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Aerosol Delivery Devices for Obstructive Lung Disease: Focus on Nebulizer Systems

By Matt Hegewald, MD

Aerosol therapy is the cornerstone for treating asthma and Chronic Obstructive Pulmonary Disease (COPD). Many aerosol devices are available, including the pressurized metered dose inhaler, the dry powder inhaler, the slow/soft mist inhaler, and the nebulizer. Each device has its particular advantages and disadvantages. The asthma and COPD guidelines stress the importance of matching the patient to the aerosol delivery device. Providers need to be aware of the advantages and disadvantages of the available devices. Given the absence of evidence that one aerosol delivery system is superior to another, as long as they are used correctly, patient preference, convenience, available drug formulations and cost will be the determining factors in choosing a device. For those patients not capable of using handheld delivery devices adequately, nebulizers are the preferred aerosol delivery devices.

Panel Discussion: New Directions in Aerosol Therapy

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

There has been a growing interest in the development of new aerosol technologies over the years. New directions and technical innovations in aerosol medicine give clinicians access to new devices. However, adopting new aerosol technologies for the treatment of patients with pulmonary diseases brings many challenges and strategic barriers such as unfamiliarity, confusion and misuse of the device by patients due to device dementia as well as lack of knowledge and experience with the novel device in clinical practice. It is important to overcome these barriers for successful implementation of new technologies in aerosol medicine. In this issue of Clinical Foundations, Drs. Bruce Rubin, James B. Fink and Sandra Adams, who have a wealth of experience and knowledge in aerosol medicine, provide valuable suggestions to clinicians who want to adopt new technologies in their clinical practice. They also provide detailed and comprehensive information on new directions in aerosol medicine, the importance of patient education and adherence, the risks with concomitant therapy and the factors that need to be considered for the selection of a nebulizer. This is your opportunity to improve your knowledge and expertise that will empower you as a clinician for the benefit of your patients.

Faculty Disclosures

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Arzu Ari, PhD, RRT, PT, CPFT, Bruce Rubin, MEngr, MD, MBA, James Fink, PhD, RRT and Sandra Adams, MD each disclosed no conflicts associated with this publication.

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Aerosol therapy is the cornerstone for treating asthma and COPD. An aerosol is defined as a suspension of liquid and solid particles produced by an aerosol generator. Aerosol therapy delivers medications directly to the airway resulting in more effective and rapid bronchodilation and anti-inflammatory effects while minimizing systemic effects compared with oral or parenteral therapy.

There are four general categories of aerosol delivery devices used to dispense inhaled medications for obstructive lung disease (OLD): 1) Pressurized metered dose inhaler (pMDI) (with or without a spacer device); 2) Dry powder inhaler (DPI); 3) Slow/soft mist inhaler (SMI); and 4) Nebulizer. Each device category has specific advantages and disadvantages (listed in TABLE 1) and healthcare providers need to be aware of the differences in order to maximize therapeutic benefit for a given patient.

The differences start with understanding some aerosol therapy terminology: Fine-particle fraction (FPF) describes the percentage of the emitted aerosol between 1-5 μm. The fine-particle dose is calculated as FPF times the emitted dose. It is the most important characteristic because particles this size deposit in the periphery of the lung and provide optimal therapeutic effects. Aerosolized particles between 5-10 μm deposit in the more proximal airways and aerosols larger than 10 μm get no farther than the upper airway. The mass median aerodynamic diameter (MMAD) describes the average aerosol particle size. It too is a useful parameter for predicting where the medication will be deposited in the lung. Optimal MMAD for lung delivery is 1-5 μm. The differences in FPF and MMAD between aerosol delivery devices results in highly variable lung deposition between different devices and ranges between 10-60%; lung deposition is also dependent on patient factors including inhalation technique and flow rate.

Table 1: Advantage and disadvantages of aerosol delivery devices

<table>
<thead>
<tr>
<th>Device</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressurized MDI</td>
<td>• Convenient</td>
<td>• Multiple steps required (coordination of actuation and slow deep inhalation, breath hold)</td>
</tr>
<tr>
<td></td>
<td>• Compact/portable</td>
<td>• High oropharyngeal drug deposition and low lung deposition</td>
</tr>
<tr>
<td></td>
<td>• Short treatment time</td>
<td>• Many patients require spacer use for optimal drug delivery</td>
</tr>
<tr>
<td></td>
<td>• No drug preparation</td>
<td>• Difficult to determine number of doses used/remaining without a dose counter</td>
</tr>
<tr>
<td></td>
<td>• Multi-dose device</td>
<td>• Priming requirements vary depending on device</td>
</tr>
<tr>
<td>DPI</td>
<td>• Convenient</td>
<td>• Multiple steps required</td>
</tr>
<tr>
<td></td>
<td>• Compact/portable</td>
<td>• Requires moderate to high inhalation flow rates (variable depending device intrinsic resistance)</td>
</tr>
<tr>
<td></td>
<td>• Short treatment time</td>
<td>• High oropharyngeal drug deposition and low lung deposition</td>
</tr>
<tr>
<td></td>
<td>• Breath actuated (no need to coordinate actuation and inhalation)</td>
<td>• Single dose devices require some preparation</td>
</tr>
<tr>
<td></td>
<td>• Multi-dose devices</td>
<td>• Affected by humidity</td>
</tr>
<tr>
<td>SMI</td>
<td>• Convenient</td>
<td>• Multiple steps required</td>
</tr>
<tr>
<td></td>
<td>• Compact/portable</td>
<td>• Not breath actuated</td>
</tr>
<tr>
<td></td>
<td>• Short treatment time</td>
<td>• Requires priming</td>
</tr>
<tr>
<td></td>
<td>• Multi dose device</td>
<td>• Aerosol duration of 1.5 seconds allowing easier coordination of actuation and inhalation</td>
</tr>
<tr>
<td></td>
<td>• Consistent drug output (dose and particle size)</td>
<td>• Increased lung deposition</td>
</tr>
<tr>
<td>Nebulizer</td>
<td>• Patient coordination not required🎓</td>
<td>• Less portable than other devices</td>
</tr>
<tr>
<td></td>
<td>• Accommodates tidal breathing; no breath hold needed</td>
<td>• Device preparation needed</td>
</tr>
<tr>
<td></td>
<td>• Allows dose modification</td>
<td>• Longer treatment time</td>
</tr>
<tr>
<td></td>
<td>• Less portable than other devices</td>
<td>• Requires frequent cleaning</td>
</tr>
<tr>
<td></td>
<td>• Device preparation needed</td>
<td>• Power source needed</td>
</tr>
<tr>
<td></td>
<td>• Longer treatment time</td>
<td>• Contamination possible (infection risk)</td>
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<tr>
<td></td>
<td>• Requires frequent cleaning</td>
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From references: 3, 4, 6, 12, 16
Optimal management of patients with OLD requires the provider to choose the ideal combination of inhaled drug and aerosol delivery device. While there has been extensive research regarding the most effective drug or drug combinations for treating OLD, there has been less rigorous evaluation of the delivery devices. The data that does exist suggests equivalent efficacy in all inhaler devices across many patient groups with two important caveats: 1) The patient is able to use the device correctly; and 2) Different devices may require different dosages.\(^7\)\(^6\)

The recent proliferation of aerosol delivery devices results in a perplexing number of choices for both patients and healthcare providers.\(^6\) The availability of multiple devices has provided improved flexibility in matching the patient with the best delivery device for their individual needs allowing for a personalized approach to therapy.\(^1\)\(^2\) However, an unintended consequence of multiple aerosol delivery devices has been the challenge for patients to use the devices correctly and for healthcare providers to not only choose the best delivery device but be able to instruct patients how to use them properly. Unfortunately, research has shown that most patients do not use their devices correctly and that providers are not able to provide proper instruction. A recent systematic review of 144 studies concluded that the overall prevalence of correct technique for pMDIs and DPIs was 31%.\(^7\) Other studies found that less than one-half of physicians and nurses are able to demonstrate proper use of pMDIs and DPIs; respiratory therapists performed better.\(^8\)\(^9\)

The choice of medication may also dictate the delivery device: Not all inhaled drug therapeutic classes and drug combinations are available in each type of aerosol delivery device. For example, inhaled corticosteroid (ICS) monotherapy and long-acting beta-agonist (LABA) plus ICS combination are not available in a SMI. The combination of LABA plus long-acting anti-muscarinic (LAMA) is not available in nebulized form. TABLE 2 lists inhaled medications for treating asthma and COPD available for each aerosol delivery device type. The lack of availability of all inhaled drug therapeutic classes in a specific type of aerosol delivery device requires that many patients utilize multiple types of delivery devices; this adds to the challenges for both patients and providers.\(^8\)\(^10\)

### Nebulizer Systems

The main advantage of nebulizers is that they are the simplest aerosol delivery devices for patients to use. While there are different types of nebulizers, they all function to convert liquid solutions or suspensions to small aerosol droplets that are delivered to the airways with minimal patient cooperation and coordination. The patient need only perform tidal breathing with occasional deep breaths; the pMDI, DPI and SMI devices require full exhalation followed by complete inhalation and a several-second breath hold.

There are three general types of nebulizer systems: 1) Jet nebulizer; 2) Ultrasonic nebulizer; and 3) Mesh nebulizer. Detailed descriptions of the available nebulizer systems is beyond the scope of this review but is described elsewhere.\(^3\) An optimal nebulizer has the following properties: 1) Consistent aerosol output (low variability) with high FPF and low MMAD, characteristics that maximize drug delivery to the lung; 2) Fast output rate allowing short treatment times; 3) Efficient drug utilization with minimal loss to the environmental and a low residual volume (defined as the amount of medication remaining in the nebulizer after treatment is completed); 4) Easy portability (determined by need for compressor, size and power source); 5) Minimal drug formulation effects; 6) Compatible with solutions and suspensions; 7) Low cost; 8) Easy to clean and maintain. The important differences in the types of nebulizer systems are listed in TABLE 3.
Jet nebulizers use compressed gas flow to entrain liquid from a reservoir and convert it to an aerosol that is then broken into small particles by passing through a baffle. Aerosol particle size characteristics and output rate are determined by the gas flow rate through the system and baffle design. The source of compressed gas can either be a compressor powered by an external power source (electricity or battery) or a pressurized gas source. The combination of the gas compressor and nebulizer device makes the system bulky and less portable. Different jet nebulizer designs have markedly different drug delivery output and aerosol efficiency with inhaled drug percentage ranging from 10-60%. Continuous output jet nebulizers are the least efficient because they generate aerosol output throughout the breathing cycle (inhalation, exhalation and breath-hold) which results in only approximately 10% of drug being delivered to the airway. Despite these drawbacks, most patients with OLD use this type of nebulizer because of its low cost. Some modifications which address these concerns are available: Continuous output jet nebulizers with a reservoir improves drug delivery efficiency. Breath-enhanced nebulizers increase airflow through the device during inhalation making them more efficient than continuous jet nebulizers. Breath-actuated nebulizers are the most efficient jet nebulizers because they generate aerosol only during inhalation, increasing inhaled drug efficiency up to 60%. Breath-enhanced and breath-actuated nebulizers are more efficient than continuous jet nebulizers but are more expensive and some are associated with longer treatment times. Ultrasonic nebulizers use a piezoelectric transducer to produce high frequency vibrations that generates an aerosol when the vibrations are transmitted to the surface of the liquid. Mesh nebulizers utilize either a piezoelectric transducer to move medication through a fine mesh to generate an aerosol (passive mesh system) or a vibrating fine mesh that draws medication through the fine apertures in the mesh (vibrating mesh system). Both ultrasonic and mesh nebulizers have advantages over jet nebulizers. They are lighter, more portable and quieter because they do not require a compressor and they have smaller residual volumes resulting in less drug wastage. Perhaps most important, they generate a more consistent aerosol with high FPF and low MMAD which improves drug deposition in the lung. Mesh nebulizers are especially efficient at producing a fine mist with very high FPF (up to 80% of the drug reaches the lung periphery). An increased efficiency allows shorter treatment times. However, despite their advantages compared with jet nebulizers, there is no evidence that ultrasonic or mesh nebulizers are more effective in treating OLD. Their main drawback is significantly increased cost.

It is vital that providers understand that the improved efficiency of ultrasonic and mesh nebulizers means that significantly lower doses of bronchodilator medications are needed compared with the less efficient jet nebulizers. Using the same doses of bronchodilator medications prescribed for jet nebulizers may result in greater toxicity.

Not all nebulizer types can deliver all the nebulized drugs available for treating OLD. All three types of nebulizer systems are capable of delivering short-acting bronchodilators (BD) (albuterol, levalbuterol and ip-
ratropium bromide) and LABAs (formoterol and aformoterol). However, the available studies for these bronchodilators have almost exclusively been performed using jet nebulizers. Again, it is important to keep in mind the differences in nebulizer drug delivery efficiency as the dose of drug may need to be adjusted to guarantee similar dose delivery to the airways. The only ICS available for nebulization (budesonide) comes in a suspension and is not compatible with an ultrasonic nebulizer. The only available nebulized long-acting muscarinic antagonist (LAMA), glycopyrrolate (Lonhala Magnair), is approved for use only with a specific mesh nebulizer (Pari eFlow).

While nebulizers are an important aerosol drug delivery device option for treating patients with OLD, there is no clear consensus about which patients benefit most from treatment with nebulizers. The primary advantage for nebulizers is that they are the easiest of the aerosol delivery devices for patients to use. Specifically, nebulizers require minimal coordination and effort to effectively deliver drugs to the airways. Their disadvantage is that they do require correct assembly, cleaning and maintenance. The main drawback for other inhaler devices (pMDI, DPI, SMI) is that they are commonly used incorrectly. As stated above, there is consistent evidence that less than one-third of patients do not use pMDI and DPI correctly. There is also evidence that poor inhaler technique is associated with worse disease control in asthma and COPD.

Patients most likely to benefit from maintenance nebulizer therapy are those that cannot correctly use other inhaler devices despite repeated instruction and those whose symptoms are not adequately controlled with other inhaler devices. Patients with the following characteristics may benefit from maintenance nebulizer therapy: 1) Extremes of age (very young and elderly); 2) Cognitive impairment; 3) Physical limitations (arthritis, stroke, Parkinson’s diseases, etc); 4) Low health literacy; 5) Severe airflow obstruction. Lack of inhaler actuation-inhalation coordination precludes effective use of pMDIs, although the use of spacer may mitigate this limitation. Inability to maintain a brief breath-hold following inhalation limits the use of all the handheld inhalers. Patients with these limitations are likely to benefit from nebulizer use. Inability to achieve peak inspiratory flow rates (PIFR) of > 30-40 L/min (optimal > 60 L/min) limits the efficacy of DPI. One study found improved lung function in COPD patients receiving nebulized LABA compared with LABA administered by DPI when PIFR was < 60 L/min against the resistance of the DPI.

Adding a home nebulizer to patients treated with pMDI or DPI may provide added benefit. Approximately one-half of patients who remain breathless despite receiving bronchodilator therapy with pMDI or DPI benefit from home nebulizer therapy. Hospitalizations were found to be significantly reduced when patients were given a home nebulizer in addition to their handheld inhaler therapy.

Several studies and meta-analyses have compared nebulizer therapy with pMDI (with and without spacers) and DPI in various clinical settings and patient types. These studies used jet nebulizers except for the LAMA glycopyrrolate (Lonhala Magnair) that requires a vibrating mesh nebulizer (Pari eFlow). For patients with asthma or COPD exacerbations treated with short-acting beta2-agonists (SABA) in the emergency department, there is no difference in efficacy or adverse events when using a nebulizer compared with a pMDI with spacer. Similarly, in the inpatient setting, there is no difference in outcomes for patients with asthma or COPD exacerbations treated with a SABA with nebulizers compared with pMDI with a spacer. For COPD maintenance therapy with a LABA, several studies have compared nebulized LABA (formoterol and aformoterol) with LABA administered using pMDI (salmeterol) or DPI (salmeterol or formoterol) and have generally found equivalent efficacy with the possible exception that older, male patients with severe COPD might fare better.
with nebulizer therapy.14 No studies have compared the combination of a nebulized LABA plus nebulized ICS (budesonide) with a LABA plus ICS in a single inhaler for maintenance therapy despite the frequent use of this combination of nebulized medications in clinical practice. The nebulized LAMA glycopyrrolate (Lonhala™ Magnair™) been compared with a DPI LAMA tiotropium (Spiriva® Handihaler®) with no significant difference in safety or efficacy.24

Cost is often a determining factor when choosing between aerosol delivery devices. For patients covered by Medicare, the nebulizer, accessories, compressor and some nebulizer medications are provided under Medicare part B durable medical equipment (DME) benefits. Medicare generally only covers jet nebulizers and not the more costly ultrasonic or mesh nebulizers. Medicare patients are responsible for 20% of the Medicare-approved amount. The local coverage determination (LCD) on nebulizers determines how often DME providers will replace the nebulizer and accessories. The nebulizer medications covered for treating OLD include SABA (albuterol and levalbuterol), LABA (formoterol and aformoterol), short-acting anti-cholinergic (ipratropium), ICS (budesonide) and cromolyn. The LCD on nebulizers identifies the maximum number of daily doses and combinations of nebulized medications that are covered by Medicare. There must be a detailed written order listing the medications with dosages and frequency of administration, and the nebulizer and accessories signed by the provider. The provider must also document in the diagnosis and clinical need for the therapies ordered. The patient may realize significant cost savings using nebulized medications covered under Medicare part B compared with medications delivered by pMDI, DPI or SMI covered under Medicare part D benefits. The LAMA glycopyrrolate (Lonhala™ Magnair™) that utilizes a vibrating mesh nebulizer (Pari eFlowR) is not covered under Medicare part B but is covered under Medicare part D.

The economic impact of utilization of a nebulizer compared with pMDI for treatment of OLD in the hospital setting has not been definitively determined. Several studies conducted in the emergency room and inpatient setting have found lower costs using a pMDI with spacer compared with nebulizer use; lower costs were attributed to decreased labor and medication costs.25-29 However, other studies have shown the opposite result with decreased costs with nebulizer use compared with pMDI or DPI.30,31 Medication costs were lower with nebulizer use. The increased labor costs (the current Joint Commission requirement is that a respiratory therapist or nurse be present during the entire nebulizer treatment) were offset by higher overall drug costs (and increased waste) when patients treated with pMDI or DPI required fewer actuations than the device contained.

The net economic benefit of treating patients in the hospital setting with a nebulizer or handheld delivery device (pMDI, DPI or SMI) depends on many institutional specific factors including labor costs, medication costs, whether or not the patient is allowed to take the inhaler home with them and if a “common canister policy” is in place. A “common canister policy” allows a single pMDI canister to be shared among patients with each patient having his/her own spacer with a one-way valve.32

The asthma and COPD guidelines stress the importance of matching the patient to the aerosol delivery device.1,2 Providers need to be aware of the advantages and disadvantages of the available devices. As long as the delivery system is used correctly, patient preference, convenience, available drug formulations and cost will be the determining factors in choosing a device. For those patients not capable of using handheld delivery devices (pMDI, DPI or SMI) adequately, nebulizers are the preferred aerosol delivery devices.

References:
10. Rootmensen GN, van Keimpema AR, Jansen HM, de Haan RJ. Predictors of incorrect inhalation technique in patients with asthma or COPD.


Panel Discussion

New Directions in Aerosol Therapy

Moderator: Arzu Ari, PhD, RRT, PT, CPFT, FAARC
Panelists: Bruce Rubin, MEng, MD, MBA, FRCPC, FAARC  
Sandra Adams, MD  
James Fink, PhD, RRT

There has been a growing interest in the development of new aerosol technologies over the years. New directions and technical innovations in aerosol medicine give clinicians access to new devices. However, adopting new aerosol technologies for the treatment of patients with pulmonary diseases brings many challenges and strategic barriers such as unfamiliarity, confusion and misuse of the device by patients due to device dementia as well as lack of knowledge and experience with the novel device in clinical practice. It is important to overcome these barriers for successful implementation of new technologies in aerosol medicine. In this issue of Clinical Foundations, Drs. Bruce Rubin, James B. Fink and Sandra Adams, who have a wealth of experience and knowledge in aerosol medicine, provide valuable suggestions to clinicians who want to adopt new technologies in their clinical practice. They also provide detailed and comprehensive information on new directions in aerosol medicine, the importance of patient education and adherence, the risks with concomitant therapy and the factors that need to be considered for the selection of a nebulizer. This is your opportunity to improve your knowledge and expertise that will empower you as a clinician for the benefit of your patients.

What are the challenges and strategic barriers to adopting new technologies for the treatment of patients with pulmonary diseases?

Rubin: There are several strategic barriers and challenges to adopting new technologies that can be meaningfully addressed. These are as follows:
1. If providers are unfamiliar with the novel platform, they are unlikely to prescribe it. Familiarity must involve not only theoretical knowledge of a platform’s advantages but practical knowledge of how to use this new technology and how to teach it to the patient.
2. Patients must be educated in the use of a novel platform. This goes without saying, but it does require familiarity by the provider and an acknowledgement that teaching a patient to use an aerosol device correctly is uncompensated provider time. With financial pressures, this may be challenging.
3. Particularly in the United States, insurance coverage for the cost of a new technology will be critical. It is rather irrelevant if a new technology is dramatically better, for unless insurance pays for this new technology, the patient may choose not to use it.
4. When new platforms are introduced they are often drug specific. Many patients with airway diseases take a variety of aerosol medications and having different medications delivered using diverse aerosol technologies can lead to confusion and misuse. Therefore, it is important that when new platforms are introduced, that they are available with most of the medication classes that we anticipate patients will be using by aerosol.
5. When introducing a new technology, it will be important to demonstrate improvement using well-defined outcomes. This has been a challenge for clinicians and investigators. Outcomes might include improved adherence, fewer hospital admissions or ED visits, better pulmonary function, and fewer adverse effects. It will be important to assess for unanticipated problems and mitigating these when possible.

Adams: Similar to the delays in implementing new technology and data
from clinical trials in any condition, it often takes many years to adopt new information into clinical practice when managing patients with pulmonary diseases. However, with the respiratory devices and aerosol drug delivery, there are specific challenges in patients that must use these devices on a daily basis. Therefore, not only do healthcare professionals need to know how to use each of these devices, but also each end-user (patient) needs to be educated and become proficient at the many steps required to effectively deliver each medication deep into the lungs.

**Fink:** High on the list is “device dementia,” a term I first heard coined by Dr. David Geller to describe the large variety of inhalers and accessory devices which are available for use by patients. Each device has a different attribute that comes with different instructions for use. With a pMDI we instruct patients to slowly inhale while with some DPIs it is “take a deep rapid breath.” As technology advances, new DPIs are less flow sensitive. So now there is even variation in the DPIs. Clinicians and patients tend to stay with what they know. The challenge is to educate both groups to the advantages of new technology with a big push to provide training aids to support acceptance.

**Cutting edge technologies and methods in aerosol medicine is improving the health of individuals and patient populations. What factors guide successful implementation of new technologies and ensure desired outcomes, and to what extent does this approach work in different patient populations?**

**Rubin:** Successful implementation of a new technology will involve overcoming the barriers mentioned above, and will also include reducing cost to the payer and the patient (copay) to be comparable to existing technologies, making the ease of use and treatment burden as simple as possible (this may include making setup, drug delivery, and cleaning efficient and easy), the technology should be easy to teach and to learn, and should be robust.

**Adams:** The most important factors in successfully implementing new technologies in patients with respiratory conditions involve, (1) getting patients to “buy-in” to the effectiveness of the inhaled medications and, (2) ensuring each patient can appropriately use every prescribed device. Adherence to inhaled medications markedly declines as time progresses, such that only a fraction of patients still uses their prescribed medications consistently after six months to a year of therapy. One of the main factors in patients’ non-compliance appears to be related to their beliefs that these medications are not helpful and/or useful. Once the patients and their families believe these medications will help and are needed, meticulous patient education on the proper use of each device with return demonstration, i.e., “teach back” is critical to ensure the medicine is appropriately delivered to the lungs. Prescribing the appropriate devices to patients with limitations due to cognitive dysfunction and/or impaired manual dexterity or pain is particularly challenging. These factors need to be carefully considered and should be important factors to consider when choosing devices for patients.

**Fink:** Access to healthcare – countries with universal healthcare tend to have greater benefit simply because they tend to get diagnosed and treated earlier in the course of their disease. Also, systems to support training of patients to properly use and maintain their devices, in adherence to their prescription. Person-to-person training, with periodic refresher training seems to work best. Affordability of the new technology – even with health insurance, some device and drug/device options may require considerable “out of pocket” expenses that may exceed patient’s ability to pay.

**With the current standard of care recommendation to discontinue concomitant therapy, (i.e., treatment-stacking) would a faster nebulizer help? If so, how?**

**Rubin:** Although standard of care does not allow concomitant therapy, a faster nebulizer is unlikely to make a great deal of difference. Much of the time related to the use of a nebulizer is removing it from storage, setting it up, then using it, and then finally cleaning and putting it away. It is un-
likely that even a very fast nebulizer will be more efficient than a pressurized metered dose inhaler (pMDI) or a dry powder inhaler (DPI).

Adams: While treatment stacking would be more convenient for patients and their caregivers, this really needs to be studied to ensure the potential risk of toxicities does not markedly increase and that the effectiveness of each individual medication is not significantly decreased (with possible oropharyngeal deposition, etc.)

Fink: For patients receiving multiple formulations via nebulizer, combining treatments in the same nebulizer may reduce time of administration, but has the risk of unanticipated chemical interactions with potential risk of toxicity. Some comparison of drug interactions has been reported which might provide guidance, however, it should be clear that such practices while "practical" would be off-label.

A more rapid nebulizer could reduce time for both individual and combined treatments and reducing time for administration is generally a good thing for patients who spend too much of their time with a nebulizer in their mouth. However, if the trade-off for faster dosing and reduced dosing time is larger particles, higher oropharyngeal deposition, and reduced drug delivery to the targeted areas of the lung (or airways), faster may not be better.

What factors should be considered when selecting a nebulizer? What product specifications are important when selecting a nebulizer?

Rubin: Several factors must be considered:
1. Is a nebulizer truly the best choice for drug delivery or would a pMDI or DPI be as effective, and potentially at a lower cost?
2. How easy is it to set up, use, clean and store the nebulizer? In other words, what is the total treatment time?

It has been estimated that 60% or more of hospital admissions are due to non-adherence to prescribed therapy.

- Rubin -

3. Is the cost covered by insurance and does this include periodic replacement costs?
4. Is the nebulizer portable, and during transport is it appropriately protected from contamination?

Adams: An ideal nebulizer would be extremely easy to assemble, use, and clean. Other desirable factors include small size/portable, short treatment time (i.e., fast administration), and not costly so that it can be accessible to everyone.

Fink: Here are some factors to consider:
- Ease of use – setup, administration, cleaning and maintenance
- Portability
- Cost
- Patient choice
- Particle size distribution and output rate with the prescribed formulations (Particle size is more of an issue in Third World medical environments where manufacturers are still allowed to sell mismatched nebulizers and compressors that have not been shown to produce respirable particles for the formulation with which they are intended to be used.)

How will patient education and adherence impact the effectiveness of new technologies in aerosol drug delivery?

Rubin: Adherence to therapy is essential. The best technology with optimal drug mass that can be delivered to the lower respiratory tract is entirely worthless if the nebulizer is not used. It has been estimated that 60% or more of hospital admissions are due to non-adherence to prescribed therapy. A corollary to this is that the more steps that are involved in using the therapy, the less likely there is to be full adherence. Adherence and effective use of a technology will only be appropriate if there is education not only for the patient, but also of the provider so that the education given to the patient is accurate.

Adams: As above, patient education with demonstration and repeat demonstration are key to successfully delivering medication into the lungs of each patient. Because there is attrition in knowledge and competency over time, it is critical to assess and reinforce proper technique at each visit. However, time limitations contribute to the difficulty in implementing these strategies in busy clinics throughout the US and the world. For the patients/caregivers who are computer savvy, online videos may be useful in reinforcing key points for each inhaled delivery device.

Fink: If aerosols don't get to the lungs (or target organ) they don't have much of an opportunity to work. Patient education is key to adherence. When the aerosol device is not used properly there is a good chance that the medication will not have the desired therapeutic effect. Up to 60% of patients fail to use their inhaler in a way to gain clinical benefit of the drug. This correlates with up to 60% of healthcare providers who also do not properly use the device. Drug labels are often the primary means for patients to learn about their new device. Unfortunately, they are all too often written in
an overly complex manner. Add this to the fact that many Americans only read at the third-grade level and have difficulty understanding the product label.

**Personalized medicine has the potential to transform aerosol therapy and healthcare in the future. How will pharma, providers and innovators deliver personalized medicine products and services in aerosol therapy to patients?**

**Rubin:** The term “personalized medicine” or precision medicine is defined as genotype- or phenotype-specific directed therapy. Aerosol devices are not genotype-specific so will not be part of the accepted definition of personalized medicine. However, we can focus on prescribing the right aerosol device to the right patient, to be used at the right time, and ensure that it continues to be used correctly and improve outcomes. Smart devices are being developed that will evaluate inhalation techniques, measure the amount of medication that is actually inhaled by the patient, and provide feedback to the patient that can help them improve their technique and adherence. These devices can provide personalized instruction that potentially could help a patient use their aerosol device more effectively.

**Adams:** Forming a tight connection between the patients/caregivers and healthcare professionals, as well as providing resources for these groups to develop a teamwork attitude, are critical factors to ensure that personalized medicine can be successfully applied. Creating an atmosphere where dialogues are routine – through techniques such as motivational interviewing and where patients and their caregivers feel they are valuable members of this healthcare team improve the chances for successful management of respiratory diseases. Accounting for various characteristics within the different phenotypes of patients is important so that the best medicine can be prescribed. These conversations between all members of the healthcare team are key factors to ensure patients “buy in” to taking various medications which will likely lead to improved adherence. Making regimens simple and easy to take will also likely lead to improved adherence/compliance. All team members need to work together to effectively deliver personalized medicine products and services to patients with respiratory conditions to ultimately improve outcomes.

**Fink:** There are already devices with GPS’s that record and report where a dose was taken. For drugs like short-acting bronchodilators, this can help identify what locales are associated with increased irritation of airways. Establishing a bond between user and prescriber is a first step to determine when and how often drugs are taken, and how that might relate to improvement (or lack thereof) of the patient over time. Even simple reminders to take your next dose can be helpful. Many patients adhere better to QD and BID dosing than other frequencies across the day. A simple reminder from your phone or app might help remind you that it is time for your next dose.

**Arzu Ari, PhD, RRT, PT, CPT, FAARC**
Dr. Arzu Ari is currently a professor at Texas State University in Round Rock, TX. She is a physical therapist and a respiratory therapist by training with 24 years of experience as a manager, clinician, educator and researcher. Dr. Ari’s primary area of research is aerosol medicine. In particular, she evaluates in-vitro characterization of medical aerosols from various types of aerosol delivery systems used in the treatment of pulmonary diseases to help improve drug delivery in adult, pediatrics and infants. Her research laboratory is one of only a few in the world that can bring together the pharmaceutical, aerosol and respiratory care talent and infrastructure needed to support innovative research, build consensus and make strides in the field. Dr. Ari has published clinical practice guidelines on aerosol drug delivery and has published a range of abstracts, original research and review articles in numerous peer-reviewed journals. She has spoken on these topics at a variety of national and international medical conferences.

**Bruce Rubin, MD, MEng**
Dr. Rubin is the Jessie Ball duPont Distinguished Professor and Chair of Pediatrics at Virginia Commonwealth University and Physician in Chief of the Children’s Hospital of Richmond. He is also Professor of Biomedical Engineering and Physiology at VCU and has been named a Virginia Eminent Scholar by the Governor. Prof. Rubin received Lifetime Scientific Achievement Awards from the AARC and CIPP. He holds honorary appointments in 4 medical schools, is on the editorial board of 11 pulmonary journals, has published more than 300 original research papers and chapters, and holds nine patents. He is on the Board of the NIH funded Atlantic Pediatric Device Consortium. His research focus is regulation of mucus clearance in health and disease, airway inflammation, and aerosol delivery of medications.

**Sandra G. Adams, MD, MS**
Dr. Adams is a Professor of Medicine in the Pulmonary/Critical Care Division of UT Health in San Antonio and Staff Physician at The South Texas Veterans Health Care System. Dr. Adams is an internationally recognized leader and educator in Chronic Obstructive Pulmonary Disease (COPD), asthma and the chronic care model. She is actively involved in COPD research as a principal Investigator and co-investigator for local, state and federally funded research projects. Additionally, Dr. Adams received the Distinguished Scholar Award in Respiratory Health from the Chest Foundation in 2010 and the University of Texas Patient Safety Grant in 2012. Dr. Adams is the founder and President of the not-for-profit WipeDiseases™ Foundation. The Foundation’s mission is to continually develop high-quality education in order to facilitate actual changes in behavior, promote lifelong learning, improve clinical outcomes, and enhance the live of patients and their families. The website can be viewed at https://wipediseases.org.

**James B. Fink, PhD, RRT, NPS, FAARC, FCCP**
Currently serves as Chief Scientific Officer for Aerogen Pharma Corporation in San Mateo, CA. Dr. Fink is an Adjunct Professor of Respiratory Therapy at Rush Medical School, Chicago, IL and Texas State University, San Marcos, TX. A respiratory care clinician, supervisor, manager, educator and researcher for 45+ years with the past 25 years dedicated to understanding aerosol device/patient interface and design in both critical care and ambulatory settings. Dr. Fink is a Fellow of both the American Association of Respiratory Care (FAARC) and the College of Chest Physicians (FCCP). Dr. Fink has authored 3 textbooks and over 120 chapters and peer reviewed papers. He serves on the editorial board for the Journal of Aerosol Medicine and Pulmonary Drug Delivery and Inhalation. He recently received the ARCF’s 2017 Forest Bird Lifetime Scientific Achievement Award.
1. What particle size is optimal for delivering medications from an aerosol delivery device to the distal airways?
   a. 5-10 μm
   b. 1-5 μm
   c. 10-20 μm
   d. 0.5-1 μm

2. What percentage of patients use their prescribed pressurized metered dose inhaler (pMDI) of dry powder inhaler (DPI) correctly?
   a. 50%
   b. 70%
   c. 30%
   d. 10%

3. For patients with Medicare part B benefits, significant cost savings associated with inhaled drug therapy may be realized with use of what aerosol delivery device?
   a. Nebulizer
   b. pMDI
   c. SMI
   d. DPI

4. What patients are likely to benefit from bronchodilator maintenance therapy delivered by nebulizer?
   a. Extremes of age (very young and very old)
   b. Severe airflow obstruction
   c. Parkinson’s disease
   d. All of the above

5. What is the peak inspiratory flow rate (PIFR) required for optimal drug delivery when using a DPI?
   a. 20 L/min
   b. 40 L/min
   c. 60 L/min
   d. 80 L/min

6. Which of the following is NOT an advantage of SMIs?
   a. Compact and portable
   b. Short treatment time
   c. Requires priming
   d. Consistent drug output (dose and particle size)

7. Nebulizer selection in patients with obstructive disease should be based on________?
   a. Ease of use
   b. Portability
   c. Cost
   d. All of the above

8. Which of the following is NOT a correct statement about aerosol therapy in spontaneously breathing adults?
   a. Many factors influence aerosol drug delivery to patients with obstructive disease.
   b. Nebulizers, pMDIs and DPIs are not equally efficacious in aerosol drug delivery to this patient population, even if they are age appropriate and used correctly.
   c. One-on-one individualized education sessions should be prepared to achieve effective educational interventions and optimize aerosol drug delivery to spontaneously breathing adults.
   d. Optimal management of patients with obstructive lung disease requires the provider to choose the ideal combination of inhaled drug and aerosol delivery device.

9. Which of the following is/are the challenges to adopting new technologies for the treatment of patients with pulmonary diseases?
   a. Unfamiliarity with the new technology
   b. Device dementia
   c. Lack of patient education and misuse
   d. All of the above
   e.

10. An optimal nebulizer has__________?
    a. Inconsistent aerosol output (high variability with high fine particle fraction)
    b. Slow output rate allowing short treatment times
    c. Efficient drug utilization with minimal loss to the environmental and low residual volume.
    d. Incompatible with solutions and suspensions

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