Aerosol Therapy and Humidification

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Elena Fernández Fernández and Ronan MacLoughlin

35.1 Humidification in the Intensive Care Unit

As discussed in greater detail throughout this book, humidification of the patient airway is a critical component of many respiratory support interventions, especially in those patients in receipt of therapy over extended periods. Broadly, humidification is classified as (a) active or (b) passive. Active humidification typically employs the use of a heating plate which is used to vaporize sterile water, hence the common term of heated humidification (HH). This heated vapor is then introduced to the patient airways on appliance of the positive pressure or gas flow during the inhalation phase of the breath. The heater element is typically placed away from the patient, for reasons of practicality and safety. Given its placement, it is also less likely that the patient's own secretions will contaminate the heated water column. Passive humidification makes use of heat and moisture exchangers (HMEs) which are essentially compiled of a hydrophobic porous material that allows for patient-appropriate gas flows to pass through, but not the patient's own exhaled moisture. They capture heat and moisture from the patient's exhaled gas and return up to 70%

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E. F. Fernández
Medical Affairs, Aerogen Limited, Galway, Ireland

R. MacLoughlin (✉)
Research and Development, Science and Emerging Technologies, Aerogen Limited, Galway, Ireland

School of Pharmacy and Biomolecular Sciences, Royal College of Surgeons in Ireland, Dublin, Ireland

School of Pharmacy and Pharmaceutical Sciences, Trinity College, Dublin, Ireland
e-mail: rmacloughlin@aerogen.com

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of both to the next inhalation [1–4]. Often, these HMEs are primed with sterile water prior to use as part of the manufacturing process. HMEs are placed between the patient wye and patient interface, for example, the endotracheal tube or tracheostomy tube. HME may also be combined with a filter layer in order to prevent microbiological contamination of the patient ventilatory circuit. This potential for contamination stems from the increased likelihood of patient secretions impacting on the HME itself and thereafter migrating through the porous materials to the oxygen source side. Such HMEs are referred to as HMEF.

The comparative clinical efficacy with respect to active (HH) versus passive (HME) humidification systems has been reported to be similar. In one meta-analysis and meta-regression of randomized controlled trials, no superiority of HMEs or HHs, in terms of artificial airway occlusion, pneumonia, and mortality, was found. It was noted that a trend favoring HMEs was observed in studies including a high percentage of patients with pneumonia diagnosis at admission and those with prolonged mechanical ventilation [5]. A randomized multicenter trial investigating the impact of HH or HME on ventilator-associated pneumonia rates in adults found no difference between the two [6]. A more recent study in 20 subjects positive for SARS-Cov-2 reported a greater incidence of endotracheal tube occlusions (ETOs) with HH. Following an investigation, a strong correlation between heater plate temperatures of the HH and humidity delivered was seen. Subsequently, measures to avoid under-humidification were implemented (including heater plate temperature monitoring), and no more ETOs occurred [7]. Similar variability in humidification levels has been noted also for various combinations of gas flow rate, humidifier type, and circuit type [8]. Intuitively, it would be expected that variations in humidification levels would have varying effects on hygroscopic growth of aerosol droplets. Finally, unconditioned gases, that is to say, no heating and no humidity added above ambient or dry, are not generally used in neonates for reasons that include the increased body temperature recorded in infants with HH and the resulting reduction in cases of hypothermia on admission to the neonate ICU [9]. HH versus HME was assessed in one recent study in rabbits and found that HH increased the highest absolute humidity levels, followed by HME, with unconditioned gases recording the lowest. The study concluded that the use of a T-piece resuscitator with HME could be a good alternative to HH given that positive-pressure ventilation is used ideally for short periods of time in the delivery room [10].

HH and HME may be used together inadvertently, and this dual humidification in ventilation circuits is considered an under-recognized error in the ICU, in operating room, or during patient transfer, and correspondingly there have been reports of critical airway occlusions within 24 h [11, 12]. In this scenario, unless the aerosol device is placed between the HME and endotracheal tube, no aerosol would likely be delivered to the patient given the HME would prevent aerosol transit to the patient.

One other consideration in the selection of either HH or HME that does not relate to humidification is the potential effect on ventilatory function and gas exchange. In 24 patients with acute respiratory failure (ARF), Jaber et al. report a negative effect of HME usage. They found that the increased dead space of the HME decreased the

efficiency of non-invasive ventilation (NIV) in those patients [13]. As these effects would likely happen over time, the implication for aerosol therapy is that the delivered dose would change over time also.

In a prospective, randomized, controlled physiologic study in difficult-to-wean chronic respiratory failure (CRF) patients, HME usage was associated with significantly increased inspiratory effort variables as well as dynamic intrinsic positive end-expiratory pressure and severe respiratory acidosis. The authors, therefore, concluded that the type of airway humidification device used may negatively influence the mechanical efficacy of ventilation and, unless the pressure support ventilation level is considerably increased, the use of a heat and moisture exchanger should not be recommended in difficult or potentially difficult-to-wean patients with CRF [14]. Additional dead space and variation in ventilation function, as identified in those studies, have been shown to affect the amount of aerosol delivered to the patient lung [15, 16].

35.2 Aerosol Therapy Combined with Humidification

Aerosol therapy during respiratory support in the intensive care unit (ICU) is a commonly prescribed intervention in the treatment of both respiratory (local targeting) and non-respiratory (systemic targeting) conditions. International surveys on aerosol therapy in the ICU suggest that between 90% and 99% of healthcare professionals (HCPs) administer aerosol therapy during both invasive and non-invasive mechanical ventilations and approximately 24% administer aerosol therapy during high-flow nasal oxygen (HFNO) therapy [17–19]. The direct access to the lung offers the potential for targeted high-dose delivery direct to the site of action, for example, topical administration of bronchodilators, ionic solutions, steroids, mucociliary modulators and anti-infectives, or targeting the site of absorption for systemically acting drugs, such as prostanoids, anticoagulants, and diuretics.

From these surveys, the primary aerosol delivery devices used in the ICU include pressurized metered dose inhalers (pMDI), Venturi jet nebulizers (JN), and vibrating mesh nebulizers (VMN). Each may be included in the patient circuit during mechanical ventilation, both invasive and non-invasive. However, following from COVID-19 renewed focus on HCP safety during aerosol therapy, the VMN has become the favored device as it has been shown to maintain a closed ventilator circuit during drug refill, unlike the JN which must be disassembled for drug refill, nor does the VMN need to be removed from the circuit between doses, as is the case with pMDI [20, 21]. This is reflected in several guidance and recommendation documents issued around the world [22–28]. Whilst no additional steps are mandated during HH, between 22% (international) and 62.7% (China) of HCPs reported that they turned off the humidifier during concurrent use of aerosol therapy [17, 18]. Concurrent use of each of pMDI, JN, and VMN has been described in the literature, and apart from selected HME, there are no contraindications against their use. All three of these aerosol device types are also suited for use with HH circuits and with no specific contraindications against their use. Figures 35.1, 35.2, and 35.3 detail the potential placement location options for aerosol delivery devices (indicated by

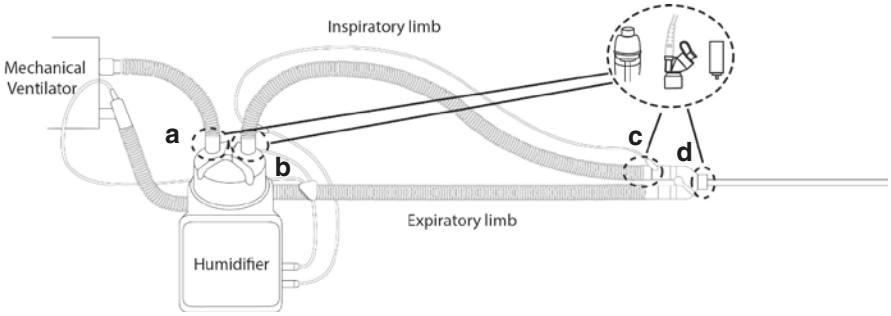

Fig. 35.1 Locations where aerosol devices may be included in the active, heated humidified (HH) mechanical ventilation setup. (**a**) Ventilator or dry side of humidifier, (**b**) patient or wet side of humidifier, (**c**) inspiratory limb at the patient wye, and (**d**) between the patient wye and patient interface, e.g., endotracheal tube (shown here), tracheostomy

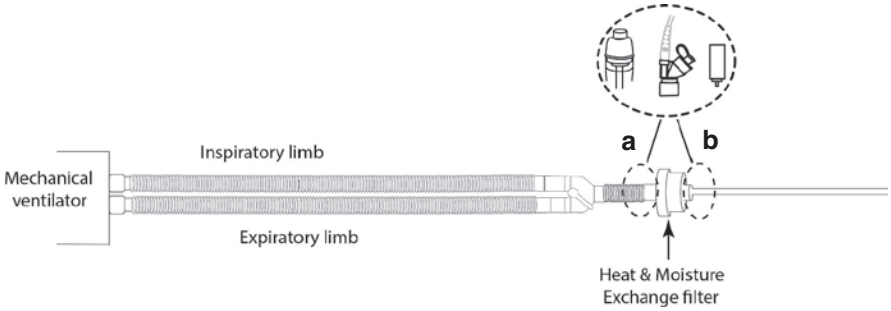

Fig. 35.2 Locations where aerosol devices may be included in the passive, heat and moisture exchange (HME) mechanical ventilation setup. (**a**) Ventilator side of the HME. *Note*: This is only suitable when aerosol therapy is being administered in combination with a bypass HME or HME that allows aerosol to pass through the porous materials. (**b**) Patient side of the HME, between HME and patient interface, e.g., endotracheal tube (shown here), tracheostomy

the device in the dotted circle) in the HH mechanical ventilation, HME mechanical ventilation, and HFNO configurations, respectively.

HME may require additional interventions on behalf of the HCP. For example, increased frequency of HME replacement given the potential for increased resistance to flow across the HME as the exhaled fraction of medical aerosol makes the HME wetter over time. It must be noted however that this exposure to exhaled medical aerosol is not necessarily catastrophic, and the outcome will vary by drug, dosing regimen, and HME type (large surface area pleated paper versus small surface area sponge) [29, 30]. Indeed, some HME manufacturers, such as Intersurgical (UK) and PALL (USA), indicate that a selection of their HME is suitable for repeated use in combination with aerosol therapy and maintain the same (typically 24 h) life as those HME not approved for use with aerosol therapy.

HME designs exist that facilitate concurrent aerosol therapy, without the need for removal of the HME or the potential increased frequency of replacement. One such

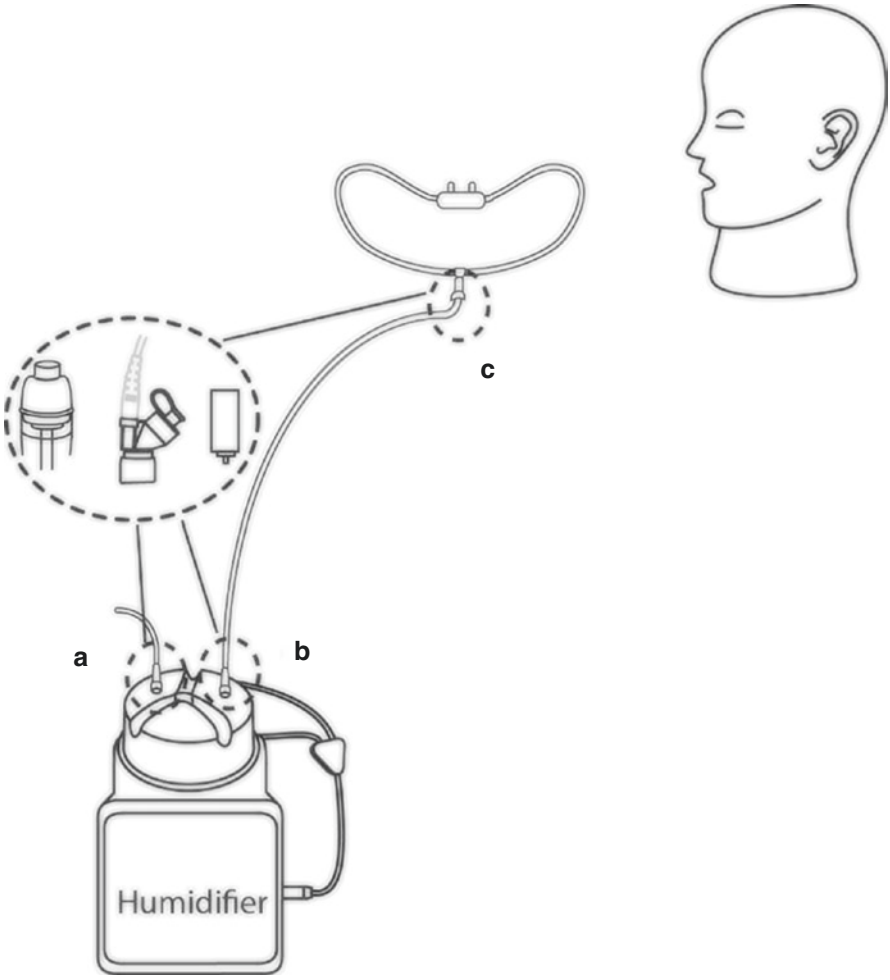

Fig. 35.3 Locations where aerosol devices may be included in the high-flow nasal oxygen (HFNO) setup. (**a**) Gas source/dry side of the humidifier, (**b**) patient/wet side of the humidifier, and (**c**) between the patient circuit and patient interface, e.g., nasal cannula (shown here), tracheostomy, mask

design is known as the bypass HME where a manually actuated mechanical valve can direct air through the HME membrane or, during aerosol therapy, bypass the membrane so that it does not come into contact with the exhaled medical aerosol. Examples of bypass HMEs include, but are not limited to, CircuVent® HME/HCH (ICU Medical, USA), AirLife® Filtered Bypass HME (Vyaire Medical, USA), and Gibeck® Humid-Flo® HME (Teleflex, USA).

There is also an alternate HME design that claims compatibility with aerosol therapy but relies on the porous materials, with no filter as opposed to a bypass mechanism. In this design, aerosol droplets pass through the porous materials. The

ThermoFlo® HN (Arc Medical, Ireland) claims only a "moderate" reduction in aerosol delivery through the HME with no significant increase in resistance measures.

VMN is the predominant delivery device used during HFNO as it does not influence gas flow or applied pressures, facilitates constant applied pressure during the drug refill process, and is increasingly recommended for use and integrated into self-contained blower-based HFNO systems [19, 31, 32]. Those systems include the Fisher & Paykel Airvo™ system, the Vapotherm Precision Flow Hi-VNI™, and Inspired Medical O2FLO™ system as examples. JN are contraindicated against for connection to HFNO systems by some manufacturers given that the additional air required for the nebulizer's operation alters gas flow and the titered oxygen mixes, especially at lower applied gas flow rates. HFNO systems are exclusively HH systems that incorporate the humidifier in the patient circuit and with gas flowing in one direction only. Thus, HME usage during HFNO is nil.

35.3 Effect of Humidification on Aerosol Drug Delivery

Across all respiratory interventions whether invasive or non-invasive, there are several contributors to aerosol drug delivery performance, such as aerosol device, patient interface, aerosol generator position in the circuit, gas flow rates, and breathing and ventilation parameters that have been shown to affect aerosol drug delivery to the patient lung in the critical care setting [31, 33–39]. However, what remains less clear is whether the hygroscopic growth of aerosol droplets that happens when aerosol is exposed to a humidified patient circuit has an appreciable effect on the dose delivered to the lung. A review of the published literature suggests that there is little consensus between (a) the various published human studies, (b) the chosen respiratory support intervention (e.g., HFNO or MV), and (c) the in vitro bench studies. Selected studies are summarized below in order to inform the readers understanding of the current state of the art.

35.4 Effect on Aerosol Droplet Diameters

Hygroscopic growth of aerosols itself is well described in the literature where, briefly, the greater the temperature and relative humidity, the greater the increase in droplet diameter, and thus the greater the droplet mass (mass median aerodynamic diameter (MMAD)) [40–44]. In relation to aerosol-mediated drug delivery, an increase in droplet and mass increases the ballistic aerosol fraction within the patient circuit that is then more likely to impact and rain out, thus becoming unavailable to the patient for inhalation as an aerosol, or in the case of a spontaneous breathing patient inhaling via mouthpiece, the larger droplets may deposit high up in the respiratory tract [34, 45]. This basic understanding is likely the rationale for HCPs being noted to turn off humification during aerosol therapy.

The timescale for water condensation on a growing droplet can depend not only on the starting droplet size and the rate of gas-phase moisture transport but also on the surface and bulk composition of the droplet [46]. Thus, growth can be controlled to some degree by formulation design, for example, the addition of fatty acids or amphiphilic surfactants [47]. Empirical characterization of the timescale for droplet growth was performed in one study for saline, tobramycin plus saline, and tobramycin alone. Droplets were seen to grow from approximately 1 μm to between 3 and 4 μm (depending on the formulation) within 5–6 s when relative humidity was raised from 50% to 99.5% [48]. This is a significant increase in droplet diameter and such growth, or at least a portion of it is entirely feasible as a droplet is transported down a HH HFNO circuit or the inspiratory limb of a HH mechanical ventilator circuit.

Interestingly, exploitation of hygroscopic growth of therapeutic aerosols for increased aerosol delivery has been proposed. In these systems, small droplets capable of distal distribution within the lung are generated and, as they are exposed to the humid environment of the lung, undergo hygroscopic growth. As a consequence, these now bigger heavier droplets deposit on the lung surface on exhalation [49, 50].

35.5 Spontaneous Breathing: Mouthpiece

A small number of human studies have been published looking at the effect of hygroscopic growth itself and do provide some insight into the combination of humidification and aerosol therapy. One dynamic SPECT study in six spontaneously breathing healthy subjects (no respiratory intervention) assessed the effect of hygroscopic growth on aerosol deposition in the lung. Changes in regional deposition with increasing hygroscopic growth were recorded [51]. In line with the published literature looking at differences in regional deposition with differing droplet sizes, the results in this study revealed significant differences in aerosol deposition resulting from the controlled hygroscopic growth of droplets, thus demonstrating the potential effect of humidification on aerosol therapy [52].

35.6 Spontaneous Breathing: HFNO

To these authors' knowledge, there is no study that has looked directly at the comparative effect of both HH and HME on aerosol droplet size under fully controlled study conditions; however, it has been investigated under HFNO conditions where the gas was both heated and unheated. In that study, the MMAD of the aerosol droplets was significantly higher in the HH condition. With respect to aerosol delivery to the lung, unheated gas was associated with aerosol delivery performance similar to that recorded for heated humidified gas but only at 10 L/min. At higher gas flow rates (30 and 50 L/min), aerosol delivery performance was significantly higher when the gas was unheated [53]. A small preliminary bench study of the effect of

humidifier temperature was conducted during HFNO, and no difference was noted in aerosol delivery for two temperatures (34 and 37 °C) when assessed across three gas flow rates (10, 30, and 60 L/min) [54].

35.7 Mechanical Ventilation

There are several published in vitro reports on the impact of humidification on aerosol delivery performance during mechanical ventilation; however, the findings are not all in agreement.

Lin et al. demonstrated on the bench that turning off the humidifier for up to 40 min prior to pMDI administration on ventilator did not increase aerosol delivery [55]. This finding was contrary to that of Lange and Finlay where on ventilator an increase in pMDI MMAD was seen with increasing temperature and relative humidity, resulting in a significant reduction in inhaled mass [43].

Studies directly comparing several different aerosol generator devices in humidified and non-humidified ventilator circuits have also been conducted. These also suggest that in a non-humidified circuit the inhaled dose was greater than that with a humidified circuit, and this was consistent across each of pMDI, ultrasonic nebulizer (USN), JN, and VMN [56].

The effect of HME design has also been assessed. Ari et al. studied the aerosol delivery performance of a VMN when used concurrently with three different types of bypass HME. Results indicate that there was no difference between the CircuVent, Humid-Flo, and AirLife [57]. This in vitro study also looked at the effect of simulated exhaled humidity from the patient in an effort to understand what effects that may have on reported aerosol delivery. It was noted that when simulated exhaled humidity was added to the ventilator circuit, aerosol drug delivery was significantly reduced but more consistent. The authors posit that the simulated exhaled humidity may make the bench setup more consistent with the circuit environment of the real ventilated patient. In another, preliminary bench study, the choice of HME design with varying materials (pleated paper, sponge, filter) was not seen to have a significant effect on the amount of aerosol delivered to the end of the endotracheal tube [58]. Separately, a single study reported the aerosol loss whilst passing through the ThermoFlo was in the order of <40%, with no significant increase in airflow resistance [25]. Considering this finding, it is clear that when assessing the potential effect of the type of humidification (HH or HME), one must also consider the intricacies of the components involved. Here the HME design, not passive humidification, was the cause of the reduced aerosol delivery.

In a randomized crossover design involving 36 asthmatic patients in receipt of mechanical ventilation, urinary salbutamol was used as a measure of the amount of aerosol delivered to the lung under “dry” and “humidified” (HH) conditions. In this study, no significant difference was noted between the two. The authors suggest that in vitro reports overestimate the impact of dry non-humidified versus heated humidified conditions on the delivery of aerosol during invasive mechanical ventilation, thus further undermining the practice of turning the humidifier off [59].

A further study conducted by the same group in 72 asthmatic subjects receiving invasive mechanical ventilation compared VMN to pMDI, under 2 humidity conditions, that is to say, with and without humidification. Results indicated that VMN resulted in a trend to shorter ICU days compared to pMDI and that this trend held for both humidification conditions [60].

Moraine et al. investigated the placement of an USN (a) before the humidifier (which was turned on) and (b) at the end of the inspiratory limb, at the patient wye, with the humidifier turned off during aerosol delivery. In this 38-subject study, the pulmonary bioavailability of ipratropium, assessed by urine concentrations of the drug, was similar for both conditions, suggesting again that in the clinical setting, there may be little beneficial effect in turning off the humidifier [61].

Similar findings were again noted during a study of 48 COPD patients in receipt of single-limb non-invasive ventilation (NIV). Assessing the effect of turning off the humidifier, no difference was seen in the urine levels of salbutamol compared to having the humidifier on [62]. This group also reports no difference in a bench model of single-limb NIV, under three heat and humidification conditions, that is to say, (a) no heat and no humidification, (b) humidification with no-heat, and (c) heat with humidification [63]. Importantly, those findings were replicated in an ex vivo setup wherein subjects inhaled ipratropium via an aerosol capture filter and the potential dose of inhaled ipratropium quantified [62].

A final NIV study in 36 COPD patients in receipt of automatic continuous positive airway pressure (auto-CPAP) looked at the effect of humidification on salbutamol levels in the urine following delivery using VMN, JN, and pMDI. The findings in this study once again recorded no difference in the urinary excreted salbutamol levels post inhalation between the humidified and dry conditions [64].

A summary of the relevant studies relating to the effect of humidification on aerosol therapy is illustrated in Table 35.1.

In summary, studies in invasively and non-invasively mechanically ventilated patients observed no significant difference in the amount of drug delivered to the lung, which is counter to the findings of the study conducted in spontaneously breathing patients and several of the published in vitro and in silico studies. This may suggest that other factors contribute to the experimental findings, such as lack of paired controls for variables such as position of nebulizer in the circuit, the combination of humidification on or off and where the nebulizer is positioned, and the use of simulated exhaled humidity. In addition, variables not discussed here but mentioned in the literature include the pre-conditioning of the circuit for sufficient amounts of time to allow for the HH or HME or un-humidified conditions to reach a point at which they are truly representative of the intended state and experimental setup for each intervention that are consistent with those seen in a clinical practice. Finally, given that the majority of the in vivo and a portion of the in vitro studies suggest that there is no difference in clinical endpoint or reported dose delivered, the practice of turning the humidifier off during aerosol therapy in order to maximize the delivered dose should be reconsidered. Indeed, any potential increase in the efficiency of aerosol delivery must be weighed against the potential deleterious effects of ventilation with under humidified dry gases [65, 66].

Table 35.1 Graphical summary of the findings on the effect of humidification on aerosol therapy reported by studies cited in this chapter. Effect is defined as a statistically significant value in the respective studies

Reference	Study type	Measure	No effect	Effect		*p* value
				Humidity	No humidity	
Hadrell et al. [40]	In vitro	Droplet size analysis		▬		NS
Peng et al. [42]	In vitro	Droplet size analysis		▬		NS
Lang et al. [43]	In vitro—MV	Predicted delivered dose -pMDI		▬		<0.01
Lin et al. [55]	In vitro—MV	Predicted delivered dose -pMDI	▬			NS
Ari et al. [56]	In vitro—MV	Predicted delivered dose			▬	<0.01
Ari et al. [57]	In vitro—MV	Predicted delivered dose - VMN			▬	<0.01
Ari et al. [57]	In vitro—MV	Predicted delivered dose - exh humidity	▬			>0.5
Batemen et al. (2016)	In vitro—MV	Predicted delivered dose - VMN	▬			0.488
Murphy et al. [38]	In vitro—HFNO	Predicted delivered dose -VMN	▬			>0.5
Saeed et al. [63]	In vitro—NIV	Predicted delivered dose		▬		NS
Chan et al. (2004)	In vivo imaging—tidal	Deposition pattern		▬		NS
Alcoforado [53]	In vivo imaging—HFNO	Lung dose - 30 + 50 LPM			▬	0.015/<0.001
Alcoforado [53]	In vivo imaging—HFNO	Lung dose -10 LPM	▬			0.531
Moustafa et al. [59, 60]	In vivo—human MV	Urinary salbutamol	▬			NS
Moustafa et al. [59, 60]	In vivo—human MV	Urinary salbutamol	▬			<0.5
Moraine et al. [61]	In vivo—human MV	Urinary ipratropium	▬			<0.5
Saeed et al. [62]	In vivo—human NIV	Urinary salbutamol	▬			NS
Abdelrahim et al. [64]	In vivo—human CPAP	Urinary salbutamol	▬			NS

pMDI pressurized metered dose inhaler, *VMN* vibrating mesh nebulizer, *MV* mechanical ventilation, *HFNO* high-flow nasal oxygen, *NIV* non-invasive ventilation, *CPAP* continuous positive airway pressure

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