Demystifying medical aerosols in acute and critical care

As guest editors of this special series of the *Annals of Translational Medicine* (*ATM*), we would like to share with the readers at large the contributions from invited authors who provided their unique and expert perspectives on the important and critical topics of this focus series titled "*Medical Aerosols in Acute and Critical Care*".

This special series was intended to meet a heretofore largely unmet need for clinicians, researchers and drug developers to clarify the special challenges of aerosol administration to patients in the acute and critical care settings. Patients in this environment often have severe airway obstruction, edematous and inflamed airways, distressed breathing patterns and require supplemental oxygen and ventilatory support. These combine to compromise aerosol drug delivery efficiency and distribution and airway response to deposited drug.

Medical aerosols play an important role in the treatment and management of patients with asthma, COPD and Cystic Fibrosis with an estimated global revenue of $31.5 billion US in 2019 (1). While many patients depend on these drugs to ameliorate symptoms, reduce inflammation and control infections, the basis of regulatory approval and label dosages are based, with few exceptions, on clinical trials conducted using patients with mild to moderate disease in the ambulatory setting, in simple terms "patients who are not very sick and are at home" (2). It has been noted over several decades that these same drugs appear to be less effective in treating patients during exacerbations and particularly while receiving oxygen and ventilatory support in the acute and critical care environment (3). While authors have hypothesized that some drugs, such as short acting bronchodilators, don't work during severe exacerbation, others have demonstrated that with changes in dosage and frequency of administration, modification or substitution of the delivery device specified on the drug label, renders the drugs effective (4). Administration of oxygen and air during ventilatory support may dilute, divert or impact medical aerosols during administration, drastically reducing drug delivered to the target in the airways (5).

It should be noted that as of this writing no medical aerosol has been approved specifically for administration to mechanically ventilated patients, or for use in acute and critical care, and none for term and preterm infants. Consequently, physicians and health care providers in the acute and critical care environments have resorted to diverging from the drug label approved by regulators, entering the realm of "off label use" to provide effective therapy, with a range or practices (6). This special edition seeks to review the available research as a basis to inform readers of ways to optimize their practice.

With the introduction of positive airway pressure ventilators in the 1950s and their adoption for increasing critically ill patients, there has been interest in administering a range of medications as medical aerosols. While methods for nebulizer operation were integrated into many ventilator designs and nebulizers were commonly used, their performance was poorly characterized for the first three decades after their introduction (7). In 1985, Macintyre and colleagues reported the delivery efficiency and distribution of radiolabeled aerosol comparing spontaneously breathing ambulatory subjects (11.9%) and intubated mechanically ventilated patients (2.9%) (8). This 75% reduction of delivered lung dose during mechanical ventilation raised awareness that different dosing strategies were required for effective aerosol delivery. As many drugs were approved in ambulatory patients with jet nebulizers, it became clear that multiples of the approved dose may be required in ventilated patients to achieve lung doses and effects associated with the drug administered at home. It should be noted that reduced delivery was initially credited to the narrow diameter of the endotracheal tube, however subsequent reports suggested that while efficiency from jet nebulizer was reduced, deposition from metered dose inhaler during mechanical ventilation was similar to reports in spontaneously breathing subjects (9). Over the next 35 years researchers have engaged a variety of *in vitro* and *in vivo* methods to quantify and optimize medical aerosol formulations while innovating technologies to improve aerosol delivery efficiency with a variety of oxygen and ventilator support modalities.

We begin with invasive mechanical ventilation, the practice of applying intermittent positive pressure ventilation to a secure airway for extended duration, as it historically represents the first and most common form of ventilatory support. Lin and colleagues review how the state of available evidence has evolved over the last 4 decades and helped us identify and better understand the various barriers which impact medical aerosol delivery, as well as factors that facilitate consistent and higher efficiency administration for the intubated, mechanically ventilated adult.

Noninvasive ventilation provides oxygen and ventilatory support without use of secure invasive airways relying on properly fitted masks to interface with the patient. Commonly used for patients at risk for developing ventilator dependency with

inability to be weaned from both ventilator and invasive airways. Because it is difficult to maintain a secure facial fit with masks during noninvasive ventilation, some level of leak compensation requires a different flow dynamic from standard invasive ventilation. Use of single limb circuits with fixed leaks and vortex flow generators present obstacles for aerosol delivery. Dr. Harb and colleagues review the range of setups, methods and implications on aerosol delivery efficiency using methods ranging *in vitro* testing with simulators and filters, PK/PD, and imaging.

High flow nasal cannula (HFNC) delivering oxygen at flows up to 60 L/min are commonly used to treat hypoxic patients as an intervention prior to deterioration requiring full ventilatory support, many of which might benefit from inhaled medications. Interrupting oxygen therapy to administer medical aerosols can place patient at risk, while inhalation of aerosol via a mouthpiece during HFNC greatly decreases drug delivery efficiency (10). This has led to multiple studies to determine the possibilities and best methods for transnasal pulmonary aerosol delivery identifying strategies for achieving lung delivery via HFNC that are equivalent to standard aerosol via mouthpiece. Drs. Li and Fink provide a pragmatic review of the evidence, oriented towards best clinical practice.

It is not uncommon for patients with bronchospastic disease to have taken multiple inhaled bronchodilators prior to presenting to the emergency department with the complaint that their inhaler is not working. Patients with obstructed airway disease who benefit from inhaled medications when they are stable, may not respond to those same drugs at the standard doses and frequencies during exacerbation. The emergency department is the common point of entry into the acute care setting, where effective treatment can make the difference between a few hours with a return to home, or escalation of symptoms and admission into the intensive care unit for days. Authors Dailey and Shockley provide evidence and rationale for selection of devices, and dosing strategies for effective treatment in the Emergency Department.

With the advent of COVID-19, there have been increased concerns about aerosol generating procedures and transmission of virus from both patient generated bioaerosol and potentially contaminated medical aerosols. Medical aerosols are prescribed for the individual patient who may benefit from their administration, however only a small fraction of emitted aerosols actually deposits in patient lungs and airways, with larger proportion released into the immediate environment of the patient. This results in care workers, support staff and other patients being exposed to a drug or infected aerosol that may put them at risk. The containment of these aerosols and reduction of fugitive emissions are essential to reduction of risk for both secondhand exposure to medical aerosol and dispersion of bioaerosols generated by patients with potential transmission of airborne pathogens. O'Toole and colleagues address this in their review of fugitive medical aerosols in the intensive care unit.

The majority of drugs for inhalation were approved based on clinical trials in adults. Only a few aerosol drugs have been approved for use in pediatric patients, and even fewer for infants. It is fair to say that aerosol devices were designed primarily for adults, with accessories designed to allow administration to smaller patients. Consequently, the selection of drug and devices with appropriate interfaces for smaller patients is critical for successful therapy. Dr. Arzu Ari provides a review of the evidence supporting appropriate selection of devices, drug formulations, interfaces and training strategies to support this underserved patient population.

Infants, both term and preterm, provide unique obstacles for effective pulmonary aerosol delivery with early studies reporting pulmonary deposition of less than 1% of dose in preterm infants whether spontaneously breathing or intubated and mechanically ventilated, with delivery from inhalers and nebulizers. Over recent decades, investigators have explored methods to increase inhaled dose to double digits in this population, as higher delivery efficiency is required to make applications such as inhaled surfactant practical and cost effective. Dr. Clark presents a model that identifies key parameters for enhancing delivery to these smallest of patients).

Much of what we know about aerosol delivery efficiency to infants and small children has been limited to *in vitro* testing and theoretical modeling. Use of radiolabeled aerosol has been limited in this population. As imaging technology advances researchers such as Dr. Corcoran are advancing methods for safe and ethical imagining in these smallest of patients.

Dry powder inhalers have dominated the development of novel inhaled medications over the last 4 decades. However, the requirement for active inspiration to generate aerosol and has limited their use in patients with limited inspiratory pressures and flows, such as small children and patients in acute respiratory distress. DPIs have largely been excluded from the discussion of aerosol delivery options for patients requiring ventilatory support. Consequently, use of DPI has not been clinically adopted and aerosol delivery in patients requiring ventilatory support has been largely limited to liquid solution and suspension administration via nebulizer and other active inhalers such pMDIs. This is unfortunate as there are drugs that

have only been developed as DPI and not available as liquid formulations. Re and colleagues describe how DPIs might be effectively used for patient requiring ventilatory support. While not ready for prime time in the ICU, it provides provocative potential that merits future methods development.

Inhaled pulmonary vasodilators have played a major role in treatment of primary pulmonary hypertension for ambulatory patients as well as cardiac surgery patients with increase pulmonary artery pressures and critically ill infants and adults. In the critical care environment, there are number of drugs that have potential to benefit patients, in acute care albeit they are not approved for delivery via aerosol in the ICU. Liu *et al.* provide perspective on the options and opportunities for use of inhaled pulmonary vasodilator in the ICU.

Last but not least, Drs. Desgrouas and Ehrman explore the administration of inhaled antibiotics to mechanically ventilated patients. While several antibiotics have been approved for inhalation for ambulatory patients for treatment of persistent bacterial infection, their use in treatment of critically ill patients with severe infections, such as ventilator associated pneumonia, has met with only limited success in reducing the high mortality rates. Ventilator associated pneumonia impacts a high percentage of patients with extended need of mechanical ventilation with mortality of up to 50%. The appeal of antibiotic aerosols is high concentrations in the lung with relatively low systemic toxicity. Despite several large clinical trials that have failed to achieve mortality endpoints, the authors provide their insights as to why future trials of inhaled antibiotics could be effective.

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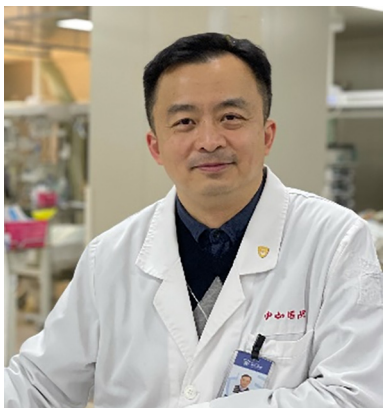

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