Aerosol Therapy in Pulmonary Critical Care

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Overview

- Introduction
- Mechanism of aerosol deposition
- Types of nebulizers
- Ventilator parameters affecting aerosol deposition
- Drugs for aerosol therapy

Introduction

- An aerosol is defined as a suspension of liquid or solid in a gaseous medium
- The aim of aerosol therapy is to deliver a therapeutic dose of the drug to the desired site of action

Advantages of pulmonary delivery of drug

- Deliver high drug concentrations directly to the disease site
- Minimizes risk of systemic side-effects
- Rapid clinical response
- Bypass barriers to therapeutic efficacy, such as poor gastrointestinal absorption and first-pass metabolism in liver
- Achieve a similar or superior therapeutic effect at a fraction of the systemic dose

Aerosol system includes

- The drug
- The aerosol device
- The patient’s respiratory system
- The ventilator system

Pharm Res. 2007;24(2):203–27

Efficiency of the aerosol system

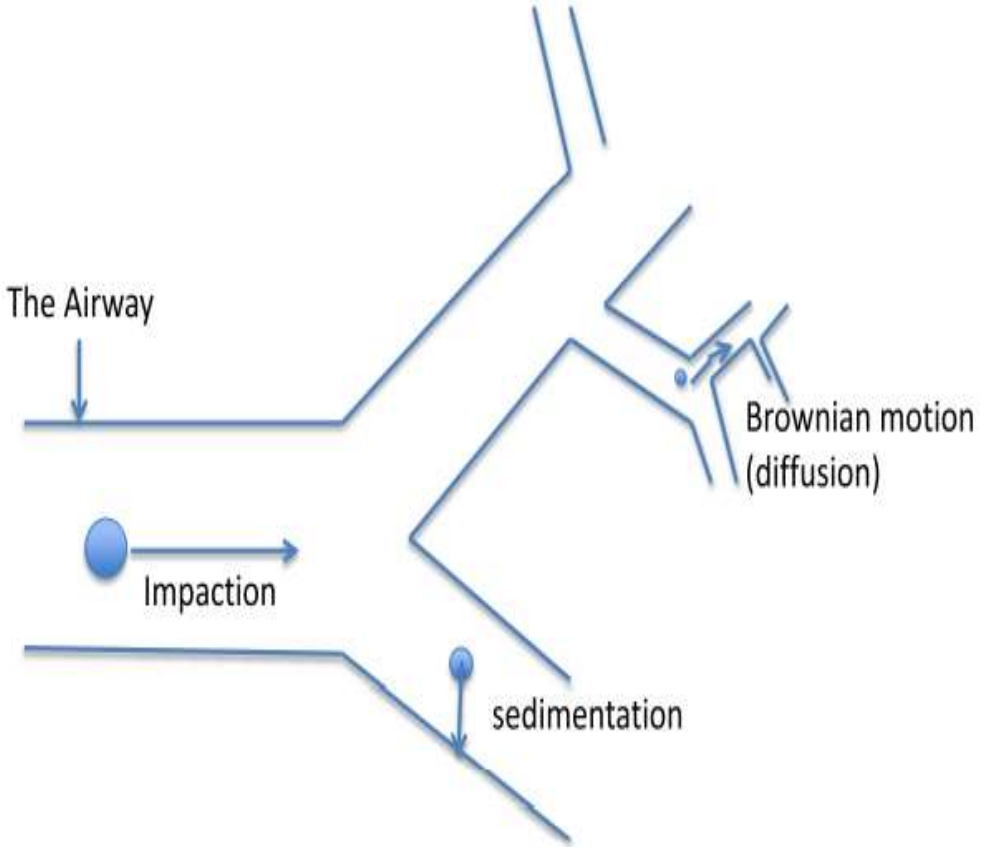
- The aim of aerosol system is to produce aerosols with characteristics suitable for drug delivery to the lungs
- Aerosol system performance
- Emitted dose (ED)—the amount of drug exiting the delivery device
- Fine particle fraction (FPF)—the mass of particles below a cut-off diameter
- The overall efficiency of the aerosol system is a composite of the ED, the dose delivered to the lung (FPF as a surrogate marker) and lung bioavailability

Characteristics of therapeutic aerosols

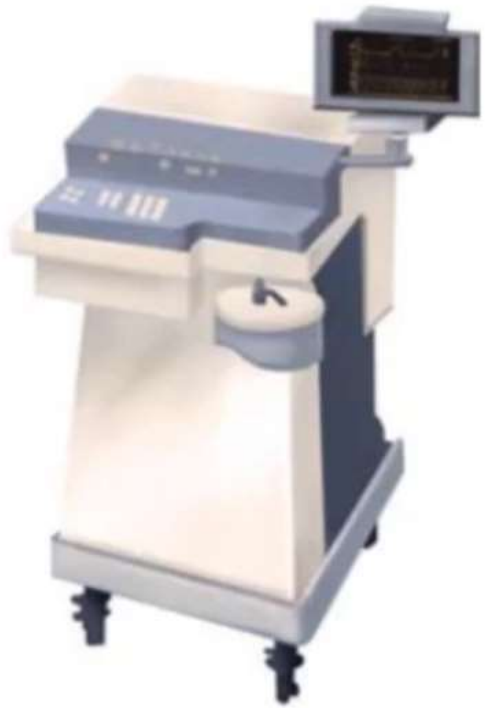
- Aerosol output
- Particle size
- Deposition
- Changes in the aerosol over time (aging)

Mechanism of Aerosol Deposition

- **Impaction**
  - Turbulence and high air velocity associated with aerosolization, is predominant in the first 10 branching's of the airway
- **Sedimentation**
  - In the distal five to six airway generations, however, predominates due to lower air velocity
- **Diffusion**
  - Diffusion is the predominant mechanism for lung deposition
  - 2–5 µm



Ventilator-related
- Ventilation mode
- Tidal volume
- Respiratory rate
- Duty cycle
- Inspiratory waveform
- Breath-triggering mechanism

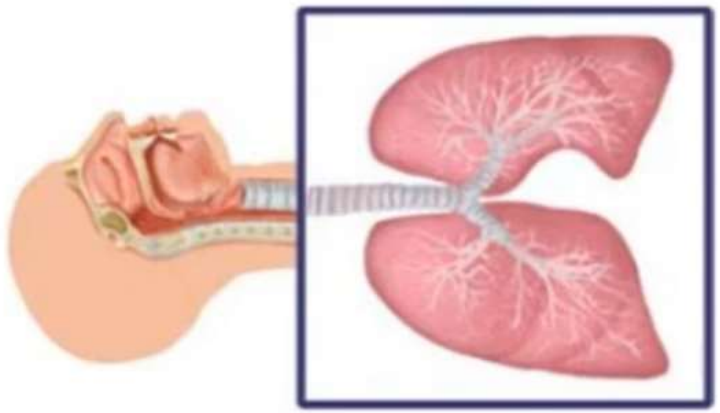


Circuit-related
- Endotracheal tube size
- Humidity of inhaled gas
- Density of inhaled gas

Device-related—MDI
- Type of spacer or adapter
- Position of spacer in circuit
- Timing of MDI actuation
- Type of MDI

Device-related—nebulizer
- Type of nebulizer
- Fill volume
- Gas flow
- Cycling: inspiration vs. continuous
- Duration of nebulization
- Position in the circuit

Drug-related
- Dose
- Formulation
- Aerosol particle size
- Targeted site for delivery
- Duration of action



Patient-related
- Severity of airway obstruction
- Mechanism of airway obstruction
- Presence of dynamic hyperinflation
- Patient–ventilator synchrony

Respir Care.2004;49(6):611-622

General factors affecting aerosolized drug delivery

- **Airway anatomy and physiology**

- Abnormal airways and impaired mucociliary clearance serve as a barrier to effective aerosolized drug therapy

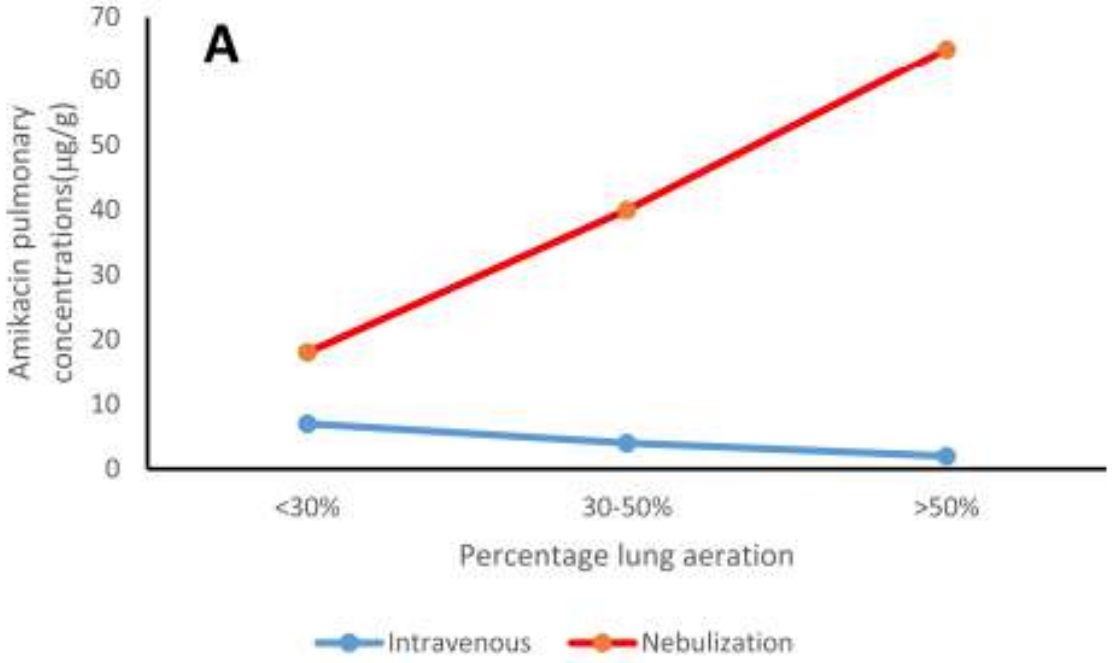
- **Regional lung aeration**

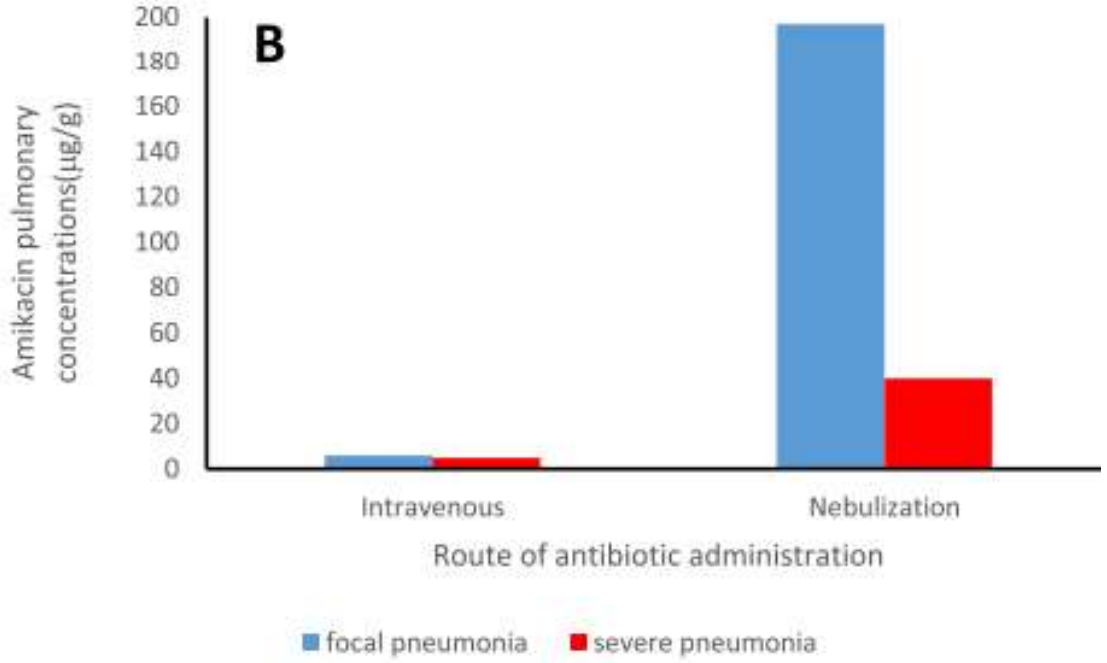
- Airflow is not homogeneous throughout the lungs

- Lung diseases are regional which adds to the heterogeneity to regional airflow

Anesthesiology. 2003;98(4):1016–9.
Ann Intern Med. 1990;113(9):677–83.

Effects of regional lung aeration and pneumonia on drug concentration in lungs





Elman et al. Anesthesiology. 2002;97(1):199–206

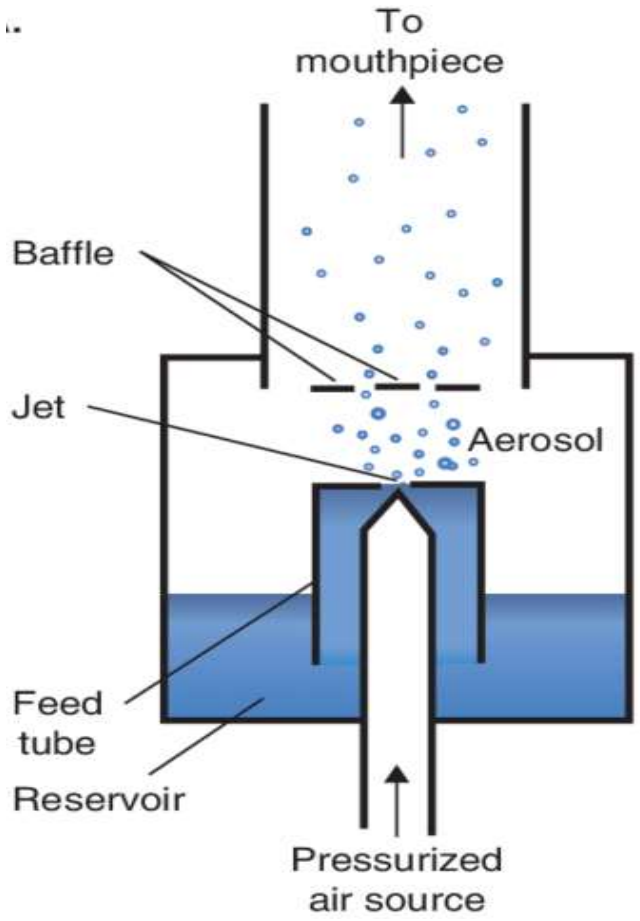
Aerosol Device

- Nebulizers
  - Jet nebulizers
  - Ultrasonic nebulizers
  - Mesh nebulizers
- Pressurized metered dose inhalers (pMDIs)

Jet Nebulizers

- Aerosols are generated by passing pressurized gas at a high velocity through a small “jet” orifice

- Pressurized gas shear liquid into droplets due to surface tension



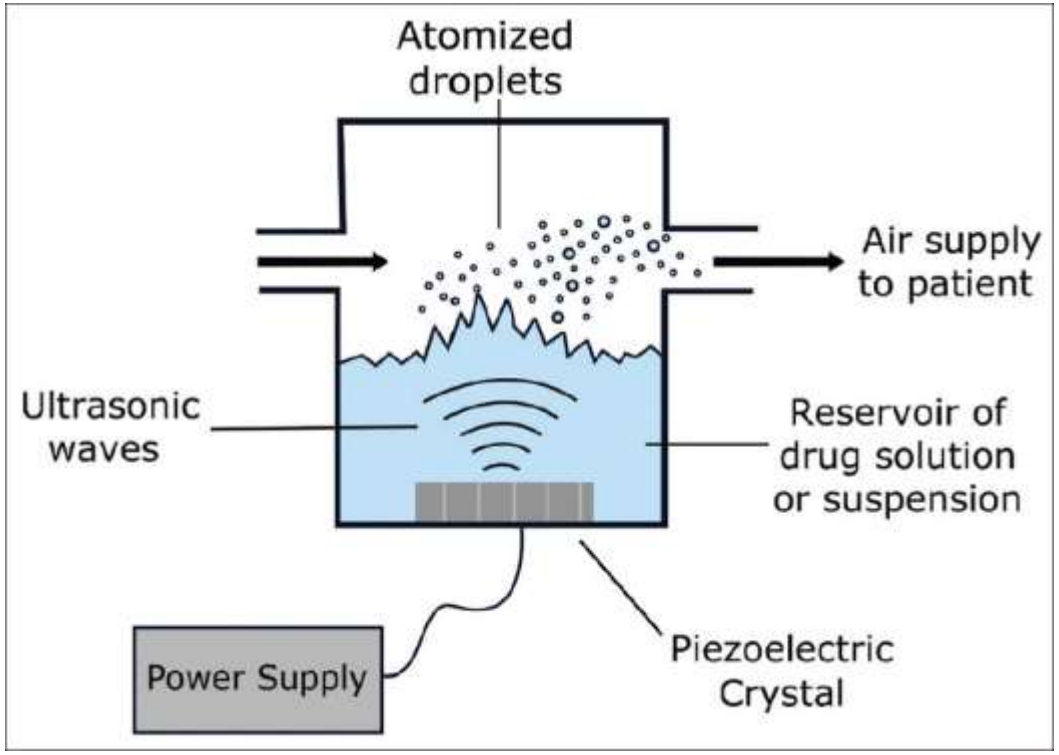
Jet Nebulizers

- Designed for delivery of drugs such as SABAs and corticosteriods
- Only about 5% of the aerosol is respirable, the remainder is removed by impaction and returned to the reservoir
- Cleaning is typically to rinse after each use and boil wash weekly
- Nebulizer replacement typically after 30 days (disposable) or 6 months (durable)

Ultrasonic nebulizer

- Ultrasonic nebulizer uses a piezoelectric transducer that produces ultrasonic waves

- The frequency of ultrasonic waves is inversely related to the particle size of aerosols whereas the amplitude of crystal vibration is directly related to drug output delivered by the nebulizer



Ultrasonic nebulizer

- **Factors affecting output from ultrasonic nebulizers**:
  - Characteristics of the liquid solution (viscosity, density, surface tension)
  - The piezoelectric transducer (vibration frequency, vibration amplitude)
  - Medication chamber (size and baffles)

Ultrasonic nebulizer

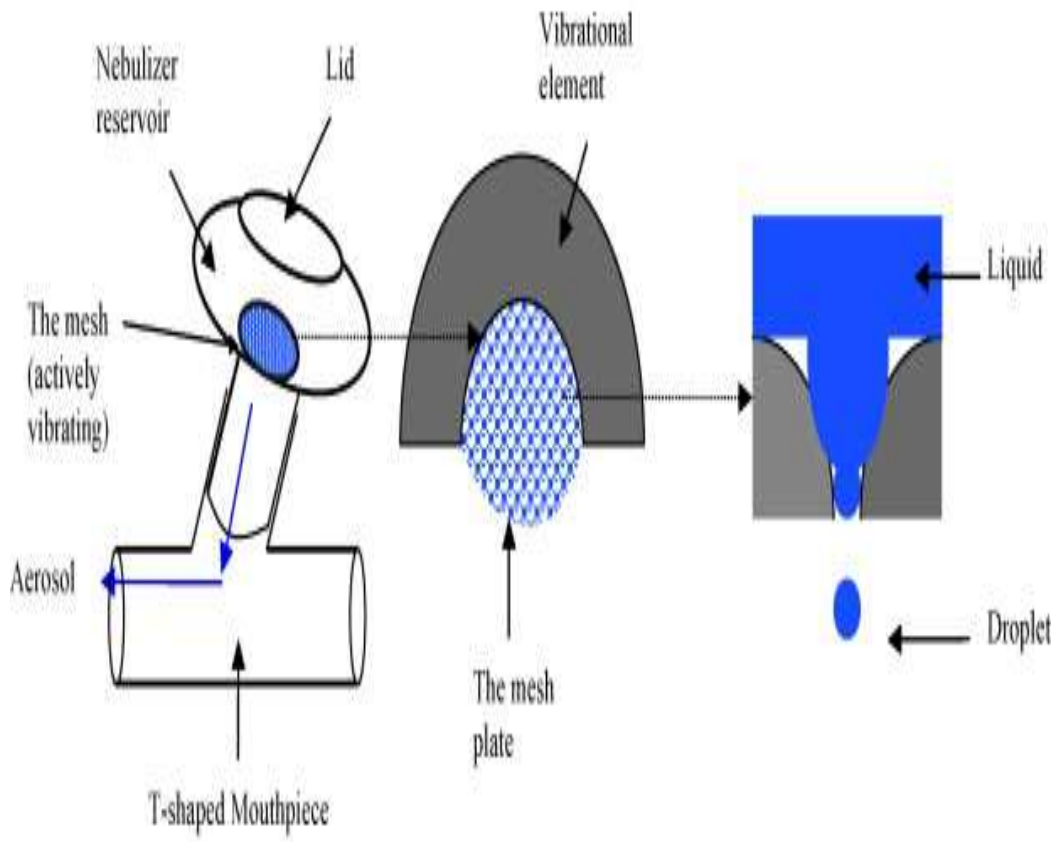
- Problem with ultrasonic nebulizers is that the drug solution becomes more concentrated during operation, and the solution temperature increases by 10°C to 15°C after a few minutes of ultrasonic nebulization

- The increase in temperature has the potential to denature some drug formulations

Vibrating Mesh Nebulizer

- Piezo element vibrates the mesh, this vibration pumps liquid drug through the mesh, the liquid is emitted from the mesh in droplets generating the aerosol

- 100% of the aerosol produced by the mesh is respirable



Vibrating Mesh Nebulizer

- Cleaning : rinse after every use, wash daily and boil weekly, often using distilled water

- Mesh replacement typically after 6 or 12 months

Pressurized Metered-Dose Inhalers (pMDIs)

- pMDIs are small, portable, convenient, multi-dose devices that use a propellant under pressure to deliver a metered dose of an aerosol

- Propellants
- Chlorofluorocarbon or
- Hydrofluoroalkane

Pressurized Metered-Dose Inhaler-Related Factors

Priming and Shaking pMDIs

- Priming the pMDI before first treatment and every time when it has not been used for 24 h

- Total and respirable doses with pMDIs are reduced by 26% and 36%, respectively, if the pMDI is not shaken before use

- 2 or more rapid actuations of a pMDI may lead to a decrease in drug delivery due to turbulence and coalescence

- **Timing of pMDI Actuation**

- Delay between a pMDI actuation and inspiration decreases aerosol deposition due to sedimentation and electrostatic charge

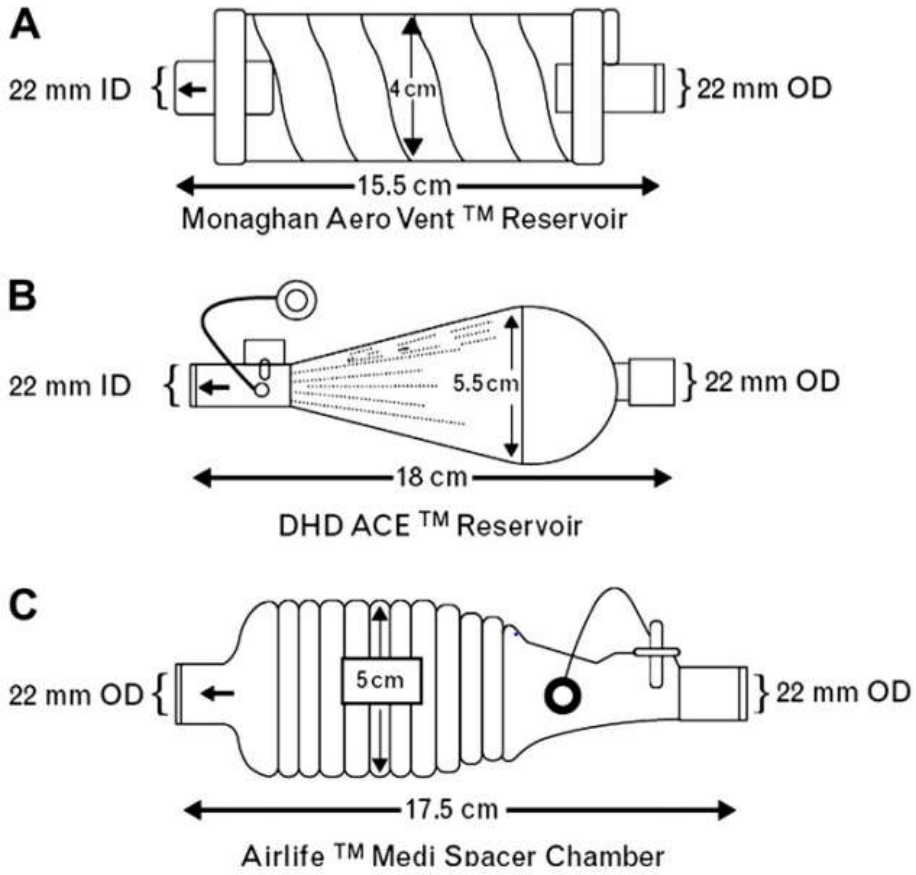
- Failure to synchronize pMDI actuation with inspiration decreases aerosol delivery by 35%

Spacer

- The types of spacers - Unidirectional adapters
  - Bidirectional adapters, and
  - Chamber spacers
- Large-volume spacers retain more of the aerosols delivered by pMDIs compared with small-volume spacers, decreasing the amount of aerosol available from the pMDI

- Non-electrostatic material, aerosols remain suspended for longer periods within the space

Type of spacer

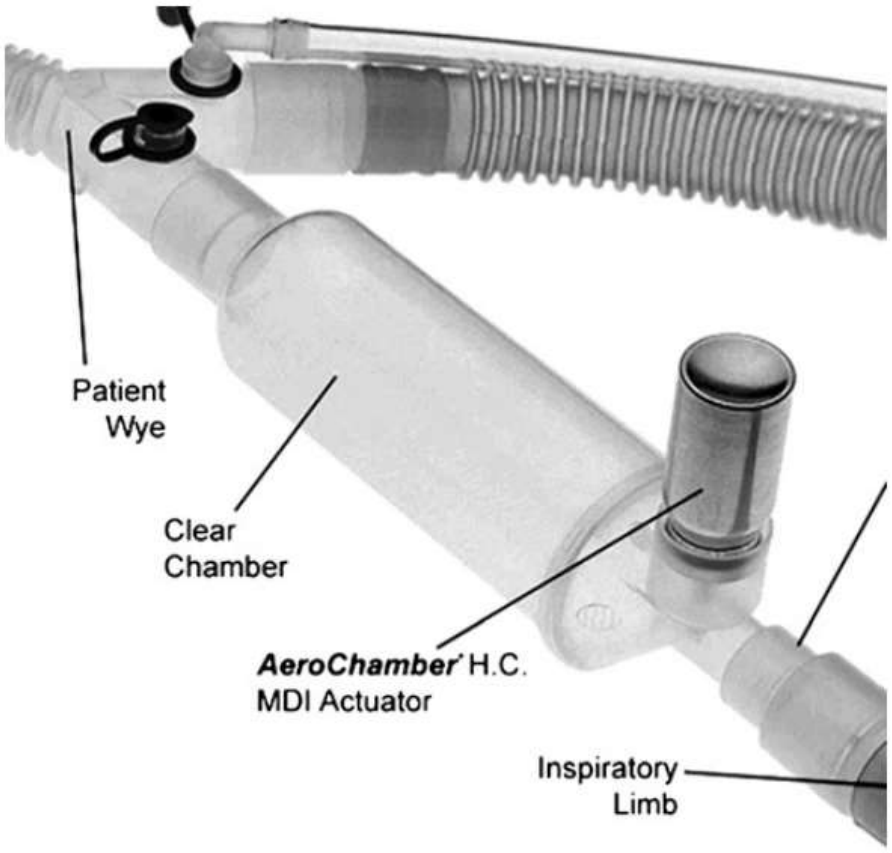


Clin Chest Med 29 (2008) 277–296

Placement of pMDI in the Ventilator Circuit

- 15 cm from the Y-adapter achieve deposition efficiencies of 17% as compared to 7.6% between the ETT and Y-adapter

Respir Care 2010;55(7):837-844



- The Aerochamber HC MV is designed for use during mechanical ventilation

Clin Chest Med 29 (2008) 277–296

Characteristics of Aerosol Devices Used in Critical Care

Feature	Jet Nebulizers	Ultrasonic Nebulizers	Mesh Nebulizers	pMDIs
Power source	Compressed gas or electrical mains	Electrical mains	Batteries or electrical mains	NA
Portability	Restricted	Restricted	Portable	Portable
Noise level	Noisy	Quiet	Quiet	Quiet
Aerosol temperature	Low	High	Ambient	Ambient
Residual volume (mL)	0.8–2.0	0.8–1.2	<0.2	NA
Performance variability	High	Low	Low	Low
Drug preparation	Needed	Needed	Needed	Not needed
Emitted dose	High	High	High	Low
Combination of therapies	Possible if drugs are compatible	Possible if drugs are compatible	Possible if drugs are compatible	Impossible
Treatment time	Long	Intermediate	Short	Short
Output rate	Low	High	High	High
Contamination	Common	Common	Less common	Impossible
Device cost	Very low	High	High	Medium

Nebulizer-Related Factors

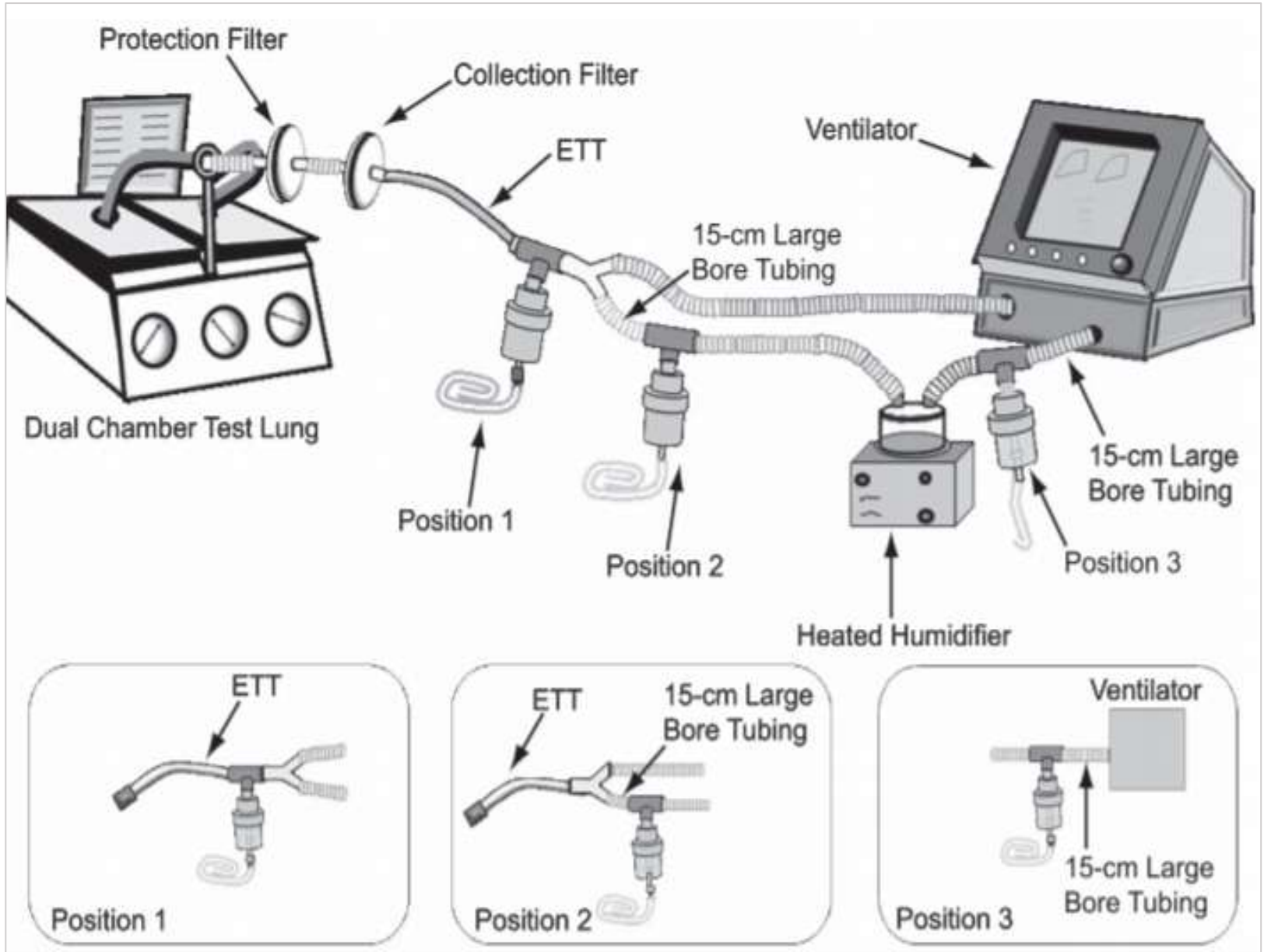
Fill Volume

- Aerosol output from jet nebulizers are directly related
- Treatment time increases with a greater fill volume
- Fill volume of 4 –5 mL is recommended to increase output from jet nebulizers

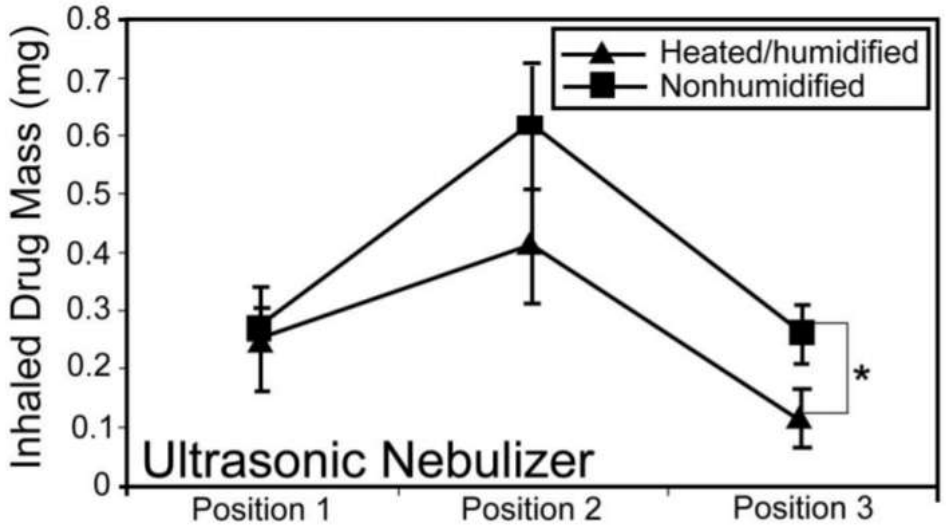
Residual volume

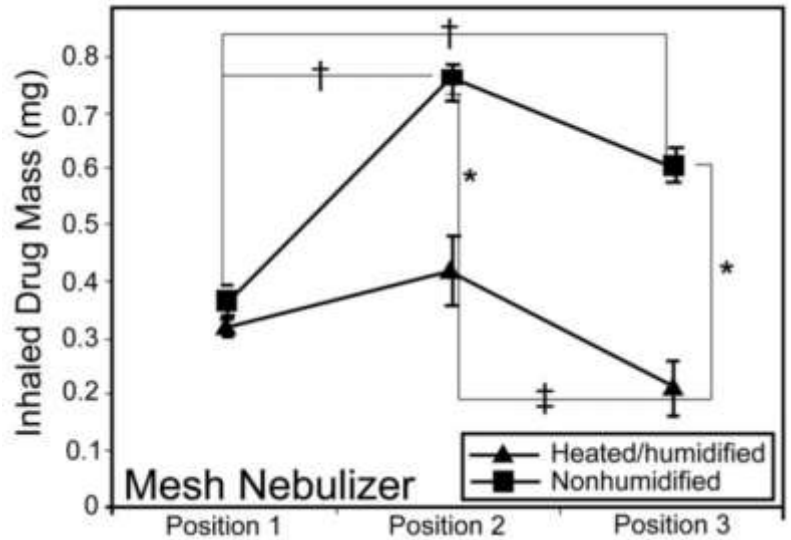
- Amount of drug that remains in nebulizer at the end of aerosol therapy
- Residual volume ranges from 0.5 to 2.5 mL depending on type of nebulizer used
- This is a major factor associated with the lower aerosol delivery efficiency of jet nebulizer

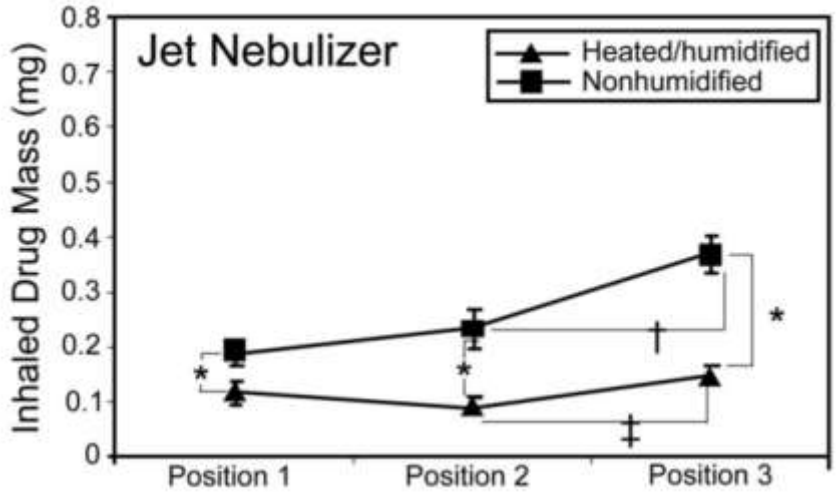
Position of the aerosol generator



Respir Care 2010;55(7):837– 844.







Respir Care 2010;55(7):837– 844.

- Jet nebulizer deliver maximum aerosol - at position 3

- It has been hypothesized that the continuous gas flow driving the jet nebulizer allows aerosol to charge (fill) the inspiratory limb of the ventilator circuit and function as a reservoir. , so improves the aerosol delivery

- In contrast, aerosol from the ultrasonic and vibrating-mesh nebulizers at position 3 tends to collect at the aerosol generator and not to be transported to the patient until gas from the ventilator flows from the ventilator.

Respir Care 2010;55(7):837– 844.

Nebulizer-Related Factors

Intermittent or Continuous Nebulization

- Intermittent nebulization during mechanical ventilation provides as much as 4-fold greater inhaled dose compared with continuous nebulization

Am J Respir Crit Care Med 2003;168(10):1205-1209.

Circuit Related Factors

Gas Density

- The delivery efficiency of aerosol devices during mechanical ventilation and the gas density in the ventilator circuit are inversely related

Heliox

- has lower density
- is not effective in generating aerosols with jet nebulizers
- Therefore, it should not be used to power jet nebulizers

Am J Respir Crit Care Med 2001;163(1):109-114

Circuit Related Factors

Endotracheal tube

- Aerosol deposition has been found to be significantly lower with smaller ETT
- Delivery efficiency of a jet nebulizer with a 7-mm inner diameter ETT was similar compared with a 9-mm inner diameter ETT in ventilator dependent subjects

Ari A et al Respir Care. 2012;57(7):1066–70

Tracheostomy

- Patients who are not mechanically ventilated, a T-piece interface between the tracheostomy tube and the nebulizer has been demonstrated to be more effective than a tracheostomy mask

- Tracheostomy tube was not a barrier to lung deposition because 3% of aerosols deposited on the tracheostomy tube

- Aerosol delivery through a tracheostomy tube was greater than that through an ETT due to the shorter length of the tracheostomy tube

Respir Care 2012;57(7):1066-1070

Ventilation Mode

- Aerosol deposition within the lower respiratory tract more with CPAP than with controlled mechanical ventilation

- The use of PEEP during aerosol therapy improved lung function in spontaneously breathing adults more than administering therapy without PEEP

Am J Respir Crit Care Med 1999;159(1): 63-68.

Ventilator Parameters

Tidal volume (V_T)

- V_T is not directly proportional to aerosol drug delivery during mechanical ventilation as long as the V_T is greater than the internal volume of the ventilator tubing and artificial airways

- V_T of 8 –10 mL/kg can result in volutrauma and should not be used to improve the delivery efficiency of aerosol devices during mechanical ventilation

J Aerosol Med Pulm Drug Deliv 2008;21(1):85-96.

Ventilator Parameters

Inspiratory time

- Directly related to aerosol deposition in ventilator-dependent patients
- Use of a duty cycle 0.3 is suggested for aerosol therapy during mechanical ventilation
- Monitor the degree of intrinsic PEEP
- Because it may worsen dynamic hyperinflation in patients with air-flow limitation

J Aerosol Med Pulm Drug Deliv 2008;21(1):85-96.

Ventilator Parameters

Inspiratory flow

- Lower inspiratory flows increase aerosol delivery to ventilator-dependent patients

- Peak inspiratory flows should be decreased as much as possible if this is tolerated by the patient

- Decreasing inspiratory flow from 80 to 40 L/min improved aerosol deposition by 2- fold in subjects receiving ventilatory support

Nurs Crit Care 2010;15(4):192-203

Ventilator Parameters

- Although low inspiratory flow rates improves the aerosol delivery but also increases the intrinsic PEEP

- Square wave airflow pattern enable generation of laminar airflow to improve drug deposition in the lungs

Heat and Humidity

- Heated and humidified ventilator circuit leads to decrease in aerosol deposition by changes in aerosol particle size during mechanical ventilation.

- Humidity during aerosol therapy in ventilator-dependent subjects increased particle size from 1.5 to 2.3

- 40% less aerosol deposition with heated and humidified gas compared with unheated and non-humidified ventilator circuit

Respir Care 2010;55(7):837-844
Am J Respir Crit Care Med 2003;168(10):1205-1209

Heat and Humidity

- Dry circuit use may be cost-effective with expensive drugs such as antibiotics, to complete aerosol therapy in 10 min to minimize the effect of dry gas on the airway mucosa

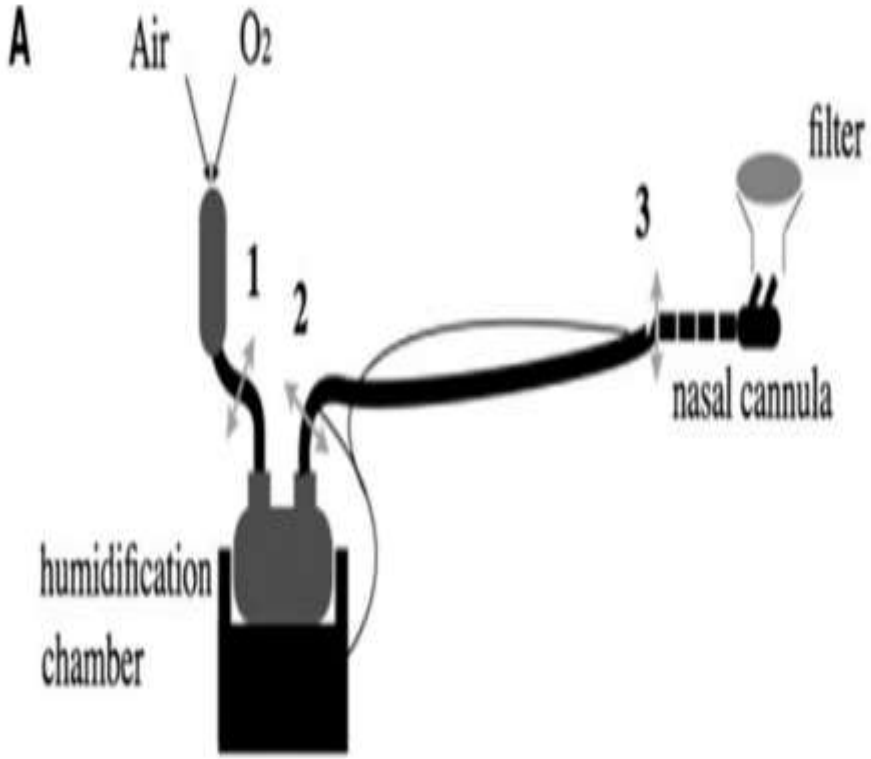
Clin Chest Med 2008;29(2):277- 296

Heat-and-moisture exchangers (HMEs)

- HME filter acts as a barrier to drug delivery, HMEs should not be placed between the artificial airway of the patient and the aerosol device

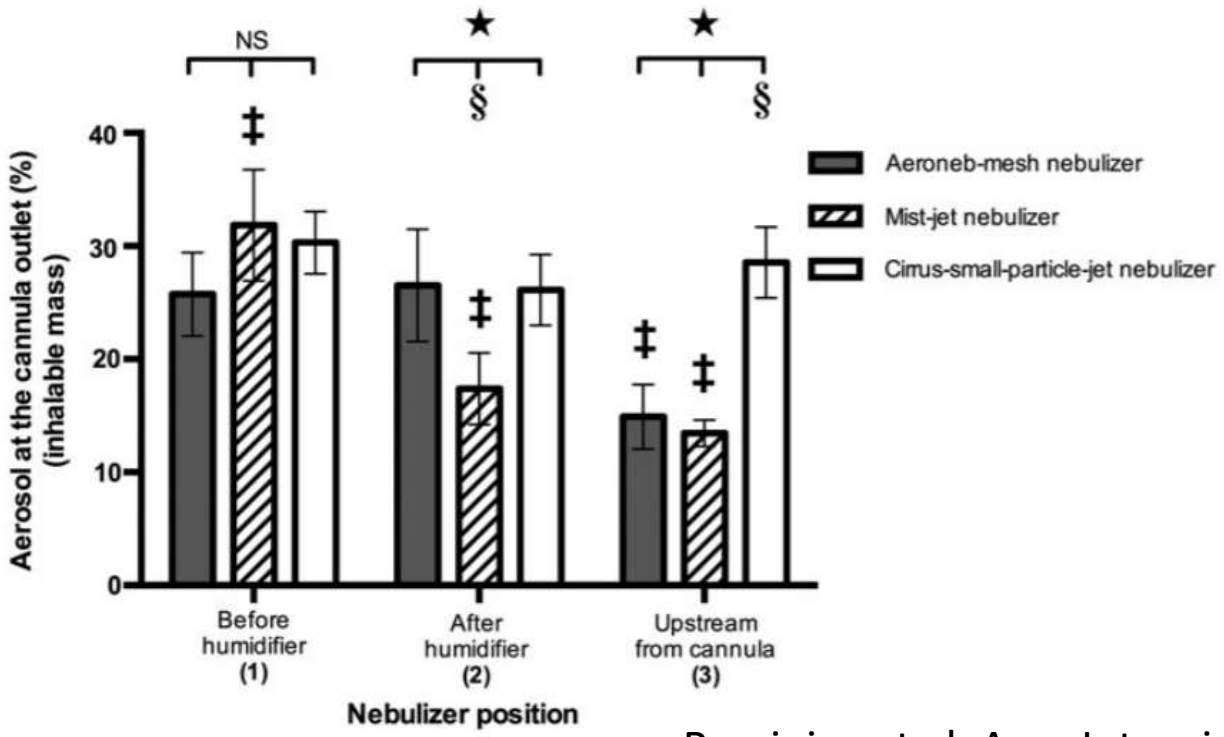
Effect of high-flow nasal cannula

- RE´ MINIAC ET AL. assessed the mass and the particle size distribution of the aerosol emitted from the nasal cannula using nebulizers placed at three positions in the HFNC circuit
- (1) before the humidification chamber
- (2) after the chamber
- (3) immediately upstream from the nasal cannula



Reminiac et al. Ann. Intensive Care (2018) 8:128

- Connecting the nebulizer close to the humidification chamber seems to outperform more distal placement



Reminiac et al. Ann. Intensive Care (2018) 8:128

Effect of high-flow nasal cannula

- Position of the nebulizer
  - A position closer to the patient improved delivery of the drug upstream
- Nebulizer type
  - VMNs demonstrated improved delivery as compared with jet nebulizers
- Airflow
  - The delivery of respirable mass is lower with higher airflow and improves at a lower airflow

Drugs used in inhalation route in critical care

Anti-infective agents	Anti-coagulants	Broncho-dilators	Corticosteroids	Mucolytics	Ionic solutions	Prostanoids	Surfactants
Amikacin Amphotericin B Ampicillin Cefazolin Colistin Gentamycin Imipenem and cilastatin Netilmicin Pentamidine Ribavirin Vancomycin	Heparin	Albuterol Atropine Epinephrine Fenoterol Formoterol Ipratropium Magnesium Terbutaline	Beclomethasone Budesonide Dexamethasone Fluticasone Hydrocortisone	Acetylcysteine Ambroxol Bromhexine Dornase Alfa Gomenol Mesna Tyloxapol	Hypertonic sodium chloride Isotonic sodium chloride Sodium bicarbonate	Epoprostenol Iloprost Treprostinil	Synthetic Bovine-derived Porcine-derived

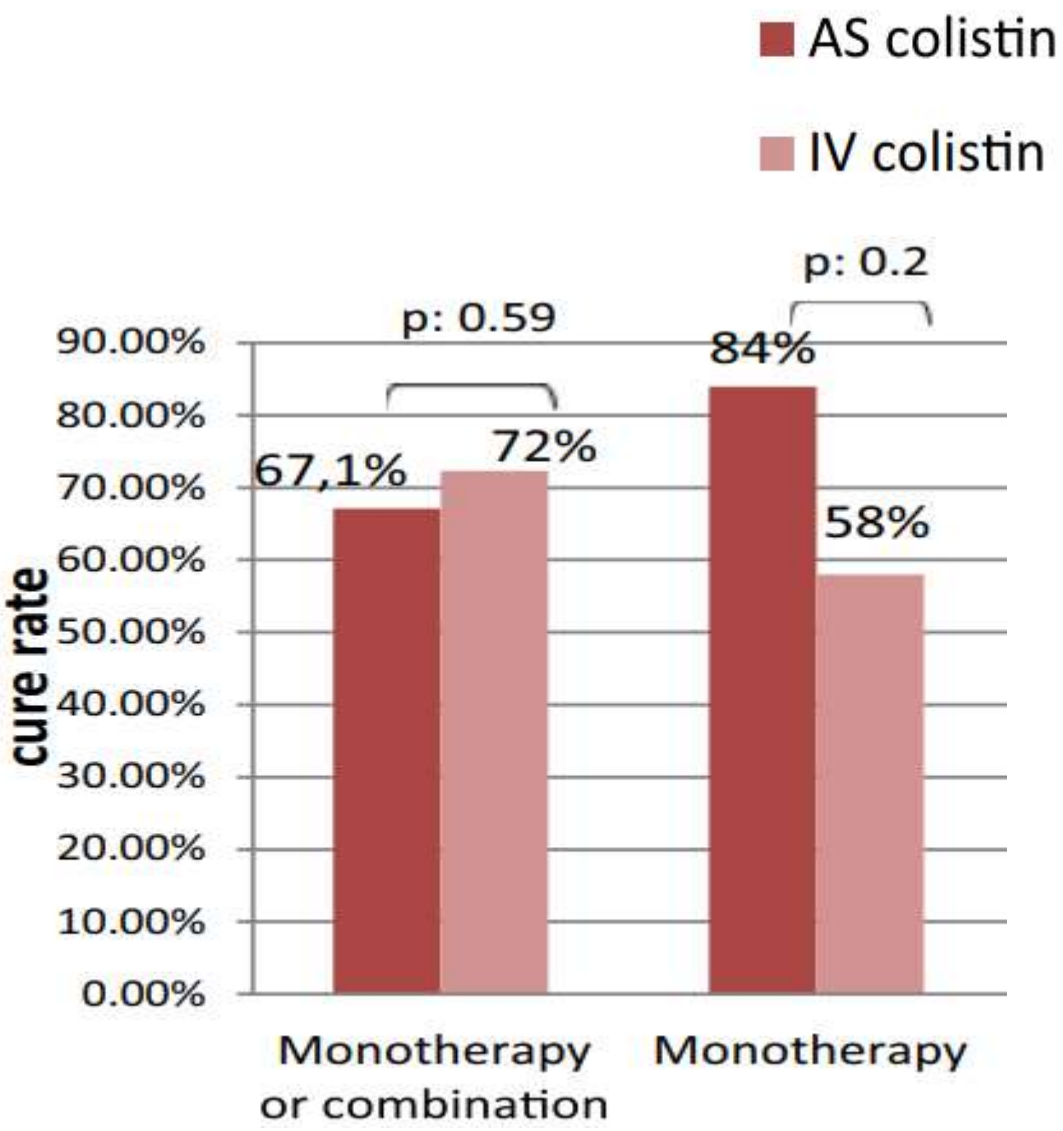
Efficacy and toxicity of aerosolized colistin in ventilator-associated pneumonia: a prospective, randomized trial

Population	Intervention	Control	Outcome
149 patients Randomized Single-blind study	4 million units of aerosolised colistin three times per day + imipenem 1g three times per day (N = 73)	IV colistin as a loading dose of 9 MU during 60 min followed by 4.5 MU two times per day + IV imipenem 1 g three times per day (N= 76)	Cure of VAP assessed at day 14 of therapy

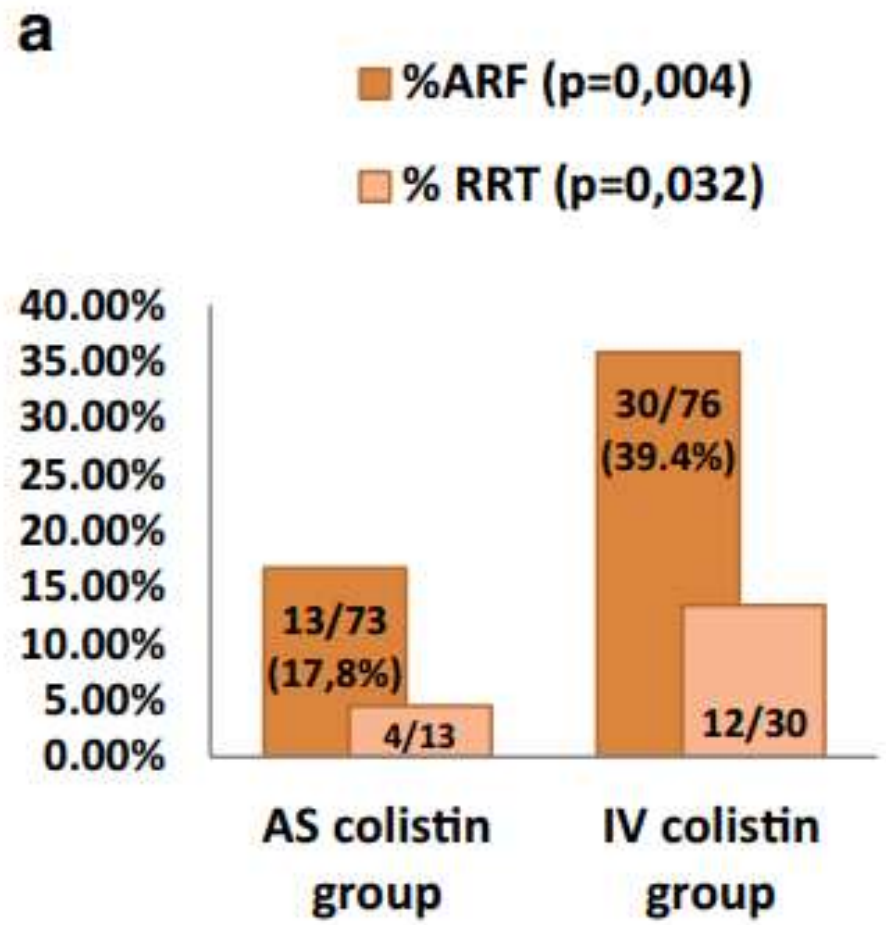
Abdellatif et al. Ann. Intensive Care (2016) 6:26

Result

- Efficacy of aerosolised colistin in treatment of VAP was not inferior to IV colistin



- Incidence of acute renal failure (ARF) and necessity of replacement renal therapy (RRT) lower in aerosolised colistin



The Role of Aerosolized Colistin in the Treatment of Ventilator-Associated Pneumonia

A Systematic Review and Metaanalysis*

Valachis, Antonis MD, PhD[1]; Samonis, George MD, PhD[2]; Kofteridis, Diamantis P. MD, PhD[2]

- 16 studies
- Total patients – 690

Primary outcome –

- A significant improvement in clinical response (odds ratio=1.57; p=0.006)

Secondary outcome

- Microbiological eradication (odds ratio=1.61; p =.01)
- Infection-related mortality (odds ratio, 0.58; p=.04)
- Overall mortality was not affected

Dose of colistin

- No recommended doses for colistin or aminoglycoside nebulization
- VAP patients who were administered 1 million international units (MIU, ie, 80 mg) of colistimethate sodium (CMS), via a vibrating-mesh nebulizer every 8 hours, peak ELF concentrations were high but then decreased to less than the sensitivity breakpoint at 4 hours
- Steady-state plasma concentrations of colistin, were significantly higher in studies evaluating high doses of nebulized CMS (4–5 MIU/8 h)compared with 2 MIU/8 h

Intensive Care Med 2012;38(11): 1779–86.
Antimicrob Agents Chemother 2014;58(12):7331–9.

International Consensus Guidelines for the Optimal Use of the Polymyxins

- Patients requiring IV polymyxin therapy for suspected or documented XDR gram-negative HAP or VAP should receive adjunctive polymyxin aerosol therapy
- Weak recommendation, low-quality evidence

Pharmacotherapy 2019;39(1):10–39

Inhaled Amikacin

Population	Intervention	control	Results
RCT Double blind trial (n = 52 subjects)	Inhaled aerosolized amikacin 400 mg every 8 h Inhaled	normal saline 4 mL every 8 h	Bacterial eradication in 41% of aerosolized amikacin group vs 14% of placebo group (41% vs. 14%, *P* = 0.024) No difference weaning rate, clinical cure rate, and mortality observed between the 2 group (22% vs. 32%, *P* = 0.427)

Chin Med J (Engl) 2017; 130(10):1196-1201

Tobramycin

Population	Intervention	Control	Outcome
Double-blind Randomized controlled trial	Twice daily Tobramycin inhalation 300 mg and standard IV antibiotic therapy	Twice daily placebo inhalation besides standard IV antibiotic treatment	Treatment failure was seen in 4 patients (31%) of the inhalation antibiotic group and in 8 patients (62%) of the control group (p=0.238)

European Respiratory Journal 2019 54: PA4026

Limitation of antibiotic aerosolization

	Aerosol (n = 20)	Intravenous (n = 20)	P Value
Duration of MV	29 (22–38)	18 (13–31)	0.13
Length of stay in ICU after inclusion, median (IQR)	24 (18–48)	16 (11–23)	0.08
Mortality on Day 28	2	1	0.55

- RCT
- Population = 40
- VAP = P. aeruginosa
- Inhaled ceftazidime + amikacin vs

I/v ceftazidime + amikacin

Am J Respir Crit Care Med 2011;184(1):106–15.

- Bronchospasm during aerosolization imposes the immediate withdrawal of the aerosol and b-agonist nebulization

- In case of bronchospasm occurring during antibiotic nebulization, reintroduction of the same drug by the same route should be avoided.

Expert Rev Anti Infect Ther 2013;11(5):511–21.

- Most dreadful complications of antibiotic nebulization is the obstruction of the expiratory filter, which can lead to cardiac arrest and death

- This complication can be avoided by a systematic change of the expiratory filter after each aerosol

Am J Respir Crit Care Med 2011;184(1):106–15.

Nebulized heparin for inhalation injury in burn patients: a systematic review and meta-analysis

- Nine trials
- 609 burn patients
- Mortality in the heparin treated group was lower than that of the traditional treatment group (relative risk (RR) 0.75).
- The duration of mechanical ventilation was shorter in the heparin-treated group compared to the traditional treatment group
- Length of hospital stay was significantly shorter than that in the traditional treatment group

Burns & Trauma, 2020, Vol. 8, tkaa015

RICU practice

- Nebulised colistin 2.5 MU with i/v colistin 9MU