IMPORTANCE OF NEBULIZER SELECTION TO IMPROVE SAFETY IN THE DELIVERY OF INHALED MEDICATIONS

Introduction

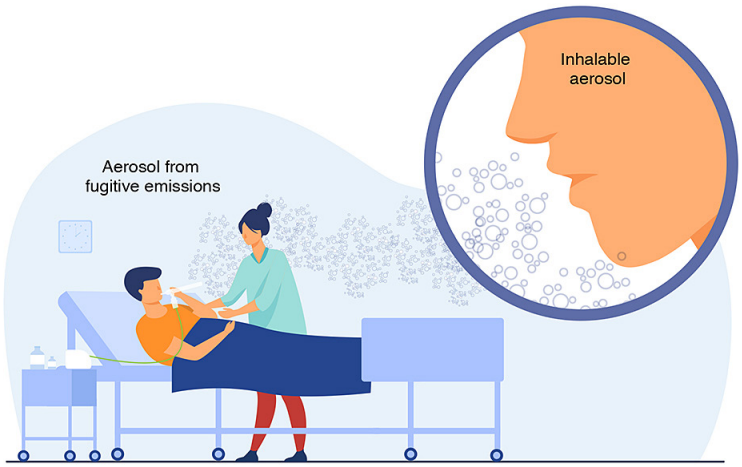
Delivery of inhaled medications by nebulizer for the treatment of respiratory diseases is widespread in both home and clinical settings for acute and long-term treatments. Nebulizers convert liquid medication into medicinal aerosols with particle size distribution typically in the range of 1–5 µm considered ideal for therapeutic response. When patients exhale, they can expel bioaerosols that are comprised of small droplets of airway-lining fluid which may [1] also carry airborne pathogens.

Fugitive emissions are aerosols [2] that may have been inhaled but did not deposit on the airway surface or were generated by the nebulizer during the inspiratory phase which were released before they could be inhaled. Studies have shown that up to 50% of the aerosol generated during constant output nebulizer therapy is released as fugitive emissions and can remain airborne in the indoor environment for several hours [3,4,5]. This process represents a potential risk factor in both clinical and homecare settings, particularly in the context of magnifying the spread of certain infectious diseases such as influenza or SARS-CoV-2 and are important when considering the safety of frontline workers and bystanders such as other patients or family members.

Inhalation of fugitive emissions has been highlighted as a significant occupational hazard in both clinical and homecare settings [6,7]. An excess risk of asthma among respiratory therapists has been reported and may increase the risk of asthma-like symptoms and/or cause occupational asthma [8,9].

Due to their ease of use and relatively cheap cost, jet nebulizers (JN) are frequently utilized [10]. Earlier work into exhaled droplets found that they can be transmitted over both short and long distances [11]. In a hospital outbreak in Hong Kong, a study of medical students exposed to a SARS patient found that their proximity to the patient was the main risk factor. In addition, the duration of contact did not appear to be associated with transmission. The study concluded that the mode of transmission was probably through droplets and/or contact, however, since nebulizer therapy was conducted 4 times per day airborne transmission could not be excluded [12]. In 2009 Hui *et al.* [13] conducted experiments within a hospital isolation room and found that healthcare workers could be exposed to exhaled air from a patient receiving a nebulizer treatment within 31.1 inches (79 cm).

The secondary exposure (bystander/caregiver) mode is not widely understood, and research has primarily focused on infection control models. The current study aimed to improve the understanding of secondary exposure in a caregiver setting to fugitive aerosols that may be emitted during respiratory nebulizer treatments with the variables being; different commonly used device types and locations tested with in the treatment area.



Materials and Methods

Nebulizers

Three predominant nebulizer technologies that are currently employed in practice were assessed for their emission of exhaled aerosol. Nebulizer types included a breath actuated small volume nebulizer (BA, AEROECLIPSE® II, Monaghan Medical, New York, USA), a breath enhanced small volume nebulizer (BE, NebuTech† HDN† Salter Labs†, California, USA) and a vibrating mesh nebulizer used with its aerosol chamber (VM, Aerogen† Solo/Ultra, Aerogen, Galway, Ireland). All devices used a mouthpiece as the patient interface. The AEROECLIPSE® II BAN™ Nebulizer and NebuTech† HDN† were operated at 8 Lpm/50 psi and the Aerogen† Ultra was run with a supplemental air flow rate of 2 Lpm as per manufacturer instructions.

Simulated Patient Breathing

Each nebulizer type was connected to a breathing simulator (ASL 5000, Ingmar Medical, Pittsburgh, PA, USA) via an absolute filter (GlobalMed 55004150) and set to simulate adult tidal breathing (tidal volume = 600 cc, 10 breaths/min, 1:2 inspiratory:expiratory ratio, *n*=3 devices per type).

Measurement of Aerosol Dose Distribution

Aerosolized albuterol was used as a model aerosol to demonstrate the potential mass and dispersion from the nebulizers on test to the surrounding environment. To ensure sufficient analytical sensitivity, each nebulizer was filled with 3 mL of 5 mg/mL albuterol sulfate solution. Aerosol delivery performance was evaluated by coupling a bacterial filter to the mouthpiece to collect the aerosolized droplets and the nebulizer was operated until sputter, which was defined and standardized as the point at which aerosolization audibly or visibly became inconsistent. Data continued to be collected for the remaining minute following this event.

Albuterol mass expressed as micrograms was extracted from the filter using methanol and quantified using an HPLC UV-VIS spectrophotometric assay [XDB-C18 (Agilent, 150 × 4.6mm, 5 µm); Mobile phase: 0.08 mol/L sodium dihydrogen phosphate solution (pH 3.10 ± 0.05) and methanol (85:15, v/v); UV detection wavelength: 276 nm; Flow rate: 1.0 mL/min; Injection volume: 20 µL; Column temperature: 40°C; Injection time: 15 min].

Categorization of Fugitive Emissions

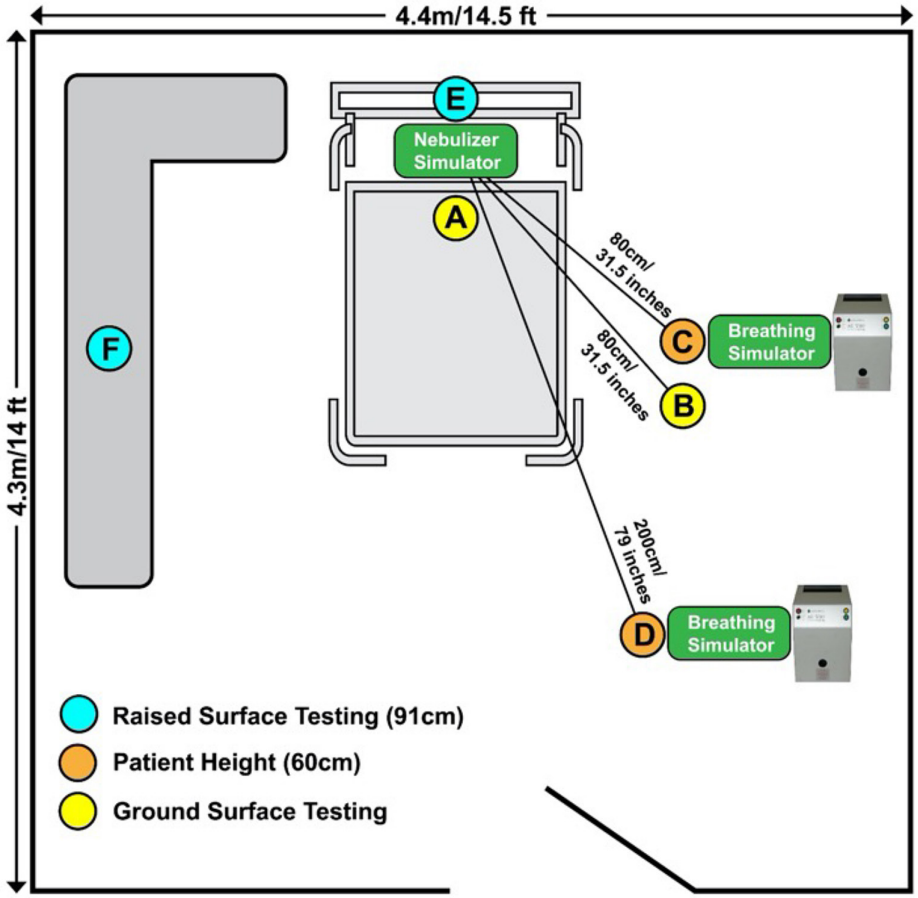
Simulation Facility

A small 1,412.6 ft^3 room (14 ft (Length) × 14.5 ft (Width) × 9.0 ft (Height)) with one internal door was used to simulate an ICU (intensive care unit) space. Ambient temperature and relative humidity in the room during the test period were 72°F and 40%, respectively. The heating, ventilation, and air conditioning (HVAC) system was turned off to eliminate additional variables within the room and to ensure that air recirculation or flow conditions did not contribute to differences in aerosol distribution based on those airflow patterns.

Estimation of Fugitive Emissions to Caregiver or Adjacent Patient

To generate the aerosol, one ASL breathing simulator was coupled to the nebulizer under evaluation, representing the patient receiving an aerosol treatment (E). This simulator was intended to mimic the breathing of a standard adult patient and to provide a constant exhalation during every cycle.

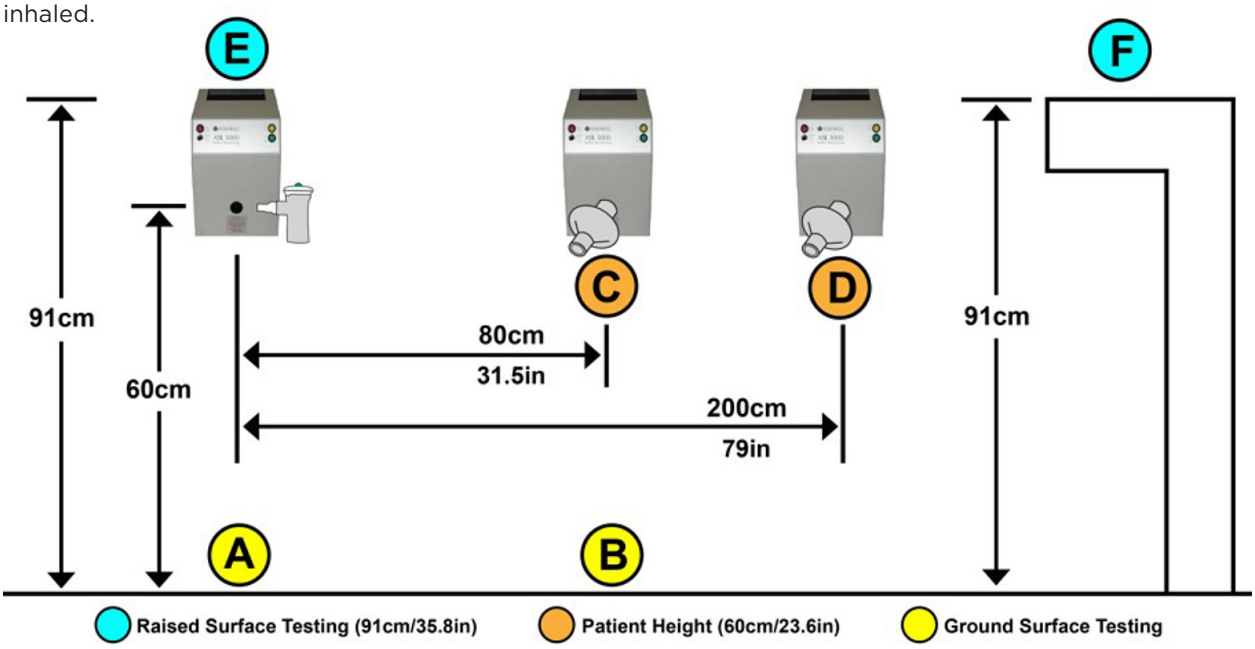
Following a previous example [5] a second breathing simulator was positioned 31.5 inches (0.8 m) away to approximate one arm's length, modeling a caregiver working closely at the bedside (B, C). To estimate the potential unintended delivery to another patient in a neighboring bed, a third breathing simulator was placed at a distance of 79 inches (2 m) away. Both of these simulators were set to simulate adult tidal breathing (tidal volume = 600 cc, 10 breaths/min, 1:2 inspiratory:expiratory ratio). All testing was carried out in triplicate.



Estimation of Room Contamination from Fugitive Emissions

In addition to the use of the breathing simulators to characterize the exposure of a spontaneously breathing subject, collection surfaces were also established within the test space.

Since gravity plays a role in the sedimentation of aerosols, collection points were established directly below the nebulizer (A) and below breathing simulator #2 (B) to collect emissions that may have reached the caregiver but have not been inhaled.



The HVAC system had been turned off within the room to prevent aerosol recirculation and dispersion from an unintended mechanism, sample collection took place from the top of the patient breathing simulator (E) as well as a counter surface 79 inches (2 m) away (F).

Location #	Location description	Sampled Area Dimension [in²]
A	Surface 1 Floor below Nebulizer	18.6
B	Surface 2 Floor below Simulator 2	25.9
C	Breathing Filter (31.5 inch distance)	9.6
D	Breathing Filter (79 inch distance)	9.6
E	ASL top surface (sampled after 3 reps)	48.4
F	Counter surface (sampled after 3 reps)	48.4

Results

Aerosol Distribution

The collection filters were analyzed in terms of the drug mass and are summarized below.

Location #	Location description	AEROECLIPSE® II [µg]	NebuTech† HDN† [µg]	Aerogen† Ultra [µg]
A	Surface 1 Floor below Nebulizer	1.8 ± 1.0	0.9 ± 0.6	*2,769.0 ± *262.4
B	Surface 2 Floor below Simulator 2	1.7 ± 1.0	1.6 ± 1.7	3.4 ± 2.0
C	Breathing Filter (31.5 inch distance)	3.1 ± 0.3	25.0 ± 12.2	14.5 ± 4.7
D	Breathing Filter (79 inch distance)	3.0 ± 0.4	19.3 ± 8.0	17.2 ± 5.8
E	ASL top surface (sampled after 3 reps)	1.1	6.3	7.4
F	Table surface (sampled after 3 reps)	0.1	1.4	0.9

Potential Inhalation Exposure

The percentage of the drug mass originally placed in the nebulizer that could have potentially been inhaled by a caregiver or adjacent patient is reported in the table below, showing the two different distances from nebulizer source evaluated.

Location #	Location description	AEROECLIPSE® II [%]	NebuTech† HDN† [%]	Aerogen† Ultra [%]
C	Breathing Filter (31.5 inch distance)	2.1%	17.0 %	10.0 %
D	Breathing Filter (79 inch distance)	2.0%	13.0 %	11.0 %

Potential Room Contamination

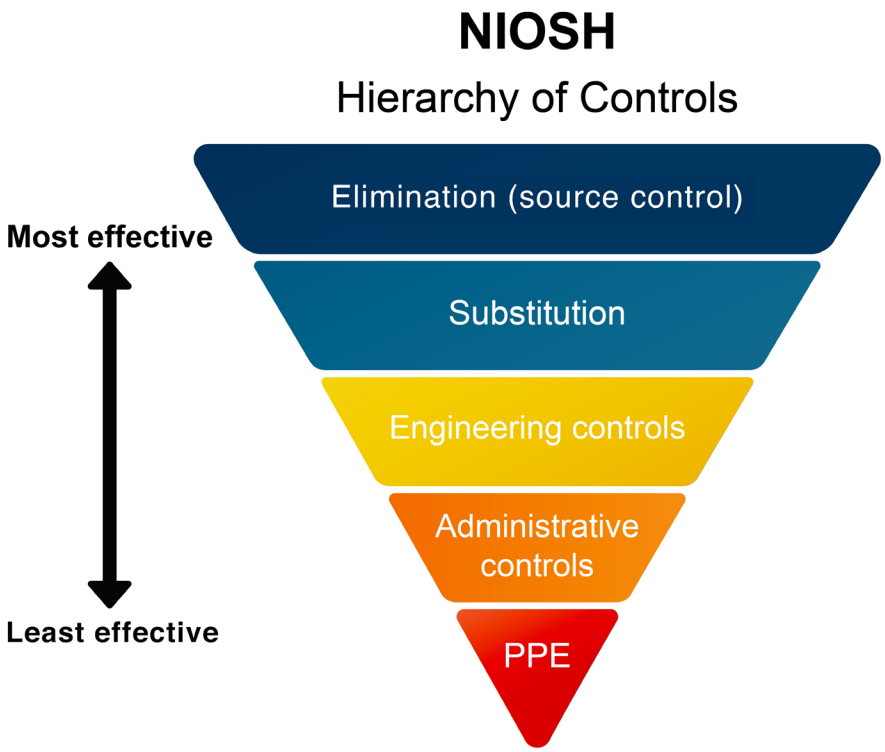
The mass of albuterol recovered from surfaces at various positions within the test area is reported in the table below.

Location #	Location description	AEROECLIPSE® II [µg]	NebuTech† HDN† [µg]	Aerogen† Ultra [µg]
A	Surface 1 Floor below Nebulizer	1.8 ± 1.0	0.9 ± 0.6	*2,769.0 ± *262.4
B	Surface 2 Floor below Simulator 2	1.7 ± 1.0	1.6 ± 1.7	3.4 ± 2.0
E	ASL top surface (sampled after 3 reps)	1.1	6.3	7.4
F	Table surface (sampled after 3 reps)	0.1	1.4	0.9

*The Aerogen† Ultra was found to have drug dripping from the exhalation valve of the holding chamber (Location A, 2,769 ± 262 µg). This is likely due to aerosol impaction within the chamber walls ultimately condensing into a liquid pool.

Discussion

This study used albuterol as a model aerosol as it represents a commonly delivered solution medication while still providing sufficient analytical sensitivity. Such a model aerosol can capture the relative potential risks associated with other aerosolized drugs and bacterial/viral transmission.



With this knowledge, a proper health and safety plan can be developed for the hazards, elimination or control at source. This could potentially include engineering controls such as filtration, reducing or eliminating aerosol exposure by isolating the hazard from the patient/caregiver, and eliminating all losses to the environment; thereby creating a safe workspace for staff.

Prior to the SARS-CoV-2 pandemic, several studies had been published that many respiratory therapists had reported not wearing the appropriate Personal Protective Equipment (PPE) while administering nebulizer treatments due to the assumption that exposures are inconsequential [9, 14].

This study highlights the potential secondary inhalation exposure to fugitive emissions for bystanders during a standard nebulizer treatment, as well as the potential for environmental contamination from other non-aerosol sources. It provides real mass quantities of inhalable material instead of relying on concentration measurements that are difficult to relate to traditional methods. Environmental factors such as HVAC performance, room construction and layout are additional factors that could impact fugitive emissions. Similarly, the amount and length of treatments within a respiratory treatment environment can vary dramatically depending on the drugs being delivered. Therefore, these current results should be viewed as potential evidence for the unintended delivery to both caregivers and other patients. Similarly, these results reflect the potential delivery from a single treatment, whereas depending on the drugs being delivered the respiratory therapist may deliver several such treatments in a single day.

With respect to the nebulizer type, the results demonstrate that both the Breath Enhanced and Vibrating Mesh Nebulizers could expose caregivers/bystanders to as much as 5-8 times the amount of fugitive aerosol/bioaerosol than the Breath Actuated device and, in addition to an aerosol route, caregivers need to be mindful of the potential for biological contamination from emissions and surfaces. Contaminated surfaces can act as a reservoir for the spread of pathogens through patient contact with the environment or indirectly through contamination of healthcare workers' hands or gloves.

Conclusions

In summary, inhalable aerosols that can be suspended and breathed could be a mode of transmission for SARS-CoV-2 like viruses. Though the potential for a secondary exposure pathway is not widely understood, these findings suggest that fugitive aerosols are a potential risk to caregivers and other bystanders, as bioaerosols are exhaled into the medicinal aerosol pathway and act as a viral/bacterial carrier. These results also highlight that the choice of nebulizer is an important factor to reduce risk of secondary exposure as the breath actuated device showed 5-8 times lower risk of inhalation from room contamination.

The purpose of this study is to aid in developing approaches for healthcare organizations to inform better policy and best practices for risk mitigation from fugitive emissions. Future studies should focus on investigating these factors in a real-life clinical scenario.

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