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Containment of procedure-associated aerosols by an extractor tent: effect on nebulized drug particle dispersal

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SUMMARY

Background: Several medical procedures involving the respiratory tract are considered as ‘aerosol-generating procedures’. Aerosols from these procedures may be inhaled by bystanders, and there are consequent concerns regarding the transmission of infection or, specific to nebulized therapy, secondary drug exposure.

Aim: To assess the efficacy of a proprietary high-efficiency-particulate-air-filtering extractor tent on reducing the aerosol dispersal of nebulized bronchodilator drugs.

Methods: The study was conducted in an unoccupied outpatient room at St. James’s Hospital, Dublin, Ireland. A novel real-time, fluorescent particle counter, the Wideband Integrated Bioaerosol Sensor (WIBS), monitored room air continuously for 3 h. Baseline airborne particle count and count during nebulization of bronchodilator drug solutions were recorded.

Findings: Nebulization within the tent prevented any increase over background level. Nebulization directly into room air resulted in mean fluorescent particle counts of 4.75 x 10^5/m^3 and 4.21 x 10^5/m^3 for Ventolin and Ipramol, respectively, representing more than 400-fold increases over mean background level. More than 99.3% of drug particles were <2 μm in diameter and therefore small enough to enter the lower respiratory tract.

Conclusion: The extractor tent was completely effective for the prevention of airborne spread of drug particles of respirable size from nebulized therapy. This suggests that extractor tents of this type would be efficacious for the prevention of airborne infection from aerosol-generating procedures during the COVID-19 pandemic.

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Introduction

Infectious aerosols are airborne particles containing pathogens. Infectious aerosols from coughing, sneezing and talking can transmit disease from person-to-person by deposition in the respiratory tract. While numerous particle sizes are generated by these activities, particles <10μm in diameter (conventionally called ‘aerosols’) remain suspended in air for long periods of time, increasing the risk of inhalation by those more than 1 m away. Particles <5μm are most likely to cause infection in the lower respiratory tract [1]. The severe acute respiratory syndrome (SARS) pandemic in 2003, the emergence of multi-drug resistant Mycobacterium tuberculosis and the current SARS coronavirus-2 (SARS-CoV-2) pandemic have heightened interest in the aerosol transmission of disease. Evidence exists supporting the aerosol transmission of SARS [2] and tuberculosis (TB) [3,4]. Preliminary data indicate that SARS-CoV-2 could also be spread in this manner [5], including the demonstration that airborne particles <5μm in diameter carry the highest coronavirus RNA titres [5].

Several medical procedures involving the respiratory tract, including intubation, non-invasive ventilation and nebulizer therapy, are known to generate aerosols [6]. These aerosol-generating procedures create aerosols in addition to those from breathing and speaking. Aerosols from these procedures may be exhaled from patients being treated and inhaled by bystanders. To date, the only airway treatment delivery procedure for which there is clear evidence for aerosol production is endotracheal intubation [7]. Bronchoscopy and sputum induction have long been associated with nosocomial transmission of TB [8,9]. More recently, bronchoscopy, and respiratory and airway suctioning have resulted in above baseline (background) values for the detection of H1N1 influenza aerosols [10].

Deliberate aerosolization by a nebulizer is a common method of drug delivery to the respiratory tract [11]. A nebulizer is a device that converts liquid into polydisperse aerosol droplets suitable for inhalation [11]. In the most common type, a jet nebulizer, the liquid drug solution is broken up into polydisperse droplets by compressed air or oxygen, and the larger droplets are then removed by baffles where they amalgamate and fall back into the reservoir to be recirculated. Most of the drug released from nebulizers is in particles 1–5μm in diameter, as required for therapeutic efficiency. Studies with radiolabelled inhaled aerosolized drug particles show that only 44% of inhaled aerosols with mass median diameter (MMD) of 10.3μm reach the lungs during inhalation, while 79% of aerosols with MMD of 1.8μm are deposited in the lungs [12]. Up to two-thirds of the prescribed dose is released from the nebulizer or exhaled, passing into the surrounding air [13,14].

There has been some concern about nebulized drug therapy and transmission of SARS-CoV-2 [15], and most countries have reduced nebulized bronchodilator treatment for common conditions such as asthma [16] during the pandemic, preferentially using inhalers. Systematic reviews [17–19] have characterized clinical evidence that nebulized drug therapy could transmit viral respiratory infection as inconsistent and of poor quality. A case–control study of transmission from the first community-acquired case of coronavirus disease 2019 (COVID-19) in the USA found that exposure to the patient during nebulizer therapy was associated with acquisition of disease [20].

In the UK, guidance has been issued from the New and Emerging Respiratory Virus Threats Advisory Group that nebulizer use does not constitute an infectious aerosol-producing procedure [21].

Several studies have highlighted concerns regarding the adverse effects of secondary exposure to nebulized aerosols (inhalation by people other than the intended patient), mainly with respect to allergy [22], or toxicity of drugs such as cisplatin [23], pentamidine [24] or ribavirin [25]. In the USA, the National Institute for Occupational Safety and Health guidelines for administration of cytotoxic drugs by nebulizer recommend the use of engineering controls [26]. Likewise, the use of nebulized sterile hypertonic saline to induce sputum for the diagnosis of TB is known to carry consequent risks of TB transmission [27]. The two main types of controls used to prevent airborne drug or infectious particle dispersion are local exhaust ventilation (LEV) devices and negative pressure isolation rooms. LEV devices are, in principle, the most efficient control method, capturing infectious particles close to the point of generation. The preferred type of LEV is a complete enclosure (booth or tent) surrounding the patient, with exhaust air passage via a high-efficiency particulate air (HEPA) filter [28,29]. Tents have flexible walls with rigid frames, and require minor assembly and disassembly [29].

Although LEV devices of this type are in widespread use, efficacy for reducing dispersal has been assessed by chemical quantitation [23] rather than direct aerosol particle detection. Direct, continuous bioaerosol sampling is an established technology for ambient air characterization in widely differing external environments [30]. Therefore, the objective of this study was to examine the efficacy of an extractor tent (Demistifier 2000; Peace Medical, Wharton, NJ, USA) for reducing aerosol dispersal of nebulized bronchodilator drugs by continuous monitoring of particle dispersal from a nebulizer using a bioaerosol detector.

Methods

This study was conducted in an unoccupied TB outpatient room at St. James’s Hospital, Dublin, Ireland on 19th July 2019 (Figure 1). The room did not have an active heating, ventilation and air conditioning system, and the windows were sealed due to external building work.

Real-time airborne particle data were recorded using a Wideband Integrated Bioaerosol Sensor (WIBS)-4a (Droplet Measurement Technologies, Longmont, CO, USA). This uses light-induced fluorescence to detect single fluorescent aerosol particles in real-time. It provides particle size (0.5–12μm), shape and fluorescent intensity in three channels. Fluorescence emission following excitation at the maximal absorption wavelengths of tryptophan (280 nm) and NAD(P)H (370 nm) is detected in two bands: 310–400 nm (Band I) and 420–650 nm (Band II) [30]. WIBS was placed approximately 1 m from the extractor tent at a height of 40 cm (Figure 1).

Continuous measurements were taken with WIBS counting particles over a pre-nebulization period to establish background level, during nebulization with and without tent enclosure, and after nebulization (Table I and Figure 2). After both open-tent nebulizations, fluorescent particle counts returned to background level (Figure 3), within mean ± 3 standard deviations (Table I).
Table I
Fluorescent particle statistics

| Tent | Type     | Mean ± SD | Maximum | % Increase without tent |
|------|----------|-----------|---------|-------------------------|
|      |          | Particles/m³ × 10⁴ | Particle count/s | Particles/m³ × 10⁴ | Particle count/s |
| NA   | Background | 0.091 ± 0.20 | 0.026 ± 0.055 | 1.07 | 0.3 | NA |
|      | Change    | 0.261 ± 0.35 | 0.073 ± 0.097 | 1.42 | 0.4 |
|      | Nurse entry | 0.43 ± 0.36 | 0.119 ± 0.1 | 1.43 | 0.4 |
| Yes  | Ventolin  | 0.065 ± 0.16 | 0.018 ± 0.44 | 0.71 | 0.2 |
|      | Ipramol   | 0.057 ± 0.15 | 0.16 ± 0.043 | 0.71 | 0.2 |
| No   | Ventolin  | 47.51 ± 23.47 | 11.3 ± 6.57 | 87.13 | 24.4 | 99.18 |
|      | Ipramol   | 42.11 ± 37.43 | 11.79 ± 10.48 | 123.2 | 34.5 | 99.42 |

SD, standard deviation; NA, not applicable.

Figure 1. Demistifier 2000 arrangement in outpatient consulting room. (A) Filtration system containing the pre-filter, high-efficiency particulate air filter and carbon filter. (B) Plastic tent covering. (C) Nebulizer pump on chair. The Wideband Integrated Bioaerosol Sensor is on a chair in the bottom right corner (out of picture). Note the tent is loose-footed and does not touch the floor.
A PARI LC SPRINT jet nebulizer placed on a chair 40 cm above the ground (Figure 1) was used with a PARI TurboBOY SX compressor (PARI Medical Ltd, West Byfleet, UK), and the nebulizer solutions were Ventolin Nebules (GlaxoSmithKline Ltd, Dublin, Ireland) and Ipramol Steri-Neb (IVAX Pharmaceuticals UK, Runcorn, UK). The nebulizer air flow was approximately 10 L/min, and nebulization was commenced by turning on the air flow and continuing until reservoir dryness. No experimental subject or mannequin was used.

Extractor tent

The LEV device used was the Demistifier 2000, a tent-style mobile filtered-air isolation device (Peace Medical) (Figure 1). An extractor fan expels air from the enclosure via a filter pack incorporating a carbon (charcoal) pre-filter which captures large airborne particles and a HEPA fibre silicate filter that removes 99.99% of particles ≥0.3 μm in diameter. The pre-filter incorporates the Aegis Antimicrobial System (quaternary silane compound, Croda International, Snaith, UK). The patient sits or stands in a loose-footed PVC enclosure which reaches almost to the floor. As the fan operates, air is expelled through the HEPA filter system at a rate of 240–360 enclosure air changes/h, and is drawn inwards from the surroundings underneath the loose-footed enclosure. This continuous circulation does not alter room air pressure.

Bronchodilator drugs

Ventolin Nebules (GlaxoSmithKline Ltd) have 2.5 mg salbutamol (sulphate) as the active ingredient in each ampoule. Ipramol Steri-Nebs (IVAX Pharmaceuticals UK) have 0.5 mg of ipratropium bromide (monohydrate) and 2.5 mg of salbutamol (sulphate) as active ingredients. Other ingredients are sodium
chloride, water for injections and dilute hydrochloric acid. Prior experiments (Fennelly et al., submitted) confirmed light-induced fluorescence of these drugs when aerosolized, facilitating WIBS-4A detection.

**Statistical analysis**

WIBS-4A records raw data as CSV files on a directly connected laptop (Fennelly et al., submitted). A single CSV file records a maximum of 30,000 particles or up to a maximum duration of 3 h. During the 3-h measurement period, a total of 22 raw Excel files were collected, comprising a total of 162,487 individual particles. The data were imported into MATLAB (MathWorks Inc., Natick, MA, USA) and processed further into appropriate files, subsets and matrices. They were then summed into 10-s intervals and analysed and graphed using R Studio 1.1.383. P-values were calculated using Student’s t-test (parametric) or Mann–Whitney U-test (non-parametric).

**Results**

The study observation timeline is shown in Figure 2, starting at 11:42 h and finishing at 14:11 h. Background level was measured for 21 min before nebulization of drugs. WIBS was in the same location for both in-tent and out-of-tent nebulizer analysis. Ipramol was nebulized, followed by Ventolin, twice inside the tent and then once outside the tent.

There was no increase in fluorescent particle count over background level associated with nebulization of drugs inside the tent (Table I and Figure 2). Nebulization of drugs directly into room air resulted in a >700-fold increase in fluorescent particle count over background level for Ventolin and Ipramol (Table I and Figure 2).

Regarding laboratory in-vitro experiments with nebulized Ventolin and Ipramol (Fennelly et al., submitted), 100% of particles counted following open nebulization were fluorescent in all channels, but the highest intensity was found in the FL1 channel. Less than 1% of background particles were fluorescent. Mean particle size was 1.26 μm and 1.27 μm with size range of ±0.06 μm and ±0.19 μm for Ventolin and Ipramol, respectively. Tent enclosure of an operating nebulizer therefore prevents exposure to these small drug particles outside the tent (Table I).

The mean fluorescent particle count in the room during operation of the tent was slightly (but significantly) lower than background level with the tent filter pump off for both in-tent nebulized drug time periods (P<0.001) (Table I and Figure 2).

There were two potential confounding events. First, after a drug sample had run dry while nebulizing in the tent, the tent had to be breached (opened) in order to change the nebulizer solution. The time during drug solution change is referred to as 'change'. During nebulizer changeover, a significant increase in fluorescent particle count was observed compared with background level (P<0.001) (Table I and Figure 2). However, it must be noted that although this increase was significant, it was quite small in terms of particle count, on average increasing by 0.047/s, and the maximum count observed differed by only one particle. Second, the entry of a nurse to the room from 12:22 h to 12:26 h (Figure 2) was associated with a significant two-fold increase in mean fluorescent particles on a very low background level from 12:23 min after Ventolin nebulization commenced to Ventolin + 6.00 min. However, a simultaneous statistically significant 12.5-fold increase in non-fluorescent particles was observed from 0.11/s to 1.31/s (P<0.001) consistent with nurse entry-associated particles comprising dust.

**Discussion**

WIBS monitoring showed 100% efficacy of the tent in restricting the spread of nebulized drug particles. The only time an increase in fluorescent particles was detected in room air over background level when nebulization was underway was during external events (i.e. nurse’s entry). The mean fluorescent particle count was significantly lower than background level for both in-tent nebulized drug time periods. The likely explanation for this is indirect filtration of room air by the extractor tent.

Previous experiments assessing the efficiency of the Demistifier 2000 in limiting cisplatin secondary exposure from sustained-release lipid-inhalation-targeting treatment used inductively coupled plasma mass spectrometry measurement of platinum content of air samples [21]. No detectable cisplatin escaped the tent during 14 h of patient dosing [23]. The present findings using a different (particle counting) method are consistent with this. After nebulization, a small but significant increase in fluorescent particle count occurred at one point compared with the background level, but this time point corresponded with an event outside the tent that was likely to increase airborne particles (i.e. room door opening when a nurse entered).

These data demonstrate that the Demister 2000 extractor tent was completely effective in the prevention of airborne spread of drug particles from nebulized therapy. Particles retained within the tent fell within the size range of airborne particles of probable respiratory origin shown to contain SARS-CoV-2 RNA in clinical studies, including those <5 μm in diameter shown to carry the highest coronavirus titres [5,31]. Although this study was not conducted with infectious particles or human subjects, this suggests that the Demister 2000, like other portable isolation devices employing filtered extraction [32], would prevent the dispersal of respiratory viruses such as SARS-CoV-2 from aerosols generated from infected patients. By expanding isolation capacity effectively without building or structural alterations, these devices have potential to increase treatment capacity during respiratory pandemics whilst protecting healthcare staff and patients from infection.

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**Conflict of interest statement**

None declared.

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References

[1] Seto W. Airborne transmission and precautions: facts and myths. J Hosp Infect 2015;89:225–8.
[2] Yu IT, Li Y, Wong TW, Tam W, Chan AT, Lee JH, et al. Evidence of airborne transmission of the severe acute respiratory syndrome virus. N Engl J Med 2004;350:1731–9.
[3] Fennelly KP, Martyny JW, Fulton KE, Orme IM, Cave DM, Heifets LB. Cough-generat ed aerosols of Mycobacterium tuberculosis: a new method to study infectiousness. Am J Respir Crit Care Med 2004;169:604–9.
[4] Fennelly KP, Jones-López EC, Ayakaka I, Kim S, Menhya H, Kirenga B, et al. Variability of infectious aerosols produced during coughing by patients with pulmonary tuberculosis. Am J Respir Crit Care Med 2012;186:450–7.
[5] Liu Y, Ning Z, Chen Y, Guo M, Liu Y, Gali NK, et al. Aerodynamic analysis of SARS-CoV-2 in two Wuhan hospitals. Nature 2020;582:557–60.
[6] Davies A, Thomson G, Walker J, Bennett A. A review of the risks and disease transmission associated with aerosol generating medical procedures. J Infect Prev 2009;10:122–6.
[7] Bivas-Benita M, Zwier R, Junjinger HE, Borchard G. Non-invasive pulmonary aerosol delivery in mice by the endotracheal route. Eur J Pharm Biopharm 2005;61:214–8.
[8] Larson JL, Lambert L, Stricof RL, Driscoll J, McGarry MA, Ridzon R. Potential nosocomial exposure to Mycobacterium tuberculosis from a bronchoscope. Infect Control Hosp Epidemiol 2003;24:825–30.
[9] McWilliams T, Wells A, Harrison A, Lindstrom S, Cameron R, Foskin E. Induced sputum and bronchoscopy in the diagnosis of pulmonary tuberculosis. Thorax 2002;57:1010–4.
[10] Thompson K-A, Pappachan JV, Bennett AM, Mittal H, Macken S, Dove BK, et al. Influenza aerosols in UK hospitals during the H1N1 (2009) pandemic — the risk of aerosol generation during medical procedures. PLoS One 2013;8:e56278.
[11] O’Callaghan C, Barry PW. The science of nebulised drug delivery. Thorax 1997;52:531.
[12] Clay MM, Clarke SW. Effect of nebulised aerosol size on lung deposition in patients with mild asthma. Thorax 1987;42:190–4.
[13] Ari A, Fink JB, Pilbeam SP. Secondhand aerosol exposure during mechanical ventilation with and without expiratory filters: an in vitro study. Ind J Respir Care 2016;5:677–82.
[14] McGrath JA, O’Sullivan A, Bennett G, O’Toole C, Joyce M, Byrne MA, et al. Investigation of the quantity of exhaled aerosols released into the environment during nebulisation. Pharmaceutics 2019;11:75.
[15] Ari A. Use of aerosolised medications at home for COVID-19. Lancet Respir Med 2020;8:754–6.
[16] Levin M, Morais-Almeida M, Anstogeui IJ, Bernstein J, Chang Y-S, Chikhladze M, et al. Acute asthma management during SARS-CoV2-pandemic 2020. World Allergy Organ J 2020;13:100123.

[17] Harding H, Broom A, Broom J. Aerosol-generating procedures and infective risk to healthcare workers from SARS-CoV-2: the limits of the evidence. J Hosp Infect 2020;105:719–25.
[18] Schünemann HJ, Khabsa J, Solo K, Khamis AM, Brignardello-Petersen R, El-Harakeh A, et al. Ventilation techniques and risk for transmission of coronavirus disease, including COVID-19: a living systematic review of multiple streams of evidence. Ann Intern Med 2020;173:204–16.
[19] Tran K, Cimon K, Severn M, Pessoa-Silva CL, Conly J. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. PLoS One 2012;7:e35797.
[20] Tashkin DP, Barjaktarevic IZ. Nebulized treatments and the possible risk of coronavirus transmission: where is the evidence? Chron Obstr Pulmon Dis 2020;7:136–8.
[21] Public Health England. COVID-19: infection prevention and control guidance. London: PHE; 2020.
[22] Delclos GL, Gimeno D, Arif AA, Burau KD, Lusk C, Stock T, et al. Occupational risk factors and asthma among health care professionals. Am J Respir Crit Care Med 2007;175:667–75.
[23] Wittgen BP, Kunst PW, Perkins WR, Lee JK, Postmus PE. Assessing a system to capture stray aerosol during inhalation of nebulized liposomal cisplatin. J Aerosol Med 2006;19:385–91.
[24] O’Riordan TG, Smaldone GC. Exposure of health care workers to aerosolized pentamidine. Chest 1992;101:1494–9.
[25] Kriol LR. Safety issues related to the administration of ribavirin. Pediatr Infect Dis J 2002;21:479–81.
[26] Connor TH, Leone MM, McDiamid MA, Polovich M, Power LA, Reed LD, et al. Personal protective equipment for health care workers who work with hazardous drugs. Report: 2009–106. Cincinnati, OH: NIOSH, Department of Health and Human Services; 2008. Available at: https://goo.gl/TJLrwD [last accessed January 2021].
[27] Weiszhar Z, Horvath I. Induced sputum analysis: step by step. Breathe 2013;9:300–6.
[28] Francis J, Curry National Tuberculosis Center, Institutional Consultation Services. Conducting sputum induction safely. Berkeley, CA: Francis J. Curry National Tuberculosis Center; 1999.
[29] Curry International Tuberculosis Center. Tuberculosis infection control: a practical manual for preventing TB, 2011. Berkeley, CA: Francis J. Curry National Tuberculosis Center; 2011.
[30] Fennelly MJ, Sewell G, Prentice MB, O’Connor DJ, Sodeau JR. The use of real-time fluorescence instrumentation to monitor ambient primary biological aerosol particles (PBAP). Atmosphere 2017;9:1.
[31] Leung NHL, Chu DKW, Shiu EYC, Chan K-H, McDevitt JJ, Hau BJP, et al. Respiratory virus shedding in exhaled breath and efficacy of face masks. Nat Med 2020;26:676–80.
[32] Phu H-T, Park Y, Andrews AJ, Marabella I, Abraham A, Mimmack R, et al. Design and evaluation of a portable negative pressure hood with HEPA filtration to protect health care workers treating patients with transmissible respiratory infections. Am J Infect Control 2020;48:1237–43.