

# Inhalation (Aerosol) therapy in mechanical ventilation

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# Outlines

## Introduction

- Advantages and aims of inhaled therapy

- Delivery methods

## Factors influencing aerosol delivery in mechanical ventilation

- Ventilator/ Circuit-related**

- Drug/ Device-related**

- Patient-related**

## Problems about nebulizers vs. MDI

## Recent advances

# Introduction

- Inhaled therapy has been employed for years in ambulatory patients with respiratory disorders
- Inhaled drug therapy is also employed in ventilated patient in ICU

# What are the advantages of inhaled therapy?

- Direct delivery of drug to site of action
- Rapid onset of action
- Lower dose (than systemic administration) to produce desired effects
- Minimizes systemic adverse effects

## Bronchodilator

Beta-agonist (albuterol, terbutaline, metaproteronol, fenoterol)

Anticholinergic (ipratropium bromide)

Combination beta-agonist and anticholinergic (albuterol sulfate + ipratropium bromide)

Combination long-acting beta-agonist and inhaled corticosteroid (salmeterol + fluticasone; formoterol + budesonide)

## Prostaglandins

## Mucoactive agents

Dornase alpha

## Surfactant

## Antibiotics

Antibacterial

Antiviral

Antifungal

Corticosteroids (beclomethasone; budesonide, fluticasone)

Anticoagulants (Heparin)

## Miscellaneous

# Delivery methods

- Nebulizer
- Metered dose inhaler (MDI)
- Dry powder inhaler

# **Factors influencing aerosol delivery in mechanical ventilation**

# Factors influencing aerosol delivery

- **Ventilator/ Circuit-related**

- Ventilator setting
- Characteristics of the ventilator circuit and endotracheal tube
- Humidity of the inspired air

- **Drug/ Device-related**

- Physical and chemical properties of the medications
- Characteristics of aerosol-generating device
- Position of the aerosol-generating device in the circuit

- **Patient-related**

# Ventilator-related

- Tidal volume
- Ventilation mode
- Respiratory rate

# Circuit-related

- Compare the delivery of aerosolized radiotracer to lower respiratory tracts
- Non-intubated subjects
  - 11.9%
- Intubated subjects
  - 2.9%
- The radiotracer was deposited on
  - Endotracheal tube (ETT)
  - Ventilator circuit

# Circuit-related

- Endotracheal tube size
  - Smaller the size of ETT, greater the particle impaction (esp in pediatric ETT)

# Circuit-related

- **Heating and Humidity** of inhaled gas
  - Greater aerosol deposition in the ventilator circuit and ETT with heated and humidified gas
  - Both diminishes pulmonary deposition of aerosols ~40%

# Circuit-related

- Effect of humidity on aerosol delivery

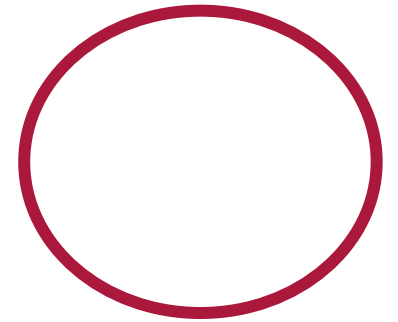
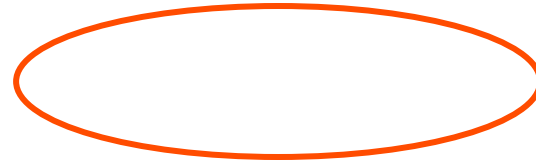
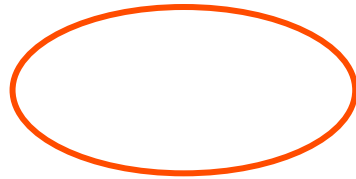
# Circuit-related

- Under humidified condition



# Circuit-related

- Under dry condition



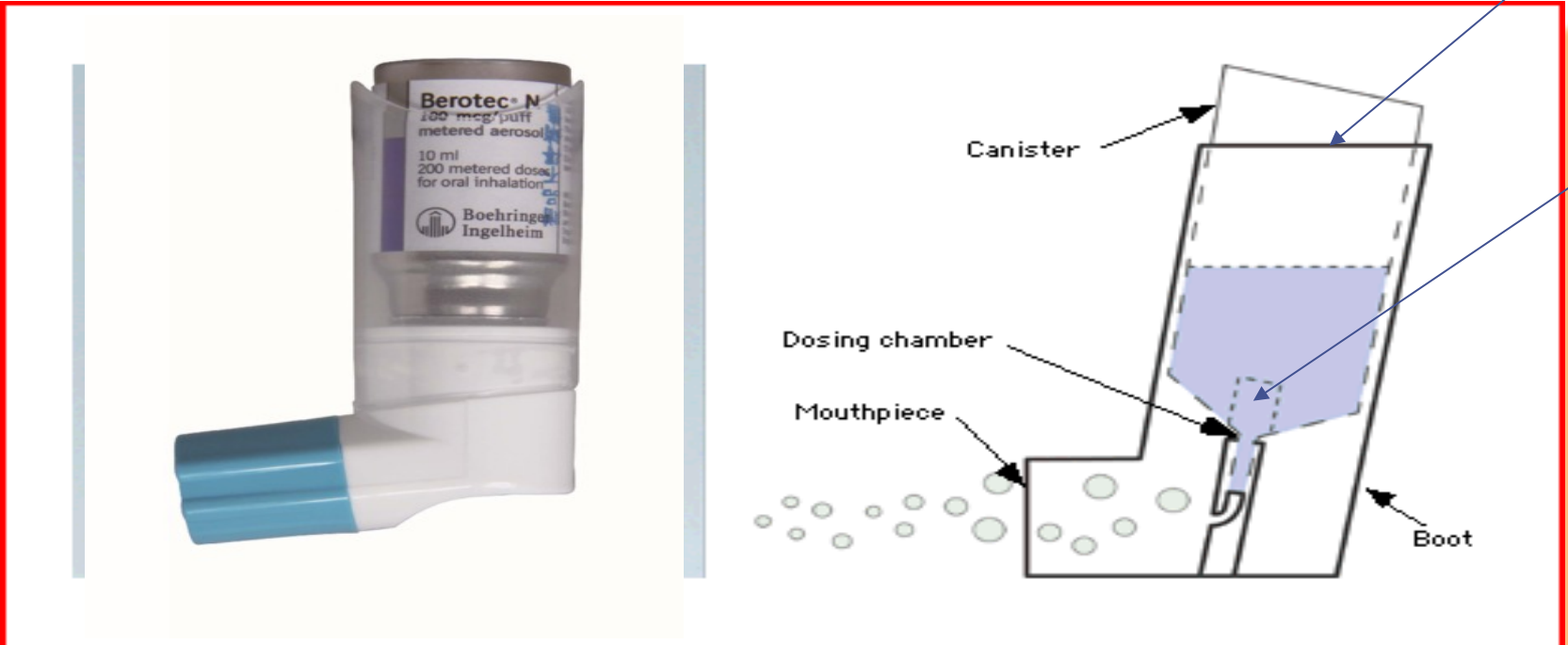
Fink JB, Dhand R, Grychowski J, Fahey PJ, Tobin MJ.  
Reconciling in vitro and in vivo measurements of aerosol delivery from a metered- dose inhaler during mechanical ventilation and defining efficiency enhancing factors. *Am J Respir Crit Care Med* 1999;159(1): 63–68.

# Device-related: MDI

- 

Pressurized canister

Metering valve



**Metered dose inhaler** Medication is stored under pressure in the canister and released in fixed volumes from the dosing chamber following actuation.

# Device-related: MDI

- After volatilization of the propellant, the final volume emitted from the MDI is **15 to 20 ml per dose**
- It can be actuated as frequent as **every 15 seconds**

# Device-related: MDI

- Commercially available MDIs are designed for ambulatory patients
- In a ventilator circuit, the canister must be removed from the actuator



# Device-related: MDI

- MDI generate aerosol with mass median aero-dynamic diameter of 1-5 $\mu$ m
- Larger aerosol particles
  - More likely to be trapped in the ventilator circuit and ETT
- Aerosols with mass median aerodynamic diameter <2  $\mu$ m are more efficient during MV

# Device-related: MDI

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

# Device-related: Nebulizer

- Nebulizer
  - Jet, vibrating mesh and ultrasonic nebulizers
  - Connected in the inspiratory limb of the ventilator circuit or at the patient Y-piece

# Device-related: Nebulizer

- Nebulizer
  - Type of nebulizer
  - Fill volume
  - Gas flow
  - Duration of nebulization
  - Position in the circuit

# Drug-related

- Dose
- Formulation
- Duration of action

# Patient-related

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

# **Choice of aerosol-generating devices in mechanical ventilation**

# MDI vs Nebulizer

- Both MDI and nebulizers are used to deliver inhaled therapies to mechanically ventilated patients
- Traditionally, nebulizers were employed for inhalation therapy during MV
- However, more centers have switched to MDIs for routine bronchodilator therapy

# MDI vs Nebulizer

- Many studies suggested that MDI with spacer is a reliable route in delivering bronchodilator

In vitro evaluation of aerosol bronchodilator delivery during mechanical ventilation: PC vs VC ventilation  
Intensive Care Med 2003; 29:1145

# Problems about nebulizers

## 1. Contamination and VAP

- Use of aerosol was one of the independent factor associated with VAP
- Need to be cleaned and disinfected to minimize the risk

# Problems about nebulizers

## 2. Difficulty triggering

- In patient on PS mode, airway pressure must be generated before the ventilator deliver a breath
- A continuous-flow nebulizer between the patient and the sensor in the ventilator makes it more difficult for the patient to generate the pressure
- May lead to under-ventilation of the patients

# Problems about nebulizers

3. Damage to expiratory transducer
  - In some ventilator brand only
4. Variable rate and particle size (depends on the brand)
5. Operational efficiency of nebulizer changes with the pressure of the driving gas and with different fill volumes

# Problems about nebulizers

6. FiO<sub>2</sub> change

7. Increase tidal volume and/ or airway pressure

8. Cost

- Time consuming (prepare the drug, disinfection...)
- Purchasing the aerosol generating device

# Advantages of MDIs

- Decreased cost
- Reliability of dosing
- Ease of administration
  - Less personnel time
- Freedom from contamination
  - The ventilator circuit need not be disconnected
  - Reduce VAP

# More about MDIs in mechanical ventilated patients

Use of spacer

Timing of actuation

# MDI-Spacer

- Allow MDI aerosol to have an opportunity to slow down
- Propellant evaporation in the expanding flume decreases the size of the aerosol particles
  - The aerosol emerging from the distal end of the ETT has a mass median aerodynamic diameter of  $\sim 2\mu\text{m}$
  - Decrease the drug loss

# MDI-Spacer

- Use of spacer significant improved aerosol delivery
- With the use of spacer
  - Increase **4-6 fold** aerosol drug delivery

Efficiency of bronchodilator aerosol delivery to the lungs from the metered dose inhaler in mechanically ventilated patients: a study comparing four different actuator devices. *Chest* 1994; 105: 214-218

# MDI-Spacer

- In general
  - An MDI with chamber spacer connected to the circuit at ~ 15cm from the ETT
  - 
  - It provides efficient aerosol delivery to MV patients

# Synchronize with inspiratory airflow

- The actuation of an MDI must be precisely synchronized with the onset of inspiratory airflow from the ventilator
- Failure to synchronize actuations with inspiration resulted in significant reduction in inhaled mass (35% vs 72%)

# **Options of inhaled drug delivery during NIPPV**

- Remove patient from ventilator and administer drug by nebulizer or MDI
- Administer nebulizer therapy inline with NIPPV
- Administer MDI therapy inline with NIPPV

# Inhalation therapy in ICU

Bronchodilator  
Antibiotic

# Bronchodilators

- Common indications
  - Asthma
  - COPD
  - Acute bronchospasm or wheezing
  - Difficulty in weaning
  - Elevated airway resistance
- Common bronchodilators
  - B2 agonist
  - Anti-cholinergic bronchodilators
  - Combination of both

# Bronchodilator dosing

- Based on the finding that aerosol deposition is lower in MV patients than in non-intubated patients
  - higher dose of BD were recommended

What is the precise dosing regimen?

# Bronchodilator dosing

- In general, significant BD effects occur after administration of
  - **4 puffs albuterol** with a MDI+spacer
  - **2.5mg of albuterol** with a standard nebulizer
  - Potential side effects were increased if administered higher doses

# Bronchodilator:Duration of effect

- Duration of action (e.g. Ventolin)
  - Ambulatory patients: 4-6hrs
  - Mechanical ventilated: 2-4hrs vs 4-6hrs
- Ventilated patients need more frequent administration of BD (short-acting)
  - E.g. every 3-4 hrs

# Bronchodilators: Use of heliox

- Heliox: Helium-oxygen mixtures
- Lower density
  - Facilitate ventilation in MV patients with asthma due to a reduction in airway resistance
  - Improve drug delivery from a MDI

Drug delivery from a MDI was 50% higher with a helium-oxygen 80/20 mixture than the oxygen

# Inhaled antibiotics

- Inhalation of aerosolized antibiotics
  - Allow direct delivery of antibiotics to the lung
  - Inhaled tobramycin is now routinely employed in patients in cystic fibrosis
- However...
  - The efficacy of inhaled antibiotic therapy in MV patients is less well defined and controversial

# Inhaled antibiotics

- In 1975, Feely and colleagues found that...
  - Increased mortality after administration of inhaled polymyxin to patients admitted to ICU
  - Increase incidence of polymyxin-resistant organisms

# Inhaled antibiotics

- More recently, some studies found that...
  - In patients with pneumonia due to MDR G-ve bacteria, the combination of aerosolized colistin with IV antibiotics had beneficial effects without leading to emergence of resistant organisms

Treatment of Nosocomial Pneumonia and Tracheobronchitis Caused by Multidrug-Resistant *Pseudomonas aeruginosa* with Aerosolized Colistin  
AJRCCM 2000; 162: 328

Aerosolized colistin for the treatment of nosocomial pneumonia due to multidrug-resistant Gram-negative bacteria in patients without cystic fibrosis

Critical Care 2005; 9: 53-59 48

# Inhaled antibiotics

- Reduce microbial biofilm formation on the inner wall of the endotracheal tube
  - Reduce bacterial seeding of the lung parenchyma

# Inhaled antibiotics

- However, the above studies were small studies or only animal model.
- In the absence of convincing clinical data, the use of aerosolized antibiotics at the present time should be limited to
  - Adjunction therapy for patients with MDR organisms
  - Patients with severe pneumonia not responding to conventional therapy
  - Patients developed tracheo-bronchitis

**Chart 1.** Strategies to improve lung drug deposition during mechanical ventilation.

### Ventilator-related strategies

- Deliver a tidal volume > 500 mL<sup>a</sup>
- 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

psi: pound-force per square inch. <sup>a</sup>In patients with obstructive lung disease, a tidal volume > 500 mL can result in auto-PEEP (dynamic hyperinflation). In such cases, respiratory mechanics should be monitored, tidal volume being controlled in order to avoid barotrauma.

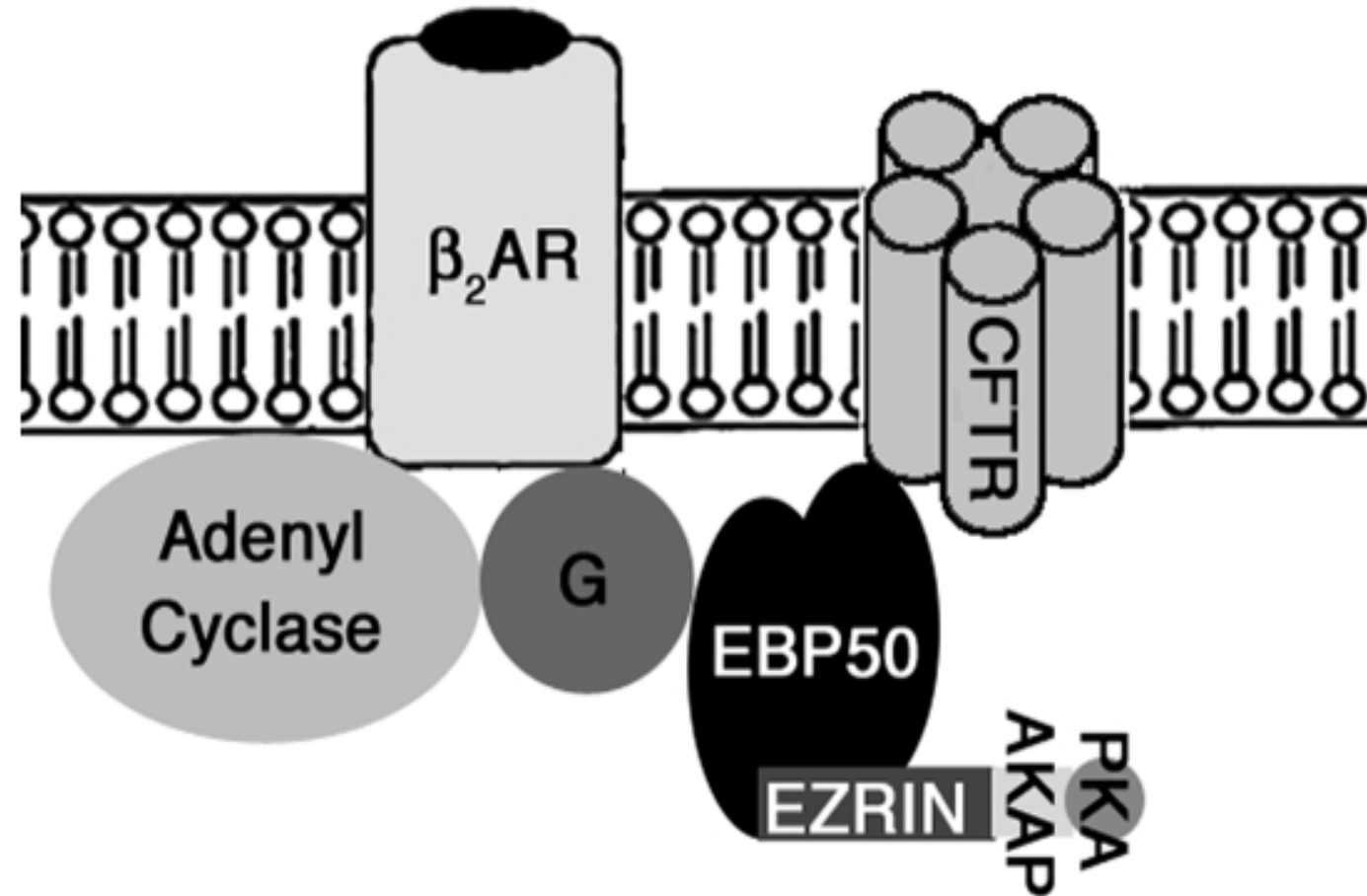
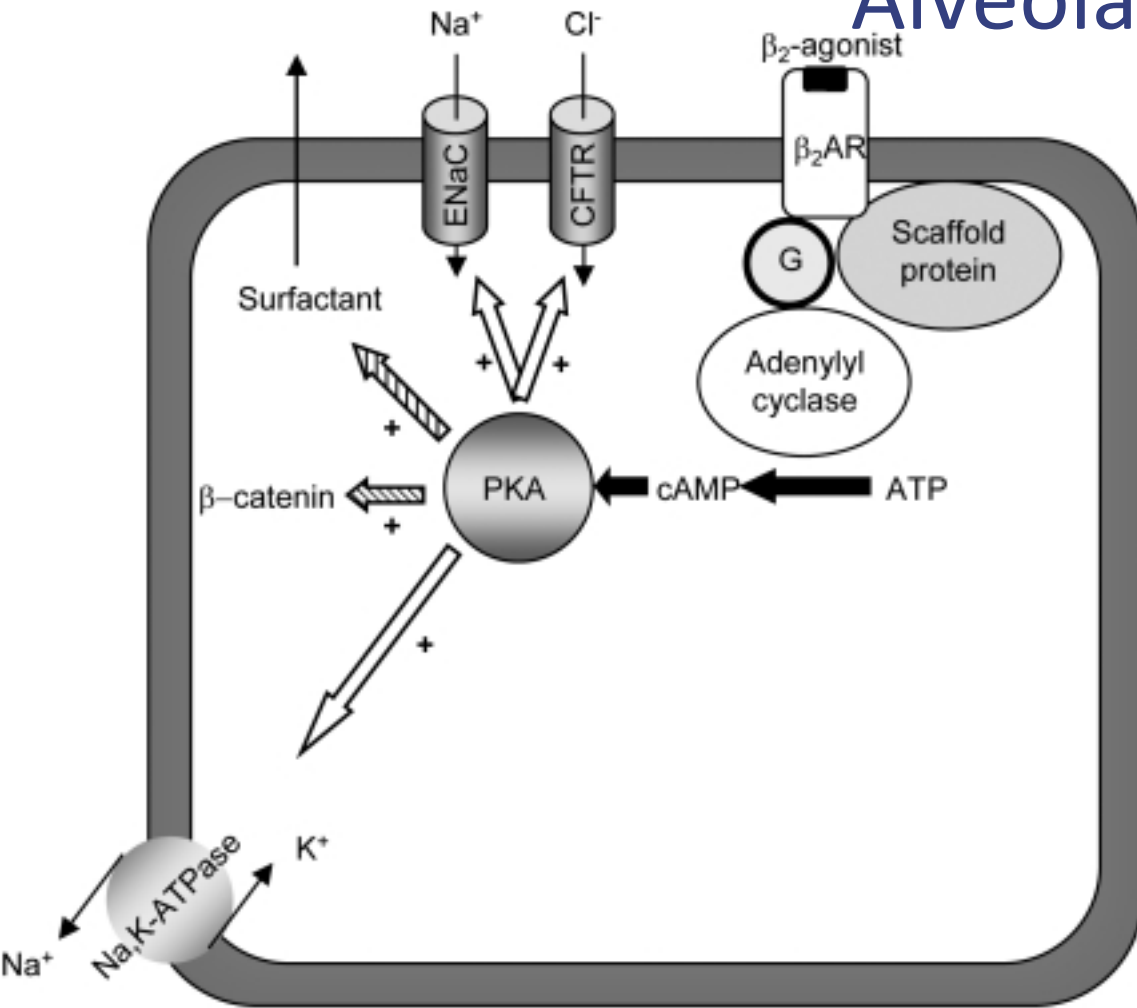
**Chart 2.** Doses and duration of action of the inhaled bronchodilators most commonly administered to patients on mechanical ventilation.

Drug	Formulation	Dose	Onset of action, min	Time to peak effect, min	Frequency of use, number of times/day
$\beta_2$ agonist					
Fenoterol hydrobromide	Solution: 5 mg/mL	5-8 drops	5-10	15	3-6
	Aerosol: 100 $\mu$ g/jet	1 jet every 5 min			
Albuterol	Aerosol: 100 $\mu$ g/jet	2 jets	5-15	30-60	4-6
Anticholinergic agent					
Ipratropium bromide	Solution: 0.25 mg/mL	20-40 drops	15	90-120	4-6
	Aerosol: 20 $\mu$ g/jet	4 jets			

**Chart 3.** Factors influencing aerosol deposition in the airways during mechanical ventilation.

Factors	Parameters	Influence on aerosol deposition
Ventilator-related	Ventilation mode Tidal volume Respiratory rate Inspiratory/expiratory time ratio Inspiratory flow Inspiratory trigger	In vitro studies have shown that aerosol deposition varies depending on the ventilation mode.  A longer inspiratory time translates to better drug delivery.
Circuit-related	Endotracheal tube size Inhaled gas humidity Inhaled gas density	A larger tube translates to a more turbulent flow and worse drug delivery.
Nebulizer-related	Nebulizer type Inhaled volume Gas flow Nebulization cycling: inspiratory vs. continuous Duration of nebulization Position in the ventilator circuit	High, turbulent flows increase drug deposition in the proximal airways, thus reducing drug efficacy.
Metered dose inhaler-related	Type of spacer and connector Position of the spacer Coordination of actuation with inhalation Type of metered dose inhaler	Failure to coordinate actuation with inhalation results in lower lung drug deposition.
Drug-related	Dose Formulation Aerosol particle size Duration of action	During mechanical ventilation, higher doses of inhaled bronchodilators are required.
Patient-related	Severity of airway obstruction Mechanism of airway obstruction Dynamic hyperinflation Patient-ventilator synchrony	Severe airway obstruction and auto-PEEP reduce deposition of bronchodilators in the more distal airways, thus reducing drug efficacy.

# Alveolar Epithelial $\beta_2$ -Adrenergic Receptors



$\beta_2$ -adrenergic receptor signaling is required for up-regulation of alveolar epithelial active ion transport in the setting of excess alveolar edema fluid. The positive, protective effects of  $\beta_2$ AR signaling on alveolar active Na<sup>+</sup> transport in normal and injured lungs provide substantial support for the use of  $\beta$ -adrenergic agonists to accelerate alveolar fluid clearance in patients with cardiogenic and noncardiogenic pulmonary edema.

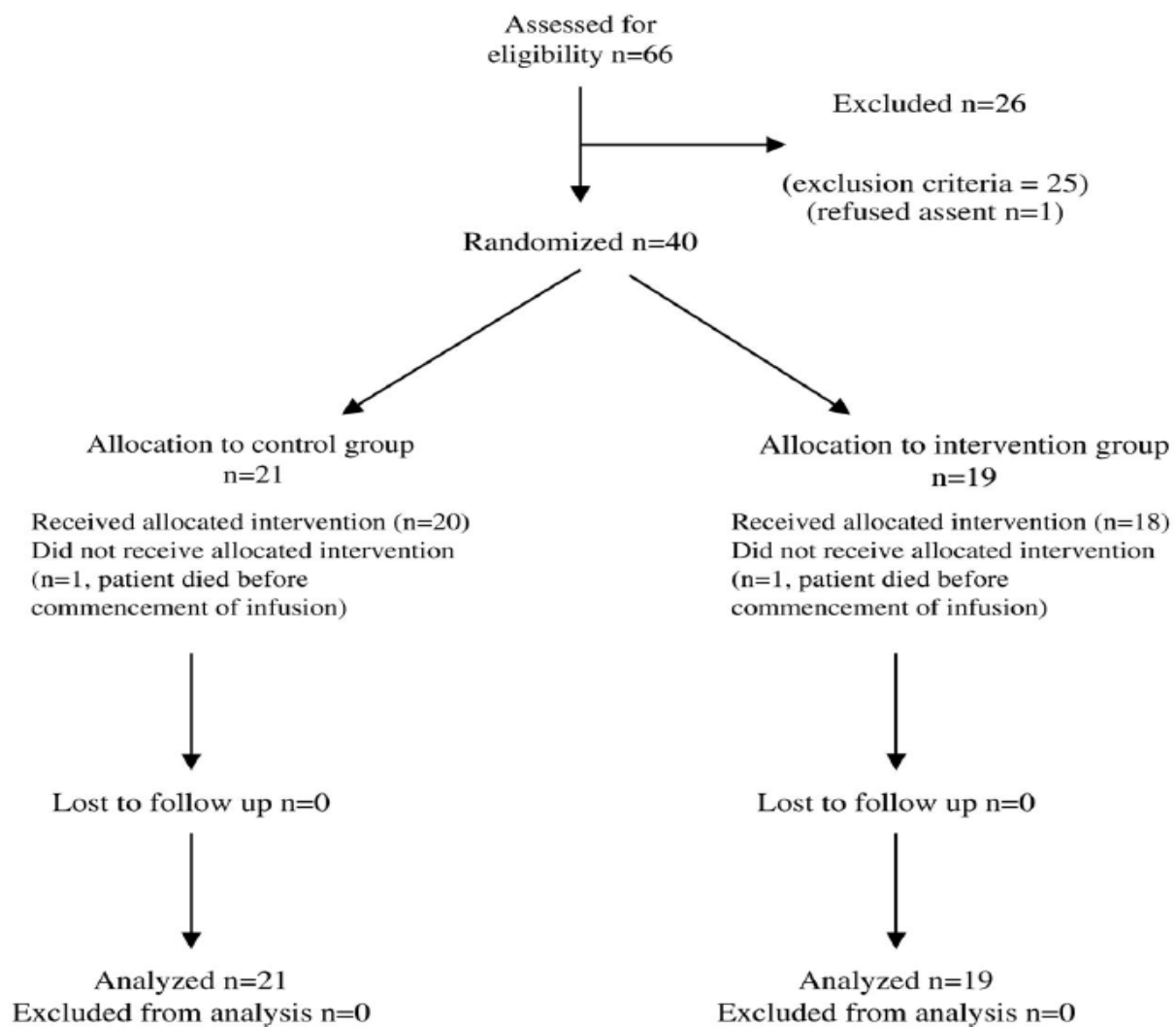


TABLE 1. BASELINE PATIENT DEMOGRAPHICS

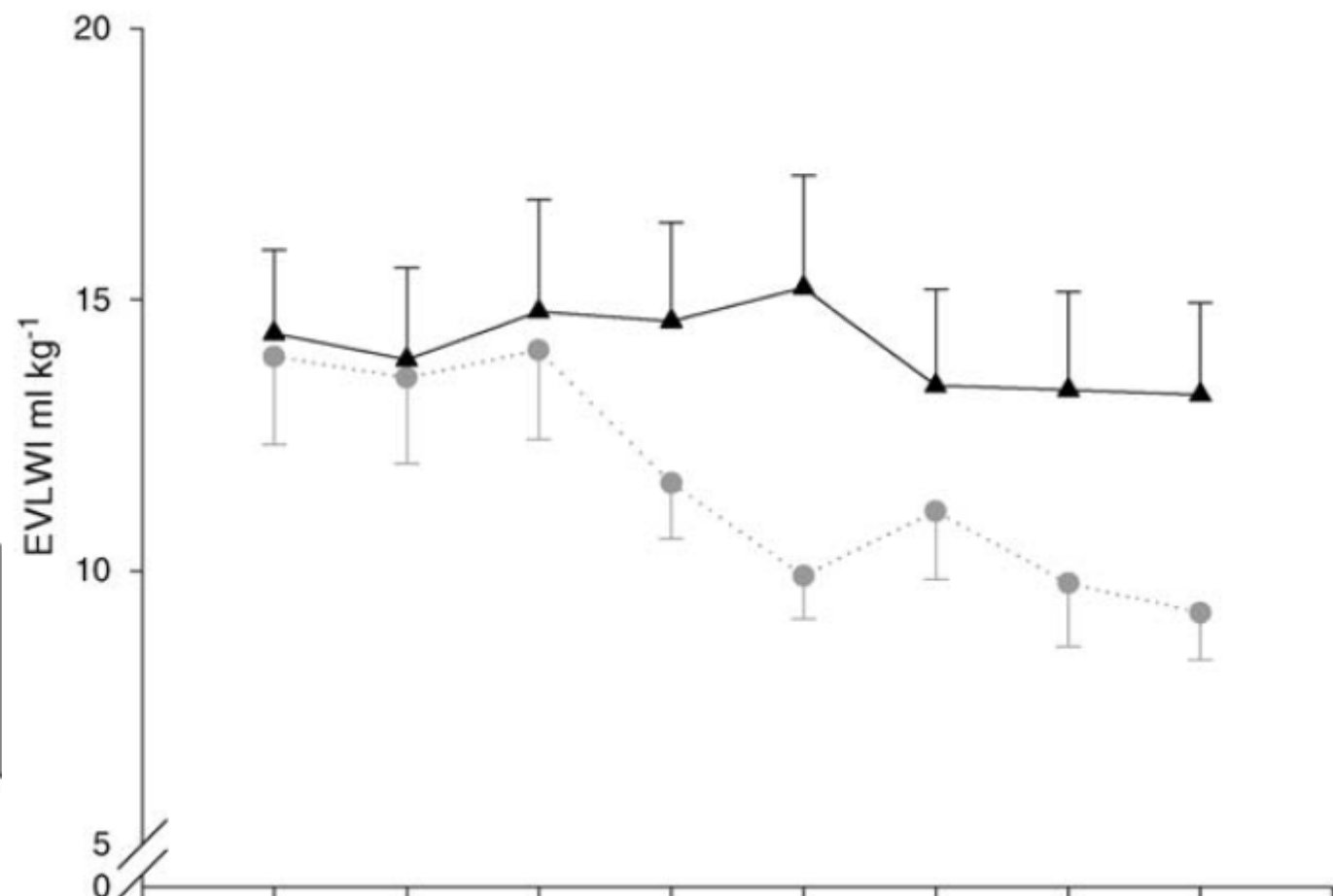
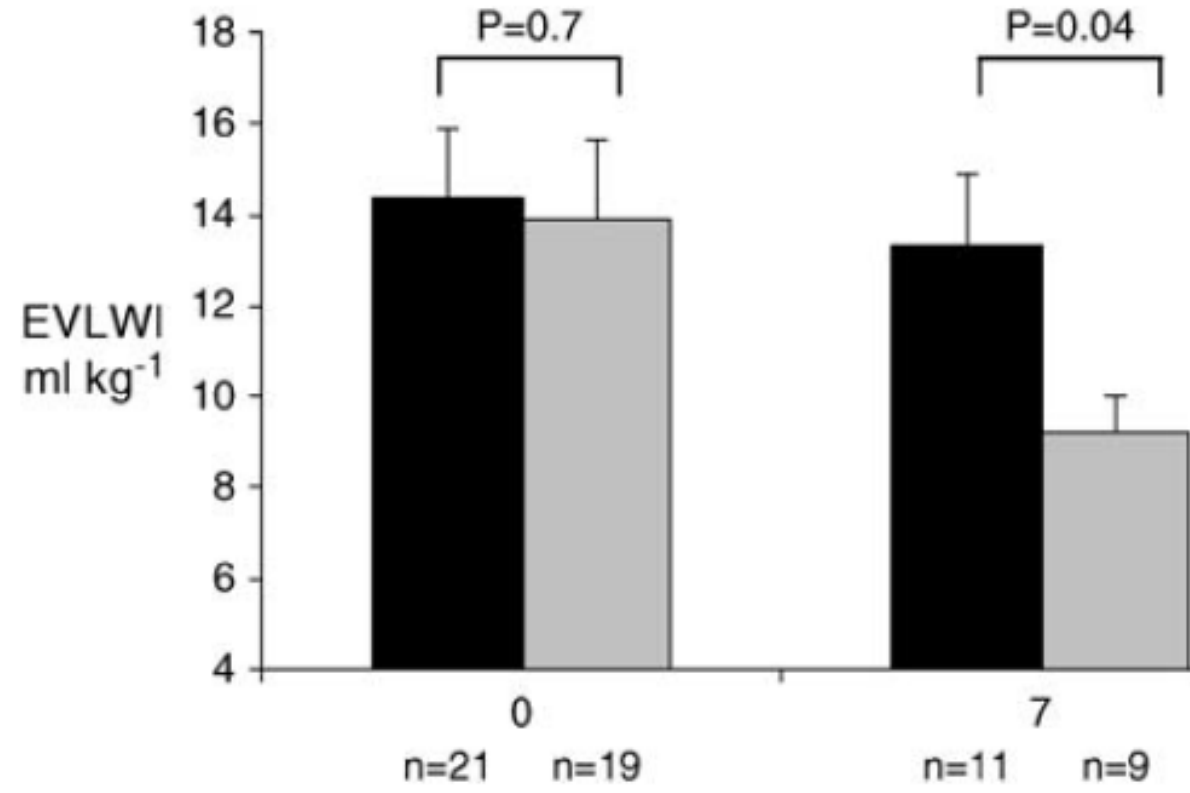
Parameter	Salbutamol	Placebo	p Value	95% CI
Age, yr	68.7 (16.0)	57.0 (14.7)	0.021	1.8–21.5
Pa <sub>O<sub>2</sub></sub> :Fi <sub>O<sub>2</sub></sub> ratio, kPa	15.6 (6.6)	13.7 (4.9)	0.326	
LIS	2.8 (0.7)	3.0 (0.4)	0.447	
APACHE II	24.9 (6.4)	22.5 (6.5)	0.243	
APACHE predicted mortality	51.8 (19.1)	44.6 (20.4)	0.257	
SAPS II	55.6 (15.1)	49.3 (14.7)	0.198	
SAPS predicted mortality	56.7 (27.3)	49.3 (14.7)	0.204	

Definition of abbreviations: APACHE II = Acute Physiology and Chronic Health Evaluation II; CI = confidence interval; LIS = Murray lung injury score; SAPS II = Simplified Acute Physiology Score II.

TABLE 2. ETIOLOGY AND SEVERITY OF LUNG INJURY

Parameter	Salbutamol n (%)	Placebo n (%)	p Value
<b>Gas exchange</b>			
Pa <sub>O<sub>2</sub></sub> /Fi <sub>O<sub>2</sub></sub> , kPa			
26.8–40	1 (5.3)	0 (0)	0.501
13.46–26.8	10 (52.6)	10 (47.6)	
< 13.46	8 (42.1)	11 (52.4)	
PEEP, cm H <sub>2</sub> O			
0–5	7 (36.8)	4 (19)	0.453
6–10	7 (36.8)	10 (47.6)	
> 10	5 (26.3)	7 (33.3)	
<b>Organ failure</b>			
Lung + 1 organ	13 (68.4)	16 (76.2)	0.442
Lung + 2 organs	6 (31.6)	5 (23.8)	
<b>Cause</b>			
<b>Direct</b>			
Pneumonia	3 (15.8)	9 (43)	0.105
Aspiration	0 (0)	2 (9.5)	
<b>Indirect</b>			
Sepsis	13 (68.4)	8 (38)	
Trauma	1 (5.3)	0 (0)	
Transfusions	1 (5.3)	2 (9.5)	
Other	1 (5.3)	0 (0)	
<b>Associated diseases</b>			
No coexisting diseases	13 (68.4)	16 (76.2)	
Coexisting disease that will cause death within 5 yr	6 (31.6)	5 (23.8)	
Coexisting disease that will cause death within 6 mo	0 (0)	0 (0)	

Definition of abbreviation: PEEP = positive end-expiratory pressure.



Day	0	1	2	3	4	5	6	7
Salbutamol (n=alive)	19	18	16	13	13	11	10	9
Placebo (n=alive)	21	18	16	15	14	12	12	11

# Inhaled Adrenergics and Anticholinergics in Obstructive Lung Disease: Do They Enhance Mucociliary Clearance?

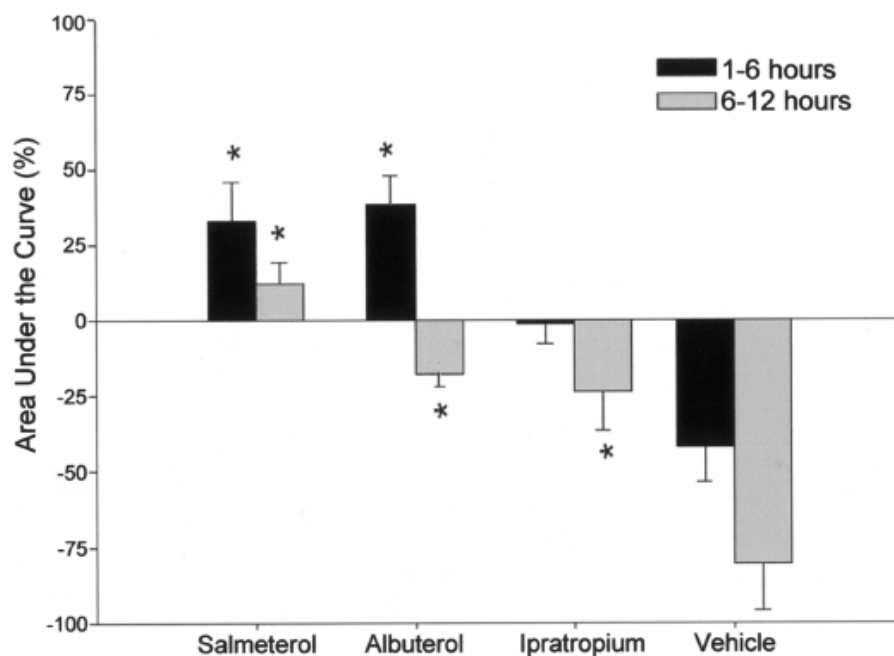
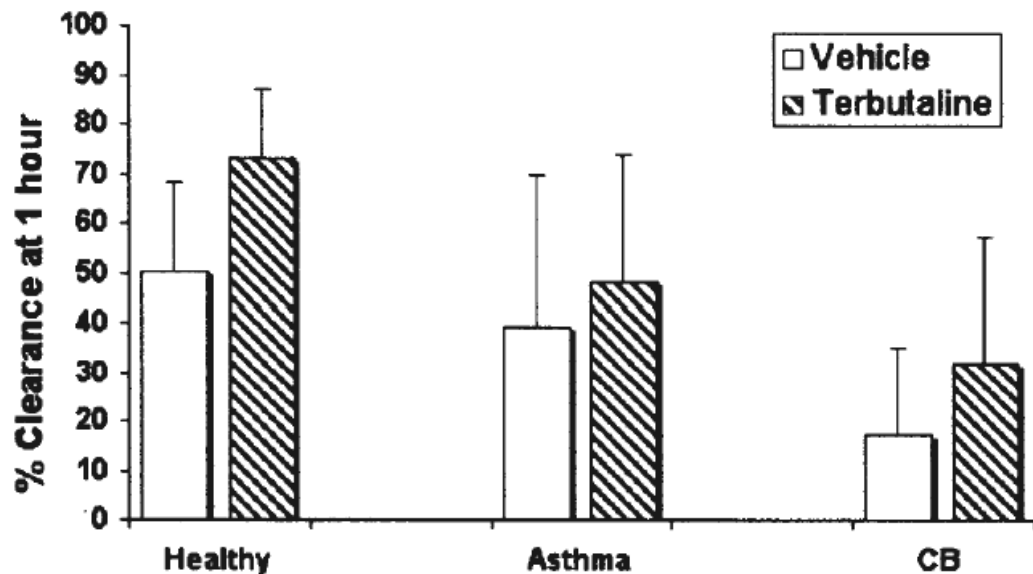


Table 1. Summary of Human and Animal Trials on the Effects of  $\beta_2$  Adrenergics and Anticholinergics on Mucociliary Clearance.

First Author	Year	Agent(s)	n	Subjects	Results
Mossberg <sup>59</sup>	1976	Terbutaline	12	Asthma vs healthy subjects	Significant increase in mucociliary clearance but significantly less than in healthy subjects. Significantly less response in subjects with impaired mucociliary clearance.
Sutton <sup>83</sup>	1988	Terbutaline	8	Bronchiectasis	Significantly increased sputum production
Mortensen <sup>63</sup>	1991	Terbutaline	10	Asthma vs healthy subjects	Significant increase in mucociliary clearance in healthy subjects
Mortensen <sup>112</sup>	1993	Terbutaline	10	Cystic fibrosis	No significant increase in mucociliary clearance
Mortensen <sup>64</sup>	1994	Terbutaline	62	Healthy subjects	Significant increase in mucociliary clearance
Daviskas <sup>78</sup>	2005	Terbutaline	16	Asthma	Little or no stimulation of mucociliary clearance
Jones <sup>87</sup>	1979	Albuterol		Rat epithelium	Significant increase in number of secretory cells
Devalia <sup>68</sup>	1992	Albuterol Salmeterol		Human bronchial epithelial cells	Albuterol produced a transient but significant increase in ciliary beat frequency. Salmeterol produced a significantly rapid and prolonged increase in ciliary beat frequency.
Frohock <sup>91</sup>	2002	Albuterol Levalbuterol		Ovine tracheal epithelium	R-albuterol is more efficacious than racemic albuterol in stimulating ciliary beat frequency
Guleria <sup>88</sup>	2003	Albuterol Ipratropium Beclomethasone	8	Chronic airway disease	No significant difference in mucociliary clearance vs placebo
Guleria <sup>89</sup>	2003	Albuterol Ipratropium Beclomethasone	8	Asthma	No significant difference in mucociliary clearance vs placebo
Sabater <sup>26</sup>	2005	Albuterol Salmeterol Ipratropium	6	Sheep	Significant increase in tracheal mucus velocity and reversion of human-neutrophil-elastase-induced depression of tracheal mucus velocity with salmeterol and albuterol. Ipratropium had no effect.
O'Riordan <sup>92</sup>	2006	Albuterol Levalbuterol	14	Long-term ventilated patients	No significant differences in volume, electrolyte concentration, or inflammatory indexes of sputum
Cleary <sup>93</sup>	2007	Albuterol Levalbuterol	10	Healthy subjects	No significant differences in mucociliary clearance vs placebo
Laube <sup>90</sup>	2007	Albuterol	7	Lung transplant	Significant improvement in mucociliary clearance
Wong <sup>94</sup>	1988	Fenoterol	9	Healthy beagles	Significant increase in ciliary beat frequency
Weich <sup>96</sup>	1988	Fenoterol	12	Chronic bronchitis	Significant increase in mucociliary clearance
Moretti <sup>95</sup>	1997	Fenoterol	26	Chronic bronchitis	Patients with FEV <sub>1</sub> changes > 15% had significant increase in mucociliary clearance, more coughs, and larger 24-h sputum production
Hasani <sup>103</sup>	2003	Salmeterol	11	Asthma	No significant increase in mucociliary clearance
Piatti <sup>74</sup>	2005	Salmeterol	10	COPD	Significant dose-dependent increase in ciliary beat frequency in all groups. No rheological changes.
Bennett <sup>101</sup>	2006	Salmeterol	14	8 Healthy subjects Chronic bronchitis	No significant overall increase in mucociliary clearance vs placebo. Significant increase in lung periphery clearance.
Melloni <sup>113</sup>	1992	Formoterol	10	Chronic bronchitis	Significant increase in mucociliary clearance
Francis <sup>122</sup>	1977	Ipratropium	12	Healthy subjects	No significant difference in mucociliary clearance vs placebo
Pavia <sup>125</sup>	1979	Ipratropium	12	Reversible airway obstruction	No significant difference in mucociliary clearance vs placebo
Miyata <sup>129</sup>	1989	Ipratropium Oxitropium Atropine	14	Pigeons and rabbits	No depression of mucociliary clearance with ipratropium and oxitropium
Bennett <sup>127</sup>	1993	Ipratropium	15	COPD	Significant decrease in cough clearance vs placebo
Tamaoki <sup>23</sup>	1994	Oxitropium	17	Chronic bronchitis	Significant decrease in sputum production
Hasani <sup>133</sup>	2004	Tiotropium	34	COPD	No depression of mucociliary clearance


FEV<sub>1</sub> = forced expiratory volume in the first second

RESEARCH

Open Access

# Aerosol delivery during invasive mechanical ventilation: a systematic review



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**Conclusions:** Lung deposition was lower than 20% of nominal dose delivered with nebulizers and mostly occurred in proximal airways. Further studies are needed to link substantial concentrations of antibiotics in infected pulmonary fluids to pulmonary deposition. The administration technique with nebulizers should be improved in ventilated patients in order to ensure an efficient but safe, feasible and reproducible technique.

**Table 2** Drugs of interest

	Drugs
Antibiotics	Amikacin and amikacin sulfate [27, 28, 32, 34, 39, 40, 43, 44, 49], colistin or colistimethate sodium [14, 16, 46], ceftazidime [38, 41, 42, 48, 49], pentamidine [21], gentamycin [31, 36], tobramycin [15, 25], vancomycin [31], fosfomycin [32], imipenem [15] or teicoplanin [45]
Tracer labeled with technetium-99 m	Diethylenetriaminepentaacetic acid [18, 24, 25, 29], pertechnetate [19], sulfur colloid [19], albumin [22, 23, 35, 37] or fenoterol [20]
Bronchodilators	Albuterol [17, 30], fenoterol [20] or ipratropium bromide [26, 33]
Other	Cisplatin [47]

Identification

Studies identified through database searching (n = 1498)

- PubMed (n = 586)
- Scopus (n = 108)
- Science Direct (n = 754)
- PEDro (n = 50)

Additional studies identified through other sources (n = 1)

Screening

Records after duplicates removal (n = 880)

Records screened (n = 880)

Records excluded (n = 646)

- Language (n = 30)
- Unrelated to AT during IMV (n = 430)
- In vitro, review, letter,... (n = 186)

Eligibility

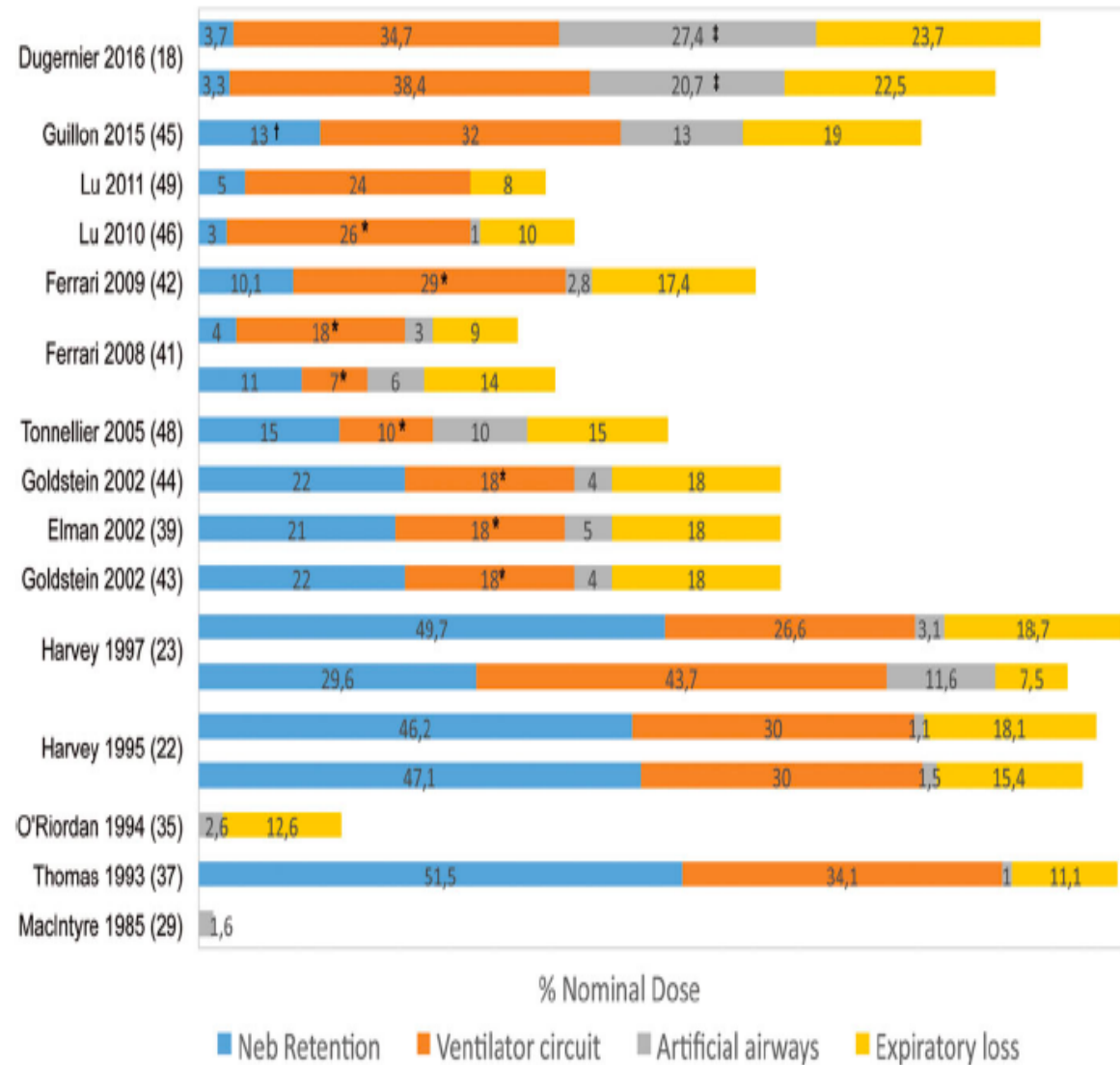
Full-text articles assessed for eligibility (n = 234)

Full-text articles excluded (n = 198)

- Subjects aged <18 or pediatric models (n = 111)
- No data on lung delivery (n = 87)

Included

Studies included in qualitative synthesis (n = 36)



### **Table 3** Practical recommendations to improve inhaled drug deposition with nebulizers

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Using vibrating-mesh nebulizers with minimal drug retention and no risk of protein denaturation as observed with ultrasonic nebulizers

[18, 27, 28, 34, 41]

Promoting inspiratory synchronized nebulizers [27, 28, 31, 35]

Combining an inhalation chamber with constant-output nebulizers (to be confirmed in further studies) [22]

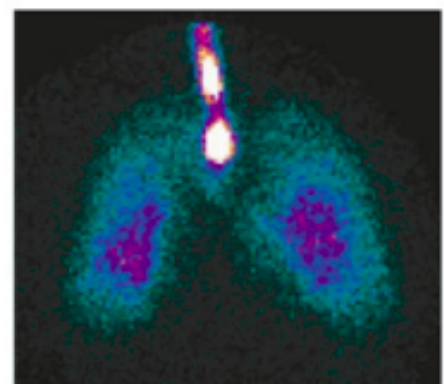
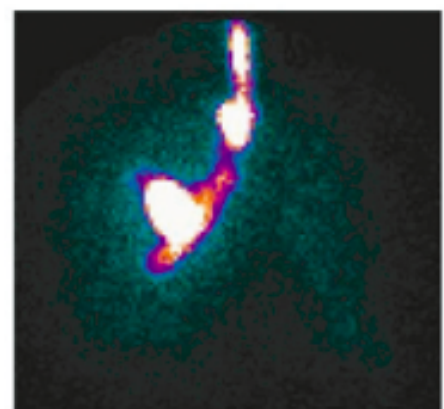
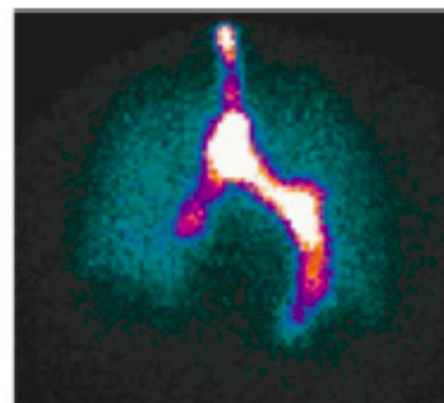
Generating aerosol particles in a dry circuit<sup>a</sup> [31]

Controlling the breathing pattern (high  $T_{\text{insp}}/T_{\text{TOT}}^a$ , low inspiratory flow) in volume control mode [18]

Using a helium-oxygen mixture as inhaled gas [48]

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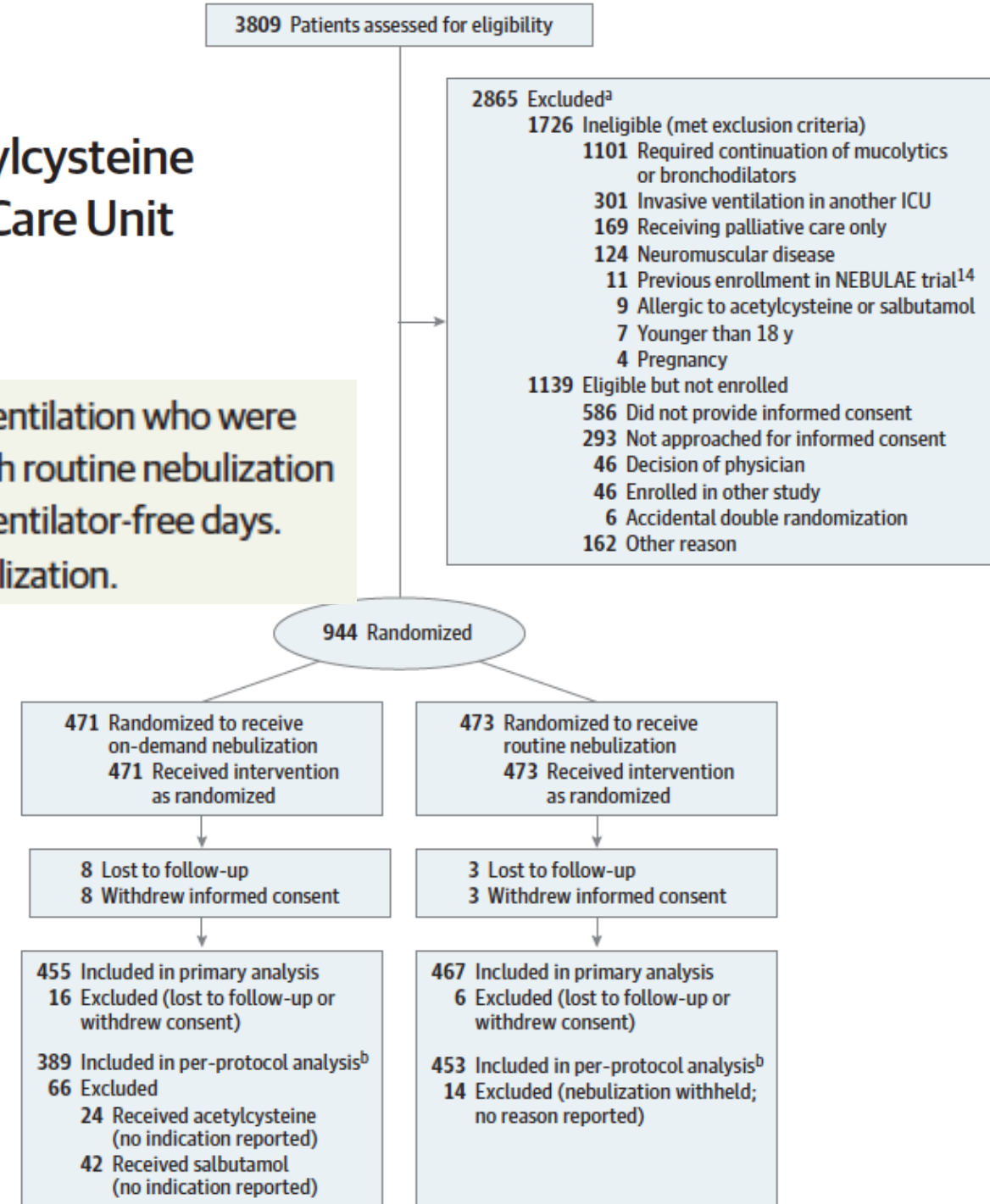
<sup>a</sup>Probably not relevant with a recent prototype of inspiratory synchronized vibrating-mesh nebulizer, as suggested by Luyt et al. [27]

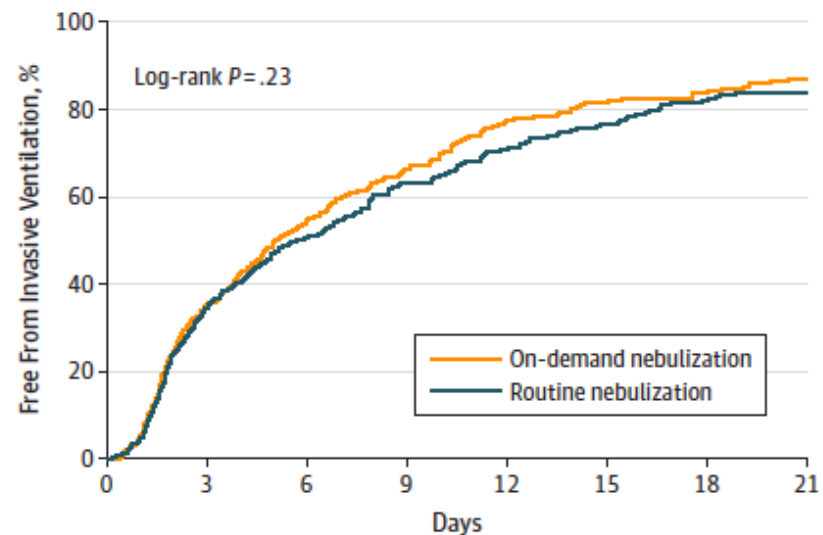


# Effect of On-Demand vs Routine Nebulization of Acetylcysteine With Salbutamol on Ventilator-Free Days in Intensive Care Unit Patients Receiving Invasive Ventilation

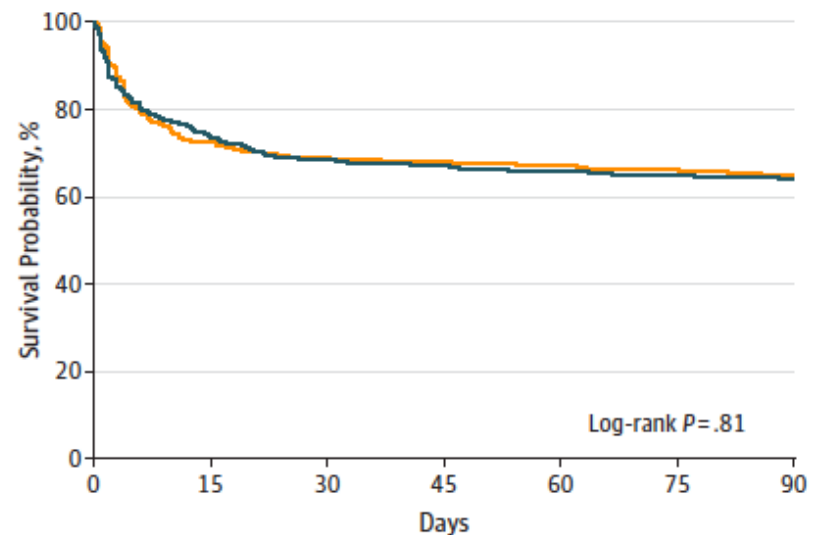
## A Randomized Clinical Trial

**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.

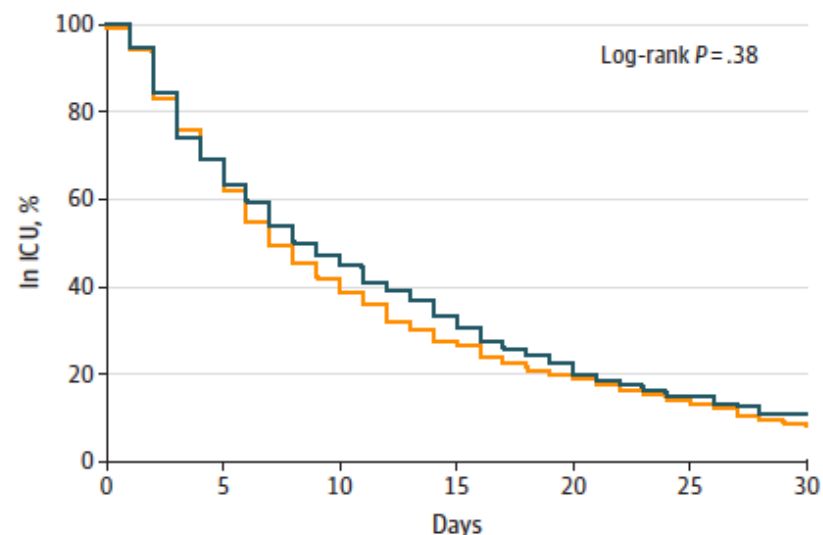


**A** Freedom from invasive ventilation

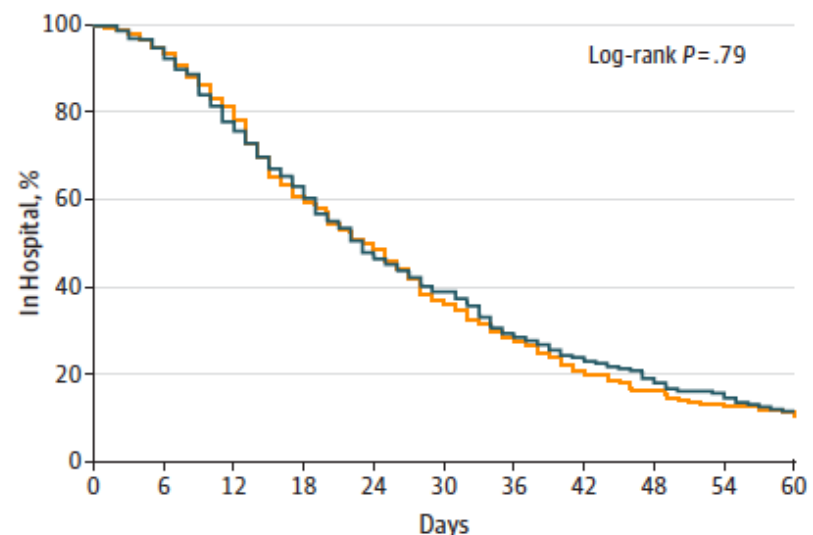
No. at risk		0	3	6	9	12	15	18	21
On-demand	455	252	139	88	53	39	31	23	
Routine	467	254	163	108	79	55	37	31	

**B** 90-Day mortality

No. at risk		0	15	30	45	60	75	90
On-demand	455	330	275	271	267	265	259	
Routine	467	346	285	279	274	270	267	

**C** ICU Length of stay

No. at risk		0	5	10	15	20	25	30
On-demand	455	241	123	71	46	31	16	
Routine	467	258	156	99	59	33	18	

**D** Hospital length of stay

No. at risk		0	6	12	18	24	30	36	42	48	54	60
On-demand	455	326	242	167	125	82	60	43	31	24	19	
Routine	467	348	258	183	124	95	69	55	40	30	21	

Table 1. Baseline Patient Characteristics

Characteristic	On-Demand Nebulization (n = 455)	Routine Nebulization (n = 467)
Age, median (IQR), y	66 (56 to 75)	65 (54 to 74)
Women, No. (%)	155 (34.1)	165 (35.3)
BMI, median (IQR), kg/m <sup>2</sup>	26 (23 to 29)	26 (24 to 29)
APACHE II, median (IQR) <sup>a</sup>	24 (18 to 31)	23 (17 to 30)
Reason of ICU admission, No. (%)		
Medical	350 (76.9)	349 (74.7)
Surgical	105 (23.1)	118 (25.3)
Reason of invasive ventilation, No. (%)		
OHCA	139 (30.5)	126 (27.0)
Postoperative ventilation	59 (13.0)	77 (16.5)
Head trauma or brain surgery	53 (11.6)	52 (11.1)
Pneumonia	46 (10.1)	41 (8.8)
Sepsis	41 (9.0)	49 (10.5)
Cardiac failure	28 (6.2)	23 (4.9)
Trauma	25 (5.5)	27 (5.8)
Respiratory insufficiency	15 (3.3)	13 (2.8)
Aspiration	11 (2.4)	14 (3.0)
Airway protection	6 (1.3)	13 (2.8)
ARDS	2 (0.4)	3 (0.6)
Other	25 (5.5)	29 (6.2)
Comorbidity, No. (%)		
Diabetes mellitus	86 (18.9)	89 (19.1)
Cardiovascular disease	77 (16.9)	86 (18.4)
Pulmonary disease	33 (7.3)	40 (8.6)
Immunosuppression	37 (8.1)	32 (6.9)
Duration of invasive ventilation prior to randomization, median (IQR), hours	9 (4-15)	9 (3-15)
Nebulization prior to randomization, median (IQR), No.	0 (0-0)	0 (0-0)
Respiratory measures, median (IQR)		
Pao <sub>2</sub> to Fio <sub>2</sub> ratio	204 (133-307)	199 (129-303)
Fio <sub>2</sub> , %	50 (40-70)	50 (40-62)
Tidal volume, mL/kg predicted body weight	6.9 (6.1-7.9)	6.9 (6.1-7.8)
Plateau airway pressure, cm H <sub>2</sub> O <sup>b</sup>	22 (18-27)	22 (18-27)
Positive end-expiratory pressure, cm H <sub>2</sub> O	8 (5-10)	8 (5-10)
Respiratory rate, breaths/min	19 (15-22)	18 (15-22)

Table 3. Secondary Outcomes of Patients Receiving On-Demand Nebulization vs Routine Nebulization

Outcome	On-Demand Nebulization (n = 455)	Routine Nebulization (n = 467)	Absolute Difference (95% CI)	P Value <sup>a</sup>
Mortality, No. of events/total No. (%)				
28-d	141/455 (31.0)	149/467 (31.9)	-0.9 (-6.9 to 5.1)	.78
ICU	135/455 (29.7)	137/467 (29.3)	0.3 (-5.6 to 6.2)	.94
90-d <sup>b</sup>	160/415 (38.5)	156/425 (36.7)	1.8 (-4.7 to 8.4)	.62
Hospital <sup>b</sup>	161/416 (38.7)	165/438 (37.7)	1.0 (-5.5 to 7.5)	.78
Duration of invasive ventilation, median (IQR)	4 (2-8)	4 (2-10)	-0.5 (-1.3 to 0.2)	.28
Length of stay, median (IQR), d				
ICU	5 (2-10)	5 (2-13)	-0.8 (-1.8 to 0.2)	.49
Hospital	15 (7-27)	14 (6-27)	-0.9 (-3.0 to 1.2)	.57
Pulmonary complications, No. (%) <sup>c</sup>				
Moderate or severe ARDS <sup>d</sup>	23 (5.1)	30 (6.4)	-1.4 (-4.4 to 1.6)	.40
VAP <sup>e</sup>	14 (3.1)	10 (2.1)	0.9 (-1.1 to 3.0)	.41
Severe atelectasis <sup>f</sup>	175 (38.5)	200 (42.8)	-4.4 (-10.7 to 2.0)	.18
Pneumothorax <sup>g</sup>	25 (5.5)	22 (4.7)	0.8 (-2.1 to 3.6)	.65
Tube occlusion <sup>h</sup>	1 (0.2)	2 (0.4)	-0.2 (-0.9 to 0.5)	.99
Adverse events, No. (%) <sup>i</sup>				
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
Hypoxemia	9 (2.0)	20 (4.3)	-2.3 (-4.5 to -0.1)	.06
Dyspnea	1 (0.2)	5 (1.1)	-0.9 (-1.9 to 0.2)	.22
Bronchospasm	1 (0.2)	4 (0.9)	-0.6 (-1.6 to 0.3)	.37
Apnea	0	3 (0.6)	-0.6 (-1.4 to 0.1)	.25
Self-extubation	0	4 (0.9)	-0.9 (-1.7 to 0.0)	.06
Vomiting	1 (0.2)	6 (1.3)	-1.1 (-2.2 to 0.0)	.17

# Conclusion

- Aerosol therapy is common in mechanical ventilated patients, however many factors can affect the efficiency of drug delivery. Vibrating mesh may be better than Jet nebulizer.
- MDIs with spacer are more efficient and convenient to use than nebulizers in MV patients. However, not all medications could be applied by MDI spacer.
- Proper technique of administration is important, and team work is necessary.
- Numerous medications can be administered via inhalation route but further studies to confirm the efficacy and safety remain mandatory.
- Effect of routine use of aerosol therapy may be not better than on- demand.