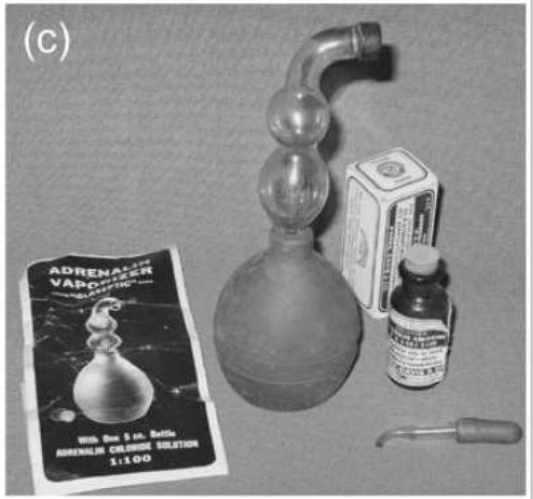
AEROSOL THERAPY IN ICU

DR. VAIBHAV KAJARIA



A Mudge -type Pewter inhaler

B Nelson-type Earthenware inhaler

C Hand-bulb nebuliser

D Pneumostat nebuliser 1930

E Medihaler-ISO (The first MDI) 1956

COMMON TERMINOLOGY

- **Aerosol:** Suspension of liquid droplets or solid particles in a gaseous medium

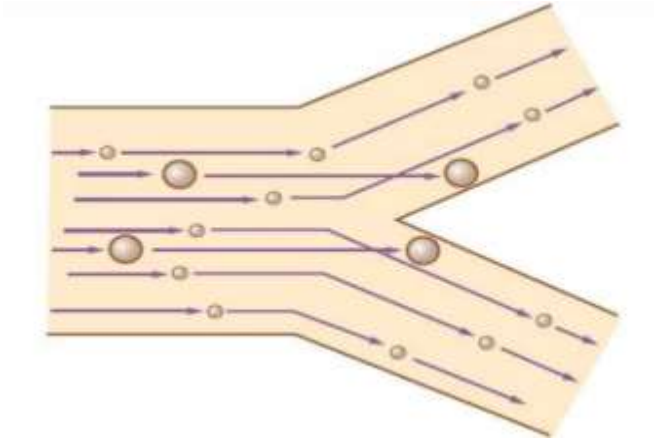
  Coarse particles: 1-10 µm, **Fine particles** 1- 0.1 µm & **Ultra fine particles** < 0.1µm

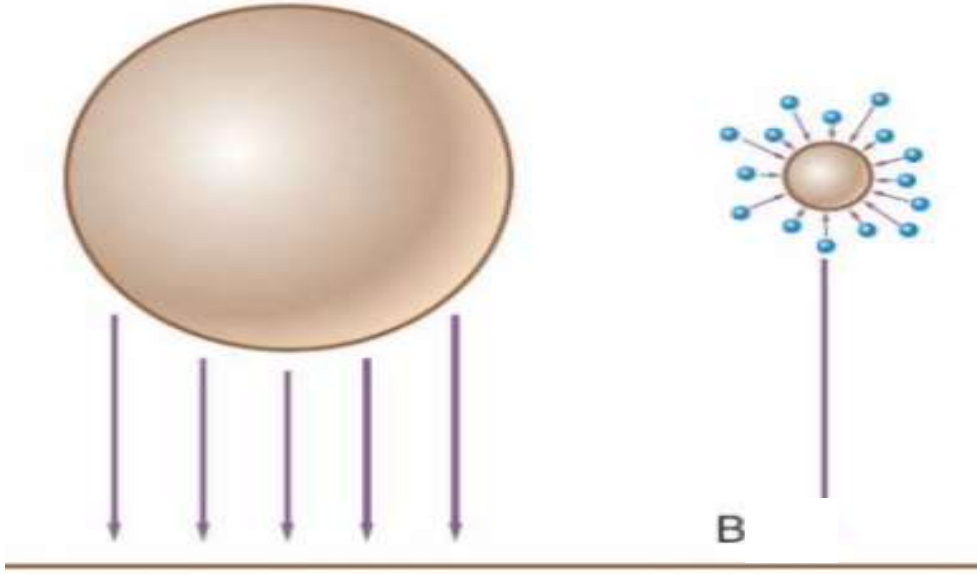
- **Mass Median Aerodynamic Diameter (MMAD)** : The MMAD divides the aerosol size distribution in half. Its the diameter at which 50% of the particles of an aerosol by mass are larger and 50% smaller
- **Aerosol Output** : Mass per minute of particles in aerosol form produced by the nebulizer
- **Respirable Particles** : Particles < 5µm in diameter
- **Respirable Fraction** : The mass of respirable particles expressed as a % of the aerosol output
- **Residual Volume :** This is the volume of liquid remaining in the nebulizer reservoir after nebulization

  RV < 1ml, fill volume 2.5-3ml & RV > 1ml then the fill volume 4 ml

Aerosol deposition

- **Inertial impaction** : suspended particles collide and deposit on the surface. Particle larger than 3-5µm. Mostly in the pharynx and large airways
- **Sedimentation** : aerosol particles settle out of suspension due to gravity, 1-3µm size particles. Large airways, breath holding during aerosol therapy help in sedimentation
- **Brownian diffusion** : in the alveoli for small particles < 3µm, mainly by diffusion
- Particles 1- 0.5µm remain suspended and may be exhaled
- Smaller than 0.5µm may get retained in the lungs





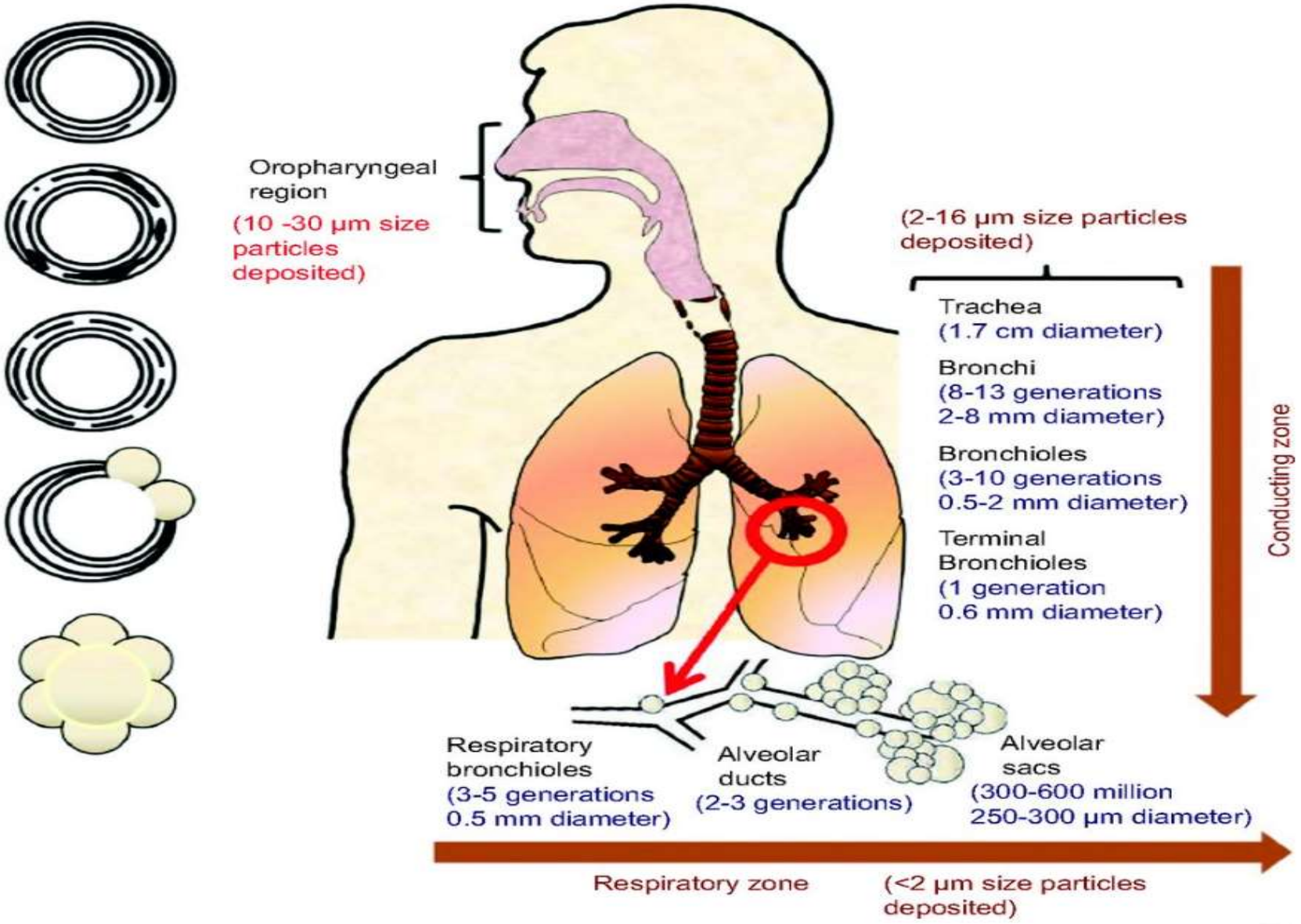
Trachea
(Crescent of cartilage, band of smooth muscle and columnar epithelium)

Intrapulmonary bronchus
(Cartilage plates, BSM, submucosal glands, ciliated goblet and basal cells)

Bronchiolus
(BSM, ciliated epithelium with Clara cells)

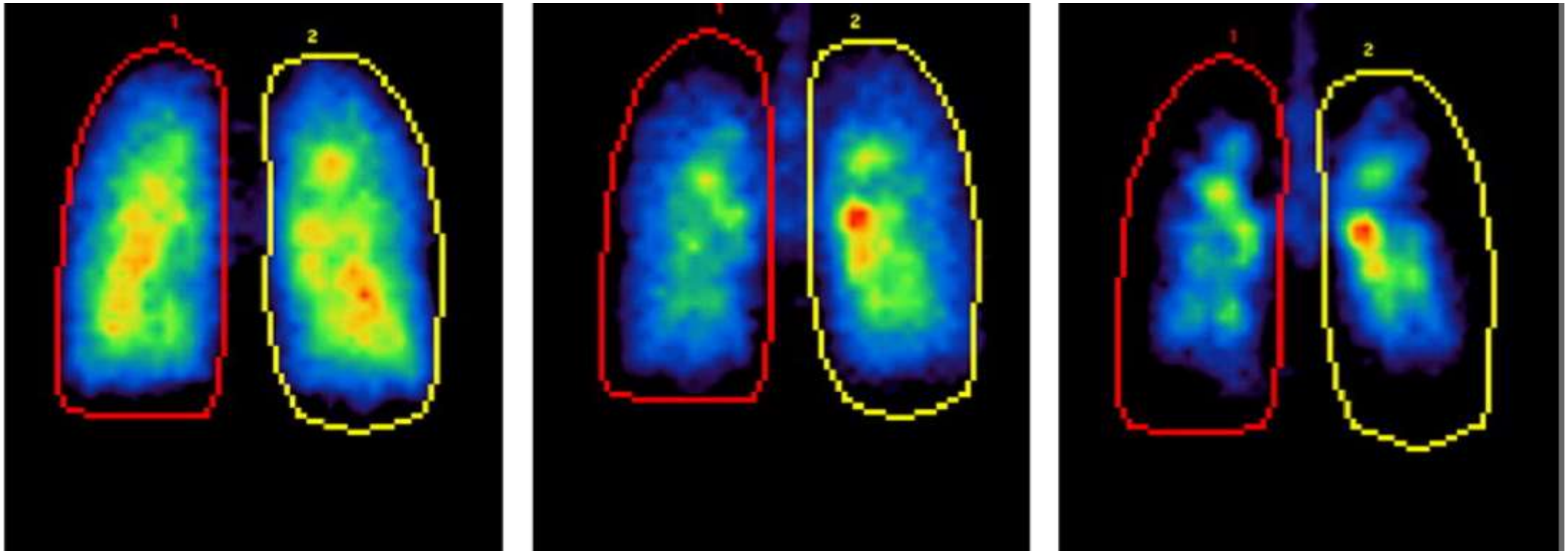
Respiratory bronchiolus
(BSM, ciliated epithelium and alveolar epithelium)

Alveolar duct
(Alveolar epithelium, Type I and Type II and pneumocytes)



Nahar K etal.,Eur J Pharmaceutical Sci 2013;49(5):805–818

- The ideal aerosol MMAD recommended : while using bronchodilators in OAD, is between 3 and 6 µm. Though smaller particles achieve greater total lung deposition, the larger particles are more efficacious achieving greater bronchodilation
- For drugs requiring peripheral intrapulmonary deposition (antimicrobials), ideal aerosol MMAD recommended is < 2 µm



- Smaller particles achieved greater total lung deposition (1.5 µm [56%], 3 µm [50%], and 6 µm [46%])
- Small particles were exhaled more (1.5 µm [22%], 3 µm [8%], 6 µm [2%]

Am J Respir Crit Care Med. 2005 Dec 15;172(12):1497-504

Indications

- Broncho-dilation: To relieve the bronchospasm
- Anti-inflammatory: To control the airway inflammation
- Mucolytic: To liquefy tenacious and impacted secretions
- Anti-microbial: To treat pneumonia and other lower respiratory tract infections
- Vasoactive: For treatment of pulmonary arterial hypertension
- Miscellaneous: Heliox, surfactant, humidification etc

- Common use in indian setting in an ICU

  59% combination drugs and 41% single agent

  Amongst single agent 51% SABA/SAMA, 23% ICS, mucolytics 16%

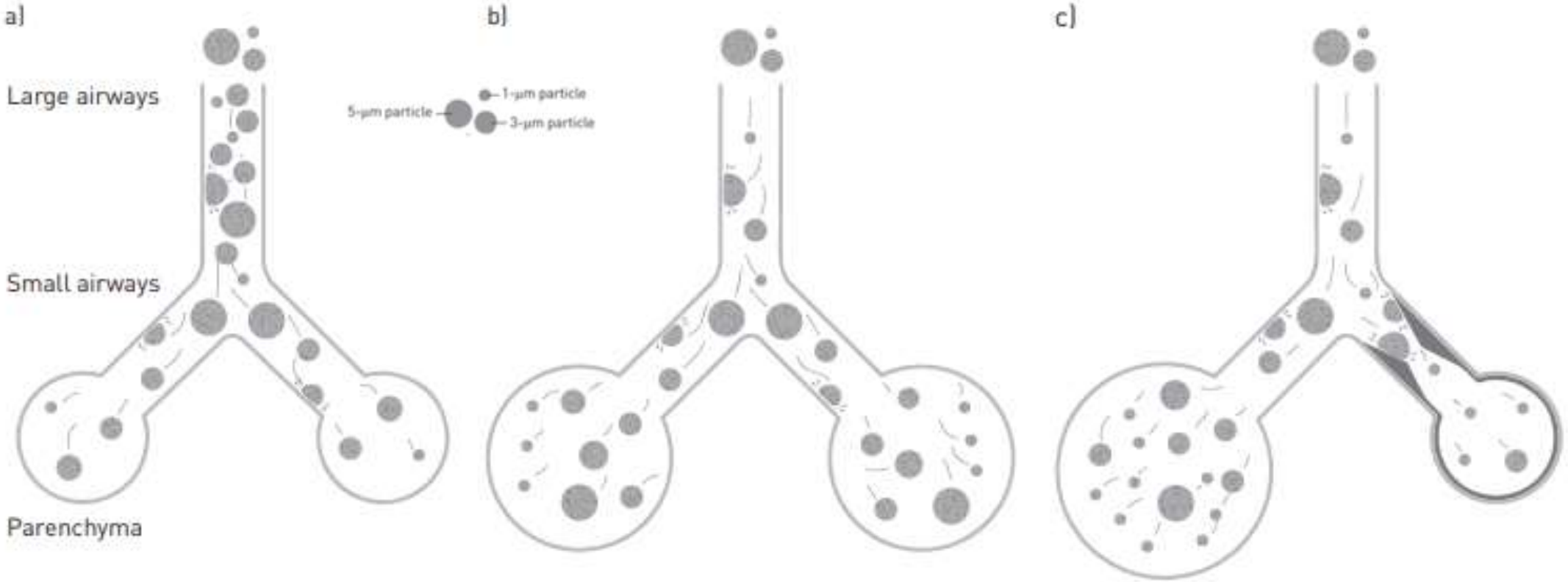
  Amongst combination drugs 70% SABA+SAMA, LABA+ICS 19%

- JET nebulizer 55% , US nebulizer 18% and VMN 17%
- 72% placed at the Y-junction and 28% 15-30cms from Y junction
- suctioning in 65.8%, HME removed in 99% , humidification continued uninterrupted

- **Aero-in-ICU study lung india 2024 april**

Class of drugs	Name of the drugs
Antimicrobials	Amikacin, Ampicillin, Aztreonam, Cefazolin, Colistin, Gentamicin, Imipenem and cilastatin, Netilmicin, Vancomycin, Tobramycin, Fosfomycin, Levofloxacin, Ciprofloxacin, Amphotericin B, Pentamidine, Ribavirin, Zanamivir, Laninamivir
Anticoagulants	Heparin
Bronchodilator	Albuterol (salbutamol), Levalbuterol (Levosalbutamol), Terbutaline, Atropine, Epinephrine, Fenoterol, Formoterol, Arformoterol, Ipratropium, Glycopyrronium, Magnesium sulfate,
Corticosteroids	Beclomethasone, Budesonide, Fluticasone, Flunisolide, Dexamethasone, Hydrocortisone
Diuretics	Frusemide
Mucolytics	N-acetylcysteine, Ambroxol, Bromhexine, Dornase Alfa, Gomenol, Mesna, Tyloxapol, Mannitol.
Ionic solutions	Hypertonic sodium chloride, Isotonic sodium chloride, Sodium bicarbonate
Anti-diabetic	Insulin
Prostanoids	Epoprostenol, Iloprost, Treprostinil
Surfactant	Synthetic, Bovine-derived, Porcine-derived
Miscellaneous	Perfluorocarbons, Biologicals, Interferon beta-1a, PDE-3 inhibitors, Mycobacterium vaccae, Lignocaine, Tranexamic acid, Opioids, Genes, Heliox

- Bland aerosols like nebulized normal saline is sometimes used for humidification
- However other pharmaco-active drugs (antibiotics etc) may cause local reaction, bronchospasm and increased risk of infection if not handled aseptically
- Inhaled drug is delivered directly to the target site causing fewer systemic side effects, and a quicker onset of action – commonly bronchodilators , inhaled corticosteroids and antibiotics are used in our RICU
- 1st pass metabolism is skipped and higher drug concentration are achieved
- Adequate dosing to the desired site may not be achieved



Tidal volume breathing

Deep inhalation

Diseased lung

Diseased lung portions may get sub inhibitory concentration of the drug

ERJ Express. Published on October 16, 2014 Inhaled antibiotics: dry or wet?

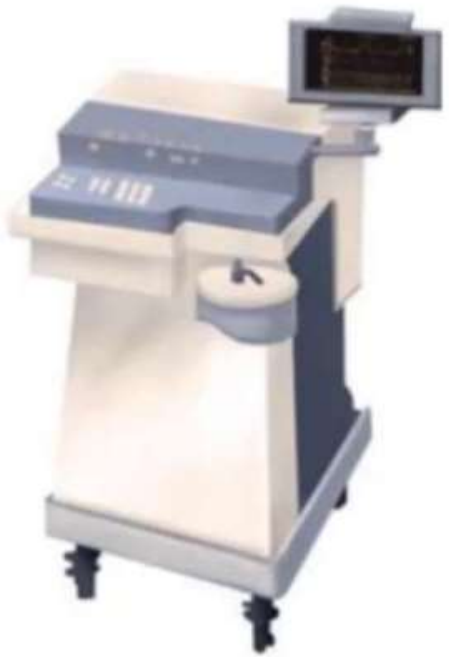
An evaluation of nebulised amphotericin B deoxycholate (Fungizone®) for treatment of pulmonary aspergillosis in the UK National Aspergillosis Centre

- Retrospective analysis of 177 patients
- 1st dose challenge test with fungizone (10 mg in 4 mL water for injection) by simple jet nebuliser
- Recorded pre and post spirometry, pre neb with SABA, follow up at 4-6 weeks
- Eighteen (10.2%) patients continued nebulisation of Fungizone® 10 mg twice a day for >3 months
- 11 - ABPA, 5 - SAFS and 2 *Aspergillus* bronchitis

	Increase	Decrease	Unchanged
AF igG	5	5	1
AF IgE	3	11	1
Total IgE	6	11	

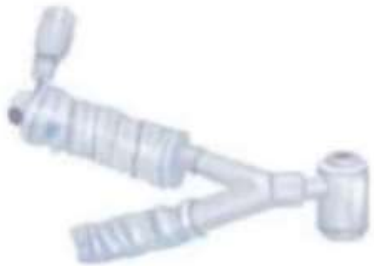
Otu AA etal., Mycoses. 2019 Nov;62(11):1049-1055

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



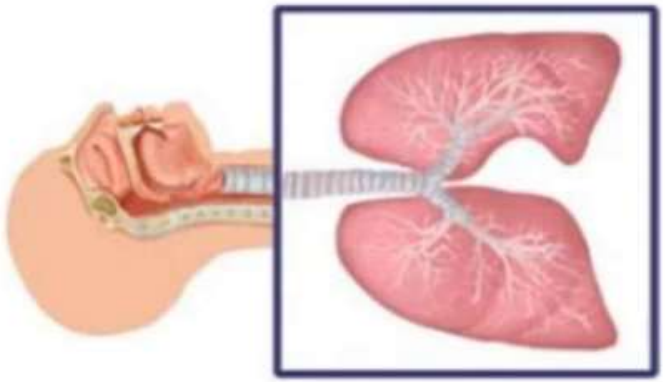
Circuit-related
- Endotracheal tube size
- Humidity of inhaled gas
- Density of inhaled gas

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

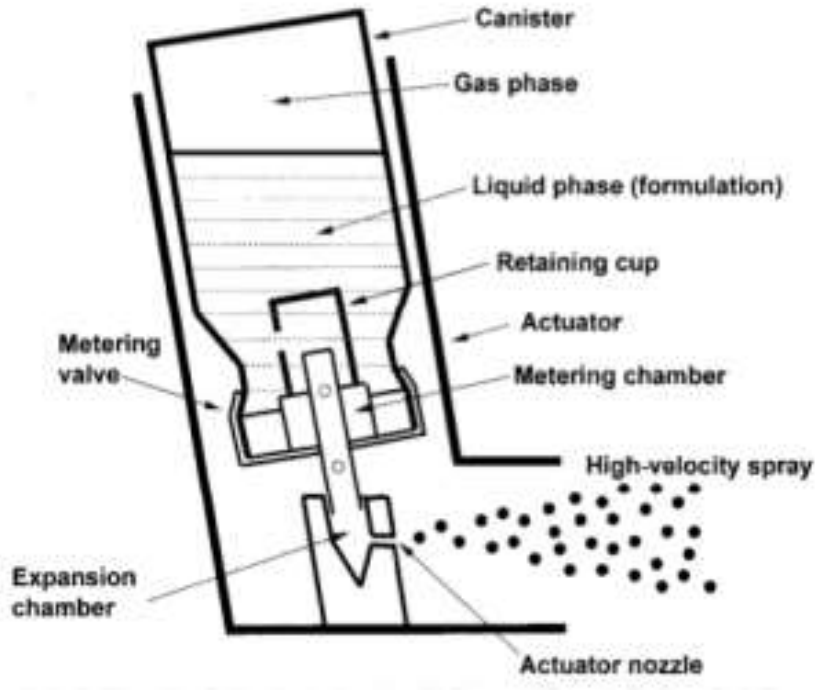


Patient-related
- Severity of airway obstruction
- Mechanism of airway obstruction
- Presence of dynamic hyperinflation
- Patient–ventilator synchrony

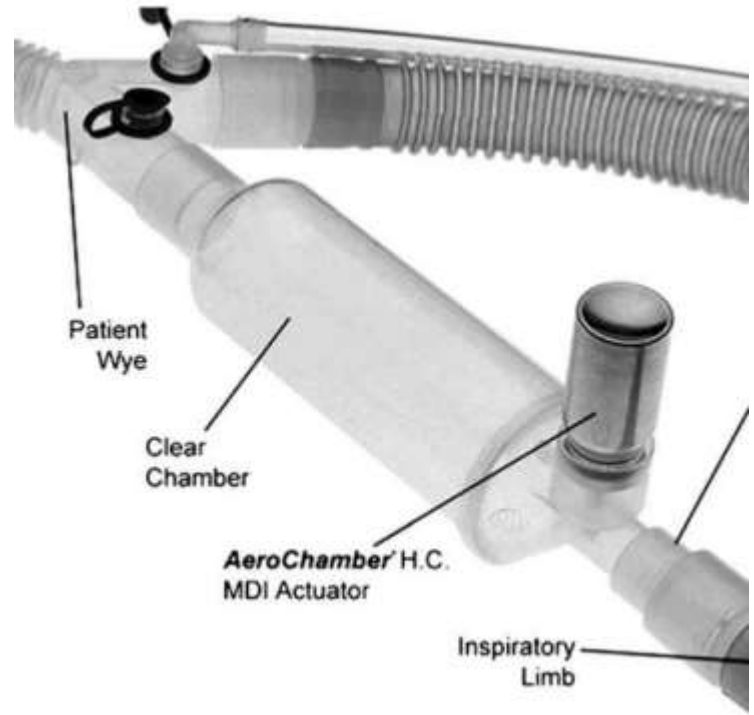
Respir Care.2004;49(6):611-622

pMDI

- Cost-effective, convenient, reliable dosing
- pMDI with a spacer chamber increases aerosol deposition
- The types of adapters available for clinical use , elbow adapter , inline devices that may be unidirectional or bidirectional, and chamber or reservoir adapters

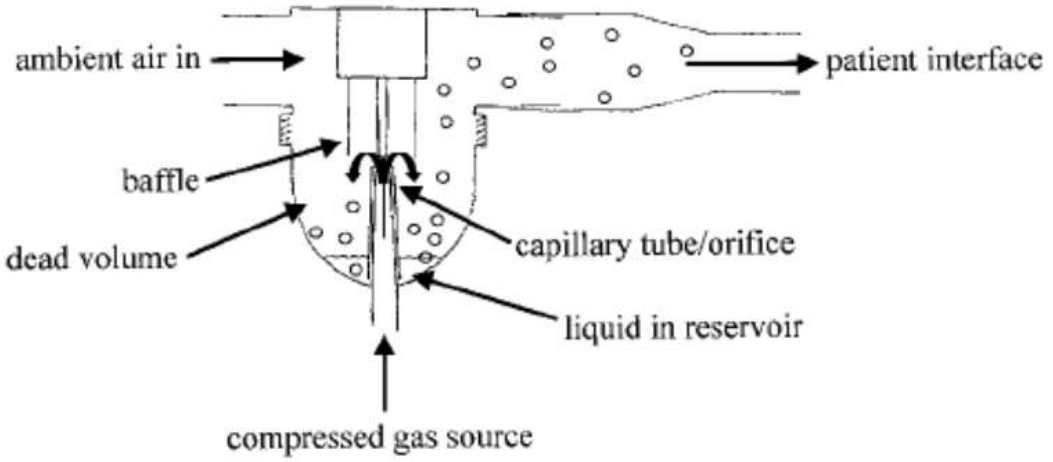



AeroChamber® MV


Patient
Wye
Clear
Chamber
AeroChamber H.C.
MDI Actuator
Inspiratory
Limb

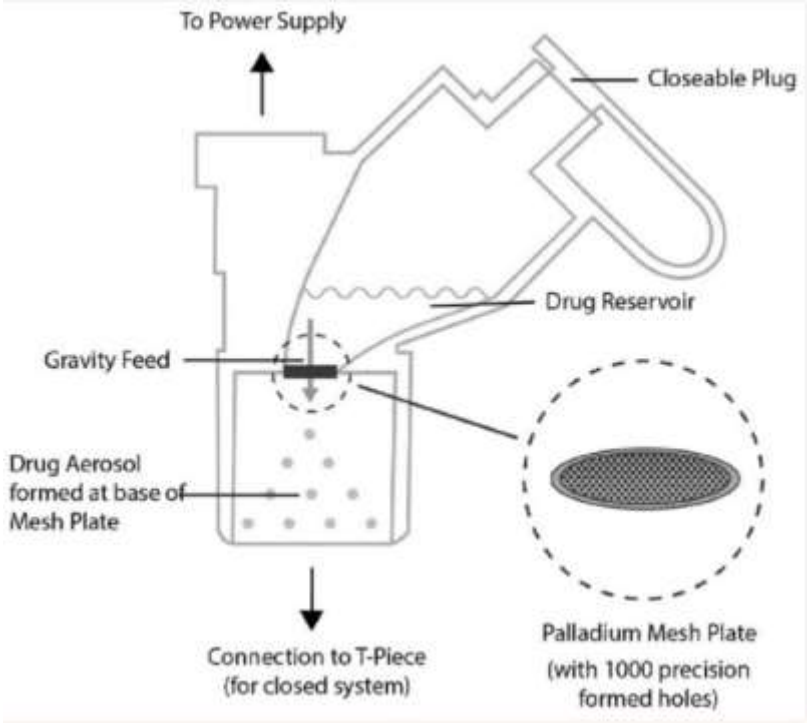
JET nebulizers

- Gas flow by an external device or via ventilator integrated system
- Additional flow hampers the ventilation by altering TV , pressures, trigger and even O2 concentration
- Higher residual volume and fall in temperature by 15C during nebulisation may denature some drugs
- Cheaper and widely available
- Large residual volume
- Should be placed 80cm away from the Y piece



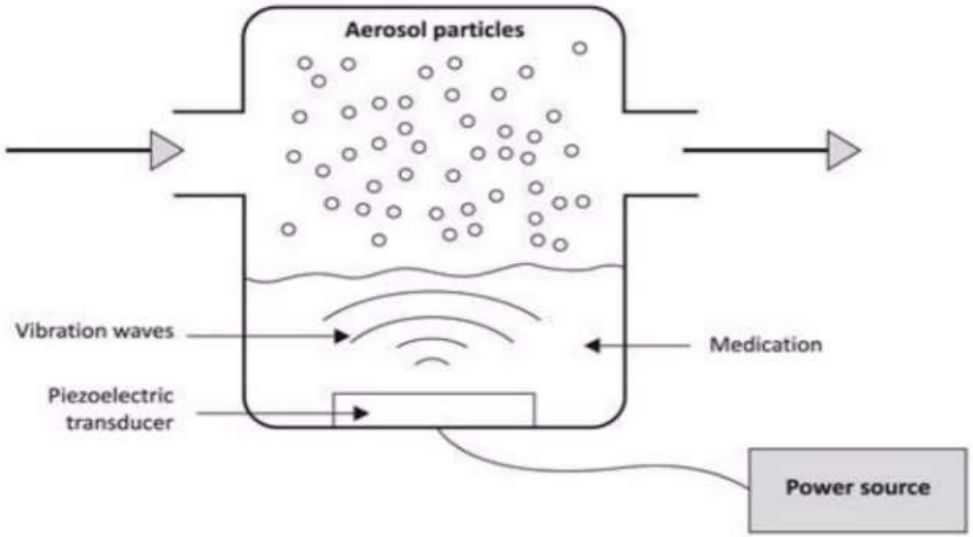
Vibrating mesh nebulizer

- VMNs generate an aerosol via a rapidly vibrating mesh or plate (also known as a piezo element) with thousands of tiny apertures
- VMNs produce a precisely sized low velocity aerosol which reduces circuit condensation and increases drug delivery to the lungs
- lower residual drug volumes
- Vibrating mesh nebulizers effectively nebulize solutions and suspen sions; as well as liposomal formulations; proteins, such as a-1 antiprotease, dornase alfa; and antibiotics.



Ultrasonic nebulizer

- A piezo electric crystal vibrates at high frequency creating standing waves on the surface of the drug
- Operates at frequency > 1MHz
- Higher frequency = smaller particles
- Temperature rises upto 10C or more with time & so is unfit for temperature sensitive drugs or suspensions (eg.budesonide) proteins, viscous solutions



Type	Advantage	Disadvantage
JET nebulizer	• Low cost • Low dimension at bedside • Single use • Widely available	• About 15% of drug delivery into lungs • Highly variable delivery, depending on gas source • *Interference of gas flow with flow delivered by ventilator* • Nonhomogeneous droplet diameter • Long duration of nebulization
Vibrating mesh nebulizer	• 40-60% drug delivery into lungs • Homogeneous droplet diameter. • Temperature stable • Good synchrony with ventilator • Low residual volume (0,5ml) • Easy to use	• High cost • Not suitable for concentrated and viscous solutions
Ultrasonic nebuliser	• low flow containing aerosol particles does not interfere with flow delivered by ventilator • 30-40% drug delivery into lungs	• Droplet diameter depends on amplitude and frequency of vibration • Increase in drug temperature. • High cost • Large dimension at bedside • Proper sterilization

Advantages	Disadvantages
Aerosol doses are generally smaller than systemic doses.	Lung deposition is a relatively low fraction of the total dose.
Onset of effect with inhaled drugs is faster than with oral dosing.	A number of variables (correct breathing pattern, use of device) can affect lung deposition and dose reproducibility.
Drug is delivered directly to the lungs, with minimal systemic exposure.	The difficulty of coordinating hand action and inhalation with the pMDIs reduces effectiveness.
Systemic side effects are less frequent and severe with inhalation when compared to systemic delivery.	The lack of knowledge of correct or optimal use of aerosol devices by patients and clinicians decreases effectiveness.
Inhaled drug therapy is less painful than injection and is relatively comfortable.	The number and variability of device types confuses patients and clinicians.
	The lack of standardized technical information on inhalers for clinicians reduces effectiveness.

Evaluation of Aerosol Generator Devices at 3 Locations in Humidified and Non-humidified Circuits During Adult Mechanical Ventilation

- Albuterol (2.5mg/3ml) delivery from jet (8L/min), vibrating-mesh(128 kHz), ultrasonic nebulizers (1.2Mhz) and pMDI with spacer was compared in a model of adult mechanical ventilation, via heated/humidified and non-humidified ventilator circuits

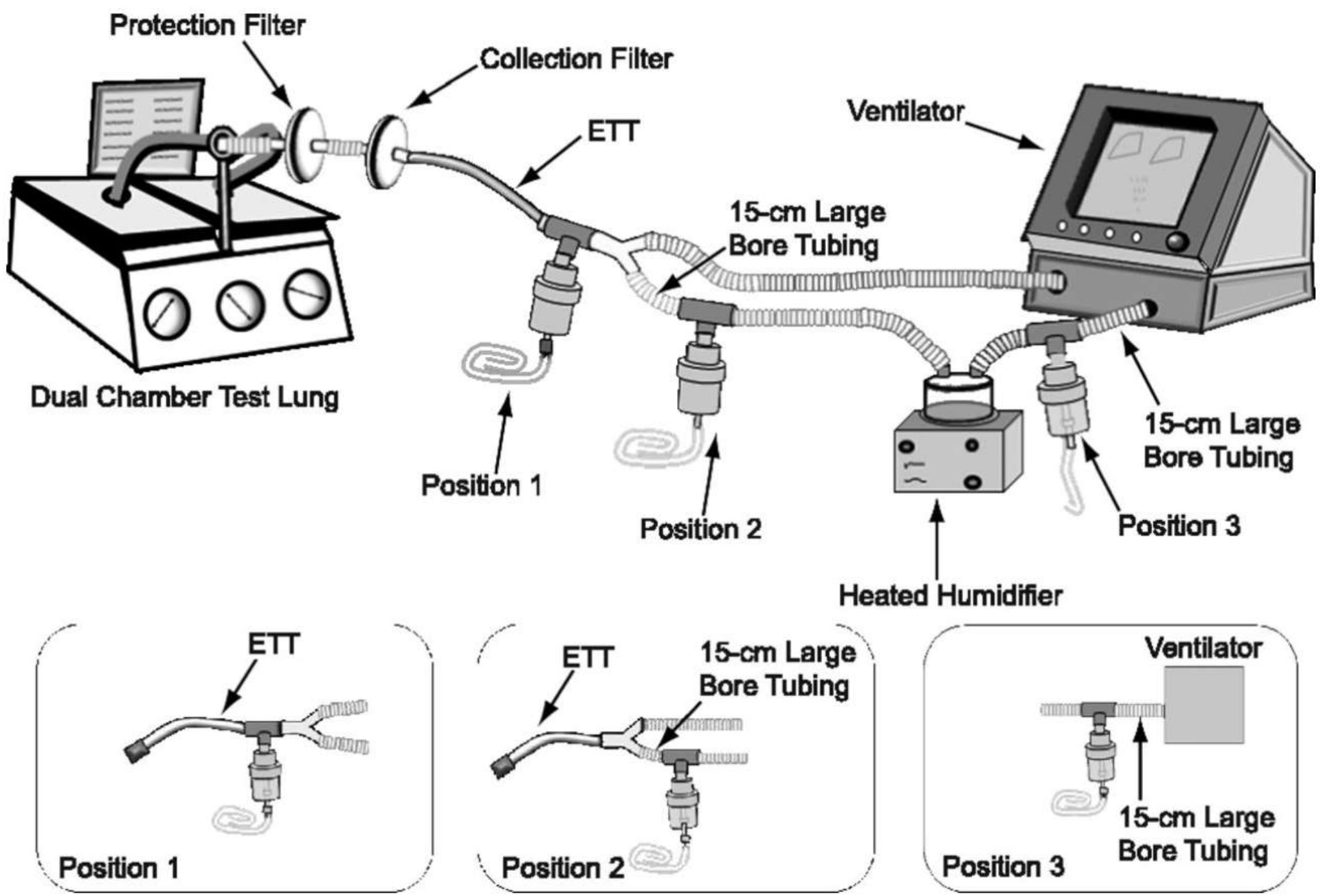
1. Between the endotracheal tube and the Y-piece
2. 15 cm from Y-piece
3. 15 cm from the ventilator

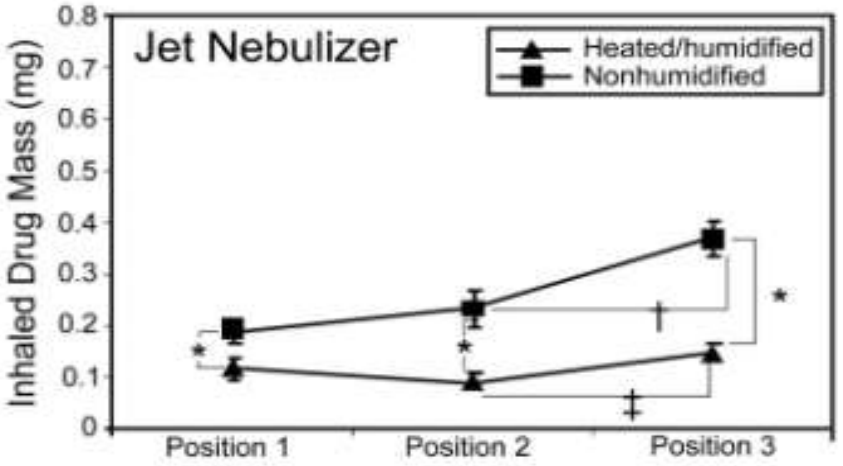
TV 500ml
RR 15/min
Flow 60L/min
PEEP 5 cmH2O

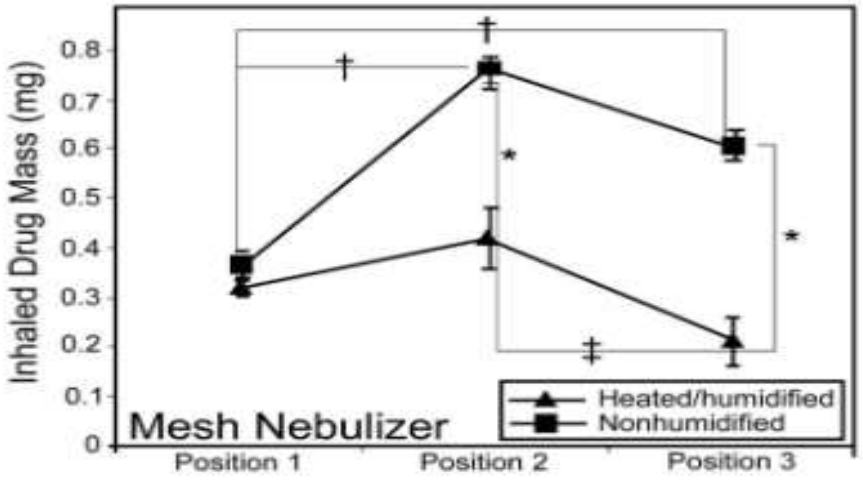
The drug deposited on an absolute filter distal to an 8.0-mm inner-diameter endotracheal tube was eluted and analyzed via spectrophotometry (276 nm)

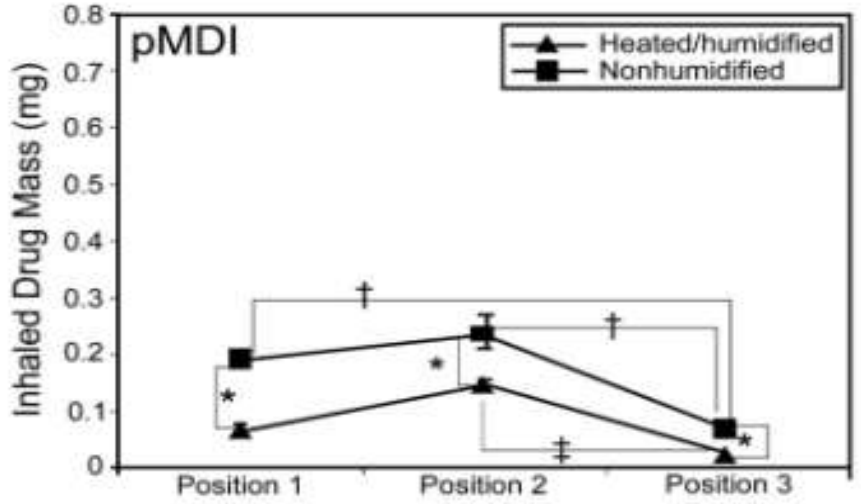
	Percent of Nominal or Emitted Dose (mean ± SD %)					
	Position 1 (between ETT and Y-piece)		Position 2 (15 cm from Y-piece)		Position 3 (15 cm from ventilator)	
	Heated/ Humidified	Non-humidified	Heated/ Humidified	Non-humidified	Heated/ Humidified	Non-humidified
Jet nebulizer	4.7 ± 0.5	7.6 ± 0.9	3.6 ± 0.2	9.7 ± 1.5	6.0 ± 0.1	14.7 ± 1.5
Vibrating-mesh nebulizer	12.8 ± 0.5	14.5 ± 1.0	16.8 ± 2.6	30.2 ± 1.0	8.4 ± 2.1	24.2 ± 1.2
Ultrasonic nebulizer	10.1 ± 3.9	10.7 ± 1.5	16.5 ± 4.3	24.7 ± 4.4	4.6 ± 2.0	10.5 ± 0.3
Pressurized metered-dose inhaler	7.6 ± 1.3	22.1 ± 1.5	17.0 ± 1.0	27.8 ± 3.3	2.5 ± 0.8	7.9 ± 1.5

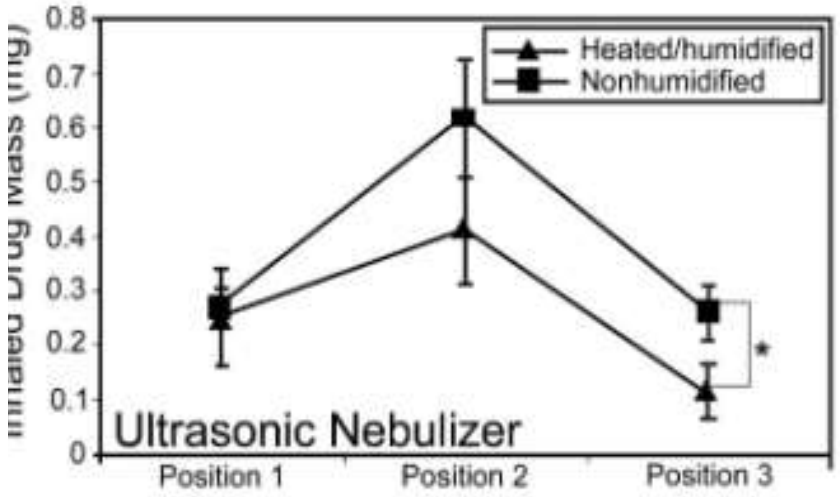
Ari A etal., Evaluation of aerosol generator devices at 3 locations in humidified and non-humidified circuits during adult mechanical ventilation. Respir Care. 2010 Jul


Protection Filter
Collection Filter
ETT
Ventilator
15-cm Large
Bore Tubing
Dual Chamber Test Lung
Position 1
Position 2
15-cm Large
Bore Tubing
Position 3
Heated Humidifier
ETT
Position 1
ETT
15-cm Large
Bore Tubing
Position 2
Ventilator
15-cm Large
Bore Tubing
Position 3









At Position 1. In the non-humidified circuit, the pMDI deposited a higher proportion of medication than the other aerosol generators ($P = .001$). The vibrating-mesh nebulizer was more efficient than the ultrasonic or jet nebulizer ($P = .001$ for each comparison). In the heated/humidified ventilator circuit the percentage of drug delivered by the pMDI sharply decreased, and the only significant difference was between the vibrating-mesh nebulizer and the jet nebulizer ($P = .01$).

At Position 2. Using the non-humidified circuit, the vibrating-mesh nebulizer delivered the greatest amount of drug, while in the heated/humidified circuit the percent of dose delivered with the vibrating-mesh and ultrasonic nebulizers and the pMDI were similar. The jet nebulizer delivered far less medication than the other aerosol generators ($P < .002$), regardless of the presence of heat and humidity.

At Position 3. In the non-humidified circuit, the vibrating-mesh nebulizer delivered a higher percent of nominal dose than the other devices ($P = .001$), while the jet nebulizer was greater than ultrasonic ($P = .03$), and pMDI was lowest ($P = .002$). With the heated/humidified circuit the vibrating-mesh nebulizer delivered more than the pMDI ($P = .01$).

Lung deposition and systemic bioavailability of different aerosol devices with and without humidification in mechanically ventilated patients

- Randomised cross over design of 36 patients on MV- 3 groups , Groups 1 and 2 received 5000 mcg salbutamol using vibrating mesh (VM) and jet nebulizers (JN), group 3 received 1600 mg (16 puffs) of salbutamol via MDI with AeroChamber Vent (MDI-AV), device downstream in inspiratory limb
- Each subject received aerosol with and without humidity at >24 h intervals with >12 hr washout periods between salbutamol doses, in between ipratropium was given
- Patients voided urine 15 min before each study dose and urine samples were collected at 0.5 h post dosing and pooled for the next 24 h. All samples were measured and assayed for salbutamol using HPLC

heart and lung November–December 2017, Pages 464-467
https://doi.org/10.1016/j.hrtlng.2017.08.004

	JN humidity	JN dry	VM humidity	VM dry	MDI-AV humidity	MDI-AV dry
URSAL0.5%	0.7 (0.5)	0.9 (0.6)	1.7 (0.8)	1.8 (1.1)	2.0 (1.1)	2.5 (1.3)
URSAL24%	6.2 (3.3)	6.6 (4.1)	10.1 (6.9)	10.5 (4.0)	7.8 (2.5)	8.0 (3.4)

- MDI-AV resulted in a higher URSAL0.5% compared to the JN and VM ($p < 0.001$ and $p = 0.041$).

  The VM resulted in significantly higher URSAL 0.5% compared to JN ($p = 0.001$).

- The URSAL 24% was greater with the VM than the JN and MDI-AV ($p = 0.002$ and $p = 0.048$)

- For each device, USAL0.5% and USAL24% were similar with both dry and humid conditions

heart and lung November–December 2017, Pages 464-467
https://doi.org/10.1016/j.hrtlng.2017.08.004

- *Heated humidifiers need to be turned off during the brief periods of nebulization (10-15 min), avoiding longer periods, however, usefulness of this practice is questionable as it takes up to 20 min. for heat and humidity to settle*
- *Higher doses of the drug may be used if the heated humidifier is not switched off during nebulization to compensate for the loss, but these must be switched off for drugs which are costly and heat unstable (e.g. antibiotics)*

Drug delivery in VCV vs PSV

- Spontaneous breathing activity of the patient (uncontrolled respiratory rate, inspiratory flow rate) in the PSV mode may affect aerosol delivery to the lungs.
- Double blind RCT of 19 patients, VMN put between catheter mount and ET tube (*flow sensor*)
- Healthy lung , neuro Sx patients, radio labelled drug TC99M DTPA was administered, Time – 9min
- Drug deposition by single planar detector gamma camera
- Propofol infusion was used , VCV – TV 8ml/kg/ MV - 8L/min/ no insp pause/ flow 30L/min

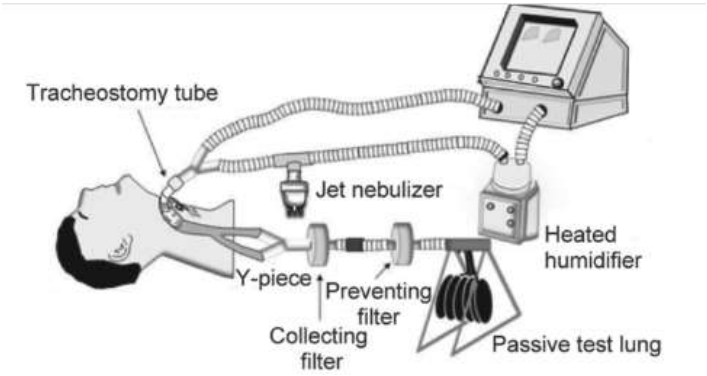
  PSV – PS titrated to generate TV 8ml/kg, PEEP 5 and bias flow 10L/min
- Expiratory trigger was set to obtain an I/E ratio of 30 %
- The system was non humidified/ heated circuit. HME in the expiratory limb to trap exhaled drug

Dugernier J *et al.* . *Ann. Intensive Care* **6**, 73 (2016)

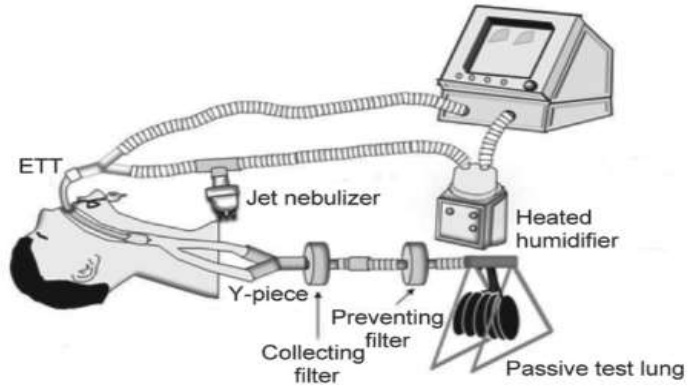
	PSV (*n* = 8)	VCV (*n* = 9)	*p* value
Pulmonary deposition (%)	*10.5 ± 3.0 (28)*	*15.1 ± 5.0 (33)*	*0.038*
Extrapulmonary deposition (%)	*89.5 ± 3.0*	*84.9 ± 5.0*	*0.038*
ETT and tracheal area	27.4 ± 6.6 (24)	20.7 ± 6.0 (29)	*0.043*
Expiratory filter	23.7 ± 5.3 (22)	22.5 ± 7.6 (34)	0.710
Ventilator circuit	34.7 ± 8.7 (25)	38.4 ± 12.3 (32)	0.486
Proximal pieces	32.0 ± 7.4 (23)	35.9 ± 12.5 (35)	0.451
Insp–expi tubing	2.7 ± 1.9 (70)	2.5 ± 1.7 (68)	0.833
Nebulizer retention	3.7 ± 0.9 (24)	3.3 ± 0.7 (21)	0.334

Pressurized Metered-Dose Inhalers Versus Nebulizers in the Treatment of Mechanically Ventilated Subjects With Artificial Airways: An In Vitro Study

- ET tube vs TT tube of size 8, breath actuated mdi & continuous jet nebs
- Nebulised albuterol 2.5mg in 3ml or albuterol 4 puffs (108 µg/puff)



TV 450ml
RR 20/min
Flow 40L/min
I:E – 1:3



	TT			ETT		
	Jet Nebulizer	pMDI	*P*	Jet Nebulizer	pMDI	*P*
Inhaled mass, mean ± SD µg	97.3 ± 14.0*	63.6 ± 0.4†	.01	79.6 ± 3.8	50.1 ± 8.2	.005
Lung dose, mean ± SD %	3.9 ± 0.5‡	14.7 ± 0.1§	.001	3.2 ± 0.1	11.6 ± 1.9	.002

* The difference between a tracheostomy tube (TT) and an endotracheal tube (ETT) in inhaled mass using a jet nebulizer ($P = .10$).
† The difference between a TT and an ETT in inhaled mass using a pressurized metered-dose inhaler (pMDI; $P = .046$).
‡ The difference between a TT and an ETT in lung dose using a jet nebulizer ($P = .10$).
§ The difference between a TT and an ETT in lung dose using a pMDI ($P = .046$).

Respiratory Care November 2015, 60 (11) 1570-1574; DOI: https://doi.org/10.4187/respcare.04125

- Drug delivery distal to the bronchi trended higher with a TT than with an ETT with both devices, but only the pMDI was significant (*P* = .046), not the jet nebulizer (*P* = .10)
- The delivery efficiency of aerosols with the pMDI and spacer was up to 3-fold greater compared with the jet nebulizer with both a TT and an ETT (*P* = .001 and .002, respectively), the jet nebulizer delivered more drug than the pMDI with both a TT (*P* = .01) and an ETT (*P* = .005)
- With both the device inhaled mass with a TT was greater compared with an ETT (*P* < .05)

During mechanical ventilation of this in vitro model, aerosol delivery to filters distal to the bronchi of the model ranged from 3.18 to 14.73% of the emitted (pMDI) or nominal (jet nebulizer) dose

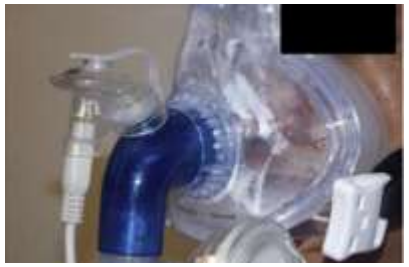
Continuous vs intermittent nebulization

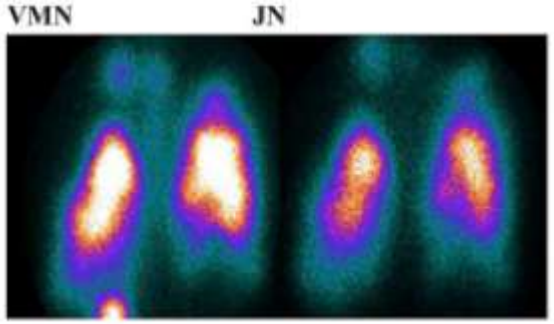
- *Intermittent nebulization with a breath actuated ventilator integrated system is always superior to a continuous nebulization via a external device*

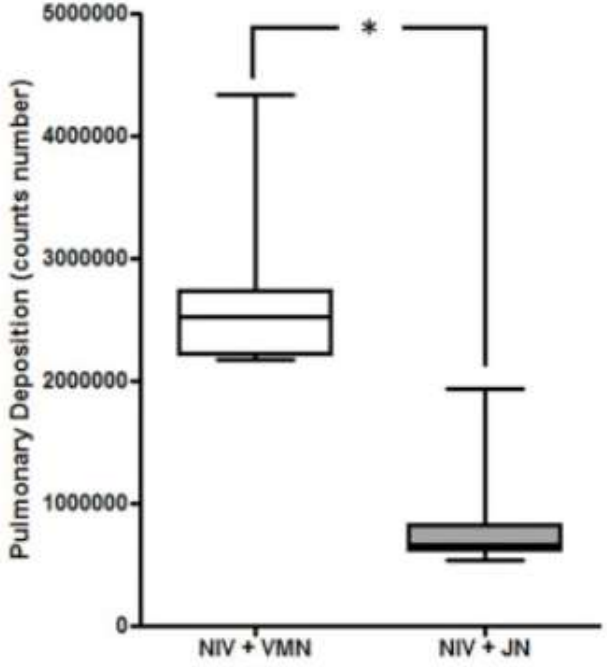
Am J Respir Crit Care Med 2003;168(10):1205-1209.

A mesh nebulizer is more effective than jet nebulizer to nebulize bronchodilators during non-invasive ventilation of subjects with COPD: A randomized controlled trial with radiolabeled aerosols

- Crossover single dose study involving 9 stable subjects with moderate to severe COPD
- Radiolabelled salbutamol and ipratropium 3ml was used with NIV pressures (12/5)
- Radioactivity counts were performed using a gamma camera
- Both inhaled and lung doses were greater with VMN (22.78 ± 3.38% and 12.05 ± 2.96%, respectively) than JN (12.51 ± 6.31% and 3.14 ± 1.71%; p = 0.008)
- Residual drug volume was lower in VMN than in JN (3.08 ± 1.3% versus 46.44 ± 5.83%, p = 0.001)



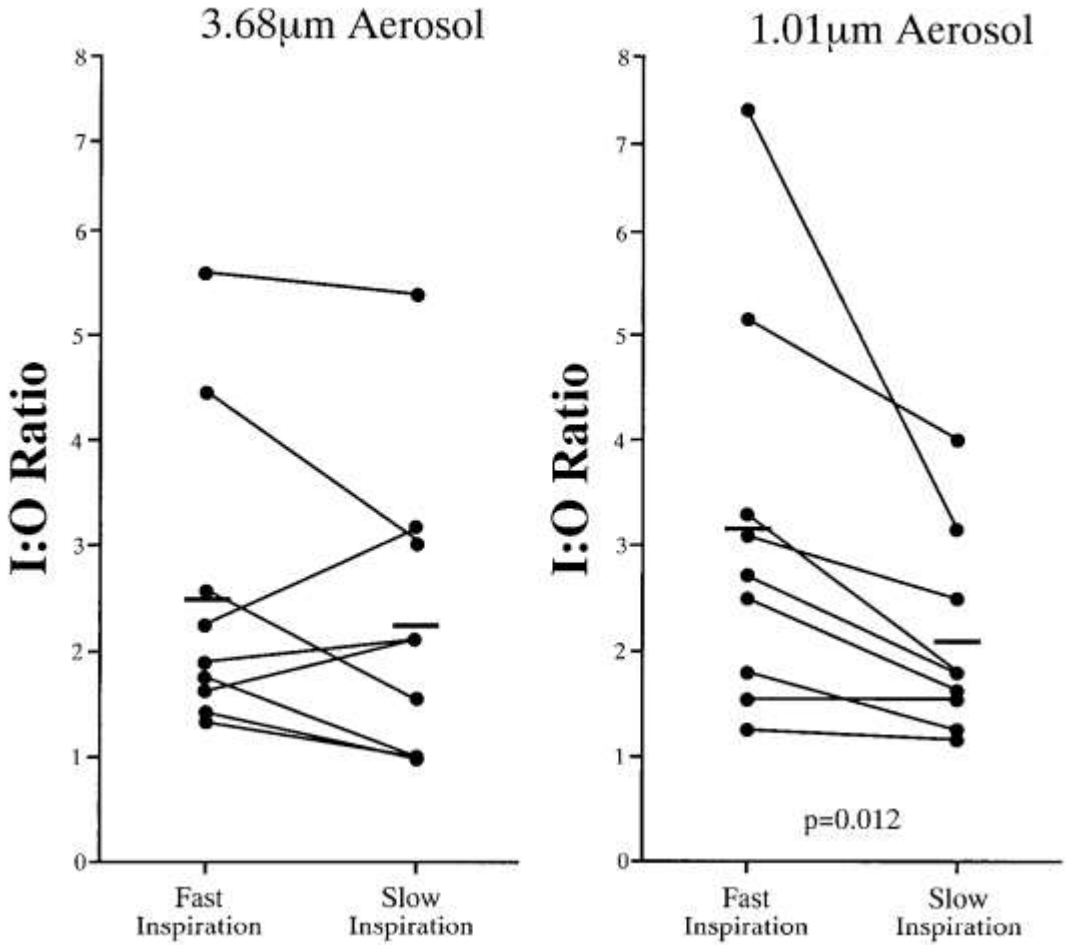




Galindo-Filho Vcetal., Respir Med. 2019 Jul;153:60-67

Targeting aerosol deposition in patients with cystic fibrosis: effects of alterations in particle size and inspiratory flow rate

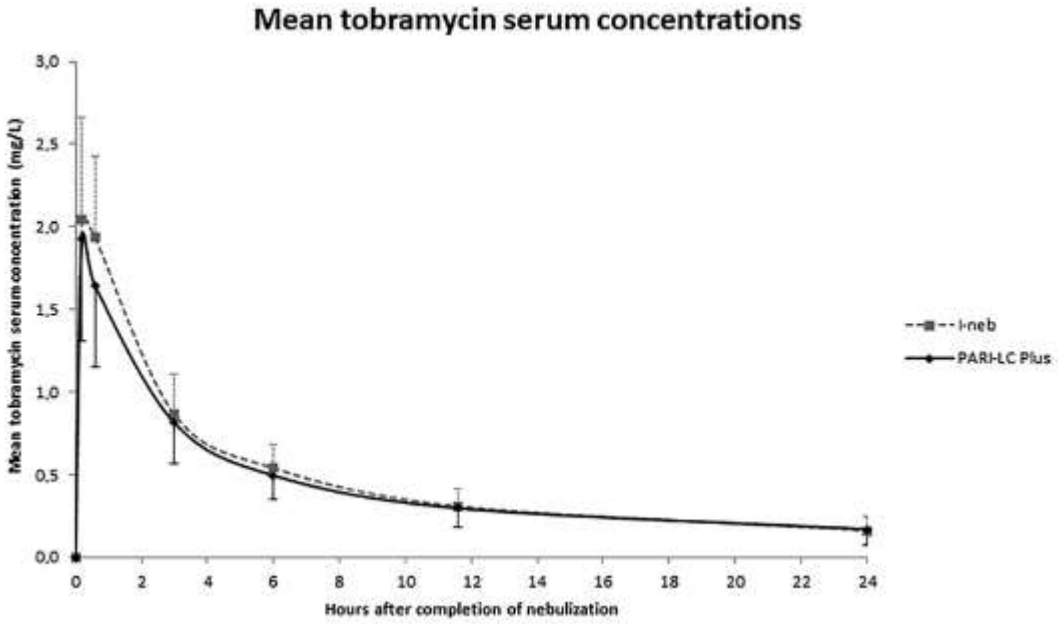
- RCT of aerosol of 2 MMAD (3.68+/-0.04 um or 1.01+/- 0.2, saline solution droplets ^{99m}Tc-DTPA) and two flow rates (12+/-2 L/min vs. 31+/-5 L/min) effecting drug delivery in CF patients (JN)
- Pari and Medicator nebulizers(patients practiced inhaling with the nebulizer system so that peak inspiration approximated a readout of 10 L/min or 25 L/min) -> Gamma Camera Imaging
- The average MMAD for the Pari nebulizer (n - 3) was 3.68 um. This MMAD was significantly larger than that of the Medicator nebulizer (n -4), which averaged 1.01 um (p - 0.034)
- Patients inhaled the aerosol for 30 s, starting from functional residual capacity and breathing at a slow or faster inspiratory flow rate
- Flow and aerosol size will alter the deposition of aerosol in the TB tree

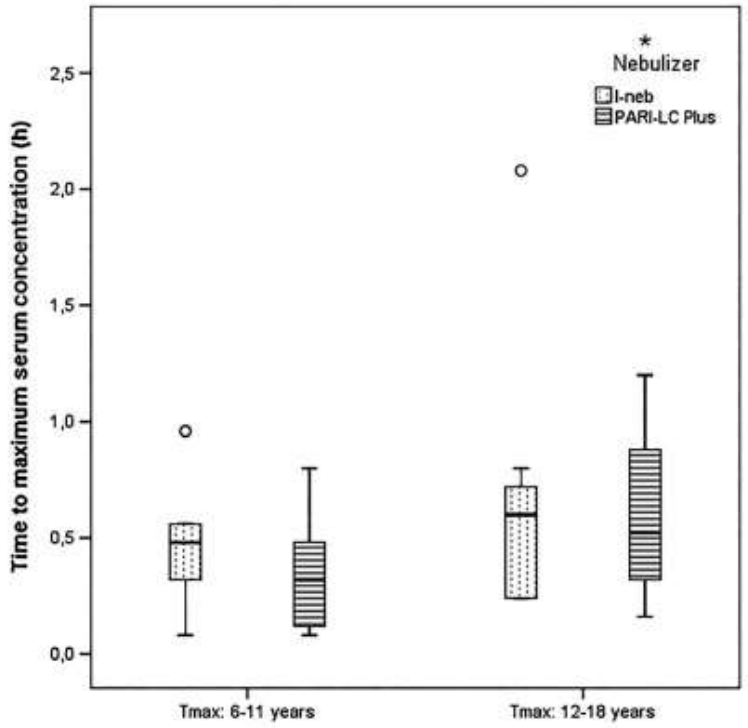


- Deposition images were analyzed in terms of the, inner zone (large, central airways) vs an outer zone (small airways and alveoli) (I:O) ratio
- For the 3.68-µm aerosol, I:O ratios averaged 2.29 +/- 1.45 and 2.54 +/- 1.48 ($p > 0.05$)
- For the 1.01 µm aerosol, I:O ratios averaged 2.09 +/- 0.96 and 3.19 +/- 1.95 ($p = 0.012$)

Pharmacokinetics and safety of tobramycin nebulization with the I-neb and PARI-LC Plus in children with cystic fibrosis: A randomized, crossover study

- Randomized, open-label, crossover study, CF children 6–18 years
- Blood samples from 22 children were collected following TIS nebulization with I-neb - VMN (75 mg) and PARI-LC Plus – breath enhanced JN (300 mg)





	Geometric mean		Ratio geometric mean (90% CI)	Bioequivalent?[a]
	I-neb	PARI-LC Plus	I-neb vs PARI-LC Plus	
C_{max} (mg/L) study population	1.70	1.61	1.06 (0.76–1.47)	Yes
6–11 y	1.43	1.60	0.89 (0.52–1.55)	Yes
12–18 y	2.10	1.62	1.29 (0.92–1.82)	Yes
AUC_{0-24} h (h*mg/L) study population	10.19	9.32	1.09 (0.86–1.39)	Yes
6–11 years	9.30	9.37	0.99 (0.66–1.50)	Yes
12–18 years	11.37	9.26	1.23 (0.97–1.56)	Yes

AUC_{0-24h} = area under the concentration–time curve from 0 to 24 h.

	I-neb (*n* = 16)	PARI-LC Plus (*n* = 6)	*P*-value
Tolerability (scale 0–10)[a]			
Coughing during nebulization	4.2 ± 2.9	4.0 ± 3.6	.860
Coughing after nebulization	3.6 ± 3.0	3.7 ± 3.1	.952
Dyspnoea during nebulization	1.3 ± 1.8	1.6 ± 0.7	.726
Dyspnoea after nebulization	1.1 ± 1.0	1.6 ± 1.4	.341
Dizziness during nebulization	0.8 ± 1.2	0.9 ± 0.8	.822
Dizziness after nebulization	0.5 ± 0.5	0.8 ± 0.7	.300

	I-neb (*n* = 16)	PARI-LC Plus (*n* = 6)	*P*-value
Nebulizer satisfaction (scale 0–10)[c]			
Size	9.3 ± 0.8	2.8 ± 2.3	<.001
Noisiness	9.3 ± 0.9	3.6 ± 3.2	<.001
Look	8.5 ± 1.5	5.6 ± 1.8	.001
Nebulization time	6.7 ± 2.8	2.6 ± 1.4	.003
Final grade	8.2 ± 0.9	5.5 ± 1.6	<.001
Cleaning time (min)	9.3 ± 8.2	9.2 ± 10.3	.975

longer nebulization time for the PARI-LC Plus (approximately 19 mins vs 13 minutes for the I-neb)

HFNC and aerosol therapy

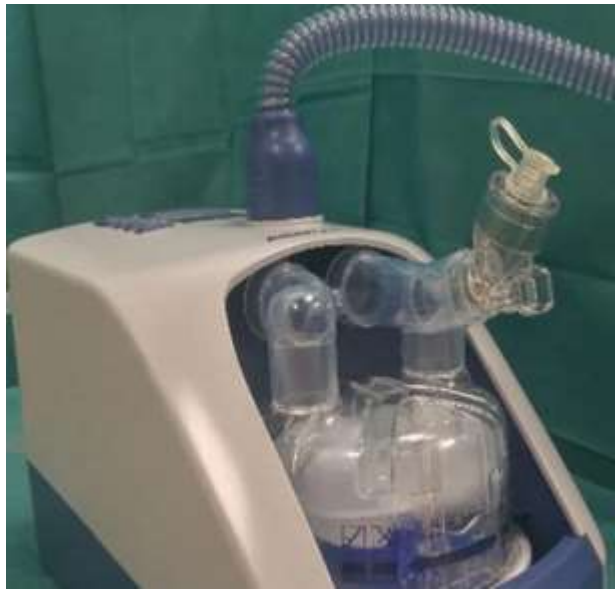
(1) 2.5 mg albuterol delivered via a jet nebulizer with a facial mask

(2) 2.5 mg albuterol delivered via a VMN placed downstream of a HFNC humidification chamber (30 L/min and 37 °C)

(3) HFNC without nebulization

median change was similar after facial mask nebulization [+ 350 mL (+ 180; + 550); + 18% and HFNC with nebulization [+ 330 mL (+ 140; + 390); + 16% (+ 5; + 24)], p = 0.11

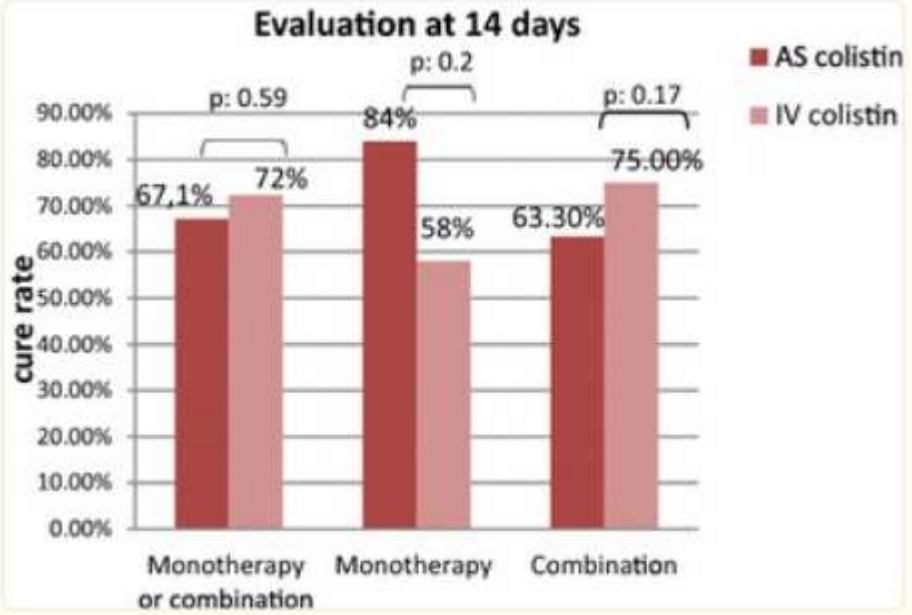
HFNC without nebulization [+ 50 mL (− 10; + 220); + 3% (− 1; + 8)], *p* = 0.0009

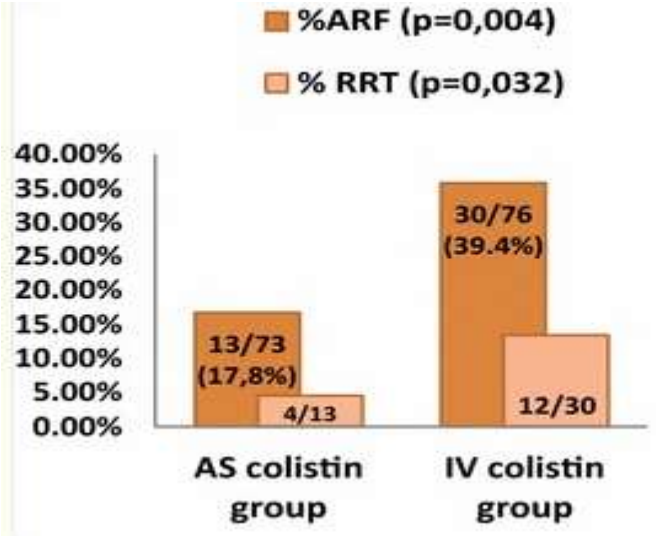


Reminiac et al. Ann. Intensive Care (2018) 8:128

Efficacy and toxicity of aerosolised colistin in ventilator-associated pneumonia: a prospective, randomised trial

- Randomised, single-blind study for VAP patients
- N-73(4mu inh colistin TID – 30mins + imipenem) vs n-76(IV 4.5mu BD colistin + imipenem)
- Treatment duration was maintained at least 14 days
- 2.7 % of patients presented a moderate bronchospasm





MV days (13.8 ± 7 vs 16.5 ± 10, p = 0.083)

ICU stay (25.9 ± 17 vs 26.07 ± 17, p = 0.9)

All cause D28 mortality (27.4 vs 23.7 %, p = 0.7)

Abdellatif S, etal., Ann Intensive Care. 2016 Dec;6(1):26

Inhaled antifungal

- In 12 lung transplant patients 7ml of technetium labeled amphotericin-B lipid complex was administered @ dose of 35 mg with JN, drug deposition measured by laser diffraction
- In single lung recipients average total deposited dose in the single lung recipients was 8.3 ± 0.6 mg (SD) which represents 23.7 ± 1.7% of the dose loaded in the nebulizer
- The average allograft dose was 3.9 ± 1.6 mg versus a native average of 2.1± 1.1 mg (p = 0.2)
- Double lung recipients: on average 2.8 ± 0.8 mg (left lung) and 4.0 ± 1.3 mg (right lung)
- Percentage of drug delivered to the central lung was similar for the transplanted and native lungs (56.9 ± 8.8% vs. 58.3 ± 11.9%; p = 0.7).
- Peripheral lung dose 0.7 to 2.7 mg in the allografts and from 0.3 to 1.5 mg in the native lungs (averages: 1.6 ± 0.7 mg, 0.8 ± 0.5 mg; p = 0.13)

American Journal of Transplantation 2006; 6: 2765–2773
Aerosol Deposition of Lipid Complex Amphotericin-B (Abelcet) in Lung Transplant Recipients

- Inhaled Ampho B deoxycholate/ lipid complex or liposomal forms have been studied and minimal systemic absorption and side effects have been demonstrated in numerous studies
- Some have suggested twice or thrice weekly regimen may be sufficient as prophylaxis
- In a study from 8 lung transplant patients, nebulised amphoB 30mg was followed 60 mins later by BAL / TBLB and serum collection.
- Mean amphotericin B concentration in the upper and lower lobe BAL samples were 0.68 +/- 0.36 and 0.50 +/- 0.31 microgram/mL. plasma detection of ampho B only in 1 patient

Marra F etal., Ann Pharmacother. 2002 Jan;36(1):46-51

Ref	Type of IFD	n-AmB	Evidence
Patterson, 2016 [86]	TBA in lung transplants associated with anastomotic endobronchial ischemia or ischemic reperfusion injury due to airway ischemia	Adjunctive inhaled AmB is recommended in association with a systemic antimold antifungal (strong recommendation; moderate-quality evidence).	"No consistent evidence"
Husain, 2016 [87]	TBA	n-AmB alone is not recommended as a primary treatment of TBA (C-III). Although it has been proposed as an adjunctive therapy in an endobronchial prothesis infection, more evidence is needed.	Morales, 2009 [80]
	IPA	Addition of n-AmB to a standard regimen of treatment is not routinely recommended (C-III). However, the authors also declare that n-AmB could be used in combination with voriconazole/other systemic antifungal drugs, depending on the severity of IFD, or possibly in situations in which large cavitary lesions might render the penetration of systemic agents difficult.	Additional evidence would be helpful
Husain, 2019 [85]	TBA associated with anastomotic endo-bronchial ischemia, or ischemic reperfusion injury due to airway ischemia associated with lung transplant	Inhaled AmB (in conjunction with systemic antifungal therapy) may be used (weak; low).	

Brunet K,etal.,Inhaled Antifungal Agents for Treatment and Prophylaxis of Bronchopulmonary Invasive Mold Infections. Pharmaceutics. 2022 Mar 14;14(3):641

Ref	Criteria	n-AmBd	n-AmB Lipid Formulation
Husain, 2016 [87]	Lung transplant recipients	n-AmB ± fluconazole or an echinocandin should be used in the first 2–4 weeks post-transplantation (B-I)	
Patterson, 2016 [86]	Lung transplant recipients	n-AmB may be considered (weak recommendation; low-quality evidence) AmB lipid formulations are generally better tolerated than AmBd	
Ullman, 2018 [124]	Lung transplant recipients	B-II 25 mg/day for 4 days, followed by 25 mg/week for 7 weeks	Recommended A-I (first choice) More AEs with AmBd but similar efficacy; various possible protocols: ABLC 50 mg/d for 4 d, then 50 mg/w for 7 w. ABLC 50 mg/day for 2 w., then 1×/w for 10 w. L-AmB 25 mg × 3/w. (day 1–60) post SOT, then 1×/w. (day 60–180)
	Heart transplant recipients	n-AmB universal prophylaxis is recommended in second choice (C-I). First choice is targeted prophylaxis with echinocandins	
Husain and Camargo, 2019 [85]	Lung transplant recipients	AmBd 20 mg × 3/d or 25 mg/d (weak; low)	ABLC 50 mg 1×/2d for 2 w., then 1×/w for 13 w. (week; low) L-AmB 25 mg × 3/w. for 2 months, then 1×/w. for 6 m., then 2×/m. thereafter (weak; low)
	Heart transplant recipients	Not cited Targeted prophylaxis with itraconazole or voriconazole or echinocandins is recommended in patients at risk	

Recommendations

- Proper suctioning should be done prior to nebulisation A good airway suction prior to nebulization is essential to ensure adequate ventilation and delivery of aerosol
- Right angled elbow connectors; sudden changes in the diameter, narrowing and rough inner surface of ventilator circuit components; connection between Y piece and endotracheal tube, and in-line suction catheters; reduce the nebulized drug delivery to the lungs
- Y piece should be directly connected to the TT / ET tube
- Patients on mechanical ventilation, for the aerosol therapy, are recommended to be kept in semi-recumbent position with head end elevated to 20 to 30 degrees above horizontal position

Indian Guidelines on Nebulization Therapy 2022

Li et al. Annals of Intensive Care (2023) 13:63 https://doi.org/10.1186/s13613-023-01147-4

- VCV is preferred to PSV & with higher TV 8ml/kg , RR 12-15/min, I:E 1:1, flow 30-50L/min, low Bias flow, longer I time (I:E 1:1) , I pause, PEEP of 5-10 and to avoid asynchrony , VMN
- Inline jet nebuliser cause change in volume and pressures and should be avoided if possible
- pMDI with spacer or VMN should be used, preferably 15 cm from the Y piece on the inspiratory limb
- When JN is utilized during invasive ventilation, it is recommended to be placed near the ventilator
- The efficiency of aerosol delivery in dry ventilator circuits is higher than that in humidified ventilator circuits.
- Heated humidifiers are recommended to be switched off during nebulization for brief periods (10-15 min.), but longer periods need to be avoided.

Indian Guidelines on Nebulization Therapy 2022

Li et al. Annals of Intensive Care (2023) 13:63 https://doi.org/10.1186/s13613-023-01147-4

- Considering the potential harms of dry gas on patient airway, and the time lapse required for a humidifier and circuits to cool down, turning of humidifier is not recommended for routine aerosol therapy. Except for costly drugs like antibiotics
- When aerosol device is placed in the inspiratory limb, removing or bypassing the heat moisture exchanger is recommended
- Increasing dilutent volume in VMN to improve aerosol delivery efficiency is not recommended
- It is not recommended to change the ventilator mode for the purpose of improving aerosol delivery
- Filter should be placed on the expiratory limb to trap generated aerosol during expiration and periodic change of the HME is recommended

Indian Guidelines on Nebulization Therapy 2022

Li et al. Annals of Intensive Care (2023) 13:63 https://doi.org/10.1186/s13613-023-01147-4

- Placing the nebulizer inline with NIV has similar or higher aerosol delivery efficiency than using the nebulizer with a mask or mouthpiece. Interrupting or discontinuing NIV to administer aerosol via a mask or mouthpiece is debatable depending on the condition of the patient
- During NIV using single limb circuit, the continuous nebulizer is recommended to be placed between the exhalation valve and the mask
- The aerosol delivery efficiency with a nebulizer via HFNC at flow ≤35 L/min is similar to that with a nebulizer and a mask or mouthpiece
- Routine use of heliox in mechanically ventilated patients, though may improve nebulized drug deposition, is not recommended for being more expensive and technically complex to use

Indian Guidelines on Nebulization Therapy 2022

Li et al. Annals of Intensive Care (2023) 13:63 https://doi.org/10.1186/s13613-023-01147-4

- It is recommended that a minimal fill volume of 4 - 6 ml and a flow rate between 6 - 8 L/min using compressed air may be used for obstructive airway disorder with nebulization time of 10 mins
- It is recommended that higher flow rates between 8 - 10 L/min and greater fill volumes may be used for administration of antibiotics targeting intrapulmonary deposition
- Mouthpiece is recommended as the preferred interface over face masks having improved drug delivery during nebulization therapy in non intubated
- Oxygen should only be used as the preferred driving gas for nebulization in hypoxemic patients with asthma exacerbations

Indian Guidelines on Nebulization Therapy 2022

Li et al. Annals of Intensive Care (2023) 13:63 https://doi.org/10.1186/s13613-023-01147-4

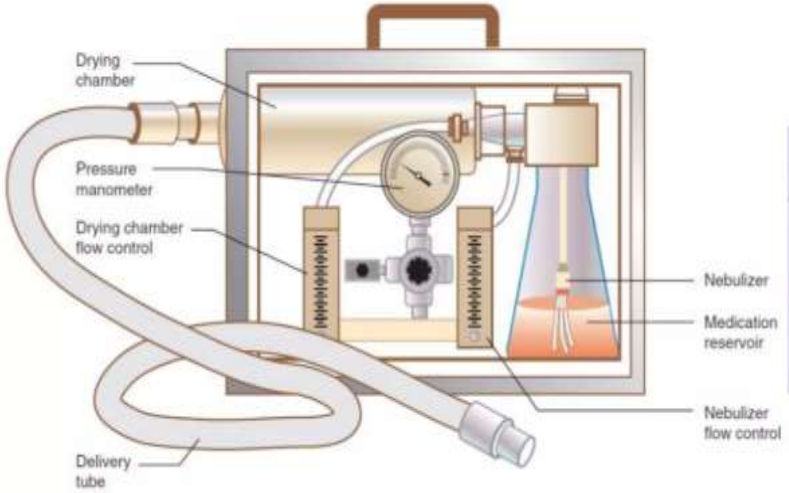
Particulars
Check patient ID (Identify the case), re-check the orders and assess the need for bronchodilator
Proper hand wash
Adjust ventilator settings for nebulization
Check sedation status (indicated to adapt the patient to the ventilator/not indicated)
Make the patient seated in an erect (if possible) or semi-recumbent position with head end elevated 20 to 30 degrees (unless contraindicated)
Suction of endotracheal and airway secretions
Proper placement of nebulizer in the ventilator circuit
Add and dilute drug as per manufacturer instructions (fill volume of 4 to 6 ml)
Switch off the heated humidifier/Remove HME from the circuit
Check bias flow
Check for proper aerosolization
Ensure peak expiratory flow within limits
Set gas flow to nebulizer (Jet) at 6 - 8 L/min and adjust ventilator volume or pressure limit to compensate for added flow
Tap nebulizer chamber periodically until it begins to sputter
Check residual volume in drug chamber
Check vital parameters at end of procedure
Return to original ventilator settings
Adequate washing, disinfection of nebulizer, and having a dry run before storage
Record any adverse reactions

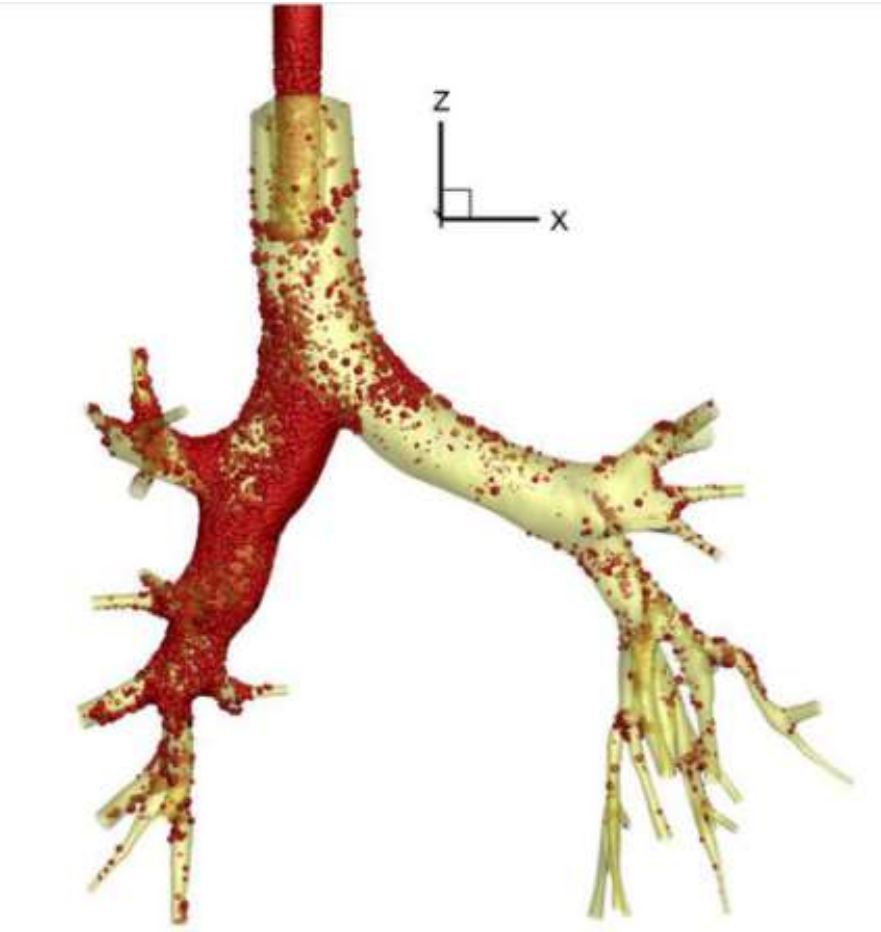
Checklist before aerosol therapy in mechanically ventilated

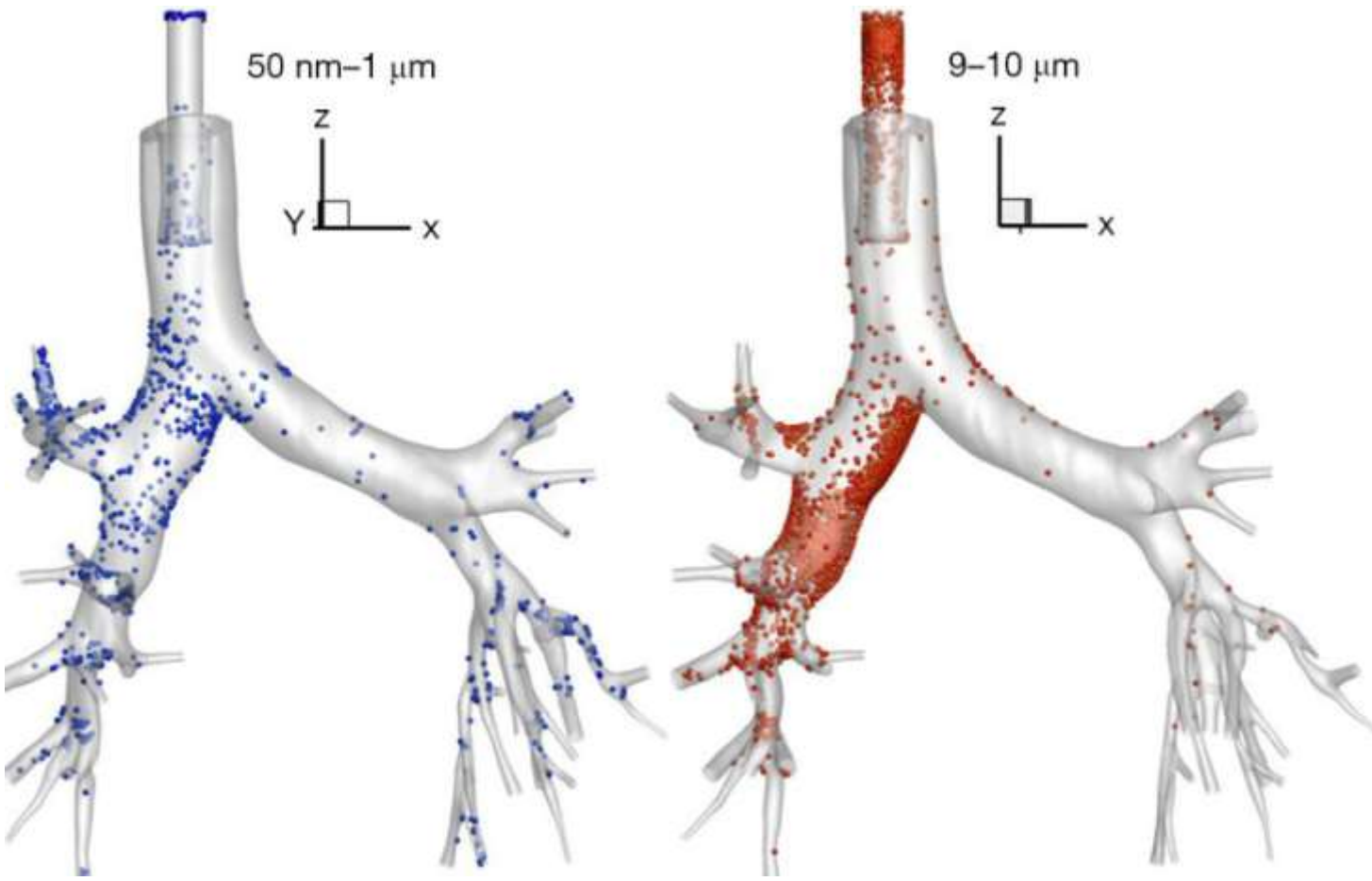
Formulation	Brand Name	Nebulizer
Tobramycin	Tobi	Pari LC
Dornase alfa	Pulmozyme	Hudson T Up-draft II, Marquest Acorn II, Pari LC, Durable Sidestream, Pari Baby
Pentamadine	NebuPent	Marquest Respirgard II
Ribavirin	Virazole	Small Particle Aerosol Generator
Iloprost	Ventavis	I-neb
Aztreonam	Cayston	Altera
Treprostinil	Tyvaso	Tyvaso Inhalation System
Glycopyrrolate	Lonhala	Magnair

Ribavirin

- The small-particle aerosol generator (SPAG) is a large-volume nebulizer designed solely to deliver aerosolized ribavirin (Virazole®, Valeant Pharmaceuticals, Aliso Viejo, CA) for prolonged periods of nebulization. It consists of a nebulizer and a drying chamber that reduces the MMAD to about 1.3 µm. Because of teratogenic characteristics of ribavirin, a scavenging system is strongly recommended for use during its administration







As consequences of intubation orientation toward right bronchus, the total deposition inside right lung was drastically higher (~12 times) than that inside left lung

Flow-controlled ascending ramp, volume-controlled ramp and pressure-controlled constant result in similar total deposition fraction and was ~43.65 % greater than using pressure-controlled sinusoidal waveform

Alzahrany M etal., Med Biol Eng Comput. 2016 Jul;54(7):1097-109.

THANK YOU