Nebulizers and techniques of administration

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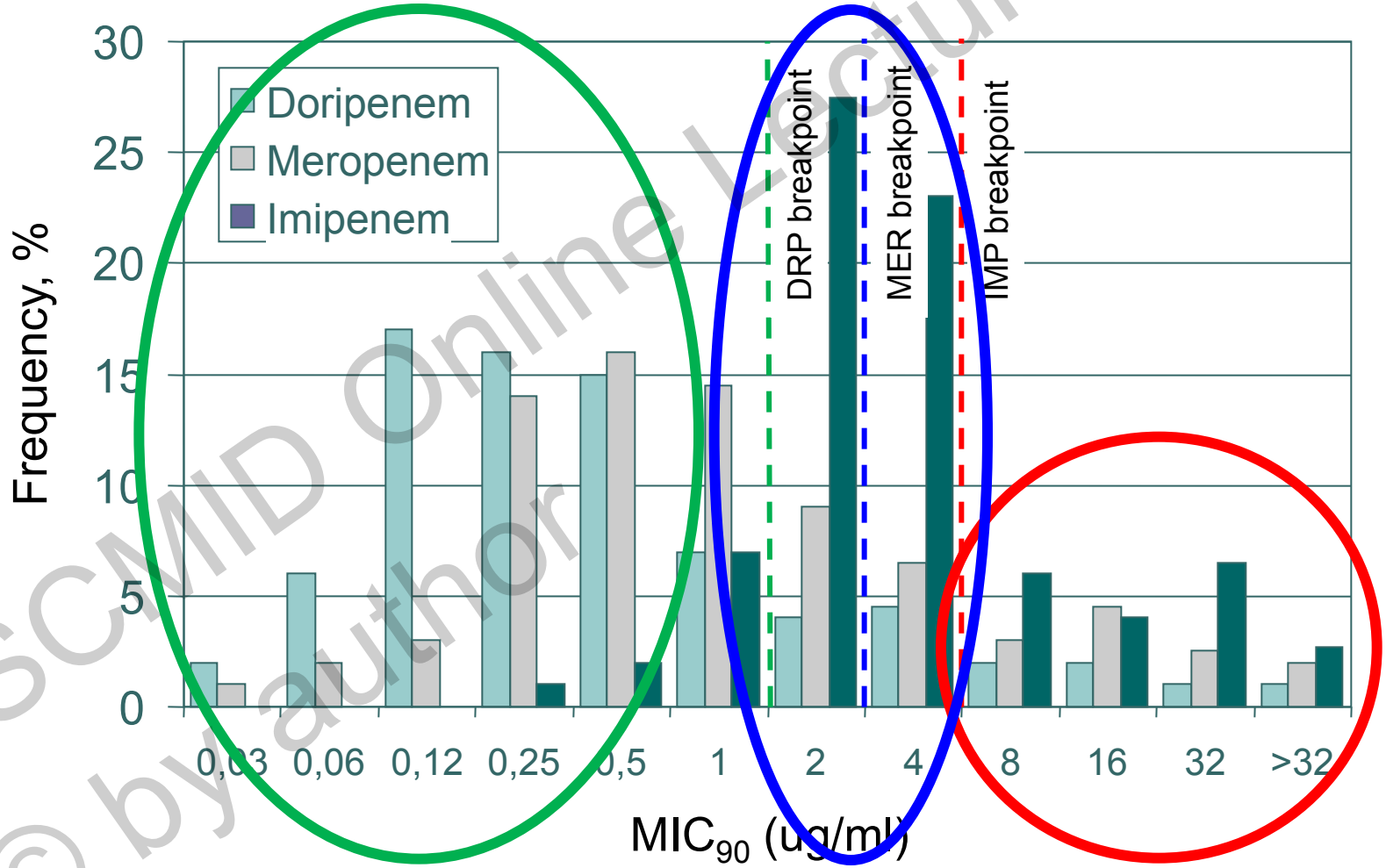
Competing interests:

Dr. Chastre has received speaker honoraria and research funding by Nektar-Bayer, the manufacturer of the PDDS device.

Aerosolized Antibiotics for HAP/VAP. *The Rationale*

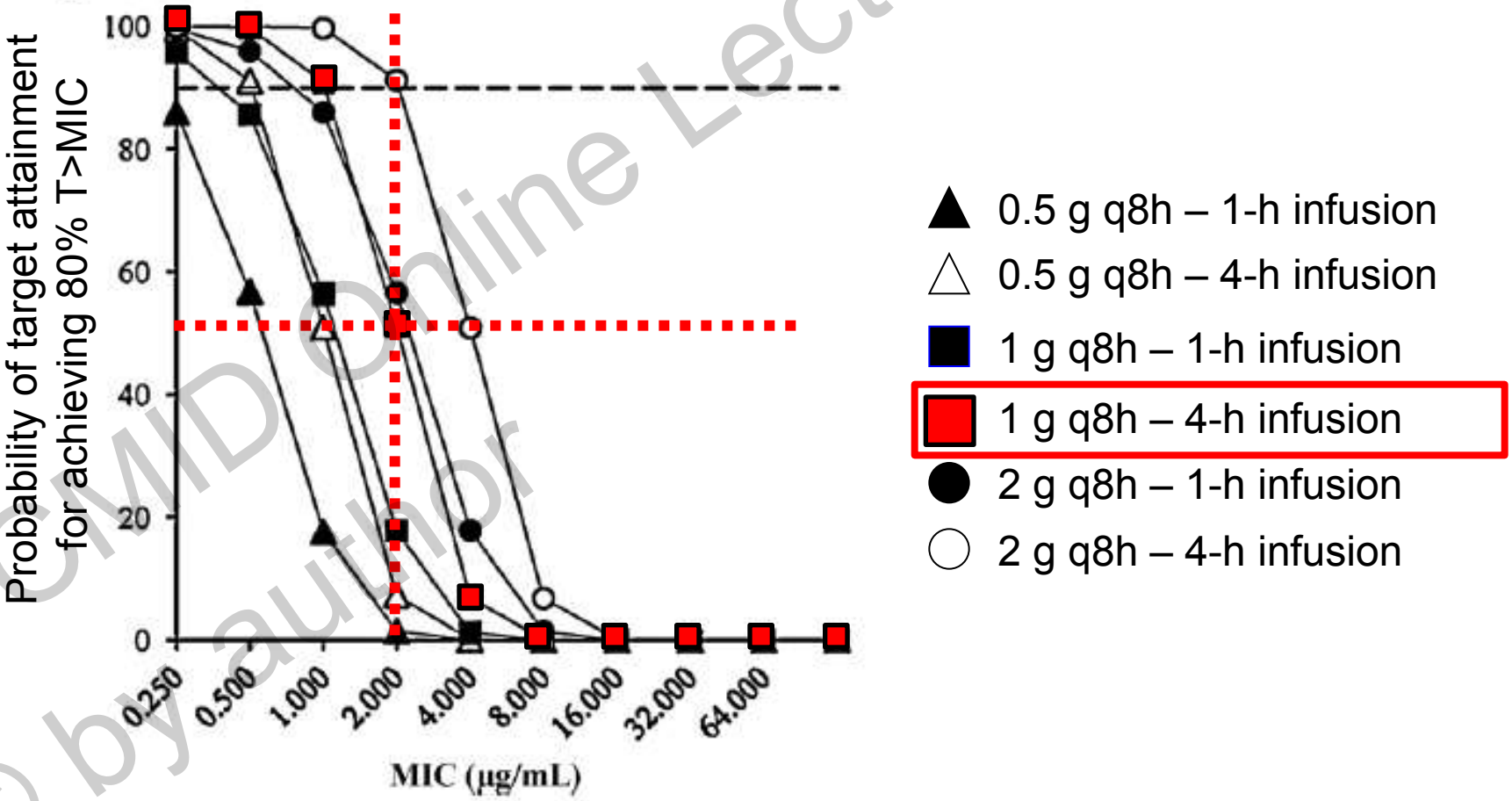
- **Directly delivering antibiotics** to the lung via **aerosolization,** as an adjunctive therapy to IV administration, may allow **increased drug concentrations at the infected site**.
- **By limiting systemic exposure**, it could also allow the administration of ABs characterized by a **high systemic toxicity**, such as AG or polymixins.

MIC Distribution of Doripenem, Meropenem and Imipenem in 873 *P. aeruginosa* Isolates in US



Pharmacodynamics of doripenem in critically ill patients with VAP caused by Gram-negative bacilli

Jaruratanasirikul S, et al. Int J Antimicrob Agents 2012;40:434-9



Doripenem Intrapulmonary Pharmacokinetics in Healthy Adult Subjects

Justo J, et al. ICAAC 2011 Abstract A1-1748

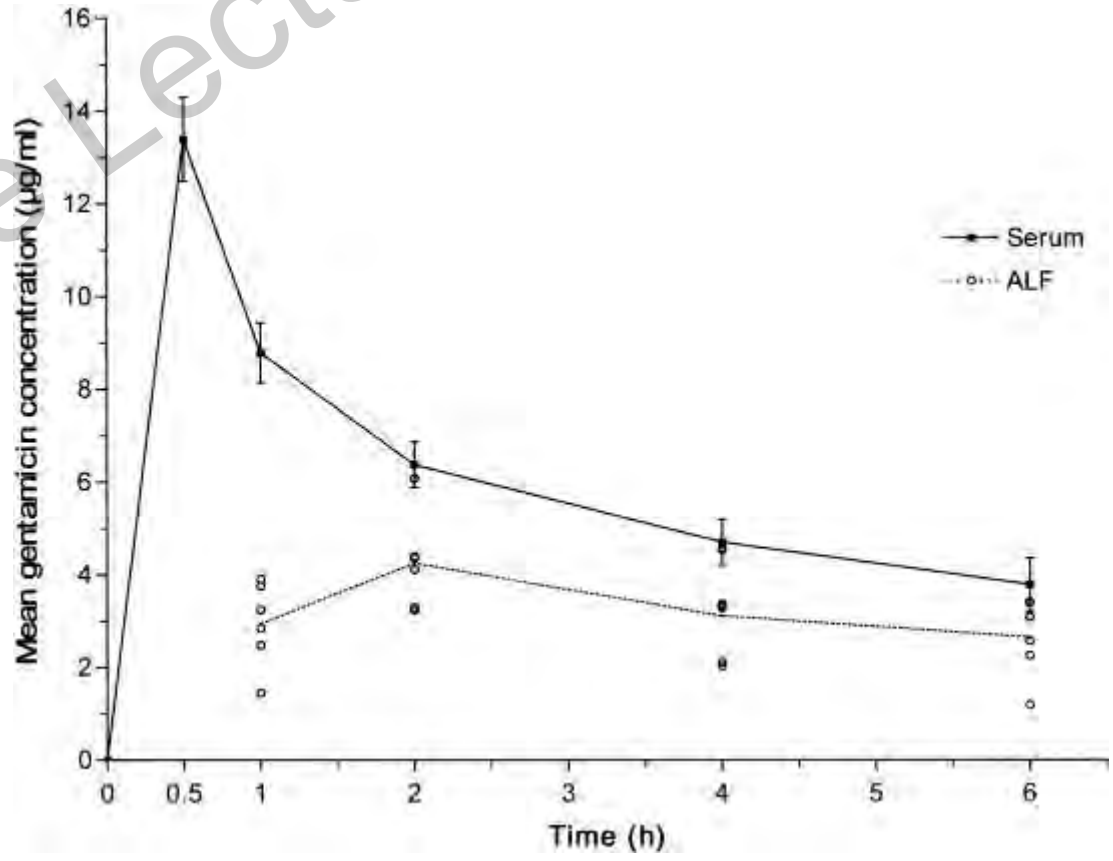
Doripenem 1000 mg IV as a 4-hr extended infusion every 8 hrs (n=20)

Sampling Time (n=5 per arm)	Plasma Concentration (mg/L)	ELF Concentration (mg/L)	Ratio ELF:Plasma
3 hours	13.85 ± 1.26	3.80 ± 0.66	0.28 ± 0.05
4.5 hours	10.92 ± 1.81	3.50 ± 0.78	0.32 ± 0.06
6 hours	3.57 ± 0.31	1.98 ± 0.54	0.56 ± 0.17
8 hours	1.06 ± 0.26	0.46 ± 0.38	0.49 ± 0.43

Penetration of Gentamicin into the Alveolar Lining Fluid of Patients with VAP

Panidis et al. Chest 2005

- **24 patients with VAP** who received a once-daily, 240-mg dose of gentamicin
- **Bronchoscopy with BAL** to determine gentamicin concentration in ALF at 1, 2, 4, and 6 h after the start of antibiotic infusion
- **Average peak antibiotic concentration in ALF** was only **4.24 ug/ml**, giving a **penetration ratio of 0.32**

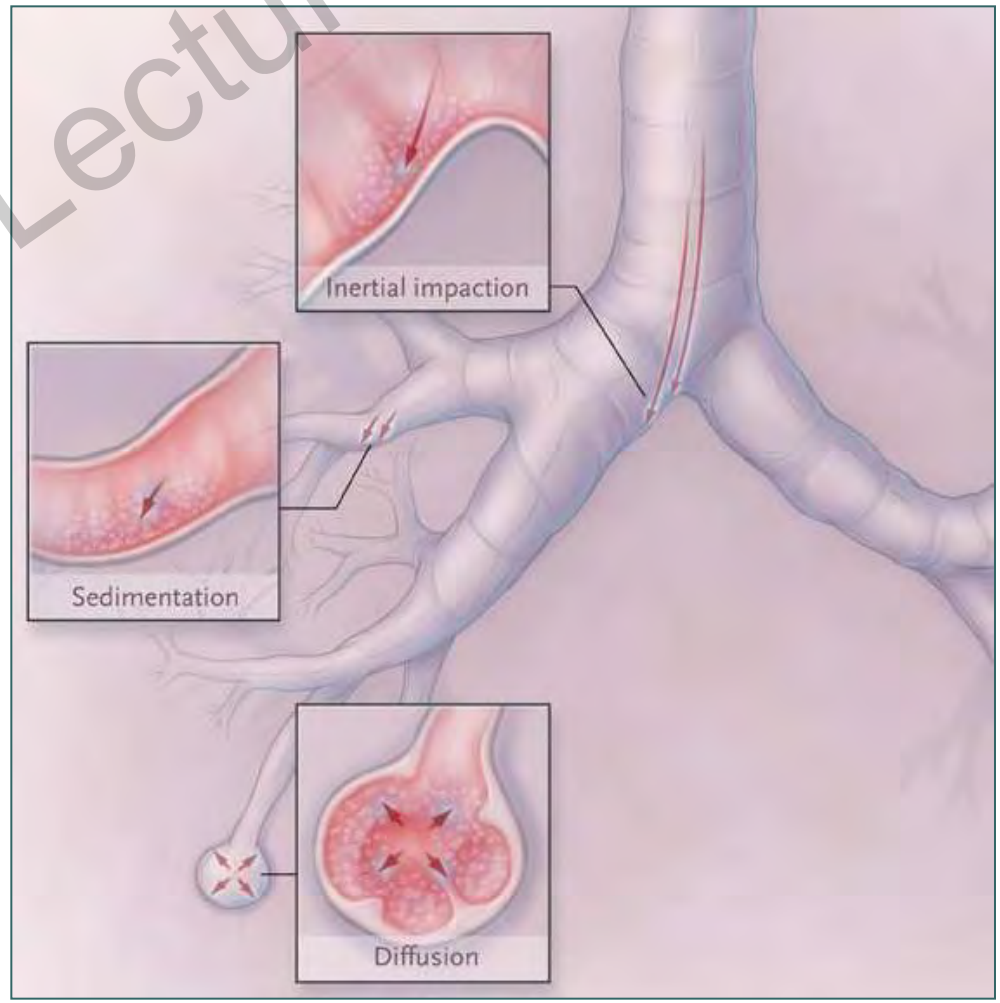


Depositing Drugs in the Lung

Coates A. N Engl J Med 2008;358:304-305

The deposition of an inhaled aerosol occurs through 3 mechanisms:

- by inertial ***impaction***, in which a droplet fails to turn a corner and impacts the wall of the airway.
- by ***sedimentation***, in which the droplets "rain out" under the influence of gravity.
- by ***diffusion*** caused by Brownian motion, which results in collisions of the droplets with the airway wall

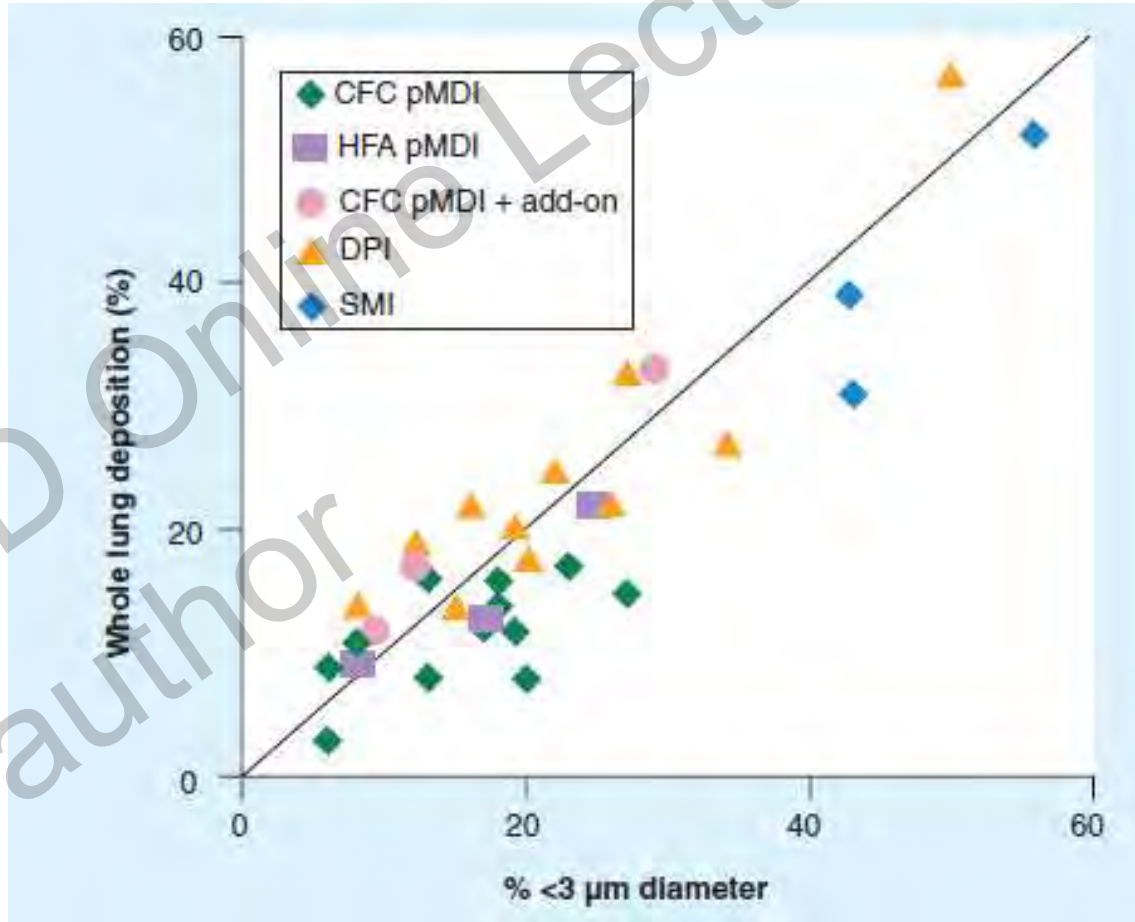


Factors influencing nebulization efficiency

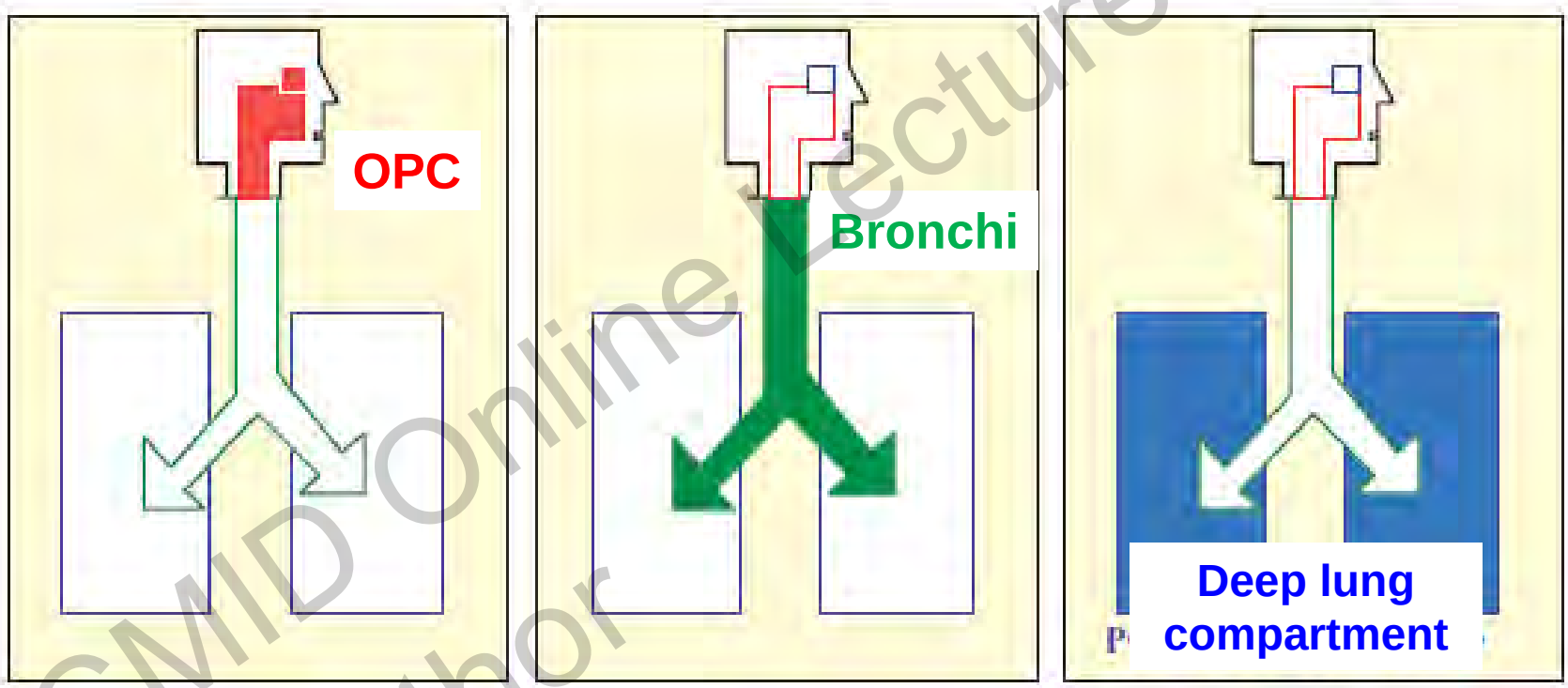
- **Size of the particles**
- Aerosol generator
- Ventilator circuit
- Ventilator settings
- Type and severity of lung lesions

Correlation between lung deposition as determined by gamma scintigraphy and mean percentage dose <3 µm

Newman SP, et al. J Aerosol Med Pulm Drug Deliv 2008;21:77-84



Particles deposition in the airways is directly related to their size



Size >5 µm

Size 2-5 µm

Size 1-3 µm

Size <1 µm: droplets exhaled with expiratory gases

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- **Aerosol generator**
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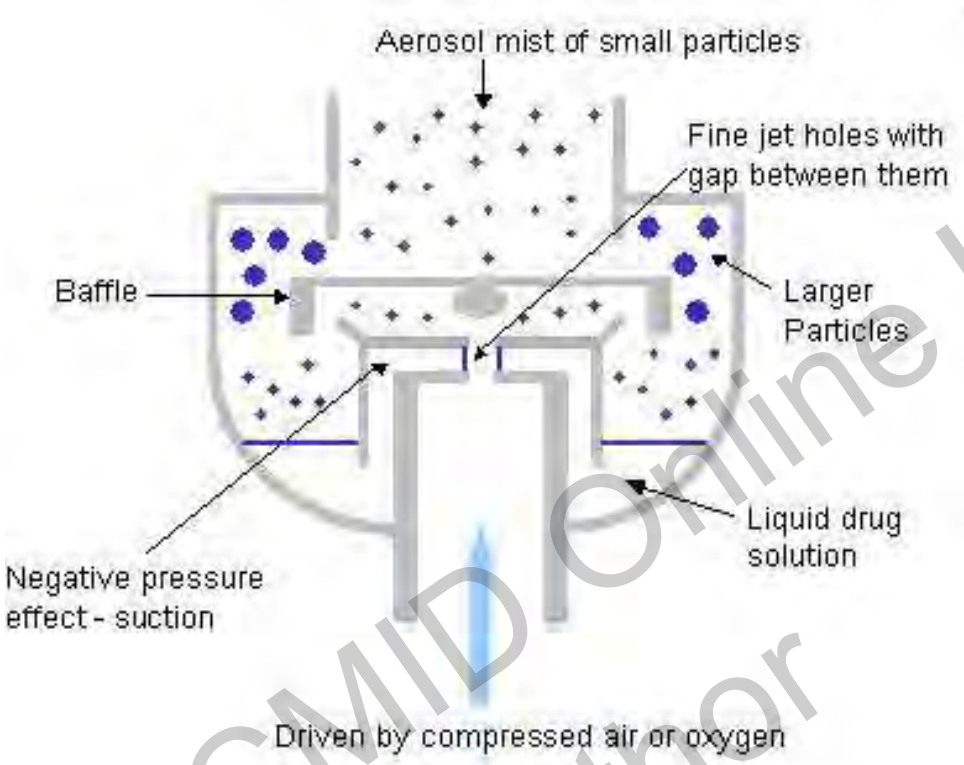
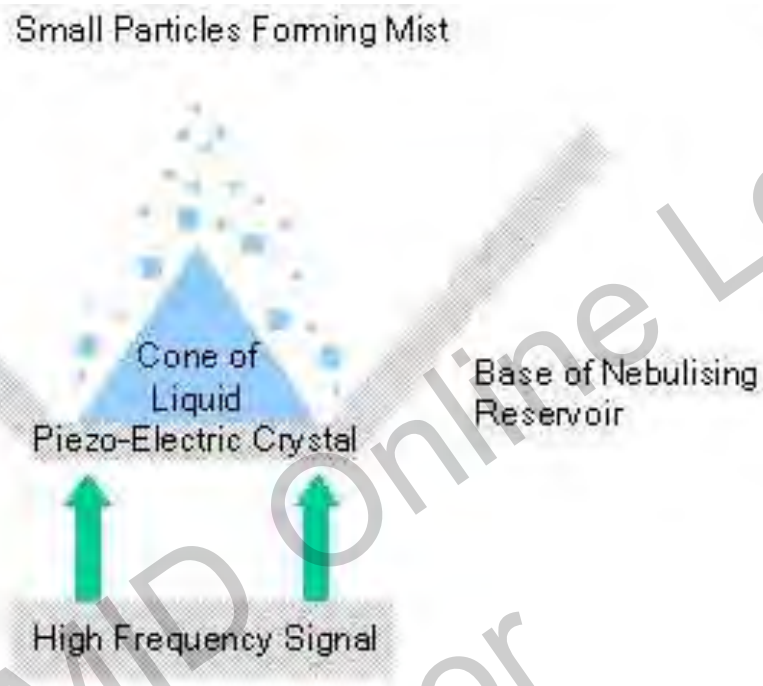
Jet nebulizers



- Aerosol generated by gas either continuously (wall system), or during inspiration (gas flow from the ventilator)
- Although particles size are usually small, it can vary from one brand to another

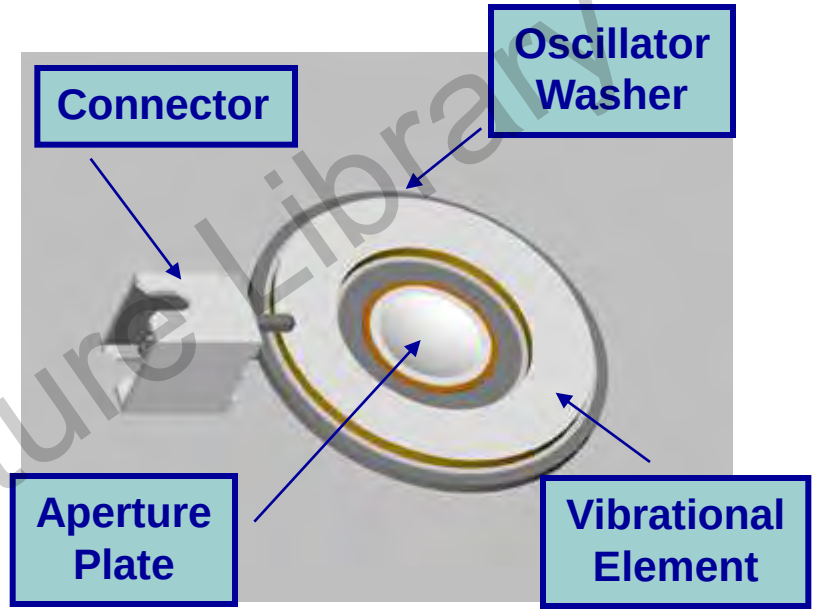
Ultrasonic nebulizers

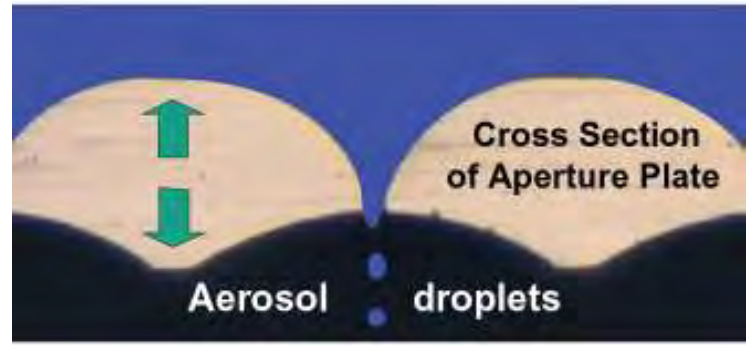


Vibrating-mesh nebulizers

Potentials advantages:

- Aerosol generated by the vibration of an aperture plate
- **Droplet size** is small and very well calibrated
- Antibiotic solution is **not heated**
- the aerosol generation can be **synchronized with inspiration** minimizing aerosol waste during exhalation.





Factors influencing nebulization efficiency

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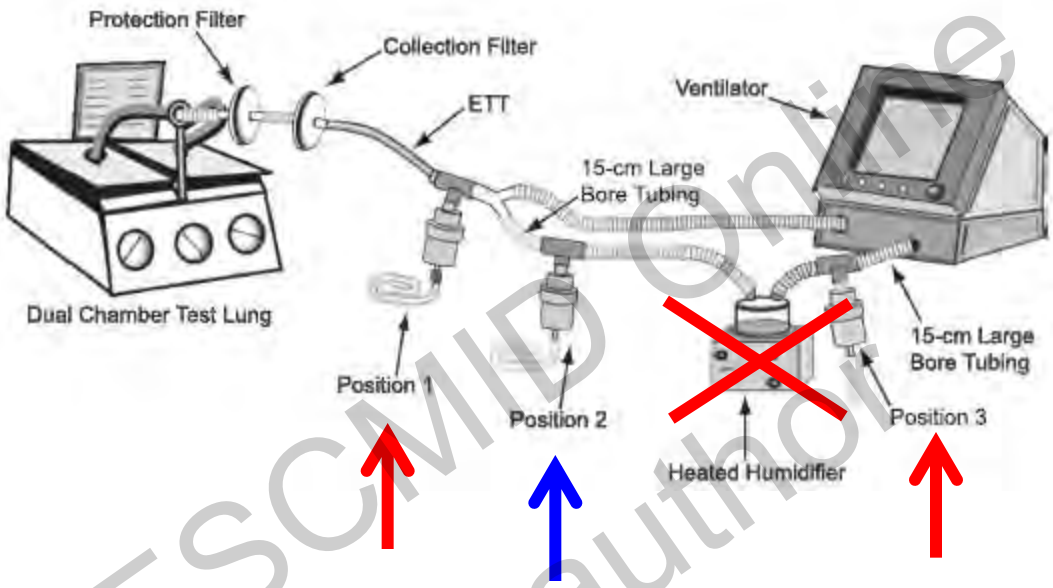
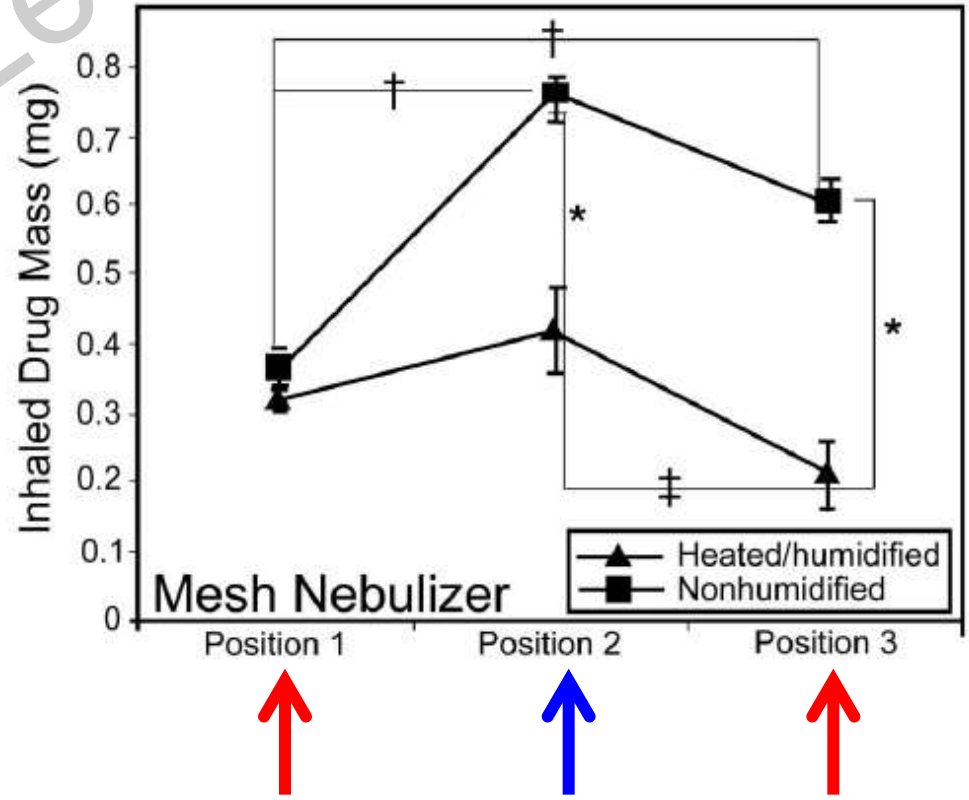
- **Ventilator circuit**
- Ventilator settings
- Type and severity of lung lesions

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

Ari A, et al. Respir Care. 2010 Jul;55(7):837-44





Device position in the circuit inspiratory limb

By courtesy of Prof. JJ Rouby

Factors influencing nebulization efficiency

- Size of the particles
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- Ventilator circuit
- **Ventilator settings**
- Type and severity of lung lesions

Optimizing Aerosol Delivery During Mechanical Ventilation: *Respiratory Settings*

- **Specific ventilator settings** should be used **to decrease turbulences and proximal deposition of aerosol droplets**:
  - Volume-controlled mode,
  - Low (6L/min) minute ventilation,
  - Inspiratory flow kept below 40L/min,
  - Inversed inspiratory to expiratory ratio of 50%
  - Low (<12/min) respiratory frequency,
  - High tidal volume (500 ml or more)
  - Humidification system discontinued.
- Applying these recommendations provides the possibility of **delivering ~25%-40% of the initial dose**.

Use ultrasonic or vibrating plate nebulizer, producing aerosols whose particles have a mass median aerodynamic diameter < 5 µm.

Remove heat and moisture exchanger and conventional humidifier and stop humidification during the period of nebulization.

Place the nebulizer on the inspiratory limb, 20 cm from the Y piece.

Determine in vitro the extrapulmonary deposition in the ventilator circuits using ventilator settings applied during the nebulization period:

The amount of antibiotic deposited into inspiratory and expiratory circuits should be measured after lavage of each part of the circuit with a known volume of water.

Determine the daily dose to be placed in the nebulizer chamber

If the aminoglycoside is administered exclusively by nebulization, the dose should be calculated as the intravenous dose x 1/extrapulmonary deposition (%). If the aminoglycoside is concomitantly intravenously administered, then the determination of the appropriate dosage is difficult. Through plasma concentrations should be daily monitored in order to avoid systemic accumulation.

If colistin is administered exclusively by nebulization, the dose should range between 6 and 15 millions International Units / day. If it is also intravenously administered, then the determination of the appropriate dosage is difficult. Through plasma concentrations should be daily monitored in order to avoid systemic accumulation.

Determine the interval between each nebulization:

For aminoglycosides, a single daily nebulization.
For colistin, 3 daily nebulizations (every 8 h).

Use a controlled mode of mechanical ventilation with the following ventilator settings:

- *Constant inspiratory flow*
- *Tidal volume of 7- 9 ml/kg*
- *Respiratory frequency 12 bpm*
- *Inspiratory to Expiratory ratio 1/1*
- *Inspiratory plateau pressure 20 %*
- *Remove any humidification system*
- *Optimize alveolar recruitment*

Avoid assisted modes of mechanical ventilation where the patient triggers flow during spontaneous inspiratory efforts

Avoid discoordination of the patient with the ventilator

If necessary, provide sedation with a continuous infusion of propofol during the nebulization period

Rouby JJ, et al. Anesthesiology 2012;117:1364-80

Factors influencing nebulization efficiency

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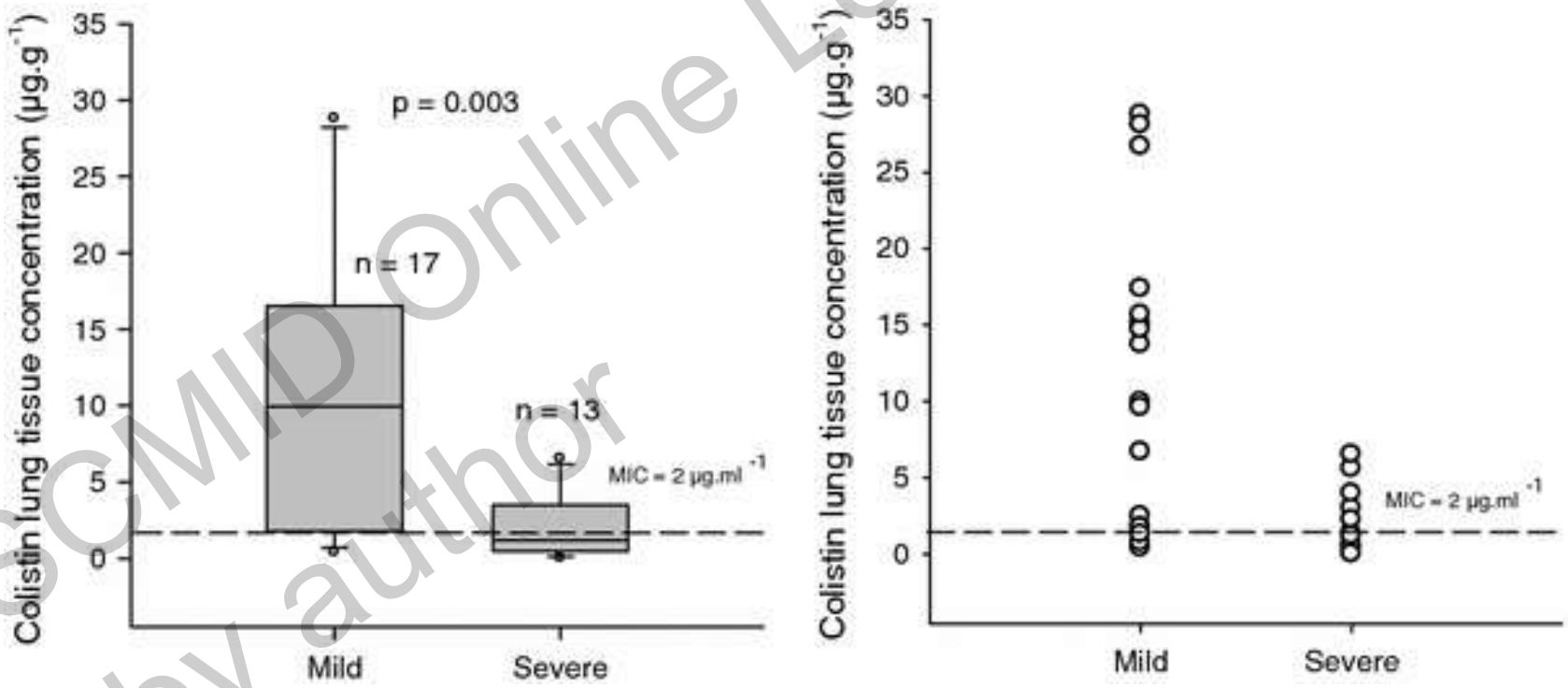
- Ventilator circuit
- Ventilator settings
- **Type and severity of lung lesions**

Nebulized and intravenous colistin in experimental pneumonia caused by *Pseudomonas aeruginosa*

Lu Q. et al. Intensive Care Med 2010;36:1147-55



Choice of antibiotics

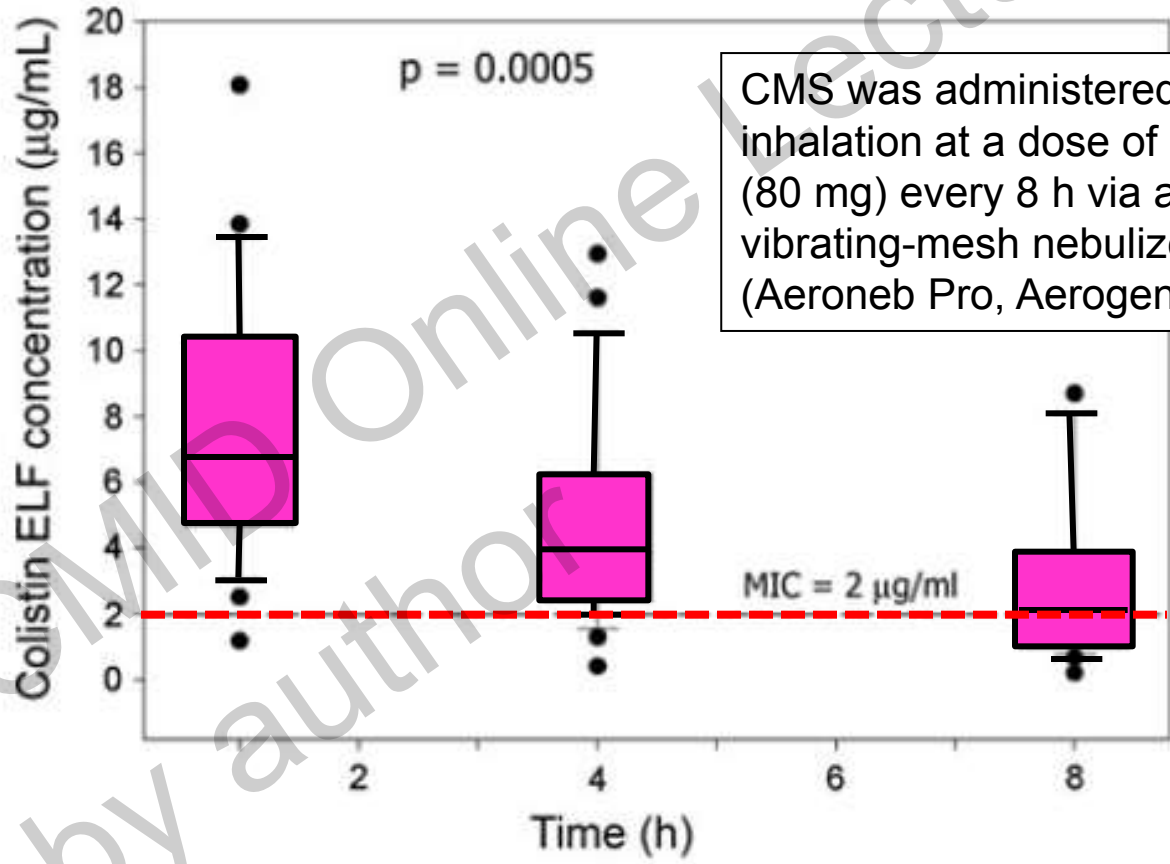
- **Several antibiotics** have been studied as aerosolized agents:
  - **colistin,**
  - **aminoglycosides**,
  - betalactams,
  - monobactams,
  - carbapenems,
  - vancomycin,
  - and fosfomycin.

Colistin (polymyxin E)

- **Colistimethate** (CMS) is a chemically derived inactive **prodrug of colistin**.
- **Colistin at high concentrations** can cause airway and alveolar damage.
- **Dose differs by country**. In the US, the dose represents the active moiety (CBA), not the prodrug. Therefore, **150mg in the US is equivalent to 390–400mg in the EU**.
- **Pharmacokinetic evaluation is problematic** because samples can continue to convert to the active form after recovery, thereby preventing elucidation of active drug levels in vivo.

PKs of inhaled colistimethate sodium (CMS) in ventilated ICU patients

Athenassa ZE, et al. Intensive Care Med 2012;38:1778-86



CMS was administered by inhalation at a dose of 1 MU (80 mg) every 8 h via a vibrating-mesh nebulizer (Aeroneb Pro, Aerogen)

EUCAST breakpoints for *A. baumannii* and *K. pneumoniae*

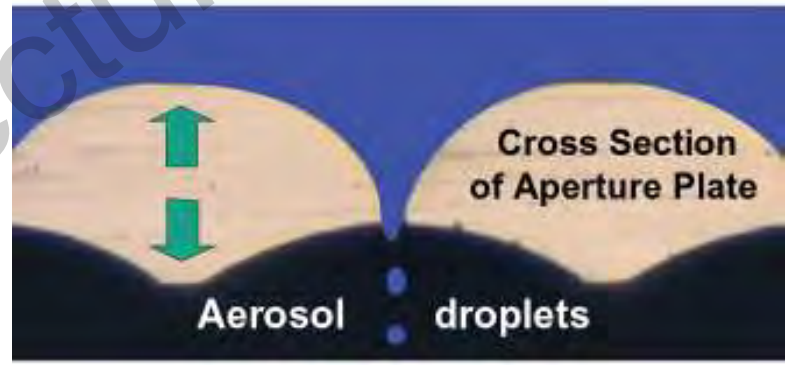
Aminoglycosides

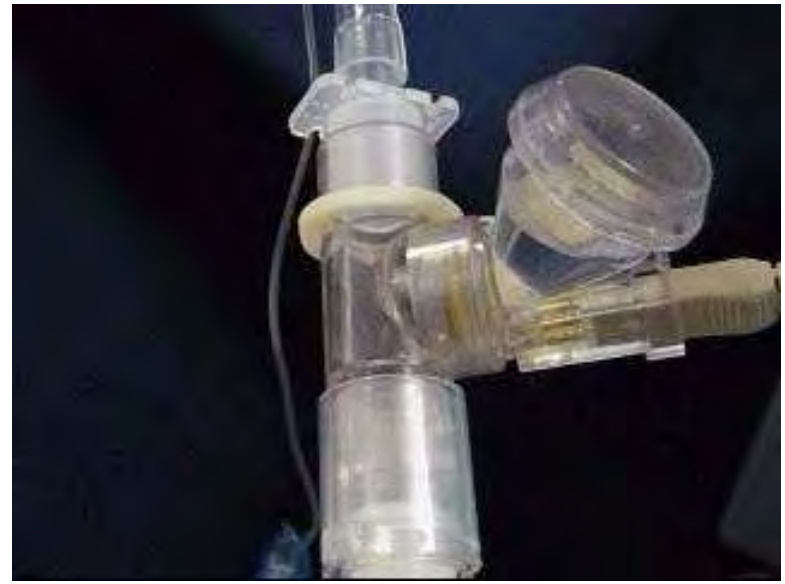
- They are very well suited for aerosolized use because of their **concentration-dependent bactericidal action:**
  - aerosolized delivery typically yields **high endobronchial peak levels** but **short half-lives**.
- The **main drawback** to their use is **sputum antagonism**, which requires **a dose up to 25 times the MIC** to achieve bactericidal concentrations.

Optimizing Aerosol Delivery During MV: The Vibrating Plate Aerosol (Nektar-Aerogen®)

Potential advantages:

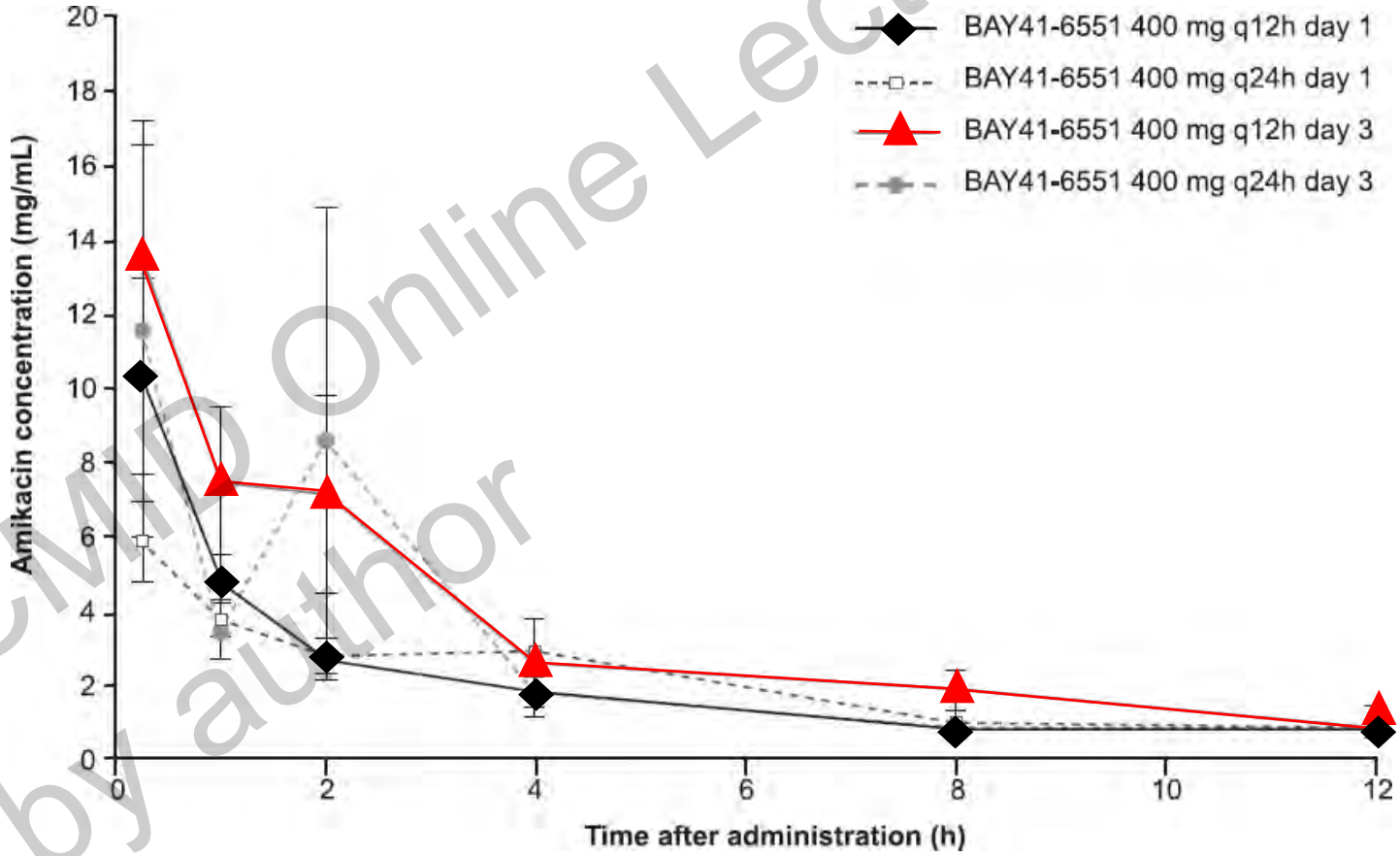
- The aerosol is generated by a **ceramic vibrating element** and a domed aperture plate through which the solution is micropumped;
- the antibiotic solution is **not heated**;
- the aerosol generation **can be synchronized with inspiration** minimizing aerosol waste during exhalation.





BAY41-6551 achieves bactericidal tracheal aspirate amikacin concentrations in ventilated patients with GNB pneumonia

Niederman MS, et al. Intensive Care Med. 2012;38(2):263-71



Target Cmax of 6,400 ug/mL

Proportion of patients in each arm who achieve on Day 1:

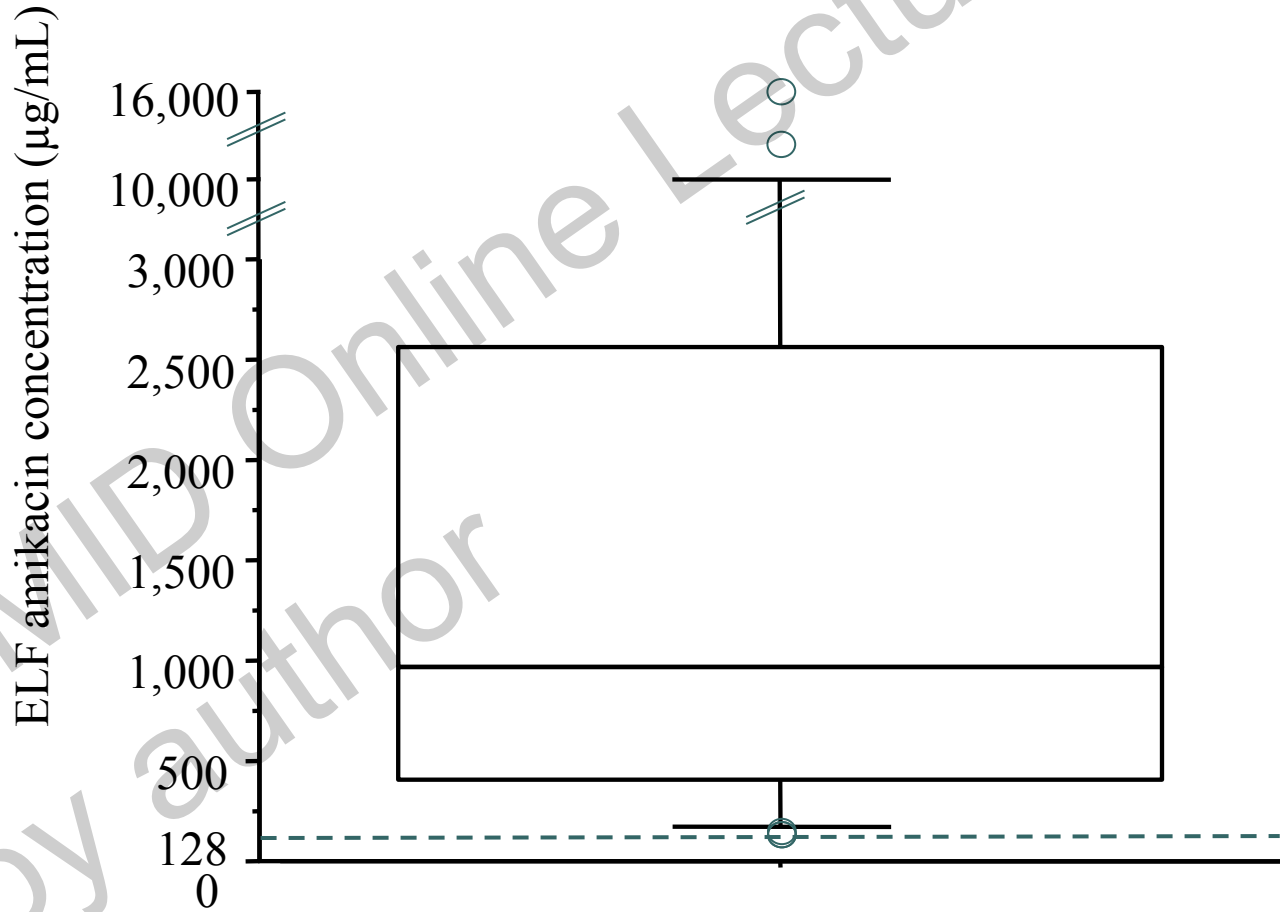
Cmax (tracheal aspirate) ≥ 25x the reference MIC (256)
for hospital-acquired organisms, i.e., 6,400 ug/mL

	400mg Q12		400mg QD	
	Mean Cmax	% of Total ≥6400 ug/ml	Mean Cmax	% of Total ≥6400 ug/ml
Day 1	11,903 ug/ml	70% (14/20)	6,083 ug/ml	39% (9/23)
Day 3: Steady State	16,212 ug/ml	74% (14/19)	6,893 ug/ml	40% (8/20)

Lowest concentration was 1,100ug/mL = 4X reference MIC AND
34X Amikacin breakpoint MIC of 32

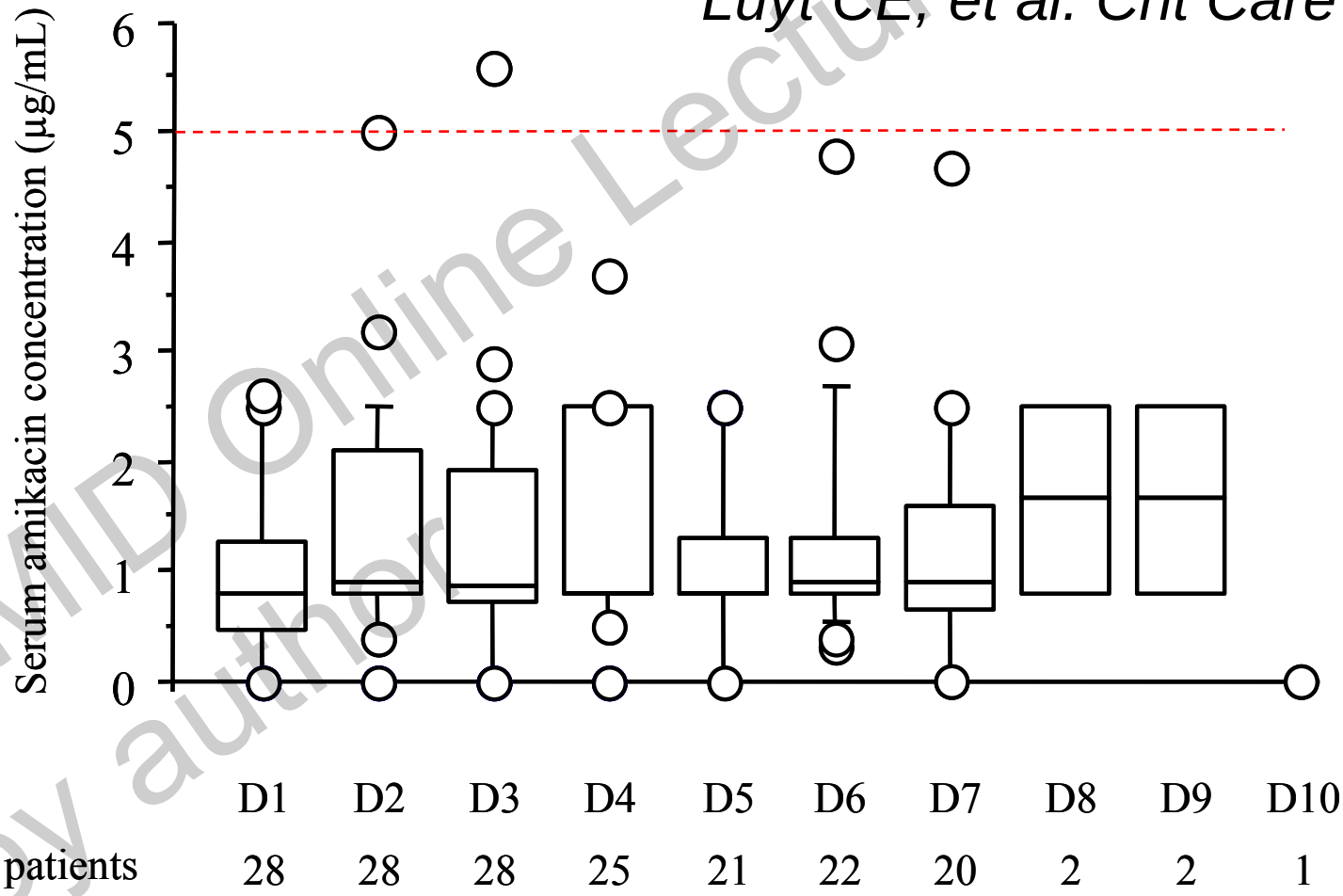
ELF Amikacin Concentrations in 28 Patients with GNB VAP Having Received Nebulized amikacin (400 mg bid) for 7–14 days

Luyt CE, et al. Crit Care 2009



Serum Amikacin Concentrations in 28 Patients with GNB VAP Having Received Nebulized amikacin (400 mg bid) for 7–14 days

Luyt CE, et al. Crit Care 2009



Betalactams

- **Efficacy** requires **frequent (every 3h) administration** because the bactericidal activity of betalactams depends on time above MIC and because of rapid airway clearance, **which is impractical** in most patients.
- **Carbapenems, like penicillins**, can cause **allergies.**

Trial record **1 of 2** for: Drusano

Previous Study | Return to List | Next Study ▸

Clinical Trials to Reduce the Risk of Antimicrobial Resistance

This study is currently recruiting participants.

Verified March 2014 by University of Florida

Sponsor:
University of Florida

ClinicalTrials.gov Identifier:
NCT01570192

First received: March 22, 2012
Last updated: March 7, 2014
Last verified: March 2014