AEROECLIPSE® II
Breath Actuated Nebulizer

Study Summary

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FOREWORD

Monaghan Medical and its affiliate company Trudell Medical have an enviable history of strong leadership in creating innovative medical devices that enhance the quality of life for people of all ages. We focus our efforts on the well-being of our employees and customers, and provide safe, valuable and easy to use devices for a global market.

Monaghan Medical Corporation designs, develops and manufactures innovative aerosol drug delivery devices for human health applications. We supply the pharmaceutical and healthcare industry with devices and solutions to help ease the burden that respiratory challenges bring to patients and their caregivers. With a dedication to providing unsurpassed quality products, we take our role within respiratory disease management very seriously.

Our product portfolio includes a number of specialty medical devices including the AEROCHAMBER® Brand of Valved Holding Chamber, TRUZONE® and STRIVE® Peak Flow Meters, and the AEROBIKA® Oscillating Positive Expiratory Pressure Device. We recognized the need for a more efficient nebulizer, so in response the AEROECLIPSE® II Breath Actuated Nebulizer (BAN) was developed.

The AEROECLIPSE® II BAN is the most significant advancement in the history of small volume nebulizers, generating aerosol only in response to the patient's inspiratory maneuver. Since virtually no aerosol is produced during exhalation or at rest, clinicians can be confident that the dose prescribed is the dose delivered.

The AEROECLIPSE® II BAN is designed to deliver an exceptional respirable dose. Superior aerosol performance means shorter treatment times with the likelihood of better patient care and outcomes. This Study Summary is designed to identify how the AEROECLIPSE® II Breath Actuated Nebulizer (BAN) has performed in both *in vitro* and *in vivo* studies with various formulations and versus other nebulizers.

The following sections are included in the summary:

1. Financial Evaluations
Studies showing cost savings related to use of the AEROECLIPSE® II BAN.

2. Summary by Active Pharmaceutical Ingredient
Divided by drug formulation, the studies are listed in chronological order with the most recent studies appearing first.

3. Comparison of AEROECLIPSE® II BAN to Valved Holding Chamber with Metered Dose Inhaler (MDI)
Comparison of results using our AEROCHAMBER® Valved Holding Chamber and MDI versus results using the AEROECLIPSE® II BAN and another competitive device.

4. Comparison of AEROECLIPSE® II BAN to Large Volume Nebulizers
Efficacy of the AEROECLIPSE® II BAN versus commonly used large volume nebulizers.

5. Combined Therapy
A summary of studies investigating if nebulized drug delivery is affected when the AEROECLIPSE® II BAN is paired with the AEROBIKA® Oscillating Positive Expiratory Pressure (OPEP) device.

6. Aerosolized Emissions
A summary of studies focused on exposure to fugitive aerosolized emissions and how this may cause adverse effects to health care providers.

7. Guidelines
A summary of Guidelines supporting the safe and effective use of nebulizers.

8. AEROECLIPSE® BAN Equivalence to AEROECLIPSE® II BAN
A summary of the work being conducted by the European Pharmaceutical Aerosol Group (EPAG) with respect to nebulization.

9. General Information
A summary of the work being conducted by the European Pharmaceutical Aerosol Group (EPAG) with respect to nebulization.

This Study Summary was updated to the end of June 2020.

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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.

Introduction: 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 (BAN) 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 (ED) of a mid-sized hospital on either continuous or BAN-based therapy. This facility pays 1.5 times standard rate for 'call in' staff together with the normal time rate for the person sick, resulting in an overall charge of 2.5 times standard rate per event. The hospital Infection Control department was consulted and supported this prospective study. **NEBULIZATION AND DROPLET GENERATION – Continuous Nebulization:** In a continuously operating nebulizer, aqueous droplets containing medication are produced throughout the patient tidal-breathing cycle **(Figure 1)**. Droplet generation continues during each exhalation. There is the possibility that virus particles, such as influenza may also be entrained with these droplets. They rapidly evaporate into the surroundings and the very fine residual particles can be transported tens of meters by local air currents, conveying infection to others in the vicinity. Medical grade facemasks afford protection to the patient from larger droplets conveying bacteria/virus particles emitted from caregivers, but do not necessarily protect the caregiver from these evaporated nebulizer-generated droplets. **Breath Actuated Nebulization:** In a BAN, aqueous droplets containing medication are ONLY produced during the inhalation portion of the tidal breathing cycle **(Figure 2)**. Droplet generation therefore does not occur during exhalation.

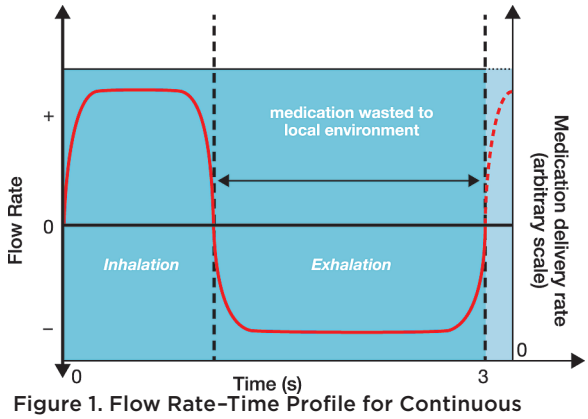


Figure 1. Flow Rate–Time Profile for Continuous Nebulization
Droplets containing virus particles may be emitted to the local environment during the exhalation phase of each breathing cycle.

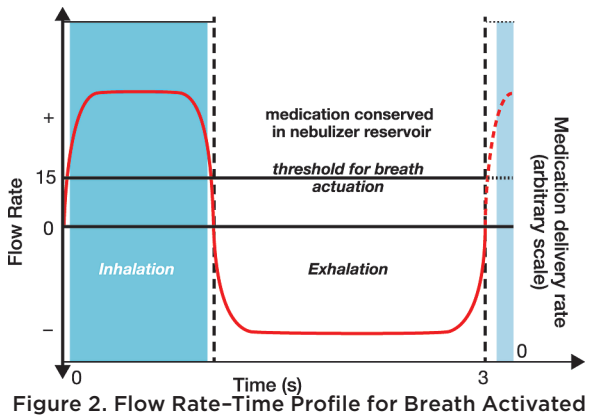


Figure 2. Flow Rate–Time Profile for Breath Activated Nebulization
Droplets are not produced during the exhalation phase.

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 Airlife† MistyMax-10† (Nov 2016 – Mar 2017) for level 1 surgical procedure face mask for only the patients undergoing continuous nebulizer-based therapy. Group 2 Airlife† MistyMax-10† (Nov 2017 – Dec 2017) for level 1 surgical procedure face mask for both staff and patients, the latter on continuous nebulizer therapy. Group 3 AEROECLIPSE® II BAN (Jan 2018 – March 2018) for level 1 surgical procedure face mask for both staff and patients, the latter on BAN-based therapy.

Table 1: Summary of Findings

Outcomes	Group 1 Continuous	Group 2 Continuous	Group 3 BAN
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
Cost-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

RESULTS AND DISCUSSION: While the use of facemasks by both staff and patients reduced the number of positive influenza tests, implementation of BAN-based therapy resulted in a further improvement protecting caregivers. The influenza treatment protocol did not change, with the exception of the use of facemasks and the BAN, as shown in **Table 1**. The same staff were involved throughout the investigation, and all members were vaccinated against influenza. The influenza season for 2018 was worse than in 2017 before the BAN was introduced, but fewer therapists reported sick with influenza. **CONCLUSIONS:** Implementation of BAN-based therapy has the potential to reduce costs associated with acquisition of nosocomial influenza in the ED.

TRANSITIONING TO A BREATH-ACTUATED PNEUMATIC NEBULIZER IN THE EMERGENCY DEPARTMENT 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 nebulizer (BAN) 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 (Monaghan Medical Corp., 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 **(Table 1)**.

Table 1: Nebulizer Supplies Budget (2012)

	Number of Nebulizers Used in 2012	Comparative Cost
AEROECLIPSE® II BAN	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 **(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	$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; 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; *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® II BAN 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 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.

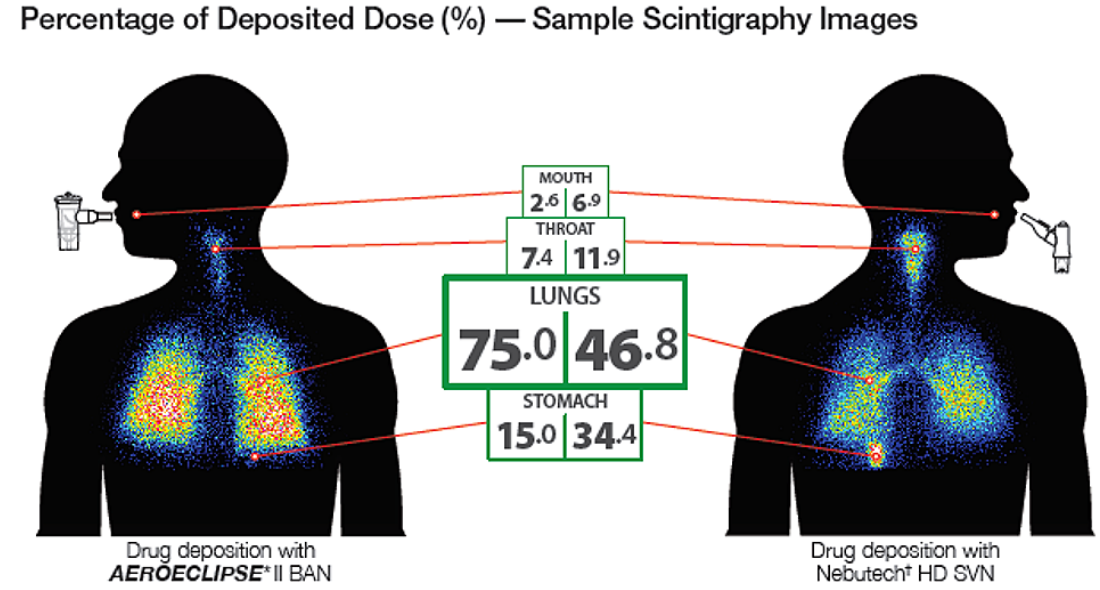
Summary by Active Pharmaceutical Ingredient

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

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 breath-actuated nebulizer (BAN) 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 BAN (AEROECLIPSE® II) and SVN (NebuTech† HD). 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 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	NebuTech† HD 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 (75.0%) demonstrated increased aerosol deposition to the lungs in healthy subjects as compared to the SVN (46.8%) ($p < .006$). 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 ($p < .005$).

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 breath actuated (Monaghan Medical Corp., 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, 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, Pittsburgh, PA) simulating tidal breathing (V_t = 600 mL; 10 cycles/min; 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 nebulizer 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 (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's (MMC) Speaker Bureau. J Mitchell is a consultant to MMC.

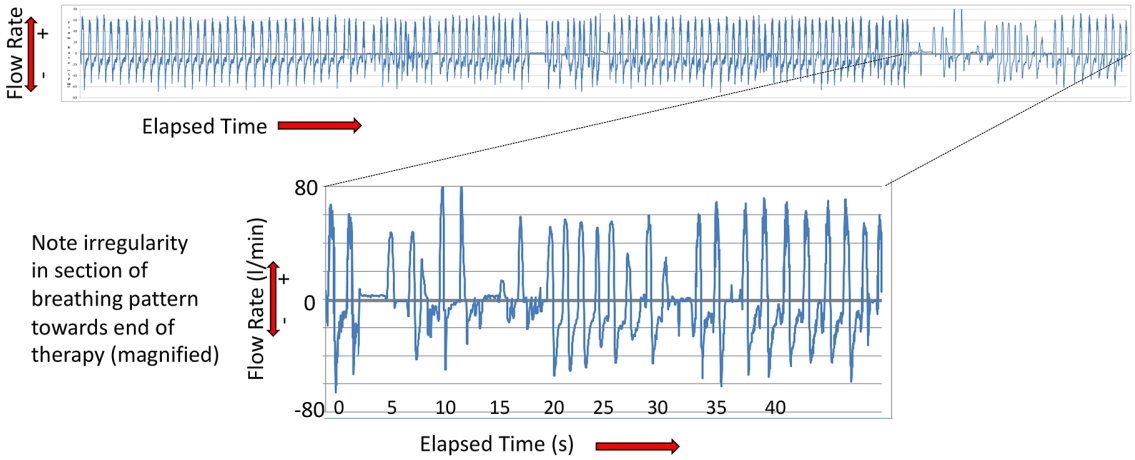
INVESTIGATION OF MEDICATION DELIVERY FROM SMALL VOLUME NEBULIZERS (SVN) AND A BREATH-ACTUATED NEBULIZER (BAN) USING IN VIVO GENERATED BREATHING PROFILES.

J Schloss, DP Coppolo, J Suggett, VT Wang, C Doyle, MW Nagel. Respiratory Care 2015;60(10):OF9.

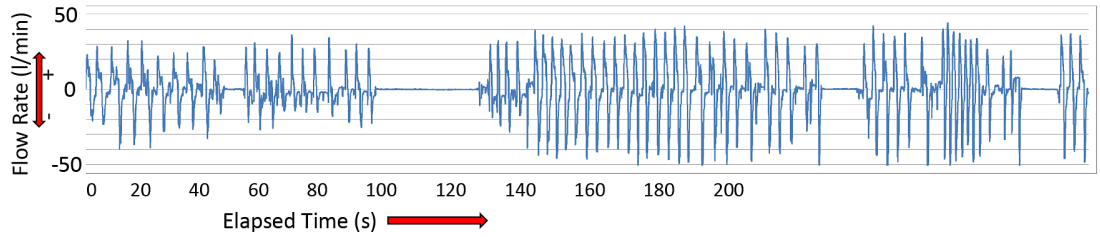
Background: Several international standards provide idealized breathing patterns to demonstrate nebulizer performance (e.g.: ISO 27427:2013 – Anaesthetic and respiratory equipment – Nebulizing systems and components). However, such

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 nebulizer (AEROECLIPSE® II BAN, 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 BAN 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 breath actuated nebulizer (BAN)/50psi Medical Air (Monaghan Medical Corporation); Circulaire† II Hybrid continuously operating, small volume nebulizer (SVN)/50psi Medical Air (Westmed Inc.); NebuTech† HDN† continuously operating, small volume nebulizer (SVN)/50psi 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, 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 (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 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 (Nikander, K, Denyer, J. Eur.Respir.Rev. 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/min respectively, delivered by breathing simulator (ASL5000, IngMar Medical, 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 ($FDF_{<4.7\mu m}$) were determined by laser diffractometry. **Results:** Fine droplet mass ($FDM_{<4.7\mu m}$, mean ± SD) values (µg) obtained as the product of TM and FDF<4.7 µm 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 $FDM_{<4.7\mu m}$ from the reference condition (I:E = 1:1), Δ $FDM_{<4.7\mu m}$ 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%. $FDM_{<4.7\mu m}$ 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 $FDF_{<4.7\mu m}$) was -42% for the Misty Fast† and -46%, 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 under-dosing. One potential solution to this clinical challenge would be the use of a breath actuated nebulizer (Schneider, J *et al.* Abstract 52461, ATS Annual Meeting, San Diego May 2014).

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 BANs. HFNC or Heliox use are currently limited to the hospital environment, however, BANs 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.

Arunthari V, Bruinsma RS, Lee AS, Johnson MM. Respir Care. 2012;57(8):1242-7.

Background: Nebulized drug delivery is a cornerstone of therapy for obstructive lung disease, but the ideal nebulizer design is uncertain. The breath-actuated nebulizer (BAN) may be superior to conventional nebulizers. This study compared the BAN 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 or standard nebulizer and were surveyed at the completion of each treatment. BAN 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 was superior to conventional nebulizer therapy; 68% indicated that duration was preferable with the BAN. RTs were more satisfied with the BAN, 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 (4.1 min vs 9.9 min, P < .001). Additionally, the BAN was associated with a lower occurrence of adverse events. **Conclusions**: Patients and RTs expressed greater satisfaction with the BAN, compared with standard nebulizer. Pre- and post-treatment vital signs did not differ between groups, but use of the BAN was associated with a shorter duration and a lower occurrence of adverse events. Taken together, these data support the use of the BAN for nebulized medication delivery.

RANDOMIZED CONTROLLED TRIAL OF A BREATH-ACTIVATED NEBULIZER IN PATIENTS WITH EXACERBATION OF COPD.

Haynes JM. Respir Care. 2012;57(9):1385-90.

Background: Exacerbations of COPD (ECOPD) are characterized by increased dyspnea due to dynamic pulmonary hyperinflation. This study sought to determine whether the AEROECLIPSE® II breath-activated nebulizer (BAN) 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 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 6.25 ± 0.55, control 6.2 ± 0.7, P = .80). Following completion of the study protocol the BAN group had a higher IC than the SVN group (1.83 ± 0.65 L vs 1.42 ± 0.49 L, P = .03, respectively). The change in IC was higher in the BAN group (0.33 ± 0.31 L than in the SVN group (0.15 ± 0.19 L, P = .03). The BAN group also had a lower respiratory rate (19 ± 3.3 breaths/min vs 22 ± 5.3 breaths/min, P = .03, respectively). There was no difference in resting dyspnea as measured with the Borg scale (BAN 3.3 ± 2.1, SVN 3.5 ± 2.4, P = .69) or stay (BAN 4.6 ± 2.6 d, SVN 5.7 ± 2.8 d, P = .21). **Conclusions:** In this cohort of patients with ECOPD, a BAN was more effective in reducing lung hyperinflation and respiratory frequency than a continuous-flow SVN.

GOING WITH THE FLOW: RESPIRATORY CARE IN THE PEDIATRIC EMERGENCY DEPARTMENT.

Canares TL, Tucker C, Garro A. R I Med J. 2014;97(1):23-6.

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 ED has incorporated several treatment adjuncts including HFNC, Heliox, and BANs. HFNC or Heliox use are currently limited to the hospital environment, however, BANs are a simple and cost- effective device that can be integrated into the primary care, urgent care, or community ED setting.

EFFECTIVENESS OF A BREATH-ACTUATED NEBULIZER DEVICE ON ASTHMA CARE IN THE PEDIATRIC EMERGENCY DEPARTMENT.

Titus MO, Eady M, King L, Bowman CM. Clin Pediatr (Phila) 2012;51(12):1150-4.

The breath-actuated nebulizer (BAN) is a new respiratory device to deliver short-acting ß-agonists to patients with asthma exacerbations. This pediatric convenience sample experimental study compares the BAN with conventional nebulizers and demonstrates that the BAN allows for shorter treatment times to achieve improved clinical asthma scores with less albuterol, shorter emergency department length of stay, and fewer hospitalizations.

RANDOMIZED CONTROLLED TRIAL OF BREATH-ACTIVATED NEBULIZER IN PATIENTS WITH EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE.

Haynes JM. Respiratory Care 2012;57(9):1385-1390.

Background: Exacerbations of chronic obstructive pulmonary disease (ECOPD) are characterized by increased dyspnea due to dynamic pulmonary hyperinflation. This study sought to determine whether the AEROECLIPSE® II breath-activated nebulizer (BAN) 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 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, respiratory frequency and pulse rate measurements were repeated. **Results:** Both groups received an equal number of nebulizer treatments over the study period (BAN 6.25 ± 0.55, control 6.2 ± 0.7, p = 0.8). Following completion of the study protocol the BAN group had a higher inspiratory capacity (IC) than the SVN (1.83 ± 0.65 L vs. 1.42 ± 0.49 L, p = 0.03, respectively). The change in IC was higher in the BAN group (0.33 ± 0.31) than in the SVN group (0.15 ± 0.19; p = 0.03). The BAN group also had a lower respiratory rate (19 ± 3.3 b/min vs. 22 ± 5.3 b/min, p = 0.03, respectively). There was no difference in resting dyspnea as measured with the Borg scale (BAN 3.3 ± 2.1, SVN 3.5 ± 2.4, p = 0.69) or length-of-stay (BAN 4.6 ± 2.6 days, SVN 5.7 ± 2.8 days, p = 0.21). **Conclusions:** In this cohort of patients with ECOPD, a BAN was more effective in reducing lung hyperinflation and respiratory frequency than a continuous-flow SVN.

RANDOMIZED CONTROLLED TRIAL OF A BREATH-ACTUATED NEBULIZER IN PEDIATRIC ASTHMA PATIENTS IN THE EMERGENCY DEPARTMENT.

Sabato K, Ward P, Hawk W, Gildengorin V, Asselin J. Respir 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® breath-actuated 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® 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®, and adverse effects. **Results:** We enrolled 149 patients between October 14, 2004 and November 11, 2005, and we randomized 84 patients to AEROECLIPSE® 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® group, and 5.1 ± 2.1 in the standard-therapy group. Time in the emergency department was not different (AEROECLIPSE® 102 min, standard therapy 125 min, P = .10), but the AEROECLIPSE® group had a significantly greater improvement in clinical asthma score (1.9 ± 1.2 vs 1.2 ± 1.4, P = .001) and respiratory rate (P = .002), and significantly lower admission rate (38% vs 57%, P = .03). There was no difference in adverse effects. **Conclusions:** Although AEROECLIPSE® did not reduce the time in the ED, it significantly improved clinical asthma score, decreased admissions, and decreased respiratory rate.

REDUCING TOTAL COSTS OF AEROSOLIZED MEDICATION DELIVERY USING THE AEROECLIPSE® II BREATH ACTUATED NEBULIZER.

Wilson J. Resp Care 2011;56(10):1634.

Introduction: We hypothesized the AEROECLIPSE® II breath actuated 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 1ml 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. BANs 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 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 Breath Actuated 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.

Ros JA, Cancelliere S, Matye P, Nair S and O'Riordan M. Presented at the American Academy of Pediatrics National Conference, San Francisco, CA, 2010.

Purpose: A Breath-Actuated Nebulizer (BAN) is a newer type of nebulizer that creates aerosol only during a patient's inhalation. Theorized advantages of BANs 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 BAN devices in treating pediatric asthma patients. No known studies have compared patient satisfaction with BANs versus continuous-output nebulizers. The purpose of this ongoing randomized controlled trial is to compare effectiveness of and patient satisfaction with a BAN 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 BAN 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 BAN 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 BAN group, and 8.03 for participants assigned to the continuous nebulizer group. Overall, 25 (32.9%) of 76 patients in the BAN 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 BAN 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 BAN 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 BAN device.

A BREATH-ACTUATED JET NEBULIZER (BAN) HAS DOSIMETRIC CAPABILITY FOR A SOLUTION FORMULATION BASED ON DIFFERING VOLUME FILL OF MEDICATION AS WELL AS RUN TIME.

Malpass J, Nagel MW, Doyle C, Ali R, Avvakoumova V and Mitchell JP. Primary Care Respiratory Journal 2009;19(2):A21.

Aim: The ability to deliver a suspension formulation dosimetrically by nebulizer is important when titrating a patient to the minimum effective dose. Ideally such a device should provide a medication delivery rate independent of fill volume to simplify the treatment process, especially if diluted respirator solution is being used. **Method:** We report a study in which we evaluated delivery of a widely prescribed solution formulation (Ventolin†, GSK Canada Inc., 833 µg/mL albuterol (salbutamol)) by BAN (AEROECLIPSE® II, Trudell Medical International, London, Canada, n=3) operated at 50 psig. Emitted droplets were collected onto a filter at the nebulizer mouthpiece. Tidal breathing was simulated (Vt=600 cc; rate = 10 cycles/min; I/E ratio = 1:2), varying the volume fill in the nebulizer reservoir from 1.0 to 3.0 mL in 0.5 mL increments. The total droplet mass of albuterol collected at minute intervals (TDM) until sputtering was assayed by a validated HPLC-UV spectrophotometric technique. Fine droplet fraction FDF<4.7 µm was determined by laser diffractometry in parallel experiments. **Results:** FDF<4.7 µm was 87.1 ± 0.5% (mean ± SD). Fine droplet mass (FDM<4.7 µm) was linear with elapsed time, and almost independent of volume fill within the range studied at 102.9 ± 7.5 µg/min. **Conclusion:** The BAN provides predictable FDM <4.7 µm based on volume fill and time, thereby assisting the clinician with dose titration.

STAFF AND PATIENT SATISFACTION WITH A BREATH ACTUATED NEBULIZER PERFORMANCE IMPROVEMENT.

Emberger J, Brown J, Killian L and Maheshwari V – Christiana Care Health System. Resp 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 nebulizer (AEROECLIPSE® II, Monaghan Medical) approved by our Pharmacy and Therapeutics Committee was performed at our hospital. We investigated if a breath actuated nebulizer (BAN) would improve the satisfaction of the patients and the respiratory staff for aspects of care associated with the nebulizer therapy. **Methods:** An IRB approved retrospective review of the surveys from our BAN patients and surveys of the respiratory therapists who performed BAN 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 was superior to standard nebulizer, 1 being BAN 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 therapy. There were 70 patients surveyed about BAN therapy. Patients were satisfied with the BAN 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 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 nebulizers 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 therapy in our performance improvement project.

IMPACT OF A BREATH ACTUATED NEBULIZER PERFORMANCE IMPROVEMENT ON HOSPITAL LENGTH OF STAY.

Emberger J, Brown J, Killian L and Maheshwari V. Resp 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 nebulizer (AEROECLIPSE® II, Monaghan Medical). We wanted to determine if timed breath actuated nebulizer (BAN) therapy impacted patient length of stay in the hospital.

Populations Defined for Data Analysis:

- "PRE-BAN" 2 months of patients on the BAN floor prior to BAN
- "BAN" Patients – 3 months during the BAN evaluation
- "Reference Floor" – Similar reference floor for the entire 5 months (none using BAN)

Methods: We performed an IRB approved retrospective review of the following patient populations: 1) Patients in the BAN approved area that received 3 minutes timed BAN treatments (BAN Patients) 2) Patients on standard nebulizers in the BAN approved area before the BAN project was initiated (PRE-BAN 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 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 code for comparison analysis. **Results:** We identified 365 BAN patients for inclusion. The BAN, PRE-BAN 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 breath actuated nebulizers versus small volume nebulizers to evaluate the primary endpoint of hospital LOS 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 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.

Bong CJH, Eady M, Bowman CM and Titus MO. Presented at the Pediatric Academic Society Annual Meeting, Baltimore, MD, 2009.

Background:

• Breath actuated nebulizers have improved asthma care in adults

• Children's Hospital and ResearchCenter at Oakland-reduced clinical asthma scores (CAS), hospitalization rates, and respiratory rates with AEROECLIPSE® II Breath Actuated Nebulizer (BAN)

Objective:

• To determine if albuterol (ALB) delivery via BAN vs. conventional continuous nebulizer optimizes care and reduces cost in pediatric patients treated for wheeze/asthma in the MUSC Pediatric Emergency Department (PED)

Conclusions:

• Shorter PED LOS & shorter treatment times

• BAN treated patients spent ~1/3 less time in PED (53 min shorter LOS)

• Decreases wait time for PED care with more rapid room turn over

• Improved delivery, less waste

• Decreased ambient loss of medication: BAN ~4% vs. ~30% with CNB

• Reusable device can be used for up to 1 week in hospital or home

• Moderate group used 47% 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.

Coppolo DP, Mitchell JP, Ali RS, Mackay HA and Nagel MW. Resp Care 2008;53(11):1522.

Background: Breath-actuated nebulizers (BANs) 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. **Methods:** We investigated the delivery of diluted generic respirator solution albuterol by a continuous jet nebulizer (NebuTech HDN†, Salter Labs., Arvin, CA with a recently introduced BAN (AEROECLIPSE® II, Monaghan Medical Corp., Plattsburgh, NY). 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/min). 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 and NebuTech HDN were 78.4 ± 1.8% and 51.3 ± 5.2% respectively. **Conclusion:** The BAN delivered 490 ± 48.5 µg as fine droplets after 5-min (delivery rate of 98 ± 10 µg/min), compared to 236 ± 23 µg (47 ± 5 µg/min) in the same period by the continuous nebulizer.

IN VITRO PERFORMANCE COMPARISON OF A BREATH-ACTUATED NEBULIZER (BAN) FOR THE DELIVERY OF ALBUTEROL OPERATED WITH COMPRESSED HELIOX OR AIR.

Coppolo D, Mitchell J, Avvakoumova V and Nagel M. Presented at the American Council of Clinical Pharmacy Annual Meeting, Philadelphia, PA, 2008.

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 BAN as guidance to clinicians. **Methods:** AEROECLIPSE® II BANs (*n*=5 devices, Monaghan Medical Corp., 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 at 1-min 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<4.7µm) was determined by laser diffractometry (*n*=3 replicates with 1 device). Total fine droplet delivery (FDM<4.7µm) was calculated as the product of TEM and FDF<4.7µm. **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 BANs operated for 10-min, 19-min and 11-min 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 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. **Clinical Implication:** Clinicians should be mindful of the need to set the flow rate of Heliox to the BAN at maximum to maintain aerosol delivery characteristics established for air.

NEBULIZER-BASED AEROSOL DELIVERY IN CONJUCTION WITH CONTINUOUS POSITIVE EXPIRATORY PRESSURE (CPEP) USING A NOVEL BRONCHIAL HYGIENE DEVICE.

Hewitt MJ, Coppolo DP, Mitchell JP and Nagel MW. Presented at the American Thorasic Society International Conference, Toronto, ON, 2008.

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 nebulizer 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 ofalbuterol from the AEROECLIPSE® II BAN/CPEP combination with that from the Salter 8900† jet nebulizer (Salter Labs, Arvin, CA) also used with the CPEP device:
  - The AEROECLIPSE® II BAN 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 8900† nebulizer operates at constant air flow rate provided by its supply gas source, without air entrainment

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.

Coppolo DP, Mitchell JP, Wiersema KJ, Doyle CC and Nagel MW. Presented at the American Association for Respiratory Care Open Forum, Orlando, FL, 2007.

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 nebulizer (AEROECLIPSE® II, Monaghan Medical Corp., Plattsburgh, NY (AEIIBAN)) 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 (MiniHeart† Hi-Flo, Westmed Corp., Tucson, AZ (CONT) with that from the AEII-BAN. **Method:** The continuous nebulizers (*n*=5) 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 AEII-BANs 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/min) 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 (mass % < 4.7 µm diameter) likely to penetrate to the airways of the lungs (FDF) could be determined. **Results**: Values of FDF for the AEII-BAN and CONT were 78.4% and 62.0% respectively. The AEII-BAN delivered 758 ± 36 µg as fine droplets after 4-min (delivery rate of 190 ± 9 µg/min), compared to 180 ± 76 µg in the same period by CONT (delivery rate of 45 ± 19 µg/min). **Conclusions:** The faster delivery rate from the AEIIBAN/high albuterol concentration modality (un-paired 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.

Simmons L and Thigpen K. Presented at the American Association for Respiratory Care Open Forum, Orlando, FL, 2007.

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 it's 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 nebulizer (Monaghan AEROECLIPSE® Breath-actuated Nebulizer, BAN) 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. We performed a separate, retrospective study on the average length of stay (ALOS) on patients receiving aerosol therapy with UDN and with BAN both with a primary diagnosis of COPD (51cases) 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. 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 was made. Treatments administered during hospitalization decreased from 24.5 using the UDN to 20.45 using the BAN. The other study demonstrated a reduction inALOS for those patients with a primary diagnosis ofCOPD from 4.81 days with the UDN to 4.41 days with the BAN, 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 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.

Coppolo DP, Nagel MW, Doyle CC, Avvakoumova VA and Mitchell JP. Presented at the American Thoracic Society International Conference, San Francisco, CA, 2007.

A new breath actuated nebulizer (AEROECLIPSE® II BAN, Monaghan Medical Corp., Plattsburgh, NY) has been developed to deliver medication only when the patient inhales. 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. 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/min; 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 was 791 ± 84 µg, delivered in 8 minutes. Corresponding values (FDM in time from start to sputter) for the VixOne† (Westmed, Tucson, AZ), MicroMist† (Hudson RCI, Temecula CA), Misty Max 10† (Cardinal Health, McGaw Park (IL) and model 8900† (Salter Labs, Arvin, CA) were 267 ± 11 µg in 6 min, 133 ± 8 µg in 4 min, 249 ± 10 µg in 6 min and 161 ± 10 µg in 5 min. Aside from dosage assurance imparted by breath-actuation, the AEROECLIPSE® II BAN 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 (BAN) OFFERS A RAPID ALTERNATIVE TREATMENT MODALITY FOR THE DELIVERY OF BRONCHODILATORS FOR ASTHMATIC PATIENTS IN A SEVERE EXACERBATION.

Coppolo DP, Mitchell JP, Wiersema KJ, Doyle CC and Nagel MW. Presented at the American Association for Respiratory Care, Las Vegas, NV, 2006.

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 relive symptoms from bronchospasm in a shorter period of time. 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 nebulizer (BAN) (AEROECLIPSE®, Monaghan Medical Corp., 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 BANs 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 BANs was sampled onto electret filters using a breathing simulator (600-ml tidal volume, inspiratory/expiratory ratio 1:2, rate 10 cycles/min) 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-min, 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 BANs delivered 810.0 ± 20.4 µg in a 10-min period, equivalent to a rate of 81.0 ± 2.0 µg/min. The significantly higher delivery rate from the BAN group (un-paired 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. **Reference:** McPeck M, Tandon R, Hughes K and Smaldone GC. *Aerosol delivery during continuous nebulization.* CHEST 1997;111:1200-1205.

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.

Sabato K, Ward P, Hawk W. Resp 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® breath actuated small volume 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: 0.5cc (2.5 mg) Albuterol in 0.5cc normal saline for patients < 20 kg, and 1cc (5.0 mg) undiluted Albuterol for patients > 20 kg. Bronchodilators given via the CONT method used 2.0cc (10 mg) Albuterol in 18cc 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 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 and CONT/SSVN groups respectively. After treatment, the BAN 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 group (-3.9 vs 0.5, p=0.002), there were no differences in side effects. **Conclusions:** Use of the Monaghan breath-actuated AEROECLIPSE® 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 patients were able to breath-activate their treatment. We contend that the Monaghan AEROECLIPSE® 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.

Rau JL, Ari A, Restrepo RD. Resp 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 LCD), and 2 dosimetric (Circulaire and AEROECLIPSE®). 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: Misty-Neb 17.2 ± 0.4%, SideStream 15.8 ± 2.8%, Pari LCD 15.2 ± 4.2%, Circulaire 8.7 ± 1.0%, and AEROECLIPSE® 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 LCD 18.3 ± 0.8%, Circulaire 12.3 ± 0.8%, and AEROECLIPSE® 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 LCD 62.5 ± 4.0%, Circulaire 75.8 ± 0.5%, and AEROECLIPSE® 51.0 ± 2.1%. Duration of nebulization was shortest with the Circulaire and longest with the AEROECLIPSE® (p <0.05 via 1-way analysis of variance). **Conclusions:** The nebulizers we tested differ significantly in overall drug disposition. The dosimetric AEROECLIPSE® 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 (BAN) IN 'CONTINUOUS DELIVERY' MODE WITH OTHER CONTINUOUS DELIVERY NEBULIZERS.

Mitchell JP, Wiersema KJ, Doyle CC, Nagel MW. Respiratory Care 2003;48(11):S1077.

The AEROECLIPSE® BAN (Monaghan Medical Corp., Plattsburgh, N.Y.) 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 Micromist† (Hudson RCI, Temecula, CA), Misty-Neb† (Allegience Healthcare Corp., McGaw Park, IL) and the LCD† (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/min, 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 (Tmed) were as follows:

Solution (mg/ml)	AEROECLIPSE®		LCD†		Micromist†		MistyNeb†	
	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
Tmed (min)	3	<1	2	<1	7	<1	4	<1

The AEROECLIPSE® 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). Tmed from the AEROECLIPSE® nebulizer was comparable with the best performing continuous nebulizer (LCD†).

BREATH-ACTUATED NEBULIZER DELIVERS BRONCHO-DILATOR MORE EFFICIENTLY THAN CONVENTIONAL JET NEBULIZER IN A SIMULATION OF AN ADULT TIDAL-BREATHING PATIENT.

Nagel MW and Mitchell JP. Am. J. Resp. Crit. Care Med., 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 (BAN), 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/min respectively. Total emitted dose (TED) was determined for 5-AEROECLIPSE® BANs (Monaghan Medical Corp., N.Y., 1.5 ml solution) and 5 Micromist† 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 mm aerodynamic diameter. **Results:** After 3 minutes, the AEROECLIPSE® BAN delivered 282 ± 10 mg FPD (mean ± SD) and the Micromist† 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® nebulizer and the reduced time to deliver a specific equivalent dose of medication compared with a conventional nebulizer will improve cost effectiveness of treatment.

SAFETY AND EFFICACY OF FIVE-MINUTE TIMED AEROSOL ADMINISTRATION WITH THE AEROECLIPSE® BREATH ACTUATED NEBULIZER: COMPARISON OF LEVALBUTEROL WITH RACEMIC ALBUTEROL.

Pikarsky RS, Acevedo R, Roman C, Fascia W, Farrell T. Resp Care 2002;47(9):1075.

Purpose: Beta2-agonist Racemic Albuterol has been used extensively in the performance of pre & 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® Breath Actuated Nebulizer (BAN) (Monaghan Medical Corp. Plattsburgh, N.Y.). **Methods:** A consecutive, non-randomized, mostly COPD population (*n* = 93) receiving pre & post bronchodilator testing in our Pulmonary Function Lab were studied. Two different Levalbuterol medication dosages were administered: 0.63mg Levalbuterol UD or 1.25mg UD Levalbuterol. The Racemic Albuterol dosage was 2.5mg UD. All 5 minute timed aerosol treatments were administered using the BAN with an oxygen flow rate of 8L/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 1.25mg Levalbuterol UD group (7.2 vs. 3.4, $p<.05$*; 7.2 vs. 2.2, $p<.01$**). 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)	0.63mg UD	7.8	6.2	5	4	3.4*
Levalbuterol (29)	1.25mg UD	7.7	16.6	5	2	7.2
Racemic Albuterol (26)	2.25mg UD	12.2	10.5	5	0	2.2**

Conclusion: Five minute timed administration of Levalbuterol and Racemic Albuterol using the BAN 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 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 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.

Pikarsky RS, Acevedo RA and Roman C. 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® Breath Actuated Nebulizer (BAN). 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<.001)*. The breakthrough rate with Albuterol was significantly reduced with the addition of Ipratropium (*p*<.001)**. Ipratropium did not significantly change the breakthrough rate when added to Levalbuterol groups.

Medication	Total Tx	Break-through	Rate/ 1000	Tx/Pt/ day	Rate/100 Pt day	
Alb Q4h	3832	47	12.27	6	7.36**	5.29*
Alb/Ipra Q4h	3767	20	5.31	6	3.19**	
Lev 0.63mg Q6h	3592	24	6.68	4	2.67	2.29*
Lev 0.63 mg/Ipra Q6h	1821	7	3.84	4	1.54	
Lev 1.25mg Q8h	1791	17	9.49	3	2.85	2.43*
Lev 1.25mg/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 re-allocating of workforce needs while maintaining, or improving, quality of aerosol administration, as evidenced by the decrease in breakthrough requirements.

BREATH-ACTUATED NEBULIZER HELPS AVOID INTUBATION.

Klopf S, Schramm C. Advance for Managers of Respiratory Care 2001:68.

Patients with acute exacerbation of asthma represent more than 1.5 million visits to the emergency department annually. Many of them are admitted to the ICU after intubation, which is traumatic for the patient and potentially costly to the provider. Keeping this in mind, clinicians are always seeking new ways and technologies that deliver better outcomes for asthmatics experiencing acute exacerbation. A recently available breath-actuated nebulizer, the AEROECLIPSE® BAN by Monaghan Medical Corp., has a number of features we evaluated as suitable for meeting our goals with highly compromised asthmatics in the ED. The device provides a very high rate of delivery of respirable drug in match with the patients' breathing patterns, works at low fill volumes with concentrated drug and has a biofeedback mechanism to encourage effective breathing. We conducted a formal evaluation of 55 patients who used the AEROECLIPSE® in the ED at Miami Valley Hospital, Dayton, Ohio. Overall, patients responded positively to the breath-actuated therapy, and many stated they felt better more quickly than with past exacerbations. One of the patients in the study, a female in her upper 30's, presented to the emergency room at 11:05 a.m. as an asthmatic in crisis. Her vital signs were as follows: respiratory rate 40 plus, heart rate 120 to 150, blood pressure dangerously elevated and breath sounds diminished to absent. Her skin color was gray with purple nail beds, and her oxygen saturation was 90 percent on a 100 percent nebulizer. A medic had brought her in on a nebulizer treatment with 0.5 cc albuterol sulfate. The patient already had taken two home handheld treatments and her inhaler. The emergency room physician requested an intubation kit and a respiratory therapist at the patient's bedside. After evaluation, the RT suggested the patient switch to the AEROECLIPSE® nebulizer and convinced the physician to hold intubation until after the first treatment. Although she was unable to do peak flow prior to the first treatment, the patient was able to trigger the AEROECLIPSE®. She received 0.5cc albuterol sulfate with a half-unit dose of ipratropium bromide. The patient was still unable to do peak flow after the treatment, but her respiratory rate was now in the 30's with little retracting. Also, the RT noted a small amount of air movement. Ten to 15 minutes later, the RT administered a second treatment of 0.5 cc albuterol sulfate with 0.5 cc saline. The patient was able to speak in complete sentences and had good aeration with the inspiratory and expiratory wheezes. She received two more treatments at 10 to 15 minute intervals, totaling four treatments in her first hour in the emergency room.

The RT then placed her on a cannula. Oxygen saturation was 93 percent to 98 percent. The emergency room team monitored her for four hours, and she maintained this status. After a fifth treatment of 0.5 cc albuterol sulfate and 0.5 cc saline, the patient's breath sounds were clear to auscultation. She had a peak flow of 300, respiratory rate of 20, and she was on room air. Shortly after the fifth treatment the physician released the patient to home on prednisone and albuterol inhaler with spacer. The patient commented that she had not performed more than 260 on a peak flow meter in many years. She could never recall rebounding from an attack so quickly. Her only complaint was that the facility was unable to accommodate her request to purchase the AEROECLIPSE® or to take the one she had used home with her. She was very thankful and satisfied, which is crucial in achieving good patient care. Treatment time was cut in half for this patient, who didn't have insurance. The nebulizer saved the hospital thousands of dollars because without it the patient would have most likely ended up in the ICU on a ventilator.

THE DELIVERY TIME, EFFICACY, AND SAFETY OF BETA AGONIST BRONCHODILATOR ADMINISTRATION WITH THE AEROECLIPSE® BREATH-ACTUATED NEBULIZER ("BAN").

Pikarsky RS, Farrell T, Acevedo R, Fascia W, Roman C. 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® Breath Actuated Nebulizer as compared to both an MDI with AEROCHAMBER® VHC (both from Monaghan Medical Corp. Plattsburgh, N.Y.) and the Airlife Misty-Neb Nebulizer (SVN) (Allegiance Healthcare Corporation). **Methods:** A consecutive, non-randomized, mostly COPD population receiving pre & post bronchodilator testing in our Pulmonary Function Lab were studied. Three different Albuterol medication dosages were administered with the BAN: 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(min)	Tremulousness
AEROECLIPSE® BAN (12)	0.5 ml + 0.5 ml NS	8.2%	2.67*	0
AEROECLIPSE® BAN (64)	1.0 ml undil.	10.9%	3.29*	17
AEROECLIPSE® BAN (23)	0.75 ml undil.	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 patients was 2.78 minutes as compared to 8.33 minutes with the SVN (p<.001) *. The mean treatment time with the MDI was 2.86 minutes as compared to 8.33 minutes with the SVN (p<.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 l 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 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 under-performed. Delivering 0.5 ml Albuterol (2.5 mg) with 0.5 ml Normal Saline using the BAN offered the best delivery time, efficacy and safety profile of the nebulizer trials. The BAN 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 ("BAN") IN PULMONARY LAB TESTING AND IMPLICATIONS FOR GENERAL USE.

Christensen YM, Flanigan CJ, Ravenscraft SA. Resp 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® Breath Actuated Nebulizer ("BAN") (Monaghan Medical Corp.) 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 (*n*=40) 2.5mg Albuterol (0.5ml) in 0.5cc saline run to sputter, or the SVN (*n*=40) 2.5mg Albuterol in 2.5cc saline (3ml 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 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 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), and total test time was reduced from 30 minutes (SVN) to 15 minutes (BAN).

SPIROMETRY RESULTS

	Absolute % Change by Device		% Difference BAN	
	SVN	BAN	BAN	
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 2.5mg of albuterol with the BAN produced improved results in FVC, FEV_1 and FEF 25-75%. Substantially shorter test times delivered by the BAN would allow for more tests and associated revenue. These data support the thesis that the BAN can reduce costs of care by delivering clinically acceptable outcomes in significantly less time.

BREATH-ACTUATED VS RESERVOIR NEBULIZERS FOR UNDILUTED ALBUTEROL.

Geller D, Kesser B. Presented at the International Congress on Aerosols in Medicine, Interlaken, Switzerland, 2001.

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® Breath-Actuated Nebulizer ("BAN"); 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 yr 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. **Background:** Many nebulizers are designed to decrease the amount of drug that is lost during exhalation. The Circulaire† (Westmed) and AeroTee† (Hudson) incorporate a 750 ml bag on the expiratory side of the nebulizer that collects aerosol while the patient exhales, making it available for inhalation on the next breathing cycle. The Salter HDN† (Salter) has a 50 ml tower that acts as a reservoir. The AEROECLIPSE® BAN (Trudell/Monaghan) has a spring mechanism that allows generation of aerosol during inhalation only, so no drug waste occurs during exhalation. We recently reported the aerosol characteristics with these devices nebulizing unit-dose albuterol sulfate (2.5 mg/3 ml).1 Delivery time with unit-dose (0.083%) albuterol can be long, which may increase personnel costs. To maintain lung-dose delivery and minimize the treatment time, some hospitals use drug-conserving nebulizers with small

fill-volumes of undiluted (0.5%) albuterol for patients presenting with acute bronchospasm. We measured the particle size distributions and used a child's breathing pattern to compare albuterol output of these 4 drug-conserving nebulizers, using unit-dose albuterol 2.5 mg (3ml), 0.5% albuterol 5 mg (1ml) and 10 mg (2ml) nominal doses. We calculated the fine particle dose and measured the dose of drug remaining within the nebulizer and all attachments to determine the residual dose. For reference, we compared these results to those of a T-piece (Hudson Micromist) nebulizer using unit-dose albuterol to simulate conventional dosing. **Materials and Methods:** Drug: Albuterol Sulfate 0.083% unit-dose (2.5mg/3ml); Albuterol Sulfate 0.5% (5mg/ml) 1 & 2cc fill volumes. Nebulizers: Circulaire† (Model 0260), AeroTee† with Micromist Nebulizer (Model 1002), Salter HDN† (Model 8960), and AEROECLIPSE® BAN **(Figure 1)**. Compressor: PARI PRONEB TURBO. 4 nebulizers of each type studied in duplicate; Particle size by laser diffraction (Malvern Insitec); Breathing pattern from 9 year old male volunteer, using the PARI breath simulator (RR 19 bpm, Vt 421 cc, Ti 1.3 seconds). Definitions: Inspired dose = drug on inspiratory filter; Residual dose = drug collected from nebulizer and accessory components after completion of nebulization; Fine particle dose (FPD) = (Inspired dose) x (% of particles <5 µm) Figure 1; Duration = time (minutes) from the beginning of nebulization to 1 minute past the onset of sputter; Samples assayed with spectrophotometer at 228 λ

Results:

		AEROECLIPSE® BAN	AeroTee†	Circulaire†	Salter HDN†
Particle	MMD	3.87	4.80	2.47	8.46
Sizing	GSD	2.3	2.0	2.1	2.0
	% < 5 µm	61.7%	52.9%	83.6%	30.0%
2.5 mg	Duration (minutes)	14.7	7.2	7.0	3.6
Unit	Inspired Dose (mg)	0.77	0.37	0.14	0.30
Dose†	Residual Dose (mg)	1.5	1.8	2.1	1.9
	Fine Particle Dose (mg)	0.52	0.19	0.12	0.10
5 mg	Duration (minutes)	3.8	2.0	2.0	2.0
(1 ml)	Inspired Dose (mg)	0.97	0.06	0.11	0.28
Dose	Residual Dose (mg)	3.5	4.9	4.6	4.4
	Fine Particle Dose (mg)	0.60	0.03	0.09	0.08
10 mg	Duration (minutes)	11.0	3.2	3.7	3.7
(2ml)	Inspired Dose (mg)	3.9	1.2	0.8	1.9
Dose	Residual Dose (mg)	5.8	8.7	8.6	6.9
	Fine Particle Dose (mg)	2.40	0.60	0.60	0.60

†Unitdose data presented at ATS 2001[1]

For comparison, the Hudson Micromist conventional T-Piece Nebulizer (with Unit-Dose 2.5 mg Albuterol) produced a fine-particle dose of 0.14 mg in 7.0 minutes.

Discussion:

- **AEROECLIPSE® BAN had highest FPD with all nominal doses:**
  - o FPD was 2.7 to 5.2 times higher with unit-dose; 6.7 to 20 times higher with 5 mg dose; 4 times higher with 10 mg dose
  - o Lowest residual dose
  - o Higher fine particle fraction except for Circulaire†
- **Nebulizer Inefficiencies:**
  - o AeroTee† and Circulaire† had high residual doses in part due to valves and collection bags
  - o Salter HDN† produces larger particles
  - o These inefficiencies were partially compensated for by increasing nominal dose to 10 mg (2 ml)
- **Duration of Nebulization:**
  - o AEROECLIPSE® BAN had longer delivery time because it is breath actuated; no waste during exhalation
  - o Using 0.5% albuterol, all nebulizers produced 0.6 mg fine-particle dose in < 4 minutes, but the AEROECLIPSE® BAN only required half the nominal dose to accomplish this
- **Comparison to Unit-Dose 2.5 mg:**
  - o AEROECLIPSE® BAN produced comparable FPD with unit-dose and 5 mg (1 ml) nominal dose, but delivery time was less than a third with undiluted drug

- **Comparison to conventional nebulizers:**
  - o The FPD with the Hudson and unit-dose drug was 0.14 mg, similar to the reservoir-type nebulizers with unit-dose
  - o The higher FPD with AEROECLIPSE® BAN (all doses) and the reservoir nebs (10 mg dose) may result in better and longer lasting bronchodilation than the Hudson with conventional dosing, thus reducing number of treatments, therapist time, and total costs

Conclusion:

- AEROECLIPSE® BAN was superior to the reservoir-type nebulizers at all nominal doses
- AEROECLIPSE® BAN has the additional advantage of being a dosimetric device, i.e. it will not operate or waste drug while the patient is coughing or resting. The patient and health care providers get visual feedback of adequate inspiratory effort necessary to actuate the nebulizer
- Use of undiluted 0.5% albuterol may result in higher lung doses in a shorter amount of time. These results can be used as a guide when developing bronchodilator protocols for the hospital or E.D. setting

Funded by the Nemours Foundation

1 Geller D, Kesser B. Am J Respir Crit Care Med 2001;163:A444 and Journal of Aerosol Medicine 2001;14(3):395:1-41.

THE DELIVERY TIME, EFFICACY, AND SAFETY OF BETA AGONIST BRONCHODILATOR ADMINISTRATION WITH THE AEROECLIPSE® BREATH ACTUATED NEBULIZER ("BAN") VERSES A CONVENTIONAL T-TYPE SMALL VOLUME NEBULIZER.

Pikarsky RS, Farrell T, Acevedo R, Fascia W, Roman C. Resp 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, non-randomized, mostly COPD population receiving pre & 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® Breath Actuated Nebulizer ("BAN") (Monaghan Medical Corp. Plattsburgh, N.Y.) 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 Sensormedics 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 patients was 2.67 minutes as compared to 8.33 minutes with the SVN (p<.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 was equally efficacious as the SVN UD. Delivering 0.5 ml Albuterol (2.5 mg) with 0.5 ml Normal Saline using the BAN 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 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 (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.

Geller DE, Kesser B. Am J Resp Crit Care 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 Aero Tee† nebulizers use a 750 cc reservoir bag to accumulate nebulized drug, while the Salter HDN† uses a 50ml tower to serve as a reservoir. The AEROECLIPSE® 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 mgs albuterol sulfate in 3cc's. Sizing studies were averaged values preformed over 5 minute runs on each nebulizer with a Malvern Spray Tec 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 & <5M	Respirable Dose	Residual Dose
AEROECLIPSE®	0.64 ± 0.06 mg	52.7 ± 2 0.	0.34 ± 0.03 mg	1.27 ± 0.09
Aero Tee	0.31 ± 0.09 mg	41.2 ± 7	0.13 ± 0.04 mg	1.51 ± 0.11
Circulaire	0.12 ± 0.03 mg	61.9 ± 1	0.07 ± 0.02 mg	1.72 ± 0.13
Salter HDN	0.25 ± 0.05 mg	24.7 ± 5	0.06 ± 0.02 mg	1.59 ± 0.10

Conclusion: The AEROECLIPSE® delivers a greater total dose of drug as well as a greater amount of drug in the fine particle range, most likely to deposit in the lower airways.

CLINICAL EVALUATION OF A BREATH ACTUATED SMALL VOLUME NEBULIZER (BA-SVN).

Klopf S, Scneiderman N, Payne H, Schramm C, Nagel MW, Mitchell JP. Resp Care 2000;45(8):979.

Background: In prior in-vitro studies using laser diffractometry, the aerosol produced by a novel breath-actuated nebulizer (BAN), the AEROECLIPSE® (Monaghan Medical Corp. 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 oro-pharyngeal 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 in the delivery of a beta2-agonist (albuterol 2.5 mg/ml) accompanied by anticholeninergic (ipratroprium 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. 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 ipratroprium 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 (min)	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 BA-SVN. **Conclusions:** Use of the AEROECLIPSE® BAN 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.

Mitchell JP, Nagel MW, Archer A, Coppolo DP. Am J Resp Crit Care Med 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:

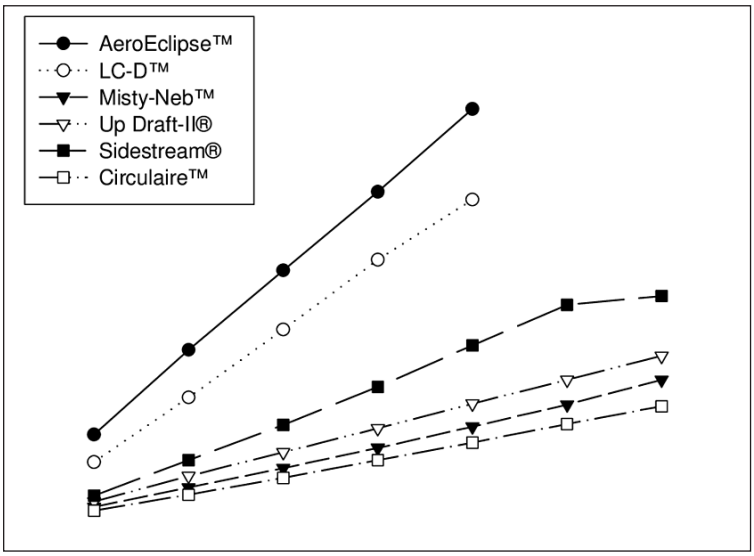
Drug	TM (µg/s)	FPM (µg/s)	MMD (µm)
Ventolin†	32.4 ± 3.1	27.6 ± 1.3	3.0 ± 0.1
Intal†	138.6 ± 10.2	109.7 ± 8.3	3.2 ± 0.1

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.

Hess D, Mitchell JP , Coppolo D, Nagel MW, Archer AD, Blacker R. Resp 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 Updraft-II Neb-U-Mist†), breath-enhanced nebulizers (Pari-LC-D†), nebulizers with collection bags (Westmed Circulaire†), and a Trudell AEROECLIPSE® (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/min, TI 2 s). 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® nebulizer was greater than that from the other nebulizers (P<0.001) **(see Figure)**. **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® is warranted.



PERFORMANCE OF A NEW AIR ENTRAINMENT SMALL VOLUME NEBULIZER.

Archer A, Mitchell JP, Nagel MW, Verdun AMW. Eur Resp J 1998;12(28):68.

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 s 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.

Blacker R, Morton RW, Mitchell JP, Nagel MW, Hess DR. J Aerosol Med 1998;13(1):65.

Fine particle mass delivery was compared from six different SVNs, including continuous un-enhanced flow designs (Hudson Updraft-II Neb-U-Mist†), breath-enhanced nebulizers (Pari-LC-D†, Medic-Aid Sidestream†), nebulizers with aerosol collection bag (Westmed Circulaire†), and an AEROECLIPSE® 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/min, TI = 2 s). 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 diffractrometer. Fine particle mass delivery rates varied significantly from each of the SVNs from more than 110 µg/min (AEROECLIPSE®) to ca. 20 µg/min (Circulaire†).

PERFORMANCE OF A NEW BREATH-ACTUATED SMALL VOLUME NEBULIZER UNDER CONDITIONS THAT SIMULATE USE BY AN ADULT PATIENT.

Blacker R, Mitchell JP, Nagel MW, Verdun AMW. Eur Resp J 1997;10(25):235.

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/min) 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 min 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.

Blacker R, Mitchell JP, Nagel MW and Verdun AMW. Presented at the American Association For Respiratory Care, New Orleans, LA, 1997.

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/min) 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 min (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 care-giver.

Budesonide (Pulmicort†, AstraZeneca†)

DELIVERY OF BUDESONIDE INHALATION SOLUTION (BIS) THROUGH AN INFANT UPPER AIRWAY MODEL.

Geller DE, Kesser KC , Janssens HM, Tiddens HAWM. Am J Respir Crit Care Med 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-mo old infant (RR=30, Vt=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: VIX1/aerosol mask (AM), PediNeb pacifier device (PN) or blow-by (BB); AEROECLIPSE® neb and mask (AE); PARI LC+ and PARI LC†/ PARI Baby mask (PB), Fish mask (FM), and AE masks. The AE neb/mask was also studied with an ill breathing pattern (RR=50, Vt=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%) > VIX1 (3.5%), LC+/FM (3.2%), LC*/PB (2.9%), and LC+/PB (2.8%). Also, VIX1/AM (3.5%)>VIX1/PN (2.5%)>VIX1/BB (2.0%). The lung dose of the LC+ and LC* 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.

Nagel MW, Wiersema KJ, Bates SL and Mitchell JP. J Resp Crit Care Med 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® BA SVNs (Monaghan Medical Corp., Plattsburgh, N.Y.) and 5-LC-D† AE SVNs (PARI Respiratory Equipment, Inc., Monterey, CA), nebulizing 4ml 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/min. FPD was determined by cascade impactor at 28.3 ± 0.5 l/min. **Results**: From the beginning of nebulization until sputtering, the AEROECLIPSE® and the LC-D† SVNs produced 164 ± 3 and 71 ± 4 µg FPD of budesonide respectively. During the first 5 minutes (after which time the LC-D†s sputtered), values of FPD for the AEROECLIPSE® and the LC-D† SVNs were 76 ± 4 and 71 ± 4 µg budesonide respectively. **Conclusion:** The AEROECLIPSE® was more efficient than the LCD† SVN for this suspension formulation [Mann-Whitney rank sum test, $p < 0.001$]. Almost no medication delivery took place from the AEROECLIPSE® 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	283 ± 33	80 ± 11
LCD†	97 ± 7	305 ± 2

DELIVERY OF A SUSPENSION CORTICOSTEROID FORMULATION BY SMALL VOLUME NEBULIZERS: A COMPARATIVE BENCH STUDY.

Mitchell JP, Nagel MW, Wiersema KJ, Bates SL. Presented at ERS Annual Congress, Berlin, Germany, 2001.

We report a study of the delivery of 0.25% mg/ml budesonide suspension (Pulmicort†, Nebuamp† (2 x 2-ml), Astra-Zeneca, Canada) by two types of small volume nebulizer (SVN), simulating adult breathing conditions ((tidal volume = 600-ml, duty cycle = 1:2 (2-s 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® BANs (Trudell Medical International, London Canada) delivered 283 ± 32 mg prior to sputtering, and 80 ± 11 mg were lost to the environment. Corresponding data for the LCD† SVNs (Pari Respiratory Equipment Inc., Richmond, VA, USA) were 97 ± 7 mg and 305 ± 2 mg respectively. The breath-actuation feature of the AEROECLIPSE® 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. Eur Resp J 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, Monaghan/Trudell 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 (0.25mg/ml in 2ml) delivered via three patterns of breathing (Vt f: 50ml, 40; 200ml, 25; 440ml, 19; duty cycle 0.50). The 50 and 200ml Vt patterns were delivered using continuous nebulization, while 440 was breath-actuated. IM was measured at 1 min intervals using a low deadspace filter with drug activity analyzed by HPLC. Low flow cascade impaction measured aerodynamic diameters (MMAD) and fine particle fraction (FPF, cutpoint 6.0 µm). 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 (J. Aerosol Med. 1998, 11:113-125). MMAD averaged 3.55±0.07 µm, 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.

Mitchell JP, Nagel MW, Archer AD. Chest 1998;114(4S):295; and Eur Resp J 1998;12(S29):7.

Purpose: To compare the performance of a new air entrainment small volume nebulizer (AE-SVN, Trudell Medical International with other widely used SVNs (LC-Star† (PARI Respiratory Equipment), Updraft† Neb-U-Mist† (Hudson Oxygen Therapy Sales Co.), Circulaire† (Westmed), Sidestream† (Medic-Aid), Airlife† Misty-Neb† (Baxter Healthcare Corp.)) for the delivery of a suspension formulation (0.25 mg/ml budesonide (Astra Pharma Inc.)). **Methods:** Each SVN (*n* = 5 devices for each group, 3 replicates per device) was operated with compressed air at 50 psig at a flow rate of 8 l/min. The total mass of budesonide nebulized from 2 x 2 ml ampoules was determined by filter collection at the mouthpiece at a flow rate of 28.3 l/min. The SVN was operated until it spluttered, was then tapped gently to dislodge droplets back to the reservoir. Nebulization was deemed complete 20 seconds later. The mass of budesonide collected was determined by HPLC-UV spectrophotometry. **Results:** The delivery rate ((mean ± 1 S.D) µg budesonide/min) from the AE-SVN (102 ± 9) was significantly greater than with the other groups: (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 s), compared with LC-Star† (229 ± 10 s), Sidestream† (365 ± 19 s), Circulaire† (420 ± 84 s), Misty-Neb† (477 ± 25 s) and Neb-U-Mist† (639 ± 15 s). **Conclusions:** The new AE-SVN is highly efficient at entraining the budesonide particles into the liquid droplets at these conditions. Clinical Implications: The good delivery rate combined with comparatively short duration of delivery offers the potential for rapid treatment and patient convenience.

THE DELIVERY OF BUDESONIDE SUSPENSION VIA SMALL VOLUME NEBULIZERS – THE RELATIONSHIP BETWEEN NEBULIZED DROPLET SIZE AND THE PARTICLE SIZE OF THE SUSPENSION.

Mitchell JP, Nagel MW, Archer AD. J Aerosol Med 1999;12(3):208.

A new air entrainment small volume nebulizer (AE-SVN) has been compared with two other SVNs (Neb-U-Mist† and Misty-Neb†) for the delivery of a suspension of 0.25 µg/ml budesonide. Each SVN was operated at 8 l/min with compressed oxygen (50 psig). The total mass of budesonide was determined by filter collection at the mouthpiece at a flow rate of 28.3 l/min. The time-averaged delivery rate over the period of nebulization ((mean ± 1 S.D.) µg budesonide/min) from the AE-SVN (102 ± 9) was greater than with the Misty-Neb† (49 ± 2), or Neb-U-Mist† (25 ± 6). Duration of nebulization was shortest with the AE-SVN (221 ± 14 s), compared with the Misty-Neb† (477 ± 25 s) and Neb-U-Mist† (639 ± 15 s). The mass median diameter (MMD) of the droplets from the AE-SVN measured using a laser diffractometer (2.9 ± 0.1 µm), was significantly finer compared with those from the Misty-Neb† (4.5 ± 0.9 µm) and Neb-U-Mist† (5.6 ± 0.6 µm) and closest to the size of the micronized budesonide particles in the original suspension. The efficient delivery of medication formulated as micronized powder in aqueous suspension necessitates that the droplets produced upon nebulization are large enough so that single particles are efficiently entrained during atomization, but not so coarse that they cannot leave the nebulizer, extending nebulization time.

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

A PROSPECTIVE, COMPARATIVE TRIAL OF STANDARD AND BREATH-ACTUATED NEBULIZER: EFFICACY, SAFETY, AND SATISFACTION.

Arunthari V, Bruinsma RS, Lee AS, Johnson MM. Resp Care. 2012;57(8):1242-7.

Background: Nebulized drug delivery is a cornerstone of therapy for obstructive lung disease, but the ideal nebulizer design is uncertain. The breath-actuated nebulizer (BAN) may be superior to conventional nebulizers. This study compared the BAN 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 or standard nebulizer and were surveyed at the completion of each treatment. BAN 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 was superior to conventional nebulizer therapy; 68% indicated that duration was preferable with the BAN. RTs were more satisfied with the BAN, 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 (4.1 min vs 9.9 min, $P < .001$). Additionally, the BAN was associated with a lower occurrence of adverse events. **Conclusions:** Patients and RTs expressed greater satisfaction with the BAN, compared with standard nebulizer. Pre- and post-treatment vital signs did not differ between groups, but use of the BAN was associated with a shorter duration and a lower occurrence of adverse events. Taken together, these data support the use of the BAN for nebulized medication delivery.

RANDOMIZED CONTROLLED TRIAL OF A BREATH-ACTIVATED NEBULIZER IN PATIENTS WITH EXACERBATION OF COPD.

Haynes JM. Resp Care. 2012;57(9):1385-90.

Background: Exacerbations of COPD (ECOPD) are characterized by increased dyspnea due to dynamic pulmonary hyperinflation. This study sought to determine whether the AEROECLIPSE® II breath-activated nebulizer (BAN) 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 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 6.25 ± 0.55, control 6.2 ± 0.7, $P = .80$). Following completion of the study protocol the BAN group had a higher IC than the SVN group (1.83 ± 0.65 L vs 1.42 ± 0.49 L, $P = .03$, respectively). The change in IC was higher in the BAN group (0.33 ± 0.31 L than in the SVN group (0.15 ± 0.19 L, $P = .03$). The BAN group also had a lower respiratory rate (19 ± 3.3 breaths/min vs 22 ± 5.3 breaths/min, $P = .03$, respectively). There was no difference in resting dyspnea as measured with the Borg scale (BAN 3.3 ± 2.1, SVN 3.5 ± 2.4, $P = .69$) or stay (BAN 4.6 ± 2.6 d, SVN 5.7 ± 2.8 d, $P = .21$). **Conclusions:** In this cohort of patients with ECOPD, a BAN was more effective in reducing lung hyperinflation and respiratory frequency than a continuous-flow SVN.

A PROSPECTIVE, COMPARATIVE TRIAL OF STANDARD AND BREATH ACTUATED NEBULIZER: EFFICACY, SAFETY, AND SATISFACTION.

Arunthari V, Bruinsma RS, Lee AS, Johnson MM. Resp Care 2012;57(8):1242-7.

Background: Nebulized drug delivery is a cornerstone of therapy for obstructive lung disease, but the ideal nebulizer design is uncertain. The breath-actuated nebulizer (BAN) may be superior to conventional nebulizers. This study compares the BAN to standard nebulizer with regards to efficacy, safety, and patient and respiratory therapists (RT) satisfaction. **Methods:** Adults admitted where nebulizer therapy was prescribed were enrolled. Patients were randomly assigned to either AEROECLIPSE® II (Monaghan Medical) or standard nebulizer and were surveyed at the completion of each treatment. BAN delivered albuterol of 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. RT assessed each patient's heart rate, respiratory rate, and peak expiratory

flow rate (PEFR) 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 patients were studied. Mean age was 69 years. 54% of patients indicated that overall the BAN was superior to conventional nebulizer therapy; 68% indicated that duration was preferable with the BAN. RTs were more satisfied with the BAN based on overall performance, treatment duration, and ease of use. There were no significant differences in heart rate, PEFR, or respiratory rate before or after nebulization therapy with either device. The duration of treatment was significantly lower with the BAN (4.1 vs. 9.9 min p=<0.001). Additionally, the BAN was associated with a lower occurrence of adverse events. **Conclusion:** Patients and RTs expressed greater satisfaction with the BAN compared with standard nebulizer. Pre- and post-treatment vital signs did not differ between groups but use of the BAN was associated with a shorter duration and a lower occurrence of adverse events. Taken together, these data support the use of the BAN for nebulized medication delivery.

RANDOMIZED CONTROLLED TRIAL OF BREATH-ACTIVATED NEBULIZER IN PATIENTS WITH EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE.

Haynes JM. Resp Care 2012;57(9):1385-90.

Background: Exacerbations of chronic obstructive pulmonary disease (ECOPD) are characterized by increased dyspnea due to dynamic pulmonary hyperinflation. This study sought to determine whether the AEROECLIPSE® II breath-activated nebulizer (BAN) 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 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, respiratory frequency and pulse rate measurements were repeated. **Results:** Both groups received an equal number of nebulizer treatments over the study period (BAN 6.25 ± 0.55, control 6.2 ± 0.7, p = 0.8). Following completion of the study protocol the BAN group had a higher inspiratory capacity (IC) than the SVN (1.83 ± 0.65 L vs. 1.42 ± 0.49 L, p = 0.03, respectively). The change in IC was higher in the BAN group (0.33 ± 0.31 than in the SVN group (0.15 ± 0.19; p = 0.03). The BAN group also had a lower respiratory rate (19 ± 3.3 b/min vs. 22 ± 5.3 b/min, p = 0.03, respectively). There was no difference in resting dyspnea as measured with the Borg scale (BAN 3.3 ± 2.1, SVN 3.5 ± 2.4, p = 0.69) or length-of-stay (BAN 4.6 ± 2.6 days, SVN 5.7 ± 2.8 days, p = 0.21). **Conclusions:** In this cohort of patients with ECOPD, a BAN 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.

Pikarsky RS, Acevedo RA, Farrell T, Bear R, Fascia W. Resp Care 2003;48(11):1080.

Purpose: In order to meet our adult 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. Different dosing schedules for Levalbuterol were evaluated. **Methods:** Racemic Albuterol (Alb) 2.5 mg Q4h was converted to either Levalbuterol (Lev) 0.63 mg Q6h or Levalbuterol 0.63 mg Q8h. Patients dosed Q8h who required more frequent aerosol administration received Levalbuterol 0.63 mg Q6h (cardiac patients) or Levalbuterol 1.25 mg Q8h (all others). If ordered, Ipratropium (Ipra) 0.5 mg was administered at the same frequency as the Levalbuterol. A majority of aerosol therapy was provided with the use of the AEROECLIPSE® Breath Actuated Nebulizer (BAN). All aerosol treatments, including breakthrough treatments, delivered between June 1, 2002 and September 30, 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 all Levalbuterol groups (25.8 vs. 18.43, 25.8 vs. 18.43, 25.8 vs. 5.96 p<.001)*. The breakthrough rate with Albuterol was significantly reduced with the addition of Ipratropium (40.76 vs. 13.35 p<.001)**. The 1.25 mg dose of Levalbuterol outperformed both 0.63 mg dosage groups (3.78 vs. 13.48 p<.02, 3.78 vs. 21.36 p<.001) ***. Ipratropium did not significantly change the breakthrough rate when added to Levalbuterol groups.

Medication	Total Tx	Break-through	Rate/ 1000	Tx/Pt/ Tday	Rate/100 Pt/day	
Alb Q4h	3832	47	12.27	6	7.36**	5.29*
Alb/Ipra Q4h	3767	20	5.31	6	3.19**	
Lev 0.63mg Q6h	3592	24	6.68	4	2.67	2.29*
Lev 0.63 mg/Ipra Q6h	1821	7	3.84	4	1.54	
Lev 1.25mg Q8h	1791	17	9.49	3	2.85	2.43*
Lev 1.25mg/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. Levalbuterol at the 1.25 mg dose performed better than the 0.63 dose for Q8h administration. 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 re-allocating of workforce needs while maintaining, or improving, quality of aerosol administration, as evidenced by the decrease in breakthrough requirements.

PERFORMANCE OF A NEW BREATH-ACTUATED SMALL VOLUME NEBULIZER (SVN) FOR THE DELIVERY OF A COMBINATION ANTICHOLINERGIC/BRONCHODILATOR.

Nagel MW, Wiersema KJ, Bates SL and Mitchell JP. Am J Resp Crit Care Med 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 (Monaghan Medical Corp., N.Y.) and 5-PARI LCD† 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	ED = 102 ± 7 µg	FPD = 82 ± 6 µg
IPR	PARI LCD† SVNs	ED = 55 ± 7 µg	FPD = 45 ± 5 µg
ALB	AEROECLIPSE® BAN	ED = 581 ± 17 µg	FPD = 471 ± 14 µg
ALB	PARI LCD† 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 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).

Klopf S, Scneiderman N, Payne H, Schramm C, Nagel MW, Mitchell JP. Resp Care 2000;45(8):979.

Background: In prior *in-vitro* studies using laser diffractometry, the aerosol produced by a novel breath-actuated nebulizer (BAN), the AEROECLIPSE® (Monaghan Medical Corp. 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 oro-pharyngeal 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 in the delivery of a beta2-agonist (albuterol 2.5 mg/ml) accompanied by anticholeninergic (ipratroprium 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. Stage 1 asthmatics were given 0.5-ml of albuterol with 0.5-ml normal saline delivered until

sputter. Patients ca5egorized in stage two and three were given 0.5-ml albuterol with the addition of 1.5-ml of ipratroprium 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 (min)	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 BA-SVN. **Conclusions:** Use of the AEROECLIPSE® BAN 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.

Ipratropium Bromide (Atrovent†, Boehringer Ingelheim†)

REDUCING TOTAL COSTS OF AEROSOLIZED MEDICATION DELIVERY USING THE AEROECLIPSE® II BREATH ACTUATED NEBULIZER.

Wilson J. Resp Care 2011;56(10):1634.

Introduction: We hypothesized the AEROECLIPSE® II breath actuated 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 1ml 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. BANs 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 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 breath actuated 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.

Mitchell JP, Nagel MW, MacIntyre NR. Presented at Drug Delivery to the Lungs 16, 2005.

A mechanically operated, breath-actuated nebulizer (BAN) 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 BAN (AEROECLIPSE®) 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 with expensive medications, such as antibiotics, if less volume fill is required per treatment.

SIMILAR DELIVERY OF IPRATROPIUM BROMIDE IS POSSIBLE AT APPROXIMATELY ONE-HALF DOSE VIA A BREATH-ACTUATED NEBULIZER COMPARED WITH A CONTINUOUS NEBULIZER.

Mitchell JP, Nagel MW, MacIntyre NR and Sharpe R. Presented at European Respiratory Society Annual Congress, Copenhagen, Denmark, 2005.

Delivery of aerosols via continuous nebulizers wastes medication during patient exhalation. Breath-actuated nebulizers (BAN) minimize waste, since they only operate when the patient inhales. We describe a study in which a BAN (AEROECLIPSE®, Trudell Medical International, 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, USA, 0.5-mg/2.5-ml)). Each device was operated with air at 50 psig at 7 L/min (BAN) 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/min). 1.25-ml was placed in the BAN 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 delivered 61.7 5.2 g IPR in 2-3 min, of which 50.0 4.2 g was in fine droplets 4.8 m diameter. The VIX delivered a total mass of 57.2 5.5 g in 3-4 min, of which 46.9 4.5 g was contained in fine droplets. The BAN delivered a similar amount of medication as fine droplets with approximately one-half of the dose in the reservoir.

Metaproternol Sulphate (Alupent†, Boehringer Ingelheim†)

PERFORMANCE OF A NEW AIR ENTRAINMENT SMALL VOLUME NEBULIZER.

Archer A, Mitchell JP, Nagel MW, Verdun AMW. Eur Resp J 1998;12(28):68.

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 s 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.

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.

Mitchell JP, Nagel MW, Archer A, Coppolo D. Am J Resp Crit Care Med 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.

Archer A, Mitchell JP, Nagel MW, Verdun AMW. Eur Resp J 1998;12(28) 68.

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 s 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 hyper-responsiveness (AHR). Each step was then expanded with supporting information. **Results:** Using independently referenced (within the ERS standard) validation data from a breath actuated nebulizer (AEROECLIPSE® BAN) 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-27 2017; DOI:10.13140/RG.2.2.12626.04807.

Summary: The assessment through a challenge test of severity of reversible broncho-constrictive 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 s (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 step-wise 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 hyper-responsiveness. 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 nebulizer (AEROECLIPSE® II BAN) as was used, through references, in the new guidance. **Introduction:** The assessment through a challenge test of severity of reversible broncho-constrictive 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 min [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-s (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 s (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 FEV1 (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, step-wise, 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 nebulizer (AEROECLIPSE® II BAN, Trudell Medical International, London, 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 Effective Dilution (mL)	Obtain Diluted Concentration (CMC) (mg/mL)	Code Letter to Provide Order of Dilution (see Second column)
	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
100	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 (DDMC) 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: For 20 seconds of tidal breathing, the delivery rate (RMC) of methacholine at the mouthpiece of the high output device (BAN) is 2.70 mg/min for a solution concentration (CMC) 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-emitted droplets made by laser diffractometry as being 0.76 [3].

Hence the DD_{MC} for t(s) can be calculated as $DD_{MC} = R_{MC} \times FDF \times (t/60)$, 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 as: $DD_{MC} = [C_{MC}/16\ mg/ml] \times 680\ µg$. **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. **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.

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

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

Consequently, from this particular example above, the bronchial responsiveness (PD_{20}) is determined as 61 µg. **5) Assessment of Airway Hyper-Responsiveness (AHR)** The PD_{20} value can then be used to interpret the degree of AHR using values from the ERS document3 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 hyper-responsiveness. 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. Available at: *http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/visited June 22 2017*. 2 Cockcroft DW, Swystun VA, Bhagat RG. Interaction of inhaled beta-2 agonist and inhaled corticosteroid on airway responsiveness to allergen and methacholine. American Journal of Respiratory and Critical Care Medicine 1995; 152: pp1485–1489. 3 Coates AL, Leung K, Dell SD. Developing alternative delivery systems for methacholine challenge tests. Journal of Aerosol Medicine and Pulmonary Drug Delivery 2014; 27: pp.66–70. 4 Dole SD, Bola SS, Foty RG, Marshall LC, Nelligan KA, Coates AL. Provocative dose of methacholine causing a 20% drop in FEV_1 should be used to interpret methacholine challenge tests with modern nebulizers. Annals of the American Thoracic Society 2015; 12(3): pp 357–363. 5 El-Gammal AI, Killian KJ, Scime TX, Beaudin S, Schlatman A, Cockcroft DW, Gauvreau GM. 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. Annals of the American Thoracic Society 2015; 12(7): pp 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 and the Bronchoprovocation Testing Task Force: KH Carlsen, Z Diamant, G Gauvreau, GL Hall, TS Hallstrand, I Horvath, FHC de Jongh, G Joos, DA Kaminsky, BL Laube, JD Leuppi and PJ Sterk. Eur Respir J 2017; 49: 1601526.

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 s (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 min (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.

PROVOCATIVE DOSE OF METHACHOLINE CAUSING A 20% DROP IN FEV_1 SHOULD BE USED TO INTERPRET METHACHOLINE CHALLENGE TESTS WITH MODERN NEBULIZERS.

Dell SD, Bola SS, Foty RG, Marshall LC, Nelligan KA, Coates AL. Ann Am Thorac Soc 2015;12(3):357-63.

RATIONALE: 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 (Aero; Trudell Medical International, London, ON, Canada) nebulizer compared with use of the reference standard EW nebulizer. **METHODS:** Subjects with asthma (10-18 yr old) participated in randomized, controlled cross-over 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 PD20 did not (0.06 vs. 0.08 mg). PC_{20} differed with the EW versus the Aero nebulzer 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}.

DEVELOPING ALTERNATIVE DELIVERY SYSTEMS FOR METHACHOLINE CHALLENGE TESTS.

Coates AL, Leung K, Dell SD. J Aerosol Med Pulm Drug Deliv. 2014 Feb;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 nonstandardized nebulizers. Of the two recommended devices, one is the English Wright nebulizer used in the 2-min 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 as a potential delivery system for the 2-min tidal breathing, and the second was the automated system by VIASYS as an alternative to either the 2-min 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 sec, the AEROECLIPSE® II BAN would be expected to have a pulmonary deposition equivalent to the 2-min tidal breathing with the English Wright, whereas the VIASYS system would take approximately 40 sec 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 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).

Coates AL, Leung K, Dell S. Am J Respir Crit Care Med 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 (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 ≤ 5μm was the estimated pulmonary deposition. **Results:** For a concentration of 16 mg/mL the rates of deposition for the EW and AER weres 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.

Bola SS, Foty R, Marshall L, Nelligan K, Coates AL, Dell S. Am J Respir Crit Care Med 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 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 PD20 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.

Mitchell JP, Nagel MW, Bates SL, Doyle CC. Respir Care 2003;48(1):46–51.

Backgroud: 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 nebulizer (AEROECLIPSE®) may offer bronchoprovocation testers an alternative to existing devices. **Methods:** We studied the

performance of 5 AEROECLIPSE® 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 (r2 = 0.9999) with MC concentration, within the range studied. FDM also showed a linear correlation (r2 = 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®'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® could be used to coach the patient to inhale for a specific period, thereby controlling MC delivery per breathing cycle.

PREDICTING LUNG DEPOSITION WITH A CASCADE IMPACTOR.

Sangwan S, Hull F, Condos R and Smaldone GC. J Aerosol Med 2001; 14(3):421.

Introduction: In recent deposition studies of interferon-ß, 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 (Gurses BK 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® Breath-Actuated Nebulizer ("BAN")) were studied. Mass median aerodynamic diameter (MMAD) and mass balance were measured under standing cloud and ventilation using a piston pump. Deposition images were obtained using gamma camera.

Results:

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

†Calculated by adding T connector deposition to the first stage (>8µm) 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.

Amphotericin (Ablecet†, Enzon† Pharmaceuticals)

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 pre-exposure prophylaxis to prevent infection. We made a very low MWt 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 immuno-suppression 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 immuno-pathology. 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.

Kamalaporn H, Leung K, Nagel M, Kittanakom S, Calvieri B, Reithmeier RA, Coates AL. Pediatr Pulmonol. 2014;49(6):574-80.

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 nebulizer (AEROECLIPSE®; 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.**

Alexander BD, Winkler TP, Shi S, Dodds Ashley ES, Hickey AJ. Pharm Dev Technol. 2011;16(6):577-82.

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 min 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 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.

Husain S, Capitano B, Corcoran T, Studer SM, Crespo M, Johnson B, Pilewski JM, Shutt K, Pakstis DL, Zhang S, Carey ME, Paterson DL, McCurry KR and Venkataramanan R. Transplantation. 2010;90(11):1215-9.

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®), of amphotericin B lipid complex at 1 mg/kg every 24 hr for 4 days in 35 lung transplant recipients. One brochoalveolar 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 mphotericin B. **Results:** Concentrations of amphotericin B in ELF (median, 25-75 IQR) were at 4 hr (*n*=5) 7.20 µg/mL (1.3-17.6), 24 hr (*n*=6) 8.26 µg/mL (3.9-82.7), 48 hr (*n*=5) 2.15 µg/mL (1.4-5.5), 72 hr (*n*=4) 1.25 µg/mL (0.75-5.5), 96 hr (*n*=6) 0.86 µg/mL (0.55-1.4),

120 hr (*n*=4) 1.04 µg/mL (0.44-1.6), 144 hr (*n*=1), 4.25 µg/mL, 168 hr (*n*=3) 1.14 µg/mL, and 192 hr (*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 sec. **Conclusions:** We conclude that administration through aerosolized nebulization of amphotericin B lipid complex every 24 hr for 4 days in lung transplant recipients achieved amphotericin B concentrations in ELF above minimum inhibitory concentration of the Aspergillus nearly at 168 hr 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.

Dodds ES, Petry NA, Davies JD, Zaas DW, Palmer SM, Shipes SW, Drew RH, Alexander BD, Coleman RE and Perfect JR. Presented at the American Association for Respiratory Care Congress, Orlando, FL, 2007.

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 (BAN's) 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 nebulizer (BAN): AEROECLIPSE® II (Monaghan Medical, Plattsburgh, NY). ABLC 20 mg/4mL was mixed with prepared 99mTc-ABLC (Abelcet†-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. Immediately following inhalation, drug product distribution image 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 (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 Devlivery†	% 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 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]Hussain S, Zaldonis D, Kusne S et al. Variation in antifungal prophylaxis strategies in lung transplantation. Transpl Infect Dis 2006:213-8.
[2]Drummer JS. A survey of fungal management in lung transplantation. Journal of Heart and Lung Transplantation 2004;23:1376-81.

SIMILAR DELIVERY OF AMPHOTERICIN LIPID COMPLEX IS POSSIBLE AT ONE-HALF DOSE VIA A BREATH-ACTUATED NEBULIZER COMPARED WITH A CONTINUOUSLY OPERATING NEBULIZER.

MacIntyre NR, Mitchell JP, Nagel MW and Coppolo DP. Presented at the 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 (BAN) 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 BAN (AEROECLIPSE®, Monaghan Medical Corp., 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) 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/min). 5-ml AMP was placed in the BAN and 10-ml in the VIX (5-ml initially, followed by a further 5-ml after 4-min). Each nebulizer was operated for 1-min 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 was 7274 123 g, delivered in 10-min, 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 min, of which 4326 457 g was contained in fine droplets. The BAN 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.

Mitchell JP, Nagel MW and MacIntyre NR. Presented at Drug Delivery to the Lungs Conference 16, 2005.

A mechanically operated, breath-actuated nebulizer (BAN) 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 BAN (AEROECLIPSE®) 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 with expensive medications, such as antibiotics, if less volume fill is required per treatment.

Measles Vaccine (Placebo)

THE DELIVERY OF PLACEBO MEASLES VACCINE BY A MECHANICALLY-OPERATED BREATH-ACTUATED NEBULIZER (BAN).

Malpass J, Mitchell JP and Nagel MW. Presented at the European Respiratory Society, Munich, Germany, 2006.

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 BAN (AEROECLIPSE®, Trudell Medical International) was evaluated in comparison with a continuously operating jet nebulizer (Aeromist†, IPI Medical Products Inc., Chicago, 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†, De Vilbiss 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. Mass output rate was quantified gravimetrically, and a laser diffractometer was used to determine droplet size distributions. The aerosol produced by the BAN (mass median diameter (MMD) = 4.3 ± 0.23 μm) was finer than the mass output rate of the BAN (0.40 ± 0.01ml/min) significantly exceeded that from the CMD (0.15 ± 0.03 ml/min) (p<0.001). The BAN 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.

Recombinant Interferon-y1B

IMMUNOMODULATION WITH RECOMBINANT INTERFERON-y1B IN PULMONARY TUBERCULOSIS.

Dawson R, Condos R, Tse D, Huie ML, Ress S, Tseng CH, Brauns C, Weiden M, Hoshino Y, Bateman E and Rom WN. 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-y1b (rIFN-yb) 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-y1b 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-1ß, IL-6, IL-8, and IL-10 in 24-hour BAL supernatants only in the nebulized rIFN-y1b group from baseline to week 16. Both rIFN-y1b 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 Mtb from the sputum smear at 4 weeks for the nebulized rIFN-y1b adjuvant group compared to DOTS or DOTS with subcutaneous rIFN-y1b. In addition, there was significant reduction in the prevalence of fever, wheeze, and night sweats at 4 weeks among patients receiving rFN-y1b versus DOTS alone. **Conclusion:** Recombinant interferon-y1b adjuvant therapy plus DOTS in cavitary pulmonary tuberculosis can reduce inflammatory cytokines at the site of disease, improve clearance of Mtb from the sputum, and improve constitutional symptoms.

IMMUNOMODULATION WITH PHARMACOLOGIC IFN-GAMMA AND ITS EFFECT ON THE LUNG-SPECIFIC IMMUNE RESPONSE IN PULMONARY TB.

Condos R, Huie ML, Dawson R, Ress S, Brauns C, Tseng CH, Weiden M, Bateman E and Rom RN. Presented at the American Thoracic Society, San Francisco, CA, 2007.

Background: In a randomized clinical trial of TB patients treated with interferon gamma (IFN-), we have shown safety and efficacy (faster culture conversion). We hypothesize that pharmacological IFN- stimulates a TH1 environment in situ in the lung. **Methods:** 24 patients with cavitary TB randomized to DOTS alone or DOTS plus IFN- (either by aerosol or by sc injection). Bronchoscopy done at baseline and 16 weeks of treatment. BAL cell differential and 24 hour supernatants were prepared and spontaneous expression of cytokines/chemokines were assayed by Beadlyte multiplex assay on the Luminex 200 platform. Results were reported as averages SEM. **Results:** 12 patients were randomized to DOTS plus aerosol IFN- ; 5 patients were randomized to DOTS plus sc IFN- ; and 5 were randomized to DOTS alone. BAL cell differentials showed in increase in % lymphocytes in all groups (10.% 3%pre, 22% 3%post). Several cytokines/ chemokines were differentially expressed between groups. Eotaxin increases with IFNtreatment (47 11pg/ml to 92 44pg/ml) but not with DOTS alone (64 31pg/ml to 61 10pg/ml). IL-4 was low in all patients (pre- 5 1 to post- 9 2pg/ml). IL1- decreased with IFN- treatment (186 132 to 21 7pg/ml), but increased on DOTS alone (20 7 to 163 156pg/ml) as did TNF- (IFN- group: 119 85 to 43 28pg/ml; DOTS alone 13 5 to 202 200pg/ml) and MIP1. IFN- increased in the aerosol group (148 111pg/ml to 229 85pg/ml) and the DOTS only group (38 16pg/ml to 111 76pg/ml), but not in the sq group (217 96pg/ml to 99 40pg/ml). IP-10 levels increased in all groups(117 55 to 401 93pg/ml). **Conclusion:** Immunomodulation with IFN- leads to a decrease in pro-inflammatory chemokines/cytokines independent of changes in cell differential or IFN- levels.

Saline

EVALUATION OF A NEW AIR ENTRAINMENT SMALL VOLUME NEBULIZER (AE-SVN) WHEN USED WITH OXYGEN AS A DRIVING GAS UNDER CONDITIONS OF HOSPITAL USE.

Mitchell JP and Nagel MW. Presented at ALA/ATS International Conference, Chicago, 1998.

Purpose: To compare the delivery of saline (0.9% w/v NaCl) by a new AE-SVN (Trudell Medical Int.) with that from two other representative SVNs (UpDraft Neb-U-Mist† (Hudson Oxygen Therapy Sales Co.) and Airlife† Misty-Neb† (Baxter Healthcare Corp.)) using oxygen delivered at 50 psig at 8 l/min to simulate hospital use. **Methods:** 5 AE-SVNs were tested using a laser diffractometer (Malvern Mastersizer-X) to determine the size distribution of droplets emitted at the mouthpiece. The total mass output was determined gravimetrically in a parallel series of tests. 5, Neb-U-Mist† and a similar number of MistyNeb† SVNs were also evaluated. **Results:** Total (TM) and respirable ((RM), droplets finer than 4.8 µm diameter) mass output rates and droplet mass median diameter (MMD) were as follows: AE-SVN: TM = 671 ± 26 µg/min, RM = 542 ± 23 µg/min (80.8 ± 1.3% respirable), MMD = 2.88 ± 0.09 µm; Neb-U-Mist†: TM = 266 ± 13 µg/min, RM = 119 ± 16 µg/min (42.1 ± 5.2% respirable), MMD = 5.6 ± 0.6 µm; Misty-Neb†: TM = 336 ± 60 µg/min, RM = 178 ± 43 µg/min (53.1 ± 8.5 % respirable), MMD =4.5 ± 0.9 µm. **Conclusion:** TM from the new AE-SVN was substantially greater than those from either the Neb-U-Mist† or Misty-Neb† (1-way ANOVA, $p < 0.001$). The finer MMD produced from the AE-SVN resulted in a significantly greater RM compared with either of the other SVNs ($p < 0.001$).

PERFORMANCE OF A NEW BREATH-ACTUATED SMALL VOLUME NEBULIZER (BA-SVN) WHEN USED WITH OXYGEN AS A DRIVING GAS UNDER CONDITIONS OF HOSPITAL USE.

Verdun AM, Mitchell JP and Nagel MW. Presented at ALA/ATS International Conference, Chicago, 1998.

Purpose: To compare the delivery of saline (0.9% w/v NaCl) by a new BA-SVN (Trudell Medical Int.) with that from two other representative SVNs (LC-JET† (PARI Respiratory Products Inc., Canada) and reusable Sidestream† (MedicAid, UK)) using oxygen delivered at 50 psig at 8 l/min to simulate hospital use. **Methods:** 5 BA-SVNs were tested using a laser diffractometer (Malvern Mastersizer-X) to determine the size distribution of droplets emitted at the mouthpiece. The total mass output was determined gravimetrically in a parallel series of tests. 5, LC-JET† and 5, Sidestream† SVNs were also tested similarly. The BA-SVN was operated with manual over-ride engaged (continuous delivery of aerosol). **Results:** Total (TM) and respirable (RM), droplets finer than 4.8 µm diameter) mass output rates and droplet mass median diameter (MMD) were as follows: BA-SVN: TM = 672 ± 23 µg/min, RM = 545 ± 31 µg (80.9 ± 2.4% respirable), MMD = 2.79 ± 0.15 µm; LC-JET†: TM = 675 ± 69 µg/min, RM = 449 ± 41 µg/min (66.7 ± 1.8% respirable), MMD = 3.39 ± 0.08 µm; Sidestream†: TM = 442 ± 26 µg/min, RM = 358 ± 38 µg/min (80.8 ± 4.2 %respirable), MMD =2.94 ± 0.03 µm. **Conclusion:** Although TM from the new BA-SVN was comparable with that from the LC-JET† (Mann-Whitney rank sum test, $p = 0.84$), the finer MMAD produced from the BA-SVN resulted in a significantly greater RM ($p < 0.001$). Both TM and RM from the BA-SVN were greater than those from the Sidestream† SVN ($p < 0.001$).

COMPARISON OF A NEW AIR ENTRAINMENT SMALL VOLUME NEBULIZER (AE-SVN) WITH OTHER SVNS WHEN USED WITH OXYGEN AS DRIVING GAS UNDER CONDITIONS OF HOSPITAL USE.

Mitchell JP and Nagel MW. Presented at the Annual Meeting of the American Association of Asthma, Allergy and Immunology, Washington, DC, 1998.

The performance of a prototype novel AE-SVN (Trudell Medical International ($n = 5$)) with normal saline (0.9% w/v NaCl) operating at 20 ± 2ºC, 50 ± 10% RH, has been evaluated with oxygen (50 psig, 8 l/min) as driving gas to simulate hospital use. Comparison testing was also undertaken with two other representative AE-SVNs, (a) LC-JET† (Pari Respiratory Equipment Inc.), without inspiratory valve cap which would otherwise restrict aerosol output, (b) SideStream† (MedicAid, UK). A laser diffractometer (Malvern Mastersizer-X) was used to determine the size distribution of droplets emitted at the mouthpiece. The total mass output was determined gravimetrically in a parallel series of tests. Total (T) and respirable ((R), droplets finer than 4.8 µm aerodynamic diameter) mass output rates and droplet mass median aerodynamic diameter (MMAD) for the new AE-SVN (5 replicate measurements/device) were: 671 ± 26 µg/min (T), 542 ± 23 µg/min (R) and 2.88 ± 0.09 µm (MMAD). Corresponding data for the LC-JET† were: 675 ± 65 µg/min (T), 450 ± 45 µg/min (R) and 3.39 ± 0.14 µm (MMAD), and for the SideStream† were: 442 ± 27 µg/min (T), 357 ± 28 µg/min (R) and 2.95 ± 0.13 µm (MMAD). The total aerosol delivery rate from the new AE-SVN matched that of the LC-JET† (un-paired t-test, $p = 0.79$) and exceeded that from the SideStream† ($p < 0.001$). The finer MMAD of the aerosol provided by the new AE-SVN resulted in a significantly greater respirable mass fraction, increasing the respirable mass delivery rate compared with the other SVNs ($p < 0.001$).

COMPARISON OF A NEW BREATH ACTUATED SMALL VOLUME NEBULIZER (BA-SVN) WITH AN SVN SUPPLIED WITH COMPRESSOR INTENDED FOR HOME CARE USE.

Verdun AM, Mitchell JP and Nagel MW. Presented at the Annual Meeting of the American Association of Asthma, Allergy and Immunology, Washington, DC, 1998.

The performance of a prototype novel BA-SVN (Trudell Medical International (*n* = 5 devices)) with normal saline (0.9% w/v NaCl) operating at 20 ± 2ºC, 50 ± 10% RH, has been evaluated with an air compressor widely used in home care (Proneb†, Pari Respiratory Equipment Inc.). A laser diffractometer (Malvern Mastersizer-X) was used to determine the size distribution of droplets emitted at the mouthpiece (5 replicates per device). The total mass output was determined gravimetrically in a parallel series of tests. The BA-SVN was operated with manual over-ride engaged (continuous delivery of aerosol). Total (T) and respirable ((R), droplets finer than 4.8 µm aerodynamic diameter) mass output rates, respirable mass fraction (RM) and droplet mass median aerodynamic diameter (MMAD) were 167 ± 6 µg/min (T) , 96 ± 5 µg/min (R), 57.5 ± 2.1% (RM) and 4.40 ± 0.11 µm (MMAD). In comparison, under similar conditions, a Pari LC-JET† SVN with Proneb† (*n* = 5 replicate measurements) provided 211 ± 3 µg/min (T), 65 ± 4 µg/min (R), 30.9 ± 1.5% (RM) and 6.94 ± 0.20 µm (MMAD). The new BA-SVN provided aerosol having a finer MMAD and greater RM (un-paired t-test, $p < 0.001$ for each variable) which resulted in an improved respirable mass output rate compared with the LC-JET† SVN. The BA-SVN also has the advantage that no aerosol is produced to waste during the exhalation portion of each breathing cycle.

Levalbuterol (Xopenex†, Sepracor†)

CLINICAL AND ECONOMIC OUTCOMES WITH A CONVERSION TO ARFORMOTEROL ONCE OR TWICE DAILY FROM LEVALBUTEROL USING BREATH ACTUATED NEBULIZERS.

Pikarsky RS, Acevedo RA, Farrell T, Fascia W and Bear R. Presented at the American Association for Respiratory Care, 2008.

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 in-patient COPD patients are for maintenance bronchodilatation. This pilot protocol evaluated the conversion from Levalbuterol (Lev) to Arformoterol (Arf) for maintenance. **Methods:** COPD in-patients assessed to be on maintenance bronchodilators were converted from Lev to Arf. All treatments (tx) were delivered using the Monaghan Medical AEROECLIPSE® Breath Activated Nebulizer (BAN). 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 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 Qday: 376 scheduled, 32 prn (8.5 per 100 pt-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 pt-days), and 2 refusals. Lev (BAN & mask) TID: 4,281 scheduled, 153 prn (10.7 per 100 pt-days) and 254 refusals. Economic results: See Table. **Conclusion:** Using Arformoterol Qday with BAN 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, by allowing Qday treatments, was extremely cost effective.

Economic Evaluation	Arformorterol QDay BAN	Arformoterol BID BAN	Levalbuterol TID BAN	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

Economic Evaluation	Out patient		
NEB	Brovana Qday BAN	Brovana BID BAN	Brovana BID Misty
# tx	141	272	272
Ave Tx/day	1.04	2.00	2.00
Daily device cost	$0.70	$0.70	$0.12
Daily drug cost	$4.43	$8.68	$8.68
Daily cost	$5.13	$9.38	$8.80

LEVALBUTEROL 1 ML (0.42 MG) Q8H DOSING USING THE AEROECLIPSE® BREATH-ACTUATED NEBULIZER IN A COPD INPATIENT POPULATION.

Pikarsky RS, Acevedo RA, Farrell T, Fascia W. Presented at CHEST Pulmonary-Critical Care, Salt Lake City, UT, 2006.

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® Breath Actuated Nebulizer (BAN) in a predominantly COPD in-patient 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. Lev was poured from a standard 3 ml unit dose vial to the 1 ml line in the BAN 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 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 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 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 is a very cost effective delivery method. Smaller doses in the BAN lead to shorter administration times. Clinical Implications: When utilizing the BAN, 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.

SAFETY AND EFFICACY OF FIVE-MINUTE TIMED AEROSOL ADMINISTRATION WITH THE AEROECLIPSE® BREATH ACTUATED NEBULIZER: COMPARISON OF LEVALBUTEROL WITH RACEMIC ALBUTEROL.

Pikarsky RS, Acevedo R, Roman C, Fascia W, Farrell T. Resp Care 2002;47(9) 1075.

Purpose: Beta2-agonist Racemic Albuterol has been used extensively in the performance of pre & 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® Breath Actuated Nebulizer (BAN) (Monaghan Medical Corp. Plattsburgh, N.Y.). **Methods:** A consecutive, non-randomized, mostly COPD population (*n* = 93) receiving pre & post bronchodilator testing in our Pulmonary Function Lab were studied. Two different Levalbuterol medication dosages were administered: 0.63mg Levalbuterol UD or 1.25mg UD Levalbuterol. The Racemic Albuterol dosage was 2.5mg UD. All 5 minute timed aerosol treatments were administered using the BAN with an oxygen flow rate of 8L/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 1.25mg Levalbuterol UD group (7.2 vs. 3.4, p<.05*; 7.2 vs. 2.2, p<.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 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 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 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.

Pikarsky RS, Acevedo RA, Roman C and Farrell T. CHEST 2002;22(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® Breath Actuated Nebulizer (BAN). 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<.001)*. The breakthrough rate with Albuterol was significantly reduced with the addition of Ipratropium (*p*<.001)**. Ipratropium did not significantly change the breakthrough rate when added to Levalbuterol groups.

Medication	Total Tx	Break-through	Rate/ 1000	Tx/Pt/ day	Rate/100 Pt/day	
Alb Q4h 25.80*	898	61	67.93	6	40.76**	
Alb/Ipra Q4h	1079	24	22.24	6	13.35**	
Lev 0.63mg Q6h	2047	69	33.71	4	13.48***	18.43*
Lev 0.63 mg/Ipra Q6h	2728	151	55.35	4	22.14	
Lev 0.63mg Q8h	660	47	71.21	3	21.36***	18.43*
Lev 0.63 mg/Ipra Q8h	707	37	52.33	3	15.70	
Lev 1.25mg Q8h	238	3	12.61	3	3.78***	5.96*
Lev 1.25mg/Ipra Q8h	215	6	27.91	3	8.37	

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 re-allocating 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.

Lewis MA, Harris DD, Campbell DL, Hodges AL, Clark DM. Resp 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® Breath Actuated Nebulizer ("BAN") (Monaghan Medical Corp., Plattsburgh, NY). Both pilot projects were approved by the Respiratory Care Advisory Committee. **Methods:** LEV 1.25mg delivered via nebulization q6h was substituted for albuterol 2.5mg ordered q4h in October 1999. Patients could also receive LEV as needed. A standardized subjective questionnaire to determine side effects of LEV was completed. BANs 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 BANs versus 322 delivered using a standard nebulizer. The average time per treatment using BANs 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 BANs 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 has decreased the time to deliver therapy by 33%.

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.

Miner JR, Kletti C, Herold M, Hubbard D, Biros MH. Acad Emerg Med 2007;14(10):895-8.

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 eight 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.

Liposome-Encapsulated Fentanyl (AeroLEF†, YM Biosciences)

A RANDOMIZED CONTROLLED TRIAL DEMONSTRATES THE EFFICACY, SAFETY AND TOLERABILITY OF AEROSOLIZED FREE AND LIPOSOME-ENCAPSULATED FENTANYL (AeroLEF†) VIA PULMONARY ADMINISTRATION.

Brull R, Chan V. Presented at the American Pain Society's Annual Scientific Meeting, Tampa, FL, 2008.

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 breathactuated 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 1500 µg AeroLEF† (≤1000 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/min or SpO2<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-TITRAATE TO EFFECTIVE ANALGESIA.

Clark A, Rossiter-Rooney M, Valle-Leutri F. Presented at the American Pain Society's Annual Scientific Meeting, Tampa, FL, 2008.

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 micro-doses 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 (1000µg 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 2.7min. Mean plasma fentanyl concentration at first perceptible analgesia was 0.801ng.mL-1. Median time to effective analgesia was 17min. At analgesia, the mean plasma fentanyl level was 1.30ng. mL-1but 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 3.7h and the request for additional analgesics was associated with a decrease in mean plasma fentanyl levels to 0.887ng.mL-1(ranging from o.36ngmL-1to 1.584ngmL-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 1.58ng.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.

Hung O, Pliura D. Presented at the American Pain Society's Annual Scientific Meeting, Tampa, FL, 2008.

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 1500µg AeroLEF vs. 200µg bolus IV fentanyl; values are mean (± SD). Healthy, opiate-naïve volunteers inhaled microdoses of AeroLEF (≤ 5µg/breath; total emitted fentanyl dose ≤ 1000µg) over 7-15 min. Within 4 min 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 min) occurred shortly after completion of AeroLEFTMinhalation (mean of 12 min), indicating rapid absorption from the lung. Cp values in the effective range persisted for several hours with AeroLEF (at 4 hr, Cp was 0.525 ± 0.180 ng.mL-1) but not with IV administration (at 1 hr, 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 FEF25%-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.

Arformoterol (Brovana†, Sunovion Pharmaceuticals)

CLINICAL AND ECONOMIC OUTCOMES WITH A CONVERSION TO ARFORMOTEROL ONCE OR TWICE DAILY FROM LEVALBUTEROL USING BREATH ACTUATED NEBULIZERS.

Pikarsky RS, Acevedo RA, Farrell T, Fascia W, Bear R. Presented at American Association for Respiratory Care, 2008.

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 in-patient COPD patients are for maintenance bronchodilatation. This pilot protocol evaluated the conversion from Levalbuterol (Lev) to Arformoterol (Arf) for maintenance. **Methods:** COPD in-patients assessed to be on maintenance bronchodilators were converted from Lev to Arf. All treatments (tx) were delivered using the Monaghan Medical AEROECLIPSE® Breath Activated Nebulizer (BAN). 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 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 Qday: 376 scheduled, 32 prn (8.5 per 100 pt-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 pt-days), and 2 refusals. Lev (BAN & mask) TID: 4,281 scheduled, 153 prn (10.7 per 100 pt-days) and 254 refusals. Economic results: See Table. **Conclusion:** Using Arformoterol Qday with BAN 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, by allowing Qday treatments, was extremely cost effective.

Economic Evaluation	Arformorterol QDay BAN	Arformoterol BID BAN	Levalbuterol TID BAN	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
Economic Evaluation	**Arformorterol QDay BAN**	**Arformoterol BID BAN**	**Levalbuterol TID BAN**	**Arformoterol BID SVN**
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

Economic Evaluation	Out patient		
	Brovana Qday BAN	**Brovana BID BAN**	**Brovana BID Misty NEB**
# tx	141	272	272
Ave Tx/day	1.04	2.00	2.00
Daily device cost	$0.70	$0.70	$0.12
Daily drug cost	$4.43	$8.68	$8.68
Daily cost	$5.13	$9.38	$8.80

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):684-91.

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 s (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). 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 FEV1 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.

Davies LA, Nunez-Alonso GA, McLachlan G, Hyde SC, Gill DR. Hum Gene Ther Clin Dev. 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 nebulizer operating at 50 psi generated stable pDNA/GL67A aerosols suitable for delivery to the CF lung (mass median aerodynamic diameter 3.4±0.1μm). 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±0.01ml/min), the breath-actuated AEROECLIPSE® II 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 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.

Manunta MDI, McAnulty RJ, Tagalakis AD, Bottoms SE, Campbell F, Hailes HC, Tabor AB, Laurent GJ, O'Callaghan C, Hart SL. PlosOne 2011;6(10):e26768.

Background: Gene therapy mediated by synthetic vectors may provide opportunities for new treatments for cystic fibrosis (CF) via aerosolisation. 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 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.

Bacteriophage

BACTERIOPHAGE DELIVERY BY NEBULIZATION AND EFFICACY AGAINST PHENOTYPICALLY DIVERSE PSEUDOMONAS AERUGINOSA FROM CYSTIC FIBROSIS PATIENTS.

Sahota JS, Smith CM, Radhakrishnan P, Winstanley C, Goderdzishvili M, Chanishvili N, Kadioglu A, O'Callaghan C, Clokie MR. J Aerosol Med Pulm Drug Deliv. 2015;28:1-8.

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 and 12% AEROECLIPSE® 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.

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 h after the first dose. Participants were reviewed every week for 6 weeks, except at 4 weeks. Plasma cysteamine concentrations were measured 8 h after dosing when reviewed at 1, 2 and 3 weeks and 6 h 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 Cmax (T_{max}) was 1.2 (0.7) h, the half-life ($t_{½}$) was 3.7 (1.7) h, clearance (CL/F) 89.9 (30.5) L/h and volume of distribution (Vd/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.

Comparison of AEROECLIPSE® II BAN to Valved Holding Chamber with Metered Dose Inhaler (MDI)

COMBINING TREATMENT WITH PRESSURIZED METERED DOSE INHALER-VALVED HOLDING CHAMBER (PMDI+VHC) WITH DOSIMETRIC THERAPY VIA A BREATH ACTUATED NEBULIZER (BAN) 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 BAN 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, 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-s 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/3mL) from AEROECLIPSE® II BANs (*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 (ASL5000, Ingmar Medical, Pittsburgh, PA), used to generate adult breathing (tidal volume = 600-mL; duty cycle = 33%; rate = 10-cycles/min). 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 was independent of volume fill and linear with time until sputter. The Table illustrates the relationships between ex VHC and treatment time ex BAN 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

pMDI + VHC (salbutamol: 100 μg/actuation label claim) with 2 s delay		BAN (2.5 mg/3 mL salbutamol)
Number of actuations	$FPM_{<4.7\mu m}$ (μg)	Treatment time (min:sec)
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 offers the clinician new possibilities in titrating the adult tidal-breathing patient through exacerbations of broncho-constrictive 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 nebulizer (BAN - AEROECLIPSE® II, Monaghan Medical, Syracuse, 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 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 for 5 minutes; 2) 0.5 ml levalbuterol + 0.5 ml ipratropium by BAN 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 4590 L to 7545 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 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 does is recommended, we report a study in which the delivery of salbutamol sulphate by breath-actuated nebulizer (BAN) was studied as a function of volume fill, simulating representative child and adult tidal breathing. **Methods:** Three AEROECLIPSE® II BANs (Monaghan Medical Corp., 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/min, duty cycle = 33% inhalation/ 67% exhalation), followed by a child pattern (V_t = 250 mL, rate = 25 cycles/min, 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).

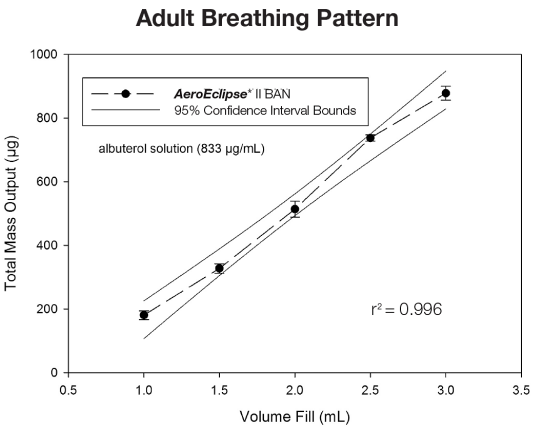


Figure 1a: Albuterol Delivery as a Function of Fill Volume: Adult Simulation

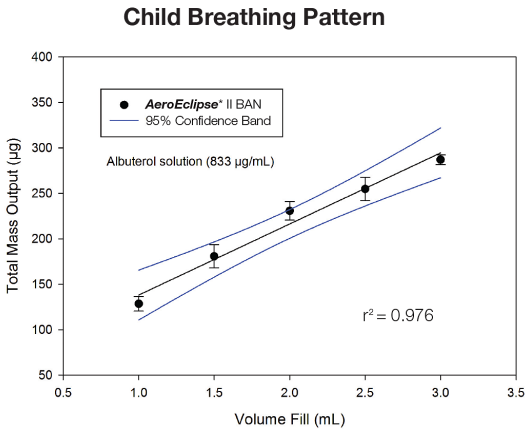


Figure 1b: Albuterol Delivery as a Function of Fill Volume: Child Simulation

Conclusions: These *in vitro* measurements simulating child and adult tidal breathing demonstrate that the AEROECLIPSE® II BAN 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 look-up 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 Look-Up Table (adult user)

pMDI + ***AeroChamber Plus**** VHC	 FPM$_{<4.7\ \mu m}$ 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; Mitchell, J.P. et al. Respiratory Drug Delivery Europe 2009; 383-386.
** Data from Mitchell, J.P. et al. Drug Delivery to the Lungs-20, Edinburgh, UK, 2009:Part B, 1-4.

THE DELIVERY TIME, EFFICACY, AND SAFETY OF BETA AGONIST BRONCHODILATOR ADMINISTRATION WITH THE AEROECLIPSE® BREATH-ACTUATED NEBULIZER ("BAN").

Pikarsky RS, Farrell T, Acevedo R, Fascia W, Roman C. 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® Breath Actuated Nebulizer as compared to both an MDI with AEROCHAMBER® VHC (both from Monaghan Medical Corp. Plattsburgh, N.Y.) and the Airlife Misty-Neb Nebulizer (SVN) (Allegiance Healthcare Corporation). **Methods**: A consecutive, non-randomized, mostly COPD population receiving pre & post bronchodilator testing in our Pulmonary Function Lab were studied. Three different Albuterol medication dosages were administered with the BAN: 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 (min)	Tremulousness
AEROECLIPSE® BAN (12)	0.5 ml + 0.5 ml NS	8.2%	2.67*	0
AEROECLIPSE® BAN (64)	1.0 ml undil.	10.9%	3.29*	17
AEROECLIPSE® BAN (23)	0.75 ml undil.	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 patients was 2.78 minutes as compared to 8.33 minutes with the SVN (p<.001) *. The mean treatment time with the MDI was 2.86 minutes as compared to 8.33 minutes with the SVN (p<.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 l 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 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 under-performed. Delivering 0.5 ml Albuterol (2.5 mg) with 0.5 ml Normal Saline using the BAN offered the best delivery time, efficacy and safety profile of the nebulizer trials. The BAN 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 to Large Volume Nebulizers

RAPID DELIVERY OF BRONCHODILATOR MEDICATION IS POSSIBLE USING A BREATH-ACTUATED SMALL VOLUME NEBULIZER AS AN ALTERNATIVE TO EXTENDED.

Mitchell J, Coppolo D, Doyle C, Nagel MW, Wiersema KJ. Presented at the American Association for Respiratory Care, Orlando, FL, 2007.

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 nebulizer (AEROECLIPSE® II, Monaghan Medical Corp., Plattsburgh, NY (AEII BAN)) 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 (MiniHeart† Hi-Flo, Westmed Corp., Tucson, AZ (CONT) with that from the AEII BAN. **Method**: The continuous nebulizers (n=5) 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 AEII BANs 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/min) 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 (mass % < 4.7 µm diameter) likely to penetrate to the airways of the lungs (FDF) could be determined. **Results**: Values of FDF for the AEII BAN and were 78.4% and 62.0% respectively. The AEII BAN delivered 758 ± 36 µg as fine droplets after 4-min (delivery rate of 190 ± 9 µg/min), compared to 180 ± 76 µg in the same period by (delivery rate of 45 ± 19 µg/min). **Conclusions**: The faster delivery rate from the AEII BAN/high albuterol concentration modality (un-paired t-test, $p < 0.001$) may offer an important clinical alternative to CONT/low concentration treatment modality.

A BREATH-ACTUATED SMALL VOLUME NEBULIZER (BAN) OFFERS A RAPID ALTERNATIVE TREATMENT MODALITY FOR THE DELIVERY OF BRONCHODILATORS FOR ASTHMATIC PATIENTS IN A SEVERE EXACERBATION.

Coppolo DP, Doyle CC, Mitchell JP, Nagel MW, Wiersema KJ. Presented at the American Association for Respiratory Care, 2006.

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 relive symptoms from bronchospasm in a shorter period of time. 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 nebulizer (BAN) (AEROECLIPSE®, Monaghan Medical Corp., 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 BANs 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 BANs was sampled onto electret filters using a breathing simulator (600-ml tidal volume, inspiratory/expiratory ratio 1:2, rate 10 cycles/min) 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-min, 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 BANs delivered 810.0 ± 20.4 µg in a 10-min period, equivalent to a rate of 81.0 ± 2.0 µg/min. The significantly higher delivery rate from the BAN group (un-paired 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.

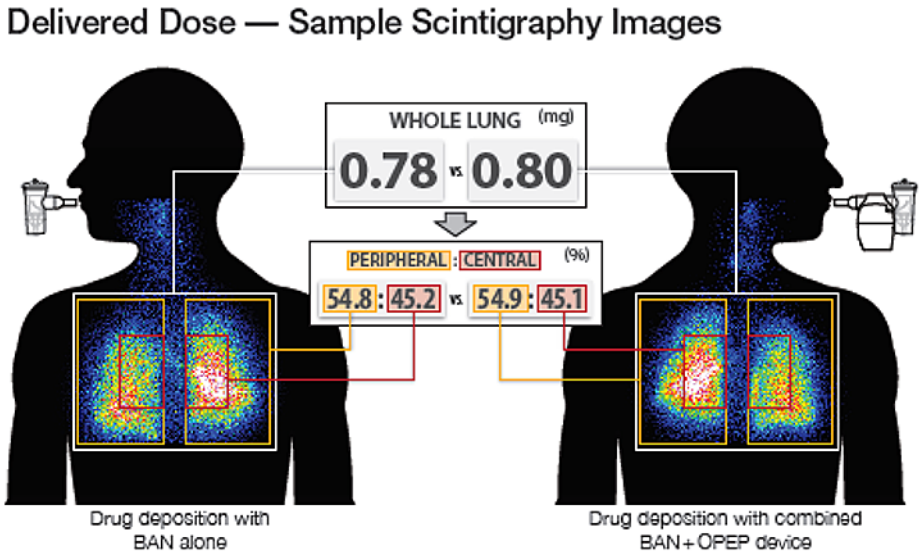
Reference: McPeck M, Tandon R, Hughes K, Smaldone GC. Aerosol delivery during continuous nebulization. Chest. 1997;111:1200-1205.

Combined 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®) with a breath actuated nebulizer (BAN) (AEROECLIPSE® II) 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 alone and again when the BAN 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 alone and BAN+OPEP respectively. Peripheral:Central deposition of the lung dose was found to be 54.8% : 45.2% (BAN alone) and 54.9% : 45.1% (BAN+OPEP). **Conclusions:** The delivery of medication from the AEROECLIPSE® II BAN 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+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.

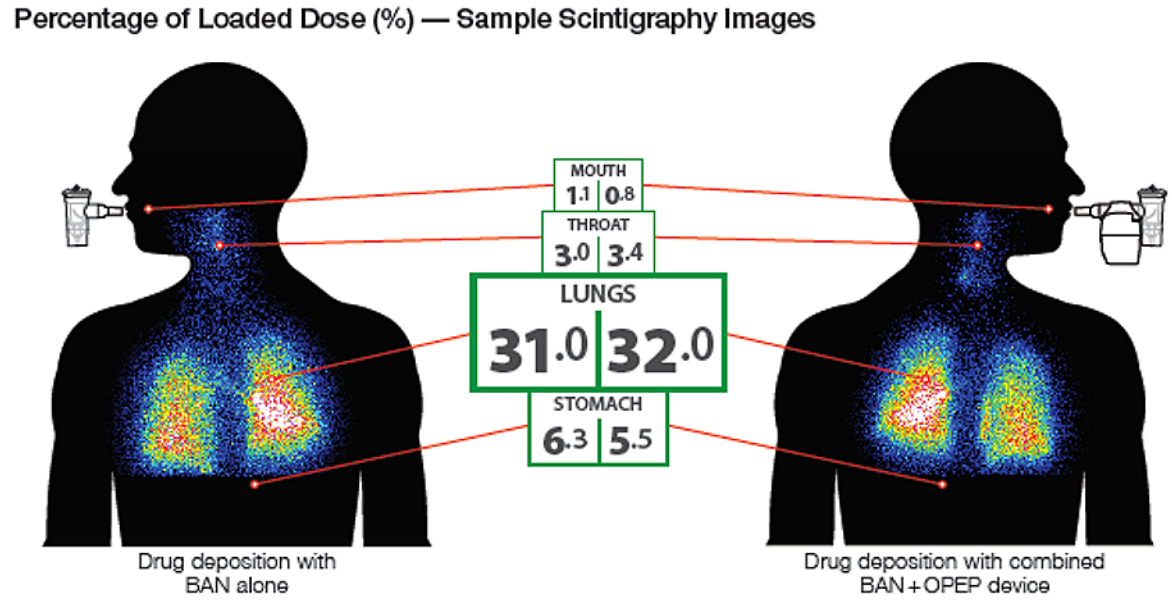


COMBINING INHALATION BY A BREATH ACTUATED NEBULISER (BAN) WITH EXHALATION THROUGH AN OSCILLATING POSITIVE EXPIRATORY PRESSURE DEVICE (OPEP) OFFERS THE POTENTIAL FOR OPTIMAL COMBINED THERAPY.

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 BAN (AEROECLIPSE® II) coupled to an OPEP device (Aerobika®) compared to deposition from the nebuliser alone. **Methods:** Eight healthy subjects received albuterol (2.5 mg/3mL) admixed with 2 mCi of Tc-DTPA (Technetium-99m bound to diethylenetriaminepentaacetic acid) administered using the BAN alone and again when the BAN 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 alone and BAN+OPEP respectively. **Conclusions:** The delivery of medication from the AEROECLIPSE® II BAN 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 (ASL5000 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-s breath hold between inhalation and exhalation). 2 different OPEP/SVN devices (Aerobika® (TMI, Canada) + AEROECLIPSE® II Breath-Actuated 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 (2.5mg/3mL). 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 alone	with Aerobika® OPEP	VixOne† SVN alone	with acapella† choice OPEP
869.8 ± 46.0µg	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 (BAN) (AEROECLIPSE® II, Monaghan Medical Corp.(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 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, with a vPEP† (D R Burton Healthcare LLC, Farmville, NC) device, might influence medication delivery. **Methods:** An AEROECLIPSE® II BAN (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® device. The mass of albuterol recovered from each filter was quantified by an HPLC-UV spectrophotometric assay. **Results:** Using the BAN mean delivered mass as the reference, the output only decreased by 4.9% with the Aerobika® OPEP in tandem, but fell substantially further by 67.6% when the vPEP† was substituted (un-paired t-test, $p < 0.001$). **Conclusions:** Pairing the BAN with the vPEP† device greatly impaired the output of medication. Clinicians should be aware not to substitute alternative OPEP devices for the Aerobika® when seeking to take advantage of concomitant therapy.

COMBINING INHALATION BY A BREATH-ACTUATED NEBULIZER (BAN) 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, Trudell Medical International (TMI)] with OPEP (Aerobika®, TMI), both therapies can be delivered concurrently. We investigated if the BAN output is affected by use with the Aerobika® 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-aerosol (3×3 replicates/device) operated by compressed air at 50 psig. The BAN 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 and induction port, and (b) substituting the acapella† duet OPEP device. The BAN was run to sputter, and the therapeutically beneficial fine particle mass <5.4 mm diameter (FMipr) determined. **Results:** FMipr (mean ± SD) via the BAN alone, with the BAN-Aerobika®, and the BAN-acapella† duet OPEP devices were 452 ± 28, 426 ± 27 and 308 ± 23 mg respectively. The BAN-Aerobika® combination marginally reduced delivery (paired t-test, $p = 0.043$), whereas the BAN-acapella† duet configuration resulted in substantial losses ($p < 0.001$). **Conclusion:** An AEROECLIPSE® II BAN-Aerobika® OPEP combination offers combined aerosol/OPEP therapy with minimal medication loss. Substitution with the acapella† duet OPEP results in substantial reduction in BAN-output that may have adverse clinical implications.

COMBINING INHALATION BY A BREATH-ACTUATED NEBULIZER (BAN) 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 hand-held oscillating positive expiratory pressure (OPEP) therapy device (Aerobika®, Trudell Medical International (TMI), London, Canada) has been developed that can be used in conjunction with the AEROECLIPSE® II breath actuated nebulizer (BAN, 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 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 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® 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®, Trudell Medical International, London, Canada) has recently been developed to provide patients undergoing secretion management the opportunity to receive therapy using a hand-held device (6). If the Aerobika® 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 breath actuated nebulizer (BAN) 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 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 Deliver from the AEROECLIPSE® II BAN with and without Aerobika® OPEP Therapy Device

Formulation	API	Aerobika® OPEP present	TEM (µg API)	$FPF_{<5.4\mu m}$ (%)	$FPF_{<5.4\mu m}$ (µg API)
Ventolin† Nebule†	salbutamol sulphate	NO	1288 ± 79	78.0 ± 1.2	1004 ± 70
		YES	1258 ± 60	82.8 ± 1.2	1042 ± 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 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® 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-based therapy will be established by individual clinical experience. In this context, it is important to note that the Aerobika® 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 with negligible impact on the performance of the latter, it may be tempting to combine the BAN 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 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 broncho-constriction and inflammation. **References:** 1 Rubin, B.K. Emerging therapies for cystic fibrosis lung disease. CHEST 1999;115:1120-1126. 2 Prasad, S.A. and Main, E. Finding evidence to support airway clearance techniques in cystic fibrosis. Disability and Rehabilitation 1998,20(6-7):235-246. 3 O'Donnell AE. Bronchiectasis. CHEST 2008;134:815–823. 4 McCool, F.D and Rosen, M.J. ACCP Evidence-based clinical practice guidelines: Nonpharmacologic airway clearance therapies. CHEST 2006;129:250S-259S. 5 Myers, T.R. Positive expiratory pressure and oscillatory positive expiratory pressure therapies. Respiratory Care 2007;52(10):1308-1327. 6 Schmidt, J., Nagel, M., Schneider, H., Avvakoumova, V., Doyle C., Wang, V., Ali, R., Meyer, A., Kopala, R. and Mitchell, J.P. 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. In: Respiratory Drug Delivery-Europe 2013, Eds., R.N. Dalby, P.R. Byron, J. Peart, J.D.Suman, D. Traini and P.M. Young, Davis Healthcare International Publishing LLC, RiverGrove, Illinois, USA, 2013, pp. 369-372. 7 Svenningsen, S., Jobse, B.N., Hasany, A., Kanhere, N., Kirby, M., Suggett, J., McCormack, D.G. and Parraga, G. Hyperpolarized 3He magnetic resonance imaging following oscillatory positive expiratory pressure treatment in GOLD stage II & III COPD. American Journal of Respiratory and Critical Care Medicine 013;187:A4116 (abstract). 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 (BAN) 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 BAN. **Study Objective:** To determine the effect of imposing an oscillating positive expiratory pressure device (Aerobika® OPEP, Trudell Medical International (TMI), London, Ontario) between the mouthpiece of a breath actuated jet nebulizer (AEROECLIPSE*® II BAN, 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 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 and inlet to the impactor. The BAN 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 alone and for the BAN-OPEP combination were 1288 ± 79 µg and 1258 ± 60 µg respectively. Corresponding values of the therapeutically beneficial FM_{alb} were 1004 ± 70 µg and 1042 ± 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 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 broncho-constriction [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 hand-held oscillatory positive expiratory pressure device (Aerobika® OPEP, Trudell Medical International (TMI), London, Canada) has been developed that can be connected directly to the AEROECLIPSE® II Breath-Actuated Nebulizer (BAN, TMI), so that the patient can receive both treatments concurrently. **BAN-OPEP System:** The Aerobika® OPEP device can also be used with any continuous nebulizer. We report the outcome of in vitro measurements of BAN 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 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 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 alone performed at the Robarts Research Institute, London, 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 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 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 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 in order to examine what might happen if a clinician was to make this substitution. The BAN 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 alone, for the BAN-Aerobika®, and for the BAN-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 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-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 is only marginally reduced by combining the BAN 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 Gonzalez P, Sara Cuccurullo C, Jafri I, Luciano L. Pulmonary/Cardiac/Cancer Rehabilitation. In Physical Medicine and Rehabilitation Board Review. Edited by Cuccurullo S. Demos Medical Publishing, NY, USA: 2004:643-712. 2 Nowobilski R, Włoch T, Płaszewski M, Szczeklik A. Efficacy of physical therapy methods in airway clearance in patients with chronic obstructive pulmonary disease: A critical review. Polskie Archiwum Medycyny Wewnetrznej 2010,120(11):468-478. 3 West K, Wallen M, Follett J. Acapella† vs. PEP mask therapy: a randomised trial in children with cystic fibrosis during respiratory exacerbation. Physiotherapy Theory and

Practice. 2010, 26(3):143-149. 4 International Physiotherapy Group for Cystic Fibrosis (IPG/CF). Physiotherapy for people with cystic fibrosis: From infant to adult. IPG/CF, 2009, available on-line at: http://www.cfww.org/docs/ipg-cf/bluebook/bluebooklet2009websiteversion.pdf , visited December 13th, 2012. 5 Kanhere N, Hasany A, Kirby M, Suggett J, McCormack D, Parrago G. Hyperpolarized 3He magnetic resonance imaging following oscillatory positive expiratory pressure treatment in GOLD stage II and III COPD. Submitted to the American Thoracic Society Annual Meeting, 2013.

COMBINING INHALATION BY A BREATH ACTUATED NEBULIZER (BAN) 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 BAN (AEROECLIPSE® II, Trudell Medical International (TMI), London Canada) with OPEP (Aerobika®, 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 is unaffected by the OPEP addition, and to compare this condition with the BAN 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 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 was initially connected directly to the induction port via a leak-tight fitting, then the measurements were repeated with the Aerobika® device inserted between the BAN and induction port. Finally, measurements were made with the acapella† substituted for the Aerobika® device. The BAN 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 alone, for the BAN-Aerobika®, and for the BAN-acapella† were 1288 ± 79, 1258 ± 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 with the Aerobika® OPEP did not affect aerosol delivery (paired t-test, $p = 0.38$), whereas substitution by the acapella† device resulted in a significant loss of medication (un-paired t-test, $p < 0.001$). **Conclusions**: The delivery of medication from the AEROECLIPSE® II BAN is not significantly affected by combining the BAN with the Aerobika® OPEP device compared with the BAN 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.

Aerosolized Emissions

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. Published online: 05 Mar 2020. https://doi.org/10.1080/15459624.2020.1724297.

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 mid-sized hospital on either continuous or BAN-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) Nov 2016 – Mar 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) Nov 2017 – Dec 2017 for level 1 surgical procedure face mask for both staff and patients, the latter on continuous nebulizer therapy (as in (1)); (Group 3) Jan 2018 – March 2018 for level 1 surgical procedure face mask for both staff and patients, the latter on BAN-based therapy (AEROECLIPSE® II, Monaghan Medical, 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 BAN-based therapy resulted in a further improvement protecting caregivers. **Conclusions**: Implementation of BAN-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 BAN
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 Secondhand 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, it may also increase the risk of asthma-like symptoms and cause occupational asthma. The development and implementation of an occupational health and safety policy in respiratory therapy departments can minimize exposure to secondhand 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®). 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: Misty-Neb† 17.2 ± 0.4%, SideStream† 15.8 ± 2.8%, PARI LC† D 15.2 ± 4.2%, Circulaire† 8.7 ± 1.0%, and AEROECLIPSE® 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® 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® 51.0 ± 2.1%. Duration of nebulization was shortest with the Circulaire† and longest with the AEROECLIPSE® ($p < 0.05$ via 1-way analysis of variance). **Conclusions**: The nebulizers we tested differ significantly in overall drug disposition. The dosimetric AEROECLIPSE® 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. Presented at ERS Annual Congress, Berlin, Germany, 2001. .

We report a study of the delivery of 0.25% mg/ml budesonide suspension (Pulmicort†, Nebuamp† (2 x 2-ml), Astra-Zeneca, Canada) by two types of small volume nebulizer (SVN), simulating adult breathing conditions ((tidal volume = 600-ml, duty cycle = 1:2 (2-s 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® BANs (Trudell Medical International, London 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® SVN minimizes aerosol release to the environment during exhalation, which may cause adverse effects to both patient and health care provider.

Guidelines

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).

AEROECLIPSE® BAN Equivalence to AEROECLIPSE® II BAN

TRANSFER FROM THE MALVERN MASTERSIZER-X TO MALVERN SPRAYTEC LASER DIFFRACTOMETERS: EXPERIENCE WITH TWO BREATH-ACTUATED NEBULIZERS (BAN).

Mitchell JP, Wiersema KJ, Doyle CC, Nagel MW, Kippax P and Krarup H. Presented at Respiratory Drug Delivery, Boca Raton, FL, 2006.

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, Trudell Medical International, London, Ontario, 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® BANs (*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.

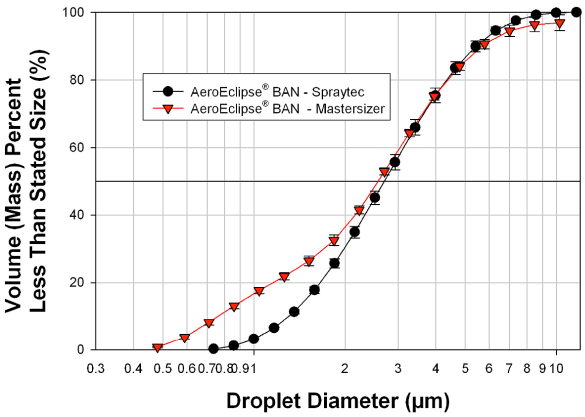


Figure 1. LD-measured size distributions from the AEROECLIPSE® BAN.

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 COMPARISON

In the second part of the study we compared saline droplet size distributions from the original AEROECLIPSE® BAN with those produced by a second generation BAN (AEROECLIPSE® II) 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 (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.

These measurements were made with only one solution (saline), and further work with other solution formulations is therefore merited.

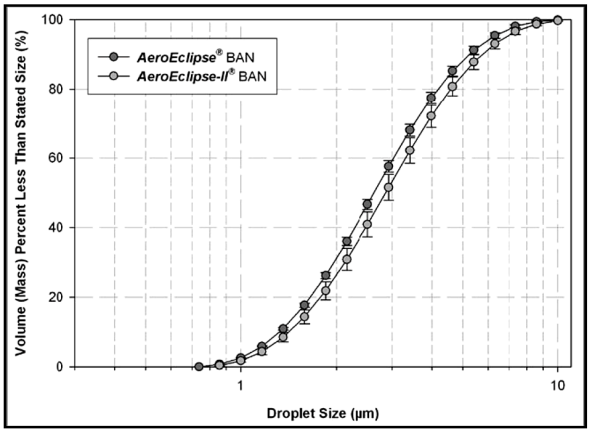


Figure 2. Spraytec LD-measured size distributions for BANs.

ARE FIRST AND SECOND GENERATION, MECHANICALLY-OPERATED BREATH-ACTUATED NEBULIZERS (BAN) COMPARABLE BASED ON IN-VITRO PERFORMANCE?

Schmidt J, Pevler J, Doyle C, Wiersema K, Nagel M, Mitchell J. Presented at Respiratory Drug Delivery, Boca Raton, FL, 2006.

Introduction: The original AEROECLIPSE® nebulizer (Monaghan Medical Corp., Plattsburgh, NY) introduced a few years ago was the first mechanically-operated BAN 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 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 BAN was evaluated with a 3 mL fill, corresponding to a single unit dose ampule (0.83 mg/mL albuterol sulfate) in widespread use within the US (1). Previously published data for the original BAN (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 nebulizers (*n*=3 replicates/device) using a piston-driven breathing simulator (Compas†, 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<4.8 µm) was also determined by laser

diffractometry (Mastersizer-X, Malvern Instruments plc, 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<4.8 µm). 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 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 was achieved throughout the 10 min. delivery period **(Figure 1)**.

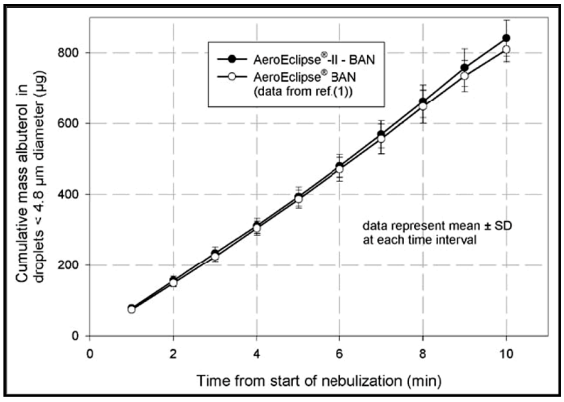


Figure 1. Comparative delivery of albuterol solution (0.83 mg/mL) \with 3-mL fill in reservoir.

Mean FDF<4.8 µm 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 by the time that audible sputtering occurred was 842 ± 50 µg compared with 810 ± 34 µg for the original BAN. In the case of the measurements made with the 1 mL fill (2.5 mg/mL albuterol), the new BAN 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. In contrast, only 67 ± 10 µg of albuterol was obtained as fine droplets from the LC PLUS† (mean FDF<4.8 µm 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 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.

General Information

THE NEBULISER SUB-TEAM OF THE EUROPEAN PHARMACEUTICAL AEROSOL GROUP (EPAG).

E Berg, J Mitchell, J Dennis, C Kreher, J Jauernig, P Lamb, M Karlsson, K Nikander, M Tservistas. Drug Delivery to the Lungs 2007;1:71-74.

Summary: The EPAG Nebuliser sub-team was formed just over 2 years ago to address four specific needs concerning the development of a new monograph 2.9.44: “Preparations for Nebulisation” in the European Pharmacopeia. These objectives were:

1. Establish the need for cooling the Next Generation Pharmaceutical Impactor (NGI) recommended as the apparatus of choice for the assessment of aerodynamic droplet size distribution;
2. Establish the need to coat the collection cup surfaces of the NGI with a viscous agent to mitigate possible bias arising from droplet bounce;
3. Develop a position statement on the possible choice of paediatric breathing patterns for the assessment of active substance delivery rate and total active substance delivered;
4. Develop a position statement on the role of laser diffraction to augment cascade impaction in the aerodynamic assessment of Nebuliser aerosols.

A progress statement on the work of the sub-team was delivered at Drug Delivery to the Lungs-17 last year. Since then, the sub-team has completed each of the objectives and presented its recommendations to the Inhalanda Committee responsible for the development of the monograph. These suggestions have been accepted and publications relating to each objective are in the process of being published or have already been published in peer-reviewed journals. The successful collaboration between the sub-team representatives from a mixture of nebuliser manufacturers, pharmaceutical companies and Swedish Medical Products Agency illustrates one process by which EPAG is providing expert guidance in the development of better standards and pharmacopeial monographs for the community involved with aerosol-based inhalation therapy.

Introduction: The EPAG Nebuliser sub-team was formed just over 2 years ago to address four specific needs concerning the development of a new monograph 2.9.44: "Preparations for Nebulisation" in the European Pharmacopeia [1]. This presentation updates the progress statement that was provided at Drug Delivery to the Lungs-17 last year [2].

Sub-team Composition: Members: Jolyon Mitchell (Sub-team chair, Trudell Medical International, Canada), Elna Berg (AstraZeneca†, Lund, Sweden), John Dennis (University of Calgary, Canada), Jüergen Jauernig (Novartis†, Switzerland), Christophe Kreher (Boehringer Ingelheim†, Germany), Mona Karlsson (MAP, Sweden), Paul Lamb (Teva†, UK), Kurt Nikander (Respironics†, US), Steve Nichols (Sanofi† Aventis, UK), Markus Tservistas (PARI Pharma, Germany) and David Wyatt (GSK†, UK) Statisticians: Dennis Sandell (Siegfried Pharma Development, Germany) and Aziz Ali (AstraZeneca†, Charnwood, UK).

Objectives: Definition and Purpose

1. **Establish the need for cooling the Next Generation Pharmaceutical Impactor (NGI) recommended as the apparatus of choice for the assessment of aerodynamic droplet size distribution.** The Next Generation Pharmaceutical Impactor (NGI) is likely to become the accepted measurement device for quantifying the aerodynamic size distribution of nebuliser-produced aerosols, particularly when operated at 15 L/min [3] in accordance with EN-13544-1:2001 [4]. However, it has been reported in the context of the Andersen 8-stage impactor (ACI) that heat transfer from the impactor to the aerosol droplets being measured can bias their measurements to finer sizes [5]. The NGI is larger and has greater mass than the ACI, and transit times within the NGI impactor body for droplets of a given size are likely to be longer. Hence, the NGI may be more susceptible to this phenomenon. This effect appears also to be dependent upon the nebuliser type, being most apparent with devices that do not entrain air as part of the nebulisation process. There are several potential solutions to the problem, in particular involving cooling of the impactor [6], or humidifying the droplet stream to close to saturation [7]. However, there is currently a lack of peer-reviewed experimental data that could be used to develop guidance on when the various techniques are applicable and with which types of nebuliser. The Inhalanda committee therefore concluded that work is urgently needed to establish the most practical configuration for the routine assessment of preparations for nebulisation in the context of defining a methodology for the proposed monograph.
2. **Establish the need to coat the collection cup surfaces of the NGI with a viscous agent to mitigate possible bias arising from droplet bounce.** The need to coat the collection cups of the NGI for nebuliser-based droplet size distribution measurements was also identified by the Inhalanda committee as an uncertain aspect of the methodology that is proposed in the proposed monograph. The sub-team was therefore tasked with investigating how this impactor responds with and without collection surface coating.
3. **Develop a position statement on the possible choice of paediatric breathing patterns for the assessment of active substance delivery rate and total active substance delivered.** Another area of controversy is the choice of breathing parameters for the laboratory-based assessment of aerosols from nebulisers that might be used with preparations that have specific indications for paediatric use. The performance of this class of inhaler can be critically dependent upon breathing pattern. At present there is a lack of authoritative guidance on appropriate breathing parameters (i.e. tidal volume, duty cycle, respiratory rate) that can be used in laboratory-based measurements as surrogates for neonates, infants and small children. The sub-team was tasked with examining the clinical and laboratory testing literature to establish evidence-based breathing patterns that could be included in the monograph as options that augment the existing adult-based pattern in the context of assessing active substance delivery rate and total active substance delivered.
4. **Develop a position statement on the role of laser diffraction to augment cascade impaction in the aerodynamic assessment of Nebuliser aerosols.** It was recognized by the Inhalanda committee that the appropriate use of optical methods, in particular laser diffractometry, would be a significant advantage to industry in the context of routine nebuliser droplet size testing for drug product quality control purposes. At present, laser diffractometers are widely used for the assessment of aqueous droplet aerosols, and the technique has received limited recognition as a measurement tool in the regulatory literature, provided that it is supported by measurements using cascade impaction, where active substance traceability is achieved. The sub-team has sought to achieve an understanding of the evidence to support laser diffractometry as the alternative method of choice to cascade impaction for solution-based products. It is well known that for solution formulations, the mass of active substance is directly associated with droplet size. In principle, laser diffractometry should be capable of providing a close approximation to the aerodynamic mass-weighted size distribution

of the active substance in aqueous solution because volume-weighted size distributions are derived from the raw angular light scattering data.

Experimental Studies:
Objective 1: A multi-centre experimental study was performed in which droplet size distributions from three nebuliser types (Aeroneb† Go – vibrating mesh, MistyMax† – continuous jet, and PARI LC PLUS† – air entrainment jet) were evaluated using a common formulation (salbutamol sulfate solution) with the NGI operated at 15L/min. Each laboratory initially undertook aerosol size determinations with the impactor at room ambient temperature and also with the impactor cooled in a refrigerator (set to 5°C for not less than 90 minutes.) before the measurements were made. Three nebulisers in each group were evaluated by every participant. **Results**: Analysis of individual and composite results all showed a similar trend that an NGI at ambient temperature yielded a significantly finer nebulised aerosol than that obtained by the cooled NGI. Mass median aerodynamic diameter (MMAD), taken as the primary metric, was reduced by between 9.5% and 21.9%, depending upon participant. Correspondingly, the Fine Droplet Fraction (<5 µm) increased by between 5.5% and 17.4% for all the nebuliser designs studied, when comparing ambient to cooled NGI data. Despite the more laborious procedure of cooling the impactor, variability in data was generally similar to that obtained with the NGI at ambient. An additional and unexpected finding was the presence of accumulated deposits of dried residues comprising mainly sodium chloride on the interior passageways and surfaces of the impactor, if cleaning was not undertaken on a regular basis. The NGI, including the inter-stage passageways, should be fully cleaned in view of the greater risk of corrosion caused by the interaction between ionic solutes and water either present as deposited droplets or formed by vapour condensation associated with cooling the impactor.
Objective 2: A two-centre experimental study was performed in which two types of device (SideStream† and PARI LC PLUS†, representing a relatively low output conventional jet nebuliser and a higher output air entrainment jet nebulizer respectively) were tested again using a common formulation (salbutamol sulfate solution). Droplet size distributions of the generated aerosols were measured with the NGI operated at 15L/min at room ambient conditions, with each laboratory undertaking two series of measurements with (a) coated and (b) un-coated collection cups. A thin layer of high viscosity (12,500 centi-Stokes) silicone grease was applied to the collection cups for the measurements where a coating was present. Three nebulisers of each type were evaluated in duplicate. Results: The mass percentages of droplets contained in droplets < 3.0 µm and < 5.0 µm aerodynamic diameter, used as metrics to assess if significant shifts in measured droplet size distributions occurred, were generally equivalent with or without coating. Data for one of the laboratories with the PARI LC PLUS† nebulisers failed to meet the criteria for statistical equivalence, however, closer inspection of the data revealed the cause to be the greater inter-nebuliser variability for these particular measurements rather than a trend that might have been associated with increased droplet bounce when uncoated cups were used. From theoretical considerations [8], liquid droplet bounce is unlikely because impaction is likely to be inelastic. Furthermore, in previously reviewed work with cascade impactors [9], and also in recently published data pertaining specifically to the NGI [6], there is no indication of biased stage deposition associated with systematic shifts in measured size distributions when uncoated surfaces were used to size nebuliser-generated liquid droplets.

Position Statements:
Objective 3: The treatment of infants and small children with nebuliser-based therapy is commonplace. However, the breathing pattern proposed for the draft monograph is that of an adult at rest. A literature survey was undertaken to establish the evidence base in support of recommendations for three breathing patterns that would be applicable to a neonate, a 12-month old infant, and a child approximately 4 years of age. The resulting position statement was developed with input from clinical experts, and provides assistance to those involved with the evaluation of preparations for paediatric use in the choice of more appropriate breathing patterns for the assessment of active substance delivery rate and total active substance delivered.
Objective 4: The position paper that has recently been published [10] is a concise summary of key aspects relating to both cascade impaction and laser diffractometry as applied to the measurement of nebuliser-generated droplets. Justification for the choice of 15L/min for the NGI is provided in the context of the flow rate ex nebuliser chosen in the European Standard for nebuliser systems [4]. The non-invasive nature and rapidity of measurements are identified as distinct advantages associated with laser diffractometry. However, this technique is not active substance-specific, and therefore inapplicable for the assessment of preparations that are suspensions rather than true solutions. Careful set-up is also needed to avoid bias arising either from the instrument itself (choice of model to interpret the light scattering data as well as input values such as droplet refractive index), or from external causes, most notably evaporation with aqueous droplets.

Recommendations: The following specific recommendations to the Inhalanda committee arose as a result of the work of the sub-team.

Objective 1:

1. Pre-cool the assembled NGI and induction port in a refrigerator (set at about +5°C) for not less than 90 minutes and start the determination within about 5 minutes of removal of the impactor from the refrigerator. Other methods, which maintain the impactor at a constant temperature below room ambient (e.g. use of a cooling cabinet) can also be employed when validated.
2. After each measurement, all visible surfaces exposed to the droplets should be dried using compressed air, and at the end of each day the seal body should be separated from the lid of the impactor so that all surfaces exposed to the droplets can be thoroughly cleaned with water, rinsed with ethanol and dried.

Objective 2:

1. NGI collection cups do not require coating for nebuliser aerosol assessments with an agent to create a viscous/tacky surface in order to mitigate possible droplet bounce and re-entrainment.

Objective 3:

1. Although a multitude of different paediatric breathing patterns have been reported, those recommended in the monograph for neonate, infant and child age categories should be harmonised with those in a Canadian Standard for spacers and holding chambers used with pressurized metered dose inhalers [11]. These patterns are similar to those of Stocks and Hislop [12], and based on normal anatomical development without the presence of obstructive disease.

Objective 4:

1. Laser Diffractometry is a suitable alternative to cascade impaction for preparations that are solutions. However, this technique should be validated back to the cascade impactor method that is regarded as the reference procedure, given its capabilities for both traceable assay of drug substance and measurement of aerodynamic size.

Current Status: The sub-team has completed each objective identified in its work plan and presented its recommendations last June to the Inhalanda Committee responsible for the development of the monograph. These suggestions have been accepted and publications relating to each objective are in the process of being published or have already been published. The successful collaboration between the sub-team members, comprising representation from a mixture of nebuliser manufacturers and pharmaceutical companies and also including a member from the Swedish Medical Products Agency, illustrates one process by which EPAG is providing expert guidance in the development of better standards and pharmacopeial monographs for the community involved with aerosol-based inhalation therapy. **References**: 1 Preparations for nebulisation: Characterization, monograph 2.9.44. Pharmeuropa 2006;18(2):280-2. 2 Dennis, J., Berg, E., Sandell, D., Krejer, C., Karlsson, M., Lamb, P., Jauernig, J., Nichols, S., Tservistas, M. and Mitchell, J. 2006. European Pharmaceutical Aerosol Group (EPAG) Nebuliser Sub-Team: Assessment of proposed European Pharmacopeial (Ph. Eur.) monograph 'Preparations for Nebulisation'. Drug Delivery to the Lungs 17, The Aerosol Society, Edinburgh, UK:146-149. 3 Marple, V.A., Olson, B.A., Santhanakrishnan, K. et al. 2004. Next generation pharmaceutical impactor: a new impactor for pharmaceutical inhaler testing. Part III. Extension of archival calibration to 15 L/min. J Aerosol Med. 17(4):335–43. 4 Comité Européen de Normalisation (CEN). 2001. Respiratory therapy equipment. Part 1: Nebulizing systems and their components. Ref: prEN 13544-1, 33-38. 5 Stapleton, K.W. and Finlay, W.H. 1999. Undersizing of droplets from a vented nebuliser caused by aerosol heating during transit through an Andersen impactor. J. Aerosol Sci. 30(1):105-109. 6 Berg, E., Svensson, J.O. and Asking, L. 2007. Determination of nebulizer droplet size distribution: A method based on impactor refrigeration. J. Aerosol Med. 20(2):97-103. 7 Jauernig, J., Ohl, S.,Knoch, and Keller, M. 2004. Effects of the test set-up, formulation, and nebulizer type on aerodynamic droplet characteristics. In R.N. Dalby, P.R. Byron, J. Peart, and S.J. Farr, eds. Respiratory Drug Delivery IX, Vol. III, Davis Horwood International Publishing Ltd, Raleigh, NC, 609-12. 8 Podczeck, F. 1997. Optimization of the operation conditions of an Andersen cascade impactor and the relationship to centrifugal adhesion measurements to aid in the development of dry powder inhalations. Int. J. Pharm. 149:51-61. 9 Mitchell, J.P. and Nagel, M.W. 2003. Cascade Impactors for the size characterization of aerosols from medical inhalers: Their use and limitations. J. Aerosol Med. 16(4):341-77. 10 Mitchell, J.P and Tservistas, M. 2006. Laser diffractometry and cascade impaction for nebulizer product characterization. Pharmeuropa Scientific Notes. 2:49-52. 11 Canadian Standards Association. 2002. Spacers and holding chambers for use with metered-dose inhalers. Mississauga, Ontario, Canada. CAN/CSA/Z264.1-02. 12 Stocks, J and Hislop, A.A. 2002. Structure and function of the human respiratory system. In: H Bisgaard, O'Callaghan C, Smaldone GC Eds. Drug Delivery to the Lung. New York. Marcel Dekker Inc. 47-104.

EUROPEAN PHARMACEUTICAL AEROSOL GROUP (EPAG) NEBULIZER SUB-TEAM: ASSESSMENT OF PROPOSED EUROPEAN PHARMACOPEIAL (PH. EUR.) MONOGRAPH 'PREPARATIONS FOR NEBULIZATION.

E Berg, J Dennis, J Jauernig, M Karlsson, C Kreher, P Lamb, JP Mitchell, S Nichols, D Sandell, M Tservistas. Presented at Drug Delivery to the Lungs, 2006.

Summary: The EPAG Nebulizer Sub-Team was formed to develop industry best practices for the evaluation of nebulizer systems. Its primary objective is to support the development of a new monograph for the European Pharmacopeia concerned with the characterization of preparations for nebulization. Specific tasks are: (1) to establish when it is appropriate to chill the Next Generation Pharmaceutical Impactor (NGI) to avoid bias due to heat-transfer related evaporation; (2) to validate the use of uncoated collection cups for the NGI; (3) to produce a position statement concerning the appropriate use of cascade impaction and laser diffractometry for nebulizer characterization; (4) to establish appropriate breathing patterns for nebulizer mass output testing by breathing simulator. The sub-team is also assisting EPAG develop expert commentary in relation to the development of a proposed international standard (ISO 27427) that will focus on establishing the performance of nebulizing systems during their design verification.

Introduction: Jet and ultrasonic nebulizers continue to be widely used modalities for inhaled aerosol therapy, with new designs such as vibrating mesh and membrane systems being marketed [1], despite the widespread availability of pressurized metered dose inhalers (pMDIs) and dry powder inhalers (DPIs). This is largely because they can be used to deliver almost all therapeutic classes of drugs to the respiratory tract whether the patient is ambulatory or on mechanical ventilation [2]. Nebulizers are typically manufactured for use with a variety of drug products often from different pharmaceutical companies, depending upon the judgment of the prescribing clinician. This contrasts with the situation for pMDIs and DPIs, where the device and drug product are directly linked, and are almost always the responsibility of the pharmaceutical company manufacturing the drug product. As a result, the regulation of nebulizers has traditionally taken place through the devices part of the various agencies, following processes that are separate from those used to regulate the drug products with which they are used. In a departure from this practice, nebulizers are now being included with the other classes of portable inhaler in a joint Health Canada-EMEA regulatory guidance on Pharmaceutical Quality of Inhalation and Nasal Products [3, 4].

In terms of nebulizers as drug delivery devices, European-wide guidelines were developed about 5 years ago that established setting uniform standards for their use [5], with performance testing undertaken in accordance with a regional (CEN) standard [6]. At the pharmacopeial compendia level, a monograph on the characterization of preparations for nebulization is in the process of being reviewed by the Inhalanda committee for possible inclusion in the European [7] and US [8] Pharmacopeias. Recognizing the need for harmonization between device- and drug product focused standards where practical, much of the proposed methodology in the draft monograph is based on the procedures described in the CEN standard [6]. However, the advent of the Next Generation Pharmaceutical Impactor (NGI) [9] took place after this standard had been issued. The ability of the NGI to operate at flow rates as low as 15 L/min [10], the flow rate adopted in the CEN standard as representative of adult inhalation, has made it possible to propose this impactor as an apparatus that is suitable for droplet aerodynamic size characterization in the monograph.

The Nebulizer Sub-Team of EPAG was formed in 2005 to reappraise methods that are used for in vitro characterization of nebulizers in the context of the above developments. This was deemed both timely and necessary in view of the increased attention being paid to these devices by both the compendia and regulatory agencies, coupled with the development of new types of devices, including breath-actuated and adaptive aerosol delivery-based systems. For instance, methods that are based on constant flow rate sampling are unable to assess properly the function of nebulizers that are either breath-enhanced or breath-actuated. As a further example, optical methods for droplet size characterization, in particular laser diffractometry, are rapid and therefore potentially useful as a tool for assessing quality control of drug product used with a nebulizer. However, without appropriate precautions, such methods are inappropriate for nebulizer designs that allow inherent evaporation of nebulized aerosol, which includes all constant output nebulizers. They are also particularly unsuitable for suspension-based formulations where droplets may include no active drug particles or may contain more than one such particle per droplet. This limitation is not always evident in industry guidance and standards documentation.

Specific Work Being Undertaken Currently by the Nebulizer Sub Team: The sub team started work by addressing four specific work packages that each relate to the proposed pharmacopeial monograph.

1. Assessment of the Need to Chill the NGI to Prevent Heat-Transfer-Related Evaporation

In the late 1990s, Finlay and Stapleton reported that the effect of heat transfer from the impactor to the aerosol droplets being measured can be to bias measurements to finer sizes, when working with the Andersen 8-stage impactor (ACI) [11].

The NGI has significantly greater mass than the ACI, and may therefore be more susceptible to this phenomenon. Attempts to cool the impactor to the temperature of the nebulizer-produced aerosol by immersion in a water bath, though feasible, are awkward and time consuming to perform [12]. Chilling the impactor to a temperature close to +5ºC has therefore been proposed as a simpler alternative to water immersion [13]. Although, operating the impactor with air close to saturation is also a practical alternative to minimize evaporative changes [14, 15], there is the risk of condensational growth of droplets and the complication of testing nebulizers in laboratory conditions that do not simulate actual clinical use. Evaporative effects appear also to be dependent upon the nebulizer type, being most apparent with devices that do not entrain air as part of the nebulization process [16]. In summary, there is currently a lack of peer-reviewed experimental data that could be used to develop guidance on when the various techniques are applicable and with which types of nebulizer.

The sub-team has organized a series of experiments to evaluate the effect on NGI-measured droplet size distributions using a cooled impactor (5ºC) compared with impactor operated at room ambient temperature (20ºC). Included in this experimental are three nebulizer types that represent different categories in terms of droplet formation. These are the MistyMax† (Cardinal Health, USA), which is a conventional non air entrainment jet nebulizer, the LC-Plus† (PARI GmbH, Germany), which is an air entrainment jet nebulizer, and the AeroNeb† (Nektar Therapeutics USA), representing newer vibrating mesh/membrane systems. This latter nebulizer is non-air entrainment in design.

Measurements are being made with a generic salbutamol solution formulation, and up to six laboratories are collaborating so that both inter- and intra-nebulizer variability can be assessed. Although data are currently undergoing statistical analysis, preliminary findings are that chilling the NGI may be necessary in determining aerosol size distributions for some nebulizer systems.

2. Assessment of the Need to Coat the Collection Cup Surfaces of the NGI to Mitigate Droplet Bounce

It is well known that impactors are vulnerable to particle bounce and blow-off, biasing particle size distribution data to finer sizes. Various methods have been proposed to mitigate the effect; including coating the collection surfaces with grease or using non-volatile agents that create a tacky surface [17]. Liquid droplet bounce is unlikely but not proven. A study to confirm that coating is not needed was therefore included in the work of the sub-team. This is a two centre experimental evaluation of the behavior of aerosols of a generic salbutamol generated by two different jet nebulizers (Sidestream† (Respironics Ltd., UK) representing a relatively low output conventional device, LC-plus† (PARI GmbH, Germany), representing a higher output air entrainment nebulizer). Coating has been undertaken with a thin layer of silicone oil. Although the data are currently undergoing evaluation, initial indications are that coating NGI collection cups is unnecessary, irrespective of nebulizer type, for the collection of aerosol droplets.

3. The Choice of Appropriate Breathing Patterns for Nebulizer Testing

The breathing pattern (tidal volume = 500 mL, inspiratory/expiratory ratio 1:1 (sinusoidal), rate = 15 breaths/min) currently specified in the draft monograph for the determination of active substance delivery rate and total active substance delivered is the same as that adopted in the CEN standard [6], which is based on a normal adult at rest. This pattern was adopted in the CEN standard because it is simple to simulate and reproduce within a test laboratory [18], and the group developing the monograph felt it highly desirable to retain harmonization, given the desirability to have comparable tests for both nebulizers as delivery devices and for the drug products that may be used with them. However, formulations have been marketed that are specifically targeted at infants and young children, whose breathing patterns are very different to those of adults [19]. The sub-team is therefore in the process of developing an evidence-based position statement that will recommend appropriate breathing conditions for these classes of patient. In addition, they are examining the feasibility of capturing exhaled medication during nebulizer operation on a breathing simulator with a view to quantifying mass recovery of active substance, where this is feasible. Such a test might also be indicative of fugitive droplet emission from nebulizers, which is a concern in some countries, post the SARS outbreaks that occurred in 2003-4.

4. The Application of Laser Diffractometry and Cascade Impaction to Nebulizer Testing

The appropriate use of optical methods, in particular low angle laser light scattering (laser diffractometry), would be a significant advantage to industry in the context of routine droplet size testing that involves nebulizer-generated aerosols for drug product quality control purposes [20]. It is well known that the drug product is directly associated with droplet size with solution formulations, so that laser diffractometry should provide a close approximation to the aerodynamic size distribution of the drug product itself [21]. At present, laser diffractometers are used for nebulizer-generated aerosol

characterization [22, 23], and the technique has also received limited recognition as a measurement tool in the regulatory literature, provided that it is supported by measurements using cascade impaction, where drug substance traceability is achieved [3, 4]. The sub-team is therefore developing an evidence-based position statement that addresses points to consider for the use of laser diffractometry as an adjunct to support cascade impaction for droplet size distribution measurement where appropriately validated.

5. The Sub-Team as a Source of Expertise on Nebulizer-Related Issues

In addition to the specific tasks already described, the sub-team which is comprised of individuals with experience in both formulation and device aspects is tasked to provide on-going expert comment as needed to help develop an EPAG position in relation to future regulatory, compendial and national/international standards that relate to nebulizers. In this context, the imminent development of a new international standard for nebulizing systems (ISO 27427) through committee ISO-TC121/SC2 is providing the opportunity to develop a consensus input into the process at the public comment stages via participating national standards bodies of countries which have EPAG members.

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