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SPECIAL ISSUE INSIGHT

Optimising aerosolized therapies in critically ill patients

Jayesh Dhanani[1,2*], Leandro U. Taniguchi[3,4] and Otavio T. Ranzani[5,6]

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Amongst the machines that help save lives in the intensive care unit (ICU) environment, aerosol drug delivery devices play a special role. Aerosolization can rapidly achieve high-effective local drug concentration at the site of action with minimal side effects for treating respiratory conditions such as reactive airways diseases [1]. The vast alveolar surface area (100 m^2) and pulmonary blood flow (entire cardiac output) provide an alternative avenue for effective systemic therapy as well [1]. However, effective aerosol therapy in ICU is affected by the complex interplay with other machines [invasive mechanical ventilation (IMV), non-invasive ventilation (NIV), high flow nasal cannula (HFNC)] as well as the patient factors [1]. Various aspects of aerosol therapy are covered extensively elsewhere [1]. We provide a summary of the aerosolized therapy in ICU.

Aerosol drug formulations and dosing

In ICU, aerosolized drugs consist of specific aerosol formulations, such as bronchodilators and off-label use of intravenous formulations, e.g., tobramycin. Aerosolized drugs in ICU belong to established drug classes, such as bronchodilators (e.g., salbutamol), anti-infectives (e.g., colistin) and other less common agents such as anticoagulants (e.g., heparin). Ideal characteristics of aerosol formulations especially for off-label uses include preservative-free, non-pyrogenic, sterile, adjusted osmolality (150–1200 mOsm/L) and pH (4.0–8.0) [2]. Ideal aerosol characteristics consist of particle size (1–5 μm), electrical charge, lipophilicity, solubility, and molecular weight (< 40 kDa) [1].

While pulmonary and systemic pharmacokinetic data can guide optimal aerosol drug dosing in the critically ill, there are limited pharmacokinetic–pharmacodynamic data with aerosolized therapy in ICU affecting effective drug dosing.

These and other regulatory aspects should be considered when choosing a formulation for aerosol drug therapy in ICU.

Aerosol delivery devices

Pressurized metered dose inhalers (pMDI) and nebulizers [jet (JN), ultrasonic and vibrating mesh (VMN)] are the common aerosol devices used in ICU. These are covered in detail elsewhere [3] and summarized in Table 1.

As VMN provides optimal aerosol characteristics, where possible, it is the preferred nebulizer. Whilst pMDI can be used in most critical care settings, it is limited in its application due to few available formulations. Choice of aerosol devices depends on the formulation (limited formulations with pMDI, heat degradation of proteins with ultrasonic nebulizer), ease of use, availability, and cost considerations.

Optimising factors for effective aerosol therapy in ICU

As aerosol therapy is often used with devices, such as IMV, NIV and HFNC, it is necessary to optimize related factors to provide effective therapy.

1. Aerosol therapy is commonly used with IMV, yet challenging due to the interplay between ventilator, circuit, and nebulizer. Airway size, nebulizer position, heated humidification (HH), bias flow, and patient–ventilator dyssynchrony are some factors affecting aerosol drug delivery [1].

*Correspondence: j.dhanani@uq.edu.au
[1] UQ Centre for Clinical Research, Faculty of Medicine, The University of Queensland, Brisbane, QLD 4029, Australia
Full author information is available at the end of the article

Table 1 Summary of aerosol delivery devices for use in ICU (generated from references [3–5]

	pMDI	Jet nebuliser	Ultrasonic nebuliser	Vibrating mesh nebuliser
Mechanism	Liquefied compressed gas used as a propellant Propellant-drug mixture is released on depressing the canister into the actuator The mixture expands and vaporises to generate the aerosol	Operated by compressed air or oxygen Gas through a jet entrains liquid which is broken into droplets Droplets impact a baffle and create small particles	Uses electrical energy Electrical energy converts to high frequency vibrations using a transducer Vibrations create a standing wave on the solution surface that generates aerosol	Uses electricity Electricity vibrates a piezo element (at ~ 128 kHz) Vibration moves the liquid formulation through a fine mesh to generate aerosol
Advantages	Portable and light Short treatment time Multiple doses and no preparation required	Least expensive nebuliser Easy to assemble and use Widely available	More efficient than JN Ease of use Shorter treatment time	Highest respirable fraction (~ 20–30%) Short treatment time No heating involved
Disadvantages	Propellant reactions Breath co-ordination required (resolved with spacer) High oral impaction	Long treatment times High residual volume Lower respiratory fraction (~ 10% of nebuliser charge	Heat denaturation (10–14 °C higher temperature than JN) High residual volume	Expensive Difficult cleaning Cannot use highly viscous liquids
IMV	Used with in-line spacer chamber in the inspiratory limb before the Y-piece Co-ordinate actuation with start of inspiration Wait 15 s between actuations	Place nebuliser in the inspiratory limb, 15–20 cm from the Y-piece Nebuliser gas flow 6–8 L/min	Place nebuliser in the inspiratory limb, 15–20 cm from Y-piece	Nebuliser placed in the inspiratory limb 15–20 cm from Y-piece if there is no bias flow or dry side of the humidifier with bias flow Remove HME
NIV	pMDI with spacer connected to face mask Actuation with the start of inspiration	Between leak port and mask Although respiratory pressure values might affect drug delivery, one should not change ventilatory setting for the sole purpose of nebulization	Between leak port and mask Although respiratory pressure values might affect drug delivery, one should not change ventilatory setting for the sole purpose of nebulization	Between leak port and mask Although respiratory pressure values might affect drug delivery, one should not change ventilatory setting for the sole purpose of nebulization
HFNC	Used with in-line spacer close to the nasal cannula Actuation with the start of inspiration	Nebuliser placed on the dry side of the humidifier	Nebuliser placed on the dry side of the humidifier Flow rate 30 L/min during delivery[a]	Nebuliser placed on the dry side of the humidifier Flow rate 30 L/min during delivery[a]

pMDI pressurized metered dose inhaler, *JN* jet nebulizer, *VMN* vibrating mesh nebulizer, *IMV* invasive mechanical ventilation, *NIV* non-invasive ventilation, *HFNC* high flow nasal cannula, *HME* heat and moisture exchanger

[a] Lower flow rates increase drug delivery and could be applied during nebulization in patients who did not improve

Whilst generally larger artificial airways are likely to reduce the airflow resistance and likely to yield better delivery, other studies showed no difference. In vitro studies indicate that positioning the VMN 15 cm from the Y-piece in the inspiratory limb of circuit with bias flow-off provides highest drug delivery [1, 5]. In in vitro studies, high bias flow has been shown to reduce drug delivery [7]. Heat and moisture exchanger (HME) placed between the nebulizer and patient results in lower drug delivery [1, 6]. Turning off the HH during nebulization may not provide significant advantages for aerosol delivery and hence not recommended. Patient–ventilator synchrony likely improves drug delivery. In vitro experiments showed, volume control, slower inspiratory flow and increased inspiratory pause might augment distal delivery of drugs and deposition. However, clinical studies failed to translate these findings [8].

2. Aerosol therapy with NIV avoids the need for disconnecting the patient from the NIV and patient discomfort. Special attention is required in two technical aspects: (1) type of NIV interface, and (2) position of the nebulizer.

It has been shown that nasal passage of the gas reduces drug delivery to the lungs [9]. And the presence of open leak or exhalation ports directly on the face mask also leads to a higher percentage of drug loss before reaching the patient's lung [10]. Therefore, inhalation with nasal masks or with vented interfaces is not recommended. Some interfaces have open ports in the mask to prevent CO_2 rebreathing, suggest capping the ports during aerosol delivery to reduce aerosol loss. Another key aspect is in single-limb non-invasive ventilators, VMN should be positioned between mask and exhalation port to provide optimal drug delivery [11]. At this position, between 5 and 25% of intended dose is delivered [12]. Aerosol therapy is affected by other ventilatory settings, such as inspiratory pressure (higher pressures are associated with higher delivered doses), expiratory pressure (lower pressures are associated with higher delivery), and type of nebulizer (VMN deliver higher doses than JN) [12, 13]. When a dual-limb ventilator is used, the same configuration as suggested for invasive mechanical ventilation is suggested (i.e. VMN 15 cm from the Y-piece in the inspiratory limb of circuit).

3. HFNC use is increasingly prevalent worldwide in many critical care settings.

There is a growing literature for inhaled therapies with HFNC. Two major barriers for effective drug delivery are the nasal passage of the gas (which entraps a high percentage of the aerosol) and the range of clinically useful gas flow during HFNC. Aerosol drug delivery was better at lower airflow as shown in an in vivo scintigraphy study [14]. Even with these limitations, a small clinical study using a VMN placed downstream the humidification chamber to deliver albuterol suggests bronchodilation effect similar to standard facial mask jet nebulization [15]. VMN provides 2–3-fold higher delivery than JN.

Safety considerations of aerosol therapy in ICU

Certain precautions should be taken to ensure safe aerosol therapy in the ICU. Nebulization with mechanical ventilation should include regular change of exhalation filter to prevent barotrauma [6]. Adequate sterility measures should be followed with reusable nebulizers. The ventilator settings should be reset if changed during nebulization [6]. Finally, measures to prevent fugitive emissions and aerosolization of infective particles should be included [16].

Aerosolized therapy provides a rapid, safe, and effective alternative mode of drug delivery in the ICU setting. Future research with newer formulations and devices needs to undergo adequately powered, well-designed randomised controlled trials to improve clinical outcomes.

Author details
[1] UQ Centre for Clinical Research, Faculty of Medicine, The University of Queensland, Brisbane, QLD 4029, Australia. [2] Department of Intensive Care Medicine, Royal Brisbane and Women's Hospital, Brisbane, Australia. [3] Emergency Medicine Discipline, Clinical Hospital, University of São Paulo, São Paulo, Brazil. [4] Syrian-Lebanese Institute of Teaching and Research, São Paulo, Brazil. [5] Barcelona Institute for Global Health, ISGlobal, Universitat Pompeu Fabra (UPF), CIBER Epidemiología Y Salud Pública (CIBERESP), Barcelona, Spain. [6] Pulmonary Division, Heart Institute, Faculty of Medicine, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.

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Declarations

Conflicts of interest
All authors declare no conflict of interest in relation to this paper.

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