Studies Using the Medicator®

Peer-Reviewed Articles:

1. Chatburn, Robert. L. and McPeck, Michael. "A New System for Understanding Nebulizer Performance." *Respiratory Care* 2007. 52.8: 1037-1050.

Abstract: We have developed a conceptual and mathematical model for nebulizer performance that attempts to provide a unifying theoretical framework for subsequent in vitro studies. Specifically, we have created a lexicon and a way to describe the effects of a standardized breathing pattern for evaluating small-volume jet nebulizers. This model should help researchers communicate more clearly and study planners to design experiments whose data may be more comparable and thus amenable to meta-analysis.

"A slightly more sophisticated approach is to use valves to separate inspiratory from expiratory flow… Another example is the Healthline Medicator, which has a valve and an elastic reservoir bag. With this device the physical reservoir (bag) is the both the aerosol and flow reservoir" (1038).

2. Corcoran TE, Shortall BP, Kim IK, Meza MP and Chigier N. "Aerosol Drug Delivery Using Heliox and Nebulizer Reservoirs: Results from an MRI-Based Pediatric Model". *Journal of Aerosol Medicine* 2003. 16: 263-271.

Abstract: An MRI-based model of the mouth, throat, and upper airways of a 5-year-old boy is used to evaluate methods for increasing the nebulized drug dose delivered to the lungs. Four methods are considered: (1) standard nebulizer delivery with air, (2) delivery with 70/30 helium- oxygen (heliox), (3) delivery with air and an aerosol-conserving reservoir, and (4) delivery with heliox and a reservoir. When comparing air and heliox, delivery flow rates were adjusted so that the aerosols produced were of similar size. The reservoir utilized was the Medicator Aerosol Maximizer (Healthline Medical, Baldwin Park, CA). It conserves the aerosol generated by the nebulizer during exhalation and makes it available for the next inhalation. Technetium-DTPA was utilized. The standard nebulizer driven by air delivered 2.2% of the dose loaded into the nebulizer to the lungs as fine droplets, versus 3.3% for the nebulizer with heliox (50% increase; *p* 5 0.002 vs. air), 2.9% for the nebulizer plus reservoir driven by air (32% increase; *p* 5 0.02 vs. no reservoir), and 4.0% for the nebulizer plus reservoir driven by heliox (82% increase; *p* 5 0.002 vs. air without reservoir). The increased pulmonary dose when heliox was utilized occurred because of decreased deposition within the nebulizer and other delivery equipment. The increased pulmonary dose when the reservoirs were utilized occurred due to a decrease in the dose expelled from the nebulizer by exhalation.

"The use of a nebulizer reservoir with air produced a 31.8% increase in the fine droplet dose delivered to the lungs. This increased delivery was the result of conserving drug dose that would have otherwise been lost to the atmosphere between breaths or expelled by exhalation. The amount of aerosol conserved and then delivered using the reservoir was in excess of the dose lost within the device itself. All reservoirs must be evaluated on an individual basis in this regard. The Medicator device demonstrated low levels of internal deposition (8.1 ± 1.7% of the loaded dose when driven with air and 4.3 ± 0.5% with heliox)" (269).

"The additional dose per breath provided by these devices would potentially increase the effectiveness of medications needed for quick administration (such as bronchodilators for asthma). The increase in deposition and decrease in exhalational losses also implies that they would allow for more efficient administration of expensive medications" (269).

3. Corcoran, T. E., Venkataramanan, R., Mihelc, K. M., Marcinkowski, A. L., Ou, J., McCook, B. M., Weber, L., Paterson, D. L., Pilewski, J. M., McCurry, K. R., and Husain, S. "Aerosol Deposition of Lipid Complex Amphotericin-B (Abelcet) in Lung Transplant Recipients". *American Journal of Transplantation* 2006. 6: 2765-2773.

Abstract: Lung transplant recipients exhibit a high incidence of invasive aspergillosis. The inhalation of lipid complex amphotericin-B (*Abelcet;* ABLC) offers a possible prophylactic strategy. The goals of this study were to select the optimal nebulizer delivery system for ABLC and to measure deposited aerosol dose in 12 lung transplant recipients. *In vitro* testing was performed to select a nebulizer delivery system, and an empirical model was used to estimate lung deposition. Estimated pulmonary doses varied by as much as 2-fold between different nebulizers. Aerosol deposition testing was performed in six single and six double lung recipients, each of whom received one 7 mL (35 mg) nebulized dose of Technetium-labeled ABLC using the selected nebulizer. In single lung recipients, the aver- age deposited doses were 3.9 ± 1.6 mg (mean ± S.D.) in the allograft versus 2.1 ± 1.1 mg in the native lung. Double lung recipients deposited on average 2.8 ± 0.8 mg (left lung) and 4.0 ± 1.3 mg (right lung). The drug was well distributed throughout the lungs, but delivery to the native lung was in some cases suboptimal. These studies provide an important precursor to studies of the efficacy of inhaled ABLC as a prophylaxis of invasive aspergillosis after lung transplant.

"Based on the model estimates, this system provided the best combination of high pulmonary dose (5.7mg; second highest after CIS-US AeroTech II with DeVilbliss Pulmoaide Compressor and Medicator Nebulizer Adjunct…" (2768).

4. Laube BL, Benedict GW and Dobs AS. "Time to Peak Insulin Level, Relative Bioavailability, and Effect of Site of Deposition of Nebulized Insulin in Patients with Noninsulin-Dependent Diabetes Mellitus". *Journal of Aerosol Medicine* 1998. 11: 153-173.

Abstract: Seven fasting patients with noninsulin-dependent diabetes mellitus (NIDDM) inhaled 1.0 U/kg of body weight of nebulized regular pork insulin by mouth or were subcutaneously (sc) injected with 0.1 U/kg of body weight of insulin in the upper arm on two different occasions. The time to peak insulin level was compared for the two treatment modalities. Insulin bioavailability after inhalation was quantified relative to sc injected insulin. Deposition of a radiolabeled insulin surrogate aerosol (insulin diluent) in the larger central airways versus the peripheral airways, expressed as the inner-to-outer (I:O) ratio, and in the lung apex versus the lung base, expressed as the apex-to-basal (A:B) ratio, was quantified with gamma scintigraphy. Ratios were related to glucose responses after inhalation of insulin. Times to peak insulin level were similar for the two methods of treatment, averaging 43 +/- 16 and 64 +/- 40 minutes after inhalation and sc injection of insulin, respectively. The bioavailability of inhaled insulin averaged 14.7% +/- 5.8% relative to sc injected insulin. This was significantly less than the average bioavailability of deposited drug (18.9% +/- 5.3%) relative to sc injected insulin ($P < 0.05$). I:O and A:B ratios for the surrogate aerosol averaged 1.3 +/- 0.4 and 0.7 +/- 0.2, respectively. Linear regression analysis revealed that the maximum percentage of decrease in glucose after insulin inhalation was significantly related to the A:B ratio such that percentage decrease in glucose was greater in patients who demonstrated a lower A:B ratio ($P = 0.003$). Percentage decrease in glucose was not related to the I:O ratio. These results indicate that the bioavailability of nebulized insulin inhaled by mouth is approximately 20% when calculated in terms of drug deposited and suggest that increasing the distribution of insulin aerosol to the base of the lung enhances the glucose response in patients with NIDDM during the fasting state.

"… We chose to deliver aerosol with the Medicator device for several reasons. First, it generated an aerosol that was comprised of small particles" (157).

"In addition to its capability of generating an aerosol comprised of small particles, we chose the Medicator device over other aerosol generators because it had the capability of delivering the entire dose in less than 5 minutes, thereby enhancing patient compliance" (158).

"Third, aerosol generated during the exhalation phase of breathing was captured in a reservoir bag and was not lost to the atmosphere during exhalation" (158).

5. Laube BL, Jashnani R, Dalby RN and Zeitlin PL. "Targeting Aerosol Deposition in Patients with Cystic Fibrosis: Effects of Alterations in Particle Size and Inspiratory Flow Rate". *Chest* 2000. 118: 1069-1076.

Abstract:
Study Objective: To determine if aerosolized medications can be targeted to deposit in the smaller, peripheral airways or the larger, central airways of adult cystic fibrosis (CF) patients by varying particle size and inspiratory flow rate.
Design: Randomized clinical trial.
Setting: Outpatient research laboratory.
Patients: Nine adult patients with CF.
Interventions: Patients inhaled an aerosol comprised of 3.68+/-0.04 microm saline solution droplets (two visits) or 1.01+/- 0.2 microm saline solution droplets (two visits) for 30 s, starting from functional residual capacity and breathing at a slow or faster inspiratory flow rate. On all visits, the saline solution was admixed with the radioisotope (99m)Tc. Immediately after inhalation, a gamma camera recorded the deposition pattern of the radioaerosol in the lungs. Deposition images were analyzed in terms of the inner:outer zone (I:O) ratio, a measure of deposition in an inner zone (large, central airways) vs. an outer zone (small airways and alveoli).
Measurements and Results: For the 3.68-microm aerosol, I:O ratios averaged 2.29+/-1.45 and 2.54+/-1.48 ($p>0.05$), indicating that aerosol distribution within the lungs was unchanged while breathing at 12+/-2 L/min vs. 31+/-5 L/min, respectively. For the 1.01-microm aerosol, I:O ratios averaged 2.09+/-0.96 and 3.19+/-1.95 ($p<0.05$), indicating that deposition was predominantly in the smaller airways while breathing at 18+/-5 L/min and in the larger airways while breathing at 38+/-8 L/min, respectively.
Conclusions: These results suggest that the targeted delivery of an aerosol to the smaller, peripheral airways or the larger, central airways of adult CF patients may be achieved by generating an aerosol comprised of approximately 1.0-microm particles and inspiring from functional residual capacity at approximately 18 L/min and approximately 38 L/min, respectively. *Study objective:* To determine if aerosolized medications can be targeted to deposit in the smaller, peripheral airways or the larger, central airways of adult cystic fibrosis (CF) patients by varying particle size and inspiratory flow rate.

"We chose to use these two nebulizer/compressor systems (Pari LC Plus and Healthline Medicator) because they produced aerosols with significantly different particle size characteristics ... These differences made it possible to compare the effect of targeting the airway with a fine-particle aerosol (Healthline Medicator) vs an aerosol with larger particles (Pari LC Plus)" (1070).

"The average MMAD for the Pari nebulizer (n=3) was 3.68 ± 0.04 microns. This MMAD was significantly larger than that of the Medicator nebulizer (n=4), which averaged 1.01 ± 0.2 micrometers ($p = 0.034$). These results indicate that 50% of the aerosol particles generated by the Pari nebulizer were <3.68 micrometers. For the Medicator nebulizer, 50% of the particles were <1.01 micrometers" (1072).

"Results from our study suggest that targeted delivery of aerosol to the larger, central airways vs the smaller, peripheral airways of adult CF patients may best be achieved by inhaling fine droplets (MMAD approximately 1.0 micrometers) at approximately 38 L/min and approximately 18 L/min peak inspiratory flow rates, respectively" (1074).

"The results from the present study suggest that it may be possible to target the delivery of aerosolized medications to the smaller peripheral airways or larger, central airways of adult patients with CF by generating aerosols comprised of fine particles…" (1076).

6. Rau, Joseph L. "The Inhalation of Drugs: Advantages and Problems". *Respiratory Care* 2005. 50.3:367-382.

Abstract: Inhalation is a very old method of drug delivery, and in the 20th century it became a mainstay of respiratory care, known as aerosol therapy. Use of inhaled epinephrine for relief of asthma was reported as early as 1929, in England. An early version of a dry powder inhaler (DPI) was the Aerohalor, used to administer penicillin dust to treat respiratory infections. In the 1950s, the Wright nebulizer was the

precursor of the modern hand-held jet-venturi nebulizer. In 1956, the first metered-dose inhaler (MDI) was approved for clinical use, followed by the SpinHaler DPI for cromolyn sodium in 1971. The scientific basis for aerosol therapy developed relatively late, following the 1974 Sugarloaf Conference on the scientific basis of respiratory therapy. Early data on the drug-delivery efficiency of the common aerosol delivery devices (MDI, DPI, and nebulizer) showed lung deposition of approximately 10–15% of the total, nominal dose. Despite problems with low lung deposition with all of the early devices, evidence accumulated that supported the advantages of the inhalation route over other drug-administration routes. Inhaled drugs are localized to the target organ, which generally allows for a lower dose than is necessary with systemic delivery (oral or injection), and thus fewer and less severe adverse effects. The 3 types of aerosol device (MDI, DPI, and nebulizer) can be clinically equivalent. It may be necessary to increase the number of MDI puffs to achieve results equivalent to the larger nominal dose from a nebulizer. Design and lungdeposition improvement of MDIs, DPIs, and nebulizers are exemplified by the new hydrofluoroalkane-propelled MDI formulation of beclomethasone, the metered-dose liquid-spray Respimat, and the DPI system of the Spiros. Differences among aerosol delivery devices create challenges to patient use and caregiver instruction. Potential improvements in aerosol delivery include better standardization of function and patient use, greater reliability, and reduction of drug loss.

“Theoretically, the most efficient nebulizer is a breath-actuated ‘dosimeter’ that generates aerosol and makes it available only during inspiration” (377).

”If a dosimetric nebulizer is defined as one that releases aerosol only during inhalation, the recently marketed Medicator models from Healthline Medical are dosimetric. The Medicator employs a reservoir bag, 1-way [valve], and can add an exhalation filter” (377).

White Papers:

7. McPeck, Michael. “Healthline Medical Aerosol Laboratory Testing of Hudson #1755 Iso-Neb for City of Hope Respiratory Care Department”. 19 August 2005.

Summary: The City of Hope RC department trialed the Healthline Model #AM-602 Medicator Aerosol Maximizer on August 18, 2005 to deliver pentamadine. The Medicator was loaded with the same amount of drug (300mg) with which City of Hope typically loads into the Hudson #1755 Iso-Neb aerosol device. This test compared the Medicator Aerosol Maximizer to the Hudson UpDraft II tee nebulizer and the Hudson #1755 Iso-Neb. The Hudson UpDraft II began sputtering around 6 minutes and stopped producing aerosol at 9 minutes, in which the Inhaled Mass was 12.1 percent. The Hudson #1755 Iso-Neb sputtered at 4.5 minutes and stopped producing aerosol by 9 minutes, resulting in an Inhaled Mass of about 12.1 percent. In contrast, the Medicator using a MistyMax 10 nebulizer sputtered around 2 minutes and stopped producing aerosol by 9 minutes, resulting in an Inhaled Mass of approximately 30 percent. The results of this test show that the Medicator Aerosol Maximizer is a much more efficient system of aerosol delivery.

8. McPeck, Michael. “Waste Not, Want Not: How the Medicator Maximizer® Aerosol Delivery Device Tackles an Old Problem”. FOCUS: Journal for Respiratory Care and Sleep Medicine, Winter 2005.

Summary: The Medicator® Aerosol Maximizer can be used for aerosol delivery of a variety of drugs, such as bronchiodialators, antimicrobials (e.g., tobramycin, pentamadine), morphone and fentanyl, and experimental drugs. The Medicator® includes an elastic reservoir bag and a unique valve to double the amount of aerosolized drug that is inhaled by the patient, while significantly reducing the amount of aerosol released into the atmosphere. This product stores the aerosol that is generated during the patient’s exhalation phase into the non-latex elastic reservoir bag, and releases it to the patient on the subsequent breath, with a slight boost from the elastic recoil of the expanded bag, along with the other aerosol that the nebulizer is generating. The implications of the Medicator’s® new approach to aerosol delivery are many: 1) simple, inexpensive nebulizers can be attached to the Medicator® Maximizer, which will approximately double delivery or halve the amount of time it takes to deliver an equivalent effective dose of medication, 2) delivery time can be shortened to about three minutes for routine bronchiodialator therapy and to about seven minutes for rescue therapy with bronchiodialators, 3) expensive concentrated

medications in unit dose ampoules can be avoided in favor of less expensive counterparts, 4) when drugs other than bronchiodialators (e.g., antimicrobials) it makes sense to use a system that can deliver as much of the drug as possible for maximum therapeutic value, and 5) the Medicator's® quasi-closed system resulting in consistent aerosol delivery at different times in the same patient, even when the breathing pattern has changed due to disease, anxiety or distress.

Conference Presentations and Abstracts:

9. Chatburn, Robert L. and Williams, Thomas, J. "Effect of Conserver Systems on Jet Nebulizer Performance". AARC Open Forum. *Respiratory Care* 2009.

Summary: The purpose of the study was to compare four different nebulizer configurations: 1) a standard continuous flow nebulizer with a simple flex tube reservoir, 2) a standard continuous flow nebulizer with a valve/bag conserver system (Healthline Medicator Plus), 3) a dosimetric nebulizer operated in a breath actuated mode, and 4) a dosimetric nebulizer operated in the continuous flow mode. Differences among the nebulizer configurations for system efficiency and component efficiencies (i.e., nebulizer, delivery and conserver efficiency) were tested. For the systems tested, the bag/valve conservers improve nebulizer performance compared to the standard flex tube.

10. McPeck, Michael, King, Russell, and Samford, Glenn. "Can Aerosol Drug Delivery in SVN be Predicted?" *Respiratory Care* 2003. 48.11: 1080.

Summary: Accurate predictions of inhaled mass (IMp) has been impractical because the efficiency of small-volume nebulizers (SVNs) and their delivery systems is generally low and drug delivery is variable and imprecise due to differences in patients' breathing patterns. The purpose of the study was to determine whether a high-efficiency aerosol system (Healthline Medicator® Aerosol Maximizer) that negated the effect of different breathing patterns would reduce the variability and permit application of a predictive formula. A formula that predicted Inhaled Mass for aerosolized albuterol using the Medicator® Plus Aerosol Maximizer was proposed. To test the validity of the proposed formula, six volunteer subjects received a "treatment" of radiolabeled unit-dose albuterol administered by the Medicator® Plus. Findings suggested that because the Medicator® stores the aerosol generated during exhalation for the subsequent inhalation in the reservoir bag, the effect of breathing pattern on aerosol delivery, increase System Efficiency fraction, and may make the application of this or other prediction formulas for Inhaled Mass possible.

11. McPeck, Michael, Potter, Ross, and Samford, Glenn. "Reservoir Bag in Medicator Aerosol Delivery System Does Not Contaminate the Nebulizer or the Patient". AARC Open Forum. Las Vegas, NV. December 8-11, 2003.

Summary: This study sought to examine whether any microbiologic contamination that may be present in the reservoir bag of the Healthline Medicator aerosol delivery system may be inhaled by the patient. The Medicator utilizes a reservoir bag, as well as a manifold, specifically designed so that aerosols and particulate matter exhaled by the patient are 1) channeled through a specific exhalation port to the atmosphere and 2) segregated from both the nebulizer and reservoir bag by a unidirectional diaphragm to ensure that the reservoir bag does not become contaminated. Testing of the manifold in preventing contamination of the reservoir bag utilized a radioactive tracer as a surrogate for microorganisms. Findings from this study showed that the radioactivity that was intentionally placed in the bags did not contaminate the nebulizer or the HEPA filter. The study concluded that even though it is likely for contamination to reach the reservoir bag in the first place, contamination of the reservoir bag will not result in contamination of the nebulizer or the patient.

12. McPeck, Michael, Samford, Glenn, Potter, and King, Russell. "Can a 'Holding Chamber' Improve Nebulizer Performance?" *Respiratory Care* 2004. 49.11: 1393.

Summary: Holding chambers are now commonly used to increase the aerosol delivery performance of metered-dose inhalers (MDIs). The Healthline Medicator® Aerosol Maximizer is claimed to act like a holding chamber for small-volume medication nebulizers (SVNs). The Inhaled Mass output of a variety of

typical Tee-style SVNs, and whether and how much the Medicator® can increase the aerosol delivery of those SVNs were tested using nine different models of plastic disposable jet SVNs. Results showed that the Medicator® Aerosol Maximizer increases the delivery of aerosol to the mouth by an average of 2.4 times that of conventional SVNs on Tee setups.

13. McPeck, Michael, Samford, Glenn, Potter, Ross, and Snitily, Timothy. "Is a Noseclip Necessary for Small Volume Nebulizer Treatments?" *Respiratory Care* 2003. 48.11: 1079.

Summary: Many patients do not use noseclips when receiving aerosol therapy via a small-volume nebulizer (SVN), so this study sought to investigate whether the use of noseclips improved aerosol delivery. Six subjects received aerosolized albuterol by mouth (HEPA filters placed at the mouthpiece) using the Healthline Medicator® Plus Aerosol Maximizer. The subjects did not use noseclips during the first treatment, but did use noseclips during the second treatment. After each treatment the filters were measured. Although aerosol delivery increased, the results were not statistically significant, possibly due to the small sample size. The use of noseclips may modestly increase aerosol delivery and may reduce variability, especially among occasional patients and predominately nose-breathers.

14. McPeck, Michael, Samford, Glenn, Potter, Ross, and King, Russell. "Mitigation of Occupational Exposure to Aerosolized Medication". *Respiratory Care* 2004. 49.11: 1390.

Summary: Although there is sparse data on occupational exposure to aerosolized medication, a link to occupational asthma in respiratory therapists has been suggested. Nine different plastic disposable nebulizers were tested to measure waste aerosol during exhalation during the breathing cycle. The waste aerosol for the nine nebulizers varied from 21.7 to 36.0% on the Tee set-up and 7.6 to 12.9% on the Medicator®. The Medicator®, with and without a filter, retained the aerosol generated by exhalation and inhaled during the subsequent breath, which significantly reduced waste aerosol.

15. McPeck, Michael, Potter Ross, and Samford, Glenn. "Validation of the Medicator® Plus 'Aerosol Maximizer': Comparison to a Commercial Reservoir-Type Delivery System and a Standard 'Tee' System". *Respiratory Care* 2003. 48.11: 1080.

Summary: This purpose of this study was to compare the Medicator® Plus to other commercially available aerosol delivery systems. The comparison showed that Inhaled Mass was 24.8%, 18%, and 14.6% for the Medicator®, "tee", and Circulaire, respectively. The Medicator®, used with the same nebulizer as the other two systems, delivered 2.1 times as much total albuterol as the Circulaire and 1.4 times as much as the "tee". Additionally, the Medicator® delivered 1.8 times as much albuterol in 6 minutes as the Circulaire and standard "tee".

16. McPeck, Michael. "An Improved Device and Patient Interface for Delivering Aerosolized Medications to Patients with Tracheotomies". AARC Open Forum. *Respiratory Care* 2005.

Summary: This study sought to answer the following questions: 1) How much aerosol is typically delivered via a Tee nebulizer connected to a trach collar? And 2) Does the Medicator® aerosol delivery system improve aerosol drug delivery with a direct connection to the trach tube? When connected directly to the trach tube with a special adapter, the Medicator® rendered 6.4 times greater albuterol delivery than with the same nebulizer on a Tee with a trach collar. This finding suggests that the Medicator® could be useful for improving and guaranteeing the efficacy of aerosol drug delivery to spontaneously breathing patients with artificial airways.

17. McPeck, Michael. "Room Air Entrainment Threshold of the Medicator Mobius". AARC Open Forum. *Respiratory Care* 2007.

Summary: This study asked the following question: Does the low-flow paradigm of the Mobius to room air entrainment (RAE) that would dilute the He portion of the HeO2 mixture to unacceptable levels? Testing conditions included tidal volumes (VT) of 200, 300, 400, and 500 mL with respiratory frequencies (f) of 10, 20, 25, 30, 35, 40, and 45 BPM resulting in minute volumes (Vmin) of 2.0 to 22.5 L/min.,

generated by a sine wave piston ventilator at I:E of 1:1. A 6 in. corrugated tube was used to connect the piston ventilator to the mask (patient) position on the patient tee. The Mobius was operated with an 80/20 HeO2 mixture powering 90mL capacity nebulizer at a flow of 8 L/min. Data from this study indicate that the threshold for clinically significant air entrainment with the Medicator Mobius is at a VT of 400 mL and a f of at least 30 BPM (Vmin=12 L/min.). The Medicator Mobius can be used in acute asthmatics with tidal volumes as high as 200-400 mL with no clinically significant RAE, even at breathing rates up to 30 BPM.

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