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

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**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>5,4,9</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.

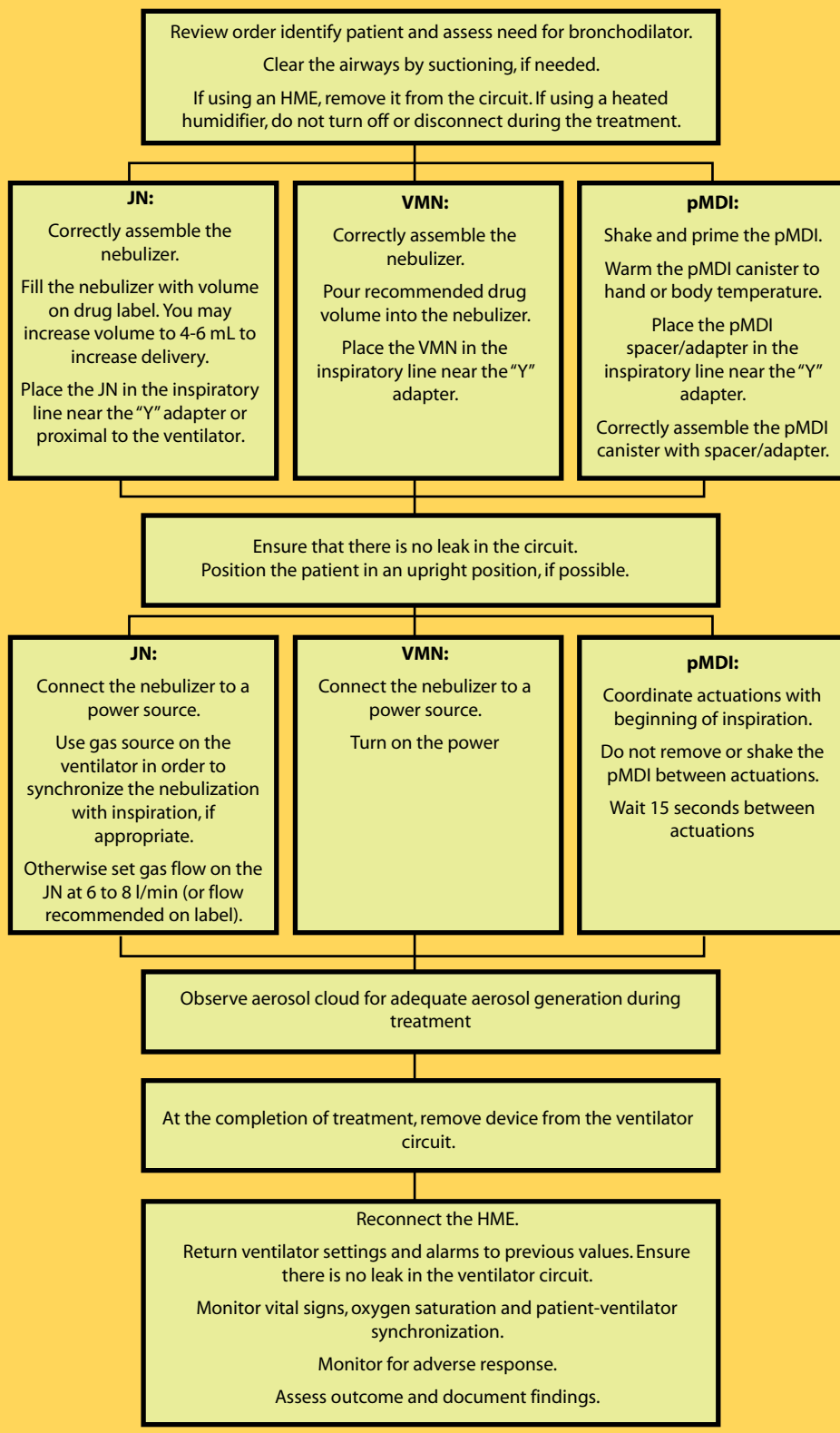
**Patient position:** Studies have shown that drug delivery to patients in a semi-fowler and sitting position produces a significant response.<sup>61-65</sup> Therefore, if the patient cannot sit in the bed during inhalation therapy, a semi-fowler position with the head of the bed elevated to 20° to 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: Circuitvent 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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