National Taiwan University
School of Pharmacy

機械通氣重症繼續教育課程

Inhalation Therapy for Critically Ill Patients

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Outline

- Spontaneous Breathing vs. Mechanical Ventilation
  - Differences in delivery efficiency
- Inhaled Drug Dosage Considerations
  - Determining MDI Doses During Ventilation
  - Inhaled Antibiotics in Ventilated Patients
    - Formulation, delivery methods, and pharmacokinetics
- Placement of Aerosol Devices in the Ventilator Circuit
  - Impact on drug delivery and system performance
- Synchronization with Ventilation
  - Timing of actuation to optimize lung deposition

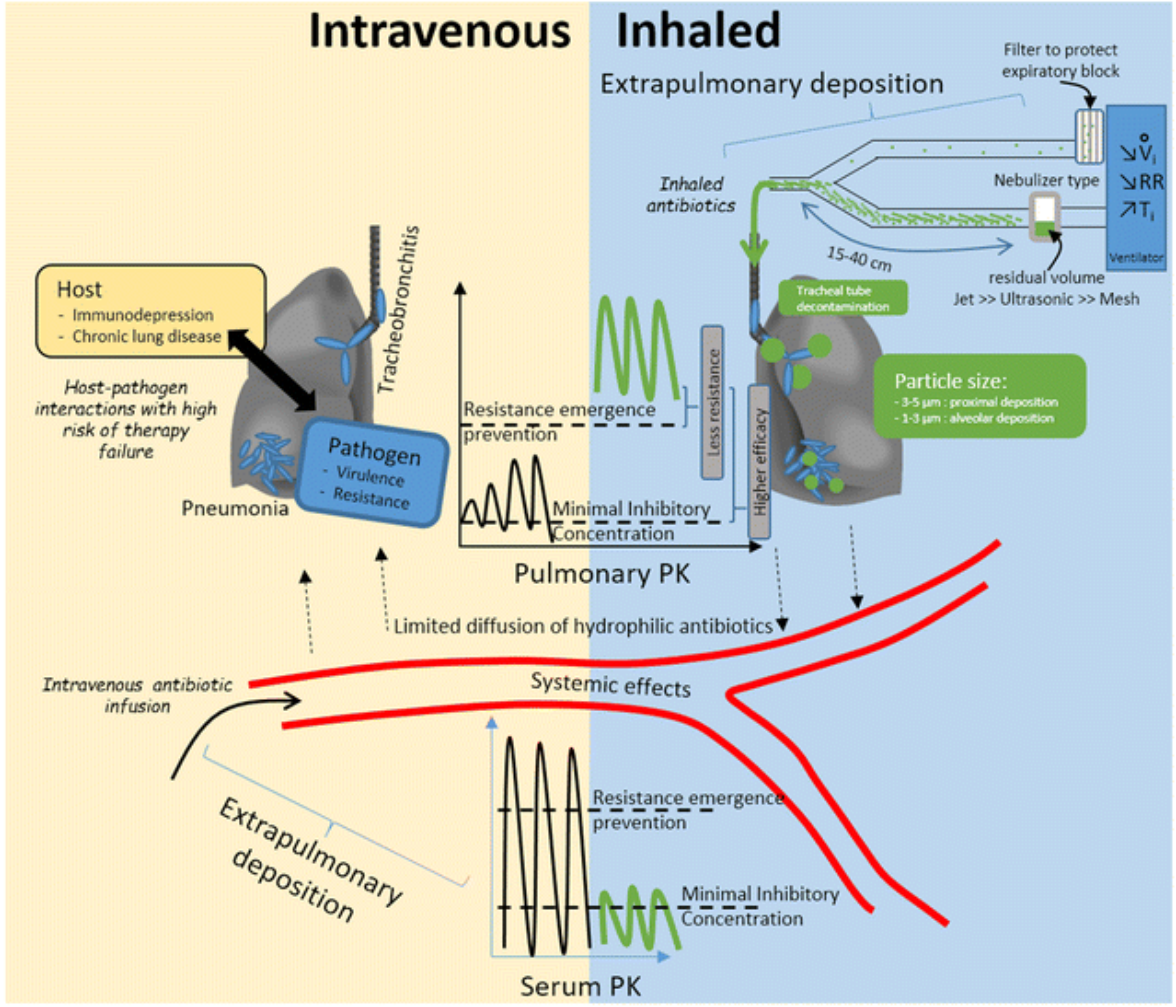
Pulmonary drug delivery

Pulmonary Delivery for Local Target

- Inhalation therapy delivers medication directly to the lungs, making it an effective strategy for treating lung diseases such as:
  - Asthma, chronic obstructive pulmonary disease (COPD), bronchitis, pneumonia, lung fibrosis…

- Advantages of the inhalation route:
  - ✓ Shortening of the delivery path
  - ✓ Achieves high local drug concentration
  - ✓ Reducing systemic exposure and side effects

- **Challenges in aerosol delivery system development:**
  - Producing small, uniform aerosol particles
  - Ensuring consistent and targeted deposition in the respiratory tract



(Ehrmann et al *Annals Intensive care*, 2017)

JN: jet nebulizer
VMN: vibrating mesh nebulizer
MDI: metered-dose inhaler
SMI: soft mist inhaler

Inhalation devices and their formulations

Nebulizers

Advantages
- Easy to use
- No strong inspiration effort
- No need for patient education
- Used in emergency

Disadvantages
- Needs regular maintenance
- Inaccurate drug doses
- Bulky and expensive

Pressurized metered dose inhalers

Advantages
- Multi-dose delivery ability
- Portable
- Low cost
- Low inspiratory flow rate needed

Disadvantages
- Needs a propellant
- High oropharyngeal deposition
- Technique dependent

Soft mist inhalers

Advantages
- A lower dose is needed
- Higher drug deposition
- No patient coordination is needed

Disadvantages
- More expensive
- Needs basic assembly and priming

Dry powder inhalers

Advantages
- Propellant-free
- Provides accurate doses
- Easy to use and portable
- Rapid and efficient delivery

Disadvantages
- Requires high inspiratory flow rate
- Emitted dose can be affected by humidity and heat

Delivered dose (%) through MV

JN	VMN	MDI	SMI	?
5-10%	15-25%	10-15%	5-10%	

Aerosol Delivery Characteristics in Spontaneously Breathing and Ventilated Patients

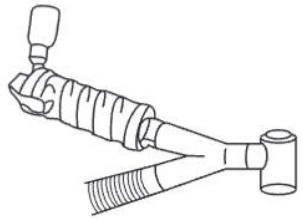
Table 1 Characteristics of aerosol delivery to spontaneously breathing and invasively ventilated patients

Characteristics	Spontaneously breathing	Invasive ventilation
Airway	Oro-nasal upper airway	Artificial airway
Inspiration flow waveform	Sinusoidal	Descending, ascending or square
Inspiratory flow rate	15–40 L/min	Up to 100 L/min
Interface of delivery	Mouthpiece/mask/nasal prongs	An adapter at airway or vent circuit
Inhaled Aerosol Temperature	Ambient	Heated to ~37 ℃
Surrounding Humidity	Ambient	Humidified to 95–99% relative humidity
Aerosol particle size to reach lower airways	2–5 μm	~2 μm
Aerosol reservoir	Mouth and pharynx (~90 mL)	Circuit (ID: 15mm; 180 cm; ~300 mL)
Aerosol loss	Upper airways, exhalation to ambient	Artificial airway, ventilator circuit impaction/ sedimentation
Patient Position	Sitting, semi-recumbent	Semirecumbent, supine, lateral, prone

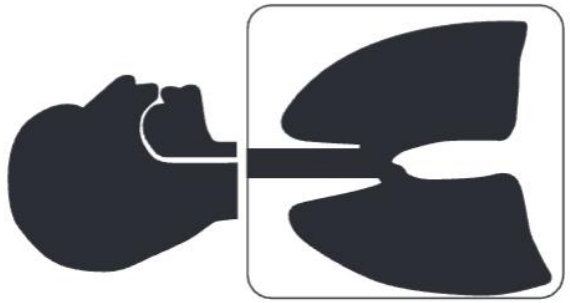
Factors Influencing Aerosol Delivery During Invasive Ventilation

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

Device-Related - MDI
- Type of spacer or adapter (>150 mL)
- Position of spacer in circuit
- Timing of MDI actuation
- Type of MDI



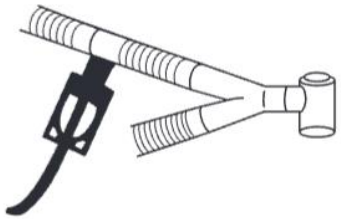
Drug-Related
- Dose
- Formulation
- Aerosol particle size
- Targeted site for delivery
- Duration of action



Device-Related - Nebulizer
- Type of nebulizer
- Fill volume
- Gas flow
- Cycling: inspiration vs continuous
- Duration of nebulization
- Position in the circuit

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

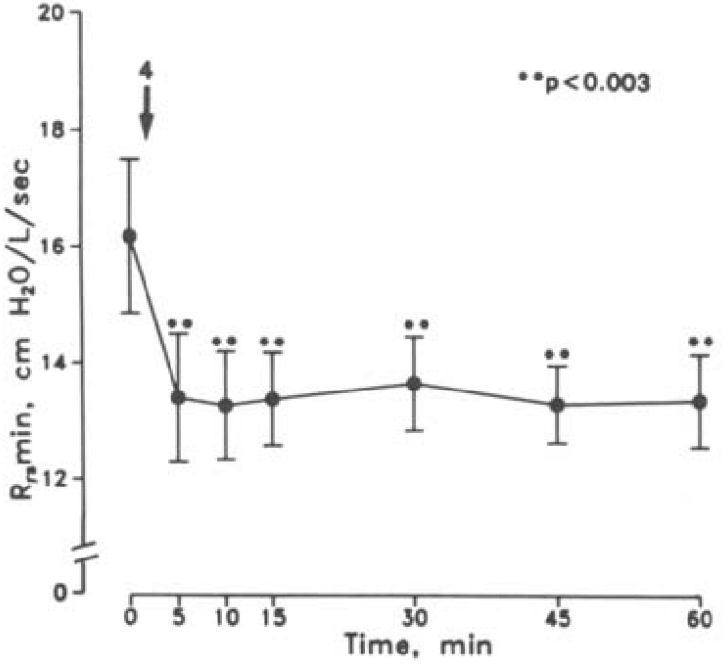
Circuit-Related
- Endotracheal tube size
- Humidity of inhaled gas
- Density of inhaled gas



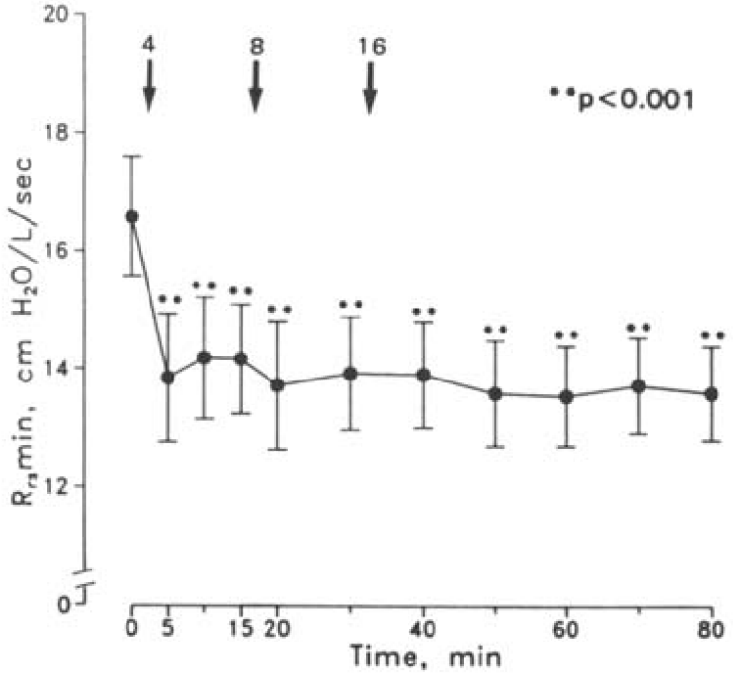
Determining MDI Doses During Ventilation

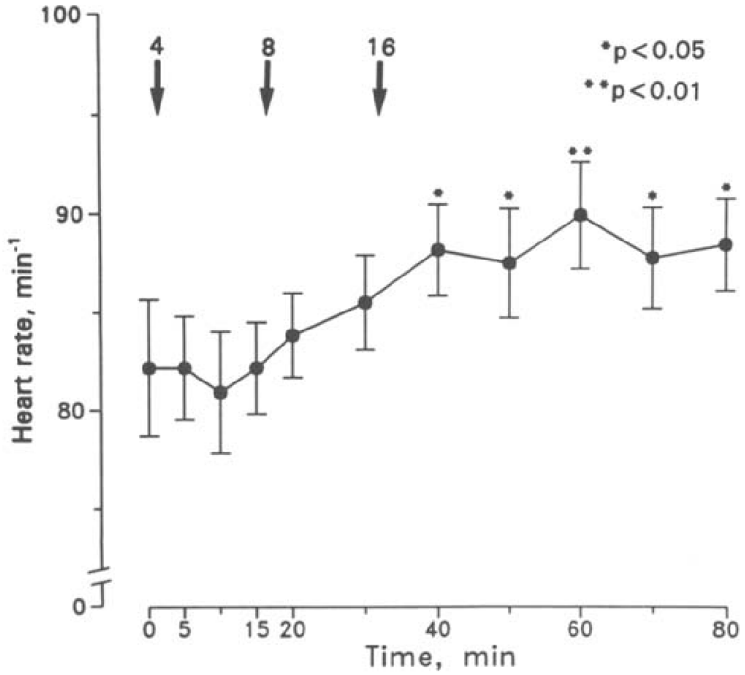
- Airway resistance reduction after 4 puffs of albuterol MDI in ventilated patients
  - Additional doses did not enhance bronchodilation but resulted in increased heart rate.

4 puffs in total



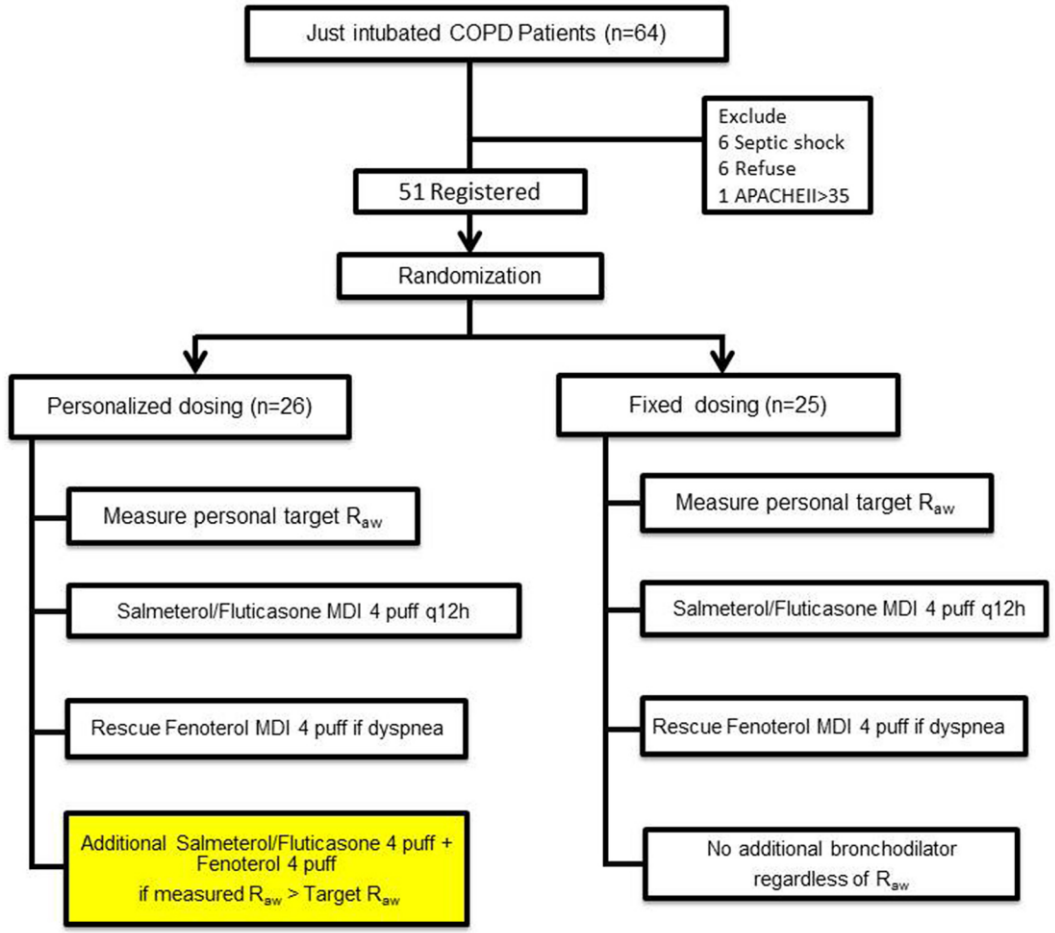
28 puffs in total





Determining MDI Doses During Ventilation

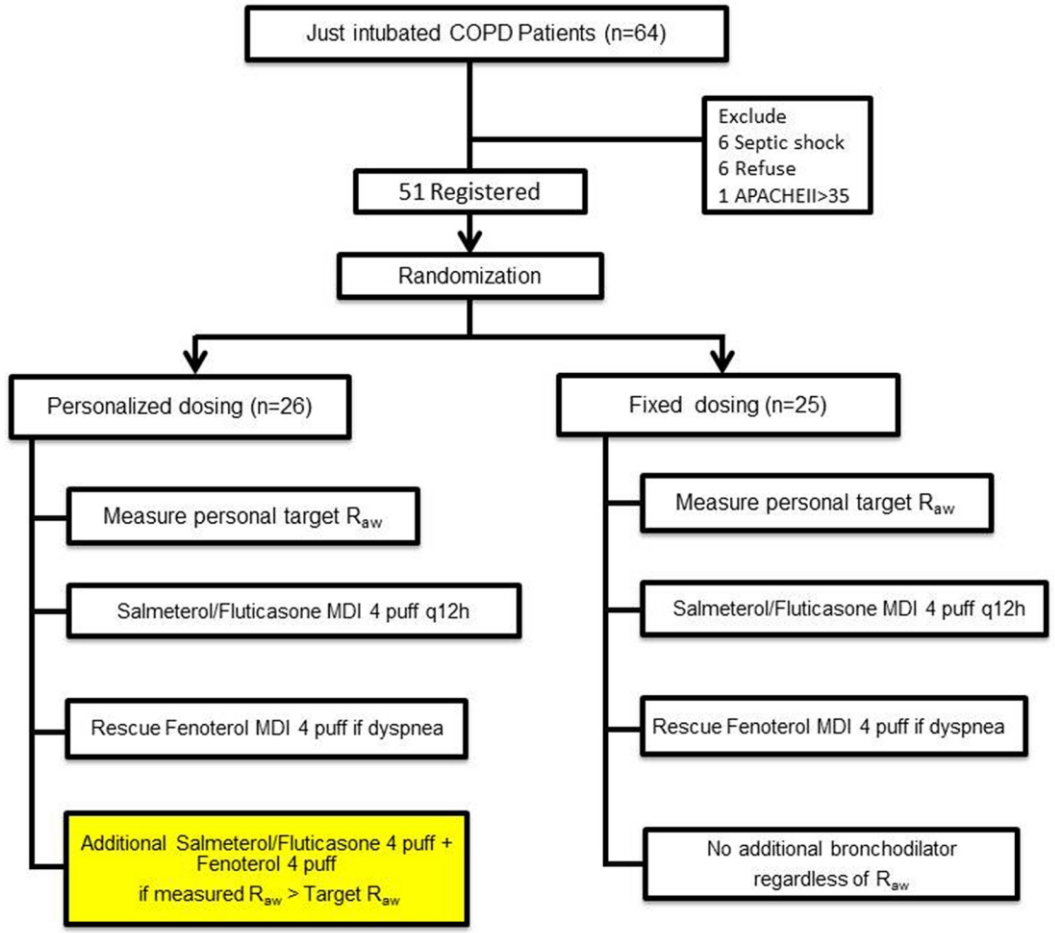
- **Determination of Personal Target Raw**
  - Within **72 hours of ICU admission**, after withholding bronchodilators:
    - **Fenoterol withheld ≥2 h**
    - **Salmeterol/fluticasone withheld ≥12 h**
  - **Stepwise intensive bronchodilation** using **fenoterol MDI**:
    - 4 puffs → 8 puffs at 15 min → 16 puffs at 30 min (Total: 28 puffs)
  - **Raw measured 15 minutes after final dose**
    - Considered the **lowest achievable Raw**
    - Assigned as **personal target Raw** for individualized dosing decisions



Determining MDI Doses During Ventilation

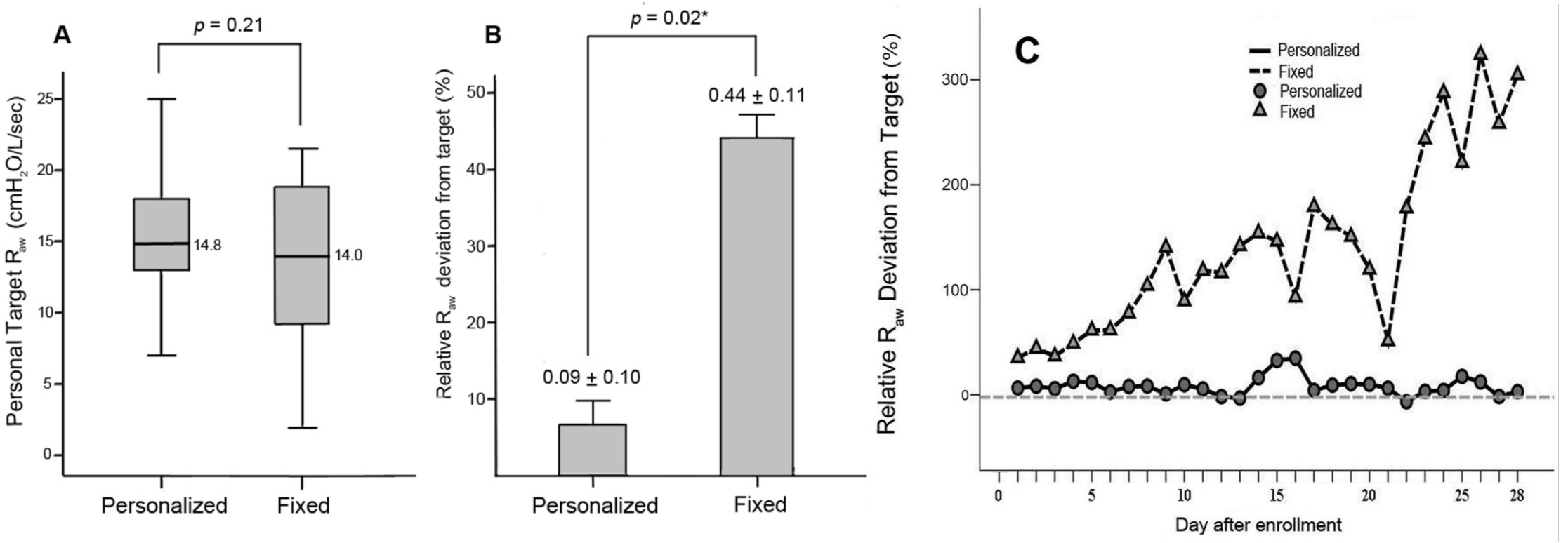
- **Routine Treatment for All Patients (Both Groups):**
  - **Seretide (Salmeterol 25 μg / Fluticasone 250 μg)**
    – 4 puffs every 12 h
  - **Combivent (Ipratropium bromide 0.5 mg + Salbutamol sulfate 2.5 mg)**
    – 1 vial every 6 h via nebulization
  - **Methylprednisolone (IV, 40 mg)**
    – Every 8 h for first 3 days
  - **Short-acting bronchodilators**
    – PRN use not restricted

- **Personalized-Dosing Group:**
  - **Additional Dosing Based on Airway Resistance (Raw) every 8 h**
    If Raw > personal target →
    +4 puffs Salmeterol/Fluticasone
    +4 puffs Fenoterol (0.1 mg/puff)



Determining MDI Doses During Ventilation

- Relative Raw deviation of the personalized-dosing group was significantly smaller than that of the fixed-dosing group.



Determining MDI Doses During Ventilation

Dosing Outcomes and Clinical Impact

- Rescue bronchodilator use (PRN):
  - No significant difference between personalized- and fixed-dosing groups
- Daily Seretide use:
  - Personalized-dosing group: 9.2 puffs
  - Fixed-dosing group: 7.6 puffs

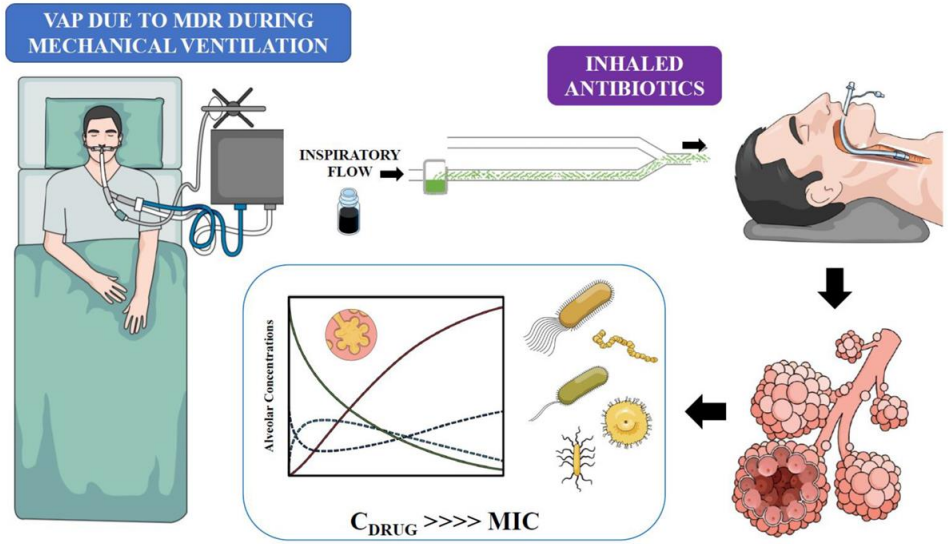
  (Significantly higher in personalized group)
- Post-extubation noninvasive ventilation duration:
  - Shorter in the personalized-dosing group than in the fixed-dosing group.

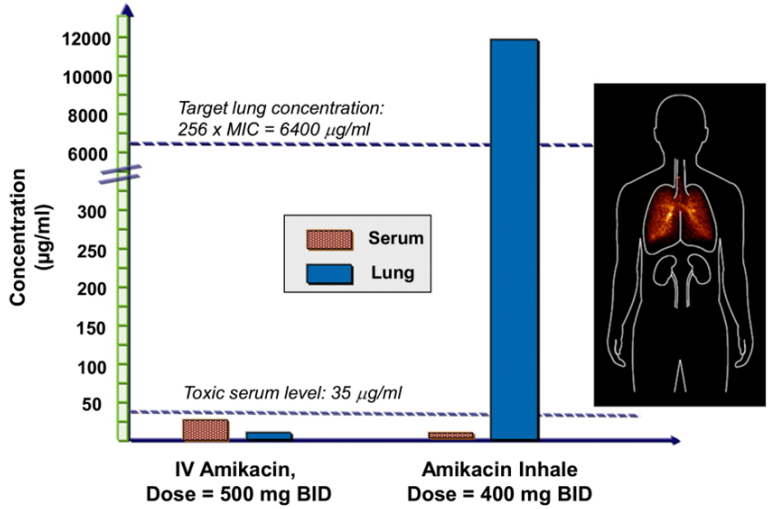
Table 2
Outcome comparisons.

	Personalized dosing (N = 26)	Fixed dosing (N = 25)	*P* value
Primary Outcome			
Relative R_{aw} deviation[a] from target	0.09 ± 0.10	0.44 ± 0.11	0.02*
Trend of relative R_{aw} deviation (per day)	−0.03	+0.004	0.80
Secondary Outcome			
No ventilator need by 28th day (%)	19 (73)	22 (88)	0.29
Ventilator-free day from day 1–28, median (IQR)	18 (9, 23)	22 (17, 26)	0.16
Total rescue bronchodilator (puff)	0 (0, 4)	0 (0, 0)	0.07
Nosocomial pneumonia	0	0	
Adverse drug effect	0	0	
ICU mortality (%)	4 (15)	1 (4)	0.17
Hospital mortality (%)	9 (35)	7 (28)	0.61
Mortality at 180th day (%)	9 (35)	10 (40)	0.69
NIV[b] after extubation (%)	15 (58)	12 (48)	0.49
NIV after extubation (hr), median (IQR)	48 (24, 48)	60 (48, 120)	0.04*

*$P < 0.05$.
[a] Relative R_{aw} deviation from target = (measured R_{aw} − target R_{aw})/target R_{aw}.
[b] NIV: Noninvasive ventilation.

Inhaled antibiotics

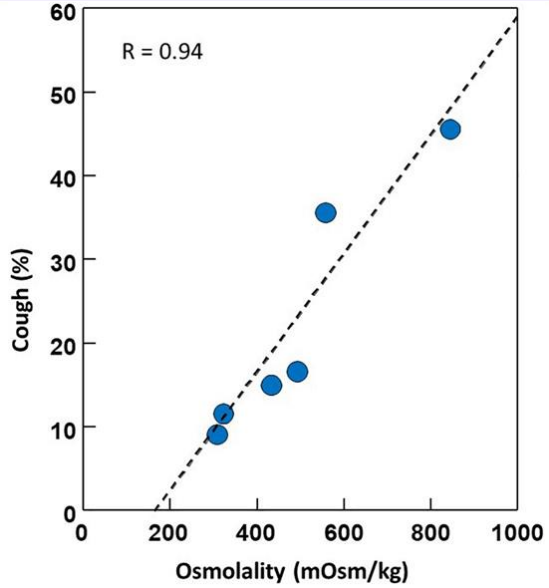


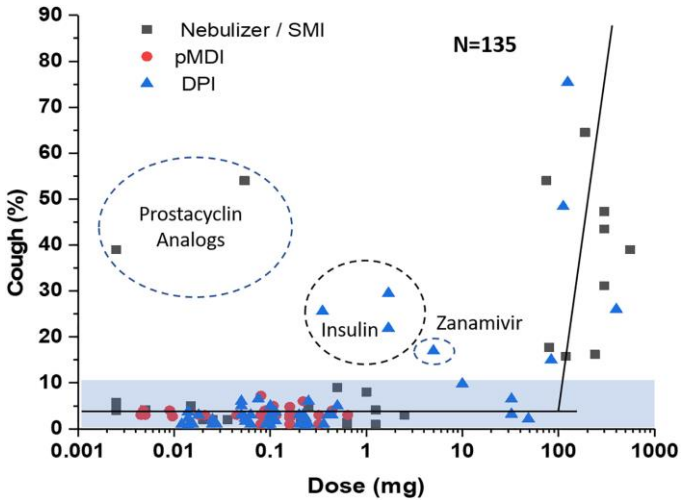


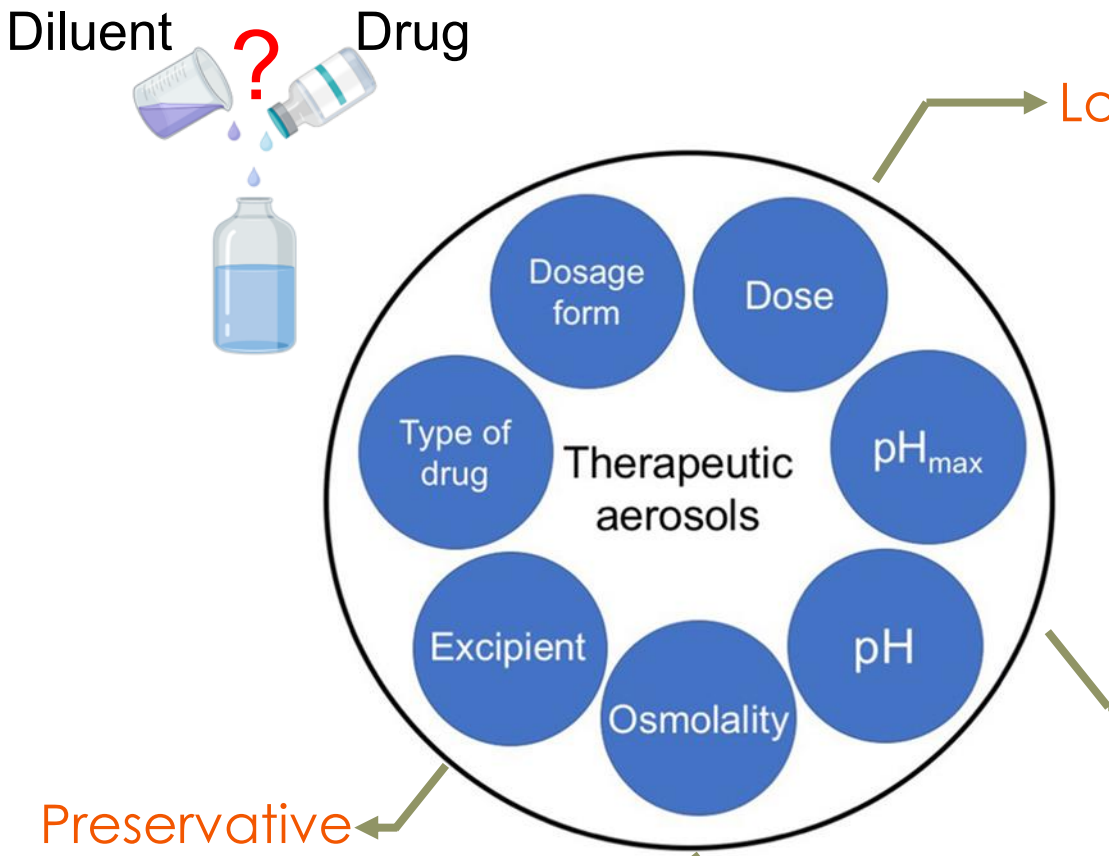
Weers, 2015. Adv. Drug Deliv. Rev. 85: 24-43

- Several antibiotics designed for parenteral administration have been repurposed for inhalation to treat lower airway infection.
- Inhaled antibiotics provide several distinct advantages over iv. administration, including:
  1. Bypassing the alveolar-capillary barrier
  2. Directly delivering high doses of antibiotics to the infected area (lungs)
  3. Rapid attainment of the minimum inhibitory concentration (MIC) in the infected area
  4. Reducing systemic adverse effects

Inhaled antibiotics







Loading mass: < 1 mg

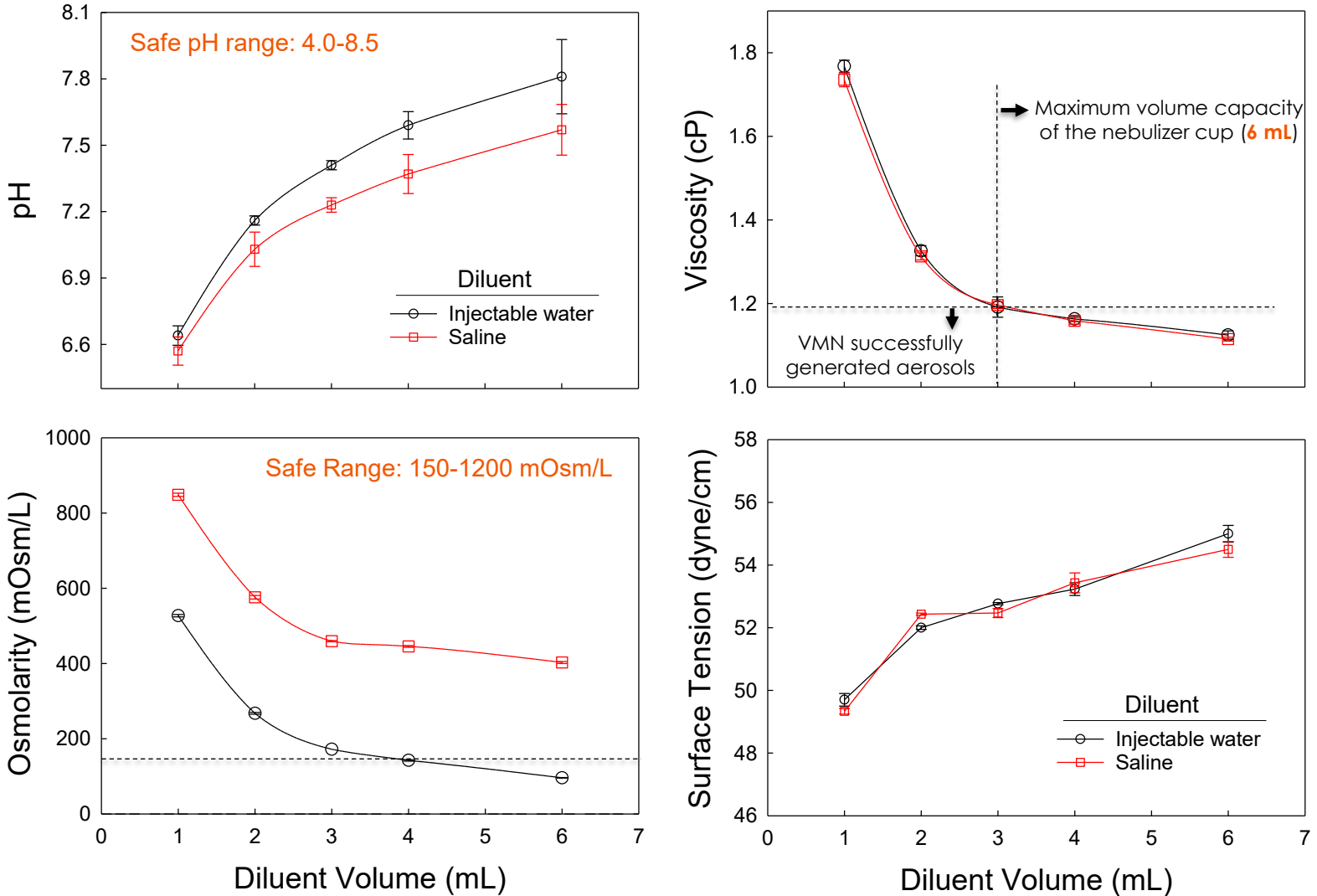
pH: 4 - 8.5

Preservative

Osmolarity: 150 – 1200 mOsm/kg

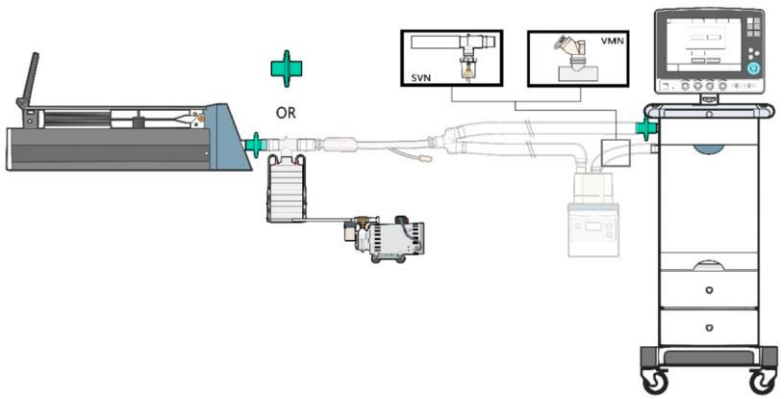
Inhaled antibiotics - colistin

VMN: vibrating mesh nebulizer



Inhaled antibiotics - colistin

- Comparisons of aerosolized colistin generated by VMN and JN



- VMN-L: 1 vial colistin (200 MIU) / Diluted to 6 mL
- JN-L: 1 vial colistin (200 MIU) / Dilute to 6 mL
- JN-H: 2 vial colistin (400 MIU) / Dilute to 6 mL

Table 1. Nebulizer performance on the delivery of colistin.

Variables	VMN-L	JN-L	JN-H	*P*-Value
Inhaled mass (mg)	53.80 ± 14.79	19.82 ± 3.34 *	31.72 ± 4.48 *	<0.001
Inhaled mass (%)	34.44 ± 9.47	12.69 ± 2.14 †	10.15 ± 1.43 †	<0.001
Nebulization time (min)	42.35 ± 2.30	21.12 ± 0.86 ‡	21.65 ± 0.42 ‡	<0.001
Delivery efficiency (mg/min)	1.27 ± 0.32	0.94 ± 0.17	1.46 ± 0.20 §	0.023
Delivery efficiency (%/min)	0.81 ± 0.20	0.60 ± 0.1	0.47 ± 0.06 ‖	0.014

- VMN delivered a greater inhaled mass but required a longer nebulization time.

Inhaled antibiotics - colistin

i.v. CMS dose of 150 mg (5 million IU)

Nebulized CMS dose of 60 mg (2 million IU)

Nebulized CMS dose of 120 mg (4 million IU)

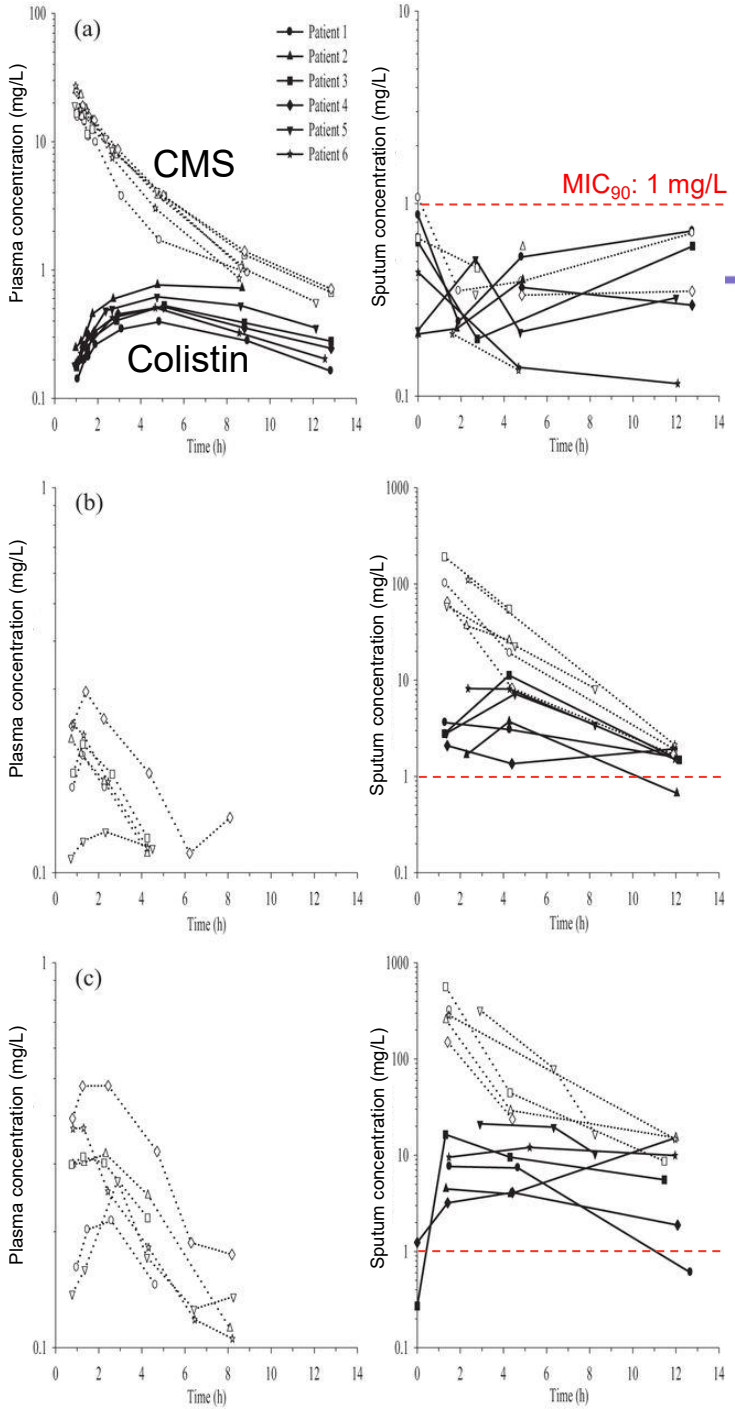


TABLE 6 Lung function parameters and glomerular filtration rates following administration of CMS by nebulization or i.v. infusion[a]

	Effects with nebulized administration of CMS at dose of:				Effects with i.v. infusion of 150 mg of CBA[c]	
	2 million IU		4 million IU			
Respiratory parameters[b]	Predose	Postdose[d]	Predose	Postdose[d]	Predose	Postdose[d]
FEV_1[e]	2.0 ± 0.65	1.9 ± 0.65	2.0 ± 0.61	2.1 ± 0.64[f]	2.1 ± 0.62	2.1 ± 0.62
FVC[e]	3.6 ± 0.85	3.5 ± 0.94	3.9 ± 0.87	3.8 ± 0.93[f]	3.9 ± 0.78	3.9 ± 0.88
MIP[e]	155 ± 64	151 ± 44	160 ± 40	161 ± 33	148 ± 39	153 ± 36
MEP[e]	157 ± 56	157 ± 55	158 ± 30	166 ± 38	152 ± 29	164 ± 30
eGFR[g]	127 ± 18	121 ± 20[h]	133 ± 22	121 ± 37	145 ± 22	127 ± 31[h]

[a] Data represented as mean ± SD ($n = 6$).
[b] FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; MIP, minimum inspiratory pressure; MEP, maximum expiratory pressure.
[c] For lung function parameters, $n = 5$, as subject 2 did not undergo lung function tests since he presented with hemoptysis.
[d] One to two hours postadministration for lung function test; 12 h postadministration for eGFR.
[e] No statistically significant difference between pre- and postdose measurements for FEV_1, FVC, MIP, and MEP.
[f] Due to time constraints in the lung function laboratory, $n = 5$, as FEV_1 and FVC could not be carried out for subject 2.
[g] No statistically significant difference was found between pre- and postdose measurements for eGFR following nebulized CMS delivery. A statistically significant difference was found between pre- and postdose measurements for eGFR following i.v. CMS delivery.
[h] $n = 4$ for nebulized 2 million IU CMS and $n = 5$ for i.v. 150 mg of CBA.

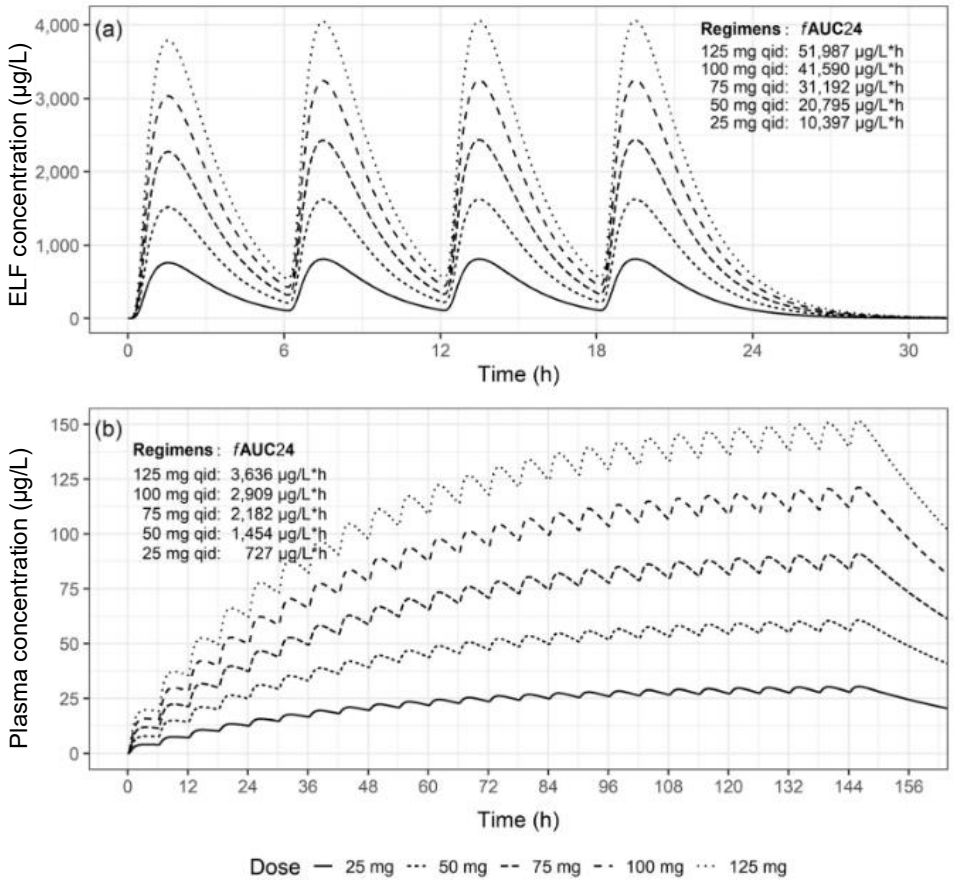
Inhaled antibiotics - colistin

- Evaluate pharmacokinetics (PK) of inhaled low-dose CMS (3.75 MIU Q6H by a JN) in VAP caused by *carbapenem-resistant A. baumannii*.

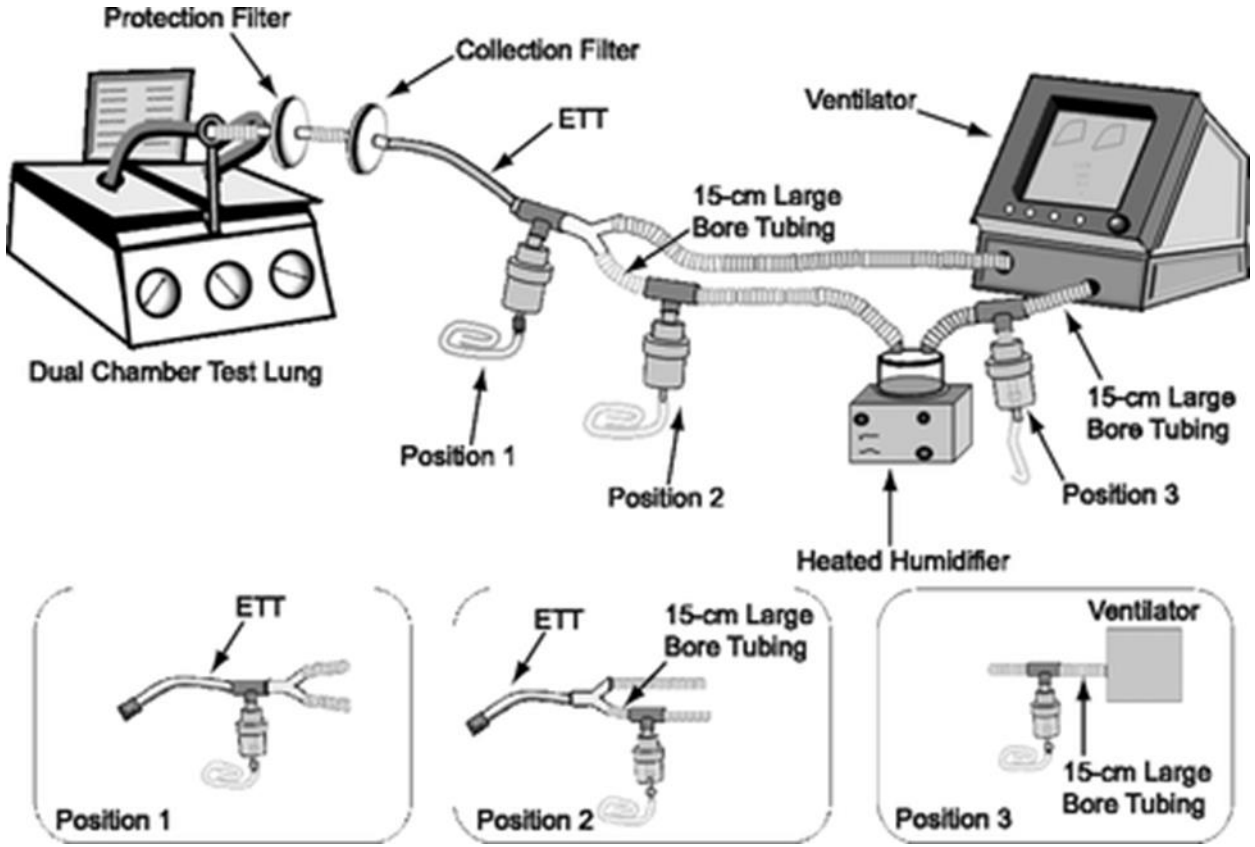
Table 3. Comparison of clinical and microbiological outcomes based on *f*AUC (mg/L·h) with a total of 3.75 MIU of colistimethate sodium administered at 6 h intervals four times a day.

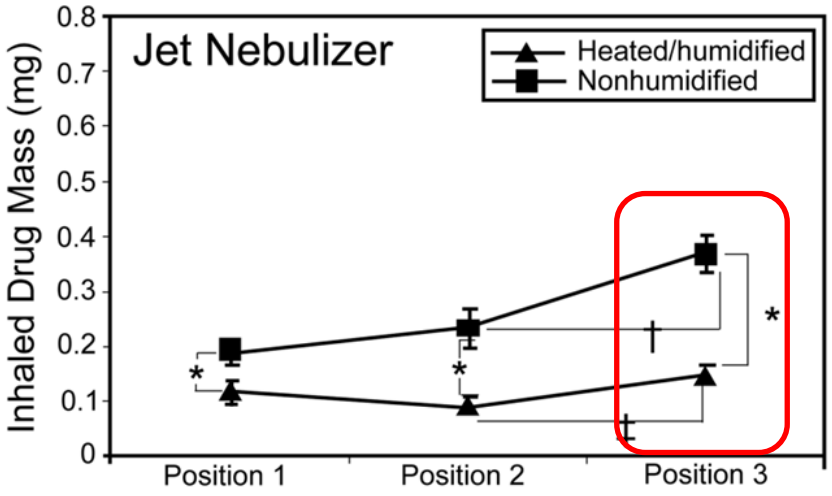
Outcome	No.	Epithelial Lining Fluid Median (IQR)	Plasma Median (IQR)
Clinical outcomes			
Cured/Improved	16	36.7 (18.2–62.9)	1.40 (0.752–3.74)
Failed	4	31.7 (15.4–47.8)	2.00 (1.87–2.38)
		p-value = 0.6366 ‖	*p*-value = 0.7055 ‖
Microbiological outcomes			
Eradicated	8	61.2 (12.5–111)	2.36 (0.645–4.11)
Persistent	10	28.5 (17.7–50.5)	1.56 (1.00–2.05)
Indeterminate	2	33.9 (30.0–37.9)	5.96 (5.00–6.91)
		p-value = 0.5977 ¶	*p*-value = 0.1163 ¶

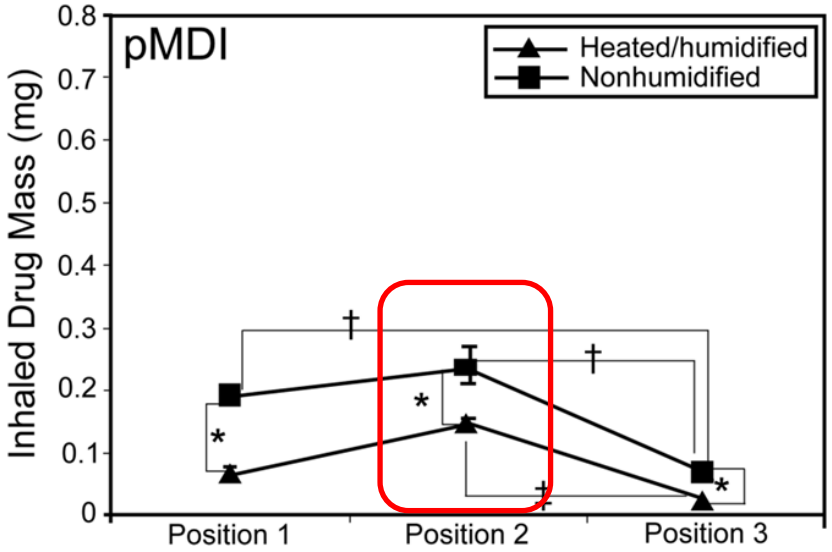
*f*AUC, area under the free colistin concentration–time curve at steady state over 24 h; IQR, interquartile range; ‖ Wilcoxon Rank-sum test; ¶ Kruskal–Wallis test.



Placement of Aerosol Device



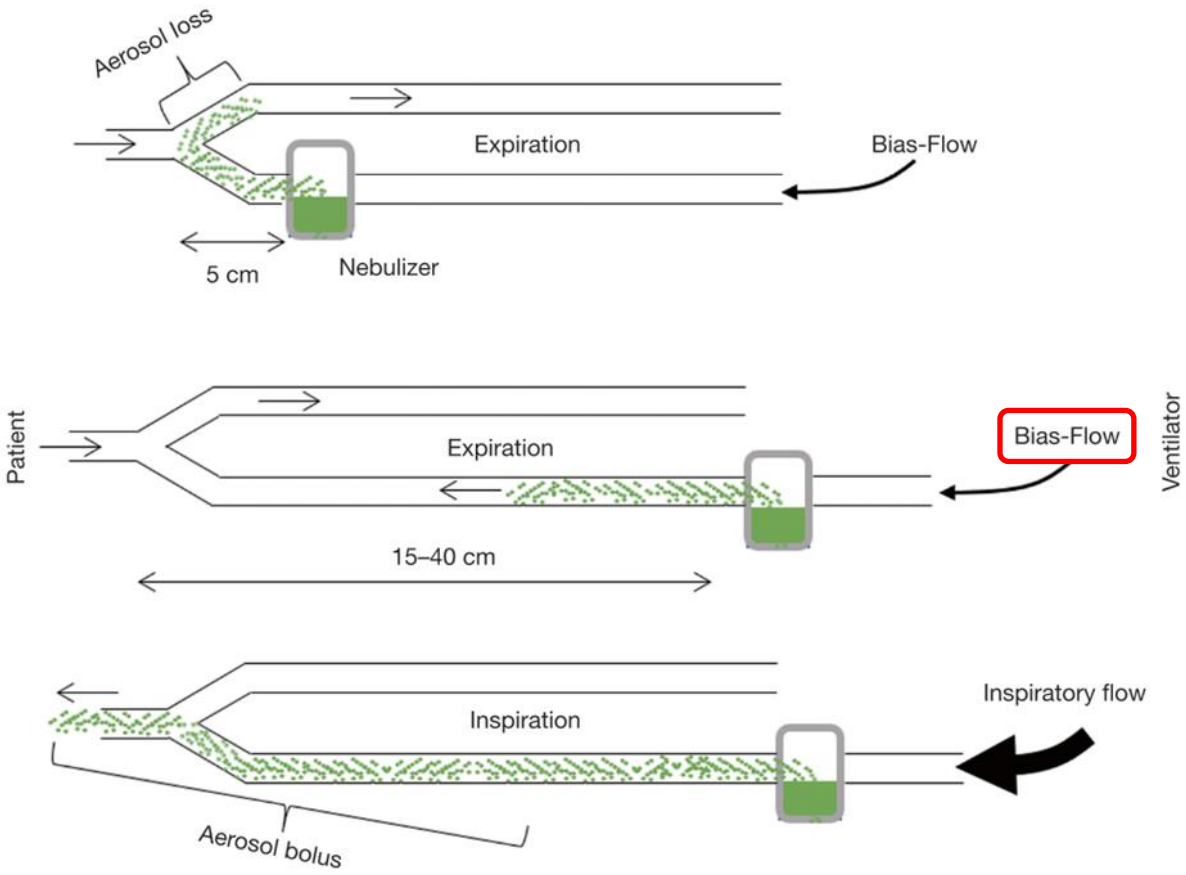




Placement of Aerosol Device

Optimal Nebulizer Position in the MV Circuit for Aerosol Delivery

- Upstream positioning (in the inspiratory limb):
  - Reduces aerosol losses during expiration
  - Allows the inspiratory limb to act as a **spacer/reservoir**
  - **Stores aerosol** during expiration
  - Enables **bolus delivery** at the next inhalation



Placement of Aerosol Device

- Benefits of Placing Nebulizer at Inlet of Heated Humidifier (HH)

➢ Increases delivered drug dose

➢ Avoids condensate accumulation in the nebulizer

➢ Prevents condensate splash-out

➢ Reduces initial aerosol impaction losses

Jet nebulizer
- At the heater chamber inlet
- T adaptor

Mesh nebulizer
- At the heater chamber inlet
- Designed T adaptor

Synchronization with ventilation

Performance of Pneumatic Nebulization Modes (JN) in Adult Lung Model

- Inhaled dose (% of total):
  - From 7.0 to 7.7% across all three modes
  - No statistically significant difference observed
- Median Nebulization Time:
  - IIM (Inspiratory Intermittent Mode): 38.9 min
  - CM (Continuous Mode): 14.3 min
  - EIM (Expiratory Intermittent Mode): 17.7 min
- Conclusion:
  - Although delivery efficiency was similar, EIM and CM significantly reduced nebulization time
  - These modes may be preferred for faster treatment in clinical settings

4 mL Salbutamol
(5 mg / 2.5 mL)

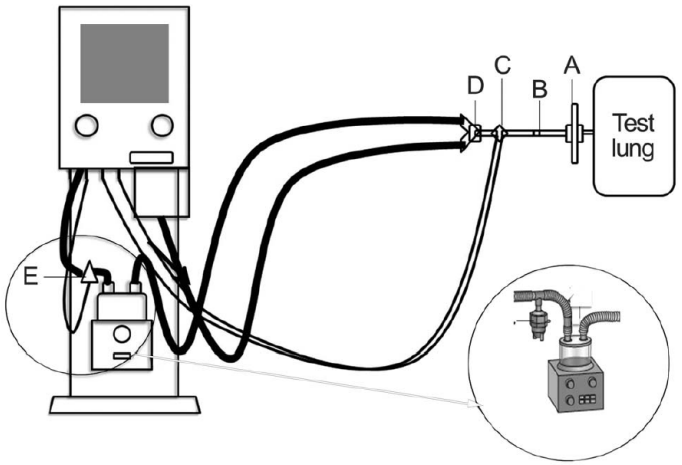
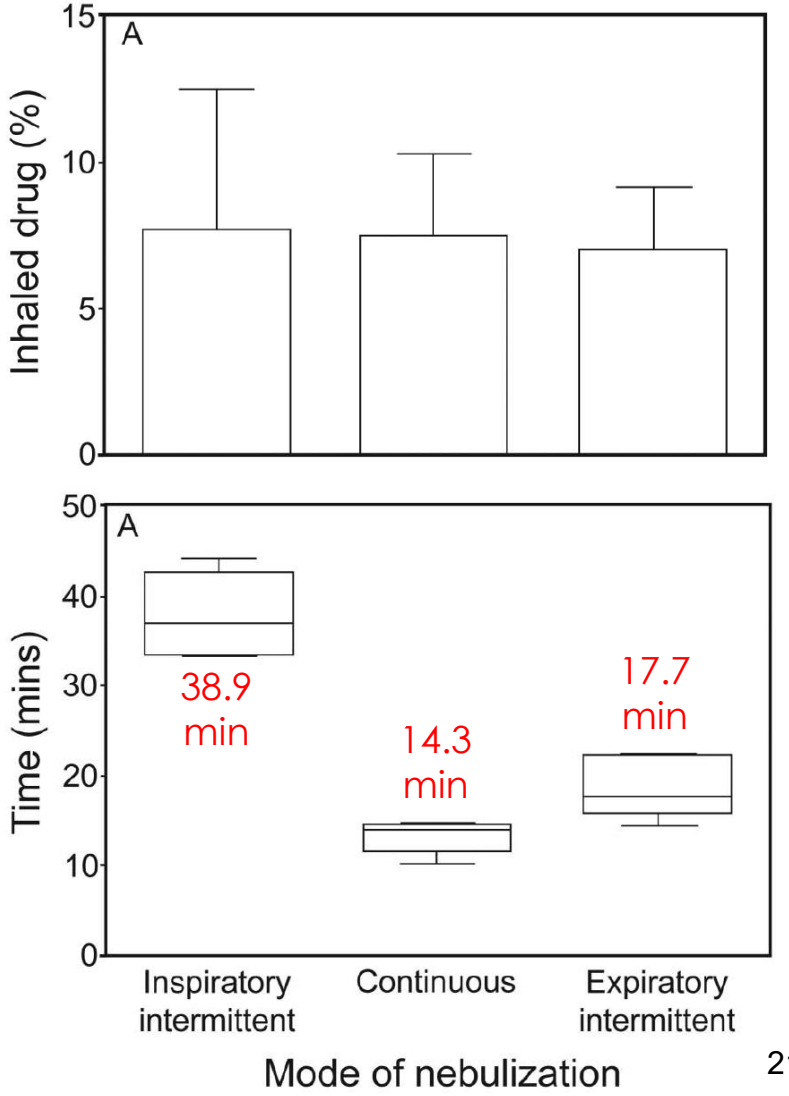


Fig. 1. Diagram of experimental apparatus. A jet nebulizer (E) powered by the ventilator nebulization function was placed in the ventilator outlet 15 cm from the heater, and a filter for aerosol collection (A) was placed distal to the endotracheal tube (B). Also shown are the flow sensor (C) and the Y-piece (D).



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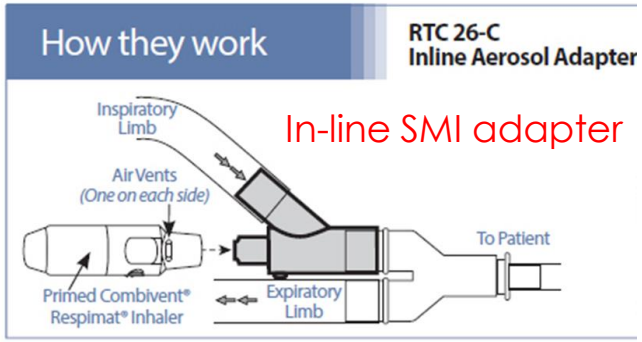
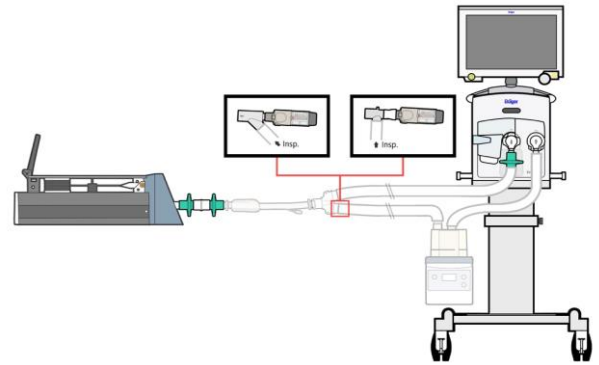
Synchronization with ventilation

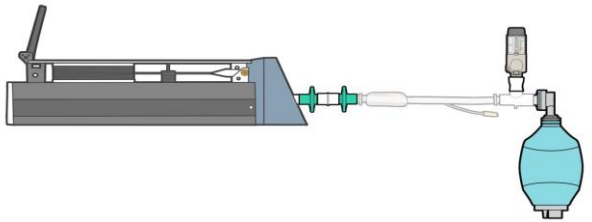
Soft Mist Inhaler (SMI) Delivery via Endotracheal Tube

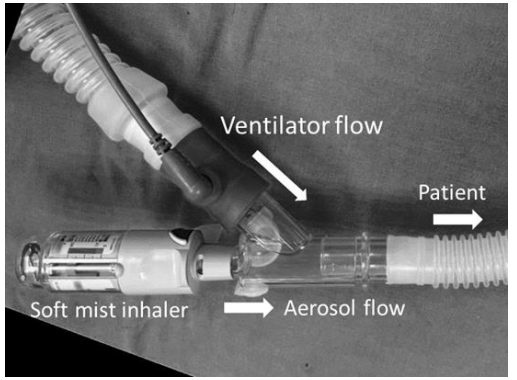
- The optimal method and timing for delivering inhaled drugs via SMIs in mechanically ventilated patients remains unclear.

- This study aimed to evaluate SMI drug delivery through an endotracheal tube using different adapters and actuation timings during mechanical ventilation.

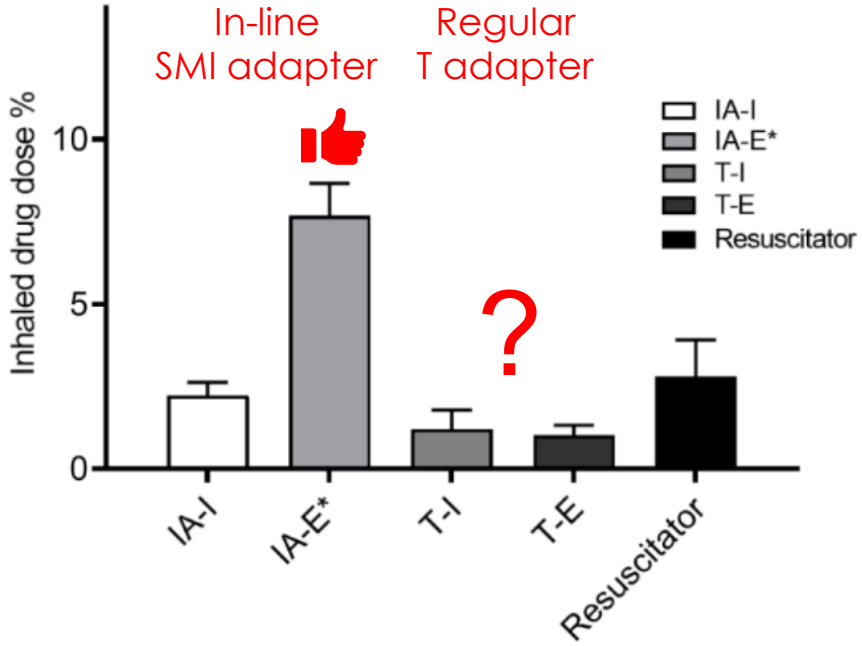






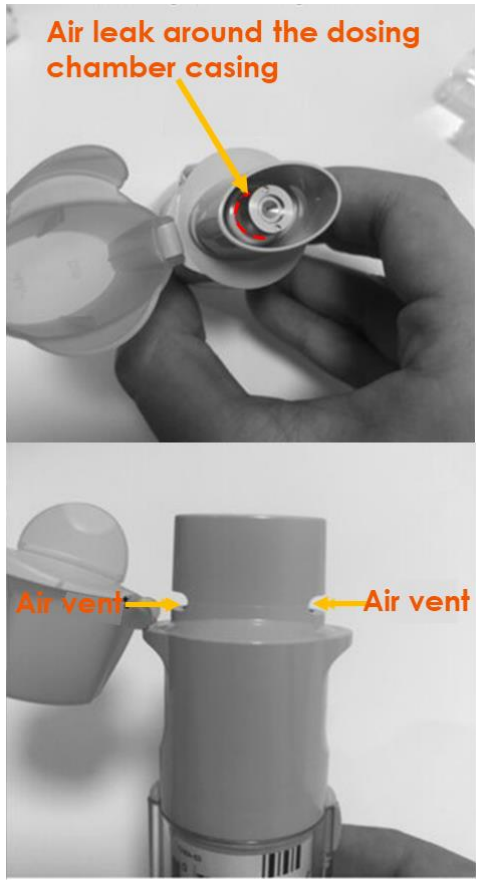


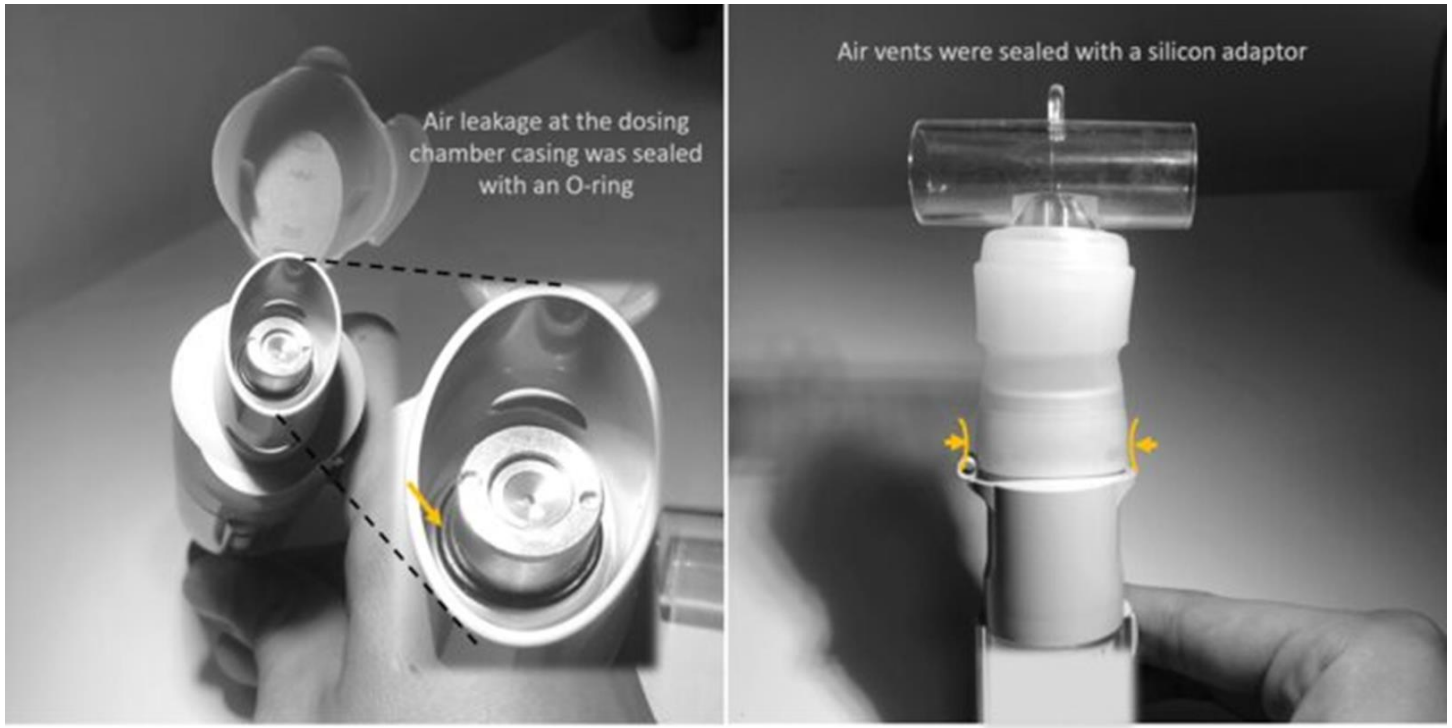
Comparison of drug dose



Synchronization with ventilation

Soft Mist Inhaler (SMI) Delivery via Endotracheal Tube

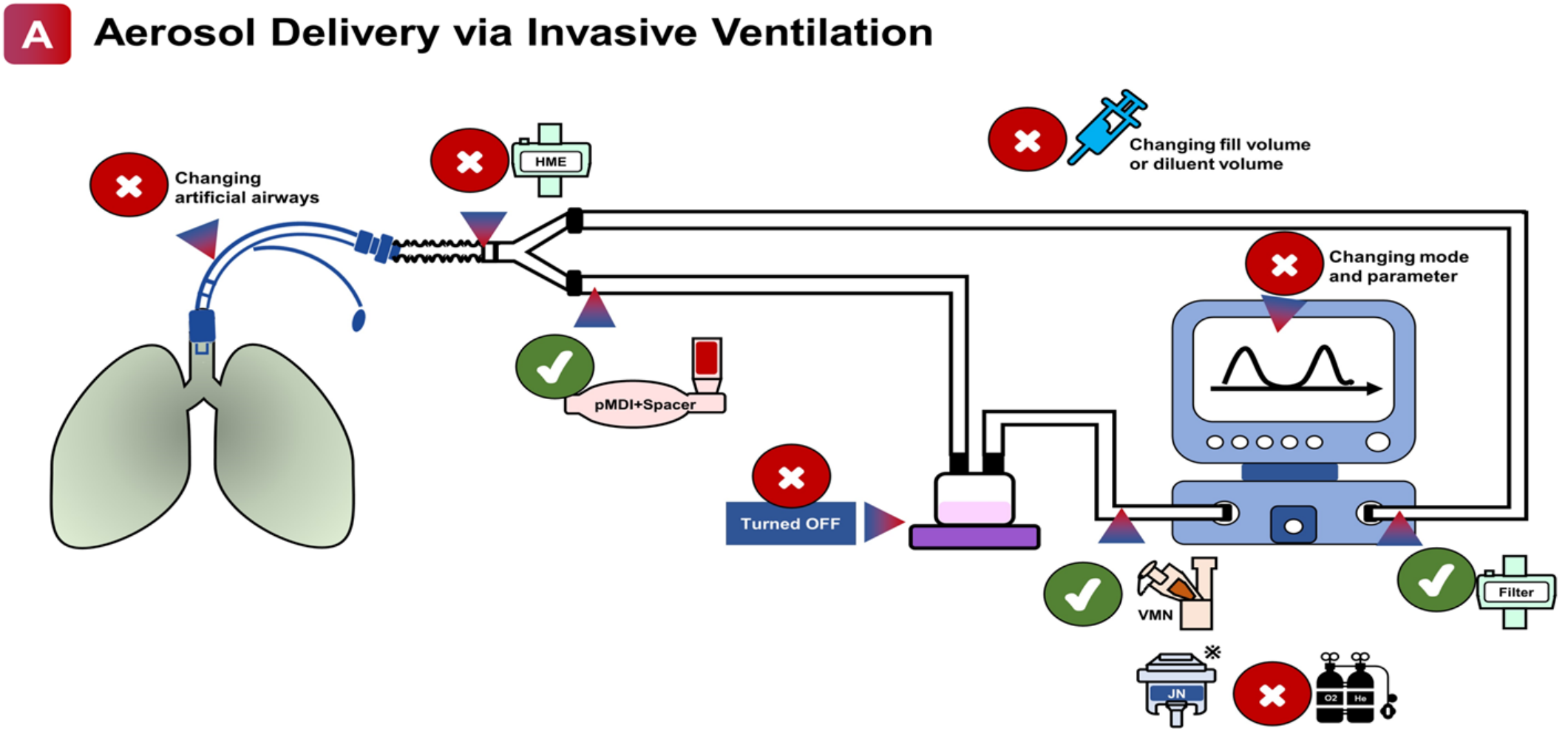




Synchronization with ventilation

- The synchronization during mechanical ventilation depends on the characteristics of the device
  - pMDI- actuated at the beginning of inspiration
  - SVN- synchronized with continuous or expiration
  - SMI- actuated at the beginning of expiration

Summary



※ in some in vitro experiments a continuous JN placed in those positions is less efficient than VMN for aerosol delivery.

Thank You

For Your Attention

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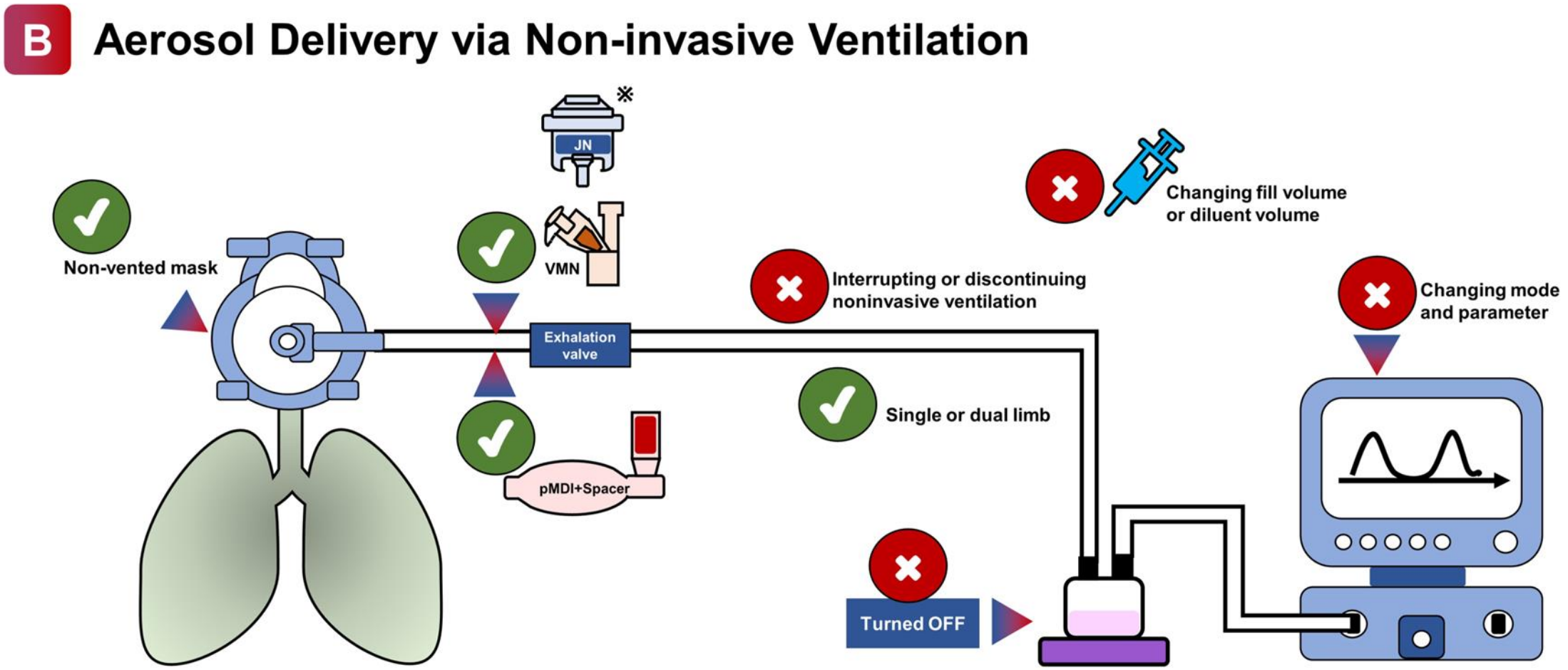
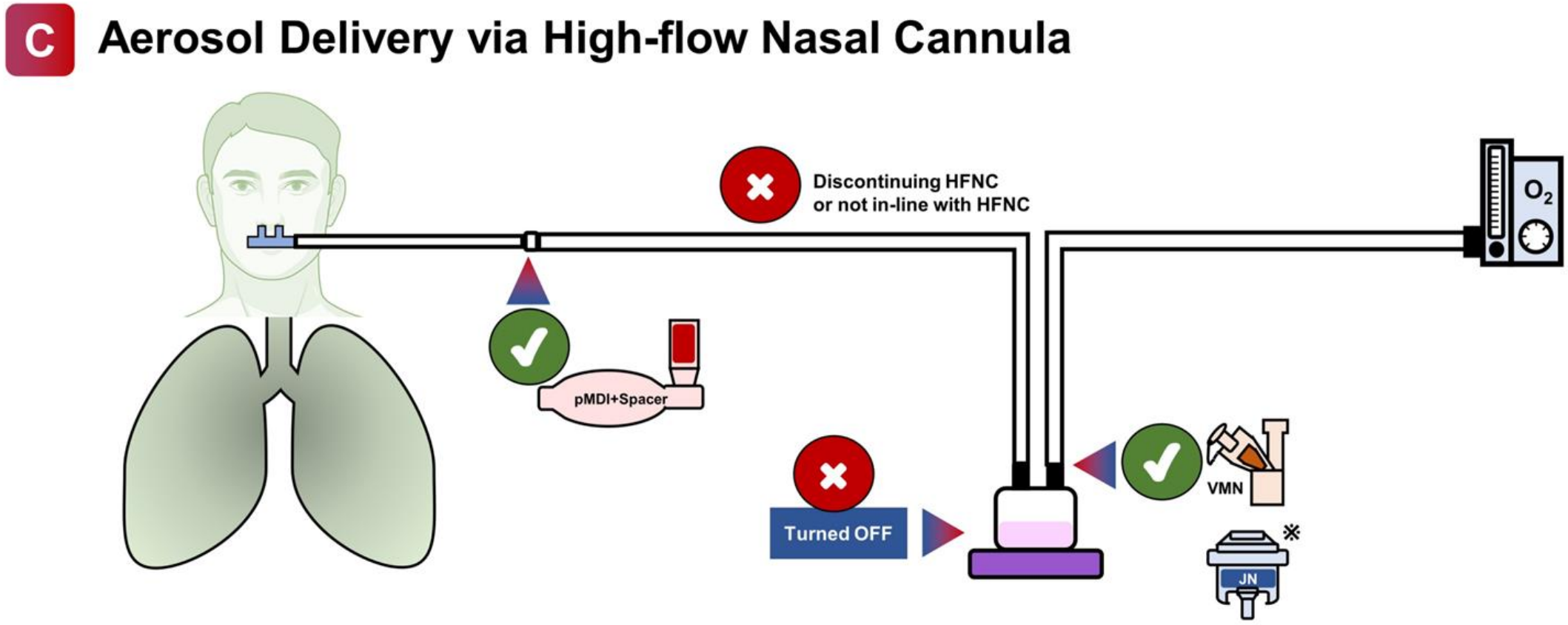
Summary



※ in some in vitro experiments a continuous JN placed in those positions is less efficient than VMN for aerosol delivery.

Summary



※ in some in vitro experiments a continuous JN placed in those positions is less efficient than VMN for aerosol delivery.