Nebulizers for mechanically ventilated patients: useful or useless

2019. 04. 27

서울의대 호흡기내과

이 상 민

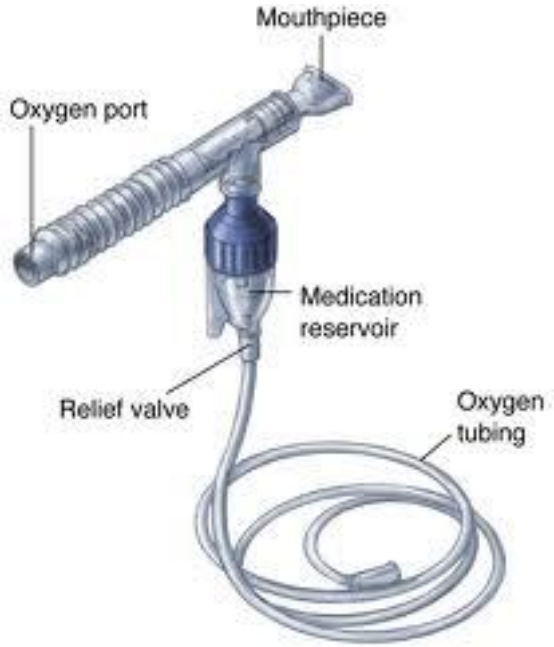
What is current status of aerolized therapy in ICU?

Administering Aerosols

Meter Dose Inhaler (MDIs)

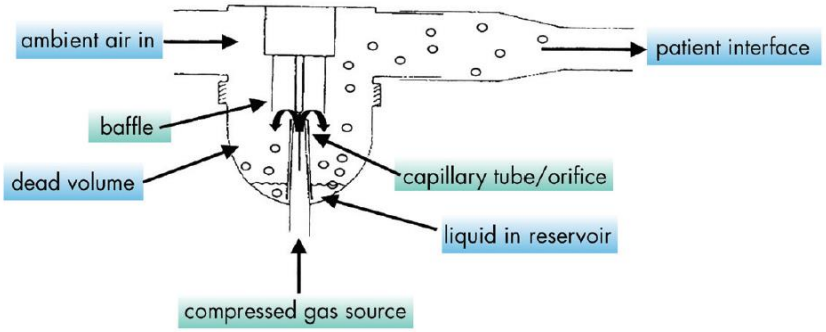
vs

Nebulizers

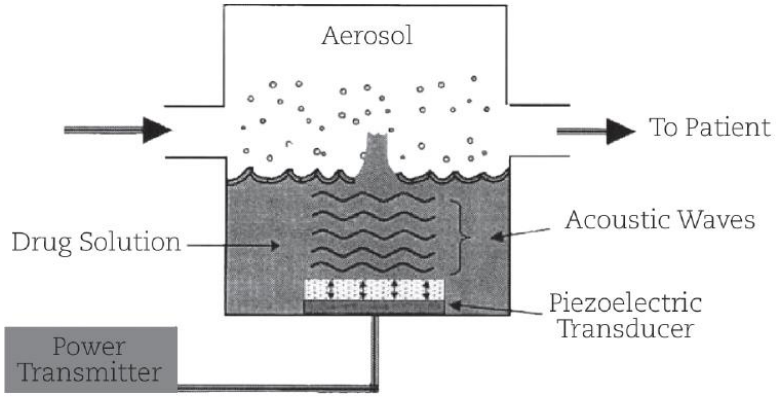


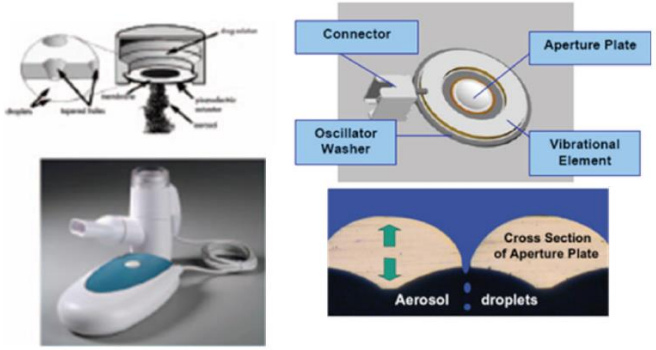
Types of Nebulizer

Jet



Ultrasonic





Vibrating Mesh

From A Guide To Aerosol Delivery Devices for Respiratory Therapists, 4th Ed

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

pMDIs = pressurized metered-dose inhalers
NA = not applicable

RESPIR CARE 2015;60:858

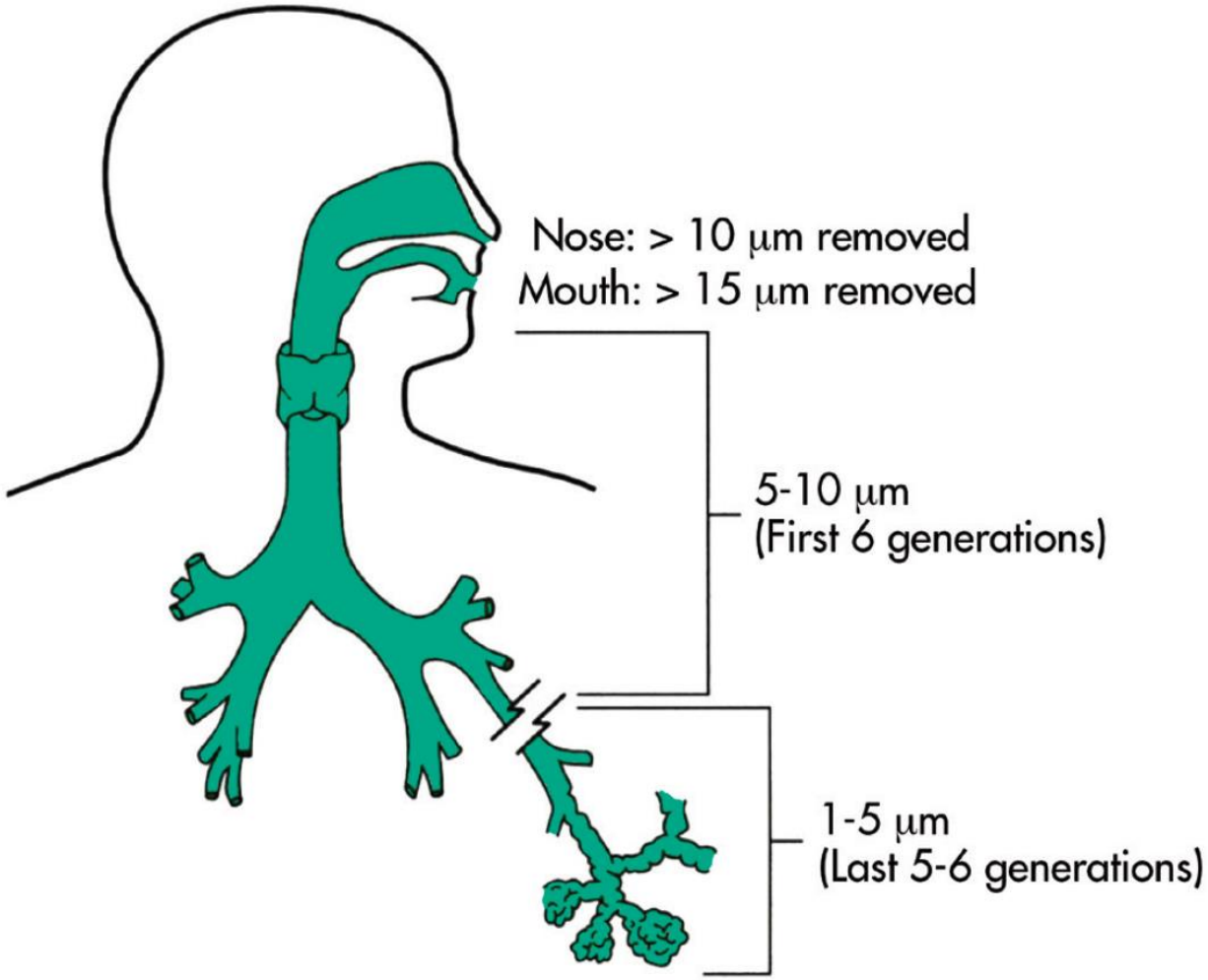
Aerosol Delivery in SB vs MV Patient

	Spontaneously Breathing Patient	Mechanically Ventilated Patient
Position of the patient	Sitting or standing	Supine or semi-recumbent
Aerosol generator	pMDI/pMDI and spacer/dry powder inhaler/nebulizer	pMDI and spacer/nebulizer
Method of delivery	By mouthpiece/facemask	Connected to endotracheal tube/inspiratory limb of ventilator circuit
Humidity	Ambient humidity	Humidifed (~97% relative humidity)
Temperature	Room/ambient	Warmed to ~35°C
Inspiratory airflow	Sinusoidal	Constant or ramp flow
Breath configuration	Controlled by patient	Controlled by ventilator*
Aerosol administration	Self-administered	Administered by nurse/therapist
Airway	Oral/nasal cavity and upper airway	Artificial airway

* In mandatory modes of mechanical ventilation, the ventilator controls the breath configuration. In spontaneous modes of ventilation, the breath configuration is influenced by the patient's effort.
pMDI = pressurized metered-dose inhaler
Adapted from Reference 23.

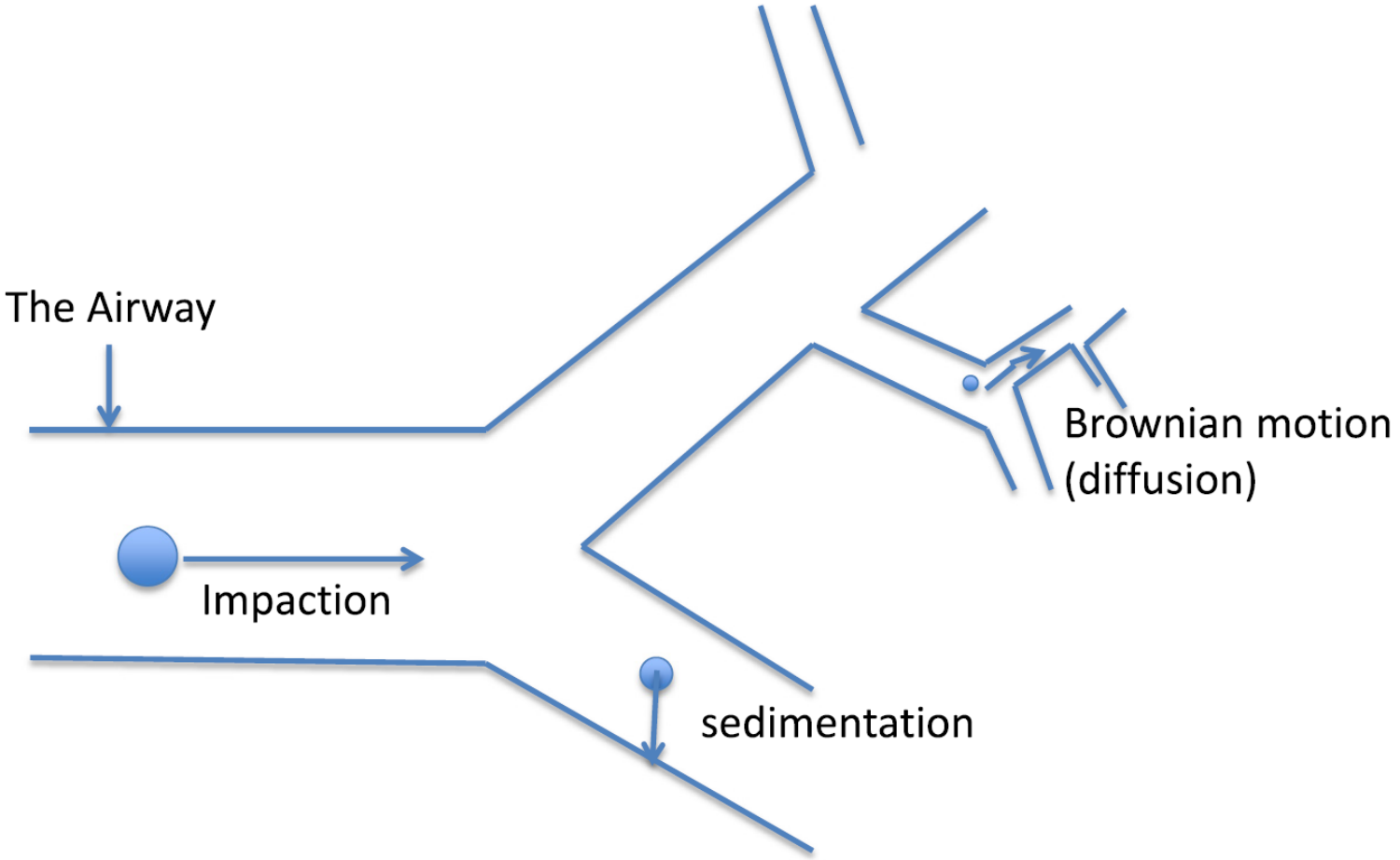
RESPIR CARE 2017;62:1343

Effect of Aerosol Size on Deposition Site



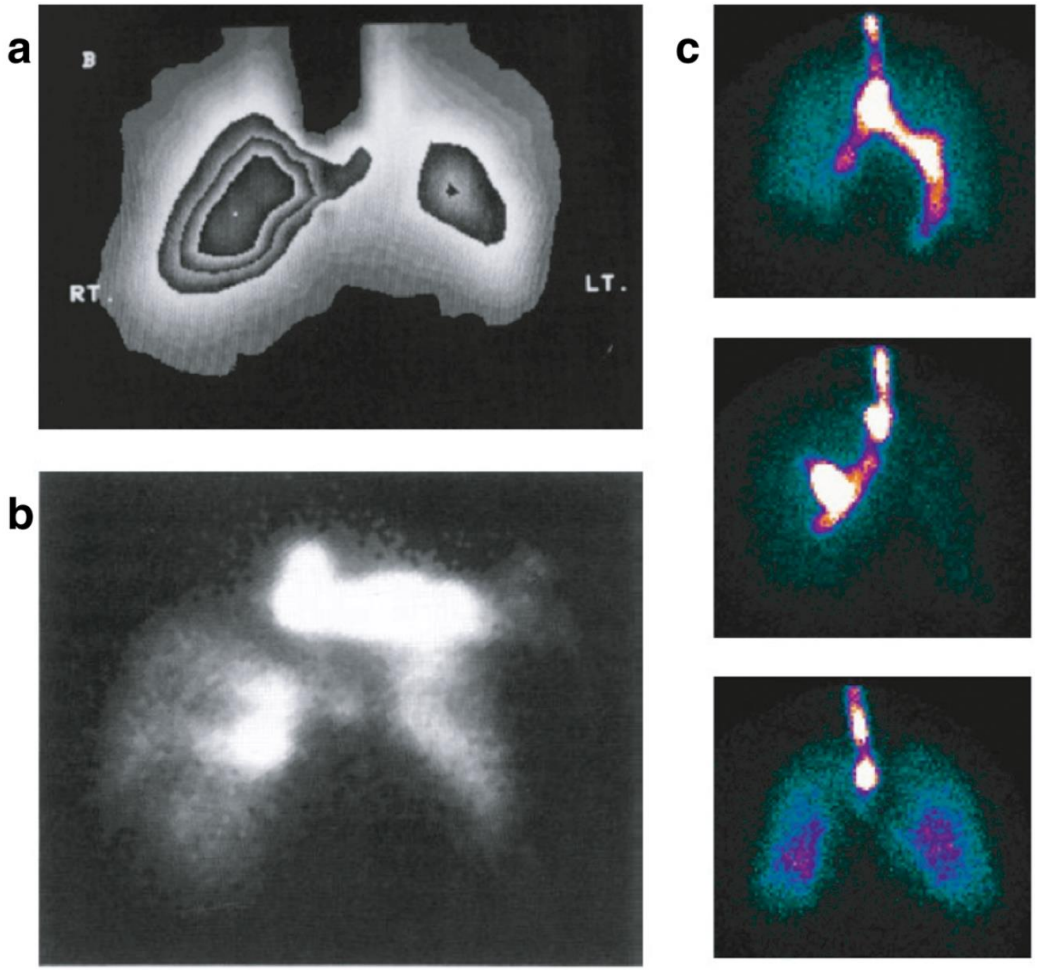
From A Guide To Aerosol Delivery Devices for Respiratory Therapists, 4th Ed

Mechanisms of Particle Deposition



Crit Care 2016;20:269

Aerosol Deposition in Intubated Patient



Imaging deposition studies revealed that the trachea and large bronchi represent the major site of drug deposition.

Crit Care 2017;21;264

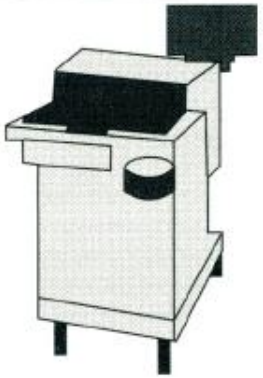
Factors on Aerosol Drug Efficacy

- Drug-related factors
  - ✓ Particle size
  - ✓ Molecular weight
- Device factors
- Patient-related factors
  - ✓ Airway anatomy
  - ✓ Inhalation patterns
- Mechanical ventilation-related factors
  - ✓ Humidification
  - ✓ Airway

Factors that Influence Aerosol Delivery

Ventilator related

- Mode of ventilation
- Tidal volume
- Respiratory rate
- Duty cycle
- Inspiratory waveform
- Breath-triggering mechanism

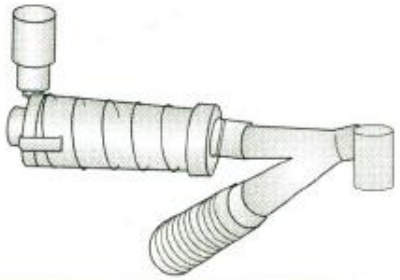


Circuit related

- Endotracheal tube
- Inhaled gas humidity
- Inhaled gas density/viscosity

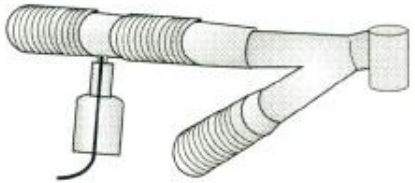
Device related—MDI

- Type of spacer or adapter used
- Position of spacer in circuit
- Timing of MDI actuation



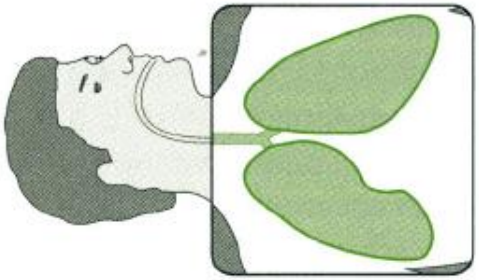
Device related—nebulizer

- Type of nebulizer used
- Continuous/intermittent operation
- Duration of nebulization
- Position in the circuit



Drug related

- Dose
- Aerosol particle size
- Duration of action

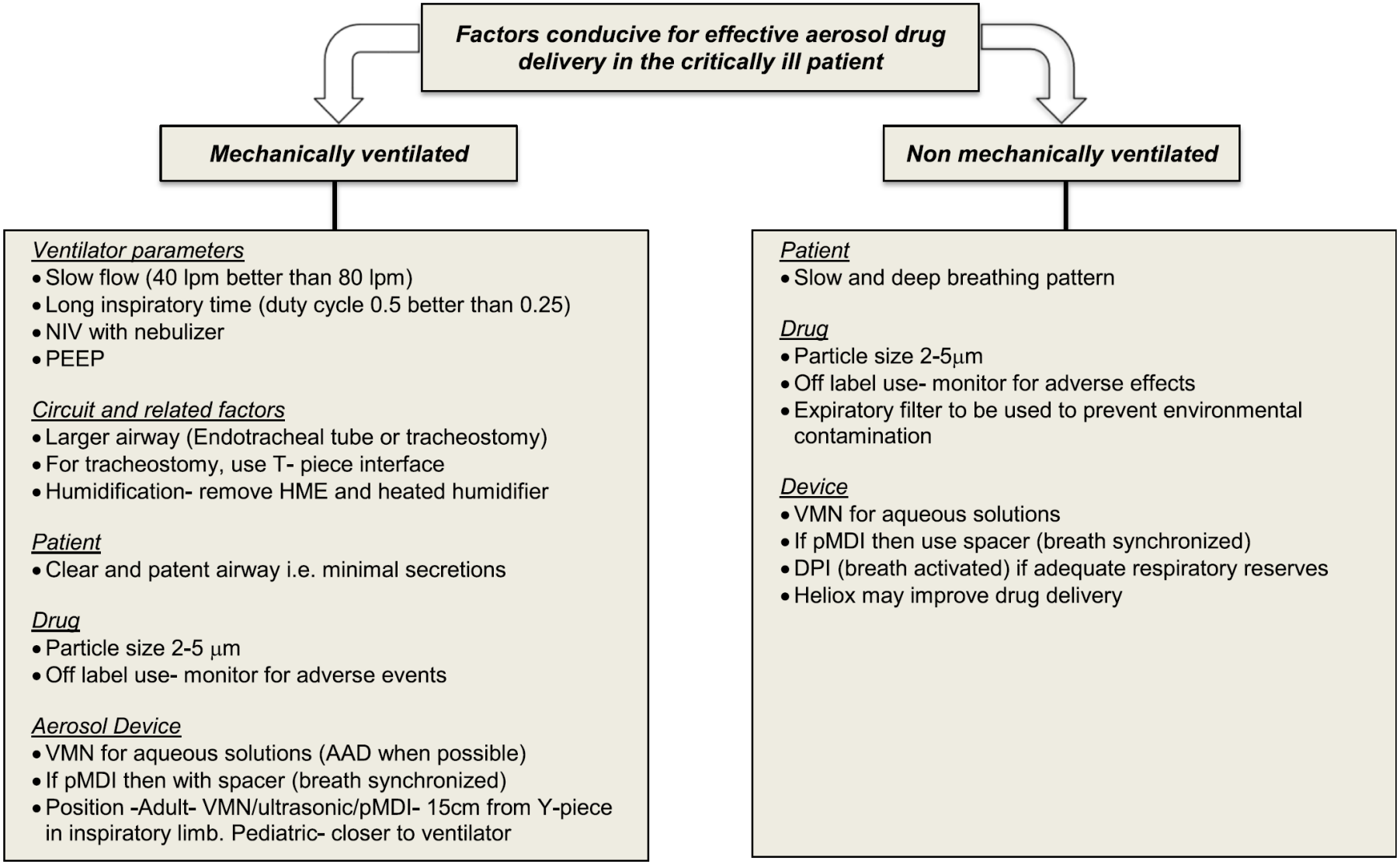


Patient related

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

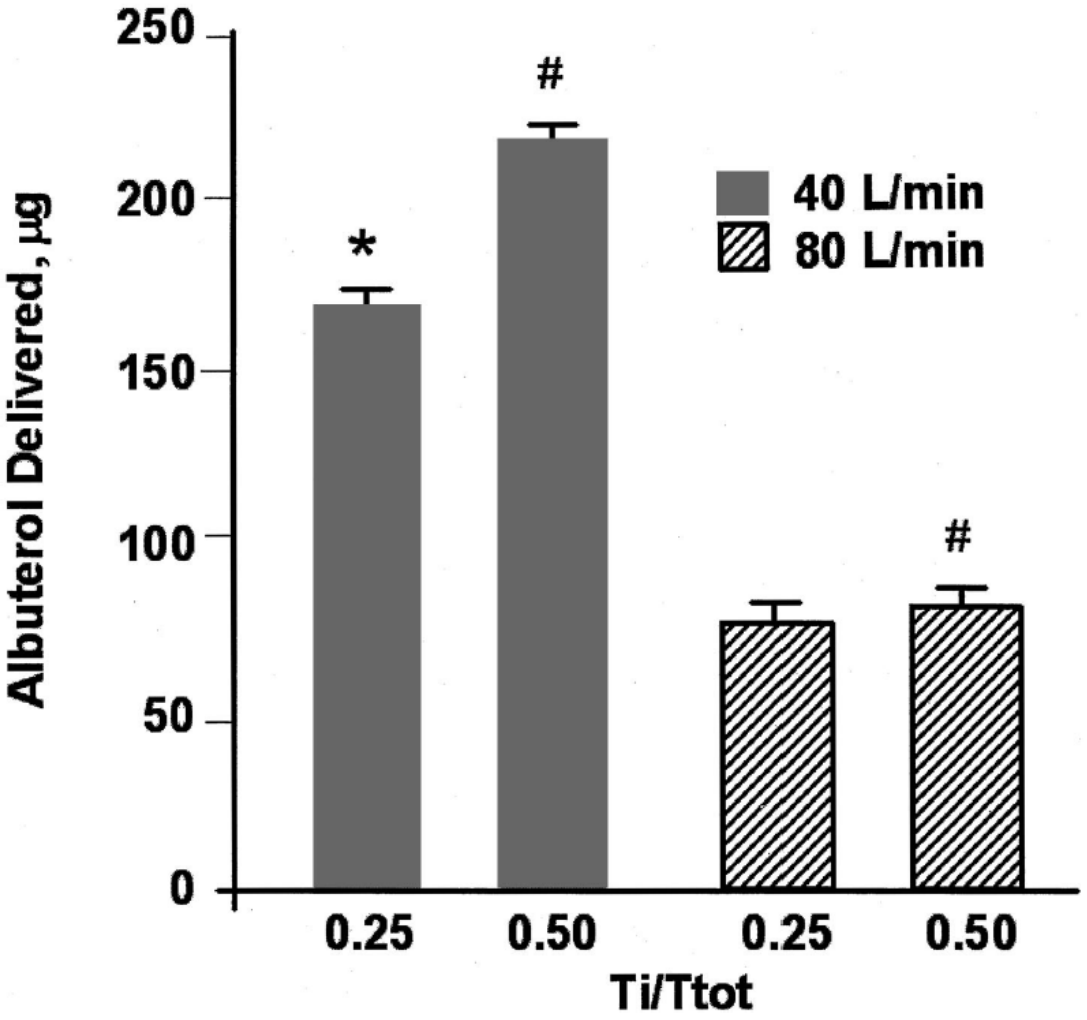
Eur Resp J 1996;9;585

Factors for Aerosol Delivery in ICU



Crit Care 2016;20:269

Aerosol Delivery at Different Insp Flows



RESPIR CARE 2004 ;49:611

How to Improve Drug Deposition during MV

Ventilator-related strategies
Deliver a tidal volume > 500 mL[a]
Maintain an inspiratory flow of 30-50 L/min
Avoid delays between actuation and inhalation
Circuit-related strategies
Remove the filter or deliver the drug at a location more proximal to the filter
Turn the humidifier off 10 min before aerosol delivery
Install the aerosol generator 15 cm proximal to the Y-piece
Device-related strategies
Metered dose inhaler
Heat it and shake it before actuation
Use an appropriate connector
Use a spacer
Coordinate actuation with inhalation
Nebulizer
Use an intermittent-flow nebulizer system only if the gas source is > 15 psi
If an external flow source is used, use a flow rate of 6-8 L/min
Complete the volume by adding 2.5 mL of saline solution

J Bras Pneumol. 2015;41(5):467

Intensive Care Med (2016) 42:192–201
DOI 10.1007/s00134-015-4114-5

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Aerosol therapy in intensive and intermediate care units: prospective observation of 2808 critically ill patients

Intensive Care Med 2016;42:192

- Two-week cross-sectional study in 81 ICU of 22 countries.
- A total of 9714 aerosols were administered to 678 of the 2808 admitted patients (24 %).
- Among intubated patients, 22 % received aerosols.
- Bronchodilators & corticosteroids were the most frequently delivered drugs (88 % overall).
- Only 106 (<1 %) mild side effects were observed.

Intensive Care Med (2016) 42:192–201
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Table 2 Characteristics of aerosols

	$n = 9714$
Aerosol generation devices	
Jet nebulizer	5436 (56 %)
Ultrasonic nebulizer	940 (10 %)
Vibrating mesh nebulizer	999 (10 %)
Hand held devices[a]	2216 (23 %)
Instillation[b]	123 (1 %)
Ventilation during aerosol delivery	
Spontaneous breathing	4832 (50 %)
NIV[c]	350 (4 %)
Invasive ventilation	4532 (47 %)
Number of molecules within one aerosol[d]	
1	5583 (57%)
2	3657 (38 %)
≥3	474 (5 %)

Table 4 Drugs delivered as aerosols

	Aerosols ($n = 9714$)
Bronchodilators	7960 (82 %)
Short acting beta-2-adrenergic agonists	6780 (95 %)
Long acting beta-2-adrenergic agonists	88 (1 %)
Anticholinergic drugs	4958 (70 %)
Corticosteroids	1233 (13 %)
Beclomethasone dipropionate	269 (22 %)
Budesonide	897 (74 %)
Fluticasone	60 (5 %)
Other	5 (<1 %)
Anti-infectious drugs	509 (5 %)
Amikacin	31 (6 %)
Amphotericin B	33 (6 %)
Colistin	400 (79 %)
Gentamicin	21 (4 %)
Ceftazidime	6 (1 %)
Tobramycin	14 (4%)
Mucus modulating drugs	241 (3 %)
Acetylcysteine	136 (61 %)
Recombinant human deoxyribonuclease	12 (5 %)
2-Mercapto ethane sodium sulfonate (Mesna)	93 (42 %)
Electrolyte solutions	503 (5 %)
0.9 % sodium chloride[a]	440 (87 %)
Hypertonic sodium chloride	16 (3 %)
Sodium bicarbonate	47 (9 %)
Other	14 (<1 %)

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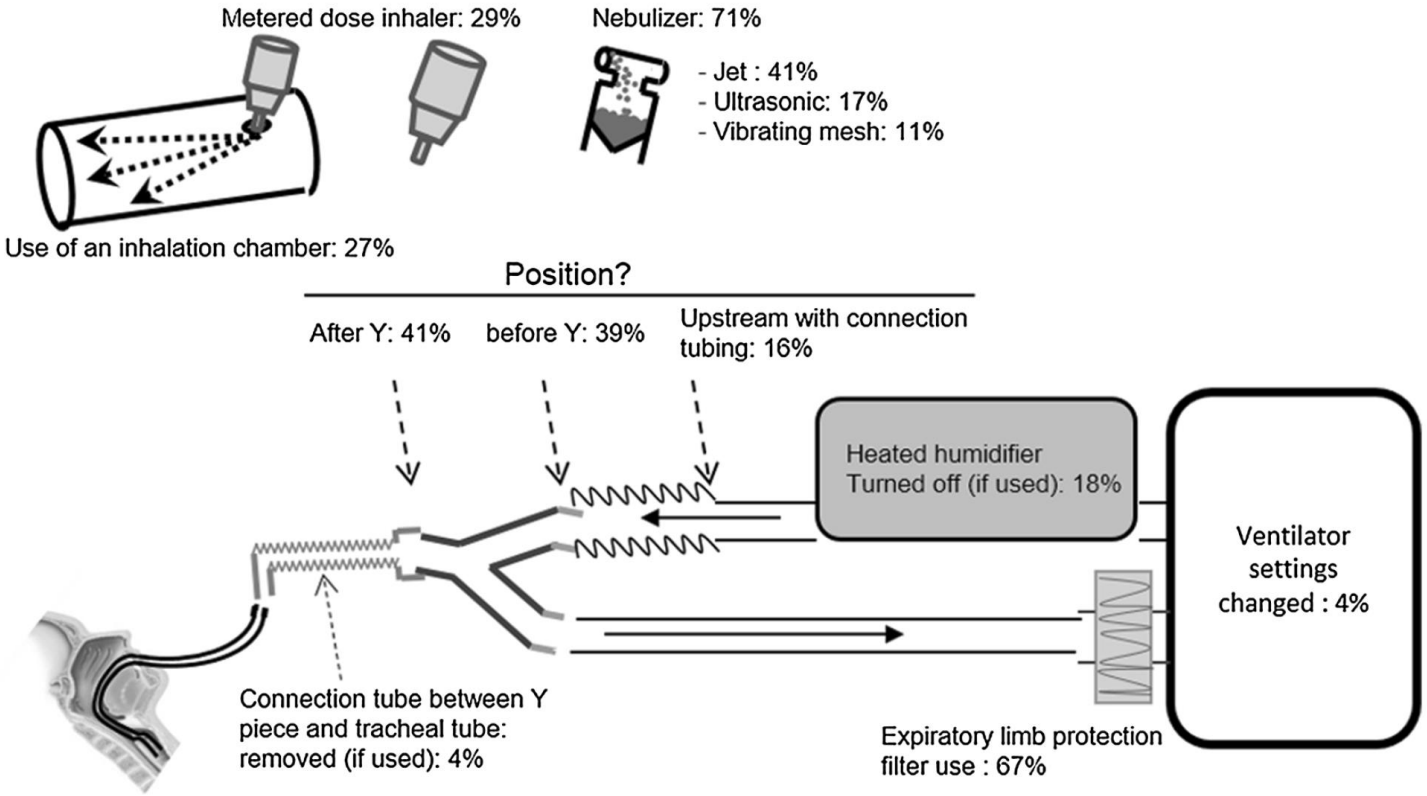


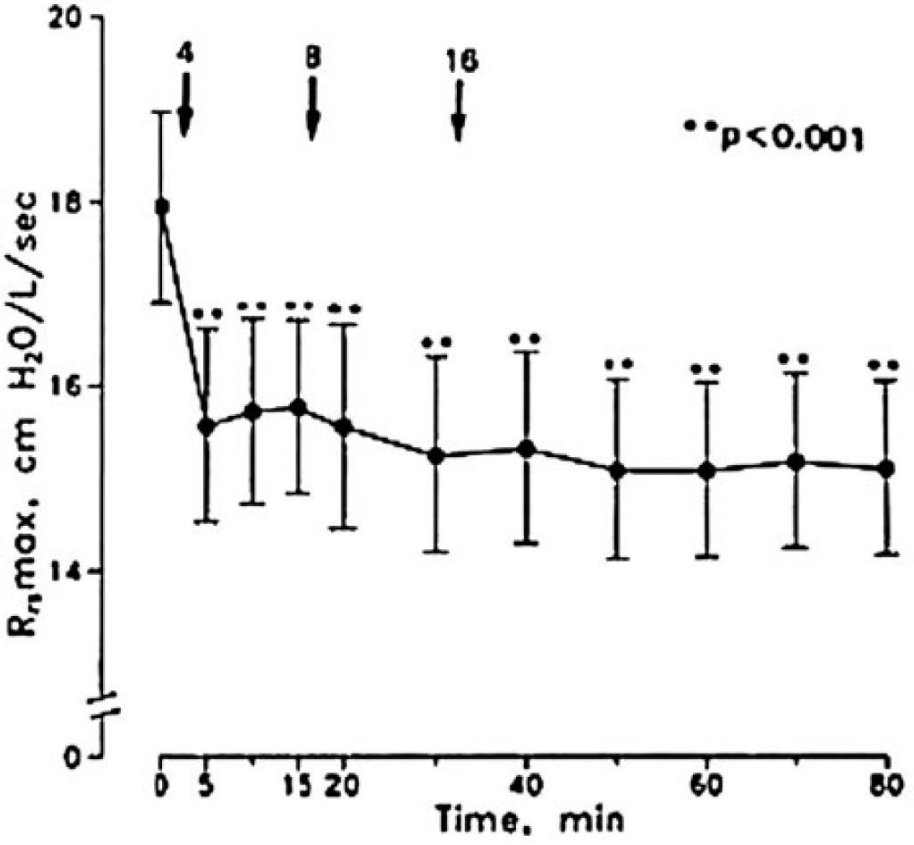
How about bronchodilator using nebulizer in ICU?

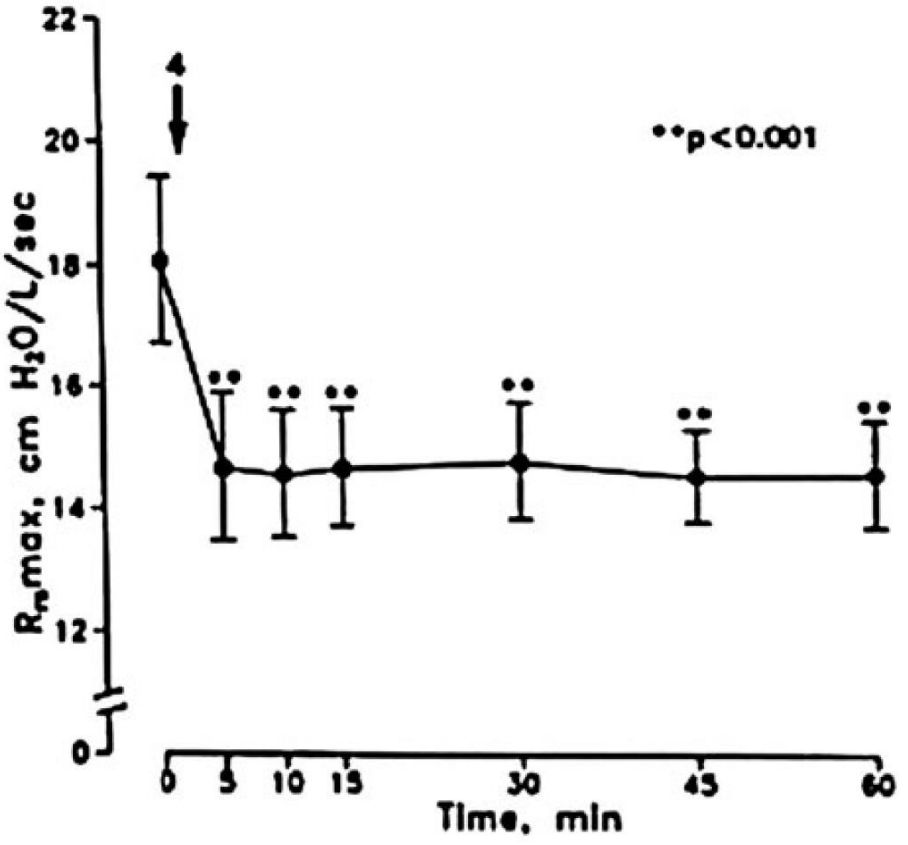
Indications for Bronchodilator in MV

1. Severe asthma
2. COPD
3. Acute bronchospasm or wheezing
4. Elevated airway resistance
5. Dynamic hyperinflation/intrinsic PEEP
6. Difficulty in weaning

Effect of Albuterol in COPD with MV

Maximal inspiratory resistance (Rrs max)





J Aerosol Med Pulm Drug Deliv 2012;25:319

Airway Response of Bronchodilator in MV

Author, year (reference #)	*Drug (dose, mg)*	*Aerosol device*	*Response*
Mouloudi, 2000[89]	Albuterol (0.2, 0.6 mg)	pMDI-spacer	Significant reduction in airway resistance. No effect of decelerating flow pattern (pressure control) versus square wave flow pattern (volume control)
Mouloudi, 2001[111]	Albuterol (0.6 mg)	pMDI-spacer	Significant reduction in airway resistance for up to 2 h, but the duration of effect was variable and unpredictable in individual patients.
Mouloudi, 2001[90]	Albuterol (0.4 mg)	pMDI-spacer	Significant reduction in airway resistance. No effect of inspiratory flow rate (0.6 L/s versus 1.2 L/s constant flow, volume control ventilation)
Tzoufi, 2005[91]	Albuterol (5 mg)	Nebulizer	Significant reduction in airway resistance. Application of external PEEP to counterbalance intrinsic PEEP provided additional benefits
Guerin, 2005[102]	Fenoterol (10 mg)	Nebulizer	Application of external PEEP did not provide additional benefits in reducing airway resistance or lung hyperinflation. External PEEP levels may need readjustment during treatment to prevent further hyperinflation
Malliotakis, 2007[92]	Albuterol (0.4 mg)	pMDI-spacer	Significant reduction in airway resistance for up to 2 hours, but there was no difference in the response during volume control versus pressure support ventilation with similar tidal volumes
Malliotakis, 2008[93]	Salmeterol (0.1 mg)	pMDI-spacer	Significant reduction in airway resistance for up to 8 h, but the duration of effect was variable and unpredictable in individual patients.
Kondili, 2011[109]	Albuterol (0.4 mg)	pMDI-spacer	Expiratory resistance of the respiratory system (expiratory Rrs) was several-fold higher than inspiratory resistance. After albuterol, there was significant reduction in expiratory Rrs with increase in the rate of lung emptying toward the end of expiration. Changes in expiratory Rrs did not correlate with changes in end-inspiratory inspiratory resistance after albuterol

J Aerosol Med Pulm Drug Deliv 2012;25:319

special report

Device Selection and Outcomes of Aerosol Therapy: Evidence-Based Guidelines*

Chest 2005; 127:335

- Both nebulizers and MDIs can be used to deliver beta2-agonists to ventilated patients.
- Cannot use DPI during mechanical ventilation.
- Careful attention to the details of technique is critical, since multiple technical factors may have clinically important effects on the efficiency of aerosol delivery.

Metered dose inhalers versus nebulizers for aerosol bronchodilator delivery for adult patients receiving mechanical ventilation in critical care units (Review)

Holland A, Smith F, Penny K, McCrossan G, Veitch L, Nicholson C

Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD008863.

Authors' conclusions

Existing randomized controlled trials, including randomized cross-over trials where the order of the intervention was randomized, comparing nebulizer and MDI for aerosol bronchodilation in mechanically ventilated adult patients do not provide sufficient evidence to support either delivery method at this time.

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of On-Demand vs Routine Nebulization of Acetylcysteine With Salbutamol on Ventilator-Free Days in Intensive Care Unit Patients Receiving Invasive Ventilation

A Randomized Clinical Trial

JAMA. 2018;319(10):993

- To determine if a strategy that uses nebulization for clinical indication (on-demand) is noninferior to one that uses preventive (routine) nebulization.
- Adult patients expected to need invasive ventilation for more than 24 hours at 7 ICUs in the Netherlands.
- On-demand nebulization of acetylcysteine or salbutamol (based on strict clinical indications, n = 471) or routine nebulization of acetylcysteine with salbutamol (every 6 hours until end of invasive ventilation, n = 473).

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of On-Demand vs Routine Nebulization of Acetylcysteine With Salbutamol on Ventilator-Free Days in Intensive Care Unit Patients Receiving Invasive Ventilation

A Randomized Clinical Trial

JAMA. 2018;319(10):993

Table 2. Primary Analysis and Subgroup Analyses

	No. of Patients		Ventilator-Free Days			
			Median (IQR)			
	On-Demand Nebulization	Routine Nebulization	On-Demand Nebulization	Routine Nebulization	Estimate of Difference (95% 1-Sided CI)[a]	*P* Value for Interaction
Primary Analysis						
Intention-to-treat	455	467	21 (0-26)	20 (0-26)	-0.00001 (-0.00003 to ∞)	NA
Per-protocol	389	453	23 (0-26)	20 (0-26)	-0.00004 (-0.00005 to ∞)	NA
Adverse events, No. (%)[i]		63 (13.8)		137 (29.3)	-15.5 (-20.7 to -10.3)	<.001
Tachyarrhythmia		57 (12.5)		121 (25.9)	-13.4 (-18.4 to -8.4)	<.001
Agitation		1 (0.2)		20 (4.3)	-4.1 (-5.9 to -2.2)	<.001

CONCLUSIONS AND RELEVANCE Among ICU patients receiving invasive ventilation who were expected to not be extubated within 24 hours, on-demand compared with routine nebulization of acetylcysteine with salbutamol did not result in an inferior number of ventilator-free days. On-demand nebulization may be a reasonable alternative to routine nebulization.

Aerosolized Bronchodilator in MV

- Administration of either aerosolized β-adrenergic or anticholinergic drugs produces significant bronchodilator responses in ventilated patients.

- However, widespread use of β-agonists in mechanically ventilated patients who do not have clear indications for their use, especially in high doses, have not been shown to lead to improvement in clinical outcomes and have the potential to be harmful.

- Thus, frequent and high doses of nebulized β-agonists should be avoided in mechanically ventilated patients unless there are specific indications for their use.

Side Effects of Aerosolized Bronchodilator

- Administration of high doses of β-agonists causes tachycardia, and has the potential to cause atrial and ventricular arrhythmias.

- High risk patients
  - ✓ elderly patients
  - ✓ preexisting heart disease
  - ✓ atrial fibrillation
  - ✓ prior history of ventricular tachycardia

How about antibiotics using nebulizer in ICU?

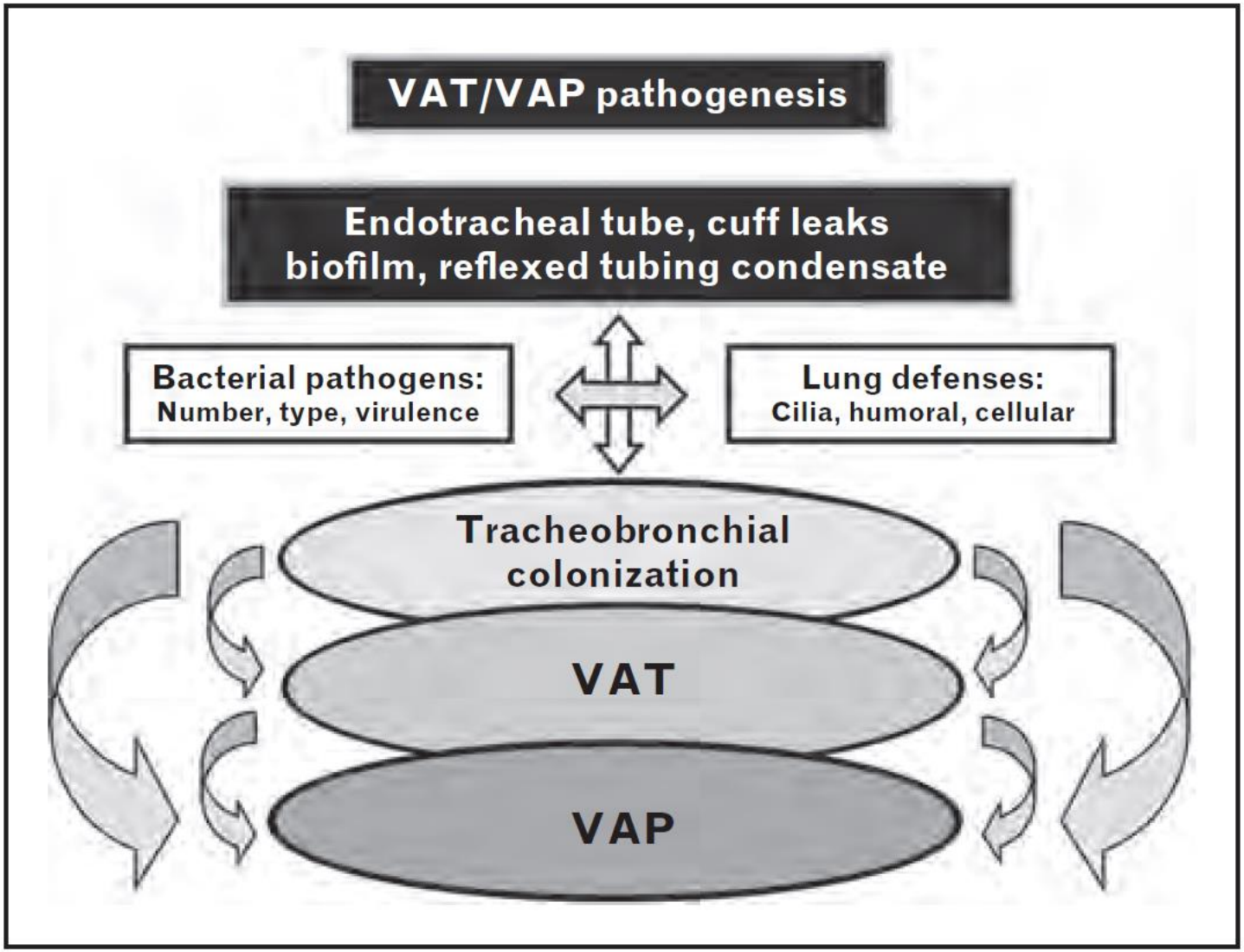
Rationale for Aerosolized Antibiotics

1. Aerosolized antibiotics reach the infected lung parenchyma without crossing the pulmonary alveolar capillary barrier

2. Aerosolized antibiotics increase anti-bacterial efficacy through increased local antibiotic concentration

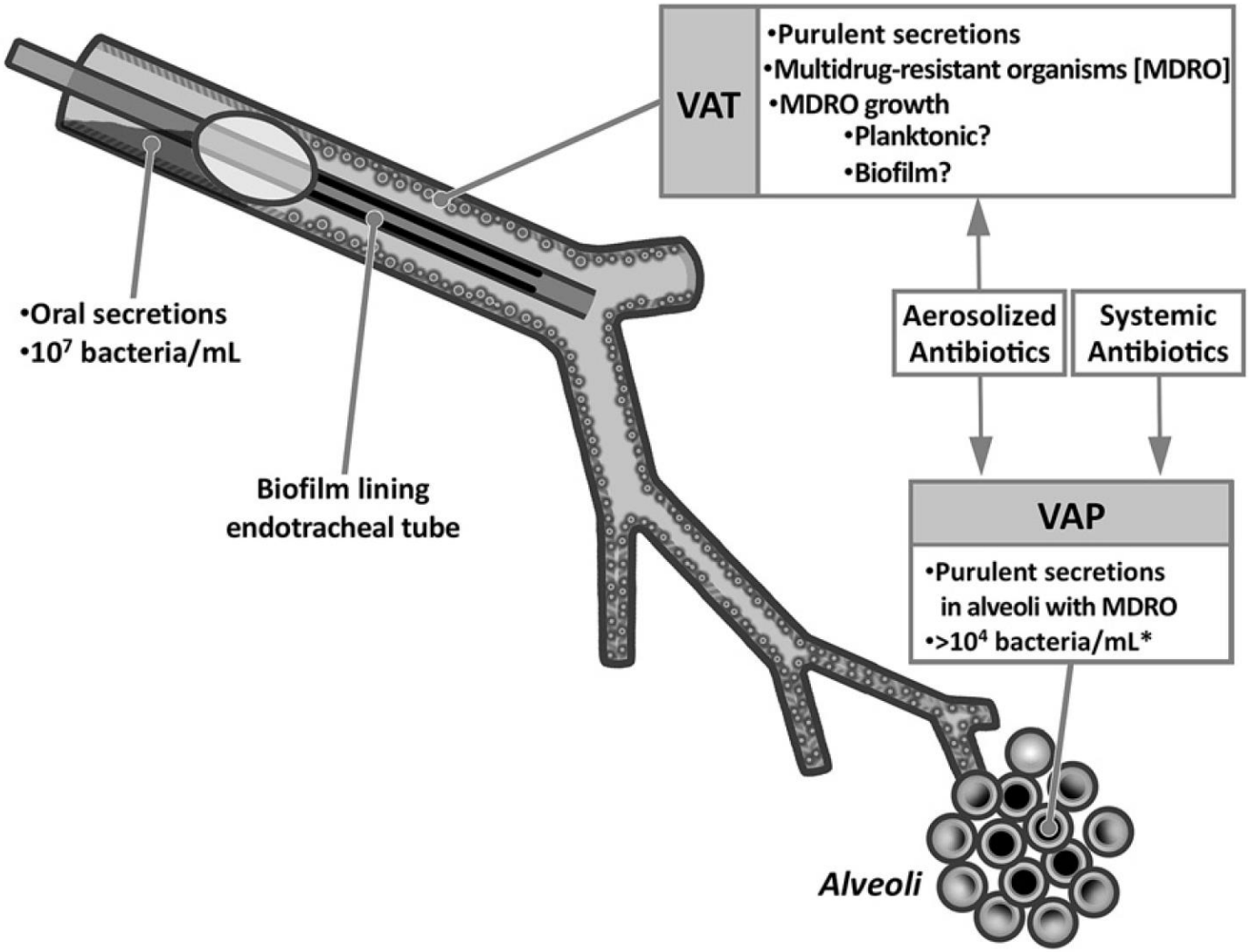
3. Aerosolized antibiotics decrease systemic toxicity

Pathogenesis of VAT/VAP



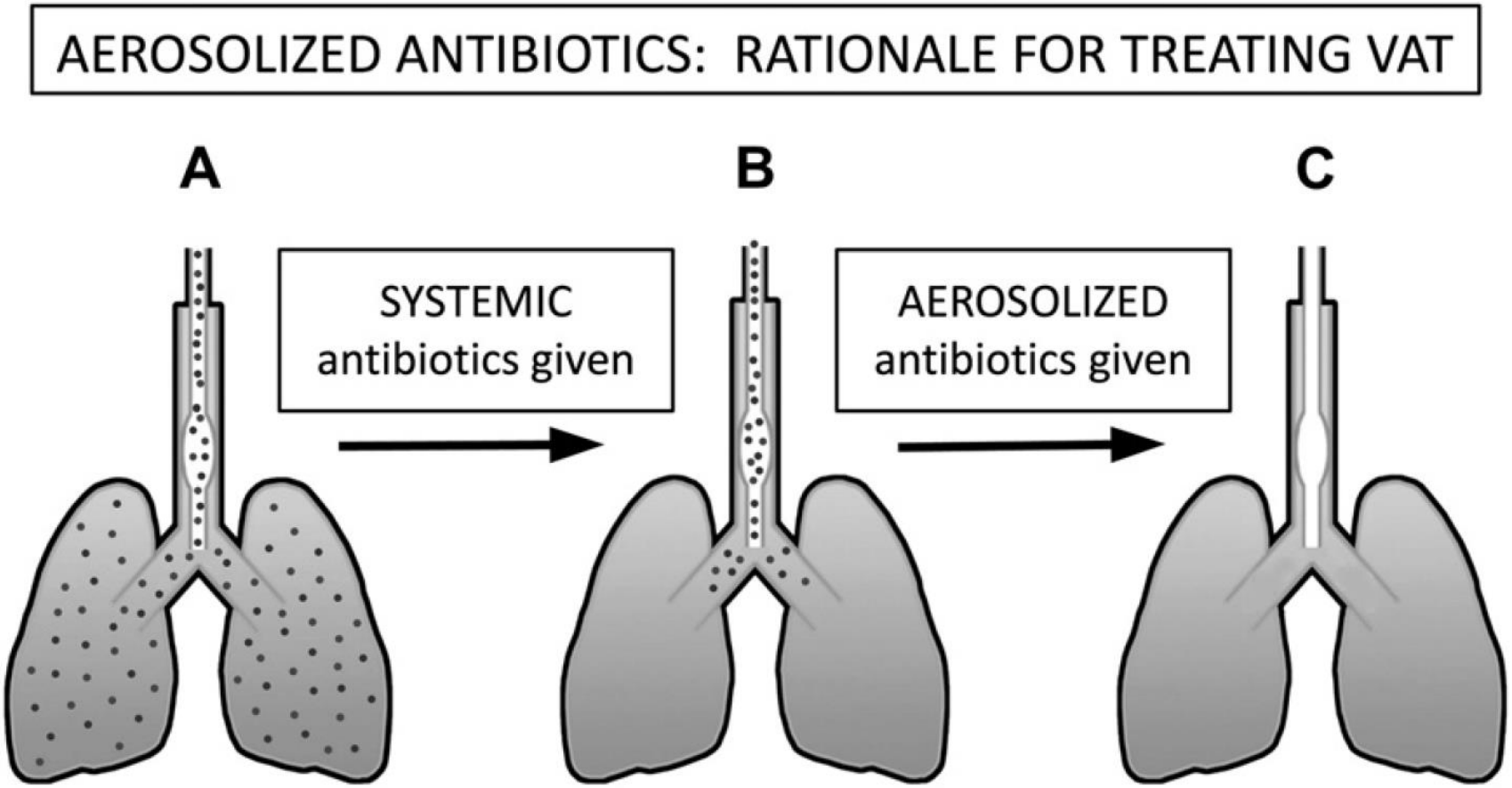
Curr Opin Crit Care 2014, 20:532

Pathogenesis of VAT/VAP



Clin Chest Med 2011;32:559

Rationale for Treating VAT



Clin Chest Med 2011;32:559

Aerosolized Antibiotics in Literature

- Cystic fibrosis
  - Gentamicin
  - Amikacin
  - Tobramycin[a]
  - Aztreonam lysine[b]
  - Liposomal amikacin[c]
- Mechanically ventilated patients
  - Sisomicin
  - Gentamicin
  - Amikacin
  - Cefuroxime/ceftazidime
  - Colistin–polymyxin B
  - Vancomycin
  - Amikacin proprietary preparation[d]

Clin Chest Med 2011;32:559

Microbiological Response to AA

Authors	Year	Setting	Design	Indication	Method of Aerosolization; Drug	Number of Patients	Number of Patients on Systemic Antibiotic Use	Number of Organisms in Patients	Patients with Eradication of Causative Organism	Number of Patients with Resistant Organisms
Michalopoulos et al[66]	2005	ICU, Greece	Retrospective chart review	VAP for 6 patients, HAP for 2 patients	Aerosolized via Siemens Servo Ventilator; colistin	8	7/8	7, *Acinetobacter*; 1, *Pseudomonas*	4/5	None
Kwa et al[65]	2005	ICU, Singapore	Retrospective chart review	VAP	Aerosolized colistin; no data on method	21	Yes, but not active against causative organism	17, *Acinetobacter*; 4, *Pseudomonas*	11/11 available cultures	Not described
Berlana et al[64]	2005	ICU, Spain	Retrospective chart review	Pulmonary infection	Aerosolized with various compressors; colistin	71	78% of patients	60, *Acinetobacter*; 11, *Pseudomonas*	*Acinetobacter* (33/33); *Pseudomonas* (4/7)	Not described
Michalopoulos et al[68]	2008	ICU, Greece	Prospective	VAP	Aerosolized via Siemens Servo Ventilator; colistin	60	57	37, *Acinetobacter*; 12, *Pseudomonas*; 11, *Klebsiella*	50/60	Not described
Palmer et al[35]	2008	ICU, United States	Randomized, double blind, placebo controlled	VAT≥2-mL sputum/4 h and organism on Gram stain	AeroTech jet nebulizer; vancomycin and/or gentamicin	24, placebo; 19, AA	32/43	Multiple species of gram-negative and gram-positive organisms	See **Table 1**	Placebo (8/24), AA (0/19)
Kofteridis et al[72]	2010	ICU, Greece	Retrospective review, matched case control	VAP	Aerosolized colistin; no details on method	43 IV & aerosolized colistin; 43 IV colistin	All patients	66, *Acinetobacter*; 12, *Klebsiella*; 8, *Pseudomonas*	Placebo, 17 (50%); aerosolized 19 (45%)	Not described
Korbila et al[73]	2010	ICU, Greece	Retrospective review, matched case control	VAP	Aerosolized via Siemens Servo Ventilator; colistin	43 IV colistin 78 aerosolized colistin + IV	All patients	MDR gram-negative organisms	Placebo, 26 (60.5%); aerosolized, 62 (79.5%)	Not described

Clin Chest Med 2011;32:559

Clinical Trials about Aerolized Antibiotics

Study and Year	Patient Population	Nebulized Antibiotic(s) Dose	Results	Conclusions
Le Conte et al (2000)[31]	Nosocomial pneumonia	Tobramycin (6 mg/kg/d)	The extubation rate at day 10 in the tobramycin group and placebo group was 35 and 18.5%, respectively, which did not statistically differ.	Aerosolized tobramycin was well tolerated in ventilated subjects with documented nosocomial pneumonia.
Hallal et al (2007)[32]	VAP caused by *Pseudomonas* or *Acinetobacter*	Tobramycin (600 mg/d)	In subjects treated with inhaled tobramycin, there was no significant decrease in ventilator-free days compared with those receiving I.V. tobramycin.	Aerosolized tobramycin for the treatment of VAP appeared to be safe in this pilot study.
Ghannam et al (2009)[33]	Gram-negative bacteria VAP	1. Tobramycin (300 mg/12 h) 2. Colistin (100 mg/8 h) 3. Gentamicin (100 mg/8 h) 4. Amikacin (100 mg/8 h)	The use of inhaled antibiotics was safe (absence of renal injury). Subjects treated with inhaled antibiotics were more likely to have complete resolution of clinical and microbiologic infection.	Inhaled aminoglycosides were well tolerated in critically ill Gram-negative VAP subjects without serious toxicity.
Kofteridis et al (2010)[34]	Multidrug-resistant VAP due to Gram-negative bacteria	Colistin (150 mg/d)	No significant differences between the I.V. plus inhaled antibiotic group and the I.V. antibiotic group were observed regarding eradication of pathogens, clinical cure, and mortality.	The addition of inhaled colistin to I.V. colistin did not provide additional therapeutic benefit to subjects with multidrug-resistant VAP due to Gram-negative bacteria.
Korbila et al (2010)[35]	Microbiologically documented VAP	Colistin (150 mg/d)	The outcome of infection was cure for 79.5% of subjects who received I.V. plus inhaled colistin vs 60.5% of subjects who received I.V. colistin alone.	Time on the ventilator was reduced in subjects receiving supplemental inhaled colistin.
Rattanaumpawan et al (2010)[36]	Gram-negative bacteria VAP	Colistin (75 mg/12 h)	The addition of nebulized colistin did not relieve pneumonia symptoms but increased the bacterial eradiation rate from 38.2 to 60.9%.	The use of nebulized colistin as adjunctive therapy of Gram-negative VAP was safe.
Lu et al (2011)[37]	VAP caused by *Pseudomonas*	Ceftazidime (15 mg/kg/3 h) Amikacin (25 mg/kg/d)	The addition of inhaled antibiotics was not superior to I.V. antibiotics alone. Rates of treatment failure and superinfection were similar in both groups.	Nebulization and I.V. infusion of ceftazidime and amikacin provide similar efficiency for treating VAP caused by *Pseudomonas aeruginosa*.
Niederman et al (2012)[38]	Mechanically ventilated subjects with Gram-negative pneumonia	Amikacin (400 mg/12 h or 400 mg/24 h)	Pneumonia was cured in 93.8% (Amikacin, 400 mg/12 h), 75.0% (Amikacin, 400 mg/24 h), and 87.5% (placebo group).	Adjunctive nebulized amikacin in mechanically ventilated subjects with Gram-negative pneumonia may increase the cure rate.
Doshi et al (2013)[39]	Multidrug-resistant VAP due to Gram-negative bacteria	Colistin (150–300 mg/d)	Clinical cure was achieved in 39.2% of subjects receiving I.V. colistin and 54.5% receiving I.V. colistin plus nebulization. No difference in microbiologic cure rates was found between the I.V. colistin and I.V. colistin plus nebulization groups.	The addition of aerosolized colistin to I.V. colistin may improve clinical cure and mortality for subjects with pneumonia.
Tumbarello et al (2013)[40]	Subjects with VAP caused by *Acinetobacter*, *Pseudomonas*, or *Klebsiella*	Colistin (225 mg/d)	Compared with the I.V. colistin group, the nebulizer plus I.V. colistin group had a higher clinical cure rate of 15% and required 4 days less of mechanical ventilation after VAP onset.	Inhalation of colistin might be a beneficial addition to I.V. colistin infusion in the management of VAP caused by colistin-only-susceptible Gram-negative bacteria.
Palmer et al (2014)[41]	Subjects with high risk for multidrug-resistant organisms in the respiratory tract	Vancomycin (360 mg/d) Gentamicin (240 mg/d) Amikacin (1,200 mg/d)	In the antibiotic nebulized group, 96% of bacterial isolates cultured at randomization were eradicated, but only 8.7% in placebo nebulization. Resistance to systemic antibiotics significantly decreased in the group receiving nebulized antibiotics.	Nebulized antibiotics are effective in eradicating existing multidrug-resistant organisms.

VAP = ventilator-associated pneumonia
I.V. = intravenous

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hivma hiv medicine association

OXFORD

Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society

- **Treatment of Ventilator-Associated Tracheobronchitis**
- **VIII. Should Patients With Ventilator-Associated Tracheobronchitis (VAT) Receive Antibiotic Therapy?**
- **Recommendation**

1. In patients with VAT, we suggest not providing antibiotic therapy *(weak recommendation, low-quality evidence)*.

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- **XIX. Which Antibiotic Should Be Used to Treat Patients With HAP/VAP Due to *Acinetobacter* Species?**
- **Recommendations**

1. In patients with HAP/VAP caused by *Acinetobacter* species, we suggest treatment with either a carbapenem or ampicillin/sulbactam if if the isolate is susceptible to these agents *(weak recommendation, low-quality evidence)*.
2. In patients with HAP/VAP caused by *Acinetobacter* species that is sensitive only to polymyxins, we recommend intravenous polymyxin (colistin or polymyxin B) *(strong recommendation, low-quality evidence)*, and we suggest adjunctive inhaled colistin *(weak*

Aerosolized Antibiotics during MV

- Treating VAP with aerosolized antibiotics combined with systemic antibiotics has bactericidal advantages compared with conventional treatment with intravenous antibiotics alone.

- To date, however, clinical trials are insufficient to support the broad use of inhaled antibiotics in critically ill patients with a diagnosis of VAP.

- Future studies should focus on improving delivery systems, patient selection, and patient respiratory optimization prior to drug nebulization.

Take Home Message

- Nebulizers or inhalers can be used effectively during mechanical ventilation
- Correct technique is most important when using these devices
- Frequent and high doses of nebulized β-agonists should be avoided in mechanically ventilated patients unless there are specific indications for their use
- Clinical trials are insufficient to support the broad use of inhaled antibiotics in critically ill patients with a diagnosis of VAP

Thank you for your attention !