Adjunctive Inhaled Antibiotics for Severe Pneumonia

Korea University Guro Hospital

Jae Kyeom Sim

Rationale for inhaled antibiotics

Definition

- **Adjunctive**
- Nebulized antibiotics administered to patients already receiving same antibiotics intravenously

- **Substitution**
- Nebulized antibiotics administered to patients not receiving same antibiotics intravenously

Clin Microbiol Infect. 2017 Sep;23(9):629-639.

Toxicity

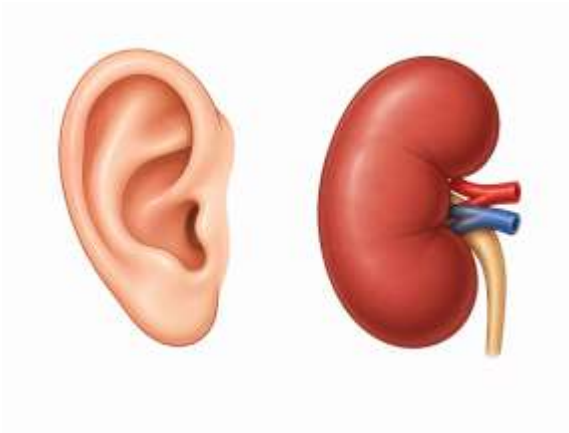
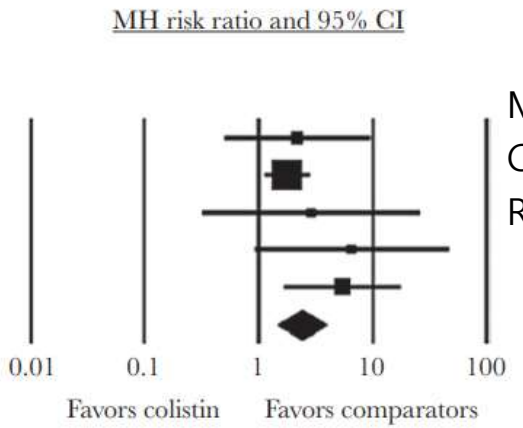


Table 2 Selected studies investigating the prevalence of hearing loss in cystic fibrosis (CF)

Author	Study methods	Definition of HI	Results
Forman-Franco *et al*, 1979[49]	PTA using frequencies 250, 500, 1000, 2000, 4000, 8000 Hz. Recruited from a CF clinic (n=80)	Air conduction thresholds for ≥2 frequencies >25 dB	1/80 (1%) had HI
Pedersen *et al*, 1987[11]	PTA (frequency range 125–8000 Hz). High-frequency audiogram from 4000–20 000 Hz. All patients had chronic *P aeruginosa* (n=42)	Threshold increased by ≥15 dB in one or both ears at two or more adjacent frequencies	2/42 patients (5%) had high-frequency HI. Both patients had normal thresholds <8000 Hz
Mulheran *et al*, 2001[30]	PTA over frequencies 250–8000 Hz. High-frequency PTA over 10 000–16 000 Hz (n=70)	≥2 thresholds in either ear of ≥20 dB or one frequency of ≥25 dB over the frequency range 250–8000 Hz	17% had HI
Conrad *et al*, 2008[40]	Annual audiometric assessment of patients at two CF clinics with PTA over frequency range 1000–8000 Hz. DPOAE were measured over the frequency range 841–7996 Hz (n=153)	Either one PTA threshold >25 dB or abnormal DPOAE thresholds	50.8% had abnormal hearing

DPOAE, distortion product otoacoustic emissions; HI, hearing impairment; PTA, pure tone audiogram.

	Nephrotoxicity/total		Statistics for each study				
	Colistin	Comparators	Relative weight	MH risk ratio	Lower limit	Upper limit	*P*-value
Betrosian 2008	5/15	2/13	10.38	2.17	0.50	9.35	0.30
Cisneros 2019	40/120	21/112	62.87	1.78	1.12	2.82	0.01
Khalili 2018	3/24	1/23	4.82	2.88	0.32	25.68	0.34
Mosaed 2018	6/111	1/12	6.01	6.55	0.93	46.12	0.06
Motsch 2019	9/16	3/29	15.92	5.44	1.71	17.26	0.00
Overall	63/186	28/189		2.40	1.47	3.91	0.00

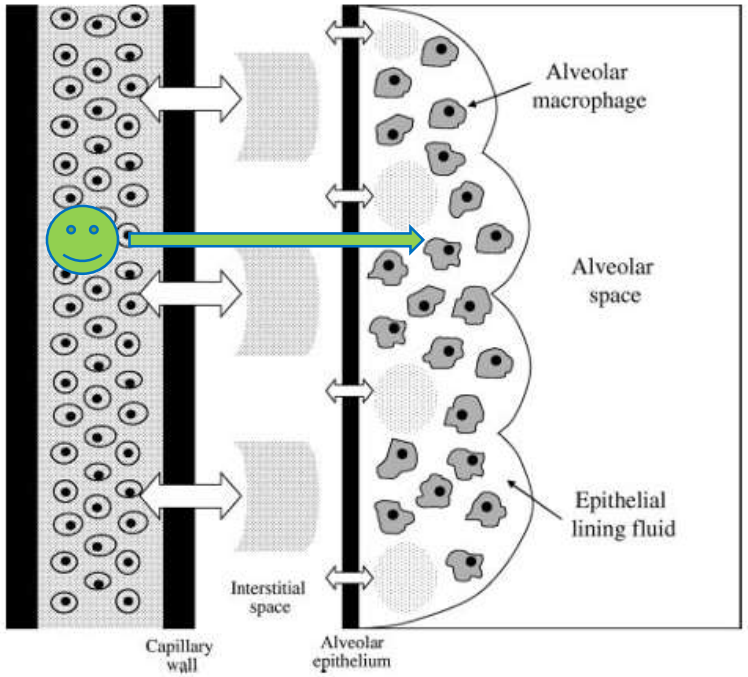


Meta-analysis of 5 RCTs,
Colistin-induced nephrotoxicity rate: 36.2%
Relative risk 2.40 (vs beta-lactam)

Thorax. 2010 Jul;65(7):654-8.
Open Forum Infect Dis. 2021 Jan 21;8(2):ofab026.

Pharmacokinetics

- Concentration of antibiotics in **epithelial lining fluid (ELF)** for extracellular pathogens and in alveolar macrophages for intracellular pathogens is thought to reflect antibiotic activity in pneumonia
- Concentration in the ELF relative to plasma (**ELF penetration ratio**) varies upon the degree of protein binding, lipophilicity, and ionization of antibiotics



Antimicrob Agents Chemother. 2008 Jan;52(1):24-36.
Semin Respir Crit Care Med. 2022 Apr;43(2):255-270.

Pharmacokinetics

Low ELF penetration ratio in beta-lactams, aminoglycosides and glycopeptides

Table 1
Ratios of main antibiotics concentration (AUC) in epithelial lining fluid/serum.

Class	Antibiotic	AUC elf/serum	Reference
beta-lactams	*amoxycillin*	0.53	[17]
	piperacillin/tazobactam	0.56–0.90	[80]
	cefaclor	0.88–3.2	[81]
	cefepime	1.04	[18]
	ceftaroline	0.23	[82]
	ceftobiprole	0.69	[83]
	meropenem	0.19–1.04	[84–86]
macrolides	*azithromycin*	13.31–24.10	[19–22]
	clarithromycin	8.34–30.27	[19,20]
quinolones	*moxifloxacin*	4.92–6.95	[22,30–33]
	levofloxacin	1.59–4.9	[21,22,32,33]
	ciprofloxacin	0.82–2.13	[87,88]
aminoglycosides	*amikacin*	0.1–0.18	[34]
	gentamicin	0.30–1.14	[35]
	tobramycin	0.1–1.6	[36,37]
oxazolidones	*linezolid*	1.04–8.35	[23–25]
glycopeptides	*vancomycin*	0.18	[38]

Steady-State Pharmacokinetics and BAL Concentration of Colistin in Critically Ill Patients After IV Colistin Methanesulfonate Administration

Roberto Imberti, MD; Maria Cusato, PharmD; Paola Villani, BiolD; Livio Carnevale, MD; Giorgio A. Iotti, MD; Martin Langer, MD; and Mario Regazzi, PharmD

VAP (n = 13)

Colistin was undetectable in BALF after IV colistin

Colistin Penetration in the Alveolar Lining Fluid of Critically Ill Patients Treated With IV Colistimethate Sodium

VAP (n = 1) alveolar lining fluid/serum ratio 7.42

BSI (n =1) alveolar lining fluid/serum ratio 1.70

Pulm Pharmacol Ther. 2020 Feb:60:101885.
Chest. 2010 Dec;138(6):1333-9.
Chest. 2011 Jan;139(1):232-3.

Pharmacodynamics

Aminoglycoside is suitable for intermittent nebulization

Beta-lactam is not suitable because time is important

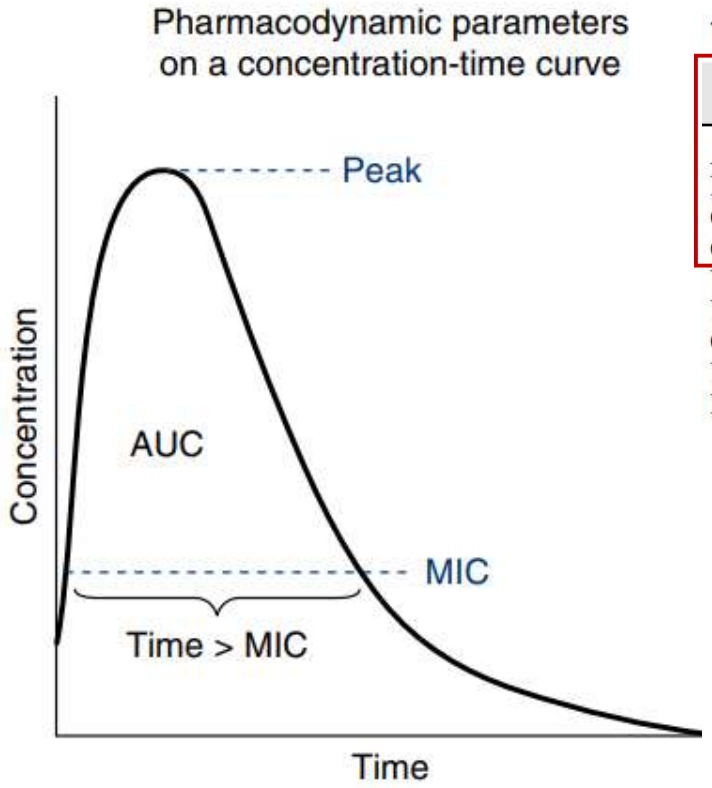
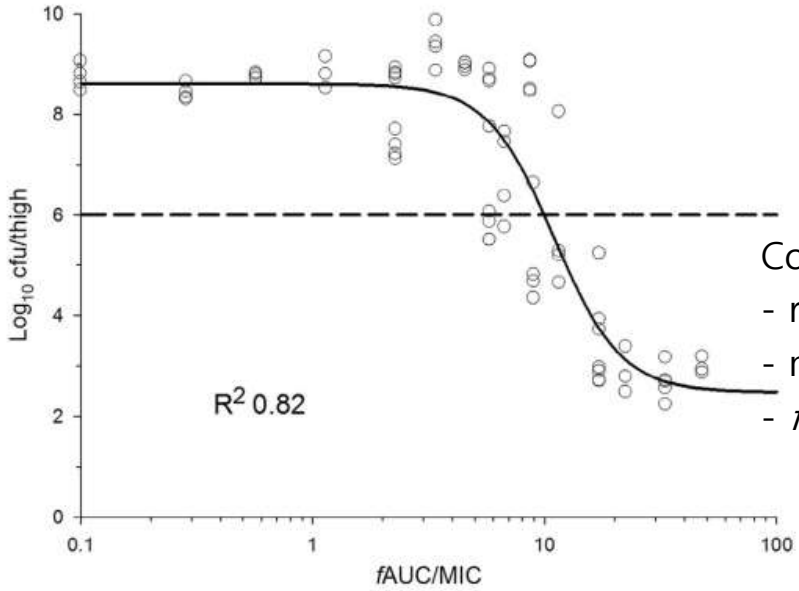


Table 1. Pharmacodynamics of common antibiotic classes (5,6)

Antibiotic Class	Pharmacodynamic Profile	Pharmacodynamic Parameter to Optimize
Aminoglycosides	Concentration-dependent	Peak:MIC
Penicillins	Time-dependent	Time>MIC
Cephalosporins	Time-dependent	Time>MIC
Carbapenems	Time-dependent	Time>MIC
Vancomycin	Time-dependent	AUC:MIC
Lipopeptides	Concentration-dependent	AUC:MIC; peak:MIC
Oxazolidinones	Time-dependent	AUC:MIC
Lipoglycopeptides	Concentration-dependent	AUC:MIC
Fluoroquinolones	Concentration dependent	AUC:MIC
		AUC:MIC
		Limited data (65)



Colistin
- rapid concentration-dependent killing
- minimal post-antibiotic effect
- *f*AUC/MIC is best index

Clin J Am Soc Nephrol. 2019 Jul 5;14(7):1080-1090.
Int J Antimicrob Agents. 2016 Dec;48(6):592-597.

Drug delivery during mechanical ventilation

Particle size

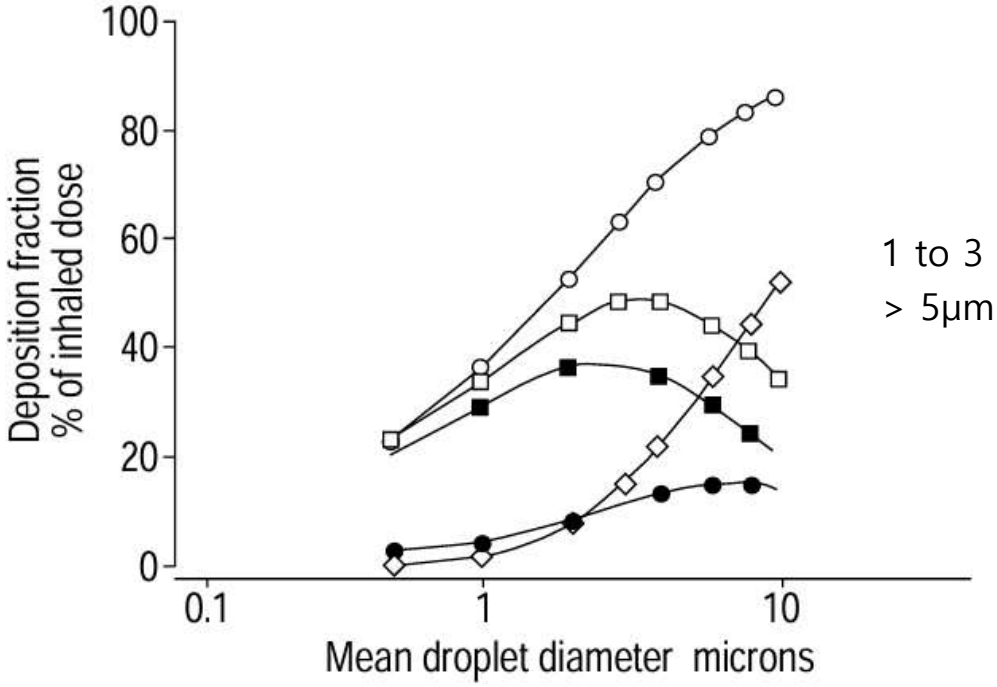


Fig. 1.–Relationship between aerosol aerodynamic diameter and deposition in the healthy adult lung (based on *in vitro* models). ○: total body; □: total lung; ◇: oropharyngeal; ●: central airways; ■: peripheral airways. Reproduced with permission [5].

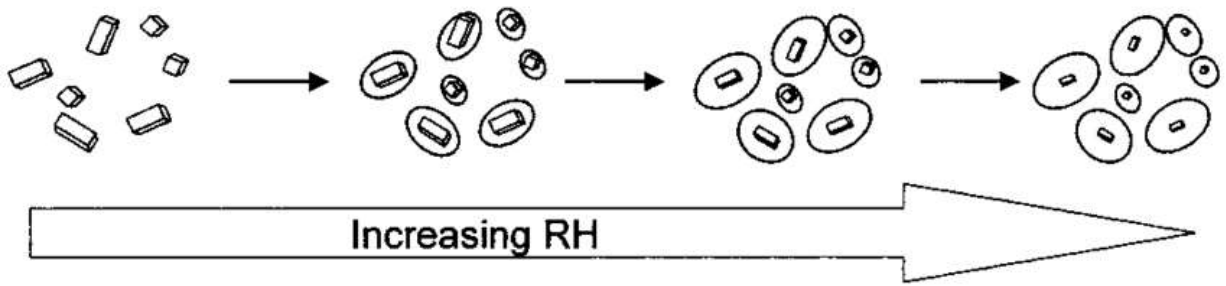
1 to 3 μm for distal lung deposition

> 5μm ventilator circuit or larger airway

Eur Respir J. 2001 Jul;18(1):228-42.

Humidification

- Increases the size of the aerosol particles through hygroscopic water absorption



Hygroscopic growth. Particles absorb moisture as they traverse the humid environment of the airways, resulting in increased particle size.

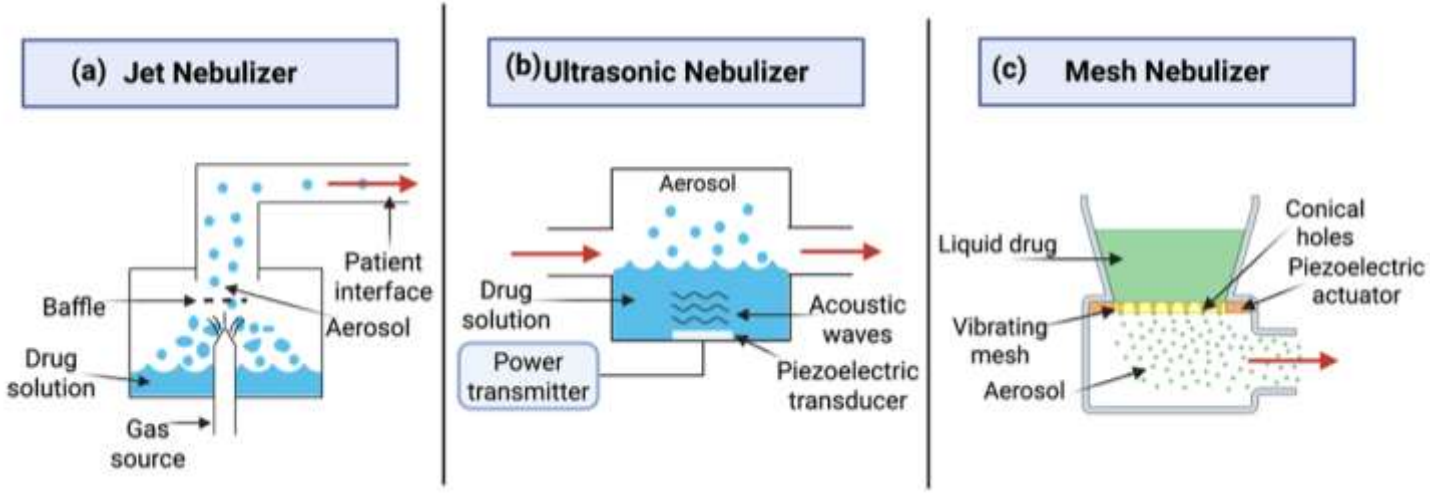
- Remove or bypass heat-moisture exchange
- Switch off active heated humidifier during nebulization

  - wait until circuit to dry? replace circuit? risk of forgetting switch on

  - not recommend in recent consensus statement

Respir Care. 2005 Sep;50(9):1209-27.
Ann Intensive Care. 2017 Dec;7(1):78.
Ann Intensive Care. 2023 Jul 12;13(1):63.

Nebulizer



Residual volume	Large	Medium	Small
Medication restriction	None	Heat-sensitive drug	Highly concentrated or viscous solution
Ergonomics	Need compressed gas Loud Disposable Inference with MV	Bulky Silent Need for decontamination	Portable, small Silent Disposable

Pharmaceutics. 2025 Jul 9;17(7):893.
Ann Intensive Care. 2017 Dec;7(1):78.

Nebulizer position

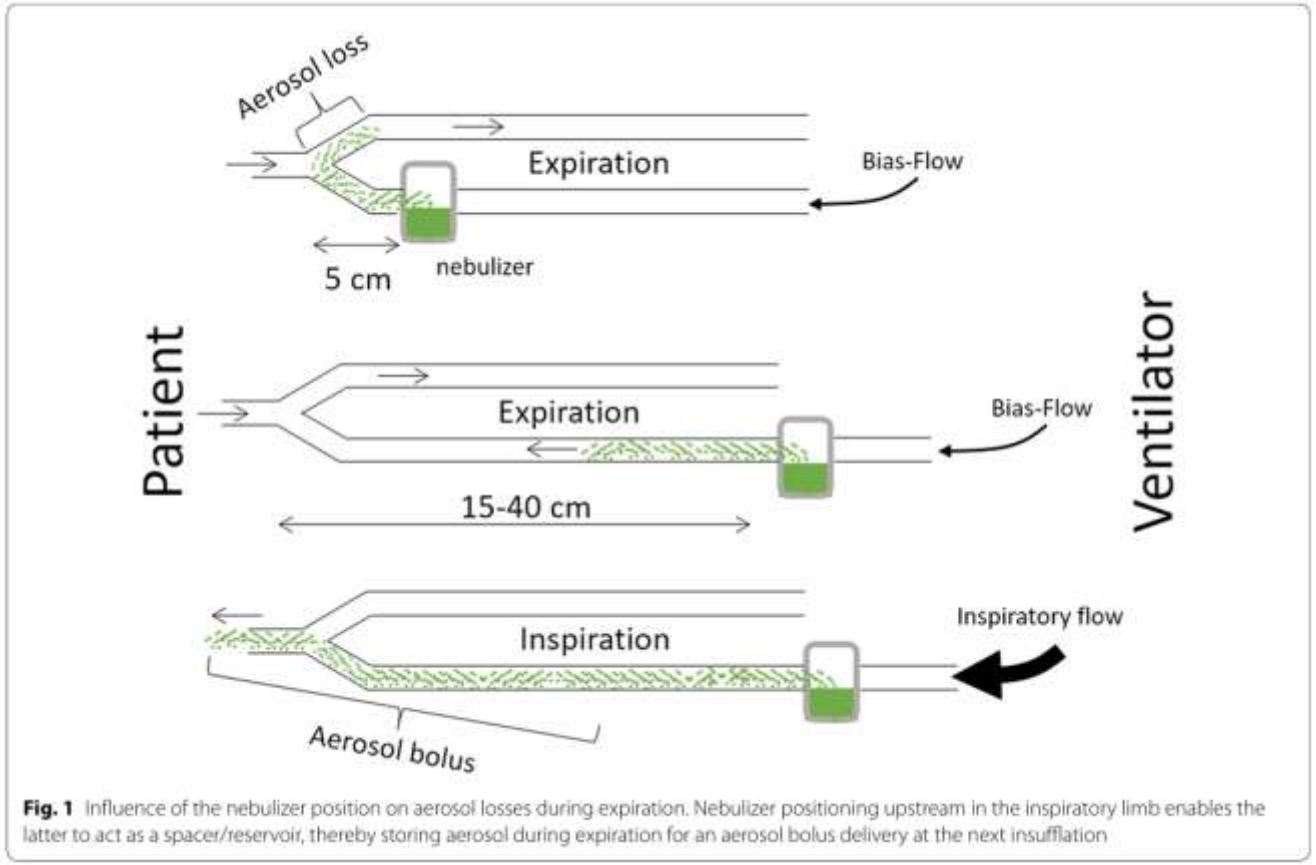
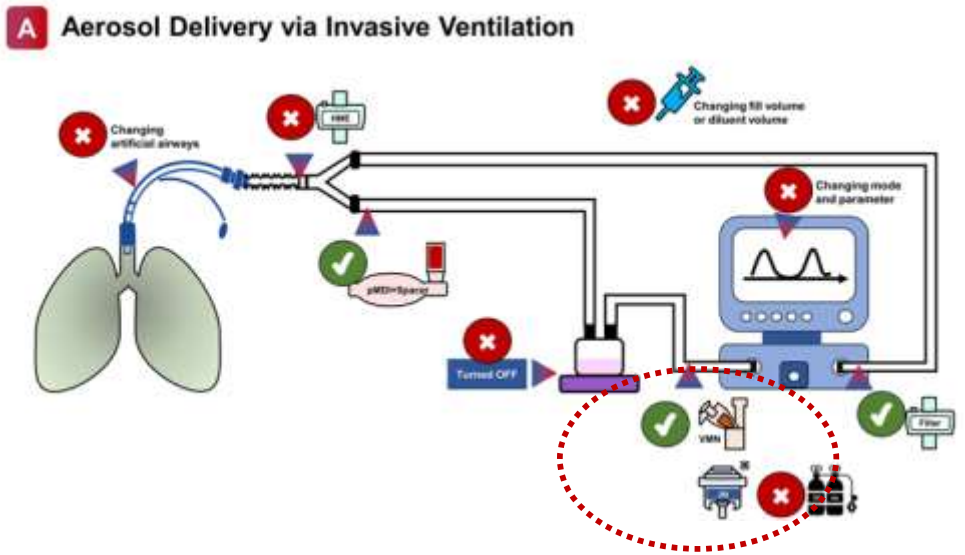


Fig. 1 Influence of the nebulizer position on aerosol losses during expiration. Nebulizer positioning upstream in the inspiratory limb enables the latter to act as a spacer/reservoir, thereby storing aerosol during expiration for an aerosol bolus delivery at the next insufflation

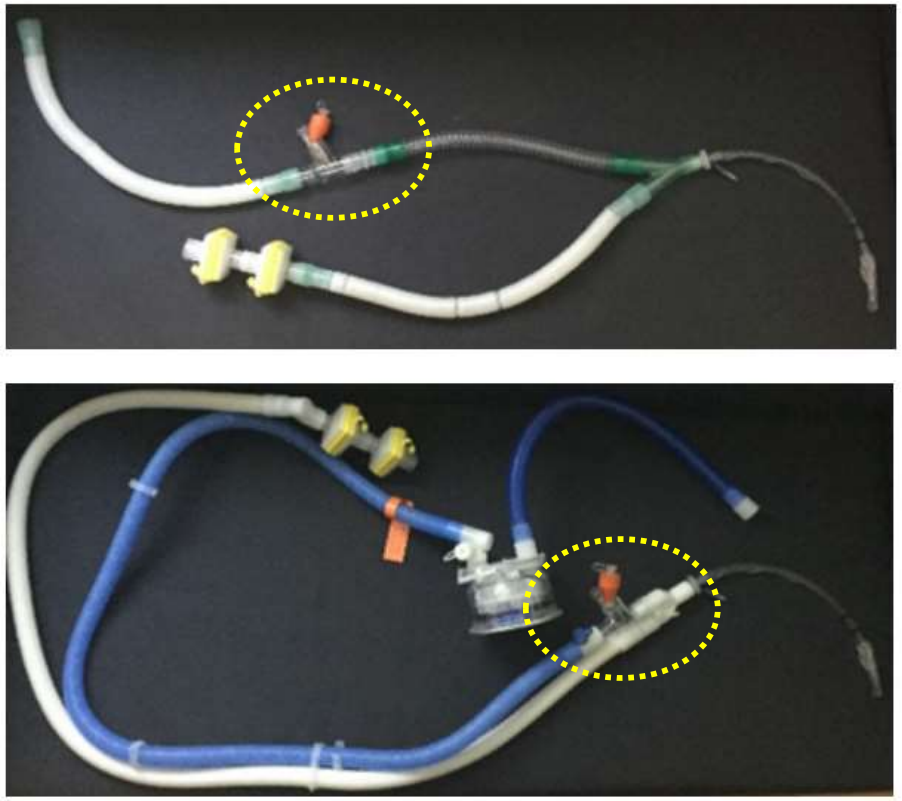
Recent consensus statement
Place the VMN or JN in the inspiratory limb,
away from the Y-piece and toward the ventilator



Ann Intensive Care. 2017 Dec;7(1):78.
Ann Intensive Care. 2023 Jul 12;13(1):63.

Circuit setup

Figure S1: Ventilator circuit setup



Top: Dry circuit; Bottom: humidified circuit.

Table S2: *In vitro* evaluation of the nebulization setup

	Nebulization duration (min)	Amikacin delivery (%)
	Humidified circuit	
1 g Amikacin	29±3	47.1±3.3
2 g Amikacin	64±8	46.7±3.2
9 mL 0.9% NaCl	27±5	na
17 mL 0.9% NaCl	69±12	na
	Dry circuit	
1 g Amikacin	29±5	56.8±7.5
2 g Amikacin	56±2	50.9±2.9
9 mL 0.9% NaCl	27±6	na
17 mL 0.9% NaCl	61±8	na

Amikacin was diluted at 125 mg per mL resulting in a total solution volume of 9 mL and 17 mL. Amikacin delivery was expressed as the percentage of the amount of drug placed in the nebulizer. na: not applicable

N Engl J Med. 2023 Nov 30;389(22):2052-2062.

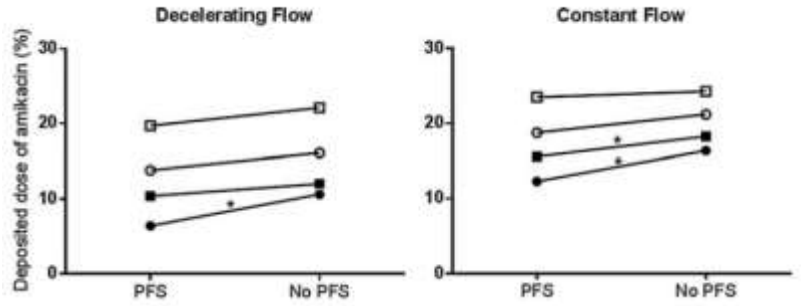
Ventilator setting

- Laminar low inspiratory flow is required for distal lung aerosol deposition
  - Volume-controlled ventilation with constant flow rate
  - Low RR
  - Low inspiratory flow (long inspiratory time) ± inspiratory pause
- Patient-ventilator synchrony may reduce turbulent flow (sedative)

- Contradictory reports about ventilator setting

Table 3 Aerosol deposition in seventeen postoperative neurological patients

	PSV ($n = 8$)	VCV ($n = 9$)	p value
Pulmonary deposition (%)	*10.5 ± 3.0 (28)*	*15.1 ± 5.0 (33)*	*0.038*



Ann Intensive Care. 2017 Dec;7(1):78.
Ann Intensive Care. 2016 Dec;6(1):73.
J Aerosol Med Pulm Drug Deliv. 2015 Jun;28(3):229-36.

Ventilator setting

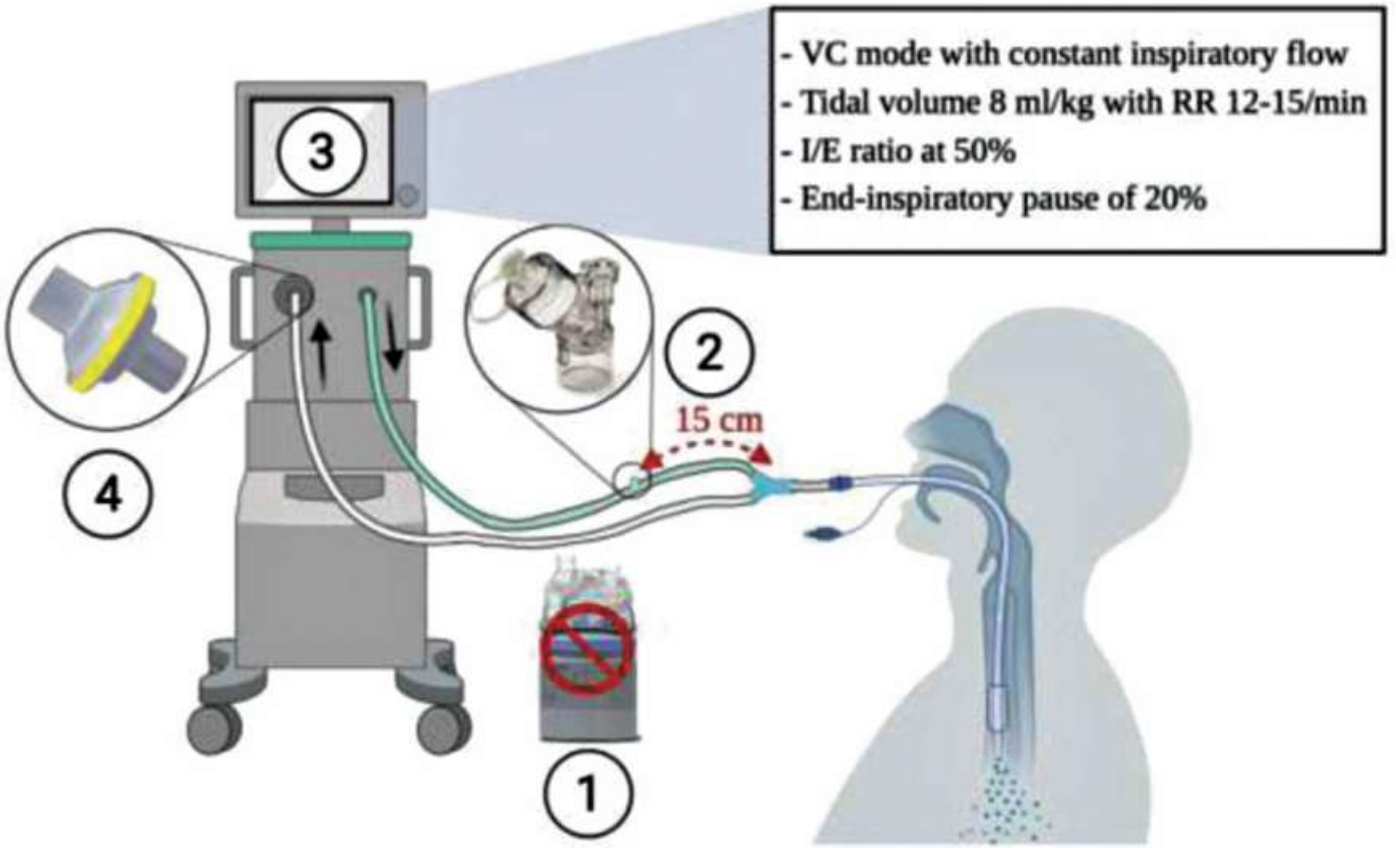


Fig. 3 Optimal ventilation settings for the optimization of nebulization. (1) Remove heated humidifier, (2) use vibrating-mesh nebulizer set at 15 cm from the endotracheal tube on the inspiratory limb, without heat and moisture filter and limit the sharp angles, (3) use optimal ventilator settings (VC = volume controlled, RR = respiratory rate, I/E = inspiratory/expiratory), (4) change the expiratory ventilator filter after each nebulization.

Semin Respir Crit Care Med. 2022 Apr;43(2):255-270.

Drug characteristics

- IV drug formulation is not optimal for nebulization
- Specific formulation of colistin, aztreonam, and tobramycin for use in cystic fibrosis
- Off-label use of colistin (CMS) in Korea

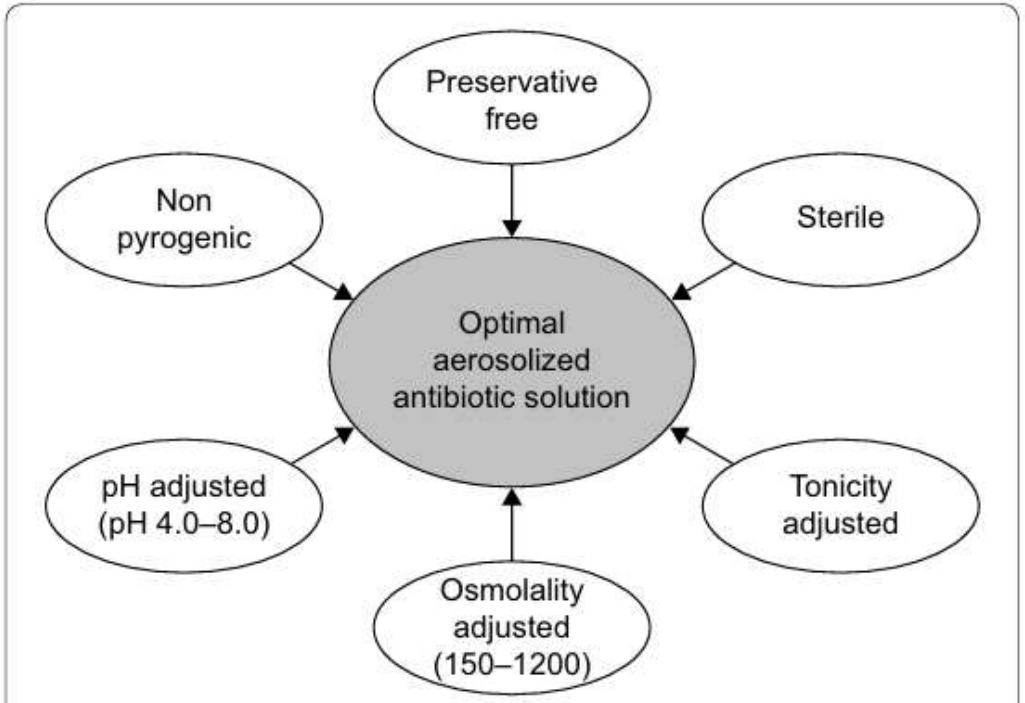


Fig. 2 Ideal properties of an antibiotic solution for aerosolization. Adapted from information in references [26, 27, 29]

Ann Intensive Care. 2016 Dec;6(1):35.

RCTs and guidelines

Nebulized Ceftazidime and Amikacin in Ventilator-associated Pneumonia Caused by *Pseudomonas aeruginosa*

- VAP caused by susceptible *P. aeruginosa*
- Nebulized ceftazidime + amikacin (n = 20)
- IV ceftazidime (ciprofloxacin) + amikacin (n = 20)
- **Vibrating plate nebulizer with standardized protocol**

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

Medical orders

Physician _____ **Date** _____

Dosages	**Ventilation before aerosol**	**Ventilation during aerosol**	**Sedation during aerosol**
☐ **Ceftazidime** _____ mg every 3 h Diluted in _____ ml ☐ **Amikacin** _____ $mg.day^{-1}$ Diluted in _____ ml	☐ Mode _____ ☐ RR _____/min ☐ I/E ratio _____ ☐ Plateau _____% ☐ TV_____ml ☐ FiO_2 = _____ %	☐ VC ; TV= 8 $ml.kg^{-1}$ ☐ RR =12.min^{-1} ☐ I/E ratio = 50% ☐ Plateau 20% ☐ constant flow ☐ FiO_2 = _____ %	☐ propofol _____$mg.h^{-1}$ (if patient desynchronized with the ventilator)

Checklist form

Nurse _____ **Date** _____

		__ h __ min ☐Cefta/AMK	__ h __ min ☐ Cefta/AMK	__ h __ min ☐Cefta/AMK	__ h __ min ☐Cefta/AMK
Before aerosol	Removal of moisture exchanger	☐	☐	☐	☐
	Removal of connecting tube	☐	☐	☐	☐
	Nebulizer inserted 10 cm before Y piece	☐	☐	☐	☐
	Connection of expiratory filter positioned between expiratory circuit and ventilator	☐	☐	☐	☐
	Ventilator settings (see medical order)	☐	☐	☐	☐
	Patient desynchronized with the ventilator : start propofol	☐	☐	☐	☐
After aerosol	Connection of moisture exchanger	☐	☐	☐	☐
	Reinsertion of connecting tube	☐	☐	☐	☐
	Removal of nebulizer	☐	☐	☐	☐
	Removal of expiratory filter	☐	☐	☐	☐
	Initial ventilator settings (see medical order)	☐	☐	☐	☐
	Stop propofol	☐	☐	☐	☐

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

Nebulized Ceftazidime and Amikacin in Ventilator-associated Pneumonia Caused by *Pseudomonas aeruginosa*

- **Extrapulmonary deposition of nebulized antibiotics**

  - Ceftazidime: 5% (nebulizer chamber) + 24% (inspiratory limb) + 8% (expiratory filter) → **37%**

  - Amikacin: 5% (nebulizer chamber) + 25% (inspiratory limb) + 7% (expiratory filter) → **37%**

TABLE 4. AMIKACIN AND CEFTAZIDIME PLASMA CONCENTRATIONS MEASURED ON DAYS 3 AND 4

	Aerosol	Intravenous	*P* Value
Ceftazidime			
Daily dose, $mg \cdot kg^{-1}$	76*	90	
C_{peak}, $mg \cdot L^{-1}$	12.1 ± 8.4		
C_{trough}, $mg \cdot L^{-1}$	8.1 (6.0–12.4)	32.2 ± 9	<0.001
Amikacin			
Daily dose, $mg \cdot kg^{-1}$	15.7*	15.0	
C_{peak}, $mg \cdot L^{-1}$	8.9 (5–11)	45.1 (33–58)	<0.001
C_{trough}, $mg \cdot L^{-1}$	2.4 (1.7-5.9)	3.3 (1.9–5.8)	0.742

Antibiotic plasma concentration was lower in nebulizer group

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

Nebulized Ceftazidime and Amikacin in Ventilator-associated Pneumonia Caused by *Pseudomonas aeruginosa*

- **Cure of VAP on day 9: 14 (70%) vs. 11 (55%) (*P* = 0.33)**
- Rapid initial eradication in nebulizer group, but similar final positivity (re-appearance)
- MV duration: 29 day vs. 18 days (*P* = 0.13)
- ICU LOS: 38 day vs. 29 day (*P* = 0.08)
- 28-day mortality: 2 (10%) vs. 1 (5%) (*P* = 0.55)

- Bronchospasm: None
- No overall ABGA change before and after nebulization
- 25% decrease of PaO_2 in 3 patients with P/F ratio <200
- Severe hypoxemia related to nebulization-induced alveolar de-recruitment in one
- Obstruction of expiratory filter in 3 patients: cardiac arrest in one patient

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

BAY41-6551 achieves bactericidal tracheal aspirate amikacin concentrations in mechanically ventilated patients with Gram-negative pneumonia

- Gram-negative HAP, VAP, or HCAP
- IV antibiotics + nebulized amikacin q 12hr (n = 21) vs q 24hr (n = 24)
- IV antibiotics + nebulized placebo (n = 22)
- **Specially formulated amikacin via proprietary vibrating mesh nebulizer**

- **Achieving target amikacin concentration in tracheal aspirate : 50% vs. 16.7% (*P* = 0.102)**
- Clinical cure: 93.8% vs. 75.0% vs. 87.5% (*P* = 0.467)
- Microbiologic eradication: 68.8% in nebulized amikacin vs. 62.5% in placebo (*P* > 0.999)
- Bronchospasm: 5 episodes in 4 participants

Intensive Care Med. 2012 Feb;38(2):263-71.

Pressure monitor senses a change in airway pressure

Aerosol is generated and provided during in inspiratory phase

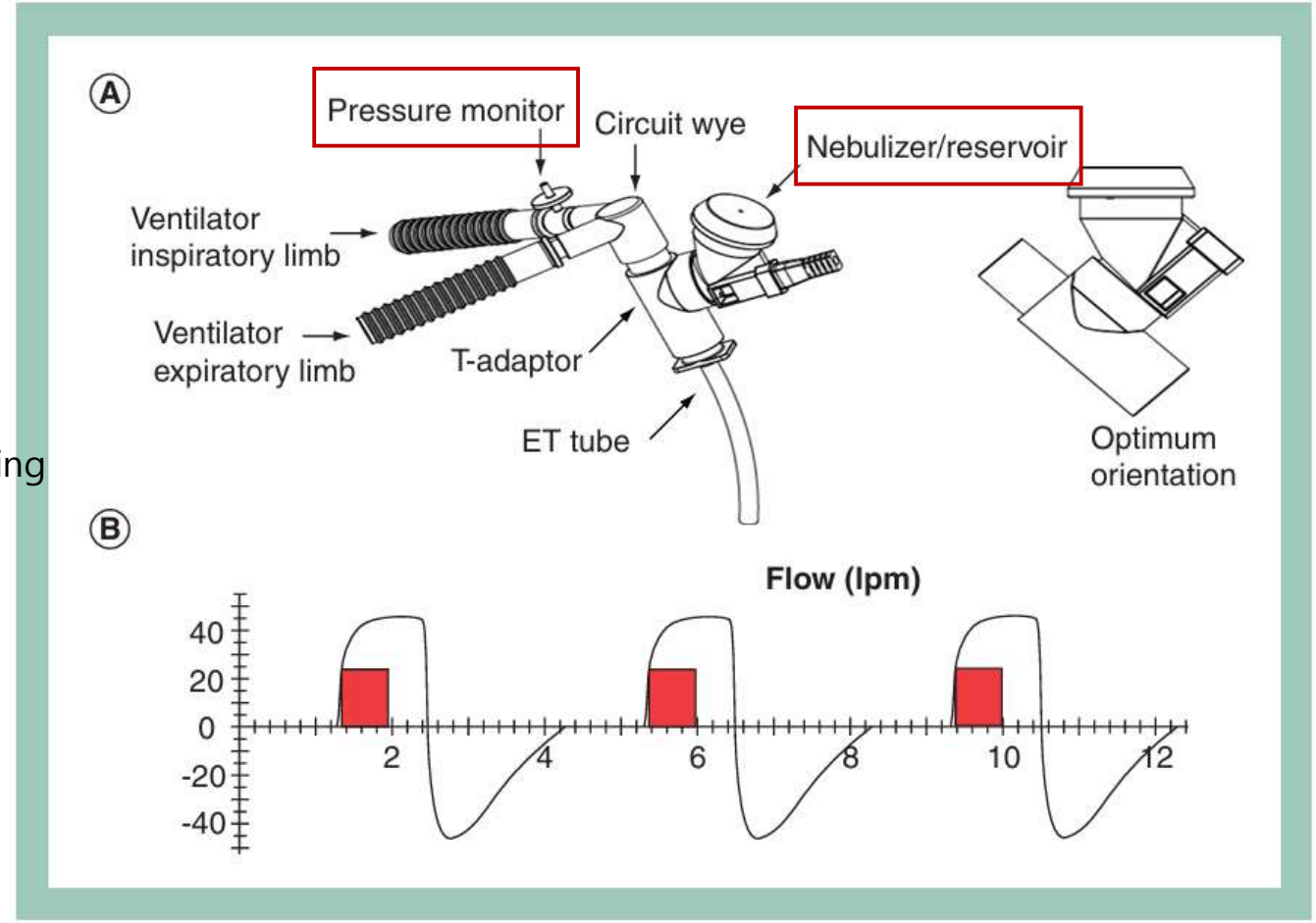


Figure 2. The Pulmonary Drug Delivery System device connected in a ventilator circuit. (A) The aerosol generator connects to a low volume adapter that is in turn connected to the patient's airway between the circuit wye and endotracheal tube. The optimum orientation of the device is shown. **(B)** Aerosol of a specific size is generated only during a specific portion, as indicated by the shaded bar, of the inspiratory cycle. By these techniques, aerosol delivery to the lower respiratory tract can be optimized in mechanically ventilated patients.
Reproduced with permission from Nektar Therapeutics.

Expert Rev Med Devices. 2008 Jan;5(1):9-18.

Inhaled amikacin adjunctive to intravenous standard-of-care antibiotics in mechanically ventilated patients with Gram-negative pneumonia (INHALE): a double-blind, randomised, placebo-controlled, phase 3, superiority trial

- Gram-negative pneumonia + mechanical ventilation
- IV standard antibiotics + nebulized amikacin (n = 354; 255)
- IV standard antibotics + nebulized saline (n = 363; 253)
- **Specially formulated amikacin via proprietary vibrating mesh nebulizer**

- **Survival at late follow-up (day 28-32): 191/255 (75%) vs. 196/253 (77%) (*P* = 0.43)**
- Early clinical response: 149/253 (58%) vs. 145/253 (57%)
- MV duration: 20.6 days vs. 20.2 days
- Bronchospasm: 15 (4%) vs. 4 (1%)
- Device-related serious AE: 4 (1%) vs. 0 (0%)
- Drug-related serious AE: 7 (2%) vs. 2 (1%)

Lancet Infect Dis. 2020 Mar;20(3):330-340.

A Randomized Trial of the Amikacin Fosfomycin Inhalation System for the Adjunctive Therapy of Gram-Negative Ventilator-Associated Pneumonia

IASIS Trial

- Gram-negative VAP
- IV carbapenem + nebulized amikacin fosfomycin (n = 71)
- IV carbapenm + nebulized saline (n = 71)
- **Amikacin Fosfomycin inhalation system (AFIS), experimental drug-device combination**

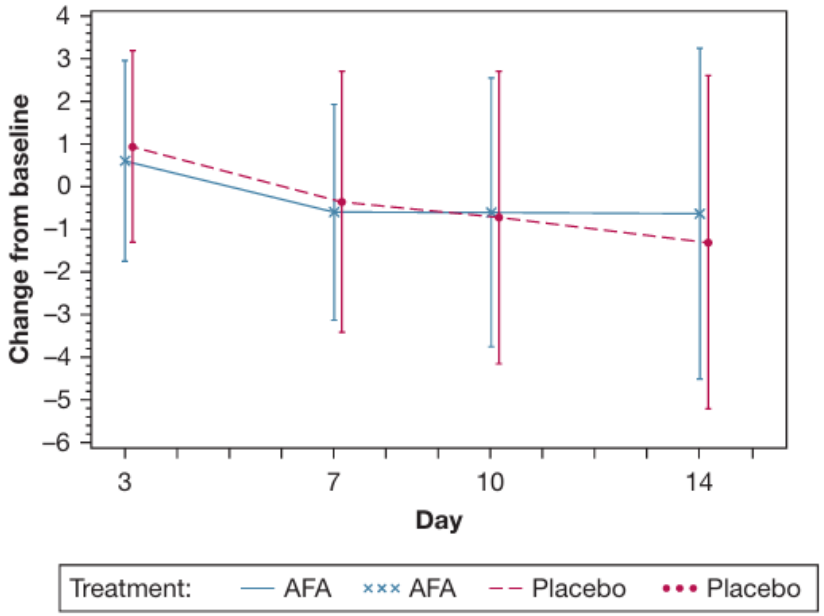
- pH and osmolality adjusted by hydrochloric acid, preservative-free
- Investigational inline **vibrating plate electronic nebulizer** (eFlow Inline System; PARI GmbH)
- Proximal to Y-connector (inspiratory limb); nebulization over 12 minutes
- Nebulizer was left in place during treatment period (no disconnection from circuit).
- **Ventilator settings unchanged**
- Humidity maintained

Chest. 2017 Jun;151(6):1239-1246.

A Randomized Trial of the Amikacin Fosfomycin Inhalation System for the Adjunctive Therapy of Gram-Negative Ventilator-Associated Pneumonia

IASIS Trial

- **No difference in CPIS improvement between group (*P* = 0.70)**
- MV free days (day 1-28): 9.8 days vs. 12.5 days (*P* = 0.02)
- Mortality (day 1-28): 17 (24%) vs. 12 (17%) (*P* = 0.32)
- Tracheal culture of GNR at day 7: 12 (17%) vs. 29 (41%) (*P* = 0.002)
- Bronchospasm in one patient in each group



Chest. 2017 Jun;151(6):1239-1246.

Randomized controlled trial of nebulized colistimethate sodium as adjunctive therapy of ventilator-associated pneumonia caused by Gram-negative bacteria

- Gram-negative VAP
- IV antibiotics + nebulized colistimethate sodium (CMS) (n = 51)
- IV antibiotics + nebulized normal saline (n = 49)
- **Jet or ultrasonic nebulizer**

- **Favorable clinical outcome (resolution of pneumonia): 51.0% vs. 53.1% (*P* = 0.84)**
- Death due to VAP: 39.2% vs. 36.7%, (*P* = 0.80)
- Favorable microbiological outcome (eradication): 60.9% vs. 38.2%, (P = 0.03)
- Bronchospasm: 7.8% vs. 2.0% (*P* = 0.36) (5 in total 100)

J Antimicrob Chemother. 2010 Dec;65(12):2645-9.

2016 IDSA/ATS guideline

- XIV. Should Patients With **VAP Due to Gram-Negative Bacilli** Be Treated With a Combination of Inhaled and Systemic Antibiotics, or Systemic Antibiotics Alone?

- 1. For patients with VAP due to gram-negative bacilli that are susceptible to only aminoglycosides or polymyxins (colistin or polymyxin B), **we suggest both inhaled and systemic antibiotics**, rather than systemic antibiotics alone (weak recommendation, very low-quality evidence).

- Improved the clinical cure rate (ie, resolution of signs and symptoms of respiratory infection)
- No definitive effects on mortality or nephrotoxicity.

Clin Infect Dis. 2016 Sep 1;63(5):e61-e111.

2016 IDSA/ATS guideline

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

- 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 recommendation, low-quality evidence).

- Higher clinical response
- No significant difference in mortality

Clin Infect Dis. 2016 Sep 1;63(5):e61-e111.

2016 IDSA/ATS guideline

- XX. Which Antibiotic Should Be Used to Treat Patients With **HAP/VAP Due to Carbapenem-Resistant Pathogens**?

- 1. In patients with HAP/VAP caused by a carbapenem-resistant pathogen that is sensitive only to polymyxins, we recommend intravenous polymyxins (colistin or polymyxin B) (strong recommendation, moderate-quality evidence), and we **suggest adjunctive inhaled colistin** (weak recommendation, low-quality evidence).

- Improved clinical cure rate
- Trend toward improved mortality

Clin Infect Dis. 2016 Sep 1;63(5):e61-e111.

2017 ESCMID position paper

- **Adjunctive strategy in VAP caused by resistant pathogens**

- **We suggest avoiding the use of nebulized antibiotics** such as colistin or aminoglycosides, added to conventional IV antibiotic therapy already including IV colistin or aminoglycosides.
- Weak recommendation; Very low quality of evidence

- Higher clinical resolution rate, shorter MV duration, lower VAP-related mortality in observational studies
- No difference in clinical resolution rate in RCT
- Higher incidence of respiratory complications in safety analysis (low quality of evidence)
- No difference in nephrotoxicity or neurotoxicity in safety analysis

Clin Microbiol Infect. 2017 Sep;23(9):629-639.

2017 ESCMID position paper

- **Substitution strategy in VAP caused by resistant pathogens**

- **We suggest avoiding the use of nebulized antibiotics** such as colistin or aminoglycosides instead of their IV administration.
- Weak recommendation; Very low quality of evidence

- Higher clinical resolution rate in one observational study
- Higher incidence of respiratory complications in safety evaluation (low quality of evidence)
- Reduced nephrotoxicity in safety evaluation (low quality evidence)

Clin Microbiol Infect. 2017 Sep;23(9):629-639.

2017 ESCMID position paper

- **Adjunctive strategy in VAP caused by susceptible pathogens**

- **We recommend avoiding the use of nebulized antibiotics** such as colistin or aminoglycosides, added to conventional IV antibiotic therapy already including IV colistin or aminoglycosides.
- Strong recommendation; No available evidence

- Against nebulization because of safety concern

Clin Microbiol Infect. 2017 Sep;23(9):629-639.

2017 ESCMID position paper

- **Substitution strategy in VAP caused by susceptible pathogens**

- **We suggest avoiding the use of nebulized antibiotics** such as colistin or aminoglycosides instead of their IV administration.
- Weak recommendation; Very low quality of evidence

- No differences in clinical resolution, mortality, MV duration, ICU stay, and occurrence of superinfection
- Higher incidence of respiratory complications in safety evaluation (low quality of evidence)
- Reduced nephrotoxicity in safety evaluation (low quality evidence)

Clin Microbiol Infect. 2017 Sep;23(9):629-639.

2024 IDSA guidance

- Question 4.9: What Is the Role of Nebulized Antibiotics for the Treatment of **Respiratory Infections Caused by DTR *P. aeruginosa***?

- **The panel does not suggest the use of nebulized antibiotics** for the treatment of respiratory infections caused by DTR P. aeruginosa.

- Favors clinical resolution
- No survival benefit, reduction in ICU stay, or MV duration
- Concerns for unequal distribution and respiratory complications such as bronchoconstriction

Clin Infect Dis. 2024 Aug 7:ciae403.

2024 IDSA guidance

- Question 5.10: What Is the Role of Nebulized Antibiotics for the Treatment of **Respiratory Infections Caused by CRAB**?

- **Nebulized antibiotics are not suggested** for the treatment of respiratory infections caused by CRAB.

- No survival benefit, reduction in ICU stay, or MV duration
- Concerns for unequal distribution and respiratory complications such as bronchoconstriction

Clin Infect Dis. 2024 Aug 7:ciae403.

2025 KATRD guideline

- Key question 8. Should inhaled colistin be added to systemic colistin therapy for **VAP caused by carbapenem-resistant gram-negative bacteria (CRGNB)**?

- **We suggest systemic plus inhaled colistin therapy (adjunctive therapy)** for patients with VAP caused by CRGNB (conditional recommendation, low-quality evidence).

- No significant difference in mortality
- Higher clinical cure rate, shorter mechanical ventilation
- Concerns for unequal distribution and respiratory complications such as bronchoconstriction

Tuberc Respir Dis (Seoul). 2025 Jan;88(1):69-89.

Table 7. Comparison of patients with VAP who presented with carbapenem-resistant gram-negative bacilli treated with colistin systemic therapy alone versus systemic plus inhaled colistin therapy (adjunctive therapy)

Study	Study design/no. of patients (systemic therapy+inhaled therapy vs. systemic therapy alone)	Pathogens	Outcome measures (systemic plus inhaled therapy vs. systemic therapy alone)		
			Clinical response, %	Mortality, %	Nephrotoxicity, %
Rattanaumpawan et al. (2010)[79]	Randomized controlled trial (51 vs. 49)	*Acinetobacter baumanii* *Pseudomonas aeruginosa* *Klebsiella pneumoniae*	51 vs. 53	39 vs. 45	22 vs. 27
Korbila et al. (2010)[73]	Retrospective cohort study (78 vs. 43)	*A. baumanii* *P. aeruginosa* *K. pneumoniae*	79 vs. 60	40 vs. 44	-
Kofteridis et al. (2010)[74]	Case-control study (43 vs. 43)	*A. baumanii* *P. aeruginosa* *K. pneumoniae*	74 vs. 60	23 vs. 42	19 vs. 19
Naesens et al. (2011)[75]	Retrospective cohort study (9 vs. 5)	*P. aeruginosa*	78 vs. 40	67 vs. 100	11 vs. 60
Kalin et al. (2012)[76]	Retrospective cohort study (29 vs. 15)	*A. baumanii*	14 vs. 40	55 vs. 47	41 vs. 20
Doshi et al. (2013)[77]	Retrospective cohort study (44 vs. 51)	*A. baumanii* *P. aeruginosa* *K. pneumoniae*	100 vs. 100	36 vs. 53	-
Tumbarello et al. (2013)[78]	Case-control study (104 vs. 104)	*A. baumanii* *P. aeruginosa* *K. pneumoniae*	69 vs. 55	43 vs. 46	25 vs. 22
Demirdal et al. (2016)[83]	Matched case-control study (43 vs. 80)	*A. baumanii*	40 vs. 56	53 vs. 48	49 vs. 54
Choe et al. (2019)[81]	Retrospective cohort study (35 vs. 86)	*A. baumanii* *P. aeruginosa* *K. pneumoniae*	49 vs. 42	23 vs. 49	59 vs. 38
Feng et al. (2021)[82]	Retrospective cohort study (181 vs. 326)	*A. baumanii* *P. aeruginosa* *K. pneumoniae*	59 vs. 54	31 vs. 33	-
Bao et al. (2022)[84]	Propensity score-matched case-control study (31 vs. 31)	Multidrug-resistant gram-negative bacteria	68 vs. 32	32 vs. 45	16 vs. 10

VAP: ventilator-associated pneumonia.

Tuberc Respir Dis (Seoul). 2025 Jan;88(1):69-89.

Trials reported on clinicaltrials.gov investigating inhaled antibiotics for VAP.

NCT Number	Country	Title	Status	Enrolment	Drug Intervention
NCT02440828	Spain & Netherlands	Addition of Tobramycin Inhalation in the Treatment of Ventilator-Associated Pneumonia	Complete	80	Inhaled **Tobramycin** in addition to standard IV antibiotics for the **treatment** of VAP in adults
NCT06488794	Tunisia	Inhaled Colistin to Prevent Paediatric Ventilator-associated Pneumonia	Pending	100	Inhaled **Colistin** for the **prevention** of VAP in children
NCT03622450	Egypt	The Effect of Colistin Inhalation on Ventilator-Associated Pneumonia	Complete	40	Inhaled **Colistin** for the treatment of suspected MDR gram negative VAP in adults
NCT03921645	China	Use of Aerosol Combined With Intravenous Antibiotics for the Treatment of Multidrug Resistant GNB Pneumonia	Recruiting	60	Aerosol **Amikacin** combined with IV antibiotics for the **treatment** of MDR gram negative VAP in adults
NCT01025921	Greece	Tracheobronchitis Prevention Trial	Complete	84	Inhaled **Colistin** for the **prevention** of VAP in mechanically ventilated adults
NCT02478710	USA	Aerosolised Antibiotics in the Treatment of Ventilator Associated Pneumonia	Terminated	16	Aerosolised **Tobramycin or Vancomycin** in conjunction with IV antibiotics for the **treatment** of VAP in adults
NCT02515448	France	A Pharmacokinetic-pharmacodynamic Dose Comparison Study of 8 mg/kg of Inhaled or Parenteral Gentamicin in 12 Mechanically Ventilated Critically Ill Patients Treated for Ventilator-associated Pneumonia	Complete	12	Inhaled **Gentamicin** for the **treatment** of VAP in adults
NCT03149640	France	Study Comparing Inhaled Amikacin Versus Placebo to Prevent Ventilator-Associated Pneumonia	Complete	850	Inhaled **Amikacin** for the **prevention** of VAP in adults
NCT03749226	Spain	Nebulised Aztreonam for Prevention of Gram-Negative Ventilator-associated Pneumonia	Terminated	9	Nebulised **Aztreonam Lysine** for the **prevention** of gram-negative VAP in adults
NCT02683603	Tunisia	Effect of Aerosolised Colistin in Ventilator Associated Pneumonia	Complete	133	Aerosolised **Colistin** for the **treatment** of VAP in adults
NCT04208945	Greece	Nebulised Colistin for Gram Negative VAP Prevention.	Recruiting	152	Nebulised **Colistin** for the **prevention** of gram-negative VAP in adults
NCT01878643	USA	Reduction of Bacterial Resistance With Inhaled Antibiotics in the Intensive Care Unit	Complete	47	Inhaled **Vancomycin** or **Gentamicin** for the **prevention** of VAP in adults
NCT00645723	Spain	Intravenous Colistin Versus Intravenous Colistin Plus Nebulised Colistin in VAP Due MDR Acinetobacter Baumannii	Recruiting	67	Inhaled **Colistin** combined with IV Colistin for the **treatment** of Multi-resistant Acinetobacter Baumanii VAP in adults

Other considerations

Clinical resolution

- **Definition of clinical resolution in RCTs**
- Decrease in modified CPIS < 6, significant lung CT reaeration, and LRT specimens either sterile or with nonsignificant concentrations
- CPIS
- Complete resolution of all signs and symptoms of pneumonia, and improvement or lack of progression of all abnormalities on CXR

Double-Blind Study of Endotracheal Tobramycin in the Treatment of Gram-Negative Bacterial Pneumonia

- Suspected GNR pneumonia with endotracheal or tracheostomy tube
- Tobramycin vs saline through small-bore plastic cannula

- Symptomatic improvement: 53% vs 45%
- Pathogen elimination: 56% vs 25% ($P < 0.005$)

Antimicrob Agents Chemother. 1990 Feb;34(2):269-72.

Nebulized Ceftazidime and Amikacin in Ventilator-associated Pneumonia Caused by *Pseudomonas aeruginosa*

- Cure of VAP on day 9: 14 (70%) vs. 11 (55%) (P = 0.33)
- **Rapid initial eradication in nebulizer group, but similar final positivity (re-appearance)**

TABLE 3. MICROBIOLOGICAL RESPONSE TO TREATMENT AND ANTIBIOTIC SUSCEPTIBILITY OF *PSEUDOMONAS AERUGINOSA* IN EACH GROUP OF PATIENTS

	Baseline	Day 3	Day 5	Day 7	Day 9
Aerosol Group					
BAL, n	20	17	16	12	12
BAL *P. aeruginosa* + *P. aeruginosa* susceptibility, n	20	1	0	2	5*
CAZ–AMK					
S–S	16	1		2	5
S–I†	1				
I‡–S	2				
I§–I†	1				
Intravenous Group					
BAL, n	20	16	15	10	11
BAL *P. aeruginosa* + *P. aeruginosa* susceptibility, n	20	8	8	5	6
CAZ–AMK					
S–S	17	6	5	1	3
S–I	3	2		1	
I–S			1	2	1
R–S			2	1	1
R–I					1

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

Microbiological eradication

- True eradication of bacteria?
- (False) Negative culture because of antibiotics in specimen?

Fungal pneumonia

Guidelines

- 2016 IDSA
- We also **recommend adjunctive inhaled AmB in the setting of TBA** associated with anastomotic endobronchial ischemia or ischemic reperfusion injury due to airway ischemia associated with **lung transplant** (strong recommendation; moderate-quality evidence).

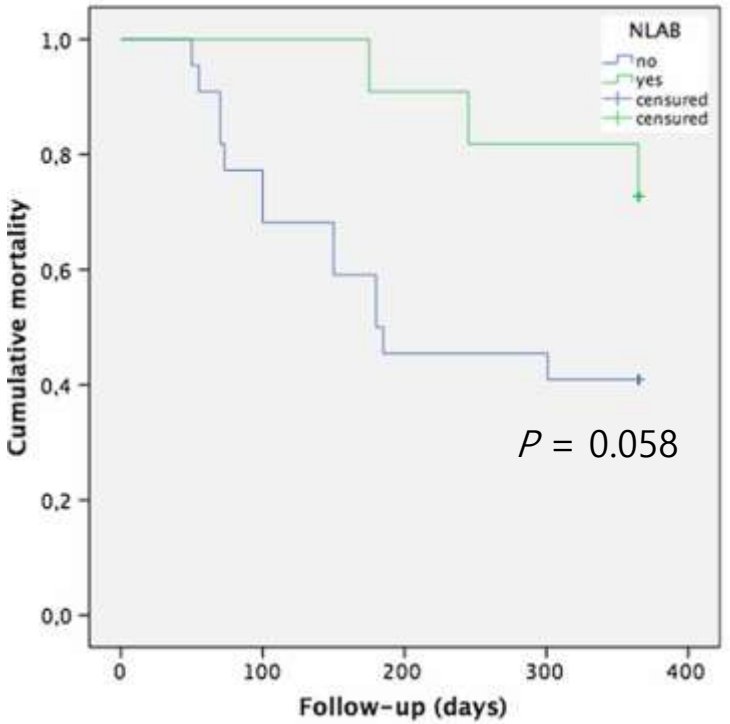
- 2019 American Society of Transplantation
- **Inhaled AmB** (in conjunction with systemic antifungal therapy) **may be used in the setting of tracheobronchial aspergillosis** associated with anastomotic endobronchial ischemia, or ischemic reperfusion injury due to airway ischemia associated with **lung transplant** (Weak; low)

Clin Infect Dis. 2016 Aug 15;63(4):e1-e60.
Clin Transplant. 2019 Sep;33(9):e13544.

Aerosolized Lipid Amphotericin B for Complementary Therapy and/or Secondary Prophylaxis in Patients with Invasive Pulmonary Aspergillosis: A Single-Center Experience

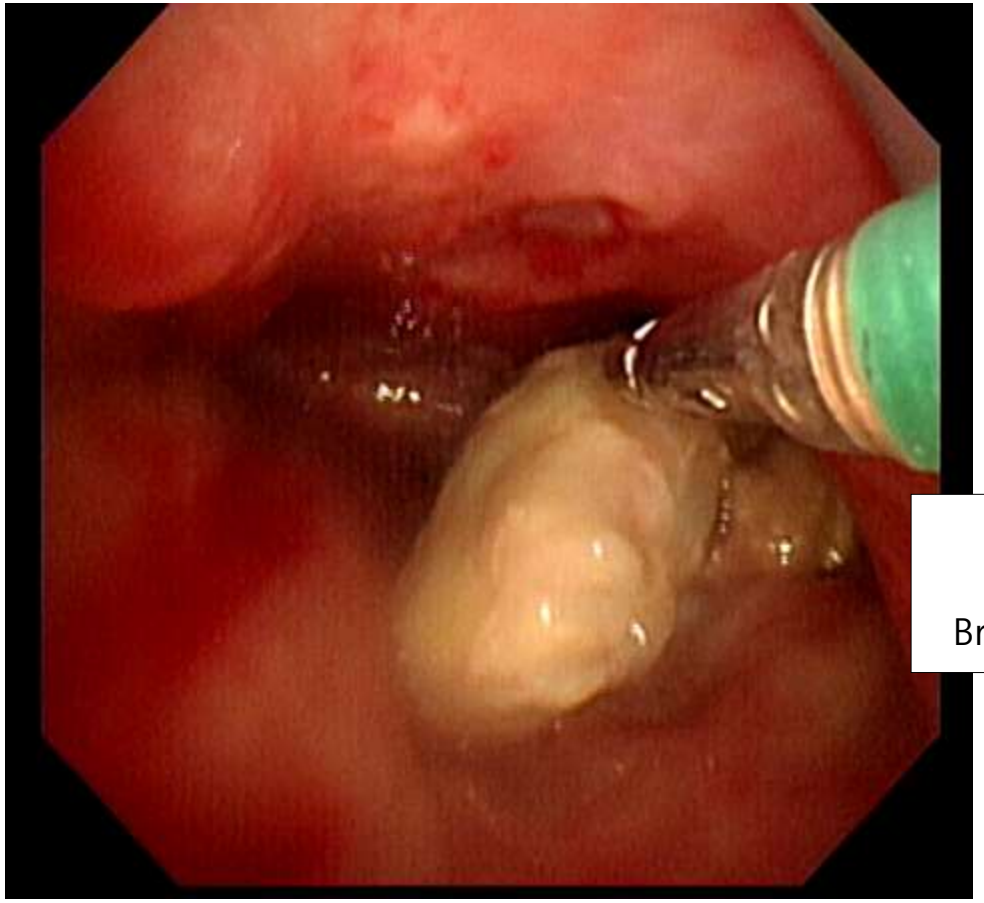
- Retrospective study
- EORTC proven or probable IPA (hematologic malignancy, solid cancer, COPD)
- Group A: systemic therapy + aerosolized amphotericin
- Group B: systemic therapy alone

	Group A (n = 11)	Group B (n = 22)	p
Primary end-point			
Clinical response[a] (3 months)	10 (91%)	14 (64%)	0.21
Secondary end-point			
Global mortality (3 months)	2 (18.2%)	7 (31.8%)	0.16
Clinical response[a] (12 months)	8 (73%)	8 (36%)	0.07
Global mortality (12 months)	3 (27%)	13 (59%)	0.14
Related mortality (12 months)	0	8 (36%)	0.03
Uncontrolled baseline condition	5 (45%)	12 (54%)	0.72
Airway colonization (other mold)	7 (64%)	2 (9%)	0.002

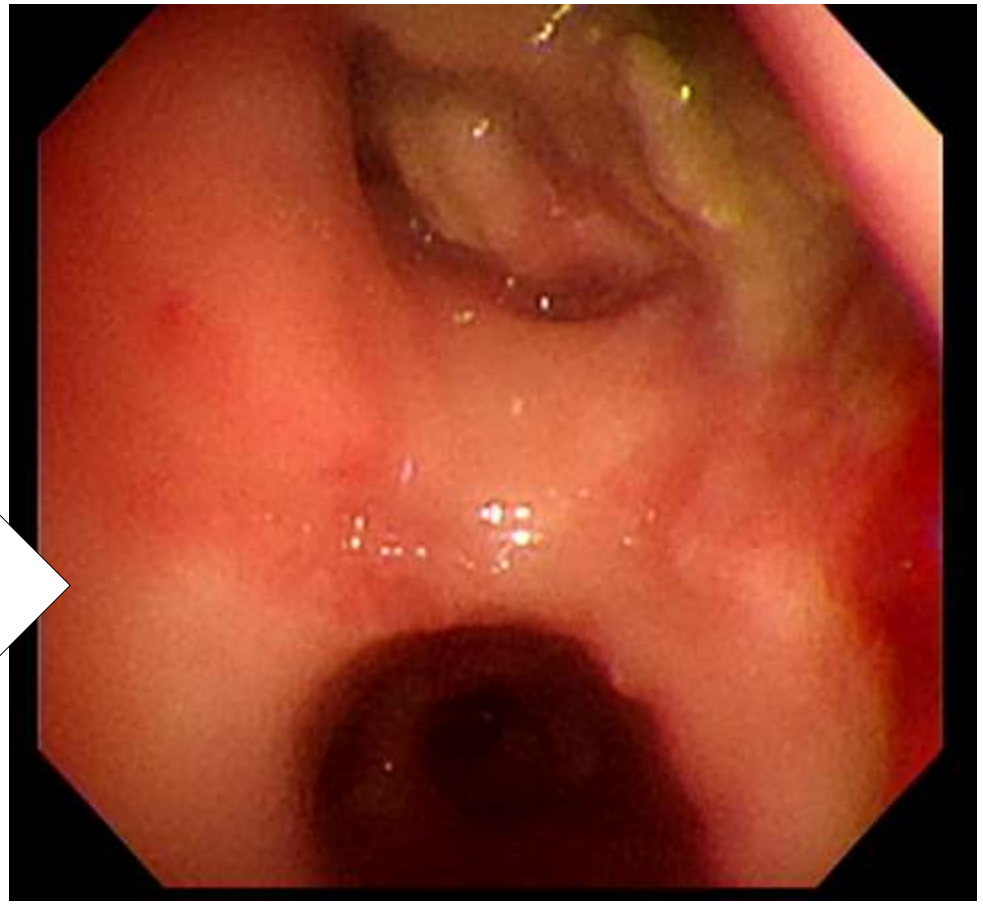


Clin Infect Dis. 2016 Aug 15;63(4):e1-e60.

F/14, Leukemia



Voriconazole IV
AmB-L nebulization
Bronchoscopic debriment



THANK YOU