TRUDELL MEDICAL INTERNATIONAL

AeroEclipse*

BAN* Nebulizers

Study Summary

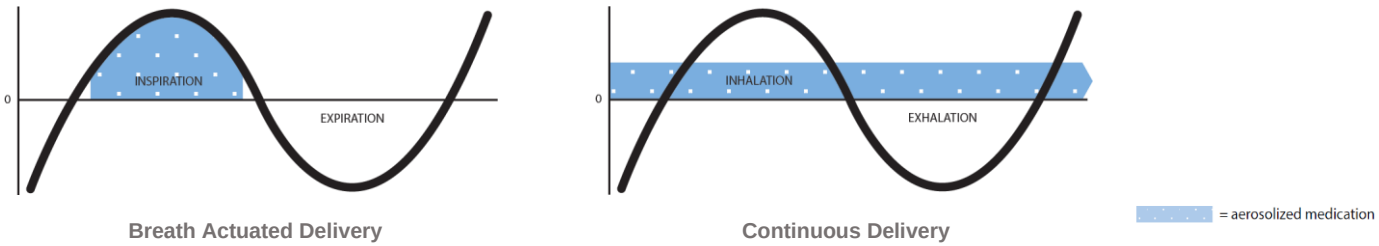
May 2023

Study Summary Outline

AeroEclipse **BAN**** Nebulizers only generate aerosol in response to the patient's inspiratory maneuver. Medication is not generated during exhalation or breaks in the patient's treatment. ***AeroEclipse*** **BAN**** Nebulizers' ability to conserve medication for delivery only when the patient inhales results in:

- Respirable dose assurance[1]
- Greater lung deposition[2]
- Reduced environmental losses[3]

Traditional nebulizers produce aerosol continuously regardless of whether the patient is inhaling, exhaling or taking a break, resulting in medication being lost to the environment instead of delivered to the lungs.



Breath Actuated Delivery **Continuous Delivery**

References: [1] Dose Assurance With Nebulizer Therapy – A Laboratory Investigation Into The Medication Delivery Performance Of A Range Of Different Nebulizers At Different Inspiratory/Expiratory Ratios. M Nagel, N Hoffman, J Suggett, V Wang. American Journal of Respiratory and Critical Care Medicine 2021;203:A4672. [2] Comparative Scintigraphic Assessment Of Deposition Of Radiolabeled Albuterol Delivered From A Breath Actuated Nebulizer And A Small Volume Jet Nebulizer To Healthy Subjects. T Corcoran, A Wesolowski, M Nagel, J Suggett, V Kushnarev, D Coppolo. Respiratory Care 2019;64(10);3235398. [3] A Laboratory-Based Examination Of The Potential For Fugitive Emission Of Aerosols To The Local Environment From A Range Of Commercially Available Nebulizer Systems. MW Nagel, JA Suggett, JP Mitchell. Respiratory Drug Delivery 2021;1:287-292.

AeroEclipse® II

BAN* Nebulizer

The ***AeroEclipse*** **II BAN**** Nebulizer has been designed for hospital use with wall air. This single patient device can be reused for up to 7 days. Refer to the instructions for use for additional information.

AeroEclipse® XL

BAN* Nebulizer

AeroEclipse **XL BAN**** Nebulizer shown with ***Ombra**** Table Top Compressor

The ***AeroEclipse*** **XL BAN**** Nebulizer single patient device can be reused for up to 6 months. The device can be paired with an ***Ombra**** Table Top Compressor for a complete home delivery system. Refer to the instructions for use for additional information.

This study summary identifies how ***AeroEclipse**** ***BAN**** Nebulizers have performed in both *in vitro* and *in vivo* studies with various formulations and versus other nebulizers.

The following sections are included within this summary:

1. ***AeroEclipse**** ***II BAN**** **Nebulizer**
    - **Financial Evaluations –** Studies reporting the impact on costs associated with the implementation of breath actuated based therapy.
    - **Summary by Active Pharmaceutical Ingredient –** Divided by drug formulation, the studies are listed in chronological order with the most recent studies appearing first.
    - **Comparison of *AeroEclipse**** ***II BAN**** **Nebulizer to Valved Holding Chamber with Metered Dose Inhaler (MDI) –** Comparison of results using the ***AeroChamber**** Valved Holding Chamber and MDI versus results using the ***AeroEclipse**** ***II BAN**** Nebulizer and another competitive device.
    - **Comparison of *AeroEclipse**** ***II BAN**** **Nebulizer to Large Volume Nebulizers –** Efficacy of the ***AeroEclipse**** ***II BAN**** Nebulizer versus commonly used large volume nebulizers.
    - **Equivalence of the *AeroEclipse**** ***BAN**** **Nebulizer to the *AeroEclipse**** ***II BAN**** **Nebulizer –** *In vitro* studies showing the equivalence of the original ***AeroEclipse**** ***BAN**** Nebulizer device and the ***AeroEclipse**** ***II BAN**** Nebulizer.
    - **Combined Therapy –** Studies investigate if nebulized drug delivery is affected when a nebulizer is paired with an oscillating positive expiratory pressure (OPEP) device.
2. ***AeroEclipse**** ***XL BAN**** **Nebulizer**
    - **Summary by Active Pharmaceutical Ingredient –** Divided by drug formulation, the studies are listed in chronological order with the most recent studies appearing first.
    - **Combined Therapy –** The performance of the ***AeroEclipse**** ***XL BAN**** Nebulizer in conjunction with the ***Aerobika**** oscillating positive expiratory pressure (OPEP) device.
3. **Aerosolized Emissions**
    - Studies report exposure to fugitive aerosolized emissions may cause adverse effects to health care providers.
    - *In vitro* studies compare aerosolized emissions for the ***AeroEclipse**** ***BAN**** Nebulizer with competitive devices.
    - Efficiency of filters used with nebulizers is evaluated.
4. **Guidance**

- Guidance on the use of nebulizers.

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AeroEclipse II BAN** Nebulizer

FINANCIAL EVALUATIONS

IMPLEMENTATION OF A BREATH-ACTUATED NEBULIZER REGIMEN MAY REDUCE NOSOCOMIAL INFLUENZA ACQUIRED BY EXPOSURE TO FUGITIVE DROPLET EMISSIONS FROM CONTINUOUS NEBULIZERS WHOSE DROPLETS PRODUCED DURING EXHALATION ARE VENTED TO THE ENVIRONMENT. D Copelin. Respiratory Care 2018;63(10):3016143.

Background: Most nebulizers generate aerosol continuously, resulting in the expulsion of droplets to the environment during each exhalation. Influenza virus particles attached to such droplets is a potential cause of infection for hospital staff. The influenza virus can survive up to 2 - 3 hours following droplet attachment. Transfer from continuous to breath actuated based therapy might be beneficial in terms of reducing staff-acquired infections. The present study examined comparative costs associated with the care of patients in the emergency department of a mid-sized hospital on either continuous or breath actuated based therapy. **Methods:** Attendance records were examined for staff associated with the care of patients known to be carrying influenza virus and therefore isolated from the general population undergoing care in the ED. The following conditions were evaluated: (Group 1) November 2016 - March 2017 for level 1 surgical procedure face mask for only the patients undergoing continuous nebulizer based therapy (AirLife† Misty Max 10† disposable nebulizer, CareFusion, San, Diego, CA); (Group 2) November 2017 - December 2017 for level 1 surgical procedure face mask for both staff and patients, the latter on continuous nebulizer therapy (as in (1)); (Group 3) January 2018 - March 2018 for level 1 surgical procedure face mask for both staff and patients, the latter on breath actuated based therapy (***AeroEclipse* II BAN**** Nebulizer, Monaghan Medical Corporation, Plattsburgh, NY). **Results:** Table 1 summarizes the findings: While the use of facemasks by both staff and patients reduced the number of positive influenza tests, implementation of breath actuated based therapy resulted in a further improvement protecting caregivers. **Conclusions:** Implementation of breath actuated based therapy has the potential to reduce costs associated with acquisition of nosocomial influenza in the ED.

Table 1: Summary and Findings

Outcomes	Group 1 Continuous	Group 2 Continuous	Group 3 Breath Actuated
Precautions to reduce virus spread	Facemask for patients only	Facemask for patients and staff	Facemask for patients and staff
Staff 'sick' days	17	8	2
Cost of 'sick' days	$4,471	$2,444	$284
Call-back pay-days	17	8	2
Cost of call-back pay-days	$7,632	$3,762	$1,254
Positive influenza tests for staff	9	5	2

TRANSITIONING TO A BREATH-ACTUATED PNEUMATIC NEBULIZER IN THE ED AND IN-PATIENT SETTINGS: EXPERIENCE GAINED FROM STAKEHOLDERS INVOLVED WITH THE PROCESS. DN Saunders. Respiratory Care 2015;60(10):OF9.

Background: We report experience gained in a recent transition from a conventional continuously operating nebulizer to a breath actuated device for the rapid treatment and rescue of patients in the ED (emergency department) and In-Patient settings of a 310 inpatient bed community hospital with an additional 60 bed ED and ED Observation unit. We are located in southeast Virginia in the City of Chesapeake. **Methods:** Our Respiratory Department transitioned from a continuously operating jet nebulizer to the routine use of the disposable ***AeroEclipse* II BAN**** Nebulizer (Monaghan Medical Corporation, Plattsburgh, NY) in the ED during October of 2011, and on the inpatient side in January of 2012. Following a 2 year period of use, we surveyed the various stakeholders involved with the transition. **Clinical Considerations:** Admissions to the hospital floors from the ED for patients diagnosed with COPD or asthma through 2011 to 2014 declined from 66.0% to 33.2% and from 5.7% to 1.2% respectively. **Economic Considerations:** There was an initial supplies cost increase associated with the change to the more complex ***BAN**** Nebulizer (Table 1).

Table 1: Nebulizer Supplies Budget (2012)

	Number of Nebulizers Used in 2012	Comparative Cost
AeroEclipse* II BAN* **Nebulizer**	9,000	$40,500
Original Jet Nebulizer	9,000	$6,750
Cost Increase		**$33,750**

This increase was however more than offset by a variety of savings associated with the delivery of the therapy by the ***BAN**** Nebulizer (Table 2). In particular the cost of re-admissions was a major benefit both in financial savings and also as a direct benefit to the patients themselves.

Table 2: Cost Savings Associated with Nebulizer Conversion

Item	Change Effected	Comments
Saving in Staff Salary	Changing majority of treatments to Q6 hours instead of Q4 hours	$73,000.00 annual salary
Decrease in Hospital Admissions from ED	From 66% **-** 37% (1,420 to 536 patients)	884 admissions
Average Reimbursement of COPD admission in 2012 minus Average Cost of COPD Admission in 2012	$5,371 - $6,269 = -$898	884(number of saved admissions) x -$898 (money lost on each admission) = $793,832
TOTAL SAVED	**$866,832**	**$866,832 (savings) - $33,750 (cost – Table 1) = Total Savings of $833,082**

Note: The saving in staff salary was achieved by decreasing the day shift by 1 full-time equivalent position.

Overall Outcomes: The following major observations were made:

Efficacy – we observed on average that treatment-to-effect was completed in one-third of the time with the ***BAN****** Nebulizer; *ED Use* – Admissions in 2012 for COPD decreased 65.94% to 36.7%. Likewise, admissions in 2012 for asthma decreased from 5.71% to 1.6%. The following years have shown the same trend. ED admissions for COPD and asthma in 2013 were 34.5% and 1.4% respectively, and in 2014 were 33.2% and 1.2% respectively. *Therapy frequency* – the majority of treatments were switched from Q4 to Q6 saving 1 x 8 hour/day RT position with a net-of-benefits saving estimated at $73k; *Quality of Care* – HFAP (Healthcare Facilities Accreditation Program) and JCAHO (Joint Commission on the Accreditation of Healthcare Organizations) standards were met by completing all treatments one-on-one with the patient, which could not be achieved with the previous nebulizer because of time constraints of the nebulizer and average patient load; *Patient Acceptance* – Customer Service was improved. Patients felt like they were receiving more medication in less time. In fact, we had to move up the time frame of the inpatient trial due to the patients that came from the ED did not want to be changed back to the continuous jet nebulizer. They preferred the ***BAN****** Nebulizer; *Continuum-of-Care* – We asked Patient First Choice Home Care and ABC HealthCare two of our homecare providers to carry in stock the reusable ***AeroEclipse****** ***XL BAN****** Nebulizer intended for 6 months of home use, so that patients will continue to receive the benefits in terms of efficacy, with the ultimate aim of decreasing their readmissions rate. **Conclusions:** The adoption of the ***BAN****** Nebulizer as our primary device for delivery inhaled therapy to patients with severely obstructed airways has resulted in significant quality, clinical, financial, and patient satisfaction benefits. We intend to follow up this study by measuring if reduced hospital readmission rates can be correlated with this approach.

SUMMARY BY ACTIVE PHARMACEUTICAL INGREDIENT

Albuterol Sulfate/Salbutamol Sulfate (Ventolin†, GSK† Inc.)

DRUG DELIVERY PERFORMANCE AND FUGITIVE EMISSION COMPARISON OF TWO COMMERCIALLY AVAILABLE NEBULIZER SYSTEMS. M Nagel. N Hoffman, J Suggett. European Respiratory Journal 2021;58(65):PA3402.

Background: Delivery of inhaled medications by nebulizer for the treatment of respiratory disease is widespread. Important factors to consider in a delivery system are amount and consistency of drug delivered to the lungs as well as the amount of drug/droplets that are emitted to the local environment (fugitive emissions). **Methodology:** Nebulizers (***AeroEclipse****** ***II BAN****** Nebulizer and Aerogen† Ultra) were evaluated with 2.5 mg/3.0 mL fill of salbutamol and connected to a breathing simulator mimicking adult tidal volume (500 mL) with I:E ratios of 1:1, 1:2 and 1:3. Emitted aerosol was captured by filter at 1 minute intervals until sputtering to determine total mass (TM_{sal}). The percentage of drug mass lost to the environment (EL_{sal}) was determined by combining the TM_{sal} recovered from the inhalation filters along with the residual mass recovered from the nebulizer and subtracting that from the initial 2.5 mg salbutamol placed in the nebulizer. Salbutamol assay was undertaken by HPLC. Fine droplet mass (FDM_{sal} µg) was determined by laser diffractometry as the product of TM_{sal} and fine droplet fraction (% < 4.7µm).

Results: Average ± SD FDM_{sal} and EL_{sal} at extended I:E ratios are reported in the table.

I:E Ratio	***BAN**** Nebulizer		Aerogen† Ultra	
	FDM_{sal} (µg)	**EL_{sal} (%)**	**FDM_{sal} (µg)**	**EL_{sal} (%)**
1:1	803 ± 76	4.1 ± 1.0	503 ± 31	23.8 ± 1.6
1:2	715 ± 82	5.2 ± 2.7	316 ± 12	34.0 ± 2.8
1:3	695 ± 52	4.2 ± 1.3	234 ± 13	37.8 ± 3.4

Conclusions: Higher and more consistent delivery was achieved by ***AeroEclipse****** ***II BAN****** Nebulizer as well as lower fugitive emissions. Clinicians should be aware of the ability to get increased amounts of medication to the lungs while maintaining a safer work environment for staff with use of the ***BAN****** Nebulizer.

EFFICIENCY OF A NEBULIZER FILTER KIT TO PREVENT ENVIRONMENTAL CONTAMINATION DURING NEBULIZER THERAPY. M Nagel, N Hoffman, J Suggett. European Respiratory Journal 2021;58(65):PA3401.

Background: The SARS-CoV-2 pandemic has highlighted the need to improve safety for frontline workers and avoid environmental contamination with aerosols. To aid in this, a nebulizer with breath actuated technology is available with a filter set to capture any exhaled aerosol. **Objective:** To determine the aerosol amounts emitted to the environment during nebulizer therapy with ***BAN****® Nebulizers and to test the efficiency of the nebulizer filter system. **Methods:** The ***AeroEclipse****® **II BAN**** Nebulizer was operated at 50 psig on its own without its optional filter kit (n = 5). Devices with the filter kit were also repeatedly tested, 2 hours apart, up to five times. Each device was evaluated with 2.5 mg/3.0 mL fill of salbutamol and connected to a simulator mimicking adult tidal breathing. In addition to inspiratory and expiratory filters, the nebulizer was placed under an extraction system to capture any aerosol emitted through leakages or exhalation. Salbutamol assay was undertaken by HPLC-UV spectrophotometry. **Results:** The mass of salbutamol captured from the extraction system with the ***BAN****® Nebulizer alone was found to be 2.6 ± 0.4% of the initial dose. When the filter kit was added, zero fugitive emissions were recovered. Even after four subsequent treatments no salbutamol was recovered.

	BAN*® Nebulizer Alone	***BAN****® Nebulizer with Filter Kit				
		Treatment 1	**Treatment 2**	**Treatment 3**	**Treatment 4**	**Treatment 5**
Device 1	2.1%	0%	0%	0%	0%	0%
Device 2	2.9%	0%	0%	0%	0%	0%
Device 3	3.0%	0%	0%	0%	0%	0%
Device 4	2.6%	0%	0%	0%	0%	0%
Device 5	2.2%	0%	0%	0%	0%	0%
Average	**2.6% ± 0.4%**	**0% ± 0%**	**0% ± 0%**	**0% ± 0%**	**0% ± 0%**	**0% ± 0%**

Conclusion: The ***BAN****® Nebulizer alone had environmental losses of less than 3%, which in itself is at least five times less than reported for continuous nebulizers and is consistent with previous data for this device. The filter kit eliminated all losses, and even if the filter was not replaced each treatment (label use), the efficiency appeared to be maintained for at least five uses.

A LABORATORY-BASED EXAMINATION OF THE POTENTIAL FOR FUGITIVE EMISSION OF AEROSOLS TO THE LOCAL ENVIRONMENT FROM A RANGE OF COMMERCIALLY AVAILABLE NEBULIZER SYSTEMS. MW Nagel, JA Suggett, JP Mitchell. Respiratory Drug Delivery 2021;1:287-292.

Introduction: The delivery of inhaled medications by nebulizer for the treatment of respiratory disease is widespread, in part because many medications are only available for inhalation via this dosage form[1]. Further, this form of medication delivery may be the best route of administration for the very young patient who might not be capable of using other inhaler classes[2], or the elderly with cognitive or motor function impairment[3,4]. However, an unintended consequence is the potential for fugitive emissions to the local environment during patient treatment[5]. This process is a potential risk factor in both clinical and homecare settings, particularly in the context of spreading SARS-CoV-2 virus particles in the context of the present COVID-19 pandemic[6]. The purpose of the present laboratory based investigation was to compare the potential for fugitive emissions from a variety of widely encountered compressed air-driven jet nebulizers and one example vibrating mesh nebulizer during simulated adult tidal breathing, using the short-acting bronchodilator, salbutamol (sulphate), as the tracer aerosol. **Materials and Methods:** The nebulizers studied in this adult use simulation (n = 5/device), together with their operating modes, are listed in Table 1. The mouthpiece of the nebulizer on test was connected to a breathing simulator (ASL 5000, IngMar Medical Ltd., Pittsburgh, PA, USA) (Figure 1), set to operate in accordance with the conditions summarized in Table 2, in order to simulate realistic variations in inspiratory/expiratory (I:E) ratio associated with different patients' disease states[7], and the potential for short pauses in therapy.

Figure 1: Nebulizer Testing by Breathing Simulator: Set-up Showing Collection of Salbutamol During Inspiratory and Expiratory Phases of Each Breathing Cycle

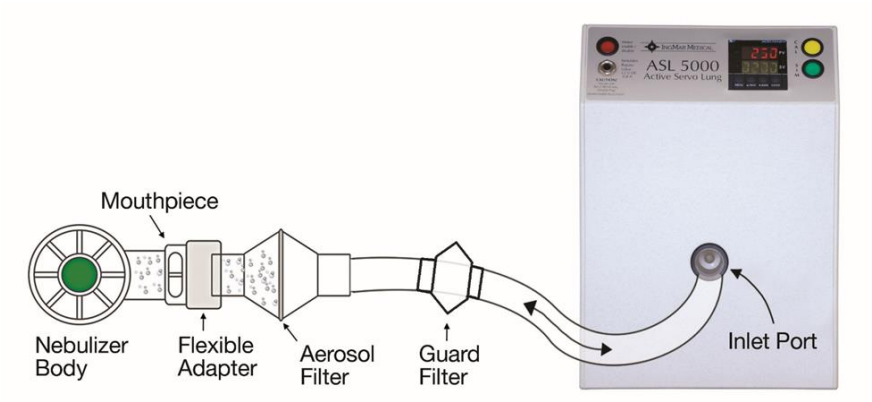


Table 1: Nebulizers Evaluated for Comparative Fugitive Emissions

Name	Manufacturer	Abbreviation	Operating Mode
AeroEclipse** *II BAN* Nebulizer	Trudell Medical International	AE-II	Breath actuated/Jet
NebuTech† HDN†	Salter Labs	NTEC	Continuous/Jet
Salter Labs† 8900	Salter Labs	8900	Continuous/Jet
Circulaire† II	Westmed Inc.	CIRC	Continuous with reservoir/Jet
Hudson RCI† MICRO MIST†	Hudson RCI	MIST	Continuous/Jet
AirLife† Sidestream† High-Efficiency	Vyaire Medical, Inc.	SSHE	Continuous/Jet
Vyaire† AirLife† Misty Fast†	Vyaire Medical, Inc.	AIRMF	Continuous/Jet
Philips SideStream† Disposable	Philips Healthcare	SS-D	Continuous/Jet
AirLife† Misty Max 10†	Carefusion/Becton Dickinson	AIR-MM	Continuous/Jet
Aerogen† Ultra	Aerogen Corporation	ULTRA	Continuous/Vibrating mesh

Table 2: ASL 5000 Breathing Simulator Operating Conditions

Tidal Volume (mL)	Respiration Rate (cycles/minute)	I:E Ratio	Minute Volume (mL)
500	15	1:1	7,500
	10	1:2	5,000
	7	1:3	3,500
	6	1:4	3,000

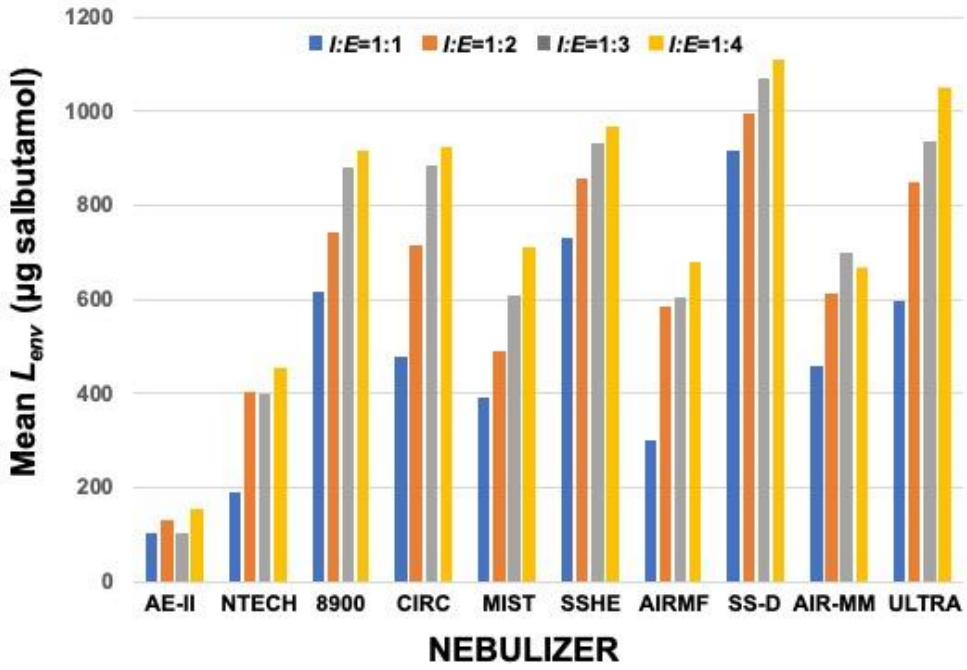
Each nebulizer was evaluated with a 3 mL fill of salbutamol solution (833 µg/mL) from a commercially available source. The mass of salbutamol recovered from the bacterial/viral filter located at the nebulizer mouthpiece (inspiratory filter) was assayed by an internally validated HPLC-UV spectrophotometric procedure. This filter was replaced after each minute of nebulization and the process continued until sputter. The environmental loss of salbutamol was quantified by difference calculation based on 2,500 µg salbutamol inserted in the nebulizer less the total mass recovered from the inhalation filter together with the residual mass recovered from the nebulizer, in accordance with the arrangement shown in Figure 1. This indirect approach was adopted because direct collection of the exhaled droplets by imposing a filter at the nebulizer exhalation port biases the outcome by altering the pressure balance at that location. This process results in a reduction in flow rate and associated 'exhaled' droplet collection. **Results:** The outcomes from the breathing simulator measurements are summarized in Table 3 with TD representing total dose emitted from nebulizer mouthpiece and L_{env} representing the calculated environmental loss.

Table 3: Disposition of Salbutamol Delivered by Each Nebulizer (µg; mean ± SD) to the Respiration Simulator Mimicking Respiration with V_t Fixed at 500 mL

Nebulizer	Metric	RR = 15/min I:E ratio = 1:1	RR = 10/min I:E ratio = 1:2	RR = 7/min I:E ratio = 1:3	RR = 6/min I:E ratio = 1:4
AE-II	TD	966 ± 91	860 ± 9	837 ± 63	724 ± 43
	L_{env}	103 ± 25	131 ± 68	105 ± 32	153 ± 36
NTECH	TD	507 ± 85	354 ± 63	298 ± 46	264 ± 34
	L_{env}	189 ± 63	404 ± 39	398 ± 138	454 ± 83
8900	TD	450 ± 14	312 ± 5	240 ± 15	195 ± 7
	L_{env}	617 ± 21	741 ± 28	882 ± 53	916 ± 43
CIRC	TD	685 ± 91	449 ± 33	303 ± 13	250 ± 26
	L_{env}	478 ± 62	717 ± 29	886 ± 10	925 ± 72
MIST	TD	418 ± 31	272 ± 21	224 ± 21	176 ± 10
	L_{env}	393 ± 72	490 ± 50	607 ± 77	711 ± 26
SSHE	TD	309 ± 10	213 ± 12	150 ± 8	126 ± 7
	L_{env}	729 ± 63	856 ± 58	933 ± 46	967 ± 79
AIRMF	TD	465 ± 30	329 ± 11	230 ± 9	203 ± 13
	L_{env}	300 ± 65	584 ± 72	605 ± 34	680 ± 127
SS-D	TD	433 ± 14	281 ± 14	207 ± 11	175 ± 10
	L_{env}	918 ± 32	994 ± 46	1,071 ± 78	1,108 ± 29
AIR-MM	TD	462 ± 32	340 ± 26	248 ± 22	193 ± 19
	L_{env}	459 ± 63	613 ± 110	698 ± 72	668 ± 97
ULTRA	TD	954 ± 59	598 ± 23	442 ± 25	357 ± 24
	L_{env}	596 ± 40	850 ± 71	936 ± 86	1,052 ± 133

Discussion: Overall, the results highlight the wide variation in TD across the different nebulizer types, a feature that has also been identified in previous laboratory based comparisons[9,10]. More important in the context of the goal of the present study, was the finding that the metric, L_{env}, not only varied considerably between nebulizer systems, but was influenced by the change in I:E ratio, in general increasing, as might be expected, as the proportion of each respiration cycle associated with exhalation increased (Figure 2). Breath actuation (AE-II) substantially reduced but did not totally eliminate environmental aerosol emissions.

Figure 2: Variation of Environmental Loss of Salbutamol Tracer (L_{env}) for the Nebulizers Studied, Showing the Influence of I:E Ratio



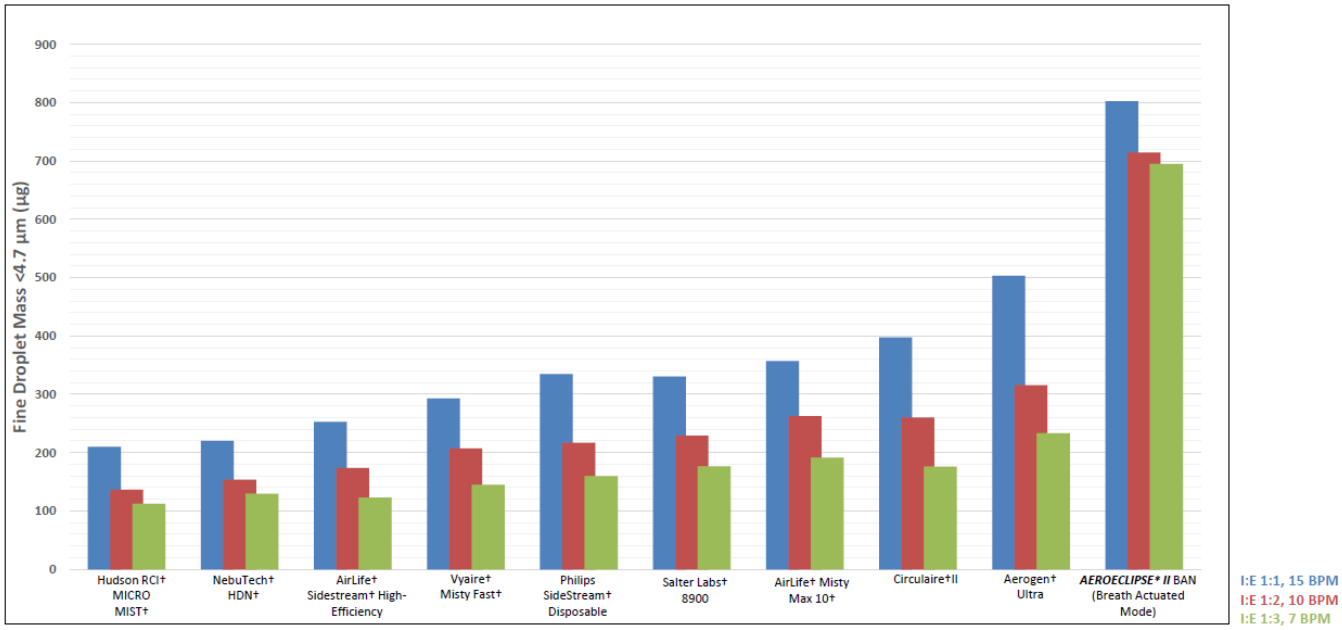
These outcomes highlight the need to consider the risk of secondary inhalation of fugitive emissions released from nebulizing systems, especially when the expiratory portion of the breathing cycle is long with respect to the inhalation portion.

Conclusions: The findings are intended to assist in developing policy and best practice for risk mitigation of fugitive emissions from nebulizing systems, both in the context of managing symptomatic patients infected with COVID-19 or other airborne pathogens, and also in relation to the goal of minimizing emissions of drugs into the local environment where they may come into contact with health care professionals or care providers. **References:** [1] Rethinking The Paradigm For The Development Of Inhaled Drugs. JN Pritchard. International Journal of Pharmaceutics 2015;496(2):1069-1072. [2] Drug Administration By Jet Nebulization. AL Coates, SL Ho. Pediatric Pulmonology 1998;26(6):412-423. [3] Device Selection And Outcomes Of Aerosol Therapy: Evidence-Based Guidelines. MB Dolovich, RC Ahrens, DR Hess, P Anderson, R Dhand, JL Rau, GC Smaldone, G Guyatt. CHEST 2005;127(1):335-371. [4] A Patient's Guide To Aerosol Drug Delivery – 4th Edition. DS Gardenhire, D Burnett, S Strickland, TR Myers. American Association for Respiratory Care, 2017. [5] Fill Volume, Humidification And Heat Effects On Aerosol Delivery And Fugitive Emissions During Noninvasive Ventilation. H Saeed, M Mohsen, JB Fink, P Dailey, EA Salah, MM Abdelrahman, AA Elberry, H Rabea, RRS Hussein, MEA Abdelrahim. Journal of Drug Delivery Science and Technology 2017;39:372-378. [6] The Use Of Nebulized Pharmacotherapies During The Covid-19 Pandemic. S Sethi, IZ Barjaktarevic, DP Tashkin. Therapeutic Advances in Respiratory Disease 2020;14:1-9. [7] Acute Respiratory Distress Syndrome: Diagnosis And Management. A Saguil, M Fargo. American Family Physician 2012;85(4):352-358. [8] An Investigation Of *In Vitro*/*In Vivo* Correlations For Salbutamol Nebulized By Eight Systems. VL Silkstone, JH Dennis, CA Pieron, H Chrystyn. Journal of Aerosol Medicine and Pulmonary Drug Delivery 2002;15(3):251-259. [9] Performance Comparison Of Nebulizer Designs: Constant-Output, Breath-Enhanced, And Dosimetric. JL Rau, A Ari, RD Restrepo. Respiratory Care 2004;49(2):174-179.

DOSE ASSURANCE WITH NEBULIZER THERAPY – A LABORATORY INVESTIGATION INTO THE MEDICATION DELIVERY PERFORMANCE OF A RANGE OF DIFFERENT NEBULIZERS AT DIFFERENTINSPIRATORY/EXPIRATORY RATIOS. M Nagel, N Hoffman, J Suggett, V Wang. American Journal of Respiratory and Critical Care Medicine 2021;203:A4672.

Rationale: Nebulizers with breath actuated technology only deliver medication during inhalation. Most nebulizers deliver aerosol continuously during inhalation and exhalation. The inspiratory/expiratory (I:E) ratio of a patient can change due to the lengthening expiration in obstructive lung disease, or as a result of distractions to the patient during treatment. These changes may consequently decrease the delivery efficiency by nebulization. This study compared the delivery of albuterol via a range of different types of nebulizer in a lab study. **Methods:** Nebulizers (*n* = 5/group) were evaluated with 3 mL fill of 0.25 mg albuterol solution. The nebulizer was connected to a simulator (ASL 5000, IngMar Medical Ltd.) mimicking adult (tidal volume = 500 mL) tidal breathing, with I:E ratios of 1:1, 1:2 and 1:3. Emitted aerosol was captured by filter at 1 minute intervals until sputtering to determine total mass of drug delivered. Albuterol assay was undertaken by HPLC-UV spectrophotometry. Fine droplet mass (µg < 4.7µm) was determined by laser diffractometry as the product of total mass and fine droplet fraction (% < 4.7µm).

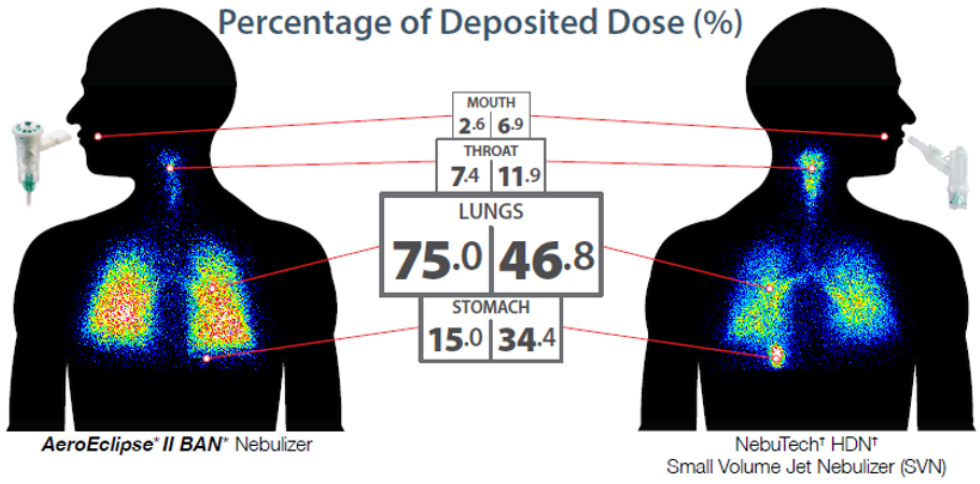
Results: Average fine droplet albuterol mass at extended I:E ratios are shown in the Figure.



Conclusions: Higher and more consistent dose delivery was achieved by the ***AeroEclipse* II BAN**** Nebulizer across the range of I:E ratios tested compared to all other types of nebulizers. Clinicians should be aware of the opportunity to deliver effective and consistent doses more assuredly without the risk of potential under-dosing as disease progresses or if patient pauses during treatment.

COMPARATIVE SCINTIGRAPHIC ASSESSMENT OF DEPOSITION OF RADIOLABELED ALBUTEROL DELIVERED FROM A BREATH ACTUATED NEBULIZER AND A SMALL VOLUME JET NEBULIZER TO HEALTHY SUBJECTS. T Corcoran, A Wesolowski, M Nagel, J Suggett, V Kushnarev, D Coppolo. Respiratory Care 2019;64(10);3235398.

Background: Medication nebulizers are commonly used to delivery aerosolized medications to patients with respiratory disease. To compare *in vivo* aerosol delivery characteristics of a nebulizer with breath actuated technology to that of a standard small volume jet nebulizer (SVN) we evaluated output and regional lung deposition of indirectly radiolabeled albuterol. **Methods:** Eight healthy subjects received albuterol (2.5 mg/3 mL) admixed with 2 mCi of Tc-DTPA (Technetium-99m bound to diethylenetriaminepentaacetic acid) administered using both the ***AeroEclipse* II BAN**** Nebulizer and SVN (NebuTech† HDN†). Regional doses were then determined from anterior and posterior gamma camera images collected after delivery. Lung perimeters were defined using Cobalt-57 transmission scans and applied to Tc-DTPA deposition images. The study was approved by the University of Pittsburgh Institutional Review Board. **Results:** Average age of the 8 subjects (4 male, 4 female) was 33 years. The dose deposited in each subject, on average, was 1.03 ± 0.14 mg vs. 0.89 ± 0.15 mg for the ***BAN**** Nebulizer and SVN respectively. The dose deposited in each subject regionally quantified into the following regions and averages were expressed as percentage of deposited dose (%) ± one standard deviation.



Percentage of Deposited Dose (%)		
Location	***AeroEclipse*** **II BAN**** Nebulizer	**NebuTech† HDN† SVN**
Mouth	2.6 ± 1.5	6.9 ± 3.9
Throat	7.4 ± 2.5	11.9 ± 6.0
Lungs	75.0 ± 15.5	46.8 ± 17.1
Left	35.9 ± 9.2	21.7 ± 8.2
Right	39.1 ± 7.8	25.0 ± 8.9
Stomach	15.0 ± 13.2	34.4 ± 17.0

Conclusions: The ***BAN**** Nebulizer (75.0%) demonstrated increased aerosol deposition to the lungs in healthy subjects as compared to the SVN (46.8%) ($p < 0.006$). Further studies in patients are needed to confirm the clinical benefit of this increased lung deposition. *In vivo* deposition patterns also demonstrated that the SVN delivered significantly more aerosol to the upper respiratory tract as indicated by deposition found in both the stomach and tracheo-esophageal regions ($p < 0.005$).

EVALUATING UPPER AND LOWER AIRWAY NEBULIZER-DELIVERY OF AN INHALED RELIEVER MEDICATION FOR BRONCHOCONSTRICTIVE DISEASE IN THE LABORATORY, SIMULATING ADULT TIDAL BREATHING AND USING AN ANATOMIC OROPHARYNGEAL MODEL. J Schloss, JP Mitchell. Respiratory Care 2016;61(10):OF21.

Background: Delivery of inhaled medication for the treatment of bronchoconstrictive disease in the ED is complicated by the loss of some of the inhaled dose to the upper airway. This laboratory based study mimicking adult use sought to evaluate the magnitude of such losses from different nebulizer types in relation to delivery to the lungs using a new anatomic upper airway model. **Methods:** Three different nebulizers ($n = 9$ replicates/device type) were evaluated with albuterol sulfate solution (2.5 mg/3 mL). Nebulizer types included Solo/Ultra vibrating mesh with Pro-X Controller, Aerogen Ltd. Ireland; NebuTech† HDN† continuous jet (Salter Labs, Arvin, CA), operated with 50 psig compressed air at 7 L/min; ***AeroEclipse*** **II BAN**** Nebulizer (Monaghan Medical Corporation, Plattsburgh, NY) operated with compressed air under similar conditions. The neb mouthpiece was attached to the mouth opening of the Aerosol Delivery to Anatomic Model (ADAM-III) adult upper airway model (Trudell Medical International, London, ON, Canada), where a filter was located at the airway outlet, representing the carina. The filter was connected to a breathing simulator (ASL 5000, IngMar Medical Ltd., Pittsburgh, PA) simulating tidal breathing (V_t = 600 mL; 10 cycles/minute; inspiratory: expiratory ratio 1:2). 5 breathing cycles were undertaken, following which the model was disconnected from the test apparatus and the mass of albuterol deposited in the model airway (O-P) and on the filter (CARINA) assayed by HPLC-UV spectrophotometry. **Results:** The table contains measurements of total mass albuterol (mg; mean ± SD) recovered from the model. All nebulizer types generated droplets that were large enough to deposit in the model oropharynx and would therefore be unavailable for delivery to the lungs. More importantly, there were differences between nebulizer types and the mass of medication that penetrated as far as the 'carina', with the breath actuated device delivering significantly more albuterol than the other two devices (1-way ANOVA, $p < 0.001$).

Table 1:

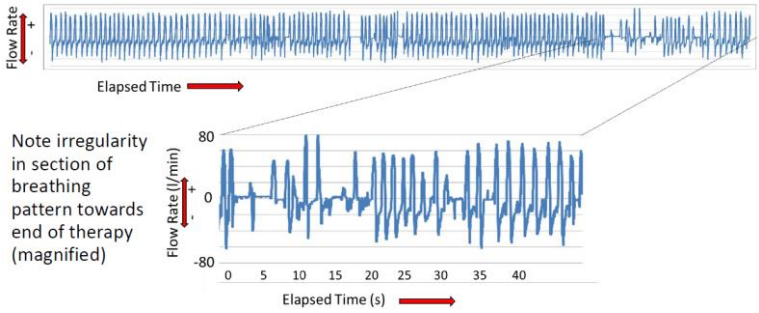
Nebulizer/Type	O-P	Carina
Aerogen† Solo-Ultra (Vibrating Mesh)	31.2 ± 5.6	22.1 ± 4.4
NebuTech† HDN† (Continuous Jet)	32.8 ± 8.3	15.8 ± 2.2
AeroEclipse **II BAN**** Nebulizer (Breath Actuated)	20.3 ± 2.0	30.7 ± 1.9

Conclusion: Nebulizer type is a consideration for the delivery of rescue medication where the goal is to deliver as much drug to the constricted airways rapidly. This *in vitro* study indicated that the breath actuated nebulizer has the potential for optimizing medication delivery, but clinical studies would be required to confirm this finding. **Disclosure:** J Schloss participates in Monaghan Medical Corporation's (MMC) Speaker Bureau. J Mitchell is a consultant to MMC.

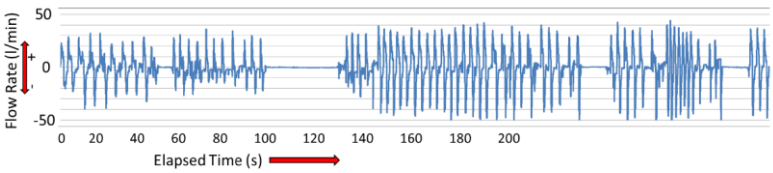
INVESTIGATION OF MEDICATION DELIVERY FROM SMALL VOLUME NEBULIZERS (SVN) AND A BREATH-ACTUATED NEBULIZER USING *IN VIVO* GENERATED BREATHING PROFILES. J Schloss, DP Coppolo, J Suggett, VT Wang, C Doyle, MW Nagel. Respiratory Care 2015;60(10):OF9.

Background: Several international standards provide idealized breathing patterns to demonstrate nebulizer performance (e.g.: ISO 27427:2013 – Anaesthetic and respiratory equipment — Nebulizing systems and components). However, such continuous patterns based on a sinusoidal waveform, even with extended exhalation compared to inhalation phase, fail to capture the nuances affecting therapy, such as difficulty in inhaling, coughing, or pausing to catch the breath. It is important to be able to assess how such realistic situations may influence nebulizer performance, as they are commonly encountered during inhaled therapy. It is therefore desirable to use *in vivo* breathing profiles obtained in the appropriate clinical setting to effectively evaluate the *in vitro* nebulized delivered dose obtained using the technology available with current breathing simulators. The aim of this study was to develop a methodology that could be used to capture multiple *in vivo* breathing patterns taken from patients having defined disease conditions. This system was then used to simulate such breathing patterns *in vitro*, measuring medication delivery from a breath actuated device (***AeroEclipse*** **II BAN**** Nebulizer, Monaghan Medical Corporation) as an example nebulizing system. **Study Objectives:** (1) To capture a series of patient-derived tidal-breathing patterns during nebulizer based therapy in a hospital environment. (2) To use selected patterns to evaluate representative breath actuated devices and SVN nebulizers as proof of concept that patient-derived patterns are more useful than continuous standard waveforms at predicting likely performance of these devices. **Recording Patient Breathing Waveforms:** Breathing patterns were recorded from patients with various disease modalities using a RSS 100 Research Pneumotach Instrumentation system.

Pattern 1: 32 year old female with an acute exacerbation of CF (cystic fibrosis) likely from a bacterial pneumonia. She has severe obstructive lung disease



Pattern 2: 62 year old male post op liver transplant on 12/23/14 (day 7) for liver cirrhosis secondary to Hepatitis C: dyspnea with productive mucus cough.



Again, note irregularities, including a lengthy pause almost mid-way through treatment. This interruption could be associated with coughing or mouthpiece removal to speak with the care-giver or another patient. **Simulated Nebulizer Therapy:** Two jet nebulizers (*n* = 5 devices; 1 measurement per device) were evaluated with 3 mL of salbutamol (albuterol) (2.5 mg/3 mL), each operated with compressed air: ***AeroEclipse*** **II BAN**** Nebulizer/50 psi Medical Air (Monaghan Medical Corporation); Circulaire† II Hybrid continuously operating, small volume nebulizer (SVN)/50 psi Medical Air (Westmed Inc.); NebuTech† HDN† continuously operating, small volume nebulizer (SVN)/50 psi Medical Air (Salter Labs). An electret filter was attached to the mouthpiece to capture nebulized droplets. This filter was replaced at minute intervals during the simulated treatment. Measurements were curtailed at onset of sputter, defining treatment duration. The patient breathing patterns were played back to operate each nebulizer-on-test by means of a breathing simulator (Model ASL 5000, IngMar Medical Ltd., Pittsburgh, PA, USA). The flow rate-time profiles produced in playback mode through the breathing simulator corresponded to patient-recorded patterns. **Results:** Total mass medication delivered (µg) from start to sputter onset.

Breathing Pattern Origin	***AeroEclipse*** **II BAN**** Nebulizer (breath actuated mode)	NebuTech† HDN†	Circulaire† II Hybrid
Pattern 1	830 ± 37	445 ± 19	374 ± 25
Pattern 2	819 ± 29	219 ± 16	182 ± 15

Conclusion: We were successfully able to generate reproducible patient-generated breathing waveforms that were used to probe how the emitted dose from the nebulizer varied from one waveform to another. In general, the ***BAN**** Nebulizer provided more reproducible delivered mass than the SVN, even in instances, such as the pattern from Pattern 2, in which there were significant pauses in between breathing cycles. Clinicians should be aware that *in vitro* data from standardized breathing simulations does detect such behavior.

UNDER-DOSING OF INHALED MEDICATION DELIVERED BY CONTINUOUS NEBULIZERS IS POSSIBLE AS THE RESULT OF CHANGES TO INSPIRATORY:EXPIRATORY (I:E) RATIO BROUGHT ABOUT BY OBSTRUCTIVE LUNG DISEASE. DP Coppolo, MW Nagel, H Schneider, J Suggett, JP Mitchell. CHEST 2014;146(4):519A.

Purpose: To demonstrate the likely variability of medication delivery from continuously operating pneumatic nebulizers at different I:E ratios as adult patient I:E ratios are known to vary widely in advanced obstructive disease (K Nikander, J Denyer. European Respiratory Journal 2000;10(76):576-579). **Methods:** Two continuously operating jet nebulizers (*n* = 5/group; AirLife† Misty Fast†, CareFusion, San Diego, CA and NebuTech† HDN†, Salter Labs, Arvin, CA) operated with compressed air at 50 psig were evaluated with an adult tidal breathing waveform (tidal volume = 50.0 mL) with I:E ratios = 1:1, 1:2, 1:3, and 1:4 with 15, 10, 7 and 6 breaths/minute respectively, delivered by breathing simulator (ASL 5000, IngMar Medical Ltd., Pittsburgh, PA). These I:E ratios were chosen to represent the various patient disease states. An electret filter at the mouthpiece of the nebulizer captured emitted aerosol containing 2.5 mg albuterol sulfate (ALD) in a 3 mL fill (Hi-Tech Pharmacal, Amityville, NY) at minute intervals until onset of sputter. Total mass (TM) was calculated after assaying for ALB by a validated HPLC based procedure. In parallel experiments fine droplet fraction < 4.7 µm ($FDF_{<4.7µm}$) were determined by laser diffractometry. **Results:** Fine droplet mass ($FDM_{<4.7µm}$, mean ± SD) values (µg) obtained as the product of TM and $FDF_{<4.7µm}$ were as follows: Misty Fast†: I:E = 1:1, 183 ± 28; I:E = 1:2, 139 ± 11; I:E = 1:3, 102 ± 4; I:E = 1:4, 107 ± 2. NebuTech† HDN†: I:E = 1:1, 206 ± 21; I:E = 1:2, 151 ± 21; I:E = 1:3, 140 ± 9; I:E = 1:4, 112 ± 15. The percentage decreases in mean $FDM_{<4.7µm}$ from the reference condition (I:E = 1:1), Δ $FDM_{<4.7µm}$ were: Misty Fast†: I:E = 1:2, 75.9%; I:E = 1:3, 55.7%; I:E = 1:4, 58.4%. NebuTech† HDN†: I:E = 1:2, 73.3%; I:E = 1:3, 68.0%; I:E = 1:4, 54.3%. $FDM_{<4.7µm}$ decreased with increasing I:E ratio for both nebulizer groups (1-way RMANOVA, $p < 0.001$), the decline across the range studied taking I:E = 1:1 as reference (100-Δ $FDF_{<4.7µm}$) was -42% for the Misty Fast† and -46%, NebuTech† HDN†. **Conclusions:** Significantly less medication was delivered per treatment by either nebulizer with increasing I:E ratio, due to wastage during each exhalation. **Clinical Implications:** This is a likely clinical scenario as disease state worsens or in patients with a compromised respiratory condition, and

could result in potential underdosing. One potential solution to this clinical challenge would be the use of a breath actuated device (H Schneider, *et al*. American Journal of Respiratory and Critical Care Medicine 2014;189:A3035.).

GOING WITH THE FLOW: RESPIRATORY CARE IN THE PEDIATRIC EMERGENCY DEPARTMENT. TL Canares, C Tucker, A Garro. Rhode Island Medical Journal 2014;97(1):23-26.

Abstract: Providers in pediatric emergency departments (ED) frequently encounter a variety of life-threatening respiratory illnesses. This article reviews current updates on the management and unique adjuncts for 3 common respiratory illnesses. Discussed first is bronchiolitis and the impact of high flow nasal cannula on reducing the need for intubation. Next, the current therapy for croup and the adjunctive use of Heliox and finally, the ED approach to asthma and treatment with breath actuated nebulizers. **Conclusion:** Respiratory illnesses are common pediatric conditions that often require emergency treatment. Unique modalities are available in a tertiary pediatric emergency department for the care of children with 3 common respiratory illnesses: bronchiolitis, croup and asthma. In addition to traditional guideline based therapies, the HCH (Hasbro Children's Hospital) ED has incorporated several treatment adjuncts including HFNC (high flow nasal cannula), Heliox, and breath actuated nebulizers. HFNC or Heliox use are currently limited to the hospital environment, however, breath actuated nebulizers are a simple and cost-effective device that can be integrated into the primary care, urgent care, or community ED setting.

A PROSPECTIVE, COMPARATIVE TRIAL OF STANDARD AND BREATH-ACTUATED NEBULIZER: EFFICACY, SAFETY, AND SATISFACTION. V Arunthari, RS Bruinsma, AS Lee, MM Johnson. Respiratory Care 2012;57(8):1242-1247.

Background: Nebulized drug delivery is a cornerstone of therapy for obstructive lung disease, but the ideal nebulizer design is uncertain. The breath actuated device may be superior to conventional nebulizers. This study compared the breath actuated device to standard nebulizer with regard to efficacy, safety, and patient and respiratory therapist (RT) satisfaction. **Methods:** Adults admitted to the hospital and for whom nebulizer therapy was prescribed were enrolled. Subjects were randomly assigned to either ***AeroEclipse*** **II BAN**** Nebulizer or standard nebulizer and were surveyed at the completion of each treatment. The ***BAN**** Nebulizer delivered albuterol 2.5 mg or albuterol 2.5 mg plus ipratropium 0.25 mg. Standard nebulizer delivered albuterol 2.5 mg or albuterol plus ipratropium 0.5 mg. An RT (respiratory therapist) assessed each subject's heart rate, respiratory rate, and peak expiratory flow rate prior to and following treatment. Treatment time and adverse events were recorded. Each RT was asked to assess his/her satisfaction with each of the nebulizers. **Results:** Twenty-eight subjects were studied. The mean age was 69 years. Fifty-four percent of the subjects indicated that overall the ***BAN**** Nebulizer was superior to conventional nebulizer therapy; 68% indicated that duration was preferable with the ***BAN**** Nebulizer. RTs were more satisfied with the ***BAN**** Nebulizer, based on overall performance, treatment duration, and ease of use. There were no significant differences in heart rate, peak expiratory flow rate, or respiratory rate before or after nebulization therapy with either device. The duration of treatment was significantly lower with the ***BAN**** Nebulizer (4.1 minutes vs. 9.9 minutes, $p < 0.001$). Additionally, the ***BAN**** Nebulizer was associated with a lower occurrence of adverse events. **Conclusions:** Patients and RTs expressed greater satisfaction with the ***BAN**** Nebulizer, compared with standard nebulizer. Pre- and post-treatment vital signs did not differ between groups, but use of the ***BAN**** Nebulizer was associated with a shorter duration and a lower occurrence of adverse events. Taken together, these data support the use of the ***BAN**** Nebulizer for nebulized medication delivery.

RANDOMIZED CONTROLLED TRIAL OF A BREATH-ACTIVATED NEBULIZER IN PATIENTS WITH EXACERBATION OF COPD. JM Haynes. Respiratory Care 2012;57(9):1385-1390.

Background: Exacerbations of COPD (ECOPD) are characterized by increased dyspnea due to dynamic pulmonary hyperinflation. This study sought to determine whether the ***AeroEclipse*** **II BAN**** Nebulizer would produce greater bronchodilator responses than a continuous flow small-volume nebulizer (SVN) in patients with ECOPD. **Methods:** Prospective randomized controlled trial. Forty patients with ECOPD were recruited to participate in the trial. The primary study outcomes were inspiratory capacity (IC) and dyspnea via the Borg scale. Subjects were randomized to receive bronchodilator from either a ***BAN**** Nebulizer or a continuous flow SVN. Subjects in both groups received 2.5 mg albuterol sulfate and 0.5 mg ipratropium bromide by nebulizer every 4 hours, and 2.5 mg albuterol every 2 hours as needed. Approximately 2 hours after the subject's 6th scheduled nebulizer treatment, IC, dyspnea, and respiratory frequency measurements were repeated. **Results:** Both groups received an equal number of nebulizer treatments over the study period (***BAN**** Nebulizer 6.25 ± 0.55, control 6.2 ± 0.7, $p = 0.80$). Following completion of the study protocol the ***BAN**** Nebulizer group had a higher IC than the SVN group (1.83 ± 0.65 L vs. 1.42 ± 0.49 L, $p = 0.03$, respectively). The change in IC was higher in the ***BAN**** Nebulizer group (0.33 ± 0.31 L than in the SVN group (0.15 ± 0.19 L, $p = 0.03$). The ***BAN**** Nebulizer group also had a lower respiratory rate (19 ± 3.3 breaths/minute vs. 22 ± 5.3 breaths/minute, $p = 0.03$, respectively). There was no difference in resting dyspnea as measured with the Borg scale (***BAN**** Nebulizer 3.3 ± 2.1, SVN 3.5 ± 2.4, $p = 0.69$) or stay (***BAN**** Nebulizer 4.6 ± 2.6 d, SVN 5.7 ± 2.8 d, $p = 0.21$). **Conclusions:** In this cohort of patients with ECOPD, a ***BAN**** Nebulizer was more effective in reducing lung hyperinflation and respiratory frequency than a continuous flow SVN.

EFFECTIVENESS OF A BREATH-ACTUATED NEBULIZER DEVICE ON ASTHMA CARE IN THE PEDIATRIC EMERGENCY DEPARTMENT. MO Titus, M Eady, L King, CM Bowman. Clinical Pediatrics 2012;51(12):1150-1154.

Abstract: The breath actuated nebulizer is a new respiratory device to deliver short-acting β-agonists to patients with asthma exacerbations. This pediatric convenience sample experimental study compares the breath actuated device with conventional nebulizers and demonstrates that the breath actuated device allows for shorter treatment times to achieve improved clinical asthma scores with less albuterol, shorter emergency department length of stay, and fewer hospitalizations. **Conclusion:** The use of the breath actuated device allows for shorter treatment times to achieve improved CAS (clinical asthma score) with less albuterol, shorter ED (emergency department) length of stay, and fewer hospitalizations. If results similar to ours are found in further studies, it would appear that the breath actuated device has significant advantages over continuous nebulization for the administration of albuterol in the management of acute asthma exacerbations in children.

RANDOMIZED CONTROLLED TRIAL OF A BREATH-ACTUATED NEBULIZER IN PEDIATRIC ASTHMA PATIENTS IN THE EMERGENCY DEPARTMENT. K Sabato, P Ward, W Hawk, V Gildengorin, J Asselin. Respiratory Care 2011;56(6):761-770.

Background: Bronchodilator treatment for asthma can be provided with various aerosol-generating devices and methods. There have been no randomized trials of a breath actuated nebulizer versus continuous 1 hour nebulization and/or small volume constant output nebulizer in pediatric asthma patients. **Methods:** We conducted a randomized study of one-time albuterol treatment with the ***AeroEclipse*** **II BAN**** Nebulizer versus standard therapy (single treatment via small volume nebulizer or 1 hour of continuous nebulized albuterol) in pediatric asthma patients in the emergency department. Eligible patients were those admitted to the emergency department, 0 months to 18 years of age, who presented with asthma or wheezing. We assessed all the patients with our clinical asthma scoring system and peak-flow measurement if possible. We stratified the patients by clinical asthma score and weight, and then randomized them to receive their initial albuterol treatment in the emergency department via either ***AeroEclipse*** **II BAN**** Nebulizer or standard therapy. We recorded time in the emergency department, change in clinical asthma score, need for additional bronchodilator treatments, need for admission, patient response, ability to actuate the ***AeroEclipse*** **II BAN**** Nebulizer, and adverse effects. **Results:** We enrolled 149 patients between October 14, 2004 and November 11, 2005, and we randomized 84 patients to ***AeroEclipse*** **II BAN**** Nebulizer and 65 to standard therapy. The cohort's average age was 5.5 years. There were no significant differences in demographics. The initial mean clinical asthma scores were 5.1 ± 2.4 in the ***AeroEclipse*** **II BAN**** Nebulizer group, and 5.1 ± 2.1 in the standard-therapy group. Time in the emergency department was not different (***AeroEclipse*** **II BAN**** Nebulizer 102 minutes, standard therapy 125 minutes, $p = 0.10$), but the ***AeroEclipse*** **II BAN**** Nebulizer group had a significantly greater improvement in clinical asthma score (1.9 ± 1.2 vs. 1.2 ± 1.4, $p = 0.001$) and respiratory rate ($p = 0.002$), and significantly lower admission rate (38% vs. 57%, $p = 0.03$). There was no difference in adverse effects. **Conclusions:** Although ***AeroEclipse*** **II BAN**** Nebulizer did not reduce the time in the ED (emergency department), it significantly improved clinical asthma score, decreased admissions, and decreased respiratory rate.

REDUCING TOTAL COSTS OF AEROSOLIZED MEDICATION DELIVERY USING THE *AEROECLIPSE* //* BREATH ACTUATED NEBULIZER. J Wilson. Respiratory Care 2011;56(10):1634.

Introduction: We hypothesized the ***AeroEclipse*** **II BAN**** Nebulizer combined with an aggressive dosing and frequency protocol would result in cost savings. **Methods:** We transitioned a 38 bed pulmonary unit from traditional jet nebulizers to ***BAN**** Nebulizers and developed a medication dosing and frequency protocol. Albuterol was converted to 0.5 mL of a 0.5% solution with 1 mL normal saline. Atrovent† was converted to one half unit dose. The breath actuated mode via mouthpiece or mask interface with normal saline increased to 2 mL and continuous mode was used. Frequencies were changed from Q4 to Q6 and QID to TID. ***BAN**** Nebulizers were changed weekly versus daily with traditional nebulizers. Average hourly rate, treatment time, drug costs, and device costs for June through November 2008 were compared to 2007. To ensure effectiveness of therapy we compared the average number of both scheduled and PRN treatments per patient per day. Subsequently, we utilized this model to convert all impatient beds to ***BAN**** Nebulizer in June 2010 and compared data to a similar time period in 2009. **Results:** Our initial 2008 conversion resulted in a 20% decrease in total costs with an annualized savings of $52,360. Additionally, a 31% decrease in minutes per day in therapist time to administer medications and 21% increase in duration between treatments was realized. The average number of scheduled treatments per patient per day was 3.4 and 2.8 in 2007 and 2008 respectively while the average number of PRN treatments was 0.16 and 0.15 in 2007 and 2008 respectively. In the 2010 analysis ***BAN**** Nebulizers account for an 18% decrease in total costs, and a 19% decrease in total treatment time. Use of ***BAN**** Nebulizers resulted in an annual savings at Forsyth Medical Center of $186,789 and estimated savings of $475,411 across Novant Health facilities. Average number of scheduled treatments per patient per day was 3.3 and 3.1 in 2009 and 2010 respectively while the average number of PRN treatments was 0.24 and 0.27 in 2007 and 2008 respectively. Additionally, we compared 2010 data from the units in our initial 2008 group to ensure the improvement reported was maintained in that area. **Conclusions:** Using the ***AeroEclipse*** **II BAN**** Nebulizer in conjunction with an aggressive medication dosing and frequency reduction protocol provides significant savings. Greater gains have been realized for the pulmonary specific unit which treats patients with more severe pulmonary conditions.

COMPARISON OF A BREATH-ACTUATED NEBULIZER VERSUS A CONVENTIONAL CONTINUOUS-OUTPUT NEBULIZER IN TREATING ACUTE ASTHMA IN A PEDIATRIC EMERGENCY DEPARTMENT: AN ONGOING RANDOMIZED CONTROLLED TRIAL. JA Rose, S Cancelliere, P Matye, S Nair, M O'Riordan. American Academy of Pediatrics National Conference and Exhibition, San Francisco, CA, 2010.

Purpose: A breath actuated nebulizer is a newer type of nebulizer that creates aerosol only during a patient's inhalation. Theorized advantages of breath actuated nebulizers over conventional continuous output nebulizers include delivery of a higher percentage of aerosolized drug doses to patients' lungs and decreased loss of drug to the environment. Little is known regarding effectiveness of breath actuated nebulizer devices in treating pediatric asthma patients. No known studies have compared patient satisfaction with breath actuated nebulizers versus continuous output nebulizers. The purpose of this ongoing randomized controlled trial is to compare effectiveness of and patient satisfaction with a breath actuated nebulizer versus a standard continuous output nebulizer for treatment of acute asthma in a pediatric emergency department (ED). **Methods:** Participants are children aged 1 through 17 years presenting to a pediatric ED for treatment of acute asthma. Following an initial bronchodilator treatment with a conventional continuous output nebulizer, participants requiring further treatments are randomly assigned to receive treatments with either a breath actuated nebulizer or standard continuous output nebulizer until meeting established discharge criteria. In each group, participants are treated with an identical regimen of frequent bronchodilator treatments and oral dexamethasone with clinical reassessment every twenty minutes according to a standardized asthma care algorithm. In addition, participants complete a survey regarding satisfaction with the assigned device at the end of their ED visit. **Results:** A total of 151 children aged 1 to 17 years have participated to date (76 in the breath actuated nebulizer group; 75 in the continuous nebulizer group). Target study enrollment is 240 participants. Study groups are similar thus far in terms of demographics and baseline asthma severity. The initial mean Pulmonary Index Score is 8.09 for participants in the breath actuated nebulizer group, and 8.03 for participants assigned to the continuous nebulizer group. Overall, 25 (32.9%) of 76 patients in the breath actuated nebulizer group have required hospitalization compared with 33 (44%) of 75 in the

continuous nebulizer group. Completed satisfaction surveys are available for 150 participants (99.3%). Forty-one (53.9%) out of 76 respondents in the breath actuated nebulizer group "strongly agreed" that they would feel comfortable receiving treatments with the same type of nebulizer in the future, compared to 20 (27%) of 74 respondents in the continuous group. **Conclusion:** Among participants enrolled thus far, the rate of hospitalization for acute asthma is lower in those assigned to the breath actuated nebulizer group compared to those in the continuous output nebulizer group. A greater percentage of participants have indicated a high level of comfort with use of the breath actuated nebulizer device.

A BREATH-ACTUATED JET NEBULIZER HAS DOSIMETRIC CAPABILITY FOR A SUSPENSION FORMULATION BASED ON DIFFERING VOLUME FILL OF MEDICATION AS WELL AS RUN TIME. J Malpass, MW Nagel, C Doyle, R Ali, V Avvakoumova, JP Mitchell. European Respiratory Journal 2010;36(54):4543.

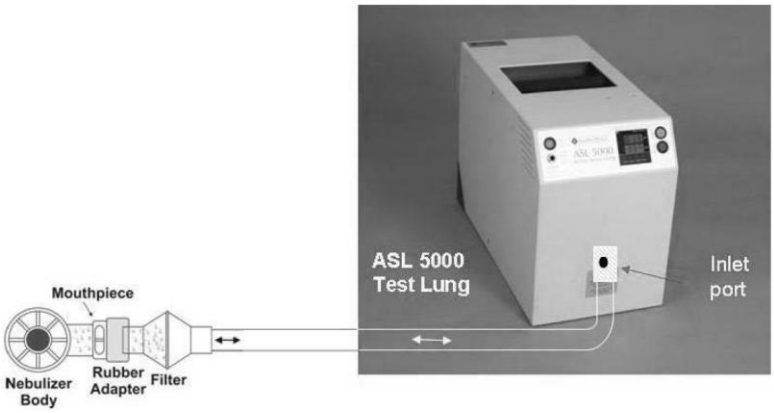
Introduction: The ability to deliver a suspension formulation dosimetrically by nebulizer is important when titrating a patient to the minimum efficacious dose. **Study Purpose:** We report a study in which we evaluated delivery of a widely prescribed budesonide suspension formulation (Pulmicort† Nebuamp†, AstraZeneca† Canada, 500 µg/mL) by breath actuated ***AeroEclipse** *II BAN**** Nebulizer, Trudell Medical International, London, ON, Canada, *n* = 3) operated at 50 psig. Emitted droplets were collected onto a filter at the nebulizer mouthpiece. Tidal breathing was simulated (V_t = 600 cc; rate = 10 cycles/minute; I:E ratio = 1:2), varying the volume fill in the nebulizer reservoir from 2.0 to 4.0 mL in 1.0 mL increments. The total droplet mass of budesonide collected at minute intervals (TDM) until sputtering was assayed by a validated HPLC-UV spectrophotometric technique. **Results:** Fine droplet fraction ($FDF_{<4.7\mu m}$) was determined by laser diffractometry in parallel experiments and was 87.1 ± 0.5% (mean ± SD). Fine droplet mass ($FDM_{<4.7\ \mu m}$) was linear with elapsed time, and almost independent of volume fill at 50.4 ± 1.9 µg/min. **Conclusions:** Settling of the budesonide particles in the reservoir of the ***BAN**** Nebulizer was minimal during the delivery process. The ***BAN**** Nebulizer therefore provides predictable $FDM_{<4.7\ \mu m}$ based on volume fill and time, thereby assisting the clinician with dose titration.

A MECHANICALLY OPERATED BREATH-ACTUATED JET NEBULIZER HAS DOSIMETRIC CAPABILITY BASED ON DIFFERING VOLUME FILL OF MEDICATION AS WELL AS RUN TIME. JP Mitchell, CC Doyle, V Avvakoumova. Drug Delivery to the Lungs-20 2009;2:1-4.

Summary: In an ideal clinical setting, it should be possible to specify a given mass of medication given by nebulizer to compare with an equivalent amount of the same drug product delivered by pressurized metered dose inhaler or dry powder inhaler. Under such circumstances, provided delivery of medication via the nebulizer only occurs during inhalation, and is dosimetric with respect to volume fill, it is a simple task to calculate from the label claim drug concentration the volume fill that will provide the required mass of drug, allowing the patient to breath tidally until the nebulizer sputters. We report a study in which the delivery of salbutamol sulphate and budesonide, representing solution and suspension formulations respectively was separately studied, simulating adult tidal breathing, as a function of volume fill with the ***AeroEclipse** *II BAN**** Nebulizer operated with compressed air (50 psig) from a wall outlet. The relationship between total inhaled mass and volume fill (1.0 - 3.0 mL salbutamol sulphate; 1.0 - 4.0 mL budesonide) throughout the stable nebulization period was linear, with the delivery rate dependent upon the mass concentration of active pharmaceutical ingredient in the formulation added to the reservoir. Interestingly, linearity was preserved with the suspension formulation, indicating that settling of the API in the reservoir was not occurring to a significant extent during the delivery process. This finding, taken with the fact that the delivery rate of either medication was constant as a function of delivery time, indicates that the ***BAN**** Nebulizer functions as a fully dosimetric device within the range of volume fills examined. **Introduction:** In an ideal clinical setting, it should be possible to specify a given mass of medication given by nebulizer to compare with an equivalent amount of the same drug product delivered either by pressurized metered dose inhaler or dry powder inhaler[1]. In practice, such comparisons are difficult because the amount of medication wasted during exhalation has a large and variable influence on the relationship between mass inserted in the reservoir at the start of treatment and the mass that is actually inhaled. However, provided delivery of medication via the nebulizer only takes place during inhalation and is dosimetric with respect to volume fill, it should be a simple task to calculate from the label claim drug concentration the volume fill that will provide the required mass of drug, assuming the patient is able to breath tidally from the nebulizer until the device sputters. The delivery rate from the ***BAN**** Nebulizer will depend upon the physical properties of the formulation (viscosity, surface tension, particle size distribution if a suspension), as well as the mass concentration of the active pharmaceutical ingredient. The original ***AeroEclipse** *BAN**** Nebulizer introduced a few years ago was the first mechanically operated breath actuated device that was shown, simulating adult tidal breathing, to provide a near constant delivery rate of medication between the onset of nebulization and first sputter from a variety of aqueous solution formulations used in current hospital practice[2]. A comprehensive study using a methacholine challenge agent also established its dosimetric capability with a fixed fill of a solution formulation (2.0 mL) as a function of mass concentration of API and delivery duration, when operated under similar conditions[3]. Since then, an improved version of the device (***AeroEclipse** *II BAN**** Nebulizer, Trudell Medical International, London, ON, Canada) with equivalent *in vitro* performance[4-6] has become available. The present study investigated the delivery of commercially available solution and suspension preparations for nebulization, also simulating tidal breathing, as a function of volume fill with the ***AeroEclipse** *II BAN**** Nebulizer operated with compressed air (50 psig) from a wall outlet as would be the case in a hospital setting. These preparations were used as model compounds to compare nebulizer performance at a benchmark condition where particle sedimentation in the preparation placed in the nebulizer reservoir was not possible (salbutamol sulphate) and where sedimentation might take place (budesonide). **Materials and Methods:** Three ***AeroEclipse** *II BAN**** Nebulizers were evaluated, operating them with medical air at their maximum flow rate (7 - 8 L/min). The mouthpiece from the nebulizer on test was connected to a breathing simulator (ASL 5000, IngMar Medical Ltd., Pittsburgh, PA, USA) via an electret bacterial/viral filter (RespirGard II†, Vital Signs Inc., Totowa, NJ, USA) upon which the 'inhaled' aerosol deposited (Figure 1). An adult tidal breathing pattern was simulated for all measurements (tidal volume (Vt) = 600 mL, rate = 10 cycles/minute, duty cycle = 33% inhalation/ 67% exhalation). In the first part of the study, various volume fills of salbutamol sulphate solution (833 µg/mL salbutamol base equivalent) ranging from 1.0 to 3.0 mL in 0.5 mL increments were introduced into the reservoir of the nebulizer and the device operated on each occasion until first sputter, defining the point at which non-linear delivery of medication would be expected. The maximum fill equates with the ampoule size for commercially available salbutamol solution in the US. The aerosol filters were replaced at 1 minute intervals to prevent overloading and to provide time dependent information. The mass of salbutamol collected on each filter was subsequently

assayed by a validated HPLC-UV spectrophotometric technique. In the second part of the study, the same procedure was repeated with budesonide suspension (500 µg/mL), this time varying the volume fill from 1.0 to 4.0 mL in 1.0 mL increments. The commercially available ampoule size for this preparation is 2 mL, making the maximum fill equal to two complete ampoules. The mass of budesonide collected was also assayed by a validated HPLC-UV spectrophotometric technique.

Figure 1: Schematic of Nebulizer Test Set-Up



Results: Medication delivery as a function of elapsed time and fill volume are presented in Tables 1 and 2 for the measurements made with salbutamol sulphate and budesonide respectively.

Table 1: Medication Delivery via ***AeroEclipse**** ***II BAN**** Nebulizer - Salbutamol Sulphate

	3.0 mL Fill			**2.5 mL Fill**			**2.0 mL Fill**			**1.5 mL Fill**			**1.0 mL Fill**		
Device	16405	16406	16407	16405	16406	16407	16405	16406	16407	16405	16406	16407	16405	16406	16407
Filter 1	128.9	131.9	120.1	127.2	129.6	100.9	126.7	133.4	113.0	136.2	134.4	112.7	141.7	136.3	106.5
Filter 2	117.6	160.1	115.2	127.0	130.6	101.8	114.1	128.3	110.2	118.6	116.6	103.9	54.1	39.5	63.2
Filter 3	91.1	119.6	110.2	104.0	111.4	102.2	96.9	116.6	100.5	84.4	80.6	94.3	0.0	0.0	0.0
Filter 4	85.1	113.3	110.3	118.4	112.2	102.5	88.5	91.1	94.2	0.0	0.0	0.0	0.0	0.0	0.0
Filter 5	95.0	110.2	102.3	98.3	103.5	89.0	59.3	53.3	69.9	0.0	0.0	0.0	0.0	0.0	0.0
Filter 6	77.2	119.3	97.5	82.7	91.3	84.7	0.0	0.0	44.9	0.0	0.0	0.0	0.0	0.0	0.0
Filter 7	72.8	86.0	80.4	72.4	70.0	81.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Filter 8	92.7	32.4	78.1	0.0	0.0	70.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Filter 9	98.6	0.0	83.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Filter 10	0.0	0.0	3.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total (µg)	**859.0**	**873.0**	**901.7**	**730.1**	**748.5**	**733.0**	**485.5**	**522.6**	**532.7**	**339.2**	**331.6**	**310.9**	**195.8**	**175.8**	**169.8**
Mean	**877.9 (µg)**			**737.2 (µg)**			**513.6 (µg)**			**327.2 (µg)**			**180.5 (µg)**		
Standard Deviation	**21.8 (µg)**			**9.9 (µg)**			**24.9 (µg)**			**14.6 (µg)**			**13.6 (µg)**		

Note: Mean and standard deviation values represent performance during stable nebulisation (i.e. before first sputter).

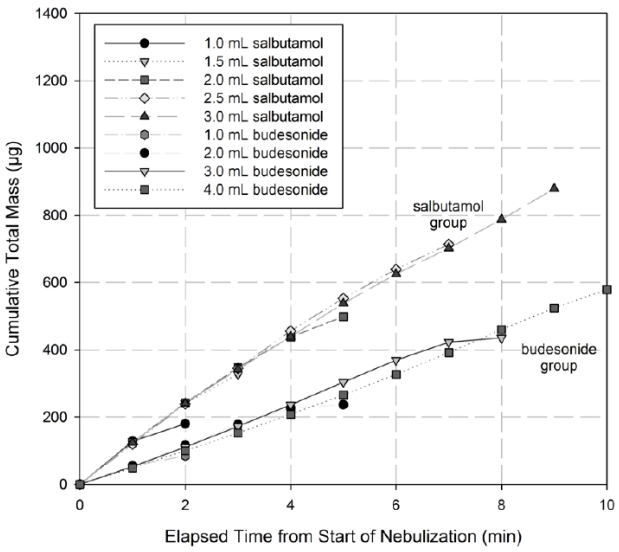
Table 2: Medication Delivery via ***AeroEclipse**** ***II BAN**** Nebulizer - Budesonide

	4.0 mL Fill			**3.0 mL Fill**			**2.0 mL Fill**			**1.0 mL Fill**		
Device	S 16405	S 16406	S 16407	S 16405	S 16406	S 16407	S 16405	S 16406	S 16407	S 16405	S 16406	S 16407
Filter 1	48.2	50.4	48.4	53.1	54.3	51.9	54.7	60.8	49.7	53.1	58.1	54.9
Filter 2	51.1	52.5	49.3	57.3	60.8	55.6	59.7	68.2	55.9	25.9	33.3	28.7
Filter 3	53.6	54.0	50.1	60.5	65.2	58.6	61.1	64.8	59.2	0.0	0.0	0.0
Filter 4	56.7	56.0	53.9	64.7	67.4	60.1	49.2	46.2	49.8	0.0	0.0	0.0
Filter 5	59.0	57.2	55.8	68.5	72.6	60.4	0.0	0.0	30.5	0.0	0.0	0.0
Filter 6	64.7	58.9	60.4	68.6	65.4	63.4	0.0	0.0	0.0	0.0	0.0	0.0
Filter 7	67.7	62.5	64.4	60.8	51.5	47.2	0.0	0.0	0.0	0.0	0.0	0.0
Filter 8	71.4	64.1	68.8	0.0	0.0	38.4	0.0	0.0	0.0	0.0	0.0	0.0
Filter 9	66.7	56.6	69.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Filter 10	66.0	44.2	54.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Filter 11	58.2	28.5	40.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total (µg)	**605.2**	**556.5**	**575.0**	**433.5**	**437.1**	**435.7**	**224.6**	**240.0**	**245.0**	**79.0**	**91.4**	**83.6**
Mean	**578.9 (µg)**			**435.4 (µg)**			**236.5 (µg)**			**84.7 (µg)**		
Standard Deviation	**24.6 (µg)**			**1.8 (µg)**			**10.7 (µg)**			**6.3 (µg)**		

Note: Mean and standard deviation values represent performance during stable nebulisation (i.e. before first sputter).

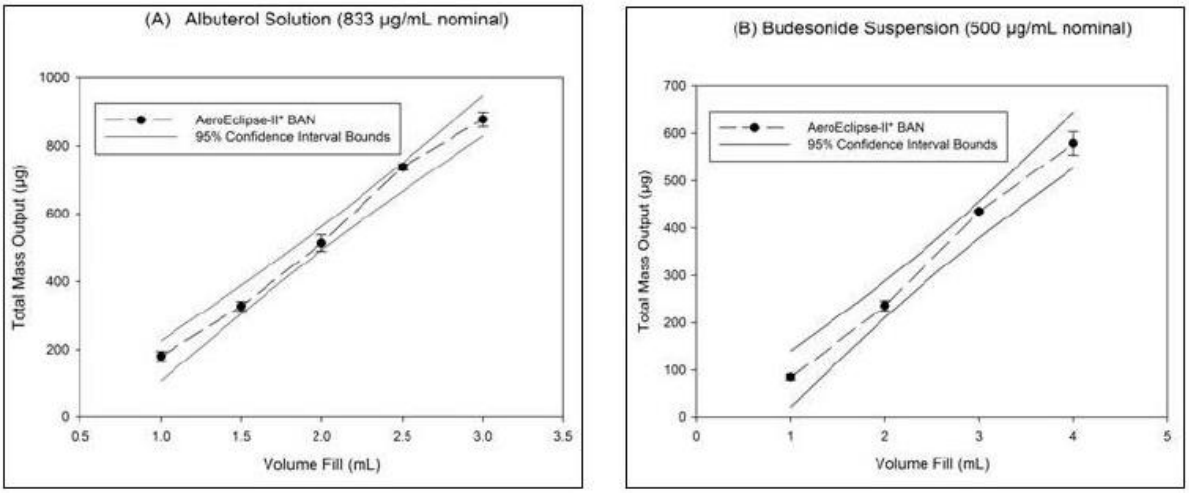
Discussion: The time based delivery of medication between onset of nebulization and first sputter was linear for both preparations (Figure 2), similar behaviour to that observed in previous studies[3,6].

Figure 2: Delivery of Medication from the ***AeroEclipse**** ***II BAN**** Nebulizer as a Function of Elapsed Time



Similarly, linear relationships between cumulative emitted mass (total mass output) and volume fill were observed for both solution and suspension formulations (Figures 3a and 3b).

Figure 3: Delivery of Medication from the ***AeroEclipse** *II BAN**** Nebulizer as a Function of Fill Volume



These data indicate that dosimetric delivery can be anticipated from the ***BAN**** Nebulizer whether the preparation being delivered is a solution or a suspension. Further work is needed to extend the knowledge base to include fill volumes up to 6 mL (the capacity of the reservoir) and to investigate how the nebulizer performs when simulating breathing patterns of other age groups who might be prescribed treatment using this device. **Conclusions:** These *in vitro* measurements simulating adult tidal breathing have demonstrated that the ***AeroEclipse** *II BAN**** Nebulizer has the capability to deliver medication to start of sputter in a predictable manner in terms of both elapsed time from start of treatment and fill volume of medication placed in the reservoir. Where equivalent drug products are available in multiple inhaler formats (pMDI, DPI, nebulizer), clinicians could convert patients currently on other inhalers who require nebulization by means of a lookup table that equates the mass of medication prescribed by the other inhaler to the fill volume and mass concentration of the preparation for nebulization. **References:** [1] Comparing Clinical Features Of The Nebulizer, Metered-Dose Inhaler, And Dry Powder Inhaler. DE Geller. Respiratory Care 2005;50(10):1313-1322. [2] An *In Vitro* Investigation Of Common Nebulizer Dosing Protocols, Comparing A Breath-Actuated With A Conventional Pneumatic Small Volume Nebulizer (SVN). MW Nagel, CC Doyle, SL Bates, JP Mitchell. Respiratory Drug Delivery 2002;2:627-629. [3] An *In Vitro* Study To Investigate The Use Of A Breath-Actuated, Small-Volume, Pneumatic Nebulizer For The Delivery Of Methacholine Chloride Bronchoprovocation Agent. JP Mitchell, MW Nagel, SL Bates, CC Doyle. Respiratory Care 2003;48(1):46-51. [4] Are First And Second Generation, Mechanically-Operated Breath-Actuated Nebulizers Comparable Based On *In Vitro* Performance**?** J Schmidt, J Pevler, C Doyle, K Wiersema, M Nagel, J Mitchell. Respiratory Drug Delivery 2006;3:817-819. [5] Transfer From The Malvern Mastersizer-X To Malvern Spraytec Laser Diffractometers: Experience With Two Breath-Actuated Nebulizers. JP Mitchell, KJ Wiersema, CC Doyle, MW Nagel, P Kippax, H Krarup. Respiratory Drug Delivery 2006;3:813-815. [6] Using Two Strengths Of Levalbuterol Solution And A Breath-Actuated Nebulizer To Modify Medication Delivery Profiles. MW Nagel, CC Doyle, VA Avvakoumova, JP Mitchell. Respiratory Drug Delivery 2008;3:789-792.

STAFF AND PATIENT SATISFACTION WITH A BREATH ACTUATED NEBULIZER PERFORMANCE IMPROVEMENT. JS Emberger, J Brown, V Maheshwari, L Killian. Respiratory Care 2009;54(11):1572.

Background: New advanced nebulizer designs have been developed to improve delivery of medications. Patients with chronic obstructive lung disease as well as respiratory care practitioners are accustomed to standard nebulizers for medication therapy. A performance improvement project evaluating a breath actuated device (***AeroEclipse** *II BAN**** Nebulizer, Monaghan Medical Corporation) approved by our pharmacy and therapeutics committee was performed at our hospital. We investigated if a breath actuated device would improve the satisfaction of the patients and the respiratory staff for aspects of care associated with the nebulizer therapy. **Methods:** An IRB (institutional review board) approved retrospective review of the surveys from our ***BAN**** Nebulizer patients and surveys of the respiratory therapists who performed ***BAN**** Nebulizer therapy was conducted. All of the survey questions were in a Likert scale format: "On a scale of 1 to 5, 5 being the ***BAN**** Nebulizer was superior to standard nebulizer, 1 being ***BAN**** Nebulizer was inferior to the standard nebulizer". Rating categories included: Relief of symptoms, Ease of use, Time of treatment, Care given by the respiratory therapist and Overall rating. **Results:** There were 43 respiratory therapists surveyed about ***BAN**** Nebulizer therapy. There were 70 patients surveyed about ***BAN**** Nebulizer therapy. Patients were satisfied with the ***BAN**** Nebulizer therapy over standard nebulizer therapy averaging scores from 4.3 to 4.9 out of 5.0 for the aspects surveyed. Respiratory staff was satisfied with ***BAN**** Nebulizer therapy over standard nebulizer therapy with survey scores ranging from 4.0 to 4.7 out of 5.0 for the aspects surveyed. There were no survey results from patients or respiratory staff lower than a score of 3. **Conclusions:** Bronchodilator treatment for patients with obstructive diseases such as asthma and COPD have conventionally used standard small volume nebulizers. Our study evaluated surveys for use of breath actuated devices to assess the satisfaction of both patients and respiratory care staff. No surveys from staff or patients reflected preference of standard nebulizers. Patients and therapists were satisfied with ***BAN**** Nebulizer therapy in our performance improvement project.

IMPACT OF A BREATH ACTUATED NEBULIZER PERFORMANCE IMPROVEMENT ON HOSPITAL LENGTH OF STAY. JS Emberger, J Brown, V Maheshwari, L Killian. Respiratory Care 2009;54(11):1571.

Background: Newer nebulizer technologies have been developed that may improve delivery of medications as well as shorten the duration of therapy time. We have been investigating ways that we can provide better care and eliminate concurrent respiratory therapy. A performance improvement project was approved by our pharmacy and therapeutics committee to evaluate performing one-on-one nebulizer therapy with a breath actuated device (***AeroEclipse*** ***II BAN*** Nebulizer, Monaghan Medical Corporation). We wanted to determine if timed breath actuated therapy impacted patient length of stay in the hospital. **Methods:** We performed an IRB (institutional review board) approved retrospective review of the following patient populations: 1) Patients in the ***BAN*** Nebulizer approved area that received 3 minutes timed ***BAN*** Nebulizer treatments (***BAN*** Nebulizer Patients) 2) Patients on standard nebulizers in the ***BAN*** Nebulizer approved area before the ***BAN*** Nebulizer project was initiated (PRE- ***BAN*** Nebulizer Patients) 3) Patients on a similar reference floor that used standard nebulizers (Reference Patients). Primary end point was hospital length of stay. We excluded patients with invasive or non-invasive mechanical ventilation, tracheotomy and ICU (intensive care unit) visit. We analyzed characteristics such as: oxygen use, combination controller medication use and home bronchodilator use to determine if the populations are "like" patients. We identified each patient's primary diagnosis and DRG (diagnostic related group) code for comparison analysis. **Results:** We identified 365 ***BAN*** Nebulizer patients for inclusion. The ***BAN*** Nebulizer, PRE- ***BAN*** Nebulizer and Reference Patients had similar percentages of the "like" characteristics listed in the methods section. There was a similar distribution of patients with COPD DRG, asthma DRG and COPD primary diagnosis in each of the three populations. **Conclusions:** Bronchodilator treatment for patients with obstructive diseases such as asthma and COPD have conventionally used standard small volume jet nebulizers. Our study compared the use of ***BAN*** Nebulizer versus small volume nebulizers to evaluate the primary endpoint of hospital LOS (length of stay) in patients with COPD, asthma or both. Actual treatment time was 3 minutes or less which allowed respiratory staff to eliminate concurrent therapy. Treatment with ***BAN*** Nebulizer resulted in a statistically significant reduction in hospital LOS when compared to historical reference and concurrent reference patients with COPD and asthma. Wider prospective studies to evaluate this therapy are needed.

BREATH ACTUATED NEBULIZER IMPROVES QUALITY OF CARE IN PEDIATRIC EMERGENCY DEPARTMENT ASTHMA AND LEADS TO SYSTEM WIDE IMPLEMENTATION. CJH Bong, M Eady, CM Bowman, MO Titus. Pediatric Academic Society Annual Meeting, Baltimore, MD, 2009.

Background: Nebulizers with breath actuated technology have improved asthma care in adults. Children's Hospital and Research Center at Oakland- reduced clinical asthma scores (CAS), hospitalization rates, and respiratory rates with ***AeroEclipse*** ***II BAN*** Nebulizer. **Objective:** To determine if albuterol (ALB) delivery via ***BAN*** Nebulizer vs. conventional continuous nebulizer (CNB) optimizes care and reduces cost in pediatric patients treated for wheeze/asthma in the MUSC pediatric emergency department (PED). **Conclusions:** Greater first response, significant & ~50% lower CAS after 1st treatment in MOD (moderate) exacerbation, despite fewer patients on inhaled controller therapy. Fewer hospitalizations, ~50% fewer admits for MOD. Shorter length of stay (LOS), significant in MOD and SEVERE groups. ***BAN*** Nebulizer treated patients spent ~1/3 less time in PED (54 - 72 minute shorter LOS). Decreases wait time for PED care with more rapid room turn over. Improved delivery, less waste. Decreased ambient loss of medication: ***BAN*** Nebulizer ~4% vs. ~30% with CNB. Reusable device can be used for up to 1 week in hospital or home. Moderate group used 50% less albuterol per treatment compared to CNB group.

BRONCHODILATOR TREATMENT TIME WITH A BREATH-ACTUATED SMALL VOLUME NEBULIZER NEED NOT BE LONGER THAN A CONTINUOUSLY OPERATING NEBULIZER. DP Coppolo, JP Mitchell, RS Ali, HA Mackay, MW Nagel. Respiratory Care 2008;53(11):1522.

Background: Breath actuated nebulizers only operate during inhalation, increasing the perception that treatment times for a given mass of inhaled bronchodilator should be longer than with a continuously operating nebulizer. This is of concern in the emergency treatment of patients with severe reversible airways disease where time-to-deliver a given dose is important. We investigated the delivery of generic diluted albuterol solution by a continuous jet nebulizer (NebuTech† HDN†, Salter Labs, Arvin, CA with a recently introduced breath actuated device (***AeroEclipse*** ***II BAN*** Nebulizer, Monaghan Medical Corporation, Plattsburgh, NY). **Method:** Both nebulizer groups (n = 5) were operated with 8 L/min air supplied at 50 psig with a 3 mL fill (albuterol concentration of 0.83 mg/mL). Aerosol from both nebulizers was sampled onto electret filters using a breathing simulator mimicking adult use (600 mL tidal volume, duty cycle 33%, rate 10 cycles/minute). Assay for albuterol was undertaken by UV spectrophotometry. In a parallel study, droplet size distributions were determined by laser diffractometry, so that the fine droplet fraction < 4.7 µm diameter likely to penetrate to the airways of the lungs (FDF) could be determined. **Results:** Values of FDF (mean ± SD) for the ***AeroEclipse*** ***II BAN*** Nebulizer and NebuTech† HDN† were 78.4 ± 1.8% and 51.3 ± 5.2% respectively. The ***BAN*** Nebulizer delivered 490 ± 48.5 µg as fine droplets after 5 minutes (delivery rate of 98 ± 10 µg/min), compared to 236 ± 23 µg (47 ± 5 µg/min) in the same period by the continuous nebulizer. **Conclusion:** The ***BAN*** Nebulizer offers an important alternative to continuous devices by delivering a higher fine droplet output in less time and in ensuring patient compliance.

IN VITRO **PERFORMANCE COMPARISON OF A BREATH-ACTUATED NEBULIZER FOR THE DELIVERY OF ALBUTEROL OPERATED WITH COMPRESSED HELIOX OR AIR.** D Coppolo, J Mitchell, V Avvakoumova, M Nagel. CHEST 2008;134(4):p93002.

Purpose: The NAEPP Guidelines for the Diagnosis and Management of Asthma were revised in 2007 to include the use of Heliox (21%v/v oxygen/79%v/v helium) for treatment of severe exacerbations that are unresponsive to initial treatments. We report data for delivery of a beta-2 adrenergic agonist by breath actuated nebulizer as guidance to clinicians. **Methods:** ***AeroEclipse*** ***II BAN*** Nebulizers (n = 5 devices, Monaghan Medical Corporation, Plattsburgh, NY) were operated simulating adult tidal breathing (tidal volume = 600 mL, 10 bpm, 33% duty cycle) and delivering 3 mL albuterol (0.83 mg/mL). Each nebulizer was powered at 50 psig by compressed air at 8 L/min (condition A, maximum achievable); Heliox at 8 L/min (condition B); Heliox at 16 L/min (condition C, maximum achievable). Emitted droplets were collected on separate filters at the mouthpiece of the ***BAN*** Nebulizer at 1 minute

intervals and recovered albuterol assayed by HPLC-UV spectrophotometry. The nebulizers were operated until onset of sputtering to determine total emitted mass (TEM). In a parallel study the emitted fine droplet fraction < 4.7 µm diameter obtained at each condition (FDF < 4.7 µm) was determined by laser diffractometry (*n* = 3 replicates with 1 device). Total fine droplet delivery (FDM < 4.7 µm) was calculated as the product of TEM and FDF < 4.7 µm. **Results:** FDF < 4.7 µm (mean ± SD) was 78.4 ± 1.8% (condition A); 68.7 ± 2.9% (condition B) and 84.8 ± 3.2% (condition C). The ***BAN**** Nebulizers operated for 10 minutes, 19 minutes and 11 minutes with corresponding values of FDM < 4.7 µm (mean ± SD) of 90.2 ± 3.3, 28.8 ± 2.0 and 80.3 ± 4.5 µg/min at conditions A, B and C respectively. **Conclusion:** Fine droplet delivery from the ***BAN**** Nebulizer can be maintained at a near equivalent delivery rate with Heliox if the flow rate is set to maximum. The reduction in aerosol output if flow rate is unchanged between air and Heliox reflects the lower density of the latter driving gas.

NEBULIZER-BASED AEROSOL DELIVERY IN CONJUNCTION WITH CONTINUOUS POSITIVE EXPIRATORY PRESSURE (CPEP) USING A NOVEL BRONCHIAL HYGIENE DEVICE. MJ Hewitt, DP Coppolo, JP Mitchell, MW Nagel. American Journal of Respiratory and Critical Care Medicine 2008;177;A863.

Background: Nebulized aerosols are commonly used to deliver aerosols into the lungs of patients with cystic fibrosis (CF). Effective mobilization of secretions is essential if ventilation is to be improved through the administration of bronchodilation agents. We report a laboratory study in which a breath actuated device operated in continuous mode is used in conjunction with a new device capable of providing continuous positive expiratory pressure (CPEP) to mobilize secretions during exhalation. **Study Purpose:** This study was intended to compare the delivery of albuterol from the ***AeroEclipse**** ***II BAN**** Nebulizer/CPEP combination with that from the Salter Labs† 8900 jet nebulizer (Salter Labs, Arvin, CA) also used with the CPEP device. The ***AeroEclipse**** ***II BAN**** Nebulizer operates with entrainment of room ambient air even in continuous mode, improving the efficiency of aerosol generation during the inspiratory portion of each breathing cycle; The Salter Labs† 8900 nebulizer operates at constant air flow rate provided by its supply gas source, without air entrainment. **Conclusions:** The CPEP device used in conjunction with the ***AeroEclipse**** ***II BAN**** Nebulizer with air entrainment during inhalation offers the potential of greater delivery of medication as fine droplets < 4.7 µm aerodynamic diameter to be achieved than with a conventional constant output nebulizer.

RAPID DELIVERY OF BRONCHODILATOR MEDICATION IS POSSIBLE USING A BREATH-ACTUATED SMALL VOLUME NEBULIZER AS AN ALTERNATIVE TO EXTENDED DELIVERY OF MEDICATION BY LARGE VOLUME NEBULIZER. DP Coppolo, JP Mitchell, KJ Wiersema, CC Doyle, MW Nagel. Respiratory Care 2007;52(11):1582.

Background: Inhaled beta-2 adrenergic agonist bronchodilators are often given to patients with severe reversible airways disease by continuous nebulization in extended treatments. However, data are limited as to whether or not shorter, but higher concentration delivery is as an effective treatment modality. The development of a new breath actuated device (***AeroEclipse**** ***II BAN**** Nebulizer, Monaghan Medical Corporation, Plattsburgh, NY (AE II)) provided an opportunity to compare the two treatment methods in a laboratory study before undertaking a clinical comparison. We investigated the delivery of diluted generic respirator solution albuterol by a widely used continuous jet nebulizer (Hi-Flo MiniHEART†, Westmed Corp., Tucson, AZ (CONT)) with that from the AE II. **Method:** The continuous nebulizers (*n* = 3) were operated with 8 L/min air supplied at 50 psig with a 20 mL fill (albuterol concentration of 0.5 mg/mL). A similar number of AE II nebulizers were operated with ca. 8.0 L/min air at 50 psi with a 1 mL fill (albuterol concentration of 5 mg/mL). Aerosol from both nebulizers was sampled onto electret filters using a breathing simulator mimicking small child use (250 mL tidal volume, inspiratory/expiratory ratio 1:2, rate 12 cycles/minute) until onset of sputtering. Assay for albuterol was undertaken by UV spectrophotometry. In a parallel study, droplet size distributions were determined by laser diffractometry, so that the fine droplet fraction < 4.7 µm diameter likely to penetrate to the airways of the lungs (FDF) could be determined. **Results:** Values of FDF for the AE II and CONT were 78.4% and 62.0% respectively. The AE II delivered 758 ± 36 µg as fine droplets after 4 minutes (delivery rate of 190 µg/min), compared to 180 ± 76 µg in the same period by CONT (delivery rate of 45 µg/min). **Conclusions:** The faster delivery rate from the AE II high albuterol concentration modality (unpaired t-test, $p < 0.001$) may offer an important clinical alternative to CONT/low concentration treatment modality.

REDUCTION OF NEBULIZATION TIME, NUMBER OF TREATMENTS, AND LENGTH OF STAY CAN BE ACHIEVED WITH A BREATH-ACTUATED NEBULIZER. K Thigpen, L Simmons. Respiratory Care 2007;52(11):1591.

Background: Patient response to therapy is affected by many factors including nebulizer design, particle size, patient technique, nebulization time*, et al.* A predominant goal in aerosol therapy since its inception has revolved around maximum efficacy in a reasonable manner. We report our findings on nebulization time, average number of treatments per admission and length of stay based on our experience utilizing an updraft nebulizer (UDN) and since our conversion to a breath actuated device (Monaghan Medical Corporation ***AeroEclipse**** ***II BAN**** Nebulizer) in October 2003. **Methods:** We performed a retrospective study on nebulization time and average number of treatments administered to a randomized sample of 50 adult patients on our COPD Clinical Path using the UDN and ***BAN**** Nebulizer. We performed a separate, retrospective study on the average length of stay (ALOS) on patients receiving aerosol therapy with UDN and with ***BAN**** Nebulizer both with a primary diagnosis of COPD (51 cases) as well as a secondary diagnosis (2375 cases) in 2003 and 2006. **Results:** Treatment times were significantly reduced from an average of approximately 10 minutes with the UDN to < 5 minutes with the ***BAN**** Nebulizer. These times were based on a policy to administer our unit dose medications for 5 minutes or until nebulizer-sputter, whichever came first, once the conversion to the ***BAN**** Nebulizer was made. Treatments administered during hospitalization decreased from 24.5 using the UDN to 20.45 using the ***BAN**** Nebulizer. The other study demonstrated a reduction in ALOS for those patients with a primary diagnosis of COPD from 4.81 days with the UDN to 4.41 days with the ***BAN**** Nebulizer, a decrease of 0.4 days or 9%. There was a reduction in ALOS for those patients with a secondary diagnosis of COPD from 7.76 days with the UDN to 7.18 days, a decrease of 0.58 days or 8%. **Conclusions:** The ***BAN**** Nebulizer had a desirable impact on decreasing the time required for nebulization while reducing the number of treatments required for our patients as well as the ALOS required for hospitalization prior to discharge.

DELIVERY OF ALBUTEROL VIA A NEW BREATH ACTUATED NEBULIZER: COMPARISON WITH CONTINUOUS JET NEBULIZERS. DP Coppolo, MW Nagel, CC Doyle, VA Avvakoumova, JP Mitchell. American Thoracic Society International Conference, San Francisco, CA, 2007.

Background: A new breath actuated device (***AeroEclipse*** ***II BAN**** Nebulizer, Monaghan Medical Corporation, Plattsburgh, NY) has been developed to deliver medication only when the patient inhales. **Study Purpose:** This study sought to determine the delivery of albuterol (3 mL fill of diluted solution (0.83 mg/mL)) as fine droplets < 4.7 µm aerodynamic diameter, and compare this fine droplet mass (FDM) with equivalent data from 4 widely available continuous jet nebulizers as benchmark devices. **Study Design:** Each nebulizer (*n* = 5; 3 replicates/device) was operated with compressed air at 50 psig at ca. 8 L/min to simulate hospital wall outlet conditions. The nebulizer on test was coupled to a breathing simulator set to mimic adult use (tidal volume = 600 mL, rate = 10 breaths/minute; duty cycle = 0.33), and the emitted droplets were collected on an electret filter at the mouthpiece. The total mass of albuterol (TM) was assayed subsequently by HPLC-UV spectrophotometry. In a separate study, the droplet size distribution was determined by laser diffractometry so that the fine droplet fraction (FDF) could be obtained. FDM was determined as the product of TM and FDF. FDM (mean SD) from the ***BAN**** Nebulizer was 791 ± 84 µg, delivered in 8 minutes. Corresponding values (FDM in time from start to sputter) for the VixOne† (Westmed, Tucson, AZ), MICRO MIST† (Hudson RCI, Temecula CA), Misty Max 10† (Cardinal Health, McGaw Park IL) and model 8900 Series (Salter Labs, Arvin, CA) were 267 ± 11 µg in 6 minutes, 133 ± 8 µg in 4 minutes, 249 ± 10 µg in 6 minutes and 161 ± 10 µg in 5 minutes. **Conclusions:** Aside from dosage assurance imparted by breath actuation, the ***AeroEclipse*** ***II BAN**** Nebulizer delivered substantially more FDM/min than the other devices. The clinician is now able to treat either for extended high dose delivery (potentially eliminating the need for additional therapy), or titrate to a shorter interval based on response.

A BREATH-ACTUATED SMALL VOLUME NEBULIZER OFFERS A RAPID ALTERNATIVE TREATMENT MODALITY FOR THE DELIVERY OF BRONCHODILATORS FOR ASTHMATIC PATIENTS IN A SEVERE EXACERBATION. DP Coppolo, JP Mitchell, KJ Wiersema, CC Doyle, MW Nagel. Respiratory Care 2006;51(11):1318.

Large volume continuous nebulizers (LVNs) are often used for the delivery of beta-2 adrenergic agonist bronchodilators in the emergency department to treat severe, reversible airways disease, in particular asthma[1]. Treatment time, however, can be lengthy for delivery of the typical LVN fill volume from 20 to 120 mL. Quick delivery of a bronchodilator with an efficient nebulizer may help relieve symptoms from bronchospasm in a shorter period of time.[2] We report a study in which the delivery of diluted generic respirator solution albuterol by LVN (Hope, B&B Medical Technologies Inc., Loomis, CA) was compared with that from a small volume breath actuated device (***AeroEclipse*** ***II BAN**** Nebulizer, Monaghan Medical Corporation, Plattsburgh, NY). The LVNs (*n* = 5) were operated with 10 L/min air supplied at 50 psig with a 20 mL fill (albuterol concentration of 0.167 mg/mL). A similar number of ***BAN**** Nebulizers were operated with 8.0 L/min air at 50 psi with a 3 mL fill (albuterol concentration of 0.833 mg/mL). The aerosol from the LVNs was sampled continuously until onset of sputtering at 12 L/min via a Dreschel filter/bottle where the albuterol was captured quantitatively. Aerosol from the ***BAN**** Nebulizers was sampled onto electret filters using a breathing simulator (600 mL tidal volume, inspiratory/expiratory ratio 1:2, rate 10 cycles/minute) until onset of sputtering, so that operation of the breath actuation mechanism was affected. Assay for albuterol was undertaken by UV spectrophotometry. In a parallel study droplet size distributions were determined by laser diffractometry, so that the fine droplet fraction < 4.8 µm diameter likely to penetrate to the airways of the lungs could be determined. Fine droplet albuterol delivery rates were constant as a function of time for all nebulizers. After 15 minutes, the LVNs had supplied 127.3 ± 37.4 µg as fine droplets at a rate of 8.5 ± 2.5 µg/min. In contrast, the ***BAN**** Nebulizers delivered 810.0 ± 20.4 µg in a 10 minute period, equivalent to a rate of 81.0 ± 2.0 µg/min. The significantly higher delivery rate from the ***BAN**** Nebulizer group (unpaired t-test, $p < 0.001$) offers an important clinical alternative to the LVN in the emergency department where rapid delivery of a bronchodilator is critical. **References:** [1] Aerosol Delivery During Continuous Nebulization. M McPeck, R Tandon, K Hughes, GC Smaldone. CHEST 1997;111:1200-1205. [2] Clinical Evaluation of a Breath Actuated Small Volume Nebulizer (BA-SVN). S Klopf, N Schneiderman, H Payne, C Schramm, MW Nagel, JP Mitchell. Respiratory Care 2000;45(8):979.

A RANDOMIZED CONTROLLED TRIAL COMPARING A BREATH ACTIVATED NEBULIZER TO STANDARD INTERMITTENT AND ONE-HOUR CONTINUOUS ALBUTEROL IN THE TREATMENT OF EMERGENCY ROOM PEDIATRIC ASTHMA. K Sabato, P Ward, W Hawk. Respiratory Care 2005;50(11):1489.

Background: Bronchodilator treatments for asthma can be provided by a various number of aerosol generating devices and methods. To date, there are few large randomized, controlled trials comparing the efficacy, effectiveness and safety of undiluted and continuous diluted administration of albuterol in the treatment of pediatric asthma. Data are also limited on whether certain nebulizers and their masks are more effective than others and whether blow-by treatments area at all effective. Children's Hospital and Research Center at Oakland (CHRCO) respiratory care department is currently conducting a large randomized controlled study comparing the efficacy of a one-time treatment with the ***AeroEclipse*** ***II BAN**** Nebulizer (BA SVN) used with mask or mouthpiece, to a one-time treatment with a standard small volume nebulizer (SSVN) or a one-hour continuous treatment (CONT) for asthmatics presenting to the emergency room (ER). **Methods:** Patients were eligible for inclusion if they were admitted to the ER for respiratory distress, were between 0 months to 18 years of age, and had wheezing or status asthmaticus. Patients were objectively assessed utilizing a CHRCO designed clinical asthma score (CAS) and peak flows when possible. The CAS scores clinical wheezing on a scale from 0 to 11, with 11 representing the most severe distress. Patients were stratified by CAS score (CAS < 4 and > 4) and weight (< 20 kg and > 20kg). Patients were randomized to receive their first bronchodilator treatment in the ER via the BA SVN or standard therapy (CONT or SSVN). Bronchodilator doses for the BA SVN and SSVN were: 0.5 cc (2.5 mg) albuterol in 0.5 cc normal saline for patients < 20 kg, and 1 cc (5.0 mg) undiluted albuterol for patients > 20 kg. Bronchodilators given via the CONT method used 2.0 cc (10 mg) albuterol in 18 cc normal saline. Patients were evaluated at baseline and again 10 minutes after completion of the assigned treatment. Primary endpoints include change in CAS pre/post treatment, need for additional bronchodilator treatments, and time spent in the emergency room. Secondarily, we evaluated the ability of infants to breath activate the BA SVN, the effectiveness of different aerosol interface adapters (patients utilizing the mouthpiece, vented and non-vented aerosolized masks versus blow-by administration), and incidence of side effects documented with each of the approaches. **Results:** Between 10/14/04 and 11/11/05, we enrolled 151 patients into

the study. 2 patients were dropped due to consent issues. The remaining 149 represented 90 male and 59 female patients with an average age of 5.5 years. 84 patients were randomized to the ***BAN**** Nebulizer and 65 were randomized to CONT/SSVN (57 CONT and 8 SSVN). There were no differences in demographics between the groups. Initial CAS scores were 5.3 and 5.2 for the ***BAN**** Nebulizer and CONT/SSVN groups respectively. After treatment, the ***BAN**** Nebulizer group showed significant improvement in their CAS (38% vs. 24%, $p < 0.003$), and the number of patient requiring admission (31 vs. 37, $p = 0.03$). Other than a significant decrease in respiratory rate in the ***BAN**** Nebulizer group (-3.9 vs. 0.5, $p = 0.002$), there were no differences in side effects. **Conclusions:** Use of the Monaghan (Monaghan Medical Corporation) breath actuated ***AeroEclipse**** ***II BAN**** Nebulizer resulted in significant improvements in CAS ($p < 0.003$), need for admission ($p = 0.03$), and decrease in respiratory rate ($p = 0.002$) as compared to our standard treatments (CONT/SSVN). 66% of the ***BAN**** Nebulizer patients were able to breath activate their treatment. We contend that the Monaghan ***AeroEclipse**** ***II BAN**** Nebulizer is a safe and effective nebulizer for the administration of bronchodilator aerosols in pediatrics and may be more effective than continuous aerosols in the treatment of emergency room pediatric asthma.

PERFORMANCE COMPARISON OF NEBULIZER DESIGNS: CONSTANT-OUTPUT, BREATH-ENHANCED, AND DOSIMETRIC. JL Rau, A Ari, RD Restrepo. Respiratory Care 2004;49(2):174-179.

Introduction: Design differences among pneumatically powered, small volume nebulizers affect drug disposition (percentage of the dose delivered to the patient, lost to deposition in the equipment, and lost via exhalation to ambient air) and thus affect drug availability and efficacy. **Objective:** Evaluate *in vitro* the dose disposition with 5 nebulizer models, of 3 types (constant output, breath enhanced, and dosimetric), using simulated normal, adult breathing. **Methods:** We compared 5 nebulizer models: 2 constant output (Misty-Neb† and Sidestream†), 1 breath enhanced (PARI LC† D), and 2 dosimetric (Circulaire† and ***AeroEclipse**** ***BAN**** Nebulizer). Each nebulizer was filled with a 3 mL unit dose of albuterol sulfate and powered by oxygen at 8 L/min. The nebulizers were connected to an induction throat, connected to a breathing simulator. We measured (1) inhaled drug (subdivided into mass deposited in the induction throat and mass deposited in the filter at the distal end of the induction throat), (2) exhaled drug (lost to ambient air), (3) drug lost to deposition in the apparatus, and (4) drug left in the unit dose bottle. The duration of nebulization (until sputter) was measured with a stopwatch. All drug amounts were analyzed via spectrophotometry and expressed as a percentage of the total dose. **Results:** The mean ± SD inhaled drug percentages were: AirLife† Misty-Neb† 17.2 ± 0.4%, AirLife† Sidestream† 15.8 ± 2.8%, PARI LC† D 15.2 ± 4.2%, Circulaire† 8.7 ± 1.0%, and ***AeroEclipse**** ***BAN**** Nebulizer 38.7 ± 1.3%. The mean ± SD percentages of drug lost to ambient air were: Misty-Neb† 26.8 ± 0.7%, Sidestream† 17.3 ± 0.4%, PARI LC† D 18.3 ± 0.8%, Circulaire† 12.3 ± 0.8%, and ***AeroEclipse**** ***BAN**** Nebulizer 6.6 ± 3.3%. The mean ± SD percentages of drug lost to deposition in the apparatus were: Misty-Neb† 52.3 ± 0.6%, Sidestream† 63.4 ± 3.0%, PARI LC† D 62.5 ± 4.0%, Circulaire† 75.8 ± 0.5%, and ***AeroEclipse**** ***BAN**** Nebulizer 51.0 ± 2.1%. Duration of nebulization was shortest with the Circulaire† and longest with the ***AeroEclipse**** ***BAN**** Nebulizer ($p < 0.05$ via 1-way analysis of variance). **Conclusions:** The nebulizers we tested differ significantly in overall drug disposition. The dosimetric ***AeroEclipse**** ***BAN**** Nebulizer provided the largest inhaled drug mass and the lowest loss to ambient air, with the test conditions we used.

COMPARISON OF BREATH-ACTUATED JET NEBULIZER IN 'CONTINUOUS DELIVERY' MODE WITH OTHER CONTINUOUS DELIVERY NEBULIZERS. JP Mitchell, KJ Wiersema, CC Doyle, MW Nagel. Respiratory Care 2003;48(11):1077.

The ***AeroEclipse**** ***BAN**** Nebulizer (Monaghan Medical Corporation, Plattsburgh, NY) has been equipped with an optional blue cap whose purpose is to retain the actuator piston in the position it would occupy during inhalation in breath actuated mode, so that the nebulizer operates continuously. The present study compared the delivery of a bronchodilator from diluted albuterol sulfate respirator solutions (3 mL of 0.83 and 1 mL of 2.5 mg/mL albuterol in physiologically normal saline (0.9% w/v NaCl)), via this nebulizer, the MICRO MIST† (Hudson RCI, Temecula, CA), Misty-Neb† (Allegiance Healthcare Corp., McGaw Park, IL) and the LC† D (PARI Respiratory Equipment, Monterey, CA). Each nebulizer was tested using a breathing simulator set to the following parameters representative of adult use: tidal volume = 600 mL, rate = 10 breaths/minute, inspiratory/expiratory ratio 1:2. The total mass of albuterol (TM) delivered to the first sputter was determined by filter collection at the mouthpiece of the nebulizer operated with compressed air supplied at 50 psig at 8 L/min ($n = 5$ devices/group, 3 replicates/device). The fraction of the aerosol contained in droplets finer than 4.8 µm aerodynamic diameter (FPF) was determined by laser diffractometry in a parallel study, so that the fine droplet mass (FM) could be calculated as the product of TM and FPF. Values of FM (mean ± SD) and time to deliver medication (T_{med}) were as follows:

Solution	***AeroEclipse**** ***BAN**** **Nebulizer**		**LC† D**		**MICRO MIST†**		**Misty-Neb†**	
(mg/mL)	0.83	2.50	0.83	2.50	0.83	2.50	0.83	2.50
FM (µg)	360 ± 22	263 ± 26	149 ± 16	108 ± 4	209 ± 12	15.4 ± 5.9	82 ± 9	31 ± 5
T_{med} (min)	3	< 1	2	< 1	7	< 1	4	< 1

The ***AeroEclipse**** ***BAN**** Nebulizer delivered significantly more FM in continuous delivery mode than the other nebulizers when operated in continuous mode with either solution strength (1-way repeated measures ANOVA, $p < 0.05$). T_{med} from the ***AeroEclipse**** ***BAN**** Nebulizer was comparable with the best performing continuous nebulizer (LC† D).

COMPARISON IN RATES OF BREAKTHROUGH TREATMENTS DURING A CONVERSION FROM RACEMIC ALBUTEROL TO LEVALBUTEROL. RS Pikarsky, RA Acevedo, C Roman. CHEST 2002;122(4):146S.

Purpose: In order to meet our patient care demands, Crouse Hospital approved an automatic conversion from racemic albuterol to levalbuterol. This study compares the breakthrough rates of racemic albuterol and levalbuterol, with and without ipratropium. **Methods:** Racemic albuterol (Alb) 2.5 mg Q4h was converted to either levalbuterol (Lev) 0.63 mg Q6h or levalbuterol 1.25 mg Q8h. If ordered, ipratropium (Ipra) 0.5 mg was administered at the same frequency as the levalbuterol. Patients with acute coronary syndromes, need for cardiac monitoring, or requiring more frequent aerosol administration received the lower levalbuterol dose Q6h. A majority of aerosol therapy was provided with the use of the ***AeroEclipse**** ***II BAN**** Nebulizer. All aerosol treatments, including breakthrough treatments, delivered between July 1, 2001 and February 28, 2002 were recorded. **Results:** Tx/Pt/day represents the number of treatments delivered per patient per day. Rate/100 Pt/days = (Breakthrough) / (Total Tx / Tx/Pt/day) x 100. Rate/100

Pt/days corrects for the differences in daily administration frequency, and may better reflect the daily impact of the breakthrough rate. The breakthrough rate of the combined albuterol group was significantly greater than both levalbuterol groups (5.29 vs. 2.29, 5.29 vs. 2.43, $p < 0.001$)*. The breakthrough rate with albuterol was significantly reduced with the addition of ipratropium ($p < 0.001$)**. Ipratropium did not significantly change the breakthrough rate when added to levalbuterol groups.

Medication	Total Tx	Breakthrough	Rate/1,000	Tx/Pt/day	Rate/100 Pt/day	
Alb Q4h	3,832	47	12.27	6	7.36**	5.29*
Alb/Ipra Q4h	3,767	20	5.31	6	3.19**	
Lev 0.63 mg Q6h	3,592	24	6.68	4	2.67	2.29*
Lev 0.63 mg/Ipra Q6h	1,821	7	3.84	4	1.54	
Lev 1.25 mg Q8h	1,791	17	9.49	3	2.85	2.43*
Lev 1.25 mg/Ipra Q8h	678	3	4.42	3	1.33	

Conclusions: The conversion from racemic albuterol to levalbuterol allowed for a decreased frequency of daily medication administrations and a significant decrease in breakthrough requirements. Ipratropium showed a significant benefit in breakthrough reduction for the racemic albuterol group. **Clinical Implications:** The efficiencies gained by decreasing the daily frequency of aerosol administration can have a significant impact on resource utilization. The conversion to levalbuterol allows for decreased respiratory therapy time or the reallocating of workforce needs while maintaining, or improving, quality of aerosol administration, as evidenced by the decrease in breakthrough requirements.

SAFETY AND EFFICACY OF FIVE MINUTE TIMED AEROSOL ADMINISTRATION WITH THE *AEROECLIPSE BREATH ACTUATED NEBULIZER: COMPARISON OF LEVALBUTEROL WITH RACEMIC ALBUTEROL.** RS Pikarsky, R Acevedo, C Roman, W Fascia, T Farrell. Respiratory Care 2002;47(9):1075.

Purpose: Beta-2 agonist racemic albuterol has been used extensively in the performance of pre and post bronchodilator studies in the pulmonary function laboratory. This study evaluated the safety and efficacy of timed nebulization of the two dosages of levalbuterol (Sepracor† Inc., Marlborough, MA) as compared to racemic albuterol (Dey, Napa, CA) with the use of the ***AeroEclipse*** **BAN**** Nebulizer (Monaghan Medical Corporation, Plattsburgh, NY). **Methods:** A consecutive, nonrandomized, mostly COPD population ($n = 93$) receiving pre and post bronchodilator testing in our pulmonary function lab were studied. Two different levalbuterol medication dosages were administered: 0.63 mg levalbuterol UD or 1.25 mg UD levalbuterol. The racemic albuterol dosage was 2.5 mg UD. All 5 minute timed aerosol treatments were administered using the ***BAN**** Nebulizer with an oxygen flow rate of 8 L/min. The Sensormedics Vmax 22 Pulmonary Function System was utilized to measure both FEV_1 and PEFR. A standardized subjective questionnaire to determine side effects was completed. **Results:** The table shows the levalbuterol and racemic albuterol dosages, mean % change of FEV_1 and PEFR from pre-treatment to 10 minute post treatment, administration time, tremulousness and increase in heart rate. There was no significant difference in % change in FEV_1 or PEFR. There was a significant increase in heart rate with the 1.25 mg levalbuterol UD group (7.2 vs. 3.4, $p < 0.05$*; 7.2 vs. 2.2, $p < 0.01$**). There was no difference in respiratory rate, tremulousness, or nausea.

Nebulizer (*n*)	Dose	% Change FEV_1	% Change PEFR	Time (min)	Trem.	HR (Inc.)
Levalbuterol (38)	0.63 mg UD	7.8	6.2	5	4	3.4*
Levalbuterol (29)	1.25 mg UD	7.7	16.6	5	2	7.2
Racemic Albuterol (26)	2.25 mg UD	12.2	10.5	5	0	2.2**

Conclusion: Five minute timed administration of levalbuterol and racemic albuterol using the ***BAN**** Nebulizer was equally efficacious and had similar safety profiles. The change in FEV_1 and PEFR are consistent with our mostly COPD population. The increase in heart rate was greatest with the levalbuterol 1.25 mg dosage. **Clinical Implications:** Five minute timed administration of levalbuterol and racemic albuterol using the ***BAN**** Nebulizer is a safe and efficient alternative to the use of small volume nebulizers. Additional caution should be taken when administering levalbuterol at the 1.25 mg dosage utilizing the ***BAN**** Nebulizer in cardiac patients. The efficiency of timed aerosol administration could have significant impact on resource utilization while maintaining the quality of aerosol delivery. This may be one of several strategies to address the problems of respiratory care staff shortages or high seasonal effect in the acute care facility.

BREATH ACTUATED NEBULIZER DELIVERS BRONCHODILATOR MORE EFFICIENTLY THAN CONVENTIONAL JET NEBULIZER IN A SIMULATION OF AN ADULT TIDAL BREATHING PATIENT. MW Nagel, JP Mitchell. American Journal of Respiratory and Critical Care Medicine 2002;165(8):A189.

Rationale: To compare delivery of albuterol sulfate inhalation solution (2.5 mg/3 mL vial equivalent to 0.083% w/v albuterol, Zenith Goldline Pharmaceuticals, Miami, FL) by conventional and breath actuated nebulizer simulating adult use. **Methods:** Each SVN ($n = 5$/group, 3 replicates/nebulizer) was operated with 8 L/min air at 50 psig and simulating breathing at tidal volume, I:E ratio and rate of 600 mL, 1:2 and 10/minute respectively. Total emitted dose (TED) was determined for 5 ***AeroEclipse*** **BAN**** Nebulizers (Monaghan Medical Corporation, Plattsburgh, NY, 1.5 mL solution) and 5 MICRO MIST† nebulizers (Hudson RCI, Temecula, CA, 3.0 mL solution) by filter collection, and droplet size distributions were measured in a parallel study by laser diffractometer. Fine particle dose (FPD) was calculated as the product of TED and the percentage by mass of droplets finer than 4.8 µm aerodynamic diameter. **Results:** After 3 minutes, the ***AeroEclipse*** **BAN**** Nebulizer delivered 282 ± 10 mg FPD (mean ± SD) and the MICRO MIST† delivered 209 ± 12 mg albuterol after 7 minutes. **Conclusion:** Dose delivery and patient compliance are assured by virtue of the breath actuation feature of the ***AeroEclipse*** **BAN**** Nebulizer and the reduced time to deliver a specific equivalent dose of medication compared with a conventional nebulizer will improve cost effectiveness of treatment.

AN *IN VITRO* INVESTIGATION OF COMMON NEBULIZER DOSING PROTOCOLS, COMPARING A BREATH-ACTUATED WITH CONVENTIONAL PNEUMATIC SMALL VOLUME NEBULIZER (SVN). MW Nagel, CC Doyle, SA Bates, JP Mitchell. Respiratory Drug Delivery 2002;2:627-629.

Introduction: Several protocols for the delivery of bronchodilator and/or anticholinergic therapy by nebulizer are in widespread use; making use of different combinations of formulation type for the bronchodilator (respirator solution or fixed concentration in ampoule) delivered alone, diluted with physiologically normal saline, or mixed with the anticholinergic component. The purpose of this investigation was to compare medication delivery as a function of elapsed time using these common protocols with a new breath actuated SVN (***AeroEclipse***** ***BAN****** Nebulizer, Monaghan Medical Corporation, Plattsburgh, NY, USA, and a conventional SVN (MICRO MIST†, Hudson RCI, Temecula, CA, USA) used as a benchmark device. **Materials and Methods:** Five SVNs of each type were tested using a piston driven breathing simulator (Kompass, PARI GmbH, Starnberg, Germany) set to the following conditions deemed representative of adult use: tidal volume = 600 mL, inspiratory/expiratory ratio 1:2, rate = 10 breaths/minute.

Table 1: Test Matrix for Nebulizer Dosing Protocol Evaluation

Dosing Protocol		**SVN**	
		AeroEclipse **BAN**** **Nebulizer**	**MICRO MIST†**
A	1 unit dose albuterol (ALB) ampoule (2.5 mg albuterol sulfate/3 mL)	5	5
B	0.5 unit dose albuterol (ALB) ampoule (2.5 mg albuterol sulfate/3 mL)	5	not tested
C	0.5 mL of albuterol sulfate (ALB) respirator solution (5 mg/mL) and 0.5 mL of normal saline (0.9% NaCl solution)	5	not tested
D	0.5 mL of albuterol sulfate (ALB) respirator solution (5mg/mL) and 1 unit dose ipratropium bromide (IPR (0.5 mg/2.5 mL)) ampoule	5	5
E	0.5 mL of albuterol sulfate (ALB) respirator solution (5 mg/mL) and 0.5 unit dose ipratropium bromide (IPR (0.5 mg/2.5 mL)) ampoule	5	not tested

A bacterial/viral filter (model 303 RespirGard II†, Marquest Medical, Englewood, CO, USA) was located to cover the mouthpiece of each SVN to collect the emitted aerosol stream. The mouthpiece was, in turn, coupled directly to the breathing simulator. The measurements with each dosing protocol (Table 1) were made with the SVN operated with 8.0 ± 0.2 L/min compressed air, delivered at 50.0 ± 0.5 psig. Each SVN (n = 5 nebulizers, 3 replicates/device) was allowed to operate until first sputter (defined to be the point at which nebulization changed audibly or visibly). The aerosol collection filter was replaced at 1 minute intervals. Following completion of each test, a constant volume (20 mL) of methanol (100% v/v) was added to the filter in its holder, and an aliquot of the resulting solution was assayed by HPLC-UV spectrophotometry to permit the cumulative mass of albuterol (ALB) and/or ipratropium bromide (IPR) to be determined as a function of the elapsed time since start of nebulization. Measurements were made with ALB in ampoule form (2.5 mg albuterol sulfate/3 mL, Zenith Goldline Pharmaceuticals (ZGP)), Miami, FL, USA), ALB supplied as respirator solution (5 mg/mL albuterol sulfate, Warrick Pharmaceuticals, Reno, NV, USA) alone or mixed with IPR from an ampoule (0.5 mg/2.5 mL, ZGP). In a parallel study, representative droplet size distributions in the range from 0.5 to 180 µm diameter of the aerosol emitted by each SVN (n = 5 nebulizers, 3 replicates/device) were measured by laser diffractometer (Mastersizer-X, Malvern Instruments Ltd., UK). These measurements were made between 15 seconds and 2 minutes after onset of nebulization, as pilot studies had not shown significant changes in size distribution with either nebulizer during the period of operation until sputtering occurred. **Results and Discussion:** The mass of drug delivered as fine particles was calculated at each time interval as the product of the total mass delivery (breathing simulator) and the average value of the volume (mass) fraction < 4.8 µm diameter (Mastersizer measurements). Fine particle mass delivered increased with time in a linear manner for both nebulizers for pure ALB and the mixtures of ALB/IPR (Figures 1, 2a, and 2b), as might be expected for solution based formulations. The ***AeroEclipse***** ***BAN****** Nebulizer delivered an equivalent mass of ALB or IPR in a significantly shorter time period than the MICRO MIST† nebulizer (unpaired t-test at each time interval, $p < 0.001$), probably due to the air entrainment capability of the former device. The use of a 0.5 unit dose (treatment A) rather than full unit dose ALB ampoule (treatment B) with the ***AeroEclipse***** ***BAN****** Nebulizer resulted in a similar outcome in terms of delivery rate, although nebulization ceased after 3 minutes with the smaller volume of solution. The higher ALB concentration in the diluted respirator solution (2.5 mg/mL) compared with that in the ampoules (0.83 mg/mL) resulted in more rapid delivery of medication (compare treatments B and C). Halving the volume of the IPR component in the ALB/IPR mixtures used with the ***AeroEclipse***** ***BAN****** Nebulizer had negligible impact on the delivery of this component (compare treatments D and E (Figure 2b)), but doubled the delivery rate for the ALB component (Figure 2a), associated with an effective ALB concentration increase from 0.83 mg/mL to 1.43 mg/mL.

Figure 1: Fine Particle Delivery with ALB Based Formulations

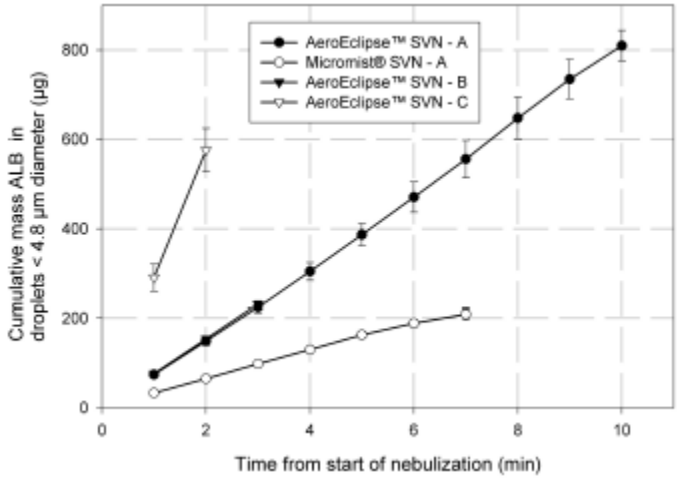


Figure 2a: Fine Particle Delivery with ALB/IPR Mixtures: ALB Component

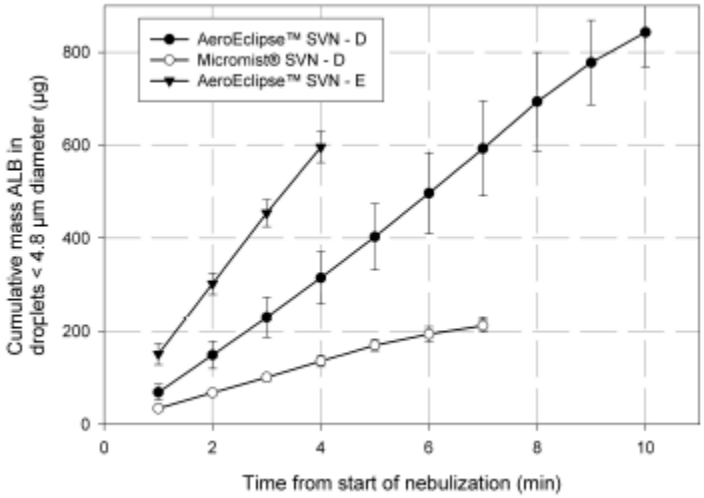
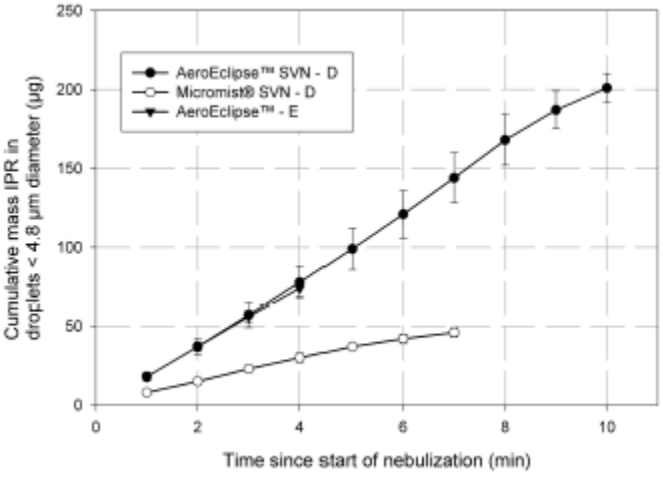


Figure 2b: Fine Particle Delivery with ALB/IPR Mixtures: IPR Component



Conclusions: The caregiver can alter either the drug concentration or volume placed in the reservoir of the ***AeroEclipse**** ***BAN**** Nebulizer to achieve a desired dosing regimen. This nebulizer delivered a comparable mass of albuterol in a significantly shorter time than with the benchmark non breath actuated SVN following protocols A and D.

THE DELIVERY TIME, EFFICACY, AND SAFETY OF β-AGONIST BRONCHODILATOR ADMINISTRATION WITH THE *AEROECLIPSE BREATH-ACTUATED NEBULIZER.** RS Pikarsky, T Farrell, R Acevedo, W Fascia, C Roman. CHEST 2001;120(4):218S.

Purpose: Aerosol delivery consumes the highest level of respiratory care resources. This study evaluated the delivery time, efficacy, and safety of rapidly nebulized albuterol with the use of the ***AeroEclipse** *BAN**** Nebulizer as compared to both an MDI with ***AeroChamber**** VHC (both from Monaghan Medical Corporation, Plattsburgh, NY) and the AirLife† Misty-Neb† Nebulizer (SVN) (Allegiance Healthcare Corporation). **Methods:** A consecutive, nonrandomized, mostly COPD population receiving pre and post bronchodilator testing in our pulmonary function lab were studied. Three different albuterol medication dosages were administered with the ***BAN**** Nebulizer: 0.5 mL albuterol (2.5 mg) with 0.5 mL normal saline, 1.0 mL (5 mg) of undiluted albuterol, and 0.75 mL albuterol (3.75 mg) using an oxygen flow rate of 8 L/min. Two puffs of albuterol were administered by MDI with ***AeroChamber**** VHC. Treatments with the SVN consisted of nebulizing 2.5 mg of albuterol diluted with 3 mL of normal saline unit dose (UD) using an oxygen flow rate of 8 L/min. The Sensormedics Vmax 22 Pulmonary Function System was utilized to measure FEV_1. A standardized subjective questionnaire to determine side effects was completed.

Nebulizer (*n*)	Dose	% Change FEV_1	Time (minutes)	Tremulousness
AeroEclipse** *BAN* Nebulizer (12)	0.5 mL + 0.5 mL NS	8.2%	2.67*	0
AeroEclipse** *BAN* Nebulizer (64)	1.0 mL undiluted	10.9%	3.29*	17
AeroEclipse** *BAN* Nebulizer (23)	0.75 mL undiluted	5.6%	1.30*	5
MDI (21)	2 puffs	8.5%	2.86**	1
Misty-Neb† (52)	2.5 mg UD	9.1%	8.33	2

Results: The table shows the albuterol dosages, mean % change of FEV_1 from pre-treatment and 10 minute post treatment, mean administration time and tremulousness. The mean treatment time with all ***BAN**** Nebulizer patients was 2.78 minutes as compared to 8.33 minutes with the SVN ($p < 0.001$)*. The mean treatment time with the MDI was 2.86 minutes as compared to 8.33 minutes with the SVN ($p < 0.001$)**. The changes in FEV_1 were not significant. There was no difference in heart rate, respiratory rate or nausea. Seventeen patients receiving the 1.0 mL undiluted albuterol indicated an increase in tremulousness. **Conclusion:** The rapid administration of albuterol in the 0.5 mL + 0.5 mL NS and 1.0 mL undiluted doses using the ***BAN**** Nebulizer was equally efficacious as the MDI with ***AeroChamber**** VHC and SVN UD. The 1.0 mL albuterol dosage has the highest incidence of tremulousness. The 0.75 mL albuterol dosage underperformed. Delivering 0.5 mL albuterol (2.5 mg) with 0.5 mL normal saline using the ***BAN**** Nebulizer offered the best delivery time, efficacy and safety profile of the nebulizer trials. The ***BAN**** Nebulizer performance was comparable to the MDI with ***AeroChamber**** VHC. **Clinical Implications:** In a health care facility that delivers large volumes of aerosol treatments, the decrease in delivery time could have a significant impact on resource utilization. The results supported changes in the respiratory care practice throughout Crouse Hospital. Further studies evaluating additional medication dosing regimens measuring safety, efficacy and resource utilization are needed.

THE CLINICAL EFFICACY OF USING THE *AEROECLIPSE BREATH ACTUATED NEBULIZER IN PULMONARY LAB TESTING AND IMPLICATIONS FOR GENERAL USE.** YM Christensen, CJ Flanigan, SA Ravenscraft. Respiratory Care 2001;46(10):1084.

Purpose: To compare the clinical efficacy and delivery time of nebulization of beta agonist bronchodilator with the use of the ***AeroEclipse** *BAN**** Nebulizer (Monaghan Medical Corporation) as compared to the AirLife† Misty-Neb† Nebulizer(SVN) (Allegiance Healthcare Corporation). **Methods:** Adult patients (n = 40) presenting with asthma (50%), COPD (10%) and other pulmonary disorders (40%); receiving pre and post bronchodilator spirometry testing in our pulmonary function lab were included in the study. Each patient received both nebulizers on two separate visits (less than 24 hours apart). Patient received a nebulizer treatment with the ***BAN**** Nebulizer (n = 40) 2.5 mg albuterol (0.5 mL) in 0.5 cc saline run to sputter, or the SVN (n = 40) 2.5 mg albuterol in 2.5 cc saline (3 mL unit dose) run to sputter. FVC, FEV_1, FEV_1% ratio and $FEF_{25-75\%}$ spirometry was conducted using the Medical Graphics 1085DX pre and 5 minutes post treatment with the ***BAN**** Nebulizer and 10 minutes post treatment with the SVN. **Results:** The results demonstrated that FVC, FEV_1 and $FEF_{25-75\%}$ for patients using the ***BAN**** Nebulizer were substantially higher while FEV_1% ratio favored the SVN (Table and Chart). Importantly, total nebulization time was reduced from 22 minutes (SVN) to 7 minutes (***BAN**** Nebulizer), and total test time was reduced from 30 minutes (SVN) to 15 minutes (***BAN**** Nebulizer).

Spirometry Results				
	Absolute % Change by Device		**% Difference *BAN** Nebulizer**	
	SVN	***BAN** Nebulizer**		***BAN** Nebulizer**
FVC	5.3	10.2	FVC	91.3
FEV_1	7.3	13.1	FEV_1	79.8
FEV_1%ratio	3.0	2.3	FEV_1%	-25.1
$FEF_{25-75\%}$	29.8	57.7	$FEF_{25-75\%}$	93.3

Conclusion: The administration of 2.5 mg of albuterol with the ***BAN**** Nebulizer produced improved results in FVC, FEV_1 and $FEF_{25-75\%}$. Substantially shorter test times delivered by the ***BAN**** Nebulizer would allow for more tests and associated revenue. These data support the thesis that the ***BAN**** Nebulizer can reduce costs of care by delivering clinically acceptable outcomes in significantly less time.

BREATH-ACTUATED VS RESERVOIR NEBULIZERS FOR UNDILUTED ALBUTEROL. D Geller, B Kesser. Journal of Aerosol Medicine 2001;14(3):395.

Aim: Some emergency departments use undiluted albuterol in nebulizers designed to conserve drug during exhalation. We compared the *in vitro* performance of 4 devices to estimate which would be most effective clinically: ***AeroEclipse** *BAN**** Nebulizer (AE); Circulaire† (C) and AeroTee† (AT) which use a 750 mL reservoir bag to conserve drug during exhalation; and Salter HDN† (S)

with a 50 mL tower reservoir. **Method:** We studied 4 units of each nebulizer type in duplicate, using a PARI PRONEB† TURBO compressor. Nebulizers were filled with undiluted 0.5% albuterol, 1 mL (5 mg) or 2 mL (10 mg). Particle size distributions were measured by laser diffraction (Malvern Spraytec). Drug output (1 minute after "sputter") was captured on a filter between the device mouthpiece and a PARI breath simulator, which used a recorded waveform from a 9 year old male. Albuterol was measured by spectrophotometry, and fine particle dose (FPD) (mg of drug < 5 mm in size) was calculated.

Results:

Neb	MMAD	FPD (1cc)	Minutes	FPD (2cc)	Minutes
AE	3.9	0.60	3.8	2.41	11.0
AT	4.8	0.03	2.0	0.62	3.2
C	2.5	0.09	2.0	0.65	3.7
S	8.5	0.08	2.0	0.57	3.7

Conclusions: The AE was superior to the reservoir type nebulizers in fine particle output for each fill volume. The AT and C had large dead volumes, and the S produced larger particles. These shortcomings were overcome with larger nominal doses. Each nebulizer produced 0.6 mg FPD of albuterol over 3½ minutes, but the AE required only half the starting dose. Albuterol 0.6 mg is a reasonable clinical respirable dose in a child with acute asthma. These findings must be taken into account when designing clinical treatment protocols for acute asthma.

THE DELIVERY TIME, EFFICACY, AND SAFETY OF BETA AGONIST BRONCHODILATOR ADMINISTRATION WITH THE *AEROECLIPSE BREATH ACTUATED NEBULIZER VERSUS A CONVENTIONAL T-TYPE SMALL VOLUME NEBULIZER.** RS Pikarsky, T Farrell, R Acevedo, W Fascia, C Roman. Respiratory Care 2001;46(10):1085.

Purpose: Aerosol delivery consumes the highest level of respiratory care resources. This study evaluated the delivery time, efficacy, and safety of rapidly nebulized albuterol with the use of a novel breath actuated nebulizer compared to a standard small volume nebulizer. **Methods:** A consecutive, nonrandomized, mostly COPD population receiving pre and post bronchodilator testing in our pulmonary function lab were studied. 0.5 mL albuterol (2.5 mg) with 0.5 mL normal saline (NS) was administered with the ***AeroEclipse** *BAN**** Nebulizer (Monaghan Medical Corporation, Plattsburgh, NY) using an oxygen flow rate of 8 L/min. Treatments with the AirLife† brand Misty-Neb† small volume nebulizer (SVN) (Allegiance Healthcare Corporation) consisted of nebulizing 2.5 mg of albuterol diluted with 3 mL of normal saline unit dose (UD) using an oxygen flow rate of 8 L/min. The Vmax 22 Pulmonary Function System was utilized to measure FEV_1. A standardized subjective questionnaire to determine side effects was completed. **Results:** The table shows the albuterol dosages, mean % change of FEV_1 from pre-treatment and 10 minute post treatment, mean administration time and tremulousness. The mean treatment time with all ***BAN**** Nebulizer patients was 2.67 minutes as compared to 8.33 minutes with the SVN ($p < 0.001$)*. The changes in FEV_1 were not significant. There was no difference in heart rate, respiratory rate or nausea. **Conclusion:** The rapid administration of albuterol in the 0.5 mL + 0.5 mL NS dose using the ***BAN**** Nebulizer was equally efficacious as the SVN UD. Delivering 0.5 mL albuterol (2.5 mg) with 0.5 mL normal saline using the ***BAN**** Nebulizer offered the best delivery time, efficacy and safety profile between the two devices. **Clinical Implications:** In a health care facility that delivers large volumes of aerosol treatments, the decrease in delivery time achieved with the ***BAN**** Nebulizer could have a significant impact on resource utilization. The results supported changes in the respiratory care practice throughout Crouse Hospital. Further studies evaluating additional medication dosing regimens measuring safety, efficacy and resource utilization are needed.

Nebulizer (*n*)	Dose	% Change FEV_1	Time (min)	Tremulousness
AeroEclipse** *BAN* Nebulizer (12)	2.5 mg (0.5 mL albuterol + 0.5 mL NS)	8.2%	2.67*	0
Misty-Neb† (52)	2.5 mg (3 mL unit dose)	9.1%	8.33	2

COMPARISON OF DRUG OUTPUT FROM 4 DIFFERENT RESERVOIR TYPE NEBULIZERS. DE Geller, B Kesser. American Journal of Respiratory and Critical Care Medicine 2001;163(5):A444.

Rationale: Many nebulizers currently being marketed utilize different techniques to conserve drug that would normally be lost during exhalation. The Circulaire† and AeroTee† nebulizers use a 750 cc reservoir bag to accumulate nebulized drug, while the Salter HDN† uses a 50 mL tower to serve as a reservoir. The ***AeroEclipse** *BAN**** Nebulizer uses breath actuated nebulization to deliver drug only during inspiration. We evaluated all 4 nebulizers using a recorded pediatric breathing pattern to measure total drug output. We additionally measured the particle size characteristics of each type with the laser diffraction technique. **Methods:** 4 nebulizers of each type were studied in duplicate for sizing and total output characteristics. Each nebulizer was charged with a unit dose of 2.5 mg albuterol sulfate in 3 cc's. Sizing studies were averaged values performed over 5 minute runs on each nebulizer with a Malvern Spraytec laser. Drug output was as calculated as the assayed amount of albuterol collected on a filter distal to the mouthpiece of the nebulizer. Simulated breathing was performed through the nebulizer by a PARI breath simulator from waveforms originally recorded from a healthy 9 year old male.

Results:

	Inspired dose	% > 1 & < 5 µ	Respirable Dose	Residual Dose
***AeroEclipse** *BAN** Nebulizer**	0.77 ± 0.07 mg	52.7 ± 2	0.41 ± 0.04 mg	1.53 ± 0.09
AeroTee†	0.37 ± 0.10 mg	41.2 ± 7	0.15 ± 0.04 mg	1.82 ± 0.11
Circulaire†	0.14 ± 0.03 mg	61.9 ± 1	0.09 ± 0.02 mg	2.07 ± 0.13
Salter HDN†	0.30 ± 0.06 mg	24.7 ± 5	0.08 ± 0.02 mg	1.91 ± 0.10

Conclusion: The breath actuated ***AeroEclipse**** ***BAN**** Nebulizer with PARI PRONEB† TURBO compressor is far more efficient than reservoir type nebulizers at producing a respirable aerosol of albuterol for children.

CLINICAL EVALUATION OF A BREATH ACTUATED SMALL VOLUME NEBULIZER (BA-SVN). S Klopf, N Schneiderman, H Payne, C Schramm, MW Nagel, JP Mitchell. Respiratory Care 2000;45(8):979.

Background: In prior *in vitro* studies using laser diffractometry, the aerosol produced by a novel breath actuated device, the ***AeroEclipse**** ***BAN**** Nebulizer (Monaghan Medical Corporation, Plattsburgh, NY) has been shown to contain a high proportion of droplets < 4.8 µm diameter (80.9% ± 2.4%). Such droplets are more likely to penetrate beyond the oropharyngeal region where bronchodilation is achieved. These *in vitro* results should therefore be predictive of improved *in vivo* delivery of nebulized medications to the respiratory tract. This study explored the clinical performance of the ***AeroEclipse**** ***BAN**** Nebulizer in the delivery of a beta-2 agonist (albuterol 2.5 mg/mL) accompanied by anticholinergic (ipratropium bromide 250 µg/mL) bronchodilator in some cases. **Methods:** Patients (*n* = 48) with a previous diagnosis for asthma presenting to the emergency department for acute exacerbation of asthma were included in this study. Upon presentation, an asthma care path, an assessment driven, algorithm based tool was used to place patients in one of three stages of severity as recommended by the NIH-NAEPP Guidelines for the Diagnosis of Asthma. Each patient was assigned to receive inhaled aerosol treatment using the ***AeroEclipse**** ***BAN**** Nebulizer. Stage 1 asthmatics were given 0.5 mL of albuterol with 0.5 mL normal saline delivered until sputter. Patients categorized in stage two and three were given 0.5 mL albuterol with the addition of 1.5 mL of ipratropium bromide unit dose. Treatments repeated every 20 minutes times three if necessary, by protocol.

Results:

Asthma Severity	Stage 1	Stage 2	Stage 3
Number	10	30	8
Treatments Given	2.4	2.03	2.25
Treatment Duration (minutes)	3.7	3.78	5
Increase in PEF (mean, range (%))	44 (0 - 120)	67.7 (-2.7 - 580)	120.7 (28 - 420)

Four patients had greater than 20% increase in heart rate, three patients noted tremor following treatment. Twenty-four patients had positive comments about the device focused on shorter treatment time and improved relief from dyspnea. Two imminent intubations were avoided with the use of the ***BAN**** Nebulizer. **Conclusions:** Use of the ***AeroEclipse**** ***BAN**** Nebulizer appears to result in good clinical outcomes. Minimum number of treatments, shorter treatment duration and minimal side effects were noticed with this device. Further outcome studies are needed to assess this impact on other groups of patients.

EVALUATION OF A NEW AIR ENTRAINMENT SMALL VOLUME NEBULIZER (AE-SVN) FOR THE DELIVERY OF ALBUTEROL SULFATE AND CROMOLYN SODIUM. JP Mitchell, MW Nagel, A Archer, DP Coppolo. American Journal of Respiratory and Critical Care Medicine 1999;159(3):A120.

Purpose: To evaluate the delivery of Ventolin† (0.2% v/v, albuterol sulfate, GlaxoSmithKline†, Canada) and Intal† (1.0% v/v cromolyn sodium, Fisons Pharmaceuticals Ltd., Canada) by a prototype AE-SVN (Trudell Medical International) using oxygen delivered at 50 psig at 8 L/min to simulate hospital use. **Methods:** 5 AE-SVNs were tested using an Andersen Mark II Cascade Impactor operated at 28.3 ± 0.5 L/min to determine the size distribution of droplets emitted at the mouthpiece during the first 10 seconds following nebulization. The mass of drug emitted was determined directly by HPLC-UV spectrophotometry. **Results:** Total (TM) and fine particle ((FPM), droplets finer than 4.7 µm diameter) mass output rates and droplet mass median diameter (MMD) were as follows:

Drug	TM (µg/s)	FPM (µg/s)	MMD (µm)
Ventolin†	32.4 ± 3.1	27.6 ± 1.3	3.0 ± 0.1
Intal†	138.6 ± 10.2	109.7 ± 8.3	3.2 ± 0.1

Conclusion: The fine MMD produced from the AE-SVN resulted in an improved FPM output rate, which is likely to produce increased lung deposition.

EFFECT OF NEBULIZER DESIGN ON FINE PARTICLE MASS. D Hess, JP Mitchell, D Coppolo, MW Nagel, AD Archer, R Blacker. Respiratory Care 1999;44(10):1289.

Background: Nebulizer design is known to affect performance. In this study, we compared fine particle mass from nebulizers of four designs. **Methods:** We tested traditional disposable nebulizers (Baxter Misty-Neb†, Hudson UP-DRAFT† II Neb-U-Mist†), breath enhanced nebulizers (PARI LC† D), nebulizers with collection bags (Westmed Circulaire†), and a Trudell ***AeroEclipse**** ***BAN**** Nebulizer (with breath actuation disabled). Five of each device with three replicates (*n* = 15) were tested using an *in vitro* model of spontaneous breathing. A rigid bar was placed between the two compartments of a test lung (Michigan Instruments TTL). The drive lung was attached to a ventilator (Infrasonics Infant Star†) to simulate spontaneous breathing (tidal volume 0.6 L, rate 10/minute, T_I 2 seconds). A bacterial/viral filter (Trudell MT3000) was placed between the nebulizer and slave lung. Flow was monitored between the test lung and filter (Novametrix VentCheck†). Albuterol solution (0.625 mg/mL) was placed into the nebulizers (4 mL), which were powered with air (8 L/min). Filters were replaced at one minute intervals (flow to the nebulizer was discontinued during filter replacement) until sputtering occurred. The filter was washed with methanol (20 mL) and albuterol concentration was measured with HPLC-UV spectrophotometry. Particle size was measured using a Malvern Mastersizer. Fine particle mass was calculated as the product of mass % < 4.7 µm and total nebulizer output. **Results:** Fine particle mass from the ***AeroEclipse**** ***BAN**** Nebulizer was greater than that from the other nebulizers ($p < 0.001$). **Conclusions:** Fine particle mass was affected by nebulizer design. The clinical relevance of this finding awaits further investigation. Further evaluation of the breath actuated feature of the ***AeroEclipse**** ***BAN**** Nebulizer is warranted.

PERFORMANCE OF A NEW AIR ENTRAINMENT SMALL VOLUME NEBULIZER (AE-SVN). A Archer, JP Mitchell, MW Nagel, AMW Verdun. European Respiratory Journal 1998;12(28):68s.

We report an *in vitro* investigation in which the performance of a new disposable AE-SVN (*n* = 3 devices) has been assessed with salbutamol sulphate (Ventolin†: 5 µg/2.5 mL, GlaxoSmithKline† Inc.), metaproterenol sulphate (Alupent†: 10 µg/2.5 mL, Boehringer Ingelheim† Pharmaceuticals Inc.) and cromolyn sodium (Intal†: 20 µg/2 mL, Fisons Pharmaceuticals) nebules. Each AE-SVN was filled with 2 nebules and operated continuously with oxygen supplied at 50 psig and 8 L/min. The AE-SVN was coupled directly to an Andersen cascade impactor, sampling at 28.3 L/min. Total and fine particle (< 4.7 µm aerodynamic diameter) delivery rates were 33.5 ± 1.8 µg/s and 27.6 ± 1.3 µg/s (Ventolin†); 54.2 ± 10.6 µg/s and 45.0 ± 7.8 µg/s (Alupent†); 138.6 ± 10.2 µg/s and 109.7 ± 8.3 µg/s (Intal†) over a 10 second period following the start of nebulization. The mass median aerodynamic diameter (MMAD) and mass % contained in fine droplets were 3.0 ± 0.1 µm and 82.4 ± 1.2% (Ventolin†); 2.9 ± 0.2 µm and 83.3 ± 2.6% (Alupent†); 3.1 ± 0.1 µm and 79.2 ± 1.9% (Intal†). This new nebulizer appears to perform well with all three formulations.

THE EFFECT OF SMALL VOLUME NEBULIZER (SVN) DESIGN ON FINE PARTICLE MASS DELIVERY OF A BRONCHODILATOR. R Blacker, RW Morton, JP Mitchell, MW Nagel, DR Hess. Journal of Aerosol Medicine 1998;13(1):65.

Fine particle mass delivery was compared from six different SVNs, including continuous unenhanced flow designs (Hudson UP-DRAFT† II Neb-U-Mist†), breath enhanced nebulizers (PARI LC† D, Medic-Aid Sidestream†), nebulizers with aerosol collection bag (Westmed Circulaire†), and an ***AeroEclipse*** **BAN**** Nebulizer with breath actuation disabled (Trudell Medical International). Five of each type of SVN were tested operating with air (8 L/min, 50 psig), using an *in vitro* model that simulated spontaneous breathing by an adult (tidal volume 0.6 L, rate 10/minute, T_I = 2 seconds). A bacterial/viral filter was placed between the nebulizer and breathing simulator. In each case, salbutamol sulphate (Ventolin†) respirator solution (0.625 mg/mL, 4 mL) was placed into the reservoir of the SVN. The filters were replaced at one minute intervals until sputtering occurred. The salbutamol collected on the filter was assayed by HPLC-UV spectrophotometry. Particle size was measured using a Malvern Mastersizer laser diffractometer. Fine particle mass delivery rates varied significantly from each of the SVNs from more than 110 µg/min (***AeroEclipse*** **BAN****** Nebulizer) to ca. 20 µg/min (Circulaire†).

PERFORMANCE OF A NEW BREATH-ACTUATED SMALL VOLUME NEBULIZER UNDER CONDITIONS THAT SIMULATE USE BY AN ADULT PATIENT. R Blacker, JP Mitchell, MW Nagel, AMW Verdun. European Respiratory Journal 1997;10(25):235s-236s.

The development of pneumatic small volume nebulizers (SVNs) in which atomization is enabled during the inhalation portion of a patient's breathing cycle has important ramifications in terms of the efficiency at which medication can be delivered. We report an investigation in which the effectiveness for the delivery of salbutamol (Ventolin† nebules: 5 mg/2.5 mL, GlaxoSmithKline†, Canada) via a prototype breath actuated SVN (Trudell Medical, Canada (TRU) was compared with that of a high performance closed system SVN (Ventstream†, Medic-Aid, Pagham, U.K. (VEN)). Each device was connected in turn to a ventilator test lung apparatus in such a way that aerosol delivered on inhalation (800 mL tidal volume, I:E of 1:1, 15 breaths/minute) was collected on a filter (Filtrete†, 3M Corp., St Paul, MN) located at the mouthpiece. Oxygen (440 kPa, 8 L/min) was supplied to operate each SVN, and the contents of a single nebule (2.5 mL) were added to the reservoir at the start of each test. Over a 5 minute period of use, the TRU SVN provided 1.74 ± 0.04 mg salbutamol to the filter (*n* = 5 replicates). In comparison, the VEN delivered 1.28 ± 0.01 mg in 3.5 minutes after which the device sputtered dry (*n* = 5 replicates). These data indicate that the new breath actuated device has important benefits in reducing wastage of medication by operating more efficiently, as well as an optimal impact on the environment.

A NOVEL BREATH-ACTUATED SMALL VOLUME NEBULIZER UNDER SIMULATED ADULT USE CONDITIONS. R Blacker, JP Mitchell, MW Nagel, AMW Verdun. Respiratory Care 1997;42(11):1091.

Pneumatic small volume nebulizers (SVNs) in which atomization only occurs during the inhalation phase of the breathing cycle have important ramifications in terms of the efficiency of medication delivery. We report an investigation in which the effectiveness for the delivery of salbutamol (Ventolin† nebules: 5 mg/2.5 mL, GlaxoSmithKline†, Canada) via a prototype breath actuated SVN (Trudell Medical, Canada (TRU) was compared with that of a high performance closed system SVN (Ventstream†, Medic-Aid, Pagham, U.K. (VEN)). Each nebulizer was connected in turn to a dual chambered test lung with one chamber driven by a ventilator and the other connected to the SVN mouthpiece. Aerosolized salbutamol delivered on inhalation (800 mL tidal volume, I:E of 1:1, 15 breaths/minute) was collected on a filter (Filtrete†, 3M Corp., St Paul, MN) located at the mouthpiece. Oxygen (440 kPa, 8 L/min) was used to operate each SVN, and the contents of a single nebule (2.5 mL) were added to the reservoir at the start of each test. Over a 5 minute period of use, the TRU SVN provided 1.74 ± 0.04 mg salbutamol to the filter (*n* = 5 replicates), significantly more than the VEN which delivered 1.28 ± 0.01 mg in 3.5 minutes (Mann Whitney Rank Sum Test, *p* = 0.008), after which the device sputtered dry (*n* = 5 replicates). These data indicate that the new breath actuated device may have important benefits in reducing wastage of medication by operating more efficiently, as well as reducing exposure to the caregiver.

Albuterol Sulfate/Salbutamol Sulfate (Ventolin†, GSK† Inc.) and Hypertonic Saline

NEW **BRONCHODILATOR RESPONSE TO ALBUTEROL NEBULIZED WITH HYPERTONIC SALINE IN ASTHMATIC CHILDREN.** A Teper, C Kofman, J Alchundia Moreira, T Köhler, F García Bournissen. Pediatric Pulmonology 2021;56(12):3714-3719.

Introduction: Asthma is distinguished by bronchial obstruction reversible by bronchodilators. The first-line treatment for asthmatic exacerbations is the use of inhaled beta agonists, by pressurized metered dose inhalers or nebulized with normal saline solution (NSS). There are no reports of nebulized beta agonists' efficacy in asthmatic children when administered with hypertonic saline solution (HSS). **Objective:** To evaluate bronchodilator responses (BDR) to albuterol nebulized with 3%-HSS in asthmatic children, compared to albuterol nebulized with NSS. **Population and Methods:** In a prospective, experimental, double-blind, randomized clinical study, children with a confirmed diagnosis of asthma with mild or moderate bronchial obstruction (FEV_1 40% - 79% of

predicted) were randomized to receive a nebulization with 2.5 mg of albuterol diluted in 3 cc of 3%-HSS or NSS (0.9%), by means of a jet nebulizer. After 30 minutes, the BDR was assessed. **Results:** Fifty patients (mean age 12.0 ± 3 years, 29 males) were enrolled; 25 were randomized to the 3%-HSS group (FEV_1 65.2% ± 10) and 25 to the NSS group (FEV_1 69.1% ± 7.1). The BDR of FEV_1 was 41.2% (SD: ± 20.1; 95% confidence interval [CI]: 35.1 - 50.4) and 17.3% (SD: ± 19.4; 95% CI: 9.7 - 24.9) ($p < 0.0001$) and of maximum mid-expiratory flow was 130% (SD: ± 90.8; 95% CI: 94.6 - 166) and 69.8% (SD: ± 72.5; 95% CI: 41.4 - 98.2) ($p < 0.01$), for the 3%-HSS and NSS groups, respectively. **Conclusion:** Albuterol produces a greater BDR when nebulized with 3%-HSS compared to NSS in asthmatic children with mild or moderate bronchial obstruction.

Amphotericin (Ablecet†, Enzon Pharmaceuticals)

NEW **PRECLINICAL STUDIES OF THE NEBULIZED DELIVERY OF LIPOSOMAL AMPHOTERICIN B.** S Kothari, SG Kefalos, ND Hages, TE Corcoran, S Husain. Journal of Aerosol Medicine and Pulmonary Drug Delivery 2022;35(6):307-312.

Background: Intravenous liposomal amphotericin B (L-AMB) has accompanying side effects that may be diminished when administering an inhaled form. Delivery systems for inhaled or aerosolized L-AMB vary, and there has not been a recent comparison of available systems to date. **Methods:** We compared three differently designed nebulizer delivery systems for the inhaled delivery of L-AMB to determine the best combination of efficient lung dosing and treatment time. Aerosol size was measured using a Malvern Mastersizer, and five separate nebulizers were tested. For drug output measurements, a Harvard Lung was used, and aerosol was collected using HEPA filters. **Results:** Overall aerosol size characteristics were similar for all devices with volume median diameters in the 4 - 5 µm range. The highest inhaled dose was delivered by the ***AeroEclipse*** **BAN**** Nebulizer. The Aerogen† Ultra and the ***AeroEclipse*** **BAN**** Nebulizer had similar predicted pulmonary doses, and the ***AeroEclipse*** **BAN**** Nebulizer had the highest pulmonary delivery rates. **Conclusion:** The ***AeroEclipse*** **BAN**** Nebulizer may provide more efficient delivery in a shorter amount of time; however, human studies are warranted to assess the safety, tolerability, and efficacy of inhaled delivery of L-AMB from this system.

NEBULISED AMPHOTERICIN B-POLYMETHACRYLIC ACID NANOPARTICLE PROPHYLAXIS PREVENTS INVASIVE ASPERGILLOSIS. K Shirkhani, I Teo, D Armstrong-James, S Shaunak. Nanomedicine: Nanotechnology, Biology, and Medicine 2015;11:1217-1226.

Aspergillus species are the major life threatening fungal pathogens in transplant patients. Germination of inhaled fungal spores initiates infection, causes severe pneumonia, and has a mortality of > 50%. This is leading to the consideration of preexposure prophylaxis to prevent infection. We made a very low molecular weight amphotericin B-polymethacrylic acid nanoparticle. It was not toxic to lung epithelial cells or monocyte derived macrophages *in vitro*, or in an *in vivo* transplant immunosuppression mouse model of life threatening invasive aspergillosis. Three days of nebuliser based prophylaxis delivered the nanoparticle effectively to lung and prevented both fungal growth and lung inflammation. Protection from disease was associated with > 99% killing of the aspergillus and a 90% reduction in lung TNF-α; the primary driver of tissue destructive immunopathology. This study provides *in vivo* proof of principle that very small and cost effective nanoparticles can be made simply, and delivered safely and effectively to lung by the aerosol route to prevent fungal infections.

AEROSOLIZED LIPOSOMAL AMPHOTERICIN B: A POTENTIAL PROPHYLAXIS OF INVASIVE PULMONARY ASPERGILLOSIS IN IMMUNOCOMPROMISED PATIENTS. H Kamalaporn, K Leung, M Nagel, S Kittanakom, B Calvieri, RA Reithmeier, AL Coates. Pediatric Pulmonology 2014;49(6):574-580.

Background: Aerosolized liposomal amphotericin B may reduce the incidence of invasive pulmonary Aspergillosis in adults with chemotherapy induced prolonged neutropenia with less nephrotoxicity. The breath actuated ***AeroEclipse*** **BAN**** Nebulizer is very efficient and minimizes environmental drug contamination since no aerosol is produced, unless the patient is inspiring through the device. Our aim is to develop an appropriate delivery system suitable for children that does not disrupt the liposomes due to the shear forces in nebulization. **Methods:** This is an *in vitro* experimental study *in vitro*. Six mL of 4 mg/mL liposomal amphotericin B solution (AmBisome†; Astellas† Pharma Inc., Markham, Ontario, CA) was nebulized with the breath actuated device (***AeroEclipse*** **BAN**** Nebulizer; Trudell Medical International, Canada) and captured by the glass liquid impinger. Sodium dodecyl sulfate was used as detergent to disrupt the liposomes in control samples. Gel filtration, electron microscopy, and high performance liquid chromatography (HPLC) were used to compare the size and shape of the liposomes, and amount of the drug before and after nebulization. The aerosol particle size was obtained by the laser diffraction. **Results:** After nebulization, 97.5% of amphotericin B was captured by the liquid impinger and detected by HPLC. Gel filtration and electron microscopy demonstrated that the drug remained in its liposomal configuration after nebulization. The mass median diameter (MMD) was 3.7 µm and 66% of aerosol particles were less than 5 µm in diameter. **Conclusions:** We demonstrated that liposomal amphotericin B can be nebulized successfully without disrupting the liposomes and minimize drug loss by using the breath actuated nebulizer.

IN VITRO **CHARACTERIZATION OF NEBULIZER DELIVERY OF LIPOSOMAL AMPHOTERICIN B AEROSOLS.** BD Alexander, TP Winkler, S Shi, ES Dodds Ashley, AJ Hickey. Pharmaceutical Development and Technology 2011;16(6):577-582.

Pharmaceutical aerosols have the potential to prevent pulmonary infectious diseases. Liposomal amphotericin B (LAMB, AmBisome†, Astellas† Pharma US, Deerfield, IL, USA) is approved as an intravenous infusion for empiric treatment of presumed fungal infections in neutropenic, febrile patients, as well as patients infected with aspergillus, cryptococcus, and other fungal pathogens. In this study, four different nebulizers were tested for their ability to deliver LAMB in aerodynamic droplet size ranges relevant to lung deposition by an inertial sampling technique. Mass median aerodynamic diameter (MMAD) and fine particle fraction percent < 3.3 µm (FPF(3.3)) and < 5.8 µm (FPF(5.8)) were determined by cascade impaction during a 2 minute sampling period for each of three trials of all nebulizers. The MMADs for all nebulizers ranged from 1.72 ± 0.11 µm to 2.89 ± 0.12 µm; FPF(3.3) and FPF(5.8) were approximately

80% and 90%, respectively. Although all nebulizers appear acceptable for delivery of LAMB, the PARI LC† Star and the ***AeroEclipse*** **II BAN**** Nebulizer were considered the best in terms of delivery of aerosol efficiently and the proportion suitable for lung deposition. Additional research on pulmonary delivery and clinical tolerability is warranted.

INTRAPULMONARY DISPOSITION OF AMPHOTERICIN B AFTER AEROSOLIZED DELIVERY OF AMPHOTERICIN B LIPID COMPLEX (ABELCET; ABLC) IN LUNG TRANSPLANT RECIPIENTS. S Husain, B Capitano, T Corcoran, SM Studer, M Crespo, B Johnson, JM Pilewski, K Shutt, DL Pakstis, S Zhang, ME Carey, DL Paterson, KR McCurry, R Venkataramanan. Transplantation 2010;90(11):1215-1219.

Background: Inhaled amphotericin preparations have been used for prophylaxis against invasive aspergillosis in lung transplant recipients. However, no published data exist regarding the pharmacokinetic profile of amphotericin B lipid complex in lung transplant recipients. **Methods:** We prospectively determined the concentrations of amphotericin B in the epithelial lining fluid (ELF) and plasma after aerosolized nebulization (***AeroEclipse*** **BAN**** Nebulizer), of amphotericin B lipid complex at 1 mg/kg every 24 hours for 4 days in 35 lung transplant recipients. One bronchoalveolar lavage sample and a simultaneous blood sample were collected at various time points after the fourth dose from each subject. High performance liquid chromatography and high performance liquid chromatography-MS-MS were used to measure amphotericin B. **Results:** Concentrations of amphotericin B in ELF (median, 25 - 75 IQR) were at 4 hours (*n* = 5) 7.20 µg/mL (1.3 - 17.6), 24 hours (*n* = 6) 8.26 µg/mL (3.9 - 82.7), 48 hours (*n* = 5) 2.15 µg/mL (1.4 - 5.5), 72 hours (*n* = 4) 1.25 µg/mL (0.75 - 5.5), 96 hours (*n* = 6) 0.86 µg/mL (0.55 - 1.4), 120 hours (*n* = 4) 1.04 µg/mL (0.44 - 1.6), 144 hours (*n* = 1), 4.25 µg/mL, 168 hours (*n* = 3) 1.14 µg/mL, and 192 hours (*n* = 1) 1 µg/mL. The plasma concentration of the drug remained below 0.08 µg/mL at all time points. During the study, the side effects noted included wheezing, coughing, and 12% decline in forced expiratory volume in 1 second. **Conclusions:** We conclude that administration through aerosolized nebulization of amphotericin B lipid complex every 24 hours for 4 days in lung transplant recipients achieved amphotericin B concentrations in ELF above minimum inhibitory concentration of the aspergillus nearly at 168 hours after the last inhaled dose and is well tolerated.

AEROSOLIZED AMPHOTERICIN B LIPID COMPLEX (AABLC) DISTRIBUTION IN LUNG TRANSPLANT RECIPIENTS: A COMPARISON OF CONTINUOUS VERSUS BREATH ACTUATED NEBULIZERS. ES Dodds, NA Petry, JD Davies, DW Zaas, SM Palmer, SW Shipes, RH Drew, BD Alexander, RE Coleman, JR Perfect. Respiratory Care 2007;52(11):1590.

Background: Aerosolized amphotericin B has become an attractive option for antifungal prophylaxis following solid organ and stem cell transplantation.[1,2] This therapeutic strategy facilitates localized delivery of antifungal agent, thereby minimizing toxicities and drug-drug interactions associated with currently available systemic antifungal agents. Determining drug delivery characteristics, including dose and nebulizer system, for aerosol drug administration is important to ensure optimal drug delivery. Newer, breath actuated nebulizers are available and, in theory, provide the ability to limit environmental exposure and also deliver a higher percentage of the prepared dose to the patient. **Objective:** To characterize the distribution of aerosolized ABLC immediately following nebulization in bilateral lung transplant recipients via 2 different nebulizer systems – continuous nebulizer (CN): UP-DRAFT†, Model 1724 (Hudson RCI, Temecula, CA) and breath actuated device: ***AeroEclipse*** **II BAN**** Nebulizer (Monaghan Medical Corporation, Plattsburgh, NY). ABLC 20 mg/4 mL was mixed with prepared 99mTc-ABLC (Ablecet†, Enzon Pharmaceuticals) prior to loading into the radioaerosol delivery system. **Methods:** Nebulizer assignment was performed sequentially with the first 5 subjects receiving treatment via the continuous flow nebulizer and the subsequent 5 subjects receiving study drug treatment via the ***BAN**** Nebulizer. Immediately following inhalation, drug product distribution images were obtained with patients in the supine position. Subjects were then placed on the table of a dual head gamma camera system (General Electric Healthcare, Milwaukee, WI). Total delivered dose (TDD) was calculated by determining the difference in the known starting counts for the medication vial and counts of the nebulizer apparatus, including filter, subject waste materials and empty medication vials, obtained after study medication administration. Gastric activity of 99mTc-ABLC was also measured. Drug exposure was reported as: TDD: total delivered dose; Drug delivery to each of the following lung regions was reported as a percentage of TDD: right lung (RL), left lung (LL) and GI tract; the two nebulizer groups were compared for differences in mean TDD and regional distribution using student's t-test. **Results:** Total drug delivery (as percent of prepared dose) was significantly higher for the ***BAN**** Nebulizer (20.7% versus 3.5%, *p* = 0.01). Mean regional distribution (as percent of total delivered dose) did not differ between the two nebulizer devices for the left lung, right lung, or GI tract.

Subject	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
	Continuous Nebulizer					**Breath Actuated Nebulizer**				
Drug Delivery‡	**% of total dose in vial**					**% of total dose in vial**				
RL	NR	1.6	1.2	0.4	1.2	7.4	9.6	5.2	5.8	11.3
LL	NR	1.4	0.9	0.3	0.7	6.4	5.5	5.4	6.0	8.9
GI	NR	3.6	1.3	0.6	0.5	5.1	5.1	7.2	11.2	3.5
Total Drug Delivery (TDD)	NR	6.6	3.4	1.3	2.4	18.9	20.2	17.8	23.0	23.7
Regional Delivery**										
Right	50	24	35	31	49	39	47	29	25	48
Left	17	21	27	23	29	34	27	30	26	37
Esophagus and Stomach	32	55	39	46	22	27	25	40	49	15

‡ As percent of prepared dose

** As a percentage of the total delivered dose

Conclusion: Use of the ***BAN**** Nebulizer resulted in a larger portion of the drug being deposited into the lungs. Since GI distribution was similar between the nebulizers, it appeared that more drug was vented to the surrounding atmosphere with the continuous system. **References:** [1] Variation In Antifungal Prophylaxis Strategies In Lung Transplantation. S Hussain, D Zaldonis, S Kusne, *et*

al. Transplant Infectious Disease 2006:213-218. [2] A Survey Of Anti-Fungal Management In Lung Transplantation. Drummer JS, *et al*. Journal of Heart and Lung Transplantation 2004;23:1376-1381.

SIMILAR DELIVERY OF AMPHOTERICIN LIPID COMPLEX IS POSSIBLE AT ONE-HALF DOSE VIA A BREATH-ACTUATED NEBULIZER COMPARED WITH A CONTINUOUSLY OPERATING NEBULIZER. NR MacIntyre, JP Mitchell, MW Nagel, DP Coppolo. American Thoracic Society International Congress, San Diego, CA, 2005.

Delivery of aerosolized antibiotics via continuous nebulizers wastes these expensive medications during patient exhalation. Breath actuated nebulizers can minimize waste with significant cost savings in medication, since they only operate when the patient inhales. Furthermore, medication is not emitted into the environment during exhalation. We describe a study in which dose delivery from a breath actuated device (***AeroEclipse*** ***BAN**** Nebulizer, Monaghan Medical Corporation, Plattsburgh, NY) was compared with that from a continuously operating nebulizer (VixOne†, Westmed Corp., Engelwood, CO (VIX)) (*n* = 3/group) for the delivery of amphotericin lipid complex ((AMP) Ablecet†, Enzon Pharmaceuticals, Piscatawny, NY, 5 mg/mL)). Each device was operated with air at 50 psig at 7 L/min (***BAN**** Nebulizer) or 8 L/min (VIX), with the mouthpiece connected to a breathing simulator (Compass, PARI, Germany) set to replicate adult use (500 mL tidal volume, 1:2 inspiratory/expiratory ratio, 20 breaths/minute). 5 mL AMP was placed in the ***BAN**** Nebulizer and 10 mL in the VIX (5 mL initially, followed by a further 5 mL after 4 minutes). Each nebulizer was operated for 1 minute past first sputter. The mass of AMP collected on a filter at the mouthpiece was determined by HPLC-UV spectrophotometry (3 replicates/nebulizer). Droplet size distributions were determined by laser diffractometer in a separate study. Total emitted mass from the ***BAN**** Nebulizer was 7274 ± 123 g, delivered in 10 minutes, of which 5892 ± 100 g was in fine droplets 4.8 m diameter. The VIX delivered a total mass of 5276 ± 557 g in 10 - 14 minutes, of which 4326 ± 457 g was contained in fine droplets. The ***BAN**** Nebulizer was therefore capable of delivering 36% more medication as fine droplets with only one half of the dose inserted in the reservoir.

A MECHANICALLY OPERATED BREATH-ACTUATED NEBULIZER ENABLES BOTH IMPROVED CONTROL OF DOSING AND DELIVERY EFFICIENCY. JP Mitchell, MW Nagel, NR MacIntyre. Drug Delivery to the Lungs-16 2005;1:181-184.

Summary: A mechanically operated, breath actuated nebulizer offers the clinician the prospect of being able to control the rate and duration of medication delivery dosimetrically, providing greater precision when titrating patients to establish an appropriate treatment regimen. We describe an *in vitro* study obtained with two formulations that are representative of formulations available for nebulization (amphotericin B and ipratropium bromide), in which a breath actuated device (***AeroEclipse*** ***BAN**** Nebulizer) delivered slightly more medication as fine droplets < 4.8 µm aerodynamic diameter with approximately one half of the dose in the reservoir compared with a continuously operating nebulizer (VixOne†). These measurements were made simulating use by an adult (500 mL tidal volume, inspiratory/expiratory ratio 1:2, 20 breaths/minute). Significant cost savings are therefore possible with the ***BAN**** Nebulizer with expensive medications, such as antibiotics, if less volume fill is required per treatment. **Introduction:** The delivery of medications in aerosol form from solution and suspension formulations by pneumatic (jet) nebulizer is widely practiced in the hospital setting[1], and in many instances alternative delivery devices, such as pressurized metered dose inhalers or dry powder inhalers are unavailable[2]. However, continuously operating devices continue to generate droplets of formulation when the patient exhales, resulting in both waste of medication and the possibility of exposure of health care providers to the treatment being offered[3], unless measures are taken to prevent escape of droplets, such as the use of an external exhalation filter. A mechanically operated, breath actuated device also offers the clinician the prospect of being able to control the rate and duration of medication delivery dosimetrically[4], providing greater precision when titrating patients to establish an appropriate treatment regimen. We report a laboratory study in which a breath actuated device (***AeroEclipse*** ***BAN**** Nebulizer, Trudell Medical International, London, ON, Canada) was compared with a continuously operating small volume nebulizer (VixOne†, Westmed Inc., Tucson, AZ, USA) for the delivery of two formulations that are representative of likely treatments in hospital. Ipratropium bromide is an anticholinergic widely prescribed for the treatment of chronic obstructive pulmonary disease[5], whereas, amphotericin B has been prescribed as an antifungal agent for respiratory tract infections since the 1950s[5]. **Materials and Methods:** Each nebulizer (*n* = 3 devices/group) was operated with compressed air supplied at 50 psig and operated at a flow rate of either 7.0 L/min (***AeroEclipse*** ***BAN**** Nebulizer) or 8.0 L/min (VixOne† continuous nebulizer). The mouthpiece of the device under evaluation was connected to a breathing simulator (Compass system, PARI, Starnberg, Germany) set to mimic adult use (500 mL tidal volume, 1:2 inspiratory/expiratory time ratio, 20 breaths/minute). Figure 1 is a schematic of the nebulizer breathing simulator arrangement. For the tests with the 0.02% w/v ipratropium bromide solution (Nephron Pharmaceuticals, Orlando, FL, USA), one 2.5 mL vial containing 500 µg ipratropium bromide was placed in the reservoir of the VixOne† nebulizer and one half a vial (250 µg ipratropium bromide) in the ***AeroEclipse*** ***BAN**** Nebulizer. In the corresponding investigation with the 0.5% w/v amphotericin B lipid complex suspension (Ablecet†, Enzon Pharmaceuticals, Piscatawny, NY, USA), 5 mL were withdrawn from a 20 mL vial after gentle shaking in accordance with manufacturer instructions to ensure thorough mixing of the contents, and placed in the reservoir of the VixOne† nebulizer and a further 5 mL added after 4 minutes of use to prevent overloading the reservoir. Only 5 mL of this formulation was inserted in the reservoir of the ***AeroEclipse*** ***BAN**** Nebulizer before the start of nebulization. The nebulizer on test (3 replicates/device) was allowed to operate for one minute past first sputter (defined to be the point at which nebulization changed (audibly or visibly) or became intermittent). At 1 minute intervals a bacterial/viral filter (MT3000, Trudell Medical Marketing Limited, London, ON, Canada) located to cover the mouthpiece of the nebulizer on test to collect the aerosol, was replaced with a fresh filter to prevent overloading. Subsequently, the mass of either ipratropium bromide or amphotericin B on each filter was determined by HPLC-UV spectrophotometry. The combined mass from all filters was calculated to determine the total mass delivered per nebulization 'treatment' (TEM). In a separate study, representative droplet size distribution data for each nebulizer were obtained by laser diffractometry (Mastersizer-X, Malvern Instruments Ltd., UK), so that the fine pp.181 - 184 droplet fraction < 4.8 µm diameter ($FDF_{<4.8\mu m}$), most likely to penetrate into the airways beyond the oropharynx, could be determined. **Results:** Mean values of $FDF_{<4.8\mu m}$ for the ***AeroEclipse*** ***BAN**** Nebulizer and VixOne† continuous nebulizer were comparable, at 81% and 82% respectively. Comparative values of TEM and fine droplet mass (FDM), calculated as the product of TEM and FDF (expressed as a fraction) are summarized in Tables 1 and 2 for ipratropium bromide and amphotericin B respectively.

Table 1: Delivery of Ipratropium Bromide by Continuous and Breath Actuated Nebulizers (*n* = 3 devices/group; 3 replicates/device: mean ± SD)

Nebulizer	Mass Ipratropium Bromide (µg)		Delivery Time (min)
	TEM	FDM	
***AeroEclipse** *BAN** Nebulizer (1.25 mL fill)**	61.7 ± 5.2	50.0 ± 4.2	2 - 3
VixOne† continuous (2.5 mL fill)	57.2 ± 5.5	46.9 ± 4.5	3 - 4

Table 2: Delivery of Amphotericin B by Continuous and Breath Actuated Nebulizers (*n* = 3 devices/group; 3 replicates/device: mean ± SD)

Nebulizer	Mass Amphotericin B (µg)		Delivery Time (min)
	TEM	FDM	
***AeroEclipse** *BAN** Nebulizer (5 mL fill)**	7274 ± 123	5892 ± 100	10
VixOne† continuous (2 x 5 mL fill)	5276 ± 557	4326 ± 457	10 - 14

Delivery times were significantly longer for the amphotericin B complex with both nebulizer types, reflecting the larger volumes of liquid that were nebulized with this formulation. In the case of the measurements with ipratropium bromide, the ***AeroEclipse** *BAN**** Nebulizer delivered a similar amount of medication as fine droplets in slightly less time as the VixOne† continuous nebulizer. However, only one half of the volume fill was required with the ***BAN**** Nebulizer. The ***BAN**** Nebulizer delivered 36% more amphotericin B as fine droplets in approximately equivalent time as the continuous nebulizer, again with only one half the volume fill of medication in the reservoir. **Conclusions:** This study has demonstrated that the breath actuated device is capable of delivering as much or slightly more mass of medication as fine droplets with one half the fill compared with a continuously operating nebulizer. Cost savings with more expensive medications, such as antibiotics, could therefore be significant. Previously published data[6] have confirmed that the delivery rate from the ***AeroEclipse** *BAN**** Nebulizer is constant during operation until sputtering occurs, and similar behaviour was observed in the present investigation (data not shown). This nebulizer is therefore a candidate device for the delivery of other medications, such as for pain control or vaccination by inhalation, where precise control of drug mass delivered is important.
References: [1] Consensus Statement: Aerosols And Delivery Devices. M Dolovich, NR MacIntyre, PJ Anderson, *et al*. Respiratory Care 2000;45(6):589-596. [2] Theory And Science Of Nebulizer Use. JH Dennis. In: Eds. J Boe, BR O'Driscoll, JH Dennis. Practical Handbook of Nebulizer Therapy. Martin Dunitz, London, UK, 2004:3-17. [3] Nebulizers: Principles And Performance. DR Hess. Respiratory Care 2000;45(6):609-622. [4] An *In Vitro* Study To Investigate The Use Of A Breath-Actuated, Small-Volume, Pneumatic Nebulizer For The Delivery Of Methacholine Chloride Bronchoprovocation Agent. JP Mitchell, MW Nagel, SL Bates, CC Doyle. Respiratory Care 2003;48(1):46-51. [5] Respiratory Care Pharmacology. JL Rau. 5th Edition, Mosby-Year Book Inc., St. Louis, MO, USA, 1998. [6] An *In Vitro* Investigation Of Common Nebulizer Dosing Protocols, Comparing A Breath-Actuated With A Conventional Pneumatic Small Volume Nebulizer (SVN). MW Nagel, CC Doyle, SL Bates, JP Mitchell. Respiratory Drug Delivery 2002;2:627-629.

Arformoterol (Brovana†, Sunovion† Pharmaceuticals)

CLINICAL AND ECONOMIC OUTCOMES WITH A CONVERSION TO ARFORMOTEROL ONCE OR TWICE DAILY FROM LEVALBUTEROL USING BREATH ACTUATED NEBULIZERS. RS Pikarsky, RA Acevedo, T Farrell, W Fascia, R Bear. Respiratory Care 2008;53(11):1545.

Background: For COPD patients using liquid nebulization, a long acting effect is achieved by using short acting bronchodilators on a scheduled basis. A large number of treatments for inpatient COPD patients are for maintenance bronchodilatation. This pilot protocol evaluated the conversion from levalbuterol (Lev) to Arformoterol (Arf) for maintenance. **Methods:** COPD inpatients assessed to be on maintenance bronchodilators were converted from Lev to Arf. All treatments (tx) were delivered using the Monaghan Medical Corporation ***AeroEclipse** *BAN**** Nebulizer. If the patient could use a mouthpiece device, they received Arf 15 mcg once daily. If a mask was used, they received Arf 15 mcg twice daily. Arf and Lev treatments delivered from 12/23/07 to 5/25/08 were recorded in a database as scheduled, prn breakthrough, or refused treatments. Prn rates are calculated in 100 patient days to correct for different treatment frequencies. Average tx per day includes scheduled and prn tx. Labor hours were obtained from the AARC Uniform Reporting Manual. RT salary and benefits averaged $31/hr. The device cost per tx was derived from the device cost divided by the change out interval and then divided by number of treatments per day. ***BAN**** Nebulizer cost = $4.88, Misty-Neb† = $0.36. In 2007 38,533 Lev treatments were delivered. We estimate that 60% of treatments can be converted to Arf. The Arf SVN column is for comparison only. **Results:** Clinical: Arf 15 mcg ***BAN**** Nebulizer Qday: 376 scheduled, 32 prn (8.5 per 100 patient days), and 8 refusals. 13 of the 32 prn treatments came from 3 patients. Arf 15 mcg mask BID: 185 scheduled, 4 prn (4.3 per 100 patient days), and 2 refusals. Lev (***BAN**** Nebulizer & mask) TID: 4,281 scheduled, 153 prn (10.7 per 100 patient days) and 254 refusals. Economic results: See table. **Conclusion:** Using Arformoterol Qday with ***BAN**** Nebulizer or BID with mask decreased the number of treatments delivered and total cost of delivery with prn treatments that compared favorably with Lev. Better patient selection may decrease the prn rate in the Qday group. The large number of refusals in the Lev group would suggest more patients could be converted to Arf. The ***BAN**** Nebulizer, by allowing Qday treatments, was extremely cost effective.

Economic Evaluation	Arformoterol Qday *BAN** Nebulizer	Arformoterol BID *BAN** Nebulizer	Levalbuterol TID *BAN** Nebulizer	Arformoterol BID SVN
Number tx	418	184	4,434	
Ave tx/day	1.08	2.04	3.11	2.04
Labor hrs/tx	0.133	0.133	0.133	0.155
Labor cost/tx	$4.13	$4.13	$4.13	$4.80
Device cost/tx	$1.08	$0.57	$0.39	$0.07
Drug cost/tx	$4.34	$4.34	$2.52	$4.34

Total tx cost	$9.55	$9.04	$7.04	$9.02
Daily tx cost	$10.34	$18.48	$21.86	$18.82
Assume 60% Arf conversion on 38,533 treatments				
tx%	68%	32%	100%	100%
# Arf tx	5,203	4,926		15,490
# Lev tx	15,413		38,533	15,413
Total # of tx	25,543		38,533	30,903
Arf cost	$94,198			$142,575
Lev cost	$38.841		$271,122	$38,841
Total cost	$133.039		$271,122	$181,416
Labor hours	3,400		5,129	4,781

Bacteriophage

BACTERIOPHAGE DELIVERY BY NEBULIZATION AND EFFICACY AGAINST PHENOTYPICALLY DIVERSE PSEUDOMONAS AERUGINOSA FROM CYSTIC FIBROSIS PATIENTS. JS Sahota, CM Smith, P Radhakrishnan, C Winstanley, M Goderdzishvili, N Chanishvili, A Kadioglu, C O'Callaghan, MR Clokie. Journal of Aerosol Medicine and Pulmonary Drug Delivery 2015;28(5):353-360.

Background: The rise in antibiotic resistant Pseudomonas aeruginosa and the considerable difficulty in eradicating it from patients has re-motivated the study of bacteriophages as a therapeutic option. For this to be effective, host range and viability following nebulization need to be assessed. Host range has not previously been assessed for the Liverpool Epidemic Strain (LES) isolates that are the most common cystic fibrosis related clone of P. aeruginosa in the UK. Nebulization studies have not previously been linked to clinically relevant phages. **Methods:** 84 phenotypically variable isolates of the LES were tested for susceptibility to seven bacteriophages known to have activity against P. aeruginosa. Five of the phages were from the Eliava Institute (IBMV) and 2 were isolated in this study. The viability of the two bacteriophages with the largest host ranges was characterized further to determine their ability to be nebulized and delivered to the lower airways. Phages were nebulized into a cascade impactor and the phage concentration was measured. **Results:** The bacteriophages tested killed between 66% - 98% of the 84 Liverpool Epidemic Strain isolates. Two isolates were multi phage resistant, but were sensitive to most first line anti-Pseudomonal antibiotics. The amount of viable bacteriophages contained in particles that are likely to reach the lower airways (< 4.7 µm) was 1% for the Omron† MicroAIR† U22 and 12% ***AeroEclipse**** ***BAN**** Nebulizer. **Conclusions:** Individual P. aeruginosa bacteriophages can lyse up to 98% of 84 phenotypically diverse LES strains. High titers of phages can be effectively nebulized.

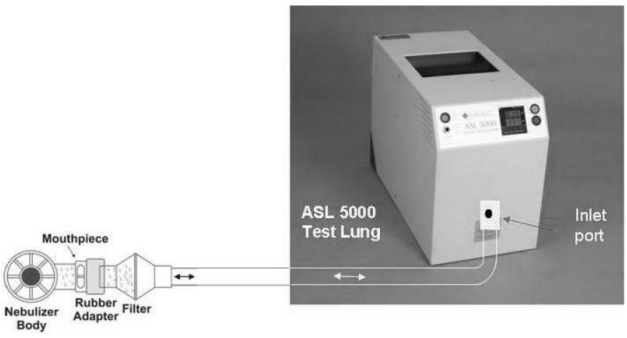
Budesonide (Pulmicort†, AstraZeneca†)

A MECHANICALLY OPERATED BREATH-ACTUATED JET NEBULIZER HAS DOSIMETRIC CAPABILITY BASED ON DIFFERING VOLUME FILL OF MEDICATION AS WELL AS RUN TIME. JP Mitchell, CC Doyle, V Avvakoumova. Drug Delivery to the Lungs-20 2009;2:1-4.

Summary: In an ideal clinical setting, it should be possible to specify a given mass of medication given by nebulizer to compare with an equivalent amount of the same drug product delivered by pressurized metered dose inhaler or dry powder inhaler. Under such circumstances, provided delivery of medication via the nebulizer only occurs during inhalation, and is dosimetric with respect to volume fill, it is a simple task to calculate from the label claim drug concentration the volume fill that will provide the required mass of drug, allowing the patient to breath tidally until the nebulizer sputters. We report a study in which the delivery of salbutamol sulphate and budesonide, representing solution and suspension formulations respectively was separately studied, simulating adult tidal breathing, as a function of volume fill with the ***AeroEclipse**** ***II BAN**** Nebulizer operated with compressed air (50 psig) from a wall outlet. The relationship between total inhaled mass and volume fill (1.0 - 3.0 mL salbutamol sulphate; 1.0 - 4.0 mL budesonide) throughout the stable nebulization period was linear, with the delivery rate dependent upon the mass concentration of active pharmaceutical ingredient in the formulation added to the reservoir. Interestingly, linearity was preserved with the suspension formulation, indicating that settling of the API in the reservoir was not occurring to a significant extent during the delivery process. This finding, taken with the fact that the delivery rate of either medication was constant as a function of delivery time, indicates that the ***BAN**** Nebulizer functions as a fully dosimetric device within the range of volume fills examined. **Introduction:** In an ideal clinical setting, it should be possible to specify a given mass of medication given by nebulizer to compare with an equivalent amount of the same drug product delivered either by pressurized metered dose inhaler or dry powder inhaler[1]. In practice, such comparisons are difficult because the amount of medication wasted during exhalation has a large and variable influence on the relationship between mass inserted in the reservoir at the start of treatment and the mass that is actually inhaled. However, provided delivery of medication via the nebulizer only takes place during inhalation and is dosimetric with respect to volume fill, it should be a simple task to calculate from the label claim drug concentration the volume fill that will provide the required mass of drug, assuming the patient is able to breath tidally from the nebulizer until the device sputters. The delivery rate from the ***BAN**** Nebulizer will depend upon the physical properties of the formulation (viscosity, surface tension, particle size distribution if a suspension), as well as the mass concentration of the active pharmaceutical ingredient. The original ***AeroEclipse**** ***BAN**** Nebulizer introduced a few years ago was the first mechanically operated breath actuated device that was shown, simulating adult tidal breathing, to provide a near constant delivery rate of medication between the onset of nebulization and first sputter from a variety of aqueous solution formulations used in current hospital practice[2]. A comprehensive study using a methacholine challenge agent also established its dosimetric capability with a fixed fill of a solution formulation (2.0 mL) as a function of mass concentration of API and delivery duration, when operated under similar conditions[3]. Since then, an improved version of the device (***AeroEclipse**** ***II BAN**** Nebulizer, Trudell Medical International,

London, ON, Canada) with equivalent *in vitro* performance[4-6] has become available. The present study investigated the delivery of commercially available solution and suspension preparations for nebulization, also simulating tidal breathing, as a function of volume fill with the ***AeroEclipse*** **II BAN**** Nebulizer operated with compressed air (50 psig) from a wall outlet as would be the case in a hospital setting. These preparations were used as model compounds to compare nebulizer performance at a benchmark condition where particle sedimentation in the preparation placed in the nebulizer reservoir was not possible (salbutamol sulphate) and where sedimentation might take place (budesonide). **Materials and Methods:** Three ***AeroEclipse*** **II BAN**** Nebulizers were evaluated, operating them with medical air at their maximum flow rate (7 - 8 L/min). The mouthpiece from the nebulizer on test was connected to a breathing simulator (ASL 5000, IngMar Medical Ltd., Pittsburgh, PA, USA) via an electret bacterial/viral filter (RespirGard II†, Vital Signs Inc., Totowa, NJ, USA) upon which the 'inhaled' aerosol deposited (Figure 1). An adult tidal breathing pattern was simulated for all measurements (tidal volume (Vt) = 600 mL, rate = 10 cycles/minute, duty cycle = 33% inhalation/ 67% exhalation). In the first part of the study, various volume fills of salbutamol sulphate solution (833 µg/mL salbutamol base equivalent) ranging from 1.0 to 3.0 mL in 0.5 mL increments were introduced into the reservoir of the nebulizer and the device operated on each occasion until first sputter, defining the point at which nonlinear delivery of medication would be expected. The maximum fill equates with the ampoule size for commercially available salbutamol solution in the US. The aerosol filters were replaced at 1 minute intervals to prevent overloading and to provide time dependent information. The mass of salbutamol collected on each filter was subsequently assayed by a validated HPLC-UV spectrophotometric technique. In the second part of the study, the same procedure was repeated with budesonide suspension (500 µg/mL), this time varying the volume fill from 1.0 to 4.0 mL in 1.0 mL increments. The commercially available ampoule size for this preparation is 2 mL, making the maximum fill equal to two complete ampoules. The mass of budesonide collected was also assayed by a validated HPLC-UV spectrophotometric technique.

Figure 1: Schematic of Nebulizer Test Set Up



Results: Medication delivery as a function of elapsed time and fill volume are presented in Tables 1 and 2 for the measurements made with salbutamol sulphate and budesonide respectively.

Table 1: Medication Delivery via ***AeroEclipse*** **II BAN**** Nebulizer - Salbutamol Sulphate

	3.0 mL Fill			**2.5 mL Fill**			**2.0 mL Fill**			**1.5 mL Fill**			**1.0 mL Fill**		
Device	16405	16406	16407	16405	16406	16407	16405	16406	16407	16405	16406	16407	16405	16406	16407
Filter 1	128.9	131.9	120.1	127.2	129.6	100.9	126.7	133.4	113.0	136.2	134.4	112.7	141.7	136.3	106.5
Filter 2	117.6	160.1	115.2	127.0	130.6	101.8	114.1	128.3	110.2	118.6	116.6	103.9	54.1	39.5	63.2
Filter 3	91.1	119.6	110.2	104.0	111.4	102.2	96.9	116.6	100.5	84.4	80.6	94.3	0.0	0.0	0.0
Filter 4	85.1	113.3	110.3	118.4	112.2	102.5	88.5	91.1	94.2	0.0	0.0	0.0	0.0	0.0	0.0
Filter 5	95.0	110.2	102.3	98.3	103.5	89.0	59.3	53.3	69.9	0.0	0.0	0.0	0.0	0.0	0.0
Filter 6	77.2	119.3	97.5	82.7	91.3	84.7	0.0	0.0	44.9	0.0	0.0	0.0	0.0	0.0	0.0
Filter 7	72.8	86.0	80.4	72.4	70.0	81.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Filter 8	92.7	32.4	78.1	0.0	0.0	70.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Filter 9	98.6	0.0	83.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Filter 10	0.0	0.0	3.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total (µg)	**859.0**	**873.0**	**901.7**	**730.1**	**748.5**	**733.0**	**485.5**	**522.6**	**532.7**	**339.2**	**331.6**	**310.9**	**195.8**	**175.8**	**169.8**
Mean	**877.9 (µg)**			**737.2 (µg)**			**513.6 (µg)**			**327.2 (µg)**			**180.5 (µg)**		
Standard Deviation	**21.8 (µg)**			**9.9 (µg)**			**24.9 (µg)**			**14.6 (µg)**			**13.6 (µg)**		

Note: Mean and standard deviation values represent performance during stable nebulisation (i.e. before first sputter).

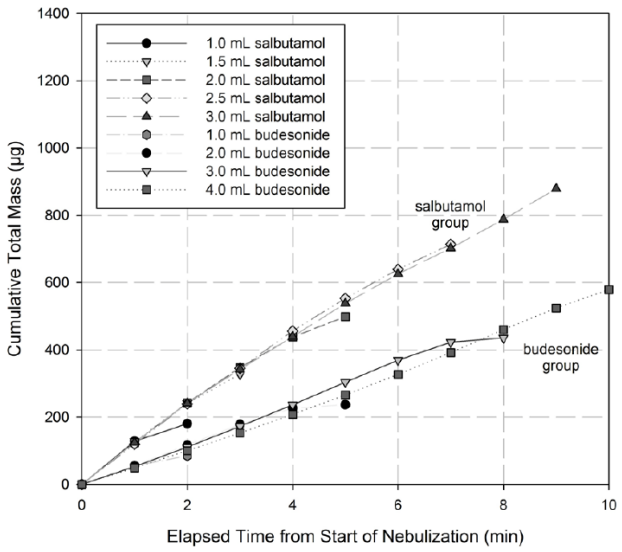
Table 2: Medication Delivery via ***AeroEclipse**** ***II BAN**** Nebulizer - Budesonide

	4.0 mL Fill			**3.0 mL Fill**			**2.0 mL Fill**			**1.0 mL Fill**		
Device	S 16405	S 16406	S 16407	S 16405	S 16406	S 16407	S 16405	S 16406	S 16407	S 16405	S 16406	S 16407
Filter 1	48.2	50.4	48.4	53.1	54.3	51.9	54.7	60.8	49.7	53.1	58.1	54.9
Filter 2	51.1	52.5	49.3	57.3	60.8	55.6	59.7	68.2	55.9	25.9	33.3	28.7
Filter 3	53.6	54.0	50.1	60.5	65.2	58.6	61.1	64.8	59.2	0.0	0.0	0.0
Filter 4	56.7	56.0	53.9	64.7	67.4	60.1	49.2	46.2	49.8	0.0	0.0	0.0
Filter 5	59.0	57.2	55.8	68.5	72.6	60.4	0.0	0.0	30.5	0.0	0.0	0.0
Filter 6	64.7	58.9	60.4	68.6	65.4	63.4	0.0	0.0	0.0	0.0	0.0	0.0
Filter 7	67.7	62.5	64.4	60.8	51.5	47.2	0.0	0.0	0.0	0.0	0.0	0.0
Filter 8	71.4	64.1	68.8	0.0	0.0	38.4	0.0	0.0	0.0	0.0	0.0	0.0
Filter 9	66.7	56.6	69.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Filter 10	66.0	44.2	54.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Filter 11	58.2	28.5	40.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total (µg)	**605.2**	**556.5**	**575.0**	**433.5**	**437.1**	**435.7**	**224.6**	**240.0**	**245.0**	**79.0**	**91.4**	**83.6**
Mean	**578.9 (µg)**			**435.4 (µg)**			**236.5 (µg)**			**84.7 (µg)**		
Standard Deviation	**24.6 (µg)**			**1.8 (µg)**			**10.7 (µg)**			**6.3 (µg)**		

Note: Mean and standard deviation values represent performance during stable nebulisation (i.e. before first sputter).

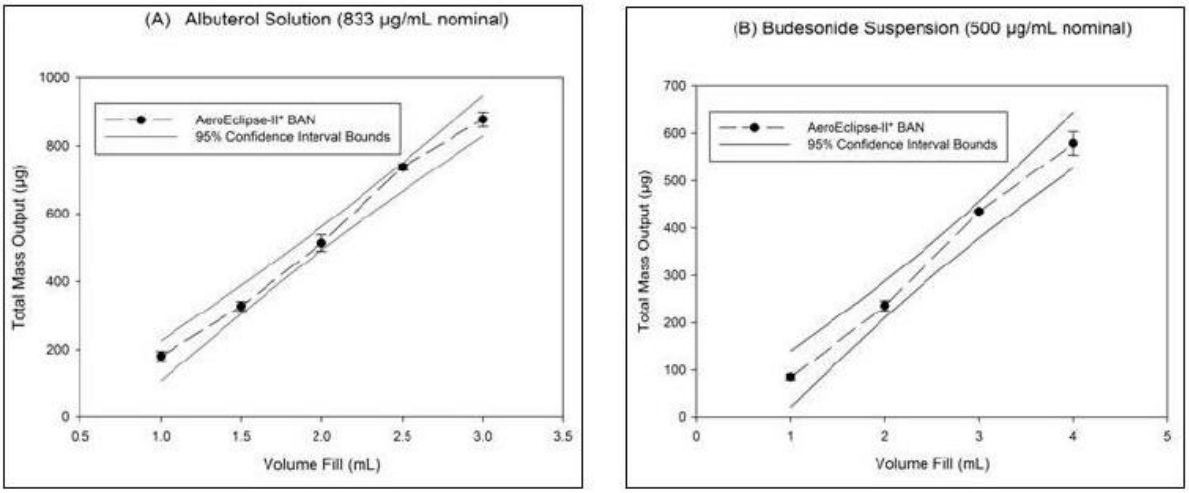
Discussion: The time based delivery of medication between onset of nebulization and first sputter was linear for both preparations (Figure 2), similar behaviour to that observed in previous studies[3,6].

Figure 2: Delivery of Medication from the ***AeroEclipse**** ***II BAN**** Nebulizer as a Function of Elapsed Time



Similarly, linear relationships between cumulative emitted mass (total mass output) and volume fill were observed for both solution and suspension formulations (Figures 3a and 3b).

Figure 3: Delivery of Medication from the ***AeroEclipse**** ***II BAN**** Nebulizer as a Function of Fill Volume



These data indicate that dosimetric delivery can be anticipated from the ***BAN**** Nebulizer whether the preparation being delivered is a solution or a suspension. Further work is needed to extend the knowledge base to include fill volumes up to 6 mL (the capacity of the reservoir) and to investigate how the nebulizer performs when simulating breathing patterns of other age groups who might be prescribed treatment using this device. **Conclusions:** These *in vitro* measurements simulating adult tidal breathing have demonstrated that the ***AeroEclipse**** ***II BAN**** Nebulizer has the capability to deliver medication to start of sputter in a predictable manner in terms of both elapsed time from start of treatment and fill volume of medication placed in the reservoir. Where equivalent drug products are available in multiple inhaler formats (pMDI, DPI, nebulizer), clinicians could convert patients currently on other inhalers who require nebulization by means of a lookup table that equates the mass of medication prescribed by the other inhaler to the fill volume and mass concentration of the preparation for nebulization. **References:** [1] Comparing Clinical Features Of The Nebulizer, Metered-Dose Inhaler, And Dry Powder Inhaler. DE Geller. Respiratory Care 2005;50(10):1313-1322. [2] An *In Vitro* Investigation Of Common Nebulizer Dosing Protocols, Comparing A Breath-Actuated With A Conventional Pneumatic Small Volume Nebulizer (SVN). MW Nagel, CC Doyle, SL Bates, JP Mitchell. Respiratory Drug Delivery 2002;2:627-629. [3] An *In Vitro* Study To Investigate The Use Of A Breath-Actuated, Small-Volume, Pneumatic Nebulizer For The Delivery Of Methacholine Chloride Bronchoprovocation Agent. JP Mitchell, MW Nagel, SL Bates, CC Doyle. Respiratory Care 2003;48(1):46-51. [4] Are First And Second Generation, Mechanically-Operated Breath-Actuated Nebulizers Comparable Based On *In Vitro* Performance**?** J Schmidt, J Pevler, C Doyle, K Wiersema, M Nagel, J Mitchell. Respiratory Drug Delivery 2006;3:817-819. [5] Transfer From The Malvern Mastersizer-X To Malvern Spraytec Laser Diffractometers: Experience With Two Breath-Actuated Nebulizers. JP Mitchell, KJ Wiersema, CC Doyle, MW Nagel, P Kippax, H Krarup. Respiratory Drug Delivery 2006;3:813-815. [6] Using Two Strengths Of Levalbuterol Solution And A Breath-Actuated Nebulizer To Modify Medication Delivery Profiles. MW Nagel, CC Doyle, VA Avvakoumova, JP Mitchell. Respiratory Drug Delivery 2008;3:789-792.

DELIVERY OF BUDESONIDE INHALATION SOLUTION (BIS) THROUGH AN INFANT UPPER AIRWAY MODEL. DE Geller, KC Kesser, HM Janssens, HAWM Tiddens. American Journal of Respiratory and Critical Care Medicine 2003;167(7):A508.

We investigated variables that may be important in the delivery of BIS to the lungs of infants, a challenging population for aerosol delivery. **Methods:** The Sophia Anatomical Infant Nose Throat (SAINT) airway model mounted on a breath simulator mimicked the breathing pattern of a 9 month old infant (RR = 30, V_t = 100 mL, I:E ratio = 1:1.3). Nebulizers were charged with BIS 0.25 mg and run continuously until dry. Drug captured on a filter distal to the SAINT model was the lung dose. Compressor: PARI PRONEB† TURBO. Nebulizer/mask systems studied: VixOne†/aerosol mask (AM), PediNeb† pacifier device (PN) or blowby (BB); ***AeroEclipse**** ***BAN**** Nebulizer and mask (AE); PARI LC PLUS† and PARI LC† Star/PARI Baby† mask (PB), Fish mask (FM), and AE masks. The AE neb/mask was also studied with an ill breathing pattern (RR = 50, V_t = 100, I:E = 1:2). **Results:** Lung dose ranged from 2.0 to 7.6% of the neb charge. Lung dose was AE (5.0%) > VixOne† (3.5%), PARI LC PLUS†/FM (3.2%), PARI LC† Star/PB (2.9%), and PARI LC PLUS†/PB (2.8%). Also, VixOne†/AM (3.5%) > VixOne†/PN (2.5%) > VixOne†/BB (2.0%). The lung dose of the PARI LC PLUS† and PARI LC† Star more than doubled (6.8 and 6.3%) when used with the AE mask. Lung dose increased with the ill breath pattern in proportion to increased minute ventilation (7.6%). **Conclusion:** 1) The AE system provided higher lung dose than other nebulizers with standard masks. 2) Mask design and fit can substantially impact nebulizer performance. 3) PN performed better than BB, but not as good as a mask. If crying decreases lung dose by 75%, we speculate that the PN and BB (non crying) may improve lung dose vs. mask with a crying infant. 4) An increase in lung dose may occur in ill infants if minute ventilation is elevated.

THE DELIVERY OF BUDESONIDE SUSPENSION VIA A BREATH-ACTUATED SMALL VOLUME NEBULIZER (SVN): A COMPARATIVE *IN VITRO* ASSESSMENT. MW Nagel, KJ Wiersema, SL Bates, JP Mitchell. American Journal of Respiratory and Critical Care Medicine 2001;163(5):A442.

Rationale: To compare the delivery of budesonide suspension in terms of fine particle dose (< 4.7 µm aerodynamic diameter (FPD)) from a breath actuated (BA) SVN with that from a continuous flow air entrainment (AE) SVN. **Methods:** FPD values were determined for 5 ***AeroEclipse**** ***BAN**** Nebulizer BA SVNs (Monaghan Medical Corporation, Plattsburgh, NY) and 5 PARI LC† D AE SVNs (PARI Respiratory Equipment, Inc., Monterey, CA), nebulizing 4 mL of a suspension formulation (0.25 mg/mL budesonide (Astra Pharma Inc.)). Each SVN was operated with air at 50 psig, 8 L/min until sputtering occurred. Breathing parameters were: tidal volume = 600 mL, I:E = 1:2 rate = 10/minute. FPD was determined by cascade impactor at 28.3 ± 0.5 L/min. **Results:** From the beginning of

nebulization until sputtering, the ***AeroEclipse*** **BAN**** Nebulizer and the PARI LC† D SVNs produced 164 ± 3 and 71 ± 4 µg FPD of budesonide respectively. During the first 5 minutes (after which time the PARI LC† Ds sputtered), values of FPD for the ***AeroEclipse*** **BAN**** Nebulizer and the PARI LC† D SVNs were 76 ± 4 and 71 ± 4 µg budesonide respectively. **Conclusion:** The ***AeroEclipse*** **BAN**** Nebulizer was more efficient than the PARI LC† D SVN for this suspension formulation [Mann-Whitney rank sum test, $p < 0.001$]. Almost no medication delivery took place from the ***AeroEclipse*** **BAN**** Nebulizer SVN during the exhalation portion of the breathing cycle, thereby providing important benefits to both patient and care giver.

Results:

Nebulizer	FILT (µg)	ENV (µg)
AeroEclipse **BAN**** Nebulizer	283 ± 33	80 ± 11
PARI LC† D	97 ± 7	305 ± 2

DELIVERY OF A SUSPENSION CORTICOSTEROID FORMULATION BY SMALL VOLUME NEBULIZERS: A COMPARATIVE BENCH STUDY. JP Mitchell, MW Nagel, KJ Wiersema, SL Bates. European Respiratory Journal 2001;16(31):903.

We report a study of the delivery of 0.25% mg/mL budesonide suspension (Pulmicort†, Nebuamp† (2 x 2 mL), AstraZeneca†, (Canada) Inc.) by two types of small volume nebulizer (SVN), simulating adult breathing conditions ((tidal volume = 600 mL, duty cycle = 1:2 (2 second inspiration), PIFR = 31 L/min). Each SVN was operated by compressed air (8 L/min at 50 psig). Budesonide delivery was determined by filter collection (n = 5 SVNs/group, 3 replicates/device). The breath actuated ***AeroEclipse*** **BAN**** Nebulizer SVNs (Trudell Medical International, London, ON, Canada) delivered 283 ± 32 µg prior to sputtering, and 80 ± 11 µg were lost to the environment. Corresponding data for the PARI LC† D SVNs (PARI Respiratory Equipment Inc., Richmond, VA, USA) were 97 ± 7 µg and 305 ± 2 µg respectively. The breath actuation feature of the ***AeroEclipse*** **BAN**** Nebulizer SVN minimizes aerosol release to the environment during exhalation, which may cause adverse effects to both patient and health care provider.

ENHANCED *IN VITRO* DELIVERY OF BUDESONIDE VIA CONTINUOUS AND BREATH-ACTIVATED NEBULIZATION. Smaldone GC. European Respiratory Journal 2000;16(31):540s.

In vitro bench testing designed to mimic clinical aerosol delivery is predictive of *in vivo* delivery of nebulized medications to the respiratory tract. This study tested a new nebulizer designed for either continuous or breath actuated use (***AeroEclipse*** **BAN**** Nebulizer, Monaghan Medical Corporation/Trudell Medical International). Using a piston pump and PARI Master compressor, a range of breathing patterns were utilized to estimate drug delivery [Inhaled mass (IM)] to pediatric patients over a wide range of breathing patterns. 500mg of budesonide comprised the nebulizer charge (0.25 mg/mL in 2mL) delivered via three patterns of breathing (V_t, f: 50 mL, 40; 200 mL, 25; 440 mL, 19; duty cycle 0.50). The 50 and 200 mL V_t patterns were delivered using continuous nebulization, while 440 was breath actuated. IM was measured at 1 minute intervals using a low dead space filter with drug activity analyzed by HPLC. Low flow cascade impaction measured aerodynamic diameters (MMAD) and fine particle fraction (FPF, cut point 6.0µm). For the three breathing patterns IM averaged (mean ± SD), 11.1 ± 0.74%, 22.9 ± 2.74%, and 36.3 ± 1.22% respectively. These values exceed by 35% those previously reported for the most efficient devices (Journal of Aerosol Medicine 1998;11:113-125). MMAD averaged 3.55 ± 0.07µm, GSD 2.55 FPF 0.72. When corrected for FPF, pulmonary delivery is estimated to be 60% higher than that reported for conventional and air entrained nebulization.

THE DELIVERY OF BUDESONIDE SUSPENSION VIA SMALL VOLUME NEBULIZERS: A COMPARATIVE *IN VITRO* ASSESSMENT. JP Mitchell, MW Nagel, AD Archer. European Respiratory Journal 1998;12(S29):7s.

We report an investigation in which a new air entrainment small volume nebulizer (AE-SVN) (Trudell Medical International, Canada) was compared with the PARI LC† Star (PARI Respiratory Equipment Inc., Canada), UP-DRAFT† Neb-U-Mist† (Hudson Oxygen Therapy Sales Co., USA), Circulaire† (Westmed, USA), Sidestream† (Medic-Aid, UK), AirLife† Misty-Neb† (Baxter Healthcare Corp., USA) n = 5 devices for each group, 3 replicates per device) for the delivery of Pulmicort† (0.25 mg/mL budesonide suspension (Astra Pharma Inc. Canada). Each nebulizer was filled 2 x 2 mL nebules and operated with compressed air (50 psig) at a flow rate of 8.0 ± 0.1 L/min. Air was drawn through the mouthpiece of the nebulizer at 28.3 L/min and the aerosol was collected by a filter located close to the mouthpiece. The nebulizer was operated until it spluttered, was then tapped gently to dislodge droplets back to the reservoir. Nebulization was deemed complete after a further 20 seconds. The mass of budesonide on the filter was determined by HPLC-UV spectrophotometry. The delivery rate ((mean ± 1 S.D) µg budesonide/minute) from the AE-SVN (102 ± 9) was significantly greater than with the other groups: (PARI LC† Star (91 ± 6), Misty-Neb† (49 ± 2), Sidestream† (46 ± 4), Circulaire† (26 ± 4) and Neb-U-Mist† (25 ± 6)), (1-way ANOVA, $p < 0.02$). Duration of nebulization was shortest with the AE-SVN (221 ± 14 seconds), compared with PARI LC† Star (229 ± 10 seconds), Sidestream† (365 ± 19 seconds), Circulaire† (420 ± 84 seconds), Misty-Neb† (477 ± 25 seconds) and Neb-U-Mist† (639 ± 15 seconds).

Cromolyn Sodium (Intal†, Fisons Pharmaceuticals)

EVALUATION OF A NEW AIR ENTRAINMENT SMALL VOLUME NEBULIZER (AE-SVN) FOR THE DELIVERY OF ALBUTEROL SULFATE AND CROMOLYN SODIUM. JP Mitchell, MW Nagel, A Archer, DP Coppolo. American Journal of Respiratory and Critical Care Medicine 1999;159(3):A120.

Purpose: To evaluate the delivery of Ventolin† (0.2% v/v, albuterol sulfate, GlaxoSmithKline†, Canada) and Intal† (1.0% v/v cromolyn sodium, Fisons Pharmaceuticals Ltd., Canada) by a prototype AE-SVN (Trudell Medical International) using oxygen delivered at 50 psig at 8 L/min to simulate hospital use. **Methods:** 5 AE-SVNs were tested using an Andersen Mark II Cascade Impactor operated at 28.3 ± 0.5 L/min to determine the size distribution of droplets emitted at the mouthpiece during the first 10 seconds following

nebulization. The mass of drug emitted was determined directly by HPLC-UV spectrophotometry. **Results:** Total (TM) and fine particle ((FPM), droplets finer than 4.7 µm diameter) mass output rates and droplet mass median diameter (MMD) were as follows:

Drug	TM (µg/s)	FPM (µg/s)	MMD (µm)
Ventolin†	32.4 ± 3.1	27.6 ± 1.3	3.0 ± 0.1
Intal†	138.6 ± 10.2	109.7 ± 8.3	3.2 ± 0.1

Conclusion: The fine MMD produced from the AE-SVN resulted in an improved FPM output rate, which is likely to produce increased lung deposition.

PERFORMANCE OF A NEW AIR ENTRAINMENT SMALL VOLUME NEBULIZER (AE-SVN). A Archer, JP Mitchell, MW Nagel, AMW Verdun. European Respiratory Journal 1998;12(28):68s.

We report an *in vitro* investigation in which the performance of a new disposable AE-SVN (*n* = 3 devices) has been assessed with salbutamol sulphate (Ventolin†: 5 µg/2.5 mL, GlaxoSmithKline† Inc.), metaproterenol sulphate (Alupent†: 10 µg/2.5 mL, Boehringer Ingelheim† Pharmaceuticals Inc.) and cromolyn sodium (Intal†: 20 µg/2 mL, Fisons Pharmaceuticals) nebules. Each AE-SVN was filled with 2 nebules and operated continuously with oxygen supplied at 50 psig and 8 L/min. The AE-SVN was coupled directly to an Andersen cascade impactor, sampling at 28.3 L /min. Total and fine particle (< 4.7 µm aerodynamic diameter) delivery rates were 33.5 ± 1.8 µg/s and 27.6 ± 1.3 µg/s (Ventolin†); 54.2 ± 10.6 µg/s and 45.0 ± 7.8 µg/s (Alupent†); 138.6 ± 10.2 µg/s and 109.7 ± 8.3 µg/s (Intal†) over a 10 second period following the start of nebulization. The mass median aerodynamic diameter (MMAD) and mass % contained in fine droplets were 3.0 ± 0.1 µm and 82.4 ± 1.2% (Ventolin†); 2.9 ± 0.2 µm and 83.3 ± 2.6% (Alupent†); 3.1 ± 0.1 µm and 79.2 ± 1.9% (Intal†). This new nebulizer appears to perform well with all three formulations.

Cysteamine Bitartrate (Cystagon†, Mylan† Pharmaceuticals Inc.)

AN OPEN-LABEL INVESTIGATION OF THE PHARMACOKINETICS AND TOLERABILITY OF ORAL CYSTEAMINE IN ADULTS WITH CYSTIC FIBROSIS. G Devereux, S Steele, K Griffiths, E Devlin, D Fraser-Pitt, S Cotton, J Norrie, H Chrystyn, D O'Neil. Clinical Drug Investigation 2016;36:605-612.

Background and Objective: Cysteamine is licensed for use in nephropathic cystinosis but preclinical data suggest a role in managing cystic fibrosis (CF). This study aimed to determine whether oral cysteamine is absorbed in adult CF patients and enters the bronchial secretions. Tolerability outcomes were also explored. **Methods:** Patients ≥ 18 years of age, weighing > 50 kg with stable CF lung disease were commenced on oral cysteamine bitartrate (Cystagon†) 450 mg once daily, increased weekly to 450 mg four times daily. Serial plasma cysteamine concentrations were measured for 24 hours after the first dose. Participants were reviewed every week for 6 weeks, except at 4 weeks. Plasma cysteamine concentrations were measured 8 hours after dosing when reviewed at 1, 2 and 3 weeks and 6 hours after dosing when reviewed at 5 weeks. Sputum cysteamine concentration was also quantified at the 5 week assessment. **Results:** Seven of the ten participants reported adverse reactions typical of cysteamine, two participants discontinued intervention. Following the first 450 mg dose, mean (SD) maximum concentration (C_{max}) was 2.86 (1.96) mg/l, the time corresponding to C_{max} (T_{max}) was 1.2 (0.7) hours, the half life ($t_{½}$) was 3.7 (1.7) hours, clearance (CL/F) 89.9 (30.5) L/hour and volume of distribution (V_d/F) 427 (129) L. Cysteamine appeared to accumulate in sputum with a median (interquartile range) sputum:plasma cysteamine concentration ratio of 4.2 (0.98 - 8.84). **Conclusion:** Oral cysteamine is absorbed and enters the bronchial secretions in patients with CF. Although adverse reactions were common, the majority of patients continued with cysteamine. Further trials are required to establish the risk benefit ratio of cysteamine therapy in CF.

Fentanyl

NEBULIZED FENTANYL FOR RELIEF OF ABDOMINAL PAIN. JM Bartfield, RD Flint, M McErlean, J Broderick. Academic Emergency Medicine 2003;10(3):215-218.

Objective: To compare the efficacies of nebulized vs. intravenous fentanyl for the relief of abdominal pain. **Methods:** This randomized, double blind, double placebo controlled study compared nebulized and intravenous fentanyl (1.5 mg/kg). Group I received intravenous fentanyl and nebulized saline. Group II received nebulized fentanyl and intravenous saline. Pain scores were measured at baseline and at 15 and 30 minutes after the study drug, using a 100 mm visual analog scale. Thirty minutes after the study drug, the subjects were offered rescue medication. The groups were compared for changes in pain scores at 30 minutes (primary outcome, t-test), changes in pain scores at 15 minutes (t-test), and need for rescue medication (Fisher's exact test). Significance was defined as $p < 0.05$. **Results:** Fifty subjects (24 group I, 26 group II) were enrolled. The groups were similar with respect to mean baseline pain (72 mm group I, 74 mm group II) and demographics. A statistically significant difference in changes in pain scores at 15 minutes favoring group I (25 mm vs. 10 mm, $p = 0.005$) was not evident by 30 minutes (25 mm vs. 16 mm, $p = 0.24$). The groups were not different with respect to need for rescue medication (50% in group I compared with 69% in group II, $p = 0.25$). **Conclusions:** Nebulized fentanyl provides comparable analgesia to that of intravenous fentanyl.

Fentanyl Citrate (Actiq†, Abbott† Laboratories)

RANDOMIZED CLINICAL TRIAL OF NEBULIZED FENTANYL CITRATE VERSUS IV FENTANYL CITRATE IN CHILDREN PRESENTING TO THE EMERGENCY DEPARTMENT WITH ACUTE PAIN. JR Miner, C Kletti, M Herold, D Hubbard, MH Biros. Academic Emergency Medicine 2007;14(10):895-898.

Objectives: To compare the pain relief achieved with nebulized fentanyl citrate with intravenous (IV) fentanyl citrate in children presenting to the emergency department (ED) with painful conditions to determine if nebulized fentanyl is a feasible alternative to IV fentanyl for the treatment of acute pain in children. **Methods:** This was a randomized controlled trial in an urban county medical center ED with an annual census of 99,000 visits. ED patients, aged 6 months to 17 years, presenting with acute pain who were going to be treated with IV pain medications, were eligible for enrollment. After the parents had provided informed consent, and children older than 6 years had provided assent, patients were randomized (1:2) to receive either fentanyl citrate IV (1.5 µg/kg) or fentanyl citrate by breath actuated nebulizer (3.0 µg/kg). Patients aged 6 years and older completed a 100 mm visual analog scale (VAS) describing their pain, and patients younger than 6 years had their pain assessed by the treating physician using the Children's Hospital of Eastern Ontario Pain Scale. Additionally, treating physicians used a 100 mm VAS to describe their perception of the patients' pain. These pain measurements were taken before treatment and every 10 minutes thereafter for 30 minutes. Baseline blood pressure, heart rate, and oxygen saturation were also measured before treatment and every 10 minutes for 30 minutes. After 30 minutes, physicians were asked whether or not they believed the medication provided adequate pain relief for the patient. Parents were asked to rate their satisfaction with the treatment using a five point scale. Patients who received additional pain medications by any method before the 30 minute measurement period was completed were considered treatment failures. Data were compared using descriptive statistics and 95% confidence intervals; the rates of adequate pain relief between the groups were compared using Fisher exact tests. **Results:** Forty-one patients were enrolled in the study; 14 were randomized to IV fentanyl (ten actually received it), and 27 patients were randomized to nebulized fentanyl (31 actually received it). In the four patients who were randomized to IV fentanyl but received nebulized fentanyl, the parents requested the nebulized medication after being told their child had been randomized to IV fentanyl. Baseline pain VAS scores were 82.8 mm (SD ± 14.3, 69 - 100) in the IV group and 76.2 mm (SD ± 20.5, 34 - 100) in the nebulized group. There were five treatment failures: one who received IV fentanyl and four who received nebulized fentanyl. The four patients who were considered treatment failures in the nebulized fentanyl group were all younger than 3 years and had difficulty triggering the breath actuated nebulizer. The mean decrease in pain for patients remaining in the study was 55.1 mm (95% CI = 40.3 to 70.0) for the IV group and 77.8 mm (95% CI = 67.4 to 88.4) for the nebulized group. The pain treatment was described as adequate by the treating physician in 8 of 14 patients in the IV group and 20 of 27 patients in the nebulized group (p = 0.42). No adverse events were detected. **Conclusions:** Nebulized fentanyl citrate 3 µg/kg through a breath actuated nebulizer appears to be a feasible alternative to IV fentanyl citrate for a variety of painful conditions in patients older than 3 years.

Flecainide

NEW **OPEN-LABEL, MULTICENTER STUDY OF FLECAINIDE ACETATE ORAL INHALATION SOLUTION FOR ACUTE CONVERSION OF RECENT-ONSET, SYMPTOMATIC ATRIAL FIBRILLATION TO SINUS RHYTHM.** HJGM Crijns, A Elvan, N Al-Windy, YS Tuininga, E Badings, I Aksoy, IC Van Gelder, P Madhavapeddi, AJ Camm, PR Kowey, JN Ruskin, L Belardinelli, INSTANT Investigators. Circulation: Arrhythmia and Electrophysiology 2022;15(3):e010204.

Background: Oral and intravenous flecainide is recommended for cardioversion of atrial fibrillation. In this open label, dose escalation study, the feasibility of delivering flecainide via oral inhalation (flecainide acetate inhalation solution) for acute conversion was evaluated. We hypothesized that flecainide delivered by oral inhalation would quickly reach plasma concentrations sufficient to restore sinus rhythm in patients with recent onset atrial fibrillation. **Methods:** Patients (n = 101) with symptomatic atrial fibrillation (for ≤ 48 hours) self administered flecainide acetate inhalation solution using a nebulizer (30 mg [n = 10], 60 mg [n = 22], 90 mg [n = 21], 120 mg [n = 19], and 120 mg in a formulation containing saccharin [n = 29]). Electrocardiograms and flecainide plasma concentrations were obtained, cardiac rhythm using 4 hour Holter was monitored, and adverse events were recorded. **Results:** Conversion rates increased with dose and with the maximum plasma concentrations of flecainide. At the highest dose, 48% of patients converted to sinus rhythm within 90 minutes from the start of inhalation. Among patients who achieved a maximum plasma concentration > 200 ng/mL, the conversion rate within 90 minutes was 50%; for those who achieved a maximum plasma concentration < 200 ng/mL, it was 24%. Conversion was rapid (median time to conversion of 8.1 minutes from the end of inhalation), and conversion led to symptom resolution in 86% of the responders. Adverse events were typically mild and transient and included: cough, throat pain, throat irritation; at the highest dose with the formulation containing saccharin, these adverse events were reported by 41%, 14%, and 3% of patients, respectively. Cardiac adverse events consistent with those observed with oral and intravenous flecainide were uncommon and included post conversion pauses (n = 2), bradycardia (n = 1), and atrial flutter with 1:1 atrioventricular conduction (n = 1); none required treatment, and all resolved without sequelae. **Conclusions:** Administration of flecainide via oral inhalation was shown to be safe and to yield plasma concentrations of flecainide sufficient to restore sinus rhythm in patients with recent onset atrial fibrillation.

PULMONARY DELIVERY OF ANTIARRHYTHMIC DRUGS FOR RAPID CONVERSION OF NEW-ONSET ATRIAL FIBRILLATION. RL Verrier, L Belardinelli. Journal of Cardiovascular Pharmacology 2020;75(4):276-283.

Pharmacologic management of atrial fibrillation (AF) is a pressing problem. This arrhythmia afflicts > 5 million individuals in the United States and prevalence is estimated to rise to 12 million by 2050. Although the pill in the pocket regimen for self administered AF cardioversion introduced over a decade ago has proven useful, significant drawbacks exist. Among these are the relatively long latency of effects in the range of hours along with potential for hypotension and other adverse effects. This experience prompted development of a new strategy for increasing plasma concentrations of antiarrhythmic drugs rapidly and for a limited time, namely, pulmonary delivery. In preclinical studies in Yorkshire pigs, intratracheal administration of flecainide was shown to cause a rapid, reproducible increase in plasma drug levels. Moreover, pulmonary delivery of flecainide converted AF to normal sinus rhythm by

prolonging atrial depolarization, which slows intra-atrial conduction and seems to be directly correlated with efficacy in converting AF. The rapid rise in plasma flecainide levels optimizes its anti-AF effects while minimizing adverse influences on ventricular depolarization and contractility. A more concentrated and soluble formulation of flecainide using a novel cyclodextrin complex excipient reduced net drug delivery for AF conversion when compared to the acetate formulation. Inhalation of the beta adrenergic blocking agent metoprolol slows ventricular rate and can also terminate AF. In human subjects, oral inhalation of flecainide acetate with a handheld, breath actuated nebulizer results in signature prolongation of the QRS complex without serious adverse events. Thus, pulmonary delivery is a promising advance in pharmacologic approach to management of AF.

Gene Therapy

REPEATED NEBULISATION OF NON-VIRAL CFTR GENE THERAPY IN PATIENTS WITH CYSTIC FIBROSIS: A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 2B TRIAL. EWFW Alton, DK Armstrong, D Ashby, KJ Bayfield, D Bilton, EV Bloomfield, AC Boyd, *et al* on behalf of the UK Cystic Fibrosis Gene Therapy Consortium. Lancet Respiratory Medicine 2015;3(9):684-691.

Background: Lung delivery of plasmid DNA encoding the CFTR gene complexed with a cationic liposome is a potential treatment option for patients with cystic fibrosis. We aimed to assess the efficacy of non-viral CFTR gene therapy in patients with cystic fibrosis. **Methods:** We did this randomised, double blind, placebo controlled, phase 2b trial in two cystic fibrosis centres with patients recruited from 18 sites in the UK. Patients (aged ≥ 12 years) with a forced expiratory volume in 1 second (FEV_1) of 50 - 90% predicted and any combination of CFTR mutations, were randomly assigned, via a computer based randomisation system, to receive 5 mL of either nebulised pGM169/GL67A gene-liposome complex or 0.9% saline (placebo) every 28 days (plus or minus 5 days) for 1 year. Randomisation was stratified by % predicted FEV_1 (< 70 vs. ≥ 70%), age (< 18 vs. ≥ 18 years), inclusion in the mechanistic sub-study, and dosing site (London or Edinburgh, UK). Participants and investigators were masked to treatment allocation. The primary endpoint was the relative change in % predicted FEV_1. The primary analysis was per protocol. This trial is registered with ClinicalTrials.gov, number NCT01621867. **Findings:** Between June 12, 2012, and June 24, 2013, we randomly assigned 140 patients to receive placebo (*n* = 62) or pGM169/GL67A (*n* = 78), of whom 116 (83%) patients comprised the per protocol population. We noted a significant, albeit modest, treatment effect in the pGM169/GL67A group versus placebo at 12 months' follow up (3.7%, 95% CI 0.1 - 7.3; *p* = 0·046). This outcome was associated with a stabilisation of lung function in the pGM169/GL67A group compared with a decline in the placebo group. We recorded no significant difference in treatment attributable adverse events between groups. **Interpretation:** Monthly application of the pGM169/GL67A gene therapy formulation was associated with a significant, albeit modest, benefit in FEV_1 compared with placebo at 1 year, indicating a stabilisation of lung function in the treatment group. Further improvements in efficacy and consistency of response to the current formulation are needed before gene therapy is suitable for clinical care; however, our findings should also encourage the rapid introduction of more potent gene transfer vectors into early phase trials.

AEROSOL DELIVERY OF DNA/LIPOSOMES TO THE LUNG FOR CYSTIC FIBROSIS GENE THERAPY. LA Davies, GA Nunez-Alonso, G McLachlan, SC Hyde, DR Gill. Human Gene Therapy Clinical Development 2014;25(2):97-107.

Lung gene therapy is being evaluated for a range of acute and chronic diseases, including cystic fibrosis (CF). As these therapies approach clinical realization, it is becoming increasingly clear that the ability to efficiently deliver gene transfer agents (GTAs) to target cell populations within the lung may prove just as critical as the gene therapy formulation itself in terms of generating positive clinical outcomes. Key to the success of any aerosol gene therapy is the interaction between the GTA and nebulization device. We evaluated the effects of aerosolization on our preferred formulation, plasmid DNA (pDNA) complexed with the cationic liposome GL67A (pDNA/GL67A) using commercially available nebulizer devices. The relatively high viscosity (6.3 ± 0.1 cP) and particulate nature of pDNA/GL67A formulations hindered stable aerosol generation in ultrasonic and vibrating mesh nebulizers but was not problematic in the jet nebulizers tested. Aerosol size characteristics varied significantly between devices, but the ***AeroEclipse* II BAN**** Nebulizer operating at 50 psi generated stable pDNA/GL67A aerosols suitable for delivery to the CF lung (mass median aerodynamic diameter 3.4 ± 0.1 μm). Importantly, biological function of pDNA/GL67A formulations was retained after nebulization, and although aerosol delivery rate was lower than that of other devices (0.17 ± 0.01 mL/min), the breath actuated ***AeroEclipse* II BAN**** Nebulizer generated aerosol only during the inspiratory phase and as such was more efficient than other devices with 83 ± 3% of generated aerosol available for patient inhalation. On the basis of these results, we have selected the ***AeroEclipse* II BAN**** Nebulizer for the delivery of pDNA/GL67A formulations to the lungs of CF patients as part of phase IIa/b clinical studies.

NEBULISATION OF RECEPTOR-TARGETED NANOCOMPLEXES FOR GENE DELIVERY TO THE AIRWAY EPITHELIUM. MDI Manunta, RJ McAnulty, AD Tagalakis, SE Bottoms, F Campbell, HC Hailes, AB Tabor, GJ Laurent, C O'Callaghan, SL Hart. PloS ONE 2011;6(10):e26768.

Background: Gene therapy mediated by synthetic vectors may provide opportunities for new treatments for cystic fibrosis (CF) via aerosolization. Vectors for CF must transfect the airway epithelium efficiently and not cause inflammation so they are suitable for repeated dosing. The inhaled aerosol should be deposited in the airways since the cystic fibrosis transmembrane conductance regulator gene (CFTR) is expressed predominantly in the epithelium of the submucosal glands and in the surface airway epithelium. The aim of this project was to develop an optimized aerosol delivery approach applicable to treatment of CF lung disease by gene therapy. **Methodology:** The vector suspension investigated in this study comprises receptor targeting peptides, cationic liposomes and plasmid DNA that self-assemble by electrostatic interactions to form a receptor targeted nanocomplex (RTN) of approximately 150 nm with a cationic surface charge of +50 mV. The aerodynamic properties of aerosolized nanocomplexes produced with three different nebulisers were compared by determining aerosol deposition in the different stages of a Next Generation Pharmaceutical Impactor (NGI). We also investigated the yield of intact plasmid DNA by agarose gel electrophoresis and densitometry, and transfection efficacies *in vitro* and *in vivo*. **Results:** RTNs nebulized with the ***AeroEclipse* II BAN**** Nebulizer were the most effective, compared to other nebulisers tested, for gene delivery both *in vitro* and *in vivo*. The biophysical properties of the nanocomplexes

were unchanged after nebulization while the deposition of RTNs suggested a range of aerosol aerodynamic sizes between 5.5 µm - 1.4 µm cut off (NGI stages 3 - 6) compatible with deposition in the central and lower airways. **Conclusions:** RTNs showed their ability at delivering genes via nebulization, thus suggesting their potential applications for therapeutic interventions of cystic fibrosis and other respiratory disorders.

Interferon-γ

LUNG DEPOSITION AND RESPIRABLE MASS DURING WET NEBULIZATION. S Sangwan, R Condos, GC Smaldone. Journal of Aerosol Medicine 2003;16(4):379-386.

For metered dose inhalers (MDIs), high flow cascade impaction with a United States Pharmacopeia (USP) throat provides a useful prediction of *in vivo* lung and oropharyngeal aerosol deposition. Particles expected to deposit in the lung are included in the "fine particle fraction" measured on the bench. Comparable *in vitro* standards are not available for nebulizers. The present study compared aerosol deposition in an *in vitro* model using low flow cascade impaction with deposition *in vivo* in human subjects. A low flow (1 L/min), 10 stage cascade impactor measured aerodynamic distributions of aerosolized interferon-gamma (IFN-γ) from two nebulizers (Misty-Neb† and ***AeroEclipse*** **BAN**** Nebulizer). (99m)Technetium diethylenetriaminepentaacetic acid ((99m)Tc-DTPA) was used as the radiolabel. Two bench conditions were specified: no breathing (standing cloud) and simulated ventilation with a piston pump (tidal volume 750 mL frequency 25 per minute and duty cycle 0.5). Mass median aerodynamic diameter (MMAD) for both nebulizers was affected by ventilation (Misty-Neb† vs. ***AeroEclipse*** **BAN**** Nebulizer: 5.2 vs. 4.6 µm for standing cloud and 3.1 vs. 2.2 µm during ventilation). In three subjects, measured values of oropharyngeal deposition averaged 68.1 ± 0.08% for Misty-Neb† and 30.9 ± 0.03% for ***AeroEclipse*** **BAN**** Nebulizer. *In vivo* deposition patterns compared to aerosol distributions from both nebulizers indicated that, for wet nebulization, penetration of aerosol beyond the upper airways (fine particle fraction) will occur only for aerosol particles below 2.5 µm. This assessment requires that the bench aerosol distribution be measured under conditions of clinical use (i.e., during tidal breathing).

PREDICTING LUNG DEPOSITION WITH A CASCADE IMPACTOR. S Sangwan, F Hull, R Condos, GC Smaldone. Journal of Aerosol Medicine 2001;14(3):421.

Introduction: In recent deposition studies of interferon-γ, we failed to predict the deposition pattern from bench studies of aerosols using multistage cascade impaction (MCI). Recent mass balance studies have identified impaction in connecting tubing and effects of breathing on interpretation of cascade data (BK Gurses, *et al*. AJRCC 163; 5(A166). 2001). In the present study we related MCI data using our new bench test protocol directly to lung scans in humans. This protocol emphasizes deposition of large particles in connecting tubing and influence of conditions internal to the nebulizer during breathing. **Methods:** Two devices (Misty-Neb† and ***AeroEclipse*** **BAN**** Nebulizer) were studied. Mass median aerodynamic diameter (MMAD) and mass balance were measured understanding cloud and ventilation using a piston pump. Deposition images were obtained using gamma camera.

Results:

Nebulizer & method of assessment		**Respirable Mass‡ (< 6 µm)**	**Regional Deposition**	
			Lung Deposition**	**Throat Deposition****
Misty-Neb†	Standing Cloud	46.2%	32%	68%
	Ventilated	24.6%		
***AeroEclipse* BAN* Nebulizer**	Standing Cloud	48.3%	72%	28%
	Ventilated	71.2%		

‡*Calculated by adding T connector deposition to the first stage (> 8 µm) of cascade*

** *Expressed as percent of total deposition in the body*

Conclusion: Regional deposition (upper airway vs. lung) was predicted by analysis only when effects of both connecting tubing and breathing were considered in the bench protocol.

Ipratropium Bromide (Atrovent†, Boehringer Ingelheim†)

REDUCING TOTAL COSTS OF AEROSOLIZED MEDICATION DELIVERY USING THE *AEROECLIPSE* II* BREATH ACTUATED NEBULIZER. J Wilson. Respiratory Care 2011;56(10):1634.

Introduction: We hypothesized the ***AeroEclipse*** **II BAN**** Nebulizer combined with an aggressive dosing and frequency protocol would result in cost savings. **Methods:** We transitioned a 38 bed pulmonary unit from traditional jet nebulizers to ***BAN**** Nebulizers and developed a medication dosing and frequency protocol. Albuterol was converted to 0.5 mL of a 0.5% solution with 1 mL normal saline. Atrovent† was converted to one half unit dose. The breath actuated mode via mouthpiece or mask interface with normal saline increased to 2 mL and continuous mode was used. Frequencies were changed from Q4 to Q6 and QID to TID. ***BAN**** Nebulizers were changed weekly versus daily with traditional nebulizers. Average hourly rate, treatment time, drug costs, and device costs for June through November 2008 were compared to 2007. To ensure effectiveness of therapy we compared the average number of both scheduled and PRN treatments per patient per day. Subsequently, we utilized this model to convert all impatient beds to ***BAN**** Nebulizer in June 2010 and compared data to a similar time period in 2009. **Results:** Our initial 2008 conversion resulted in a 20% decrease in total costs with an annualized savings of $52,360. Additionally, a 31% decrease in minutes per day in therapist time to

administer medications and 21% increase in duration between treatments was realized. The average number of scheduled treatments per patient per day was 3.4 and 2.8 in 2007 and 2008 respectively while the average number of PRN treatments was 0.16 and 0.15 in 2007 and 2008 respectively. In the 2010 analysis ***BAN**** Nebulizers account for an 18% decrease in total costs, and a 19% decrease in total treatment time. Use of ***BAN**** Nebulizers resulted in an annual savings at Forsyth Medical Center of $186,789 and estimated savings of $475,411 across Novant Health facilities. Average number of scheduled treatments per patient per day was 3.3 and 3.1 in 2009 and 2010 respectively while the average number of PRN treatments was 0.24 and 0.27 in 2007 and 2008 respectively. Additionally, we compared 2010 data from the units in our initial 2008 group to ensure the improvement reported was maintained in that area. **Conclusions:** Using the ***AeroEclipse**** ***II BAN**** Nebulizer in conjunction with an aggressive medication dosing and frequency reduction protocol provides significant savings. Greater gains have been realized for the pulmonary specific unit which treats patients with more severe pulmonary conditions.

A MECHANICALLY OPERATED BREATH-ACTUATED NEBULIZER ENABLES BOTH IMPROVED CONTROL OF DOSING AND DELIVERY EFFICIENCY. JP Mitchell, MW Nagel, NR MacIntyre. Drug Delivery to the Lungs-16 2005;1:181-184.

Summary: A mechanically operated, breath actuated nebulizer offers the clinician the prospect of being able to control the rate and duration of medication delivery dosimetrically, providing greater precision when titrating patients to establish an appropriate treatment regimen. We describe an *in vitro* study obtained with two formulations that are representative of formulations available for nebulization (amphotericin B and ipratropium bromide), in which a breath actuated device (***AeroEclipse**** ***BAN**** Nebulizer) delivered slightly more medication as fine droplets < 4.8 µm aerodynamic diameter with approximately one half of the dose in the reservoir compared with a continuously operating nebulizer (VixOne†). These measurements were made simulating use by an adult (500 mL tidal volume, inspiratory/expiratory ratio 1:2, 20 breaths/minute). Significant cost savings are therefore possible with the ***BAN**** Nebulizer with expensive medications, such as antibiotics, if less volume fill is required per treatment. **Introduction:** The delivery of medications in aerosol form from solution and suspension formulations by pneumatic (jet) nebulizer is widely practiced in the hospital setting[1], and in many instances alternative delivery devices, such as pressurized metered dose inhalers or dry powder inhalers are unavailable[2]. However, continuously operating devices continue to generate droplets of formulation when the patient exhales, resulting in both waste of medication and the possibility of exposure of health care providers to the treatment being offered[3], unless measures are taken to prevent escape of droplets, such as the use of an external exhalation filter. A mechanically operated, breath actuated device also offers the clinician the prospect of being able to control the rate and duration of medication delivery dosimetrically[4], providing greater precision when titrating patients to establish an appropriate treatment regimen. We report a laboratory study in which a breath actuated device (***AeroEclipse**** ***BAN**** Nebulizer, Trudell Medical International, London, ON, Canada) was compared with a continuously operating small volume nebulizer (VixOne†, Westmed Inc., Tucson, AZ, USA) for the delivery of two formulations that are representative of likely treatments in hospital. Ipratropium bromide is an anticholinergic widely prescribed for the treatment of chronic obstructive pulmonary disease[5], whereas, amphotericin B has been prescribed as an antifungal agent for respiratory tract infections since the 1950s[5]. **Materials and Methods:** Each nebulizer (*n* = 3 devices/group) was operated with compressed air supplied at 50 psig and operated at a flow rate of either 7.0 L/min (***AeroEclipse**** ***BAN**** Nebulizer) or 8.0 L/min (VixOne† continuous nebulizer). The mouthpiece of the device under evaluation was connected to a breathing simulator (Compass system, PARI, Starnberg, Germany) set to mimic adult use (500 mL tidal volume, 1:2 inspiratory/expiratory time ratio, 20 breaths/minute). Figure 1 is a schematic of the nebulizer-breathing simulator arrangement. For the tests with the 0.02% w/v ipratropium bromide solution (Nephron Pharmaceuticals, Orlando, FL, USA), one 2.5 mL vial containing 500 µg ipratropium bromide was placed in the reservoir of the VixOne† nebulizer and one half a vial (250 µg ipratropium bromide) in the ***AeroEclipse**** ***BAN**** Nebulizer. In the corresponding investigation with the 0.5% w/v amphotericin B lipid complex suspension (Ablecet†, Enzon Pharmaceuticals, Piscatawny, NY, USA), 5 mL were withdrawn from a 20 mL vial after gentle shaking in accordance with manufacturer instructions to ensure thorough mixing of the contents, and placed in the reservoir of the VixOne† nebulizer and a further 5 mL added after 4 minutes of use to prevent overloading the reservoir. Only 5 mL of this formulation was inserted in the reservoir of the ***AeroEclipse**** ***BAN**** Nebulizer before the start of nebulization. The nebulizer on test (3 replicates/device) was allowed to operate for one minute past first sputter (defined to be the point at which nebulization changed (audibly or visibly) or became intermittent). At 1 minute intervals a bacterial/viral filter (MT3000, Trudell Medical Marketing Limited, London, ON, Canada) located to cover the mouthpiece of the nebulizer on test to collect the aerosol, was replaced with a fresh filter to prevent overloading. Subsequently, the mass of either ipratropium bromide or amphotericin B on each filter was determined by HPLC-UV spectrophotometry. The combined mass from all filters was calculated to determine the total mass delivered per nebulization 'treatment' (TEM). In a separate study, representative droplet size distribution data for each nebulizer were obtained by laser diffractometry (Mastersizer-X, Malvern Instruments Ltd., UK), so that the fine droplet fraction < 4.8 µm diameter ($FDF_{<4.8\mu m}$), most likely to penetrate into the airways beyond the oropharynx, could be determined. **Results:** Mean values of $FDF_{<4.8\mu m}$ for the ***AeroEclipse**** ***BAN**** Nebulizer and VixOne† continuous nebulizer were comparable, at 81% and 82% respectively. Comparative values of TEM and fine droplet mass (FDM), calculated as the product of TEM and FDF (expressed as a fraction) are summarized in Tables 1 and 2 for ipratropium bromide and amphotericin B respectively.

Table 1: Delivery of Ipratropium Bromide by Continuous and Breath Actuated Nebulizers (*n* = 3 devices/group; 3 replicates/device: mean ± SD)

Nebulizer	Mass Ipratropium Bromide (µg)		Delivery Time (minutes)
	TEM	FDM	
AeroEclipse* ***BAN**** **Nebulizer (1.25 mL fill)**	61.7 ± 5.2	50.0 ± 4.2	2 - 3
VixOne† continuous (2.5 mL fill)	57.2 ± 5.5	46.9 ± 4.5	3 - 4

Table 2: Delivery of Amphotericin B by Continuous and Breath Actuated Nebulizers (*n* = 3 devices/group; 3 replicates/device: mean ± SD)

Nebulizer	Mass Amphotericin B (µg)		Delivery Time (minutes)
	TEM	FDM	
***AeroEclipse** *BAN** Nebulizer (5 mL fill)**	7274 ± 123	5892 ± 100	10
VixOne† continuous (2 x 5 mL fill)	5276 ± 557	4326 ± 457	10 - 14

Delivery times were significantly longer for the amphotericin B complex with both nebulizer types, reflecting the larger volumes of liquid that were nebulized with this formulation. In the case of the measurements with ipratropium bromide, the ***AeroEclipse** *BAN**** Nebulizer delivered a similar amount of medication as fine droplets in slightly less time as the VixOne† continuous nebulizer. However, only one half of the volume fill was required with the ***BAN**** Nebulizer. The ***BAN**** Nebulizer delivered 36% more amphotericin B as fine droplets in approximately equivalent time as the continuous nebulizer, again with only one half the volume fill of medication in the reservoir. **Conclusions:** This study has demonstrated that the breath actuated device is capable of delivering as much or slightly more mass of medication as fine droplets with one half the fill compared with a continuously operating nebulizer. Cost savings with more expensive medications, such as antibiotics, could therefore be significant. Previously published data[6] have confirmed that the delivery rate from the ***AeroEclipse** *BAN**** Nebulizer is constant during operation until sputtering occurs, and similar behaviour was observed in the present investigation (data not shown). This nebulizer is therefore a candidate device for the delivery of other medications, such as for pain control or vaccination by inhalation, where precise control of drug mass delivered is important. **References:** [1] M Dolovich, NR MacIntyre, PJ Anderson, *et al*. Consensus Statement: Aerosols And Delivery Devices. Respiratory Care 2000;45(6):589-596. [2] JH Dennis. Theory And Science Of Nebulizer Use. In: Eds. J Boe, BR O'Driscoll, JH Dennis. Practical Handbook of Nebulizer Therapy. Martin Dunitz, London, UK, 2004:3-17. [3] Nebulizers: Principles And Performance. DR Hess. Respiratory Care 2000;45(6):609-622. [4] JP Mitchell, MW Nagel, SL Bates, CC Doyle. An *In Vitro* Study To Investigate The Use Of A Breath-Actuated, Small-Volume, Pneumatic Nebulizer For The Delivery Of Methacholine Chloride Bronchoprovocation Agent. Respiratory Care 2003;48(1):46-51. [5] JL Rau. Respiratory Care Pharmacology. 5th Edition, Mosby-Year Book Inc., St. Louis, MO, USA, 1998. [6] MW Nagel, CC Doyle, SL Bates, JP Mitchell. An *In Vitro* Investigation Of Common Nebulizer Dosing Protocols, Comparing A Breath-Actuated With A Conventional Pneumatic Small Volume Nebulizer (SVN). Respiratory Drug Delivery 2002,2:627-629.

SIMILAR DELIVERY OF IPRATROPIUM BROMIDE IS POSSIBLE AT APPROXIMATELY ONE-HALF DOSE VIA A BREATH-ACTUATED NEBULIZER COMPARED WITH A CONTINUOUS NEBULIZER. JP Mitchell, MW Nagel, NR MacIntyre, R Sharpe. European Respiratory Journal 2005;26(49):306s.

Delivery of aerosols via continuous nebulizers wastes medication during patient exhalation. Breath actuated nebulizers minimize waste, since they only operate when the patient inhales. We describe a study in which a breath actuated device (***AeroEclipse** *BAN**** Nebulizer, Trudell Medical International, London, ON, Canada) was compared with a continuous nebulizer (VixOne†, Westmed Corp., Engelwood, CO (VIX)) (*n* = 3 /group) for the delivery of ipratropium bromide ((IPR), Nephron Pharmaceuticals, Orlando, FL, USA, 0.5 mg/2.5 mL). Each device was operated with air at 50 psig at 7 L/min (***BAN**** Nebulizer) or 8 L/min (VIX), with the mouthpiece connected to a breathing simulator (Compass, PARI, Germany) set to replicate adult use (500 mL tidal volume, 1:2 inspiratory/expiratory ratio, 20 breaths/minute). 1.25 mL was placed in the ***BAN**** Nebulizer and 2.5 mL in the VIX. The mass of IPR collected on a filter at the mouthpiece was assayed by HPLC-UV spectrophotometry (3 replicates). Droplet size distributions were separately determined by laser diffractometry. The ***BAN**** Nebulizer delivered 61.7 ± 5.2 µg IPR in 2 - 3 minutes, of which 50.0 ± 4.2 µg was in fine droplets ≤ 4.8 µm diameter. The VIX delivered a total mass of 57.2 ± 5.5 µg in 3 - 4 minutes, of which 46.9 ± 4.5 µg was contained in fine droplets. The ***BAN**** Nebulizer delivered a similar amount of medication as fine droplets with approximately one half of the dose in the reservoir.

Ipratropium Bromide And Albuterol Sulfate (Combivent†, Boehringer Ingelheim†)

A PROSPECTIVE, COMPARATIVE TRIAL OF STANDARD AND BREATH-ACTUATED NEBULIZER: EFFICACY, SAFETY, AND SATISFACTION. V Arunthari, RS Bruinsma, AS Lee, MM Johnson. Respiratory Care 2012;57(8):1242-1247.

Background: Nebulized drug delivery is a cornerstone of therapy for obstructive lung disease, but the ideal nebulizer design is uncertain. The breath actuated nebulizer may be superior to conventional nebulizers. This study compared the breath actuated nebulizer to standard nebulizer with regard to efficacy, safety, and patient and respiratory therapist (RT) satisfaction. **Methods:** Adults admitted to the hospital and for whom nebulizer therapy was prescribed were enrolled. Subjects were randomly assigned to either ***AeroEclipse** *II BAN**** Nebulizer or standard nebulizer and were surveyed at the completion of each treatment. ***BAN**** Nebulizer delivered albuterol 2.5 mg or albuterol 2.5 mg plus ipratropium 0.25 mg. Standard nebulizer delivered albuterol 2.5 mg or albuterol plus ipratropium 0.5 mg. An RT assessed each subject's heart rate, respiratory rate, and peak expiratory flow rate prior to and following treatment. Treatment time and adverse events were recorded. Each RT was asked to assess his/her satisfaction with each of the nebulizers. **Results:** Twenty-eight subjects were studied. The mean age was 69 years. Fifty-four percent of the subjects indicated that overall the ***BAN**** Nebulizer was superior to conventional nebulizer therapy; 68% indicated that duration was preferable with the ***BAN**** Nebulizer. RTs were more satisfied with the ***BAN**** Nebulizer, based on overall performance, treatment duration, and ease of use. There were no significant differences in heart rate, peak expiratory flow rate, or respiratory rate before or after nebulization therapy with either device. The duration of treatment was significantly lower with the ***BAN**** Nebulizer (4.1 minutes vs. 9.9 minutes, $p < 0.001$). Additionally, the ***BAN**** Nebulizer was associated with a lower occurrence of adverse events. **Conclusions:** Patients and RTs expressed greater satisfaction with the ***BAN**** Nebulizer, compared with standard nebulizer. Pre- and post-treatment vital signs did not differ between groups, but use of the ***BAN**** Nebulizer was associated with a shorter duration and a lower occurrence of adverse events. Taken together, these data support the use of the ***BAN**** Nebulizer for nebulized medication delivery.

RANDOMIZED CONTROLLED TRIAL OF A BREATH-ACTIVATED NEBULIZER IN PATIENTS WITH EXACERBATION OF COPD. JM Haynes. Respiratory Care 2012;57(9):1385-1390.

Background: Exacerbations of COPD (ECOPD) are characterized by increased dyspnea due to dynamic pulmonary hyperinflation. This study sought to determine whether the breath actuated ***AeroEclipse**® **II BAN**®* Nebulizer would produce greater bronchodilator responses than a continuous flow small volume nebulizer (SVN) in patients with ECOPD. **Methods:** Prospective randomized controlled trial. Forty patients with ECOPD were recruited to participate in the trial. The primary study outcomes were inspiratory capacity (IC) and dyspnea via the Borg scale. Subjects were randomized to receive bronchodilator from either a ***BAN**®* Nebulizer or a continuous flow SVN. Subjects in both groups received 2.5 mg albuterol sulfate and 0.5 mg ipratropium bromide by nebulizer every 4 hours, and 2.5 mg albuterol every 2 hours as needed. Approximately 2 hours after the subject's 6th scheduled nebulizer treatment, IC, dyspnea, and respiratory frequency measurements were repeated. **Results:** Both groups received an equal number of nebulizer treatments over the study period (***BAN**®* Nebulizer 6.25 ± 0.55, control 6.2 ± 0.7, $p = 0.80$). Following completion of the study protocol the ***BAN**®* Nebulizer group had a higher IC than the SVN group (1.83 ± 0.65 L vs. 1.42 ± 0.49 L, $p = 0.03$, respectively). The change in IC was higher in the ***BAN**®* Nebulizer group (0.33 ± 0.31 L than in the SVN group (0.15 ± 0.19 L, $p = 0.03$). The ***BAN**®* Nebulizer group also had a lower respiratory rate (19 ± 3.3 breaths/minute vs. 22 ± 5.3 breaths/minute, $p = 0.03$, respectively). There was no difference in resting dyspnea as measured with the Borg scale (***BAN**®* Nebulizer 3.3 ± 2.1, SVN 3.5 ± 2.4, $p = 0.69$) or stay (***BAN**®* Nebulizer 4.6 ± 2.6 days, SVN 5.7 ± 2.8 days, $p = 0.21$). **Conclusions:** In this cohort of patients with ECOPD, a ***BAN**®* Nebulizer was more effective in reducing lung hyperinflation and respiratory frequency than a continuous flow SVN.

COMPARISON IN RATES OF BREAKTHROUGH TREATMENTS DURING A CONVERSION FROM RACEMIC ALBUTEROL TO LEVALBUTEROL. RS Pikarsky, RA Acevedo, C Roman. CHEST 2002;122(4):146S.

Purpose: In order to meet our patient care demands, Crouse Hospital approved an automatic conversion from racemic albuterol to levalbuterol. This study compares the breakthrough rates of racemic albuterol and levalbuterol, with and without ipratropium. **Methods:** Racemic albuterol (Alb) 2.5 mg Q4h was converted to either levalbuterol (Lev) 0.63 mg Q6h or levalbuterol 1.25 mg Q8h. If ordered, ipratropium (Ipra) 0.5 mg was administered at the same frequency as the levalbuterol. Patients with acute coronary syndromes, need for cardiac monitoring, or requiring more frequent aerosol administration received the lower levalbuterol dose Q6h. A majority of aerosol therapy was provided with the use of the ***AeroEclipse**® **II BAN**®* Nebulizer. All aerosol treatments, including breakthrough treatments, delivered between July 1, 2001 and February 28, 2002 were recorded. **Results:** Tx/Pt/day represents the number of treatments delivered per patient per day. Rate/100 Pt/days = (Breakthrough) / (Total Tx / Tx/Pt/day) x 100. Rate/100 Pt/days corrects for the differences in daily administration frequency, and may better reflect the daily impact of the breakthrough rate. The breakthrough rate of the combined albuterol group was significantly greater than both levalbuterol groups (5.29 vs. 2.29, 5.29 vs. 2.43, $p < 0.001$)*. The breakthrough rate with albuterol was significantly reduced with the addition of ipratropium ($p < 0.001$)**. Ipratropium did not significantly change the breakthrough rate when added to levalbuterol groups.

Medication	Total Tx	Breakthrough	Rate/1,000	Tx/Pt/day	Rate/100 Pt/day	
Alb Q4h	3,832	47	12.27	6	7.36**	5.29*
Alb/Ipra Q4h	3,767	20	5.31	6	3.19**	
Lev 0.63 mg Q6h	3,592	24	6.68	4	2.67	2.29*
Lev 0.63 mg/Ipra Q6h	1,821	7	3.84	4	1.54	
Lev 1.25 mg Q8h	1,791	17	9.49	3	2.85	2.43*
Lev 1.25 mg/Ipra Q8h	678	3	4.42	3	1.33	

Conclusions: The conversion from racemic albuterol to levalbuterol allowed for a decreased frequency of daily medication administrations and a significant decrease in breakthrough requirements. Ipratropium showed a significant benefit in breakthrough reduction for the racemic albuterol group. **Clinical Implications:** The efficiencies gained by decreasing the daily frequency of aerosol administration can have a significant impact on resource utilization. The conversion to levalbuterol allows for decreased respiratory therapy time or the reallocating of workforce needs while maintaining, or improving, quality of aerosol administration, as evidenced by the decrease in breakthrough requirements.

AN *IN VITRO* INVESTIGATION OF COMMON NEBULIZER DOSING PROTOCOLS, COMPARING A BREATH-ACTUATED WITH CONVENTIONAL PNEUMATIC SMALL VOLUME NEBULIZER (SVN). MW Nagel, CC Doyle, SA Bates, JP Mitchell. Respiratory Drug Delivery 2002;2:627-629.

Introduction: Several protocols for the delivery of bronchodilator and/or anticholinergic therapy by nebulizer are in widespread use; making use of different combinations of formulation type for the bronchodilator (respirator solution or fixed concentration in ampoule) delivered alone, diluted with physiologically normal saline, or mixed with the anticholinergic component. The purpose of this investigation was to compare medication delivery as a function of elapsed time using these common protocols with a new breath actuated SVN (***AeroEclipse**® **BAN**®* Nebulizer, Monaghan Medical Corporation, Plattsburgh, NY, USA, and a conventional SVN (MICRO MIST†, Hudson RCI, Temecula, CA, USA) used as a benchmark device. **Materials and Methods:** Five SVNs of each type were tested using a piston driven breathing simulator (Kompass, PARI GmbH, Starnberg, Germany) set to the following conditions deemed representative of adult use: tidal volume = 600 mL, inspiratory/expiratory ratio 1:2, rate = 10 breaths/minute.

Table 1: Test Matrix for Nebulizer Dosing Protocol Evaluation

Dosing Protocol		SVN	
		AeroEclipse* ***BAN**** **Nebulizer**	**MICRO MIST†**
A	1 unit dose albuterol (ALB) ampoule (2.5 mg albuterol sulfate/3 mL)	5	5
B	0.5 unit dose albuterol (ALB) ampoule (2.5 mg albuterol sulfate/3 mL)	5	not tested
C	0.5 mL of albuterol sulfate (ALB) respirator solution (5 mg/mL) and 0.5 mL of normal saline (0.9% NaCl solution)	5	not tested
D	0.5 mL of albuterol sulfate (ALB) respirator solution (5mg/mL) and 1 unit dose ipratropium bromide (IPR (0.5 mg/2.5 mL)) ampoule	5	5
E	0.5 mL of albuterol sulfate (ALB) respirator solution (5 mg/mL) and 0.5 unit dose ipratropium bromide (IPR (0.5 mg/2.5 mL)) ampoule	5	not tested

A bacterial/viral filter (model 303 Respirgard II†, Marquest Medical, Englewood, CO, USA) was located to cover the mouthpiece of each SVN to collect the emitted aerosol stream. The mouthpiece was, in turn, coupled directly to the breathing simulator. The measurements with each dosing protocol (Table 1) were made with the SVN operated with 8.0 ± 0.2 L/min compressed air, delivered at 50.0 ± 0.5 psig. Each SVN (n = 5 nebulizers, 3 replicates/device) was allowed to operate until first sputter (defined to be the point at which nebulization changed audibly or visibly). The aerosol collection filter was replaced at 1 minute intervals. Following completion of each test, a constant volume (20 mL) of methanol (100% v/v) was added to the filter in its holder, and an aliquot of the resulting solution was assayed by HPLC-UV spectrophotometry to permit the cumulative mass of albuterol (ALB) and/or ipratropium bromide (IPR) to be determined as a function of the elapsed time since start of nebulization. Measurements were made with ALB in ampoule form (2.5 mg albuterol sulfate/3 mL, Zenith Goldline Pharmaceuticals (ZGP)), Miami, FL, USA), ALB supplied as respirator solution (5 mg/mL albuterol sulfate, Warrick Pharmaceuticals, Reno, NV, USA) alone or mixed with IPR from an ampoule (0.5 mg/2.5 mL, ZGP). In a parallel study, representative droplet size distributions in the range from 0.5 to 180 µm diameter of the aerosol emitted by each SVN (n = 5 nebulizers, 3 replicates/device) were measured by laser diffractometer (Mastersizer-X, Malvern Instruments Ltd., UK). These measurements were made between 15 seconds and 2 minutes after onset of nebulization, as pilot studies had not shown significant changes in size distribution with either nebulizer during the period of operation until sputtering occurred. **Results and Discussion:** The mass of drug delivered as fine particles was calculated at each time interval as the product of the total mass delivery (breathing simulator) and the average value of the volume (mass) fraction < 4.8 µm diameter (Mastersizer measurements). Fine particle mass delivered increased with time in a linear manner for both nebulizers for pure ALB and the mixtures of ALB/IPR (Figures 1, 2a, and 2b), as might be expected for solution based formulations. The ***AeroEclipse**** ***BAN**** Nebulizer delivered an equivalent mass of ALB or IPR in a significantly shorter time period than the MICRO MIST† nebulizer (unpaired t-test at each time interval, $p < 0.001$), probably due to the air entrainment capability of the former device. The use of a 0.5 unit dose (treatment A) rather than full unit dose ALB ampoule (treatment B) with the ***AeroEclipse**** ***BAN**** Nebulizer resulted in a similar outcome in terms of delivery rate, although nebulization ceased after 3 minutes with the smaller volume of solution. The higher ALB concentration in the diluted respirator solution (2.5 mg/mL) compared with that in the ampoules (0.83 mg/mL) resulted in more rapid delivery of medication (compare treatments B and C). Halving the volume of the IPR component in the ALB/IPR mixtures used with the ***AeroEclipse**** ***BAN**** Nebulizer had negligible impact on the delivery of this component (compare treatments D and E (Figure 2b)), but doubled the delivery rate for the ALB component (Figure 2a), associated with an effective ALB concentration increase from 0.83 mg/mL to 1.43 mg/mL.

Figure 1: Fine Particle Delivery with ALB Based Formulations

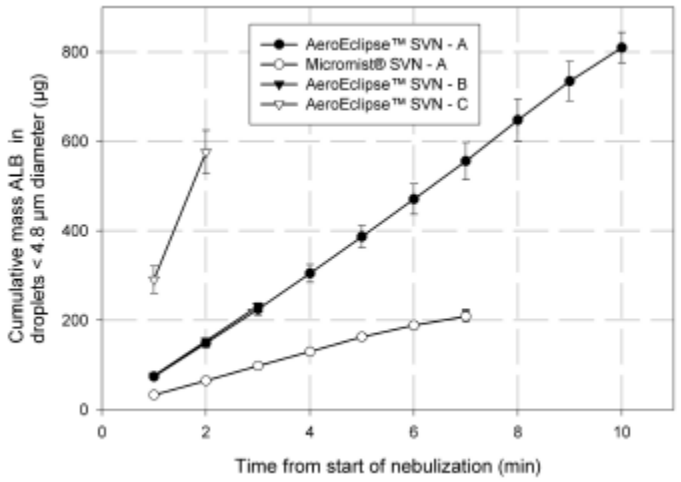


Figure 2a: Fine Particle Delivery with ALB/IPR Mixtures: ALB Component

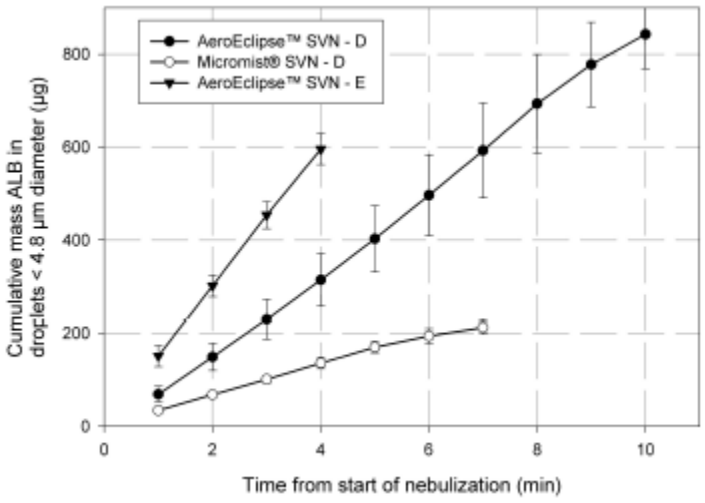
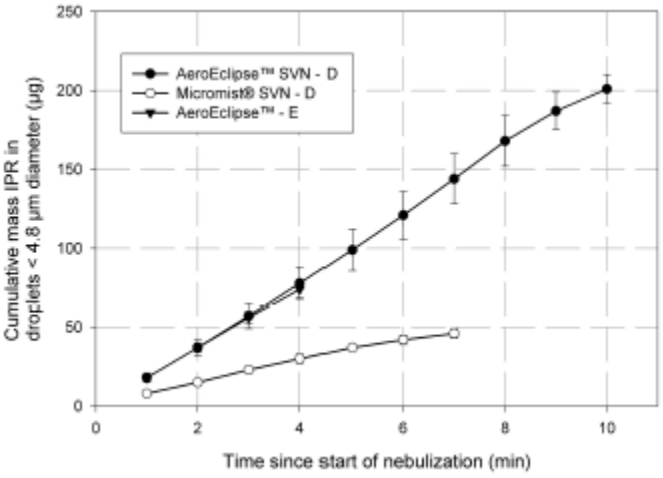


Figure 2b: Fine Particle Delivery with ALB/IPR Mixtures: IPR Component



Conclusions: The caregiver can alter either the drug concentration or volume placed in the reservoir of the ***AeroEclipse**** ***BAN**** Nebulizer to achieve a desired dosing regimen. This nebulizer delivered a comparable mass of albuterol in a significantly shorter time than with the benchmark non-breath actuated SVN following protocols A and D.

PERFORMANCE OF A NEW BREATH-ACTUATED SMALL VOLUME NEBULIZER (SVN) FOR THE DELIVERY OF A COMBINATION ANTICHOLINERGIC/BRONCHODILATOR. MW Nagel, KJ Wiersema, SL Bates, JP Mitchell. American Journal of Respiratory and Critical Care Medicine 2001;163(5):A443.

Purpose: To compare the delivery of ipratropium bromide (IPR) and albuterol sulfate (ALB) as fine droplets (< 4.8 µm diameter (FPD)) and as total emitted dose (ED) from a breath actuated (BA-SVN) with that from a continuous flow air entrainment (AE-SVN) after 5 minutes of operation. **Methods:** FPD and ED were determined for 5 ***AeroEclipse**** ***BAN**** Nebulizers (Monaghan Medical Corporation, NY) and 5 PARI LC† D SVNs (PARI Respiratory Equipment, Inc., CA) nebulizing Combivent† (2.5 mL, 0.2 mg/mL IPR and 1.0 mg/mL ALB; Boehringer Ingelheim† (Canada) Inc.). Each SVN was operated with 8 L/min air at 50 psig, simulating breathing at tidal volume, I:E ratio and rate of 750 mL, 1:2 and 10/min respectively. Droplet size distributions were measured by laser diffractometer. **Results:** (ED) and (FPD) were as follows:

IPR	***AeroEclipse**** ***BAN**** Nebulizer	ED = 102 ± 7 µg	FPD = 82 ± 6 µg
IPR	PARI LC† D SVNs	ED = 55 ± 7 µg	FPD = 45 ± 5 µg
ALB	***AeroEclipse**** ***BAN**** Nebulizer	ED = 581 ± 17 µg	FPD = 471 ± 14 µg
ALB	PARI LC† D SVNs	ED = 279 ± 33 µg	FPD = 226 ± 26 µg

Differences in ED and FPD between SVNs for IPR and ALB components were statistically significant (unpaired t-test for each variable, $p < 0.001$). Mass median aerodynamic diameters were close to 2.8 mm for both SVN groups. **Conclusion:** The ***AeroEclipse**** ***BAN**** Nebulizer is significantly more efficient for the delivery of this combination anticholinergic/bronchodilator than a conventional AE-SVN.

CLINICAL EVALUATION OF A BREATH ACTUATED SMALL VOLUME NEBULIZER (BA-SVN). S Klopf, N Schneiderman, H Payne, C Schramm, MW Nagel, JP Mitchell. Respiratory Care 2000;45(8):979.

Background: In prior *in vitro* studies using laser diffractometry, the aerosol produced by a novel breath actuated device, the ***AeroEclipse***** **BAN**** Nebulizer (Monaghan Medical Corporation, Plattsburgh, NY) has been shown to contain a high proportion of droplets < 4.8 µm diameter (80.9% ± 2.4%). Such droplets are more likely to penetrate beyond the oropharyngeal region where bronchodilation is achieved. These *in vitro* results should therefore be predictive of improved *in vivo* delivery of nebulized medications to the respiratory tract. This study explored the clinical performance of the ***AeroEclipse***** **BAN**** Nebulizer in the delivery of a beta-2 agonist (albuterol 2.5 mg/mL) accompanied by anticholinergic (ipratropium bromide 250 µg/mL) bronchodilator in some cases. **Methods:** Patients (*n* = 48) with a previous diagnosis for asthma presenting to the emergency department for acute exacerbation of asthma were included in this study. Upon presentation, an asthma care path, an assessment driven, algorithm based tool was used to place patients in one of three stages of severity as recommended by the NIH-NAEPP Guidelines for the Diagnosis of Asthma. Each patient was assigned to receive inhaled aerosol treatment using the ***AeroEclipse***** **BAN**** Nebulizer. Stage 1 asthmatics were given 0.5 mL of albuterol with 0.5 mL normal saline delivered until sputter. Patients categorized in stage two and three were given 0.5 mL albuterol with the addition of 1.5 mL of ipratropium bromide unit dose. Treatments repeated every 20 minutes times three if necessary, by protocol.

Results:

Asthma Severity	Stage 1	Stage 2	Stage 3
Number	10	30	8
Treatments Given	2.4	2.03	2.25
Treatment Duration (minutes)	3.7	3.78	5
Increase in PEF (mean, range (%))	44 (0 - 120)	67.7 (-2.7 - 580)	120.7 (28 - 420)

Four patients had greater than 20% increase in heart rate, three patients noted tremor following treatment. Twenty-four patients had positive comments about the device focused on shorter treatment time and improved relief from dyspnea. Two imminent intubations were avoided with the use of the ***BAN***** Nebulizer. **Conclusions:** Use of the ***AeroEclipse***** **BAN**** Nebulizer appears to result in good clinical outcomes. Minimum number of treatments, shorter treatment duration and minimal side effects were noticed with this device. Further outcome studies are needed to assess this impact on other groups of patients.

Ketamine

NEW **PARAPHIMOSIS PAIN TREATMENT WITH NEBULIZED KETAMINE IN THE EMERGENCY DEPARTMENT.** C Barberan Parraga, Y Peng, E Cen, D Dove, C Fassassi, A Davis, J Drapkin, R Hossain, E Mahl, S Motov. The Journal of Emergency Medicine 2022;62(3):e57-e59.

Background: Paraphimosis is an acute urological emergency occurring in uncircumcised males that can lead to strangulation of the glans and painful vascular compromise. Ketamine has been used in the emergency department (ED) as an anesthetic agent for procedural sedation, and when administrated in a sub-dissociative dose (low dose) at 0.1 - 0.3 mg/kg, ketamine has been utilized in the ED and prehospital settings for pain control as an adjunct and as an alternative to opioid, as well as for preprocedural sedation. This report details the case of a pediatric patient who presented to our Pediatric ED with paraphimosis and had his procedural pain treated with ketamine administrated via a breath actuated nebulizer. **Case report:** This case report illustrates the potential use of ketamine via breath actuated nebulizer to effectively achieve minimal sedation for a procedure in pediatric patients in the ED. The patient was a 15 year old boy admitted to the Pediatric ED complaining of groin pain due to paraphimosis. The patient was given 0.75 mg/kg of nebulized ketamine via breath actuated nebulizer, and 15 minutes after the medication administration the pain score was reduced from 5 to 1 on the numeric pain rating scale. The patient underwent a successful paraphimosis reduction without additional analgesic or sedative agents 20 minutes after the administration of nebulized ketamine. The patient was subsequently discharged home after 60 minutes of monitoring, with a pain score of 0. WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS? The use of nebulized ketamine via breath actuated nebulizer might represent a viable, non-invasive way to provide a mild sedative and be an effective analgesic option for managing a variety of acute painful conditions and procedures in the pediatric ED.

COMPARISON OF NEBULIZED KETAMINE AT THREE DIFFERENT DOSING REGIMENS FOR TREATING PAINFUL CONDITIONS IN THE EMERGENCY DEPARTMENT: A PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND CLINICAL TRIAL. D Dove, C Fassassi, A Davis, J Drapkin, M Butt, R Hossain, S Kabariti, A Likourezos, A Gohel, P Favale, M Silver, J Marshall, S Motov. Annals of Emergency Medicine 2021;78(6)779-787.

Study objective: We aimed to assess and compare the analgesic efficacies and adverse effects of ketamine administered through a breath actuated nebulizer at 3 different dosing regimens for emergency department patients presenting with acute and chronic painful conditions. **Methods:** This was a prospective, randomized, double blinded trial comparing 3 doses of nebulized ketamine (0.75 mg/kg, 1 mg/kg, and 1.5 mg/kg) administered through breath actuated nebulizer in adult emergency department patients aged 18 years and older with moderate to severe acute and chronic pain. The primary outcome included the difference in pain scores on an 11 point numeric rating scale between all 3 groups at 30 minutes. Secondary outcomes included the need for rescue analgesia (additional doses of nebulized ketamine or intravenous morphine) and adverse events in each group at 30 and 60 minutes. **Results:** We enrolled 120 subjects (40 per group). The difference in mean pain scores at 30 minutes between the 0.75 mg/kg and 1 mg/kg groups was 0.25 (95% confidence interval [CI] 1.28 to 1.78); between the 1 mg/kg and 1.5 mg/kg groups was -0.225 (95% CI -1.76 to 1.31); and between the 0.75 mg/kg and 1.5 mg/kg groups was 0.025 (95% CI -1.51 to 1.56). No clinically concerning changes in vital signs occurred. No serious adverse events occurred in any of the groups. **Conclusion:** We found no difference between all 3

doses of ketamine administered through breath actuated nebulizer for short term treatment of moderate to severe pain in the emergency department.

NEBULIZED KETAMINE USED FOR PAIN MANAGEMENT OF ORTHOPEDIC TRAUMA. C Fassassi, D Dove, AR Davis, A Ranginwala, E Khordipour, S Motov. The Journal of Emergency Medicine 2021;60(3):365-367.

Background: Ketamine is a non-competitive N-methyl-D-aspartate/glutamate receptor complex antagonist that decreases pain by diminishing central sensitization and hyperalgesia. When administered via IV (push dose, short infusion, or continuous infusion) or intranasal routes, ketamine has shown to be effective in patients with acute traumatic pain. However, when IV access is not attainable or readily available, the inhalation route of ketamine administration via breath actuated nebulizer provides a non-invasive and titratable method of analgesic delivery. The use of nebulized ketamine has been studied in areas of post operative management of sore throat and acute traumatic musculoskeletal and abdominal pain. To our knowledge, this is the first case series describing the use of nebulized ketamine for analgesia and orthopedic reduction. **Case Series:** We describe 4 patients who presented to the emergency department with acute traumatic painful conditions (one patellar dislocation, one shoulder dislocation, and two forearm fractures) and received nebulized ketamine for management of their pain. WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS? Administration of nebulized ketamine via breath actuated nebulizer can be used as analgesic control for musculoskeletal trauma, as it can be administrated to patients with difficult IV access, has a rapid onset of analgesic effects with minimal side effects, and remains opioid sparing.

ADMINISTRATION OF NEBULIZED KETAMINE FOR MANAGING ACUTE PAIN IN THE EMERGENCY DEPARTMENT: A CASE SERIES. J Drapkin, A Masoudi, M Butt, R Hossain, A Likourezos, S Motov. Clinical Practice and Cases in Emergency Medicine 2020;4(1):16-20.

Ketamine is a non-competitive N-methyl-D-aspartate/glutamate receptor complex antagonist that decreases pain by diminishing central sensitization, hyperalgesia, and “wind-up” phenomenon at the level of the spinal cord (dorsal ganglion) and central nervous system.[1] Ketamine administration in sub-dissociative (SDK) dose (0.1 - 0.3 milligrams per kilogram (mg/kg)) in the emergency department (ED) results in effective pain relief in patients with acute traumatic and non-traumatic pain, chronic non-cancer and cancer pain, and opioid tolerant pain by virtue of providing anti-hyperalgesia, anti-allodynia, and anti-tolerance.[2,3] Two commonly employed administration strategies of SDK administration in the ED include an intravenous (IV) route (push dose, short infusion, or continuous infusion), and intranasal route.[4,5] However, in situations when IV access is unobtainable and /or mucosal atomization device is not readily available, nebulized routes of analgesic administration can be used. The nebulization of analgesics in the ED provides rapid, effective, and titratable analgesic delivery. It also results in less painful methods of analgesic delivery, minimizes analgesic toxicity and side effects (for example, opioids), and improves overall management of a variety of painful conditions in the ED.[6] Nebulized administration of ketamine has been studied in the areas of palliative care, therapy for asthma, and acute postoperative management of sore throat.[7-9] To our knowledge, there is no literature regarding analgesic efficacy and safety of nebulized ketamine’s role in managing acute painful conditions in the ED. The following cases describe five patients presenting to the ED of a tertiary medical center between May - June 2019 with acute painful conditions and receiving nebulized ketamine at three different dosing regimens of 0.75 mg/kg, 1 mg/kg, and 1.5 mg/kg via breath actuated nebulizer.

Levalbuterol (Xopenex†, Sepracor† Inc.)

CLINICAL AND ECONOMIC OUTCOMES WITH A CONVERSION TO ARFORMOTEROL ONCE OR TWICE DAILY FROM LEVALBUTEROL USING BREATH ACTUATED NEBULIZERS. RS Pikarsky, RA Acevedo, T Farrell, W Fascia, R Bear. Respiratory Care 2008;53(11):1545.

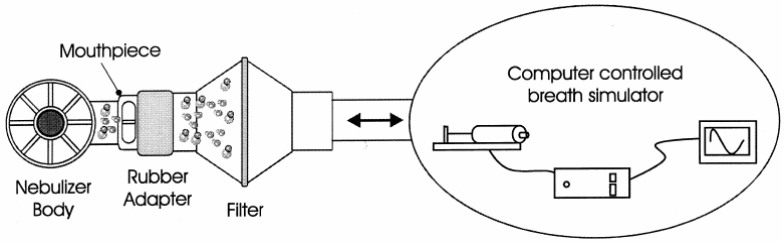
Background: For COPD patients using liquid nebulization, a long acting effect is achieved by using short acting bronchodilators on a scheduled basis. A large number of treatments for inpatient COPD patients are for maintenance bronchodilatation. This pilot protocol evaluated the conversion from levalbuterol (Lev) to Arformoterol (Arf) for maintenance. **Methods:** COPD inpatients assessed to be on maintenance bronchodilators were converted from Lev to Arf. All treatments (tx) were delivered using the Monaghan Medical Corporation ***AeroEclipse***** **BAN**** Nebulizer. If the patient could use a mouthpiece device, they received Arf 15 mcg once daily. If a mask was used, they received Arf 15 mcg twice daily. Arf and Lev treatments delivered from 12/23/07 to 5/25/08 were recorded in a database as scheduled, prn breakthrough, or refused treatments. Prn rates are calculated in 100 patient days to correct for different treatment frequencies. Average tx per day includes scheduled and prn tx. Labor hours were obtained from the AARC Uniform Reporting Manual. RT salary and benefits averaged $31/hr. The device cost per tx was derived from the device cost divided by the change out interval and then divided by number of treatments per day. ***BAN***** Nebulizer cost = $4.88, Misty-Neb† = $0.36. In 2007 38,533 Lev treatments were delivered. We estimate that 60% of treatments can be converted to Arf. The Arf SVN column is for comparison only. **Results:** Clinical: Arf 15 mcg ***BAN***** Nebulizer Qday: 376 scheduled, 32 prn (8.5 per 100 patient days), and 8 refusals. 13 of the 32 prn treatments came from 3 patients. Arf 15 mcg mask BID: 185 scheduled, 4 prn (4.3 per 100 patient days), and 2 refusals. Lev (***BAN***** Nebulizer & mask) TID: 4,281 scheduled, 153 prn (10.7 per 100 patient days) and 254 refusals. Economic results: See table. **Conclusion:** Using Arformoterol Qday with ***BAN***** Nebulizer or BID with mask decreased the number of treatments delivered and total cost of delivery with prn treatments that compared favorably with Lev. Better patient selection may decrease the prn rate in the Qday group. The large number of refusals in the Lev group would suggest more patients could be converted to Arf. The ***BAN***** Nebulizer, by allowing Qday treatments, was extremely cost effective.

Economic Evaluation	Arformoterol Qday *BAN** Nebulizer	Arformoterol BID *BAN** Nebulizer	Levalbuterol TID *BAN** Nebulizer	Arformoterol BID SVN
Number tx	418	184	4,434	
Ave tx/day	1.08	2.04	3.11	2.04
Labor hrs/tx	0.133	0.133	0.133	0.155
Labor cost/tx	$4.13	$4.13	$4.13	$4.80
Device cost/tx	$1.08	$0.57	$0.39	$0.07
Drug cost/tx	$4.34	$4.34	$2.52	$4.34
Total tx cost	$9.55	$9.04	$7.04	$9.02
Daily tx cost	$10.34	$18.48	$21.86	$18.82
Assume 60% Arf conversion on 38,533 treatments				
tx%	68%	32%	100%	100%
# Arf tx	5,203	4,926		15,490
# Lev tx	15,413		38,533	15,413
Total # of tx	25,543		38,533	30,903
Arf cost	$94,198			$142,575
Lev cost	$38.841		$271,122	$38,841
Total cost	$133.039		$271,122	$181,416
Labor hours	3,400		5,129	4,781

USING TWO STRENGTHS OF LEVALBUTEROL SOLUTION AND A BREATH-ACTUATED NEBULIZER TO MODIFY MEDICATION DELIVERY PROFILES. MW Nagel, CC Doyle, VA Avvakoumova, JP Mitchell. Respiratory Drug Delivery 2008;3:789-792.

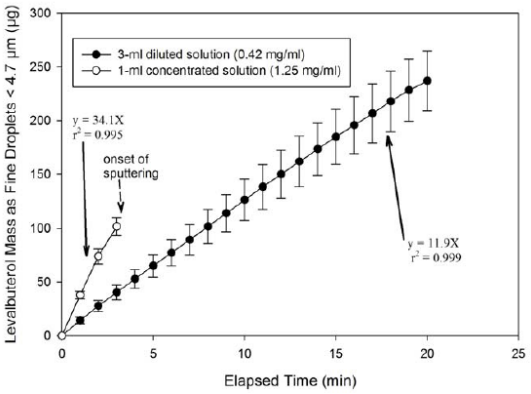
Introduction: Delivery of bronchodilators by jet nebulizer is widely practiced for the treatment of obstructive lung diseases, because certain drugs are only available as inhalation solutions and some patients are unable to master the correct use of either pressurised metered dose inhalers (pMDIs) or dry powder inhalers[1]. Nebulizer treatment times are long compared with pMDI and DPI use[2] leading to interest in shortening them[3] and improving nebulizer efficiency[4]. One way to achieve shorter nebulizer delivery times is the use of a concentrated inhalation solution[5]. We studied delivery times and the medication delivery profiles of two levalbuterol strengths in an efficient breath actuated nebulizer to determine if the same amount of medication could be delivered during each simulated breath by dosimetric delivery[6]. **Materials and methods:** A group of ***AeroEclipse** II BAN** Nebulizers (n = 5 devices; 3 replicates/device) were evaluated using a piston driven breathing simulator (Compass, PARI GmbH, Starnberg, Germany) set to provide conditions appropriate to adult use (tidal volume of 600 mL, inspiratory/expiratory ratio of 1:2, rate of 10 breaths/minute), based on a previous investigation[7]. All measurements were made under ambient conditions (22 ± 1ºC, 38 ± 2% RH). Each nebulizer was operated with a portable compressor (PRONEB† Ultra, PARI GmbH, Starnberg, Germany). Before connecting the nebulizer to the simulator, the reservoir was filled with either 1 unit dose (3 mL) of levalbuterol inhalation solution (0.42 mg/mL levalbuterol base equivalent; Xopenex†, Sepracor† Inc., Marlborough, MA, "dilute solution") or 1 unit dose vial of 0.5 mL levalbuterol inhalation solution (2.5 mg/mL levalbuterol base equivalent; Xopenex†, Sepracor† Inc. diluted with the same volume of physiologically normal saline to make 1 mL of 1.25 mg/mL of levalbuterol solution, "concentrated solution"). The mouthpiece of the nebulizer was connected to the breathing simulator with a bacterial/viral filter (Figure 1) between the two components to collect the total mass of medication delivered.

Figure 1: Schematic of Collection Apparatus for Nebulized Levalbuterol Using Adult Breath Simulation Conditions



The filter was changed at one minute intervals, based on internal validation studies that confirmed overloading did not occur within this time interval, until 4 minutes past the point at which sputtering occurred or 20 minutes elapsed, whichever occurred first. Levalbuterol extracted from the filter was assayed by HPLC-UV spectrophotometry. Under the same ambient conditions the average fine droplet fraction < 4.7 µm diameter ($FDF_{<4.7\mu m}$) was determined by laser diffractometry (Spraytec, Malvern Instruments Ltd., UK) using the Lorenz-Mie optical model, with the refractive index of the droplets considered to be that of water (1.333)[8]. At minute intervals the mass of drug delivered as fine particles (FPD) was calculated as the product of total mass recovered from the filter and the mean $FDF_{<4.7\ \mu m}$. **Results:** $FDF_{<4.7\mu m}$ was 63 ± 3% (mean ± SD) for the diluted and concentrate drug solutions. Fine droplet delivery of levalbuterol from either 3 mL diluted or 1 mL concentrate levalbuterol solutions was a near linear function of time until the onset of sputtering (Figure 2), with calculated total fine particle delivery of 237 ± 28 µg in 20 minutes from 3 mL dilute solution and 102 ± 8 µg in the first 3 minutes from the 1 mL concentrated solution.

Figure 2: Calculated Fine Particle Mass of Levalbuterol Delivered by ***AeroEclipse**** ***II BAN**** Nebulizer with PARI PRONEB† Ultra Portable Compressor



Calculated fine particle delivery rates averaged 12.7 µg/min (range 11.9 - 14.3 µg/min) over the 20 minutes during delivery from the 3 mL dilute solution, and 36.3 µg/min (range 33.9 - 37.9 µg/min) for the first 3 minutes of delivery from the 1 mL concentrated solution. The difference in mean delivery rates was in direct proportion to the three-fold increase in levalbuterol concentration between the diluted and concentrated drug solutions. **Conclusions:** The ***AeroEclipse**** ***II BAN**** Nebulizer can enable two distinctly different treatment modalities to be used in conjunction with both available levalbuterol formulations. When used with the 3 mL dilute levalbuterol solution, it delivers approximately 240 µg of medication as fine droplets at a near constant rate over a 20 minute period. About 100 µg levalbuterol can be delivered as fine droplets in 3 minutes from the 1 mL concentrate solution. **References:** [1] Nebulizers: Principles And Performance. DR Hess. Respiratory Care 2000;45(6):609-622. [2] Device Selection And Outcomes Of Aerosol Therapy: Evidence-Based Guidelines. MB Dolovich, RC Ahrens, DR Hess, P Anderson, R Dhand, JL Rau, GC Smaldone, G Guyatt. CHEST 2005;127(1):335-371. [3] Optimizing Nebulisation Practice. A Kendrick, E Smith. Respiratory Medicine 1996;90(5):315-316. [4] The Future Of Nebulization. PW Barry. Respiratory Care 2003;47(12):1459-1470. [5] Expert Panel Report 3: Guidelines For The Diagnosis And Management Of Asthma. US Department of Health and Human Services. National Heart, Lung and Blood Institute 2007. an Services. [6] An *In Vitro* Study To Investigate The Use Of A Breath-Actuated, Small-Volume, Pneumatic Nebulizer For The Delivery Of Methacholine Chloride Bronchoprovocation Agent. JP Mitchell, MW Nagel, SL Bates, CC Doyle. Respiratory Care 2003;48(1):46-51. [7] Effect Of Nebulizer Design On Fine Particle Mass. D Hess, JP Mitchell, D Coppolo, MW Nagel, AD Archer, R Blacker. Respiratory Care 1999;44:1289. [8] Particle Size Analysis – Laser Diffraction Methods. International Standards Organization, Geneva, Switzerland ISO 13320-1:1999.

LEVALBUTEROL 1 ML (0.42 MG) Q8H DOSING USING THE *AEROECLIPSE® BREATH-ACTUATED NEBULIZER IN A COPD INPATIENT POPULATION.** RS Pikarsky, RA Acevedo, T Farrell, W Fascia. CHEST 2006;130(4):182S.

Purpose: In order to maximize therapist time, an auto-conversion from levalbuterol (Lev) 1.5 mL (0.63 mg) Q8h to Lev 1 mL (0.42 mg) Q8h using the ***AeroEclipse**** ***BAN**** Nebulizer in a predominantly COPD inpatient population was evaluated. **Methods:** All patients with orders for Lev assessed by respiratory therapists with the ability to perform aerosol treatments by mouthpiece were converted to 1 mL Lev using the ***BAN**** Nebulizer. Lev was poured from a standard 3 mL unit dose vial to the 1 mL line in the ***BAN**** Nebulizer and administered. All protocol treatments, including breakthrough treatments, delivered during the two month pilot were recorded. The breakthrough data for racemic albuterol (Alb) Q4h and Lev 0.63 mg Q8h was from our previous studies. **Results: Clinical:** Lev 1 mL (0.42 mg) Q8h had similar daily breakthrough rates per 100 treatments as did Lev 1.5 mL (0.63 mg) Q8h and significantly lower breakthroughs rates than Alb 2.5 mg Q4h (6.0, 4.9, 13.7 respectively, both compared to Alb $p < 0.05$). **Economic:** Time to deliver 1 mL by ***BAN**** Nebulizer was 2.67 minutes as compared with 8.33 minutes using a standard small volume nebulizer (SVN). The time saved per treatment multiplied by the number of treatments and the hourly therapist cost annualized to a personnel cost savings of $54,693. The increased cost of ***BAN**** Nebulizer vs. SVN annualized to $10,851. Net savings $43,842 per year. Pharmacy costs did not change. **Conclusion:** The conversion from 1.5 mL (0.63 mg) to 1 mL (0.42 mg) Lev using the ***BAN**** Nebulizer had similar clinical performance in breakthrough requirements. The savings in personnel cost more than offset the increase in device cost. Lev 1 mL delivered by the ***BAN**** Nebulizer is a very cost effective delivery method. Smaller doses in the ***BAN**** Nebulizer lead to shorter administration times. **Clinical Implications:** When utilizing the ***BAN**** Nebulizer, the 1 mL Lev dose showed similar clinical efficacy and economic advantages when compared to our prior use of the 1.5 mL Lev dose, Alb, and a standard SVN.

BREAKTHROUGH TREATMENTS RATES DURING A CONVERSION TO LEVALBUTEROL, TIOTROPIUM AND BREATH ACTUATED NEBULIZERS. RS Pikarsky, RA Acevedo, T Farrell, W Fascia. CHEST 2005;128(4):259S.

Purpose: In order to maximize therapist time, an auto-conversion to levalbuterol (Lev) Q8h, Tiotropium (Tio) QD and ***AeroEclipse**** ***BAN**** Nebulizer usage in mouthpiece (MP) mode was evaluated. **Methods:** All patients assessed by Respiratory Therapists with the ability to perform aerosol treatments by mouthpiece were converted to Lev 0.63 mg Q8h by ***BAN**** Nebulizer MP. If ordered, ipratropium (Ipra) 0.5 mg was converted to Tio 18 mcg QD. If unable to perform the MP treatment patients were converted to Lev 1.25 mg Q8h delivered by mask. If ordered, Ipra 0.5 mg was converted to Ipra 0.25 mg Q8h. All protocol treatments, including breakthrough treatments delivered between 10/04 and 4/05 were recorded. Treatment refusals and omitted treatments were recorded. The breakthrough data for racemic albuterol (Alb) was from our previous studies. **Results:** The table shows the number of treatments (tx), the number of prn breakthrough treatments and the per treatment and daily rates of breakthroughs per 100 treatments. Lev 0.63 mg Q8h MP had significantly lower breakthroughs rates than the Alb 2.5 mg Q4h, both in per treatment and daily rates ($p < 0.05$). Alb/Ipra Q4h had significantly lower per treatment rates when compared with Lev/Tio Q8h and Lev/Ipra Q8h

($p < 0.01$); the daily breakthrough rates were not significantly different. Omitted treatments decreased from 2.28% to 1.95%. Patients refused 3.81% of scheduled treatments. **Conclusion:** The conversion from Alb Q4h to Lev Q8h allowed for a decreased frequency of daily medication administrations and a decrease in breakthrough requirements. Ipratropium showed a significant benefit in breakthrough reduction for the Alb group. Lev 0.63 mg MP performed as well as Lev 1.25 mg via mask. **Clinical Implications:** The efficiencies gained by decreasing the daily frequency of aerosol administration can have a significant impact on resource utilization. The conversion to Lev allows for decreased respiratory therapy time or the reallocating of workforce needs while maintaining, or improving, quality of aerosol administration, as evidenced by the decrease in breakthrough requirements. Smaller doses in the ***BAN**** Nebulizer lead to shorter administration times.

SAFETY AND EFFICACY OF FIVE MINUTE TIMED AEROSOL ADMINISTRATION WITH THE *AEROECLIPSE BREATH ACTUATED NEBULIZER: COMPARISON OF LEVALBUTEROL WITH RACEMIC ALBUTEROL.** RS Pikarsky, R Acevedo, C Roman, W Fascia, T Farrell. Respiratory Care 2002;47(9):1075.

Purpose: Beta-2 agonist racemic albuterol has been used extensively in the performance of pre and post bronchodilator studies in the pulmonary function laboratory. This study evaluated the safety and efficacy of timed nebulization of the two dosages of levalbuterol (Sepracor† Inc., Marlborough, MA) as compared to racemic albuterol (Dey, Napa, CA) with the use of the ***AeroEclipse**** ***BAN**** Nebulizer (Monaghan Medical Corporation, Plattsburgh, NY). **Methods:** A consecutive, nonrandomized, mostly COPD population ($n = 93$) receiving pre and post bronchodilator testing in our pulmonary function lab were studied. Two different levalbuterol medication dosages were administered: 0.63 mg levalbuterol UD or 1.25 mg UD levalbuterol. The racemic albuterol dosage was 2.5 mg UD. All 5 minute timed aerosol treatments were administered using the ***BAN**** Nebulizer with an oxygen flow rate of 8 L/min. The Sensormedics Vmax 22 Pulmonary Function System was utilized to measure both FEV_1 and PEFR. A standardized subjective questionnaire to determine side effects was completed. **Results:** The table shows the levalbuterol and racemic albuterol dosages, mean % change of FEV_1 and PEFR from pre-treatment to 10 minute post treatment, administration time, tremulousness and increase in heart rate. There was no significant difference in % change in FEV_1 or PEFR. There was a significant increase in heart rate with the 1.25 mg levalbuterol UD group (7.2 vs. 3.4, $p < 0.05$*; 7.2 vs. 2.2, $p < 0.01$**). There was no difference in respiratory rate, tremulousness, or nausea.

Nebulizer (*n*)	Dose	% Change FEV_1	% Change PEFR	Time (minutes)	Trem.	HR (Inc.)
Levalbuterol (38)	0.63 mg UD	7.8	6.2	5	4	3.4*
Levalbuterol (29)	1.25 mg UD	7.7	16.6	5	2	7.2
Racemic Albuterol (26)	2.25 mg UD	12.2	10.5	5	0	2.2**

Conclusion: Five minute timed administration of levalbuterol and racemic albuterol using the ***BAN**** Nebulizer was equally efficacious and had similar safety profiles. The change in FEV_1 and PEFR are consistent with our mostly COPD population. The increase in heart rate was greatest with the levalbuterol 1.25 mg dosage. **Clinical Implications:** Five minute timed administration of levalbuterol and racemic albuterol using the ***BAN**** Nebulizer is a safe and efficient alternative to the use of small volume nebulizers. Additional caution should be taken when administering levalbuterol at the 1.25 mg dosage utilizing the ***BAN**** Nebulizer in cardiac patients. The efficiency of timed aerosol administration could have significant impact on resource utilization while maintaining the quality of aerosol delivery. This may be one of several strategies to address the problems of respiratory care staff shortages or high seasonal effect in the acute care facility.

COMPARISON IN RATES OF BREAKTHROUGH TREATMENTS DURING A CONVERSION FROM RACEMIC ALBUTEROL TO LEVALBUTEROL. RS Pikarsky, RA Acevedo, C Roman. CHEST 2002;122(4):146S.

Purpose: In order to meet our patient care demands, Crouse Hospital approved an automatic conversion from racemic albuterol to levalbuterol. This study compares the breakthrough rates of racemic albuterol and levalbuterol, with and without ipratropium. **Methods:** Racemic albuterol (Alb) 2.5 mg Q4h was converted to either levalbuterol (Lev) 0.63 mg Q6h or levalbuterol 1.25 mg Q8h. If ordered, ipratropium (Ipra) 0.5 mg was administered at the same frequency as the levalbuterol. Patients with acute coronary syndromes, need for cardiac monitoring, or requiring more frequent aerosol administration received the lower levalbuterol dose Q6h. A majority of aerosol therapy was provided with the use of the ***AeroEclipse**** ***II BAN**** Nebulizer. All aerosol treatments, including breakthrough treatments, delivered between July 1, 2001 and February 28, 2002 were recorded. **Results:** Tx/Pt/day represents the number of treatments delivered per patient per day. Rate/100 Pt/days = (Breakthrough) / (Total Tx / Tx/Pt/day) x 100. Rate/100 Pt/days corrects for the differences in daily administration frequency, and may better reflect the daily impact of the breakthrough rate. The breakthrough rate of the combined albuterol group was significantly greater than both levalbuterol groups (5.29 vs. 2.29, 5.29 vs. 2.43, $p < 0.001$)*. The breakthrough rate with albuterol was significantly reduced with the addition of ipratropium ($p < 0.001$)**. Ipratropium did not significantly change the breakthrough rate when added to levalbuterol groups.

Medication	Total Tx	Breakthrough	Rate/1,000	Tx/Pt/day	Rate/100 Pt/day	
Alb Q4h	3,832	47	12.27	6	7.36**	5.29*
Alb/Ipra Q4h	3,767	20	5.31	6	3.19**	
Lev 0.63 mg Q6h	3,592	24	6.68	4	2.67	2.29*
Lev 0.63 mg/Ipra Q6h	1,821	7	3.84	4	1.54	
Lev 1.25 mg Q8h	1,791	17	9.49	3	2.85	2.43*
Lev 1.25 mg/Ipra Q8h	678	3	4.42	3	1.33	

Conclusions: The conversion from racemic albuterol to levalbuterol allowed for a decreased frequency of daily medication administrations and a significant decrease in breakthrough requirements. Ipratropium showed a significant benefit in breakthrough reduction for the racemic albuterol group. **Clinical Implications:** The efficiencies gained by decreasing the daily frequency of aerosol administration can have a significant impact on resource utilization. The conversion to levalbuterol allows for decreased respiratory

therapy time or the reallocating of workforce needs while maintaining, or improving, quality of aerosol administration, as evidenced by the decrease in breakthrough requirements.

IMPROVING RESOURCE UTILIZATION WITH NEW TECHNOLOGIES. MA Lewis, SS Harris, SL Campbell, AL Hodges, DM Clark. Respiratory Care 2000;45(8):981.

Background: To meet patient care needs during the peak respiratory season using levalbuterol (LEV) (Sepracor† Inc., Marlboro, MA) and ***AeroEclipse**** ***BAN**** Nebulizer (Monaghan Medical Corporation, Plattsburgh, NY). Both pilot projects were approved by the respiratory care advisory committee. **Methods:** LEV 1.25 mg delivered via nebulization Q6h was substituted for albuterol 2.5 mg ordered Q4h in October 1999. Patients could also receive LEV as needed. A standardized subjective questionnaire to determine side effects of LEV was completed. ***BAN**** Nebulizers were utilized on patients meeting specified criteria during November 1999. Standard nebulizers were used for all other patients who required nebulized treatments. Treatment times were extracted from the CliniVision Information Management System database. **Results:** LEV was substituted for albuterol in 25 patients. Indications for nebulizer therapy included asthma (8%), COPD (32%), community acquired pneumonia (20%), and other (40%). The average number of LEV treatments per day was 3.7. This compared favorably to albuterol, which historically required = 6 treatments per day. No patients requested breakthrough treatments or noted side effects due to LEV. A total of 298 treatments were delivered using ***BAN**** Nebulizers versus 322 delivered using a standard nebulizer. The average time per treatment using ***BAN**** Nebulizers was 9.9 minutes versus 14.76 minutes with the standard nebulizer. The results of these pilot programs prompted changes in respiratory therapy practice throughout the hospital. LEV was added to the patient driven protocols and ***BAN**** Nebulizers are now used for nebulizer treatments in patients meeting criteria. Hospital census data indicate a 13.5% increase for 2000 versus 1999. Thus, total treatments for January and February 1999 and 2000 were 30,089 and 32,923 respectively. During this period 16,000 LEV vials were dispensed from an automated dispensing unit vs. 8,900 vials of albuterol. Concurrently, overtime (OT) hours utilized in 2000 were decreased by 693 hours, resulting in a savings of $16,632, despite the increased number of treatments. Therefore, treatments were delivered to more patients with less OT utilized in 2000. **Conclusions:** These data illustrate the cost effectiveness of two technologies utilized in our hospital, while patient care and satisfaction were maintained. OT hours decreased by 25% while treatments were delivered to more patients throughout the hospital. The use of LEV has resulted in a 33% decrease in the number of treatments per day with few “prn” treatments, while ***BAN**** Nebulizer has decreased the time to deliver therapy by 33%.

Liposome-Encapsulated Fentanyl (AeroLEF†, YM BioSciences Inc.)

A RANDOMIZED CONTROLLED TRIAL DEMONSTRATES THE EFFICACY, SAFETY AND TOLERABILITY OF AEROSOLIZED FREE AND LIPOSOME-ENCAPSULATED FENTANYL (AEROLEF†) VIA PULMONARY ADMINISTRATION. R Brull, V Chan. Journal of Pain 2008;9(4):42.

Pain following orthopedic surgery can be severe, requiring rapid onset and prolonged analgesia. The ideal analgesic has rapid onset of action, sustained effect, self-titratable dosing and minimal adverse effects (AEs). Inhalation of opioids is conceptually appealing as the alveolar surface permits rapid absorption. We report a prospective randomized, blinded, placebo controlled study of AeroLEF† administered via breath actuated nebulizer. Ninety-nine ASA PS I-II patients aged 18 - 81 years undergoing elective orthopedic surgery under GA were randomized to AeroLEF† or placebo (2:1 stratification). Nebulizers contained 1,500 µg AeroLEF† (≤ 1,000 µg available for nebulization) or placebo; during each treatment session, a second nebulizer was provided if requested. Treatment was initiated when patients reported ≥ moderate pain. Up to three treatment sessions were permitted over 8 - 12 hours. Rescue medication was IV morphine. The primary efficacy endpoint, SPRID4, was better with AeroLEF† (mean scores of 7.02 vs. 3.35, $p < 0.02$). There was no difference between groups in clinically significant respiratory depression (< 8 breaths/minute or SpO_2 < 90% for > 20 sec). No patient received opioid antagonists or ventilatory support. Nausea (11% vs. 3%) and vomiting (31% vs. 21%) were more common with AeroLEF† than with placebo. Following the first dose of study drug, more patients given AeroLEF† reported mild or no pain (59% vs. 27%; $p < 0.01$). Time to effective pain relief after the first dose of study drug was shorter with AeroLEF† group ($p < 0.005$). More patients given AeroLEF† reported moderate to complete pain relief (60% vs. 32%, $p < 0.02$). This study suggests that patient controlled inhalational analgesia with free and liposome encapsulated fentanyl can provide safe and effective pain relief following orthopedic surgery. Industry support provided by YM BioSciences Inc.

AEROSOLIZED LIPOSOME-ENCAPSULATED FENTANYL (AEROLEF†) VIA PULMONARY ADMINISTRATION ALLOWS PATIENTS WITH MODERATE TO SEVERE POST-SURGICAL ACUTE PAIN TO SELF-TITRATE TO EFFECTIVE ANALGESIA. A Clark, M Rossiter-Rooney, F Valle-Leutri. Journal of Pain 2008;9(4):42.

Acute pain is characterized by rapid onset, unpredictable and variable intensity confounded by highly variable patient responses to analgesics. Consequently, a successful dose is difficult to predict and maintain. AeroLEF†, a proprietary combination of free and liposome encapsulated fentanyl for inhalation provides microdoses of fentanyl per breath designed to allow real time patient controlled dose selection. In this study, nineteen post-surgical patients with moderate to severe pain following ACL surgery, were instructed to self-administer AeroLEF† via breath actuated nebulizer until they had achieved analgesia, experienced dose limiting side effects, or completed the maximum available dose (1,000 µg emitted per nebulizer, ≤ 2 nebulizers allowed). Eighteen (95%) of the patients achieved analgesia following self-administration of AeroLEF†. The median time to first perceptible analgesia was 2.7 minutes. Mean plasma fentanyl concentration at first perceptible analgesia was 0.801 $ng.mL^{-1}$. Median time to effective analgesia was 17 minutes. At analgesia, the mean plasma fentanyl level was 1.30 $ng.mL^{-1}$ but varied widely among patients, covering a 6.5-fold concentration range (0.39 to 2.5 $ng.mL^{-1}$) The mean duration of analgesia was 3.7 hours and the request for additional analgesics was associated with a decrease in mean plasma fentanyl levels to 0.887 $ng.mL^{-1}$ (ranging from 0.36 $ngmL^{-1}$ to 1.584 $ngmL^{-1}$), comparable to the concentrations at first perceptible analgesia and consistent with reported ranges for minimal effective plasma fentanyl in post surgical patients (0.34 to 1.58 $ng.mL^{-1}$). A 9-fold dosing range was selected by patients in order to obtain analgesia with AeroLEF†, emphasizing the inter-patient variability associated with opioid use. AeroLEF†, at doses sufficient to establish analgesia, was well tolerated with no serious adverse events were reported. Adverse events were generally mild and commonly

associated with opioid use in the post operative period. These data suggest that self-titration to analgesia with AeroLEF† offers a novel and effective approach to address the variability inherent in pain. Industry support provided by YM BioSciences Inc.

COMPARATIVE PHASE I PK STUDY OF AEROSOLIZED FREE AND LIPOSOME-ENCAPSULATED FENTANYL (AEROLEF†) DEMONSTRATES RAPID AND EXTENDED PLASMA FENTANYL CONCENTRATIONS FOLLOWING INHALATION. O Hung, D Pliura. Journal of Pain 2008;9(4):36.

AeroLEF† is a proprietary combination of free and liposome encapsulated fentanyl for inhalation via breath actuated nebulizers. We report the pharmacokinetics, safety, and tolerability of 1,500 µg AeroLEF† vs. 200 µg bolus IV fentanyl; values are mean (± SD). Healthy, opiate naïve volunteers inhaled microdoses of AeroLEF† (≤ 5 µg/breath; total emitted fentanyl dose ≤ 1,000 µg) over 7 - 15 minutes. Within 4 minutes of initiating AeroLEF† inhalation, subjects attained plasma fentanyl concentrations (Cp) of 0.734 ng.mL^{-1}. Maximum Cp was similar with AeroLEF† and IV fentanyl (2.53 vs. 2.80 ng.mL^{-1}). Cmax (mean of 15 minutes) occurred shortly after completion of AeroLEF† inhalation (mean of 12 minutes), indicating rapid absorption from the lung. Cp values in the effective range persisted for several hours with AeroLEF† (at 4 hours, Cp was 0.525 ± 0.180 ng.mL^{-1}) but not with IV administration (at 1 hour, Cp was 0.559 ± 0.209 ng.mL^{-1}). Similar inter-subject variability in exposure was observed in both treatment arms: coefficient in variation of AUC was 24% with IV administration vs. 29% with AeroLEF†. Subjects were monitored continuously for adverse respiratory events. No severe adverse events were observed. Mild hypoxia was observed in both treatment groups. Mild bradycardia was observed in one subject receiving IV fentanyl. Spirometry measurements (FVC, FEV_1 and $FEF_{25-75\%}$) before and after AeroLEF† indicated no significant changes in lung function. In summary, AeroLEF† achieves rapid and persistent fentanyl concentrations in the therapeutic range and appears to be well tolerated. Industry support provided by YM BioSciences Inc.

Measles Vaccine (Placebo)

THE DELIVERY OF PLACEBO MEASLES VACCINE BY A MECHANICALLY-OPERATED BREATH-ACTUATED NEBULIZER. J Malpass, JP Mitchell, MW Nagel. European Respiratory Journal 2006;28(S50):2647.

Nebulizer delivered vaccination offers the potential for the mass immunization of children. We report the outcome of a study in which the delivery of a placebo measles vaccine by a novel breath actuated nebulizer (***AeroEclipse***** **BAN**** Nebulizer, Trudell Medical International, London, ON, Canada) was evaluated in comparison with a continuously operating jet nebulizer (AeroMist†, IPI Medical Products Inc., Chicago, IL, USA), used successfully to deliver aerosol in the so-called Classic Mexican Device (CMD) in previous World Health Organization (WHO) sponsored studies. Each nebulizer (n = 5 devices/group) was operated by portable compressor (PulmoMate†, DeVilbiss† Corp.), with a 3 mL fill of reconstituted placebo vaccine in sterile water. The emitted droplets were drawn at 30 L/min ± 5% through an electret filter located at the distal end of either a 15 cm length of corrugated tubing forming the outlet of the CMD, or a 5 cm tube with inhalation valve attached to the ***BAN**** Nebulizer. Mass output rate was quantified gravimetrically, and a laser diffractometer was used to determine droplet size distributions. The aerosol produced by the ***BAN**** Nebulizer (mass median diameter (MMD) = 4.3 ± 0.23 µm) was finer than that emitted by the CMD (MMD = 5.9 ± 0.16 µm) (unpaired t-test, $p < 0.01$), and the mass output rate of the ***BAN**** Nebulizer (0.40 ± 0.01 mL/min) significantly exceeded that from the CMD (0.15 ± 0.03 mL/min) ($p < 0.001$). The ***BAN**** Nebulizer is dosimetric, so that an estimated mass output/breath close to that from the CMD can be anticipated when used by a tidally breathing patient with duty cycle of 33%. Furthermore, the breath actuation feature avoids the risk of exposing the health care giver to medication when the patient is not inhaling.

Metaproterenol Sulphate (Alupent†, Boehringer Ingelheim†)

PERFORMANCE OF A NEW AIR ENTRAINMENT SMALL VOLUME NEBULIZER (AE-SVN). A Archer, JP Mitchell, MW Nagel, AMW Verdun. European Respiratory Journal 1998;12(28):68s.

We report an *in vitro* investigation in which the performance of a new disposable AE-SVN (n = 3 devices) has been assessed with salbutamol sulphate (Ventolin†: 5 µg/2.5 mL, GlaxoSmithKline† Inc.), metaproterenol sulphate (Alupent†: 10 µg/2.5 mL, Boehringer Ingelheim† Pharmaceuticals Inc.) and cromolyn sodium (Intal†: 20 µg/2 mL, Fisons Pharmaceuticals) nebules. Each AE-SVN was filled with 2 nebules and operated continuously with oxygen supplied at 50 psig and 8 L/min. The AE-SVN was coupled directly to an Andersen cascade impactor, sampling at 28.3 L/min. Total and fine particle (< 4.7 µm aerodynamic diameter) delivery rates were 33.5 ± 1.8 µg/s and 27.6 ± 1.3 µg/s (Ventolin†); 54.2 ± 10.6 µg/s and 45.0 ± 7.8 µg/s (Alupent†); 138.6 ± 10.2 µg/s and 109.7 ± 8.3 µg/s (Intal†) over a 10 second period following the start of nebulization. The mass median aerodynamic diameter (MMAD) and mass % contained in fine droplets were 3.0 ± 0.1 µm and 82.4 ± 1.2% (Ventolin†); 2.9 ± 0.2 µm and 83.3 ± 2.6% (Alupent†); 3.1 ± 0.1 µm and 79.2 ± 1.9% (Intal†). This new nebulizer appears to perform well with all three formulations.

Methacholine Chloride

A PRACTICAL GUIDE FOR INTERPRETATION OF ERS GUIDELINES FOR METHACHOLINE CHALLENGE TEST. J Suggett, M Nagel. European Respiratory Journal 2018;52(62):5484.

Rationale: A new ERS standard was published in 2017 providing guidance on how to perform the MCT, incorporating a change from evaluating the provocation concentration to the provocation dose (PD_{20}). The standard includes significant useful detail and considerations regarding how one might undertake the MCT, with numerous appendices providing additional detail. The purpose of this abstract was to identify a small number of steps within the MCT process and provide a practical example of how the test could then be performed. **Methods:** The ERS standard/appendices was reviewed and the MCT process was broken down into the following discrete steps: a) preparation of methacholine solutions, b) calculation of doses at each concentration c) performance of actual

challenge test, d) determination of PD_{20} and e) assessment of airway hyperresponsiveness (AHR). Each step was then expanded with supporting information. **Results:** Using independently referenced (within the ERS standard) validation data from a breath actuated device (***AeroEclipse*** **BAN****** Nebulizer) and 1 minute tidal breathing, it was possible to expand upon the five identified steps in order to provide example methacholine concentrations, dilutions and associated delivered doses. This then enabled an example test protocol to be formulated with the subsequent determination of PD_{20} and interpretation in terms of AHR. **Conclusions:** A five step guide to the 2017 ERS standard has been developed. This could either be used directly with the example nebulizer, or modified with alternative delivery systems once such systems have validated methacholine delivery data available.

THE METHACHOLINE CHALLENGE TEST FOR REVERSIBLE AIRWAYS DISEASE ASSESSMENT: A PRACTICAL GUIDE ON HOW TO INTERPRET NEW 2017 ERS GUIDELINES. JA Suggett, MW Nagel, JP Mitchell. Drug Delivery to the Lungs-28 2017:270-273.

Summary: The assessment through a challenge test of severity of reversible bronchoconstrictive disease, such as asthma, is an important part of the diagnosis process as well as defining treatment therapy. Methacholine is frequently used as the inhaled challenge substance and is given by inhalation via a nebulizer for a fixed exposure time to the methacholine concentration. The challenge test involves progressively increasing the concentration of methacholine and measuring the forced expiratory volume in 1 second (FEV_1) after exposure at each concentration level. The test is terminated after the first instance at which FEV_1 decreases by more than 20% from the pre-test reference value. New recommendations from the European Respiratory Society (ERS) have recommended basing the result upon the delivered dose (µg) of methacholine causing a 20% fall in FEV_1, termed the provocative dose (PD_{20}), rather than the former metric of methacholine concentration (mg/mL), causing the same fall in FEV_1 (PC_{20}). Given the detail and complexity of the recent guidance, we follow a stepwise approach to explain each stage of the new bronchial challenge test, then illustrate how PD_{20} is calculated and used to interpret the degree of airway hyperresponsiveness. Although any nebulizer with validated methacholine delivery data could be used to deliver the agent, we illustrate how to apply the methodology, based on the same breath actuated device (***AeroEclipse*** **II BAN****** Nebulizer) as was used, through references, in the new guidance. **Introduction:** The assessment through a challenge test of severity of reversible bronchoconstrictive disease, such as asthma, is an important part of the diagnosis process as well as defining treatment therapy[1]. Methacholine is frequently used as the inhaled challenge substance, because the onset of symptoms upon inhalation of an appropriate concentration is rapid, and spontaneous recovery post methacholine testing usually occurs within 45 - 60 minutes[2]. In practice, however, patients are usually given a bronchodilator at the end of testing to relieve challenge induced bronchoconstriction more rapidly[2]. The bronchial challenge agent is given by inhalation via a nebulizer for a fixed exposure time to the concentration of methacholine. The provocation test involves progressively doubling the concentration of methacholine and measuring the forced expiratory volume in 1 second (FEV_1) after exposure at each concentration level. The test is terminated after the first instance at which FEV_1 decreases by more than 20% from the pre-test reference value. New recommendations from an international European Respiratory Society task force have been published this year[3]. This technical standard, also endorsed by the American Thoracic Society, recommends basing the result of the bronchial challenge upon the delivered dose (mass expressed in µg) of methacholine causing a 20% fall in forced expiratory volume in 1 second (FEV_1). This is termed the provocative dose (PD_{20}), and replaces the former definition based on the provocative concentration of challenge agent resulting in a 20% reduction in FEV_1 (PC_{20}). This new end point allows comparable results from either different aerosol delivery devices or protocols. Hence, the standard notes that any suitable nebuliser or dosimeter may be used, so long as the delivery characteristics are known[3]. It is recognized however that the change in approach to assess PD_{20} rather than PC_{20} has the potential to cause some confusion in how to execute the protocol in a practical manner. The purpose of the present interpretation is therefore to provide a simplified explanation with a practical, stepwise, example of how the test can be performed to meet the new standard. **Bronchial Challenge Testing – Drug Delivery System:** The new standard allows for 'any suitable nebulizer or dosimeter' but does require characterization of the device output and particle size to be demonstrated. The example provided in this abstract uses data from the breath actuated device (***AeroEclipse*** **II BAN****** Nebulizer, Trudell Medical International, London, ON, Canada) that is specifically referenced in the new 2017 standard, using independently reported tidal breathing data (both *in vitro* and *in vivo*). Such a breath actuated device, that only delivers the medication when the patient inhales, has the additional benefit of affording minimal exposure of health care personnel to fugitive emissions[4], although a filter can be placed on the expiratory limb to eliminate such exposure altogether[3]. At least two independent clinical studies have recommended using this breath actuated nebulizer for methacholine challenge testing[4,5]. **How To Perform The Challenge Test – Example calculation of PD_{20}: 1) Prepare the methacholine solutions for challenge test** The dilutions of methacholine concentrate can be prepared in the same way as with the previous 1999 guidance, prior to performing the challenge test and measurements of FEV_1. Table 1 shows an example of a schedule, based on the guidance in the new ERS document[3].

Table 1: Methacholine Concentrate Dilution Schedule in Which the Challenge Agent Concentration is Increased Four-Fold for Each Exposure

Label Mass of Concentrate (mg)	Start with:	Normal Saline Added to Effect Dilution (mL)	Obtain Diluted Concentration (CMC) (mg/mL)	Code Letter to Provide Order of Dilution (see second column)
100	100 mg	+ 6.25	16.0	A
	3 mL of A	+ 9.0	4.0	B
	3 mL of B	+ 9.0	1.0	C
	3 mL of C	+ 9.0	0.25	D
	3 mL of D	+ 9.0	0.0625	E
	3 mL of E	+ 9.0	0.015625	F

2) Calculate the delivered doses at different methacholine concentrations In order to establish the delivered dose to the lungs (DD_{MC}) during a defined delivery duration, several key parameters regarding the nebulizer's output characteristics need to be known. For example, Appendix D of the new ERS standard[3] provides the following information for the ***BAN****** Nebulizer:

- For 20 seconds of tidal breathing, the delivery rate (R_{MC}) of methacholine at the mouthpiece of the high output device (***BAN**** Nebulizer) is 2.70 mg/min for a solution concentration (C_{MC}) of 16 mg/mL when operated from a 50 psi dry gas source.
- The fine droplet fraction (FDF), defined as those droplets less than 5 µm aerodynamic diameter, is reported from *in vitro* measurements of ***BAN**** Nebulizer emitted droplets made by laser diffractometry as being 0.76[3].

Hence the DD_{MC} for t(s) can be calculated as $DD_{MC} = R_{MC}$ x FDF x (t/60), and in the example provided for 20 seconds with the 16mg/mL concentration, DD_{MC} would therefore be: 2.70 mg/min X 0.76 X 20/60 = 680 µg. This can further be generalized for any MC concentration using 20 seconds tidal breathing with the ***BAN**** Nebulizer as: $DD_{MC} = [C_{MC}/16$ mg/mL] X 680 µg. **3) Perform the bronchial challenge test** Once the calculations of DD_{MC} are completed for all the concentrations prepared as part of the test phase in Table 1, the measurement of FEV_1 can be conducted at increasing concentrations. Table 2 is an example of a bronchial challenge report taken from Appendix F of the ERS standard[3]. The DD_{MC} values in this case are based upon a 1 minute tidal breathing test duration as recommended in the standard. The test begins with a 'Pre-Challenge' to confirm that the patient can perform acceptable and repeatable spirometry, and ensure they have sufficient airflow at baseline. Increasing amounts of DD_{MC} are delivered until such time as FEV_1 has fallen > 20% from the reference (baseline) condition. In this particular example, in Table 2, the test was terminated after exposure to 127 µg (D_2) and the dose at the second to last exposure D_1 is 31.8 µg.

Table 2: Example Bronchial Challenge Report

Time of Exposure	Test Phase	DD_{MC} (µg) (1 minute tidal breathing)	FEV_1 (L)	FEV_1 (% of reference)	Change in FEV_1 (% pre-challenge value)
T_0	Pre-challenge	N/A	3.10	N/A	N/A
T_0 + 10 minutes	Post diluent (reference condition)	N/A	3.00	100	N/A
T_0 + 15 minutes	0.015625 mg/mL	1.9	3.05	102	-2
T_0 + 20 minutes	0.0625 mg/mL	7.65	2.94	98	2
T_0 + 25 minutes	0.25 mg/mL	31.8	2.62	87	13
T_0 + 30 minutes	1.0 mg/mL	127	2.16	72	28
T_0 + 45 minutes	After bronchodilator administration	N/A	3.20	107	-7

4) Determination of PD_{20} The PD_{20} calculation is shown below and is illustrated using the example data from Table 2 where R_1 and R_2 are the percentage decreases in FEV_1 for D_1 and D_2, respectively.

$$PD_{20} = antilog\left\{\log D_1 + \frac{(\log D_2 - \log D_1)(20 - R_1)}{(R_2 - R_1}\right\}$$

$$PD_{20} = antilog\left\{3.46 + \frac{(4.84 - 3.46)(20 - 13)}{(28 - 13}\right\}$$

Consequently, from this particular example above, the bronchial responsiveness (PD_{20}) is determined as 61 µg. **5) Assessment of airway hyperresponsiveness (AHR)** The PD_{20} value can then be used to interpret the degree of AHR using values from the ERS document[3] represented below in Table 3. Based on the given example, the patient would be considered to have mild AHR.

Table 3: Categorization of AHR to PD_{20} of Methacholine

PD_{20} (µg)	Interpretation
>400	Normal
100 - 400	Borderline AHR
25 - 100	Mild AHR
6 - 25	Moderate AHR
< 6	Marked AHR

Conclusions: The new ERS standard allows the use of a more appropriate PD_{20} endpoint to assess airway hyperresponsiveness. The methacholine challenge test procedure, calculation and interpretation have been described in an attempt to provide a meaningful practical demonstration of how the new guideline could be put into practice clinically. **References:** [1] Global Initiative for Asthma (GINA). Global Strategy For Asthma Management And Prevention. 2017 Update. [2] Interaction Of Inhaled Beta-2 Agonist And Inhaled Corticosteroid On Airway Responsiveness To Allergen And Methacholine. DW Cockcroft, VA Swystun, RG Bhagat. American Journal of Respiratory and Critical Care Medicine 1995;152:1485-1489. [3] Developing Alternative Delivery Systems For Methacholine Challenge Tests. AL Coates, K Leung, SD Dell. Journal of Aerosol Medicine and Pulmonary Drug Delivery 2014;27(1):66-70. [4] Provocative Dose Of Methacholine Causing A 20% Drop In FEV_1 Should Be Used To Interpret Methacholine Challenge Tests With Modern Nebulizers. SD Dole, SS Bola, RG Foty, LC Marshall, KA Nelligan, AL Coates. Annals of the American Thoracic Society 2015;12(3):357-363. [5] Comparison Of The Provocative Concentration Of Methacholine Causing A 20% Fall In FEV_1 Between The ***AeroEclipse**** II Breath-Actuated Nebulizer And The Wright Nebulizer In Adult Subjects With Asthma. AI El-Gammal, KJ Killian, TX Scime, S Beaudin, A Schlatman, DW Cockcroft, GM Gauvreau. Annals of the American Thoracic Society 2015;12(7):1039-1043.

ERS TECHNICAL STANDARD ON BRONCHIAL CHALLENGE TESTING: GENERAL CONSIDERATIONS AND PERFORMANCE OF METHACHOLINE CHALLENGE TESTS. AL Coates, J Wanger, DW Cockcroft, BH Culver, Bronchoprovocation Testing Task Force: K-H Carlsen, Z Diamant, G Gauvreau, GL Hall, TS Hallstrand, I Horvath, FHC de Jongh, G Joos, DA Kaminsky, BL. Laube, JD Leuppi, PJ Sterk. European Respiratory Journal 2017;49:1601526.

Abstract: This international task force report updates general considerations for bronchial challenge testing and the performance of the methacholine challenge test. There are notable changes from prior recommendations in order to accommodate newer delivery devices. Rather than basing the test result upon a methacholine concentration (provocative concentration (PC_{20}) causing a 20% fall in forced expiratory volume in 1 second (FEV_1)), the new recommendations base the result upon the delivered dose of methacholine causing a 20% fall in FEV_1 (provocative dose (PD_{20})). This end point allows comparable results from different devices or protocols, thus any suitable nebuliser or dosimeter may be used, so long as the delivery characteristics are known. Inhalation may be by tidal breathing using a breath actuated or continuous nebuliser for 1 minute (or more), or by a dosimeter with a suitable breath count. Tests requiring maximal inhalations to total lung capacity are not recommended because the bronchoprotective effect of a deep breath reduces the sensitivity of the test.

COMPARISON OF THE PROVOCATIVE CONCENTRATION OF METHACHOLINE CAUSING A 20% FALL IN FEV1 BETWEEN THE AEROECLIPSE II BREATH-ACTUATED NEBULIZER AND THE WRIGHT NEBULIZER IN ADULT SUBJECTS WITH ASTHMA. Al El-Gammal, KJ Killian, TX Scime, S Beaudin, A Schlatman, DW Cockcroft, GM Gauvreau. Annals of the American Thoracic Society 2015;12(7):1039-1043.

Rationale: The American Thoracic Society guidelines for methacholine testing for the diagnosis of asthma recommends the 2 minute tidal breathing protocol with the Wright† nebulizer, which produces more aerosol than required, generates a small particle size, and requires cleaning between tests. **Objectives:** To evaluate methacholine testing using a disposable, breath actuated ***AeroEclipse**** ***II BAN**** Nebulizer, which produces aerosol during inspiration and was developed for single patient use. **Methods:** Forty-six adult subjects with asthma (19 men), aged 27.3 (SD, 9.5) years, with FEV_1 98.5 (SD, 18.1) % predicted participated in a randomized, crossover, observational study. Subjects were first screened using the Wright† nebulizer, then assigned to 2 minutes of tidal breathing from the Wright† or 20 seconds of tidal breathing from the ***AeroEclipse**** ***II BAN**** Nebulizer on 2 separate days, in random order. Provocative concentration of methacholine causing a 20% fall in FEV_1 (PC_{20}) values were calculated by linear interpolation of log dose versus response curves, log transformed, and compared using paired Student t-test and Pearson correlation. **Measurements and Main Results:** The 38 subjects demonstrating reproducible PC_{20} measurements of within 1.5 doubling concentrations were included in the comparison. The geometric mean methacholine PC_{20} measured with the ***AeroEclipse**** ***II BAN**** Nebulizer was approximately 1 doubling concentration lower than the geometric mean methacholine PC_{20} of the Wright† nebulizer (*p*, 0.05). The Pearson correlation coefficient between the two nebulizers was 0.86 (*p*,0.05). **Conclusions:** The PC_{20} measurements using the two nebulizers were highly correlated; however, the PC_{20} determined with the ***AeroEclipse**** ***II BAN**** Nebulizer was significantly lower than those determined using the Wright† nebulizer. Clinical trial registered with www.clinicaltrials.gov (NCT 01919424).

PROVOCATIVE DOSE OF METHACHOLINE CAUSING A 20% DROP IN FEV_1 SHOULD BE USED TO INTERPRET METHACHOLINE CHALLENGE TESTS WITH MODERN NEBULIZERS. SD Dell, SS Bola, RG Foty, LC Marshall, KA Nelligan, AL Coates. Annals of the American Thoracic Society 2015;12(3):357-363.

Rational: The American Thoracic Society guidelines (1999) for methacholine challenge tests (MCTs) using the 2 minute tidal breathing protocol were developed for the now obsolete English Wright† (EW) nebulizer. In addition, the guideline recommendation to use the provocative concentration of methacholine causing a 20% drop in FEV_1 (PC_{20}) rather than the provocative dose of methacholine causing a 20% drop in FEV_1 (PD_{20}) for determining the level of bronchial hyperresponsiveness has been challenged. **Objectives:** To determine if cumulative dose or concentration of methacholine delivered to the airways is the determinant for airway responsiveness and to validate use of the ***AeroEclipse**** ***II BAN**** Nebulizer (Aero; Trudell Medical International, London, ON, Canada) compared with use of the reference standard EW nebulizer. **Methods:** Subjects with asthma (10 - 18 years old) participated in randomized, controlled crossover experiments comparing four MCT protocols using standard methacholine concentrations, but varying: (1) methacholine starting concentration (testing for cumulative effect); (2) nebulizer (EW versus Aero); and (3) inhalation time. PD_{20} was calculated using nebulizer output rate, inhalation time, and preceding doses delivered. ANOVA analyses were used to compare geometric means of PC_{20} and PD_{20} between protocols. **Results:** A total of 32 subjects (17 male) participated. PC_{20} differed when starting concentration varied (0.46 vs. 0.80 mg/mL; $p < 0.0001$), whereas PD_{20} did not (0.06 vs. 0.08 mg). PC_{20} differed with the EW versus the Aero nebulizer with 30 second inhalation (1.19 vs. 0.43 mg/mL; $p = 0.0006$) and the EW versus the Aero nebulizer with 20 second inhalation (1.91 vs. 0.89 mg/mL; $p = 0.0027$), whereas PD_{20} did not (0.07 vs. 0.06 mg and 0.11 vs. 0.09 mg, respectively). **Conclusions:** In MCTs, the cumulative dose (PD_{20}), not the PC_{20}, determines bronchial responsiveness. Modern nebulizers may be used for the test if clinical interpretation is based on PD_{20}.

30 SECONDS TIDAL BREATHING METHOD WITH *AEROECLIPSE* // NEBULIZER (AE) VERSUS AEROSOL PROVOCATION SYSTEM (APS) IN METHACHOLINE CHALLENGE TESTING. E Ruberg, I Steenbruggen, J Willem van den Berg. European Respiratory Journal 2014;44(S58):P1830.

Introduction: Methacholine challenge tests (MCT) are often used to rule out asthma. Recently it has been recommended that for a high-sensitive test the methacholine should be inhaled without deep inhalations. **Aim:** Our objective was to compare the methacholine PD_{20} performed with an AE, with the standard APS method. **Methods:** From November to December 2013, 100 patients (mean age 54 ± 17), 30 m, performed a MCT using a 30 second tidal breathing (TB) method with an AE. From November to December 2012, 100 patients (mean age 50 ± 16), 34 m, used a dosimeter method on APS. The nebulizers were calibrated and outputs were calculated to administer the same cumulative dose (2.27 mg). A maximum of 9 doubling concentrations of methacholine was used. FEV_1 was measured by spirometry after each dose. The PD_{20} is a calculated value of the dosage of methacholine required

to cause a 20% fall in the subject's FEV_1. The number of patients with a positive tests (PD_{20} < 2.0) was compared between the two groups. **Results:** In the 30 second TB group we found positive tests in 65% (mean PD_{20} 0.360 mg) whereas only 40% in the group of APS (mean PD_{20} 0.673 mg) had a positive test. This difference of 25% between the two groups was statistically significant (p = 0.0004, chi square test). **Conclusion:** This study found a clinically relevant and statistically significant difference in outcome of the number of positive MCT between the 30 second TB group using AE and the group using APS method. The APS method resulted in higher PD_{20} values, possibly due to a bronchodilator effect from the deep inhalations. The 30 second TB resulted in lower PD_{20} values and appears to be a more sensitive test.

DEVELOPING ALTERNATIVE DELIVERY SYSTEMS FOR METHACHOLINE CHALLENGE TESTS. AL Coates, K Leung, SD Dell. Journal of Aerosol Medicine and Pulmonary Drug Delivery 2014;27(1):66-70.

Background: The two American Thoracic Society recommended aerosol delivery devices for methacholine challenge testing are both obsolete and often very difficult to acquire, leading to the test being done with a number of non-standardized nebulizers. Of the two recommended devices, one is the English Wright† nebulizer used in the 2 minute tidal breathing method, and the other is the DeVilbiss† 646 nebulizer used in the five breath dosimeter method. The purpose of this study was to evaluate the *in vitro* performance of potential alternative devices that would be economically viable and would minimize environmental contamination. One device was the disposable breath actuated ***AeroEclipse** *II BAN**** Nebulizer as a potential delivery system for the 2 minute tidal breathing, and the second was the automated system by VIASYS as an alternative to either the 2 minute tidal breathing or the five breath dosimeter method. **Methods:** A breath simulator mimicked an adult or small child breathing pattern, and a slow inhalation for the five breath method was generated by a spirometry calibration syringe. Methacholine (Provocholine†) was eluted from filters at the "mouth" and assayed by high pressure liquid chromatography. **Results:** In 12 seconds, the ***AeroEclipse** *II BAN**** Nebulizer would be expected to have a pulmonary deposition equivalent to the 2 minute tidal breathing with the English Wright, whereas the VIASYS system would take approximately 40 seconds for the equivalent delivery. The per breath delivery of the VIASYS and the DeVilbiss† 646 was approximately the same, whereas one breath from the ***AeroEclipse** *II BAN**** Nebulizer was the equivalent of five from the DeVilbiss† 646. **Conclusions:** These data will allow for planning *in vivo* studies to develop methacholine challenge protocols using modern aerosol delivery systems.

REPLACING THE ENGLISH WRIGHT† AND THE DEVILBISS† 646 NEBULIZERS FOR METHACHOLINE CHALLENGE TESTS (MCT). AL Coates, K Leung, S Dell. American Journal of Respiratory and Critical Care Medicine 2012;185:A5753.

Rationale: In the 2000 ATS standard for performing MCT two delivery systems were proposed: the English Wright† (EW) for two minutes of tidal breathing and the DeVilbiss† 646 (DeV) for the 5 breath dosimeter method. The former is obsolete and hard to acquire, and the latter has variable output and an elaborate calibration scheme is necessary for both. Hence, many other delivery systems have come into use without standardization. This study evaluated other potential delivery systems for the MCT. **Methods:** Devices compared were the breath actuated disposable ***AeroEclipse** *II BAN**** Nebulizer (AER) and the Viasys Aerosol Provocation System† which uses the Sidestream† MedicAid Pro nebulizer to simulate the EW system. The AER only produces aerosol during inspiration which significantly limits environmental contamination. The protocol for the Viasys device suggests that 19 breaths would be equivalent to the 2 minutes EW tidal breathing method. Rates of output for the EW and AER were measured using a breathing simulator (modified Harvard Animal Ventilator, Hollistan MA) (tidal volume 750 mL, respiratory rate 15 and inspiratory time 1.6 seconds) and particle size distribution was measured by laser diffraction allowing the calculation of estimated pulmonary deposition of methacholine during *in vivo* two minute tidal breathing MCT. For the dosimeter method, an inhalation was simulated with a tidal volume of 3L over a 2 second duration, using a spirometry calibration syringe. A pulse of 0.6 seconds activated the DeV. In all cases, methacholine was eluted from filters at the "mouth" and assayed by high performance liquid chromatography (HPLC). The amount of methacholine captured at the "mouth" multiplied by the fraction of the mass of the aerosol carried in particles ≤ 5 μm was the estimated pulmonary deposition. **Results:** For a concentration of 16 mg/mL the rates of deposition for the EW and AER were 0.19 ± 0.07 vs. 2.05 ± 0.16 mg/min, indicating that 12 seconds of inhalation from the AER would be equivalent of two minutes with EW. The recommended 19 breaths for the Viasys deposited 0.80 ± 0.06 mg or 0.04 mg/breath. The estimated pulmonary deposition was 0.17 ± 0.02 mg for 5 breaths dosimeter method or 0.03 mg/breath. **Conclusions:** It is clear that the EW has a very low rate of output compared to modern nebulizers. In order to change from one delivery system to another, adjustments of inhalation duration will be necessary. From these data it will be possible to design an *in vivo* study comparing modern aerosol delivery systems for MCT.

PROVOCATIVE DOSE 20, NOT PROVOCATIVE CONCENTRATION 20, DETERMINES BRONCHIAL HYPERRESPONSIVENESS IN CHILDREN WITH ASTHMA. SS Bola, R Foty, L Marshall, K Nelligan, AL Coates, S Dell. American Journal of Respiratory and Critical Care Medicine 2012;185:A2348.

Rationale: International standards for methacholine challenge testing (MCT) to diagnose asthma recommend a 2 minute tidal breathing protocol with the English Wright† nebulizer (EW), the EW is now obsolete. Currently, the provocative concentration of methacholine causing a 20% drop in FEV_1 (PC_{20}) is recommended to determine the level of bronchial hyperresponsiveness, not the provocative dose (PD_{20}). The objectives were to (1) determine if cumulative dose or concentration was the determinant for airway hyperresponsiveness and (2) validate an MCT using a modern, faster and environmentally safer delivery system, the breath actuated ***AeroEclipse** *II BAN**** Nebulizer (Aero). **Methods:** Subjects aged 10 to 18 years, with physician diagnosed asthma, participated in multiple randomized, controlled crossover experiments comparing four different MCT protocols using standard methacholine concentrations and spirometry measurements but varying: (1) nebulizer used (EW versus Aero) (2) methacholine inhalation time (assumed to be directly related to dose delivered), and (3) methacholine starting concentration (to test for a cumulative effect). Total dose was based on total number of breaths and the *in vitro* performance characteristics of the nebulizer. **Experiment A:** 16 subjects EW protocol versus Aero with a 30 second inhalation time (Aero 30) **Experiment B:** 30 subjects EW protocol versus Aero with a 20 second inhalation time (Aero20) **Experiment C:** 13 subjects EW protocol versus Aero 30 protocol using the final methacholine concentration inhaled during experiment A as the starting concentration. Paired student t-tests, intraclass correlation coefficients

(ICC), and Bland Altman graphs were used to compare PC_{20} and PD_{20} obtained with EW versus Aero in each experiment. **Results:** 33 children (17 male), aged 14.8 ± 6.8 SD years, with median PC_{20} 1.36 mg/mL (0.143 - 32 mg/mL) participated. Comparison of PC_{20} between EW and Aero in experiments A, B and C demonstrated a statistically significant difference between the two nebulizers (Figures 1 and 2). Comparison of PD_{20} between EW and Aero in experiments A, B and C demonstrated no statistically significant difference (Figures 1 and 2). ICC for Experiment A PC_{20} and PD_{20} were 0.54 (0.11 - 0.80) and 0.64 (0.25 - 0.85) respectively and for Experiment B PC_{20} and PD_{20} were 0.62 (0.31 - 0.81) and 0.73 (0.48 - 0.87) respectively. **Conclusions:** These results demonstrate that dose, not concentration, is the important determinant for bronchial responsiveness in MCT as dose of delivered methacholine accumulates and PD_{20} more accurately accounts for this cumulative effect. Our results also validate the use of the Aero for MCT.

AN *IN VITRO* STUDY TO INVESTIGATE THE USE OF A BREATH-ACTUATED, SMALL-VOLUME, PNEUMATIC NEBULIZER FOR THE DELIVERY OF METHACHOLINE CHLORIDE BRONCHOPROVOCATION AGENT. JP Mitchell, MW Nagel, SL Bates, CC Doyle. Respiratory Care 2003;48(1):46-51.

Background: Current American Thoracic Society and American Association for Respiratory Care guidelines for the delivery of aerosol agents such as methacholine chloride (MC) for bronchoprovocation testing require the use of pneumatic jet nebulizers that have well defined droplet size and mass output. A recently developed disposable, breath actuated device (***AeroEclipse***** ***BAN***** Nebulizer) may offer bronchoprovocation testers an alternative to existing devices. **Methods:** We studied the performance of 5 ***AeroEclipse***** ***BAN***** Nebulizers with regard to mass of MC delivered with various MC solution concentrations and numbers of inhalations, using a model of adult tidal breathing. Each nebulizer was operated with compressed air (8 L/min at 50 psig) and an initial fill of 2 mL. MC solutions with mass concentrations of 0.25, 0.98, 3.85, and 15.70 mg/mL were tested. The total mass of MC delivered was determined after 5, 10, and 15 complete breathing cycles, by assaying the MC collected on a filter placed at the nebulizer mouthpiece. The aerosol droplet size distribution, fine droplet fraction (FDF) (percentage of droplets < 4.8 µm diameter), and fine droplet mass (FDM) (mass of droplets < 4.8 µm diameter) were determined by laser diffractometry, using physiologically normal saline as a surrogate for MC solution. **Results:** The mean ± SD FDM collected in 5 breathing cycles was 654 ± 29 µg with the 15.70 mg/mL solution, 158 ± 9 µg with the 3.85 mg/mL solution, 37 ± 3 µg with the 0.98 mg/mL solution, and 7 ± 2 µg with the 0.25 mg/mL solution. FDM showed a linear correlation (r^2 = 0.9999) with MC concentration, within the range studied. FDM also showed a linear correlation (r^2 = 0.999) with the number of breathing cycles. For instance, with the 15.70 mg/mL solution, FDM was 654 ± 29 µg with 5 breathing cycles, 1,228 ± 92 µg with 10 breathing cycles, and 1,876 ± 132 µg with 15 breathing cycles. **Conclusions:** Although the bronchoprovocation test procedure had to be slightly modified from the guidelines to accommodate the operation of the ***AeroEclipse***** ***BAN***** Nebulizer's breath actuation feature, our measurements indicate that a predictable dose of MC, within the useful range for bronchoprovocation testing, can be delivered to an adult patient breathing tidally. The green indicator on the ***AeroEclipse***** ***BAN***** Nebulizer could be used to coach the patient to inhale for a specific period, thereby controlling MC delivery per breathing cycle.

Recombinant Interferon-γ1b

IMMUNOMODULATION WITH RECOMBINANT INTERFERON-γ1b IN PULMONARY TUBERCULOSIS. R Dawson, R Condos, D Tse, ML Huie, S Ress, CH Tseng, C Brauns, M Weiden, Y Hoshino, E Bateman, WN Rom. PLoS ONE 2009;4(9):e6984.

Background: Current treatment regimens for pulmonary tuberculosis require at least 6 months of therapy. Immune adjuvant therapy with recombinant interferon-γ1b (rIFN-γb) may reduce pulmonary inflammation and reduce the period of infectivity by promoting earlier sputum clearance. **Methodology/Principal Findings:** We performed a randomized, controlled clinical trial of directly observed therapy (DOTS) versus DOTS supplemented with nebulized or subcutaneously administered rIFN-γ1b over 4 months to 89 patients with cavitary pulmonary tuberculosis. Bronchoalveolar lavage (BAL) and blood were sampled at 0 and 4 months. There was a significant decline in levels of inflammatory cytokines IL-1β, IL-6, IL-8, and IL-10 in 24 hour BAL supernatants only in the nebulized rIFN-γ1b group from baseline to week 16. Both rIFN-γ1b groups showed significant 3-fold increases in CD4+ lymphocyte response to PPD at 4 weeks. There was a significant (p = 0.03) difference in the rate of clearance of mycobacterium tuberculosis from the sputum smear at 4 weeks for the nebulized rIFN-γ1b adjuvant group compared to DOTS or DOTS with subcutaneous rIFN-γ1b. In addition, there was significant reduction in the prevalence of fever, wheeze, and night sweats at 4 weeks among patients receiving rFN-γ1b versus DOTS alone. **Conclusion:** Recombinant interferon-γ1b adjuvant therapy plus DOTS in cavitary pulmonary tuberculosis can reduce inflammatory cytokines at the site of disease, improve clearance of mycobacterium tuberculosis from the sputum, and improve constitutional symptoms.

Tiotropium

NEW **INCORPORATING TIOTROPIUM INTO A RESPIRATORY THERAPIST-DIRECTED BRONCHODILATOR PROTOCOL FOR MANAGING IN-PATIENTS WITH COPD EXACERBATIONS DECREASES BRONCHODILATOR COSTS.** GS Drescher, BJ Carnathan, S Imus, GL Colice. Respiratory Care 2008;53(12):1678-1684.

Background: Tiotropium is used in maintenance treatment of chronic obstructive pulmonary disease (COPD), but there are no guidelines on when to start tiotropium following an exacerbation. **Objective:** To determine whether the addition of tiotropium to a respiratory therapist directed bronchodilator protocol affects bronchodilator costs for patients hospitalized for COPD exacerbation. **Methods:** We retrospectively analyzed data on the number and type of bronchodilator treatments administered to all patients admitted for COPD exacerbation during the 3 month period (January through March 2006) after tiotropium was added to our bronchodilator protocol, and compared that data to a historical control period (January through March 2004) before tiotropium was available in our hospital. We compared the costs of bronchodilator treatments, baseline patient characteristics, comorbidities, concomitant medications, length of stay, adverse events, and in hospital deaths. **Results:** Baseline characteristics, comorbidities,

and concomitant medications were similar in the 2004 control group (*n* = 181) and the 2006 intervention group (*n* = 174). The mean ± SD number of bronchodilator treatments per admission was significantly higher in the control period (13.6 ± 15.6) than in the intervention period (10.6 ± 9.4). That difference correlated to a reduction in combination therapy (short acting inhaled beta-2 agonist plus ipratropium), which decreased from a per admission average of 6.7 ± 14.2 in the control period to 1.9 ± 5.1 in the intervention period. Calculated bronchodilator costs were significantly lower in the intervention period than in the control period. Length of stay also significantly decreased, from 6.5 ± 5.0 days to 5.5 ± 4.0 days. There were no adverse events related to tiotropium. Pulmonary related in hospital deaths were not significantly different between the 2 periods. **Conclusions:** Early addition of maintenance treatment tiotropium to a respiratory therapist directed bronchodilator protocol for patients hospitalized for COPD exacerbation reduced costs and produced no safety concerns.

COMPARISON OF *AEROECLIPSE* II BAN** NEBULIZER TO HOLDING CHAMBER WITH METERED DOSE INHALER

COMBINING TREATMENT WITH PRESSURIZED METERED DOSE INHALER-VALVED HOLDING CHAMBER (pMDI + VHC) WITH DOSIMETRIC THERAPY VIA A BREATH ACTUATED NEBULIZER IN PATIENT TITRATION FOR OBSTRUCTIVE LUNG DISEASES. J Mitchell, M Nagel. American Journal of Respiratory and Critical Care Medicine 2013;187:A4115.

Rationale: Clinical guidelines for asthma and COPD suggest health care providers titrate the patient to the least dose that is efficacious. In mild stable asthma or COPD, the dosing regimen will likely be pMDI + VHC. However, in an exacerbation, nebulizer treatment may be more appropriate. If a dosimetric breath actuated device is used, it is possible to relate the drug mass delivered in a given time to the equivalent number of pMDI actuations. We report such data here for salbutamol, which can be delivered by either pMDI + VHC or nebulizer routes. **Methods:** Fine particle mass < 4.7 µm salbutamol ex-***AeroChamber**** Plus VHC; Trudell Medical International (TMI), London, ON, Canada ($FPM_{<4.7\mu m}$; *n* = 5 devices) was determined by Andersen 8 stage cascade impactor following the pharmacopeial method, but simulating a 2 second delay between pMDI actuation and the onset of sampling to mimic the poorly coordinate patient for whom these devices are prescribed. In parallel studies, the fine particle delivery rate ($FPM_{<4.7\mu m/min}$) of salbutamol solution (2.5 mg/3 mL) from ***AeroEclipse* II BAN**** Nebulizers (*n* = 5) with 1.5, 2.0, 2.5 and 3.0 mL fill volumes operated at 50 psig was determined with the mouthpiece of the nebulizer connected via a collection filter to a breathing simulator (ASL 5000, Ingmar Medical Ltd., Pittsburgh, PA), used to generate adult breathing (tidal volume = 600 mL; duty cycle = 33%; rate = 10 cycles/minute). Assay for salbutamol in both studies was by HPLC-UV spectrophotometry. **Results:** Preliminary studies had confirmed linearity of $FPM_{<4.7\mu m}$ ex-VHC between 2 and 10 actuations. $FPM_{<4.7\mu m/min}$ for the ***BAN**** Nebulizer was independent of volume fill and linear with time until sputter. The table illustrates the relationships between ex VHC and treatment time ex ***BAN**** Nebulizer to achieve the same $FPM_{<4.7\mu m}$ from pMDI + VHC. Mean values are reported as coefficients of variation were < 10%.

Table 1: Comparison of Dosing for Salbutamol by pMDI + VHC and ***BAN**** Nebulizer

pMDI + VHC (salbutamol: 100 µg/actuation label claim) with 2 second delay		***BAN**** **Nebulizer(2.5 mg/3 mL salbutamol)**
Number of actuations	**$FPM_{<4.7\mu m}$ (µg)**	**Treatment time (minutes:seconds)**
2	70	0:53
4	140	1:45
6	210	2:38
8	280	3:30
10	350	4:20

* Values calculated based on measured $FPM_{<4.7\ \mu m}$ of 33.2 ± 3.3 µg/actuation for 5 actuations

Conclusions: The ability to transition to and from pMDI + VHC to ***BAN**** Nebulizer offers the clinician new possibilities in titrating the adult tidal breathing patient through exacerbations of bronchoconstrictive diseases such as asthma or COPD, and easing the transition from hospital to the home environment.

BRONCHODILATOR RESPONSE IN ASTHMATICS TO SHORT COURSE NEBULIZATION WITH A BREATH ACTUATED NEBULIZER. J Davies, E MacIntyre, S Shearer, NR MacIntyre. American Journal of Respiratory and Critical Care Medicine 2010;181:A1348.

Background: Aerosolized bronchodilators are often given by either pressurized metered dose inhaler (pMDI) or small volume nebulizer (SVN). The advantages to the former are portability and short treatment time (i.e. usually 2 puffs administered). The downside to the pMDI is frequent patient difficulty with the optimal inhalation technique. The advantage to the SVN is that higher doses with tidal breathing can be given which can be easier for patients to use. The downside to the SVN is that it usually requires long treatment times (e.g. > 10 - 15 minutes). A novel breath actuated device (***AeroEclipse* II BAN**** Nebulizer, Monaghan Medical Corporation, Plattsburgh, NY) does not waste aerosol during patient exhalation and thus could be used to deliver a more concentrated medication over a shorter period of time. We hypothesized that using a ***BAN**** Nebulizer with a 5 minute nebulization period using an undiluted bronchodilator solution would have equal efficacy compared to traditional pMDI techniques. **Methods:** Ten stable adult asthmatic subjects with known bronchodilator responsiveness were recruited. On five successive days, each subject received one of five aerosol treatments: 1) 0.5 mL levalbuterol + 0.5 mL saline by ***BAN**** Nebulizer for 5 minutes; 2) 0.5 mL levalbuterol + 0.5 mL ipratropium by ***BAN**** Nebulizer for 5 minutes; 3) 2 puffs levalbuterol pMDI; 4) 2 puffs levalbuterol pMDI + holding chamber; 5) 2 puffs levalbuterol pMDI + holding chamber +2 second breath hold. All subjects held their controller medications on days of testing. FEV_1, tremor scores and dyspnea scores were recorded for up to 8 hours. FEV_1 areas under the curve (AUC) were calculated for all ten patients for each treatment and compared by ANOVA. **Results:** The average peak FEV_1 response for the 5 treatment regimens ranged from 12.2% to 19.1% and were all statistically significant from baseline but not from each other. AUC for all treatment regimens

ranged from 4,590 L to 7,545 L but were not significantly different from each other. Tremor scores and dyspnea scores were also comparable across all 5 treatment regimens. **Conclusion:** The short course nebulization treatment with the ***BAN**** Nebulizer provided comparable bronchodilator responses to the standard pMDI regimens and could thus be a convenient alternative strategy for patients intolerant to pMDIs.

DOSIMETRIC DELIVERY OF BRONCHODILATATION MEDICATION BY BREATH-ACTUATED NEBULIZER SHOULD FACILITATE PATIENT TITRATION: EXAMPLE *IN VITRO* DATA FOR SIMULATED CHILD AND ADULT TIDAL BREATHING. J Mitchell, J Malpass, MW Nagel, R Ali, V Avvakoumova, C Doyle. American Journal of Respiratory and Critical Care Medicine 2010;181:A1346.

Rationale: In the context of the GINA Guidelines for Asthma in which patient titration to the lowest efficacious dose is recommended, we report a study in which the delivery of salbutamol sulphate by breath actuated nebulizer was studied as a function of volume fill, simulating representative child and adult tidal breathing. **Methods:** Three ***AeroEclipse**** ***II BAN**** Nebulizers (Monaghan Medical Corporation, Plattsburgh, NY) were evaluated, operating them at 50 psig with medical air at their maximum flow rate (7 - 8 L/min). The mouthpiece from the nebulizer on test was connected to a breathing simulator (ASL 5000, IngMar Medical Ltd., Pittsburgh, PA, USA) via an electret bacterial/viral filter (RespirGard II†, Vital Signs Inc., Totowa, NJ, USA) upon which the 'inhaled' aerosol deposited. An adult tidal breathing pattern was simulated (tidal volume (V_t) = 600 mL, rate = 10 cycles/minute, duty cycle = 33% inhalation/67% exhalation), followed by a child pattern (V_t = 250 mL, rate = 25 cycles/minute, duty cycle = 33%). Various volume fills of salbutamol sulphate solution (833 µg/mL salbutamol base equivalent) ranging from 1.0 to 3.0 mL in 0.5 mL increments were introduced into the reservoir of the nebulizer and the device operated on each occasion until first sputter, defining the point at which non-linear delivery of medication would be expected. The aerosol filters were replaced at 1 minute intervals to provide time dependent information, The mass of salbutamol collected on each filter was assayed by HPLC-UV spectrophotometry. **Results:** The variation of total mass output (mean ± SD) with volume fill was linear for both simulations (Figures 1a (r^2 = 0.996) and 1b (r^2 = 0.976).

Figure 1a: Albuterol Delivery as a Function of Fill Volume: Adult Simulation

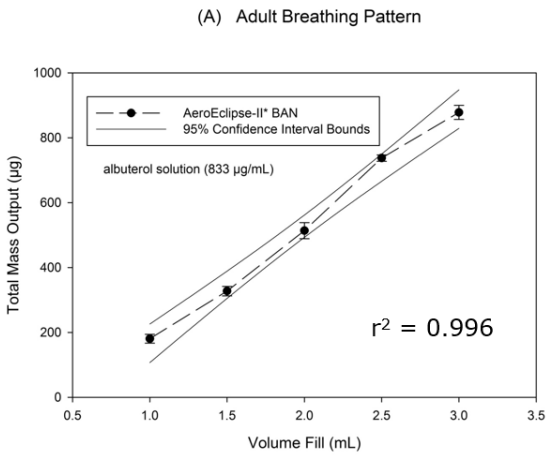
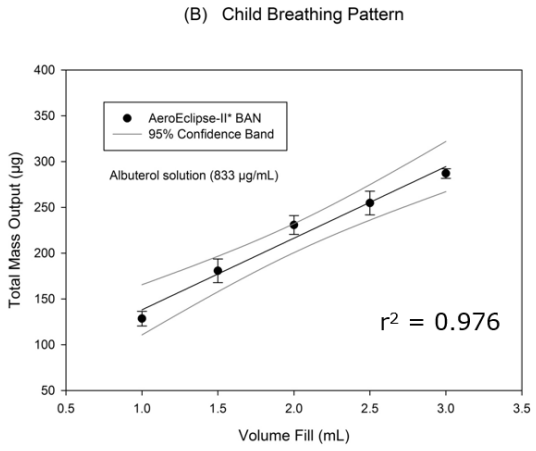
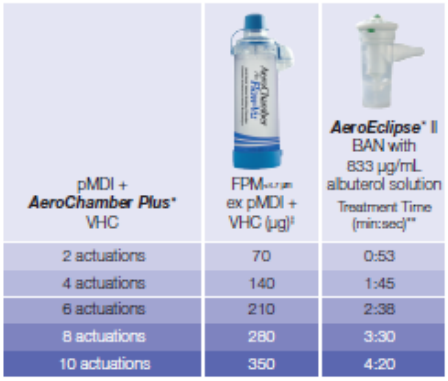


Figure 1b: Albuterol Delivery as a Function of Fill Volume: Child Simulation



Conclusions: These *in vitro* measurements simulating child and adult tidal breathing demonstrate that the ***AeroEclipse**** ***II BAN**** Nebulizer has the capability to deliver medication to start of sputter in a predictable manner in terms of both elapsed time from start of treatment and fill volume of medication placed in the reservoir. In the context of patient titration, in principle clinicians could convert patients currently on other inhalers who require nebulization by this breath actuated device by means of a lookup table. Such a table would equate the mass of medication prescribed with the other inhaler to the fill volume and mass concentration of the preparation for nebulization.

Example Lookup Table (adult user):



pMDI + *AeroChamber Plus** VHC	FPM ex pMDI + VHC (µg)‡	*AeroEclipse** II BAN with 833 µg/mL albuterol solution Treatment Time (min:sec)**
2 actuations	70	0:53
4 actuations	140	1:45
6 actuations	210	2:38
8 actuations	280	3:30
10 actuations	350	4:20

‡ Data for Ventolin†-HFA: Developing A "Universal" Valved Holding Chamber (VHC) Platform With Added Patient Benefits Whilst Maintaining Consistent *In Vitro* Performance. JP Mitchell, M Nagel, HA Mackay, V Avvakoumova, J Malpass. Respiratory Drug Delivery 2009;2:383-386.

** Data from: A Mechanically Operated Breath-Actuated Jet Nebulizer has Dosimetric Capability Based on Differing Volume Fill of Medication as Well as Run Time. JP Mitchell, CC Doyle, V Avvakoumova. Drug Delivery to the Lungs-20 2009;2:1-4.

THE DELIVERY TIME, EFFICACY, AND SAFETY OF β-AGONIST BRONCHODILATOR ADMINISTRATION WITH THE *AEROECLIPSE BREATH-ACTUATED NEBULIZER.** RS Pikarsky, T Farrell, R Acevedo, W Fascia, C Roman. CHEST 2001;120(4):218S.

Purpose: Aerosol delivery consumes the highest level of respiratory care resources. This study evaluated the delivery time, efficacy, and safety of rapidly nebulized albuterol with the use of the ***AeroEclipse** *BAN**** Nebulizer as compared to both an MDI with ***AeroChamber**** VHC (both from Monaghan Medical Corporation, Plattsburgh, NY) and the AirLife† Misty-Neb† Nebulizer (SVN) (Allegiance Healthcare Corporation). **Methods:** A consecutive, nonrandomized, mostly COPD population receiving pre and post bronchodilator testing in our pulmonary function lab were studied. Three different albuterol medication dosages were administered with the ***BAN**** Nebulizer: 0.5 mL albuterol (2.5 mg) with 0.5 mL normal saline, 1.0 mL (5 mg) of undiluted albuterol, and 0.75 mL albuterol (3.75 mg) using an oxygen flow rate of 8 L/min. Two puffs of albuterol were administered by MDI with ***AeroChamber**** VHC. Treatments with the SVN consisted of nebulizing 2.5 mg of albuterol diluted with 3 mL of normal saline unit dose (UD) using an oxygen flow rate of 8 L/min. The Sensormedics Vmax 22 Pulmonary Function System was utilized to measure FEV_1. A standardized subjective questionnaire to determine side effects was completed.

Nebulizer (*n*)	Dose	% Change FEV_1	Time (minutes)	Tremulousness
AeroEclipse** *BAN* Nebulizer (12)	0.5 mL + 0.5 mL NS	8.2%	2.67*	0
AeroEclipse** *BAN* Nebulizer (64)	1.0 mL undiluted	10.9%	3.29*	17
AeroEclipse** *BAN* Nebulizer (23)	0.75 mL undiluted	5.6%	1.30*	5
MDI (21)	2 puffs	8.5%	2.86**	1
Misty-Neb† (52)	2.5 mg UD	9.1%	8.33	2

Results: The table shows the albuterol dosages, mean % change of FEV_1 from pre-treatment and 10 minute post treatment, mean administration time and tremulousness. The mean treatment time with all ***BAN**** Nebulizer patients was 2.78 minutes as compared to 8.33 minutes with the SVN ($p < 0.001$)*. The mean treatment time with the MDI was 2.86 minutes as compared to 8.33 minutes with the SVN ($p < 0.001$)**. The changes in FEV_1 were not significant. There was no difference in heart rate, respiratory rate or nausea. Seventeen patients receiving the 1.0 mL undiluted albuterol indicated an increase in tremulousness. **Conclusion:** The rapid administration of albuterol in the 0.5 mL + 0.5 mL NS and 1.0 mL undiluted doses using the ***BAN**** Nebulizer was equally efficacious as the MDI with ***AeroChamber**** VHC and SVN UD. The 1.0 mL albuterol dosage has the highest incidence of tremulousness. The 0.75 mL albuterol dosage underperformed. Delivering 0.5 mL albuterol (2.5 mg) with 0.5 mL normal saline using the ***BAN**** Nebulizer offered the best delivery time, efficacy and safety profile of the nebulizer trials. The ***BAN**** Nebulizer performance was comparable to the MDI with ***AeroChamber**** VHC. **Clinical Implications:** In a health care facility that delivers large volumes of aerosol treatments, the decrease in delivery time could have a significant impact on resource utilization. The results supported changes in the respiratory care practice throughout Crouse Hospital. Further studies evaluating additional medication dosing regimens measuring safety, efficacy and resource utilization are needed.

COMPARISON OF *AEROECLIPSE** II BAN** NEBULIZER TO LARGE VOLUME NEBULIZERS

RAPID DELIVERY OF BRONCHODILATOR MEDICATION IS POSSIBLE USING A BREATH-ACTUATED SMALL VOLUME NEBULIZER AS AN ALTERNATIVE TO EXTENDED DELIVERY OF MEDICATION BY LARGE VOLUME NEBULIZER. DP Coppolo, JP Mitchell, KJ Wiersema, CC Doyle, MW Nagel. Respiratory Care 2007;52(11):1582.

Background: Inhaled beta-2 adrenergic agonist bronchodilators are often given to patients with severe reversible airways disease by continuous nebulization in extended treatments. However, data are limited as to whether or not shorter, but higher concentration delivery is as an effective treatment modality. The development of a new breath actuated device (***AeroEclipse** II BAN**** Nebulizer, Monaghan Medical Corporation, Plattsburgh, NY (AE II BA)) provided an opportunity to compare the two treatment methods in a

laboratory study before undertaking a clinical comparison. We investigated the delivery of diluted generic respirator solution albuterol by a widely used continuous jet nebulizer (Hi-Flo MiniHEART†, Westmed Corp., Tucson, AZ (CONT)) with that from the AE II BA. **Method:** The continuous nebulizers (*n* = 3) were operated with 8 L/min air supplied at 50 psig with a 20 mL fill (albuterol concentration of 0.5 mg/mL). A similar number of AE II BAs were operated with ca. 8.0 L/min air at 50 psi with a 1 mL fill (albuterol concentration of 5 mg/mL). Aerosol from both nebulizers was sampled onto electret filters using a breathing simulator mimicking small child use (250 mL tidal volume, inspiratory/expiratory ratio 1:2, rate 12 cycles/minute) until onset of sputtering. Assay for albuterol was undertaken by UV spectrophotometry. In a parallel study, droplet size distributions were determined by laser diffractometry, so that the fine droplet fraction < 4.7 µm diameter likely to penetrate to the airways of the lungs (FDF) could be determined. **Results:** Values of FDF for the AE II BA and CONT were 78.4% and 62.0% respectively. The AE II BA delivered 758 ± 36 µg as fine droplets after 4 minutes (delivery rate of 190 µg/min), compared to 180 ± 76 µg in the same period by CONT (delivery rate of 45 µg/min). **Conclusions:** The faster delivery rate from the ***AeroEclipse* II BAN**** Nebulizer high albuterol concentration modality (unpaired t-test, $p < 0.001$) may offer an important clinical alternative to CONT/low concentration treatment modality.

A BREATH-ACTUATED SMALL VOLUME NEBULIZER OFFERS A RAPID ALTERNATIVE TREATMENT MODALITY FOR THE DELIVERY OF BRONCHODILATORS FOR ASTHMATIC PATIENTS IN A SEVERE EXACERBATION. DP Coppolo, JP Mitchell, KJ Wiersema, CC Doyle, MW Nagel. Respiratory Care 2006;51(11):1318.

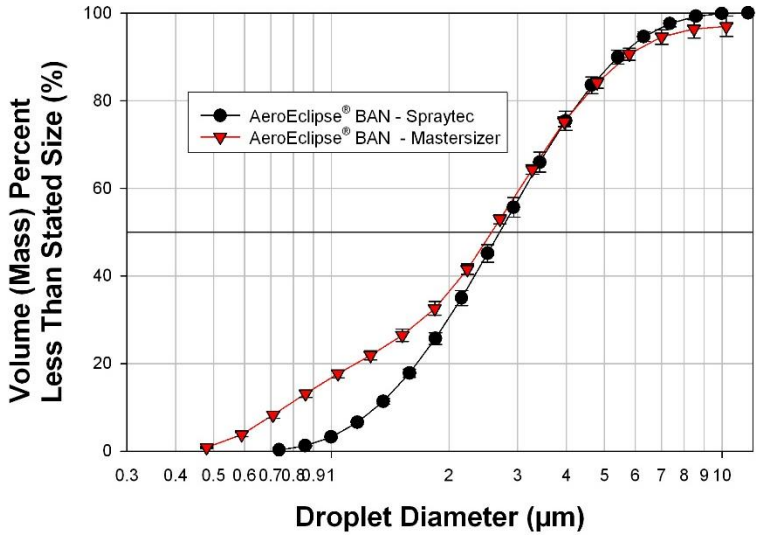
Large volume continuous nebulizers (LVNs) are often used for the delivery of beta-2 adrenergic agonist bronchodilators in the emergency department to treat severe, reversible airways disease, in particular asthma[1]. Treatment time, however, can be lengthy for delivery of the typical LVN fill volume from 20 to 120 mL. Quick delivery of a bronchodilator with an efficient nebulizer may help relieve symptoms from bronchospasm in a shorter period of time.[2] We report a study in which the delivery of diluted generic respirator solution albuterol by LVN (Hope, B&B Medical Technologies Inc., Loomis, CA) was compared with that from a small volume breath actuated device (BA) (***AeroEclipse* BAN**** Nebulizer, Monaghan Medical Corporation, Plattsburgh, NY). The LVNs (*n* = 5) were operated with 10 L/min air supplied at 50 psig with a 20 mL fill (albuterol concentration of 0.167 mg/mL). A similar number of BAs were operated with 8.0 L/min air at 50 psi with a 3 mL fill (albuterol concentration of 0.833 mg/mL). The aerosol from the LVNs was sampled continuously until onset of sputtering at 12 L/min via a Dreschel filter/bottle where the albuterol was captured quantitatively. Aerosol from the BAs was sampled onto electret filters using a breathing simulator (600 mL tidal volume, inspiratory/expiratory ratio 1:2, rate 10 cycles/minute) until onset of sputtering, so that operation of the breath actuation mechanism was effected. Assay for albuterol was undertaken by UV spectrophotometry. In a parallel study droplet size distributions were determined by laser diffractometry, so that the fine droplet fraction < 4.8 µm diameter likely to penetrate to the airways of the lungs could be determined. Fine droplet albuterol delivery rates were constant as a function of time for all nebulizers. After 15 minutes, the LVNs had supplied 127.3 ± 37.4 µg as fine droplets at a rate of 8.5 ± 2.5 µg/min. In contrast, the BAs delivered 810.0 ± 20.4 µg in a 10 minute period, equivalent to a rate of 81.0 ± 2.0 µg/min. The significantly higher delivery rate from the BA group (unpaired t-test, $p < 0.001$) offers an important clinical alternative to the LVN in the emergency department where rapid delivery of a bronchodilator is critical. **References:** [1] Aerosol Delivery During Continuous Nebulization. M McPeck, R Tandon, K Hughes, GC Smaldone. CHEST 1997;111:1200-1205. [2] Clinical Evaluation of a Breath Actuated Small Volume Nebulizer (BA-SVN). S Klopf, N Schneiderman, H Payne, C Schramm, MW Nagel, JP Mitchell. Respiratory Care 2000;45(8):979.

AEROECLIPSE BAN** NEBULIZER EQUIVALENCE TO *AEROECLIPSE* II BAN** NEBULIZER

TRANSFER FROM THE MALVERN MASTERSIZER-X TO MALVERN SPRAYTEC LASER DIFFRACTOMETERS: EXPERIENCE WITH TWO BREATH-ACTUATED NEBULIZERS. JP Mitchell, KJ Wiersema, CC Doyle, MW Nagel, P Kippax, H Krarup. Respiratory Drug Delivery 2006;3:813-815.

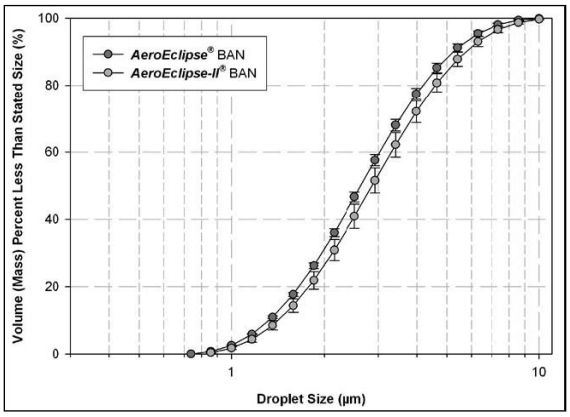
Introduction: Laser diffractometry is widely used for the measurement of droplet sizes of aqueous solution aerosols from nebulizers on account of its rapidity and size resolution capability[1], and is indicated in an Informative Annex of a European standard for the evaluation of this class of inhalers[2]. The second generation Malvern Spraytec laser diffractometer (LD) (Malvern Instruments Ltd., Malvern, UK) has recently been introduced for the purpose of size characterizing aerosols and droplet sprays, replacing earlier instruments. We describe our recent experience transferring from a Mastersizer-X LD to the Spraytec LD at the same time as bringing a second generation breath actuated nebulizer (***AeroEclipse* II BAN**** Nebulizer, Trudell Medical International, London, ON, Canada) to market. **Transfer From Mastersizer-X To Spraytec LD Systems:** In the first part of the study, we compared droplet size distributions of normal saline (0.9% w/v NaCl, 5 mL fill) determined by Mastersizer-X and Spraytec LDs, using first generation ***AeroEclipse* BAN**** Nebulizers (*n* = 3 devices, 2 measurement per device) operated at 7 to 8 L/min by compressed air supplied at 345 kPa (50 psi). The complex refractive index (RI) for saline was defined as 1.33 + 0i, with air (RI = 1.00) as support medium. Measurements were made with the Mastersizer LD in the open bench configuration with a 100 mm focal length range lens, delivering an additional flow of 20 L/min through the cap of the nebulizer containing the air entrainment entry passages to move the droplets through the measurement zone without risk of recirculation. In contrast, the aerosol from the nebulizer was drawn via the inhalation cell of the Spraytec (300 mm range lens) at 28 L/min using an external vacuum source. This arrangement is more representative of the process of inhalation.

Figure 1: LD Measured Size Distributions from the ***AeroEclipse*** **BAN**** Nebulizer



The cumulative volume (mass) weighted size distributions (Figure 1) were comparable for droplets > 3 µm, so that the Mastersizer-X determined fine droplet fraction < 4.8 µm (84.0 ± 1.2% (mean ± SD)) compared with 83.5 ± 1.9% < 4.6 µm for the Spraytec system. The cause of the 'tail' of fine droplets present in the Mastersizer data requires further investigation. Preliminary studies suggest that the cause was not multiple scattering, even though obscurations in excess of 25% were obtained. It may, however, be associated with the way the aerosol was transported to the measurement zone and the working range of the optical system. Here the Spraytec offers advantages over the Mastersizer-X in that the working range is 150 mm compared with 2.4 mm. The angular range of the scattering measurements made using the Spraytec is also greater than for the Mastersizer-X so that the former would be expected to provide a more accurate measure of the fine particle fraction. **First And Second Generation *BAN** Nebulizer Comparison:** In the second part of the study we compared saline droplet size distributions from the original ***AeroEclipse*** **BAN**** Nebulizer with those produced by a second generation breath actuated device (***AeroEclipse*** **II BAN**** Nebulizer) designed to improve actuation capability for low inhalation flow rate patients. 5 nebulizers of each type were evaluated, with the Spraytec system configured as described in the first part of the investigation. The entire size distribution profiles from the two nebulizer types were substantially similar (Figure 2), so that the fine droplet fraction < 4.6 µm from the ***AeroEclipse*** **BAN**** Nebulizer (85.2 ± 1.5%) compared with 80.7 ± 2.7% for the second generation nebulizer. In both cases, the volume (mass) median diameter was 2.5 to 2.7 µm.

Figure 2: Spraytec LD Measured Size Distributions for ***BAN**** Nebulizers



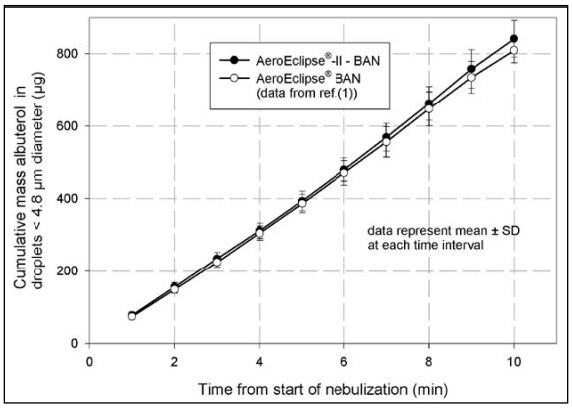
These measurements were made with only one solution (saline), and further work with other solution formulations is therefore merited. **References:** [1] Particle Size Analysis of Aerosols From Medicinal Inhalers. JP Mitchell, MW Nagel. KONA Powder and Particle 2005;22:32-65. [2] European Standard EN 13544-1:2001. Respiratory Therapy Equipment - Part 1. Nebulizing Systems And Their Components. European Committee for Standardization (CEN). Brussels, Belgium, 2001.

ARE FIRST AND SECOND GENERATION, MECHANICALLY-OPERATED BREATH-ACTUATED NEBULIZERS COMPARABLE BASED ON *IN VITRO* PERFORMANCE? J Schmidt, J Pevler, C Doyle, K Wiersema, M Nagel, J Mitchell. Respiratory Drug Delivery 2006;3:817-819.

Introduction: The original ***AeroEclipse*** **BAN**** Nebulizer (Monaghan Medical Corporation, Plattsburgh, NY) introduced a few years ago was the first mechanically operated breath actuated device with dosimetric capability, providing a near constant delivery rate of medication from a variety of solution formulations and volume fills[1]. This nebulizer required an inhalation flow rate close to 25 L/min to operate the breath actuation mechanism. The second generation ***AeroEclipse*** **II BAN**** Nebulizer now actuates at flow rates as low as 15 L/min, making it potentially more suitable for younger patients. At the same time, a control located on the nebulizer cap

enables a smooth transition to be made from breath actuated to continuous operation. We report a study in which the delivery of albuterol sulfate solution from the new ***AeroEclipse*** ***II BAN*** Nebulizer was evaluated with a 3 mL fill, corresponding to a single unit dose ampoule (0.83 mg/mL albuterol sulfate) in widespread use within the US[1]. Previously published data for the original ***AeroEclipse*** ***BAN*** Nebulizer[1] were used as a benchmark for demonstrating *in vitro* equivalence. The study was extended to examine comparative behavior with a low volume (1 mL) fill, used to reduce treatment time. **Materials and Methods:** In the first part, we evaluated 5 ***AeroEclipse*** ***II BAN*** Nebulizers (*n* = 3 replicates/device) using a piston driven breathing simulator (Compass, PARI GmbH, Starnberg, Germany) set at tidal volume of 600 mL, inspiratory/expiratory ratio of 1:2, rate of 10 breaths/minute, based on a previous study simulating adult use[2]. Each nebulizer was operated at 8.0 ± 0.2 L/min with compressed air supplied at 50 ± 0.5 psig. 3 mL albuterol solution obtained by diluting respirator solution (5 mg/mL albuterol base equivalent, Hi-Tech Pharmacal, Amityville, NY) with normal saline to the desired concentration (0.83 mg/mL) was placed in the reservoir of the nebulizer prior to test. The measurement protocol to determine the total mass of drug delivered on a minute by minute basis was as described previously[1]. Fine droplet fraction < 4.8 µm diameter ($FDF_{<4.8µm}$) was also determined by laser diffractometry (Mastersizer-X, Malvern Instruments Ltd., UK) as described previously[1]. At each minute, the mass of drug delivered as fine particles was calculated as the product of total mass and the mean ($FDF_{<4.8µm}$). Measurements were made at comparable conditions (22 ± 2ºC, 30 ± 5% RH) to those of the original study. In the second part, we followed the same protocol, except that the fill volume was decreased to 1 mL, diluting respirator solution with normal saline to achieve an albuterol concentration of 2.5 mg/mL. The delivery rate of fine droplets from the ***BAN*** Nebulizer was compared with that produced by the LC PLUS† (PARI Respiratory Equipment Inc.), chosen as a benchmark high output, continuous breath enhanced nebulizer. **Results:** Comparable fine droplet delivery with both the original and new ***BAN*** Nebulizer was achieved throughout the 10 minute delivery period (Figure 1).

Figure 1: Comparative Delivery of Albuterol Solution (0.83 mg/mL) with 3 mL Fill in Reservoir



Mean $FDF_{<4.8µm}$ for both nebulizers was within 80 ± 2%. The rate of delivery of albuterol was constant, as might be expected for a solution formulation. The cumulative mass of fine droplets from the new ***BAN*** Nebulizer by the time that audible sputtering occurred was 842 ± 50 µg compared with 810 ± 34 µg for the original ***BAN*** Nebulizer. In the case of the measurements made with the 1 mL fill (2.5 mg/mL albuterol), the new ***BAN*** Nebulizer operated for about 3 minutes before sputtering, delivering 544 ± 54 µg albuterol as fine droplets, in comparison with 576 ± 49 µg in a similar time from the original ***BAN*** Nebulizer. In contrast, only 67 ± 10 µg of albuterol was obtained as fine droplets from the LC PLUS† (mean $FDF_{<4.8µm}$ also ~80%), which operated for just over 1 minute before sputtering. The LC PLUS† operated throughout each breathing cycle, reducing delivery time, but medication emitted during exhalation was not collected since it would be wasted in normal use. **Conclusions:** The ***AeroEclipse*** ***II BAN*** Nebulizer has similar *in vitro* performance with albuterol as the original version, and treatment time can be significantly shortened by reducing the volume fill to 1 mL. The breath actuation feature avoids the escape and therefore waste of medication during patient exhalation, with attendant concerns concerning possible exposure of the care giver to medication. These considerations could be important when used with more expensive medications. **References:** [1] An *In Vitro* Investigation Of Common Nebulizer Dosing Protocols, Comparing A Breath-Actuated With A Conventional Pneumatic Small Volume Nebulizer (SVN). MW Nagel, CC Doyle, SL Bates, JP Mitchell. Respiratory Drug Delivery 2002;2:627-629. [2] Effect Of Nebulizer Design On Fine Particle Mass. D Hess, JP Mitchell, D Coppolo, MW Nagel, AD Archer, R Blacker. Respiratory Care 1999;44:1289.

COMBINED THERAPY

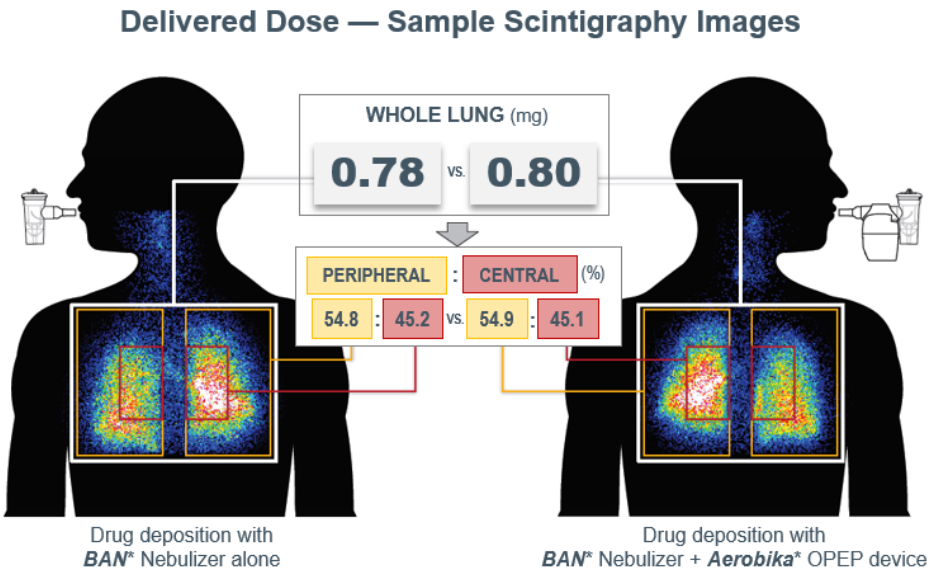
EFFECTIVENESS OF *AEROBIKA* **WITH *AEROECLIPSE*** **TO GENERATE POSITIVE EXPIRATORY PRESSURE IN CHILDREN WITH CYSTIC FIBROSIS.** A Locke, P Anderson. Journal of Cystic Fibrosis 2019;18(1):S162.

Objectives: Frequently children with cystic fibrosis (CF) are unable to tolerate nebulised hypertonic saline (HS), but we know that it can often be a beneficial aid to secretion removal. O'Connell *et al* (2011) found that HS via a positive expiratory pressure (PEP) nebuliser can be beneficial for CF patients, including improved tolerance. PEP is a well accepted tool to aid secretion clearance and it is widely recognised that when using PEP, pressures of 10 - 20 cmH2O are required to have the desired effect. ***Aerobika*** OPEP device is an oscillating PEP device that can be used to simultaneously nebulise medication using the ***AeroEclipse*** ***BAN*** Nebulizer attachment. Patients with CF often have onerous regimes and we are keen to find ways to optimize treatment, whilst keeping the burden of care to a minimum. The purpose of this study was to measure the effectiveness of the ***Aerobika*** OPEP device with ***AeroEclipse*** ***BAN*** Nebulizer to generate PEP in children with CF. **Method:** 7 patients with CF, 1 male and 6 females, aged 3 - 15 years (mean 11.7 years), participated in this study. All were existing users of the ***Aerobika*** OPEP device and ***AeroEclipse*** ***BAN*** Nebulizer, and all were using it as their method of delivering HS. A digital manometer was attached into the system and the patients

were advised to continue with their normal, tidal volume breaths, for 10 minutes. The pressures were measured for the duration of the treatment. **Results:** A peak range of 10 cmH2O - 22 cmH2O was achieved by these patients with a mean peak pressure of 13.86 cmH2O. **Conclusion:** This study shows that PEP of 10 - 22 cmH2O is achievable using the ***Aerobika**** OPEP device with ***AeroEclipse**** ***BAN**** Nebulizer at tidal volume breaths. These values are within the range of what is accepted as clinically effective. Further work is required to assess the pressures that can be achieved with PEP or forceful breaths, and to establish whether or not patients can combine HS nebulisation and PEP therapy.

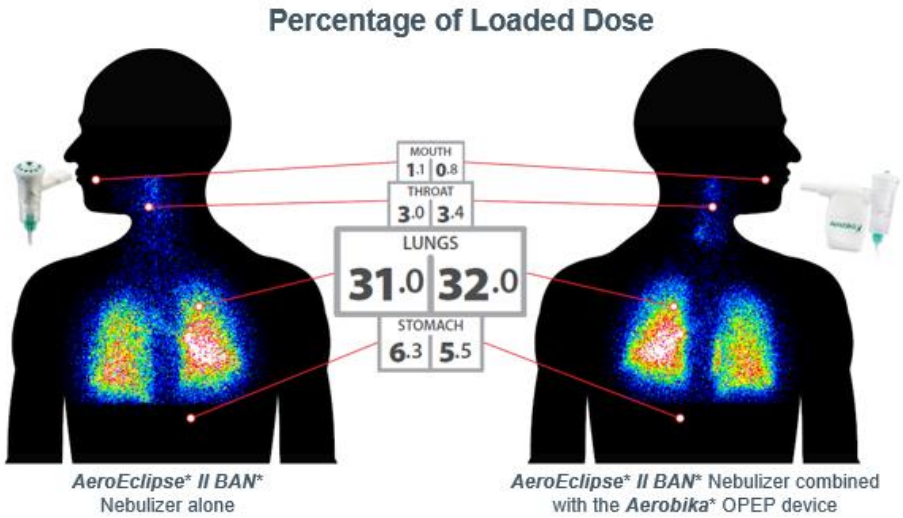
COMBINING DRUG DELIVERY BREATH ACTUATED NEBULIZER WITH EXHALATION THROUGH AN OSCILLATING POSITIVE EXPIRATORY PRESSURE DEVICE — THE POTENTIAL FOR OPTIMAL COMBINED THERAPY. M Nagel, J Suggett, V Kushnarev, DP Coppolo, A Wesolowski, T Corcoran. Pediatric Pulmonology 2019;54(S2):183.

Introduction: Pairing an oscillating positive expiratory pressure (OPEP) device (***Aerobika**** OPEP device) with a breath actuated device (***AeroEclipse**** ***II BAN**** Nebulizer) offers the opportunity to deliver bronchodilator therapy during inhalation with secretion clearance during exhalation thereby reducing combined treatment time. The aim of the study was to assess the impact on lung deposition of the nebulized medication when given in combination with the OPEP device. **Methods:** Eight healthy subjects received albuterol (2.5 mg/3 mL) admixed with 2 mCi of Tc-DTPA (technetium-99m bound to diethylenetriaminepentaacetic acid) administered using the ***BAN**** Nebulizer alone and again when the ***BAN**** Nebulizer was combined with the OPEP device. Regional doses were then determined from anterior and posterior gamma camera images collected after delivery. Lung perimeters were defined using cobalt-57 transmission scans and applied to Tc-DTPA deposition images. Results were expressed as milligrams (mg) ± one standard deviation of delivered albuterol. **Results:** Average age of all 8 subjects (4 male, 4 female) was 33 years. Whole lung deposition was, on average, 0.78 ± 0.20 mg vs. 0.80 ± 0.19 mg for the ***BAN**** Nebulizer alone and ***BAN**** Nebulizer + OPEP respectively. Peripheral: Central deposition of the lung dose was found to be 54.8%:45.2% (***BAN**** Nebulizer alone) and 54.9%:45.1% (***BAN**** Nebulizer + OPEP). **Conclusions:** The delivery of medication from the ***AeroEclipse**** ***II BAN**** Nebulizer to the lungs was not affected by the incorporation of the ***Aerobika**** OPEP device. Aerosol deposition within the lung was unaltered by the addition of the OPEP device as evidenced by the near identical percentage of the dose being deposited in both the peripheral and central airways. ***BAN**** Nebulizer + OPEP therapy could offer the clinician the opportunity for combined treatment thereby reducing the time needed for the patient to take both nebulizer and OPEP treatments separately.



COMBINING INHALATION BY A BREATH ACTUATED NEBULISER WITH EXHALATION THROUGH AN OSCILLATING POSITIVE EXPIRATORY PRESSURE DEVICE (OPEP) OFFERS THE POTENTIAL FOR OPTIMAL COMBINED THERAPY. M Nagel, J Suggett, V Kushnarev, D Coppolo, A Wesolowski, T Corcoran. European Respiratory Journal 2019;54:PA4529.

Rational: OPEP therapy when combined with nebulised drug delivery or hypertonic saline offers the potential to reduce combined treatment time. Aerosol deposition scintigraphy was undertaken to assess *in vivo* pulmonary deposition from a breath actuated device (***AeroEclipse**** ***II BAN**** Nebulizer) coupled to an OPEP device (***Aerobika**** OPEP device) compared to deposition from the nebuliser alone. **Methods:** Eight healthy subjects received albuterol (2.5 mg/3 mL) admixed with 2 mCi of Tc-DTPA (Technetium-99m bound to diethylenetriaminepentaacetic acid) administered using the ***BAN**** Nebulizer alone and again when the ***BAN**** Nebulizer was combined with the OPEP device. Regional doses were then determined from anterior and posterior gamma camera images collected after delivery. Lung perimeters were defined using Cobalt-57 transmission scans and applied to Tc-DTPA deposition images. Results were expressed as a percentage of baseline counts. **Results:** Average age of all 8 subjects (4 male, 4 female) was 33 years. Whole lung deposition was, on average, 31 ± 13 vs. 32 ± 13% of loaded dose for ***BAN**** Nebulizer alone and ***BAN**** Nebulizer + OPEP respectively. **Conclusions:** The delivery of medication from the ***AeroEclipse**** ***II BAN**** Nebulizer to the lungs was not significantly affected by the incorporation of the ***Aerobika**** OPEP device. This therapy could offer the clinician the opportunity for combined aerosol/OPEP therapy (i.e. in cystic fibrosis patients) thereby reducing the time needed for the patient to take nebuliser and OPEP treatment separately.



COMPARISON OF MEDICATION DELIVERY FROM NEBULIZERS WHEN COUPLED TO OSCILLATORY POSITIVE EXPIRATORY PRESSURE DEVICES. J Suggett, V Wang, V Avvakoumova, M Nagel. American Journal of Respiratory and Critical Care Medicine 2019;199:A5717.

Rational: Treatment of chronic lung diseases typically includes the use of a small volume nebulizer (SVN) to aerosolize medications. To reduce total therapy time nebulizers and oscillatory positive expiratory pressure (OPEP) devices can be combined, however, practitioners should also ensure that there is no meaningful change in medication delivery. **Methods:** To assess this a breathing simulator (ASL 5000 IngMar, US) was used to generate a pattern that a patient could comfortably perform over the length of the nebulizer treatment (tidal volume: 600 mL, 10 BPM, IE of 1:2 with a 2 second breath hold between inhalation and exhalation). 2 different OPEP/SVN devices (***Aerobika****** OPEP device (TMI, Canada) + ***AeroEclipse****** ***II BAN****** Nebulizer and acapella† choice (Smiths Medical, US) + VixOne† SVN (*n* = 5 devices, 1 replicate for each) were chosen for the study. For the acapella† choice the nebulizer was placed between the mouthpiece and the OPEP device. Each OPEP device was set at their highest resistance to enable direct comparison and each nebulizer was filled with 3 mL of albuterol (2.5 mg/3 mL). A filter was attached and sealed to the mouthpiece of each device and the filter connected to the breathing simulator. Each nebulizer was operated for 60 seconds using 8 L/min medical air, after which, the filter was removed, and a clean filter inserted. This process was repeated until the nebulizer began to sputter. High performance liquid chromatography was used to analyze the aerosol deposited onto the filters. **Results:** The results table show mean ± SD of medication delivery for each system. A relatively small decrease in medication delivery was observed with the addition of the ***Aerobika****** OPEP device to the nebulizer it was paired with. The nebulizer paired with the acapella† choice OPEP device, even when used alone, delivered substantially less medication. When coupled together medication delivery was reduced even further resulting in less than 10% delivery compared to the other nebulizer + OPEP combination.

AeroEclipse* ***II BAN**** **Nebulizer alone**	**with *Aerobika**** **OPEP device**	**VixOne† SVN alone**	**with acapella† choice OPEP**
869.8 ± 46.0 µg	764.0 ± 18.0 µg	207.4 ± 8.4 µg	57.4 ± 4.9 µg

Conclusions: The experiments reported in this study should caution practitioners regarding the interchangeability of OPEP and aerosol delivery devices. Our findings reinforce the message that data obtained with one combination of devices cannot be extrapolated to others.

PAIRING OF OSCILLATING POSITIVE EXPIRATORY PRESSURE (OPEP) DEVICES WITH A BREATH ACTUATED NEBULIZER: CHOICE OF OPEP DEVICE IS IMPORTANT. D Coppolo, JA Suggett, MW Nagel, JP Mitchell. Pediatric Pulmonology 2017;52(S47):397.

Background/Objective: Pairing an oscillating positive expiratory pressure (OPEP) device with a breath actuated nebulizer (***AeroEclipse****** ***II BAN****** Nebulizer, Monaghan Medical Corporation (MMC)) offers an opportunity to deliver bronchodilator therapy during inhalation with secretion clearance during exhalation, thereby optimising potential therapeutic benefit without extending treatment times. However, clinicians might wish to vary OPEP-***BAN****** Nebulizer device pairings for a variety of reasons, including cost and availability. The present study was undertaken to see how substituting the ***Aerobika****** OPEP device (MMC), that was optimized for use with the ***AeroEclipse****** ***BAN****** Nebulizer, with a vPEP† (D R Burton Healthcare LLC, Farmville, NC) device, might influence medication delivery. **Methods:** An ***AeroEclipse****** ***II BAN****** Nebulizer (MMC, *n* = 3 replicates) operated with compressed air at 50 psig was evaluated for the delivery of albuterol solution, chosen as the analyte to track aerosol delivery, with and without the ***Aerobika**** OPEP device inserted between the mouthpiece and nebulizer. The nebulized droplets were collected on a bacterial/viral filter located at the mouthpiece, sampling at a constant flow rate of 30 L/min. The test protocol was repeated with the vPEP† substituted for the ***Aerobika**** OPEP device. The mass of albuterol recovered from each filter was quantified by an HPLC-UV spectrophotometric assay. **Results:** Using the ***BAN****** Nebulizer mean delivered mass as the reference, the output only decreased by 4.9% with the ***Aerobika**** OPEP device in tandem, but fell substantially further by 67.6% when the vPEP† was substituted (unpaired t-test, $p < 0.001$). **Conclusions:** Pairing the ***BAN****** Nebulizer with the vPEP† device greatly impaired the output of medication. Clinicians should be aware not to substitute alternative OPEP devices for the ***Aerobika**** OPEP device when seeking to take advantage of concomitant therapy.

COMBINING INHALATION BY A BREATH-ACTUATED NEBULIZER AND EXHALATION WITH OSCILLATING POSITIVE EXPIRATORY PRESSURE DEVICE (OPEP) OFFERS POTENTIAL FOR SIMULTANEOUS THERAPY: A LABORATORY STUDY. R Sharpe, J Suggett, V Avvakoumova, H Schneider, R Ali, M Nagel. Journal of Cystic Fibrosis 2015;14(1):S101.

Objective: Mobilization of secretions by OPEP is often given separately to aerosol delivery. Combining a nebulizer [***AeroEclipse*** ***II BAN**** Nebulizer, Trudell Medical International (TMI)] with OPEP (***Aerobika**** OPEP device, TMI), both therapies can be delivered concurrently. We investigated if the ***BAN**** Nebulizer output is affected by use with the ***Aerobika**** OPEP device, or by substituting another OPEP product (acapella† duet, Smiths Medical). **Methods:** A Next Generation Cascade Impactor operated at 15 L/min was used in accordance with United States Pharmacopeia (USP) <1601>'Products for Nebulization' to make droplet size measurements of the ***BAN**** Nebulizer aerosol (3 × 3 replicates/device) operated by compressed air at 50 psig. The ***BAN**** Nebulizer was filled with 4 mL ipratropium bromide anticholinergic solution (0.5 mg/mL, Teva†), and connected directly to the USP induction port. Measurements were made (a) with the ***Aerobika**** OPEP device inserted between the ***BAN**** Nebulizer and induction port, and (b) substituting the acapella† duet OPEP device. The ***BAN**** Nebulizer was run to sputter, and the therapeutically beneficial fine particle mass < 5.4 mm diameter (FMipr) determined. **Results:** FMipr (mean ± SD) via the ***BAN**** Nebulizer alone, with the ***BAN**** Nebulizer-***Aerobika**** OPEP device, and the ***BAN**** Nebulizer-acapella† duet OPEP devices were 452 ± 28, 426 ± 27 and 308 ± 23 mg respectively. The ***BAN**** Nebulizer-***Aerobika**** OPEP device combination marginally reduced delivery (paired t-test, p = 0.043), whereas the ***BAN**** Nebulizer-acapella† duet configuration resulted in substantial losses (p < 0.001). **Conclusion:** An ***AeroEclipse*** ***II BAN**** Nebulizer-***Aerobika**** OPEP device combination offers combined aerosol/OPEP therapy with minimal medication loss. Substitution with the acapella† duet OPEP results in substantial reduction in ***BAN**** Nebulizer output that may have adverse clinical implications.

COMBINING INHALATION BY A BREATH-ACTUATED NEBULIZER WITH EXHALATION THROUGH AN OSCILLATING POSITIVE PRESSURE DEVICE (OPEP) OFFERS THE POTENTIAL FOR COMBINED THERAPY. JP Mitchell, J Suggett, M Nagel, V Avvakoumova, R Ali, H Schneider. Drug Delivery to the Lungs-24 2013;1:322-325.

Summary: A novel handheld oscillating positive expiratory pressure (OPEP) therapy device (***Aerobika**** OPEP device, Trudell Medical International (TMI), London, ON, Canada) has been developed that can be used in conjunction with the ***AeroEclipse*** ***II BAN**** Nebulizer (BA, TMI). The ***Aerobika**** OPEP device by itself has shown promising signs from lung imaging studies for the opening of secretion obstructed airways. A follow-on study is reported here, evaluating how the OPEP-***BAN**** Nebulizer configuration performs for the delivery of three different inhaled medications deliverable by nebulizer that might be used clinically in support of improving airway patency or reducing underlying inflammation. Combining the ***AeroEclipse*** ***II BAN**** Nebulizer with the ***Aerobika**** OPEP therapy device reduced only slightly the overall aerosol delivery in terms of either total emitted mass (TEM) with all three formulations. The resulting aerodynamic particle size distribution (APSD) data were also slightly displaced to finer sizes by the presence of the OPEP device. These size shifts represent marginally increased retention of the coarser, less therapeutically beneficial particles in transit through the OPEP device, most likely due to inertial effects at the valve support as otherwise the flow path contains no obstructions or bends that might increase turbulent deposition. Hence, in terms of fine particle mass (FPM), the presence of the ***Aerobika**** OPEP device resulted in no difference for two of the three formulations (paired t-test, $p \geq 0.38$), and only a statistically marginal reduction for the third. **Introduction:** The burden of therapy for secretion mobilization for patients with cystic fibrosis (CF) to mitigate inflammation of the airways as the result of bacterial and fungal infection[1] has a major impact on their quality of life, mainly because of treatment duration and frequency[2]. In bronchiectasis, failure to clear secretions allows bacteria and fungal spores to collect in them, which leads to the generation of more secretions accompanied by inflammation that further damages the airways, thereby causing more dilation in a vicious cycle[3]. Similar considerations apply with the management of secretions in pulmonary rehabilitation for patients with chronic obstructive pulmonary disease (COPD)[4]. Oscillating positive expiratory pressure (OPEP) therapy is an established component in secretion management therapy[5]. To date, OPEP has been routinely given at separate time to inhaled medical aerosol therapy, because the former is associated with exhalation whereas the latter can only be done effectively during inhalation. A novel OPEP therapy system (***Aerobika**** OPEP device, Trudell Medical International, London, ON, Canada) has recently been developed to provide patients undergoing secretion management the opportunity to receive therapy using a handheld device[6]. If the ***Aerobika**** OPEP device is considered by itself, when the patient exhales, the one way valve closes, diverting the flow through the body of the device, mechanically operating the vane that generates oscillatory pressure pulsations which are transmitted back to the patient (Figure 1a). Importantly, however, when the patient inhales through the device, the one way valve opens allowing inhalation air flow to pass directly through the device with the minimum of internal obstruction (Figure 1b). Lung imaging studies in adults with COPD have shown significant improvements in lung ventilation and dyspnoea when the ***Aerobika**** OPEP device was used on its own[7]. However, this device is designed so that the ***AeroEclipse*** ***II BAN**** Nebulizer can be coupled directly in tandem to its inlet (Figure 2), so that nebulized inhaled medications can be delivered upon inhalation. This combination of devices therefore offers the potential to combine secretion mobilization therapy with the administration of inhaled bronchodilators or corticosteroids to improve airway patency or inflammation respectively in one treatment. The object of this study was to evaluate the performance of this combination with three different nebulizer delivered medications that might be used in the clinic in support of bronchodilatation and reduction of inflammation in the airways of the lungs. **Materials and Methods:** Measurements were made (9 replicates/condition) in accordance with the procedure for aerodynamic particle size analysis in <1601> of the US Pharmacopeia[8], using a Next Generation Impactor (NGI) equipped with a Ph. Eur./USP induction port and operated at 15.0 L/min ± 5%. The ***BAN**** Nebulizer on test was operated by a compressed air supply at 345 kPa (50 psig). Fill volumes and concentration of active pharmaceutical ingredient(s) (APIs) are given in Table 1. Measurements were made during the entire run time of the nebulizer from start of nebulization until one minute past the onset of sputter. API recovery and subsequent assay for each solution were each undertaken by validated procedures involving HPLC spectrophotometry for API assay. Total emitted mass (TEM) and fine particle fraction < 5.4 µm aerodynamic diameter ($FPF_{<5.4\mu m}$) of recovered active pharmaceutical ingredient(s) were determined from the collected particles in the CI system, and subsequently used to calculate emitted fine particle mass ($FPM_{<5.4\mu m}$). Benchmark measurements were made with the same nebulizers without the OPEP device present.

Table 1: API Fill Volumes and Solution Concentrations Evaluated

Formulation/Manufacturer	API Mass Concentration (%w/v)	Fill Volume (mL)
Ventolin† Nebules/GSK† (Canada)	833 µg/mL albuterol sulfate	1 x 3.0 mL
Ipratroprium/Pharmascience Canada	250 µg/mL ipratropium bromide	2 x 2.0 mL
Pulmicort† Nebuamp†/AstraZeneca† Canada	250 µg/mL budesonide	2 x 2.0 mL

Results: The results of the CI measurements are summarized in Table 2. Comparative APSDs obtained with and without the ***Aerobika**** OPEP device are illustrated in Figures 3a, 3b and 3c.

Table 2: Summary of NGI Based Measurements (mean ± SD) of API Delivery from the ***AeroEclipse**** ***II BAN**** Nebulizer with and without ***Aerobika**** OPEP Therapy Device

Formulation	API	*Aerobika** OPEP device present	TEM (µg API)	$FPF_{<5.4µm}$ (%)	$FPM_{<5.4µm}$ (µg API)
Ventolin† Nebule†	salbutamol sulphate	NO	1,288 ± 79	78.0 ± 1.2	1,004 ± 70
		YES	1,258 ± 60	82.8 ± 1.2	1,042 ± 43
Ipratropium (Generic)	ipratropium bromide	NO	582 ± 30	77.6 ± 1.3	452 ± 28
		YES	515 ± 23	82.8 ± 1.0	426 ± 27
Pulmicort† Nebuamp†	budesonide	NO	488 ± 20	57.0 ± 2.6	278 ± 8
		YES	406 ± 26	61.6 ± 2.2	250 ± 21

Discussion: Combining the ***AeroEclipse**** ***II BAN**** Nebulizer with the ***Aerobika**** OPEP device had minimal effect on the overall aerosol delivery in terms of TEM with all three formulations. The resulting APSD data were also slightly displaced to finer sizes by the presence of the OPEP device. These size shifts represent marginally increased retention of the coarser, less therapeutically beneficial particles in transit through the OPEP device, most likely due to inertial effects at the valve support, since the flow path otherwise contains no obstructions or bends that might increase turbulent deposition. Hence the delivery of budesonide fine particles (FPM) was only marginally reduced by ca. 5% when the ***Aerobika**** OPEP device was present (paired t-test, $p = 0.043$), and the effect was statistically insignificant with either of the other formulations ($p \geq 0.38$). The ability to carry out inhalation therapy at the same time as receiving OPEP secretion mobilization treatment has obvious advantages for the patient and caregiver, however, the precise timing when to introduce ***BAN**** Nebulizer based therapy will be established by individual clinical experience. In this context, it is important to note that the ***Aerobika**** OPEP device is sufficiently versatile that it can be used on its own to begin with until secretion movement has become significant, indicating that airway patency is improving to the point at which bronchodilatation or anti-inflammatory inhaled aerosol therapy would be beneficial. Since this work has demonstrated that the new OPEP therapy device can be used with the ***AeroEclipse**** ***II BAN**** Nebulizer with negligible impact on the performance of the latter, it may be tempting to combine the ***BAN**** Nebulizer with an alternative OPEP device. However, *in vitro* studies have shown that such combinations are unlikely to be effective[6], unless the inhalation air flow pathway through the secretion mobilization device is optimized. **Conclusions:** This investigation of a novel OPEP therapy device used in conjunction with the ***AeroEclipse**** ***II BAN**** Nebulizer has the potential to offer the ability to give simultaneous combined secretion mobilization treatment with the delivery of inhaled medications for the treatment of the underlying bronchoconstriction and inflammation. **References:** [1] Emerging Therapies For Cystic Fibrosis Lung Disease. BK Rubin. CHEST 1999;115:1120-1126. [2] Finding Evidence To Support Airway Clearance Techniques In Cystic Fibrosis. SA Prasad, E Main. Disability and Rehabilitation 1998;20(6-7):235-246. [3] Bronchiectasis. AE O'Donnell. CHEST 2008;134:815-823. [4] ACCP Evidence-Based Clinical Practice Guidelines: Nonpharmacologic Airway Clearance Therapies. FD McCool, MJ Rosen. CHEST 2006;129:250S-259S. [5] Positive Expiratory Pressure And Oscillatory Positive Expiratory Pressure Therapies. TR Myers. Respiratory Care 2007;52(10):1308-1327. [6] Combining Oscillating Positive Expiratory Pressure Therapy With Inhalation Of Bronchodilator Via A Breath-Actuated Nebulizer: Initial Evaluation Of *In Vitro* Data To Determine Nebulizer Performance. J Schmidt, M Nagel, H Schneider, V Avvakoumova, C Doyle. Respiratory Drug Delivery 2013;2:369-372. [7] Hyperpolarized ^{3}He Magnetic Resonance Imaging Following Oscillatory Positive Expiratory Pressure Treatment In Gold Stage II and III COPD. S Svenningsen, BN Jobse, A Hasany, N Kanhere, M Kirby, J Suggett, DG McCormack, G Parraga. American Journal of Respiratory and Critical Care Medicine 2013;187:A4885. [8] United States Pharmacopeial Convention. <1602> Products for Nebulization. USP 36/NF 31. Rockville, MD, USA, 2013.

COMBINING OSCILLATING POSITIVE EXPIRATORY PRESSURE THERAPY WITH INHALATION OF BRONCHODILATOR VIA A BREATH-ACTUATED NEBULIZER AS A NEW TREATMENT MODALITY IN CYSTIC FIBROSIS (CF): *IN VITRO* DATA TO DETERMINE NEBULIZER PERFORMANCE. D Coppolo. JP Mitchell, J Schmidt, A Meyer. Pediatric Pulmonology 2013;48(S36):417.

Background: Oscillating positive expiratory pressure (OPEP) is an established treatment modality to mobilize lung secretions in CF. Bronchodilation by beta-2 adrenergic agonist formulations is also well established, but efficacy is limited due to the ability of the aerosol to penetrate only those airways that are not plugged with secretions. OPEP therapy with a breath actuated nebulizer offers the prospect of combining secretion mobilization with aerosol based therapy, but it is necessary to quantify any effect that the OPEP device may have on medication delivery from the breath actuated device. **Study Objective:** To determine the effect of imposing an oscillating positive expiratory pressure device (***Aerobika**** OPEP device, Trudell Medical International (TMI), London, ON, Canada) between the mouthpiece of a breath actuated jet nebulizer (***AeroEclipse**** ***II BAN**** Nebulizer, TMI) on the mass of model active pharmaceutical ingredient (API) available for inhalation. **Methods:** Measurements were made (9 replicates) using albuterol solution for nebulization (3 mL fill, 0.833 mg/mL API) as the model bronchodilator. Total (TM_{alb}) and fine droplet mass < 5.4 µm (FM_{alb}) were determined by Next Generation Impactor (NGI) equipped with a Ph. Eur./USP induction port and operated at 15.0 L/min ± 5%. The ***BAN**** Nebulizer alone was operated by compressed air delivered at 50 psig, with the mouthpiece connected directly to the inlet of the cascade impactor. The measurements were repeated with the OPEP device inserted between the ***BAN**** Nebulizer and inlet to the impactor. The ***BAN**** Nebulizer on test was run to onset of sputter, and the total mass of albuterol recovered and assayed by a validated HPLC-UV spectrophotometric method. **Results:** TM_{alb} (mean ± SD) via the ***BAN**** Nebulizer alone and for the ***BAN**** Nebulizer-OPEP combination were 1,288 ± 79 µg and 1,258 ± 60 µg respectively. Corresponding values of the therapeutically

beneficial FM_{alb} were 1,004 ± 70 µg and 1,042 ± 43 µg respectively. **Conclusions:** A design goal for the ***Aerobika**** OPEP device has been to make aerosol movement through the OPEP device during inhalation unrestricted, since the OPEP mechanism is not introduced to the flow pathway until exhalation takes place. The delivery of medication as fine particles from the ***BAN**** Nebulizer was confirmed comparable (paired t-test, $p = 0.221$) by combining it with the ***Aerobika**** OPEP device, offering the patient the opportunity for combined aerosol/OPEP therapy.

COMBINING OSCILLATING POSITIVE EXPIRATORY PRESSURE THERAPY WITH INHALATION OF BRONCHODILATOR VIA A BREATH-ACTUATED NEBULIZER: INITIAL EVALUATION OF *IN VITRO* DATA TO DETERMINE NEBULIZER PERFORMANCE. J Schmidt, M Nagel, H Schneider, V Avvakoumova, C Doyle. Respiratory Drug Delivery 2013;2:369-372.

Introduction: The creation of oscillating positive expiratory pressure (OPEP) is a well established therapy to mobilize secretions associated with lung diseases in pulmonary rehabilitation[1], in particular in association with COPD[2] and cystic fibrosis[3]. To date, OPEP therapy has usually been given at a separate time following initial delivery of inhaled medical aerosol therapy for the relief of bronchoconstriction[4]. The most likely reason is that the former is associated with exhalation, whereas the latter can only be done effectively during inhalation. A new handheld oscillatory positive expiratory pressure device (***Aerobika**** OPEP device, Trudell Medical International (TMI), London, ON, Canada) has been developed that can be connected directly to the ***AeroEclipse**** ***II BAN**** Nebulizer (BA, TMI), so that the patient can receive both treatments concurrently. ***BAN**** **Nebulizer-OPEP System:** The ***Aerobika**** OPEP device can also be used with any continuous nebulizer. We report the outcome of *in vitro* measurements of ***BAN**** Nebulizer performance as part of research into the capability for the new OPEP device. The ***Aerobika**** OPEP device is readily attached to the ***AeroEclipse**** ***II BAN**** Nebulizer by removing the mouthpiece and attaching the outlet of the OPEP device in its place (Figure 1). The medication containing aerosol generated from the ***BAN**** Nebulizer upon inhalation passes through the OPEP device via a short, low resistance pathway containing an open one way valve before being inhaled. In this configuration, the aerosol flow path is linear with minimal restriction to mitigate internal losses caused by inertial impaction. When the patient exhales, the one way valve closes, diverting the flow through the body of the OPEP device mechanically operating the vane that generates oscillatory pressure pulsations to mobilize secretion removal from the airways of the lungs that are transmitted back to the patient (Figure 2). Initial results from a clinical study with the ***Aerobika**** OPEP device alone performed at the Robarts Research Institute, London, ON, Canada reported improvements in pulmonary function tests and lung imaging data following use by COPD patients[5]. **Materials and Methods:** Measurements were made (9 replicates) in accordance with the procedure for droplet size analysis for Products for Nebulization in the US Pharmacopeia[6]. The Next Generation Impactor (NGI) was equipped with a Ph. Eur./USP induction port and operated at 15.0 L/min ± 5%. The ***BAN**** Nebulizer was filled with 4 mL ipratropium bromide solution (0.25 mg/mL), widely used as an anticholinergic in the treatment of COPD[7], and operated by compressed air delivered at 50 psig. The ***BAN**** Nebulizer was initially tested connected directly to the induction port via a leak tight fitting, then the measurements were repeated with the ***Aerobika**** OPEP device inserted between the ***BAN**** Nebulizer and induction port. Finally, measurements were made with a widely available alternative OPEP device in lung secretion mobilization (acapella†, Smiths Medical North America, Dublin, OH, USA[3]), substituted for the ***Aerobika**** OPEP device in order to examine what might happen if a clinician was to make this substitution. The ***BAN**** Nebulizer was run to onset of sputter, and the total mass of ipratropium bromide (TM_{ipr}) recovered and assayed by a validated HPLC-UV spectrophotometric method. **Results:** TM_{ipr} (mean ± SD) via the ***BAN**** Nebulizer alone, for the ***BAN**** Nebulizer-***Aerobika**** OPEP device, and for the ***BAN**** Nebulizer-acapella† OPEP systems were 582 ± 30, 515 ± 28 and 178 ± 21 µg respectively, equivalent to delivery rates of 1.9 ± 0.1, 1.6 ± 0.1 and 0.4 ± 0.05 µg/s. Corresponding values of the therapeutically more important fine droplet mass < 5.4 µm for bronchodilatation of the airways of the lungs (FM_{ipr})[8] were 452 ± 28, 426 ± 27 and 177 ± 21 µg respectively. Combining the ***AeroEclipse**** ***II BAN**** Nebulizer with the ***Aerobika**** OPEP device marginally reduced aerosol delivery in terms of FM_{ipr} by ca. 5% (1-way ANOVA, $p = 0.043$), whereas substitution by the acapella† device resulted in a significantly greater loss of medication ($p < 0.001$). The marginal decrease in output associated with the ***BAN**** Nebulizer-OPEP configuration is an unsurprising outcome, given that the aerosol transport pathway involves passing through the one way valve, and has also been extended by virtue of using the OPEP aid. However, the decrease when the acapella† device was substituted was much larger, being close to 60%, potentially due to a restricted aerosol pathway. **Conclusions:** The delivery of medication from the ***AeroEclipse**** ***II BAN**** Nebulizer is only marginally reduced by combining the ***BAN**** Nebulizer with the ***Aerobika**** OPEP device, offering the patient the opportunity for combined aerosol/OPEP therapy. Substitution by devices that do not allow incoming aerosol to be transported directly to the patient, are likely to result in substantial loss of aerosol from this nebulizer. **References:** [1] Pulmonary/Cardiac/Cancer Rehabilitation. P Gonzalez, SC Cuccurullo, I Jafri, L Luciano. 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American Journal of Respiratory and Critical Care Medicine 2013;187:A4885.

COMBINING INHALATION BY A BREATH ACTUATED NEBULIZER WITH EXHALATION THROUGH AN OSCILLATING POSITIVE PRESSURE DEVICE (OPEP) OFFERS THE POTENTIAL FOR OPTIMAL COMBINED THERAPY. JP Mitchell, V Avvakoumova, H Schneider, R Ali, MW Nagel. American Journal of Respiratory and Critical Care Medicine 2013;187:A4116.

Rationale: To date OPEP therapy to mobilize secretions associated with obstructive lung disease has been routinely given at separate time to inhaled medical aerosol therapy. OPEP therapy is associated with exhalation whereas medication delivery is undertaken during inhalation. A combination of breath actuated nebulizer (***AeroEclipse**** ***II BAN**** Nebulizer, Trudell Medical International (TMI), London, ON, Canada) with OPEP (***Aerobika**** OPEP device, TMI) enables both treatments to take place simultaneously. We report the outcome of an *in vitro* study to verify that output of aerosolized medication from the ***BAN**** Nebulizer is unaffected by the OPEP addition, and to compare this condition with the ***BAN**** Nebulizer` coupled to a frequently prescribed

oscillatory PEP device (acapella†, Smiths Medical North America, Dublin, OH). **Methods:** Measurements were made (9 replicates/condition) in accordance with the procedure for aerodynamic particle size analysis in <1601> of the US Pharmacopeia, using a Next Generation Impactor (NGI) equipped with a Ph. Eur./USP induction port and operated at 15.0 L/min ± 5%. The ***BAN**** Nebulizer on test was filled with 3 mL albuterol solution (2.5 mg/3 mL) and operated by compressed air delivered at 50 psig. The ***BAN**** Nebulizer` was initially connected directly to the induction port via a leak tight fitting, then the measurements were repeated with the ***Aerobika**** OPEP device inserted between the ***BAN**** Nebulizer and induction port. Finally, measurements were made with the acapella† substituted for the ***Aerobika**** OPEP device. The ***BAN**** Nebulizer on test was run to onset of sputter, and the total mass of albuterol (TM_{alb}) recovered and assayed by a validated HPLC-UV spectrophotometric method. **Results:** TM_{alb} (mean ± SD) via the ***BAN**** Nebulizer alone, for the ***BAN**** Nebulizer-***Aerobika**** OPEP device, and for the ***BAN**** Nebulizer-acapella† were 1,288 ± 79, 1,258 ± 60 and 422 ± 47 µg respectively, equivalent to delivery rates of 5.8 ± 0.3, 5.8 ± 0.3 and 1.8 ± 0.2 µg/s. Combining the ***BAN**** Nebulizer with the ***Aerobika**** OPEP device did not affect aerosol delivery (paired t-test, $p = 0.38$), whereas substitution by the acapella† device resulted in a significant loss of medication (unpaired t-test, $p < 0.001$). **Conclusions:** The delivery of medication from the ***AeroEclipse**** ***II BAN**** Nebulizer is not significantly affected by combining the ***BAN**** Nebulizer with the ***Aerobika**** OPEP device compared with the ***BAN**** Nebulizer alone, offering the patient the opportunity for combined aerosol/OPEP therapy. Substitution by other devices offering similar oscillatory therapy on exhalation results in substantial loss of aerosol from the ***BAN**** Nebulizer.

AeroEclipse XL BAN** Nebulizer

SUMMARY BY ACTIVE PHARMACEUTICAL INGREDIENT

Albuterol Sulfate/Salbutamol Sulfate (Ventolin†, GSK† Inc.)

DELIVERY OF INHALED MEDICATION IS MAINTAINED BY A BREATH-ACTUATED NEBULIZER WHEN USED BY PATIENTS WITH DIFFERING INHALATION/EXHALATION RATIOS: A LABORATORY STUDY USING ALBUTEROL SULFATE SOLUTION FOR NEBULIZATION. J Suggett, M Nagel, V Avvakoumova, V Wang, D Coppolo, JP Mitchell. American Journal of Respiratory and Critical Care Medicine 2016;193:A5843.

Rationale: Breath actuated pneumatic nebulizers only deliver aerosolized medication during the inhalation component of each tidal breathing cycle. In contrast, continuous output (CONs) and breath enhanced nebulizers (BENs), continue to deliver aerosol during exhalation. The inspiratory:expiratory (I:E) ratio may vary from 1:1 to as much as 1:4 in the presence of obstructive lung disease. This laboratory study sought to compare the output of nebulizers at different I:E ratios simulating potential real patient breathing pattern. **Methods:** Measurements were undertaken with the following nebulizer systems: ***AeroEclipse* XL BAN**** Nebulizer with ***Ombra**** Table Top Compressor, Monaghan Medical Corporation; ProBasics† Rite-Neb 3† CON with compressor, PMI; Mini nebulizer CON with compressor, Roscoe Medical Inc.; SideStream† Plus BEN with InnoSpire Essence† compressor, Phillips Healthcare. Each nebulizer (n = 3/group) was filled with 3.0 mL fill of 2.5 mg albuterol sulfate (AS) and the mouthpiece connected to a breathing simulator (ASL 5000, IngMar Medical Ltd.). Tidal volume (V_t) was fixed at 500 mL to mimic adult use, but I:E ratio and rate/minute were varied as presented in Table 1. Emitted droplets were collected at minute intervals to first sputter by a filter positioned at the mouthpiece; AS recovered from the filter was assayed by HPLC-UV spectrophotometry. **Results:** Measures of total emitted mass (TEM (µg); mean ± SD) are summarized in the Table. TEM from the ***BAN**** Nebulizer was unaffected by changes in breathing pattern (1-way ANOVA, p = 0.97), whereas the output from the other nebulizers was lower generally and decreased with increasing I:E ratio (1-way ANOVA for each nebulizer-compressor, p < 0.001).

Table 1: Total Emitted Mass from Nebulizers at Different Tidal Breathing Patterns

Nebulizers/ Compressors	**I:E ratio/rate per minute**			
	1:1/15	1:2/10	1:3/7	1:4/6
AeroEclipse* XL BAN* Nebulizer/***Ombra**** Table Top Compressor	985 ± 93	964 ± 81	960 ± 80	979 ± 37
ProBasics† Rite-Neb 3† CON/compressor	673 ± 26	528 ± 6	354 ± 4	302 ± 15
Mini nebulizer CON/compressor	441 ± 8	301 ± 14	245 ± 14	176 ± 30
SideStream† Plus BEN/InnoSpire Essence†	467 ± 23	344 ± 10	270 ± 9	231 ± 11

Conclusions: A more consistent dose delivery was achieved across the range of I:E ratios tested with the ***BAN**** Nebulizer rather than the other nebulizer types. The ability to conserve medication for delivery only when the patient inhales, would result in more consistent therapy if I:E ratio was to change in association with disease progression.

VERSATILITY OF A NEW RE-USABLE BREATH-ACTUATED NEBULIZER INTENDED FOR DOMICILIARY USE WITH ITS TABLE-TOP COMPRESSOR: *IN VITRO* COMPARISON IN BREATH-ACTUATED AND CONTINUOUS DELIVERY MODES WITH A CONTINUOUS HIGH OUTPUT JET NEBULIZER. D Coppolo, J Mitchell, V Avvakoumova, R Ali, H Schneider, M Nagel. American Journal of Respiratory and Critical Care Medicine 2013;187:A2607.

Rationale: It can be helpful in the home based situation to be able to provide rapid bronchodilator therapy by nebulizer during exacerbations of obstructive lung disease. A new reusable breath actuated nebulizer (reusable ***AeroEclipse* BAN**** Nebulizer, Monaghan Medical Corporation (MMC)) does not waste medication during exhalation, but can be converted to continuous output by rotating the green selector button in the center of the nebulizer cap when the patient cannot operate the device in breath actuated mode and/or to shorten overall treatment time. We evaluated this device operated in both modes using its table top compressor (***Ombra**** Table Top Compressor, MMC), and comparing performance with that of a reusable high output venturi jet nebulizer (SideStream†, Respironics† Inc., Pittsburgh, PA) equipped with Inspiration† Elite table top compressor, chosen as a benchmark. **Methods:** The nebulizer on test (n = 5/group) was filled with 2.5 mL, 1.0 mg/mL albuterol solution (Ventolin†, GSK† Canada Inc.), and connected to a breathing simulator (ASL 5000, IngMar Medical Ltd., Pittsburgh, PA), mimicking adult tidal breathing (V_t = 600 mL; duty cycle = 33%; rate = 10 cycles/minute). The reusable ***AeroEclipse* BAN**** Nebulizer was first operated in breath actuated mode, and testing was subsequently repeated with the same nebulizer set to continuous operation. Emitted aerosol was captured on a filter located at the mouthpiece, replaced at minute intervals until onset of sputtering, defining run time. Recovery/assay of salbutamol was undertaken by HPLC-UV spectrophotometry. Fine droplet fraction ($FDF_{<4.7µm}$) and mass median droplet diameter (MMD) were determined by laser diffractometry in a parallel study. Total fine droplet mass ($FDM_{<4.7µm}$) was the product of total mass and $FDF_{<4.7µm}$. Comparative measurements were reusable SideStream† nebulizers. **Results:** Table 1 summarizes the outcomes from these measurements.

Table 1: Performance Measures (mean ± SD) for the Nebulizer Table Top Compressor Systems Evaluated

System	Reusable *AeroEclipse* BAN** Nebulizer/*Ombra** Table Top Compressor		SideStream† Nebulizer/Inspiration† Elite Compressor
Operating Mode	Breath Actuated	Continuous	Continuous
FDF$_{<4.7\mu m}$ (%)	70.8 ± 1.0		68.6 ± 1.5
MMD (µm)	3.39 ± 0.05		3.43 ± 0.11
FDM$_{<4.7\mu m}$ (µg)	503 ± 39	349 ± 13	233 ± 6
Run time (minutes)	10	7	10

Conclusions: Treatment time with the reusable ***AeroEclipse*** **BAN**** Nebulizer/***Ombra*** Table Top Compressor was reduced by 36%, when used in continuous mode, significantly shorter than the 10 minutes required by the SideStream†/Inspiration† Elite system. The longer run time for the ***AeroEclipse*** **BAN**** Nebulizer/***Ombra*** Table Top Compressor system in the breath actuated mode reflects the fact that aerosol is only delivered during inhalation and not wasted to the environment. Both systems provided highly respirable aerosol with values of FDF$_{<4.7\mu m}$ close to 70%, but FDM$_{<4.7\mu m}$ from the ***AeroEclipse*** **BAN**** Nebulizer/***Ombra*** Table Top Compressor system in either mode of operation was significantly greater than the equivalent measure from the benchmark system (1-way ANOVA, $p < 0.001$).

EXTENDING THE CAPABILITY OF A BREATH-ACTUATED JET NEBULIZER FOR HOME AS WELL AS HOSPITAL USE – *IN VITRO* STUDIES TO CHARACTERIZE PERFORMANCE. J Malpass, J Mitchell, M Nagel, V Avvakoumova, Cathy Doyle, Rubina Ali. American Journal of Respiratory and Critical Care Medicine 2012;185:A5626.

Rationale: It is desirable that patients prescribed a breath actuated nebulizer in hospital can continue its use at home. However, domiciliary compressors typically operate at pressures < 3.4 bar associated with hospital wall outlet gas supplies. The ***AeroEclipse*** **XL BAN**** Nebulizer (Trudell Medical International, London, ON, Canada), has been developed to meet this need. This laboratory investigation was undertaken to guide transitioning patients to the new nebulizer. **Methods:** A simulator (ASL 5000, Ingmar Medical Ltd., Pittsburgh, PA) was used to generate adult breathing (tidal volume = 600 mL; duty cycle = 33%; rate = 10 cycles/minute). The nebulizer on test was coupled to the simulator via its mouthpiece and evaluated with 2.5 mL fill of salbutamol (0.1% w/v). ***AeroEclipse*** **XL BAN**** Nebulizers (n = 5) were operated by Table Top or Portable Compressor (***Ombra***, Trudell Medical International)) at ca. 1.5 and 1.2 bar respectively. Total emitted mass (TEM) of salbutamol was determined on a minute by minute basis to sputter by filter collection of the aerosol at the mouthpiece. The same procedure was undertaken for LC† Sprint breath enhanced nebulizers (n = 5) powered by PARI BOY† SX and BOY† mobile S compressors at ca. 1.5 and 1.0 bar respectively (PARI Pharma GmbH, Starnberg, Germany), as benchmarks. Salbutamol assay was undertaken by HPLC-UV spectrophotometric analysis. In parallel experiments, fine droplet fraction < 4.7 µm diameter (FDF$_{<4.7\mu m}$) was determined for each nebulizer-compressor combination by laser diffractometry (Spraytec, Malvern Instruments Ltd., UK). The performance metrics were fine droplet mass < 4.7 µm (FDM$_{<4.7\ \mu m}$) as the product of TEM and (FDF$_{<4.7\mu m}$) and run time (t), with delivery rate/minute calculated from the ratio (FDM$_{<4.7\mu m}$)/t. **Results:** FDF$_{<4.7\mu m}$ (mean ± SD) for the ***AeroEclipse*** **XL BAN**** Nebulizer with table top and portable compressors were 70.8 ± 1.0 and 68.1 ± 0.9% respectively. FDF$_{<4.7\mu m}$ for the LC† Sprint with BOY† SX and BOY† mobile S compressors were 57.9 ± 3.1 and 52.0 ± 0.7% respectively. The variation of FDM$_{<4.7\mu m}$ with run time for all systems is illustrated in the Figure. Average FDM$_{<4.7\mu m/min}$ were 43.5 and 50.4 µg/min for the ***AeroEclipse*** **XL BAN**** Nebulizer with portable and table top compressors respectively, whereas equivalent rates for the LC† Sprint nebulizers were 37.8 and 56.3 µg/min with the PARI BOY† mobile S and SX compressors respectively. Treatment times for all combinations were approximately the same. **Conclusions:** The ***AeroEclipse*** **XL BAN**** Nebulizer has superior performance to the LC† Sprint nebulizer based on FDF$_{<4.7\mu m}$, but is equivalent in terms of FDM$_{<4.7\mu m/min}$. However, the breath actuation feature ensures compliance and a safe environment, because medication is only nebulized when the patient performs the inhalation maneuver.

COMPARATIVE *IN VITRO* PERFORMANCE OF A NEW RE-USABLE BREATH-ACTUATED NEBULIZER WITH HIGH PERFORMANCE AIR ENTRAINMENT (AEN) NEBULIZER SYSTEMS INTENDED FOR DOMICILIARY USE: TABLE TOP AND PORTABLE COMPRESSOR SYSTEMS. J Mitchell, V Avvakoumova, H Schneider, R Ali, M Nagel. Journal of Aerosol Medicine and Pulmonary Drug Delivery 2012;26(5):189-192.

Summary: We evaluated a new, reusable breath actuated device (***AeroEclipse*** **XL BAN**** Nebulizer, Trudell Medical International, London, ON, Canada), optimized with both its Table Top and Portable (***Ombra***) Compressor systems. We compared *in vitro* performance for delivery of salbutamol solution for nebulization, with that of a high output air entrainment nebulizer ((AEN) LC† Sprint, PARI GmbH, Starnberg, Germany) with equivalent compressors as benchmark systems. Adult tidal breathing was simulated by means of a test lung driven system with the aerosol collected at the nebulizer mouthpiece to provide measures of total mass of salbutamol. In parallel studies, the droplet size distribution of aerosol from each nebulizer-compressor system was determined by laser diffractometry, so that the mass median droplet diameter (MMD) and fine droplet fraction < 4.7 µm diameter (FDF$_{<4.7\mu m}$) could be determined. Values of MMD and FDF$_{<4.7\mu m}$ for the ***BAN**** Nebulizer generated droplets were near to 3.5 µm and 70% respectively with either compressor system, and likely to be sufficiently fine for efficient medication delivery to patients with narrowed airways. These investigations also confirmed that for either table top or portable compressor systems, despite generating aerosol droplets only during 33% of each simulated breathing cycle, the ***BAN**** Nebulizer provided comparable therapeutically beneficial fine droplet delivery of salbutamol to the benchmark AEN. The delivery rate/minute of fine droplets was near to constant for the first 6 minutes of delivery with the ***BAN**** Nebulizer, irrespective of compressor type, suggesting that the dosimetric capability of this device is available when used with the domiciliary compressors sold with this product. **Introduction:** Treatments with portable compressor/nebulizer systems can offer very different time dependent delivery profiles based on fine droplet mass, depending upon compressor type[1], and also compared with the profile that would be obtained with compressed air driven at a typical hospital wall outlet pressure of 50 psig (340 kPa)[2]. We evaluated in the laboratory a new, reusable breath actuated device (***AeroEclipse*** **XL BAN**** Nebulizer, Trudell Medical International, London, ON, Canada) optimized with its Table Top and Portable (***Ombra***) Compressor systems. We compared its performance in terms of delivery of a beta-2 adrenergic agonist, salbutamol solution for nebulization, with that for a

high output air entrainment nebulizer (LC† Sprint, PARI GmbH, Starnberg, Germany) also with the equivalent table top and portable compressors, to represent benchmark systems that are in widespread domiciliary use[3]. **Materials and Methods:** In the first part of the investigation, we operated each ***BAN**** Nebulizer with its associated ***Ombra**** Table Top Compressor and comparative measurements were made with the AEN and PARI BOY† SX table top compressor (Figure 1). In the second part, we operated each ***BAN**** Nebulizer with its ***Ombra**** Portable Compressor and compare performance with the AEN in association with the PARI BOY† mobile S portable compressor (Figure 2). We filled the nebulizer on test (n = 5/group) with 2.5 mL, 1.0 mg/mL salbutamol solution (Ventolin†, GSK† Canada Inc.) for both parts of the investigation, and connected it to a breathing simulator (ASL 5000, IngMar Medical Ltd., Pittsburgh, PA), mimicking adult tidal breathing (tidal volume (V_t) = 600 mL; duty cycle = 33%; breathing rate = 10 cycles/minute). We captured the emitted aerosol on a filter located at the mouthpiece, replaced at minute intervals until onset of sputtering, defining the run time, t_{run} (Figure 3). Recovery/assay of salbutamol was undertaken by HPLC-UV spectrophotometry. In parallel measurements, we also determined the fine droplet fraction < 4.7 µm diameter ($FDF_{<4.7µm}$) and mass median droplet diameter (MMD) by laser diffractometry (Figure 4). We subsequently calculated the fine droplet mass ($FDM_{<4.7µm}$) as the product of total mass (TM) and fine droplet fraction ($FDF_{<4.7µm}$). **Results and Discussion:** We observed that all droplet particle size distributions were unimodal, making it possible to calculate MMD from the LD measured distributions as the size that corresponded to the 50th volume (mass) percentile reported by the Spraytec LD. The performance metrics: $FDF_{<4.7µm}$, MMD, $FDM_{<4.7µm}$, t_{run} are summarized in Table 1. We also calculated the range for fine droplet delivery rate based on the averages for the first 2 minutes (upper limit) and 6 minutes (lower limit) of operation. The variation in $FDM_{<4.7µm}$ as a function of elapsed time from start of nebulization to the onset of sputter is illustrated in Figures 5 and 6 for the nebulizer-table top and nebulizer-portable compressor systems respectively. Each compressor-type nebulizer system is a unique combination in terms of its pressure-gas flow relationship[4]. In this study, we found that both the benchmark and ***BAN**** Nebulizer systems had comparable and near to linear values of $FDM_{<4.7µm}$ delivery rate as a function of elapsed time, whether the table top or portable compressor options were chosen. The slightly lower delivery rates for both ***BAN**** Nebulizer and AEN devices with their respective portable compressor is a reflection of the fact that these air supply systems are battery driven rather than powered from a wall outlet ("mains" electricity), and therefore operate at slightly lower pressure. It is also important to note that whereas the AEN generates aerosol continuously, albeit at a lower rate during exhalation (Figure 7a), the ***BAN**** Nebulizer only generates aerosol during the inhalation portion of each breathing cycle (Figure 7b). This outcome has the advantage that medication in the reservoir is conserved for a longer treatment time, if needed, and also that fugitive emissions of drug product to the ambient environment surrounding the patient are minimized during each exhalation[5]. The significantly finer measures we observed for MMD of droplets from the ***BAN**** Nebulizer compared with AEN in association with either compressor type (unpaired t-test $p \leq 0.005$), were associated with relatively high values of $FDF_{<4.7µm}$ close to 70%. Such aerosols may be beneficial for patients whose airways are physiologically narrow, such as those of children[6,7] or narrowing caused by obstructive lung disease[8,9].

Table 1: *In Vitro* Performance Measures for Evaluated Nebulizer-Compressor Systems

Metric	Table Top Compressor Systems		Portable Compressor Systems	
	BAN* **Nebulizer/*Ombra** Compressor**	**AEN/BOY† SX**	***BAN**** **Nebulizer/*Ombra** Compressor**	**AEN/BOY† mobile S**
$FDF_{<4.7µm}$ (%)	70.8 ± 1.0	57.9 ± 3.1	68.1 ± 0.9	52.0 ± 0.7
MMD (µm)	3.39 ± 0.05	4.13 ± 0.21	3.53 ± 0.04	4.55 ± 0.05
$FDM_{<4.7µm}$ (µg)	530 ± 22	408 ± 22	474 ± 32	344 ± 20
t_{run} (min)	11	8	12	9
$FDM_{<4.7µm}$rate‡ (µg/min)	58 - 63	60 - 64	48 - 55	43 - 45

‡ The first (lower value) is average over first 6 minutes, with the second (higher value) being the average over the first 2 minutes.

Conclusions: We confirmed by these laboratory studies that for each class of compressor system (table top or portable), the B ***BAN**** Nebulizer provided comparable therapeutically beneficial fine droplet delivery of salbutamol to the benchmark AEN, despite generating aerosol droplets only during 33% of each simulated adult tidal breathing cycle. The delivery rate of fine droplets was near to constant for the first six minutes of delivery with the ***BAN**** Nebulizer, irrespective of compressor type, suggesting that dosimetric delivery is possible with this device when operated by compressor, rather than via a higher pressure wall outlet air supply.
References: [1] Characterization Of Aerosol Output From Various Nebulizer/Compressor Combinations. C Reisner, RK Katial, BB Bartelson, A Buchmeir, LJ Rosenwasser, HS Nelson. Annals of Allergy, Asthma & Immunology 2001;86(5):566-574. [2] Comparison Of Breath-Enhanced To Breath-Actuated Nebulizers For Rate, Consistency, And Efficiency. K Leung, E Louca, AL Coates. CHEST 2004;126(5);1619-1627. [3] Effective Aerosol Therapy Devices For Respiratory Disease Management – Practical Considerations Key To Successful Treatment. PARI GmbH. US Respiratory Disease 2007;Issue 1. [4] The Equivalence Of Compressor Pressure-Flow Relationships With Respect To Jet Nebulizer Aerosolization Characteristics. T Standaert, SE Bohn, ML Aitken, B Ramsey. Journal of Aerosol Medicine 2001;14(1):31-42. [5] Delivery Of Inhaled Bronchodilators By Breath-Actuated Jet Nebulizer: The Potential For Improved Adherence With Clinical Guidelines. JP Mitchell. Inhalation 2011;5(4):20-23. [6] Deposition of Aerosols in Infants and Children. KG Schüepp, D Straub, A Möller, JH Wildhaber. Journal of Aerosol Medicine 2004;17(2):153-156. [7] The Current Laboratory Determination Of "Respirable Mass" Is Not Clinically Relevant. MT Newhouse. Journal of Aerosol Medicine 1998;11S1:S122-S132. [8] The Importance Of Particle Size In Response To Inhaled Bronchodilators. PJ Rees, TJ Clark, F Moren. European Journal of Respiratory Diseases 1982;119(S):73-78. [9] Pulmonary Drug Delivery. Part I: Physiological Factors Affecting Therapeutic Effectiveness Of Aerosolized Medications. NR Labiris, MB Dolovich. British Journal of Clinical Pharmacology 2003;56(6):588-599.

COMPARATIVE *IN VITRO* PERFORMANCE OF A NEW RE-USABLE BREATH-ACTUATED NEBULIZER WITH OTHER HIGH PERFORMANCE SYSTEMS INTENDED FOR DOMICILIARY USE – 1: TABLE-TOP COMPRESSORS. J Malpass, M Nagel, V Avvakoumova, R Ali, H Schneider, J Mitchell. European Respiratory Journal 2012;40(56):P2181.

Rationale: Treatments by portable compressor/nebulizer systems can offer very different delivery characteristics. We evaluated a new, reusable breath actuated device (***AeroEclipse**** ***XL BAN**** Nebulizer, Trudell Medical International) optimized with its table top (***Ombra**** Table Top Compressor) compressor. **Methods:** Each nebulizer (n = 5/group) was filled with 2.5 mL, 1.0 mg/mL albuterol

(Ventolin†, GSK† Canada Inc.), and connected to a breathing simulator (ASL 5000, IngMar Medical Ltd., Pittsburgh, PA) mimicking adult tidal breathing (V_t = 600 mL; duty cycle = 33%; rate = 10 cycles/minute). Emitted aerosol was captured on a filter at the mouthpiece, replaced every minute until onset of sputtering, defining run time. Recovery/assay of salbutamol was undertaken by HPLC-UV spectrophotometry. Fine droplet fraction ($FDF_{<4.7\mu m}$) and mass median droplet diameter (MMD) were determined by laser diffractometry. Total fine droplet mass ($FDM_{<4.7\mu m}$) was the product of total mass and $FDF_{<4.7\mu m}$. Comparative measurements were made with the LC† Sprint (PARI, Germany) and reusable SideStream† (Philips Respironics†, Germany) air entrainment nebulizers using PARI BOY† SX and Inspiration† Elite table top compressors respectively. **Results:** See Table.

Nebulizer/Table Top Compressor Performance Data

MEAN ± SD	*AeroEclipse* XL BAN** Nebulizer	LC† Sprint	SideStream†
$FDF_{<4.7\mu m}$ (%)	70.8 ± 1.0	57.9 ± 3.1	68.6 ± 1.5
MMD (µm)	3.39 ± 0.05	4.13 ± 0.21	3.43 ± 0.11
$FDM_{<4.7\mu m}$ (µg)	530 ± 22	408 ± 22	233 ± 6
Run Time (minutes)	11	8	10

Conclusions: The ***AeroEclipse**** ***XL BAN**** Nebulizer /***Ombra**** Table Top Compressor system provided highly respirable aerosol with $FDM_{<4.7\mu m}$ greater than the benchmark systems. Its run time reflects the fact that aerosol is only delivered during inhalation and not wasted to the environment.

COMPARATIVE *IN VITRO* PERFORMANCE OF A NEW RE-USABLE BREATH-ACTUATED NEBULIZER WITH OTHER HIGH PERFORMANCE SYSTEMS INTENDED FOR DOMICILIARY USE – 2: PORTABLE BATTERY-COMPRESSOR. J Malpass, M Nagel, V Avvakoumova, R Ali, H Schneider, J Mitchell. European Respiratory Journal 2012;40(56):P2148.

Rationale: Treatments with home based compressor/nebulizer systems can offer very different delivery characteristics. We evaluated a new, reusable breath actuated device (***AeroEclipse**** ***XL BAN**** Nebulizer, Trudell Medical International) in breath actuated mode with its portable (***Ombra**** Portable Compressor) battery compressor. **Methods:** The nebulizer on test (*n* = 5/group) was filled with 2.5 mL, 1.0 mg/mL albuterol (Ventolin†, GSK† Canada Inc.), and connected to a breathing simulator (ASL 5000, IngMar Medical Ltd., Pittsburgh, PA) mimicking adult tidal breathing (V_t = 600 mL; duty cycle = 33%; rate = 10 cycles/minute). Emitted aerosol was captured on a filter at the mouthpiece, replaced at minute intervals until onset of sputtering, defining run time. Recovery/assay of salbutamol was undertaken by HPLC-UV spectrophotometry. Fine droplet fraction ($FDF_{<4.7\mu m}$) and mass median droplet diameter (MMD) were determined by laser diffractometry. Total fine droplet mass ($FDM_{<4.7\mu m}$) was the product of total mass and $FDF_{<4.7\mu m}$. Comparative measurements were made with the LC† Sprint (PARI, Germany) and MicroPlus† (Philips Respironics†, Germany) nebulizers using PARI BOY† mobile S and Inspiration MicroElite† portable compressors respectively. **Results:** See Table.

MEAN ± SD	*AeroEclipse* XL BAN** Nebulizer	LC† Sprint	MicroPlus†
$FDF_{<4.7\mu m}$ (%)	68.1 ± 0.9	52.0 ± 0.7	52.8 ± 2.8
MMD (µm)	3.53 ± 0.04	4.55 ± 0.05	4.46 ± 0.23
$FDM_{<4.7\mu m}$ (µg)	474 ± 32	344 ± 20	297 ± 20
Run Time (minutes)	12	9	11

Conclusions: The ***AeroEclipse**** ***XL BAN**** Nebulizer /***Ombra**** Portable Compressor system provided highly respirable aerosol with $FDM_{<4.7\mu m}$ substantially greater than the benchmark systems. Its run time reflects the fact that aerosol is only delivered during inhalation and not wasted to the environment.

Budesonide (Pulmicort†, AstraZeneca†)

CONSISTENT DELIVERY OF INHALED MEDICATION IS MAINTAINED BY A BREATH ACTUATED NEBULIZER WITH DIFFERING INHALATION/EXHALATION RATIOS: A STUDY USING BUDESONIDE SUSPENSION FOR NEBULIZATION. D Coppolo, J Suggett, M Nagel, C Doyle, R Ali, J Mitchell. Association of Asthma Educators Conference, Garden Grove, CA, 2015.

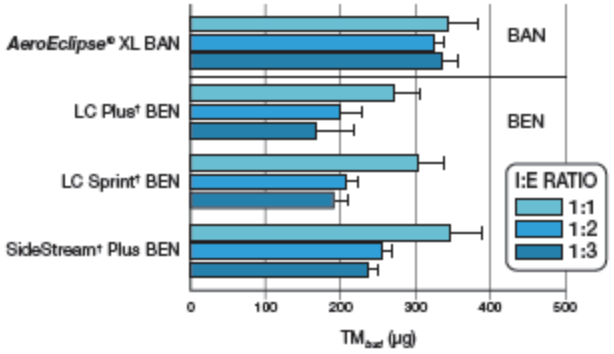
Background: In adult asthma, the inhalation/exhalation (I:E) ratio may vary due to collapse of the bronchiolar airways during exhalation. This study sought to investigate if I:E ratio changes affect medication delivery. **Introduction:** Patients receiving inhaled medications via nebulizer are often quite sick and therefore breathe tidally, rather than being asked to execute a forced breathing maneuver, such as a long slow inhalation followed by a breath hold. The I:E ratio, along with tidal volume and respiration rate, is an important descriptor of tidal breathing. Typically, nebulizers are evaluated in the laboratory, mimicking a patient having a fixed I:E ratio. However, in severe obstructive disease, such as asthma, this ratio can shift with disease progression. Breath actuated devices only deliver medication during the inhalation portion of each breathing cycle (Figure 1). This study sought to confirm the hypothesis that if the portion of each breathing cycle involved with exhalation increases, the medication is conserved and not vented to the local environment, as would be the case with breath enhanced nebulizers (BENs), whose output of medication does not fall to zero during exhalation (Figure 2). **Methods:** Measurements were undertaken with the following pneumatic nebulizers, using a 2 x 2.0 mL fill of 0.25 mg/mL budesonide (Pulmicort†, AstraZeneca† Inc., Canada):

- ***AeroEclipse**** ***XL BAN**** Nebulizer/***Ombra**** Table Top Compressor Monaghan Medical Corporation, Plattsburgh, NY – in Breath Actuated Mode (AE+)
- LC PLUS† BEN/PARI BOY† SX Table Top Compressor PARI Respiratory Equipment, Midlothian, VA (LC+)
- LC† Sprint BEN/PARI BOY† SX Compressor (LC*)

- SideStream† Plus BEN/Inspiration† Elite Table Top Compressor Philips Healthcare, Andover, MA (SS+)

Each nebulizer (*n* = 5/group) was connected to a breathing simulator (ASL 5000, IngMar Medical Ltd., Pittsburgh, PA) set at a constant tidal volume of 500 mL and rates of 15, 10 and 7 cycles/minute with I:E ratios of 1:1, 1:2 and 1:3 respectively. Budesonide mass was determined by HPLC-UV spectrophotometry using a validated procedure. **Results:** Values of total mass of budesonide delivered (TM_{bud}) (mean ± SD) from start of nebulization until first sputter are summarized in Figure 3. Average TM_{bud} from the AE+ was ~300 µg irrespective of I:E ratio. Kruskal-Wallis 1-way analysis of ranks (p = 0.264). Average decreases of 38%, 37% and 32% were observed for the LC+, LC* and SS+ BENs respectively. The change between I:E of 1:1 to 1:2 and 1:1 to 1:3 were significant (1-way ANOVA; $p \leq 0.011$).

Figure 3: TM_{bud} for the Various Nebulizers Evaluated as a Function of I:E Ratio



Conclusions: Consistent delivery was achieved by ***BAN****** Nebulizer across the range of I:E ratios, reflecting its conservation of medication during exhalation. Educators should be aware that the ***BAN****** Nebulizer's ability to conserve medication for delivery only when the patient inhales, provides greater assurance of dose consistency, resulting in more consistent therapy if I:E ratio changes with disease progression.

DELIVERY OF MEDICATION BY BREATH-ACTUATED NEBULIZER IS SIMILAR WHEN USED WITH DIFFERING INHALATION/EXHALATION RATIOS: A CONTRAST TO BREATH ENHANCED NEBULIZER (BEN) BEHAVIOR. J Suggett, M Nagel, C Doyle, R Ali, J Mitchell. European Respiratory Journal 2014;44(S58):3819.

Rationale: Nebulizers with breath actuated technology only deliver medication during inhalation. BENs continue to deliver aerosol (at a lower rate) during exhalation. If the inspiratory/expiratory (I:E) ratio of a patient decreases in obstructive lung disease, drug delivery efficiency by BEN may reduce. We compared the delivery of a corticosteroid by both types of nebulizer in a lab study. **Methods:** These nebulizer/table top compressor systems (*n* = 5/group) were evaluated: (a) ***AeroEclipse***** **XL BAN****** Nebulizer/***Ombra****** Table Top Compressor (TMI); (b) LC PLUS† BEN/PARI BOY†; (c) LC† Sprint BEN/PARI BOY† SX (PARI Respiratory Equipment); (d) SideStream† Plus BEN/Inspiration† Elite (Philips Respironics†). Each device was evaluated with 2 x 2.0 mL fill of 0.25 mg/mL budesonide (AstraZeneca†). The nebulizer was connected to a simulator (ASL 5000, IngMar Medical Ltd.) mimicking adult (tidal volume = 500 mL) tidal breathing, with I:E ratios of 1:1, 1:2 or 1:3. Emitted aerosol was captured by filter at 1 minute intervals until sputtering to determine total mass budesonide delivered (TM_{bud}), as percentage of TM_{bud} at I:E ratio = 1:1. Budesonide assay was undertaken by HPLC-UV spectrophotometry. **Results:** Average TM_{bud} at extended I:E ratios as percentage of TM_{bud} are in the Table.

Nebulizer	***AeroEclipse* XL BAN**** **Nebulizer**	**LC PLUS†**	**LC† Sprint**	**SideStream† Plus**
Type	**Breath Actuated**	**Breath Enhanced**		
I:E ratio = 1:1	100.0	100.0	100.0	100.0
I:E ratio = 1:2	95.3	73.3	68.0	73.9
I:E ratio = 1:3	98.2	61.5	62.7	68.1

Conclusions: More consistent dose delivery was achieved by ***AeroEclipse***** **XL BAN****** Nebulizer. Clinicians should be aware of the opportunity to more confidently titrate patients to the lowest effective dose. The risk of potential under dosing as disease progresses is also removed.

DELIVERY OF INHALED MEDICATION IS MAINTAINED BY A BREATH ACTUATED NEBULIZER WHEN USED BY PATIENTS WITH DIFFERING INHALATION/EXHALATION RATIOS: A LABORATORY STUDY USING BUDESONIDE SUSPENSION FOR NEBULIZATION. J Suggett, M Nagel, C Doyle, R Ali, J Mitchell. Respiratory Drug Delivery 2014;3:573-576.

Background: Nebulizers with breath actuated technology only deliver aerosolized medication during the course of the inhalation component of each tidal breathing cycle. In contrast, breath enhanced nebulizers (BEs), although utilizing entrained air to enhance the output of medication when the patient inhales, continue to deliver aerosol (at a lower rate) during exhalation and between breaths. The following benefits apply for the breath actuated device. Medication delivery is optimized by the near elimination of aerosol emitted by the nebulizer during exhalation, that would otherwise be wasted to the local environment, resulting in the potential for unnecessary caregiver exposure. Dosimetric delivery is possible, an advantage for drugs that are expensive or that have narrow therapeutic indices. In obstructive lung diseases, such as COPD, the tendency exists for the inhalation:exhalation ratio (I:E ratio) to be increased from 1:2 in the normal adult, to 1:3 or beyond. This behavior arises due to the loss of connective tissue typical of these diseases, resulting in the collapse of the bronchiolar airways during exhalation, thereby delaying this part of the respiratory cycle. There is also

anecdotal evidence from caregivers in various healthcare settings, that patients during a treatment period occasionally remove the nebulizer mouthpiece from their lips in order to engage in conversational activity or to have a self-administered pause in therapy. Under these circumstances, medication delivered by a breath actuated device will be conserved, whereas waste will inevitably occur with BE administered therapy. **Study Rationale:** A laboratory study was therefore undertaken to compare data obtained with a breath actuated device/compressor system with results from a variety of BENs. A widely prescribed formulation for nebulization budesonide (Pulmicort†, AstraZeneca† Inc., Canada) was chosen as the test product. **Materials and Methods:** Measurements were undertaken with nebulizer-compressor systems (n = 5 devices/group). Each nebulizer was tested with a 2 x 2.0 mL fill of 0.25 mg/mL budesonide. The breath actuated group (BA) were operated in breath actuated mode. Each nebulizer on test was connected to a breathing simulator set to mimic adult tidal breathing patterns (ASL 5000, IngMar Medical Ltd., Pittsburgh, PA). The tidal volume was held at 500 mL. The emitted aerosol was captured on a filter located at the mouthpiece that was replaced at one minute intervals until the onset of sputtering occurred. Recovery and subsequent assay of budesonide was undertaken by an HPLC-UV spectrophotometric procedure.

Nebulizer Systems Assessed:

Nebulizer	Type	Compressor	Manufacturer
AeroEclipse **XL BAN**** Nebulizer	BA	***Ombra**** Table Top Compressor	Trudell Medical International
LC PLUS†	BE	PARI BOY† SX Table Top Compressor	PARI
LC† Sprint	BE	PARI BOY† SX Table Top Compressor	PARI
SideStream† Plus	BE	Inspiration† Elite Table Top Compressor	Philips Respironics†

Adult Breathing Patterns Simulated:

Rate (cycles/minute)	Minute Volume (mL)	I:E Ratio
15	7,500	1:1
10	5,000	1:2
7	3,500	1:3

Results: Total mass of budesonide delivered (TM_{bud}) (mean ± SD) from start of nebulization until first audible sputter are summarized below.

Nebulizer	***AeroEclipse*** **XL BAN**** Nebulizer	LC PLUS†	LC† Sprint	SideStream† Plus
Type	**Breath Actuated**	**Breath Enhanced**		
I:E ratio = 1:1	100.0	100.0	100.0	100.0
I:E ratio = 1:2	95.3	73.3	68.0	73.9
I:E ratio = 1:3	98.2	61.5	62.7	68.1

Average TM_{bud} from the ***AeroEclipse*** **XL BAN**** Nebulizer was maintained at a constant level across the three I:E ratios, whereas average decreases of 38%, 37% and 32% were observed for the LC PLUS†, LC† Sprint and SideStream† Plus BEs, respectively. S Byrne, *et al*.[1], in a similar study observed that for two different BEs (LC PLUS† and LC† Sprint), the total mass of colistimethate sodium ($TM_{c\text{-}m}$) decreased as the I:E ratio increased mimicking adult tidal breathing with tidal volume and I:E ratios. In contrast, they found that the Adaptive Aerosol Delivery (AAD) nebulizer (I-neb, Philips Respironics†) like the ***AeroEclipse*** **XL BAN**** Nebulizer, only delivers medication during the inspiratory portion of each breathing cycle, providing constant delivery regardless of chosen I:E ratio. **Conclusions:** A more consistent dose delivery was achieved across the range of I:E ratios tested with the ***BAN**** Nebulizer rather than BE nebulizers. This study reflects the greatly reduced loss of medication from the ***BAN**** Nebulizer since aerosol is only produced during inhalation and therefore ensures that there is no risk of under dosing. Since the operation of the ***BAN**** Nebulizer is purely mechanical, it is a significant low cost alternative to AAD based nebulizers. The ability to conserve medication for delivery only when the patient inhales, provides a greater assurance of dose consistency and therefore would result in more consistent therapy if I:E ratio was to change with disease progression. **Reference:** [1] The Effect Of Inhalation:Exhalation (I:E) Ratio On The Delivered Dose Of Colistimethate Sodium From 3 Nebulizers. S Byrne, D Jeffrey, RHM Hatley. Proc. 19th Congress International Society for Aerosols in Medicine, Chapel Hill, NC, USA, 2013.

Colistimethate Sodium (Colomycin†, Forest Laboratories UK† Ltd.)

MEDICATION DELIVERY OF CF DRUGS VIA A BREATH ACTUATED NEBULIZER: REVIEW OF DELIVERY PERFORMANCE VERSUS A BREATH ENHANCED NEBULIZER (BEN) COMMONLY USED WITH SUCH MEDICATIONS. J Suggett, M Nagel, J Schloss, D Coppolo. Journal of Cystic Fibrosis 2021;20(S2):S126.

Introduction: Medications to manage care of CF patients are often delivered via a nebulizer, as such treatment is generally easy to use and enables delivery of the typical doses needed. A breath actuated nebulizer will reduce fugitive emissions and provide dose assurance (because dosing is not dependent on breathing pattern), however there are sometimes questions around the dose delivered to the patient when changing between continuous and breath actuated delivery modes. This study compares the two delivery modes for a number of commonly used CF medications in the home. **Methods:** Four different medications were evaluated. These were: a) 7% hypertonic saline, b) tobramycin, c) dornase alfa, and d) colistimethate sodium. Delivery was compared for each with a breath actuated nebulizer (***AeroEclipse*** **XL BAN**** Nebulizer/***Ombra**** Table Top Compressor, Monaghan Medical Corporation) and continuous breath enhanced nebulizer (LC PLUS† BEN/PARI BOY† SX compressor, PARI). Medication delivery was compared for each, from existing laboratory studies, in terms of the performance measures in each study. **Results:** For hypertonic saline, the ***BAN**** Nebulizer exhibited an 81.6% fine droplet fraction compared to 71.2% with the BEN, indicative of slightly smaller droplets, more likely to be delivered to the lungs. For tobramycin, the ***BAN**** Nebulizer again exhibited a slightly higher fine particle fraction than the BEN (72% vs. 64%) and delivered a total mass of 141 mg compared to 83 mg for the BEN. For dornase alfa, the ***BAN**** Nebulizer exhibited a fine droplet mass of 428 mcg compared to 349 mcg with the BEN. For colistimethate, the fine

droplet mass for the ***BAN**** Nebulizer was similar to the BEN for the first 12 minutes of delivery, with the ***BAN**** Nebulizer continuing to deliver medication for an additional 7 minutes.

Medication	Metric	*AeroEclipse** *XL BAN** Nebulizer/ *Ombra** Table Top Compressor	LC PLUS† BEN/ PARI BOY† SX Compressor
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Conclusions: Although the medication delivery in the various lab studies was reported using differing metrics, a common trend was that the ***BAN**** Nebulizer delivered at least as much or more medication than the BEN in each case. Reviewing the safety data for the drugs themselves shows that the higher delivery with the ***BAN**** Nebulizer was well within acceptable dosing ranges. On the basis of these studies, clinicians could recommend ***BAN**** Nebulizer for delivery of CF medications, with the added value of a ***BAN**** Nebulizer system offering low fugitive emissions and improved dosing consistency.

MEDICATION DELIVERY OF BRONCHIECTASIS DRUGS VIA A BREATH ACTUATED NEBULIZER: REVIEW OF DELIVERY PERFORMANCE VERSUS A BREATH ENHANCED NEBULIZER (BEN) COMMONLY USED WITH SUCH MEDICATIONS. J Suggett, D Haapanen. 2nd European NTM & Bronchiectasis Workshop 2021 Abstracts Leaflet:P.09.

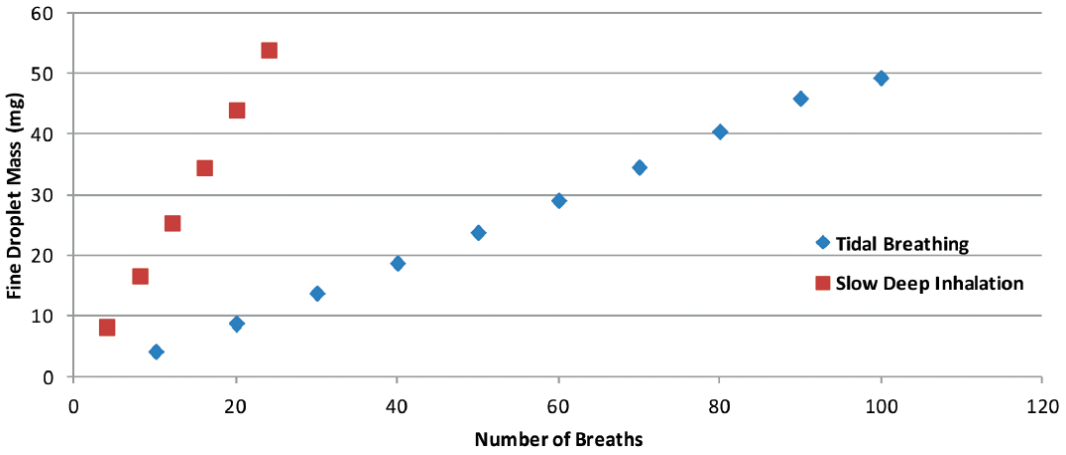
Introduction: Medications to manage care of bronchiectasis patients are often delivered via a nebulizer, as such treatment is generally easy to use and enables delivery of the typical doses needed. A breath actuated nebulizer will reduce fugitive emissions and provide dose assurance (because dosing is not dependent on breathing pattern), however there are sometimes questions around the dose delivered to the patient when changing between continuous and breath actuated delivery modes. This study compares the two delivery modes for bronchiectasis medications commonly used in the home. **Methods:** Three different medications were evaluated. These were: a) 7% hypertonic saline, b) tobramycin, and c) colistimethate sodium. Delivery was compared for each with a breath actuated nebulizer (***AeroEclipse**** ***XL BAN**** Nebulizer/***Ombra**** Table Top Compressor, Trudell Medical International) and continuous breath enhanced nebulizer (LC PLUS† BEN/PARI BOY† SX compressor, PARI). Medication delivery was compared for each, from existing laboratory studies, in terms of the performance measures in each study. **Results:** For hypertonic saline, the ***BAN**** Nebulizer exhibited an 81.6% fine droplet fraction compared to 71.2% with the BEN, indicative of slightly smaller droplets, more likely to be delivered to the lungs. For tobramycin, the ***BAN**** Nebulizer again exhibited a slightly higher fine particle fraction than the BEN (72% vs. 64%) and delivered a total mass of 141 mg compared to 83 mg for the BEN. For colistimethate, the fine droplet mass for the ***BAN**** Nebulizer was similar to the BEN for the first 12 minutes of delivery, with the ***BAN**** Nebulizer continuing to deliver medication for an additional 7 minutes. **Conclusions:** Although the medication delivery in the various lab studies was reported using differing metrics, a common trend was that the ***BAN**** Nebulizer delivered at least as much or more medication than the BEN in each case. Reviewing the safety data for the drugs themselves shows that the higher delivery with the ***BAN**** Nebulizer was well within acceptable dosing ranges. Clinicians could recommend ***BAN**** Nebulizer for delivery of bronchiectasis medications on the basis of these studies.

AN *IN VITRO* INVESTIGATION OF INHALED MEDICATION DELIVERY FROM A BREATH ACTUATED NEBULIZER COMPARING A SLOW, DEEP INHALATION WITH TIDAL BREATHING – DOES BREATHING PROFILE MATTER? MW Nagel, JA Suggett, R Ali, V Wang, JP Mitchell. Respirable Drug Delivery 2016;3:533-538.

Introduction: Breath actuated operation of a nebulizer only during inhalation affords the prospect for reduced wasted medication when the patient exhales[1]. There is also the prospect of optimizing delivery and shortening treatment time where the patient is capable of performing a trained maneuver, such as a slow deep inhalation followed by a breath hold, known to be associated with improved lung deposition[2], rather than simply tidal breathing. Whereas inhalation technique is a focus for dry powder and pressurized metered dose inhaler administration, little if any mention is made of the importance of good inhalation technique when using small volume nebulizers (SVNs). However, slow and deep inhalation using adaptive aerosol delivery devices such as the AKITA† or the I-neb† AAD System has been shown to improve lung deposition[3,4]. In addition, a shorter treatment time would be a highly desirable goal for many patients undergoing nebulizer based treatments, particularly those with cystic fibrosis (CF), who must spend a significant proportion of each day receiving therapy[5]. We report an *in vitro* study in which an antibiotic representative of those given by inhalation to patients with CF, was used to investigate medication delivery from a pneumatic breath actuated nebulizer to an adult, comparing the simulation of a slow deep inhalation with tidal breathing. **Materials and Methods:** ***AeroEclipse**** ***XL BAN**** Nebulizer (*n* = 5 devices, Trudell Medical International, London, ON, Canada), each filled with 4 mL of colistimethate sodium solution (160 mg/mL, 2 million IU, Forest Laboratories UK†), were operated at 7 - 8 L/min with medical air (50 psi). The mouthpiece from the nebulizer on test was connected to a breathing simulator (ASL 5000, IngMar Medical Ltd., Pittsburgh, PA, USA) via an electret bacterial/viral filter upon which the "inhaled" aerosol deposited (Figure 1). The aerosol filters were replaced at one minute intervals to prevent overloading and to provide time dependent information. Colistimethate sodium content collected on the filter was subsequently assayed by UV spectrophotometry. The parameters defining the adult tidal breathing pattern simulated for the first part of the study (Figure 2) were: (a) tidal volume (V_t) = 600 mL; (b) rate/minute = 10 cycles; (c) duty cycle = 33% (inspiratory/expiratory ratio = 1:2). For the second part of the investigation, an adult volunteer was instructed to exhale fully, inhale slowly and deeply, at the same time focusing on keeping the green inhalation feedback indicator on top of the breath actuated nebulizer lowered for as long as possible. A recorded representative inhalation pattern (Figure 3) was subsequently played back through the breathing simulator at a rate of four cycles per minute as this was shown to be a comfortable rate in which the volunteer had sufficient time to rest in between the slow, deep inhalations. In both cases, the nebulizer on test was operated until first sputter. The fine droplet fraction ($FDF_{<4.7\mu m}$) of the emitted size distribution from the ***BAN**** Nebulizer contained in aqueous droplets < 4.7 µm in diameter was determined in a separate series of measurements by laser diffractometry (Spraytec, Malvern Instruments Ltd., Malvern, UK). The mass of those droplets (fine droplet mass (FDM)) was calculated as the product of the FDF multiplied by the mass of colistimethate recovered from each filter. **Results:** The cumulative delivery of colistimethate as mass contained in fine droplets ($FDM_{<4.7\mu m}$) versus

number of breaths is illustrated in Figure 4 for both the tidal breathing and slow deep inhalation, respectively. $FDF_{<4.7\mu m}$ was determined to be 82%. Total $FDM_{<4.7\mu m}$ delivered to sputter by either breathing profile was comparable and close to 50 mg, however, only six minutes (24 deep inhalations) was required to achieve this delivered mass using the slow deep inhalation, compared with 10 minutes (100 breathing cycles) by tidal breathing.

Figure 4: Delivery of Colistin as Fine Droplets < 4.7µm from the ***AeroEclipse*** **XL BAN**** Nebulizer (*n* = 5/group) as a Function of the Number of Breaths

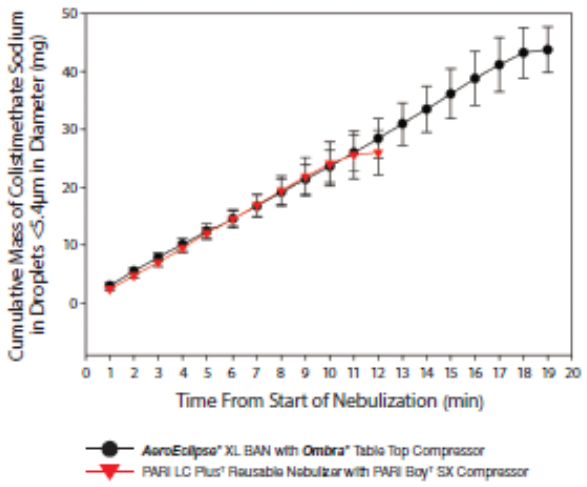


Discussion: The present investigation has shown the potential for shortening ***BAN**** Nebulizer based therapy if the patient is capable of achieving a long slow inhalation (aided by concentrating on the inhalation feedback indicator on the device), rather than merely tidal breathing, as is usual with such drug delivery devices. Poor inhalation technique is known to result, in some cases, in less than ideal control of lungs disease[6]. The European based Aerosol Drug Management Improvement Team (ADMIT) group has therefore suggested that devices which provide reassurance to patients and their physicians when inhalation is performed correctly could help improve patient compliance[7] offering the prospect of better disease management. It follows that if patients are willing to be engaged in their treatment and are capable of executing the ideal maneuver of a long, slow inhalation followed by a breath hold for fine droplet deposition to the lungs[8], the use of a pneumatic breath actuated device could lead to reduced treatment times and potentially better disease management. **Conclusions:** This study has demonstrated that the ***AeroEclipse*** **XL BAN**** Nebulizer has the potential to significantly reduce overall therapy time based on patients achieving a slow, deep inhalation, as an alternative to tidal breathing. Consequently, this could lead to potential improved patient compliance and healthcare costs of nebulizer treatments. **References:** [1] A Prospective, Comparative Trial Of Standard And Breath-Actuated Nebulizer: Efficacy, Safety, And Satisfaction. V Arunthari, RS Bruinsma, AS Lee, MM Johnson. Respiratory Care 2012;57(8):1242-1247. [2] Higher Lung Deposition With Respimat† Soft Mist† Inhaler Than HFA-MDI In COPD Patients With Poor Technique. P Brand, B Hederer, G Austen, H Dewberry, T Meyer. International Journal of Chronic Obstructive Pulmonary Disease 2008;3(4):763-770. [3] Lung Deposition After Electronically Breath-Controlled Inhalation And Manually Triggered Conventional Inhalation In Cystic Fibrosis Patients. E Köhler, V Sollich, R Schuster-Wonka, G Jorch. Journal of Aerosol Medicine 2005;18(4):386-395. [4] Adaptive Aerosol Delivery (AAD) Technology. J Denyer, K Nikander, NJ Smith. Expert Opinion on Drug Delivery 2004;1(1):165-176. [5] High Treatment Burden In Adults With Cystic Fibrosis: Challenges To Disease Self-Management. GS Sawick, DE Sellers, WM Robinson. Journal of Cystic Fibrosis 2009;8:91-96. [6] Inhaler Mishandling Remains Common In Real Life And Is Associated With Reduced Disease Control. AS Melani, M Bonavia, V Cilenti, C Cinti, M Lodi, P Martucci, M Serra, N Schichilone, P Sestini, M Aliani, M Neri. Respiratory Medicine 2011;105:930-938. [7] The Need To Improve Inhalation Technique In Europe: A Report From The Aerosol Drug Management Improvement Team. GK Crompton, PJ Barnes, M Broeders, C Corrigan, L Corbetta, R Dekhuijzen, JC Dubus, A Magnan, F Massone, J Sanchis, JL Viejo, T Voshaar. Respiratory Medicine 2006;100:1479-1494. [8] Inhaler Devices: From Theory To Practice. J Sanchis, C Corrigan, ML Levy, JL Viejo. Respiratory Medicine 2013;107:495-502.

INHALED ANTIBIOTIC DELIVERY BY PNEUMATIC NEBULIZATION: CASE STUDY COMPARING BREATH ACTUATED WITH BREATH ENHANCED NEBULIZERS FOR COLISTIMETHATE SODIUM. JA Suggett, MW Nagel, H Schneider, CC Doyle, RS Ali, JP Mitchell. Respiratory Drug Delivery 2014;3:581-584.

Background: Inhaled colistimethate sodium is a polymyxin antibiotic that is indicated for treating lung infection with Pseudomonas aeruginosa in cystic fibrosis. Although dry powder inhaler based products are available, this therapeutic agent is often given by pneumatic nebulization. To ensure optimal dosing, the possibility of using such products in conjunction with a breath actuated nebulizer may be of interest, as this type of nebulizer conserves medication during exhalation rather than allowing it to escape and disperse into the local environment. The present laboratory investigation was designed to evaluate colistimethate sodium output from a breath actuated configuration able to be used in either the hospital or home environment. Comparison measurements were also gathered for a continuous breath enhanced nebulizer (BE), to provide benchmark data. **Materials and Methods:** BA group (*n* = 5 devices) ***AeroEclipse*** **XL BAN**** Nebulizer with ***Ombra**** Table Top Compressor; AE-XL, Trudell Medical international, London, ON, Canada. BE group (*n* = 5 devices) LC PLUS† with PARI BOY† SX compressor; PARI Respiratory equipment, Midlothian, VA, USA. 4.0 mL fill colistimethate sodium from ampoule (Colomycin† for injection, Forest Laboratories UK† Ltd.) equivalent to 160 mg colistimethate sodium, representative polymyxin antibiotic (polymyxin E). Adult patient tidal breathing simulation with ASL 5000 Test Lung (IngMar Medical Ltd., Pittsburgh, PA), tidal volume = 600 mL, duty cycle = 33%, rate = 10 breathing cycles/minute. Filter collection at mouthpiece of nebulizer at 1 minute intervals from start to onset of sputter. Colistimethate sodium recovered quantitatively and assayed by HPLC-UV spectrophotometry to determine total mass of colistimethate sodium (TM_{cs}) at each time interval. The ***BAN**** Nebulizers were operated in the breath actuated mode for this part of the study. Medication is only delivered

during the inspiratory portion of each breathing cycle. There is negligible waste of medication to the ambient surroundings during exhalation. The measurements were subsequently repeated with the same nebulizers sampling continuously at 15 L/min to determine droplet size distribution by Next Generation Pharmaceutical Impactor (NGI). Fine droplet fraction < 5.4 µm diameter ($FDF_{<5.4\ \mu m}$) determined in accordance with USP Chapter 1601 (2013). Fine particle mass delivery profiles for colistimethate sodium aerosols were constructed on a minute by minute basis from the product of TM_{cs} and $FDF_{<5.4\ \mu m}$. **Results:** The figure summarizes the time dependent delivery of colistimethate sodium from BA and BE groups as fine particles < 5.4µm aerodynamic diameter.



Fine particle mass delivery rates during the first 10 minutes from start of nebulization for both BA and BE systems were comparable. This outcome might be anticipated, since both nebulizers operate as breath entrainment devices having similar droplet aerodynamic particle size distributions. TM delivered to sputter was appreciably higher for the ***AeroEclipse*** **XL BAN**** Nebulizer. **Conclusions:** Conservation of medication and associated avoidance of environmental losses from fugitive emissions with the ***BAN**** Nebulizer system was evident by the increased fine particle mass, compared with the BE nebulizer system. Mean delivery rates of the therapeutically beneficial fine droplets were, however, comparable at ca. 2.4 mg/min for both nebulizer-compressor systems. In this particular instance, the caregiver therefore has the option of stopping treatment after 12 minutes with the ***BAN**** Nebulizer if a similar dose or run time to the BE is desired, or can continue to deliver additional dose in the same treatment session if it is considered clinically desirable to maximize delivered dose. This additional dose is well within the safe and effective daily dose range reported from a colistimethate sodium marketed product registration information[1]. **Reference:** [1] Summary of Product Characteristics, Colomycin† Injection (Aerosol Inhalation), Forest Laboratories UK† Ltd.

Dornase Alfa (Pulmozyme†, Genentech† Inc.)

MEDICATION DELIVERY OF CF DRUGS VIA A BREATH ACTUATED NEBULIZER: REVIEW OF DELIVERY PERFORMANCE VERSUS A BREATH ENHANCED NEBULIZER (BEN) COMMONLY USED WITH SUCH MEDICATIONS. J Suggett, M Nagel, J Schloss, D Coppolo. Journal of Cystic Fibrosis 2021;20(S2):S126.

Introduction: Medications to manage care of CF patients are often delivered via a nebulizer, as such treatment is generally easy to use and enables delivery of the typical doses needed. A breath actuated nebulizer will reduce fugitive emissions and provide dose assurance (because dosing is not dependent on breathing pattern), however there are sometimes questions around the dose delivered to the patient when changing between continuous and breath actuated delivery modes. This study compares the two delivery modes for a number of commonly used CF medications in the home. **Methods:** Four different medications were evaluated. These were: a) 7% hypertonic saline, b) tobramycin, c) dornase alfa, and d) colistimethate sodium. Delivery was compared for each with a breath actuated nebulizer (***AeroEclipse*** **XL BAN**** Nebulizer/***Ombra**** Table Top Compressor, Monaghan Medical Corporation) and continuous breath enhanced nebulizer (LC PLUS† BEN/PARI BOY† SX compressor, PARI). Medication delivery was compared for each, from existing laboratory studies, in terms of the performance measures in each study. **Results:** For hypertonic saline, the ***BAN**** Nebulizer exhibited an 81.6% fine droplet fraction compared to 71.2% with the BEN, indicative of slightly smaller droplets, more likely to be delivered to the lungs. For tobramycin, the ***BAN**** Nebulizer again exhibited a slightly higher fine particle fraction than the BEN (72% vs. 64%) and delivered a total mass of 141 mg compared to 83 mg for the BEN. For dornase alfa, the ***BAN**** Nebulizer exhibited a fine droplet mass of 428 mcg compared to 349 mcg with the BEN. For colistimethate, the fine droplet mass for the ***BAN**** Nebulizer was similar to the BEN for the first 12 minutes of delivery, with the ***BAN**** Nebulizer continuing to deliver medication for an additional 7 minutes.

Medication	Metric	***AeroEclipse*** **XL BAN**** Nebulizer/ ***Ombra**** Table Top Compressor	LC PLUS† BEN/ PARI BOY† SX Compressor
7% Hypertonic Saline	Fine Droplet Fraction	81.6%	71.2%
Tobramycin	Fine Particle Fraction Total Mass	72% 141 mg	64% 83 mg
Dornase Alfa	Fine Droplet Mass	428 µg	349 µg
Colistimethate Sodium	Fine Droplet Mass	Approx. 26 mg at 12 minutes increasing to a little over 40 mg at sputter	Approx. 25 mg at 12 minutes (sputter)

Conclusions: Although the medication delivery in the various lab studies was reported using differing metrics, a common trend was that the ***BAN**** Nebulizer delivered at least as much or more medication than the BEN in each case. Reviewing the safety data for the drugs themselves shows that the higher delivery with the ***BAN**** Nebulizer was well within acceptable dosing ranges. On the basis of these studies, clinicians could recommend ***BAN**** Nebulizer for delivery of CF medications, with the added value of a ***BAN**** Nebulizer system offering low fugitive emissions and improved dosing consistency.

USE OF A BREATH-ACTUATED JET NEBULIZER TO DELIVER DORNASE ALFA FOR THE TREATMENT OF CYSTIC FIBROSIS: *IN VITRO* ASSESSMENT USING ADULT TIDAL BREATHING SIMULATION. JP Mitchell, D Coppolo, M Nagel. Pediatric Pulmonology 2013;48(S36):418.

Background: Dornase alfa recombinant human deoxyribonuclease I enzyme (Pulmozyme†, Genentech† Inc., South San Francisco, CA) is indicated in the management of cystic fibrosis to improve lung function. This inhaled biotherapeutic is typically delivered by continuous nebulization to tidal breathing patients, but during the exhalation phase, medication is discharged into the environment. Breath actuated nebulizers such as the reusable ***AeroEclipse*** **BAN**** Nebulizer (Monaghan Medical Corporation, Plattsburgh, NY) only operate during inhalation, thereby mitigating contamination of the local environment and exposure burden of caregivers. **Study Objective:** This study was designed to evaluate medication output from a reusable ***BAN**** Nebulizer with table top compressor (r***BAN**** Nebulizer/***Ombra**** Table Top Compressor) that is capable of being used in either the hospital or home environment, comparing its performance with that of a continuous nebulizer-compressor (LC PLUS†/BOY† SX compressor (LC+/BOY† SX), PARI Respiratory Equipment Inc., Midlothian, VA) that could be used for this therapeutic modality. **Methods:** Each nebulizer group (10 devices) was filled with a 2.5 mL Pulmozyme† ampoule (1 mg/mL dornase alfa) and run until onset of sputtering. Aerosol was captured by a filter at the mouthpiece, and the nebulizer connected to a breathing simulator (tidal volume = 600 mL; duty cycle = 33%; rate = 10 cycles/minute). Fine droplet mass (µg < 5.4 µm diameter (FM_{pulm})) and fine droplet mass fraction (% < 5.4µm, (FMF_{pulm})) were determined by Next Generation Impactor operated at 15 L/min with assay for dornase alfa by isocratic size exclusion high performance liquid chromatography. **Results:** Comparative measures of the therapeutically beneficial FMF_{pulm} and FM_{pulm} are summarized in the table.

Delivery of Dornase Alfa by Nebulizer-Compressor (values are mean ± SD)

System	FMF_{pulm} (%)	FM_{pulm} (µg)
r*BAN Nebulizer/*Ombra** Table Top Compressor**	83.3 ± 2.2	428 ± 40
LC+/BOY† SX	83.8 ± 2.2	349 ± 62

Conclusions: Both nebulizer-compressor systems offer similar aerosol quality in terms of FMF_{pulm} and FM_{pulm} for delivery of Pulmozyme†. However, clinicians should be aware that, since the operation of the reusable ***AeroEclipse*** **BAN**** Nebulizer only occurs due to patient inhalation nearly all fugitive emissions are eliminated and delivery of all the FM_{pulm} leaving the nebulizer to the patient is assured.

DELIVERY OF DORNASE ALFA VIA BREATH-ACTUATED NEBULIZER: *IN VITRO* MEASURES OF PERFORMANCE. J Suggett, J Mitchell, H Schneider, R Ali, M Nagel. European Respiratory Journal 2013;42:1186.

Rationale: Pulmozyme† is indicated in the management of cystic fibrosis to improve lung function and is typically delivered by continuous nebulization to tidal breathing patients. During the exhalation phase medication is discharged into the environment. Breath actuated nebulizers only operate during inhalation. This study was designed to evaluate medication output from a breath actuated device configuration (***AeroEclipse*** **XL BAN**** Nebulizer /***Ombra**** Compressor (AE-XL); TMI) compared with a continuous nebulizer configuration (PARI LC PLUS†/PARI BOY† SX compressor (LC+)). **Methods:** Each nebulizer was filled with a 2.5 mL Pulmozyme† ampoule (1 mg/mL dornase alfa) and run until onset of sputtering. Aerosol was captured by a filter at the mouthpiece, and the nebulizer connected to a breathing simulator (tidal volume = 600 mL; duty cycle = 33%; rate = 10 cycles/minute). Fine droplet mass (µg < 5.4 µm diameter (FM_{pulm})) and fine droplet fraction (% < 5.4µm, (FMF_{pulm}) were determined by Next Generation Impactor operated at 15 L/min with assay for dornase alfa by HPLC. **Results:**

Device (*n* = 10)	FMF_{pulm} (%)	FM_{pulm} (mg)
AE-XL/*Ombra Compressor**	83.3 ± 2.2	428 ± 40
LC+/PARI BOY† SX	83.8 ± 2.2	349 ± 62

Conclusions: The AE-XL configuration exhibited a little higher delivery of Pulmozyme† to the LC+, although well within the demonstrated patient tolerability (Pulmozyme† Nebulizer solution SPC, Roche). In addition, clinicians should be aware that, unlike the LC+, the operation of the ***BAN**** Nebulizer only occurs due to patient inhalation thereby eliminating nearly all fugitive emissions and ensuring delivery to the patient at their own pace.

Hypertonic Saline

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Medication	**Metric**	***AeroEclipse*** XL BAN**** Nebulizer/ ***Ombra**** Table Top Compressor	**LC PLUS† BEN/ PARI BOY† SX Compressor**
7% Hypertonic Saline	Fine Droplet Fraction	81.6%	71.2%
Tobramycin	Fine Particle Fraction Total Mass	72% 141 mg	64% 83 mg
Dornase Alfa	Fine Droplet Mass	428 µg	349 µg
Colistimethate Sodium	Fine Droplet Mass	Approx. 26 mg at 12 minutes increasing to a little over 40 mg at sputter	Approx. 25 mg at 12 minutes (sputter)

Conclusions: Although the medication delivery in the various lab studies was reported using differing metrics, a common trend was that the ***BAN**** Nebulizer delivered at least as much or more medication than the BEN in each case. Reviewing the safety data for the drugs themselves shows that the higher delivery with the ***BAN**** Nebulizer was well within acceptable dosing ranges. On the basis of these studies, clinicians could recommend ***BAN**** Nebulizer for delivery of CF medications, with the added value of a ***BAN**** Nebulizer system offering low fugitive emissions and improved dosing consistency.

MEDICATION DELIVERY OF BRONCHIECTASIS DRUGS VIA A BREATH ACTUATED NEBULIZER: REVIEW OF DELIVERY PERFORMANCE VERSUS A BREATH ENHANCED NEBULIZER (BEN) COMMONLY USED WITH SUCH MEDICATIONS. J Suggett, D Haapanen. 2nd European NTM & Bronchiectasis Workshop 2021 Abstracts Leaflet:P.09.

Introduction: Medications to manage care of bronchiectasis patients are often delivered via a nebulizer, as such treatment is generally easy to use and enables delivery of the typical doses needed. A breath actuated nebulizer will reduce fugitive emissions and provide dose assurance (because dosing is not dependent on breathing pattern), however there are sometimes questions around the dose delivered to the patient when changing between continuous and breath actuated delivery modes. This study compares the two delivery modes for bronchiectasis medications commonly used in the home. **Methods:** Three different medications were evaluated. These were: a) 7% hypertonic saline, b) tobramycin, and c) colistimethate sodium. Delivery was compared for each with a breath actuated nebulizer (***AeroEclipse*** XL BAN****** Nebulizer/***Ombra****** Table Top Compressor, Trudell Medical International) and continuous breath enhanced nebulizer (LC PLUS† BEN/PARI BOY† SX compressor, PARI). Medication delivery was compared for each, from existing laboratory studies, in terms of the performance measures in each study. **Results:** For hypertonic saline, the ***BAN**** Nebulizer exhibited an 81.6% fine droplet fraction compared to 71.2% with the BEN, indicative of slightly smaller droplets, more likely to be delivered to the lungs. For tobramycin, the ***BAN**** Nebulizer again exhibited a slightly higher fine particle fraction than the BEN (72% vs. 64%) and delivered a total mass of 141 mg compared to 83 mg for the BEN. For colistimethate, the fine droplet mass for the ***BAN**** Nebulizer was similar to the BEN for the first 12 minutes of delivery, with the ***BAN**** Nebulizer continuing to deliver medication for an additional 7 minutes. **Conclusions:** Although the medication delivery in the various lab studies was reported using differing metrics, a common trend was that the ***BAN**** Nebulizer delivered at least as much or more medication than the BEN in each case. Reviewing the safety data for the drugs themselves shows that the higher delivery with the ***BAN**** Nebulizer was well within acceptable dosing ranges. Clinicians could recommend ***BAN**** Nebulizer for delivery of bronchiectasis medications on the basis of these studies.

USE OF AN OSCILLATING POSITIVE EXPIRATORY PRESSURE (OPEP) DEVICE WITH A BREATH ACTUATED NEBULIZER FOR THE DELIVERY OF HYPERTONIC SALINE. DP Coppolo, JA Suggett, MW Nagel, JP Mitchell. Pediatric Pulmonology 2016;S45(51):372.

Background/Objective: Hypertonic saline is associated with increased mucociliary clearance of secretions. OPEP therapy helps to mobilize secretions mechanically. This laboratory investigation examined the performance of a breath actuated nebulizer in conjunction with OPEP for the delivery of hypertonic saline to see if the OPEP affected the emitted aerosol size distribution. **Methods:** The ***AeroEclipse*** XL BAN****** Nebulizer (MMC, *n* = 5 devices) with tabletop compressor (***Ombra****** Table Top Compressor) was evaluated for the delivery of hypertonic saline (4 mL, 7% v/w NaCl aq.) with and without the OPEP device (***Aerobika****** OPEP device, MMC) inserted between the mouthpiece and nebulizer. Aerosol from the ***BAN****** Nebulizer was "inhaled" via a vacuum source operated at 28.3 L/min, and sized by a laser diffractometer (Malvern Spraytec, Malvern, UK). Comparative measurements were also made with a widely encountered breath enhanced nebulizer (LC PLUS†, PARI Respiratory Equipment, Midlothian, VA; *n* = 5 devices) operated by tabletop compressor (BOY† SX). **Results:** Measures of the aerosol size distribution were volume median diameter (VMD) and fine droplet fraction defined as the % < 4.7 µm diameter ($FDF_{<4.7\mu m}$), and are summarized in the table. **Conclusions:** The addition of the OPEP device marginally reduced droplet size (paired t-test for each metric, $p < 0.001$), but the effect was small and likely unimportant, given that the finer droplets are more likely to penetrate further into the airways of the lungs, especially when restricted by secretions. The comparator BEN device produced similar, if slightly larger, droplet size results. Use of the ***AeroEclipse*** XL BAN****** Nebulizer with tabletop compressor, either with or without the concurrent use of the ***Aerobika****** OPEP device, would appear to be an effective method of delivering hypertonic saline to the lungs for the purpose of mucociliary clearance.

Ipratropium Bromide (Atrovent†, Boehringer Ingelheim†)

A LABORATORY STUDY COMPARING BREATH ACTUATED AND BREATH ENHANCED NEBULIZER DEVICES AT VARIOUS DUTY CYCLES ASSOCIATED WITH COPD. JA Suggett, H Schneider, R Ali, M Nagel, J Mitchell. American Journal of Respiratory and Critical Care Medicine 2014;189:A3035.

Background: Breath actuation of a nebulizer only during patient inhalation conserves medication that would otherwise go to waste as fugitive emissions during exhalation. Similarly, medication is conserved if the patient interrupts their treatment by removing the mouthpiece temporarily. This laboratory study compared the delivery of an anticholinergic [ipratropium bromide (IPR)] solution widely used in the treatment of COPD by a breath actuated jet nebulizer (***AeroEclipse**** ***XL BAN**** Nebulizer with ***Ombra**** Table Top Compressor (Trudell Medical International, London, ON, Canada) with widely used breath enhanced nebulizer (BEN)-compressor systems in home based therapy for COPD at various duty cycles (50%, 33%, 25% and 20%). **Methods:** The breath actuated nebulizer group (n = 5 devices/group) were evaluated with an adult tidal breathing waveform (tidal volume = 500 mL) with duty cycles = 50%, 33%, 25% and 20% with 15, 10, 7 and 6 breaths/minute respectively, delivered by breathing simulator (ASL 5000, IngMar Medical Ltd., Pittsburgh, PA). An electret filter at the mouthpiece of the nebulizer captured emitted aerosol containing 5,000 ug ipratropium bromide in a 2 mL fill (UDV; Ratiopharm Inc., Canada) at minute intervals until onset of sputter. Total mass delivered (TM) was calculated after assaying for IPR by a validated HPLC based procedure. Similar measurements were undertaken with an identical number of BENs (LC PLUS† and LC† Sprint with PARI BOY† SX compressor; PARI Respiratory Equipment, Midlothian, VA; SideStream† Plus with Inspiration† Elite compressor; Philips Respironics†, Murrysville, PA). **Results:** TM values are reported in Table 1. Significantly less medication (1-way ANOVA, $p < 0.001$) was delivered per treatment by each BEN group with decreasing duty cycle, due to wastage during each exhalation. In contrast, ***BAN**** Nebulizer based delivery was unaffected (p = 0.722), because medication was conserved during exhalation.

Table 1: Nebulizer Based Delivery (TM µg mean ± SD) of IPR from Breath Actuated and Breath Enhanced Devices Simulating Adult Tidal Breathing in COPD with Differing Duty Cycles

Duty Cycle		**50%**	**33%**	**25%**	**20%**
Nebulizer/Compressor		**TM_{ipr} (µg)**			
Breath Actuated	***AeroEclipse**** ***XL BAN**** Nebulizer/ ***Ombra**** Table Top Compressor	102.9 ± 9.0	98.9 ± 8.5	105.7 ±16.5	97.1 ± 15.6
Breath Enhanced	LC† Sprint/PARI BOY† SX	135.1 ± 5.7	107.0 ±9.9	84.7 ± 10.0	68.6 ± 4.1
	LC PLUS†/PARI BOY† SX	94.8 ± 13.9	76.4 ±12.2	53.3 ± 11.5	37.1 ± 8.6
	SideStream† Plus/Inspiration† Elite	144.5 ±12.4	108.4 ±7.5	81.0 ± 7.1	76.3 ± 3.6

Conclusions: Wasted medication during exhalation can markedly reduce delivery via BEN to the patient, especially at short duty cycles, and can be avoided by the use of a ***BAN**** Nebulizer. The ***BAN**** Nebulizer therefore provides assurance of dose consistency independent of the patient's duty cycle and prevents potentially harmful fugitive emissions.

Tobramycin (TOBI†, Novartis Pharmaceuticals Corporation†)

NEW **COMPARING BREATH ACTUATED AND BREATH ENHANCED JET NEBULIZERS FOR THE DELIVERY OF TOBRAMYCIN.** M Nagel, R Ali, C Doyle, J Suggett, D Coppolo. American Journal of Respiratory and Critical Care Medicine 2023;207:A4880.

Rationale: Nebulization is the mainstay of care for patients requiring inhaled antibiotic therapy in association with pulmonary diseases such as cystic fibrosis, bronchiectasis and COPD. Breath actuated (BA) technology offers more consistent dose delivery[1] and the reduction of fugitive emissions[2] into the care environment. This *in vitro* study was undertaken to determine delivery of tobramycin using a BA nebulizer/compressor system and 2 breath enhanced (BE) nebulizer/compressor systems. **Methods:** ***AeroEclipse**** ***XL BAN**** Nebulizer (BA) with ***Ombra**** Table Top Compressor (Trudell Medical International) was evaluated with 300 mg tobramycin (5 mL, Teva† Tobramycin) and an adult tidal breathing waveform (tidal volume = 500 mL; duty cycle = 33%; breaths/minute = 13) delivered by breathing simulator (ASL 5000, IngMar Medical). An electret filter at the nebulizer mouthpiece captured emitted aerosol at minute intervals until onset of sputter. Total mass delivered (TM) was determined. Average delivery rate/min (DR_{min}) was calculated after assaying for tobramycin by a validated HPLC-based procedure. Parallel measurements of fine droplet fraction <5.4µm diameter ($FDF_{<5.4µm}$) were made with each nebulizer, sampling the emitted aerosol via a chilled Next Generation Pharmaceutical Impactor at 15 L/min. Fine droplet mass delivery/min ($FDM_{<5.4µm/min}$) was determined as the product of DR_{min} and $FDF_{<5.4µm}$. Fine droplet mass ($FDM_{<5.4µm}$) was determined as the product of TM and $FDF_{<5.4µm}$. Similar measurements were undertaken with PARI LC PLUS† (BE) with DeVilbiss† Pulmo-Aide† compressor and PARI LC PLUS† (BE) with PARI Vios† compressor. **Results:** Table 1 summarizes the results. $FDM_{<5.4µm/min}$ data was similar for the BA/compressor system and one of the BE/compressor systems. However, $FDM_{<5.4µm}$ for the BA/compressor system was higher than both BE/compressor systems.

Table 1: Delivery of Tobramycin from BA and BE Systems Simulating Adult Tidal-Breathing (mean ± SD) (n = 5devices/group)

Nebulizer Type	**Breath Actuated (BA)**	**Breath Enhanced (BE)**	
	AeroEclipse* ***XL BAN**** **Nebulizer/ *Ombra**** **Table Top Compressor**	**PARI LC PLUS†/DeVilbiss† Pulmo-Aide† Compressor**	**PARI LC PLUS†/PARI Vios† Compressor**
TM (mg)	106.4 ± 18.9	100.6 ± 10.9	64.1 ± 20.1
DR_{min}(mg/min)	5.5 ± 1.3	5.9 ± 0.5	3.5 ± 1.4
$FDF_{<5.4µm}$ (%)	63.1 ± 2.6	60.6 ± 3.8	59.3 ± 4.0
$FDM_{<5.4µm/min}$ (mg/min)	3.3 ± 0.9	3.6 ± 0.3	2.0 ± 0.9
$FDM_{<5.4µm}$ (mg)	63.6 ± 12.7	60.6 ± 6.2	37.0 ± 13.1

Conclusions: The BA system performs similarly or better than both BE systems. The more significant difference in fine droplet mass delivered between the two BE systems may be due to the compressor. On the basis of this study, clinicians could select ***AeroEclipse**** ***XL BAN**** Nebulizer with ***Ombra**** Table Top Compressor for tobramycin delivery, with the added value of a breath actuated device offering improved dosing consistency[1] and low fugitive emissions[2]. [1] Dose Assurance With Nebulizer Therapy – A Laboratory Investigation Into The Medication Delivery Performance Of A Range Of Different Nebulizers At Different Inspiratory/Expiratory Ratios. M Nagel, N Hoffman, J Suggett, V Wang. American Journal of Respiratory and Critical Care Medicine 2021;203:A4672. [2] A Laboratory-Based Examination Of The Potential For Fugitive Emission Of Aerosols To The Local Environment From A Range Of Commercially Available Nebulizer Systems. MW Nagel, JA Suggett, JP Mitchell. Respiratory Drug Delivery 2021;1:287-292.

MEDICATION DELIVERY OF CF DRUGS VIA A BREATH ACTUATED NEBULIZER: REVIEW OF DELIVERY PERFORMANCE VERSUS A BREATH ENHANCED NEBULIZER (BEN) COMMONLY USED WITH SUCH MEDICATIONS. J Suggett, M Nagel, J Schloss, D Coppolo. Journal of Cystic Fibrosis 2021;20(S2):S126.

Introduction: Medications to manage care of CF patients are often delivered via a nebulizer, as such treatment is generally easy to use and enables delivery of the typical doses needed. A breath actuated nebulizer will reduce fugitive emissions and provide dose assurance (because dosing is not dependent on breathing pattern), however there are sometimes questions around the dose delivered to the patient when changing between continuous and breath actuated delivery modes. This study compares the two delivery modes for a number of commonly used CF medications in the home. **Methods:** Four different medications were evaluated. These were: a) 7% hypertonic saline, b) tobramycin, c) dornase alfa, and d) colistimethate sodium. Delivery was compared for each with a breath actuated nebulizer (***AeroEclipse**** ***XL BAN**** Nebulizer/***Ombra**** Table Top Compressor, Monaghan Medical Corporation) and continuous breath enhanced nebulizer (LC PLUS† BEN/PARI BOY† SX compressor, PARI). Medication delivery was compared for each, from existing laboratory studies, in terms of the performance measures in each study. **Results:** For hypertonic saline, the ***BAN**** Nebulizer exhibited an 81.6% fine droplet fraction compared to 71.2% with the BEN, indicative of slightly smaller droplets, more likely to be delivered to the lungs. For tobramycin, the ***BAN**** Nebulizer again exhibited a slightly higher fine particle fraction than the BEN (72% vs. 64%) and delivered a total mass of 141 mg compared to 83 mg for the BEN. For dornase alfa, the ***BAN**** Nebulizer exhibited a fine droplet mass of 428 mcg compared to 349 mcg with the BEN. For colistimethate, the fine droplet mass for the ***BAN**** Nebulizer was similar to the BEN for the first 12 minutes of delivery, with the ***BAN**** Nebulizer continuing to deliver medication for an additional 7 minutes.

Medication	**Metric**	***AeroEclipse*** XL BAN**** **Nebulizer/ *Ombra*** Table Top Compressor**	**LC PLUS† BEN/ PARI BOY† SX Compressor**
7% Hypertonic Saline	Fine Droplet Fraction	81.6%	71.2%
Tobramycin	Fine Particle Fraction Total Mass	72% 141 mg	64% 83 mg
Dornase Alfa	Fine Droplet Mass	428 µg	349 µg
Colistimethate Sodium	Fine Droplet Mass	Approx. 26 mg at 12 minutes increasing to a little over 40 mg at sputter	Approx. 25 mg at 12 minutes (sputter)

Conclusions: Although the medication delivery in the various lab studies was reported using differing metrics, a common trend was that the ***BAN**** Nebulizer delivered at least as much or more medication than the BEN in each case. Reviewing the safety data for the drugs themselves shows that the higher delivery with the ***BAN**** Nebulizer was well within acceptable dosing ranges. On the basis of these studies, clinicians could recommend ***BAN**** Nebulizer for delivery of CF medications, with the added value of a ***BAN**** Nebulizer system offering low fugitive emissions and improved dosing consistency.

MEDICATION DELIVERY OF BRONCHIECTASIS DRUGS VIA A BREATH ACTUATED NEBULIZER: REVIEW OF DELIVERY PERFORMANCE VERSUS A BREATH ENHANCED NEBULIZER (BEN) COMMONLY USED WITH SUCH MEDICATIONS. J Suggett, D Haapanen. 2nd European NTM & Bronchiectasis Workshop 2021 Abstracts Leaflet:P.09.

Introduction: Medications to manage care of bronchiectasis patients are often delivered via a nebulizer, as such treatment is generally easy to use and enables delivery of the typical doses needed. A breath actuated nebulizer will reduce fugitive emissions and provide dose assurance (because dosing is not dependent on breathing pattern), however there are sometimes questions around the dose delivered to the patient when changing between continuous and breath actuated delivery modes. This study compares the two delivery modes for bronchiectasis medications commonly used in the home. **Methods:** Three different medications were evaluated. These were: a) 7% hypertonic saline, b) tobramycin, and c) colistimethate sodium. Delivery was compared for each with a breath actuated nebulizer (***AeroEclipse**** ***XL BAN**** Nebulizer/***Ombra**** Table Top Compressor, Trudell Medical International) and continuous breath enhanced nebulizer (LC PLUS† BEN/PARI BOY† SX compressor, PARI). Medication delivery was compared for each, from existing laboratory studies, in terms of the performance measures in each study. **Results:** For hypertonic saline, the ***BAN**** Nebulizer exhibited an 81.6% fine droplet fraction compared to 71.2% with the BEN, indicative of slightly smaller droplets, more likely to be delivered to the lungs. For tobramycin, the ***BAN**** Nebulizer again exhibited a slightly higher fine particle fraction than the BEN (72% vs. 64%) and delivered a total mass of 141 mg compared to 83 mg for the BEN. For colistimethate, the fine droplet mass for the ***BAN**** Nebulizer was similar to the BEN for the first 12 minutes of delivery, with the ***BAN**** Nebulizer continuing to deliver medication for an additional 7 minutes. **Conclusions:** Although the medication delivery in the various lab studies was reported using differing metrics, a common trend was that the breath actuated nebulizer delivered at least as much or more medication than the breath enhanced nebulizer in each case. Reviewing the safety data for the drugs themselves shows that the higher delivery with the ***BAN**** Nebulizer was well within acceptable dosing ranges. Clinicians could recommend ***BAN**** Nebulizer for delivery of bronchiectasis medications on the basis of these studies.

DELIVERY OF TOBRAMYCIN VIA PNEUMATIC NEBULIZER: A LABORATORY STUDY COMPARING BREATH-ACTUATED AND BREATH-ENHANCED DEVICES. JA Suggett, H Schneider, M Nagel, J Mitchell. American Journal of Respiratory and Critical Care Medicine 2014;189:A2847.

Rationale: Pneumatic nebulization is the mainstay of care of patients requiring inhaled antibiotic therapy in association with pulmonary diseases such as cystic fibrosis and chronic obstructive pulmonary disease. Nebulizers with breath actuated technology

offer the opportunity to provide such therapy without emission of fugitive emissions to caregivers during exhalation, as well as conserving medication if the patient chooses to interrupt therapy. This bench study was undertaken to determine the delivery of tobramycin using a breath actuated device, with data from a breath entrained nebulizer (BEN) as a benchmark. **Methods:** The breath actuated device (***AeroEclipse*** **XL BAN**** Nebulizer with ***Ombra**** Table Top Compressor (AE-XL, Trudell Medical International, London, ON, Canada) was evaluated with an adult tidal breathing waveform (tidal volume = 600 mL; duty cycle = 33%; rate/minute = 10 breaths) delivered by breathing simulator (ASL 5000, IngMar Medical Ltd., Pittsburgh, PA). An electret filter at the mouthpiece of the nebulizer captured emitted aerosol containing 300 mg tobramycin in a 5 mL fill (TOBI†; Novartis Pharmaceuticals Corporation†, East Hanover, NJ) at minute intervals until onset of sputter. Average delivery rate/minute (DR_{min}) was calculated after assaying for tobramycin by a validated HPLC based procedure. Similar measurements were undertaken with an identical number of BENs (LC PLUS† with PARI BOY† SX compressor; PARI Respiratory Equipment, Midlothian, VA). Parallel measurements of fine droplet fraction < 5.4 µm diameter ($FDF_{<5.4\mu m}$) were made with each nebulizer, sampling the emitted aerosol via a Next Generation Pharmaceutical Impactor at 15 L/min in accordance with the pharmacopeial procedure. Fine droplet mass delivery/min ($FDM_{<5.4\mu m/min}$) was determined as the product of DR_{min} and $FDF_{<5.4\mu m}$. Total mass delivered (TM) was also determined. **Results:** Table 1 summarizes the results for DR_{min}, $FDF_{<5.4\mu m}$, $FDM_{<5.4\mu m/min}$ and TM. DR_{min} data was similar for the two nebulizer/compressor systems however the $FDM_{<5.4\mu m/min}$ delivery rate was a little higher with the ***BAN**** Nebulizer than with the BEN, as a result of the higher FDF. The TM delivered to sputter was appreciably higher for the ***AeroEclipse*** **XL BAN**** Nebulizer (140.9 mg compared to 83.4 mg).

Table 1: Nebulizer Based Delivery of Tobramycin from Breath Actuated and Breath Enhanced Devices Simulating Adult Tidal Breathing (mean ± SD) (*n* = 5 devices/group)

Type	Nebulizer	DR_{min} (mg/min)	$FDF_{<5.4\mu m}$ (%)	$FDM_{<5.4\mu m/min}$ (mg/min)	TM (mg)
Breath Actuated	***AeroEclipse*** **XL BAN**** Nebulizer/***Ombra**** Table Top Compressor	4.14 ± 0.18	72.1 ± 1.9	2.99 ± 0.13	140.9 ± 6.2
Breath Enhanced	LC PLUS†/PARI BOY† SX Compressor	4.17 ± 0.34	63.7 ± 2.0	2.66 ± 0.22	83.4 ± 6.9

Conclusions: The delivery rate of tobramycin using the breath actuated and breath enhanced nebulizer/compressor systems was similar with evidence of a slightly higher fine particle delivery rate for the ***BAN**** Nebulizer. The more significant difference related to the total mass delivered and is somewhat expected given the higher delivery efficiency with a breath actuated nebulizer. The potential to adjust total delivery, if required, exists through the adjustment of either delivery time or fill volume.

COMBINED THERAPY

NEW **A LABORATORY ASSESSMENT OF NEBULIZED MEDICATION DELIVERY THROUGH DIFFERENT OSCILLATING POSITIVE EXPIRATORY PRESSURE (OPEP) DEVICES – NOT ALL DEVICES ARE THE SAME.** J Suggett. 5th World Bronchiectasis & NTM Conference 2022 Abstract Book:P.73.

Rationale: Medications to manage care of bronchiectasis and NTM patients are often delivered via a nebulizer, as they are easy to use. OPEP devices are also often used for airway clearance by the same group of patients and the two treatments can be combined allowing medication delivery on inhalation and OPEP therapy on exhalation. This study compares a number of different OPEP/nebulizer combinations using salbutamol as the modelled medication. **Methods:** Four different OPEP/nebulizer systems were evaluated. These were: a) ***Aerobika**** OPEP device with ***AeroEclipse** II BAN** Nebulizer at back of OPEP b) acapella† choice OPEP with VixOne† nebulizer using t-piece at front of OPEP, c) acapella† Choice Blue OPEP with ***AeroEclipse** II BAN** Nebulizer at back of OPEP, and d) acapella† Choice Blue OPEP with Salter Labs† 8900 nebulizer using t-piece at front of nebulizer. Medication delivery (total emitted mass until sputter) of salbutamol 2.5 mg in 3 mL was determined in the lab for each system using a breathing simulator and filter collection at mouthpiece (settings 600 mL tidal volume, 1:3 I:E ratio, 2 second pause after inhalation). **Results:** The graph below reports the medication delivered via each system.

Delivery System	Emitted mass of salbutamol (mcg, ± SD)
Aerobika* OPEP device/***AeroEclipse** II BAN** Nebulizer	764 ± 18
acapella† Choice Blue OPEP/***AeroEclipse** II BAN** Nebulizer	229 ± 15
acapella† choice OPEP/VixOne† Nebulizer	248 ± 25
acapella† Choice Blue OPEP/Salter Labs† 8900 Nebulizer	214 ± 8

Conclusions: The results show that OPEP/nebulizer combination selection can have a large impact on the amount of drug delivered. The ***Aerobika**** OPEP device/breath actuated ***AeroEclipse** II BAN** Nebulizer device combination delivered more than 3x as much salbutamol in a treatment compared to the other combinations. Combining OPEP and nebulizer therapy has advantages in terms of patient efficiencies, convenience, and adherence, however care should be taken to ensure the drug delivery is not compromised.

USE OF AN OSCILLATING POSITIVE EXPIRATORY PRESSURE (OPEP) DEVICE WITH A BREATH ACTUATED NEBULIZER FOR THE DELIVERY OF HYPERTONIC SALINE. DP Coppolo, JA Suggett, MW Nagel, JP Mitchell. Pediatric Pulmonology 2016;S45(51):372.

Background/Objective: Hypertonic saline is associated with increased mucociliary clearance of secretions. OPEP therapy helps to mobilize secretions mechanically. This laboratory investigation examined the performance of a breath actuated nebulizer in conjunction with OPEP for the delivery of hypertonic saline to see if the OPEP affected the emitted aerosol size distribution. **Methods:** The ***AeroEclipse** XL BAN** Nebulizer (MMC, *n* = 5 devices) with tabletop compressor (***Ombra**** Table Top Compressor) was evaluated for the delivery of hypertonic saline (4 mL, 7% v/w NaCl aq.) with and without the OPEP device (***Aerobika**** OPEP device, MMC) inserted between the mouthpiece and nebulizer. Aerosol from the ***BAN**** Nebulizer was "inhaled" via a vacuum source operated at 28.3 L/min, and sized by a laser diffractometer (Malvern Spraytec, Malvern, UK). Comparative measurements were also made with a widely encountered breath enhanced nebulizer (LC PLUS†, PARI Respiratory Equipment, Midlothian, VA; *n* = 5 devices) operated by tabletop compressor (BOY† SX). **Results:** Measures of the aerosol size distribution were volume median diameter (VMD) and fine droplet fraction defined as the % < 4.7 µm diameter ($FDF_{<4.7\mu m}$), and are summarized in the table. **Conclusions:** The addition of the OPEP device marginally reduced droplet size (paired t-test for each metric, $p < 0.001$), but the effect was small and likely unimportant, given that the finer droplets are more likely to penetrate further into the airways of the lungs, especially when restricted by secretions. The comparator BEN device produced similar, if slightly larger, droplet size results. Use of the ***AeroEclipse** XL BAN** Nebulizer with tabletop compressor, either with or without the concurrent use of the ***Aerobika**** OPEP device, would appear to be an effective method of delivering hypertonic saline to the lungs for the purpose of mucociliary clearance.

Aerosolized Emissions

NEW **EFFICIENCY OF A NEBULIZER FILTER KIT TO PREVENT ENVIRONMENTAL CONTAMINATION DURING NEBULIZER THERAPY.** J Suggett, M Nagel. CHEST 2022;162(4):A2472.

Rationale: The SARS-CoV-2 pandemic has highlighted the need to avoid environmental contamination with aerosols. To aid in this the addition of a filter kit is intended to capture any exhaled aerosol. To determine the aerosol amounts emitted to the environment during nebulizer therapy several nebulizers were evaluated to test the efficiency of the nebulizer filter system. **Methods:** The MaxiNeb Duo†, Circulaire† II and ***AeroEclipse**** ***II BAN**** Nebulizer were operated at 50 psig with their optional filter kits (*n* = 5). Each device was evaluated with 2.5 mg/3.0 mL fill of albuterol and connected to a simulator mimicking adult tidal breathing. In addition to inspiratory and expiratory filters, the nebulizer was placed under an extraction system to capture any aerosol emitted through leakages or exhalation. Salbutamol assay was undertaken by HPLC-UV spectrophotometry. **Results:** The mass of salbutamol captured from the extraction system with the MaxiNeb Duo†, Circulaire† II and ***AeroEclipse**** ***II BAN**** Nebulizer was found to be 0.5 ± 0.2, 1.5 ± 0.6 and 0.0 ± 0.0% of the initial dose respectively. **Conclusions:** The ***BAN**** Nebulizer without filter kit has previously reported environmental losses of just under 3%[1] so it is in keeping that the addition of the filter kit eliminated all losses for this device. The other two nebulizers emitted small amounts of aerosol even when a filter kit was used, which, if replicated in a clinical setting, would need to be assessed in terms of risk to staff and patients. **Reference:** [1] Efficiency of a Nebulizer Filter Kit to Prevent Environmental Contamination During Nebulizer Therapy. M Nagel, N Hoffman, J Suggett. European Respiratory Journal 2021;58(65):PA3401.

NEW **A RISK EVALUATION FOR FUGITIVE AEROSOL EMISSIONS WHEN USING DIFFERENT NEBULIZER SYSTEMS; POTENTIAL MECHANISMS, IMPACT OF DEVICE TYPE, AND MITIGATION STRATEGIES.** J Suggett, M Nagel. J Schloss, DP Coppolo. American Journal of Respiratory and Critical Care Medicine 2022;205:A1697.

Rationale: The SARS-CoV-2 environment has brought about a heightened awareness of the potential risks of fugitive emissions associated with nebulized aerosol drug delivery. Hence it would be useful to evaluate such risks in a methodical way. **Methods:** The assessment evaluated: a) the potential mechanisms (routes) whereby nebulizers might emit aerosol or liquid medication into the local environment; b) how such mechanisms may differ depending on the type of nebulizer device; and c) what mitigation strategies exist to reduce risk. Mechanisms: Review of various nebulizer types, in their use scenarios, highlight potential fugitive emissions from a) the nebulizer when the patient is not inhaling (could be when exhaling or if taking a break during the treatment); b) the patient's exhaled breath (bioaerosols); and c) the nebulizer as leaking liquid medication and biofilm generated from condensate within the device. Mitigation Strategies: a) Use of personal protective equipment (PPE) and environmental controls are general approaches (more suitable in hospital environment). b) More specific to the nebulizer itself, in addition to using a breath actuated system, is the ability to separate the liquid aerosol waiting to be nebulized from patient expelled mucosal liquid or droplets. This has the potential to be achieved through the positioning of the liquid feed in the device or through use of a dam to stop such liquid passing back into the medication reservoir. c) Finally, there are a number of different filter kit systems available that capture exhaled aerosol and prevent drug or microbial contamination into the environment. Care should be taken though to ensure that the filter has appropriate efficiency and capacity so as to not become saturated.

Results:

Potential Fugitive Emissions by Nebulizer Type:	*AeroEclipse** *II BAN** Nebulizer	Continuous Jet Nebulizer	Continuous Vibrating Mesh Nebulizer with Spacer Component
Mechanism(s)	1) Exhaled breath	1) Exhaled breath; and 2) Medicinal aerosol during breaks in treatment or any time when not inhaling	1) Exhaled breath; 2) Medicinal aerosol during breaks in treatment or any time when not inhaling; and 3) Liquid leakage from condensate
Mitigation strategies	1) Breath actuated system 2) Drool guard 3) Exhaled breath filter kit	1) Exhaled breath filter kit	1) Positioning of liquid feed 2) Exhaled breath filter kit

Conclusions: A systematic review of nebulizer use highlighted a few different potential mechanisms for fugitive emissions. Differences in nebulizer design had an impact in the amount and type of fugitive emissions emitted. Through the choice of an appropriate nebulizer, the natural risk can be greatly reduced, and through selection of appropriate mitigation strategies, the risk can be almost eliminated.

EFFICIENCY OF A NEBULIZER FILTER KIT TO PREVENT ENVIRONMENTAL CONTAMINATION DURING NEBULIZER THERAPY. M Nagel, N Hoffman, J Suggett. European Respiratory Journal 2021;58(65):PA3401.

Background: The SARS-CoV-2 pandemic has highlighted the need to improve safety for frontline workers and avoid environmental contamination with aerosols. To aid in this, a breath actuated nebulizer is available with a filter set to capture any exhaled aerosol. **Objective:** To determine the aerosol amounts emitted to the environment during nebulizer therapy with breath actuated nebulizers

and to test the efficiency of the nebulizer filter system. **Methods:** The ***AeroEclipse*** **II BAN**** Nebulizer was operated at 50 psig on its own without its optional filter kit (*n* = 5). Devices with the filter kit were also repeatedly tested, 2 hours apart, up to five times. Each device was evaluated with 2.5 mg/3.0 mL fill of salbutamol and connected to a simulator mimicking adult tidal breathing. In addition to inspiratory and expiratory filters, the nebulizer was placed under an extraction system to capture any aerosol emitted through leakages or exhalation. Salbutamol assay was undertaken by HPLC-UV spectrophotometry. **Results:** The mass of salbutamol captured from the extraction system with the ***BAN**** Nebulizer alone was found to be 2.6 ± 0.4% of the initial dose. When the filter kit was added, zero fugitive emissions were recovered. Even after four subsequent treatments no salbutamol was recovered.

	BAN* Nebulizer Alone**	***BAN**** Nebulizer with Filter Kit**				
		Treatment 1	**Treatment 2**	**Treatment 3**	**Treatment 4**	**Treatment 5**
Device 1	2.1%	0%	0%	0%	0%	0%
Device 2	2.9%	0%	0%	0%	0%	0%
Device 3	3.0%	0%	0%	0%	0%	0%
Device 4	2.6%	0%	0%	0%	0%	0%
Device 5	2.2%	0%	0%	0%	0%	0%
Average	**2.6% ± 0.4%**	**0% ± 0%**	**0% ± 0%**	**0% ± 0%**	**0% ± 0%**	**0% ± 0%**

Conclusion: The ***BAN**** Nebulizer alone had environmental losses of less than 3%, which in itself is at least five times less than reported for continuous nebulizers and is consistent with previous data for this device. The filter kit eliminated all losses, and even if the filter was not replaced each treatment (label use), the efficiency appeared to be maintained for at least five uses.

DRUG DELIVERY PERFORMANCE AND FUGITIVE EMISSION COMPARISON OF TWO COMMERCIALLY AVAILABLE NEBULIZER SYSTEMS. M Nagel. N Hoffman, J Suggett. European Respiratory Journal 2021;58(65):PA3402.

Background: Delivery of inhaled medications by nebulizer for the treatment of respiratory disease is widespread. Important factors to consider in a delivery system are amount and consistency of drug delivered to the lungs as well as the amount of drug/droplets that are emitted to the local environment (fugitive emissions). **Methodology:** Nebulizers (***AeroEclipse*** **II BAN**** Nebulizer and Aerogen† Ultra) were evaluated with 2.5 mg/3.0 mL fill of salbutamol and connected to a breathing simulator mimicking adult tidal volume (500 mL) with I:E ratios of 1:1, 1:2 and 1:3. Emitted aerosol was captured by filter at 1 minute intervals until sputtering to determine total mass (TM_{sal}). The percentage of drug mass lost to the environment (EL_{sal}) was determined by combining the TM_{sal} recovered from the inhalation filters along with the residual mass recovered from the nebulizer and subtracting that from the initial 2.5 mg salbutamol placed in the nebulizer. Salbutamol assay was undertaken by HPLC. Fine droplet mass (FDM_{sal} µg) was determined by laser diffractometry as the product of TM_{sal} and fine droplet fraction (% < 4.7µm).

Results: Average ± SD FDM_{sal} and EL_{sal} at extended I:E ratios are reported in the table.

I:E Ratio	***BAN**** Nebulizer**		**Aerogen† Ultra**	
	FDM_{sal} (µg)	**EL_{sal} (%)**	**FDM_{sal} (µg)**	**EL_{sal} (%)**
1:1	803 ± 76	4.1 ± 1.0	503 ± 31	23.8 ± 1.6
1:2	715 ± 82	5.2 ± 2.7	316 ± 12	34.0 ± 2.8
1:3	695 ± 52	4.2 ± 1.3	234 ± 13	37.8 ± 3.4

Conclusions: Higher and more consistent delivery was achieved by ***AeroEclipse*** **II BAN**** Nebulizer as well as lower fugitive emissions. Clinicians should be aware of the ability to get increased amounts of medication to the lungs while maintaining a safer work environment for staff with use of the ***BAN**** Nebulizer.

ESTIMATED DERMAL EXPOSURE TO NEBULIZED PHARMACEUTICALS FOR A SIMULATED HOME HEALTHCARE WORKER SCENARIO. S Ishaua, J F. Reichard, A Maier, M Nianga, M Yermakova, SA Grinshpuna. Journal of Occupational and Environmental Hygiene 2020;17(4):193-205.

The duties of home healthcare workers are extensive. One important task that is frequently performed by home healthcare workers is administration of nebulized medications, which may lead to significant dermal exposure. In this simulation study conducted in an aerosol exposure chamber, we administered a surrogate of nebulizer delivered medications (dispersed sodium chloride, NaCl) to a patient mannequin. We measured the amount of NaCl deposited on the exposed surface of the home healthcare worker mannequin, which represented the exposed skin of a home healthcare worker. Factors such as distance and position of the home healthcare worker, room airflow rate and patient's inspiratory rate were varied to determine their effects on dermal exposure. There was a 2.78% reduction in dermal deposition for every centimeter the home healthcare worker moved away from the patient. Increasing the room's air exchange rate by one air change per hour increased dermal deposition by about 2.93%, possibly due to a decrease in near field particle settling. For every 10 degrees of arc the home healthcare worker is positioned from the left side of the patient toward the right and thus moving into the ventilation airflow direction, dermal deposition increased by about 4.61%. An increase in the patient's inspiratory rate from 15 - 30 L/min resulted in an average of 14.06% reduction in dermal deposition for the home healthcare worker, reflecting a relative increase in the aerosol fraction inhaled by the patient. The findings of this study elucidate the interactions among factors that contribute to dermal exposure to aerosolized pharmaceuticals administered by home healthcare workers. The results presented in this paper will help develop recommendations on mitigating the health risks related to dermal exposure of home healthcare workers.

IMPLEMENTATION OF A BREATH ACTUATED NEBULIZER REGIMEN MAY REDUCE NOSOCOMIAL INFLUENZA ACQUIRED BY EXPOSURE TO FUGITIVE DROPLET EMISSIONS FROM CONTINUOUS NEBULIZERS WHOSE DROPLETS PRODUCED DURING EXHALATION ARE VENTED TO THE ENVIRONMENT. D Copelin. Respiratory Care 2018;63(10):3016143.

Background: Most nebulizers generate aerosol continuously, resulting in the expulsion of droplets to the environment during each exhalation. Influenza virus particles attached to such droplets is a potential cause of infection for hospital staff. The influenza virus can survive up to 2 - 3 hours following droplet attachment. Transfer from continuous to breath actuated nebulizer based therapy might be beneficial in terms of reducing staff acquired infections. The present study examined comparative costs associated with the care of patients in the emergency department of a midsized hospital on either continuous or breath actuated nebulizer based therapy. **Methods:** Attendance records were examined for staff associated with the care of patients known to be carrying influenza virus and therefore isolated from the general population undergoing care in the ED. The following conditions were evaluated: (Group 1) November 2016 - March 2017 for level 1 surgical procedure face mask for only the patients undergoing continuous nebulizer based therapy (AirLife† Misty Max 10† disposable nebulizer, CareFusion, San, Diego, CA); (Group 2) November 2017 - December 2017 for level 1 surgical procedure face mask for both staff and patients, the latter on continuous nebulizer therapy (as in (1)); (Group 3) January 2018 - March 2018 for level 1 surgical procedure face mask for both staff and patients, the latter on breath actuated nebulizer based therapy (***AeroEclipse** *II BAN**** Nebulizer, Monaghan Medical Corporation, Plattsburgh, NY). **Results:** Table 1 summarizes the findings: While the use of facemasks by both staff and patients reduced the number of positive influenza tests, implementation of breath actuated nebulizer based therapy resulted in a further improvement protecting caregivers. **Conclusions:** Implementation of breath actuated nebulizer based therapy has the potential to reduce costs associated with acquisition of nosocomial influenza in the ED.

Table 1: Summary and Findings

Outcomes	Group 1 Continuous	Group 2 Continuous	Group 3 Breath Actuated Nebulizer
Precautions to reduce virus spread	Facemask for patients only	Facemask for patients and staff	Facemask for patients and staff
Staff 'sick' days	17	8	2
Cost of 'sick' days	$4,471	$2,444	$284
Call-back pay-days	17	8	2
Cost of call-back pay-days	$7,632	$3,762	$1,254
Positive influenza tests for staff	9	5	2

A GUIDE TO AEROSOL DELIVERY DEVICES FOR RESPIRATORY THERAPISTS, 4TH EDITION. DS Gardenhire, D Burnett, S Strickland, TR Myers. American Association for Respiratory Care 2017.

Exposure to Second-hand Aerosol Drugs: Care providers and bystanders have the risk of exposure to inhaled medications during routine monitoring and care of patients. While workplace exposure to aerosol may be detectable in the plasma,[26] it may also increase the risk of asthma-like symptoms and cause occupational asthma.[27-29] The development and implementation of an occupational health and safety policy in respiratory therapy departments can minimize exposure to second-hand aerosol drugs.

ASTHMA AMONG EMPLOYED ADULTS, BY INDUSTRY AND OCCUPATION — 21 STATES, 2013. KE Dodd, JM Mazurek. Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report 2016;65(47):1325-1331.

"…it is well recognized that workers in the health care and social assistance industry who are exposed to cleaning and disinfection products, powdered latex gloves, and aerosolized medications have a twofold increased likelihood of new onset asthma."

RESPIRATORY HEALTH SURVEY OF RESPIRATORY THERAPISTS. H Dimich-Ward, ML Wymar, M Chan-Yeung. CHEST 2004;126(4):1048-1053.

Study Objectives: The purpose of this study was to determine whether respiratory therapists (RTs) had an elevated risk of respiratory symptoms and to determine the association of work exposures with symptoms. **Methods:** Mailed questionnaire responses from 275 RTs working in British Columbia, Canada, were compared to those of 628 physiotherapists who had been surveyed previously. Analyses incorporated logistic regression analysis with adjustment for age, sex, smoking status, and childhood asthma. **Results:** Compared to physiotherapists, RTs had over twice the risk of being woken by dyspnea, having wheeze, asthma attacks, and asthma diagnosed after entering the profession. Among RTs, two work factors associated with asthma were sterilizing instruments with glutaraldehyde based solutions and the use of aerosolized ribavirin. RTs who used an oxygen tent or hood had the highest risk of asthma diagnosed after entering the profession (odds ratio [OR], 8.3; 95% confidence interval [CI], 12.6 to 26.0) and of asthma attacks in the last 12 months (OR, 3.6; 95% CI, 1.2 to 10.9). **Conclusions:** Our data suggest that RTs may be at an increased risk for asthma-like symptoms and for receiving a diagnosis of asthma since starting to work in their profession, possibly related to exposure to glutaraldehyde and aerosolized ribavirin.

PERFORMANCE COMPARISON OF NEBULIZER DESIGNS: CONSTANT-OUTPUT, BREATH-ENHANCED, AND DOSIMETRIC. JL Rau, A Ari, RD Restrepo. Respiratory Care 2004;49(2):174-179.

Introduction: Design differences among pneumatically powered, small volume nebulizers affect drug disposition (percentage of the dose delivered to the patient, lost to deposition in the equipment, and lost via exhalation to ambient air) and thus affect drug availability and efficacy. **Objective:** Evaluate *in vitro* the dose disposition with 5 nebulizer models, of 3 types (constant output, breath enhanced,

and dosimetric), using simulated normal, adult breathing. **Methods:** We compared 5 nebulizer models: 2 constant output (Misty-Neb† and Sidestream†), 1 breath enhanced (PARI LC† D), and 2 dosimetric (Circulaire† and ***AeroEclipse*** **BAN**** Nebulizer). Each nebulizer was filled with a 3 mL unit dose of albuterol sulfate and powered by oxygen at 8 L/min. The nebulizers were connected to an induction throat, connected to a breathing simulator. We measured (1) inhaled drug (subdivided into mass deposited in the induction throat and mass deposited in the filter at the distal end of the induction throat), (2) exhaled drug (lost to ambient air), (3) drug lost to deposition in the apparatus, and (4) drug left in the unit dose bottle. The duration of nebulization (until sputter) was measured with a stopwatch. All drug amounts were analyzed via spectrophotometry and expressed as a percentage of the total dose. **Results:** The mean ± SD inhaled drug percentages were: AirLife† Misty-Neb† 17.2 ± 0.4%, AirLife† Sidestream† 15.8 ± 2.8%, PARI LC† D 15.2 ± 4.2%, Circulaire† 8.7 ± 1.0%, and ***AeroEclipse*** **BAN**** Nebulizer 38.7 ± 1.3%. The mean ± SD percentages of drug lost to ambient air were: Misty-Neb† 26.8 ± 0.7%, Sidestream† 17.3 ± 0.4%, PARI LC† D 18.3 ± 0.8%, Circulaire† 12.3 ± 0.8%, and ***AeroEclipse*** **BAN**** Nebulizer 6.6 ± 3.3%. The mean ± SD percentages of drug lost to deposition in the apparatus were: Misty-Neb† 52.3 ± 0.6%, Sidestream† 63.4 ± 3.0%, PARI LC† D 62.5 ± 4.0%, Circulaire† 75.8 ± 0.5%, and ***AeroEclipse*** **BAN**** Nebulizer 51.0 ± 2.1%. Duration of nebulization was shortest with the Circulaire† and longest with the ***AeroEclipse*** **BAN**** Nebulizer ($p < 0.05$ via 1-way analysis of variance). **Conclusions:** The nebulizers we tested differ significantly in overall drug disposition. The dosimetric ***AeroEclipse*** **BAN**** Nebulizer provided the largest inhaled drug mass and the lowest loss to ambient air, with the test conditions we used.

DELIVERY OF A SUSPENSION CORTICOSTEROID FORMULATION BY SMALL VOLUME NEBULIZERS: A COMPARATIVE BENCH STUDY. JP Mitchell, MW Nagel, KJ Wiersema, SL Bates. European Respiratory Journal 2001;16(31):903.

We report a study of the delivery of 0.25% mg/mL budesonide suspension (Pulmicort†, Nebuamp† (2 x 2 mL), AstraZeneca†, Canada) by two types of small volume nebulizer (SVN), simulating adult breathing conditions ((tidal volume = 600 mL, duty cycle = 1:2 (2 second inspiration), PIFR = 31 L/min). Each SVN was operated by compressed air (8 L/min at 50 psig). Budesonide mass delivery was determined by filter collection (n = 5 SVNs/group, 3 replicates/device). The ***AeroEclipse*** **BAN**** Nebulizers (Trudell Medical International, London, ON, Canada) delivered 283 ± 32 mg prior to sputtering, and 80 ± 11 mg were lost to the environment. Corresponding data for the PARI LC† D SVNs (PARI Respiratory Equipment Inc., Richmond, VA, USA) were 97 ± 7 mg and 305 ± 2 mg respectively. The breath actuation feature of the ***AeroEclipse*** **BAN**** Nebulizer minimizes aerosol release to the environment during exhalation, which may cause adverse effects to both patient and health care provider.

Guidance

NEW **INFECTION PREVENTION AND CONTROL IN THE CONTEXT OF CORONAVIRUS DISEASE (COVID-19): A LIVING GUIDELINE, 13 JANUARY 2023.** World Health Organization 2023. WHO/2019-nCoV/ipc/guideline/2023.1.

> It remains unclear whether aerosols generated by nebuliser therapy or high flow oxygen delivery are infectious or whether other procedures (e.g. nasogastric tube insertion, suctioning for airway clearance, or swabbing procedures) involve the risk of aerosol generation, due to lack of evidence or low quality evidence.

NEW **INDIAN GUIDELINES ON NEBULIZATION THERAPY.** SK Katiyar, SN Gaur, RN Solanki, N Sarangdhar, JC Suri, R Kumar, GC Khilnani, D Chaudhary, R Singla, PA Koul, AA Mahashur, AG Ghoshal, D Behera, DJ Christopher, D Talwar, D Ganguly, H Paramesh, KB Gupta, TM Kumar, PD Motiani, PS Shankar, R Chawla, R Guleria, SK Jindal, SK Luhadia, VK Arora, VK Vijayan, A Faye, A Jindal, AK Murar, A Jaiswal, M Arunachalam, AK Janmeja, B Prajapat, C Ravindran, D Bhattacharyya, G D'Souza, IS Sehgal, JK Samaria, J Sarma, L Singh, MK Sen, MK Bainara, M Gupta, NT Awad, N Mishra, NN Shah, N Jain, PR Mohapatra, P Mrigpuri, P Tiwari, R Narasimhan, RV Kumar, R Prasad, R Swarnakar, RK Chawla, R Kumar, S Chakrabarti, S Katiyar, S Mittal, S Spalgais, S Saha, S Kant, VK Singh, V Hadda, V Kumar, V Singh, V Chopra, B Visweswaran. Indian Journal of Tuberculosis 2022;69(S1):S1-S191.

> **Recommendation:** The aerosol generated from nebulizer treatment carries a lower risk of infection since it is not patient derived (bioaerosols) but is produced from fluid in the nebulizer chamber (medical aerosol), and hence, does not carry viral particles.

NEW **COVID-19: INFORMATION FOR THE RESPIRATORY COMMUNITY.** British Thoracic Society. (Last accessed April 24, 2023.)

> **Advice About The Safety Of Nebuliser Use:** Advice from PHE and HPS is that nebulisation is not a VIRAL droplet generating procedure. The droplets are from the machine (liquid bronchodilator drug particles), not the patient. Nebulisation is not therefore considered a 'viral' aerosol generating procedure. Last update 23/3/20.

NEW **REDUCING AEROSOL-RELATED RISK OF TRANSMISSION IN THE ERA OF COVID-19: AN INTERIM GUIDANCE ENDORSED BY THE INTERNATIONAL SOCIETY OF AEROSOLS IN MEDICINE.** JB Fink, S Ehrmann, J Li, P Dailey, P McKiernan, C Darquenne, AR Martin, B Rothen-Rutishauser, PJ. Kuehl, S Häussermann, R MacLoughlin, GC Smaldone, B Muellinger, TE Corcoran, R Dhand. Journal of Aerosol Medicine and Pulmonary Drug Delivery 2020;33(6):300-304.

> Medical aerosols from nebulization derive from a nonpatient source (the fluid in the nebulizer chamber) and have not been shown to carry patient-derived viral particles. Concerns of medical aerosol becoming contaminated in the lungs before exhalation are not supported by evidence. Consequently, when a droplet in the aerosol coalesces with a contaminated mucous membrane, it will cease to be airborne and, therefore, will no longer be part of an aerosol.

NEW **VARIABILITY IN DELIVERED DOSE AND RESPIRABLE DELIVERED DOSE FROM NEBULIZERS: ARE CURRENT REGULATORY TESTING GUIDELINES SUFFICIENT TO PRODUCE MEANINGFUL INFORMATION?** RHM Hatley, SM Byrne. Medical Devices: Evidence and Research 2017;10:17-28.

> **Background:** To improve convenience to patients, there have been advances in the operation of nebulizers, resulting in fast treatment times and less drug lost to the environment. However, limited attention has been paid to the effects of these developments on the delivered dose (DD) and respirable delivered dose (RDD). Published pharmacopoeia and ISO testing guidelines for adult use testing utilize a single breathing pattern, which may not be sufficient to enable effective comparisons between the devices. **Materials and Methods:** The DD of 5 mg of salbutamol sulfate into adult breathing patterns with inhalation:exhalation (I:E) ratios between 1:1 and 1:4 was determined. Droplet size was determined by laser diffraction and RDD calculated. Nine different nebulizer brands with different modes of operation (conventional, venturi, breath enhanced, mesh, and breath activated) were tested. **Results:** Between the non-breath activated nebulizers, a 2.5-fold difference in DD (~750 - 1,900 µg salbutamol) was found; with RDD, there was a more than fourfold difference (~210 - 980 µg). With increasing time spent on exhalation, there were progressive reductions in DD and RDD, with the RDD at an I:E ratio of 1:4 being as little as 40% of the dose with the 1:1 I:E ratio. The DD and RDD from the breath activated mesh nebulizer were independent of the I:E ratio, and for the breath activated jet nebulizer, there was less than 20% change in RDD between the I:E ratios of 1:1 and 1:4. **Conclusion:** Comparing nebulizers using the I:E ratio recommended in the guidelines does not predict relative performance between the devices at other ratios. There was significant variance in DD or RDD between different brands of non-breath activated nebulizer. In future, consideration should be given to revision of the test protocols included in the guidelines, to reflect more accurately the potential therapeutic dose that is delivered to a realistic spectrum of breathing patterns.

EUROPEAN RESPIRATORY SOCIETY GUIDELINES ON THE USE OF NEBULIZERS. J Boe, JH Dennis, BR O'Driscoll, Members of Task Force: TT Bauer, M Carone, B Dautzenberg, P Diot, K Heslop, L Lannefors. European Respiratory Journal 2001;18:228-242.

- The most important considerations should be efficacy and patient safety.
- The three main factors which determine where in the respiratory tract a nebulized drug droplet will deposit are: droplet size, pattern of breath inhalation and age/condition of the lung.
- Lung delivery of nebulized drugs will also be increased greatly when breath activated nebulizers are used (at present, half of the nebulizer output is wasted during expiration).

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