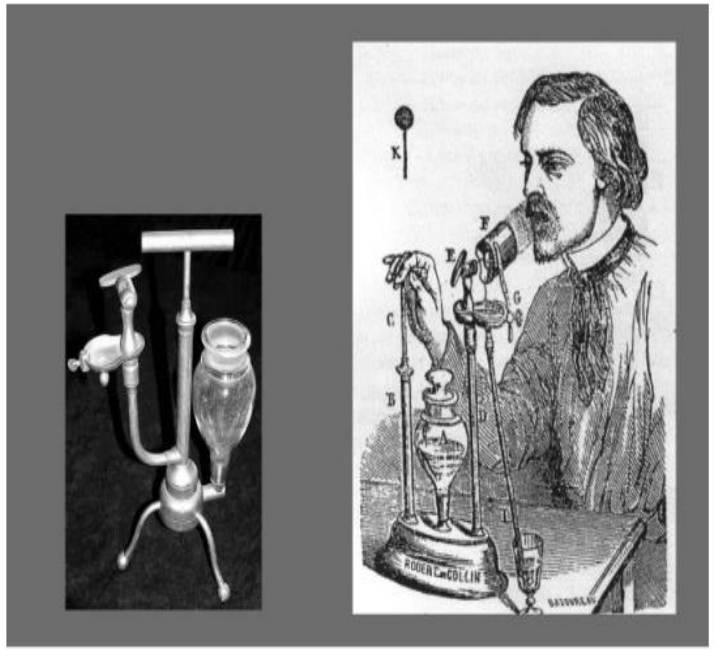


Fig. 3. Examples of earthenware inhalers from the late 19th century for inhalation of infusions. Left: The Alexandra inhaler, which has a vertical air channel at the back, through which air is drawn; a cover with a mouthpiece would complete the item. (Courtesy of Mark Sanders, Inhalatorium.com.) Right: The Maw's (or Nelson) inhaler, which would have had a stopper with a tube extending down into the liquid infusion.

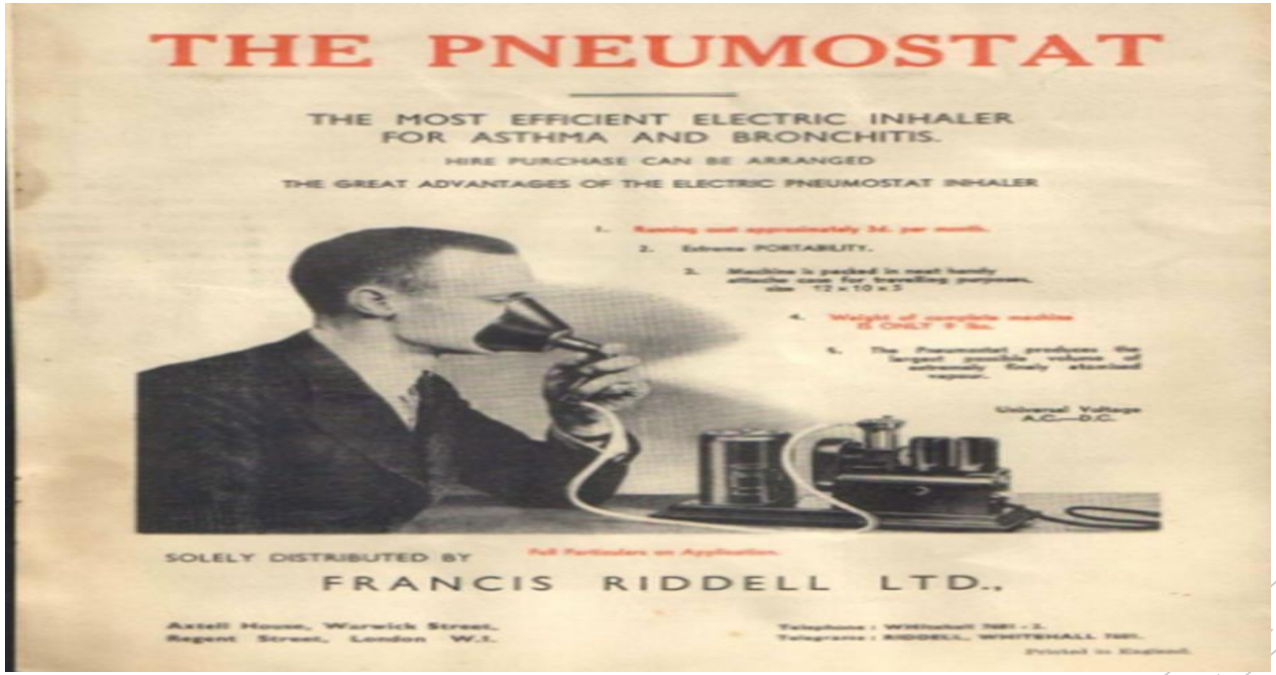
Fig. 2. The Mudge inhaler, invented by Dr John Mudge in 1778, was a pewter tankard with a mouthpiece covering the top and an air passage drilled through the handle. As the patient breathed through the mouthpiece, air was drawn through the holes in the handle and passed through the liquid at the bottom of the vessel. (Courtesy of Mark Sanders, Inhalatorium.com.)



irons "pulverisateur," which won the 1858 silver prize of the Paris Academy of Science. The pump
and forces it through an atomizer. (Courtesy of Mark Sanders, Inhalatorium.com.)

Hand-Bulb Nebulizer

Glass Nebulizer



- Variations on Hippocrates's **pot-and-reed** design were used in the late 18th and early 19th century.

Fig. 2. The Mudge inhaler, invented by Dr John Mudge in 1778, was a pewter tankard with a mouthpiece covering the top and an air passage drilled through the handle. As the patient breathed through the mouthpiece, air was drawn through the holes in the handle and passed through the liquid at the bottom of the vessel. (Courtesy of Mark Sanders, Inhalatorium.com.)

Early Atomizers and Nebulizers (Mid-to-Late 19th Century)

- Atomizers (also known as nebulizers) were developed in the **mid-1800s in France**.
- In 1858 Jean Sales-Girons introduced a portable nebulizer who won the silver prize of the **Paris Academy of Science** in 1858 for his invention.
- Used a pump handle to draw liquid from the reservoir and force it through a nozzle against a plate.

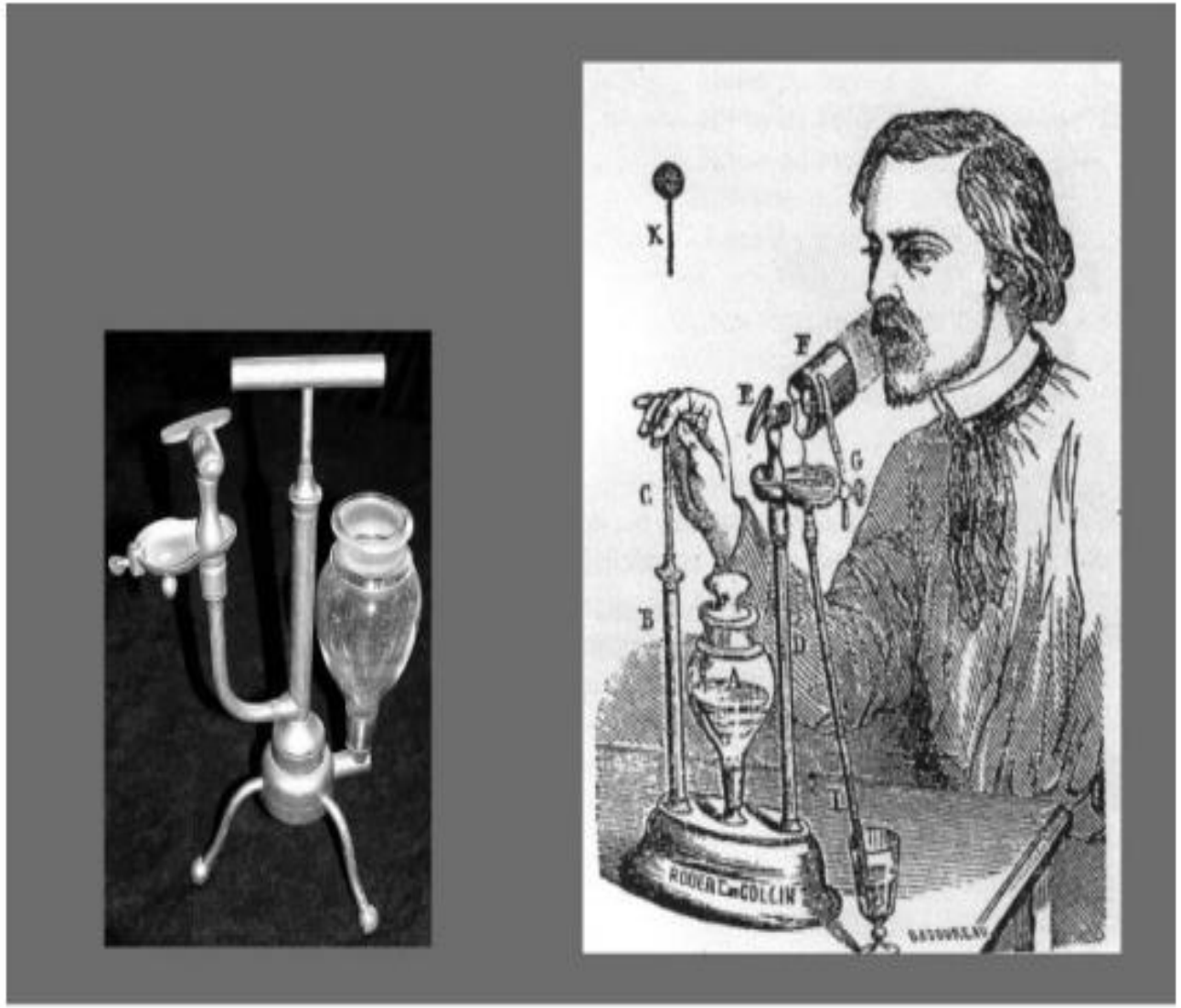
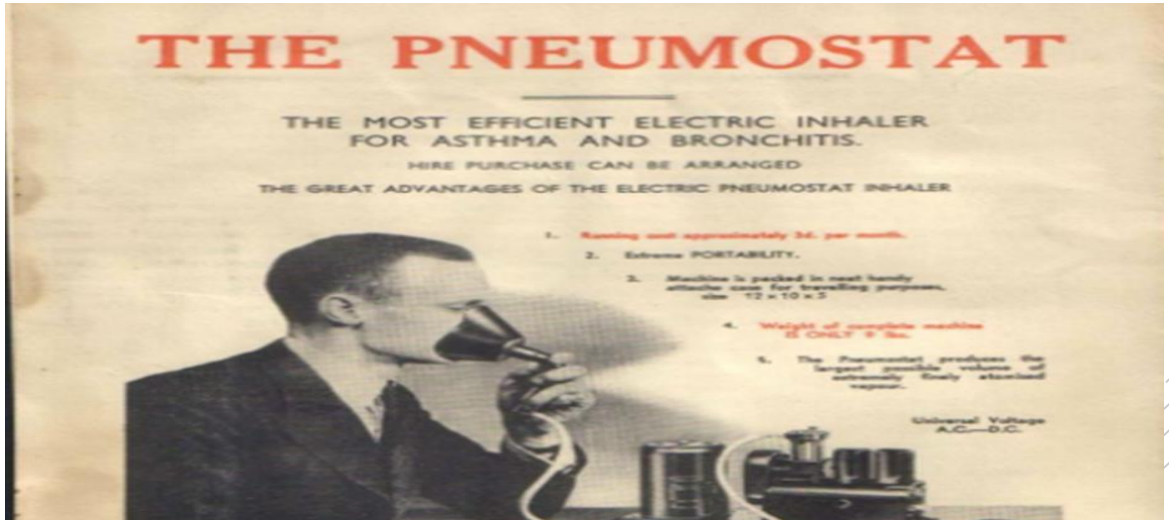


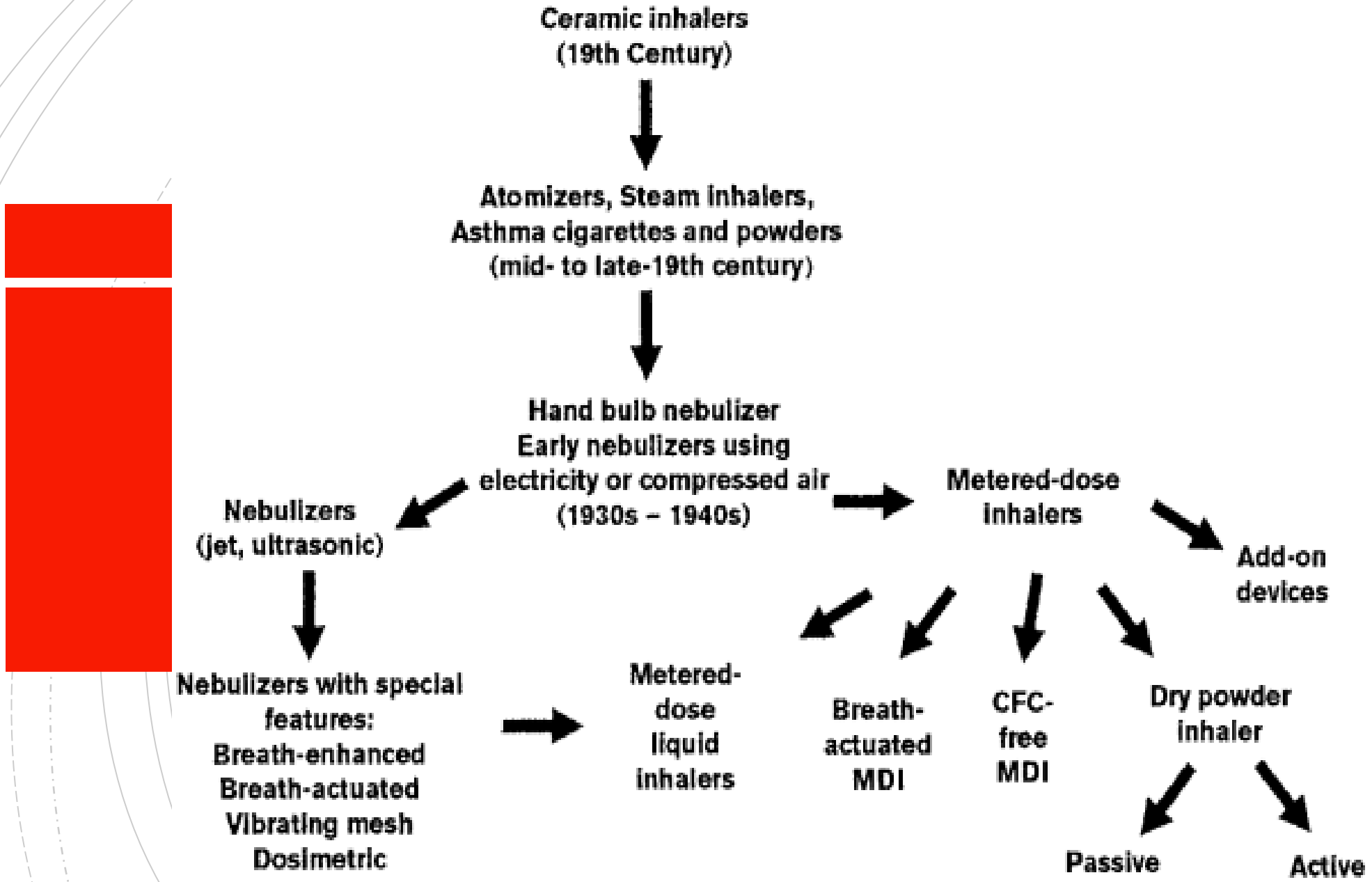
Fig. 4. The Sales-Girons "pulverisateur," which won the 1858 silver prize of the Paris Academy of Science. The pump handle draws liquid from the reservoir and forces it through an atomizer. (Courtesy of Mark Sanders, Inhalatorium.com.)


CONTENTS 6 FOR AVOIR.
DR. WHETZEL'S
POWDER
FOR
TEMPORARY RELIEF
OF PAROXYSMS OF
ASTHMA
ACTIVE INGREDIENTS IN EACH AVOIR. OUNCE: POWD. STRAMONIUM LEAVES 42.02% (CONTAINING 0.55 GRAIN OF STRAMONIUM ALKALOIDS) AND POWD. LOBELIA HERB.
Caution: Frequent or continued use of this preparation should be avoided. To temporarily relieve the paroxysms of Asthma, there should be an interval of one-half to an hour between doses and not more than three doses for an attack should be used. Use cautiously if dryness of the throat occurs; discontinue if rapid pulse or blurring of vision appears.
Warning: This preparation should not be used by elderly persons except on competent advice.
Page's Inhalers
- 20 -
(MEDICATED CIGARETTES)
- CONTAINS -
Stramonium leaves (containing Alkaloids .25% in finished product) Chestnut leaves, Tea leaves, Gum Benzoin, Kola nuts.
For the Temporary Relief of the Paroxysms of Asthma and to Aid in the Relief of the Discomforts due to Excessive Secretions in the Nasal Passage Associated with Hay Fever and Simple Nasal Irritations
Directions on back panel.
Consolidated Chemical C
Grand Rapids, Mich., U. S. A.
Est. 1892

Early electric nebulizer

In the early **1930s**, a compressor nebulizer, the **Pneumostat**, was manufactured in **Germany**. This piece of equipment had a rheostat for the power supply, allowing adjustment of the electrical voltage powering the compressor.




Ceramic inhalers
(19th Century)
Atomizers, Steam inhalers,
Asthma cigarettes and powders
(mid- to late-19th century)
Hand bulb nebulizer
Early nebulizers using
electricity or compressed air
(1930s – 1940s)
Nebulizers
(jet, ultrasonic)
Metered-dose
Inhalers
Add-on
devices
Nebulizers with special
features:
Breath-enhanced
Breath-actuated
Vibrating mesh
Dosimetric
Metered-
dose
liquid
inhalers
Breath-
actuated
MDI
CFC-
free
MDI
Dry powder
inhaler
Passive
Active

Nebulizer Advantages in pulmonary disease

- Exacerbations of asthma/COPD
- Bronchiectasis
- HAP/VAP

- There is **no special technique** for using
- Nebulizers can be used **at any age**
- Nebulizers can be used for **any disease severity**
- Can be used in paints with **cognitive, neuromuscular, or ventilatory** abnormalities
- Can be used in patients with **suboptimal PIFR** (Peak Inspiratory Flow Rate)
- **Mix** more than one medication in a nebulizer
- Contain **no propellants** that can damage the atmosphere
- Only nebulizers and pMDIs can be used in patients who are **intubated or have a tracheostomy**; DPIs are not designed for use in these patients.
- Only nebulizers can be used with **high flow nasal cannula.**
- No requirements for forceful **inspiratory maneuvers** or complex **hand-breath coordination**

Factors Affecting Penetration and Deposition

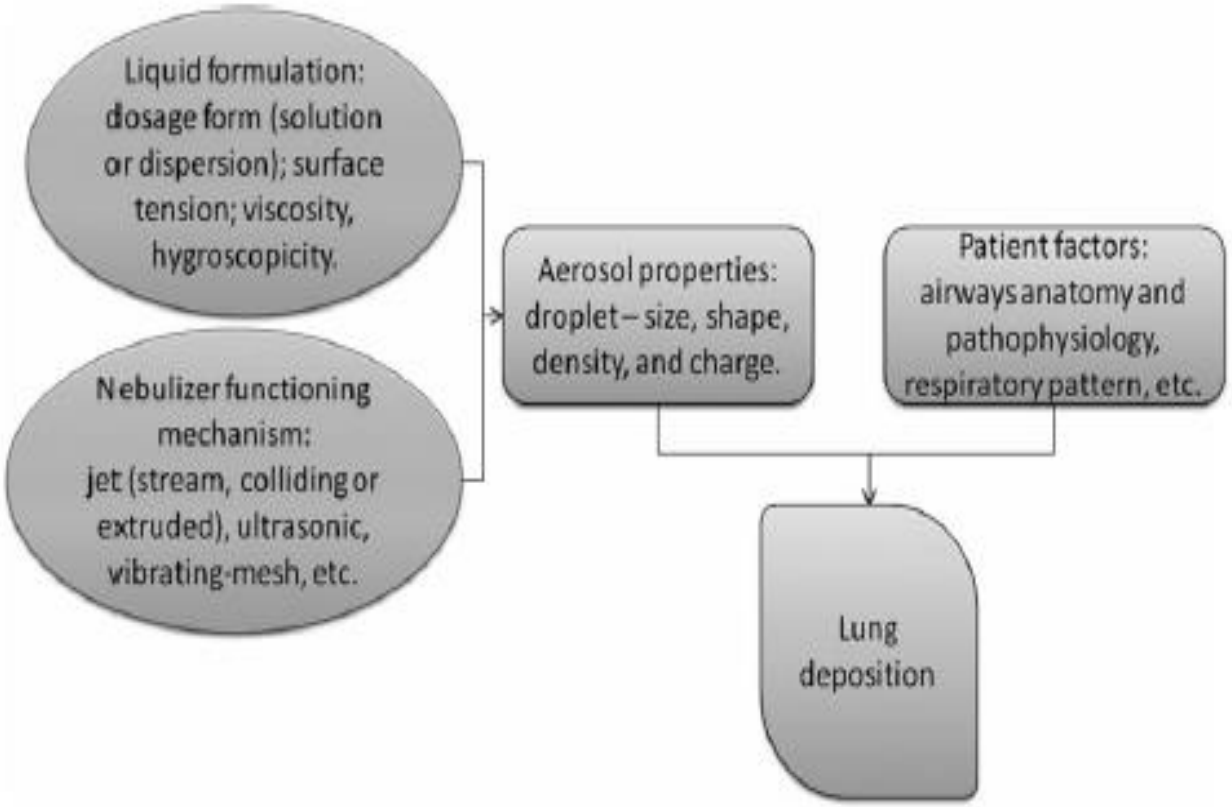
Technical Factors

- Manufacturer of nebulizer
- Gas flow used to power nebulizer
- Fill volume of nebulizer
- Solution characteristics
- Composition of the driving gas
- Continuous versus breath-actuated

Patient Factors

- Breathing pattern
- Nose versus mouth breathing
- Composition of inspired gas
- Airway obstruction
- Positive pressure delivery
- Artificial airway and mechanical ventilation

Factors influencing lung deposition from nebulizer formulations



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Respirable dose

The **most important** characteristic of nebulizer performance.

- It is a function of the mass output of the nebulizer and the size of the droplets produced.
- **2 to 5 µm** for **airway deposition** (eg, bronchodilator administration)
- **1 to 2 µm** or smaller for **parenchymal deposition** (eg, drugs intended for absorption into the bloodstream such as **pulmonary vasodilators**).
- Determinants of **droplet size** produced by nebulizers include the characteristics of the solution (density, viscosity, surface tension), the velocities of the gas and solution, and the flow rates for the gas and the solution.

Nebulization time

- Is determined by the **volume** of drug to be delivered and the flow of the driving gas into the nebulizer.
- It is an important determinant of **patient compliance** with completing a full dose in the outpatient setting.
- During nebulization, the solution within the nebulizer becomes **increasingly concentrated** as water evaporates from the solution. Thus, on a per breath basis, more medication is delivered late in the course of a treatment.

Dead volume

- The **dead volume** is typically in the range of **1 to 3 mL**.
  Although **nebulizer output** increases with a greater fill volume,
  this also results in an increase in **nebulization time**.
- Considering both factors, an initial nebulizer fill volume of **4 to 5 mL** is typically used.
- The maximum fill volume of the nebulizer is **manufacturer-determined**.
- Most do not exceed **5 mL**, but some accept a volume as great as **10 mL**.

	Albuterol (salbutamol) 2.5 mL PF	Budesonide	Fluticasone propionate	Formoterol	Ipratropium bromide 2 mL PF	Sodium chloride 5.8%
Albuterol (salbutamol)		C	C*	NR	C*	NR
Budesonide 2 mL	C		NR	C[1]	C	C
Fluticasone propionate	C*	NR		NR	C*	NR
Formoterol 2 mL	NR	C[1]	NR		NR	NR
Ipratropium bromide	C*	C	C*	NR		NR
Sodium chloride 5.8%	NR	C	NR	NR	NR	

- Factors other than physicochemical compatibility can alter drug mass delivery profile of medication mixtures. Such factors can include increased volume placed in reservoir and potential for alteration in particle size and character of mixed solutions. Except where compatible ("C") mixtures have an asterisk (*), the effect that mixing of medications has on drug mass delivery profile, relative to separate nebulization, has not been adequately studied.
- When mixing nebulized medications, use only freshly opened PF (single-use) formulations (ie, do not store mixtures or use medications or diluents containing preservatives).

Driving gas

- Increasing the flow of the driving gas results in an increase in **nebulized output** and a **reduction in particle size**. A flow of **6 to 8 L/min** is usually selected to optimize drug delivery.

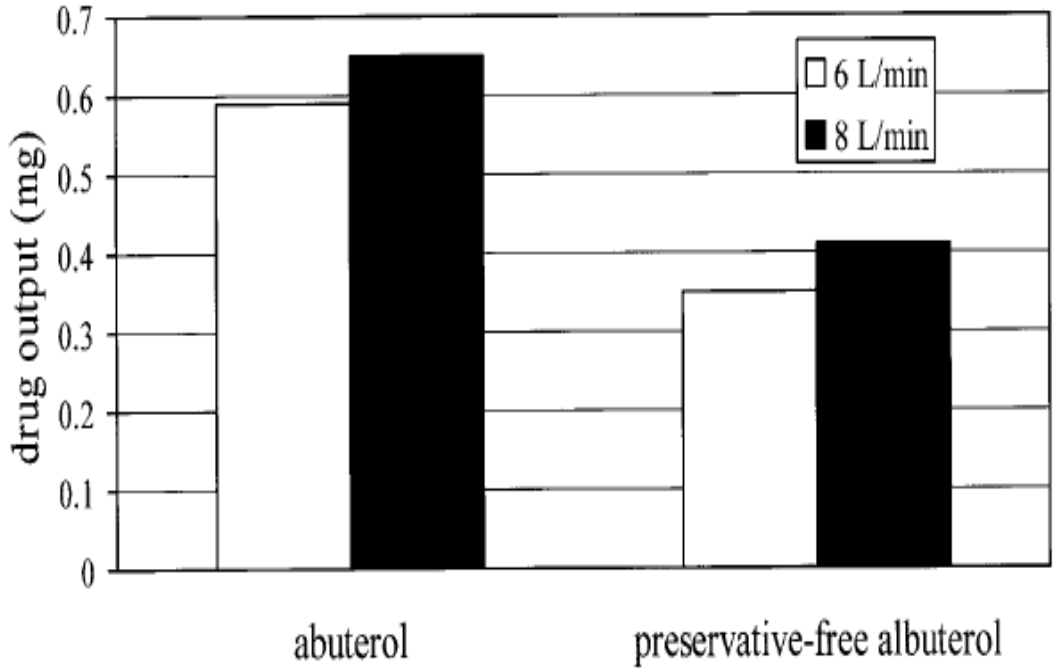
Gas density

- For example, the inhaled mass of **albuterol** is signifcantly reduced when a nebulizer is powered with a mixture of helium and oxygen (heliox). Accordingly, in the rare situation that the nebulizer is powered with heliox, the flow to the nebulizer is increased by 50 percent to **9 to 12 L/min**.
- Heliox may improve aerosol delivery to the lower respiratory tract, because the **decrease in gas density** results in creation of smaller particles; however, the clinical benefit of this approach is unclear.

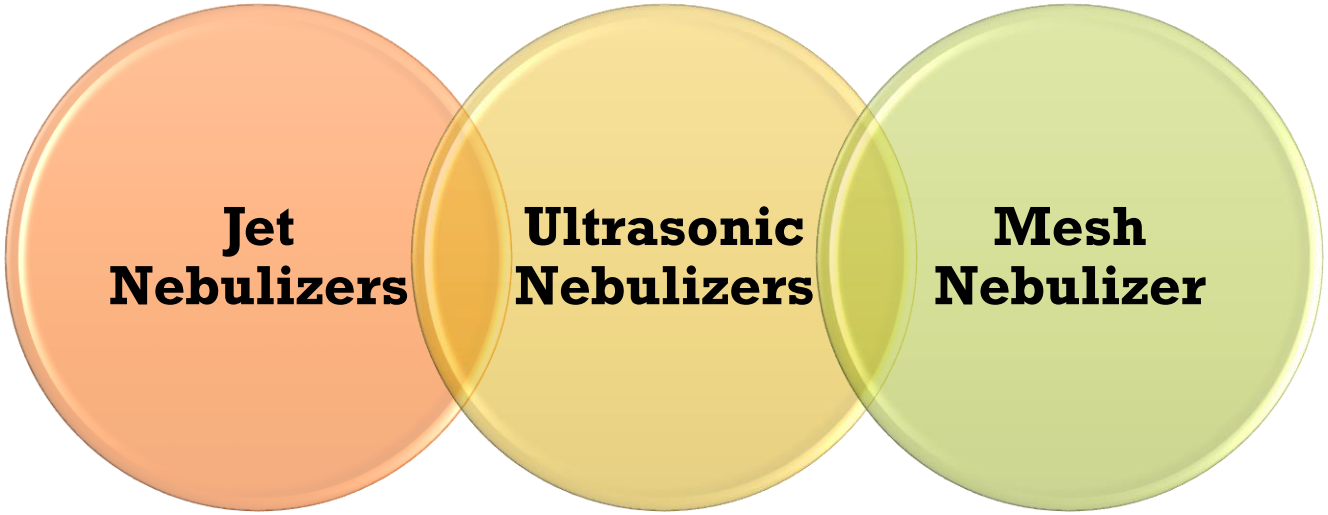
Breathing pattern

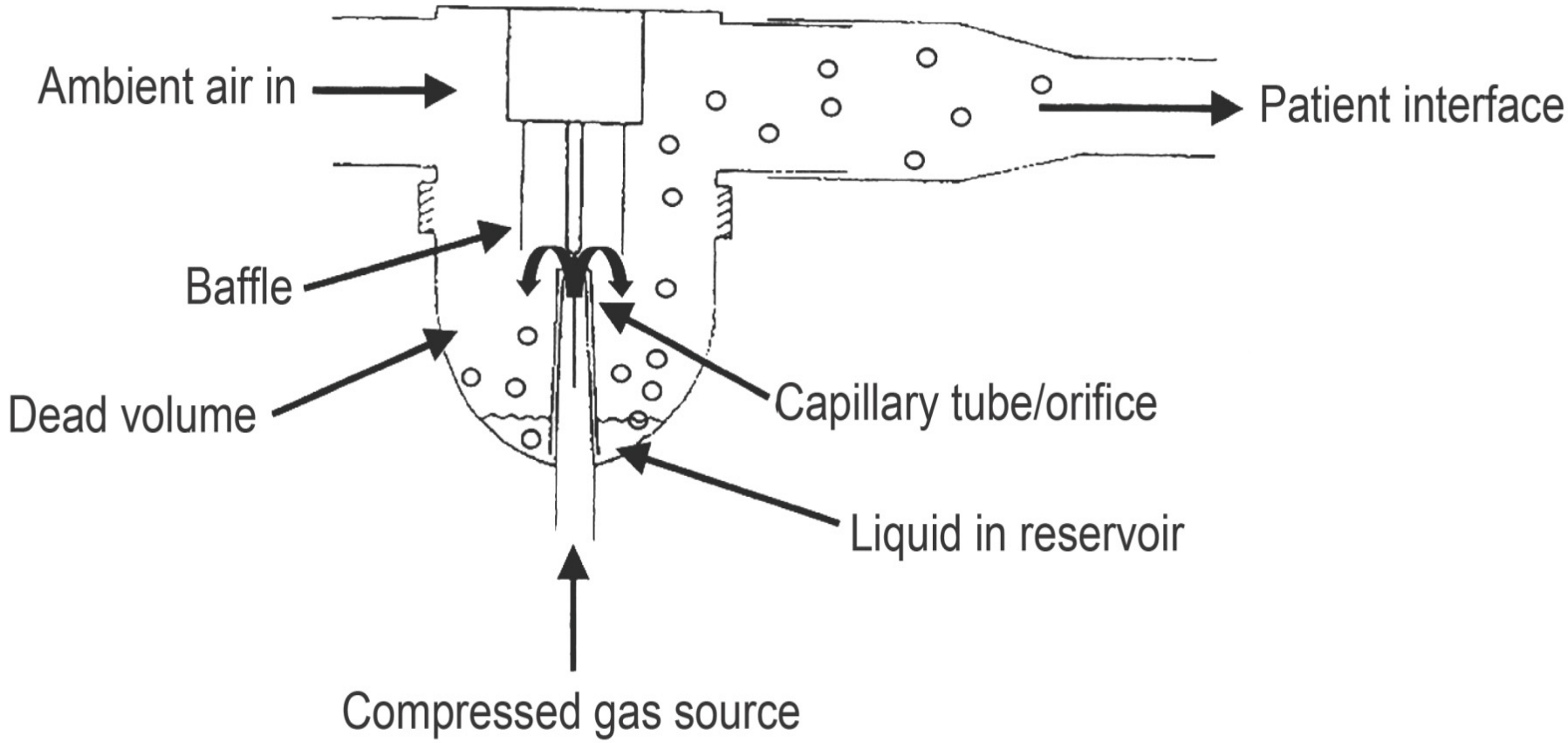
- The breathing pattern of the patient affects the amount of aerosol deposited in the lower respiratory tract.
- To improve aerosol penetration and deposition in the lungs, the patient should be encouraged to use a **slow breathing pattern with a normal tidal volume and an occasional deep breath.**

It is not commonly appreciated that the drug formulation
can affect nebulizer performance. MacNeish et al. reported differences in nebulizer output with two formulations of albuterol. Nebulizer output was significantly greater with the formulation containing the preservative **benzalkonium chloride**, probably because of its **surface activity**.



Nebulizers Types

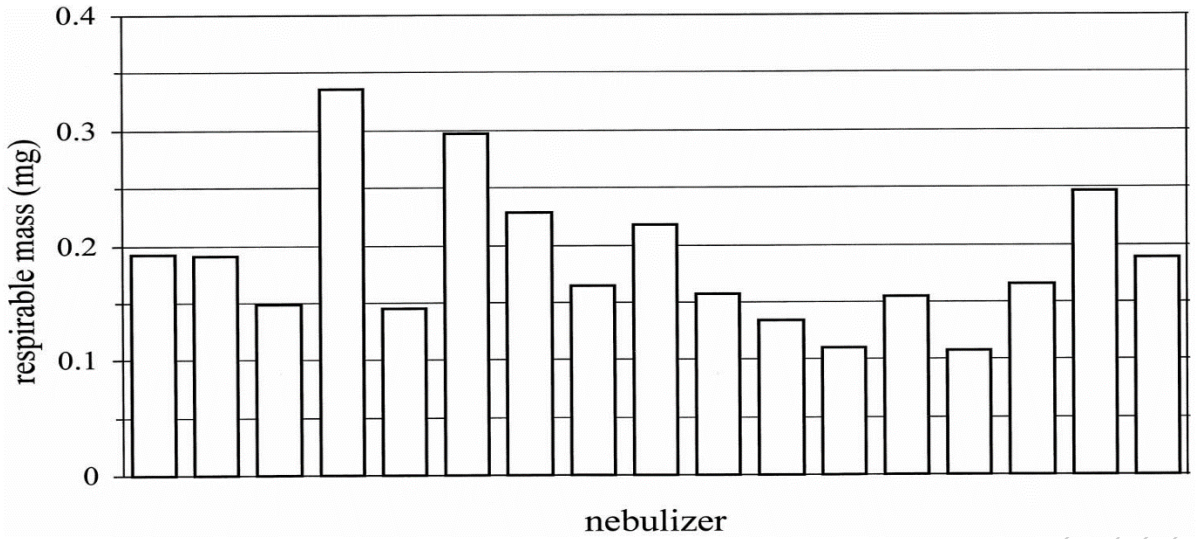



Ambient air in
Patient interface
Baffle
Dead volume
Capillary tube/orifice
Liquid in reservoir
Compressed gas source

Mechanism

- The operation of a jet nebulizer requires an air compressor or a pressurized gas supply (eg, compressed air, oxygen), which acts as the driving force for liquid atomization.
- Compressed gas is delivered as a jet through a small orifce, generating a region of negative pressure above the medication reservoir.
- The solution to be aerosolized is first entrained, or pulled into the gas stream (Venturi eſect), and then sheared into a **liquid film**. This film is unstable, and rapidly breaks into droplets due to surface tension forces.
- A **baffle** placed in the aerosol stream allows formation of smaller droplets and recycling of larger droplets into the liquid reservoir.

- The European Respiratory Society Guidelines on use of nebulizers **estimated > 10-fold differences in the amount of aerosol delivered** from different nebulizer systems in use throughout Europe.With many nebulizers only **10%** (range from 3.1 to 23.4%) of the prescribed dose may reach the lung.



The basic design of jet (pneumatic) nebulizers has changed little over the past 25 years

Differences in performance among nebulizers produced by various manufacturers:

- Deliver the dose of medication in a **shorter time**
- Deliver a more **accurate dose**
- Less **drug wastage** during exhalation
- Portability
- Battery power

- **Breath-actuated Device**
- **Breath-enhanced nebulizer systems**
- **Adaptive aerosol delivery (AAD) control system**

Breath-actuated jet nebulizers

AeroEclipse® II (Monaghan Medical Corporation, Plattsburgh, NY)

Breath-enhanced jet nebulizers

Pari LC® Sprint (PARI, Midlothian, VA)

SideStream Plus® (Philips,Murrysville, PA)

Nebulizer Type	Characteristics	Advantages	Disadvantages	Examples
Breath-enhanced JN	1. Air flows through the jet resulting in aerosolization of the drug solution; powered by compressor 2. The additional room air carried into the nebulizer during inhalation causes aerosolization 3. Drug solution cools during nebulization 4. Expired air vented outside of the device 5. Available as tabletop and portable models	1. Drug delivery during inhalation only, thus less drug wastage 2. Easy to use and quiet	1. Sufficient flow required to initiate drug delivery 2. Not ventilator-enabled 3. More expensive versus conventional JNs and ultrasonic nebulizers	1. PARI LC® Sprint NebuTech HDN® SideStream Plus®
Breath-actuated JN	1. Air flows through the tube resulting in aerosolization of the drug solution; powered by compressor 2. Aerosolization is triggered by patient inhalation 3. Available as tabletop and portable models	1. Same as breath-enhanced JN	1. Same as breath-enhanced JN	1. AeroEclipse® II BAN
Mesh nebulizer	1. Piezoelectric crystals vibrate a mesh plate resulting in aerosolization 2. Very fine droplets 3. No significant change in temperature of the solution during nebulization 4. Lower residual drug in chamber versus JNs	1. Fast, quiet, portable, and easy to use 2. Self-contained power source 3. Particle size optimized for specific medications 4. More efficient when compared other nebulizers	1. Expensive 2. Hard to clean 3. Medication dosage requires adjusting 4. Incompatible with viscous liquids or liquids that crystallize on drying	1. AKITA2®APIXNEB 2. eFlow®rapid 3. Micro Air® NE-U22

Deliver aerosols after **preprofiling a patient's breathing pattern**. The AeroEclipse nebulizer has a breath-actuated valve that triggers aerosol generation **only during inhalation**, eliminating the need for a storage bag or reservoir.

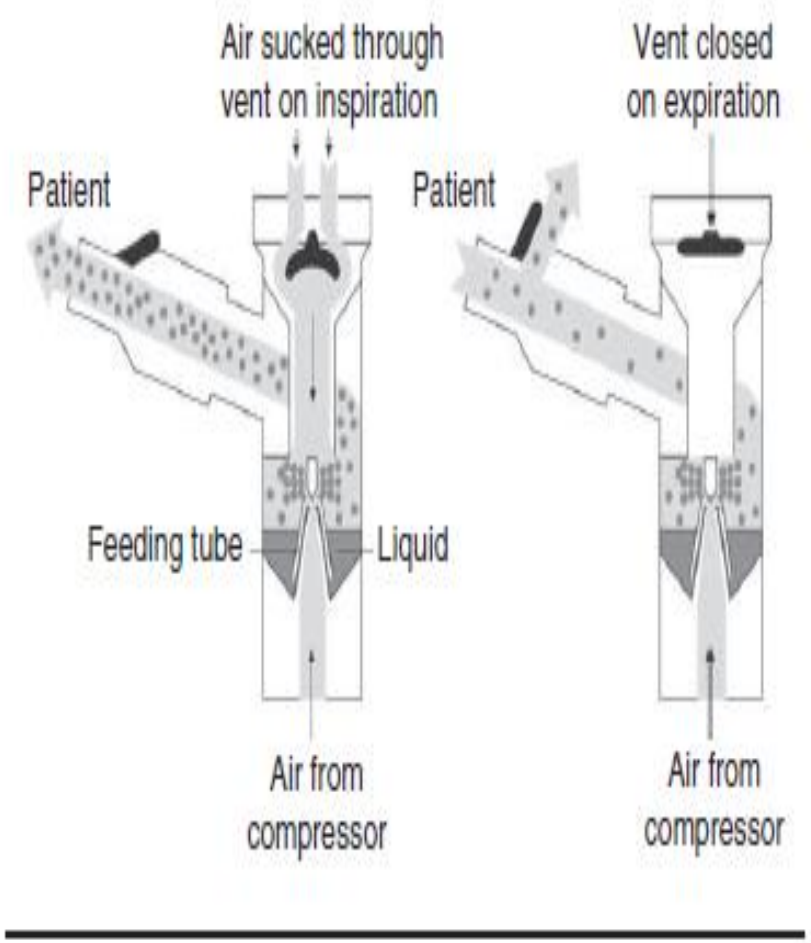
Breath-actuated jet nebulizers

AeroEclipse® II (Monaghan Medical Corporation, Plattsburgh, NY)

Breath Enhanced, Open Vent Nebulizer

During inhalation, an inspiratory valve opens to permit room air to be entrained through the main body of the nebulizer. During exhalation, this valve closes, and an expiratory valve on or near the mouthpiece opens, permitting flow of exhaled gas to bypass the droplet production region of the nebulizer and exit directly to the room environment.

Accordingly, a greater fraction of nebulized drug produced during exhalation is retained in the nebulizer and available for the subsequent



Breath-enhanced jet nebulizers

Pari LC® Sprint (PARI, Midlothian, VA)

SideStream Plus® (Philips,Murrysville, PA)

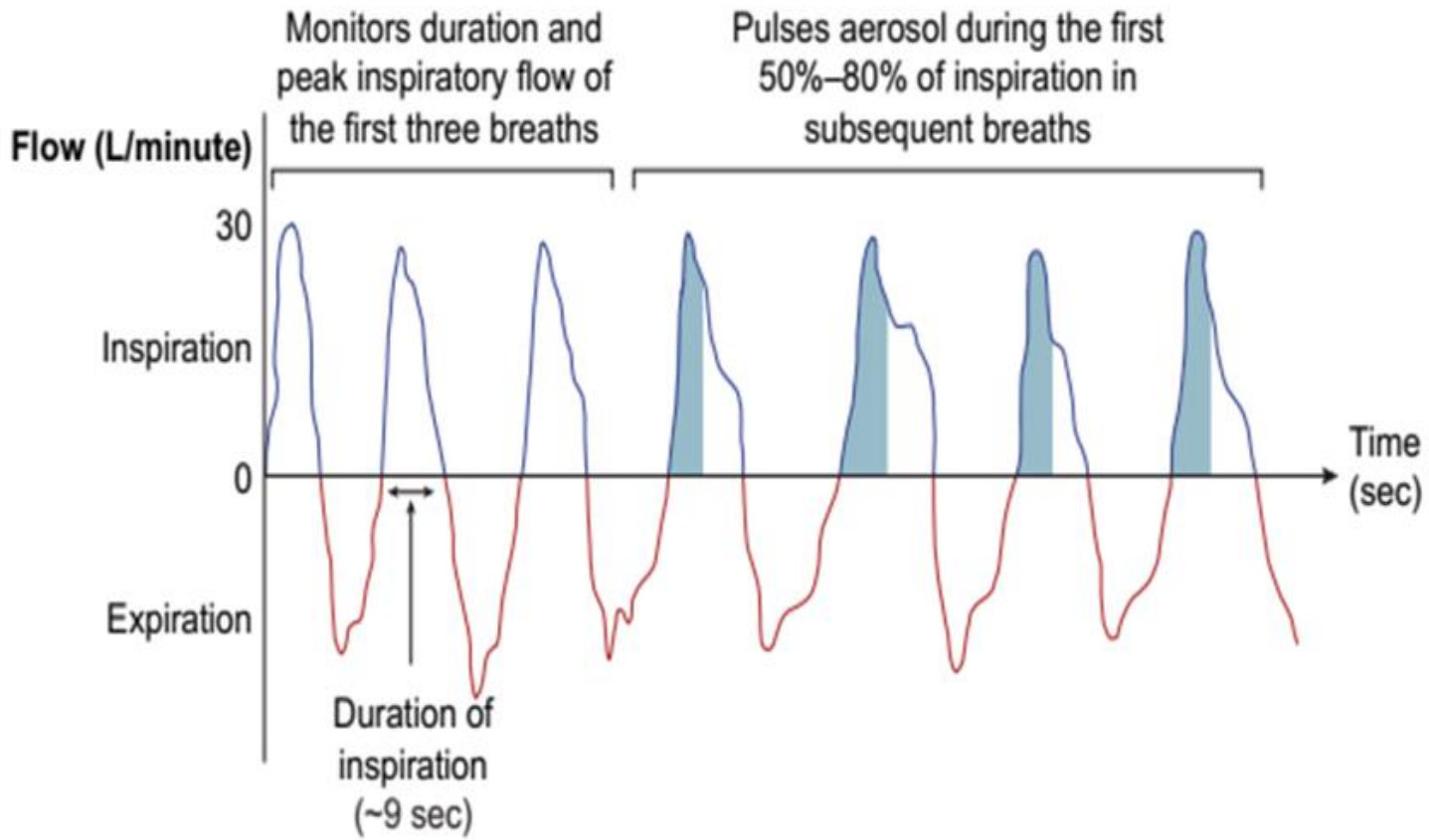


Figure 2 AAD technology used in the Akita® and I-neb® nebulizers.

Notes: During the first three breaths, AAD calculates when to pulse the aerosol. In subsequent breaths, AAD pulses aerosol during the first 50%–80% of inspiration (blue shade). Republished with permission of Respiratory Care: the official science journal of the American Association for Respiratory Care, from New Aerosol Delivery Devices for Cystic Fibrosis, KC Kesser and DE Geller, volume 54, edition 6, 2009; permission conveyed through Copyright Clearance Center, Inc.[105]

Abbreviation: AAD, adaptive aerosol delivery.

- That the additional airflow through the nebulizer draws more of the **small particles** generated out to be inspired (increased evaporation from droplets may occur so that smaller particles are produced)
- There is an increase in the amount of aerosol delivered to the patient and **less wastage** of aerosol during exhalation so that the dose of drug inspired may be doubled.
- **Lower compressors air flows** are needed to generate the respirable output, allowing cheaper compressors of lower specification to be used.

The disadvantages of the breath assisted

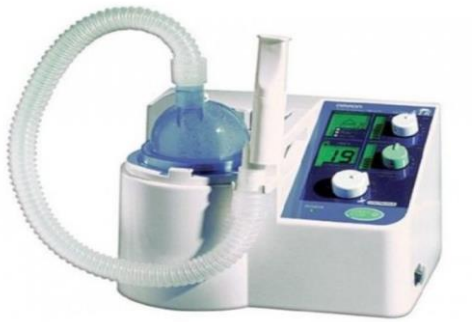
- They are dependent upon the patient’s inspiratory flow for optimum function and more information is needed before they can be recommended for young children.
- Viscous solutions (such as ceftazidime) may be nebulized slowly if a less powerful compressor is used.

Ultrasonic nebulizers

- The ultrasonic nebulizer, which uses a transducer made from a **piezoelectric crystal**, was put into production in the **1960s**, but was never as commercially successful as the jet nebulizer.
- The power unit converts **electrical energy to high-frequency ultrasonic waves**. A piezoelectric element in the transducer vibrates at the same frequency as the applied wave. Ultrasonic waves are transmitted to the surface of the solution to create an aerosol.
- A **fan** is used to deliver the aerosol to the patient, or the aerosol is evacuated from the nebulization chamber by the inspiratory flow of the patient.
- Small volume ultrasonic nebulizers **(eg, Beetle Neb, Lumiscope, Minibreeze)** are commercially available for delivery of bronchodilators.

ULTRASONIC NEBULIZERS

- Increase in solution **temperatures**
- **Incapable** of generating aerosols from **high viscosity liquids**
- **Incapable** of delivering microparticulate **dispersed dosage forms**, e.g. budesonide suspensions
- **Larger** average particle size
- **Faster**
- More **expensive**



MESH NEBULIZERS

- **Portable**
- **Battery-operated**
- **Minimal residual volume**
- Ability to deliver **expensive formulations** with **precise** dosing and **minimal** wastage
- **Reduce** the duration of each nebulizer treatment

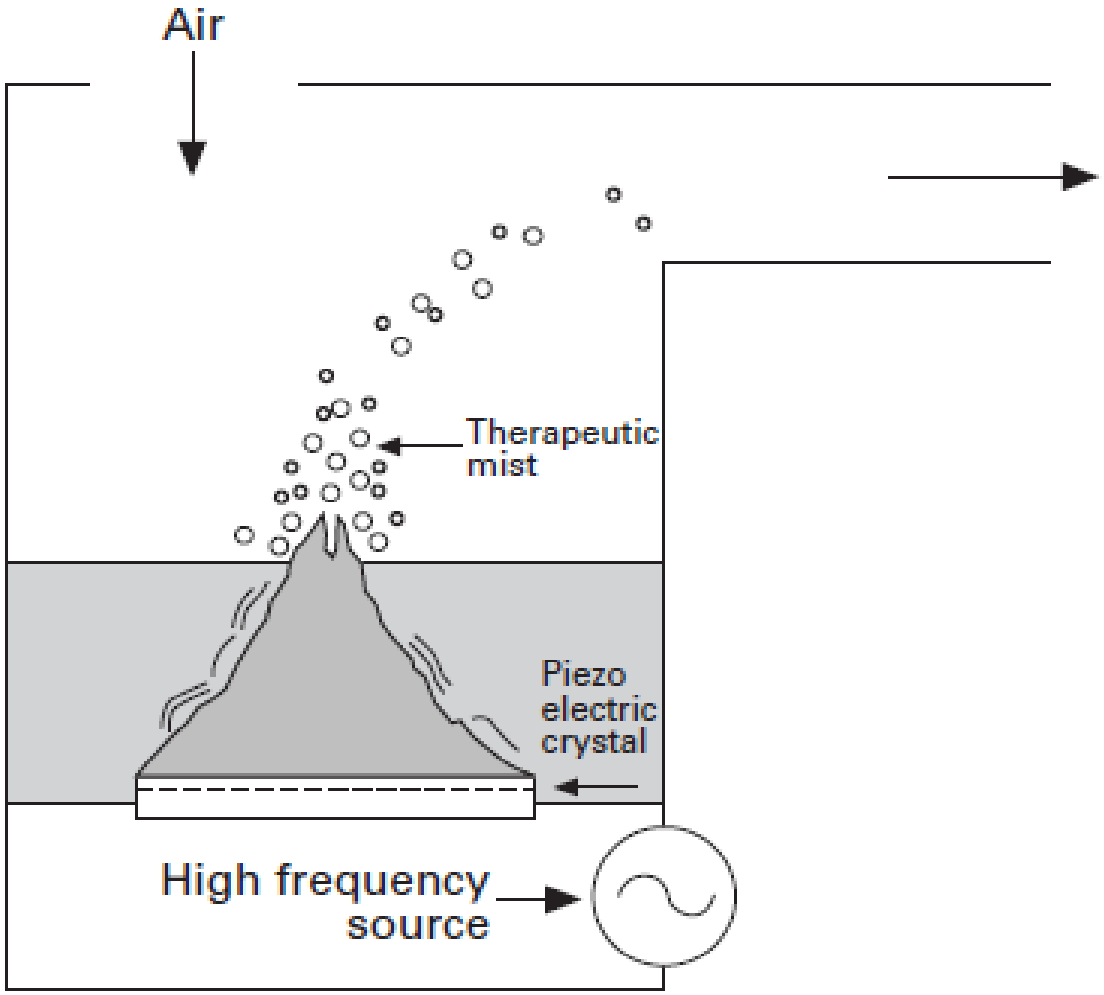
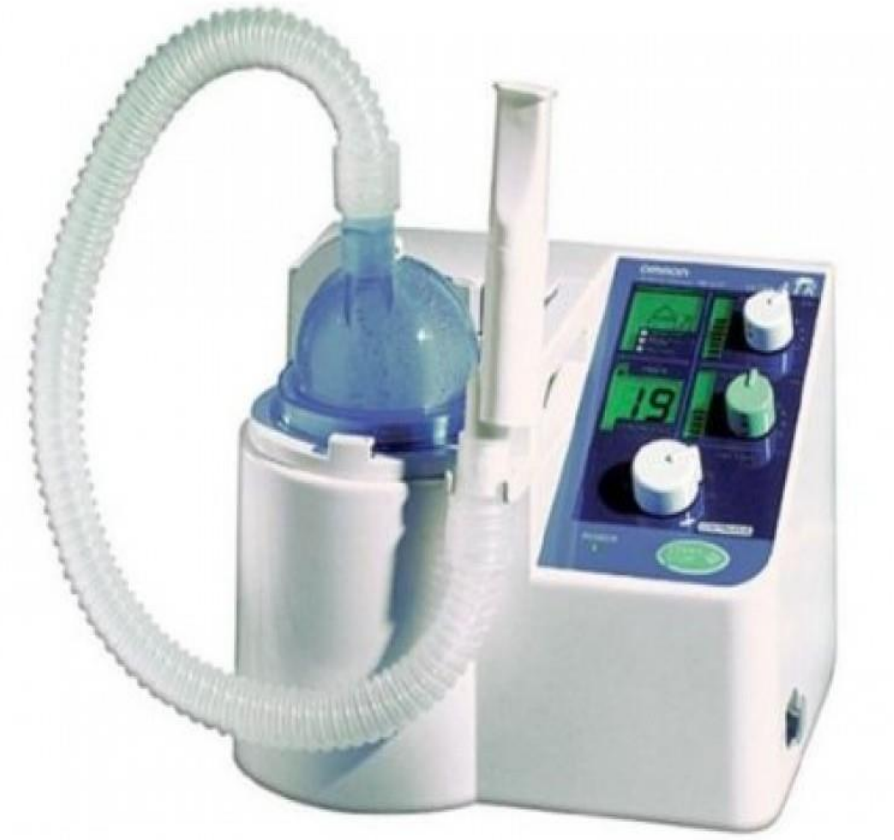
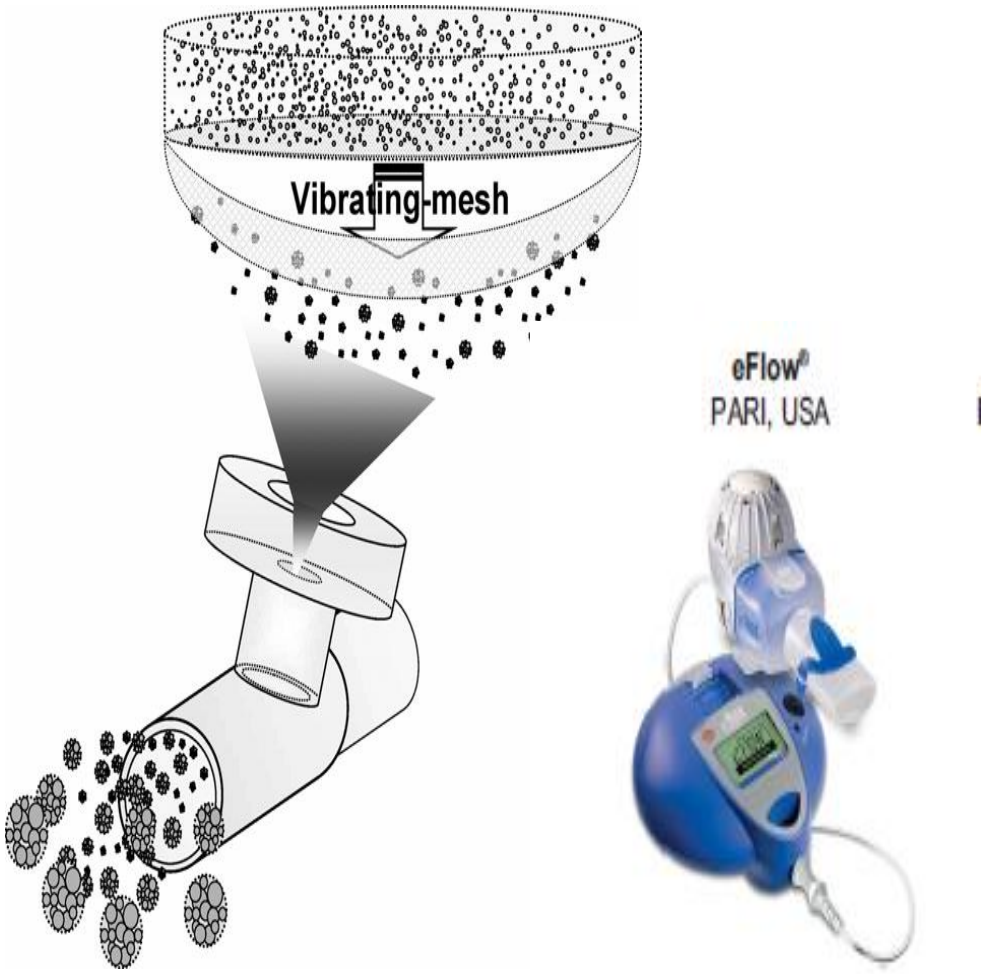


Figure 2 Schematic diagram of an ultrasonic nebuliser showing vibration of fluid with release of particles from the standing waves generated.



Ultrasonic nebulizers Considerations

- Ultrasonic nebulizers promote an **increase in solution temperatures** to as much as 10 °C above the starting temperature after a 5- to 10-min aerosolization period.
- Ultrasonic nebulizers are incapable of generating aerosols from **high viscosity liquids** (i.e. greater than 6 cP).
- Ultrasonic devices are well known for not being appropriate to deliver **microparticulate dispersed dosage forms**, such as budesonide suspensions. [ultrasonic nebulizers create aerosol droplets from the surface of the liquid. In suspensions, such as budesonide, the drug particles tend to settle and ultrasonic nebulizers are inefficient for aerosolization of suspensions.]



- Use a mesh or plate with multiple apertures to produce a liquid aerosol .
- the solution or suspension of medication is forced through the mesh to produce an aerosol, without need for an internal baffling system or compressed air source.
- A common feature of these devices is their ability to generate aerosols with a high fine-particle fraction, which results in more efficient drug delivery compared to conventional nebulizers.

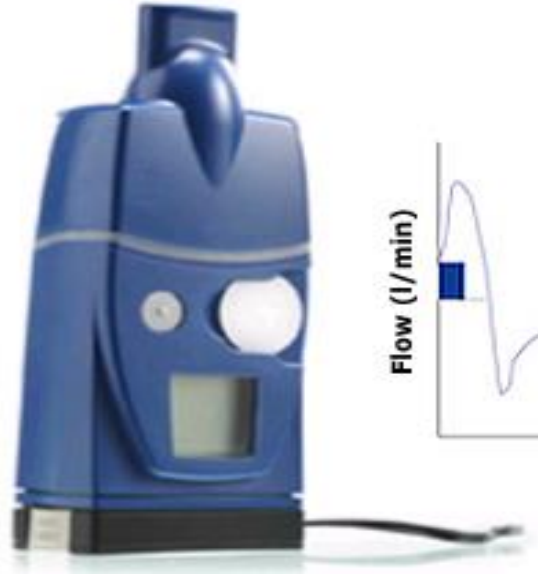
Mesh nebulizer

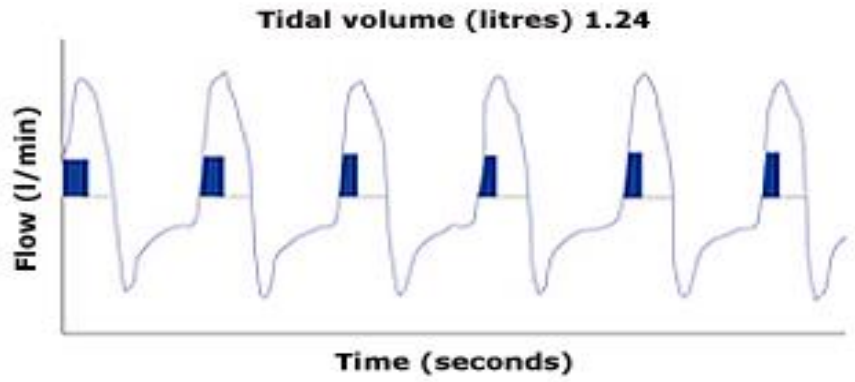
Examples of mesh nebulizers include the **eFlow** (Pari), **Aeroneb Solo** and **Aeroneb Go** (Aerogen), **MicroAIR/NE-U22** (OMRON), **InnoSpire Go**(Philips) and the **I-neb** (Respironics).

- **Portable**
- **Battery-operated**
- **Minimal residual medication volume**
- **Ability to deliver expensive formulations with precise dosing and minimal wastage**
- **Reduce the duration of each nebulizer treatment**

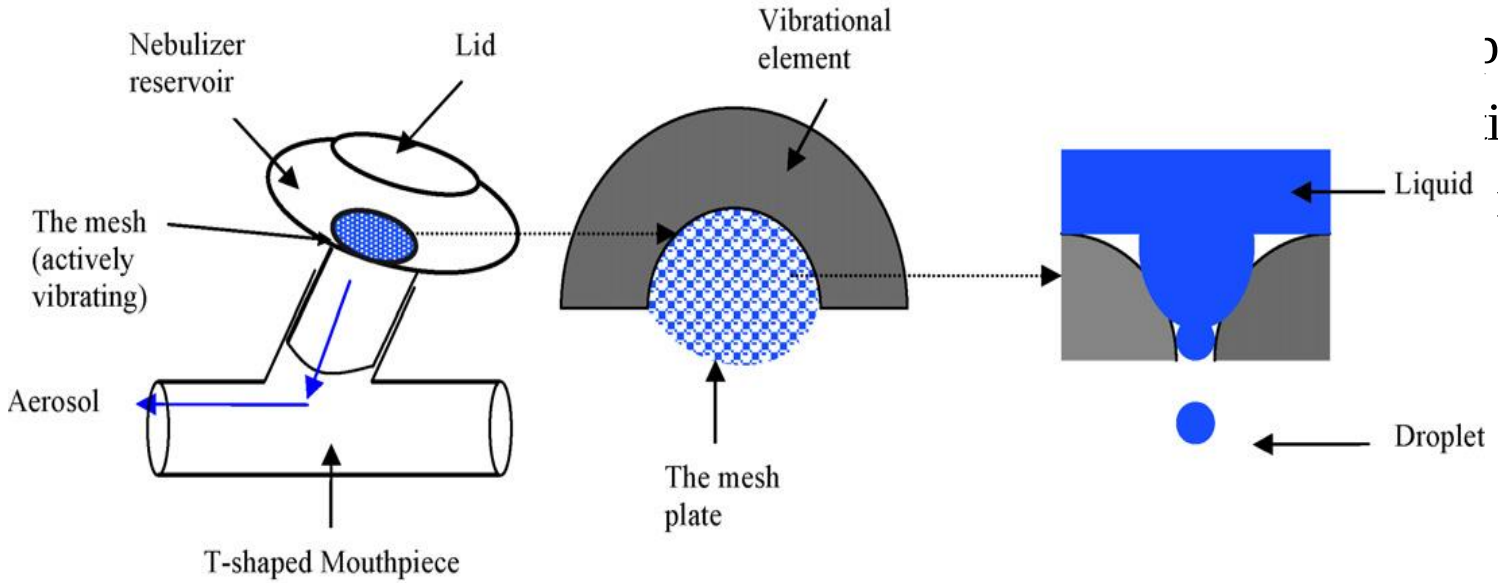
I-neb

- The I-neb nebulizer uses **mesh technology** combined with **Adaptive Aerosol Delivery (ADD).**
- This nebulizer is used specifically for the administration of **iloprost** (Ventavis) inhalation solution for the treatment of **pulmonary arterial hypertension.**





- Actively vibrating-mesh devices (e.g. Aeroneb Pro nebulizer) may emplo
  to 10
  ion of
  micro



T. Ghazanfari et al. / International Journal of Pharmaceutics 339 (2007) 103–111

Table 1. Features of different nebulizers[6]

Feature	Jet Nebulizer	Ultrasonic Nebulizer	Vibrating Mesh Nebulizer
Power source	Compressed gas or electric	Electric	Electric or battery
Portability	Limited	Limited	Portable
Treatment time (min)	15–20	4–10	<1–5
Output rate	Low	Higher	Highest
Performance variability	High	Intermediate	Low
Cleaning	Required after every use	Required after several uses	Required after every use
Environmental contamination	High with continuous use, low with breath activation	High with continuous use, low with breath activation	High with continuous use, low with breath activation
Cost	Very low	High	High
Formulation effects			
Temperature	Decreases	Increases	Minimum change
Concentration	Increases	Variable	Minimum change
Suspensions, efficiency	Low	Poor	Variable
Denaturation	Possible	Probable	Possible

فهرست تجهیزات و ملزومات پزشکی ثبت شده

در خصوص مشاهده استعلام فهرست کالاهای ثبت شده و استعلام قیمت وسیله پزشکی، اطلاعات با داشتن شرایط ذیل قابل نمایش روی سایت می باشد.

برای کالاهای وارداتی :

- در صورتیکه تاریخ اعتبار IRC یا نمایندگی منقضی شود، بعد از گذشت شش ماه در کلیه استعلام های سایت اداره غیرفعال و غیرقابل نمایش خواهد شد. بدیهی است پس از معتبر شدن IRC و یا نمایندگی، اطلاعات بصورت خودکار بروزرسانی خواهد شد و دوباره بر روی تمامی استعلامهای سایت نمایش داده می شود. در صورتیکه که شرکت تمایل به تمدید تاریخ اعتبار نداشته باشد می تواند بصورت مکتوب مشخصات و تعداد کالای در انبار خود را اعلام نماید و برای مدت مشخصی از اداره نظارت مجوز فروش دریافت نماید.

برای کالاهای تولیدی:

- در صورتیکه تاریخ اعتبار کلیه IRC منقضی شد، بعد از یکماه در استعلام های مرتبط همانند استعلام قیمت تجهیزات مصرفی مورد تایید جهت مراکز درمانی و استعلام تولید کنندگان دارای پروانه ساخت و استعلام فهرست تجهیزات پزشکی ثبت شده و ..... غیرقابل نمایش می شود. (تاریخ اعتبار IRC با تاریخ اعتبار پروانه یکسان باشد.) بدیهی است پس از معتبر شدن پروانه و IRC آن، اطلاعات بصورت خودکار بروز رسانی خواهد شد و دوباره بر روی تمامی استعلامهای سایت نمایش داده می شود. در صورتیکه که شرکت تمایل به تمدید تاریخ اعتبار نداشته باشد می تواند بصورت مکتوب مشخصات و تعداد کالای در انبار خود را اعلام نماید و برای مدت مشخصی از اداره نظارت مجوز فروش دریافت نماید.

مراجعه کننده گرامی ، شما میتوانید با انتخاب یک یا چند گزینه، به گزارش مورد نظر خود دسترسی پیدا کنید.

جستجو

گروه اصلی کالای پزشکی :

گروه فرعی کالای پزشکی :

شرکت نمایندگی :

نام کالا :

PARI eFlow Rapid

MicroAIR U100
Japan

multisonic infraControl
Germany

ME-700
Iran

Yuwell 402B
South Korea

NE-C300-E
Netherlands

Neb 1000
Italy

Pari sinus
Germany

Pro 110
Switzerland

CN-01W
Taiwan

NE-C28
Italy

- Some drug preparations are only approved for delivery with specific nebulizers due to factors such as **preventing contamination** of the ambient environment, **achieving greater precision** in dosing, or **preventing medication degradation** by the aerosol technology:

1- Aztreonam – Inhaled aztreonam is administered using the **Altera** Nebulizer System, which uses **mesh** nebulizer technology.

2- Ribavirin – A specialized jet nebulizer is used to allow the safe delivery of aerosolized ribavirin, which is potentially **teratogenic**. The Valeant Small-Particle Aerosol Generator (SPAG-2) is designed specially to aerosolize ribavirin.

4- Amikacin: Amikacin (Arikayce) **liposome inhalation suspension** is delivered once daily with the **Lamira** **mesh nebulizer system**. During nebulization, approximately 70 percent of the amikacin dose remains encapsulated within liposomes while approximately 30 percent of the dose is released as free amikacin. Nebulized amikacin is indicated for patients who remain **culture positive after six months** of multidrug treatment for ***Mycobacterium avium complex*** (MAC).

(Arikayce®) 590mg/8.4mL (623mg/8.4mL amikacin sulfate equivalent)

Mechanically ventilated patients

- One major factor is that **humidification** of inhaled gas **decreases aerosol deposition (and rise in particle size)** by approximately 40 percent due to increased particle drug deposition in the ventilator circuit. For this reason, **increased dosage** of medication is often required to achieve a therapeutic effect in mechanically ventilated patients.
- Nebulizer performance can be optimized by placing the nebulizer **30 cm from the endotracheal tube**, rather than at the Y-piece, because the inspiratory ventilator tubing acts as a spacer.
- Unlike the jet nebulizer, the **mesh nebulizer** remains in the ventilator circuit and does not interfere with ventilator function.

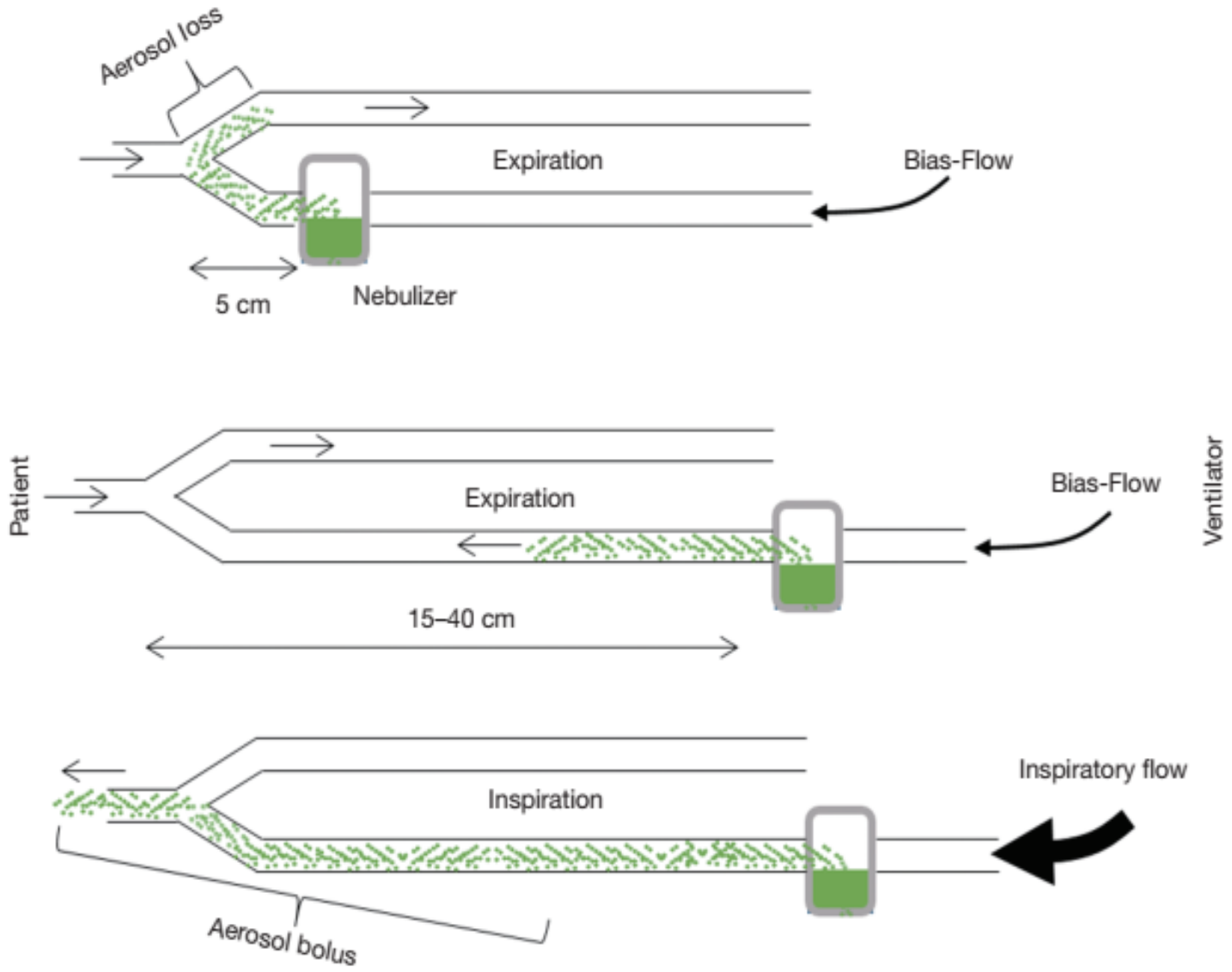


Figure 1 Influence of the nebulizer position on aerosol loss during expiration. With permission (19).

High flow nasal cannula

- When aerosols are delivered via a nebulizer and, the ratio of HFNC gas flow to patient's inspiratory flow is critical; the **optimal** inhaled dose is achieved with the **HFNC gas flow** set at about **50 percent** of patient's **inspiratory flow**.

Mouthpieces or facemasks ???

The **mouthpiece** interface is generally preferred.

Bronchodilator response appears **similar** with either interface, and some have argued that the selection of patient interface should be based upon

patient preference.

Significant **facial and eye deposition** of aerosol can occur when a face mask is used, deposition is of particular concern when aerosolized **anticholinergic agents** (eg, ipratropium) are administered, as this can result in **blurring of vision, pupil dilation, and worsening of narrow angle glaucoma**.

When a **facemask** is used, it is important to instruct the patient to inhale through the mouth to minimize nasopharyngeal deposition of medication.

Consideration

- **Nebulizer and Covid-19 ???**

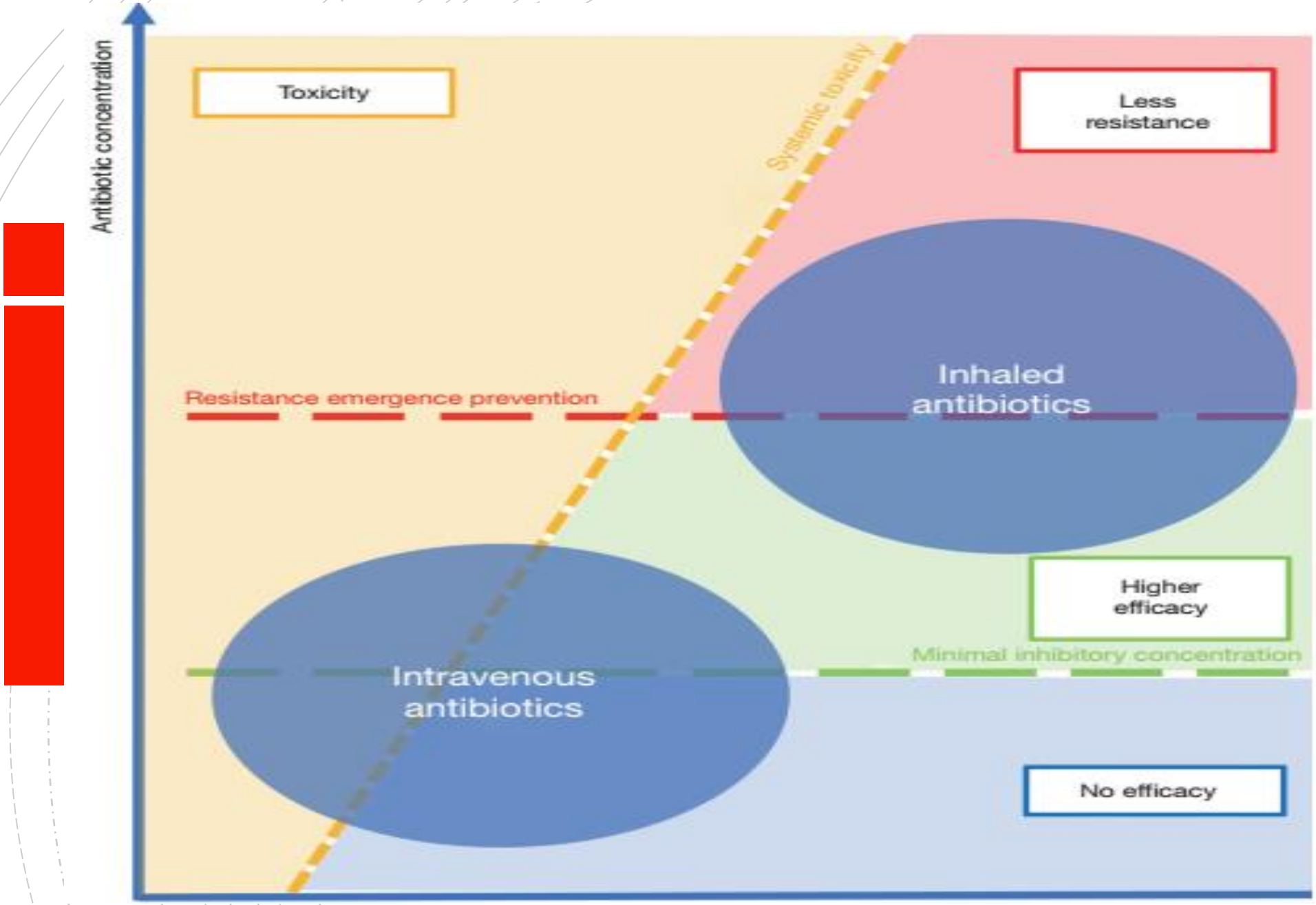
According to the Centers for Disease Control and Prevention(CDC) and World Health Organization (WHO), it is uncertain whether aerosols generated from nebulizer administration are infectious.

- Unlike jet nebulizers, **mesh nebulizers are preferred** as nebulizing device because their medication reservoir is isolated from the breathing circuit that eliminates the nebulization of contaminated fluids.

- Inhaled rather than systemic antibiotics are recommended due to their high effectiveness. **(Strong recommendation. Moderate quality evidence)**

- significant reduction of bacterial load
- decrease in local inflammation
- improved quality of life and reduction in the number of exacerbations.
- good safety profile
- High antibiotic concentrations at the infection site
- Minimal systemic side effects and lower rate of resistance

- Part of the reason for the clinical benefit of adjunctive inhaled antibiotic therapy is that the antibiotic efficacy against bacteria in purulent secretions may require an antibiotic concentration greater than **10–25 times** the minimum inhibitory concentration (MIC), which could not be achieved by intravenous treatment alone, which however inhaled antibiotic therapy may achieve.


Antibiotic concentration
Toxicity
Systemic toxicity
Less resistance
Resistance emergence prevention
Inhaled antibiotics
Higher efficacy
Minimal inhibitory concentration
Intravenous antibiotics
No efficacy

Chronic P. aeruginosa infection

- In alphabetical order:
- **Aztreonam lysine** (solution for inhalation) or
- **Ciprofloxacin** (dry powder or solution for inhalation) or
- **Colistimethate** (dry powder or solution for inhalation) or
- **Gentamicin** (**i.v. formulation** administered via inhalation) or
- **Tobramycin** (dry powder or solution for inhalation)

Chronic P. aeruginosa infection

- **Gentamicin** is an i.v. formulation delivered via the inhaled route **(80 mg, twice daily, continuous treatment).** Gentamicin is **not** marketed in a specific preparation for inhalation.
- The **colistimethate sodium** dose depends on the efficacy of the nebulizer used. Lower doses **(1 mU, twice daily)** should be used with an adaptive aerosol delivery nebulizer, such as the **I-neb**, although there is

Chronic MRSA infection

- **Vancomycin** (i.v. formulation administered via inhalation), continuous treatment, **250 mg, twice daily**.

Chronic infection with other PPM

- **Gentamicin** is an i.v. formulation used via the inhaled route (**80 mg, twice daily, continuous treatment**)

Or Any of the inhaled antibiotics used in chronic P. Aeruginosa infection:

If the response is insufficient:

(a) Try efficacy with **other i.v. formulations** of antibiotics administered **via inhalation** or

(b) Add (or switch) the inhaled antibiotic for an **oral** one according to the

antibiotic sensitivities of the PPM causing the infection.

European Respiratory Society guidelines for the management of adult bronchiectasis

Eva Polverino[1], Pieter C. Goeminne[2,3], Melissa J. McDonnell[4,5,6], Stefano Aliberti[7], Sara E. Marshall[8], Michael R. Loebinger[9], Marlene Murris[10], Rafael Cantón[11], Antoni Torres[12], Katerina Dimakou[13], Anthony De Soyza[14,15], Adam T. Hill[16], Charles S. Haworth[17], Montserrat Vendrell[18], Felix C. Ringshausen[19], Dragan Subotic[20], Robert Wilson[9], Jordi Vilaró[21], Bjorn Stallberg[22], Tobias Welte[19], Gernot Rohde[23], Francesco Blasi[7], Stuart Elborn[9,24], Marta Almagro[25], Alan Timothy[25], Thomas Ruddy[25], Thomy Tonia[26], David Rigau[27] and James D. Chalmers[28]

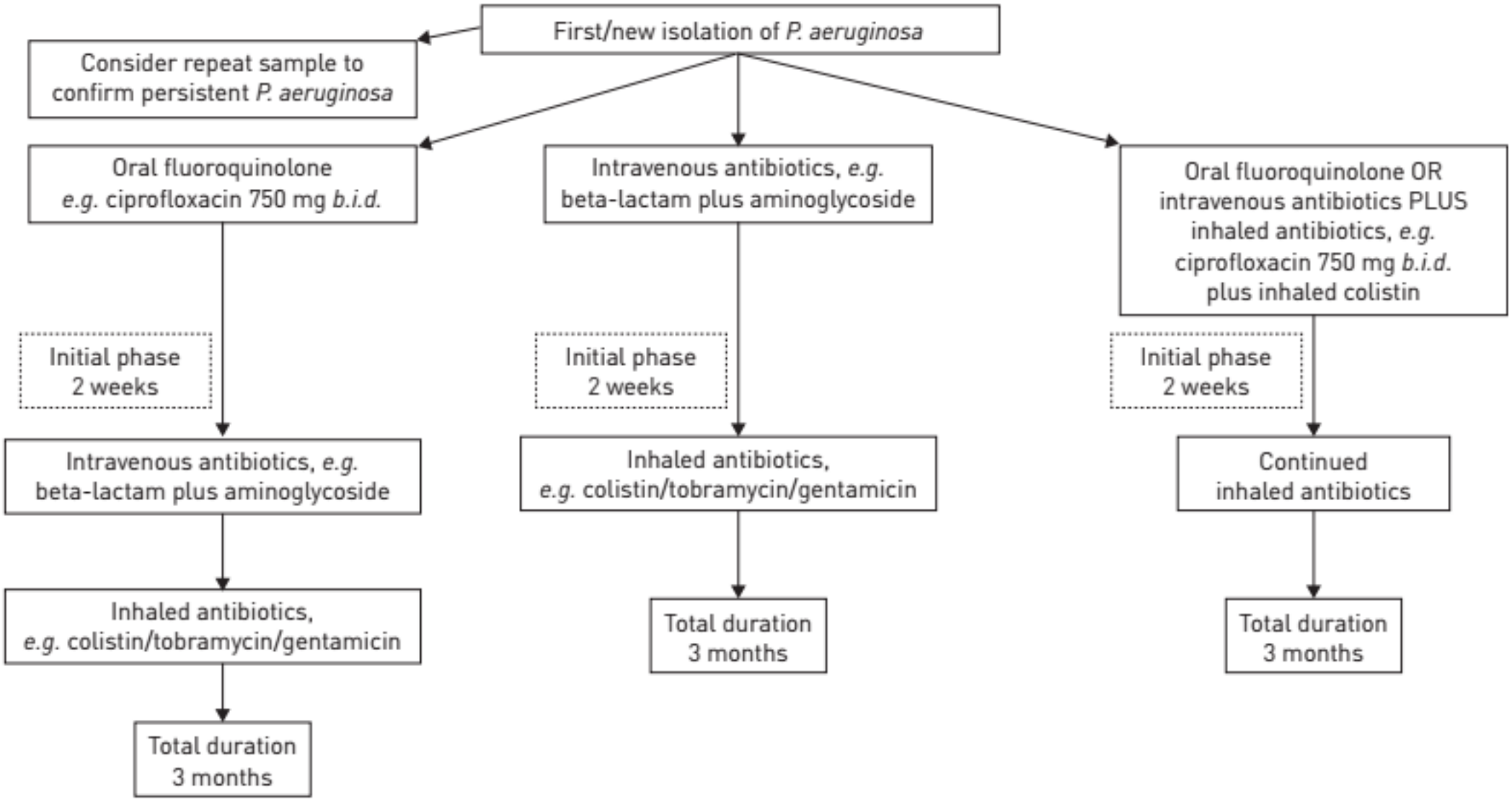


FIGURE 3 Three possible and alternative eradication treatment pathways based on what is commonly used in clinical practice. After each step it is recommended to repeat sputum sampling for *Pseudomonas aeruginosa* and to progress to the next step if the culture remains positive.

long-term antibiotic treatment (⩾3 months)

- We suggest long-term(⩾3 months) treatment **with an inhaled antibiotic** for adults with bronchiectasis and chronic **P. aeruginosa** infection **(conditional recommendation, moderate quality evidence)**
- We suggest offering long-term antibiotic treatment for adults with bronchiectasis who have **three or more exacerbations per year (conditional recommendation, moderate quality evidence).**

- For individuals with **P. aeruginosa**, the currently available evidence supports continuous use of nebulised **colistin or gentamicin**.
- **Nebulised aztreonam** is **not** recommended due to the **lack of efficacy** with regard to quality of life improvement over two treatment cycles and a **high adverse event** rate reported in the pivotal phase III trials.

Uptodate

Ceftazidime, or Aztreonam

±

systemic Aminoglycoside for 14 days

Spanish guideline

1-2 iv antibiotic with anti pseudomonas activity for 2-3 weeks plus Inhaled antibiotic **(colistimethate, tobramycin or azteronam)** as long as the benefit/risk is favorable

European guideline

Intravenous beta lactam + Aminoglycoside for 2 weeks
Followed by inhaled antibiotic **(colistimethate or gentamicin)** for at least 3 months

Consideration

Intravenous antibiotic formulations delivered via inhalation **should not** be used if **the same antibiotic** is available in a formulation for inhalation.

There are **four aerosolized antibiotics** that have received approval either from European Medicines or the U.S. Food and Drug Administration: **aztreonam, amikacin liposome, colistin, and tobramycin.**

There is **no guarantee** that the preparation is identical to that approved by the corresponding regulatory agencies; therefore, these formulations must be **administered with caution**, as they may be poorly tolerated and present a higher risk of adverse effects.

In **hemoptysis**, the use of inhaled drugs and respiratory physiotherapy should be avoided until **48 h** after resolution.

Consideration

- Patients who use inhaled antibiotics on **alternate months** and present clinical worsening during the off-months (28-day periods) could benefit from using them **continuously**, alternating or rotating them with another antibiotic with **no off-period**, or shorter breaks (14 days).
- We suggest using **bronchodilators before** physiotherapy, inhaled mucoactive drugs, as well as **before inhaled antibiotics**, in order to **increase tolerability and optimise pulmonary deposition** in diseased areas of the lungs **(good practice point, indirect evidence).**

Consideration

- Rotation or alternation of antibiotics could be useful to minimize the development of resistances. There is **no evidence** that inhalation of **2 concomitant antibiotics** is more effective than **using 1 alone**, so this practice should only be used in particularly **refractory patients** (multi-resistant microorganisms).
- **Mesh nebulizers** and dry powder inhalers are more effective than jet nebulizers. **Ultrasonic nebulizers should not** be used as they may inactivate the antibiotic.
- Relatively high doses of amikacin are typically recommended because **mucin binding may be as high as 90%.**

- 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).**
  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).
- When a 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 non-randomized).
- However, the optimal administration, **dosage, and safety** of inhaled antibiotic therapy are **not very clear**, and more research on these aspects is needed in the future.

Considerations

- To minimize adverse effects, aerosolized drug solutions should have an osmolality of **150–1200 mOsm/kg**, a sodium content of **77–154 mEq/L**, and a pH of **2.6–10.12**
- preservatives, such as **phenols and sulfites** found in some parenteral drug formulations, may contribute to **cough, airway irritation, and bronchoconstriction**.

Colistin Considerations

J. Rello, Clin Microbiol Infect 2017;23:640

- Effective pulmonary concentrations of **colistin** are typically achieved by administering **three daily doses of 80 mg** of colistimethate sodium, although this dose **might not be sufficient** to treat resistant organisms. Indeed, the **rate of conversion** from colistimethate sodium to active drug is unknown, and somewhat inconsistent data has been reported.
- **Colistimethate sodium** is administered on a **continuous basis** (with no need for on/off cycles), on account of the **low rate** of resistance of P. aeruginosa to this antibiotic.

Colistin Considerations

- **Colistimethate sodium** (the parenteral formulation) has been associated with **fewer respiratory adverse effects** compared with **colistin sulfate** (the oral formulation).
- Compared with **aminoglycosides**, colistin appears to have a **higher** rate and more severe presentation of **pulmonary adverse events**.

Colistin Considerations

- Colistin is easily **hydrolyzed** to **active drug** and a **toxic metabolite** after mixture with a diluent. If this product is not used within **24 hours** of preparation, **direct lung injury** and resultant systemic drug exposure can result. This is believed to be the mechanism attributed to the **fatal case report** described in the FDA communication to providers.
- Therefore, it is essential that colistin be **compounded immediately** before use to avoid potentially **fatal pulmonary toxicity**.

(Pharmacotherapy 2010;30(6):562–584)

Amikacin consideration

- High lung tissue concentrations of amikacin are obtained after a single daily nebulization of **15 to 30 mg/kg**.
- Such high doses provide rapid bacterial killing, and the long **postantibiotic effect** allows a single daily administration during **3 to 5 days.**
- Relatively high doses of amikacin are typically recommended because **mucin binding may be as high as 90%.**

J. Rello, Clin Microbiol Infect 2017;23:640

Consideration

- Since they can cause Provoke **coughing or sneezing, dyspnea, tachycardia, hyper- or hypotension, hypoxemia and Bronchospasm** the first dose should be given under supervision following.
- The use of inhaled antibiotics is associated with a **10–32%** risk of **bronchospasm** and a supervised test dose with pre- and post-spirometry is recommended. Prior inhalation of a **short-acting bronchodilator** may prevent bronchospasm and, therefore, is advisable.
- MCCULLOUGH et al. assessed **compliance** in 75 patients with bronchiectasis and found self-reported adherence of **52%** for inhaled antibiotics

Table 3
Inhaled Antimicrobials.

Antimicrobial and Formulation	Marketed in Spain (at the Time of Writing)	Dose, Frequency	Delivery Time	Inhalation System
Inhaled amikacin	No	400 mg, once daily, 28 days on, 28 days off	11–13 min	e-Flow® nebulizer system
Aztreonam lysine, solution for inhalation	Yes	750 mg, three times daily, 28 days on, 28-days off	2–3 min	e-Flow® nebulizer system (Altera)
Ciprofloxacin, solution for inhalation	No	150 mg (liposomal), 60 mg (non-liposomal), once daily, 28 days on, 28 days off	No data	Jet nebulizer (PARI LC Sprint®)
Ciprofloxacin, dry powder for inhalation	No	32.5 mg, twice daily, 14 days on, 14 days off[b]	No data	T-326® inhaler
Colistimethate, dry powder for inhalation	Yes	1 662 500 IU (125 mg of colistimethate), twice daily, continuous treatment	1–2 min	Turbospin®
Colistimethate, solution for inhalation[a]	Yes	2 million IU (1 million=80 mg of colistimethate), twice daily, continuous treatment	Variable, depending on the nebulizer	e-Flow® nebulizer system, Pari LC plus®
	Yes	1 million IU, twice daily, continuous treatment	3.7 ± 2.3 min	I-neb AAD®
Levofloxacin	No	240 mg, twice daily, 28 days on, 28 days off	5 min	e-Flow® nebulizer system (Zirela)
Tobramycin, dry powder for inhalation	Yes	112 mg, twice daily, 28 days on, 28 days off	~6 min	T-326 inhaler
Tobramycin, solution for inhalation	Yes	300 mg/5 mL, twice daily, 28 days on, 28 days off	Variable, depending on the nebulizer	e-Flow® nebulizer system, Pari LC plus®
	Yes	300 mg/4 mL, twice daily, 28 days on, 28 days off	Variable, depending on the nebulizer	Nebulizer system e-Flow®, Pari LC plus®

[a] The colistimethate sodium dose depends on the efficacy of the nebulizer used. Lower doses (1 mU, twice daily) should be used with an adaptive aerosol delivery nebulizer, such as the I-neb®, although there is a lack of lung deposition studies to confirm this.

[b] At the time of writing, studies have concluded that there is better efficacy with 14-day on/off cycles than with 28-day on/off cycles.

TABLE 2 Current state of development of inhaled antibiotic agents for non-cystic fibrosis bronchiectasis

Agent [ref.]	n	Current phase of development	Primary outcome	Duration	Patient population	Main results	Safety
Amoxicillin [78–80]	6 (78); 3 (79); 5 (80)	Three open label studies following failure of oral antibiotics	Sputum purulence	Continuous; 4 months/ 16 weeks	Bronchiectasis patients with purulent sputum that failed to clear following oral amoxicillin	Reduced sputum purulence; reduced neutrophil elastase activity ; reduced sputum volume; improved PEFR	No issues identified
Tobramycin [81]	A: 37; P: 37	Phase II study	*P. aeruginosa* bacterial load	28 days treatment (total duration 8 weeks)	*P. aeruginosa*-colonised patients; mean age 66 *versus* 63 years; FEV_1 mean 56 *versus* 53%	Significant reduction in *P. aeruginosa* load (mean difference 4.56 $\log_{10}$ CFU·mL^{-1}, $p<0.01$); 13/37 cleared *P. aeruginosa* from sputum; no significant change in FEV_1, $p=0.41$	Increased dyspnoea, chest pain and wheezing; new resistance to tobramycin in 4/36
Gentamicin [82]	A: 27; P: 30	Single-blind randomised controlled trial	Bacterial load	12 months	Patients colonised with any pathogens in at least three sputum samples in the preceding 12 months; two exacerbations in the previous year; able to tolerate test dose of gentamicin; FEV_1 >30% predicted; exsmokers of >1 year; not on long-term antibiotics	Significant difference in bacterial load at 12 months (2.96 $\log_{10}$ CFU·mL^{-1} *versus* 7.67 $\log_{10}$ CFU·mL^{-1}, $p<0.0001$); reduction in exacerbations (median 0 in the gentamicin group, 1.5 in the saline group, $p<0.0001$); improved SGRQ and LCQ scores; reduced airway inflammation	Bronchospasm in 21.9%, two withdrawals; elevated serum gentamicin levels required dose reduction in one patient; no resistant isolates detected

Colistin [83]	A: 73; P: 71	Phase III double-blind randomised controlled trial	Time to first exacerbation	6 months (patients withdrawn following exacerbation)	*P. aeruginosa*-colonised patients (two or more positive cultures in 12 months) and within 21 days of completing antipseudomonal antibiotics for an exacerbation	Missed primary end-point (colistin 165 days, placebo 111 days, p=0.11); improved SGRQ (mean difference −10.5 points, p=0.006); improved time to first exacerbation in patients taking >80% of doses	Five patients (7%) developed bronchoconstriction leading to discontinuation; no resistant strains at follow-up
Aztreonam [84]	AIR-BX1: A: 134; P: 132. AIR-BX2: A: 136; P: 138	2× phase III double-blind randomised controlled trial	QOL-B questionnaire score at week 4	Two 28 day treatment courses with alternating 28 day off treatment	Positive sputum for *P. aeruginosa* or other Gram-negative organisms (excluding *H. influenzae*) FEV_1 >20% predicted; chronic sputum production	No difference in QOL-B at week 4 (mean difference 0.8 [95% CI −3.1–4.7, p=0.7] in AIR-BX1 and 4.6 [1.1–8.2, p=0.011] in AIR-BX2); no difference in QOL-B in both studies at week 12 (p=0.56 in both studies); no difference in time to first exacerbation	AIR-BX1 adverse events leading to discontinuation: 22 *versus* 6%; AIR-BX2-adverse events leading to discontinuation: 10 *versus* 5%

Continued

TABLE 2 Continued

Agent [ref.]	n	Current phase of development	Primary outcome	Duration	Patient population	Main results	Safety
Ciprofloxacin DPI [86]	A: 60; P: 64	Phase II double blind randomised controlled trial	Bacterial load	28 days treatment with follow-up to 84 days	Idopathic or post-infective bronchiectasis; two or more exacerbations in the previous 12 months (one hospitalisation); able to produce sputum; culture positive for target microorganisms	Mean difference in bacterial load -3.62 $\log_{10}$ CFU·mL^{-1} *versus* -0.27 $\log_{10}$ CFU·mL^{-1}, p<0.001; no significant differences in proportion of patients with exacerbations (36.7 *versus* 39.1%, p=0.6); no significant difference in SGRQ (mean difference −3.56, p=0.059)	10% of patients developed resistance (MIC >4 mg·L^{-1}) in the ciprofloxacin group; no difference in adverse events between groups
Liposomal ciprofloxacin [87]	A: 20; P: 22	Phase II study double blind randomised controlled trial	Bacterial load after first 28-day treatment cycle with intervening 28-day off periods)	24 weeks (three 28-day treatment cycles)	*P. aeruginosa*-colonised patients; ≥2 exacerbations in previous 12 months	Reduction in *P. aeruginosa* bacterial load −4.2 *versus* -0.08 $\log_{10}$ CFU·mL^{-1}, p=0.002; reduced number of exacerbations in the active treatment group (OR 0.2 95% CI 0.04–0.89, p=0.027); median time to pulmonary exacerbations reduced in the per protocol population (p=0.046)	No significant difference in minimal inhibitory concentrations to ciprofloxacin at day 28; no increase in adverse events

PEFR: peak expiratory low rate; A: active; P: placebo; *P. aeruginosa*: *Pseudomonas aeruginosa*; FEV_1: forced expiratory volume in 1 s; SGRQ: St. Georges Respiratory Questionnaire; LCQ: Leicester Cough Questionnaire; QOL-B: quality of life bronchiectasis questionnaire; DPI: dry powder for inhalation; MIC: minimum inhibitory concentration.

American Journal of Respiratory and Critical Care Medicine

A Randomized Controlled Trial of Nebulized Gentamicin in Non-Cystic Fibrosis Bronchiectasis

Maeve P. Murray [1,2,3], John R. W. Govan [2], Catherine J. Doherty [2], A. John Simpson [3], Thomas S. Wilkinson [3], James D. Chalmers [3], Andrew P. Greening [3,4], Christopher Haslett [3], and Adam T. Hill [1,3]

+ Author Affiliations

Gentamicin has been used widely in the UK following the publication of this trial.

https://doi.org/10.1164/rccm.201005-0756OC PubMed: 20870753

Received: May 12, 2010 Accepted: September 24, 2010

- **65 patients** were randomized to either **twice-daily nebulized gentamicin, 80 mg**, or **nebulized 0.9% saline**, for **12 months**.
- Reduced **sputum bacterial density** with **30.8%** eradication in those infected with Pseudomonas aeruginosa and **92.8%** eradication in those infected with other pathogens.
- **less sputum purulence** (8.7% vs. 38.5%; P , 0.0001)
- **greater exercise capacity** (510 [350–690]m vs. 415[267.5–530] m; P 5 0.03);
- **Fewer exacerbations** (0 [0–1] vs. 1.5 [1–2]; P , 0.0001)
- increased time to first exacerbation (120 [87–161.5] d vs. 61.5 [20.7–122.7] d; P 5 0.02).
- greater improvements in **Leicester Cough Questionnaire** (81.4% vs. 20%; P , 0.01) and St. **George's Respiratory Questionnaire** (87.5% vs. 19.2%; P , 0.004) score.
- **No differences** were seen in 24-hour sputum volume, FEV1, FVC, or forced expiratory flow, midexpiratory phase.
- **No P. aeruginosa** isolates developed resistance to gentamicin.

ORIGINAL ARTICLE

Inhaled Colistin in Patients with Bronchiectasis and Chronic *Pseudomonas aeruginosa* Infection

Charles S. Haworth[1], Juliet E. Foweraker[2], Peter Wilkinson[3], Robert F. Kenyon[4], and Diana Bilton[5]

[1]Cambridge Centre for Lung Infection and [2]Department of Microbiology, Papworth Hospital, Cambridge, United Kingdom; [3]Wilkinson Associates, Radnage, Bucks, United Kingdom; [4]Profile Pharma Ltd., Tangmere, Chichester, West Sussex, United Kingdom; and [5]Host Defence Unit, Royal Brompton Hospital, London, United Kingdom

- The study was conducted at **35 centers** in the United Kingdom, Russia, and Ukraine.
- Patients with bronchiectasis (confirmed by computed tomography) and chronic P. Aeruginosa infection were enrolled within **21 days** of completing a course of antipseudomonal antibiotics for an exacerbation.
- Participants were randomized to receive **colistin (1 million IU; n = 73)** or placebo (0.45% saline; n = 71) via the **I-neb twice a day**, for up to **6 months**.
- **The median time to exacerbation** was 168 (65) versus 103 (37) days. (P = 0.038)
- **P. aeruginosa density was reduced** after 4 (P = 0.001) and 12 weeks (P = 0.008).
- The St. George's Respirator Questionnaire total score was improved after 26 weeks (P = 0.006)

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NARRATIVE REVIEW

Ventilator-associated pneumonia in adults: a narrative review

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- To date, nebulized antibiotics **cannot** be recommended as an **alternative** to the intravenous route.
- The use of nebulised antibiotics as an **adjunctive** treatment (i.e., in addition to effective intravenous therapy) is also **not** recommended.
- The use of nebulised antibiotics should therefore be **restricted** to patients with VAP to **XDR-Gram-negative** pathogens susceptible only to colistin or aminoglycosides.
- Indeed, three meta-analyses found that in patients infected with such pathogens, the use of **nebulised colistin combined with IV colistin** led to better outcomes compared to IV colistin alone.

Nebulizer in pulmonary infections

- Nebulized inhaled antibiotic is one of the methods proposed in recent years to treat resistant organisms **(including MDR, extensively drug resistant and pan-resistant organisms).**
- Results of a meta-analysis showed that adjunctive inhaled antibiotics (including amikacin liposome, gentamicin, colistin, and tobramycin) may benefit patients with VAP **caused by MDR or difficult-to-treat organisms.**

- American guidlines believe that for patients who **could not respond to intravenous antibiotics alone**, regardless of whether the infected organism is MDR, it is reasonable to consider **adjunctive inhaled antibiotic** therapy as the last treatment option.
- In contrast, recent European recommendations **do not mention** inhaled antibiotics in the setting of VAP and an ESCMID panel positioned against their use putting forward the **weak evidence** in favor of efficacy and potentially underestimated risks of adverse events.


THANKS FOR YOUR ATTENTION