*AEROECLIPSE**

Breath Actuated Nebulizer

Study Summary

FOREWORD

Trudell Medical International designs, develops and manufactures innovative aerosol drug delivery devices for human and animal 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**** Peak Flow Meter and ***AeroCount**** Dose Indicators. 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. **Equivalence of the *AeroEclipse**** **BAN to the *AeroEclipse**** **II BAN**
   In vitro studies showing the equivalence of the original ***AeroEclipse**** BAN device and 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. **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 2015, and will be updated again no later than June 2017.

*AeroEclipse** II BAN - Study Summary

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*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). JP Mitchell, KJ Wiersema, CC Doyle, MW Nagel, P Kippax and H Krarup. 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.

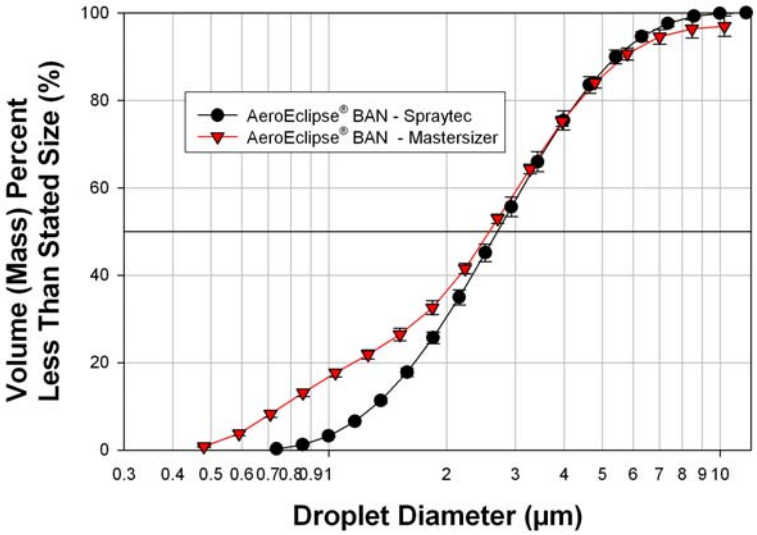

Figure 1. LD-measured size distributions from the AeroEclipse* BAN.

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.

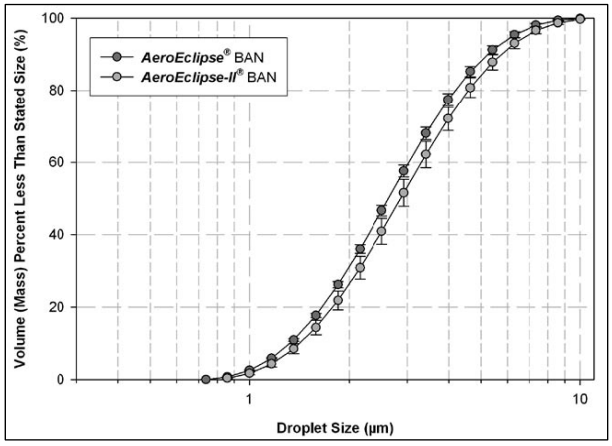

Figure 2. Spraytec LD-measured size distributions for BANs.

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

ARE FIRST AND SECOND GENERATION, MECHANICALLY-OPERATED BREATH-ACTUATED NEBULIZERS (BAN) COMPARABLE BASED ON *IN-VITRO* PERFORMANCE? J Schmidt, J Pevler, C Doyle, K Wiersema, M Nagel, J Mitchell. 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 ampoule (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 ($FDF_{<4.8\ \mu m}$) 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 ($FDF_{<4.8\ \mu m}$). 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).

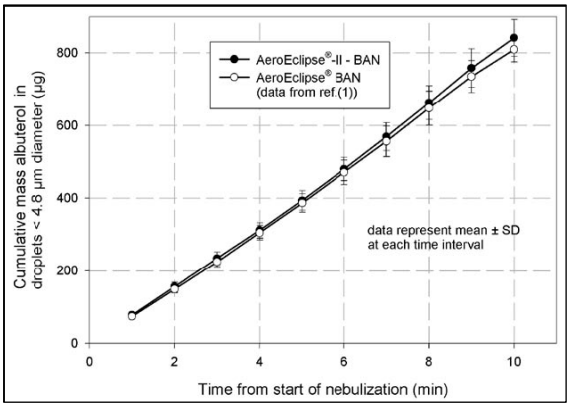

Figure 1. Comparative delivery of albuterol solution (0.83 mg/mL) with 3-mL fill in reservoir.

Mean $FDF_{<4.8\ \mu m}$ 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 $FDF_{<4.8\ \mu m}$ 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.

Summary by Active Pharmaceutical Ingredient

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

A PROSPECTIVE, COMPARATIVE TRIAL OF STANDARD AND BREATH-ACTUATED NEBULIZER: EFFICACY, SAFETY, AND SATISFACTION. V Arunthari, RS Bruinsma, AS Lee, MM Johnson. 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. JM Haynes. 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. TL Canares, C Tucker, A Garro. 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. MO Titus, M Eady, L King, CM Bowman. Clin Pediatr (Phila) 2012;51(12):1150-4.

The breath-actuated nebulizer (BAN) is a new respiratory device to deliver short-acting β-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. JM Haynes. 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. K Sabato, P Ward, W Hawk, V Gildengorin, J Asselin. 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. J Wilson. 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. JA Rose, S Cancelliere, P Matye, S Nair and M O'Riordan. 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. J Malpass, MW Nagel, C Doyle, R Ali, V Avvakoumova and JP Mitchell. 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 (V_t=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 $FDF_{<4.7\ \mu m}$ was determined by laser diffractometry in parallel experiments. **Results:** $FDF_{<4.7\ \mu m}$ was 87.1 ± 0.5% (mean ± SD). Fine droplet mass ($FDM_{<4.7\ \mu m}$) was linear with elapsed time, and almost independent of volume fill within the range studied at 102.9 ± 7.5 µg/min. **Conclusion:** The BAN provides predictable $FDM_{<4.7\ \mu m}$ based on volume fill and time, thereby assisting the clinician with dose titration.

STAFF AND PATIENT SATISFACTION WITH A BREATH ACTUATED NEBULIZER PERFORMANCE IMPROVEMENT. J Emberger, J Brown, L Killian and V Maheshwari – 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. J Emberger, J Brown, L Killian and V Maheshwari. 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. CJH Bong, M Eady, CM Bowman and MO Titus. 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. DP Coppolo, JP Mitchell, RS Ali, HA Mackay and MW Nagel. 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.** D Coppolo, J Mitchell, V Avvakoumova and M Nagel. 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 ($FDF_{<4.7\mu m}$) was determined by laser diffractometry (n=3 replicates with 1 device). Total fine droplet delivery ($FDM_{<4.7\mu m}$) was calculated as the product of TEM and $FDF_{<4.7\mu m}$. **Results**: $FDF_{<4.7\ \mu m}$ (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 $FDM_{<4.7\ \mu m}$ (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. **Disclosures**: The authors are employees of Trudell Medical Group, manufacturer of the AeroEclipse***** II BAN.

NEBULIZER-BASED AEROSOL DELIVERY IN CONJUCTION WITH CONTINUOUS POSITIVE EXPIRATORY PRESSURE (CPEP) USING A NOVEL BRONCHIAL HYGIENE DEVICE. MJ Hewitt, DP Coppolo, JP Mitchell and MW Nagel. 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. DP Coppolo, JP Mitchell, KJ Wiersema, CC Doyle and MW Nagel. 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. L Simmons and K Thigpen. 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. DP Coppolo, MW Nagel, CC Doyle, VA Avvakoumova and JP Mitchell. 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. DP Coppolo, JP Mitchell, KJ Wiersema CC Doyle and MW Nagel. 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:** M McPeck, R Tandon, K Hughes and GC Smaldone. *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. K Sabato, P Ward, W Hawk. 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. JL Rau, A Ari, RD Restrepo. 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. JP Mitchell, KJ Wiersema, CC Doyle, MW Nagel. 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 (T_{med}) 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
T_{med} (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, $p < 0.05$). T_{med} 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. MW Nagel and JP Mitchell. 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. RS Pikarsky, R Acevedo, C Roman, W Fascia, T Farrell. Resp Care 2002;47(9):1075.

Purpose: $Beta_2$-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 FEV1 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 FEV1 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 FEV1 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 FEV1	% 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 FEV1 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. RS Pikarsky, RA Acevedo and C Roman. CHEST 2002;122(4):146S.

Purpose: in order to meet our patient care demands, Crouse Hospital approved an automatic conversion from Racemic Albuterol to Levalbuterol. This study compares the breakthrough rates of Racemic Albuterol and Levalbuterol, with and without Ipratropium. **Methods:** Racemic Albuterol (Alb) 2.5 mg Q4h was converted to either Levalbuterol (Lev) 0.63 mg Q6h or Levalbuterol 1.25 mg Q8h. If ordered, Ipratropium (Ipra) 0.5 mg was administered at the same frequency as the Levalbuterol. Patients with acute coronary syndromes, need for cardiac monitoring, or requiring more frequent aerosol administration received the lower Levalbuterol dose Q6h. A majority of aerosol therapy was provided with the use of the AeroEclipse* 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	Breakthrough	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. S Klopf, C Schramm. 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"). RS Pikarsky, T Farrell, R Acevedo, W Fascia, C Roman. CHEST 2001;120(4):218S.

Purpose: Aerosol delivery consumes the highest level of Respiratory Care resources. This study evaluated the delivery time, efficacy, and safety of rapidly nebulized Albuterol with the use of the AeroEclipse* 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 FEV1. A standardized subjective questionnaire to determine side effects was completed.

Nebulizer (n)	Dose	% Change FEV1	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 FEV1 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 FEV1 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. YM Christensen, CJ Flanigan, SA Ravenscraft. 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, FEV1, FEV1% 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, FEV1 and FEF 25-75% for patients using the BAN were substantially higher while FEV1% 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
FEV1	7.3	13.1	FEV1	79.8
FEV1%ratio	3.0	2.3	FEV1%	-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, FEV1 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. D Geller, B Kesser. 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 Sizing	MMD	3.87	4.80	2.47	8.46
	GSD	2.3	2.0	2.1	2.0
	% < 5 μm	61.7%	52.9%	83.6%	30.0%
2.5 mg Unit Dose†	Duration (minutes)	14.7	7.2	7.0	3.6
	Inspired Dose (mg)	0.77	0.37	0.14	0.30
	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 (1 ml) Dose	Duration (minutes)	3.8	2.0	2.0	2.0
	Inspired Dose (mg)	0.97	0.06	0.11	0.28
	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 (2 ml) Dose	Duration (minutes)	11.0	3.2	3.7	3.7
	Inspired Dose (mg)	3.9	1.2	0.8	1.9
	Residual Dose (mg)	5.8	8.7	8.6	6.9
	Fine Particle Dose (mg)	2.40	0.60	0.60	0.60

† Unit-dose 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:
  - 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
  - Lowest residual dose
  - Higher fine particle fraction except for Circulaire®
- **Nebulizer Inefficiencies:**
  - AeroTee™ and Circulaire® had high residual doses in part due to valves and collection bags
  - Salter HDN™ produces larger particles
  - These inefficiencies were partially compensated for by increasing nominal dose to 10 mg (2 ml)
- **Duration of Nebulization:**
  - AeroEclipse* BAN had longer delivery time because it is breath actuated; no waste during exhalation
  - 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:**
  - 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:**
  - The FPD with the Hudson and unit-dose drug was 0.14 mg, similar to the reservoir-type nebulizers with unit-dose
  - 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. RS Pikarsky, T Farrell, R Acevedo, W Fascia, C Roman. 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 FEV1. A standardized subjective questionnaire to determine side effects was completed. **Results:** The table shows the albuterol dosages, mean % change of FEV1 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 FEV1 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. DE Geller, B Kesser. 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). S Klopf, N Scneiderman, H Payne, C Schramm, MW Nagel, JP Mitchell. 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. JP Mitchell, MW Nagel, A Archer, DP Coppolo. 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. D Hess, JP Mitchell, D Coppolo, MW Nagel, AD Archer, R Blacker. 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, T_I 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. A Archer, JP Mitchell, MW Nagel, AMW Verdun. 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. R Blacker, RW Morton, JP Mitchell, MW Nagel, DR Hess. 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. R Blacker, JP Mitchell, MW Nagel, AMW Verdun. 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. R Blacker, JP Mitchell, MW Nagel and AMW Verdun. 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. DE Geller, KC Kesser, HM Janssens, HAWM Tiddens. 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. MW Nagel, KJ Wiersema, SL Bates and JP Mitchell. 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. 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 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 6.0µm). For the three breathing patterns IM averaged (mean ±SD), 11.1±0.74%, 22.9±2.74%, and 36.3±1.22% respectively. These values exceed by 35% those previously reported for the most efficient devices (J. Aerosol Med. 1998, 11:113-125). MMAD averaged 3.55±0.07µm, GSD 2.55 FPF 0.72. When corrected for FPF, pulmonary delivery is estimated to be 60% higher than that reported for conventional and air-entrained nebulization.

THE DELIVERY OF BUDESONIDE SUSPENSION VIA SMALL VOLUME NEBULIZERS: A COMPARATIVE *IN-VITRO* ASSESSMENT. JP Mitchell, MW Nagel, AD Archer. 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. JP Mitchell, MW Nagel, AD Archer. 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. V Arunthari, RS Bruinsma, AS Lee, MM Johnson. 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. JM Haynes. 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. VArunthari, RS Bruinsma, AS Lee, MM Johnson. 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. JM Haynes. 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. RS Pikarsky, RA Acevedo, T Farrell, R Bear, W Fascia. 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	Breakthrough	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. 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. MW Nagel, KJ Wiersema, SL Bates and JP Mitchell. 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). S Klopf, N Scneiderman, H Payne, C Schramm, MW Nagel, JP Mitchell. 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.

Ipratropium Bromide (Atrovent™, Boehringer Ingelheim™)

REDUCING TOTAL COSTS OF AEROSOLIZED MEDICATION DELIVERY USING THE AEROECLIPSE II BREATH ACTUATED NEBULIZER. J Wilson. 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. JP Mitchell, MW Nagel, NR MacIntyre. 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. JP Mitchell, MW Nagel, NR MacIntyre and R Sharpe. 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. A Archer, JP Mitchell, MW Nagel, AMW Verdun. 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. JP Mitchell, MW Nagel, A Archer, D Coppolo. 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. A Archer, JP Mitchell, MW Nagel, AMW Verdun. 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

PROVOCATIVE DOSE OF METHACHOLINE CAUSING A 20% DROP IN FEV_1 SHOULD BE USED TO INTERPRET METHACHOLINE CHALLENGE TESTS WITH MODERN NEBULIZERS. SD Dell, SS Bola, RG Foty, LC Marshall, KA Nelligan, AL Coates. 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 PD_{20} 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. AL Coates, K Leung, SD Dell. 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). AL Coates, K Leung, S Dell. 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. SS Bola, R Foty, L Marshall, K Nelligan, AL Coates, S Dell. 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 PD_{20} more accurately accounts for this cumulative effect. Our results also validate the use of the Aero for MCT.

AN *IN VITRO* STUDY TO INVESTIGATE THE USE OF A BREATH-ACTUATED, SMALL-VOLUME, PNEUMATIC NEBULIZER FOR THE DELIVERY OF METHACHOLINE CHLORIDE BRONCHOPROVOCATION AGENT. JP Mitchell, MW Nagel, SL Bates, CC Doyle. 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 (r^2 = 0.9999) with MC concentration, within the range studied. FDM also showed a linear correlation (r^2 = 0.999) with the number of breathing cycles. For instance, with the 15.70 mg/mL solution, FDM was 654 ± 29 μg with 5 breathing cycles, 1,228 ± 92 μg with 10 breathing cycles, and 1,876

± 132 µg with 15 breathing cycles. **Conclusions:** Although the bronchoprovocation test procedure had to be slightly modified from the guidelines to accommodate the operation of the AeroEclipse*'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. S Sangwan, F Hull, R Condos and GC Smaldone. 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)

AEROSOLIZED LIPOSOMAL AMPHOTERICIN B: A POTENTIAL PROPHYLAXIS OF INVASIVE PULMONARY ASPERGILLOSIS IN IMMUNOCOMPROMISED PATIENTS. H Kamalaporn, K Leung, M Nagel, S Kittanakom, B Calvieri, RA Reithmeier, AL Coates. 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.** BD Alexander, TP Winkler, S Shi, ES Dodds Ashley, AJ Hickey. 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. S Husain, B Capitano, T Corcoran, SM Studer, M Crespo, B Johnson, JM Pilewski, K Shutt, DL Pakstis, S Zhang, ME Carey, DL Paterson, KR McCurry and R Venkataramanan. 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. ES Dodds, NA Petry, JD Davies, DW Zaas, SM Palmer, SW Shipes, RH Drew, BD Alexander, RE Coleman and JR Perfect. 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. NR MacIntyre, JP Mitchell, MW Nagel and DP Coppolo. 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. JP Mitchell, MW Nagel and NR MacIntyre. 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). J Malpass, JP Mitchell and MW Nagel. 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-γ1B

IMMUNOMODULATION WITH RECOMBINANT INTERFERON-γ1B IN PULMONARY TUBERCULOSIS. R Dawson, R Condos, D Tse, ML Huie, S Ress, CH Tseng, C Brauns, M Weiden, Y Hoshino, E Bateman and WN Rom. PLoS ONE 2009;4(9):e6984.

> **Background:** Current treatment regimens for pulmonary tuberculosis require at least 6 months of therapy. Immune adjuvant therapy with recombinant interferon-γ1b (rIFN-γb) may reduce pulmonary inflammation and reduce the period of infectivity by promoting earlier sputum clearance. **Methodology/Principal Findings:** We performed a randomized, controlled clinical trial of directly observed therapy (DOTS) versus DOTS supplemented with nebulized or subcutaneously administered rIFN-γ1b over 4 months to 89 patients with cavitary pulmonary tuberculosis. Bronchoalveolar lavage (BAL) and blood were sampled at 0 and 4 months. There was a significant decline in levels of inflammatory cytokines IL-1β, IL-6, IL-8, and IL-10 in 24-hour BAL supernatants only in the nebulized rIFN-γ1b group from baseline to week 16. Both rIFN-γ1b groups showed significant 3-fold increases in CD4+ lymphocyte response to PPD at 4 weeks. There was a significant ($p = 0.03$) difference in the rate of clearance of Mtb from the sputum smear at 4 weeks for the nebulized rIFN-γ1b adjuvant group compared to DOTS or DOTS with subcutaneous rIFN-γ1b. In addition, there was significant reduction in the prevalence of fever, wheeze, and night sweats at 4 weeks among patients receiving rFN-γ1b versus DOTS alone. **Conclusion:** Recombinant interferon-γ1b adjuvant therapy plus DOTS in cavitary pulmonary tuberculosis can reduce inflammatory cytokines at the site of disease, improve clearance of 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. R Condos, ML Huie, R Dawson, S Ress, C Brauns, CH Tseng, M Weiden, E Bateman and RN Rom. 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.JP Mitchell and MW Nagel. 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. AM Verdun, JP Mitchell and MW Nagel. 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. JP Mitchell and MW Nagel. 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. AM Verdun, JP Mitchell and MW Nagel. 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. RS Pikarsky, RA Acevedo, T Farrell, W Fascia and R Bear. 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		
	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

LEVALBUTEROL 1 ML (0.42 MG) Q8H DOSING USING THE AEROECLIPSE* BREATH-ACTUATED NEBULIZER IN A COPD INPATIENT POPULATION. RS Pikarsky, RA Acevedo, T Farrell, W Fascia. 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. RS Pikarsky, R Acevedo, C Roman, W Fascia, T Farrell. Resp Care 2002;47(9) 1075.

Purpose: $Beta_2$-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 FEV1 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 FEV1 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 FEV1 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 FEV1	% 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 FEV1 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. RS Pikarsky, RA Acevedo, C Roman and T Farrell. 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	Breakthrough	Rate/1000	Tx/Pt/day	Rate/100 Pt/day	
Alb Q4h	898	61	67.93	6	40.76**	25.80*
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. MA Lewis, SS Harris, SL Campbell, AL Hodges, DM Clark. 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. JR Miner, C Kletti, M Herold, D Hubbard, MH Biros. 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. R Brull, V Chan. 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 SpO_2<90% for >20 sec). No patient received opioid antagonists or ventilatory support. Nausea (11% vs. 3%) and vomiting (31% vs. 21%) were more common with AeroLEF™ than with placebo. Following the first dose of study drug, more patients given AeroLEF™ reported mild or no pain (59% vs. 27%; P< 0.01). Time to effective pain relief after the first dose of study drug was shorter with AeroLEF™ group (P< 0.005). More patients given AeroLEF™ reported moderate-to-complete pain relief (60% vs. 32%, P< 0.02). This study suggests that patient-controlled inhalational analgesia with free and liposome encapsulated fentanyl can provide safe and effective pain relief following orthopedic surgery. Industry support provided by YM Biosciences Inc.

AEROSOLIZED LIPOSOME-ENCAPSULATED FENTANYL (AeroLEF™) VIA PULMONARY ADMINISTRATION ALLOWS PATIENTS WITH MODERATE TO SEVERE POST-SURGICAL ACUTE PAIN TO SELF-TITRAATE TO EFFECTIVE ANALGESIA. A Clark, M Rossiter-Rooney, F Valle-Leutri. 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. O Hung, D Pliura. 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, FEV1 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. RS Pikarsky, RA Acevedo, T Farrell, W Fascia, R Bear. 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

AEROSOL DELIVERY OF DNA/LIPOSOMES TO THE LUNG FOR CYSTIC FIBROSIS GENE THERAPY. LA Davies, GA Nunez-Alonso, G McLachlan, SC Hyde, DR Gill. 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±0.1 μm). Importantly, biological function of pDNA/GL67A formulations was retained after nebulization, and although aerosol delivery rate was lower than that of other devices (0.17±0.01 ml/min), the breath-actuated AeroEclipse II 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. MDI Manunta, RJ McAnulty, AD Tagalakis, SE Bottoms, F Campbell, HC Hailes, AB Tabor, GJ Laurent, C O'Callaghan, SL Hart. 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. JS Sahota, CM Smith, P Radhakrishnan, C Winstanley, M Goderdzishvili, N Chanishvili, A Kadioglu, C O'Callaghan, MR Clokie. 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.

Comparison of *AeroEclipse** II BAN to Valved Holding Chamber with Metered Dose Inhaler (MDI)

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

Purpose: Aerosol delivery consumes the highest level of Respiratory Care resources. This study evaluated the delivery time, efficacy, and safety of rapidly nebulized Albuterol with the use of the AeroEclipse* 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 FEV1. 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 FEV1 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 FEV1 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. J Mitchell, D Coppolo, C Doyle, MW Nagel, KJ Wiersema. 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. DP Coppolo, CC Doyle, JP Mitchell, MW Nagel, KJ Wiersema. 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.

General Information

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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