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## Aerosol Therapy for Ventilator-Dependent Patients: Devices, Issues, Selection & Technique

Arzu Ari, PhD, RRT, PT, CPFT, FAARC

Many types of aerosol devices for delivering inhaled therapeutics are available for treating mechanically ventilated patients. Each type of device has advantages and disadvantages, which are discussed in this article. Many variables must be accounted for to optimize the technique of delivery and the amount of medication administered. It begins with choosing the right device based on the medication to be administered, knowing what particle size will be produced over what period of time, then determining how aspects of mechanical ventilation will affect medication delivery and deposition. Intermittent versus continuous nebulization, the nebulizer type, the type of spacer and its electrostatic charge, and the aerosol device's position in the ventilator circuit all affect the efficiency of aerosol delivery. Ventilator parameters, including flow rate, pressurization, and features like the presence of a heat-moisture exchanger also affect medication delivery. In addition, correct patient positioning can improve treatment efficacy and response.

## Aerosol Therapy In Spontaneously Breathing & Mechanically Ventilated Patients: Description, Selection & Issues

**Moderator:** Tim Myers, RRT-NPS, MBA, FAARC

**Panelists:** Ariel Berlinski, MD  
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Many issues surround the selection and use of aerosol therapy in all populations of patients. Matching the medication to the delivery device is key, as is understanding how the mechanistic attributes of nebulizers and mechanical ventilation can work together or against each other in delivering medication effectively. Each nebulizer option offers advantages and disadvantages that need to be assessed according to patient need, the medication involved, and use with mechanical ventilation (if present). Aerosol therapy for pediatric patients poses a unique set of challenges. Standards of practice are still evolving regarding minimizing the risk ventilator-associated pneumonia with aerosol treatments. Adherence to treatment regimens is a global issue that encompasses patient perceptions, patient/family education, financial concerns, insurance reimbursement, and other factors. Our panel of experts discusses a patient-focused approach to aerosol therapy in mechanically ventilated and spontaneous breathing patients.

# Aerosol Therapy for Ventilator-Dependent Patients: Devices, Issues, Selection & Technique

Arzu Ari, PhD, RRT, PT, CPFT, FAARC

**A**erosol devices have been used to administer inhaled medications since the invention of modern mechanical ventilators. Although many new aerosol devices are available for ventilator-dependent patients, successful aerosol therapy still depends on thorough clinician knowledge of aerosol devices and their proper use. This paper explains the types of aerosol devices available on the market and provides strategies for choosing the right device for optimal treatment of mechanically-ventilated patients.

## Description of Aerosol Delivery Devices

**Nebulizers:** Jet, ultrasonic and mesh nebulizers are used for aerosol drug delivery by converting liquid medications into small droplets that can be inhaled into the lower respiratory tract of ventilator-dependent patients.

To aerosolize liquid medications, jet nebulizers use a jet of compressed air or oxygen to draw on a reservoir and shear the liquid into particles. Jet nebulizers are widely used for ventilator-dependent patients because they are inexpensive and easy to use.

Ultrasonic nebulizers are powered by electricity or battery to generate high frequency vibrations with a piezo, thus creating a standing wave in the medication and aerosols at the crest of the wave.<sup>1,2</sup> Unlike jet nebulizers, they do not add gas to the ventilator circuit, rather, aerosol particle size and drug output are affected by the frequency and amplitude of vibration of the piezo-electric crystal. Aerosol particle size is inversely related to the vibration frequency of the piezo-electric crystal, while drug output is directly related to the amplitude of crystal vibration.<sup>3,4</sup>

The mesh nebulizer, also operated by electricity or battery, vibrates a piezo that

moves liquid formulations through a fine mesh to generate aerosol.<sup>1,2,5</sup> The mesh nebulizer is a single-use device with a vibrating aperture plate designed to deliver aerosolized medications to mechanically-ventilated patients. The nebulizer is compatible with conventional ventilators. Because the mesh nebulizer operates without compressed gas, it does not change ventilator parameters and the reservoir of the nebulizer can be refilled without interrupting ventilation. Furthermore, mesh nebulizers are easy to use and have a higher rate of drug output than jet nebulizers. Unlike ultrasonic nebulizers, they do not affect the temperature or concentration of the solution being delivered.<sup>6</sup>

As with other new nebulizers, mesh nebulizer designs are portable, handheld, and highly efficient with low residual volume.<sup>1,2,5</sup> They also have a silent operation and rapid output. Also, solutions, proteins and liposomal formulations can be nebulized by mesh nebulizers. Because of these advantages, mesh nebulizers are likely become popular for delivering aerosols to ventilator-dependent patients. Whereas in vitro studies have shown mesh nebulizers to be efficient in aerosol delivery during mechanical ventilation,<sup>7,8</sup> more clinical information about them is needed.

**Pressurized Metered-Dose Inhalers (pMDIs):** The pMDI is the most commonly used aerosol device for inhalation therapy worldwide; it is a compact and portable device that is easy to operate with short treatment time, multi-dose convenience and good dose consistency.<sup>9-11</sup> The basic components of a pMDI include a canister, propellants, drug formulation, metering valve and actuator. A pressurized mixture of propellants, surfactants, preservatives and active drug is released from the metering valve of the canister, which fits into an actuator boot.

Two types of propellants are used with

pMDIs: (1) chlorofluorocarbon (CFC) and (2) hydrofluoroalkane (HFA). HFA-pMDIs are different from CFC-pMDIs in terms of the formulation, metering-valve and actuator design.<sup>5,9</sup> For example, HFAs contain ethanolic solutions while CFCs use a surfactant for dispersion. HFAs have a softer and finer aerosol spray with greater lung deposition than CFCs.<sup>12-14</sup> However, despite differences in the pMDI formulations, HFA-pMDIs are similar to those of CFC pMDIs, in terms of bronchodilator response,<sup>15,16</sup> pulmonary function<sup>17,18</sup> and side effects.<sup>19</sup>

A variety of spacers are used for aerosol drug delivery in mechanically-ventilated patients. However, electrostatic charge and the type of spacer need to be considered. The electrostatic charge decreases aerosol delivery by drawing small particles to the walls of the chamber; therefore, clinicians need to review the electrostatic properties of the spacer before treatment. Spacers are made of metal, paper or plastic, each of which have different electrostatic properties. Electrostatic charge is not an issue with metal or paper spacers, but plastic spacers may have electrostatic or non-electrostatic properties. If a plastic spacer with electrostatic properties is used for aerosol therapy, clinicians should wash it with liquid detergent to reduce the electrostatic charge before treatment. Actuating the pMDI 12 or 20 times into a spacer also reduces the electrostatic charge. However, many pMDI doses are wasted with this technique, and it is less effective than washing.<sup>20,21</sup>

Types of spacers include unidirectional, bidirectional and cylindrical/reservoir adaptors. The spacer type influences the efficiency of aerosol delivery during mechanical ventilation.<sup>9,22-24</sup> While bidirectional spacers are superior to unidirectional spacers in dose delivery, cylindrical spacers have been shown to have 4-to-6 fold greater efficiency

on aerosol delivery than unidirectional and bidirectional spacers that attach directly to the endotracheal tube (ETT).<sup>25-27</sup>

### Issues with Aerosol Delivery Devices

**Problems with Nebulizers:** Jet nebulizers are bulky. They require a compressor or pressurized gas to operate, and are labor-intensive.<sup>20,28,29</sup> They are also less efficient than other aerosol devices and retain a lot of the medication in the nebulizer cup, limiting the drug available to the patient. They require more preparation to setup, and more time for cleaning and maintenance than pMDIs. Further, the additional gas flow delivered into the ventilator circuit may change the set flow and delivered volume and require adjustments of alarm settings both during and after nebulization if the ventilator does not compensate for nebulizer gas flow entering the circuit. This is especially important in ventilator-dependent children because they are affected to a greater extent when extra flow is added to the ventilator circuit. Clinicians should exercise caution when changing ventilator parameters and return to them to pretreatment levels after the treatment is completed. Since jet nebulizers are attached to the ventilator circuit with a standard T adaptor, attaching or removing the nebulizer from the ventilator circuit may interrupt ventilation. Therefore, valved T adaptors should be used in order to allow placement and removal of the jet nebulizer without loss of pressure in the ventilator circuit.

Ultrasonic nebulizers also have several problems. They are bulky and more expensive than jet nebulizers. Their particle size is larger than with jet nebulizers, and drug solutions used with ultrasonic nebulizers become more concentrated during operation. There is an increase in solution temperature after a few minutes of operation, and as a result, ultrasonic nebulizers may denature some drug formulations. Although smaller ultrasonic nebulizers are used to deliver aerosolized drugs to mechanically-ventilated patients,<sup>30</sup> the cost and size of these nebulizers make them less desirable, in addition to their inefficiency in nebulizing drug suspensions and more viscous solutions.<sup>31,32</sup> Therefore, ultrasonic nebulizers are not widely used for aerosol delivery during mechanical ventilation.

Mesh nebulizers are more expensive than jet nebulizers. Suspension or viscous drugs may clog the pores of the mesh nebulizer which may not be easily detectable by the output of the nebulizer.<sup>33</sup> Cleaning of mesh nebulizers should be gentle in order to prevent damage to the mesh.

When a nebulizer is used with mechanically-ventilated patients, escape of aerosol to the environment creates health risks to healthcare providers and bystanders.<sup>34</sup> Other problems associated with nebulizers are infection due to contamination (jet nebulizer) and increases in drug concentration in the nebulizer cup when using jet and ultrasonic nebulizers.

**Problems with pMDIs:** If a dose counter is not used with a pMDI, it is difficult to determine the dose left in the pMDI. Thus, pMDIs may be used beyond their capacity or remaining doses may be wasted. The dose counters, which are attached to the top or boot of the pMDI, are manufactured by different companies. Although use of dose counters is recommended with all pMDIs, it should be noted that newer pMDIs with dose counters may not permit removal of the canister from the actuator. In this case, the actuator itself must fit an adapter to be connected to the ventilator circuit, but the efficiency of such systems is not known. Integrating dose counters into new pMDIs is required by the FDA in order to determine the total number of doses available in the device.<sup>35</sup>

### Selection of an Aerosol Device for Mechanically-Ventilated Patients

Nebulizers or pMDIs with in-line spacers are used to administer inhaled medications during mechanical ventilation. Both nebulizers and pMDIs produce similar therapeutic effects in mechanically-ventilated patients.<sup>4,22,36-38</sup> The therapeutic aim and availability of the drug generally determine which aerosol device to use. pMDIs are preferred for inhalation therapy in ventilator-dependent patients because of problems associated with use of nebulizers and the advantages of pMDI, such as convenience, lower cost and decreased risk of damaging the flow sensor.<sup>4,39</sup> However, only a few drug formulations are available as pMDIs. Therefore, they are mainly used to deliver bronchodilators and corticosteroids

for ventilator-supported patients with airway obstruction,<sup>22,23,40</sup> while nebulizers are used to deliver a variety of drugs such as bronchodilators, corticosteroids, antibiotics, prostaglandins, surfactant, mucolytic agents and other formulations that are not available as pMDIs. A few studies have shown that use of pMDIs with ventilator-dependent patients has increased significantly over the years<sup>41,42</sup> because of their convenience, more consistent dosing and reduced chances of bacterial contamination.<sup>43,44</sup>

### Factors Affecting Aerosol Drug Delivery During Mechanical Ventilation

Aerosol delivery during mechanical ventilation depends on several factors. These can be divided into three categories: (1) ventilator-related factors, (2) circuit-related factors and (3) device-related factors.<sup>45</sup>

**Ventilator-related Factors:** Ventilator-related factors such as inspiratory flow rate, ventilator mode, inspiratory time, tidal volume, bias flow and wave patterns make a significant difference in aerosol drug delivery to ventilator-dependent patients. The lower the flow, the greater the amount of aerosol delivered to the patient. Since high inspiratory flow rates increase turbulent flow and inertial impaction of aerosol particles, aerosol deposition with high inspiratory flow rates is less than with lower flow rates. Peak flow rates of 40-50 L/min may be used to improve drug delivery during mechanical ventilation as long as this is tolerated by the patient.<sup>46,47</sup>

For critically ill patients with low compliance and low resistance, aerosol delivery through a nebulizer is more efficient with volume-controlled ventilation than pressure-controlled ventilation.<sup>48</sup> This is not the case with pMDIs. Also, it has been shown that spontaneous ventilation modes such as continuous positive airway pressure (CPAP) increase aerosol delivery by 30% compared to controlled breaths of equivalent tidal volume.<sup>49</sup> Nebulizers generate aerosol over time; therefore, using a longer inspiratory time increases the efficiency of nebulizers, in contrast, pMDIs, which have a short aerosol generation time, are not influenced by the duration of inspiratory time.

Tidal volume (Vt) is directly related to aerosol deposition. Although setting Vt

greater than 500 ml in an adult improves aerosol drug delivery during mechanical ventilation,<sup>47,49</sup> larger Vt can damage the lungs of mechanically-ventilated patients. Vt may be a problem when it is not adequate to move the aerosol from the generator to the end of the patient airway in a single breath; therefore, it is important to set the Vt larger than the volume of the ventilator circuit and artificial airway in order to increase aerosol delivery.

Although descending ramp wave patterns provide higher efficiency than square wave patterns at the same peak flow, the effect of inspiratory waveform is much less in pMDIs than in nebulizers.<sup>48</sup> Bias flow, also known as trigger sensitivity, affects the efficiency of nebulizers during mechanical ventilation. Increasing bias flow from 2 to 5 L/min decreases aerosol deposition in ventilator-dependent patients by diluting aerosols and increasing the washout into the expiratory limb between breaths.<sup>8</sup>

**Circuit-related Factors:** Using heat-moisture exchangers (HMEs) or heated humidifiers, the gas in the ventilator circuit is heated and humidified in order to avoid drying the airway mucosa. Since the filter in the HME is considered a barrier to aerosol delivery, it should not be placed between the aerosol device and the patient. Also, if a dry circuit is used, aerosol therapy should be completed in 15 minutes to minimize the effects of dry gas on the airway mucosa.<sup>40</sup>

As shown in Figure 1, some HMEs designed for aerosol delivery (HME-AD) allow inhalation therapy without removing the HME-AD from the circuit during mechanical ventilation. Although the designs of these HME-ADs are different, each HME-AD has two configurations: (1) an HME configuration that functions like a regular HME, and (2) an aerosol configuration in which inspiratory gas bypasses the HME to deliver inhaled medications to ventilator-dependent patients. It has been reported that drug delivery varies with HME-ADs because of the

design and composition of the HME-ADs,<sup>50</sup> but clinical research is needed to determine the in-vivo efficiency of aerosol delivery by different HME-ADs and the effectiveness of HME-ADs with different aerosol devices.

Several in-vitro studies have shown up to 50% reduction in aerosol delivery with heated/humidified ventilator circuits.<sup>7,22,49,51-54</sup> However, bypassing the humidifier and exposing a ventilator-dependent patient to dry and cold gas just to increase aerosol deposition is not recommended. Clinicians can increase the efficiency of aerosol therapy by paying attention to the technique of administration and increasing the dose when a heated humidifier is used.

The density of gas used with the ventilator has been shown to make a substantial difference in aerosol delivery. For instance, helium-oxygen mixtures greater than 50% increase aerosol delivery with nebulizers and pMDIs more than air or air-oxygen mixtures used to ventilate the patient.<sup>55</sup>

Aerosol deposition with artificial airways such as an endotracheal tube (ETT) or tracheostomy tube (TT) has not been studied much. Also, research on the efficiency of aerosol delivery in intubated patients has focused largely on ETT, with little analysis of effect of TT on aerosol delivery during mechanical ventilation. Since ETTs are narrower than the internal diameter of the trachea, they are associated with increased airway resistance and losses in aerosol delivery.<sup>56,57</sup> Previous in-vitro studies indicate that there is no difference in aerosol deposition between ETT with 9.0 -7.0 mmID, but aerosol delivery to ventilator-dependent patients is reduced as the inner diameter of ETT decreases from 6.0 mmID to 3.0 mmID.<sup>52,56</sup>

**Device-related Factors:** The nebulizer type and its position in the ventilator circuit have all been shown to impact the efficiency of aerosol delivery. Previous research reported variations in dose efficiency in different brands of nebulizers, and different units

of the same brand.<sup>58,59</sup> Since fill volume and nebulizer type affect drug delivery,<sup>57,60</sup> following instructions in the drug/device label is critical.

### Optimum Technique for Drug Delivery in Ventilator-Dependent Patients

Aerosol drug delivery to ventilator-dependent patients is affected by many factors. Understanding these factors has helped us to develop optimal techniques for using pMDIs and nebulizers. When proper administration technique is used, aerosol therapy in mechanically-ventilated patients is safe, convenient and effective. Figure 2 outlines the optimum administration technique with nebulizers and pMDIs.

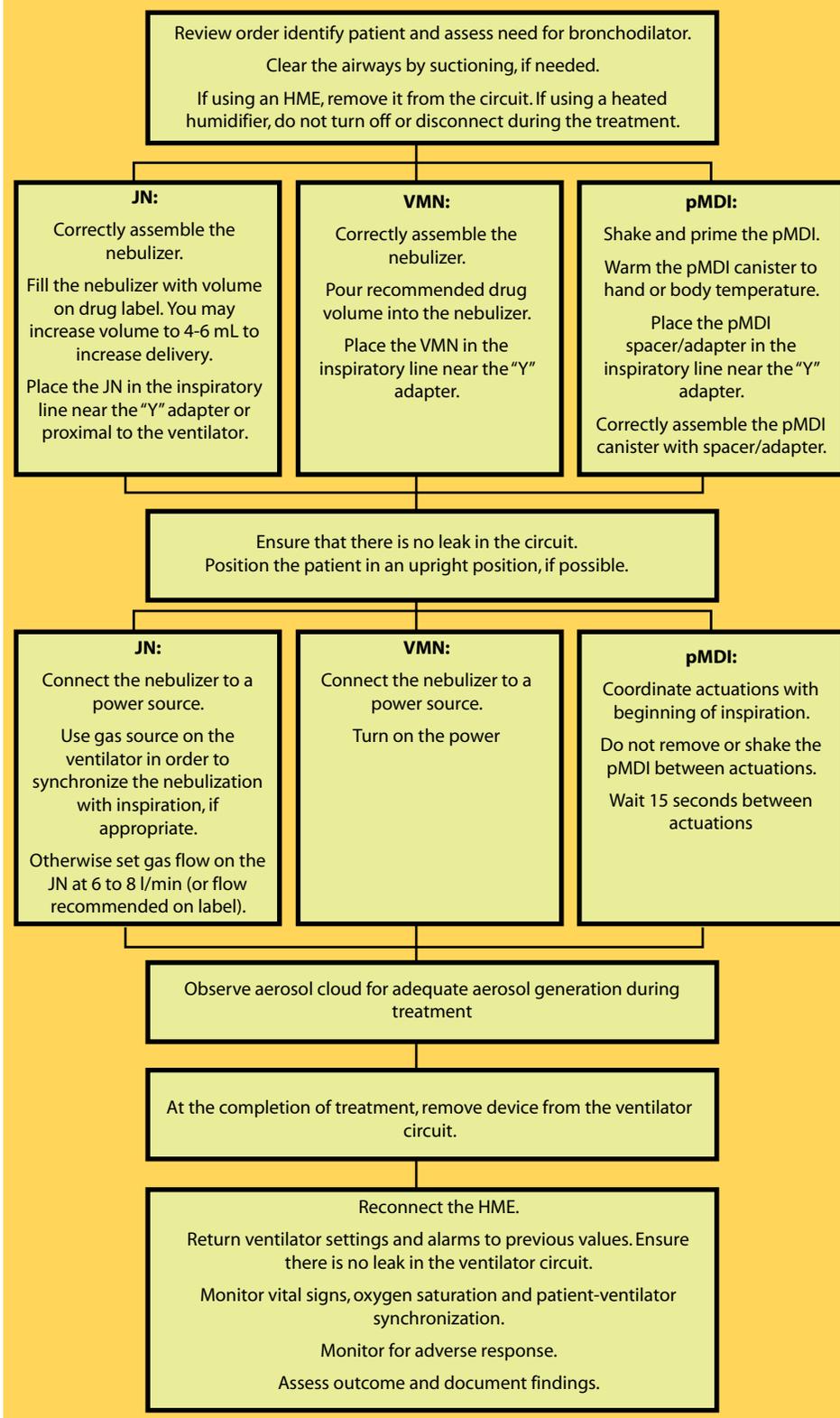
**Patient position:** Studies have shown that drug delivery to patients in a semi-fowler and sitting position produces a significant response.<sup>61-65</sup> Therefore, if the patient cannot sit in the bed during inhalation therapy, a semi-fowler position with the head of the bed elevated to 20° to 30° above the horizontal should be used for aerosol administration during mechanical ventilation.

**Optimum Technique with Nebulizers:** Jet nebulizers are operated continuously by pressurized gas or intermittently by a separate line connected to the ventilator which provides driving pressure and flow to the nebulizer. During intermittent operation (aka nebulizer function on the ventilator), the ventilator operates the nebulizer only in inspiration, thus reducing aerosol loss during expiration. When nebulizer function is used for aerosol therapy during mechanical ventilation, the ventilator compensates for the flow to the nebulizer to maintain constant tidal volume and minute ventilation. Although jet nebulizers are often operated continuously, it has been shown that intermittent nebulization increases aerosol deposition more than continuous nebulization during mechanical ventilation.<sup>51,66</sup> However, it must be noted that the lower pressure of the driving gas may affect the aerosol characteristics and delivery efficiency of a nebulizer operated through the ventilator. For instance, operating a nebulizer with a lower driving pressure (<15 psi) through a ventilator instead of using pressurized gas (≥50 psi) may generate larger particles and decrease the efficiency of the nebulizer.<sup>40</sup> However, it has been reported that the newer



Figure 1. HMEs designed for aerosol delivery during mechanical ventilation. A: Circuit HME/HCH bypass (Smiths-Medical Keene, NH) with Gibbeck Humidivent Filter Light 5 inline (Hudson RC, Arlington Heights, IL). B: Humid-Flo HME (Hudson RC, Arlington Heights, IL). C: Airlife bypass HME (Carefusion, San Diego, California). (Reproduced with permission, from Reference 70)

Figure 2. An algorithm describing steps for optimal drug administration technique by each aerosol generator (Reproduced with permission from Reference 45).



ventilators with built-in nebulizer function deliver reproducible and consistent doses to ventilator-dependent patients.<sup>51,67</sup>

When the jet nebulizer is placed closer to the ventilator and operated continuously

under heated/humidified conditions, the aerosol tubing acts as a reservoir because continuous output of the jet nebulizer charges the inspiratory limb of the ventilator circuit between inspiration and minimizes

aerosol loss during the expiratory phase of the breathing cycle.<sup>7</sup> pMDIs, mesh and ultrasonic nebulizers that do not add gas flow to the ventilator circuit appear to be most efficient when placed in the inspiratory limb, 6 inches from the Y adaptor.<sup>7</sup> With the addition of continuous bias flow in the ventilator circuit, placement of aerosol generators near the ventilator may be more efficient.<sup>8</sup>

Optimum Technique with pMDIs: Priming and shaking the canister before treatment is important, especially prior to first use and when the canister has not been used for more than 24 hours. Otherwise, the drug in the pMDI formulation may separate from the propellants, which reduces aerosol delivery.<sup>68</sup> Also, synchronizing pMDI actuation with the beginning of inspiration is required for effective aerosol therapy during mechanical ventilation. Aerosol drug delivery to ventilator-dependent patients is maximized by synchronizing the actuation of pMDI with the beginning of inspiration.<sup>69</sup> When a spacer is used with a ventilator-dependent patient, it should be placed at approximately 15 cm from the ETT in order to achieve a significant bronchodilator response.<sup>24,61</sup>

Patient Monitoring: In order to eliminate the complications caused by aerosol treatment, some institutions require respiratory therapists to stay in the room when administering aerosol therapy through nebulizers. Although this increases respiratory therapist time spent with patients, such practice assures not only patient safety but also effective aerosol therapy for critically-ill patients.

## Conclusion

In conclusion, there have been dramatic advances in aerosol drug delivery for ventilator-dependent patients over the years. However, aerosol therapy during mechanical ventilation is still complex because of challenges associated with the aerosol devices, inhaled medications, device selection and administration technique. Therefore, understanding aerosol delivery devices, potential problems and factors influencing drug delivery to mechanically-ventilated patients is crucial for the safety and effectiveness of aerosol therapy for patients in the ICU.

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## Aerosol Therapy In Spontaneously Breathing And Mechanically Ventilated Patients: Description, Selection & Issues

**Moderator:** Tim Myers, RRT-NPS, MBA, FAARC

**Panelists:** Ariel Berlinski, MD

Bruce Rubin, MD, MEng, MBA

Rajiv Dhand, MD, FCCP, FACP, FAARC

Many issues surround the selection and use of aerosol therapy in all populations of patients. Matching the medication to the delivery device is key, as is understanding how the mechanistic attributes of nebulizers and mechanical ventilation can work together or against each other in delivering medication effectively. Each nebulizer option offers advantages and disadvantages that need to be assessed according to patient need, the medication involved, and use with mechanical ventilation (if present). Aerosol therapy for pediatric patients poses a unique set of challenges. Standards of practice are still evolving regarding minimizing the risk ventilator-associated pneumonia with aerosol treatments. Adherence to treatment regimens is a global issue that encompasses patient perceptions, patient/family education, financial concerns, insurance reimbursement, and other factors. Our panel of experts discusses a patient-focused approach to aerosol therapy in mechanically ventilated and spontaneous breathing patients.

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Nebulizers that produce aerosols with a smaller particle size are better suited for aerosol delivery during mechanical ventilation.

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- Rubin -

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*The ability to match the right delivery device with the mode of ventilation of respiratory patients is imperative to insuring medication delivery. What is the key take home message for clinicians are how to select the appropriate delivery device?*

**Berlinski:** In spontaneously breathing patients, prescribe an inhalation device that either they or their caregivers can effectively assemble, operate and clean. The prescribed drug has to be available for use

with that device; and consider minimization of systemic side effects, including ocular and facial exposure, during the selection process. Do a hands-on evaluation of the patient's proficiency in using the device at each clinic visit.

Mouthpieces should be used when possible to optimize drug delivery. Tracheostomized patients can effectively use a metered-dose inhaler attached to a valved holding chamber that has a special connector for the trach. Patients receiving either invasive or non-invasive ventilator support have different considerations. Preferentially use in-line devices that avoid breaking the circuit integrity. When selecting the drug dosage, take into consideration a decrease in drug delivery due to the presence of circuit humidity. Ultrasonic and vibrating mesh nebulizers should be preferred over jet nebulizers if no additional flow within the circuit is desired.

**Rubin:** The best device under any circumstance is the one that the patient will use correctly, comfortably, and as prescribed. That helps ensure treatment adherence. I prefer devices that (1) are easy to use and clean, (2) require minimal setup and breakdown, (3) rapidly deliver a good amount of medication to the airways, and (4) are reasonably priced. For these reasons, I prefer using pressurized meter dose inhalers (pMDI) or dry-powder inhalers (DPI) whenever possible. However, some of the newer small-volume nebulizers are fast, portable, and easy to use.

**Dhand:** Another takeaway is to match the drug with the device, because sometimes a drug/device combination is not available. Many classes of aerosolized therapeutics are available today—bronchodilators, mu-

cokinetic agents, corticosteroids, surfactants, prostaglandins, antibiotics, diuretics, and anticoagulants, among others. But currently, pMDI formulations are available only for bronchodilators and corticosteroids. DPIs are not efficient for aerosol delivery in ventilated patients. So nebulizers are used by default for delivering drug solutions and suspensions for which no pMDI formulations are available. But a word of caution: some of those solutions may be formulated for intravenous rather than inhalational use.

When a pMDI is used, an appropriate adapter positioned about 15 cm from the endotracheal tube in the inspiratory limb of the ventilator circuit is ideal for efficient aerosol delivery. Moreover, device actuation must be synchronized with ventilator inspiratory airflow.

The nebulizer choice should be based on studies that demonstrate efficiency of aerosol delivery in the specific clinical situation and with the drug for which it will be employed. In general, nebulizers that produce aerosols with a smaller particle size (MMAD < 3 $\mu$ m) are better suited for aerosol delivery during mechanical ventilation than nebulizers that produce larger-particle aerosols. For routine bronchodilator therapy, pMDIs are preferred over nebulizers. A 2012 review article discusses factors influencing aerosol delivery, choice of drug delivery devices, and optimum administration techniques of inhaled drugs in mechanically ventilated patients.<sup>1</sup>

*What should clinicians be aware of regarding the inherent advantages and key differences among nebulizers as they match a device and product with patient needs?*

**Berlinski:** Two new nebulizer designs/technologies have become available in the last few years. The breath-actuated nebulizer releases aerosol only during inhalation, and it offers the advantages of decreased exposure to the healthcare provider and less drug wastage.<sup>2</sup> This type of nebulizer might not be appropriate for toddlers and younger children, due to their inability to open the inhalation valve. Such devices also deliver a less variable amount of medication. Vibrating mesh nebulizers have been released

Use the drug/device combination that was approved as a result of clinical trials that used that same combination.

- Berlinski -

as open platform or tied to specific drugs.<sup>3</sup> They are more efficient and faster at facilitating adherence to the inhaled therapy.<sup>4</sup> But their membranes need to be treated carefully and cleaned according to instructions to avoid occlusion and subsequent malfunctions. The high efficiency of these devices may predicate dosing adjustments. This is especially crucial with drugs that have a narrow therapeutic index. And, as Rajiv [Dhand] noted, use the drug/device combination that was approved as a result of clinical trials that used that same combination. Finally, some drugs like budesonide can't be used with an ultrasonic nebulizer. Methodologies to determine equivalency between different drug/device combinations are needed.

**Rubin:** New nebulizer technology allows rapid, effective airway delivery of medications, including medications that are not available in other forms. For non-intubated patients who require therapy using bronchodilators, inhaled corticosteroids, or anticholinergics, I still prefer using a pMDI with a holding chamber or for patients who can generate sufficient inspiratory flow, a DPI. For medications like aerosolized antibiotics (e.g. inhaled tobramycin and aztreonam) and medications such as dornase alfa (Pulmozyme), only a select group of nebulizers have been well studied. And, as Ariel [Berlinski] said, use only nebulizer/medication combos that have been studied in clinical trials. As more data are collected

regarding use of other medications in these newer nebulizers, the recommendations will change, giving patients and providers more choices.

Whenever possible, I prefer not to use a mix of nebulizers and devices. Each device requires slightly different steps for appropriate use. So, the more devices in the mix, the more likely it will be that certain ones simply will not be used or will be used inappropriately.

**Dhand:** Today a plethora of nebulizers are available, including jet, ultrasonic, and vibrating mesh/aperture plate nebulizers. Jet nebulizers may be constant-output, breath-enhanced or breath-actuated; each type has widely different efficiencies of drug deposition in the lung. These choices underscore the importance of matching the drug with the device. A 2012 review article discusses the difference between those devices.<sup>5</sup>

Certain patients, including (1) infants, (2) uncooperative children, (3) the elderly, (4) patients with severe lung disease and severe exacerbations, (5) patients with physical and/or cognitive impairments, (6) patients who cannot use pMDIs or DPIs optimally despite adequate instruction and training, and (7) those who have inadequate symptom relief despite appropriate use of a pMDI or DPI, should be considered for domiciliary long-term treatment with nebulizers. In addition, nebulizers are commonly used to administer drug solutions and suspensions in patients with cystic fibrosis, particularly for agents where pMDI or DPI formulations are not available.

*Clinicians caring for patients with exacerbations of chronic respiratory disease are making concerted efforts to avoid endotracheal intubation and mechanical ventilation through use of non-invasive ventilation (NIV). While this solves one problem regarding the ability to support ventilation and/or oxygenation, it presents potential problems for delivery of aerosolized medications. What are your perspectives on the most effective and efficient ways to deliver respiratory medications to patients receiving NIV?*

**Berlinski:** Despite the complex factors affecting drug delivery, aerosols can be efficiently delivered while patients are receiving NIV. Practitioners need to be aware of the conditions that optimize drug delivery.<sup>6,7,8</sup> When metered-dose inhalers are used, spacers are preferred to adaptors. Both should be designed to receive the stem of an HFA inhaler. Actuation should be performed at the beginning of the inhalation.<sup>7</sup> Position of leak (either at the mask or in the circuit) does not seem to affect delivery efficiency with inhalers.<sup>7</sup> However, when using nebulizers, drug delivery is less efficient when the leak is located in the mask.<sup>7</sup> The optimal position of the nebulizer is between the leak port and the mask.<sup>6,8</sup> When the nebulizer is placed distal to the BiPAP device, a pressure difference between EPAP and IPAP of at least 10 cm H<sub>2</sub>O is better than a lower value.<sup>6</sup> Vibrating mesh nebulizers are 2 to 3 times more efficient than a jet nebulizer.<sup>8</sup>

**Rubin:** This is an evolving science. Elegant bench studies by investigators like Jim Fink and Arzu Ari suggest that certain methods of administration may be more effective during non-invasive ventilation. If it is essential to deliver nebulized medications to these patients, my current practice is to interrupt the ventilation for a short time to administer the medication and then resume non-invasive ventilation. Most patients receiving NIV can tolerate short periods off of it, and I would rather risk having to briefly interrupt the ventilation to administer the drug than not know how much of the drug is being delivered to the patient while on ventilation. This is strictly a personal preference; administration methods are an area worthy of further study.

**Dhand:** Many factors influence aerosol delivery during NIV: (1) the type of ventilator, (2) mode of ventilation, (3) circuit conditions, (4) type of interface, (5) type of aerosol generator and its configuration, (6) drug-related factors, including aerosol particle size, (7) breathing parameters, and (8) patient-related factors. Patient factors include (1) the ability to tolerate a face mask, (2) the level of respiratory distress, (3) hemodynamic status, (4) the type and severity of lung disease, and (5) synchronization of aerosol generation with inspiratory airflow.

Whenever possible, I prefer not to use a mix of nebulizers and devices. Each device requires slightly different steps for appropriate use.

- Rubin -

When nebulizers are employed for aerosol delivery during NIV with a single-arm circuit, the position of the device in relation to the leak port also influences nebulizer efficiency.

Few studies have attempted to determine optimum settings for maximizing drug delivery with pMDIs and nebulizers during NIV. But devices vary greatly in this respect. For example, the position of the leak port in the single-arm circuit used for bilevel positive pressure ventilation influences nebulizer efficiency but does not affect drug delivery from pMDIs. Furthermore, vibrating mesh nebulizers are at least twice as efficient for drug delivery during NIV compared to traditional jet nebulizers. The factors that influence aerosol therapy and administration techniques in patients receiving NIV have been reviewed recently.<sup>9</sup>

Despite impediments to efficient aerosol delivery because of continuous gas flow, high inspiratory flow rates, air leaks, circuit humidity, and patient-ventilator asynchrony, significant therapeutic effects are achieved in patients with asthma and COPD after inhaled bronchodilator administration.

*Pediatric patients present a unique set of issues and problems surrounding effective medication delivery for respiratory illnesses. What are the contributing factors and most effective methods for ensuring delivery of respiratory medications to pediatric patients?*

**Dhand:** The most convenient method to provide efficient aerosol delivery to children under the age of 5 years is with a pMDI connected to a spacer/holding chamber and mask or spacer/holding chamber and mouthpiece. DPIs are not recommended for this patient population because children may not be able to coordinate their breathing with device actuation, and they may not be able to generate an adequate inspiratory airflow. Likewise, nebulizers could be used with a face mask in infants and children up to age 3 or 4; a mouthpiece can work with older children. But, because it's difficult to restrain infants or young children throughout a nebulizer treatment, it's preferable to administer aerosols while they are sleeping. Aerosols don't deliver drugs effectively when babies are crying or struggling during administration. Use of a high-flow nasal cannula may be considered as an alternative method of aerosol administration in infants and children. Drs. Rubin and Berlinski on this panel specialize in aerosol delivery to children, so I defer to their expertise in this field.

**Berlinski:** Delivering therapeutic aerosols to pediatric patients poses several challenges. Not only are children's airways and tidal volumes smaller, but children also present particular developmental and behavioral characteristics. Both nebulizers and metered-dose inhalers with holding chambers and masks are used in this age group. Crying and being upset during inhalation decreases lung deposition. The right facial-nebulizer interface is critical. Mask design affects facial and ocular drug deposition. This is an underappreciated problem, especially for inhaled corticosteroids. Face masks have been used extensively to overcome actuation/inhalation lack of coordination present in younger patients. However, because face masks require a tight fit, they can become part of the problem by causing some distress in this population.

Metered-dose inhalers attached to a non-electrostatic holding chamber with either a mouthpiece or a soft face mask that provides a good seal and the lowest dead space are an effective method to deliver aerosols to children. Visual feedback of the child's ventilation is key. It is also crucial that the

canister remains in vertical position during the actuation-inhalation period.

**Rubin:** My mantra is, “Make it easy to use and make it fast.” Adherence tends to be worse with nebulizers because it means dragging the nebulizer out, filling the neb cup, having the child sit still with either a mouthpiece (preferred over a mask) or wearing a mask while generally not taking deep breaths. Then the device must be cleaned and packed away for subsequent use. The fastest, easiest, most reliable and least expensive way to administer medication to most children is using a pMDI with a valved holding chamber. The patient interface is critical. A mask, if used, must provide a complete seal, comfortable fit on the face, and a minimal amount of dead space. This requires getting used to, but is no more difficult than using masks on nebulizers. Most non-adherence in children is due to the parents’ time and ability to administer and monitor the medication. Parental agreement and understanding are critical regardless of which device is used. Dr. Israel Amirav and others are developing some novel devices to administer medications to the sleeping child or by incorporating a soother into a mask so that the child will suck on the soother and breathe quietly, calmly, and comfortably through their nose.

*What are some of the primary issues that cause medication non-adherence in respiratory patients?*

**Berlinski:** One of my mentors said that it was not enough to make the right diagnosis and prescribe the right therapy. We need to ensure that the patient and his or her family are convinced that they need the medication and that it will help. Insurance and financial considerations are also important. Patients are less likely to use medications that require complex preparation and have a prolonged administration time. Frequent dosing schedules could also contribute to non-adherence. Written instructions and frequent reassessment of the inhaler are important to reduce non-adherence.

**Rubin:** A big issue is that patients often tell you what they think you want to hear so it may be difficult to determine true adher-

With the use of pMDIs,  
collapsible spacers that  
remain in-line also prevent  
frequent circuit disconnection,  
minimizing the risk of VAP.

-Dhand -

ence. This has been studied using electronic monitoring devices attached to a pMDI or to a nebulizer to measure true adherence. Even diary records of medication used often do not reflect true adherence.

The key factors to improve adherence are education, education, and education. The patient must be comfortable using the device effectively and recognize the importance of using it on a regular basis. Medication costs, misunderstanding of how to use the med, forgetfulness, and not considering the med important to use when feeling well also contribute to non-adherence. Much of this can be overcome with education reinforced at each visit. Sadly, education (which takes time and effort) is poorly reimbursed if at all.

**Dhand:** In addition, many patients hesitate to use inhalers or limit their use because of fear of dependence or because they are afraid of corticosteroid side effects—palpitations, feeling jittery or “flighty,” hoarseness, or cough. Devices that are difficult or inconvenient to use could affect treatment adherence. Patients’ perceived lack of efficacy when medications don’t produce rapid clinical effects can lead to non-adherence. And, as noted, these issues require education and frequent reinforcement to promote optimal and regular inhaler use. Newer “smart” devices can monitor a patient’s use of the

device, and the information they provide could alert clinicians to suboptimal treatment adherence. Finally, poor adherence to prescribed treatments in patients on limited incomes may be caused by their inability to afford expensive inhaled medications.

*What are the current standards of practice for delivering aerosolized medications to ventilated patients that help prevent VAP while maintaining effective and efficient aerosol delivery?*

**Berlinski:** Aerosols can be delivered to patients receiving mechanical ventilation without interrupting circuit integrity. Practitioners need to know how to optimize drug delivery with metered-dose inhalers and nebulizers. Metered-dose inhalers can be used with either rigid or collapsible spacers placed in the inspiratory limb before the wye. However, adapters are very inefficient. Coordination of actuation of the canister at the beginning of the inspiratory time is paramount for efficient delivery. Jet nebulizers attached to a spring-loaded t-piece should be positioned in the inspiratory limb closer to the ventilator. Single-use vibrating nebulizers attached to a t-piece can be positioned at the ventilator or in the inspiratory limb before the wye. Ultrasonic nebulizers with their t-piece can be placed at the humidifier. The vibrating mesh and ultrasonic nebulizers are the most efficient devices. They also offer the advantage of not adding extra flow in the circuit; therefore, ventilator settings don’t need to be adjusted. The ultrasonic nebulizer has the disadvantage of heating the liquid medication during nebulization, making it unacceptable for thermally sensitive solutions or suspensions.

**Rubin:** Personally, I believe that aerosols are prescribed to intubated and mechanically ventilated patients too often, and their use can increase cost of care. If the circuit must be broken to administer the drug, that increases the risk of infection. As with any other drug, clinicians need to assess the risk/benefit ratio associated with this route of administration. Developing true evidence-based, published standards of practice that define algorithms for delivering aerosolized medications to mechanically ventilated patients is a worthy endeavor, as data on the

clinical effectiveness of aerosol therapy in this patient population are limited.

**Dhand:** As Bruce [Rubin] said, use of aerosol-generating devices should not require frequent interruption of the ventilator circuit. Nebulizers that remain in-line between doses have been developed. With the use of pMDIs, collapsible spacers that remain in-line also prevent frequent circuit disconnection, minimizing the risk of VAP. And nebulizers must be cleaned and disinfected between uses. Contamination of nebulizer solutions could lead to aerosolization of microorganisms into the lung, with the potential to cause VAP. Contamination of solutions has not been reported with pMDIs. To the best of my knowledge, no head-to-head studies have examined the occurrence of VAP in patients receiving aerosols via pMDIs versus nebulizers. Such studies are needed to determine how or if aerosolized medications contribute to the development of VAP.

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## Questions

- Which of the following types of nebulizers are used for aerosol therapy during mechanical ventilation?
  - Jet nebulizers and pressured metered-dose inhalers
  - Jet, ultrasonic, and mesh nebulizers
  - Jet, ultrasonic, and mesh nebulizers and pressured metered-dose inhalers
  - Jet nebulizers and liquid metered-dose inhalers
- Which of the following is not a true statement about ultrasonic nebulizers?
  - Ultrasonic nebulizers are powered by electricity or battery.
  - Aerosol particle size is inversely related to the vibration frequency of the piezo-electric crystal.
  - Drug output has a direct relationship to the amplitude of crystal vibration.
  - Like jet nebulizers, ultrasonic nebulizers add gas into the ventilator circuit.
- Which one of the following statements is not true about mesh nebulizers?
  - They can nebulize solutions, proteins, and liposomal formulations.
  - They change ventilator parameters during operation.
  - They can be refilled without interrupting ventilation.
  - They generate aerosols by vibrating a piezo, moving liquid formulations through a fine mesh.
- Which of the following is an advantage of a pMDI?
  - A pMDI is compact and portable.
  - Aerosol therapy with pMDI is short compared to nebulizers.
  - A greater variety of drugs can be delivered via pMDI than by nebulizers.
  - Although a pMDI costs more than a nebulizer, a pMDI reduces the chance of bacterial contamination.
- Which of the following is not true about pMDI spacers?
  - Electrostatic charge is an issue with metal or paper spacers.
  - Electrostatic charge decreases aerosol delivery by drawing small particles to the walls of the spacer.
  - The types of spacers include unidirectional, bidirectional and chamber/reservoir adaptors.
  - The cylindrical spacers have 4- to 6-fold greater efficiency in aerosol delivery than unidirectional and bidirectional spacers.
- Aerosols cannot be efficiently delivered while patients are receiving NIV.
  - True
  - False
- Because the filter in the HME is not considered a barrier to aerosol delivery, it can be placed between the aerosol device and the patient.
  - True
  - False
- Which of the following is not true about delivering aerosolized medications to small children?
  - Crying or being upset reduces lung deposition.
  - Lack of parental commitment to time and their ability to administer and monitor the medication contribute to nonadherence.
  - DPIs are recommended over pMDIs because DPIs are easier for this patient population to use.
  - If you use a mask, it needs to fit comfortably on the face.
- Which of the following are barriers to medication adherence?
  - Lack of insurance coverage, complexity of treatments, side effects
  - Limited incomes, perceived lack of efficacy when the treatment doesn't produce immediate results
  - Lack of education about the medication's medical necessity or how to use it
  - All the above
- The high efficiency of which type of nebulizer may require dosing adjustments?
  - Breath-actuated nebulizers
  - Vibrating mesh nebulizers
  - Ultrasonic nebulizers
  - All the above

**This program has been approved for 2.0 contact hours of continuing education (CRCE) by the American Association for Respiratory Care (AARC). AARC is accredited as an approver of continuing education in respiratory care.**

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- Read the educational offering (both articles).
- Complete the post-test for the educational offering online at [www.saxetesting.com/cf](http://www.saxetesting.com/cf). The questions are the same as above
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- Faculty Disclosure. No conflicts were disclosed for any other faculty.

## Participant's Evaluation

- What is the highest degree you have earned?  
Circle one. 1. Diploma 2. Associate 3. Bachelor  
4. Masters 5. Doctorate
- Indicate to what degree the program met the objectives:

### Objectives

Upon completion of the course, the reader was able to:

- Describe aerosol devices used in ventilator-dependent patients,  

Strongly Agree	Strongly Disagree
1 2 3	4 5 6
- List the best aerosol delivery device(s) for mechanically-ventilated patients  

Strongly Agree	Strongly Disagree
1 2 3	4 5 6
- Discuss the factors affecting aerosol drug delivery during mechanical ventilation  

Strongly Agree	Strongly Disagree
1 2 3	4 5 6
- Please indicate your agreement with the following statement. "The content of this course was presented without bias toward any product or drug."  

Strongly Agree	Strongly Disagree
1 2 3	4 5 6

Please consult [www.clinicalfoundations.org](http://www.clinicalfoundations.org) for current annual renewal dates.

## Answers

- |   |  |
|---|--|
| 1 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> | 6 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>  |
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| 5 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> | 10 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> |

All tests must be taken online at  
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