

# Respiratory CRO



**Inamed Literature Service – June 2010**

## Editorial



Dear clients, dear colleagues,

We are pleased to send you today another Literature Review, a literature service that Inamed Research has been providing since five years now. This service provides periodically a collection of current publications regarding testing of inhalers, pediatric clinical trials, active agents, aerosols, lung deposition, and inhalation therapy in patients with asthma and COPD as well as studies in patients with Cystic Fibrosis. Our aim is to facilitate your orientation in the increasing amount of relevant publications and their handling, thus being up to date with the state of research.

I hope that this literature service offers you a valuable overview and that it may be helpful for your further research.

Yours sincerely



Dr. Thomas Meyer, CSO

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## Inhaler and Other Inhalation Devices

H. Adi, P. M. Young, H. K. Chan, H. Agus and D. Traini. "Co-spray-dried mannitol-ciprofloxacin dry powder inhaler formulation for cystic fibrosis and chronic obstructive pulmonary disease." 2010 *Eur J Pharm Sci* 40(3):

The aim of this study was to assess the potential of delivering a combination therapy, containing mannitol (a sugar alcohol with osmotic characteristics), and ciprofloxacin hydrochloride (an antibacterial fluoroquinolone), as a dry powder inhaler (DPI) formulation for inhalation. Single and combination powders were produced by spray drying ciprofloxacin and mannitol, from aqueous solution, at different ratios and under controlled conditions, as to obtain similar particle size distributions. Each formulation was characterised using laser diffraction, scanning electron microscopy, differential scanning calorimetry, dynamic vapour sorption, X-ray powder diffraction, and colloidal force microscopy. The *in vitro* aerosol performance of each formulation was studied using an Aerolizer DPI device and a multi-stage liquid impinger (analysed using high performance liquid chromatography). In addition, a disk diffusion test was performed to assess the *in vitro* antimicrobial activity of each formulation and starting materials. All formulations had similar particle size distributions, however, the morphology, thermal properties and moisture sorption was dependent on the relative percentages of each component. In general, the combination formulation containing 50% (w/w) mannitol appeared to have the best aerosol performance, good stability and lowest particle cohesion (as measured by colloid probe microscopy). Furthermore, of the formulations tested, mannitol did not appear to alter the effectiveness of the ciprofloxacin antimicrobial activity to *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Streptococcus pyogenes*. The combination of co-spray-dried mannitol and ciprofloxacin from a DPI is an attractive approach to promote mucous clearance in the respiratory tract while simultaneously treating local chronic infection, such as chronic obstructive pulmonary disease and cystic fibrosis.

W. E. Berger, E. R. Bleecker, L. O'Dowd, C. J. Miller and W. Mezzanotte. "Efficacy and safety of budesonide/formoterol pressurized metered-dose inhaler: randomized controlled trial comparing once- and twice-daily dosing in patients with asthma." 2010 *Allergy Asthma Proc* 31(1):

Asthma guidelines recommend titrating maintenance medications to the lowest effective dose. This study assessed the efficacy and tolerability of reducing the frequency of dosing in patients previously controlled with twice-daily budesonide/formoterol (BUD/FM) pressurized metered-dose inhaler (pMDI) to once-daily regimens of BUD/FM pMDI or BUD pMDI. This was a 12-week, randomized, double-blind, double-dummy, placebo (PBO)/active-controlled, multicenter study (N = 752) of patients aged > or =16 years with mild to moderate asthma. After 4-5 weeks on single-blind BUD/FM pMDI 160/9 micrograms twice daily (320/18 micrograms daily), patients with stable asthma received BUD/FM pMDI 160/9 micrograms twice daily (320/18 micrograms daily; morning and evening), BUD/FM pMDI 320/9 micrograms once daily (evening), BUD/FM pMDI 160/9 micrograms once daily (evening), BUD pMDI 320 micrograms once daily (evening), or PBO. BUD/FM (once or twice daily) was more effective ( $p < \text{or} = 0.003$ ) than BUD and PBO on evening peak expiratory flow (primary variable), morning pulmonary function assessments, daily symptoms, and nighttime rescue medication use. Twice-daily BUD/FM was more effective ( $p < \text{or} = 0.05$ ) than both once-daily doses for evening pulmonary function assessments and daytime rescue medication use. All treatments were well tolerated. Once- or twice-daily BUD/FM showed better efficacy than BUD once daily or PBO; results generally were more favorable with twice-daily dosing compared with both once-daily dosing regimens, which had one-half the daily FM dose.

W. E. Berger, J. G. Leflein, D. E. Geller, B. Parasuraman, C. J. Miller, C. D. O'Brien and L. O'Dowd. "The safety and clinical benefit of budesonide/formoterol pressurized metered-dose inhaler versus budesonide alone in children." 2010 Allergy Asthma Proc 31(1):

Few studies have evaluated inhaled corticosteroid (ICS)/long-acting beta(2)-adrenergic agonist combination therapy in asthmatic children. This study was designed to evaluate the safety (primary) and clinical benefits (secondary) of budesonide/formoterol pressurized metered-dose inhaler (pMDI) versus budesonide dry powder inhaler (DPI) in children with persistent asthma. This was a 26-week, multicenter, randomized, open-label U.S. study of 187 children 6-11 years of age previously receiving ICS. After 1 week of usual ICS therapy, subjects received twice-daily budesonide/formoterol pMDI 160/4.5 micrograms x 2 inhalations (320/9 micrograms; n = 124) or budesonide DPI 200 micrograms x 2 inhalations (400 micrograms [320 micrograms delivered ex-mouthpiece]; n = 63). Budesonide/formoterol and budesonide were well tolerated with a similar incidence of adverse events (AEs) (84.6% and 85.7%, respectively), most of mild or moderate intensity. Treatment-related AE incidence was low (5.4%) and similar across groups (budesonide/formoterol, 4.9%; budesonide, 6.3%). No clinically important treatment differences were observed for 12-lead electrocardiograms, hematology, serum glucose and potassium, and 24-hour urinary cortisol. Compared with budesonide, budesonide/formoterol decreased health care use (urgent care visits and interference with daily activities [child] or work [caregiver];  $p < \text{or} = 0.012$ ) and improved health-related quality of life (Pediatric Asthma Quality of Life Questionnaire [standardized] and Pediatric Asthma Caregiver Quality of Life Questionnaire overall scores;  $p < \text{or} = 0.006$ ) and pulmonary function (predose forced expiratory volume in 1 second and forced expiratory flow during the middle half of exhalation;  $p < \text{or} = 0.007$ ). In this 26-week study of asthmatic children (6-11 years), safety profiles were similar and clinical benefits were greater with budesonide/formoterol than with budesonide.

W. E. Berger and M. J. Noonan. "Treatment of persistent asthma with Symbicort (budesonide/formoterol inhalation aerosol): an inhaled corticosteroid and long-acting beta2-adrenergic agonist in one pressurized metered-dose inhaler." 2010 J Asthma 47(4):

**OBJECTIVE:** Budesonide/formoterol inhalation aerosol (Symbicort AstraZeneca, Wilmington, Delaware) is an inhaled corticosteroid (ICS) and long-acting beta(2)-adrenergic agonist (LABA) combination administered twice daily via one hydrofluoroalkane pressurized metered-dose inhaler (pMDI) approved in the United States for the long-term maintenance treatment of persistent asthma in patients  $\geq 12$  years of age whose asthma cannot be controlled by an ICS alone. The objective was to review efficacy, safety, and pharmacogenetic data on budesonide/formoterol pMDI in the treatment of persistent asthma. **METHODS:** The authors searched PubMed and respiratory meeting databases to identify asthma studies of budesonide/formoterol pMDI. Studies involving traditional and patient-reported outcomes, safety, tolerability, or pharmacogenetics were included. **RESULTS:** In two 12-week pivotal trials in adolescents and adults, treatment with budesonide/formoterol pMDI 160/4.5 microg x 2 inhalations (320/9 microg) twice daily for moderate to severe persistent asthma or 80/4.5 microg x 2 inhalations (160/9 microg) twice daily for mild to moderate persistent asthma, demonstrated greater efficacy and similar tolerability compared with placebo and the same nominal dose of its monocomponents. Comparisons with formoterol dry powder inhaler (DPI) for predose forced expiratory volume in one second (FEV<sub>1</sub>) and with budesonide pMDI for 12-hour mean postdose FEV<sub>1</sub> demonstrated the anti-inflammatory and bronchodilatory contributions of budesonide and formoterol, respectively. Evaluations of patient-reported outcomes, including asthma-specific quality of life and treatment satisfaction, further supported the clinical benefits of budesonide/formoterol pMDI. In a 52-week tolerability study of patients aged  $\geq 12$  years, budesonide/formoterol pMDI was delivered at up to double the maximum dose (640/18 microg twice daily) and demonstrated a safety profile similar to that of budesonide (640 microg twice daily), with

no unexpected pattern of abnormalities. Additional studies reported that budesonide/formoterol pMDI 320/9 microg twice daily and fluticasone propionate/salmeterol DPI 250/50 microg twice daily have similar efficacy and tolerability, with significantly more patients achieving  $\geq 15\%$  improvement in FEV<sub>1</sub> within 15 minutes with budesonide/formoterol pMDI compared with fluticasone/salmeterol DPI. Moreover, inheritance of the Gly16Arg polymorphism of the beta(2)-adrenergic receptor does not appear to affect clinical outcomes with budesonide/formoterol pMDI. CONCLUSION: Budesonide/formoterol pMDI administered twice daily is effective and generally well tolerated in patients whose asthma is not well controlled on ICS alone.

V. Giraud and F. A. Allaert. "Improved asthma control with breath-actuated pressurized metered dose inhaler (pMDI): the SYSTER survey." 2009 Eur Rev Med Pharmacol Sci 13(5):

**BACKGROUND AND OBJECTIVES:** Poor inhalation technique may impact both asthma control and compliance in patients with asthma. The SYSTER survey is therefore aimed at assessing the influence of starting or switching an existing therapy to a breath-actuated pressurized metered dose inhaler (pMDI, Autohaler) on these parameters. **MATERIALS AND METHODS:** 709 French general practitioners (GP) enrolled 2588 asthmatic patients in whom therapy with the breath-actuated pMDI was either initiated, or a switch from an existing inhalation device to the said inhaler was deemed necessary. Asthma control was assessed at inclusion and after 4 weeks of treatment with the Juniper Asthma Control Questionnaire (ACQ). In addition, patient adherence was estimated according to the self-reported Morisky scale. **RESULTS:** 1510 patients (mean age 39 years, standard deviation 18 years; 53% male) completed follow-up after 4 weeks. The main reasons for inhaler change were poor asthma control (49%) and poor coordination (40%). After 4 weeks of therapy with the breath-actuated pMDI, asthma control significantly improved from 2.35  $\pm$  1.05 to 1.32  $\pm$  0.93 in the ACQ ( $p < 0.0001$ ). Also, self-reported patient adherence improved from 2.11  $\pm$  1.43 to 1.57  $\pm$  1.53 on the Morisky scale ( $p < 0.0001$ ). **DISCUSSION:** These results suggest that by focusing on the inhalation devices, asthma control and compliance with treatment are improved.

J. Haughney, D. Price, N. C. Barnes, J. C. Virchow, N. Roche and H. Chrystyn. "Choosing inhaler devices for people with asthma: Current knowledge and outstanding research needs." 2010 Respir Med:

Recommendations in asthma guidelines presuppose that practitioners have the evidence, information, knowledge, and tools to select inhaler devices appropriate for individual patients. Randomised controlled trials usually exclude patients with suboptimal inhaler technique. There is therefore little evidence on which to base inhaler selection in the real world, where patients often use their inhalers incorrectly. The lung deposition of inhaled drug varies according to inhaler device, drug particle size, inhalation technique, and pattern of inspiratory flow. Even with training, not all patients can use their inhalers correctly and maintain inhaler technique; patients may have inability to handle the inhaler, strong negative preferences, or natural breathing patterns that do not match their prescribed inhaler. Therefore, matching device to the patient may be a better course of action than increasing therapy or training and retraining a patient to use a specific inhaler device. Several research questions require answers to meet the goal of helping prescribers make a more informed choice of inhaler type. Is the level of drug deposition in the lungs a key determinant of clinical short- and long-term outcomes? What should be measured by a clinical tool designed to check inhaler technique and therefore help with device selection? If we have a tool to help in individualising inhaler choice, will we achieve better asthma outcomes? Do we have to refine inhaler device choice for each individual, or will we get better outcomes if we select our current best option in light of current knowledge and apply this on a population level?

R. Hodder and D. Price. "Patient preferences for inhaler devices in chronic obstructive pulmonary disease: experience with Respimat Soft Mist inhaler." 2009 Int J Chron Obstruct Pulmon Dis 4:

Current guidelines for the management of chronic obstructive pulmonary disease (COPD) recommend the regular use of inhaled bronchodilator therapy in order to relieve symptoms and prevent exacerbations. A variety of inhaler devices are currently available to COPD patients, and the choice of device is an important consideration because it can influence patients' adherence to treatment, and thus potentially affect the long-term outcome. The Respimat((R)) Soft Mist Inhaler (SMI) generates a slow-moving aerosol with a high fine particle fraction, resulting in deposition of a higher proportion of the dose in the lungs than pressurized metered-dose inhalers (pMDIs) or some dry powder inhalers (DPIs). We review clinical studies of inhaler satisfaction and preference comparing Respimat((R)) SMI against other inhalers in COPD patients. Using objective and validated patient satisfaction instruments, Respimat((R)) SMI was consistently shown to be well accepted by COPD patients, largely due to its inhalation and handling characteristics. In comparative studies with pMDIs, the patient total satisfaction score with Respimat((R)) SMI was statistically and clinically significantly higher than with the pMDI. In comparative studies with DPIs, the total satisfaction score was statistically significantly higher than for the Turbuhaler((R)) DPI, but only the performance domain of satisfaction was clinically significantly higher for Respimat((R)) SMI. Whether the observed higher levels of patient satisfaction reported with Respimat((R)) SMI might be expected to result in improved adherence to therapy and thus provide benefits consistent with those recently shown to be associated with sustained bronchodilator treatment in patients with COPD remains to be proven.

M. Kaashmiri, J. Shepard, B. Goodman, W. R. Lincourt, R. Trivedi, A. Ellsworth and A. M. Davis. "Repeat dosing of albuterol via metered-dose inhaler in infants with acute obstructive airway disease: a randomized controlled safety trial." 2010 Pediatr Emerg Care 26(3):

**BACKGROUND:** Airway obstruction and bronchial hyperactivity often times lead to emergency department visits in infants. Inhaled short-acting beta2-agonist bronchodilators have traditionally been dispensed to young children via nebulizers in the emergency department. Delivery of bronchodilators via metered-dose inhalers (MDIs) in conjunction with holding chambers (spacers) has been shown to be effective. **STUDY OBJECTIVE::** Safety and efficacy evaluations of albuterol sulfate hydrofluoroalkane (HFA) inhalation aerosol in children younger than 2 years with acute wheezing caused by obstructive airway disease. **METHODS:** A randomized, double-blind, parallel group, multicenter study of albuterol HFA 180 microg (n = 43) or 360 microg (n = 44) via an MDI with a valved holding chamber and face mask in an urgent-care setting. Assessments included adverse events, signs of adrenergic stimulation, electrocardiograms, and blood glucose and potassium levels. Efficacy parameters included additional albuterol use and Modified Tal Asthma Symptoms Score ([MTASS] reduction in MTASS representing improvement). **RESULTS:** Overall, adverse events occurred in 4 (9%) and 3 (7%) subjects in the 180-microg and 360-microg groups, respectively. Drug-related tachycardia (360 microg) and ventricular extrasystoles (180 microg) were reported in 1 patient each. Three additional instances of single ventricular ectopy were identified from Holter monitoring. No hypokalemia or drug-related QT or QTc prolongation was seen; glucose values and adrenergic stimulation did not significantly differ between treatment groups. In the 180-microg and 360-microg groups, mean change from baseline in MTASS during the treatment period was -2.8 (-49.8%) and -2.9 (-48.4%), and rescue albuterol use occurred in 4 (9%) and 3 (7%) subjects, respectively. **CONCLUSIONS:** Cumulative dosing with albuterol HFA 180 microg or 360 microg via MDI-spacer and face mask in children younger than 2 years did not result in any significant safety issues and improved MTASS by at least 48%.

C. L. Leach and G. L. Colice. "A Pilot Study to Assess Lung Deposition of HFA-Beclo-methasone and CFC-Beclo-methasone from a Pressurized Metered Dose Inhaler with and without Add-On Spacers and Using Varying Breathhold Times." 2010 J Aerosol Med Pulm Drug Deliv:

**Abstract Background:** The study objective of this pilot study was to determine the lung delivery of HFA-134a-beclomethasone dipropionate (HFA-BDP; QVAR) and CFC-beclomethasone dipropionate (CFC-BDP; Becloforte) with and without the add-on spacers, Aerochamber, and Volumatic. The smaller particles of HFA-BDP were presumed to produce greater lung deposition using spacers, with and without a delay [i.e., metered dose inhaler (MDI) actuation into the spacer and subsequent inhalation 0 and 2 sec later], compared with the larger particles of CFC-BDP. The study included a comparison of breathhold effects (i.e., 1 and 10-sec breathholds) on lung deposition. **Methods:** The study was an open-label design and utilized healthy subjects (n = 12 males). Each arm of the study contained three subjects; thus, outcomes were not powered to assess statistical significance. HFA-BDP and CFC-BDP were radiolabeled with technetium-99m and delivered to subjects. **Results:** Results showed that the small particle HFA-BDP lung deposition averaged 52% and was not affected by the use of Aerochamber with or without a spacer delay. The oropharyngeal deposition of HFA-BDP was reduced from approximately 28% to 4% with the Aerochamber. Lung deposition with the large particle CFC-BDP was 3-7% and generally decreased with Aerochamber or Volumatic. A 2-sec time delay between actuation and breath plus the spacer reduced lung deposition slightly but reduced oropharyngeal deposition substantially (84% down to 3-20%) using the Aerochamber or Volumatic with and without a spacer delay. HFA-BDP lung deposition was dependent on the breathhold. Lung deposition with HFA-BDP was reduced by 16% with a 1-sec versus 10-sec breathhold. The difference was measured in the increased exhaled fraction, confirming that smaller particles need time to deposit and are exhaled if there is a reduced breathhold. The large particle CFC-BDP lung deposition was not affected by breathhold. **Conclusions:** The use of Aerochamber or Volumatic spacers with HFA-BDP did not alter lung deposition but it did reduce oropharyngeal deposition. However, HFA-BDP displayed reduced oropharyngeal deposition without a spacer

P. C. Kwok, S. J. Trietsch, M. Kumon and H. K. Chan. "Electrostatic charge characteristics of jet nebulized aerosols." 2010 J Aerosol Med Pulm Drug Deliv 23(3):

**BACKGROUND:** Liquid droplets can be spontaneously charged in the absence of applied electric fields by spraying. It has been shown by computational simulation that charges may influence particle deposition in the airways. The electrostatic properties of jet nebulized aerosols and their potential effects on lung deposition have hardly been studied. A modified electrical low pressure impactor (ELPI) was employed to characterize the aerosol charges generated from jet nebulized commercial products. **METHODS:** The charge and size measurements were conducted at 50% RH and 22 degrees C with a modified ELPI. Ventolin, Bricanyl, and Atrovent were nebulized using PARI LC Plus jet nebulizers coupled to a DeVilbiss Pulmo-Aide compressor. The aerosols were sampled in 30-sec durations. The drug deposits on the impactor stages were assayed chemically using high-performance liquid chromatography (HPLC). The charges of nebulized deionized water, isotonic saline, and the three commercial products diluted with saline were also measured to analyze the contributions of the major nebulized ingredients on charging. No mass assays were performed on these runs. **RESULTS:** All three commercial nebulizers generated net negative charges. The magnitude of the charges reduced over the period of nebulization. Ventolin and Bricanyl yielded similar charge profiles. Highly variable charges were produced from deionized water. On the other hand, nebulized saline reproducibly generated net positive charges. Diluted commercial nebulizers showed charge polarity inversion. The charge profiles of diluted salbutamol and terbutaline solutions resembled those of saline, while the charges from diluted ipratropium solutions fluctuated near neutrality. **CONCLUSIONS:** The charge profiles were shown to be influenced by the concentration and physicochemical properties of the drugs, as well as the history of nebulization. The drugs may have unique isoelectric concentrations in saline at which the nebulized droplets would carry near-zero charges. According to results

from computational simulation models in the literature, the numbers of elementary charges per droplet estimated from the data were not high enough to potentially affect lung deposition.

N. K. Leidy, B. Gutierrez, K. Lampl, T. Uryniak and C. D. O'Brien. "Can patients with asthma feel inhaler therapy working right away? Two clinical trials testing the effect of timing of assessment on patient perception." 2009 J Asthma 46(10):

**BACKGROUND:** Feeling a maintenance therapy work right away may provide positive reinforcement and may offer one way to improve adherence in patients with asthma. Precise measurement is required to accurately compare the presence of this effect across clinical trial treatment groups. **METHODS:** Two randomized, controlled studies tested whether timing of assessment (daily vs weekly, study 1; and predose vs postdose, study 2) influenced patients' reports of whether they can feel a medication working right away (perception), and their satisfaction with this perception (satisfaction). These 2-week US-based multicenter double-blind, parallel-group studies included patients  $> \text{ or } = 18$  years of age with mild to moderate persistent asthma. In each, patients were randomized to one of two drugs with different onset profiles: budesonide/formoterol pressurized metered-dose inhaler (pMDI) 80/4.5 microg x 2 inhalations (160/9 microg) twice daily or budesonide pMDI 80 microg x 2 inhalations (160 microg) twice daily. Patients were further randomized to complete previously validated perception and satisfaction questions in a cross-over fashion, either daily and weekly (N = 123) or predose and postdose (N = 134). Patient surveys also assessed perceptions of the onset of effect of medication and their value of these perceptions. **RESULTS:** No significant differences were observed in patients' reports of perception, either daily versus weekly or predose versus postdose. A statistically significant difference in satisfaction was found in study 1 only, favoring weekly recall ( $p < 0.05$ ), with sensitivity analysis showing no difference by treatment group ( $p = 0.162$ ). Across both studies, most patients (87%) who perceived their inhaler working right away (136 of 157 patients) identified positive airway sensations. Most patients reported that feeling their medication work right away is reassuring and would help them manage their asthma. **CONCLUSION:** Assessment timing has no effect on patient response to the perception of feeling a medication working right away. Differences found in satisfaction levels reported with weekly versus daily recall were consistent across treatment groups, indicating that no bias was introduced in favor of either treatment group. Patients characterized the perception of feeling a maintenance therapy working right away as easier breathing and reported this perception as beneficial to patient self-care.

D. Price, A. Robertson, K. Bullen, C. Rand, R. Horne and H. Staudinger. "Improved adherence with once-daily versus twice-daily dosing of mometasone furoate administered via a dry powder inhaler: a randomized open-label study." 2010 BMC Pulm Med 10:

**BACKGROUND:** Poor adherence with prescribed asthma medication is a major barrier to positive treatment outcomes. This study was designed to determine the effect of a once-daily administration of mometasone furoate administered via a dry powder inhaler (MF-DPI) on treatment adherence compared with a twice-daily administration. **METHODS:** This was a 12-week open-label study designed to mimic an actual clinical setting in patients  $> \text{ or } = 12$  years old with mild-to-moderate persistent asthma. Patients were randomized to receive MF-DPI 400 microg once-daily in the evening or MF-DPI 200 microg twice-daily. Adherence was assessed primarily using the number of actual administered doses reported from the device counter divided by the number of scheduled doses. Self-reports were also used to determine adherence. Health-related quality of life, healthcare resource utilization, and days missed from work or school were also reported. **RESULTS:** 1233 patients were randomized. The mean adherence rates, as measured by the automatic dose counter, were significantly better ( $P < 0.001$ ) with MF-DPI 400 microg once-daily in the evening (93.3%) than with MF-DPI 200 microg twice-daily (89.5%). Mean adherence rates based on self-reports were also significantly better ( $P < 0.001$ ) with MF-

DPI 400 microg QD PM (97.2%) than with MF-DPI 200 microg twice-daily (95.3%). Adherence rates were lower in adolescents (12-17 years old). Health-related quality of life improved by 20% in patients using MF-DPI once-daily in the evening and by 14% in patients using MF-DPI twice-daily. Very few (<8%) patients missed work/school. CONCLUSION: Mean adherence rates were greater with a once-daily dosing regimen of MF-DPI than with a twice-daily dosing regimen. This trial was completed prior to the ISMJE requirements for trial registration.

P. Quinet, C. A. Young and F. Heritier. "The use of dry powder inhaler devices by elderly patients suffering from chronic obstructive pulmonary disease." 2010 *Ann Phys Rehabil Med* 53(2):

Twenty-five COPD patients, aged 65 years or above, were recruited to test their ability to use dry powder inhaler Handihaler (Boeringher-Ingelheim) and Aerolizer (Novartis). The results of a score created to evaluate the inhalation technique were compared with age, MMSE, Barthel Index, FEV(1), maximum inspiratory and expiratory pressures, and peak inspiratory flow (PIF). RESULTS: Dry powder inhalers were correctly used by 60% of the patients (15 out of 25). Among the capable ones, 13 out of 15 were aged less than 80 years ( $p < \text{or} = 0.02$ ), 13 out of 15 had a maximum inspiratory pressure greater or equal to 53cm H(2)O ( $p < \text{or} = 0.001$ ) and a PIF greater or equal to 120l/min ( $p < \text{or} = 0.05$ ). All skilled patients had a minimum MMSE of 25 ( $p < \text{or} = 0.001$ ). CONCLUSION: In a geriatric population, age, the decrease of maximum inspiratory pressure and PIF as well as cognitive functions, limit the use of dry powder inhalers.

S. Shah, M. White, T. Uryniak and C. D. O'Brien. "The functionality of a budesonide/formoterol pressurized metered-dose inhaler with an integrated actuation counter." 2010 *Allergy Asthma Proc* 31(1):

Integration of an actuation counter into pressurized metered-dose inhalers (pMDIs) can allow patients to accurately determine the remaining number of medication doses. This study was designed to assess the functionality of budesonide/formoterol (Symbicort; AstraZeneca, Dunkerque, France) pMDI with an integrated actuation counter in a clinical setting. Children aged  $> \text{or} = 6$  years, adolescents, and adults with inhaled corticosteroid-dependent asthma participated in this 6-week, randomized, open-label, multicenter study (SD-039-0743; D5896C00743). Patients were treated with budesonide/formoterol pMDI with no actuation counter (80/4.5 micrograms x 2 inhalations [160/9 micrograms] twice daily) during a 7- to 10-day run-in period. Qualifying patients were then randomized into one of three groups treated with budesonide/formoterol pMDI with actuation counter (80/4.5 micrograms x 2 inhalations [160/9 micrograms] twice daily): group 1, 96 actuations (24 days); group 2, 120 actuations (30 days); or group 3, 128 actuations (32 days). Actuation count was assessed using position of the counter arrow, patient/caregiver reports (daily log and actuation counter final reading), and device (canister plus actuation counter assembly) weight change. Patients/caregivers rated ease of device use. There was good agreement across treatment groups ( $n = 254$ ) between patient/caregiver-reported actuation counts and counts determined by the angular position of the arrow. Analysis of device weight change versus other estimates of actuation counts in groups 1 and 2 indicated that the device did not undercount the number of actuations sprayed. Most patients (93%) indicated the device was "extremely easy" or "very easy" to use. Clinical functionality and reliability of the budesonide/formoterol pMDI device with an actuation counter were established.

S. Skaria and G. C. Smaldone. "Omron NE U22: Comparison between vibrating mesh and jet nebulizer." 2010 J Aerosol Med Pulm Drug Deliv 23(3):

**BACKGROUND:** To overcome the limitations of conventional jet nebulizers, vibrating mesh technology has been commercialized. The present article is designed to address clinically relevant issues for routine aerosol therapy for a vibrating mesh nebulizer, the Omron NE U22, compared to traditional jet nebulizers. **METHODS:** Inhaled mass (IM), residual activity, particle distribution, including mass median aerodynamic diameter (MMAD) and run time, were determined for radiolabeled albuterol (2.5 mg/3 mL). Omron NE U22, Pari LC Plus, and Sidestream nebulizers were tested. The Omron was tested in two positions, tilted and horizontal. Finally robustness of the Omron NE U22 was determined by repeating treatment 60 times. All Omron experiments were performed using continuous operation. **RESULTS:** IM for Omron and Pari were similar (20% of nebulizer charge) and greater than the Sidestream (10%). MMADs were similar for all devices but variability was much greater for Omron in the horizontal position. Run time in the tilted position was three times longer when compared to the horizontal ( $p = 0.02$ ). IM and MMAD were unchanged after Omron robustness testing. **CONCLUSION:** Position was an important factor for the mesh device affecting run time and variability in particle distribution. Using a common commercial formulation and continuous operation, drug delivery was similar to an efficient jet nebulizer. The Omron mesh tolerated repeated use with the albuterol formulation.

R. Zuwallack, M. C. De Salvo, T. Kaelin, E. D. Bateman, C. S. Park, R. Abrahams, F. Fakhri, P. Sachs, K. Pudi, Y. Zhao and C. C. Wood. "Efficacy and safety of ipratropium bromide/albuterol delivered via Respimat((R)) inhaler versus MDI." 2010 Respir Med:

We compared the efficacy and safety of ipratropium bromide/albuterol delivered via Respimat((R)) inhaler, a novel propellant-free inhaler, versus chlorofluorocarbon (CFC)-metered dose inhaler (MDI) and ipratropium Respimat((R)) inhaler in patients with COPD. This was a multinational, randomized, double-blind, double-dummy, 12-week, parallel-group, active-controlled study. Patients with moderate to severe COPD were randomized to ipratropium bromide/albuterol (20/100mcg) Respimat((R)) inhaler, ipratropium bromide/albuterol MDI [36mcg/206mcg (Combivent((R)) Inhalation Aerosol MDI)], or ipratropium bromide (20mcg) Respimat((R)) inhaler. Each medication was administered four times daily. Serial spirometry was performed over 6h (0.15min, then hourly) on 4 test days. The primary efficacy variable was forced expiratory volume in 1s (FEV(1)) change from test day baseline at 12 weeks. A total of 1209 of 1480 randomized, treated patients completed the study; the majority were male (65%) with a mean age of 64 yrs and a mean screening pre-bronchodilator FEV(1) (percent predicted) of 41%. Ipratropium bromide/albuterol Respimat((R)) inhaler had comparable efficacy to ipratropium bromide/albuterol MDI for FEV(1) area under the curve at 0-6h (AUC(0-6)), superior efficacy to ipratropium Respimat((R)) inhaler for FEV(1) AUC(0-4) and comparable efficacy to ipratropium Respimat((R)) inhaler for FEV(1) AUC(4-6). All active treatments were well tolerated. This study demonstrates that ipratropium bromide/albuterol 20/100mcg inhaler((R)) administered four times daily for 12 weeks had equivalent bronchodilator efficacy and comparable safety to ipratropium bromide/albuterol 36mcg/206mcg MDI, and significantly improved lung function compared with the mono-component ipratropium bromide 20 mcg Respimat((R)) inhaler. [Clinical Trial Identifier Number: NCT00400153].

## Pediatric Clinical Trials

M. E. Abdelrahim. "Emitted dose and lung deposition of inhaled terbutaline from Turbuhaler at different conditions." 2010 *Respir Med* 104(5):

Turbuhaler has a very high resistance hence patient inhalation flow when using it would be low. The total emitted dose (TED) of 500microg terbutaline sulphate from a Bricanyl Turbuhaler was determined using a range of inhalation flows (10-60L min<sup>(-1)</sup>) with inhalation volume of 2 and 4L using a DPI sampling apparatus after one and two inhalations. The relative lung and systemic bioavailability of terbutaline from Bricanyl Turbuhaler when used by healthy subjects and COPD patients were determined after one and two inhalations at slow and fast inhalation flows using a novel urinary terbutaline pharmacokinetic method. The TED resulted from the one and two inhalations increased significantly ( $p<0.05$ ) with the increase of the inhalation flow at both 2 and 4L inhalation volumes. The relative lung and systemic bioavailability after one inhalation at fast inhalation flow were significantly higher ( $p<0.01$ ) than at slow inhalation flow in both healthy subjects and patients. Also the healthy subjects results were significantly higher ( $p<0.05$ ) than the COPD patients after one inhalation. However after two inhalations there was no significant difference between slow and fast inhalation flow or healthy subjects and COPD patients. Hence it is essential to inhale twice and as deep and hard as possible from each dose of Turbuhaler for patients with low inspiratory flow and limited inhalation volume as they may not receive much benefit from one inhalation.

H. Adi, P. M. Young, H. K. Chan, H. Agus and D. Traini. "Co-spray-dried mannitol-ciprofloxacin dry powder inhaler formulation for cystic fibrosis and chronic obstructive pulmonary disease." 2010 *Eur J Pharm Sci* 40(3):

The aim of this study was to assess the potential of delivering a combination therapy, containing mannitol (a sugar alcohol with osmotic characteristics), and ciprofloxacin hydrochloride (an antibacterial fluoroquinolone), as a dry powder inhaler (DPI) formulation for inhalation. Single and combination powders were produced by spray drying ciprofloxacin and mannitol, from aqueous solution, at different ratios and under controlled conditions, as to obtain similar particle size distributions. Each formulation was characterised using laser diffraction, scanning electron microscopy, differential scanning calorimetry, dynamic vapour sorption, X-ray powder diffraction, and colloidal force microscopy. The in vitro aerosol performance of each formulation was studied using an Aerolizer DPI device and a multi-stage liquid impinger (analysed using high performance liquid chromatography). In addition, a disk diffusion test was performed to assess the in vitro antimicrobial activity of each formulation and starting materials. All formulations had similar particle size distributions, however, the morphology, thermal properties and moisture sorption was dependent on the relative percentages of each component. In general, the combination formulation containing 50% (w/w) mannitol appeared to have the best aerosol performance, good stability and lowest particle cohesion (as measured by colloid probe microscopy). Furthermore, of the formulations tested, mannitol did not appear to alter the effectiveness of the ciprofloxacin antimicrobial activity to *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Streptococcus pyogenes*. The combination of co-spray-dried mannitol and ciprofloxacin from a DPI is an attractive approach to promote mucous clearance in the respiratory tract while simultaneously treating local chronic infection, such as chronic obstructive pulmonary disease and cystic fibrosis.

R. Agarwal, A. Khan, A. N. Aggarwal and D. Gupta. "Is the SMART approach better than other treatment approaches for prevention of asthma exacerbations? A meta-analysis." 2009 *Monaldi Arch Chest Dis* 71(4):

**BACKGROUND AND AIMS:** The combination of inhaled corticosteroids (ICS) and long-acting beta2 agonists (LABA) has been used as a single inhaler both for maintenance and reliever therapy in asthma, the SMART approach. The administration of additional CS with each reliever inhalation in response to symptoms is expected to provide better control of airway inflammation. The aim of this meta-analysis was to evaluate the efficacy and safety of the SMART approach versus other approaches in the management of asthma in preventing asthma exacerbations. **METHODS:** We searched the MEDLINE and EMBASE databases for studies that have reported exacerbations in the SMART group versus the control group. We calculated the odds ratio (OR) and 95% confidence intervals (CI) to assess the exacerbations in the two groups and pooled the results using a random-effects model. **RESULTS:** Our search yielded eight studies. The use of SMART approach compared to fixed-dose ICS-LABA combination significantly decreased the odds of a severe exacerbation (OR 0.65; 95% CI, 0.53-0.80) and severe exacerbation requiring hospitalization/ER treatment (OR 0.69; 95% CI, 0.58-0.83). The use of SMART approach compared to fixed-dose ICS also significantly decreased the odds of a severe exacerbation (OR 0.52; 95% CI, 0.45-0.61) and severe exacerbation requiring medical intervention (OR 0.52; 95% CI, 0.42-0.65). The occurrence of adverse events was similar in the two groups. There was some evidence of statistical heterogeneity. **CONCLUSIONS:** The SMART approach using formoterol-budesonide is superior in preventing exacerbations when compared to traditional therapy with fixed dose ICS or ICS-LABA combination without any increase in adverse events.

J. Ahnert, S. Loffler, J. Muller and H. Vogel. "[Systematic literature review on interventions in rehabilitation for children and adolescents with asthma bronchiale]." 2010 *Rehabilitation (Stuttg)* 49(3):

Relevant data bases were used to collect and evaluate guidelines, meta-analyses, and reviews as well as primary studies dealing with asthma therapy for children and adolescents. Treatment approaches whose effectiveness with regard to bronchial asthma was empirically verified (i. e., evidence-based) were identified (medical and diagnostic procedures as well as drug trials were excluded from the analysis). 152 methodically sound studies referring to asthma treatment of children and adolescents were selected. Strong evidence was found for patient education, parent education, exercise therapy, inhalation, and tobacco withdrawal. Nutritional counseling and avoidance of allergens showed limited evidence. Psychotherapy, relaxation techniques, breathing exercises, climate therapy, clinical social work (social and legal counseling services, vocational reintegration counseling, aftercare) and integration counseling showed inconsistent evidence. No evidence was found for alternative medicine. Challenges regarding the development of treatment standards for children and adolescent rehabilitation are highlighted; these refer to limitations in report quality in some of the studies, the validity of treatments for comorbid conditions, a lack of differentiation for different age groups, and transferability of outpatient or international study results to inpatient rehabilitation.

S. A. Antoniu. "Effects of inhaled therapy on biomarkers of systemic inflammation in stable chronic obstructive pulmonary disease." 2010 *Biomarkers* 15(2):

In chronic obstructive pulmonary disease (COPD) airways inflammation is associated in more advanced stages with systemic inflammation. COPD-associated systemic inflammation syndrome is defined currently with rather non-specific biomarkers such as C-reactive protein (CRP) but there are also other 'organ-specific' biomarkers such as surfactant protein-D which are still not well characterized but might represent more appropriate and reliable alternatives to the non-specific biomarkers. Inhaled therapies are

the mainstay in stable COPD and they were demonstrated to reduce airway inflammation and more recently in the case of inhaled corticosteroids alone or combined with long-acting beta-2 agonists to reduce systemic inflammation as well. This paper focuses on current and potential biomarkers of systemic inflammation in COPD and on the systemic anti-inflammatory effects of inhaled therapies in stable COPD.

E. Bannier, K. Cieslar, K. Mosbah, F. Aubert, F. Duboeuf, Z. Salhi, S. Gaillard, Y. Berthezene, Y. Cremillieux and P. Reix. "Hyperpolarized  $^3\text{He}$  MR for sensitive imaging of ventilation function and treatment efficiency in young cystic fibrosis patients with normal lung function." 2010 Radiology 255(1):

**PURPOSE:** To assess the sensitivity of hyperpolarized helium 3 ( $^3\text{He}$ ) magnetic resonance (MR) imaging for the detection of peripheral airway obstruction in younger cystic fibrosis (CF) patients showing normal spirometric results (mean forced expiratory volume in 1 second [FEV(1)], 112% +/- 14.5 [standard deviation]) and to observe the immediate effects of a single chest physical therapy (CPT) session, thereby comparing two image quantification techniques. **MATERIALS AND METHODS:** Ten pediatric CF patients (age range, 8-16 years) with normal spirometric results were included in this study after approval from the local research ethics committee. Spirometry followed by proton and hyperpolarized ( $^3\text{He}$ ) three-dimensional lung imaging were performed with a 1.5-T MR unit before and after 20 minutes of CPT. The number of ventilation defects per image (VDI) and the ventilated lung fraction (VF), defined as the ratio of ventilated lung volume divided by total lung volume, were quantified. **RESULTS:** Ventilation defects were found in all patients (mean VDI, 5.1 +/- 1.9; mean global VF, 78.5% +/- 12.3; and mean peripheral VF, 75.5% +/- 17.1) despite normal spirometric results. After CPT, disparate changes in the distribution of ventilation defects were observed but the average VDI and VF did not change significantly (mean VDI, 5.1 +/- 1.1; mean global VF, 83.5% +/- 12.2; and mean peripheral VF, 80.3% +/- 12.2). There was no correlation between FEV(1) and VDI ( $\rho = -0.041$ ,  $P = .863$ ) or global VF ( $\rho = -0.196$ ,  $P = .408$ ) values but peripheral VF and VDI were correlated ( $\rho = -0.563$ ,  $P = .011$ ). **CONCLUSION:** Although spirometric results indicate normal lung function, the mean VDI in patients (5.1) found in this study is well above the VDI in healthy subjects (1.6) reported in the literature. A single CPT session induces disparate changes in the distribution and extent of ventilation defects.

W. E. Berger, E. R. Bleecker, L. O'Dowd, C. J. Miller and W. Mezzanotte. "Efficacy and safety of budesonide/formoterol pressurized metered-dose inhaler: randomized controlled trial comparing once- and twice-daily dosing in patients with asthma." 2010 Allergy Asthma Proc 31(1):

Asthma guidelines recommend titrating maintenance medications to the lowest effective dose. This study assessed the efficacy and tolerability of reducing the frequency of dosing in patients previously controlled with twice-daily budesonide/formoterol (BUD/FM) pressurized metered-dose inhaler (pMDI) to once-daily regimens of BUD/FM pMDI or BUD pMDI. This was a 12-week, randomized, double-blind, double-dummy, placebo (PBO)/active-controlled, multicenter study (N = 752) of patients aged > or =16 years with mild to moderate asthma. After 4-5 weeks on single-blind BUD/FM pMDI 160/9 micrograms twice daily (320/18 micrograms daily), patients with stable asthma received BUD/FM pMDI 160/9 micrograms twice daily (320/18 micrograms daily; morning and evening), BUD/FM pMDI 320/9 micrograms once daily (evening), BUD/FM pMDI 160/9 micrograms once daily (evening), BUD pMDI 320 micrograms once daily (evening), or PBO. BUD/FM (once or twice daily) was more effective ( $p < or = 0.003$ ) than BUD and PBO on evening peak expiratory flow (primary variable), morning pulmonary function assessments, daily symptoms, and nighttime rescue medication use. Twice-daily BUD/FM was more effective ( $p < or = 0.05$ ) than both once-daily doses for evening pulmonary function assessments and daytime rescue medication use. All treatments were well tolerated. Once- or twice-daily BUD/FM showed better efficacy than BUD once daily or

PBO; results generally were more favorable with twice-daily dosing compared with both once-daily dosing regimens, which had one-half the daily FM dose.

W. E. Berger, J. G. Leflein, D. E. Geller, B. Parasuraman, C. J. Miller, C. D. O'Brien and L. O'Dowd. "The safety and clinical benefit of budesonide/formoterol pressurized metered-dose inhaler versus budesonide alone in children." 2010 Allergy Asthma Proc 31(1):

Few studies have evaluated inhaled corticosteroid (ICS)/long-acting beta(2)-adrenergic agonist combination therapy in asthmatic children. This study was designed to evaluate the safety (primary) and clinical benefits (secondary) of budesonide/formoterol pressurized metered-dose inhaler (pMDI) versus budesonide dry powder inhaler (DPI) in children with persistent asthma. This was a 26-week, multicenter, randomized, open-label U.S. study of 187 children 6-11 years of age previously receiving ICS. After 1 week of usual ICS therapy, subjects received twice-daily budesonide/formoterol pMDI 160/4.5 micrograms x 2 inhalations (320/9 micrograms; n = 124) or budesonide DPI 200 micrograms x 2 inhalations (400 micrograms [320 micrograms delivered ex-mouthpiece]; n = 63). Budesonide/formoterol and budesonide were well tolerated with a similar incidence of adverse events (AEs) (84.6% and 85.7%, respectively), most of mild or moderate intensity. Treatment-related AE incidence was low (5.4%) and similar across groups (budesonide/formoterol, 4.9%; budesonide, 6.3%). No clinically important treatment differences were observed for 12-lead electrocardiograms, hematology, serum glucose and potassium, and 24-hour urinary cortisol. Compared with budesonide, budesonide/formoterol decreased health care use (urgent care visits and interference with daily activities [child] or work [caregiver];  $p < \text{or} = 0.012$ ) and improved health-related quality of life (Pediatric Asthma Quality of Life Questionnaire [standardized] and Pediatric Asthma Caregiver Quality of Life Questionnaire overall scores;  $p < \text{or} = 0.006$ ) and pulmonary function (predose forced expiratory volume in 1 second and forced expiratory flow during the middle half of exhalation;  $p < \text{or} = 0.007$ ). In this 26-week study of asthmatic children (6-11 years), safety profiles were similar and clinical benefits were greater with budesonide/formoterol than with budesonide.

W. E. Berger and M. J. Noonan. "Treatment of persistent asthma with Symbicort (budesonide/formoterol inhalation aerosol): an inhaled corticosteroid and long-acting beta2-adrenergic agonist in one pressurized metered-dose inhaler." 2010 J Asthma 47(4):

**OBJECTIVE:** Budesonide/formoterol inhalation aerosol (Symbicort AstraZeneca, Wilmington, Delaware) is an inhaled corticosteroid (ICS) and long-acting beta(2)-adrenergic agonist (LABA) combination administered twice daily via one hydrofluoroalkane pressurized metered-dose inhaler (pMDI) approved in the United States for the long-term maintenance treatment of persistent asthma in patients  $\geq 12$  years of age whose asthma cannot be controlled by an ICS alone. The objective was to review efficacy, safety, and pharmacogenetic data on budesonide/formoterol pMDI in the treatment of persistent asthma. **METHODS:** The authors searched PubMed and respiratory meeting databases to identify asthma studies of budesonide/formoterol pMDI. Studies involving traditional and patient-reported outcomes, safety, tolerability, or pharmacogenetics were included. **RESULTS:** In two 12-week pivotal trials in adolescents and adults, treatment with budesonide/formoterol pMDI 160/4.5 microg x 2 inhalations (320/9 microg) twice daily for moderate to severe persistent asthma or 80/4.5 microg x 2 inhalations (160/9 microg) twice daily for mild to moderate persistent asthma, demonstrated greater efficacy and similar tolerability compared with placebo and the same nominal dose of its monocomponents. Comparisons with formoterol dry powder inhaler (DPI) for predose forced expiratory volume in one second (FEV(1)) and with budesonide pMDI for 12-hour mean postdose FEV(1) demonstrated the anti-inflammatory and bronchodilatory contributions of budesonide and formoterol, respectively. Evaluations of patient-reported outcomes, including asthma-specific quality of life and treatment satisfaction, further supported the clinical benefits of budesonide/formoterol pMDI. In a 52-

week tolerability study of patients aged  $\geq 12$  years, budesonide/formoterol pMDI was delivered at up to double the maximum dose (640/18 microg twice daily) and demonstrated a safety profile similar to that of budesonide (640 microg twice daily), with no unexpected pattern of abnormalities. Additional studies reported that budesonide/formoterol pMDI 320/9 microg twice daily and fluticasone propionate/salmeterol DPI 250/50 microg twice daily have similar efficacy and tolerability, with significantly more patients achieving  $\geq 15\%$  improvement in FEV<sub>1</sub> within 15 minutes with budesonide/formoterol pMDI compared with fluticasone/salmeterol DPI. Moreover, inheritance of the Gly16Arg polymorphism of the beta(2)-adrenergic receptor does not appear to affect clinical outcomes with budesonide/formoterol pMDI. CONCLUSION: Budesonide/formoterol pMDI administered twice daily is effective and generally well tolerated in patients whose asthma is not well controlled on ICS alone.

M. T. Bigham, B. R. Jacobs, M. A. Monaco, R. J. Brill, D. Wells, E. M. Conway, S. Pettinichi and D. S. Wheeler. "Helium/oxygen-driven albuterol nebulization in the management of children with status asthmaticus: a randomized, placebo-controlled trial." 2010 *Pediatr Crit Care Med* 11(3):

OBJECTIVES: We investigated the effect of heliox-powered albuterol therapy on hospital length of stay and clinical status in children with moderate to severe status asthmaticus. DESIGN: Prospective, randomized, placebo-controlled trial. SETTING: Twenty-five-bed pediatric intensive care unit at an academic children's medical center. PATIENTS: Forty-two children (2-21 yrs of age) with moderate to severe status asthmaticus. INTERVENTIONS: Patients were randomized to receive either heliox-powered nebulized albuterol or air/oxygen-powered nebulized albuterol (placebo) until they were transitioned to albuterol delivered by a metered dose inhaler. MEASUREMENTS AND MAIN RESULTS: Clinical asthma scores were recorded on enrollment and every 4 hrs thereafter. Patients in the heliox group (n = 22) and the control group (n = 20) had similar ages (mean +/- sem: 88 +/- 9.9 vs. 98 +/- 11.1 months, respectively; p = .51), time to study enrollment (618 +/- 70.4 vs. 597 +/- 84.1 mins, respectively; p = .72), and clinical asthma scores at study entry (5.9 +/- 0.2 vs. 5.7 +/- 0.3, respectively; p = .72). There were no significant differences between groups in time to eligibility to hospital discharge (66.2 +/- 8.7 vs. 63.4 +/- 8.6 hrs, respectively; p = .61), time to clinical asthma score <3 (22 +/- 2.8 vs. 21.2 +/- 5.3 hrs, respectively; p = .27), or time to eligibility for intensive care unit discharge (34.4 +/- 6.8 vs. 33.3 +/- 8.2 hrs, respectively; p = .64). There were no significant differences in adverse events between groups. CONCLUSIONS: Despite the previously demonstrated effects of heliox on improved aerosol particle delivery into the distal airways, heliox-powered nebulized albuterol therapy for children admitted to the hospital with moderate to severe status asthmaticus does not shorten hospital length of stay or hasten rates of clinical improvement when compared with air/oxygen-powered nebulized albuterol.

C. J. Cates and T. J. Lasserson. "Regular treatment with formoterol and an inhaled corticosteroid versus regular treatment with salmeterol and an inhaled corticosteroid for chronic asthma: serious adverse events." 2010 *Cochrane Database Syst Rev*(1):

BACKGROUND: An increase in serious adverse events with both regular formoterol and regular salmeterol in chronic asthma has been demonstrated in comparison with placebo in previous Cochrane reviews. This increase was significant in trials that did not randomise participants to an inhaled corticosteroid, but less certain in the smaller numbers of participants in trials that included an inhaled corticosteroid in the randomised treatment regimen. OBJECTIVES: We set out to compare the risks of mortality and non-fatal serious adverse events in trials which have randomised patients with chronic asthma to regular formoterol versus regular salmeterol, when each are used with an inhaled corticosteroid as part of the randomised treatment. SEARCH STRATEGY: Trials were identified using the Cochrane Airways Group Specialised Register of trials. Manufacturers' web sites of clinical trial registers were checked for unpublished trial data and Food and

Drug Administration (FDA) submissions in relation to formoterol and salmeterol were also checked. The date of the most recent search was July 2009. **SELECTION CRITERIA:** Controlled clinical trials with a parallel design, recruiting patients of any age and severity of asthma were included if they randomised patients to treatment with regular formoterol versus regular salmeterol (each with a randomised inhaled corticosteroid), and were of at least 12 weeks duration. **DATA COLLECTION AND ANALYSIS:** Two authors independently selected trials for inclusion in the review and extracted outcome data. Unpublished data on mortality and serious adverse events were sought from the sponsors and authors. **MAIN RESULTS:** Eight studies met the eligibility criteria of the review recruiting 6,163 adults and adolescents. There were seven studies (involving 5,935 adults and adolescents) comparing formoterol and budesonide to salmeterol and fluticasone. All but one study administered the products as a combined inhaler, and most used formoterol 50 mcg and budesonide 400 mcg twice daily versus salmeterol 50 mcg and fluticasone 250 mcg twice daily. There were two deaths overall (one on each combination) and neither were thought to be related to asthma. There was no significant difference between treatment groups for non-fatal serious adverse events, either all-cause (Peto OR 1.14; 95% CI 0.82 to 1.59, I(2) = 26%) or asthma-related (Peto OR 0.69; 95% CI 0.37 to 1.26, I(2) = 33%). Over 23 weeks the rates for all-cause serious adverse events were 2.6% on formoterol and budesonide and 2.3% on salmeterol and fluticasone, and for asthma-related serious adverse events, 0.6% and 0.8% respectively. There was one study (228 adults) comparing formoterol and beclomethasone to salmeterol and fluticasone, but there were no deaths or hospital admissions. No studies were found in children. **AUTHORS' CONCLUSIONS:** The seven identified studies in adults did not show any significant difference in safety between formoterol and budesonide in comparison with salmeterol and fluticasone. Asthma-related serious adverse events were rare, and there were no reported asthma-related deaths. There was a single small study comparing formoterol and beclomethasone to salmeterol and fluticasone in adults, but no serious adverse events occurred in this study. No studies were found in children. Overall there is insufficient evidence to decide whether regular formoterol and budesonide or beclomethasone have equivalent or different safety profiles from salmeterol and fluticasone.

Y. S. Cheng, Y. Zhou, R. H. Pierce, M. Henry and D. G. Baden. "Characterization of Florida red tide aerosol and the temporal profile of aerosol concentration." 2010 *Toxicol* 55(5):

Red tide aerosols containing aerosolized brevetoxins are produced during the red tide bloom and transported by wind to coastal areas of Florida. This study reports the characterization of Florida red tide aerosols in human volunteer studies, in which an asthma cohort spent 1h on Siesta Beach (Sarasota, Florida) during aerosolized red tide events and non-exposure periods. Aerosol concentrations, brevetoxin levels, and particle size distribution were measured. Hourly filter samples were taken and analyzed for brevetoxin and NaCl concentrations. In addition, the aerosol mass concentration was monitored in real time. The results indicated that during a non-exposure period in October 2004, no brevetoxin was detected in the water, resulting in non-detectable levels of brevetoxin in the aerosol. In March 2005, the time-averaged concentrations of brevetoxins in water samples were moderate, in the range of 5-10 microg/L, and the corresponding brevetoxin level of Florida red tide aerosol ranged between 21 and 39 ng/m<sup>3</sup>. The temporal profiles of red tide aerosol concentration in terms of mass, NaCl, and brevetoxin were in good agreement, indicating that NaCl and brevetoxins are components of the red tide aerosol. By continuously monitoring the marine aerosol and wind direction at Siesta Beach, we observed that the marine aerosol concentration varied as the wind direction changed. The temporal profile of the Florida red tide aerosol during a sampling period could be explained generally with the variation of wind direction.

I. J. Clifton, L. A. Fletcher, C. B. Beggs, M. Denton, S. P. Conway and D. G. Peckham. "An aerobiological model of aerosol survival of different strains of *Pseudomonas aeruginosa* isolated from people with cystic fibrosis." 2010 J Cyst Fibros 9(1):

*Pseudomonas aeruginosa* is a common and important pathogen in people with cystic fibrosis (CF). Recently epidemic strains of *P. aeruginosa* associated with increased morbidity, have been identified. The method of transmission is not clear, but there is evidence of a potential airborne route. The aim of this study was to determine whether different strains of *P. aeruginosa* isolated from people with CF were able to survive within artificially generated aerosols in an aerobiological chamber. Viable *P. aeruginosa* could still be detected up to 45min after halting generation of the aerosols. All of the strains of *P. aeruginosa* expressing a non-mucoid phenotype isolated from people with CF had a reduced ability to survive within aerosols compared to an environmental strain. Expression of a mucoid phenotype by the strains of *P. aeruginosa* isolated from people with CF promoted survival in the aerosol model compared to strains expressing a non-mucoid phenotype.

E. Daviskas, S. D. Anderson, A. Jaques and B. Charlton. "Inhaled mannitol improves the hydration and surface properties of sputum in patients with cystic fibrosis." 2010 Chest 137(4):

**BACKGROUND:** The airway mucus in patients with cystic fibrosis (CF) is dehydrated and adhesive and accumulates in the airways, resulting in chronic inflammation, infection, and progressive loss of lung function. Inhaled mannitol improves mucus clearance and, when administered over 2 weeks, it improves lung function in CF (Jaques et al. Chest. 2008;133(6):1388-1396). The changes in the physical properties of sputum after a 2-week treatment with mannitol were investigated in the same subjects with CF. **METHODS:** Sputum was collected before and at the end of the 2-week treatment period from 28 subjects with CF who participated in the double-blind crossover study. Mannitol or placebo 420 mg bid was inhaled over 2 weeks. The solids content, surface tension, contact angle, and viscoelasticity were measured. **RESULTS:** Two-week treatment with mannitol reduced the solids from 7.3% +/- 3.0% to 5.7% +/- 3.0% (P = .012), surface tension from 83.1 +/- 7.2 to 78.6 +/- 8.0 mN/m (P < .039), and contact angle from 52.4 +/- 7.7 to 47.9 +/- 7.3 degrees. There was no significant change in the viscoelastic properties of sputum (P > .1). Placebo treatment had no significant effect on the sputum properties. The change in solids content correlated with the change in both FEV(1) (r = -0.78, P = .004) and forced expiratory flow in the middle half of the FVC (r = -0.80, P = .003), and the percentage change in surface tension and contact angle correlated with the percentage change in the FEV(1) (r = -0.73, P = .012 and r = -0.63, P = .03, respectively) in these subjects. **CONCLUSION:** Treatment with inhaled mannitol over 2 weeks improved the hydration and surface properties of sputum in patients with CF. This effect was sustained and correlated with airway function changes. Trial registration: clinicaltrials.gov; Identifier: NCT00455130.

W. De Backer, A. Devolder, G. Poli, D. Acerbi, R. Monno, C. Herpich, K. Sommerer, T. Meyer and F. Mariotti. "Lung deposition of BDP/formoterol HFA pMDI in healthy volunteers, asthmatic, and COPD patients." 2010 J Aerosol Med Pulm Drug Deliv 23(3):

**BACKGROUND:** When inhaling medication, it is essential that drug particles are delivered to all sites of lung inflammation, including the peripheral airways. The aim of this study was to assess the lung deposition and lung distribution of beclomethasone dipropionate (BDP)/formoterol (100/6 microg), both dissolved in hydrofluoroalkane (HFA) and delivered by pressurized metered dose inhaler (pMDI) in healthy subjects, asthmatic, and chronic obstructive pulmonary disease (COPD) patients, to investigate how the in vitro characteristics of the formulation translate into the in vivo performance in diseases with different airway obstruction. **METHODS:** Healthy volunteers (n = 8), persistent asthmatics (n = 8), and patients with stable COPD (n = 8) completed this open-label, single-dose

parallel-group study. Each patient received one single treatment of four puffs of (99 m)Tc-labeled BDP/formoterol formulation. The correlation between particle size distribution of radioactivity and of the drugs in the radiolabeled formulation was validated. Intra- and extrapulmonary deposition, amount of exhaled drug, and the central to peripheral ratio (C/P) were calculated immediately after inhalation. Patients' lung function and pharmacokinetic parameters were also assessed up to 24 h post-dose. RESULTS: The average lung deposition of BDP/formoterol was 34.08 +/- 9.30% (relative to nominal dose) in healthy subjects, 30.86 +/- 8.89% in asthmatics, and 33.10 +/- 8.90% in COPD patients. Extrathoracic deposition was 53.48% +/- 8.95, 57.64% +/- 9.92 and 54.98% +/- 7.01, respectively. C/P ratios of 1.42 +/- 0.32 in healthy subjects, 1.96 +/- 0.43 in asthmatics, and 1.94 +/- 0.69 for COPD patients confirmed drug distribution to all regions of the lungs. Forced expiratory volume in 1 sec (FEV(1)) increased in all groups after BDP/formoterol inhalation, but was more evident in the patient groups. No significant correlation between baseline lung function and drug deposition was observed. Formoterol, BDP, and beclomethasone 17 monopropionate (B17MP) plasma profiles were comparable between groups. CONCLUSION: Inhalation of BDP/formoterol HFA (100/6 microg) produces high and homogeneous deposition of BDP and formoterol in the airways, regardless of pathophysiological condition.

J. Denyer, A. Black, K. Nikander, T. Dyche and I. Prince. "Domiciliary experience of the Target Inhalation Mode (TIM) breathing maneuver in patients with cystic fibrosis." 2010 J Aerosol Med Pulm Drug Deliv 23 Suppl 1:

BACKGROUND: The time requirements for multiple daily nebulizer treatments are important impediments to the quality of life for most patients with cystic fibrosis (CF). The I-neb Adaptive Aerosol Delivery (AAD) System can be used with a new mode of breathing during inhalation of aerosol, the Target Inhalation Mode (TIM). As a function of the TIM algorithm, the patient is guided to a slow and deep inhalation, which can result in shorter treatment times. METHODS: This study was conducted as a 3-month patient handling study of the I-neb AAD System in 42 patients with CF aged 12-57 years. The I-neb AAD System was supplied in both the standard Tidal Breathing Mode (TBM), and in TIM. Patients were trained to use the I-neb AAD System in TIM for the delivery of all their inhaled medications, but if they were not comfortable with the TIM maneuver they could change to the TBM maneuver. The primary variables were compliance with the correct use of the I-neb AAD System, and treatment times. The secondary variables were based on study questionnaires at the end of the study and covered ease of use, patient confidence, and patient satisfaction with the I-neb AAD System. RESULTS: There were a total of 10,240 complete treatments and of these, 8979 (88%) were in TIM. Compliance with the correct use of the I-neb AAD System was 97.6%. The mean treatment time for complete treatments in TIM was 4.20 min, compared with 6.83 min when using the I-neb AAD System in TBM. The responses to the questionnaires indicated that over 77% of the patients found the I-neb AAD System in TIM to be either: very easy, easy, or acceptable to use. CONCLUSIONS: The results demonstrated that by using the I-neb AAD System in TIM, a 40-50% reduction of nebulizer treatment times, and a high level of compliance could be achieved. The results also showed that the patients found the I-neb AAD System easy to use.

J. Denyer, I. Prince, E. Dixon, P. Agent, J. Pryor and M. Hodson. "Evaluation of the Target Inhalation Mode (TIM) breathing maneuver in simulated nebulizer therapy in patients with cystic fibrosis." 2010 J Aerosol Med Pulm Drug Deliv 23 Suppl 1:

BACKGROUND: Adaptive Aerosol Delivery (AAD) systems provide efficient drug delivery and improved lung deposition over conventional nebulizers by combining real-time analyses of patient breathing patterns and precisely timed aerosol delivery. Delivery and deposition are further enhanced by breathing techniques involving slow, deep inhalations. METHODS: This exploratory study assessed the acceptability of slow, deep inhalations in

20 patients with cystic fibrosis (CF) during up to eight simulated nebulizer treatments with the I-neb AAD System. The breathing maneuver, Target Inhalation Mode (TIM) breathing, involved the lengthening of the patient's inhalation time over successive breaths with guidance from auditory and tactile (vibratory) feedback from the device. RESULTS: At the end of the first treatment, most patients felt that the instructions were easy to understand (90%) and that the vibratory feedback was pleasant (65%). Half of the patients found the procedure to be comfortable. At the end of the final treatment, most patients felt that the breathing maneuver was easy to understand (90%) and use (80%), but that the duration of the breath was too long (100%). Logged data revealed that 90% of patients were able to comply with the breathing maneuver. The two patients unable to comply had a forced vital capacity of <1.75 L. The average treatment time decreased from 288.4 to 141.6 sec during the first and final treatments, respectively. CONCLUSIONS: This study provides preliminary evidence of the acceptability of the TIM breathing maneuver in patients with CF and their ability to perform repeated TIM breathing during simulated nebulizer therapy with the I-neb AAD System.

F. M. Ducharme, M. Ni Chroinin, I. Greenstone and T. J. Lasserson. "Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma." 2010 Cochrane Database Syst Rev 4:

BACKGROUND: In asthmatic patients inadequately controlled on inhaled corticosteroids and/or those with moderate persistent asthma, two main options are recommended: the combination of a long-acting inhaled ss2 agonist (LABA) with inhaled corticosteroids (ICS) or use of a higher dose of inhaled corticosteroids. OBJECTIVES: To determine the effect of the combination of long-acting ss(2) agonists and inhaled corticosteroids compared to a higher dose of inhaled corticosteroids on the risk of asthma exacerbations, pulmonary function and on other measures of asthma control, and to look for characteristics associated with greater benefit for either treatment option. SEARCH STRATEGY: We identified randomised controlled trials (RCTs) through electronic database searches (MEDLINE, EMBASE and CINAHL), bibliographies of RCTs, clinical trial registries and correspondence with manufacturers until May 2008. SELECTION CRITERIA: RCTs that compared the combination of inhaled LABA and ICS to a higher dose of inhaled corticosteroids, in children and adults with asthma. DATA COLLECTION AND ANALYSIS: Two authors independently assessed methodological quality and extracted data. We obtained confirmation from the trialists when possible. The primary endpoint was the number of patients experiencing one or more asthma exacerbations requiring oral corticosteroids. MAIN RESULTS: This review included 48 studies (15,155 participants including 1155 children and 14,000 adults). Participants were inadequately controlled on their current ICS regimen, experiencing ongoing symptoms and with generally moderate (FEV1 60% to 79% of predicted) airway obstruction. The studies tested the combination of salmeterol or formoterol with a median dose of 400 mcg/day of beclomethasone or equivalent (BDP-eq) compared to a median of 1000 mcg/day of BDP-eq, usually for 24 weeks or less. There was a statistically significantly lower risk of exacerbations requiring systemic corticosteroids in patients treated with LABA and ICS (RR 0.88, 95% CI 0.78 to 0.98, 27 studies, N = 10,578) from 11.45% to 10%, with a number needed to treat of 73 (median study duration: 12 weeks). The study results were dominated by adult studies; trial data from three paediatric studies showed a trend towards increased risk of rescue oral steroids (RR 1.24, 95% CI 0.58 to 2.66) and hospital admission (RR 2.21, 95% CI 0.74 to 6.64) associated with combination therapy. Overall, there was no statistically significant difference in the risk ratios for either hospital admission (RR 1.02, 95% CI 0.67 to 1.56) or serious adverse events (RR 1.12, 95% CI 0.91 to 1.37). The combination of LABA and ICS resulted in significantly greater but modest improvement from baseline in lung function, symptoms and rescue medication use than with higher ICS dose. Despite no significant group difference in the risk of overall adverse events (RR 0.99, 95% CI 0.95 to 1.03), there was an increase in the risk of tremor (RR 1.84, 95% CI 1.20 to 2.82) and a lower risk of oral thrush (RR 0.58, 95% CI 0.40 to 0.86) in the LABA and ICS compared to the higher ICS group. There was no significant difference in hoarseness or headache between the treatment groups. The rate of withdrawals due to poor asthma control

favoured the combination of LABA and ICS (RR 0.65, 95% CI 0.51 to 0.83). **AUTHORS' CONCLUSIONS:** In adolescents and adults with sub-optimal control on low dose ICS monotherapy, the combination of LABA and ICS is modestly more effective in reducing the risk of exacerbations requiring oral corticosteroids than a higher dose of ICS. Combination therapy also led to modestly greater improvement in lung function, symptoms and use of rescue  $\beta_2$  agonists and to fewer withdrawals due to poor asthma control than with a higher dose of inhaled corticosteroids. Apart from an increased rate of tremor and less oral candidiasis with combination therapy, the two options appear relatively safe in adults although adverse effects associated with long-term ICS treatment were seldom monitored. In children, combination therapy did not lead to a significant reduction, but rather a trend towards an increased risk, of oral steroid-treated exacerbations and hospital admissions. These trends raised concern about the safety of combination therapy in view of modest improvement in children under the age of 12 years.

J. S. Elborn and N. R. Henig. "Optimal airway antimicrobial therapy for cystic fibrosis: the role of inhaled aztreonam lysine." 2010 *Expert Opin Pharmacother* 11(8):

**IMPORTANCE OF THE FIELD:** Chronic endobronchial infection in cystic fibrosis (CF) leads to progressive lung function loss and respiratory failure. Most adult CF patients are infected with *Pseudomonas aeruginosa*, an important predictor of mortality. Suppressing chronic *P. aeruginosa* infection with inhaled antibiotics is standard of care for CF patients. **AREAS COVERED IN THIS REVIEW:** This review describes the development (2003 - 2010) of aztreonam lysine 75 mg powder and solvent for nebulizer solution (AZLI; Cayston), an aerosolized formulation of the monobactam antibiotic aztreonam. **WHAT THE READER WILL GAIN:** AZLI was studied in patients with CF and chronic *P. aeruginosa* airway infection. In placebo-controlled trials, AZLI improved respiratory symptoms, increased forced expiratory volume in 1 sec (FEV<sub>1</sub>), decreased sputum *P. aeruginosa* density, and was well tolerated. An open-label follow-on trial of nine 'on/off' courses showed that AZLI was safe and the effect durable with repeated administration. AZLI was recently approved for use in CF patients in Australia and the USA, and conditionally approved in Canada and the European Union. AZLI is given three times daily for 28 days (2 - 3 min/dose), followed by 28 days off-drug. AZLI is used only with the Altera Nebulizer System, which provides appropriate particle size and small airway deposition, and has excellent portability. **TAKE HOME MESSAGE:** AZLI is a new therapy that is safe and effectively improves respiratory symptoms and FEV<sub>1</sub> in patients with CF.

M. E. Falagas, A. Michalopoulos and E. I. Metaxas. "Pulmonary drug delivery systems for antimicrobial agents: facts and myths." 2010 *Int J Antimicrob Agents* 35(2):

Inhaled antimicrobial agents are used for the treatment of respiratory tract infections due to Gram-negative bacteria, mainly *Pseudomonas aeruginosa*. The effectiveness of the inhaled antimicrobial therapy is believed to correlate with the delivery system used. The objective of this review was to search for data supporting differentiation in clinical effectiveness between systems used for pulmonary delivery of antibiotics, including delivery using disposable nebulisers and oxygen flow. Published studies in peer-reviewed journals comparing the effectiveness of pulmonary drug delivery systems for antimicrobial agents were retrieved. The studies found were either in vitro or Phase I and Phase II clinical studies. Differences in in vitro parameters may affect the in vivo efficacy of the devices, and in vivo differences may imply differences in clinical effectiveness. The main difference between newer and older devices is the time needed for antibiotic delivery. Interpretation and association with clinical effectiveness is difficult. In conclusion, Phase III clinical trials comparing the clinical effectiveness of delivery systems, including delivery using a hospital's oxygen flow and disposable nebulisers, do not exist. Cost is an important parameter, which may be counterbalanced in cystic fibrosis patients by a better quality of life and a greater adherence to treatment.

H. J. Farber. "Optimizing maintenance therapy in pediatric asthma." 2010 *Curr Opin Pulm Med* 16(1):

**PURPOSE OF REVIEW:** There are different phenotypes of asthma, with phenotype-specific differences in medication response observed. **RECENT FINDINGS:** Tobacco smoke exposure reduces corticosteroid responsiveness. Treatment for tobacco smoke-triggered asthma must start with treatment of tobacco dependence. Obesity-associated asthma responds to weight loss and treatment of comorbidities. Immunotherapy and omalizumab are specific therapies for atopic asthma, though its use is limited by expense, inconvenience, need for injections, and toxicities. Leukotriene modifier response is more prominent in viral-triggered asthma. Research on intermittent escalation of controller therapy for asthma shows best results when escalation is substantial and early. Inhaled corticosteroid medications in low-to-moderate doses remain the most important maintenance medication for a broad variety of asthma phenotypes, reducing both impairment and risk. When impairment is not fully controlled by an inhaled corticosteroid, combination with a long-acting beta-agonist, leukotriene modifier, or theophylline can be effective. Inhaled corticosteroid use in children does not appear to influence airway caliber or asthma severity after the medication is stopped. **SUMMARY:** Optimizing maintenance therapy for asthma is not one size fits all. It is important to assess the asthma phenotype in addition to the symptom pattern, in determining optimal maintenance therapy.

M. D. Frazier and I. M. Cheifetz. "The role of heliox in paediatric respiratory disease." 2010 *Paediatr Respir Rev* 11(1):

Helium-oxygen (heliox) gas mixtures have been studied for over 70 years as an adjunctive therapy for airway obstruction in a variety of respiratory diseases. The medical use of heliox is based on the physical properties of helium as its low density makes it advantageous in promoting more efficient flow through narrowed passages. Clinical evidence of the efficacy of heliox in treating paediatric respiratory diseases is increasing in the medical literature. This article consists of a comprehensive review of the literature investigating the utility of heliox in the treatment of paediatric respiratory disorders, including upper and lower airway obstruction, mechanical ventilation, and aerosol delivery.

C. Frois, E. Q. Wu, S. Ray and G. L. Colice. "Inhaled corticosteroids or long-acting beta-agonists alone or in fixed-dose combinations in asthma treatment: a systematic review of fluticasone/budesonide and formoterol/salmeterol." 2009 *Clin Ther* 31(12):

**BACKGROUND:** Inhaled corticosteroids (ICSs) and long-acting inhaled beta(2)-agonists (LABAs) are recommended treatment options for asthma. **OBJECTIVE:** This review compares the clinical effectiveness and tolerability of the ICSs fluticasone propionate and budesonide and the LABAs formoterol fumarate and salmeterol xinafoate administered alone or in combination. **METHODS:** A systematic review of the clinical studies available on MEDLINE (database period, 1950-September 2009) was conducted to assess English-language randomized controlled trials in children and adults with asthma. Treatment outcomes included lung function, symptom-free days (SFDs), use of rescue/reliever medications, asthma exacerbations, and tolerability profile. **Results:** Use of fluticasone was associated with significantly greater improvement in lung function and better asthma symptom control than budesonide. Similarly, formoterol was associated with significantly greater improvement in lung function and better asthma symptom control (as measured by less rescue medication use and more SFDs) compared with salmeterol. Single inhaler combination regimens (budesonide/ formoterol and fluticasone/salmeterol) were frequently more effective in improving all treatment outcomes than either monotherapy alone. Across all comparisons, a review of studies in adults and children did not find

statistically significant differences in outcomes between the ICS and LABA therapies considered in this research. In general, no differences in tolerability profiles were reported between the ICS and LABA options, although the risk for growth retardation was lower with fluticasone than budesonide and with budesonide/formoterol than with budesonide monotherapy. **CONCLUSIONS:** In this systematic review, fluticasone and formoterol appear to provide improved therapeutic benefits versus budesonide and salmeterol, respectively. Both fluticasone/salmeterol and budesonide/ formoterol combination therapies appeared to be associated with greater improvements in outcomes measures than the corresponding ICS and LABA monotherapies.

L. Garcia-Marcos and P. L. Brand. "The utility of sputum eosinophils and exhaled nitric oxide for monitoring asthma control with special attention to childhood asthma." 2010 *Allergol Immunopathol (Madr)* 38(1):

The monitoring of sputum eosinophils has received certain attention as a tool for improving asthma management both in children and in adults. The present paper reviews the technique and also the usefulness of induced sputum in the diagnosis and assessment of asthma, together with its ability to predict the response to treatment and to anticipate asthma exacerbations. Special attention is addressed to childhood asthma. The authors conclude that due to cost-effectiveness reasons derived from high labour costs, together with the unpleasantness of the technique and the failure to obtain adequate samples in a non-negligible percentage of children, this technique should be only used for research purposes.

D. E. Geller and K. C. Kesser. "The I-neb Adaptive Aerosol Delivery System enhances delivery of alpha1-antitrypsin with controlled inhalation." 2010 *J Aerosol Med Pulm Drug Deliv* 23 Suppl 1:

**BACKGROUND:** Inhaled alpha1-antitrypsin (AAT) is being developed for treatment of cystic fibrosis to protect the lungs from excessive free elastase. High drug costs mandate a very efficient aerosol system to deliver a high payload to the airways. The I-neb Adaptive Aerosol Delivery (AAD) System is a portable, electronic, vibrating mesh nebulizer that delivers aerosol only during inhalation. It can be operated in conventional tidal breathing mode (TBM) or in target inhalation mode (TIM) that guides the patient to inhale deeply and slowly. The purposes of this in vitro study were to determine aerosol characteristics, device efficiency, and delivery time of AAT using the I-neb AAD System with TBM and TIM. **METHODS:** We studied the I-neb AAD System in TBM and TIM (inspiratory time 6 or 9 sec) using a breath simulator. The loaded dose was 0.5 mL AAT (50 mg/mL). Nebulized drug captured on an inspiratory filter was reported as emitted dose. Particle size was measured by laser diffraction. Predicted lung doses were calculated based on the results of a prior scintigraphy study of the I-neb AAD System. **RESULTS:** Particle size (VMD) for TBM and TIM was similar (4.4-4.8 microm). The emitted doses were very high and similar between modes (82-90% of loaded dose). Predicted lung dose of AAT (percent of loaded dose) and delivery times were: TBM 56.6% in 7.5 min; TIM-6 59.9% in 4.4 min; and TIM-9 64.5% in 2.5 min. **CONCLUSIONS:** The I-neb AAD System enhanced AAT delivery by inhalation-only aerosol generation and a low-residual dose. Predicted lung dose was high for both TBM and TIM, but longer inspiratory times with TIM reduced the administration time to one-third that of tidal breathing. We conclude that slow, deep, controlled inspirations using the I-neb AAD System is an efficient method to deliver AAT.

D. A. Gentile and D. P. Skoner. "New asthma drugs: small molecule inhaled corticosteroids." 2010 *Curr Opin Pharmacol*:

Small-particle inhaled corticosteroid (ICS) metered-dose inhalers were recently developed to treat asthma as part of the CFC to HFA propellant switch mandated by the Montreal Protocol. Two such ICS, beclomethasone dipropionate (BDP) and ciclesonide (CIC), are available in the United States and are formulated in HFA solutions. A major advantage of small-particle ICS is that they have improved total lung deposition and consequently, effective asthma control is achieved at lower daily doses than the large-particle ICS. Another advantage of small-particle ICS is that they are able to reach the small airways and consequently, may result in increased efficacy. Indeed, recent studies have demonstrated the effect of small-particle ICS on asthmatic inflammation in the small airways. Another advantage of small-particle ICS is that they may have an improved safety profile. Small-particle inhalers generally deposit decreased amounts of drug in the oropharynx than their CFC counterparts possibly resulting in a lower incidence of oropharyngeal candidiasis. However, growth studies and most HPA studies do not support improved safety on the basis of particle size alone and some studies suggest even higher systemic bioavailability and safety risk with smaller particles, depending on the molecule and the formulation. Further efficacy and safety studies are clearly warranted to determine any potential advantages of small-particle ICS, particularly in long-term disease modification where large-particle ICS have failed, and in infants and pre-schoolers, in whom airway delivery is problematic with current formulations.

S. Ghdifan, L. Couderc, I. Michelet, C. Leguillon, B. Masseline and C. Marguet. "Bolus methylprednisolone efficacy for uncontrolled exacerbation of cystic fibrosis in children." 2010 *Pediatrics* 125(5):

We present here the clinical course of 4 children with cystic fibrosis, deltaF508/deltaF508, who were admitted with severe respiratory distress and in whom no improvement was obtained by intensive antibiotic therapy and systemic corticosteroids. Chest computed-tomography scans showed hyperinflation and atelectasis. The severity of these exacerbations was explained neither by visible mucus plugging nor by allergic bronchopulmonary aspergillosis. We hypothesized that these clinical features were related to a severe inflammatory process in small airways. Therefore, a high-dose short course of methylprednisolone (1 g/1.73 m<sup>2</sup>) per day for 3 days) was given; all the patients' conditions were dramatically improved, and the therapy was safe. To our knowledge, this is the first reported use of bolus methylprednisolone in the treatment of uncontrolled pulmonary exacerbation in children with cystic fibrosis.

V. Giraud and F. A. Allaert. "Improved asthma control with breath-actuated pressurized metered dose inhaler (pMDI): the SYSTER survey." 2009 *Eur Rev Med Pharmacol Sci* 13(5):

**BACKGROUND AND OBJECTIVES:** Poor inhalation technique may impact both asthma control and compliance in patients with asthma. The SYSTER survey is therefore aimed at assessing the influence of starting or switching an existing therapy to a breath-actuated pressurized metered dose inhaler (pMDI, Autohaler) on these parameters. **MATERIALS AND METHODS:** 709 French general practitioners (GP) enrolled 2588 asthmatic patients in whom therapy with the breath-actuated pMDI was either initiated, or a switch from an existing inhalation device to the said inhaler was deemed necessary. Asthma control was assessed at inclusion and after 4 weeks of treatment with the Juniper Asthma Control Questionnaire (ACQ). In addition, patient adherence was estimated according to the self-reported Morisky scale. **RESULTS:** 1510 patients (mean age 39 years, standard deviation 18 years; 53% male) completed follow-up after 4 weeks. The main reasons for inhaler change were poor asthma control (49%) and poor coordination (40%). After 4 weeks of therapy with the breath-actuated pMDI, asthma control significantly improved from 2.35 +/- 1.05 to 1.32 +/- 0.93 in the ACQ ( $p < 0.0001$ ). Also, self-reported patient adherence

improved from 2.11 +/- 1.43 to 1.57 +/- 1.53 on the Morisky scale ( $p < 0.0001$ ).

DISCUSSION: These results suggest that by focusing on the inhalation devices, asthma control and compliance with treatment are improved.

N. Goodman, M. Morgan, K. Nikander, S. Hinch and S. Coughlin. "Evaluation of patient-reported outcomes and quality of life with the I-neb AAD system in patients with chronic obstructive pulmonary disease." 2010 J Aerosol Med Pulm Drug Deliv 23 Suppl 1:

BACKGROUND: The I-neb Adaptive Aerosol Delivery (AAD) System is a novel portable mesh nebulizer that provides patient feedback regarding adherence to prescribed treatment and compliance with the correct use of the device. METHODS: This multicenter study was composed of 98 patients aged 53-80 years with Chronic Obstructive Pulmonary Disease (COPD). The primary variables were ease of use and satisfaction, which were assessed after 3 months of use of the I-neb AAD System (assessed at visit 2) and after 3 months of use of the patient's previous nebulizer system (assessed at visit 1) using matched questions from pre- and poststudy questionnaires. Quality of life was also assessed at visits 1 and 2 using the validated Chronic Respiratory Questionnaire (CRQ), which consists of dyspnea, emotional function, fatigue, and mastery domains. Differences in the distribution of responses between the pre- and poststudy ease of use and satisfaction questions were analyzed using the Marginal Homogeneity test. Differences in mean CRQ scores between the pre- and poststudy assessments were analyzed using the Wilcoxon Signed-Rank test. RESULTS: Patient responses on the ease of use and satisfaction questions significantly ( $p < \text{or} = 0.001$ ) favored the I-neb AAD System compared with the patient's previous nebulizer system. In addition, significant ( $p < \text{or} = 0.015$ ) improvements in the CRQ dimensions of dyspnea and fatigue were reported with the I-neb AAD System compared with the patients' previous nebulizer systems. CONCLUSIONS: The results from this study demonstrated that patients were more satisfied with the I-neb AAD System and found it easier to use than their previous nebulizer systems. In addition, the I-neb AAD System significantly improved dyspnea and fatigue compared with the patients' previous nebulizer systems, which may reflect improved adherence or more correct use of the nebulizer system with the I-neb AAD System.

J. Haughney, D. Price, N. C. Barnes, J. C. Virchow, N. Roche and H. Chrystyn. "Choosing inhaler devices for people with asthma: Current knowledge and outstanding research needs." 2010 Respir Med:

Recommendations in asthma guidelines presuppose that practitioners have the evidence, information, knowledge, and tools to select inhaler devices appropriate for individual patients. Randomised controlled trials usually exclude patients with suboptimal inhaler technique. There is therefore little evidence on which to base inhaler selection in the real world, where patients often use their inhalers incorrectly. The lung deposition of inhaled drug varies according to inhaler device, drug particle size, inhalation technique, and pattern of inspiratory flow. Even with training, not all patients can use their inhalers correctly and maintain inhaler technique; patients may have inability to handle the inhaler, strong negative preferences, or natural breathing patterns that do not match their prescribed inhaler. Therefore, matching device to the patient may be a better course of action than increasing therapy or training and retraining a patient to use a specific inhaler device. Several research questions require answers to meet the goal of helping prescribers make a more informed choice of inhaler type. Is the level of drug deposition in the lungs a key determinant of clinical short- and long-term outcomes? What should be measured by a clinical tool designed to check inhaler technique and therefore help with device selection? If we have a tool to help in individualising inhaler choice, will we achieve better asthma outcomes? Do we have to refine inhaler device choice for each individual, or will we get better outcomes if we select our current best option in light of current knowledge and apply this on a population level?

S. O. Henderson and T. L. Ahern. "The utility of serial peak flow measurements in the acute asthmatic being treated in the ED." 2010 Am J Emerg Med 28(2):

**BACKGROUND:** Peak flow is used extensively in emergency departments (EDs) to both assess asthma patient's status on arrival as well as to document clinical improvement during treatment. Many algorithms suggest serial peak expiratory flow (PEF) measurements during an ED stay. **OBJECTIVE:** The aim of the study was to assess the contribution of serial PEF in describing the overall improvement of asthmatics over the course of an ED visit for acute exacerbation of their asthma. **METHODS:** This was a prospective institutional review board-approved study of mild/moderate asthmatics presenting to an inner-city ED serving a large Latino population. Peak expiratory flow was measured before treatment (baseline PEF) and after each inhaled treatment (PEF post RX#1, PEF post RX#2, PEF post RX#3) while in the ED. **RESULTS:** One hundred consecutive patients made up this study cohort. The change from baseline PEF to PEF #1 represented 86% (95% confidence interval [CI], 76%-96%) of the total improvement experienced by these patients with asthma. The change from PEF post RX#1 to PEF post RX#2 represented 7.5% (95% CI, -4.2% to 26%) of the total improvement and PEF post RX#2 to PEF post RX#3 represented 8.6% (95% CI, -1% to 34%) of the total PEF improvement seen. **LIMITATION:** No correlation between outcome and PEF% of predicted was made or implied. **CONCLUSION:** The improvement in PEF seen after the first ED inhaled therapy appears to describe most of the total improvement seen in asthmatic patients. Subsequent PEFs provided little additional information.

R. Hodder and D. Price. "Patient preferences for inhaler devices in chronic obstructive pulmonary disease: experience with Respimat Soft Mist inhaler." 2009 Int J Chron Obstruct Pulmon Dis 4:

Current guidelines for the management of chronic obstructive pulmonary disease (COPD) recommend the regular use of inhaled bronchodilator therapy in order to relieve symptoms and prevent exacerbations. A variety of inhaler devices are currently available to COPD patients, and the choice of device is an important consideration because it can influence patients' adherence to treatment, and thus potentially affect the long-term outcome. The Respimat((R)) Soft Mist Inhaler (SMI) generates a slow-moving aerosol with a high fine particle fraction, resulting in deposition of a higher proportion of the dose in the lungs than pressurized metered-dose inhalers (pMDIs) or some dry powder inhalers (DPIs). We review clinical studies of inhaler satisfaction and preference comparing Respimat((R)) SMI against other inhalers in COPD patients. Using objective and validated patient satisfaction instruments, Respimat((R)) SMI was consistently shown to be well accepted by COPD patients, largely due to its inhalation and handling characteristics. In comparative studies with pMDIs, the patient total satisfaction score with Respimat((R)) SMI was statistically and clinically significantly higher than with the pMDI. In comparative studies with DPIs, the total satisfaction score was statistically significantly higher than for the Turbuhaler((R)) DPI, but only the performance domain of satisfaction was clinically significantly higher for Respimat((R)) SMI. Whether the observed higher levels of patient satisfaction reported with Respimat((R)) SMI might be expected to result in improved adherence to therapy and thus provide benefits consistent with those recently shown to be associated with sustained bronchodilator treatment in patients with COPD remains to be proven.

M. Hohenegger. "Novel and Current Treatment Concepts Using Pulmonary Drug Delivery." 2010 Curr Pharm Des:

The novel technologies in pulmonary drug delivery propelled the development of new strategies for pharmacological intervention in human diseases. In particular, this review will focus on pulmonary parameters which influence the delivery of inhaled therapeutics and summarize novel applications and recent innovations. The central issues of

pulmonary drug application are optimal effectiveness under conditions of greatest safety. They not only depend on the properties of the drug but also feature the application vehicle and drug formulation. The optimization of the whole system (drug, formulation and vehicle) is therefore a necessary prerequisite for reliable inhaling medicines. Depending on the desired locus of drug action, the inhaled medicine has to be adjusted to particle size, concentration and chemical composition to guarantee a local or systemic drug action. Local asthma therapy represents the established concept for inhalation therapy. Due to the disease status, deposition of drugs is therefore often seen in central rather than peripheral airways. Recent developments in ultrafine therapeutic particles should therefore provide enough drug deposition even in the deeper airways. Recent approvals and interesting new therapy concepts will be discussed. Beside a pulmonary drug action there is an accumulating number of applications also for systemic drug action after pulmonary drug delivery. These involve among others inhaled insulin, glucagon-like-peptide 1 or growth hormone. But also novel therapeutic systems for gene therapy and vaccination are currently under investigation. Successful feasibility of these novel concepts will be expected in the near future.

P. N. Huynh, L. G. Scott and K. Y. Kwong. "Long-term maintenance of pediatric asthma: focus on budesonide/formoterol inhalation aerosol." 2010 *Ther Clin Risk Manag* 6:

Current national and international asthma guidelines recommend treatment of children with asthma towards achieving and maintaining asthma control. These guidelines provide more stringent recommendations to increase therapy for patients with uncontrolled asthma in order to reduce asthma-related morbidity and mortality. Newer combination agents such as budesonide and formoterol have been shown to be safe and effective in treatment of asthma in children. Use of long-term controller agents like this in combination with improved compliance and treatment of co-morbid conditions have been successful in this endeavor. This review discusses control of pediatric asthma with focus on the use of budesonide in combination with formoterol.

P. Iseli. "[Chronic cough in children--what to consider and how to evaluate?]." 2009 *Praxis (Bern 1994)* 98(23):

There is a long list of differential diagnoses for chronic cough lasting longer than 4 weeks in children. Diagnostic work up starts with a detailed history taking and a clinical investigation followed by a chest X-ray (in one plane) and a spirometry. For the latter reliable results can be achieved by children older than 5 years. If the diagnostic work up is still inconclusive and if the child is in good clinical condition, a 4 weeks' course of inhalation therapy with steroids and betamimetics together with a 2 weeks' course of antibiotics with a macrolide is warranted. In case coughing persists a thorough diagnostic work up is indicated to rule out conditions like cystic fibrosis, relevant humoral immunodeficiencies, primary ciliary dyskinesia, anatomic malformation or chronic pulmonary aspiration, preferably done by a pediatric pulmonologist. Chronic cough has to be considered abnormal in any child under the age of 1 year. For this age group a final diagnosis is of special importance.

M. Kaashmiri, J. Shepard, B. Goodman, W. R. Lincourt, R. Trivedi, A. Ellsworth and A. M. Davis. "Repeat dosing of albuterol via metered-dose inhaler in infants with acute obstructive airway disease: a randomized controlled safety trial." 2010 *Pediatr Emerg Care* 26(3):

**BACKGROUND:** Airway obstruction and bronchial hyperactivity often times lead to emergency department visits in infants. Inhaled short-acting beta2-agonist bronchodilators have traditionally been dispensed to young children via nebulizers in the emergency department. Delivery of bronchodilators via metered-dose inhalers (MDIs) in conjunction

with holding chambers (spacers) has been shown to be effective. **STUDY OBJECTIVE::** Safety and efficacy evaluations of albuterol sulfate hydrofluoroalkane (HFA) inhalation aerosol in children younger than 2 years with acute wheezing caused by obstructive airway disease. **METHODS:** A randomized, double-blind, parallel group, multicenter study of albuterol HFA 180 microg (n = 43) or 360 microg (n = 44) via an MDI with a valved holding chamber and face mask in an urgent-care setting. Assessments included adverse events, signs of adrenergic stimulation, electrocardiograms, and blood glucose and potassium levels. Efficacy parameters included additional albuterol use and Modified Tal Asthma Symptoms Score ([MTASS] reduction in MTASS representing improvement). **RESULTS:** Overall, adverse events occurred in 4 (9%) and 3 (7%) subjects in the 180-microg and 360-microg groups, respectively. Drug-related tachycardia (360 microg) and ventricular extrasystoles (180 microg) were reported in 1 patient each. Three additional instances of single ventricular ectopy were identified from Holter monitoring. No hypokalemia or drug-related QT or QTc prolongation was seen; glucose values and adrenergic stimulation did not significantly differ between treatment groups. In the 180-microg and 360-microg groups, mean change from baseline in MTASS during the treatment period was -2.8 (-49.8%) and -2.9 (-48.4%), and rescue albuterol use occurred in 4 (9%) and 3 (7%) subjects, respectively. **CONCLUSIONS:** Cumulative dosing with albuterol HFA 180 microg or 360 microg via MDI-spacer and face mask in children younger than 2 years did not result in any significant safety issues and improved MTASS by at least 48%.

O. N. Keene, J. Vestbo, J. A. Anderson, P. M. Calverley, B. Celli, G. T. Ferguson, C. Jenkins and P. W. Jones. "Methods for therapeutic trials in COPD: lessons from the TORCH trial." 2009 *Eur Respir J* 34(5):

The TORCH (Towards a Revolution in COPD Health) trial has highlighted some important issues in the design and analysis of long term trials in chronic obstructive pulmonary disease. These include collection of off-treatment exacerbation data, analysis of exacerbation rates and the effect of inclusion of patients receiving inhaled corticosteroids (ICS) prior to randomisation. When effective medications are available to patients who withdraw, inclusion of off-treatment data can mask important treatment effects on exacerbation rates. Analysis of on-treatment data avoids this bias but it needs to be combined with careful analysis of withdrawal patterns across treatments. The negative binomial model is currently the best approach to statistical analysis of exacerbation rates, while analysis of time to exacerbation can supplement this approach. In the TORCH trial, exacerbation rates were higher among patients with previous use of ICS compared to those with no prior use on all study treatments. Retrospective subgroup analysis suggests ICS reduced exacerbation rates compared with placebo, regardless of prior use of ICS before entry to the study. Factorial analysis provides an alternative analysis for trials with combinations of treatments, but assumes no interaction between treatments, an assumption which cannot be verified by a significance test. No definitive conclusions can yet be drawn on whether ICS treatment has an effect on mortality.

D. B. Konga, Y. Kim, S. C. Hong, Y. M. Roh, C. M. Lee, K. Y. Kim and S. M. Lee. "Oxidative stress and antioxidant defenses in asthmatic murine model exposed to printer emissions and environmental tobacco smoke." 2009 *J Environ Pathol Toxicol Oncol* 28(4):

Exposure to particulate emissions from printer and cigarette smoke affects the structure and function of mitochondria, which may account for the pathogenesis of respiratory diseases. The addition of charge for the pollutant aerosols may increase the toxicity by their deposition in the lower respiratory tract. The mitochondrial damage in the lung of asthmatic mice was assessed by examining the levels of reactive oxygen species (ROS), lipid peroxides, reduced glutathione, and the activities of isocitrate dehydrogenase, alpha-ketoglutarate dehydrogenase, succinate dehydrogenase, malate dehydrogenase, complexes I to IV, and cytochrome c. The oxidative phosphorylation (levels of adenosine

triphosphatase) was evaluated for the assessment of mitochondrial functional capacity. We found highly significant elevated levels of ROS, lipid peroxides, and decreased levels of mitochondrial enzymes in the mice exposed to environmental tobacco smoke and printer emissions + environmental tobacco smoke (ETS). However, mice exposed to printer emissions alone exhibited slight significant variations in the parameters studied. From the results, we conclude that printer emissions exert a synergistic effect in the presence of ETS and induce intense damage to the lung mitochondria by disrupting the structural and functional integrity of the mitochondrial membrane.

C. Leach, G. L. Colice and A. Luskin. "Particle size of inhaled corticosteroids: does it matter?" 2009 J Allergy Clin Immunol 124(6 Suppl):

A question with respect to asthma therapy revolves around the issue of whether better efficacy occurs with an ultrafine-particle inhaled corticosteroid because of better lung deposition into the distal airways. This article reviews particle size and delivery devices of different steroids, clinical outcomes of small- versus large-particle steroids, and the issue of pharmacoeconomics.

N. K. Leidy, B. Gutierrez, K. Lampl, T. Uryniak and C. D. O'Brien. "Can patients with asthma feel inhaler therapy working right away? Two clinical trials testing the effect of timing of assessment on patient perception." 2009 J Asthma 46(10):

**BACKGROUND:** Feeling a maintenance therapy work right away may provide positive reinforcement and may offer one way to improve adherence in patients with asthma. Precise measurement is required to accurately compare the presence of this effect across clinical trial treatment groups. **METHODS:** Two randomized, controlled studies tested whether timing of assessment (daily vs weekly, study 1; and predose vs postdose, study 2) influenced patients' reports of whether they can feel a medication working right away (perception), and their satisfaction with this perception (satisfaction). These 2-week US-based multicenter double-blind, parallel-group studies included patients  $\geq 18$  years of age with mild to moderate persistent asthma. In each, patients were randomized to one of two drugs with different onset profiles: budesonide/formoterol pressurized metered-dose inhaler (pMDI) 80/4.5 microg x 2 inhalations (160/9 microg) twice daily or budesonide pMDI 80 microg x 2 inhalations (160 microg) twice daily. Patients were further randomized to complete previously validated perception and satisfaction questions in a cross-over fashion, either daily and weekly (N = 123) or predose and postdose (N = 134). Patient surveys also assessed perceptions of the onset of effect of medication and their value of these perceptions. **RESULTS:** No significant differences were observed in patients' reports of perception, either daily versus weekly or predose versus postdose. A statistically significant difference in satisfaction was found in study 1 only, favoring weekly recall ( $p < 0.05$ ), with sensitivity analysis showing no difference by treatment group ( $p = 0.162$ ). Across both studies, most patients (87%) who perceived their inhaler working right away (136 of 157 patients) identified positive airway sensations. Most patients reported that feeling their medication work right away is reassuring and would help them manage their asthma. **CONCLUSION:** Assessment timing has no effect on patient response to the perception of feeling a medication working right away. Differences found in satisfaction levels reported with weekly versus daily recall were consistent across treatment groups, indicating that no bias was introduced in favor of either treatment group. Patients characterized the perception of feeling a maintenance therapy working right away as easier breathing and reported this perception as beneficial to patient self-care.

C. Motala, R. J. Green, A. I. Manjra, P. C. Potter and H. J. Zar. "Guideline for the management of chronic asthma in children--2009 update." 2009 S Afr Med J 99(12 Pt 2):

**OBJECTIVE:** To revise the guideline for the diagnosis and management of chronic asthma in children in view of the following considerations: the existing South African Childhood Asthma Working Group (SACAWG) guideline was produced 10 years ago; diagnosis of asthma in young children remains a challenge; evidence-based treatment is the new paradigm; new treatment approaches to achieving and maintaining control; therapeutic roles of several medications have evolved; more studies and data on treatment in young children; new medications and formulations; a change of emphasis in assessing asthma control to guide treatment changes. The main aim of the guideline is to promote a better standard of treatment based on understanding of the pathophysiology and pharmacotherapy of asthma, and encouraging uniformity in asthma management.

**EVIDENCE:** A detailed literature review by a working group of clinicians from relevant disciplines. The strategies recommended are classified according to the evidence category in Appendix B, and denoted as Evidence A, B, C and D.

**RECOMMENDATIONS:** These include an appropriate diagnostic approach, environmental control measures, treatment options, definition of asthma control, and strategies to achieve control.

**ENDORSEMENT:** The guideline document was endorsed by the South African Thoracic Society (SATS), the National Asthma Education Programme (NAEP), the South African Paediatric Association (SAPA) and the South African Academy of Family Practice.

P. Nair, J. Hanrahan and F. E. Hargreave. "Clinical equivalence testing of inhaled bronchodilators." 2009 Pol Arch Med Wewn 119(11):

There are no standardized methods to demonstrate in-vivo bioequivalence of inhaled bronchodilators. The most practical method of showing therapeutic equivalence in vivo is by estimating their relative potencies (RP) in clinical efficacy studies. The RP of bronchodilators may be estimated by comparing either their bronchodilator or bronchoprotective properties. Bronchodilator studies are easier to perform and may better model the physiologic effect of many agents, including inhaled beta-agonists. However, it may be difficult to demonstrate steep dose-response for these outcomes, except in cumulative study designs. Bioequivalence trials may be especially challenging when involving pressurized metered-dose inhalers, as a single actuation - the lowest feasible dose to include in the evaluation, may already produce bronchodilation that is at or near the plateau of the dose-response curve. Protection against bronchoconstriction induced by a direct inhaled stimulus like methacholine or histamine affords a reliable and practical method of comparing inhaled bronchodilators and estimating their RP. Inhalational bronchoprovocation testing allows for easier repeatability and quantitation of the stimulus necessary to produce a predetermined degree of bronchoconstriction, and the degree of protection afforded by the bronchoprotection agent. RP studies using adequate methodology are necessary to compare long-acting bronchodilators and both short- and long-acting bronchodilators in patients who are also on inhaled corticosteroids.

G. Nicolini, G. Cremonesi and A. S. Melani. "Inhaled corticosteroid therapy with nebulized beclometasone dipropionate." 2010 Pulm Pharmacol Ther 23(3):

Inhaled corticosteroids (ICS) are the most effective anti-inflammatory agents for the management of chronic persistent asthma and are therefore recommended as first-line antiasthmatic therapy in children and adults. In various settings, the administration of ICS via nebulizer rather than hand-held inhaler (HHI) may have certain advantages, as many patients with HHI fail to use these devices properly or efficiently. In particular, young children, the elderly, the acutely ill, and those with restricted dexterity may be unable to coordinate inhalation with actuation of the device or to generate sufficient inspiratory flow to operate breath-actuated devices effectively. Compliance with nebulized therapy may also be better than that with a pressurized metered-dose inhaler

(pMDI) plus spacer. Systematic reviews conclude that there is no significant difference in clinical effects between nebulizers and HHI. Performance and clinical effect of nebulization are influenced by several technical aspects such as the nebulizer-drug combination, nebulizer type, output and lung deposition. Among the currently available ICS, nebulized beclometasone dipropionate (BDP) has been in clinical use for more than 35 years, and has demonstrated marked clinical efficacy and a favorable tolerability profile in children and adults with chronic persistent asthma. The clinical efficacy of nebulized beclometasone is discussed in the present review using data from 13 published studies, which included a total of 1250 patients. Three multicenter, randomized, double-blind studies showed that nebulized BDP is as effective as BDP via pMDI plus spacer in a 2:1 dose ratio. Controlled trials involving 497 adults and children demonstrated similar clinical efficacy between nebulized BDP and either nebulized fluticasone propionate or nebulized budesonide. In all these trials, treatment-related adverse effects were generally uncommon, most were mild-to-moderate in severity, and most were associated with the respiratory system. Meta-analyses show that BDP, like other inhaled corticosteroids, has no major influence on patient height, urinary cortisol concentration, or bone metabolism, thus suggesting the absence of growth retardation or any marked effect on adrenal function or the hypothalamic-pituitary-adrenal axis when used in the approved dose range. Overall, nebulized BDP appears to have a particularly important place in asthma therapy: as a general alternative to HHIs (e.g. in patients with poor HHI compliance); when patients such as children or the elderly are unable to operate HHIs because of poor hand-lung coordination, lack of cooperation, or low inspiratory flow rate; and when high dosages of ICS are required, such as in adults with severe, corticosteroid-dependent asthma.

K. Nikander, J. Denyer, M. Dodd, T. Dyche, K. Webb, P. Weller and D. Stableforth. "The adaptive aerosol delivery system in a telehealth setting: patient acceptance, performance and feasibility." 2010 J Aerosol Med Pulm Drug Deliv 23 Suppl 1:

**BACKGROUND:** The telehealth service is one of the fastest growing healthcare segments. It is increasingly utilizing computer technology and telecommunication equipment to either provide continuous vital sign monitoring or facilitate patient care at home, rather than relying solely on in-person care. **METHODS:** We conducted a 6-week open study in nineteen patients with cystic fibrosis enrolled from three centers, to investigate patient perception of a telehealth enabled nebulizer system (Prodose Adaptive Aerosol Delivery [AAD] System), which enabled the doorstep delivery of repeat medication. **RESULTS:** The results showed that patient confidence in the device and perception of ease of use was high with no significant change between the start and end of the trial. Views on the home delivery of medication were split between 'great' and 'inconvenient.' However, if the delivery system had been more flexible and delivered all the patients' drugs, the majority of patients would have had their medication delivered in this way. **CONCLUSIONS:** The trial showed that it was possible to build telehealth technology into an advanced nebulizer system, and that patient acceptance of the technology was unlikely to be a barrier to the adoption of such a telehealth system.

T. L. Noah, S. S. Ivins, K. A. Abode, P. W. Stewart, P. H. Michelson, W. T. Harris, M. M. Henry and M. W. Leigh. "Inhaled versus systemic antibiotics and airway inflammation in children with cystic fibrosis and Pseudomonas." 2010 Pediatr Pulmonol 45(3):

**RATIONALE:** Inhaled tobramycin has been shown to transiently clear Pseudomonas from lower airways in early cystic fibrosis (CF), but does not markedly reduce lung inflammation, a key factor in disease progression. **OBJECTIVE:** Test the hypothesis that systemic antibiotics are more effective than inhaled antibiotics for reducing lower airways inflammation. **METHODS:** Clinically stable CF children with recent Pseudomonas were randomized to receive 4 weeks of inhaled tobramycin or 2 weeks of systemic antibiotics (intravenous ceftazidime and tobramycin). Bronchoalveolar lavage fluid was obtained just

before and 4-6 weeks after treatment. The primary outcome was change in % neutrophils in lavage fluid. RESULTS: Fifteen subjects (inhaled = 6, systemic = 9) completed the protocol. Three Systemic Group subjects could not have central venous access established and were treated with oral ciprofloxacin (plus inhaled tobramycin) for 2 weeks as an alternative "systemic" regimen, per protocol. Groups were well matched in age, markers of disease severity, and initial % neutrophils. The Systemic Group showed a modest median change in percent neutrophils (-7%) which was not statistically significant compared to inhaled (+5.4%,  $P = 0.07$ ). However, the Systemic Group had significantly greater reductions in total cells (-50% vs. -3%,  $P < 0.01$ ) and neutrophils (-74% vs. -10%,  $P = 0.02$ ) per ml lavage fluid. Both groups had reduced bacterial quantity after treatment, but there was no significant difference between groups. CONCLUSIONS: In clinically stable children with CF, systemic antibiotics result in greater short-term reduction in lower airways inflammation than inhaled antibiotics.

P. M. O'Byrne. "Obstructive lung disease from conception to old age: differences in the treatment of adults and children with asthma." 2009 Proc Am Thorac Soc 6(8):

Achieving asthma control is the focus of asthma management. Inhaled corticosteroids are the most effective treatment for asthma in children and adults, with no evidence that the magnitude of benefit differs between adults and school-aged children. Leukotriene inhibitors are more widely used in children than in adults. This may be because provoking stimuli, such as environmental allergens and frequent exercise, are more important asthma triggers in children or because parental concerns about the side effects of treatment with ICS. Inhaled corticosteroid/long-acting inhaled beta(2)-agonist combinations may not be as effective in children as in they are adults in improving asthma control and reducing asthma exacerbations.

M. Otsuki, M. N. Eakin, C. S. Rand, A. M. Butz, V. D. Hsu, I. H. Zuckerman, J. Ogborn, A. Bilderback and K. A. Riekert. "Adherence feedback to improve asthma outcomes among inner-city children: a randomized trial." 2009 Pediatrics 124(6):

OBJECTIVE: We evaluated the longitudinal effects of home-based asthma education combined with medication adherence feedback (adherence monitoring with feedback [AMF]) and asthma education alone (asthma basic care [ABC]) on asthma outcomes, relative to a usual-care (UC) control group. METHODS: A total of 250 inner-city children with asthma (mean age: 7 years; 62% male; 98% black) were recruited from a pediatric emergency department (ED). Health-outcome measures included caregiver-frequency of asthma symptoms, ED visits, hospitalizations, and courses of oral corticosteroids at baseline and 6-, 12-, and 18-month assessments. Adherence measures included caregiver-reported adherence to inhaled corticosteroid (ICS) therapy and pharmacy records of ICS refills. Multilevel modeling was used to examine the differential effects of AMF and ABC compared with UC. RESULTS: ED visits decreased more rapidly for the AMF group than for the UC group, but no difference was found between the ABC and UC groups. The AMF intervention led to short-term improvements in ICS adherence during the active-intervention phase relative to UC, but this improvement decreased over time. Asthma symptoms and courses of corticosteroids decreased more rapidly for the ABC group than for the UC group. Hospitalization rates did not differ between either intervention group and the UC group. No differences were found between the ABC and AMF groups on any outcome. CONCLUSIONS: Asthma education led to improved adherence and decreased morbidity compared with UC. Home-based educational interventions may lead to modest short-term improvements in asthma outcomes among inner-city children. Adherence feedback did not improve outcomes over education alone.

D. Price, A. Robertson, K. Bullen, C. Rand, R. Horne and H. Staudinger. "Improved adherence with once-daily versus twice-daily dosing of mometasone furoate administered via a dry powder inhaler: a randomized open-label study." 2010 BMC Pulm Med 10:

**BACKGROUND:** Poor adherence with prescribed asthma medication is a major barrier to positive treatment outcomes. This study was designed to determine the effect of a once-daily administration of mometasone furoate administered via a dry powder inhaler (MF-DPI) on treatment adherence compared with a twice-daily administration. **METHODS:** This was a 12-week open-label study designed to mimic an actual clinical setting in patients  $\geq 12$  years old with mild-to-moderate persistent asthma. Patients were randomized to receive MF-DPI 400 microg once-daily in the evening or MF-DPI 200 microg twice-daily. Adherence was assessed primarily using the number of actual administered doses reported from the device counter divided by the number of scheduled doses. Self-reports were also used to determine adherence. Health-related quality of life, healthcare resource utilization, and days missed from work or school were also reported. **RESULTS:** 1233 patients were randomized. The mean adherence rates, as measured by the automatic dose counter, were significantly better ( $P < 0.001$ ) with MF-DPI 400 microg once-daily in the evening (93.3%) than with MF-DPI 200 microg twice-daily (89.5%). Mean adherence rates based on self-reports were also significantly better ( $P < 0.001$ ) with MF-DPI 400 microg QD PM (97.2%) than with MF-DPI 200 microg twice-daily (95.3%). Adherence rates were lower in adolescents (12-17 years old). Health-related quality of life improved by 20% in patients using MF-DPI once-daily in the evening and by 14% in patients using MF-DPI twice-daily. Very few ( $< 8\%$ ) patients missed work/school. **CONCLUSION:** Mean adherence rates were greater with a once-daily dosing regimen of MF-DPI than with a twice-daily dosing regimen. This trial was completed prior to the ISMJE requirements for trial registration.

P. Quinet, C. A. Young and F. Heritier. "The use of dry powder inhaler devices by elderly patients suffering from chronic obstructive pulmonary disease." 2010 Ann Phys Rehabil Med 53(2):

Twenty-five COPD patients, aged 65 years or above, were recruited to test their ability to use dry powder inhaler Handihaler (Boehringer-Ingelheim) and Aerolizer (Novartis). The results of a score created to evaluate the inhalation technique were compared with age, MMSE, Barthel Index, FEV(1), maximum inspiratory and expiratory pressures, and peak inspiratory flow (PIF). **RESULTS:** Dry powder inhalers were correctly used by 60% of the patients (15 out of 25). Among the capable ones, 13 out of 15 were aged less than 80 years ( $p < 0.02$ ), 13 out of 15 had a maximum inspiratory pressure greater or equal to 53 cm H<sub>2</sub>O ( $p < 0.001$ ) and a PIF greater or equal to 120 l/min ( $p < 0.05$ ). All skilled patients had a minimum MMSE of 25 ( $p < 0.001$ ). **CONCLUSION:** In a geriatric population, age, the decrease of maximum inspiratory pressure and PIF as well as cognitive functions, limit the use of dry powder inhalers.

F. Ratjen, A. Munck, P. Kho and G. Angyalosi. "Treatment of early Pseudomonas aeruginosa infection in patients with cystic fibrosis: the ELITE trial." 2010 Thorax 65(4):

**RATIONALE:** Antibiotic therapy for early Pseudomonas aeruginosa infection in patients with cystic fibrosis (CF) is effective, but the optimal therapeutic regimen and duration for early treatment remains unclear. The EarLy Inhaled Tobramycin for Eradication (ELITE) study was designed to assess the efficacy and safety of two regimens (28 and 56 days) of tobramycin inhalation solution (TIS) 300 mg/5 ml twice daily for the treatment of early onset P aeruginosa infection in patients with CF. **METHODS:** In this open-label randomised multicentre study, patients with CF (aged  $\geq 6$  months) with early P aeruginosa infection were treated for 28 days with TIS twice daily administered by the PARI LC PLUS (PARI GmbH, Starnberg, Germany) jet nebuliser. After 28 days, patients were randomised 1:1 to either stop TIS ( $n=45$ ) or to receive a further 28 days of TIS ( $n=43$ ). The primary endpoint was the median time to recurrence of P aeruginosa (any

strain). Secondary endpoints included the proportion of patients free of *P. aeruginosa* infection 1 month after cessation of therapy and safety assessments. **RESULTS:** The median time to recurrence of *P. aeruginosa* (any strain) was similar between the two groups. In total, 93% and 92% of the patients were free of *P. aeruginosa* infection 1 month after the end of treatment and 66% and 69% remained free at the final visit in the 28-day and 56-day groups, respectively. TIS was well tolerated. **CONCLUSIONS:** Treatment with TIS for 28 days is an effective and well tolerated therapy for early *P. aeruginosa* infection in patients with CF. **TRIAL REGISTRATION NUMBER:** NCT00391976.

G. J. Rodrigo, H. Neffen, F. D. Colodenco and J. A. Castro-Rodriguez. "Formoterol for acute asthma in the emergency department: a systematic review with meta-analysis." 2010 *Ann Allergy Asthma Immunol* 104(3):

**BACKGROUND:** Although several published studies have suggested that formoterol fumarate could be equivalent to short-acting beta2-agonists (SABAs) for the treatment of asthma exacerbations, its role in acute asthma treatment remains undefined. **OBJECTIVE:** To evaluate the efficacy and safety of inhaled formoterol (compared with SABAs) for the emergency department treatment of patients with acute asthma. **METHODS:** Systematic searches were conducted in MEDLINE, EMBASE, the Cochrane Controlled Trials Register, and manufactures' trial registers, without language restriction. The primary outcomes were spirometric measures. The secondary outcomes included final serum potassium level, heart rate, electrocardiographic QT interval corrected for heart rate, and total withdrawals. **RESULTS:** Nine randomized controlled trials (including 576 participants) were selected. No significant difference could be detected between formoterol and SABAs for any of the selected time points: at 30 to 40 minutes after the first administration of study drugs (standardized mean difference, -0.19; 95% confidence interval, -0.56 to 0.17; I<sup>2</sup> = 75%), at the end of treatment (standardized mean difference, -0.25; 95% confidence interval, -0.72 to 0.13; I<sup>2</sup> = 89%), and at 60 to 90 minutes after the last dose (standardized mean difference, -0.13; 95% confidence interval, -0.55 to 0.28; I<sup>2</sup> = 80%). Similarly, there were no significant differences between formoterol and SABAs regarding final serum potassium level, heart rate, QT interval, hospitalization rate, and total withdrawals. **CONCLUSIONS:** This review suggests that high-dose formoterol administered via dry powder inhaler is well tolerated and provides rapid and effective bronchodilation, similar to high-dose salbutamol or terbutaline via metered-dose inhaler or nebulizer. Formoterol may be used in the treatment of acute asthma in the emergency department setting.

E. T. Rotta, S. L. Amantea, P. E. Froehlich and A. Becker. "Plasma concentrations of salbutamol in the treatment of acute asthma in a pediatric emergency. Could age be a parameter of influence?" 2010 *Eur J Clin Pharmacol* 66(6):

**OBJECTIVE:** The objective was to determine if the plasma concentrations of salbutamol, obtained during inhalation treatment of infantile acute asthma, are influenced by age range and by the aerosol system used. **METHOD:** A randomized clinical trial was conducted in 46 children (1-5 years of age) with a diagnosis of acute asthma crisis, established in an emergency room pediatric service. Twenty-five children received salbutamol using a pressurized metered-dose inhaler with spacer (50 microg/kg), and 21 children received salbutamol by nebulization (150 microg/kg), three times during a 1-h period. At the end of the treatment, one blood sample was drawn and the plasma was stored for later determination of salbutamol concentration (liquid chromatography). Salbutamol plasma concentrations were compared in two age groups (< or =2 years and >2 years of age). The type of device used (pressurized metered-dose inhaler or nebulizer) and the need of hospitalization were also tested. The Mann-Whitney U test was used with the level of significance set at 5% (P < 0.05). **RESULTS:** No differences were detected regarding either the aerosol delivery system used or the need for hospitalization in relation to the plasma concentrations of salbutamol. However, higher plasma levels were found in

patients >2 years vs patients < or =2 years [median (IQR): 9.40 (6.32-18.22) vs. 4.65 (2.77-10.10) ng/mL], demonstrating a significance difference (P = 0.05). CONCLUSION: Salbutamol plasma concentrations were influenced by age group of the patients submitted to inhalation therapy, even with doses adjusted for body weight. After correcting for the differences in the bioavailabilities of the delivery systems, the concentrations were independent of the aerosol delivery device used.

B. L. Rottier and E. J. Duiverman. "Anti-inflammatory drug therapy in asthma." 2009 *Paediatr Respir Rev* 10(4):

Asthma is a disease with chronic inflammation of the airways and anti-inflammatory treatment is a logical treatment. Inhaled corticosteroids [ICS] remain the cornerstone of anti-inflammatory therapy in recent international guidelines. Asthma cannot be cured by any medication: if the drug is discontinued, the disease manifestations return. This has been proven at all ages. In preschool children the diagnosis of asthma is difficult to establish. In this heterogeneous group ICS or leukotriene receptor antagonists [LTRA] are just as effective as placebo; in the future it will hopefully be possible to describe characteristics of responders. LTRA are an alternative in mild asthma, especially when mono-triggered viral related wheeze is present. Theophylline is effective and also has bronchodilatory properties, which need to be balanced against the relatively frequent side effects. The working mechanisms of anti-inflammatory asthma medications including ICS, LTRA, cromones, macrolides and theophylline are described.

A. Roy, L. Lurslurchachai, E. A. Halm, X. M. Li, H. Leventhal and J. P. Wisnivesky. "Use of herbal remedies and adherence to inhaled corticosteroids among inner-city asthmatic patients." 2010 *Ann Allergy Asthma Immunol* 104(2):

**BACKGROUND:** Complementary and alternative medicines (CAM), such as herbal remedies, are widely used by patients with chronic diseases, such as asthma. However, it is unclear whether use of the herbal remedies is associated with decreased adherence to inhaled corticosteroids (ICSs), a key component of asthma management. **OBJECTIVE:** To examine the association among use of herbal remedies, adherence to prescribed ICSs, and medication and disease beliefs. **METHODS:** We surveyed 326 adults with persistent asthma who received care at 2 inner-city outpatient clinics. Patients were asked about CAM use (teas, herbs, and rubs) for the treatment of asthma in the prior 6 months. Medication adherence was assessed using the Medication Adherence Report Scale, a validated self-report measure. Univariate and multiple regression analyses were used to assess the relationship among herbal remedy use, adherence to ICSs, and medication and disease beliefs. **RESULTS:** Overall, 25.4% (95% confidence interval, 20%-30%) of patients reported herbal remedy use. Univariate analyses showed that herbal remedy use was associated with decreased ICS adherence and increased asthma morbidity. In multivariable analysis, herbal remedy use was associated with lower ICS adherence (odds ratio, 0.4; 95% confidence interval, 0.2-0.8) after adjusting for confounders. Herbal remedy users were also more likely to worry about the adverse effects of ICSs (P = .01). **CONCLUSIONS:** The use of herbal remedies was associated with lower adherence to ICSs and worse outcomes among inner-city asthmatic patients. Medication beliefs, such as worry about ICS adverse effects, may in part mediate this relationship. Physicians should routinely ask patients with asthma about CAM use, especially those whose asthma is poorly controlled.

S. R. Salpeter, A. J. Wall and N. S. Buckley. "Long-acting beta-agonists with and without inhaled corticosteroids and catastrophic asthma events." 2010 *Am J Med* 123(4):

**BACKGROUND:** It is unclear whether long-acting beta-agonists with concomitant inhaled corticosteroids increase asthma-related intubations and deaths. We pooled data on long-acting beta-agonists with variable and concomitant inhaled corticosteroids to evaluate the risk for catastrophic asthma events. **METHODS:** We conducted searches of electronic databases, the US Food and Drug Administration website, clinical-trials registries, and selected references through December 2008. We analyzed randomized controlled trials in patients with asthma, which lasted at least 3 months, evaluated long-acting beta-agonists compared with placebo or long-acting beta-agonists with inhaled corticosteroids compared with corticosteroids alone, and included at least 1 catastrophic event, defined as asthma-related intubation or death. **RESULTS:** In pooled trial data that included 36,588 participants, long-acting beta-agonists increased catastrophic events 2-fold (Peto odds ratio [OR] 2.10; 95% confidence interval [CI], 1.37-3.22). Statistically significant increases were seen for long-acting beta-agonists with variable corticosteroids compared with placebo (OR 1.83; 95% CI, 1.14-2.95) and for concomitant treatment with corticosteroids compared with corticosteroids alone (OR 3.65; 95% CI, 1.39-9.55). Similar increases in risk were seen for variable and concomitant corticosteroid use, salmeterol and formoterol, and children and adults. When the analysis was restricted to trials with controlled corticosteroid use, given as part of the study intervention, concomitant treatment still increased catastrophic events compared with corticosteroids alone (OR 8.19; 95% CI, 1.10-61.18). **CONCLUSION:** Long-acting beta-agonists increase the risk for asthma-related intubations and deaths, even when used in a controlled fashion with concomitant inhaled corticosteroids.

G. S. Sawicki, R. C. Strunk, B. Schuemann, R. Annett, S. Weiss and A. L. Fuhlbrigge. "Patterns of inhaled corticosteroid use and asthma control in the Childhood Asthma Management Program Continuation Study." 2010 *Ann Allergy Asthma Immunol* 104(1):

**BACKGROUND:** Daily controller medication use is recommended for children with persistent asthma to achieve asthma control. **OBJECTIVE:** To examine patterns of inhaled corticosteroid (ICS) use and asthma control in an observational study of children and adolescents with mild-to-moderate asthma (the Childhood Asthma Management Program Continuation Study). **METHODS:** We assessed patterns of ICS use during a 12-month period (consistent, intermittent, and none) and asthma control (well controlled vs poorly controlled). Multivariate logistic regression examined the association between pattern of ICS use and asthma control. **RESULTS:** Of 914 patients enrolled, 425 were recommended to continue receiving ICS therapy in the Childhood Asthma Management Program Continuation Study. Of these patients, 46% reported consistent ICS use and 20% reported no ICS use during year 1. By year 4, consistent ICS use decreased to 20%, whereas no ICS use increased to 57%; poorly controlled asthma was reported in 18% of encounters. In multivariate models controlling for age, sex, forced expiratory volume in 1 second, and asthma severity assessment, patients reporting consistent ICS use during a 12-month period were more likely to report poor asthma control (odds ratio, 1.6; 95% confidence interval, 1.2-2.1) compared with those reporting no ICS use. **CONCLUSIONS:** In this observational study of children and adolescents with mild-to-moderate asthma, most did not report continued use of ICS. Patients recommended to continue receiving ICS therapy and reporting consistent ICS use were less likely to report well-controlled asthma even after controlling for markers of asthma severity. Although residual confounding by severity cannot be ruled out, many children and adolescents may not achieve well-controlled asthma despite consistent use of ICS.

N. Scichilone, A. Contino, G. B. Figlioli, G. Paglino and V. Bellia. "Patient perspectives in the management of asthma: improving patient outcomes through critical selection of treatment options." 2010 Patient Prefer Adherence 4:

Asthma is a chronic inflammatory disorder of the airways that requires long-term treatment, the goal of which is to control clinical symptoms for extended periods with the least possible amount of drugs. International guidelines recommend the addition of an inhaled long-acting beta2-agonist (LABA) to a low- to medium-dose inhaled corticosteroid (ICS) when low doses of ICS fail to control asthma symptoms. The fixed combined administration of ICS/LABA improves patient compliance, reducing the risk of therapy discontinuation. The relative deposition pattern of the inhaled drug to the target site is the result of a complex interaction between the device used, the aerosol formulation and the patient's adherence to therapy. Different inhalation devices have been introduced in clinical practice over time. The new hydrofluoroalkane (HFA) solution aerosols allow for the particle size to be modified, thus leading to deeper penetration of the medication into the lung. The Modulite((R)) technology allows for the manipulation of inhaled HFA-based solution formulations, such as the fixed beclomethasone/formoterol combination, resulting in a uniform treatment of inflammation and bronchoconstriction. The success of any anti-asthmatic treatment depends on the choice of the correct device and the adherence to therapy.

S. Shah, M. White, T. Uryniak and C. D. O'Brien. "The functionality of a budesonide/formoterol pressurized metered-dose inhaler with an integrated actuation counter." 2010 Allergy Asthma Proc 31(1):

Integration of an actuation counter into pressurized metered-dose inhalers (pMDIs) can allow patients to accurately determine the remaining number of medication doses. This study was designed to assess the functionality of budesonide/formoterol (Symbicort; AstraZeneca, Dunkerque, France) pMDI with an integrated actuation counter in a clinical setting. Children aged > or =6 years, adolescents, and adults with inhaled corticosteroid-dependent asthma participated in this 6-week, randomized, open-label, multicenter study (SD-039-0743; D5896C00743). Patients were treated with budesonide/formoterol pMDI with no actuation counter (80/4.5 micrograms x 2 inhalations [160/9 micrograms] twice daily) during a 7- to 10-day run-in period. Qualifying patients were then randomized into one of three groups treated with budesonide/formoterol pMDI with actuation counter (80/4.5 micrograms x 2 inhalations [160/9 micrograms] twice daily): group 1, 96 actuations (24 days); group 2, 120 actuations (30 days); or group 3, 128 actuations (32 days). Actuation count was assessed using position of the counter arrow, patient/caregiver reports (daily log and actuation counter final reading), and device (canister plus actuation counter assembly) weight change. Patients/caregivers rated ease of device use. There was good agreement across treatment groups (n = 254) between patient/caregiver-reported actuation counts and counts determined by the angular position of the arrow. Analysis of device weight change versus other estimates of actuation counts in groups 1 and 2 indicated that the device did not undercount the number of actuations sprayed. Most patients (93%) indicated the device was "extremely easy" or "very easy" to use. Clinical functionality and reliability of the budesonide/formoterol pMDI device with an actuation counter were established.

S. Singh and Y. K. Loke. "Risk of pneumonia associated with long-term use of inhaled corticosteroids in chronic obstructive pulmonary disease: a critical review and update." 2010 Curr Opin Pulm Med 16(2):

**PURPOSE OF REVIEW:** The aim was to determine the effects of long-term inhaled corticosteroid use on pneumonia in patients with chronic obstructive pulmonary disease (COPD) via systematic searches of MEDLINE, EMBASE, ISI, regulatory documents and manufacturers' trial registries. **RECENT FINDINGS:** Our updated meta-analysis of 24

long-term randomized controlled trials involving 23 096 participants shows a significantly increased risk of pneumonia with the use of inhaled corticosteroids in COPD (relative risk 1.57, 95% confidence interval 1.41-1.75,  $P < 0.0001$ ). The increased risk of pneumonia is not accompanied by a corresponding increase in mortality. The elderly and those with more severe disease and lower forced expiratory volume in 1s are at the highest risk of pneumonia. The trials of currently available inhaled corticosteroids have included participants with varying duration of inhaled corticosteroid exposure and COPD severity, with apparent differences in the proportion of pneumonia ascertained among these trials. The absence of adequately powered long-term head-to-head trials precludes any definitive conclusions on intraclass differences in risk. SUMMARY: Clinicians should consider the long-term risks of pneumonia with the use of inhaled corticosteroids in patients with COPD. Adequately powered long-term head-to-head trials with objective pneumonia definitions, active ascertainment and radiologic and microbiologic confirmation are needed to clarify any intraclass differences in the risk of pneumonia.

D. P. Skoner, D. A. Gentile and B. Angelini. "Effect of therapeutic doses of mometasone furoate on cortisol levels in children with mild asthma." 2010 Allergy Asthma Proc 31(1):

Corticosteroids are the foundation of pharmacologic treatment for children with asthma. However, high-dose inhaled corticosteroid treatment can cause hypothalamic-pituitary-adrenal (HPA) axis suppression. We investigated the effect of three doses of mometasone furoate administered via dry-powder inhaler (MF-DPI) on the HPA axis in children. Fifty children (6-11 years) with mild asthma of  $>$  or  $=6$  months' duration were randomized to MF-DPI, 100 ( $n = 13$ ), 200 ( $n = 13$ ), or 400 micrograms b.i.d. ( $n = 12$ ), or placebo ( $n = 12$ ) for 29 days. The primary end point was change from baseline in the 12-hour area under the plasma-cortisol-concentration-time curve (AUC). Secondary parameters included plasma cortisol response to cosyntropin stimulation and 24-hour urinary free cortisol concentrations. Compared with placebo, AUC changes associated with treatments of MF-DPI, 100 or 200 micrograms b.i.d., were not significant, whereas a significant change was observed with MF-DPI, 400 micrograms b.i.d. (27%;  $p = 0.05$ ). Responses to cosyntropin stimulation and urinary cortisol measurements were similar to placebo with all MF-DPI doses. All regimens were well tolerated. MF-DPI did not have a significant effect on plasma or urinary cortisol levels at doses up to 200 micrograms b.i.d. in children with mild asthma. Higher MF-DPI doses may potentially suppress the HPA axis.

J. Spahn, K. Sheth, W. S. Yeh, D. A. Stempel and R. H. Stanford. "Dispensing of fluticasone propionate/salmeterol combination in the summer and asthma-related outcomes in the fall." 2009 J Allergy Clin Immunol 124(6):

BACKGROUND: Asthma exacerbations occur year-round; however, peak asthma-related events occur in the fall and are frequently associated with viral respiratory infections. OBJECTIVE: To compare the rates of asthma-related emergency department (ED) visits and hospitalizations in the fall (September, October, November) between users and nonusers of fluticasone propionate plus salmeterol in a single inhaler (FSC) in the preceding summer. METHODS: This was a retrospective, observational study using health care claims from a large managed care database. Patients age 4 to 55 years with both a medical claim for asthma and a pharmacy claim for FSC were categorized into 3 age groups: children (4-11 years), adolescents (12-18 years), and adults (19-55 years). RESULTS: There were 201,973 observations of FSC dispensings and 184,143 observations without FSC. Across all age groups, summertime dispensings of FSC were associated with a significantly lower ( $P < .001$ ) risk of an asthma-related ED visit (4-11 years: adjusted odds ratio [OR], 0.54, 95% CI, 0.49-0.60; 12-18 years: OR, 0.59, 95% CI, 0.54-0.64; 19-55 years: OR, 0.53, 95% CI, 0.51-0.55) or hospitalization (4-11 years: OR, 0.43, 95% CI, 0.35-0.54; 12-18 years: OR, 0.49, 95% CI, 0.40-0.60; 19-55 years: OR, 0.61, 95% CI, 0.57-0.65) in the subsequent fall. This protective effect persisted even for patients with fall dispensings of FSC. The risk of oral corticosteroid dispensing in the fall

was also significantly reduced in all age groups. CONCLUSION: Summertime dispensings of FSC were associated with a decreased risk of serious asthma-related outcomes in the subsequent fall. Continuous use of FSC before seasonal viral exposure may decrease seasonally related exacerbations.

C. R. Sudfeld, E. C. Dasenbrook, W. G. Merz, K. C. Carroll and M. P. Boyle. "Prevalence and risk factors for recovery of filamentous fungi in individuals with cystic fibrosis." 2010 J Cyst Fibros 9(2):

BACKGROUND: Filamentous fungi are frequently recovered from respiratory cultures of individuals with CF. METHODS: A CF cohort database was utilized to determine filamentous fungal prevalence and risk factors. RESULTS: The prevalence of filamentous fungal isolation increased from 2.0% in 1997 to 28.7% in 2007. The odds of isolating filamentous fungi during a quarter was greater in CF adults [ $p < 0.001$ ], during chronic oral antibiotic use [ $p = 0.002$ ] and increased with each 10% drop in FEV(1) percent predicted [ $p = 0.005$ ], while inhaled corticosteroids surprisingly decreased the likelihood [ $p = 0.012$ ]. The direction of these effects persisted after excluding individuals with ABPA. A sub-analysis determined older age [ $p = 0.019$ ] and use of inhaled antibiotics [ $p = 0.011$ ] were independent risk factors for onset of fungal colonization. CONCLUSIONS: This study suggests that isolation of filamentous fungi in CF at JHH has increased and risk factors include older age, decreased lung function, and chronic oral antibiotics.

E. R. Sutherland, C. A. Camargo, Jr., W. W. Busse, E. O. Meltzer, H. G. Ortega, S. W. Yancey, A. H. Emmett and D. A. Stempel. "Comparative effect of body mass index on response to asthma controller therapy." 2010 Allergy Asthma Proc 31(1):

Increases in body mass index (BMI) are reported to influence asthma severity and response to treatment. This analysis was designed to explore whether increasing BMI altered the comparative response to treatment with either fluticasone propionate (FP) or montelukast. Two double-blind, randomized, parallel-group trials of 12-weeks duration comparing FP, 88 micrograms, twice daily or montelukast, 10 mg, daily were evaluated. Subjects with mild-moderate persistent asthma were retrospectively stratified by BMI of  $< 20$  kg/m<sup>2</sup> (underweight), 20-24.9 kg/m<sup>2</sup> (normal weight), 25-29.9 kg/m<sup>2</sup> (overweight), and  $\geq 30$  kg/m<sup>2</sup> (obese). Outcomes included mean changes in forced expiratory volume in 1 second (FEV(1)) and morning peak flow, daily albuterol use, and daily symptom scores. There were 1052 subjects evenly distributed between FP and montelukast by baseline parameters, including BMI. FP was statistically superior to montelukast for all BMI categories of normal, overweight, and obese subjects for FEV(1) ( $p < 0.008$ ), morning peak flow ( $p < 0.002$ ), albuterol use ( $p < 0.02$ ), and symptom scores ( $p < 0.05$ ). FP produced a significantly greater clinical response for normal, overweight, and obese subjects compared with montelukast. Irrespective of BMI, FP appears to be the more effective asthma controller therapy.

M. Takemura, M. Kobayashi, K. Kimura, K. Mitsui, H. Masui, M. Koyama, R. Itotani, M. Ishitoko, S. Suzuki, K. Aihara, M. Matsumoto, T. Oguma, T. Ueda, H. Kagioka and M. Fukui. "Repeated instruction on inhalation technique improves adherence to the therapeutic regimen in asthma." 2010 J Asthma 47(2):

BACKGROUND: Adherence to inhalation therapy is a critical determinant of the success of asthma management. Reasons for nonadherence have been well studied, but reasons for good adherence are poorly understood. Understanding the mechanisms of adherence to inhalation therapy is important in developing strategies to promote adherence. The objective of this study was to assess the factors and mechanisms that contribute to and the clinical outcomes relating to adherence to inhalation therapy. METHODS: The factors and outcomes related to adherence to inhalation therapy were examined cross-sectionally

in 176 adults with asthma using a self-reported adherence questionnaire that consisted of four items dealing with the use of inhaled controller medications. A 5-point Likert scale was used for the responses to each item. Adherence was assessed based on the overall mean adherence score. RESULTS: Of the 176 patients who were potential participants, 146 (83%) responded with usable information. Significant factors associated with the overall mean adherence score were older age ( $r = .18$ ,  $p = .032$ ) and receiving repeated instruction on inhalation techniques ( $p = .0016$ ). Of the 146 respondents, 25 (17.1%) patients were given repeated verbal instruction or demonstrations of inhalation technique by a respiratory physician. On logistic regression analysis, good adherence to inhalation therapy was significantly related to the receiving of repeated instruction on inhalation technique, with an odds ratio of 2.90 (95% confidence interval 1.07-7.88;  $p = .037$ ). Furthermore, less intentional nonadherent behavior was reported in patients with repeated instruction on inhalation technique compared to those without it. A significant correlation was found between the overall mean adherence score and the frequency of asthma exacerbations ( $r = -.19$ ,  $p = .021$ ), emergency room visits ( $r = -.19$ ,  $p = .042$ ), and the health-related quality of life score (St. George's Respiratory Questionnaire: Total,  $r = -.22$ ,  $p = .024$ ; Symptoms,  $r = -.21$ ,  $p = .022$ ; Impacts,  $r = -.20$ ,  $p = .035$ ). CONCLUSIONS: Repeated instruction on inhalation techniques may contribute to adherence to inhalation therapy through decreasing intentional nonadherence. Furthermore, good adherence to the therapeutic regimen may offer good asthma-related outcomes.

E. D. Telenga, H. A. Kerstjens, D. S. Postma, N. H. Ten Hacken and M. van den Berge. "Inhaled corticosteroids in chronic obstructive pulmonary disease: a review." 2010 Expert Opin Pharmacother 11(3):

**IMPORTANCE OF THE FIELD:** Chronic obstructive pulmonary disease (COPD) is a disease characterized by chronic airflow obstruction and a progressive lung function decline. Although widely used, the efficacy of inhaled corticosteroids (ICS) in the treatment of COPD remains a matter of debate. **AREAS COVERED IN THIS REVIEW:** This article reviews the evidence about the effects of inhaled corticosteroids in the treatment of COPD. **WHAT THE READER WILL GAIN:** Short-term treatment with ICS improves lung function and quality of life; in addition, several studies with longer follow-up have shown less decline over time in quality of life, and fewer exacerbations. By contrast, long-term studies have been unable to show substantial improvement in the decline of lung function in COPD. Based on these findings, it was concluded that the use of ICS did not influence the natural course of COPD. However, this conclusion has been challenged by two subsequent studies, TORCH and GLUCOLD, which both showed a reduction in lung-function decline over time with the use of ICS. These two studies indicate that ICS might indeed influence the natural course of the disease, at least in a subgroup of COPD patients. **TAKE HOME MESSAGE:** Further studies are needed to identify which individuals have a favorable short- and long-term response to ICS treatment.

H. A. Tiddens, S. H. Donaldson, M. Rosenfeld and P. D. Pare. "Cystic fibrosis lung disease starts in the small airways: can we treat it more effectively?" 2010 Pediatr Pulmonol 45(2):

The aims of this article are to summarize existing knowledge regarding the pathophysiology of small airways disease in cystic fibrosis (CF), to speculate about additional mechanisms that might play a role, and to consider the available or potential options to treat it. In the first section, we review the evidence provided by pathologic, physiologic, and imaging studies suggesting that obstruction of small airways begins early in life and is progressive. In the second section we discuss how the relationships between CF transmembrane conductance regulator (CFTR), ion transport, the volume of the periciliary liquid layer and airway mucus might lead to defective mucociliary clearance in small airways. In addition, we discuss how chronic endobronchial bacterial infection and a chronic neutrophilic inflammatory response increase the viscosity of CF secretions and exacerbate the clearance problem. Next, we discuss how the mechanical properties of

small airways could be altered early in the disease process and how remodeling can contribute to small airways disease. In the final section, we discuss how established therapies impact small airways disease and new directions that may lead to improvement in the treatment of small airways disease. We conclude that there are many reasons to believe that small airways play an important role in the pathophysiology of (early) CF lung disease. Therapy should be aimed to target the small airways more efficiently, especially with drugs that can correct the basic defect at an early stage of disease.

M. E. Wechsler, S. J. Kunselman, V. M. Chinchilli, E. Bleecker, H. A. Boushey, W. J. Calhoun, B. T. Ameredes, M. Castro, T. J. Craig, L. Denlinger, J. V. Fahy, N. Jarjour, S. Kazani, S. Kim, M. Kraft, S. C. Lazarus, R. F. Lemanske, Jr., A. Markezich, R. J. Martin, P. Permaul, S. P. Peters, J. Ramsdell, C. A. Sorkness, E. R. Sutherland, S. J. Szeffler, M. J. Walter, S. I. Wasserman and E. Israel. "Effect of beta2-adrenergic receptor polymorphism on response to longacting beta2 agonist in asthma (LARGE trial): a genotype-stratified, randomised, placebo-controlled, crossover trial." 2009 *Lancet* 374(9703):

**BACKGROUND:** Some studies suggest that patients with asthma who are homozygous for arginine at the 16th amino acid position of the beta2-adrenergic receptor (B16 Arg/Arg) benefit less from treatment with longacting beta2 agonists and inhaled corticosteroids than do those homozygous for glycine (B16 Gly/Gly). We investigated whether there is a genotype-specific response to treatment with a longacting beta2 agonist in combination with inhaled corticosteroid. **METHODS:** In this multicentre, randomised, double-blind, placebo-controlled trial, adult patients with moderate asthma were enrolled in pairs matched for forced expiratory volume in 1 s and ethnic origin, according to whether they had the B16 Arg/Arg (n=42) or B16 Gly/Gly (n=45) genotype. Individuals in a matched pair were randomly assigned by computer-generated randomisation sequence to receive inhaled longacting beta2 agonist (salmeterol 50 microg twice a day) or placebo given in a double-blind, crossover design for two 18-week periods. Open-label inhaled corticosteroid (hydrofluoroalkane beclometasone 240 microg twice a day) was given to all participants during the treatment periods. The primary endpoint was morning peak expiratory flow (PEF). Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00200967. **FINDINGS:** After 18 weeks of treatment, mean morning PEF in Arg/Arg participants was 21.4 L/min (95% CI 11.8-31.1) higher when participants were assigned to receive salmeterol than when assigned to receive placebo (p<0.0001). In Gly/Gly participants, morning PEF was 21.5 L/min (11.0-32.1) higher when participants were assigned to receive salmeterol than when assigned to receive placebo (p<0.0001). The improvement in PEF did not differ between genotypes (difference [Arg/Arg-Gly/Gly] - 0.1, -14.4 to 14.2; p=0.99). In Gly/Gly participants, methacholine PC20 (20% reduction in forced expiratory volume in 1 s; a prespecified secondary outcome) was 2.4 times higher when participants were assigned to salmeterol than when assigned to placebo (p<0.0001). Responsiveness to methacholine did not differ between salmeterol and placebo in Arg/Arg participants (p=0.87). The 2.5 times higher genotype-specific difference in responsiveness to methacholine was significant (1.32 doubling dose difference between genotypes, 0.43-2.21, p=0.0038). Seven Arg/Arg participants (placebo, n=5; salmeterol, n=2) and six Gly/Gly participants (placebo, n=3; salmeterol, n=3) had an asthma exacerbation. Five serious adverse events were reported, one each during the pre-match and run-in phases on open-label inhaled corticosteroid, two during double-blind treatment with salmeterol/inhaled corticosteroid, and one during double-blind treatment with placebo/inhaled corticosteroid. None of the serious events was asthma-related or related to study drugs or procedures. **INTERPRETATION:** In asthma patients with B16 Arg/Arg and B16 Gly/Gly genotypes, combination treatment with salmeterol and inhaled corticosteroid improved airway function when compared with inhaled corticosteroid therapy alone. These findings suggest that patients should continue to be treated with longacting beta2 agonists plus moderate-dose inhaled corticosteroids irrespective of B16 genotype. Further investigation is needed to establish the importance of the genotype-specific difference in responsiveness to methacholine. **FUNDING:** National Institutes of Health.

J. Widger and B. Elnazir. "Survey of the management of acute asthma in children." 2009 *Ir Med J* 102(10):

Acute asthma is one of the most common reasons for children presenting to the emergency department. International guidelines for the management of acute paediatric asthma are widely available. In this study we examined how acute asthma in children is managed across hospitals in Ireland and compared Irish practice with standard international guidelines. We surveyed 54 paediatricians across 18 centres in Ireland. A total of 30 (55.5%) individual paediatricians across 17 (94%) centres replied. The majority of centres had a written protocol for the management of acute asthma. A large number of centres use MDI and spacer devices in acute management although doses used varied widely. Only 29% of centres had written asthma action plans available from the emergency department and 53% had plans available from the ward. Irish practice is largely inline with established guidelines. A national asthma strategy could further help to improve asthma care.

W. F. Wu, J. R. Wu, Z. K. Dai, C. W. Tsai, T. C. Tsai, C. C. Chen and C. Y. Yang. "Montelukast as monotherapy in children with mild persistent asthma." 2009 *Asian Pac J Allergy Immunol* 27(4):

The cysteinyl leukotrienes cause bronchoconstriction, increased mucus production and airway inflammation, three major features of asthma. Several randomized controlled trials have shown the efficacy of leukotriene receptor antagonists for improving asthma outcomes. The drug is favored for treating childhood asthma, where poor compliance with inhalation therapy is a therapeutic challenge. To assess the effectiveness of Montelukast in asthmatic children under real-life conditions, a prospective, single-arm, multicenter, open-label observational study was performed on asthmatic children 2- to 14-years-old with a history of physician-diagnosed mild persistent asthma. Montelukast was given once daily for 12 consecutive weeks. By the end a significant improvement of the daytime asthma symptom score, nighttime asthma score, peak expiratory flow rate (PEFR) and mean score of the investigators' global evaluation was noted ( $p < 0.05$ ). These results suggest that montelukast is an effective monotherapy controller in children with mild persistent asthma.

R. Zuwallack, M. C. De Salvo, T. Kaelin, E. D. Bateman, C. S. Park, R. Abrahams, F. Fakhri, P. Sachs, K. Pudi, Y. Zhao and C. C. Wood. "Efficacy and safety of ipratropium bromide/albuterol delivered via Respimat((R)) inhaler versus MDI." 2010 *Respir Med*:

We compared the efficacy and safety of ipratropium bromide/albuterol delivered via Respimat((R)) inhaler, a novel propellant-free inhaler, versus chlorofluorocarbon (CFC)-metered dose inhaler (MDI) and ipratropium Respimat((R)) inhaler in patients with COPD. This was a multinational, randomized, double-blind, double-dummy, 12-week, parallel-group, active-controlled study. Patients with moderate to severe COPD were randomized to ipratropium bromide/albuterol (20/100mcg) Respimat((R)) inhaler, ipratropium bromide/albuterol MDI [36mcg/206mcg (Combivent((R)) Inhalation Aerosol MDI)], or ipratropium bromide (20mcg) Respimat((R)) inhaler. Each medication was administered four times daily. Serial spirometry was performed over 6h (0.15min, then hourly) on 4 test days. The primary efficacy variable was forced expiratory volume in 1s (FEV(1)) change from test day baseline at 12 weeks. A total of 1209 of 1480 randomized, treated patients completed the study; the majority were male (65%) with a mean age of 64 yrs and a mean screening pre-bronchodilator FEV(1) (percent predicted) of 41%. Ipratropium bromide/albuterol Respimat((R)) inhaler had comparable efficacy to ipratropium bromide/albuterol MDI for FEV(1) area under the curve at 0-6h (AUC(0-6)), superior efficacy to ipratropium Respimat((R)) inhaler for FEV(1) AUC(0-4) and comparable efficacy to ipratropium Respimat((R)) inhaler for FEV(1) AUC(4-6). All active treatments

were well tolerated. This study demonstrates that ipratropium bromide/albuterol 20/100mcg inhaler((R)) administered four times daily for 12 weeks had equivalent bronchodilator efficacy and comparable safety to ipratropium bromide/albuterol 36mcg/206mcg MDI, and significantly improved lung function compared with the mono-component ipratropium bromide 20 mcg Respimat((R)) inhaler. [Clinical Trial Identifier Number: NCT00400153].

## Studies in Subjects with Cystic Fibrosis

H. Adi, P. M. Young, H. K. Chan, H. Agus and D. Traini. "Co-spray-dried mannitol-ciprofloxacin dry powder inhaler formulation for cystic fibrosis and chronic obstructive pulmonary disease." 2010 Eur J Pharm Sci 40(3):

The aim of this study was to assess the potential of delivering a combination therapy, containing mannitol (a sugar alcohol with osmotic characteristics), and ciprofloxacin hydrochloride (an antibacterial fluoroquinolone), as a dry powder inhaler (DPI) formulation for inhalation. Single and combination powders were produced by spray drying ciprofloxacin and mannitol, from aqueous solution, at different ratios and under controlled conditions, as to obtain similar particle size distributions. Each formulation was characterised using laser diffraction, scanning electron microscopy, differential scanning calorimetry, dynamic vapour sorption, X-ray powder diffraction, and colloidal force microscopy. The in vitro aerosol performance of each formulation was studied using an Aerolizer DPI device and a multi-stage liquid impinger (analysed using high performance liquid chromatography). In addition, a disk diffusion test was performed to assess the in vitro antimicrobial activity of each formulation and starting materials. All formulations had similar particle size distributions, however, the morphology, thermal properties and moisture sorption was dependent on the relative percentages of each component. In general, the combination formulation containing 50% (w/w) mannitol appeared to have the best aerosol performance, good stability and lowest particle cohesion (as measured by colloid probe microscopy). Furthermore, of the formulations tested, mannitol did not appear to alter the effectiveness of the ciprofloxacin antimicrobial activity to *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Streptococcus pyogenes*. The combination of co-spray-dried mannitol and ciprofloxacin from a DPI is an attractive approach to promote mucous clearance in the respiratory tract while simultaneously treating local chronic infection, such as chronic obstructive pulmonary disease and cystic fibrosis.

E. Banner, K. Cieslar, K. Mosbah, F. Aubert, F. Duboeuf, Z. Salhi, S. Gaillard, Y. Berthezene, Y. Cremillieux and P. Reix. "Hyperpolarized  $^3\text{He}$  MR for sensitive imaging of ventilation function and treatment efficiency in young cystic fibrosis patients with normal lung function." 2010 Radiology 255(1):

**PURPOSE:** To assess the sensitivity of hyperpolarized helium 3 ( $^3\text{He}$ ) magnetic resonance (MR) imaging for the detection of peripheral airway obstruction in younger cystic fibrosis (CF) patients showing normal spirometric results (mean forced expiratory volume in 1 second [FEV(1)], 112% +/- 14.5 [standard deviation]) and to observe the immediate effects of a single chest physical therapy (CPT) session, thereby comparing two image quantification techniques. **MATERIALS AND METHODS:** Ten pediatric CF patients (age range, 8-16 years) with normal spirometric results were included in this study after approval from the local research ethics committee. Spirometry followed by proton and hyperpolarized ( $^3\text{He}$ ) three-dimensional lung imaging were performed with a 1.5-T MR unit before and after 20 minutes of CPT. The number of ventilation defects per image (VDI) and the ventilated lung fraction (VF), defined as the ratio of ventilated lung volume divided by total lung volume, were quantified. **RESULTS:** Ventilation defects were found in all patients (mean VDI, 5.1 +/- 1.9; mean global VF, 78.5% +/- 12.3; and mean peripheral VF, 75.5% +/- 17.1) despite normal spirometric results. After CPT, disparate changes in the distribution of ventilation defects were observed but the average VDI and VF did not change significantly (mean VDI, 5.1 +/- 1.1; mean global VF, 83.5% +/- 12.2; and mean peripheral VF, 80.3% +/- 12.2). There was no correlation between FEV(1) and VDI ( $\rho = -0.041$ ,  $P = .863$ ) or global VF ( $\rho = -0.196$ ,  $P = .408$ ) values but peripheral VF and VDI were correlated ( $\rho = -0.563$ ,  $P = .011$ ). **CONCLUSION:** Although spirometric

results indicate normal lung function, the mean VDI in patients (5.1) found in this study is well above the VDI in healthy subjects (1.6) reported in the literature. A single CPT session induces disparate changes in the distribution and extent of ventilation defects.

I. J. Clifton, L. A. Fletcher, C. B. Beggs, M. Denton, S. P. Conway and D. G. Peckham. "An aerobiological model of aerosol survival of different strains of *Pseudomonas aeruginosa* isolated from people with cystic fibrosis." 2010 J Cyst Fibros 9(1):

*Pseudomonas aeruginosa* is a common and important pathogen in people with cystic fibrosis (CF). Recently epidemic strains of *P. aeruginosa* associated with increased morbidity, have been identified. The method of transmission is not clear, but there is evidence of a potential airborne route. The aim of this study was to determine whether different strains of *P. aeruginosa* isolated from people with CF were able to survive within artificially generated aerosols in an aerobiological chamber. Viable *P. aeruginosa* could still be detected up to 45min after halting generation of the aerosols. All of the strains of *P. aeruginosa* expressing a non-mucoid phenotype isolated from people with CF had a reduced ability to survive within aerosols compared to an environmental strain. Expression of a mucoid phenotype by the strains of *P. aeruginosa* isolated from people with CF promoted survival in the aerosol model compared to strains expressing a non-mucoid phenotype.

E. Daviskas, S. D. Anderson, A. Jaques and B. Charlton. "Inhaled mannitol improves the hydration and surface properties of sputum in patients with cystic fibrosis." 2010 Chest 137(4):

**BACKGROUND:** The airway mucus in patients with cystic fibrosis (CF) is dehydrated and adhesive and accumulates in the airways, resulting in chronic inflammation, infection, and progressive loss of lung function. Inhaled mannitol improves mucus clearance and, when administered over 2 weeks, it improves lung function in CF (Jaques et al. Chest. 2008;133(6):1388-1396). The changes in the physical properties of sputum after a 2-week treatment with mannitol were investigated in the same subjects with CF. **METHODS:** Sputum was collected before and at the end of the 2-week treatment period from 28 subjects with CF who participated in the double-blind crossover study. Mannitol or placebo 420 mg bid was inhaled over 2 weeks. The solids content, surface tension, contact angle, and viscoelasticity were measured. **RESULTS:** Two-week treatment with mannitol reduced the solids from 7.3% +/- 3.0% to 5.7% +/- 3.0% ( $P = .012$ ), surface tension from 83.1 +/- 7.2 to 78.6 +/- 8.0 mN/m ( $P < .039$ ), and contact angle from 52.4 +/- 7.7 to 47.9 +/- 7.3 degrees. There was no significant change in the viscoelastic properties of sputum ( $P > .1$ ). Placebo treatment had no significant effect on the sputum properties. The change in solids content correlated with the change in both FEV(1) ( $r = -0.78$ ,  $P = .004$ ) and forced expiratory flow in the middle half of the FVC ( $r = -0.80$ ,  $P = .003$ ), and the percentage change in surface tension and contact angle correlated with the percentage change in the FEV(1) ( $r = -0.73$ ,  $P = .012$  and  $r = -0.63$ ,  $P = .03$ , respectively) in these subjects. **CONCLUSION:** Treatment with inhaled mannitol over 2 weeks improved the hydration and surface properties of sputum in patients with CF. This effect was sustained and correlated with airway function changes. Trial registration: clinicaltrials.gov; Identifier: NCT00455130.

J. Denyer, A. Black, K. Nikander, T. Dyche and I. Prince. "Domiciliary experience of the Target Inhalation Mode (TIM) breathing maneuver in patients with cystic fibrosis." 2010 J Aerosol Med Pulm Drug Deliv 23 Suppl 1:

**BACKGROUND:** The time requirements for multiple daily nebulizer treatments are important impediments to the quality of life for most patients with cystic fibrosis (CF). The I-neb Adaptive Aerosol Delivery (AAD) System can be used with a new mode of breathing

during inhalation of aerosol, the Target Inhalation Mode (TIM). As a function of the TIM algorithm, the patient is guided to a slow and deep inhalation, which can result in shorter treatment times. **METHODS:** This study was conducted as a 3-month patient handling study of the I-neb AAD System in 42 patients with CF aged 12-57 years. The I-neb AAD System was supplied in both the standard Tidal Breathing Mode (TBM), and in TIM. Patients were trained to use the I-neb AAD System in TIM for the delivery of all their inhaled medications, but if they were not comfortable with the TIM maneuver they could change to the TBM maneuver. The primary variables were compliance with the correct use of the I-neb AAD System, and treatment times. The secondary variables were based on study questionnaires at the end of the study and covered ease of use, patient confidence, and patient satisfaction with the I-neb AAD System. **RESULTS:** There were a total of 10,240 complete treatments and of these, 8979 (88%) were in TIM. Compliance with the correct use of the I-neb AAD System was 97.6%. The mean treatment time for complete treatments in TIM was 4.20 min, compared with 6.83 min when using the I-neb AAD System in TBM. The responses to the questionnaires indicated that over 77% of the patients found the I-neb AAD System in TIM to be either: very easy, easy, or acceptable to use. **CONCLUSIONS:** The results demonstrated that by using the I-neb AAD System in TIM, a 40-50% reduction of nebulizer treatment times, and a high level of compliance could be achieved. The results also showed that the patients found the I-neb AAD System easy to use.

J. Denyer, I. Prince, E. Dixon, P. Agent, J. Pryor and M. Hodson. "Evaluation of the Target Inhalation Mode (TIM) breathing maneuver in simulated nebulizer therapy in patients with cystic fibrosis." 2010 J Aerosol Med Pulm Drug Deliv 23 Suppl 1:

**BACKGROUND:** Adaptive Aerosol Delivery (AAD) systems provide efficient drug delivery and improved lung deposition over conventional nebulizers by combining real-time analyses of patient breathing patterns and precisely timed aerosol delivery. Delivery and deposition are further enhanced by breathing techniques involving slow, deep inhalations. **METHODS:** This exploratory study assessed the acceptability of slow, deep inhalations in 20 patients with cystic fibrosis (CF) during up to eight simulated nebulizer treatments with the I-neb AAD System. The breathing maneuver, Target Inhalation Mode (TIM) breathing, involved the lengthening of the patient's inhalation time over successive breaths with guidance from auditory and tactile (vibratory) feedback from the device. **RESULTS:** At the end of the first treatment, most patients felt that the instructions were easy to understand (90%) and that the vibratory feedback was pleasant (65%). Half of the patients found the procedure to be comfortable. At the end of the final treatment, most patients felt that the breathing maneuver was easy to understand (90%) and use (80%), but that the duration of the breath was too long (100%). Logged data revealed that 90% of patients were able to comply with the breathing maneuver. The two patients unable to comply had a forced vital capacity of <1.75 L. The average treatment time decreased from 288.4 to 141.6 sec during the first and final treatments, respectively. **CONCLUSIONS:** This study provides preliminary evidence of the acceptability of the TIM breathing maneuver in patients with CF and their ability to perform repeated TIM breathing during simulated nebulizer therapy with the I-neb AAD System.

J. S. Elborn and N. R. Henig. "Optimal airway antimicrobial therapy for cystic fibrosis: the role of inhaled aztreonam lysine." 2010 Expert Opin Pharmacother 11(8):

**IMPORTANCE OF THE FIELD:** Chronic endobronchial infection in cystic fibrosis (CF) leads to progressive lung function loss and respiratory failure. Most adult CF patients are infected with *Pseudomonas aeruginosa*, an important predictor of mortality. Suppressing chronic *P. aeruginosa* infection with inhaled antibiotics is standard of care for CF patients. **AREAS COVERED IN THIS REVIEW:** This review describes the development (2003 - 2010) of aztreonam lysine 75 mg powder and solvent for nebulizer solution (AZLI; Cayston), an aerosolized formulation of the monobactam antibiotic aztreonam. **WHAT**

THE READER WILL GAIN: AZLI was studied in patients with CF and chronic *P. aeruginosa* airway infection. In placebo-controlled trials, AZLI improved respiratory symptoms, increased forced expiratory volume in 1 sec (FEV(1)), decreased sputum *P. aeruginosa* density, and was well tolerated. An open-label follow-on trial of nine 'on/off' courses showed that AZLI was safe and the effect durable with repeated administration. AZLI was recently approved for use in CF patients in Australia and the USA, and conditionally approved in Canada and the European Union. AZLI is given three times daily for 28 days (2 - 3 min/dose), followed by 28 days off-drug. AZLI is used only with the Altera Nebulizer System, which provides appropriate particle size and small airway deposition, and has excellent portability. TAKE HOME MESSAGE: AZLI is a new therapy that is safe and effectively improves respiratory symptoms and FEV(1) in patients with CF.

M. E. Falagas, A. Michalopoulos and E. I. Metaxas. "Pulmonary drug delivery systems for antimicrobial agents: facts and myths." 2010 *Int J Antimicrob Agents* 35(2):

Inhaled antimicrobial agents are used for the treatment of respiratory tract infections due to Gram-negative bacteria, mainly *Pseudomonas aeruginosa*. The effectiveness of the inhaled antimicrobial therapy is believed to correlate with the delivery system used. The objective of this review was to search for data supporting differentiation in clinical effectiveness between systems used for pulmonary delivery of antibiotics, including delivery using disposable nebulisers and oxygen flow. Published studies in peer-reviewed journals comparing the effectiveness of pulmonary drug delivery systems for antimicrobial agents were retrieved. The studies found were either in vitro or Phase I and Phase II clinical studies. Differences in in vitro parameters may affect the in vivo efficacy of the devices, and in vivo differences may imply differences in clinical effectiveness. The main difference between newer and older devices is the time needed for antibiotic delivery. Interpretation and association with clinical effectiveness is difficult. In conclusion, Phase III clinical trials comparing the clinical effectiveness of delivery systems, including delivery using a hospital's oxygen flow and disposable nebulisers, do not exist. Cost is an important parameter, which may be counterbalanced in cystic fibrosis patients by a better quality of life and a greater adherence to treatment.

D. E. Geller and K. C. Kesser. "The I-neb Adaptive Aerosol Delivery System enhances delivery of alpha1-antitrypsin with controlled inhalation." 2010 *J Aerosol Med Pulm Drug Deliv* 23 Suppl 1:

BACKGROUND: Inhaled alpha1-antitrypsin (AAT) is being developed for treatment of cystic fibrosis to protect the lungs from excessive free elastase. High drug costs mandate a very efficient aerosol system to deliver a high payload to the airways. The I-neb Adaptive Aerosol Delivery (AAD) System is a portable, electronic, vibrating mesh nebulizer that delivers aerosol only during inhalation. It can be operated in conventional tidal breathing mode (TBM) or in target inhalation mode (TIM) that guides the patient to inhale deeply and slowly. The purposes of this in vitro study were to determine aerosol characteristics, device efficiency, and delivery time of AAT using the I-neb AAD System with TBM and TIM. METHODS: We studied the I-neb AAD System in TBM and TIM (inspiratory time 6 or 9 sec) using a breath simulator. The loaded dose was 0.5 mL AAT (50 mg/mL). Nebulized drug captured on an inspiratory filter was reported as emitted dose. Particle size was measured by laser diffraction. Predicted lung doses were calculated based on the results of a prior scintigraphy study of the I-neb AAD System. RESULTS: Particle size (VMD) for TBM and TIM was similar (4.4-4.8 microm). The emitted doses were very high and similar between modes (82-90% of loaded dose). Predicted lung dose of AAT (percent of loaded dose) and delivery times were: TBM 56.6% in 7.5 min; TIM-6 59.9% in 4.4 min; and TIM-9 64.5% in 2.5 min. CONCLUSIONS: The I-neb AAD System enhanced AAT delivery by inhalation-only aerosol generation and a low-residual dose. Predicted lung dose was high for both TBM and TIM, but longer inspiratory times with TIM reduced the administration time to one-third that of tidal breathing. We

conclude that slow, deep, controlled inspirations using the I-neb AAD System is an efficient method to deliver AAT.

S. Ghdifan, L. Couderc, I. Michelet, C. Leguillon, B. Masseline and C. Marguet. "Bolus methylprednisolone efficacy for uncontrolled exacerbation of cystic fibrosis in children." 2010 *Pediatrics* 125(5):

We present here the clinical course of 4 children with cystic fibrosis, deltaF508/deltaF508, who were admitted with severe respiratory distress and in whom no improvement was obtained by intensive antibiotic therapy and systemic corticosteroids. Chest computed-tomography scans showed hyperinflation and atelectasis. The severity of these exacerbations was explained neither by visible mucus plugging nor by allergic bronchopulmonary aspergillosis. We hypothesized that these clinical features were related to a severe inflammatory process in small airways. Therefore, a high-dose short course of methylprednisolone (1 g/1.73 m<sup>2</sup> per day for 3 days) was given; all the patients' conditions were dramatically improved, and the therapy was safe. To our knowledge, this is the first reported use of bolus methylprednisolone in the treatment of uncontrolled pulmonary exacerbation in children with cystic fibrosis.

P. Iseli. "[Chronic cough in children--what to consider and how to evaluate?]." 2009 *Praxis (Bern 1994)* 98(23):

There is a long list of differential diagnoses for chronic cough lasting longer than 4 weeks in children. Diagnostic work up starts with a detailed history taking and a clinical investigation followed by a chest X-ray (in one plane) and a spirometry. For the latter reliable results can be achieved by children older than 5 years. If the diagnostic work up is still inconclusive and if the child is in good clinical condition, a 4 weeks' course of inhalation therapy with steroids and betamimetics together with a 2 weeks' course of antibiotics with a macrolide is warranted. In case coughing persists a thorough diagnostic work up is indicated to rule out conditions like cystic fibrosis, relevant humoral immunodeficiencies, primary ciliary dyskinesia, anatomic malformation or chronic pulmonary aspiration, preferably done by a pediatric pulmonologist. Chronic cough has to be considered abnormal in any child under the age of 1 year. For this age group a final diagnosis is of special importance.

P. Markart, R. Nass, C. Ruppert, L. Hundack, M. Wygrecka, M. Korfei, R. H. Boedeker, G. Staehler, H. Kroll, G. Scheuch, W. Seeger and A. Guenther. "Safety and tolerability of inhaled heparin in idiopathic pulmonary fibrosis." 2010 *J Aerosol Med Pulm Drug Deliv* 23(3):

**BACKGROUND:** Abnormalities in alveolar coagulation occur in idiopathic pulmonary fibrosis (IPF). Anticoagulants attenuate bleomycin-induced lung fibrosis in animals. In this study, we first examined the pharmacokinetics of inhaled heparin in healthy subjects. Second, we investigated the safety and tolerability of heparin inhalation in IPF patients. **METHODS:** Coagulation assays were performed in blood and bronchoalveolar lavage fluid samples from 19 healthy volunteers after inhalation of increasing amounts of unfractionated heparin. The acute effects of heparin inhalation on lung function and exercise capacity and the safety and tolerability of chronic heparin inhalation for 28 days were assessed in 20 IPF patients in an open-label exploratory pilot study. **RESULTS:** In healthy subjects, inhalation of 150,000 IU heparin ("filled dose") significantly increased the partial thromboplastin time and anti-factor Xa activity in blood samples indicating the threshold dose. The local alveolar anticoagulant effect was detectable up to 72 h, and the alveolar half-life was estimated at 28 h. In IPF-patients, no acute deleterious effects on pulmonary function, gas exchange, or exercise capacity were noted after inhalation of the threshold dose. During chronic treatment, where one-fourth of the threshold dose was

inhaled every 12 h for 28 days to obtain a steady-state anticoagulant activity in the alveolar space approximating the anticoagulant activity observed after threshold dose inhalation, no heparin-related side effects, such as hemoptysis or heparin-induced antibodies and thrombocytopenia, were detected in any patient, and median lung function values, exercise capacity, and quality of life scores appeared largely unaltered. Three adverse and one serious adverse events were noted; however, the relation of these events to the heparin inhalation was assessed as "unlikely" or "no relation" in each case. CONCLUSIONS: Inhaled heparin appears to be safe and well tolerated in IPF patients. Future clinical trials are required to demonstrate the long-term safety and efficacy of inhaled heparin in IPF.

K. Nikander, J. Denyer, M. Dodd, T. Dyché, K. Webb, P. Weller and D. Stableforth. "The adaptive aerosol delivery system in a telehealth setting: patient acceptance, performance and feasibility." 2010 J Aerosol Med Pulm Drug Deliv 23 Suppl 1:

BACKGROUND: The telehealth service is one of the fastest growing healthcare segments. It is increasingly utilizing computer technology and telecommunication equipment to either provide continuous vital sign monitoring or facilitate patient care at home, rather than relying solely on in-person care. METHODS: We conducted a 6-week open study in nineteen patients with cystic fibrosis enrolled from three centers, to investigate patient perception of a telehealth enabled nebulizer system (Prodose Adaptive Aerosol Delivery [AAD] System), which enabled the doorstep delivery of repeat medication. RESULTS: The results showed that patient confidence in the device and perception of ease of use was high with no significant change between the start and end of the trial. Views on the home delivery of medication were split between 'great' and 'inconvenient.' However, if the delivery system had been more flexible and delivered all the patients' drugs, the majority of patients would have had their medication delivered in this way. CONCLUSIONS: The trial showed that it was possible to build telehealth technology into an advanced nebulizer system, and that patient acceptance of the technology was unlikely to be a barrier to the adoption of such a telehealth system.

T. L. Noah, S. S. Ivins, K. A. Abode, P. W. Stewart, P. H. Michelson, W. T. Harris, M. M. Henry and M. W. Leigh. "Inhaled versus systemic antibiotics and airway inflammation in children with cystic fibrosis and Pseudomonas." 2010 Pediatr Pulmonol 45(3):

RATIONALE: Inhaled tobramycin has been shown to transiently clear Pseudomonas from lower airways in early cystic fibrosis (CF), but does not markedly reduce lung inflammation, a key factor in disease progression. OBJECTIVE: Test the hypothesis that systemic antibiotics are more effective than inhaled antibiotics for reducing lower airways inflammation. METHODS: Clinically stable CF children with recent Pseudomonas were randomized to receive 4 weeks of inhaled tobramycin or 2 weeks of systemic antibiotics (intravenous ceftazidime and tobramycin). Bronchoalveolar lavage fluid was obtained just before and 4-6 weeks after treatment. The primary outcome was change in % neutrophils in lavage fluid. RESULTS: Fifteen subjects (inhaled = 6, systemic = 9) completed the protocol. Three Systemic Group subjects could not have central venous access established and were treated with oral ciprofloxacin (plus inhaled tobramycin) for 2 weeks as an alternative "systemic" regimen, per protocol. Groups were well matched in age, markers of disease severity, and initial % neutrophils. The Systemic Group showed a modest median change in percent neutrophils (-7%) which was not statistically significant compared to inhaled (+5.4%,  $P = 0.07$ ). However, the Systemic Group had significantly greater reductions in total cells (-50% vs. -3%,  $P < 0.01$ ) and neutrophils (-74% vs. -10%,  $P = 0.02$ ) per ml lavage fluid. Both groups had reduced bacterial quantity after treatment, but there was no significant difference between groups. CONCLUSIONS: In clinically stable children with CF, systemic antibiotics result in greater short-term reduction in lower airways inflammation than inhaled antibiotics.

F. Ratjen, A. Munck, P. Kho and G. Angyalosi. "Treatment of early *Pseudomonas aeruginosa* infection in patients with cystic fibrosis: the ELITE trial." 2010 *Thorax* 65(4):

**RATIONALE:** Antibiotic therapy for early *Pseudomonas aeruginosa* infection in patients with cystic fibrosis (CF) is effective, but the optimal therapeutic regimen and duration for early treatment remains unclear. The Early Inhaled Tobramycin for Eradication (ELITE) study was designed to assess the efficacy and safety of two regimens (28 and 56 days) of tobramycin inhalation solution (TIS) 300 mg/5 ml twice daily for the treatment of early onset *P aeruginosa* infection in patients with CF. **METHODS:** In this open-label randomised multicentre study, patients with CF (aged  $\geq$  6 months) with early *P aeruginosa* infection were treated for 28 days with TIS twice daily administered by the PARI LC PLUS (PARI GmbH, Starnberg, Germany) jet nebuliser. After 28 days, patients were randomised 1:1 to either stop TIS (n=45) or to receive a further 28 days of TIS (n=43). The primary endpoint was the median time to recurrence of *P aeruginosa* (any strain). Secondary endpoints included the proportion of patients free of *P aeruginosa* infection 1 month after cessation of therapy and safety assessments. **RESULTS:** The median time to recurrence of *P aeruginosa* (any strain) was similar between the two groups. In total, 93% and 92% of the patients were free of *P aeruginosa* infection 1 month after the end of treatment and 66% and 69% remained free at the final visit in the 28-day and 56-day groups, respectively. TIS was well tolerated. **CONCLUSIONS:** Treatment with TIS for 28 days is an effective and well tolerated therapy for early *P aeruginosa* infection in patients with CF. **TRIAL REGISTRATION NUMBER:** NCT00391976.

C. R. Sudfeld, E. C. Dasenbrook, W. G. Merz, K. C. Carroll and M. P. Boyle. "Prevalence and risk factors for recovery of filamentous fungi in individuals with cystic fibrosis." 2010 *J Cyst Fibros* 9(2):

**BACKGROUND:** Filamentous fungi are frequently recovered from respiratory cultures of individuals with CF. **METHODS:** A CF cohort database was utilized to determine filamentous fungal prevalence and risk factors. **RESULTS:** The prevalence of filamentous fungal isolation increased from 2.0% in 1997 to 28.7% in 2007. The odds of isolating filamentous fungi during a quarter was greater in CF adults [ $p < 0.001$ ], during chronic oral antibiotic use [ $p = 0.002$ ] and increased with each 10% drop in FEV<sub>1</sub> percent predicted [ $p = 0.005$ ], while inhaled corticosteroids surprisingly decreased the likelihood [ $p = 0.012$ ]. The direction of these effects persisted after excluding individuals with ABPA. A sub-analysis determined older age [ $p = 0.019$ ] and use of inhaled antibiotics [ $p = 0.011$ ] were independent risk factors for onset of fungal colonization. **CONCLUSIONS:** This study suggests that isolation of filamentous fungi in CF at JHH has increased and risk factors include older age, decreased lung function, and chronic oral antibiotics.

H. A. Tiddens, S. H. Donaldson, M. Rosenfeld and P. D. Pare. "Cystic fibrosis lung disease starts in the small airways: can we treat it more effectively?" 2010 *Pediatr Pulmonol* 45(2):

The aims of this article are to summarize existing knowledge regarding the pathophysiology of small airways disease in cystic fibrosis (CF), to speculate about additional mechanisms that might play a role, and to consider the available or potential options to treat it. In the first section, we review the evidence provided by pathologic, physiologic, and imaging studies suggesting that obstruction of small airways begins early in life and is progressive. In the second section we discuss how the relationships between CF transmembrane conductance regulator (CFTR), ion transport, the volume of the periciliary liquid layer and airway mucus might lead to defective mucociliary clearance in small airways. In addition, we discuss how chronic endobronchial bacterial infection and a chronic neutrophilic inflammatory response increase the viscosity of CF secretions and exacerbate the clearance problem. Next, we discuss how the mechanical properties of small airways could be altered early in the disease process and how remodeling can

contribute to small airways disease. In the final section, we discuss how established therapies impact small airways disease and new directions that may lead to improvement in the treatment of small airways disease. We conclude that there are many reasons to believe that small airways play an important role in the pathophysiology of (early) CF lung disease. Therapy should be aimed to target the small airways more efficiently, especially with drugs that can correct the basic defect at an early stage of disease.

## Active Agents

H. Adi, P. M. Young, H. K. Chan, H. Agus and D. Traini. "Co-spray-dried mannitol-ciprofloxacin dry powder inhaler formulation for cystic fibrosis and chronic obstructive pulmonary disease." 2010 Eur J Pharm Sci 40(3):

The aim of this study was to assess the potential of delivering a combination therapy, containing mannitol (a sugar alcohol with osmotic characteristics), and ciprofloxacin hydrochloride (an antibacterial fluoroquinolone), as a dry powder inhaler (DPI) formulation for inhalation. Single and combination powders were produced by spray drying ciprofloxacin and mannitol, from aqueous solution, at different ratios and under controlled conditions, as to obtain similar particle size distributions. Each formulation was characterised using laser diffraction, scanning electron microscopy, differential scanning calorimetry, dynamic vapour sorption, X-ray powder diffraction, and colloidal force microscopy. The in vitro aerosol performance of each formulation was studied using an Aerolizer DPI device and a multi-stage liquid impinger (analysed using high performance liquid chromatography). In addition, a disk diffusion test was performed to assess the in vitro antimicrobial activity of each formulation and starting materials. All formulations had similar particle size distributions, however, the morphology, thermal properties and moisture sorption was dependent on the relative percentages of each component. In general, the combination formulation containing 50% (w/w) mannitol appeared to have the best aerosol performance, good stability and lowest particle cohesion (as measured by colloid probe microscopy). Furthermore, of the formulations tested, mannitol did not appear to alter the effectiveness of the ciprofloxacin antimicrobial activity to *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Streptococcus pyogenes*. The combination of co-spray-dried mannitol and ciprofloxacin from a DPI is an attractive approach to promote mucous clearance in the respiratory tract while simultaneously treating local chronic infection, such as chronic obstructive pulmonary disease and cystic fibrosis.

E. Banner, K. Cieslar, K. Mosbah, F. Aubert, F. Duboeuf, Z. Salhi, S. Gaillard, Y. Berthezene, Y. Cremillieux and P. Reix. "Hyperpolarized 3He MR for sensitive imaging of ventilation function and treatment efficiency in young cystic fibrosis patients with normal lung function." 2010 Radiology 255(1):

**PURPOSE:** To assess the sensitivity of hyperpolarized helium 3 ( $^3\text{He}$ ) magnetic resonance (MR) imaging for the detection of peripheral airway obstruction in younger cystic fibrosis (CF) patients showing normal spirometric results (mean forced expiratory volume in 1 second [FEV(1)], 112% +/- 14.5 [standard deviation]) and to observe the immediate effects of a single chest physical therapy (CPT) session, thereby comparing two image quantification techniques. **MATERIALS AND METHODS:** Ten pediatric CF patients (age range, 8-16 years) with normal spirometric results were included in this study after approval from the local research ethics committee. Spirometry followed by proton and hyperpolarized ( $^3\text{He}$ ) three-dimensional lung imaging were performed with a 1.5-T MR unit before and after 20 minutes of CPT. The number of ventilation defects per image (VDI) and the ventilated lung fraction (VF), defined as the ratio of ventilated lung volume divided by total lung volume, were quantified. **RESULTS:** Ventilation defects were found in all patients (mean VDI, 5.1 +/- 1.9; mean global VF, 78.5% +/- 12.3; and mean peripheral VF, 75.5% +/- 17.1) despite normal spirometric results. After CPT, disparate changes in the distribution of ventilation defects were observed but the average VDI and VF did not change significantly (mean VDI, 5.1 +/- 1.1; mean global VF, 83.5% +/- 12.2; and mean peripheral VF, 80.3% +/- 12.2). There was no correlation between FEV(1) and VDI ( $\rho = -0.041$ ,  $P = .863$ ) or global VF ( $\rho = -0.196$ ,  $P = .408$ ) values but peripheral VF and VDI were correlated ( $\rho = -0.563$ ,  $P = .011$ ). **CONCLUSION:** Although spirometric

results indicate normal lung function, the mean VDI in patients (5.1) found in this study is well above the VDI in healthy subjects (1.6) reported in the literature. A single CPT session induces disparate changes in the distribution and extent of ventilation defects.

I. J. Clifton, L. A. Fletcher, C. B. Beggs, M. Denton, S. P. Conway and D. G. Peckham. "An aerobiological model of aerosol survival of different strains of *Pseudomonas aeruginosa* isolated from people with cystic fibrosis." 2010 J Cyst Fibros 9(1):

*Pseudomonas aeruginosa* is a common and important pathogen in people with cystic fibrosis (CF). Recently epidemic strains of *P. aeruginosa* associated with increased morbidity, have been identified. The method of transmission is not clear, but there is evidence of a potential airborne route. The aim of this study was to determine whether different strains of *P. aeruginosa* isolated from people with CF were able to survive within artificially generated aerosols in an aerobiological chamber. Viable *P. aeruginosa* could still be detected up to 45min after halting generation of the aerosols. All of the strains of *P. aeruginosa* expressing a non-mucoid phenotype isolated from people with CF had a reduced ability to survive within aerosols compared to an environmental strain. Expression of a mucoid phenotype by the strains of *P. aeruginosa* isolated from people with CF promoted survival in the aerosol model compared to strains expressing a non-mucoid phenotype.

E. Daviskas, S. D. Anderson, A. Jaques and B. Charlton. "Inhaled mannitol improves the hydration and surface properties of sputum in patients with cystic fibrosis." 2010 Chest 137(4):

**BACKGROUND:** The airway mucus in patients with cystic fibrosis (CF) is dehydrated and adhesive and accumulates in the airways, resulting in chronic inflammation, infection, and progressive loss of lung function. Inhaled mannitol improves mucus clearance and, when administered over 2 weeks, it improves lung function in CF (Jaques et al. Chest. 2008;133(6):1388-1396). The changes in the physical properties of sputum after a 2-week treatment with mannitol were investigated in the same subjects with CF. **METHODS:** Sputum was collected before and at the end of the 2-week treatment period from 28 subjects with CF who participated in the double-blind crossover study. Mannitol or placebo 420 mg bid was inhaled over 2 weeks. The solids content, surface tension, contact angle, and viscoelasticity were measured. **RESULTS:** Two-week treatment with mannitol reduced the solids from 7.3% +/- 3.0% to 5.7% +/- 3.0% ( $P = .012$ ), surface tension from 83.1 +/- 7.2 to 78.6 +/- 8.0 mN/m ( $P < .039$ ), and contact angle from 52.4 +/- 7.7 to 47.9 +/- 7.3 degrees. There was no significant change in the viscoelastic properties of sputum ( $P > .1$ ). Placebo treatment had no significant effect on the sputum properties. The change in solids content correlated with the change in both FEV(1) ( $r = -0.78$ ,  $P = .004$ ) and forced expiratory flow in the middle half of the FVC ( $r = -0.80$ ,  $P = .003$ ), and the percentage change in surface tension and contact angle correlated with the percentage change in the FEV(1) ( $r = -0.73$ ,  $P = .012$  and  $r = -0.63$ ,  $P = .03$ , respectively) in these subjects. **CONCLUSION:** Treatment with inhaled mannitol over 2 weeks improved the hydration and surface properties of sputum in patients with CF. This effect was sustained and correlated with airway function changes. Trial registration: [clinicaltrials.gov](http://clinicaltrials.gov); Identifier: NCT00455130.

J. Denyer, A. Black, K. Nikander, T. Dyche and I. Prince. "Domiciliary experience of the Target Inhalation Mode (TIM) breathing maneuver in patients with cystic fibrosis." 2010 J Aerosol Med Pulm Drug Deliv 23 Suppl 1:

**BACKGROUND:** The time requirements for multiple daily nebulizer treatments are important impediments to the quality of life for most patients with cystic fibrosis (CF). The I-neb Adaptive Aerosol Delivery (AAD) System can be used with a new mode of breathing

during inhalation of aerosol, the Target Inhalation Mode (TIM). As a function of the TIM algorithm, the patient is guided to a slow and deep inhalation, which can result in shorter treatment times. **METHODS:** This study was conducted as a 3-month patient handling study of the I-neb AAD System in 42 patients with CF aged 12-57 years. The I-neb AAD System was supplied in both the standard Tidal Breathing Mode (TBM), and in TIM. Patients were trained to use the I-neb AAD System in TIM for the delivery of all their inhaled medications, but if they were not comfortable with the TIM maneuver they could change to the TBM maneuver. The primary variables were compliance with the correct use of the I-neb AAD System, and treatment times. The secondary variables were based on study questionnaires at the end of the study and covered ease of use, patient confidence, and patient satisfaction with the I-neb AAD System. **RESULTS:** There were a total of 10,240 complete treatments and of these, 8979 (88%) were in TIM. Compliance with the correct use of the I-neb AAD System was 97.6%. The mean treatment time for complete treatments in TIM was 4.20 min, compared with 6.83 min when using the I-neb AAD System in TBM. The responses to the questionnaires indicated that over 77% of the patients found the I-neb AAD System in TIM to be either: very easy, easy, or acceptable to use. **CONCLUSIONS:** The results demonstrated that by using the I-neb AAD System in TIM, a 40-50% reduction of nebulizer treatment times, and a high level of compliance could be achieved. The results also showed that the patients found the I-neb AAD System easy to use.

J. Denyer, I. Prince, E. Dixon, P. Agent, J. Pryor and M. Hodson. "Evaluation of the Target Inhalation Mode (TIM) breathing maneuver in simulated nebulizer therapy in patients with cystic fibrosis." 2010 J Aerosol Med Pulm Drug Deliv 23 Suppl 1:

**BACKGROUND:** Adaptive Aerosol Delivery (AAD) systems provide efficient drug delivery and improved lung deposition over conventional nebulizers by combining real-time analyses of patient breathing patterns and precisely timed aerosol delivery. Delivery and deposition are further enhanced by breathing techniques involving slow, deep inhalations. **METHODS:** This exploratory study assessed the acceptability of slow, deep inhalations in 20 patients with cystic fibrosis (CF) during up to eight simulated nebulizer treatments with the I-neb AAD System. The breathing maneuver, Target Inhalation Mode (TIM) breathing, involved the lengthening of the patient's inhalation time over successive breaths with guidance from auditory and tactile (vibratory) feedback from the device. **RESULTS:** At the end of the first treatment, most patients felt that the instructions were easy to understand (90%) and that the vibratory feedback was pleasant (65%). Half of the patients found the procedure to be comfortable. At the end of the final treatment, most patients felt that the breathing maneuver was easy to understand (90%) and use (80%), but that the duration of the breath was too long (100%). Logged data revealed that 90% of patients were able to comply with the breathing maneuver. The two patients unable to comply had a forced vital capacity of <1.75 L. The average treatment time decreased from 288.4 to 141.6 sec during the first and final treatments, respectively. **CONCLUSIONS:** This study provides preliminary evidence of the acceptability of the TIM breathing maneuver in patients with CF and their ability to perform repeated TIM breathing during simulated nebulizer therapy with the I-neb AAD System.

J. S. Elborn and N. R. Henig. "Optimal airway antimicrobial therapy for cystic fibrosis: the role of inhaled aztreonam lysine." 2010 Expert Opin Pharmacother 11(8):

**IMPORTANCE OF THE FIELD:** Chronic endobronchial infection in cystic fibrosis (CF) leads to progressive lung function loss and respiratory failure. Most adult CF patients are infected with *Pseudomonas aeruginosa*, an important predictor of mortality. Suppressing chronic *P. aeruginosa* infection with inhaled antibiotics is standard of care for CF patients. **AREAS COVERED IN THIS REVIEW:** This review describes the development (2003 - 2010) of aztreonam lysine 75 mg powder and solvent for nebulizer solution (AZLI; Cayston), an aerosolized formulation of the monobactam antibiotic aztreonam. **WHAT**

THE READER WILL GAIN: AZLI was studied in patients with CF and chronic P. aeruginosa airway infection. In placebo-controlled trials, AZLI improved respiratory symptoms, increased forced expiratory volume in 1 sec (FEV(1)), decreased sputum P. aeruginosa density, and was well tolerated. An open-label follow-on trial of nine 'on/off' courses showed that AZLI was safe and the effect durable with repeated administration. AZLI was recently approved for use in CF patients in Australia and the USA, and conditionally approved in Canada and the European Union. AZLI is given three times daily for 28 days (2 - 3 min/dose), followed by 28 days off-drug. AZLI is used only with the Altera Nebulizer System, which provides appropriate particle size and small airway deposition, and has excellent portability. TAKE HOME MESSAGE: AZLI is a new therapy that is safe and effectively improves respiratory symptoms and FEV(1) in patients with CF.

M. E. Falagas, A. Michalopoulos and E. I. Metaxas. "Pulmonary drug delivery systems for antimicrobial agents: facts and myths." 2010 Int J Antimicrob Agents 35(2):

Inhaled antimicrobial agents are used for the treatment of respiratory tract infections due to Gram-negative bacteria, mainly *Pseudomonas aeruginosa*. The effectiveness of the inhaled antimicrobial therapy is believed to correlate with the delivery system used. The objective of this review was to search for data supporting differentiation in clinical effectiveness between systems used for pulmonary delivery of antibiotics, including delivery using disposable nebulisers and oxygen flow. Published studies in peer-reviewed journals comparing the effectiveness of pulmonary drug delivery systems for antimicrobial agents were retrieved. The studies found were either in vitro or Phase I and Phase II clinical studies. Differences in in vitro parameters may affect the in vivo efficacy of the devices, and in vivo differences may imply differences in clinical effectiveness. The main difference between newer and older devices is the time needed for antibiotic delivery. Interpretation and association with clinical effectiveness is difficult. In conclusion, Phase III clinical trials comparing the clinical effectiveness of delivery systems, including delivery using a hospital's oxygen flow and disposable nebulisers, do not exist. Cost is an important parameter, which may be counterbalanced in cystic fibrosis patients by a better quality of life and a greater adherence to treatment.

D. E. Geller and K. C. Kesser. "The I-neb Adaptive Aerosol Delivery System enhances delivery of alpha1-antitrypsin with controlled inhalation." 2010 J Aerosol Med Pulm Drug Deliv 23 Suppl 1:

BACKGROUND: Inhaled alpha1-antitrypsin (AAT) is being developed for treatment of cystic fibrosis to protect the lungs from excessive free elastase. High drug costs mandate a very efficient aerosol system to deliver a high payload to the airways. The I-neb Adaptive Aerosol Delivery (AAD) System is a portable, electronic, vibrating mesh nebulizer that delivers aerosol only during inhalation. It can be operated in conventional tidal breathing mode (TBM) or in target inhalation mode (TIM) that guides the patient to inhale deeply and slowly. The purposes of this in vitro study were to determine aerosol characteristics, device efficiency, and delivery time of AAT using the I-neb AAD System with TBM and TIM. METHODS: We studied the I-neb AAD System in TBM and TIM (inspiratory time 6 or 9 sec) using a breath simulator. The loaded dose was 0.5 mL AAT (50 mg/mL). Nebulized drug captured on an inspiratory filter was reported as emitted dose. Particle size was measured by laser diffraction. Predicted lung doses were calculated based on the results of a prior scintigraphy study of the I-neb AAD System. RESULTS: Particle size (VMD) for TBM and TIM was similar (4.4-4.8 microm). The emitted doses were very high and similar between modes (82-90% of loaded dose). Predicted lung dose of AAT (percent of loaded dose) and delivery times were: TBM 56.6% in 7.5 min; TIM-6 59.9% in 4.4 min; and TIM-9 64.5% in 2.5 min. CONCLUSIONS: The I-neb AAD System enhanced AAT delivery by inhalation-only aerosol generation and a low-residual dose. Predicted lung dose was high for both TBM and TIM, but longer inspiratory times with TIM reduced the administration time to one-third that of tidal breathing. We

conclude that slow, deep, controlled inspirations using the I-neb AAD System is an efficient method to deliver AAT.

S. Ghdifan, L. Couderc, I. Michelet, C. Leguillon, B. Masseline and C. Marguet. "Bolus methylprednisolone efficacy for uncontrolled exacerbation of cystic fibrosis in children." 2010 *Pediatrics* 125(5):

We present here the clinical course of 4 children with cystic fibrosis, deltaF508/deltaF508, who were admitted with severe respiratory distress and in whom no improvement was obtained by intensive antibiotic therapy and systemic corticosteroids. Chest computed-tomography scans showed hyperinflation and atelectasis. The severity of these exacerbations was explained neither by visible mucus plugging nor by allergic bronchopulmonary aspergillosis. We hypothesized that these clinical features were related to a severe inflammatory process in small airways. Therefore, a high-dose short course of methylprednisolone (1 g/1.73 m<sup>2</sup> per day for 3 days) was given; all the patients' conditions were dramatically improved, and the therapy was safe. To our knowledge, this is the first reported use of bolus methylprednisolone in the treatment of uncontrolled pulmonary exacerbation in children with cystic fibrosis.

P. Iseli. "[Chronic cough in children--what to consider and how to evaluate?]." 2009 *Praxis (Bern 1994)* 98(23):

There is a long list of differential diagnoses for chronic cough lasting longer than 4 weeks in children. Diagnostic work up starts with a detailed history taking and a clinical investigation followed by a chest X-ray (in one plane) and a spirometry. For the latter reliable results can be achieved by children older than 5 years. If the diagnostic work up is still inconclusive and if the child is in good clinical condition, a 4 weeks' course of inhalation therapy with steroids and betamimetics together with a 2 weeks' course of antibiotics with a macrolide is warranted. In case coughing persists a thorough diagnostic work up is indicated to rule out conditions like cystic fibrosis, relevant humoral immunodeficiencies, primary ciliary dyskinesia, anatomic malformation or chronic pulmonary aspiration, preferably done by a pediatric pulmonologist. Chronic cough has to be considered abnormal in any child under the age of 1 year. For this age group a final diagnosis is of special importance.

C. L. Leach and G. L. Colice. "A Pilot Study to Assess Lung Deposition of HFA-Beclomethasone and CFC-Beclomethasone from a Pressurized Metered Dose Inhaler with and without Add-On Spacers and Using Varying Breathhold Times." 2010 *J Aerosol Med Pulm Drug Deliv*:

**Abstract Background:** The study objective of this pilot study was to determine the lung delivery of HFA-134a-beclomethasone dipropionate (HFA-BDP; QVAR) and CFC-beclomethasone dipropionate (CFC-BDP; Becloforte) with and without the add-on spacers, Aerochamber, and Volumatic. The smaller particles of HFA-BDP were presumed to produce greater lung deposition using spacers, with and without a delay [i.e., metered dose inhaler (MDI) actuation into the spacer and subsequent inhalation 0 and 2 sec later], compared with the larger particles of CFC-BDP. The study included a comparison of breathhold effects (i.e., 1 and 10-sec breathholds) on lung deposition. **Methods:** The study was an open-label design and utilized healthy subjects (n = 12 males). Each arm of the study contained three subjects; thus, outcomes were not powered to assess statistical significance. HFA-BDP and CFC-BDP were radiolabeled with technetium-99m and delivered to subjects. **Results:** Results showed that the small particle HFA-BDP lung deposition averaged 52% and was not affected by the use of Aerochamber with or without a spacer delay. The oropharyngeal deposition of HFA-BDP was reduced from approximately 28% to 4% with the Aerochamber. Lung deposition with the large particle

CFC-BDP was 3-7% and generally decreased with Aerochamber or Volumatic. A 2-sec time delay between actuation and breath plus the spacer reduced lung deposition slightly but reduced oropharyngeal deposition substantially (84% down to 3-20%) using the Aerochamber or Volumatic with and without a spacer delay. HFA-BDP lung deposition was dependent on the breathhold. Lung deposition with HFA-BDP was reduced by 16% with a 1-sec versus 10-sec breathhold. The difference was measured in the increased exhaled fraction, confirming that smaller particles need time to deposit and are exhaled if there is a reduced breathhold. The large particle CFC-BDP lung deposition was not affected by breathhold. Conclusions: The use of Aerochamber or Volumatic spacers with HFA-BDP did not alter lung deposition but it did reduce oropharyngeal deposition. However, HFA-BDP displayed reduced oropharyngeal deposition without a spacer

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**BACKGROUND:** Abnormalities in alveolar coagulation occur in idiopathic pulmonary fibrosis (IPF). Anticoagulants attenuate bleomycin-induced lung fibrosis in animals. In this study, we first examined the pharmacokinetics of inhaled heparin in healthy subjects. Second, we investigated the safety and tolerability of heparin inhalation in IPF patients. **METHODS:** Coagulation assays were performed in blood and bronchoalveolar lavage fluid samples from 19 healthy volunteers after inhalation of increasing amounts of unfractionated heparin. The acute effects of heparin inhalation on lung function and exercise capacity and the safety and tolerability of chronic heparin inhalation for 28 days were assessed in 20 IPF patients in an open-label exploratory pilot study. **RESULTS:** In healthy subjects, inhalation of 150,000 IU heparin ("filled dose") significantly increased the partial thromboplastin time and anti-factor Xa activity in blood samples indicating the threshold dose. The local alveolar anticoagulant effect was detectable up to 72 h, and the alveolar half-life was estimated at 28 h. In IPF-patients, no acute deleterious effects on pulmonary function, gas exchange, or exercise capacity were noted after inhalation of the threshold dose. During chronic treatment, where one-fourth of the threshold dose was inhaled every 12 h for 28 days to obtain a steady-state anticoagulant activity in the alveolar space approximating the anticoagulant activity observed after threshold dose inhalation, no heparin-related side effects, such as hemoptysis or heparin-induced antibodies and thrombocytopenia, were detected in any patient, and median lung function values, exercise capacity, and quality of life scores appeared largely unaltered. Three adverse and one serious adverse events were noted; however, the relation of these events to the heparin inhalation was assessed as "unlikely" or "no relation" in each case. **CONCLUSIONS:** Inhaled heparin appears to be safe and well tolerated in IPF patients. Future clinical trials are required to demonstrate the long-term safety and efficacy of inhaled heparin in IPF.

K. Nikander, J. Denyer, M. Dodd, T. Dyche, K. Webb, P. Weller and D. Stableforth. "The adaptive aerosol delivery system in a telehealth setting: patient acceptance, performance and feasibility." 2010 J Aerosol Med Pulm Drug Deliv 23 Suppl 1:

**BACKGROUND:** The telehealth service is one of the fastest growing healthcare segments. It is increasingly utilizing computer technology and telecommunication equipment to either provide continuous vital sign monitoring or facilitate patient care at home, rather than relying solely on in-person care. **METHODS:** We conducted a 6-week open study in nineteen patients with cystic fibrosis enrolled from three centers, to investigate patient perception of a telehealth enabled nebulizer system (Prodose Adaptive Aerosol Delivery [AAD] System), which enabled the doorstep delivery of repeat medication. **RESULTS:** The results showed that patient confidence in the device and perception of ease of use was high with no significant change between the start and end of the trial. Views on the home delivery of medication were split between 'great' and

'inconvenient.' However, if the delivery system had been more flexible and delivered all the patients' drugs, the majority of patients would have had their medication delivered in this way. **CONCLUSIONS:** The trial showed that it was possible to build telehealth technology into an advanced nebulizer system, and that patient acceptance of the technology was unlikely to be a barrier to the adoption of such a telehealth system.

T. L. Noah, S. S. Ivins, K. A. Abode, P. W. Stewart, P. H. Michelson, W. T. Harris, M. M. Henry and M. W. Leigh. "Inhaled versus systemic antibiotics and airway inflammation in children with cystic fibrosis and *Pseudomonas*." 2010 *Pediatr Pulmonol* 45(3):

**RATIONALE:** Inhaled tobramycin has been shown to transiently clear *Pseudomonas* from lower airways in early cystic fibrosis (CF), but does not markedly reduce lung inflammation, a key factor in disease progression. **OBJECTIVE:** Test the hypothesis that systemic antibiotics are more effective than inhaled antibiotics for reducing lower airways inflammation. **METHODS:** Clinically stable CF children with recent *Pseudomonas* were randomized to receive 4 weeks of inhaled tobramycin or 2 weeks of systemic antibiotics (intravenous ceftazidime and tobramycin). Bronchoalveolar lavage fluid was obtained just before and 4-6 weeks after treatment. The primary outcome was change in % neutrophils in lavage fluid. **RESULTS:** Fifteen subjects (inhaled = 6, systemic = 9) completed the protocol. Three Systemic Group subjects could not have central venous access established and were treated with oral ciprofloxacin (plus inhaled tobramycin) for 2 weeks as an alternative "systemic" regimen, per protocol. Groups were well matched in age, markers of disease severity, and initial % neutrophils. The Systemic Group showed a modest median change in percent neutrophils (-7%) which was not statistically significant compared to inhaled (+5.4%,  $P = 0.07$ ). However, the Systemic Group had significantly greater reductions in total cells (-50% vs. -3%,  $P < 0.01$ ) and neutrophils (-74% vs. -10%,  $P = 0.02$ ) per ml lavage fluid. Both groups had reduced bacterial quantity after treatment, but there was no significant difference between groups. **CONCLUSIONS:** In clinically stable children with CF, systemic antibiotics result in greater short-term reduction in lower airways inflammation than inhaled antibiotics.

F. Ratjen, A. Munck, P. Kho and G. Angyalosi. "Treatment of early *Pseudomonas aeruginosa* infection in patients with cystic fibrosis: the ELITE trial." 2010 *Thorax* 65(4):

**RATIONALE:** Antibiotic therapy for early *Pseudomonas aeruginosa* infection in patients with cystic fibrosis (CF) is effective, but the optimal therapeutic regimen and duration for early treatment remains unclear. The Early Inhaled Tobramycin for Eradication (ELITE) study was designed to assess the efficacy and safety of two regimens (28 and 56 days) of tobramycin inhalation solution (TIS) 300 mg/5 ml twice daily for the treatment of early onset *P. aeruginosa* infection in patients with CF. **METHODS:** In this open-label randomised multicentre study, patients with CF (aged  $\geq 6$  months) with early *P. aeruginosa* infection were treated for 28 days with TIS twice daily administered by the PARI LC PLUS (PARI GmbH, Starnberg, Germany) jet nebuliser. After 28 days, patients were randomised 1:1 to either stop TIS ( $n=45$ ) or to receive a further 28 days of TIS ( $n=43$ ). The primary endpoint was the median time to recurrence of *P. aeruginosa* (any strain). Secondary endpoints included the proportion of patients free of *P. aeruginosa* infection 1 month after cessation of therapy and safety assessments. **RESULTS:** The median time to recurrence of *P. aeruginosa* (any strain) was similar between the two groups. In total, 93% and 92% of the patients were free of *P. aeruginosa* infection 1 month after the end of treatment and 66% and 69% remained free at the final visit in the 28-day and 56-day groups, respectively. TIS was well tolerated. **CONCLUSIONS:** Treatment with TIS for 28 days is an effective and well tolerated therapy for early *P. aeruginosa* infection in patients with CF. **TRIAL REGISTRATION NUMBER:** NCT00391976.

C. R. Sudfeld, E. C. Dasenbrook, W. G. Merz, K. C. Carroll and M. P. Boyle. "Prevalence and risk factors for recovery of filamentous fungi in individuals with cystic fibrosis." 2010 J Cyst Fibros 9(2):

**BACKGROUND:** Filamentous fungi are frequently recovered from respiratory cultures of individuals with CF. **METHODS:** A CF cohort database was utilized to determine filamentous fungal prevalence and risk factors. **RESULTS:** The prevalence of filamentous fungal isolation increased from 2.0% in 1997 to 28.7% in 2007. The odds of isolating filamentous fungi during a quarter was greater in CF adults [ $p < 0.001$ ], during chronic oral antibiotic use [ $p = 0.002$ ] and increased with each 10% drop in FEV(1) percent predicted [ $p = 0.005$ ], while inhaled corticosteroids surprisingly decreased the likelihood [ $p = 0.012$ ]. The direction of these effects persisted after excluding individuals with ABPA. A sub-analysis determined older age [ $p = 0.019$ ] and use of inhaled antibiotics [ $p = 0.011$ ] were independent risk factors for onset of fungal colonization. **CONCLUSIONS:** This study suggests that isolation of filamentous fungi in CF at JHH has increased and risk factors include older age, decreased lung function, and chronic oral antibiotics.

E. R. Sutherland, C. A. Camargo, Jr., W. W. Busse, E. O. Meltzer, H. G. Ortega, S. W. Yancey, A. H. Emmett and D. A. Stempel. "Comparative effect of body mass index on response to asthma controller therapy." 2010 Allergy Asthma Proc 31(1):

Increases in body mass index (BMI) are reported to influence asthma severity and response to treatment. This analysis was designed to explore whether increasing BMI altered the comparative response to treatment with either fluticasone propionate (FP) or montelukast. Two double-blind, randomized, parallel-group trials of 12-weeks duration comparing FP, 88 micrograms, twice daily or montelukast, 10 mg, daily were evaluated. Subjects with mild-moderate persistent asthma were retrospectively stratified by BMI of  $< 20$  kg/m<sup>2</sup> (underweight), 20-24.9 kg/m<sup>2</sup> (normal weight), 25-29.9 kg/m<sup>2</sup> (overweight), and  $\geq 30$  kg/m<sup>2</sup> (obese). Outcomes included mean changes in forced expiratory volume in 1 second (FEV(1)) and morning peak flow, daily albuterol use, and daily symptom scores. There were 1052 subjects evenly distributed between FP and montelukast by baseline parameters, including BMI. FP was statistically superior to montelukast for all BMI categories of normal, overweight, and obese subjects for FEV(1) ( $p < 0.008$ ), morning peak flow ( $p < 0.002$ ), albuterol use ( $p < 0.02$ ), and symptom scores ( $p < 0.05$ ). FP produced a significantly greater clinical response for normal, overweight, and obese subjects compared with montelukast. Irrespective of BMI, FP appears to be the more effective asthma controller therapy.

E. D. Telenga, H. A. Kerstjens, D. S. Postma, N. H. Ten Hacken and M. van den Berge. "Inhaled corticosteroids in chronic obstructive pulmonary disease: a review." 2010 Expert Opin Pharmacother 11(3):

**IMPORTANCE OF THE FIELD:** Chronic obstructive pulmonary disease (COPD) is a disease characterized by chronic airflow obstruction and a progressive lung function decline. Although widely used, the efficacy of inhaled corticosteroids (ICS) in the treatment of COPD remains a matter of debate. **AREAS COVERED IN THIS REVIEW:** This article reviews the evidence about the effects of inhaled corticosteroids in the treatment of COPD. **WHAT THE READER WILL GAIN:** Short-term treatment with ICS improves lung function and quality of life; in addition, several studies with longer follow-up have shown less decline over time in quality of life, and fewer exacerbations. By contrast, long-term studies have been unable to show substantial improvement in the decline of lung function in COPD. Based on these findings, it was concluded that the use of ICS did not influence the natural course of COPD. However, this conclusion has been challenged by two subsequent studies, TORCH and GLUCOLD, which both showed a reduction in lung-function decline over time with the use of ICS. These two studies indicate that ICS might indeed influence the natural course of the disease, at least in a subgroup of COPD

patients. TAKE HOME MESSAGE: Further studies are needed to identify which individuals have a favorable short- and long-term response to ICS treatment.

H. A. Tiddens, S. H. Donaldson, M. Rosenfeld and P. D. Pare. "Cystic fibrosis lung disease starts in the small airways: can we treat it more effectively?" 2010 *Pediatr Pulmonol* 45(2):

The aims of this article are to summarize existing knowledge regarding the pathophysiology of small airways disease in cystic fibrosis (CF), to speculate about additional mechanisms that might play a role, and to consider the available or potential options to treat it. In the first section, we review the evidence provided by pathologic, physiologic, and imaging studies suggesting that obstruction of small airways begins early in life and is progressive. In the second section we discuss how the relationships between CF transmembrane conductance regulator (CFTR), ion transport, the volume of the periciliary liquid layer and airway mucus might lead to defective mucociliary clearance in small airways. In addition, we discuss how chronic endobronchial bacterial infection and a chronic neutrophilic inflammatory response increase the viscosity of CF secretions and exacerbate the clearance problem. Next, we discuss how the mechanical properties of small airways could be altered early in the disease process and how remodeling can contribute to small airways disease. In the final section, we discuss how established therapies impact small airways disease and new directions that may lead to improvement in the treatment of small airways disease. We conclude that there are many reasons to believe that small airways play an important role in the pathophysiology of (early) CF lung disease. Therapy should be aimed to target the small airways more efficiently, especially with drugs that can correct the basic defect at an early stage of disease.

M. E. Wechsler, S. J. Kunselman, V. M. Chinchilli, E. Bleecker, H. A. Boushey, W. J. Calhoun, B. T. Ameredes, M. Castro, T. J. Craig, L. Denlinger, J. V. Fahy, N. Jarjour, S. Kazani, S. Kim, M. Kraft, S. C. Lazarus, R. F. Lemanske, Jr., A. Markezich, R. J. Martin, P. Permaul, S. P. Peters, J. Ramsdell, C. A. Sorkness, E. R. Sutherland, S. J. Szeffler, M. J. Walter, S. I. Wasserman and E. Israel. "Effect of beta2-adrenergic receptor polymorphism on response to longacting beta2 agonist in asthma (LARGE trial): a genotype-stratified, randomised, placebo-controlled, crossover trial." 2009 *Lancet* 374(9703):

**BACKGROUND:** Some studies suggest that patients with asthma who are homozygous for arginine at the 16th amino acid position of the beta2-adrenergic receptor (B16 Arg/Arg) benefit less from treatment with longacting beta2 agonists and inhaled corticosteroids than do those homozygous for glycine (B16 Gly/Gly). We investigated whether there is a genotype-specific response to treatment with a longacting beta2 agonist in combination with inhaled corticosteroid. **METHODS:** In this multicentre, randomised, double-blind, placebo-controlled trial, adult patients with moderate asthma were enrolled in pairs matched for forced expiratory volume in 1 s and ethnic origin, according to whether they had the B16 Arg/Arg (n=42) or B16 Gly/Gly (n=45) genotype. Individuals in a matched pair were randomly assigned by computer-generated randomisation sequence to receive inhaled longacting beta2 agonist (salmeterol 50 microg twice a day) or placebo given in a double-blind, crossover design for two 18-week periods. Open-label inhaled corticosteroid (hydrofluoroalkane beclometasone 240 microg twice a day) was given to all participants during the treatment periods. The primary endpoint was morning peak expiratory flow (PEF). Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00200967. **FINDINGS:** After 18 weeks of treatment, mean morning PEF in Arg/Arg participants was 21.4 L/min (95% CI 11.8-31.1) higher when participants were assigned to receive salmeterol than when assigned to receive placebo (p<0.0001). In Gly/Gly participants, morning PEF was 21.5 L/min (11.0-32.1) higher when participants were assigned to receive salmeterol than when assigned to receive placebo (p<0.0001). The improvement in PEF did not differ between genotypes (difference [Arg/Arg-Gly/Gly] -0.1, -14.4 to 14.2; p=0.99). In Gly/Gly participants, methacholine PC20 (20% reduction in forced expiratory volume in 1 s; a prespecified secondary outcome) was 2.4 times higher

when participants were assigned to salmeterol than when assigned to placebo ( $p < 0.0001$ ). Responsiveness to methacholine did not differ between salmeterol and placebo in Arg/Arg participants ( $p = 0.87$ ). The 2.5 times higher genotype-specific difference in responsiveness to methacholine was significant (1.32 doubling dose difference between genotypes, 0.43-2.21,  $p = 0.0038$ ). Seven Arg/Arg participants (placebo,  $n = 5$ ; salmeterol,  $n = 2$ ) and six Gly/Gly participants (placebo,  $n = 3$ ; salmeterol,  $n = 3$ ) had an asthma exacerbation. Five serious adverse events were reported, one each during the pre-match and run-in phases on open-label inhaled corticosteroid, two during double-blind treatment with salmeterol/inhaled corticosteroid, and one during double-blind treatment with placebo/inhaled corticosteroid. None of the serious events was asthma-related or related to study drugs or procedures. INTERPRETATION: In asthma patients with B16 Arg/Arg and B16 Gly/Gly genotypes, combination treatment with salmeterol and inhaled corticosteroid improved airway function when compared with inhaled corticosteroid therapy alone. These findings suggest that patients should continue to be treated with longacting beta2 agonists plus moderate-dose inhaled corticosteroids irrespective of B16 genotype. Further investigation is needed to establish the importance of the genotype-specific difference in responsiveness to methacholine. FUNDING: National Institutes of Health.

## Reviews and Meta Analyses

R. Agarwal, A. Khan, A. N. Aggarwal and D. Gupta. "Is the SMART approach better than other treatment approaches for prevention of asthma exacerbations? A meta-analysis." 2009 *Monaldi Arch Chest Dis* 71(4):

**BACKGROUND AND AIMS:** The combination of inhaled corticosteroids (ICS) and long-acting beta2 agonists (LABA) has been used as a single inhaler both for maintenance and reliever therapy in asthma, the SMART approach. The administration of additional CS with each reliever inhalation in response to symptoms is expected to provide better control of airway inflammation. The aim of this meta-analysis was to evaluate the efficacy and safety of the SMART approach versus other approaches in the management of asthma in preventing asthma exacerbations. **METHODS:** We searched the MEDLINE and EMBASE databases for studies that have reported exacerbations in the SMART group versus the control group. We calculated the odds ratio (OR) and 95% confidence intervals (CI) to assess the exacerbations in the two groups and pooled the results using a random-effects model. **RESULTS:** Our search yielded eight studies. The use of SMART approach compared to fixed-dose ICS-LABA combination significantly decreased the odds of a severe exacerbation (OR 0.65; 95% CI, 0.53-0.80) and severe exacerbation requiring hospitalization/ER treatment (OR 0.69; 95% CI, 0.58-0.83). The use of SMART approach compared to fixed-dose ICS also significantly decreased the odds of a severe exacerbation (OR 0.52; 95% CI, 0.45-0.61) and severe exacerbation requiring medical intervention (OR 0.52; 95% CI, 0.42-0.65). The occurrence of adverse events was similar in the two groups. There was some evidence of statistical heterogeneity. **CONCLUSIONS:** The SMART approach using formoterol-budesonide is superior in preventing exacerbations when compared to traditional therapy with fixed dose ICS or ICS-LABA combination without any increase in adverse events.

J. Ahnert, S. Loffler, J. Muller and H. Vogel. "[Systematic literature review on interventions in rehabilitation for children and adolescents with asthma bronchiale]." 2010 *Rehabilitation (Stuttg)* 49(3):

Relevant data bases were used to collect and evaluate guidelines, meta-analyses, and reviews as well as primary studies dealing with asthma therapy for children and adolescents. Treatment approaches whose effectiveness with regard to bronchial asthma was empirically verified (i. e., evidence-based) were identified (medical and diagnostic procedures as well as drug trials were excluded from the analysis). 152 methodically sound studies referring to asthma treatment of children and adolescents were selected. Strong evidence was found for patient education, parent education, exercise therapy, inhalation, and tobacco withdrawal. Nutritional counseling and avoidance of allergens showed limited evidence. Psychotherapy, relaxation techniques, breathing exercises, climate therapy, clinical social work (social and legal counseling services, vocational reintegration counseling, aftercare) and integration counseling showed inconsistent evidence. No evidence was found for alternative medicine. Challenges regarding the development of treatment standards for children and adolescent rehabilitation are highlighted; these refer to limitations in report quality in some of the studies, the validity of treatments for comorbid conditions, a lack of differentiation for different age groups, and transferability of outpatient or international study results to inpatient rehabilitation.

C. Frois, E. Q. Wu, S. Ray and G. L. Colice. "Inhaled corticosteroids or long-acting beta-agonists alone or in fixed-dose combinations in asthma treatment: a systematic review of fluticasone/budesonide and formoterol/salmeterol." 2009 *Clin Ther* 31(12):

**BACKGROUND:** Inhaled corticosteroids (ICSs) and long-acting inhaled beta(2)-agonists (LABAs) are recommended treatment options for asthma. **OBJECTIVE:** This review compares the clinical effectiveness and tolerability of the ICSs fluticasone propionate and budesonide and the LABAs formoterol fumarate and salmeterol xinafoate administered alone or in combination. **METHODS:** A systematic review of the clinical studies available on MEDLINE (database period, 1950-September 2009) was conducted to assess English-language randomized controlled trials in children and adults with asthma. Treatment outcomes included lung function, symptom-free days (SFDs), use of rescue/reliever medications, asthma exacerbations, and tolerability profile. **Results:** Use of fluticasone was associated with significantly greater improvement in lung function and better asthma symptom control than budesonide. Similarly, formoterol was associated with significantly greater improvement in lung function and better asthma symptom control (as measured by less rescue medication use and more SFDs) compared with salmeterol. Single inhaler combination regimens (budesonide/ formoterol and fluticasone/salmeterol) were frequently more effective in improving all treatment outcomes than either monotherapy alone. Across all comparisons, a review of studies in adults and children did not find statistically significant differences in outcomes between the ICS and LABA therapies considered in this research. In general, no differences in tolerability profiles were reported between the ICS and LABA options, although the risk for growth retardation was lower with fluticasone than budesonide and with budesonide/formoterol than with budesonide monotherapy. **CONCLUSIONS:** In this systematic review, fluticasone and formoterol appear to provide improved therapeutic benefits versus budesonide and salmeterol, respectively. Both fluticasone/salmeterol and budesonide/ formoterol combination therapies appeared to be associated with greater improvements in outcomes measures than the corresponding ICS and LABA monotherapies.

O. N. Keene, J. Vestbo, J. A. Anderson, P. M. Calverley, B. Celli, G. T. Ferguson, C. Jenkins and P. W. Jones. "Methods for therapeutic trials in COPD: lessons from the TORCH trial." 2009 *Eur Respir J* 34(5):

The TORCH (Towards a Revolution in COPD Health) trial has highlighted some important issues in the design and analysis of long term trials in chronic obstructive pulmonary disease. These include collection of off-treatment exacerbation data, analysis of exacerbation rates and the effect of inclusion of patients receiving inhaled corticosteroids (ICS) prior to randomisation. When effective medications are available to patients who withdraw, inclusion of off-treatment data can mask important treatment effects on exacerbation rates. Analysis of on-treatment data avoids this bias but it needs to be combined with careful analysis of withdrawal patterns across treatments. The negative binomial model is currently the best approach to statistical analysis of exacerbation rates, while analysis of time to exacerbation can supplement this approach. In the TORCH trial, exacerbation rates were higher among patients with previous use of ICS compared to those with no prior use on all study treatments. Retrospective subgroup analysis suggests ICS reduced exacerbation rates compared with placebo, regardless of prior use of ICS before entry to the study. Factorial analysis provides an alternative analysis for trials with combinations of treatments, but assumes no interaction between treatments, an assumption which cannot be verified by a significance test. No definitive conclusions can yet be drawn on whether ICS treatment has an effect on mortality.

G. Nicolini, G. Cremonesi and A. S. Melani. "Inhaled corticosteroid therapy with nebulized beclometasone dipropionate." 2010 *Pulm Pharmacol Ther* 23(3):

Inhaled corticosteroids (ICS) are the most effective anti-inflammatory agents for the management of chronic persistent asthma and are therefore recommended as first-line antiasthmatic therapy in children and adults. In various settings, the administration of ICS via nebulizer rather than hand-held inhaler (HHI) may have certain advantages, as many patients with HHI fail to use these devices properly or efficiently. In particular, young children, the elderly, the acutely ill, and those with restricted dexterity may be unable to coordinate inhalation with actuation of the device or to generate sufficient inspiratory flow to operate breath-actuated devices effectively. Compliance with nebulized therapy may also be better than that with a pressurized metered-dose inhaler (pMDI) plus spacer. Systematic reviews conclude that there is no significant difference in clinical effects between nebulizers and HHI. Performance and clinical effect of nebulization are influenced by several technical aspects such as the nebulizer-drug combination, nebulizer type, output and lung deposition. Among the currently available ICS, nebulized beclometasone dipropionate (BDP) has been in clinical use for more than 35 years, and has demonstrated marked clinical efficacy and a favorable tolerability profile in children and adults with chronic persistent asthma. The clinical efficacy of nebulized beclometasone is discussed in the present review using data from 13 published studies, which included a total of 1250 patients. Three multicenter, randomized, double-blind studies showed that nebulized BDP is as effective as BDP via pMDI plus spacer in a 2:1 dose ratio. Controlled trials involving 497 adults and children demonstrated similar clinical efficacy between nebulized BDP and either nebulized fluticasone propionate or nebulized budesonide. In all these trials, treatment-related adverse effects were generally uncommon, most were mild-to-moderate in severity, and most were associated with the respiratory system. Meta-analyses show that BDP, like other inhaled corticosteroids, has no major influence on patient height, urinary cortisol concentration, or bone metabolism, thus suggesting the absence of growth retardation or any marked effect on adrenal function or the hypothalamic-pituitary-adrenal axis when used in the approved dose range. Overall, nebulized BDP appears to have a particularly important place in asthma therapy: as a general alternative to HHIs (e.g. in patients with poor HHI compliance); when patients such as children or the elderly are unable to operate HHIs because of poor hand-lung coordination, lack of cooperation, or low inspiratory flow rate; and when high dosages of ICS are required, such as in adults with severe, corticosteroid-dependent asthma.

D. Price, A. Robertson, K. Bullen, C. Rand, R. Horne and H. Staudinger. "Improved adherence with once-daily versus twice-daily dosing of mometasone furoate administered via a dry powder inhaler: a randomized open-label study." 2010 *BMC Pulm Med* 10:

**BACKGROUND:** Poor adherence with prescribed asthma medication is a major barrier to positive treatment outcomes. This study was designed to determine the effect of a once-daily administration of mometasone furoate administered via a dry powder inhaler (MF-DPI) on treatment adherence compared with a twice-daily administration. **METHODS:** This was a 12-week open-label study designed to mimic an actual clinical setting in patients  $\geq 12$  years old with mild-to-moderate persistent asthma. Patients were randomized to receive MF-DPI 400 microg once-daily in the evening or MF-DPI 200 microg twice-daily. Adherence was assessed primarily using the number of actual administered doses reported from the device counter divided by the number of scheduled doses. Self-reports were also used to determine adherence. Health-related quality of life, healthcare resource utilization, and days missed from work or school were also reported. **RESULTS:** 1233 patients were randomized. The mean adherence rates, as measured by the automatic dose counter, were significantly better ( $P < 0.001$ ) with MF-DPI 400 microg once-daily in the evening (93.3%) than with MF-DPI 200 microg twice-daily (89.5%). Mean adherence rates based on self-reports were also significantly better ( $P < 0.001$ ) with MF-DPI 400 microg QD PM (97.2%) than with MF-DPI 200 microg twice-daily (95.3%). Adherence rates were lower in adolescents (12-17 years old). Health-related quality of life

improved by 20% in patients using MF-DPI once-daily in the evening and by 14% in patients using MF-DPI twice-daily. Very few (<8%) patients missed work/school. CONCLUSION: Mean adherence rates were greater with a once-daily dosing regimen of MF-DPI than with a twice-daily dosing regimen. This trial was completed prior to the ISMJE requirements for trial registration.

G. J. Rodrigo, H. Neffen, F. D. Colodenco and J. A. Castro-Rodriguez. "Formoterol for acute asthma in the emergency department: a systematic review with meta-analysis." 2010 *Ann Allergy Asthma Immunol* 104(3):

**BACKGROUND:** Although several published studies have suggested that formoterol fumarate could be equivalent to short-acting beta2-agonists (SABAs) for the treatment of asthma exacerbations, its role in acute asthma treatment remains undefined. **OBJECTIVE:** To evaluate the efficacy and safety of inhaled formoterol (compared with SABAs) for the emergency department treatment of patients with acute asthma. **METHODS:** Systematic searches were conducted in MEDLINE, EMBASE, the Cochrane Controlled Trials Register, and manufacturers' trial registers, without language restriction. The primary outcomes were spirometric measures. The secondary outcomes included final serum potassium level, heart rate, electrocardiographic QT interval corrected for heart rate, and total withdrawals. **RESULTS:** Nine randomized controlled trials (including 576 participants) were selected. No significant difference could be detected between formoterol and SABAs for any of the selected time points: at 30 to 40 minutes after the first administration of study drugs (standardized mean difference, -0.19; 95% confidence interval, -0.56 to 0.17; I<sup>2</sup> = 75%), at the end of treatment (standardized mean difference, -0.25; 95% confidence interval, -0.72 to 0.13; I<sup>2</sup> = 89%), and at 60 to 90 minutes after the last dose (standardized mean difference, -0.13; 95% confidence interval, -0.55 to 0.28; I<sup>2</sup> = 80%). Similarly, there were no significant differences between formoterol and SABAs regarding final serum potassium level, heart rate, QT interval, hospitalization rate, and total withdrawals. **CONCLUSIONS:** This review suggests that high-dose formoterol administered via dry powder inhaler is well tolerated and provides rapid and effective bronchodilation, similar to high-dose salbutamol or terbutaline via metered-dose inhaler or nebulizer. Formoterol may be used in the treatment of acute asthma in the emergency department setting.

S. Singh and Y. K. Loke. "Risk of pneumonia associated with long-term use of inhaled corticosteroids in chronic obstructive pulmonary disease: a critical review and update." 2010 *Curr Opin Pulm Med* 16(2):

**PURPOSE OF REVIEW:** The aim was to determine the effects of long-term inhaled corticosteroid use on pneumonia in patients with chronic obstructive pulmonary disease (COPD) via systematic searches of MEDLINE, EMBASE, ISI, regulatory documents and manufacturers' trial registries. **RECENT FINDINGS:** Our updated meta-analysis of 24 long-term randomized controlled trials involving 23 096 participants shows a significantly increased risk of pneumonia with the use of inhaled corticosteroids in COPD (relative risk 1.57, 95% confidence interval 1.41-1.75, P < 0.0001). The increased risk of pneumonia is not accompanied by a corresponding increase in mortality. The elderly and those with more severe disease and lower forced expiratory volume in 1s are at the highest risk of pneumonia. The trials of currently available inhaled corticosteroids have included participants with varying duration of inhaled corticosteroid exposure and COPD severity, with apparent differences in the proportion of pneumonia ascertained among these trials. The absence of adequately powered long-term head-to-head trials precludes any definitive conclusions on intraclass differences in risk. **SUMMARY:** Clinicians should consider the long-term risks of pneumonia with the use of inhaled corticosteroids in patients with COPD. Adequately powered long-term head-to-head trials with objective pneumonia definitions, active ascertainment and radiologic and microbiologic confirmation are needed to clarify any intraclass differences in the risk of pneumonia.

D. P. Skoner, D. A. Gentile and B. Angelini. "Effect of therapeutic doses of mometasone furoate on cortisol levels in children with mild asthma." 2010 Allergy Asthma Proc 31(1):

Corticosteroids are the foundation of pharmacologic treatment for children with asthma. However, high-dose inhaled corticosteroid treatment can cause hypothalamic-pituitary-adrenal (HPA) axis suppression. We investigated the effect of three doses of mometasone furoate administered via dry-powder inhaler (MF-DPI) on the HPA axis in children. Fifty children (6-11 years) with mild asthma of > or =6 months' duration were randomized to MF-DPI, 100 (n = 13), 200 (n = 13), or 400 micrograms b.i.d. (n = 12), or placebo (n = 12) for 29 days. The primary end point was change from baseline in the 12-hour area under the plasma-cortisol-concentration-time curve (AUC). Secondary parameters included plasma cortisol response to cosyntropin stimulation and 24-hour urinary free cortisol concentrations. Compared with placebo, AUC changes associated with treatments of MF-DPI, 100 or 200 micrograms b.i.d., were not significant, whereas a significant change was observed with MF-DPI, 400 micrograms b.i.d. (27%; p = 0.05). Responses to cosyntropin stimulation and urinary cortisol measurements were similar to placebo with all MF-DPI doses. All regimens were well tolerated. MF-DPI did not have a significant effect on plasma or urinary cortisol levels at doses up to 200 micrograms b.i.d. in children with mild asthma. Higher MF-DPI doses may potentially suppress the HPA axis.

E. D. Telenga, H. A. Kerstjens, D. S. Postma, N. H. Ten Hacken and M. van den Berge. "Inhaled corticosteroids in chronic obstructive pulmonary disease: a review." 2010 Expert Opin Pharmacother 11(3):

**IMPORTANCE OF THE FIELD:** Chronic obstructive pulmonary disease (COPD) is a disease characterized by chronic airflow obstruction and a progressive lung function decline. Although widely used, the efficacy of inhaled corticosteroids (ICS) in the treatment of COPD remains a matter of debate. **AREAS COVERED IN THIS REVIEW:** This article reviews the evidence about the effects of inhaled corticosteroids in the treatment of COPD. **WHAT THE READER WILL GAIN:** Short-term treatment with ICS improves lung function and quality of life; in addition, several studies with longer follow-up have shown less decline over time in quality of life, and fewer exacerbations. By contrast, long-term studies have been unable to show substantial improvement in the decline of lung function in COPD. Based on these findings, it was concluded that the use of ICS did not influence the natural course of COPD. However, this conclusion has been challenged by two subsequent studies, TORCH and GLUCOLD, which both showed a reduction in lung-function decline over time with the use of ICS. These two studies indicate that ICS might indeed influence the natural course of the disease, at least in a subgroup of COPD patients. **TAKE HOME MESSAGE:** Further studies are needed to identify which individuals have a favorable short- and long-term response to ICS treatment.

## Aerosol

H. Adi, P. M. Young, H. K. Chan, H. Agus and D. Traini. "Co-spray-dried mannitol-ciprofloxacin dry powder inhaler formulation for cystic fibrosis and chronic obstructive pulmonary disease." 2010 Eur J Pharm Sci 40(3):

The aim of this study was to assess the potential of delivering a combination therapy, containing mannitol (a sugar alcohol with osmotic characteristics), and ciprofloxacin hydrochloride (an antibacterial fluoroquinolone), as a dry powder inhaler (DPI) formulation for inhalation. Single and combination powders were produced by spray drying ciprofloxacin and mannitol, from aqueous solution, at different ratios and under controlled conditions, as to obtain similar particle size distributions. Each formulation was characterised using laser diffraction, scanning electron microscopy, differential scanning calorimetry, dynamic vapour sorption, X-ray powder diffraction, and colloidal force microscopy. The in vitro aerosol performance of each formulation was studied using an Aerolizer DPI device and a multi-stage liquid impinger (analysed using high performance liquid chromatography). In addition, a disk diffusion test was performed to assess the in vitro antimicrobial activity of each formulation and starting materials. All formulations had similar particle size distributions, however, the morphology, thermal properties and moisture sorption was dependent on the relative percentages of each component. In general, the combination formulation containing 50% (w/w) mannitol appeared to have the best aerosol performance, good stability and lowest particle cohesion (as measured by colloid probe microscopy). Furthermore, of the formulations tested, mannitol did not appear to alter the effectiveness of the ciprofloxacin antimicrobial activity to *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Streptococcus pyogenes*. The combination of co-spray-dried mannitol and ciprofloxacin from a DPI is an attractive approach to promote mucous clearance in the respiratory tract while simultaneously treating local chronic infection, such as chronic obstructive pulmonary disease and cystic fibrosis.

W. E. Berger and M. J. Noonan. "Treatment of persistent asthma with Symbicort (budesonide/formoterol inhalation aerosol): an inhaled corticosteroid and long-acting beta2-adrenergic agonist in one pressurized metered-dose inhaler." 2010 J Asthma 47(4):

**OBJECTIVE:** Budesonide/formoterol inhalation aerosol (Symbicort AstraZeneca, Wilmington, Delaware) is an inhaled corticosteroid (ICS) and long-acting beta(2)-adrenergic agonist (LABA) combination administered twice daily via one hydrofluoroalkane pressurized metered-dose inhaler (pMDI) approved in the United States for the long-term maintenance treatment of persistent asthma in patients  $\geq 12$  years of age whose asthma cannot be controlled by an ICS alone. The objective was to review efficacy, safety, and pharmacogenetic data on budesonide/formoterol pMDI in the treatment of persistent asthma. **METHODS:** The authors searched PubMed and respiratory meeting databases to identify asthma studies of budesonide/formoterol pMDI. Studies involving traditional and patient-reported outcomes, safety, tolerability, or pharmacogenetics were included. **RESULTS:** In two 12-week pivotal trials in adolescents and adults, treatment with budesonide/formoterol pMDI 160/4.5 microg x 2 inhalations (320/9 microg) twice daily for moderate to severe persistent asthma or 80/4.5 microg x 2 inhalations (160/9 microg) twice daily for mild to moderate persistent asthma, demonstrated greater efficacy and similar tolerability compared with placebo and the same nominal dose of its monocomponents. Comparisons with formoterol dry powder inhaler (DPI) for predose forced expiratory volume in one second (FEV(1)) and with budesonide pMDI for 12-hour mean postdose FEV(1) demonstrated the anti-inflammatory and bronchodilatory contributions of budesonide and formoterol, respectively. Evaluations of patient-reported outcomes, including asthma-specific quality of life and treatment

satisfaction, further supported the clinical benefits of budesonide/formoterol pMDI. In a 52-week tolerability study of patients aged  $\geq 12$  years, budesonide/formoterol pMDI was delivered at up to double the maximum dose (640/18 microg twice daily) and demonstrated a safety profile similar to that of budesonide (640 microg twice daily), with no unexpected pattern of abnormalities. Additional studies reported that budesonide/formoterol pMDI 320/9 microg twice daily and fluticasone propionate/salmeterol DPI 250/50 microg twice daily have similar efficacy and tolerability, with significantly more patients achieving  $\geq 15\%$  improvement in FEV<sub>1</sub> within 15 minutes with budesonide/formoterol pMDI compared with fluticasone/salmeterol DPI. Moreover, inheritance of the Gly16Arg polymorphism of the beta(2)-adrenergic receptor does not appear to affect clinical outcomes with budesonide/formoterol pMDI. CONCLUSION: Budesonide/formoterol pMDI administered twice daily is effective and generally well tolerated in patients whose asthma is not well controlled on ICS alone.

M. T. Bigham, B. R. Jacobs, M. A. Monaco, R. J. Brill, D. Wells, E. M. Conway, S. Pettinichi and D. S. Wheeler. "Helium/oxygen-driven albuterol nebulization in the management of children with status asthmaticus: a randomized, placebo-controlled trial." 2010 *Pediatr Crit Care Med* 11(3):

OBJECTIVES: We investigated the effect of heliox-powered albuterol therapy on hospital length of stay and clinical status in children with moderate to severe status asthmaticus. DESIGN: Prospective, randomized, placebo-controlled trial. SETTING: Twenty-five-bed pediatric intensive care unit at an academic children's medical center. PATIENTS: Forty-two children (2-21 yrs of age) with moderate to severe status asthmaticus. INTERVENTIONS: Patients were randomized to receive either heliox-powered nebulized albuterol or air/oxygen-powered nebulized albuterol (placebo) until they were transitioned to albuterol delivered by a metered dose inhaler. MEASUREMENTS AND MAIN RESULTS: Clinical asthma scores were recorded on enrollment and every 4 hrs thereafter. Patients in the heliox group (n = 22) and the control group (n = 20) had similar ages (mean +/- sem: 88 +/- 9.9 vs. 98 +/- 11.1 months, respectively; p = .51), time to study enrollment (618 +/- 70.4 vs. 597 +/- 84.1 mins, respectively; p = .72), and clinical asthma scores at study entry (5.9 +/- 0.2 vs. 5.7 +/- 0.3, respectively; p = .72). There were no significant differences between groups in time to eligibility to hospital discharge (66.2 +/- 8.7 vs. 63.4 +/- 8.6 hrs, respectively; p = .61), time to clinical asthma score <3 (22 +/- 2.8 vs. 21.2 +/- 5.3 hrs, respectively; p = .27), or time to eligibility for intensive care unit discharge (34.4 +/- 6.8 vs. 33.3 +/- 8.2 hrs, respectively; p = .64). There were no significant differences in adverse events between groups. CONCLUSIONS: Despite the previously demonstrated effects of heliox on improved aerosol particle delivery into the distal airways, heliox-powered nebulized albuterol therapy for children admitted to the hospital with moderate to severe status asthmaticus does not shorten hospital length of stay or hasten rates of clinical improvement when compared with air/oxygen-powered nebulized albuterol.

M. Bur, H. Huwer, L. Muys and C. M. Lehr. "Drug transport across pulmonary epithelial cell monolayers: effects of particle size, apical liquid volume, and deposition technique." 2010 *J Aerosol Med Pulm Drug Deliv* 23(3):

BACKGROUND: Pulmonary cell cultures are increasingly used to predict in vivo drug absorption after inhalation, similar to intestinal cell culture models that have already been well established to predict oral drug absorption. In contrast to the intestinal barrier, however, the so-called air-blood barrier of the lung is covered only with a thin film of liquid, on which the aerosol particles are deposited. The aim of this study was to investigate the relevance of this apical liquid film on the drug absorption rate when deposited as a dry powder formulation on pulmonary epithelial cells in vitro. METHODS: Budesonide and salbutamol sulfate were chosen as model drugs, and for each drug three generic aerosol powder formulations were used. Filter-grown monolayers of the human bronchial epithelial cell line Calu-3 were used as a model, using various volumes of apical liquid. RESULTS

AND CONCLUSIONS: Although proven to be bioequivalent in vivo for each of the two drugs, the generic dry powder formulations showed strikingly different epithelial transport rates in vitro, depending on the amount of apical liquid and the deposition technique, and suggesting that the dissolution of the aerosol particles in the apical liquid volume was rate limiting for the overall absorption rate. However, we found that the absorption rates of the formulations were similar after aerosolization and deposition in a multistage liquid impinger, which simulates more realistically the detachment of the drug crystals from the carrier lactose and their aerodynamic particle size-dependent deposition in the respiratory tract following inhalation from a dry powder inhaler. These data demonstrate the need for improved in vitro test systems to allow deposition of aerosol particles on the air-liquid interface cultivated cell monolayers by simultaneously taking into account aerodynamic properties.

Y. S. Cheng, Y. Zhou, R. H. Pierce, M. Henry and D. G. Baden. "Characterization of Florida red tide aerosol and the temporal profile of aerosol concentration." 2010 *Toxicol* 55(5):

Red tide aerosols containing aerosolized brevetoxins are produced during the red tide bloom and transported by wind to coastal areas of Florida. This study reports the characterization of Florida red tide aerosols in human volunteer studies, in which an asthma cohort spent 1h on Siesta Beach (Sarasota, Florida) during aerosolized red tide events and non-exposure periods. Aerosol concentrations, brevetoxin levels, and particle size distribution were measured. Hourly filter samples were taken and analyzed for brevetoxin and NaCl concentrations. In addition, the aerosol mass concentration was monitored in real time. The results indicated that during a non-exposure period in October 2004, no brevetoxin was detected in the water, resulting in non-detectable levels of brevetoxin in the aerosol. In March 2005, the time-averaged concentrations of brevetoxins in water samples were moderate, in the range of 5-10 microg/L, and the corresponding brevetoxin level of Florida red tide aerosol ranged between 21 and 39 ng/m<sup>3</sup>. The temporal profiles of red tide aerosol concentration in terms of mass, NaCl, and brevetoxin were in good agreement, indicating that NaCl and brevetoxins are components of the red tide aerosol. By continuously monitoring the marine aerosol and wind direction at Siesta Beach, we observed that the marine aerosol concentration varied as the wind direction changed. The temporal profile of the Florida red tide aerosol during a sampling period could be explained generally with the variation of wind direction.

I. J. Clifton, L. A. Fletcher, C. B. Beggs, M. Denton, S. P. Conway and D. G. Peckham. "An aerobiological model of aerosol survival of different strains of *Pseudomonas aeruginosa* isolated from people with cystic fibrosis." 2010 *J Cyst Fibros* 9(1):

*Pseudomonas aeruginosa* is a common and important pathogen in people with cystic fibrosis (CF). Recently epidemic strains of *P. aeruginosa* associated with increased morbidity, have been identified. The method of transmission is not clear, but there is evidence of a potential airborne route. The aim of this study was to determine whether different strains of *P. aeruginosa* isolated from people with CF were able to survive within artificially generated aerosols in an aerobiological chamber. Viable *P. aeruginosa* could still be detected up to 45min after halting generation of the aerosols. All of the strains of *P. aeruginosa* expressing a non-mucoid phenotype isolated from people with CF had a reduced ability to survive within aerosols compared to an environmental strain. Expression of a mucoid phenotype by the strains of *P. aeruginosa* isolated from people with CF promoted survival in the aerosol model compared to strains expressing a non-mucoid phenotype.

W. De Backer, A. Devolder, G. Poli, D. Acerbi, R. Monno, C. Herpich, K. Sommerer, T. Meyer and F. Mariotti. "Lung deposition of BDP/formoterol HFA pMDI in healthy volunteers, asthmatic, and COPD patients." 2010 J Aerosol Med Pulm Drug Deliv 23(3):

**BACKGROUND:** When inhaling medication, it is essential that drug particles are delivered to all sites of lung inflammation, including the peripheral airways. The aim of this study was to assess the lung deposition and lung distribution of beclomethasone dipropionate (BDP)/formoterol (100/6 microg), both dissolved in hydrofluoroalkane (HFA) and delivered by pressurized metered dose inhaler (pMDI) in healthy subjects, asthmatic, and chronic obstructive pulmonary disease (COPD) patients, to investigate how the in vitro characteristics of the formulation translate into the in vivo performance in diseases with different airway obstruction. **METHODS:** Healthy volunteers (n = 8), persistent asthmatics (n = 8), and patients with stable COPD (n = 8) completed this open-label, single-dose parallel-group study. Each patient received one single treatment of four puffs of (99 m)Tc-labeled BDP/formoterol formulation. The correlation between particle size distribution of radioactivity and of the drugs in the radiolabeled formulation was validated. Intra- and extrapulmonary deposition, amount of exhaled drug, and the central to peripheral ratio (C/P) were calculated immediately after inhalation. Patients' lung function and pharmacokinetic parameters were also assessed up to 24 h post-dose. **RESULTS:** The average lung deposition of BDP/formoterol was 34.08 +/- 9.30% (relative to nominal dose) in healthy subjects, 30.86 +/- 8.89% in asthmatics, and 33.10 +/- 8.90% in COPD patients. Extrathoracic deposition was 53.48% +/- 8.95, 57.64% +/- 9.92 and 54.98% +/- 7.01, respectively. C/P ratios of 1.42 +/- 0.32 in healthy subjects, 1.96 +/- 0.43 in asthmatics, and 1.94 +/- 0.69 for COPD patients confirmed drug distribution to all regions of the lungs. Forced expiratory volume in 1 sec (FEV(1)) increased in all groups after BDP/formoterol inhalation, but was more evident in the patient groups. No significant correlation between baseline lung function and drug deposition was observed. Formoterol, BDP, and beclomethasone 17 monopropionate (B17MP) plasma profiles were comparable between groups. **CONCLUSION:** Inhalation of BDP/formoterol HFA (100/6 microg) produces high and homogeneous deposition of BDP and formoterol in the airways, regardless of pathophysiological condition.

J. Denyer, A. Black, K. Nikander, T. Dyché and I. Prince. "Domiciliary experience of the Target Inhalation Mode (TIM) breathing maneuver in patients with cystic fibrosis." 2010 J Aerosol Med Pulm Drug Deliv 23 Suppl 1:

**BACKGROUND:** The time requirements for multiple daily nebulizer treatments are important impediments to the quality of life for most patients with cystic fibrosis (CF). The I-neb Adaptive Aerosol Delivery (AAD) System can be used with a new mode of breathing during inhalation of aerosol, the Target Inhalation Mode (TIM). As a function of the TIM algorithm, the patient is guided to a slow and deep inhalation, which can result in shorter treatment times. **METHODS:** This study was conducted as a 3-month patient handling study of the I-neb AAD System in 42 patients with CF aged 12-57 years. The I-neb AAD System was supplied in both the standard Tidal Breathing Mode (TBM), and in TIM. Patients were trained to use the I-neb AAD System in TIM for the delivery of all their inhaled medications, but if they were not comfortable with the TIM maneuver they could change to the TBM maneuver. The primary variables were compliance with the correct use of the I-neb AAD System, and treatment times. The secondary variables were based on study questionnaires at the end of the study and covered ease of use, patient confidence, and patient satisfaction with the I-neb AAD System. **RESULTS:** There were a total of 10,240 complete treatments and of these, 8979 (88%) were in TIM. Compliance with the correct use of the I-neb AAD System was 97.6%. The mean treatment time for complete treatments in TIM was 4.20 min, compared with 6.83 min when using the I-neb AAD System in TBM. The responses to the questionnaires indicated that over 77% of the patients found the I-neb AAD System in TIM to be either: very easy, easy, or acceptable to use. **CONCLUSIONS:** The results demonstrated that by using the I-neb AAD System in TIM, a 40-50% reduction of nebulizer treatment times, and a high level of compliance

could be achieved. The results also showed that the patients found the I-neb AAD System easy to use.

J. Denyer, I. Prince, E. Dixon, P. Agent, J. Pryor and M. Hodson. "Evaluation of the Target Inhalation Mode (TIM) breathing maneuver in simulated nebulizer therapy in patients with cystic fibrosis." 2010 J Aerosol Med Pulm Drug Deliv 23 Suppl 1:

**BACKGROUND:** Adaptive Aerosol Delivery (AAD) systems provide efficient drug delivery and improved lung deposition over conventional nebulizers by combining real-time analyses of patient breathing patterns and precisely timed aerosol delivery. Delivery and deposition are further enhanced by breathing techniques involving slow, deep inhalations. **METHODS:** This exploratory study assessed the acceptability of slow, deep inhalations in 20 patients with cystic fibrosis (CF) during up to eight simulated nebulizer treatments with the I-neb AAD System. The breathing maneuver, Target Inhalation Mode (TIM) breathing, involved the lengthening of the patient's inhalation time over successive breaths with guidance from auditory and tactile (vibratory) feedback from the device. **RESULTS:** At the end of the first treatment, most patients felt that the instructions were easy to understand (90%) and that the vibratory feedback was pleasant (65%). Half of the patients found the procedure to be comfortable. At the end of the final treatment, most patients felt that the breathing maneuver was easy to understand (90%) and use (80%), but that the duration of the breath was too long (100%). Logged data revealed that 90% of patients were able to comply with the breathing maneuver. The two patients unable to comply had a forced vital capacity of <1.75 L. The average treatment time decreased from 288.4 to 141.6 sec during the first and final treatments, respectively. **CONCLUSIONS:** This study provides preliminary evidence of the acceptability of the TIM breathing maneuver in patients with CF and their ability to perform repeated TIM breathing during simulated nebulizer therapy with the I-neb AAD System.

J. S. Elborn and N. R. Henig. "Optimal airway antimicrobial therapy for cystic fibrosis: the role of inhaled aztreonam lysine." 2010 Expert Opin Pharmacother 11(8):

**IMPORTANCE OF THE FIELD:** Chronic endobronchial infection in cystic fibrosis (CF) leads to progressive lung function loss and respiratory failure. Most adult CF patients are infected with *Pseudomonas aeruginosa*, an important predictor of mortality. Suppressing chronic *P. aeruginosa* infection with inhaled antibiotics is standard of care for CF patients. **AREAS COVERED IN THIS REVIEW:** This review describes the development (2003 - 2010) of aztreonam lysine 75 mg powder and solvent for nebulizer solution (AZLI; Cayston), an aerosolized formulation of the monobactam antibiotic aztreonam. **WHAT THE READER WILL GAIN:** AZLI was studied in patients with CF and chronic *P. aeruginosa* airway infection. In placebo-controlled trials, AZLI improved respiratory symptoms, increased forced expiratory volume in 1 sec (FEV(1)), decreased sputum *P. aeruginosa* density, and was well tolerated. An open-label follow-on trial of nine 'on/off' courses showed that AZLI was safe and the effect durable with repeated administration. AZLI was recently approved for use in CF patients in Australia and the USA, and conditionally approved in Canada and the European Union. AZLI is given three times daily for 28 days (2 - 3 min/dose), followed by 28 days off-drug. AZLI is used only with the Altera Nebulizer System, which provides appropriate particle size and small airway deposition, and has excellent portability. **TAKE HOME MESSAGE:** AZLI is a new therapy that is safe and effectively improves respiratory symptoms and FEV(1) in patients with CF.

M. D. Frazier and I. M. Cheifetz. "The role of heliox in paediatric respiratory disease." 2010 Paediatr Respir Rev 11(1):

Helium-oxygen (heliox) gas mixtures have been studied for over 70 years as an adjunctive therapy for airway obstruction in a variety of respiratory diseases. The medical use of heliox is based on the physical properties of helium as its low density makes it advantageous in promoting more efficient flow through narrowed passages. Clinical evidence of the efficacy of heliox in treating paediatric respiratory diseases is increasing in the medical literature. This article consists of a comprehensive review of the literature investigating the utility of heliox in the treatment of paediatric respiratory disorders, including upper and lower airway obstruction, mechanical ventilation, and aerosol delivery.

D. E. Geller and K. C. Kesser. "The I-neb Adaptive Aerosol Delivery System enhances delivery of alpha1-antitrypsin with controlled inhalation." 2010 J Aerosol Med Pulm Drug Deliv 23 Suppl 1:

**BACKGROUND:** Inhaled alpha1-antitrypsin (AAT) is being developed for treatment of cystic fibrosis to protect the lungs from excessive free elastase. High drug costs mandate a very efficient aerosol system to deliver a high payload to the airways. The I-neb Adaptive Aerosol Delivery (AAD) System is a portable, electronic, vibrating mesh nebulizer that delivers aerosol only during inhalation. It can be operated in conventional tidal breathing mode (TBM) or in target inhalation mode (TIM) that guides the patient to inhale deeply and slowly. The purposes of this in vitro study were to determine aerosol characteristics, device efficiency, and delivery time of AAT using the I-neb AAD System with TBM and TIM. **METHODS:** We studied the I-neb AAD System in TBM and TIM (inspiratory time 6 or 9 sec) using a breath simulator. The loaded dose was 0.5 mL AAT (50 mg/mL). Nebulized drug captured on an inspiratory filter was reported as emitted dose. Particle size was measured by laser diffraction. Predicted lung doses were calculated based on the results of a prior scintigraphy study of the I-neb AAD System. **RESULTS:** Particle size (VMD) for TBM and TIM was similar (4.4-4.8 microm). The emitted doses were very high and similar between modes (82-90% of loaded dose). Predicted lung dose of AAT (percent of loaded dose) and delivery times were: TBM 56.6% in 7.5 min; TIM-6 59.9% in 4.4 min; and TIM-9 64.5% in 2.5 min. **CONCLUSIONS:** The I-neb AAD System enhanced AAT delivery by inhalation-only aerosol generation and a low-residual dose. Predicted lung dose was high for both TBM and TIM, but longer inspiratory times with TIM reduced the administration time to one-third that of tidal breathing. We conclude that slow, deep, controlled inspirations using the I-neb AAD System is an efficient method to deliver AAT.

N. Goodman, M. Morgan, K. Nikander, S. Hinch and S. Coughlin. "Evaluation of patient-reported outcomes and quality of life with the I-neb AAD system in patients with chronic obstructive pulmonary disease." 2010 J Aerosol Med Pulm Drug Deliv 23 Suppl 1:

**BACKGROUND:** The I-neb Adaptive Aerosol Delivery (AAD) System is a novel portable mesh nebulizer that provides patient feedback regarding adherence to prescribed treatment and compliance with the correct use of the device. **METHODS:** This multicenter study was composed of 98 patients aged 53-80 years with Chronic Obstructive Pulmonary Disease (COPD). The primary variables were ease of use and satisfaction, which were assessed after 3 months of use of the I-neb AAD System (assessed at visit 2) and after 3 months of use of the patient's previous nebulizer system (assessed at visit 1) using matched questions from pre- and poststudy questionnaires. Quality of life was also assessed at visits 1 and 2 using the validated Chronic Respiratory Questionnaire (CRQ), which consists of dyspnea, emotional function, fatigue, and mastery domains. Differences in the distribution of responses between the pre- and poststudy ease of use and satisfaction questions were analyzed using the Marginal Homogeneity test. Differences in mean CRQ scores between the pre- and poststudy assessments were analyzed using the

Wilcoxon Signed-Rank test. RESULTS: Patient responses on the ease of use and satisfaction questions significantly ( $p < \text{or} = 0.001$ ) favored the I-neb AAD System compared with the patient's previous nebulizer system. In addition, significant ( $p < \text{or} = 0.015$ ) improvements in the CRQ dimensions of dyspnea and fatigue were reported with the I-neb AAD System compared with the patients' previous nebulizer systems. CONCLUSIONS: The results from this study demonstrated that patients were more satisfied with the I-neb AAD System and found it easier to use than their previous nebulizer systems. In addition, the I-neb AAD System significantly improved dyspnea and fatigue compared with the patients' previous nebulizer systems, which may reflect improved adherence or more correct use of the nebulizer system with the I-neb AAD System.

R. Hodder and D. Price. "Patient preferences for inhaler devices in chronic obstructive pulmonary disease: experience with Respimat Soft Mist inhaler." 2009 *Int J Chron Obstruct Pulmon Dis* 4:

Current guidelines for the management of chronic obstructive pulmonary disease (COPD) recommend the regular use of inhaled bronchodilator therapy in order to relieve symptoms and prevent exacerbations. A variety of inhaler devices are currently available to COPD patients, and the choice of device is an important consideration because it can influence patients' adherence to treatment, and thus potentially affect the long-term outcome. The Respimat((R)) Soft Mist Inhaler (SMI) generates a slow-moving aerosol with a high fine particle fraction, resulting in deposition of a higher proportion of the dose in the lungs than pressurized metered-dose inhalers (pMDIs) or some dry powder inhalers (DPIs). We review clinical studies of inhaler satisfaction and preference comparing Respimat((R)) SMI against other inhalers in COPD patients. Using objective and validated patient satisfaction instruments, Respimat((R)) SMI was consistently shown to be well accepted by COPD patients, largely due to its inhalation and handling characteristics. In comparative studies with pMDIs, the patient total satisfaction score with Respimat((R)) SMI was statistically and clinically significantly higher than with the pMDI. In comparative studies with DPIs, the total satisfaction score was statistically significantly higher than for the Turbuhaler((R)) DPI, but only the performance domain of satisfaction was clinically significantly higher for Respimat((R)) SMI. Whether the observed higher levels of patient satisfaction reported with Respimat((R)) SMI might be expected to result in improved adherence to therapy and thus provide benefits consistent with those recently shown to be associated with sustained bronchodilator treatment in patients with COPD remains to be proven.

P. N. Huynh, L. G. Scott and K. Y. Kwong. "Long-term maintenance of pediatric asthma: focus on budesonide/formoterol inhalation aerosol." 2010 *Ther Clin Risk Manag* 6:

Current national and international asthma guidelines recommend treatment of children with asthma towards achieving and maintaining asthma control. These guidelines provide more stringent recommendations to increase therapy for patients with uncontrolled asthma in order to reduce asthma-related morbidity and mortality. Newer combination agents such as budesonide and formoterol have been shown to be safe and effective in treatment of asthma in children. Use of long-term controller agents like this in combination with improved compliance and treatment of co-morbid conditions have been successful in this endeavor. This review discusses control of pediatric asthma with focus on the use of budesonide in combination with formoterol.

M. Kaashmiri, J. Shepard, B. Goodman, W. R. Lincourt, R. Trivedi, A. Ellsworth and A. M. Davis. "Repeat dosing of albuterol via metered-dose inhaler in infants with acute obstructive airway disease: a randomized controlled safety trial." 2010 *Pediatr Emerg Care* 26(3):

**BACKGROUND:** Airway obstruction and bronchial hyperactivity often times lead to emergency department visits in infants. Inhaled short-acting beta2-agonist bronchodilators have traditionally been dispensed to young children via nebulizers in the emergency department. Delivery of bronchodilators via metered-dose inhalers (MDIs) in conjunction with holding chambers (spacers) has been shown to be effective. **STUDY OBJECTIVE::** Safety and efficacy evaluations of albuterol sulfate hydrofluoroalkane (HFA) inhalation aerosol in children younger than 2 years with acute wheezing caused by obstructive airway disease. **METHODS:** A randomized, double-blind, parallel group, multicenter study of albuterol HFA 180 microg (n = 43) or 360 microg (n = 44) via an MDI with a valved holding chamber and face mask in an urgent-care setting. Assessments included adverse events, signs of adrenergic stimulation, electrocardiograms, and blood glucose and potassium levels. Efficacy parameters included additional albuterol use and Modified Tal Asthma Symptoms Score ([MTASS] reduction in MTASS representing improvement). **RESULTS:** Overall, adverse events occurred in 4 (9%) and 3 (7%) subjects in the 180-microg and 360-microg groups, respectively. Drug-related tachycardia (360 microg) and ventricular extrasystoles (180 microg) were reported in 1 patient each. Three additional instances of single ventricular ectopy were identified from Holter monitoring. No hypokalemia or drug-related QT or QTc prolongation was seen; glucose values and adrenergic stimulation did not significantly differ between treatment groups. In the 180-microg and 360-microg groups, mean change from baseline in MTASS during the treatment period was -2.8 (-49.8%) and -2.9 (-48.4%), and rescue albuterol use occurred in 4 (9%) and 3 (7%) subjects, respectively. **CONCLUSIONS:** Cumulative dosing with albuterol HFA 180 microg or 360 microg via MDI-spacer and face mask in children younger than 2 years did not result in any significant safety issues and improved MTASS by at least 48%.

D. B. Konga, Y. Kim, S. C. Hong, Y. M. Roh, C. M. Lee, K. Y. Kim and S. M. Lee. "Oxidative stress and antioxidant defenses in asthmatic murine model exposed to printer emissions and environmental tobacco smoke." 2009 *J Environ Pathol Toxicol Oncol* 28(4):

Exposure to particulate emissions from printer and cigarette smoke affects the structure and function of mitochondria, which may account for the pathogenesis of respiratory diseases. The addition of charge for the pollutant aerosols may increase the toxicity by their deposition in the lower respiratory tract. The mitochondrial damage in the lung of asthmatic mice was assessed by examining the levels of reactive oxygen species (ROS), lipid peroxides, reduced glutathione, and the activities of isocitrate dehydrogenase, alpha-ketoglutarate dehydrogenase, succinate dehydrogenase, malate dehydrogenase, complexes I to IV, and cytochrome c. The oxidative phosphorylation (levels of adenosine triphosphatase) was evaluated for the assessment of mitochondrial functional capacity. We found highly significant elevated levels of ROS, lipid peroxides, and decreased levels of mitochondrial enzymes in the mice exposed to environmental tobacco smoke and printer emissions + environmental tobacco smoke (ETS). However, mice exposed to printer emissions alone exhibited slight significant variations in the parameters studied. From the results, we conclude that printer emissions exert a synergistic effect in the presence of ETS and induce intense damage to the lung mitochondria by disrupting the structural and functional integrity of the mitochondrial membrane.

P. C. Kwok, S. J. Trietsch, M. Kumon and H. K. Chan. "Electrostatic charge characteristics of jet nebulized aerosols." 2010 *J Aerosol Med Pulm Drug Deliv* 23(3):

**BACKGROUND:** Liquid droplets can be spontaneously charged in the absence of applied electric fields by spraying. It has been shown by computational simulation that charges

may influence particle deposition in the airways. The electrostatic properties of jet nebulized aerosols and their potential effects on lung deposition have hardly been studied. A modified electrical low pressure impactor (ELPI) was employed to characterize the aerosol charges generated from jet nebulized commercial products. METHODS: The charge and size measurements were conducted at 50% RH and 22 degrees C with a modified ELPI. Ventolin, Bricanyl, and Atrovent were nebulized using PARI LC Plus jet nebulizers coupled to a DeVilbiss Pulmo-Aide compressor. The aerosols were sampled in 30-sec durations. The drug deposits on the impactor stages were assayed chemically using high-performance liquid chromatography (HPLC). The charges of nebulized deionized water, isotonic saline, and the three commercial products diluted with saline were also measured to analyze the contributions of the major nebule ingredients on charging. No mass assays were performed on these runs. RESULTS: All three commercial nebulizers generated net negative charges. The magnitude of the charges reduced over the period of nebulization. Ventolin and Bricanyl yielded similar charge profiles. Highly variable charges were produced from deionized water. On the other hand, nebulized saline reproducibly generated net positive charges. Diluted commercial nebulizers showed charge polarity inversion. The charge profiles of diluted salbutamol and terbutaline solutions resembled those of saline, while the charges from diluted ipratropium solutions fluctuated near neutrality. CONCLUSIONS: The charge profiles were shown to be influenced by the concentration and physicochemical properties of the drugs, as well as the history of nebulization. The drugs may have unique isoelectric concentrations in saline at which the nebulized droplets would carry near-zero charges. According to results from computational simulation models in the literature, the numbers of elementary charges per droplet estimated from the data were not high enough to potentially affect lung deposition.

K. Nikander, J. Denyer, M. Dodd, T. Dyche, K. Webb, P. Weller and D. Stableforth. "The adaptive aerosol delivery system in a telehealth setting: patient acceptance, performance and feasibility." 2010 J Aerosol Med Pulm Drug Deliv 23 Suppl 1:

BACKGROUND: The telehealth service is one of the fastest growing healthcare segments. It is increasingly utilizing computer technology and telecommunication equipment to either provide continuous vital sign monitoring or facilitate patient care at home, rather than relying solely on in-person care. METHODS: We conducted a 6-week open study in nineteen patients with cystic fibrosis enrolled from three centers, to investigate patient perception of a telehealth enabled nebulizer system (Prodose Adaptive Aerosol Delivery [AAD] System), which enabled the doorstep delivery of repeat medication. RESULTS: The results showed that patient confidence in the device and perception of ease of use was high with no significant change between the start and end of the trial. Views on the home delivery of medication were split between 'great' and 'inconvenient.' However, if the delivery system had been more flexible and delivered all the patients' drugs, the majority of patients would have had their medication delivered in this way. CONCLUSIONS: The trial showed that it was possible to build telehealth technology into an advanced nebulizer system, and that patient acceptance of the technology was unlikely to be a barrier to the adoption of such a telehealth system.

E. T. Rotta, S. L. Amantea, P. E. Froehlich and A. Becker. "Plasma concentrations of salbutamol in the treatment of acute asthma in a pediatric emergency. Could age be a parameter of influence?" 2010 Eur J Clin Pharmacol 66(6):

OBJECTIVE: The objective was to determine if the plasma concentrations of salbutamol, obtained during inhalation treatment of infantile acute asthma, are influenced by age range and by the aerosol system used. METHOD: A randomized clinical trial was conducted in 46 children (1-5 years of age) with a diagnosis of acute asthma crisis, established in an emergency room pediatric service. Twenty-five children received salbutamol using a pressurized metered-dose inhaler with spacer (50 microg/kg), and 21

children received salbutamol by nebulization (150 microg/kg), three times during a 1-h period. At the end of the treatment, one blood sample was drawn and the plasma was stored for later determination of salbutamol concentration (liquid chromatography). Salbutamol plasma concentrations were compared in two age groups (< or =2 years and >2 years of age). The type of device used (pressurized metered-dose inhaler or nebulizer) and the need of hospitalization were also tested. The Mann-Whitney U test was used with the level of significance set at 5% ( $P < 0.05$ ). RESULTS: No differences were detected regarding either the aerosol delivery system used or the need for hospitalization in relation to the plasma concentrations of salbutamol. However, higher plasma levels were found in patients >2 years vs patients < or =2 years [median (IQR): 9.40 (6.32-18.22) vs. 4.65 (2.77-10.10) ng/mL], demonstrating a significance difference ( $P = 0.05$ ). CONCLUSION: Salbutamol plasma concentrations were influenced by age group of the patients submitted to inhalation therapy, even with doses adjusted for body weight. After correcting for the differences in the bioavailabilities of the delivery systems, the concentrations were independent of the aerosol delivery device used.

N. Scichilone, A. Contino, G. B. Figlioli, G. Paglino and V. Bellia. "Patient perspectives in the management of asthma: improving patient outcomes through critical selection of treatment options." 2010 Patient Prefer Adherence 4:

Asthma is a chronic inflammatory disorder of the airways that requires long-term treatment, the goal of which is to control clinical symptoms for extended periods with the least possible amount of drugs. International guidelines recommend the addition of an inhaled long-acting beta2-agonist (LABA) to a low- to medium-dose inhaled corticosteroid (ICS) when low doses of ICS fail to control asthma symptoms. The fixed combined administration of ICS/LABA improves patient compliance, reducing the risk of therapy discontinuation. The relative deposition pattern of the inhaled drug to the target site is the result of a complex interaction between the device used, the aerosol formulation and the patient's adherence to therapy. Different inhalation devices have been introduced in clinical practice over time. The new hydrofluoroalkane (HFA) solution aerosols allow for the particle size to be modified, thus leading to deeper penetration of the medication into the lung. The Modulite((R)) technology allows for the manipulation of inhaled HFA-based solution formulations, such as the fixed beclomethasone/formoterol combination, resulting in a uniform treatment of inflammation and bronchoconstriction. The success of any anti-asthmatic treatment depends on the choice of the correct device and the adherence to therapy.

R. Zuwallack, M. C. De Salvo, T. Kaelin, E. D. Bateman, C. S. Park, R. Abrahams, F. Fakhri, P. Sachs, K. Pudi, Y. Zhao and C. C. Wood. "Efficacy and safety of ipratropium bromide/albuterol delivered via Respimat((R)) inhaler versus MDI." 2010 Respir Med:

We compared the efficacy and safety of ipratropium bromide/albuterol delivered via Respimat((R)) inhaler, a novel propellant-free inhaler, versus chlorofluorocarbon (CFC)-metered dose inhaler (MDI) and ipratropium Respimat((R)) inhaler in patients with COPD. This was a multinational, randomized, double-blind, double-dummy, 12-week, parallel-group, active-controlled study. Patients with moderate to severe COPD were randomized to ipratropium bromide/albuterol (20/100mcg) Respimat((R)) inhaler, ipratropium bromide/albuterol MDI [36mcg/206mcg (Combivent((R)) Inhalation Aerosol MDI)], or ipratropium bromide (20mcg) Respimat((R)) inhaler. Each medication was administered four times daily. Serial spirometry was performed over 6h (0.15min, then hourly) on 4 test days. The primary efficacy variable was forced expiratory volume in 1s (FEV(1)) change from test day baseline at 12 weeks. A total of 1209 of 1480 randomized, treated patients completed the study; the majority were male (65%) with a mean age of 64 yrs and a mean screening pre-bronchodilator FEV(1) (percent predicted) of 41%. Ipratropium bromide/albuterol Respimat((R)) inhaler had comparable efficacy to ipratropium bromide/albuterol MDI for FEV(1) area under the curve at 0-6h (AUC(0-6)), superior

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efficacy to ipratropium Respimat((R)) inhaler for FEV(1) AUC(0-4) and comparable efficacy to ipratropium Respimat((R)) inhaler for FEV(1) AUC(4-6). All active treatments were well tolerated. This study demonstrates that ipratropium bromide/albuterol 20/100mcg inhaler((R)) administered four times daily for 12 weeks had equivalent bronchodilator efficacy and comparable safety to ipratropium bromide/albuterol 36mcg/206mcg MDI, and significantly improved lung function compared with the mono-component ipratropium bromide 20 mcg Respimat((R)) inhaler. [Clinical Trial Identifier Number: NCT00400153].

## Lung Deposition

M. E. Abdelrahim. "Emitted dose and lung deposition of inhaled terbutaline from Turbuhaler at different conditions." 2010 *Respir Med* 104(5):

Turbuhaler has a very high resistance hence patient inhalation flow when using it would be low. The total emitted dose (TED) of 500microg terbutaline sulphate from a Bricanyl Turbuhaler was determined using a range of inhalation flows (10-60L min<sup>(-1)</sup>) with inhalation volume of 2 and 4L using a DPI sampling apparatus after one and two inhalations. The relative lung and systemic bioavailability of terbutaline from Bricanyl Turbuhaler when used by healthy subjects and COPD patients were determined after one and two inhalations at slow and fast inhalation flows using a novel urinary terbutaline pharmacokinetic method. The TED resulted from the one and two inhalations increased significantly ( $p<0.05$ ) with the increase of the inhalation flow at both 2 and 4L inhalation volumes. The relative lung and systemic bioavailability after one inhalation at fast inhalation flow were significantly higher ( $p<0.01$ ) than at slow inhalation flow in both healthy subjects and patients. Also the healthy subjects results were significantly higher ( $p<0.05$ ) than the COPD patients after one inhalation. However after two inhalations there was no significant difference between slow and fast inhalation flow or healthy subjects and COPD patients. Hence it is essential to inhale twice and as deep and hard as possible from each dose of Turbuhaler for patients with low inspiratory flow and limited inhalation volume as they may not receive much benefit from one inhalation.

W. De Backer, A. Devolder, G. Poli, D. Acerbi, R. Monno, C. Herpich, K. Sommerer, T. Meyer and F. Mariotti. "Lung deposition of BDP/formoterol HFA pMDI in healthy volunteers, asthmatic, and COPD patients." 2010 *J Aerosol Med Pulm Drug Deliv* 23(3):

**BACKGROUND:** When inhaling medication, it is essential that drug particles are delivered to all sites of lung inflammation, including the peripheral airways. The aim of this study was to assess the lung deposition and lung distribution of beclomethasone dipropionate (BDP)/formoterol (100/6 microg), both dissolved in hydrofluoroalkane (HFA) and delivered by pressurized metered dose inhaler (pMDI) in healthy subjects, asthmatic, and chronic obstructive pulmonary disease (COPD) patients, to investigate how the in vitro characteristics of the formulation translate into the in vivo performance in diseases with different airway obstruction. **METHODS:** Healthy volunteers ( $n = 8$ ), persistent asthmatics ( $n = 8$ ), and patients with stable COPD ( $n = 8$ ) completed this open-label, single-dose parallel-group study. Each patient received one single treatment of four puffs of (99 m)Tc-labeled BDP/formoterol formulation. The correlation between particle size distribution of radioactivity and of the drugs in the radiolabeled formulation was validated. Intra- and extrapulmonary deposition, amount of exhaled drug, and the central to peripheral ratio (C/P) were calculated immediately after inhalation. Patients' lung function and pharmacokinetic parameters were also assessed up to 24 h post-dose. **RESULTS:** The average lung deposition of BDP/formoterol was 34.08 +/- 9.30% (relative to nominal dose) in healthy subjects, 30.86 +/- 8.89% in asthmatics, and 33.10 +/- 8.90% in COPD patients. Extrathoracic deposition was 53.48% +/- 8.95, 57.64% +/- 9.92 and 54.98% +/- 7.01, respectively. C/P ratios of 1.42 +/- 0.32 in healthy subjects, 1.96 +/- 0.43 in asthmatics, and 1.94 +/- 0.69 for COPD patients confirmed drug distribution to all regions of the lungs. Forced expiratory volume in 1 sec (FEV(1)) increased in all groups after BDP/formoterol inhalation, but was more evident in the patient groups. No significant correlation between baseline lung function and drug deposition was observed. Formoterol, BDP, and beclomethasone 17 monopropionate (B17MP) plasma profiles were comparable between groups. **CONCLUSION:** Inhalation of BDP/formoterol HFA (100/6 microg) produces high and homogeneous deposition of BDP and formoterol in the airways, regardless of pathophysiological condition.

M. Bur, H. Huwer, L. Muys and C. M. Lehr. "Drug transport across pulmonary epithelial cell monolayers: effects of particle size, apical liquid volume, and deposition technique." 2010 J Aerosol Med Pulm Drug Deliv 23(3):

**BACKGROUND:** Pulmonary cell cultures are increasingly used to predict in vivo drug absorption after inhalation, similar to intestinal cell culture models that have already been well established to predict oral drug absorption. In contrast to the intestinal barrier, however, the so-called air-blood barrier of the lung is covered only with a thin film of liquid, on which the aerosol particles are deposited. The aim of this study was to investigate the relevance of this apical liquid film on the drug absorption rate when deposited as a dry powder formulation on pulmonary epithelial cells in vitro. **METHODS:** Budesonide and salbutamol sulfate were chosen as model drugs, and for each drug three generic aerosol powder formulations were used. Filter-grown monolayers of the human bronchial epithelial cell line Calu-3 were used as a model, using various volumes of apical liquid. **RESULTS AND CONCLUSIONS:** Although proven to be bioequivalent in vivo for each of the two drugs, the generic dry powder formulations showed strikingly different epithelial transport rates in vitro, depending on the amount of apical liquid and the deposition technique, and suggesting that the dissolution of the aerosol particles in the apical liquid volume was rate limiting for the overall absorption rate. However, we found that the absorption rates of the formulations were similar after aerosolization and deposition in a multistage liquid impinger, which simulates more realistically the detachment of the drug crystals from the carrier lactose and their aerodynamic particle size-dependent deposition in the respiratory tract following inhalation from a dry powder inhaler. These data demonstrate the need for improved in vitro test systems to allow deposition of aerosol particles on the air-liquid interface cultivated cell monolayers by simultaneously taking into account aerodynamic properties.

J. Denyer, I. Prince, E. Dixon, P. Agent, J. Pryor and M. Hodson. "Evaluation of the Target Inhalation Mode (TIM) breathing maneuver in simulated nebulizer therapy in patients with cystic fibrosis." 2010 J Aerosol Med Pulm Drug Deliv 23 Suppl 1:

**BACKGROUND:** Adaptive Aerosol Delivery (AAD) systems provide efficient drug delivery and improved lung deposition over conventional nebulizers by combining real-time analyses of patient breathing patterns and precisely timed aerosol delivery. Delivery and deposition are further enhanced by breathing techniques involving slow, deep inhalations. **METHODS:** This exploratory study assessed the acceptability of slow, deep inhalations in 20 patients with cystic fibrosis (CF) during up to eight simulated nebulizer treatments with the I-neb AAD System. The breathing maneuver, Target Inhalation Mode (TIM) breathing, involved the lengthening of the patient's inhalation time over successive breaths with guidance from auditory and tactile (vibratory) feedback from the device. **RESULTS:** At the end of the first treatment, most patients felt that the instructions were easy to understand (90%) and that the vibratory feedback was pleasant (65%). Half of the patients found the procedure to be comfortable. At the end of the final treatment, most patients felt that the breathing maneuver was easy to understand (90%) and use (80%), but that the duration of the breath was too long (100%). Logged data revealed that 90% of patients were able to comply with the breathing maneuver. The two patients unable to comply had a forced vital capacity of <1.75 L. The average treatment time decreased from 288.4 to 141.6 sec during the first and final treatments, respectively. **CONCLUSIONS:** This study provides preliminary evidence of the acceptability of the TIM breathing maneuver in patients with CF and their ability to perform repeated TIM breathing during simulated nebulizer therapy with the I-neb AAD System.

D. A. Gentile and D. P. Skoner. "New asthma drugs: small molecule inhaled corticosteroids." 2010 *Curr Opin Pharmacol*:

Small-particle inhaled corticosteroid (ICS) metered-dose inhalers were recently developed to treat asthma as part of the CFC to HFA propellant switch mandated by the Montreal Protocol. Two such ICS, beclomethasone dipropionate (BDP) and ciclesonide (CIC), are available in the United States and are formulated in HFA solutions. A major advantage of small-particle ICS is that they have improved total lung deposition and consequently, effective asthma control is achieved at lower daily doses than the large-particle ICS. Another advantage of small-particle ICS is that they are able to reach the small airways and consequently, may result in increased efficacy. Indeed, recent studies have demonstrated the effect of small-particle ICS on asthmatic inflammation in the small airways. Another advantage of small-particle ICS is that they may have an improved safety profile. Small-particle inhalers generally deposit decreased amounts of drug in the oropharynx than their CFC counterparts possibly resulting in a lower incidence of oropharyngeal candidiasis. However, growth studies and most HPA studies do not support improved safety on the basis of particle size alone and some studies suggest even higher systemic bioavailability and safety risk with smaller particles, depending on the molecule and the formulation. Further efficacy and safety studies are clearly warranted to determine any potential advantages of small-particle ICS, particularly in long-term disease modification where large-particle ICS have failed, and in infants and pre-schoolers, in whom airway delivery is problematic with current formulations.

J. Haughney, D. Price, N. C. Barnes, J. C. Virchow, N. Roche and H. Chrystyn. "Choosing inhaler devices for people with asthma: Current knowledge and outstanding research needs." 2010 *Respir Med*:

Recommendations in asthma guidelines presuppose that practitioners have the evidence, information, knowledge, and tools to select inhaler devices appropriate for individual patients. Randomised controlled trials usually exclude patients with suboptimal inhaler technique. There is therefore little evidence on which to base inhaler selection in the real world, where patients often use their inhalers incorrectly. The lung deposition of inhaled drug varies according to inhaler device, drug particle size, inhalation technique, and pattern of inspiratory flow. Even with training, not all patients can use their inhalers correctly and maintain inhaler technique; patients may have inability to handle the inhaler, strong negative preferences, or natural breathing patterns that do not match their prescribed inhaler. Therefore, matching device to the patient may be a better course of action than increasing therapy or training and retraining a patient to use a specific inhaler device. Several research questions require answers to meet the goal of helping prescribers make a more informed choice of inhaler type. Is the level of drug deposition in the lungs a key determinant of clinical short- and long-term outcomes? What should be measured by a clinical tool designed to check inhaler technique and therefore help with device selection? If we have a tool to help in individualising inhaler choice, will we achieve better asthma outcomes? Do we have to refine inhaler device choice for each individual, or will we get better outcomes if we select our current best option in light of current knowledge and apply this on a population level?

C. L. Leach and G. L. Colice. "A Pilot Study to Assess Lung Deposition of HFA-Beclomethasone and CFC-Beclomethasone from a Pressurized Metered Dose Inhaler with and without Add-On Spacers and Using Varying Breathhold Times." 2010 *J Aerosol Med Pulm Drug Deliv*:

Abstract Background: The study objective of this pilot study was to determine the lung delivery of HFA-134a-beclomethasone dipropionate (HFA-BDP; QVAR) and CFC-beclomethasone dipropionate (CFC-BDP; Becloforte) with and without the add-on spacers, Aerochamber, and Volumatic. The smaller particles of HFA-BDP were presumed to produce greater lung deposition using spacers, with and without a delay [i.e., metered

dose inhaler (MDI) actuation into the spacer and subsequent inhalation 0 and 2 sec later], compared with the larger particles of CFC-BDP. The study included a comparison of breathhold effects (i.e., 1 and 10-sec breatholds) on lung deposition. Methods: The study was an open-label design and utilized healthy subjects (n = 12 males). Each arm of the study contained three subjects; thus, outcomes were not powered to assess statistical significance. HFA-BDP and CFC-BDP were radiolabeled with technetium-99m and delivered to subjects. Results: Results showed that the small particle HFA-BDP lung deposition averaged 52% and was not affected by the use of Aerochamber with or without a spacer delay. The oropharyngeal deposition of HFA-BDP was reduced from approximately 28% to 4% with the Aerochamber. Lung deposition with the large particle CFC-BDP was 3-7% and generally decreased with Aerochamber or Volumatic. A 2-sec time delay between actuation and breath plus the spacer reduced lung deposition slightly but reduced oropharyngeal deposition substantially (84% down to 3-20%) using the Aerochamber or Volumatic with and without a spacer delay. HFA-BDP lung deposition was dependent on the breathhold. Lung deposition with HFA-BDP was reduced by 16% with a 1-sec versus 10-sec breathhold. The difference was measured in the increased exhaled fraction, confirming that smaller particles need time to deposit and are exhaled if there is a reduced breathhold. The large particle CFC-BDP lung deposition was not affected by breathhold. Conclusions: The use of Aerochamber or Volumatic spacers with HFA-BDP did not alter lung deposition but it did reduce oropharyngeal deposition. However, HFA-BDP displayed reduced oropharyngeal deposition without a spacer

C. Leach, G. L. Colice and A. Luskin. "Particle size of inhaled corticosteroids: does it matter?" 2009 J Allergy Clin Immunol 124(6 Suppl):

A question with respect to asthma therapy revolves around the issue of whether better efficacy occurs with an ultrafine-particle inhaled corticosteroid because of better lung deposition into the distal airways. This article reviews particle size and delivery devices of different steroids, clinical outcomes of small- versus large-particle steroids, and the issue of pharmacoeconomics.

G. Nicolini, G. Cremonesi and A. S. Melani. "Inhaled corticosteroid therapy with nebulized beclometasone dipropionate." 2010 Pulm Pharmacol Ther 23(3):

Inhaled corticosteroids (ICS) are the most effective anti-inflammatory agents for the management of chronic persistent asthma and are therefore recommended as first-line antiasthmatic therapy in children and adults. In various settings, the administration of ICS via nebulizer rather than hand-held inhaler (HHI) may have certain advantages, as many patients with HHI fail to use these devices properly or efficiently. In particular, young children, the elderly, the acutely ill, and those with restricted dexterity may be unable to coordinate inhalation with actuation of the device or to generate sufficient inspiratory flow to operate breath-actuated devices effectively. Compliance with nebulized therapy may also be better than that with a pressurized metered-dose inhaler (pMDI) plus spacer. Systematic reviews conclude that there is no significant difference in clinical effects between nebulizers and HHI. Performance and clinical effect of nebulization are influenced by several technical aspects such as the nebulizer-drug combination, nebulizer type, output and lung deposition. Among the currently available ICS, nebulized beclometasone dipropionate (BDP) has been in clinical use for more than 35 years, and has demonstrated marked clinical efficacy and a favorable tolerability profile in children and adults with chronic persistent asthma. The clinical efficacy of nebulized beclometasone is discussed in the present review using data from 13 published studies, which included a total of 1250 patients. Three multicenter, randomized, double-blind studies showed that nebulized BDP is as effective as BDP via pMDI plus spacer in a 2:1 dose ratio. Controlled trials involving 497 adults and children demonstrated similar clinical efficacy between nebulized BDP and either nebulized fluticasone propionate or nebulized budesonide. In all these trials, treatment-related adverse effects were generally

uncommon, most were mild-to-moderate in severity, and most were associated with the respiratory system. Meta-analyses show that BDP, like other inhaled corticosteroids, has no major influence on patient height, urinary cortisol concentration, or bone metabolism, thus suggesting the absence of growth retardation or any marked effect on adrenal function or the hypothalamic-pituitary-adrenal axis when used in the approved dose range. Overall, nebulized BDP appears to have a particularly important place in asthma therapy: as a general alternative to HHIs (e.g. in patients with poor HHI compliance); when patients such as children or the elderly are unable to operate HHIs because of poor hand-lung coordination, lack of cooperation, or low inspiratory flow rate; and when high dosages of ICS are required, such as in adults with severe, corticosteroid-dependent asthma.

## Inhalation Therapy

S. A. Antoniu. "Effects of inhaled therapy on biomarkers of systemic inflammation in stable chronic obstructive pulmonary disease." 2010 *Biomarkers* 15(2):

In chronic obstructive pulmonary disease (COPD) airways inflammation is associated in more advanced stages with systemic inflammation. COPD-associated systemic inflammation syndrome is defined currently with rather non-specific biomarkers such as C-reactive protein (CRP) but there are also other 'organ-specific' biomarkers such as surfactant protein-D which are still not well characterized but might represent more appropriate and reliable alternatives to the non-specific biomarkers. Inhaled therapies are the mainstay in stable COPD and they were demonstrated to reduce airway inflammation and more recently in the case of inhaled corticosteroids alone or combined with long-acting beta-2 agonists to reduce systemic inflammation as well. This paper focuses on current and potential biomarkers of systemic inflammation in COPD and on the systemic anti-inflammatory effects of inhaled therapies in stable COPD.

S. Ghdifan, L. Couderc, I. Michelet, C. Leguillon, B. Masseline and C. Marguet. "Bolus methylprednisolone efficacy for uncontrolled exacerbation of cystic fibrosis in children." 2010 *Pediatrics* 125(5):

We present here the clinical course of 4 children with cystic fibrosis, deltaF508/deltaF508, who were admitted with severe respiratory distress and in whom no improvement was obtained by intensive antibiotic therapy and systemic corticosteroids. Chest computed-tomography scans showed hyperinflation and atelectasis. The severity of these exacerbations was explained neither by visible mucus plugging nor by allergic bronchopulmonary aspergillosis. We hypothesized that these clinical features were related to a severe inflammatory process in small airways. Therefore, a high-dose short course of methylprednisolone (1 g/1.73 m<sup>2</sup>) per day for 3 days) was given; all the patients' conditions were dramatically improved, and the therapy was safe. To our knowledge, this is the first reported use of bolus methylprednisolone in the treatment of uncontrolled pulmonary exacerbation in children with cystic fibrosis.

S. O. Henderson and T. L. Ahern. "The utility of serial peak flow measurements in the acute asthmatic being treated in the ED." 2010 *Am J Emerg Med* 28(2):

**BACKGROUND:** Peak flow is used extensively in emergency departments (EDs) to both assess asthma patient's status on arrival as well as to document clinical improvement during treatment. Many algorithms suggest serial peak expiratory flow (PEF) measurements during an ED stay. **OBJECTIVE:** The aim of the study was to assess the contribution of serial PEF in describing the overall improvement of asthmatics over the course of an ED visit for acute exacerbation of their asthma. **METHODS:** This was a prospective institutional review board-approved study of mild/moderate asthmatics presenting to an inner-city ED serving a large Latino population. Peak expiratory flow was measured before treatment (baseline PEF) and after each inhaled treatment (PEF post RX#1, PEF post RX#2, PEF post RX#3) while in the ED. **RESULTS:** One hundred consecutive patients made up this study cohort. The change from baseline PEF to PEF #1 represented 86% (95% confidence interval [CI], 76%-96%) of the total improvement experienced by these patients with asthma. The change from PEF post RX#1 to PEF post RX#2 represented 7.5% (95% CI, -4.2% to 26%) of the total improvement and PEF post RX#2 to PEF post RX#3 represented 8.6% (95% CI, -1% to 34%) of the total PEF improvement seen. **LIMITATION:** No correlation between outcome and PEF% of predicted

was made or implied. **CONCLUSION:** The improvement in PEF seen after the first ED inhaled therapy appears to describe most of the total improvement seen in asthmatic patients. Subsequent PEFs provided little additional information.

M. Hohenegger. "Novel and Current Treatment Concepts Using Pulmonary Drug Delivery." 2010 *Curr Pharm Des*:

The novel technologies in pulmonary drug delivery propelled the development of new strategies for pharmacological intervention in human diseases. In particular, this review will focus on pulmonary parameters which influence the delivery of inhaled therapeutics and summarize novel applications and recent innovations. The central issues of pulmonary drug application are optimal effectiveness under conditions of greatest safety. They not only depend on the properties of the drug but also feature the application vehicle and drug formulation. The optimization of the whole system (drug, formulation and vehicle) is therefore a necessary prerequisite for reliable inhaling medicines. Depending on the desired locus of drug action, the inhaled medicine has to be adjusted to particle size, concentration and chemical composition to guarantee a local or systemic drug action. Local asthma therapy represents the established concept for inhalation therapy. Due to the disease status, deposition of drugs is therefore often seen in central rather than peripheral airways. Recent developments in ultrafine therapeutic particles should therefore provide enough drug deposition even in the deeper airways. Recent approvals and interesting new therapy concepts will be discussed. Beside a pulmonary drug action there is an accumulating number of applications also for systemic drug action after pulmonary drug delivery. These involve among others inhaled insulin, glucagon-like-peptide 1 or growth hormone. But also novel therapeutic systems for gene therapy and vaccination are currently under investigation. Successful feasibility of these novel concepts will be expected in the near future.

P. Iseli. "[Chronic cough in children--what to consider and how to evaluate?]." 2009 *Praxis (Bern 1994)* 98(23):

There is a long list of differential diagnoses for chronic cough lasting longer than 4 weeks in children. Diagnostic work up starts with a detailed history taking and a clinical investigation followed by a chest X-ray (in one plane) and a spirometry. For the latter reliable results can be achieved by children older than 5 years. If the diagnostic work up is still inconclusive and if the child is in good clinical condition, a 4 weeks' course of inhalation therapy with steroids and betamimetics together with a 2 weeks' course of antibiotics with a macrolide is warranted. In case coughing persists a thorough diagnostic work up is indicated to rule out conditions like cystic fibrosis, relevant humoral immunodeficiencies, primary ciliary dyskinesia, anatomic malformation or chronic pulmonary aspiration, preferably done by a pediatric pulmonologist. Chronic cough has to be considered abnormal in any child under the age of 1 year. For this age group a final diagnosis is of special importance.

E. T. Rotta, S. L. Amantea, P. E. Froehlich and A. Becker. "Plasma concentrations of salbutamol in the treatment of acute asthma in a pediatric emergency. Could age be a parameter of influence?" 2010 *Eur J Clin Pharmacol* 66(6):

**OBJECTIVE:** The objective was to determine if the plasma concentrations of salbutamol, obtained during inhalation treatment of infantile acute asthma, are influenced by age range and by the aerosol system used. **METHOD:** A randomized clinical trial was conducted in 46 children (1-5 years of age) with a diagnosis of acute asthma crisis, established in an emergency room pediatric service. Twenty-five children received salbutamol using a pressurized metered-dose inhaler with spacer (50 microg/kg), and 21

children received salbutamol by nebulization (150 microg/kg), three times during a 1-h period. At the end of the treatment, one blood sample was drawn and the plasma was stored for later determination of salbutamol concentration (liquid chromatography). Salbutamol plasma concentrations were compared in two age groups (< or =2 years and >2 years of age). The type of device used (pressurized metered-dose inhaler or nebulizer) and the need of hospitalization were also tested. The Mann-Whitney U test was used with the level of significance set at 5% ( $P < 0.05$ ). RESULTS: No differences were detected regarding either the aerosol delivery system used or the need for hospitalization in relation to the plasma concentrations of salbutamol. However, higher plasma levels were found in patients >2 years vs patients < or =2 years [median (IQR): 9.40 (6.32-18.22) vs. 4.65 (2.77-10.10) ng/mL], demonstrating a significance difference ( $P = 0.05$ ). CONCLUSION: Salbutamol plasma concentrations were influenced by age group of the patients submitted to inhalation therapy, even with doses adjusted for body weight. After correcting for the differences in the bioavailabilities of the delivery systems, the concentrations were independent of the aerosol delivery device used.

M. Takemura, M. Kobayashi, K. Kimura, K. Mitsui, H. Masui, M. Koyama, R. Itotani, M. Ishitoko, S. Suzuki, K. Aihara, M. Matsumoto, T. Oguma, T. Ueda, H. Kagioka and M. Fukui. "Repeated instruction on inhalation technique improves adherence to the therapeutic regimen in asthma." 2010 J Asthma 47(2):

BACKGROUND: Adherence to inhalation therapy is a critical determinant of the success of asthma management. Reasons for nonadherence have been well studied, but reasons for good adherence are poorly understood. Understanding the mechanisms of adherence to inhalation therapy is important in developing strategies to promote adherence. The objective of this study was to assess the factors and mechanisms that contribute to and the clinical outcomes relating to adherence to inhalation therapy. METHODS: The factors and outcomes related to adherence to inhalation therapy were examined cross-sectionally in 176 adults with asthma using a self-reported adherence questionnaire that consisted of four items dealing with the use of inhaled controller medications. A 5-point Likert scale was used for the responses to each item. Adherence was assessed based on the overall mean adherence score. RESULTS: Of the 176 patients who were potential participants, 146 (83%) responded with usable information. Significant factors associated with the overall mean adherence score were older age ( $r = .18$ ,  $p = .032$ ) and receiving repeated instruction on inhalation techniques ( $p = .0016$ ). Of the 146 respondents, 25 (17.1%) patients were given repeated verbal instruction or demonstrations of inhalation technique by a respiratory physician. On logistic regression analysis, good adherence to inhalation therapy was significantly related to the receiving of repeated instruction on inhalation technique, with an odds ratio of 2.90 (95% confidence interval 1.07-7.88;  $p = .037$ ). Furthermore, less intentional nonadherent behavior was reported in patients with repeated instruction on inhalation technique compared to those without it. A significant correlation was found between the overall mean adherence score and the frequency of asthma exacerbations ( $r = -.19$ ,  $p = .021$ ), emergency room visits ( $r = -.19$ ,  $p = .042$ ), and the health-related quality of life score (St. George's Respiratory Questionnaire: Total,  $r = -.22$ ,  $p = .024$ ; Symptoms,  $r = -.21$ ,  $p = .022$ ; Impacts,  $r = -.20$ ,  $p = .035$ ). CONCLUSIONS: Repeated instruction on inhalation techniques may contribute to adherence to inhalation therapy through decreasing intentional nonadherence. Furthermore, good adherence to the therapeutic regimen may offer good asthma-related outcomes.

J. Widger and B. Elnazir. "Survey of the management of acute asthma in children." 2009 Ir Med J 102(10):

Acute asthma is one of the most common reasons for children presenting to the emergency department. International guidelines for the management of acute paediatric asthma are widely available. In this study we examined how acute asthma in children is managed across hospitals in Ireland and compared Irish practice with standard

international guidelines. We surveyed 54 paediatricians across 18 centres in Ireland. A total of 30 (55.5%) individual paediatricians across 17 (94%) centres replied. The majority of centres had a written protocol for the management of acute asthma. A large number of centres use MDI and spacer devices in acute management although doses used varied widely. Only 29% of centres had written asthma action plans available from the emergency department and 53% had plans available from the ward. Irish practice is largely inline with established guidelines. A national asthma strategy could further help to improve asthma care.

W. F. Wu, J. R. Wu, Z. K. Dai, C. W. Tsai, T. C. Tsai, C. C. Chen and C. Y. Yang. "Montelukast as monotherapy in children with mild persistent asthma." 2009 Asian Pac J Allergy Immunol 27(4):

The cysteinyl leukotrienes cause bronchoconstriction, increased mucus production and airway inflammation, three major features of asthma. Several randomized controlled trials have shown the efficacy of leukotriene receptor antagonists for improving asthma outcomes. The drug is favored for treating childhood asthma, where poor compliance with inhalation therapy is a therapeutic challenge. To assess the effectiveness of Montelukast in asthmatic children under real-life conditions, a prospective, single-arm, multicenter, open-label observational study was performed on asthmatic children 2- to 14-years-old with a history of physician-diagnosed mild persistent asthma. Montelukast was given once daily for 12 consecutive weeks. By the end a significant improvement of the daytime asthma symptom score, nighttime asthma score, peak expiratory flow rate (PEFR) and mean score of the investigators' global evaluation was noted ( $p < 0.05$ ). These results suggest that montelukast is an effective monotherapy controller in children with mild persistent asthma.

## Other

W. Möller, I. Heimbeck, N. Weber, G. K. Saba, B. Körner, M. Neiswirth and M. Kohlhäufel.  
"Fractionated exhaled breath condensate collection shows high hydrogen peroxide release in the airways." 2010 *J Aerosol Med Pulm Drug Deliv* 23(3):

**BACKGROUND:** Exhaled breath condensate (EBC) allows noninvasive monitoring of inflammation in the lung. Activation of inflammatory cells results in an increased production of reactive oxygen species, leading to the formation of hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>). In addition, cigarette smoking causes an influx of inflammatory cells, and higher levels of H<sub>2</sub>O<sub>2</sub> have been found in EBC of smokers. However, there are still unresolved issues reflected by large variations in exhaled H<sub>2</sub>O<sub>2</sub> and uncertainties about the origin of H<sub>2</sub>O<sub>2</sub> release in the lung. **METHODS:** We collected EBC as fractionated samples from the airways and from the lung periphery in 10 nonsmokers, eight asymptomatic smokers, and in eight chronic obstructive pulmonary disease (COPD) patients, and H<sub>2</sub>O<sub>2</sub> concentration and acidity (pH) were analyzed in the airway and the alveolar fraction. **RESULTS:** In all subjects studied, H<sub>2</sub>O<sub>2</sub> was 2.6 times higher in the airway versus the alveolar fraction. Airway H<sub>2</sub>O<sub>2</sub> was twofold higher in smokers and fivefold higher in COPD patients compared to nonsmokers. In all study groups, there was no significant difference in deaerated pH between the airway and the alveolar sample. **CONCLUSIONS:** Exhaled H<sub>2</sub>O<sub>2</sub> is released at higher concentrations from the airways of all subjects studied, implying that the airways may be the dominant location of H<sub>2</sub>O<sub>2</sub> production. Because many lung diseases cause inflammation at different sites of the lung, fractionated sampling of EBC can reduce variability and maintain an anatomical allocation of the exhaled biomarkers.

P. Nair, J. Hanrahan and F. E. Hargreave. "Clinical equivalence testing of inhaled bronchodilators." 2009 *Pol Arch Med Wewn* 119(11):

There are no standardized methods to demonstrate in-vivo bioequivalence of inhaled bronchodilators. The most practical method of showing therapeutic equivalence in vivo is by estimating their relative potencies (RP) in clinical efficacy studies. The RP of bronchodilators may be estimated by comparing either their bronchodilator or bronchoprotective properties. Bronchodilator studies are easier to perform and may better model the physiologic effect of many agents, including inhaled beta-agonists. However, it may be difficult to demonstrate steep dose-response for these outcomes, except in cumulative study designs. Bioequivalence trials may be especially challenging when involving pressurized metered-dose inhalers, as a single actuation - the lowest feasible dose to include in the evaluation, may already produce bronchodilation that is at or near the plateau of the dose-response curve. Protection against bronchoconstriction induced by a direct inhaled stimulus like methacholine or histamine affords a reliable and practical method of comparing inhaled bronchodilators and estimating their RP. Inhalational bronchoprovocation testing allows for easier repeatability and quantitation of the stimulus necessary to produce a predetermined degree of bronchoconstriction, and the degree of protection afforded by the bronchoprotection agent. RP studies using adequate methodology are necessary to compare long-acting bronchodilators and both short- and long-acting bronchodilators in patients who are also on inhaled corticosteroids.



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