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Publisher/Editor in Chief
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■ Spring 2018

Respiratory Compromise Institute Adds Expert

The Respiratory Compromise Institute (RCI) has appointed Brent Dunworth, DNP, MBA, APRN, CRNA, to its Clinical Advisory Committee. Dr Dunworth is a member of the American Association of Nurse Anesthetists (AANA), the professional association for more than 52,000 Certified Registered Nurse Anesthetists, and serves as Director of Advanced Practice and Division Chief of Nurse Anesthesia in the Department of Anesthesiology at Vanderbilt University Medical Center (VUMC) in Nashville, Tennessee. He will join a group of 13 distinguished clinicians who make up the committee, which is dedicated to addressing respiratory compromise across the care continuum via public education, research and advocacy. Respiratory compromise is a deterioration of respiratory function that poses a high risk of life-threatening respiratory failure. Respiratory failure is the second leading avoidable patient safety issue. It is one of the top five conditions leading to increasing hospital costs and the third most rapidly increasing hospital inpatient cost in the United States. General care floor patients with respiratory compromise are 29 times more likely to die. Dr Dunworth is an educator at the Vanderbilt University School of Nursing and lectures nationally on a variety of nurse anesthesia topics. He has received numerous awards, including: the Agatha Hodgins Award, presented to outstanding nurse anesthesia students; the Pennsylvania Association of Nurse Anesthetists' Didactic Instructor of the Year Award; and the University of Pittsburgh School of Nursing's Outstanding Young Alumnus Award. He has given more than 40 presentations on anesthesia-related subjects, such as difficult airway management, anesthesia ventilation, patient safety advocacy in anesthesiology, and problems associated with sleep-disordered breathing. His peer-reviewed publications and abstracts have appeared in AACN Clinical Issues: Advanced Practice in Acute and Critical Care, American Journal of Nursing, AANA Journal and Anesthesia & Analgesia. "As the Respiratory Compromise Institute continues to grow, we are pleased to have someone on our clinical advisory committee of Dr Dunworth's caliber," said, Phillip Porte, Executive Director of RCI. At VUMC, Dr Dunworth provides administrative leadership to advanced practice perioperative professionals, including certified registered nurse anesthetists (CRNAs) and certified registered nurse practitioners (CRNPs). His oversight responsibilities include preoperative evaluations, procedural assessments and postoperative recovery monitoring in order to provide safe and efficient patient care delivery. He is responsible for 160 CRNAs, 25 CRNPs and 30 anesthesia technologists. Prior to VUMC, he was Senior Director for Nurse Anesthesia at the University of Pittsburgh Medical Center. Respiratory compromise, which includes respiratory distress, insufficiency, failure and arrest, can occur across numerous clinical scenarios. Respiratory compromise may appear post-operatively or may be drug-induced by the delivery of a sedative, opioid, or analgesic to patients who were not properly assessed or properly monitored.

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According to the US Department of Health & Human Services, Agency for Healthcare Research and Quality, respiratory compromise is the third most rapidly increasing hospital inpatient cost in the United States, with $7.8 billion spent on respiratory compromise in US hospitals in 2007. Respiratory compromise increases patient mortality rates by over 30 percent and hospital and ICU stays by almost 50 percent. RCI defines respiratory compromise as a state in which there is a high likelihood of decompensation into respiratory insufficiency, respiratory failure or death that could be prevented or mitigated through specific interventions (enhanced monitoring and/or therapies). The Respiratory Compromise Institute brings together a broad-based coalition of organizations, companies, and individuals dedicated to reducing—and eventually eliminating—preventable adverse events and deaths due to respiratory compromise.

Company's First POC Introduced

ResMed has introduced Mobi, its first ResMed-branded portable oxygen concentrator (POC). Mobi offers an industry-leading balance of oxygen delivery, weight and battery life so that millions with chronic obstructive pulmonary disease (COPD) or other respiratory condition can enjoy ResMed-quality oxygen therapy at home or on the go. "We have focused decades of patient-centered ResMed technology and design innovation into this POC," said ResMed CEO Mick Farrell. "We've achieved great mobility, comfort and therapy quality in sleep apnea treatment with AirMini, the world's smallest PAP device. Mobi offers that same great balance to the many millions of people who rely on supplemental oxygen to enjoy their highest quality of life." Mobility is particularly key for oxygen patients with chronic obstructive pulmonary disease. Regular physical activity is shown to lower the risk of hospitalization and death among those with COPD, according to a 2006 study published in Thorax. "The time is now for portable oxygen," said Farrell. "Our patients demand a device that enables them to get out of their house and travel to visit friends and family. Mobi gives the gift of freedom to millions." Mobi will be available to US patients through their home medical equipment (HME) providers later this quarter. ResMed is pursuing clearance to sell in other countries in 2018. ResMed is a world-leading connected health company with more than 4 million cloud-connected devices for daily remote patient monitoring, changes lives with every breath. Its award-winning devices and software solutions help treat and manage sleep apnea, chronic obstructive pulmonary disease and other respiratory conditions. Its 6,000-member team strives to improve patients' quality of life, reduce the impact of chronic disease and save healthcare costs in more than 120 countries.

New AHRQ Report Highlights FeNO Testing

Circassia Pharmaceuticals, Inc., a specialty pharmaceutical company focused on respiratory disease, welcomes the publication of a new clinical evidence report, The Clinical Utility of Fractional Exhaled Nitric Oxide (FeNO) in Asthma Management, by the United States Agency for Healthcare Research and Quality (AHRQ). The report highlights the use of fractional exhaled nitric oxide (FeNO) testing as valuable part of comprehensive asthma diagnosis and management. Circassia's NIOX products are novel point-of-care FeNO measurement devices, which are available in the United States, many countries across Europe, China, Japan and a range of other territories. The new AHRQ report states that FeNO results can predict which patients will respond to inhaled corticosteroid therapy, and reinforces the association between a positive FeNO test result and an accurate asthma diagnosis in people 5 years and older. The research found that FeNO diagnostic accuracy was higher among steroid-naïve asthmatics, children (ages 5-18), and nonsmokers than other patients suspected to have asthma. Importantly, the report also states that using FeNO measurements to manage long-term control medications, including dose titration, weaning, and monitoring of adherence, can reduce the frequency of exacerbations. According to the AHRQ report, asthma was one of the top 20 leading diagnosis groups for primary care visits in the US in 2012 and was the main reason for 1.8 million emergency department visits and 439,000 hospitalizations. Although the severity of disease varies among patients and over time in the same patient, asthma can be fatal, accounting for approximately one death per 100,000 Americans. The AHRQ report publication comes shortly after the UK's National Institute for Health and Care Excellence (NICE) issued clinical guidelines for asthma* recommending the use of FeNO testing as part of comprehensive diagnostic

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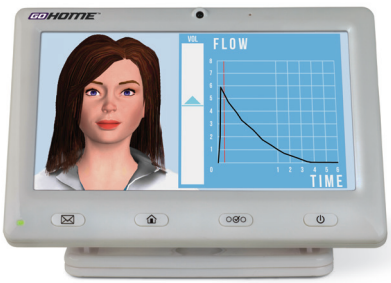

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algorithms for adults, children and young people, and is a timely addition to the growing body of evidence that supports the use of FeNO testing for asthma diagnosis and management. "The ability to predict which asthma patients will respond to corticosteroid therapy, and how well that therapy is working to reduce the frequency of exacerbations is powerful information for clinicians," said Bradley Chipps, MD, FAAP, FAAA, FCCP, Pediatric Pulmonologist, Allergist, and current President of the American College of Allergy, Asthma and Immunology. "It is exciting to see the AHRQ report support FeNO testing as a tool that can truly benefit asthma patients and improve outcomes, particularly for children." Other experts expressed similar praise. "The AHRQ report is welcome news for both clinicians and their patients, who have the right to high quality, evidence-based healthcare. I am looking forward to the National Heart, Lung, and Blood Institute using the evidence report to help develop future clinical guidelines for the use of FeNO in the diagnosis and management of asthma," said Tonya Winders, President and CEO, Allergy & Asthma Network, the leading nonprofit patient education and advocacy organization for people with asthma, allergies and related conditions. Asthma is a chronic inflammatory respiratory disease that often begins in childhood, but can affect people of any age. The disease is characterized by attacks (exacerbations) of breathlessness and wheezing of varying severity and frequency, which if left untreated can be life-threatening. Asthma is a common condition, with the World Health Organization estimating 235 million people have the condition worldwide. Asthma affects approximately 25 million people in the United States. Th2 or type 2 airway inflammation is the major underlying cause of asthma. NIOX is based on the discovery that patients with Th2 or type 2 driven airway inflammation generally have higher than normal levels of nitric oxide in their exhaled breath. By measuring the concentration of this fractional exhaled nitric oxide (FeNO), NIOX enables clinicians to evaluate airway inflammation in patients with underlying asthma. As a result, Circassia's NIOX products are used to assist asthma management around the world. Circassia markets NIOX directly to healthcare professionals in the United States, United Kingdom and Germany and through a network of distributors in a range of other countries. Circassia is a world-class specialty pharmaceutical business focused on respiratory disease. In addition to its market-leading NIOX products, the Company recently established a collaboration with AstraZeneca in the US in which it promotes the chronic obstructive pulmonary disease (COPD) treatment Tudorza (aclidinium bromide inhalation powder), and has the US commercial rights to late-stage COPD product, aclidinium bromide and formoterol fumarate inhalation powder.

Device Choice Vital in Asthma Control: Data

A recent article in Pulmonary Pharmacology and Physiology provides in vitro evidence that the AEROCHAMBER PLUS FLOW-VU valved holding chamber (or spacer) delivers aerosolized drug more effectively than other chambers, a view further supported in a new literature review published in Therapeutic Advances in Respiratory Disease. The use of spacers with Metered Dose Inhalers (MDIs) has become firmly established in the management of asthma and COPD, with guidelines such as the Global Initiative for Asthma (GINA) recommending their use to reduce oropharyngeal deposition of drug and counter the common problem of poor inhaler technique. What is not established, however, is whether there

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are any meaningful differences between the devices. While GINA guidelines do indicate that not all are the same—a view echoed by the European Medicines Agency (EMA) recommendations, which state that data for MDIs should be generated with a 'specific named spacer'—this view is not expressed in all guidelines. Two recent publications set out to address the impact of spacer design on drug delivery performance and look at potential implications for clinical use. Four similarly sized chambers were compared 'out of the box' in terms of statistical equivalence with the gold standard AEROCHAMBER PLUS chamber with respect to retention of drug particles within the device and the aerodynamic particle size distribution of the drug particles delivered. Only the AEROCHAMBER PLUS FLOW-VU chamber (Monaghan Medical Corporation) demonstrated an equivalent profile of dose retention and delivery versus the reference chamber. The Compact Space Chamber Plus (Medical Developments), the OptiChamber Diamond (Philips Respironics, Inc), and InspiraChamber (Lupin Pharmaceuticals, Inc) devices all retained approximately twice as much drug, delivering around half the dose and showing non-equivalent performance compared with the AEROCHAMBER PLUS FLOW-VU chamber and reference chamber (pretreated AEROCHAMBER PLUS chamber). Lead author Dr Sanjeeva Dissanayake has published a literature review in Therapeutic Advances in Respiratory Disease, which provides further support for these findings. In considering the important attributes of such delivery devices, the review notes a shift in emphasis from chamber size and shape to other aspects, such as consistency of drug delivery, static charge reduction, valve performance, and factors optimizing facemask effectiveness (such as flexibility and seal). Despite the general lack of published clinical studies that confirm the therapeutic benefits of such differences, the AEROCHAMBER 'family' of chambers has amassed an impressive body of clinical evidence. Most recently, a real-world database study has demonstrated improved clinical benefits and reduced resource utilization use with the AEROCHAMBER PLUS FLOW-VU chamber versus other chambers in patients with asthma. A study specifically looking at the FLOW-VU inhalation indicator has also shown benefits for carer confidence in dose delivery, and improved caregiver preference and quality of life.

Dr Dissanayake commented, "The in vitro equivalence study results and the literature review findings provide strong support for the EMA guideline recommendations that data for MDIs should be generated with specific spacer devices, and further reinforce the view that superficially similar chambers should not automatically be considered to be interchangeable—even if superficially similar."

Tender Offer Approved

Altus Capital Partners, Inc., an investment firm focused on the North American manufacturing sector, announced the successful conclusion of the tender offer for all of the outstanding shares of common stock of MGC Diagnostics Corporation, a global medical technology company dedicated to cardiorespiratory health solutions, at a price of $11.03 per share. MGC CEO Todd M. Austin commented, "We are excited about our new partnership with the Altus team. They understand and support our strategies for product innovation and growth. Their financial strength will also provide incremental funding for our product development pipeline initiatives and help to accelerate the delivery of new product offerings in 2018 and beyond." Others praised the deal. "MGC is well-positioned in an exciting diagnostics sector, both domestically and increasingly in key international markets," Altus Co-Founder and Senior

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Partner Gregory L. Greenberg said. "I look forward to working closely with a great management team, led by Todd Austin, as they continue to implement their growth strategy. At the same time, we will support the company's ongoing investments in FDA-approved diagnostics products and software platforms." Through its Medical Graphics Corporation and Medisoft SA subsidiaries MGC develops, manufactures and markets non-invasive diagnostic systems. This portfolio of products provides solutions for disease detection, integrated care, and wellness across the spectrum of cardiorespiratory healthcare and are sold internationally through distributors and, in the United States, France and Belgium, primarily through a direct sales force targeting heart and lung specialists located in hospitals, university-based medical centers, medical clinics, physicians' offices, pharmaceutical companies, medical device manufacturers, and clinical research organizations (CROs). This is Altus' second acquisition in 2017, after partnering with management to acquire Max Environmental Technologies, Inc., an integrated environmental solutions company, in February, 2017.

CPAP Safe for Obesity Hypoventilation Syndrome With Apnea

Most patients with obesity hypoventilation syndrome and sleep apnea can safely switch to continuous positive airway pressure (CPAP) ventilation therapy after at least 3 months of bilevel positive airway pressure (BiPAP) therapy, new research shows. "We were astonished," said lead investigator María Paola Arellano-Maric, MD, from Pontifical Catholic University of Chile in Santiago. "We all felt pretty neutral on this when we started, but our results were very positive." Noninvasive BiPAP ventilation provides a higher pressure for inhalation and a lower pressure for exhalation. With CPAP, pressure is consistent. There has been a belief that "if you have a pressure gradient for inhalation and exhalation, it's more comfortable for the patient, but our patients didn't find that," Dr Arellano-Maric explained at the European Respiratory Society International Congress 2017. She and her colleagues demonstrated that once patients were stabilized after using BiPAP for at least 3 months, most could be safely switched to CPAP. The patients "didn't have any respiratory insufficiency under CPAP," she reported. For their study, the team recruited 42 stable patients with obesity hypoventilation syndrome who had been receiving noninvasive ventilation at home for an average of 34 months (interquartile range, 13.7-57.4 months). All 19 women and 23 men had severe obstructive sleep apnea and 52.3% had chronic obstructive pulmonary disease (COPD) classified as GOLD stage I or II. Average body mass index (BMI) in the study cohort was 45.1 kg/mg^2, and 83% of the patients were current or ex smokers. Every patient spent one night in the hospital receiving automatic positive airway pressure (APAP) so that the proper amount of pressurized air could be determined. If blood gases, polysomnography, and lung function were adequate, patients were sent home with a CPAP machine. "Surprisingly, the pressure for many was about 14 centimeters of water," Dr Arellano-Maric reported. "That was high. We were worried they wouldn't be able to sleep." After 3 weeks, each patient returned to the hospital to undergo whole-night polysomnography. "One after the other, the patients told us they were sleeping better," she said. After 6 weeks of home CPAP, daytime levels of partial pressure of carbon dioxide in arterial blood were 45 mmHg or less in 30 of the 42 patients (71%; 95% confidence interval [CI],

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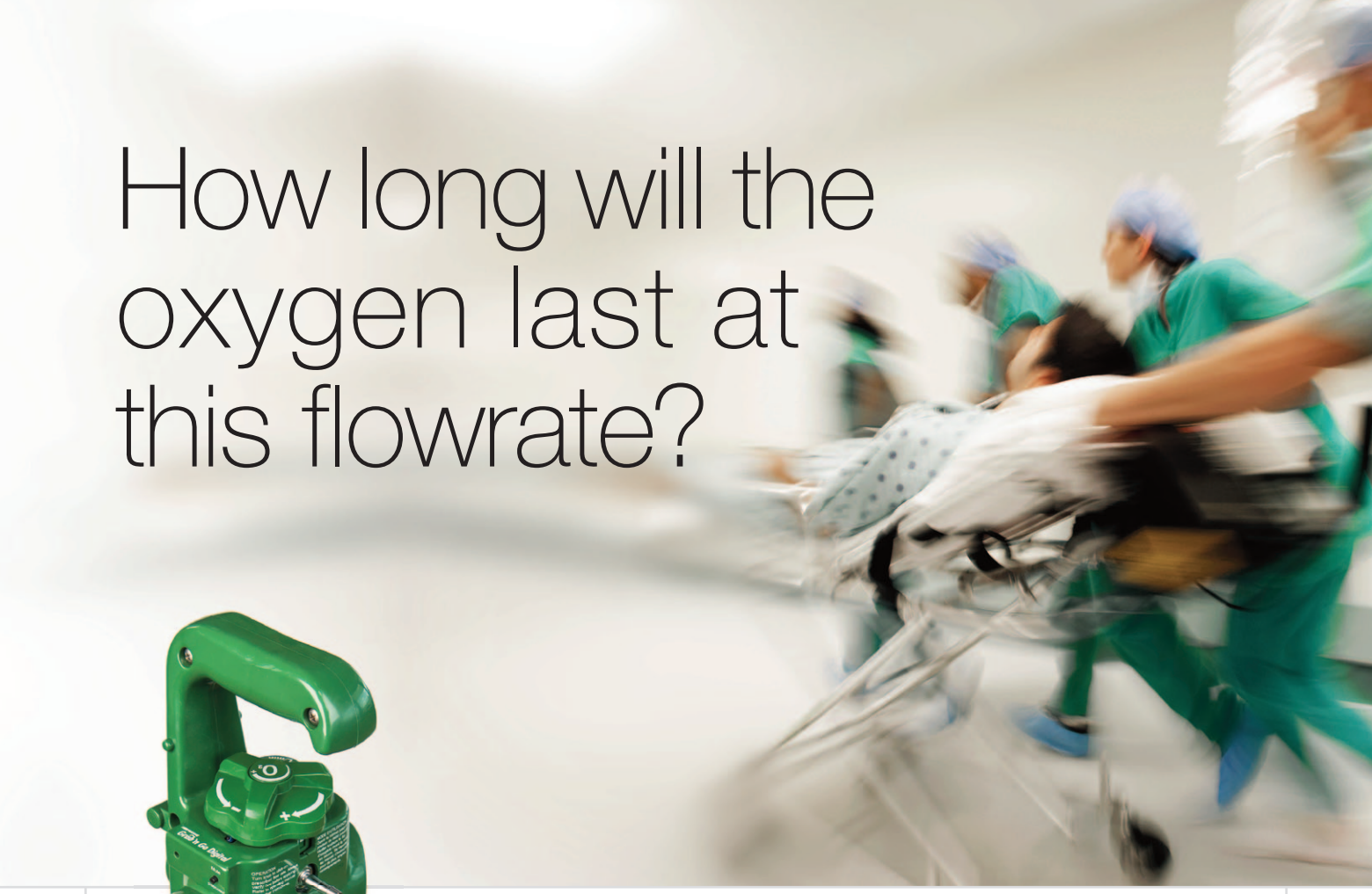

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55%-84%). Current guidelines do not recommend auto-titrating CPAP machines for patients such as the ones in this study because initial treatment with CPAP often fails, and there is a "lack of studies on switching," Dr Arellano-Maric explained.

CAIRE Appoints Authorized Provider

CAIRE, the manufacturer of the AirSep, CAIRE and SeQual brands of wearable, portable, and stationary oxygen concentrators, has appointed Altra Service Professionals, as the Authorized Service Center serving customers in New Jersey and the New England states. Altra Service Professionals will perform both warranty and non-warranty service for CAIRE products from their facility in Berlin, CT. "Altra has been performing non-warranty repairs of our products for many years and were a natural fit to bring on board in support of our warranty repairs. They have experienced technicians who we're confident will perform high quality repair work and represent CAIRE well," said Miguel Cervantes, Service Manager. Robert DeChello, President and co-owner of Altra, believes this strategic relationship with CAIRE is important for providers and customers in the region he'll be supporting and provides growth opportunities for both Altra and CAIRE. "In an industry where reimbursement continually shrinks, dealers are always looking for ways to cut costs without sacrificing quality of care. This relationship with CAIRE enables us to do this by providing exceptional training and processes so that we can provide efficient and affordable repair solutions. We are honored to have been chosen by CAIRE as the Authorized Service Center for the northeast and look forward to supporting our customers." The Berlin, CT, location will be entrusted with the repair of wearable, portable, and stationary concentrators for Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut, and New Jersey.

Chest Wall Oscillation Therapy Goes Wireless

Electromed, Inc. announced the launch of the SmartVest SQL with SmartVest Connect wireless technology, a personalized high frequency chest wall oscillation (HFCWO) therapy management portal for patients with compromised pulmonary function. The SmartVest SQL with wireless technology features built-in cellular connectivity, offering healthcare teams and patients access to treatment information to better collaborate in making patient-centered care decisions. SmartVest Connect is available online to pediatric and cystic fibrosis patients using a wirelessly enabled SmartVest SQL system. SmartVest Connect enables patients to track progress of their therapy plan and includes a real-time SmartVest Score and easy-to-read goal reports that provide an in-depth look at performance. Created to encourage patient engagement, SmartVest Connect provides feedback for patients to take an active role in their HFCWO therapy, fostering improved therapy adherence. SmartVest SQL with SmartVest Connect is simple, intuitive, and designed to automatically update following completion of a therapy session: just plug it in. "SmartVest Connect is designed to make it easy for healthcare teams and patients to track therapy performance and collaborate in treatment decisions," commented Kathleen Skarvan, President and Chief Executive Officer of Electromed. "We believe this innovation will strengthen our patient and clinician partnerships, leading to greater therapy adherence and improved quality of life for individuals with compromised pulmonary function. We're proud to stand by our commitment to 'making life's important moments possible' and continued innovation of

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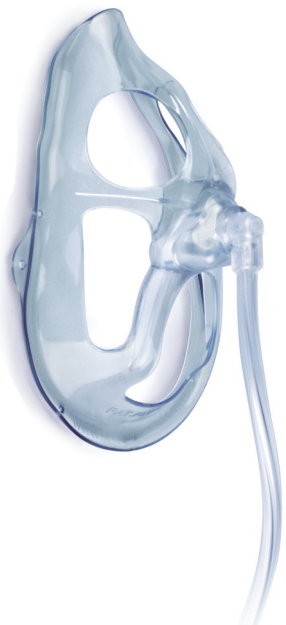

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1. 2017. Oxygen flow rate and the rebreathing of CO2 in oxygen simple masks and OxyMask™. Department of Clinical Engineering, Respiratory care division, Yokohama municipal citizens hospital, KANAGAWA JAPAN.

delivering market-driven HFCWO therapy solutions. We expect to expand SmartVest Connect availability to targeted adult pulmonary clinics throughout the year." The SmartVest System uses HFCWO, a proven therapy that helps clear the lungs of excess secretions, reducing the risk of respiratory infections and hospitalizations. HFCWO produces an alternating flow of air into a garment that rapidly compresses and releases the chest wall at a variety of selectable frequencies and pressures, resulting in an oscillation in airflow within the airways that act to loosen, thin, and propel mucus toward the major airways where it can be expectorated or suctioned away.

New CPAP Masks Approved by FDA

3B Medical announced FDA clearances for two new CPAP masks. The Viva is 3B's newest nasal mask. A light, simple and comfortable design makes this nasal mask stand out from the competition. The Numa Full Face Mask also received FDA clearance and shares the same design philosophy for simplicity, flowing lines, and lightweight. Both masks provide maximum comfort and superior sealing, to aid patient compliance. The Numa Full Face and the Viva Nasal are now available for immediate ordering. 3B Medical is a leader in the development; marketing and distribution of medical products for the treatment of sleep disordered breathing and oxygen therapy.

Company Breathes Life Into Website

CAIRE Inc,. manufacturer of oxygen therapy solutions, has rolled out new branding and content on its website. CAIRE's new look and feel was developed in partnership with advertising agency Morrison in Atlanta. Jeremy Heilpern, President of Morrison, explained, "Creatively, our goal was to speak to the human truth affecting every person that finds themselves in need of CAIRE products. We strategically decided to show people in environments that spoke to the state they're in today, with the notion that they would not be missing out on those great moments in the future. The real beneficiary of CAIRE products are the loved ones that still get to spend time with their nana, grandpa, mom, or dad." He continued, "That same sentiment comes through on the new CAIRE website with a clean user experience, detailed product information, insight and information related to oxygen therapy, and an easy ordering process." Along with powerful messaging encouraging end users to engage in ways they can improve their health by adhering to their oxygen therapy prescription, there is extensive product information allowing visitors to quickly navigate CAIRE's portfolio of products that serve low to high flow needs. Expanded educational content includes information on COPD, disease stages, treatments and tips, oxygen therapy FAQs, and links to valuable resources provided by premier health organisations who actively working to improve the lives of people suffering from a variety of respiratory diseases. Chris Southerland, Vice-President of Respiratory, Chart BioMedical, commented, "We feel this shift of reaching out directly to the end user will benefit our providers via retail sales opportunities and in garnering clinical referrals direct from physicians who view CAIRE as a quality resource for oxygen therapy solutions and educational resources."

Second-Generation Rapid Influenza Test Clears FDA

The US Food and Drug Administration (FDA) has cleared for marketing the Alere i Influenza A & B 2 rapid molecular diagnostic test for use in children and adults. This is a "second-generation rapid molecular assay, which delivers lab accurate results in less time, with the ability to report a positive result in as little as 5 minutes," the company said. An earlier version of the company's point-of-care Alere i influenza test, which was cleared by the FDA in 2014, gives results in under 15 minutes. "In acute care settings, every minute counts when assessing symptomatic patients. Alere i delivers clinically meaningful and actionable results to clinicians—enabling them to treat patients more quickly and appropriately," Avi Pelossof, Alere's global president of infectious disease, said. The clinical performance of the second-generation test was demonstrated in a multicenter, prospective clinical study conducted at 10 centers in the United States during the 2016-2017 respiratory season. In the study, 1074 prospective nasal or nasopharyngeal swab specimens collected from patients with influenza-like symptoms were evaluated with the Alere i test and compared to an FDA-cleared real-time polymerase chain reaction test. The second-generation Alere i influenza test also offers more flexible sampling features and enhanced quality control functions, the company said. The test will be available for use in hospitals in time for the 2017-2018 respiratory season. Alere plans to submit an application for a Clinical Laboratory Improvement Amendments waiver for the influenza test, which would allow it to be used in nontraditional laboratory sites, such as physician offices, hospital emergency departments, and health department clinics.

Latest Gastroenterology Data Presented at Conference

Researchers presented data from two related studies at the 25th United European Gastroenterology Week. The studies evaluated procedural sedation practices, incidence of adverse events (AEs) and costs of sedation-related AEs in France, Germany, Italy, the UK and the US based on surveys of providers (e.g., nurses, physicians and anaesthesiologists) and payers. In one study, "Clinical Practice, Monitoring, and Patient Safety During Procedural Sedation in Five Countries," researchers concluded that clinical sedation practices and AE incidence were relatively consistent across countries, yet AE incidence was influenced by monitoring modality (e.g., capnography, pulse oximetry, etc.). For example, 7 of 11 German respondents who did not use capnography as a standard of care reported severe desaturation events, compared with 0 of 9 who routinely used it. Study authors also concluded that pulse oximetry monitoring was almost universally used during sedation, while capnography use was more variable. Nonetheless, sedation monitoring technology that provided an actionable early warning of patient compromise (e.g., respiratory compromise) remained a priority for clinicians, regardless of technology employed. In another study, "Interventions and Costs Associated with SIVA-defined Adverse Events During Procedural Sedation in Five Countries," researchers found that costs of sedation-related AEs can be substantial, regardless of country of origin, especially when accounting for indirect AE expenses (i.e., fully-loaded costs), such as hospital administration fees, resolution time, inpatient stays, procedural delays and cancellations. For example, the direct costs of severe desaturation, an AE which can lead to respiratory compromise, by country were: 79 EUR (France), 92 EUR (Germany), 59 EUR (Italy), 93 GBP (UK) and 529 USD (USA). The fully-loaded costs were significantly higher: 1,994 EUR (France), 1,268 EUR (Germany), 201 EUR (Italy), 1,258 GBP (UK) and 1,715 USD (US). Based on these and other findings, researchers concluded that relatively minor events can have a substantial cost impact through disruption of patient flow and reduced provider efficiency that may add to the total burden of sedation-related AEs.

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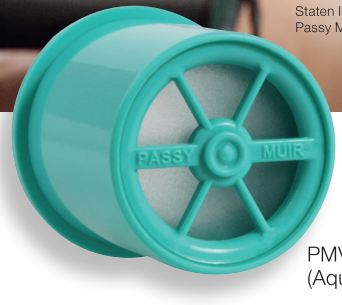

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Therapists Must be Fully Aware of the Implications of the Buildup of Biofilm and Secretions in the Endotracheal Tube

In this feature, Respiratory Therapy interviews clinicians and healthcare providers about the actual application of specific products and therapies. This interview is with Brian Wicker, RRT, Director of Respiratory Services — Wound & Hyperbaric with McLaren-Lapeer Region about the endOclear® Restore™ device.

Respiratory Therapy: You recently had an IRB approved study presented during the AARC Congress in October. Could you describe what that entailed?
Brian Wicker: The primary purpose of this study was to compare objective outcome measures before and after implementing a daily ETT cleaning protocol with the endOclear® Restore™ device, which is a sterile, single-use, mechanically operated wiper designed to remove adherent ETT secretions and biofilm invariably left behind after standard of care closed suctioning. This was a five-year retrospective, observational, single centered study to evaluate the efficacy of cleaning the ETT daily with the endOclear® Restore™ device prior to the spontaneous breathing trial. The primary endpoints were average duration of mechanical ventilation, average hospital length of stay, and average hospital direct cost per subject. Data was collected on 426 subjects prior to using the daily ETT cleaning protocol and 894 subjects after implementing the protocol. Daily use of the endOclear® Restore™ resulted in a decrease in average time on the ventilator from 4.2 to 3.5 days, a decrease in length of stay in the hospital from 9.9 to 8.3 days, and a decrease in direct cost per case from $13,101 to $12,024 — a total of $926,838 net benefit.

RT: I know that wasn't your first AARC congress as an attendee but could you tell us about your experience sharing your study in Indianapolis as a researcher?
BW: It was rewarding since this is a place where all of our colleagues, peers and educators meet to explore new technology and the latest in products, procedures and studies. Multiple facilities and several different countries were very interested in our study. It was an extremely rewarding experience as it was a way to share the success of our facility and showcase our excellent team of Respiratory Therapists and all of their hard work, which ultimately makes patients safer while improving outcomes.

RT: What led to you wanting to do the study and what challenges did you face?
BW: When I took the job as director I never knew how many hats I would wear, but one of the most important roles I found myself taking on was being my own quality manager. So, I had to collect data, show value in that data, and prove cost savings aside from managing people. One of the items that I tracked was our ventilator days, and I worked with the ICU director to ensure practices for daily weaning were consistent and accurately measured.

RT: How did you achieve product buy-in?
BW: The RT Department had taken on the responsibilities of evidence-based practices such as low tidal volume minute ventilation, early mobility, daily spontaneous awakening and breathing trials, among other things, through two projects at our hospital: Keystone, and the AHRQ CUSP project. These projects were implemented with the aim of reducing VAP and getting patients off of the ventilator sooner. I knew as Director that the best way to get the department to believe in the projects and achieve buy in was to let them take ownership. I accomplished this by having Respiratory drive the project. Every new study, product, and change encounters resistance but by empowering the staff to take ownership and by working equally with both shifts (which is critical) the RT staff bought in. Once the results started coming in, the metrics kept getting better, and the staff really saw the positive impact they were having buy in became much easier.

RT: Was there anything that you took away from the study that may not have been published?
BW: Every Therapist knows that they "own the airway" but I think too often they forget that maintenance of the airway is also their responsibility. We as therapists often pass off suctioning to nursing, or aren't fully aware of the implications of the buildup of biofilm and secretions and their contribution to some patients being unable to overcome that increased resistance during the spontaneous breathing trial. We had the Keystone and CUSP projects and stayed up on best practices but it was the maintenance of the airway — the cleaning of the ET tube — that really drove down length of stay, decreased mortality, provided better financial outcomes, and was a safer practice altogether.

RT: Since the study you have transitioned to a new product for airway maintenance. Could you describe that and your current practice and tell us how that is progressing?
BW: For the study, we used the endOclear® Restore™ device which was obviously safe and effective and led to great results for our institution, but it is also a single use device that requires breaking the circuit. Everyone in the field understands the importance of minimizing alveolar derecruitment and endOclear® took the initiative to create an entire airway management system called the Liberator®, which has been equally effective in maintaining the airway while eliminating the need to break the circuit. The Liberator® system utilizes a manifold with a stopcock

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which allows the user to switch between a normal suction catheter and a balloon wiper catheter that can be interchanged to clean the airway as often as necessary. The manifold is good for as long as the ventilator circuit unless it becomes soiled, and the catheters are good for 72 hours which has also added to our cost savings. EndOclear® has even created an accessory adapter which allows for bronchoscopies and mini-BALs without causing derecruitement as well. We have been using the Liberator® system since mid-June 2017 and have had great results, similar to the Restore™.

Dealing With a Rising Number of Bronchiectasis Cases

In this feature, Respiratory Therapy interviews clinicians and healthcare providers about the actual application of specific products and therapies. This interview is with Dr Alan F Barker, Professor of Medicine, Pulmonary and Critical Care, UHN-67, Oregon Health and Science University about the increase in cases of bronchiectasis.

Respiratory Therapy: How is Bronchiectasis clinically defined and diagnosed?
Dr Alan F Barker: Bronchiectasis (sometimes called non-cystic fibrosis bronchiectasis or NCFB) is a chronic respiratory condition manifest by symptoms of usually daily cough with copious mucopurulent phlegm expectoration. Other symptoms include dyspnea, wheeze, pleuritic chest pain, and intermittent hemoptysis. Unrelenting fatigue is a common complaint. Frequent lower respiratory tract infections are both part of the history and often exacerbate bronchiectasis. Non-contrast chest CT imaging is the gold standard test to confirm the diagnosis. Findings on chest CT include dilated and thickened airways, lower lobe involvement greater than upper lobe. Mucous plugging in small airways is an accompanying feature and is called tree-in-bud.

RT: What is the prevalence of Bronchiectasis in the overall COPD population in the US and what is the importance for clinical care?
AB: There is considerable overlap of symptoms of COPD and bronchiectasis including daily cough, sputum production, and dyspnea. The major etiology for COPD is a long history of personal cigarette smoking. In bronchiectasis, smoking is probably not an etiologic agent, but contributes to morbidity. Data from European studies of COPD patients that includes chest imaging, suggests that 20-30% will have structural changes of bronchiectasis. There is no reason to think that this percentage is much different in the US. With 19 million COPD individuals in the US, that suggests a population of bronchiectasis patients in the millions. The overlap of COPD and bronchiectasis increases exacerbations and hospitalizations, reduces pulmonary function, and increases mortality.

RT: Reference is often made to the "Vicious Cycle of Bronchiectasis." What are the elements of that cycle and what is the impact on the patient?
AB: The key pathophysiologic features include recurrent infection, reduced host defense, and inflammation in damaged airways. The initial insult and damage may occur with a virulent infection (whooping cough and tuberculosis were common 60 years ago; more recently other viral infections such as influenza or adenovirus, bacterial such as Staphylococcus aureus or Pseudomonas aeruginosa and sometimes non-tuberculous mycobacteria), residua of a foreign body aspiration obstructing an airway, humoral immunodeficiency, or genetic (alpha-1 antitrypsin deficiency, primary ciliary dyskinesia). The response to Infections includes airway infiltration with intense neutrophilic cells and accompanying potent proteases and cytokines that linger in the damaged airways. The vicious cycle refers to the recurrent exacerbations triggered by infections that attract inflammatory mediators that can further damage previously injured airways. An impaired host defense retards healing and allows further damage. The copious sputum production includes reactive mucus, inflammatory cells and mediators, and bacterial products.

RT: Recent and previous studies have emphasized the potential scope of the prevalence of bronchiectasis and the various estimates show that the number of patients diagnosed each year is significant and that the number of undiagnosed patients may range from hundreds of thousands to perhaps millions. This suggests that it is a significant healthcare problem, underdiagnosed, and that screening for bronchiectasis is critical for patients with symptoms. Can you elaborate briefly on your perspective and experience with these demographics and ways to address this?
AB: Although probably underestimated, reports from Medicare and insurance databases suggest that over 200,000- 300,000 individuals are affected with bronchiectasis in the US. That number may be increasing by 7-8%/year. The prevalence varies between 15-25/100,000 individuals below the age of 50 to greater than 300-500/100,000 individuals over the age of 60. The average age is 62-65 with a 60% female predominance. In the US, there is no ethnic proclivity, but most studies report a preponderance of Caucasians. Populations with reduced access to health care (and ability to receive prompt antibiotics for respiratory tract infections) such as Alaska natives have increased prevalence of bronchiectasis

RT: What is the impact of this situation on the patient and healthcare system in terms of hospitalizations and cost?
AB: Patients on average have 1.5-3.0 exacerbations/year depending on the severity of the underlying bronchiectasis as assessed by pulmonary function, presence of Pseudomonas aeruginosa in sputum, and comorbidities. Approximately 1/3 of those exacerbations require hospitalization because of respiratory insufficiency, need for intravenous antibiotic administration, large volume hemoptysis, frailty (being underweight), and worsening of comorbidities (arrhythmias, heart failure, etc.). The economic burden reflects the increased medical burden compared to similar age-matched individuals.

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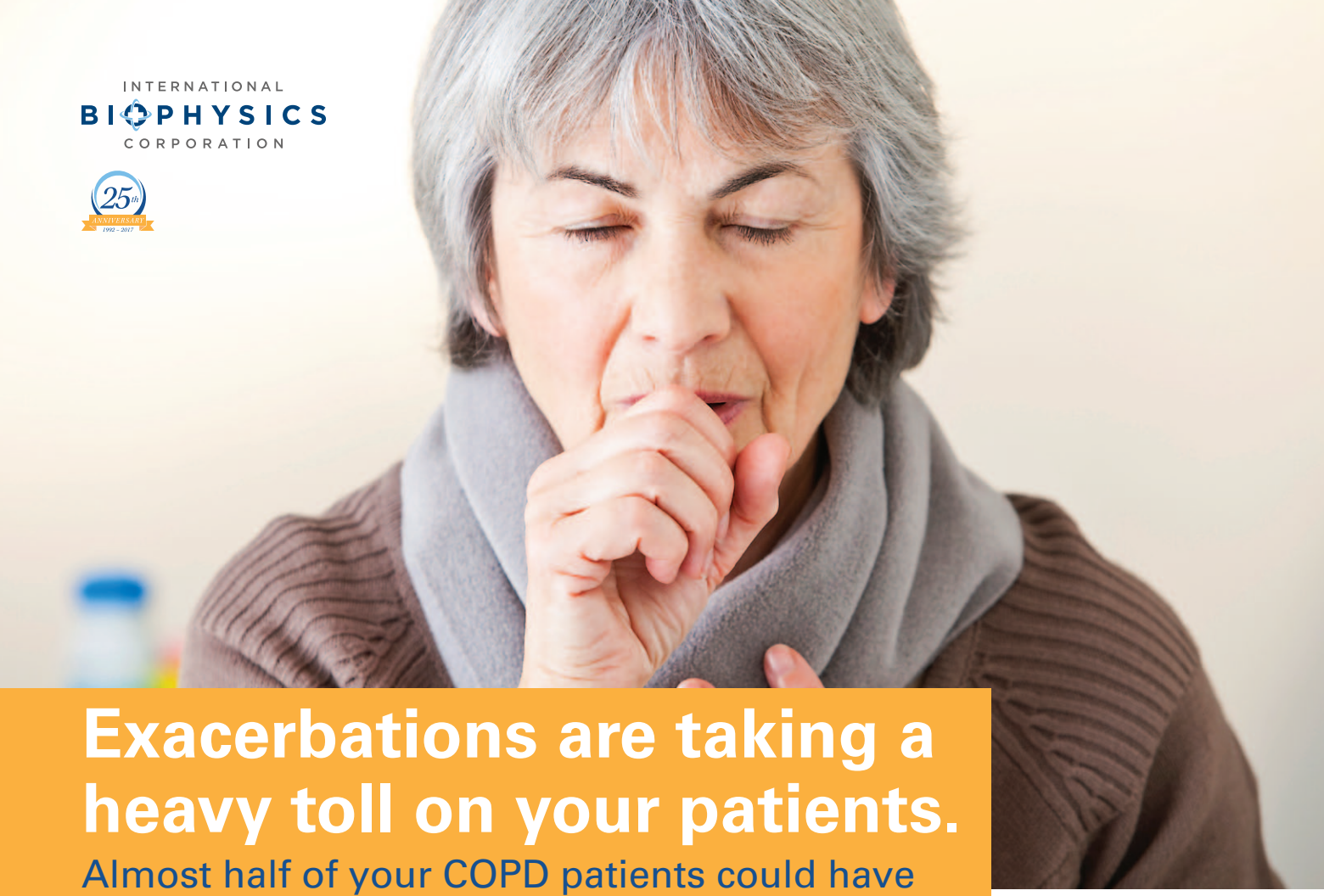

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*Demonstrated by recent clinical studies and industry papers

Bronchiectasis patients have more hospitalizations and increased days in the hospital, increased ambulatory encounters, and increased use of antibiotics, steroids, and bronchodilator medications.

RT: Bronchiectasis cannot be reversed so how do you treat bronchiectasis?
AB: Management of bronchiectasis includes several actions to treat infection and reduce inflammation: A. Treat acute exacerbations as (bacterial) infection promptly. If sputum cultures are available, administer an antibiotic targeted for the potential pathogen(s); B. Identify and treat any underlying condition. eg Humoral IgG deficiency is managed with immunoglobulin G replacement; C. Consider suppression of chronic infection. Regular macrolide administration will reduce exacerbations. Some inhaled antibiotics will reduce the sputum microbial load. No inhaled antibiotic is approved for bronchiectasis in the US; D. Bronchial hygiene is the general term to include airway clearance to enhance and promote tenacious airway secretion removal; E. Manage critical hemoptysis (usually defined as 250-300 ml/day) potentially compromising respiration. May require bronchial artery embolization or surgical extirpation of a bleeding segment or lobe; F. Resectional surgery is appropriate for some patients with critical hemoptysis, removal of a lobe or segment whose airway is obstructed and interfering with drainage, or removal of a lobe or segment containing a very resistant organism difficult to treat with antibiotics. Bilateral lung transplant may be considered for individuals with respiratory insufficiency and a paucity of comorbidities.

RT: How important is bronchial hygiene and airway clearance in helping patients live with bronchiectasis?
AB: Regular practice of bronchial hygiene is a major component of bronchiectasis management. Modalities include mechanical airway clearance to enhance secretion removal and inhalation of mucokinetic and bronchodilator medication.

RT: What are the types of airway clearance therapies available to patients?
AB: Airway clearance modalities are administered during exacerbations and during times of stability to loosen respiratory secretions and enhance their removal. Regular physical exercise must be part of the management of patients with lung disease including bronchiectasis. Stretching of respiratory muscles will induce or strengthen coughing. Cystic fibrosis and bronchiectasis are the prototypical disease for which specific attention to airway clearance is effective. Directed, huff, or forceful coughing is more effective than usual or the irregular sometimes painful cough that accompanies bronchiectasis. These techniques can be learned or practiced with a respiratory care practitioner (RCP). Traditional "chest physical therapy" including postural drainage (positional to include gravity-assist) with chest clapping (hand or mechanical percussor) has been widely practiced but is time and labor intensive (requires a trained companion or medical professional assistant). Newer modalities, after some training in their use, do not require assistance. They include positive expiratory pressure resistance devices, sometimes with an additional flutter valve. High frequency chest wall oscillatory (HFCWO) "vest" therapy allows many of the advantages of CPT but often more comfort, are home-based, and can be practiced without an assistant. The older air bladder vest utilizes an electrical generator to inflate and deflate air bladders that provide oscillatory waves to the chest. The pressure of the inflated bladders may be uncomfortable for some individuals and there is the need to be near an electrical outlet for the generator. Available and in use for several years now, a newer, and perhaps more accommodating device technology operates on a mechanical oscillator principle. Battery powered motors in the vest create direct oscillatory forces to the chest wall. There is no squeezing of the chest wall. Portability is a distinct advantage and this HFCWO can be performed during walking or performing daily activities. This device more closely mimics traditional CPT techniques.

RT: How would you suggest educating patients and clinicians on bronchiectasis and the role of airway clearance therapy?
AB: Respiratory care practioners play a key role as they are trained and charged with setting up and administering inhaled medications and performing airway clearance techniques. They are educators for patients and caregivers regarding the best strategies.

RT: What are the most important take-home points for clinicians and patients on this topic?
AB: For clinicians, consider bronchiectasis when patients complain about chronic cough or give a history of lower respiratory infections or pneumonia. The chest CT is the key to confirming the diagnosis. Presume that symptoms of an exacerbation are likely manifestations of bacterial infection and treat promptly. Airway clearance is a mainstay of acute and chronic management. Request respiratory care educator(s) to help identify the most comfortable, effective and convenient airway clearance strategy.

For patients, do not be afraid to describe the frequency of cough, the color and consistency of expectorated phlegm or even share a specimen for examination placed in a covered container. Call or come to your caregiver within 24-48 hours of a change in sputum color or tenacity, worse shortness of breath, or increased fatigue Early antibiotics may be needed. Perform some form of exercise 3 or more times/week. Ask about or utilize specific airway clearance modalities that fit your needs best.

Aerosol Deposition Measurements with ODAPT Mask Adapter

Rym Mehri, PhD[1], Kenny Lee Slew, MASc[1], Abubakar Alatrash, MSc[1], Edgar Matida, PhD[1*], and Frank Fiorenza, RRT, BHSc[2]

Abstract

Background: Aerosol is commonly used to deliver therapeutic drugs to patient suffering from asthma and chronic obstructive pulmonary disease (COPD). The purpose of this in vitro study is to characterize the effect of using the EcoMask facemask and the ODAPT adapter with the Spiriva Respimat Soft Mist Inhaler (SMI) in different environments.

Methods: An 8-stage Andersen cascade impactor, enclosed in a controlled environment, was connected in-line with a flow meter and a vacuum pump to simulate the steady inhalation of a healthy adult. The Spiriva Respimat SMI was tested at a flow rate of 28.3 L/min, with and without the use of the add-ons (ODAPT adapter and EcoMask facemask). The facemask was mounted on a 3D printed face which was modeled after an adult subject. The experiment was performed in normal (40-50% relative humidity) and humid (>90% relative humidity) environments. The aerosol depositions were then analyzed using a UV-visible spectrophotometer to obtain the particle size distribution of the medication in the cascade impactor.

Results: The particle size distribution was found to shift towards larger aerosol diameters with increasing relative humidity as a result of different water evaporation rates. Furthermore, a maximum of 10% drug delivered via the Respimat SMI was lost when using the add-ons. However, the aerosol deposition in the lungs was found to be 38.8-34.1%, which is similar to measurements without the use of add-ons.

Conclusions: For patients requiring a mask, the use of the EcoMask facemask and the ODAPT adapter is considered to be effective to help administer the medication, as this results in a difference in aerosol deposition of only approximately 7% under normal conditions.

Keywords: Chronic Obstructive Pulmonary Disease (COPD), Spiriva Respimat, Soft-Mist Inhalers (SMIs), ODAPT soft-mist adapter, UV-visible Spectrophotometry, Aerosols, Particle Size Distribution

[1]Department of Mechanical & Aerospace Engineering, Carleton University, Ottawa, ON, Canada. [2]Product Development, McArthur Medical Sales Inc., Rockton, ON, Canada and Respiratory Therapy Department, University of Ottawa Heart Institute, Ottawa, ON, Canada.

Introduction

Lung diseases such as asthma and chronic obstructive pulmonary disease (COPD) affect the respiratory system, causing breathing difficulties. Therapeutic drugs, which are prescribed for the treatment of lung diseases, are commonly delivered by means of aerosols. The amount of drug deposited in the lungs is largely influenced by the characteristic of the aerosol, the delivery method, the mode of inhalation, and the architecture of the airways.[1,2] There are several methods of delivering the drugs: pressurised metered-dose inhalers (pMDIs), dry powder inhalers (DPIs), nebulisers, and soft-mist inhalers (SMIs). The Respimat SMI (Boehringer Ingelheim, Ingelheim, Germany) is a new generation of inhaler, which generates an aerosol cloud suitable for inhalation using mechanical power from a spring in comparison to the liquid-gas propellant typically used in pMDIs.[3] The soft mist travels much slower (initial droplet velocity is approximately 10 m/s)[4] and lasts much longer (approximately 1.5 seconds),[3] thereby facilitating the coordination of actuation with inhalation for proper medication delivery. Furthermore, SMIs generate finer particles than pMDIs, thus allowing a higher dose of medication (~40% of the inhaled medication)[5] to be delivered to the lungs.[6-8]

Aerosol particles below 5.8 microns are normally regarded as the fine particle fraction, which refers to the particle mass that is able to be inhaled past the mouth-throat region. It was shown that particles between 1 to 5 microns is the optimal size for pharmaceutical aerosols to reach the lower respiratory tract whereas particles larger than 5 microns tend to impact in the upper respiratory airways and are generally swallowed.[9,10] Several previous studies were performed to characterize aerosol deposition in the lungs using the Respimat SMI. In 1998, Newman et al.[11] conducted two randomized studies using the Respimat SMI, where 12 non-smoking adult subjects were administered 100 µg of fenoterol in one study and 250 µg of flunisolide in another. The whole lung deposition, which was measured using gamma scintigraphy, was found to be 39.2% and 44.6% when administered with fenoterol and flunisolide, respectively. Pitcairn et al. (2005)[12] studied the lung deposition of 200 µg of budesonide administered to 14 mild-to-moderate asthmatic patients using the Respimat SMI. The study revealed that 51.6% of the budesonide was deposited in the lungs. A similar study was performed by Brand et al. (2008),[8] where 13 male and female subjects were administered radiolabelled Berodual (fenoterol hydrobromide 50 µg/ipratropium bromide 20 µg) using the Respimat SMI. It was found that 37% of the inhaled drug deposited in the lungs.

Figure 1 shows the ODAPT soft mist adapter and the EcoMask facemask used in this study. The ODAPT soft mist adapter (McArthur Medical Sales Inc., Rockton, ON) was designed to deliver inhaled medication via Respimat SMIs to patients requiring a facemask or tracheostomy application. ODAPT allows for the use of standard masks such as the EcoMask facemask (Intersurgical Ltd., UK). In this paper, the particle size distribution of the aerosols generated by the Spiriva Respimat SMI was studied in an in vitro set up to investigate the effect on medication delivery resulting from the addition of the ODAPT adapter and EcoMask facemask. The Spiriva Respimat SMI used in this study, contains 2.5 mcg of tiotropium bromide monohydrate, per puff, which is used in the treatment of COPD. To study the effect of the add-ons (ODAPT adapter and EcoMask facemask) on delivering inhaled pharmaceutical drugs to the lungs, the soft mist particle deposition was measured at a steady inhalation flow rate and two humidity levels (40-50% and >90%), using UV-visible spectrophotometry.

Figure 1. Add-on devices tested in this study: ODAPT soft mist adapter (left) and EcoMask facemask with ODAPT adapter (right).

Materials and Methods

Experiments were performed in both normal (40-50% relative humidity (RH)) and humid (>90% RH) air to study the aerosol deposition on the ODAPT soft mist adapter using commercially available Spiriva Respimat (2.5 mcg tiotropium bromide per puff). Table 1 outlines the four test cases carried out in the current study.

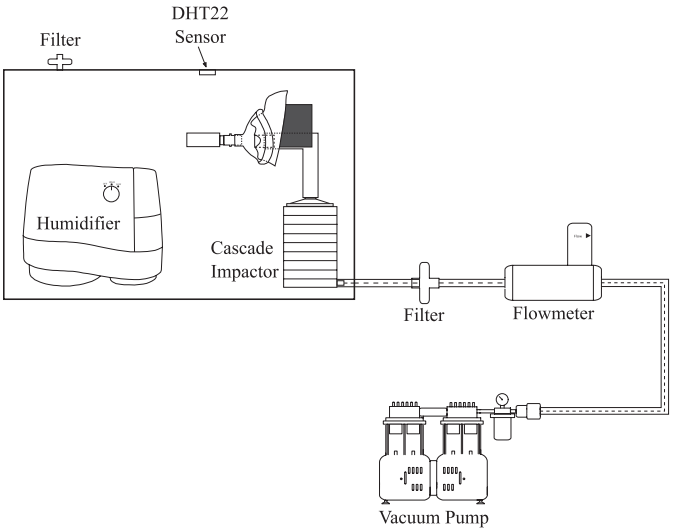
Table 1. Controlled parameters used in this study.

Test Case	Flow Rate [L/min]	Facemask	Relative Humidity [%]
1	28.3	No	40-50
2	28.3	Yes	40-50
3	28.3	No	>90
4	28.3	Yes	>90

Experimental Apparatus

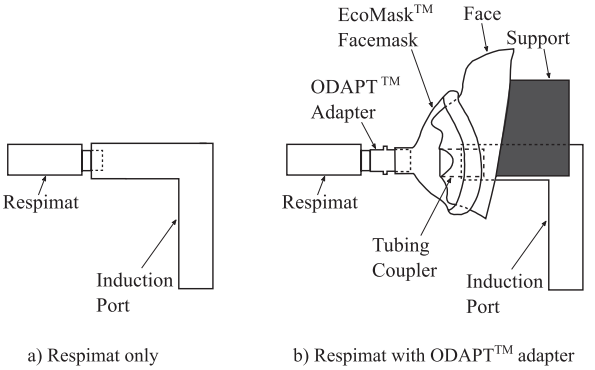
Figure 2 shows a schematic of the experimental setup used in this study. As described in Table 1, for test cases 1 and 3, the inhaler was connected directly to the induction port (IP) simulating the upper airway of an 8-stage Andersen Cascade Impactor (ACI, stages 0 to 7) (MSP Corporation, Shoreview, MN), as can be seen in Figure 3. For test cases 2 and 4, the inhaler was connected in sequence to an ODAPT soft-mist adapter (EcoMask facemask) a 3D printed face, a tubing coupler, and finally to the IP of the ACI as seen in Figure 3. The face was modeled by overlapping multiple photographs of an adult face to generate a three dimensional (3D) mesh using Autodesk Meshmixer and fabricated using the Dimension BST 3D ABS printer (Stratasys, Eden Prairie, MN). The attachment between the 3D printed face and the tubing coupler was carefully sealed to ensure no medication was released to the surroundings. In addition, a block of high density foam was mounted between the face and the IP thereby adding rigidity to the face as well as keeping proper alignment between each device.

Figure 2. Schematic of the experimental setup used in this study (not to scale).



As seen in Figure 2, the entire setup was placed in a sealed, temperature-and-humidity-controlled environment. The temperature was kept constant (22 ± 2°C) throughout the entire experiment and the humid environment was created using a Duracraft DCM200 2 Gallon Cool Mist Humidifier. A DHT22 temperature-humidity sensor (Adafruit Industries, LLC., New York, NY) connected to an Arduino UNO Rev3 (Arduino, LLC., Somerville, MA) was used to measure both the temperature and humidity of the environment. The DHT22 sensor was placed directly at the mouth level of the 3D printed face to measure the humidity of the air entering the system. To simulate the inspiratory flow rate of a healthy male subject, the method used by Alhegagi,[13] and Ogrodnik et al.,[14] was utilized, through which the ACI was connected in series to a Vital Signs RespirGard II 303 bacterial/viral filter (Vital Signs, Inc., Englewood, CO), a Brooks Mass Flow Meter 5863S (Brooks Instrument, LLC., Hatfield, PA), and a Welch Dry Vacuum Pump 2585B (Welch-

Figure 3. Schematic of the experimental setup used for (a) Respimat only (Test cases 1 and 3) and (b) Repimat with the ODAPT soft mist adapter and the EcoMask facemask (Test cases 2 and 4).



Ilmvac, Niles, IL). The filter was placed between the ACI and the flow meter to collect any unwanted particles leaving the ACI. The flow meter was connected to a National Instruments Data Acquisition USB-6009 device (National Instruments Corporation, Austin, TX) and the readings were recorded with LabVIEW software. The flow rate was monitored and maintained at 28.3 ± 0.3 L/min.

Experimental Procedure

Prior to each experiment, each device under test was washed with dish soap, rinsed with water, and allowed to air dry. The cascade impactor was assembled and the experiments were connected as described previously. The Spiriva Respimat inhaler was primed by releasing 5 puffs in open air for first time use, and loaded onto the respective device. For test case 2 and 4, the humidifier was turned on for 30 minutes to allow the relative humidity to reach a steady 98-99%. The vacuum pump was then run at a flow rate of 28.3 ± 0.3 L/min for at least 15 minutes to allow the flow to settle before starting the experiment. Twenty actuations of the Respimat were used with a 30 second intervals between each actuation. The vacuum pump was left running for an additional 60 seconds to allow the medication to properly deposit on the plates of the ACI.

The experimental setup was then disassembled and prepared for washing. The ACI deposition plates were placed into separate Petri dishes with 15 mL of distilled water and were shaken for 1 minute each. The face, facemask, and ODAPT adapter were carefully cleaned with 10 mL, 10 mL, and 8 mL of distilled water, respectively. The induction port (IP) only (for test case 1 and 3) or the IP and the tubing coupler (for the test case 2 and 4) were washed with 15 mL of distilled water. Each component was left in their respective solution for 2 hours to allow for a consistent dissolution of the medication.

Absorbance Measurement

The deposition of the tiotropium bromide monohydrate for each test case was then determined by measuring the absorbency of each wash solution using the Agilent 8453 UV-Visible Spectrophotometer (Agilent Technologies, Santa Clara, CA). A calibration curve was necessary to relate the measured absorbency to the concentration of tiotropium bromide monohydrate. To generate such curve, a stock solution of tiotropium bromide monohydrate and distilled water (using 25 mL) was prepared from 13.9 mg of pure tiotropium bromide monohydrate (Sigma Aldrich Canada, Oakville, Canada). The stock solution was then diluted to known concentrations and the absorbency of these standard solutions was obtained using the Agilent spectrophotometer. It was found that the tiotropium bromide monohydrate has an absorption wavelength of 237 nm.

Prior to measuring the absorbency of the wash solutions, each cuvette was washed 3 times with distilled water and primed 3 times with 0.5 mL of the wash solution under test. At least 2 absorbency readings were taken for each sample of the wash solutions. The concentration of tiotropium bromide could then be found using the calibration curve. The mass deposition and particle size distribution can therefore be calculated.

Data and Statistical Analyses

The drug deposition results were expressed as a percentage of the total recorded medication. The mean ± SD of the drug deposition were evaluated from at least 5 repeats for each test case. To ensure the reported results were statistically significant, t-tests were conducted for the drug deposited in the lung. For each test case, a t-value was calculated using the following equation:

$$t = \frac{\overline{X} - \mu}{S / \sqrt{n}}$$

where n is the number of samples, $\overline{X}$ is the sample mean, and S is the sample standard deviation. The hypothesis variable μ is assumed to be the expected percentage drug delivered to the lung (μ = 40%). P-values of <0.05 were considered statistically significant. Calculations were done with MATLAB R2014b software (MathWorks, Natick, MA).

To characterize the particle size distribution (PSD), the mass median aerodynamic diameter (MMAD) and the geometric standard deviation (GSD) were used. MMAD, which is based on a model that assumes a log-normal distribution of the particle size mass, is determined at the diameter corresponding to the 50th mass percentile (D_{50}). GSD describes the spread of the data in the distribution and is evaluated under the log-normal distribution using the following equation.

$$GSD = D_{84}/D_{50} = D_{50}/D_{16} = (D_{84}/D_{16})^{1/2}$$

where D_{16} and D_{84} are the diameters corresponding to the 16th and 84th mass percentile, respectively. It should be noted that all the PSD data were converted in terms of percentage of the total mass recovered at the different stages and IP of the ACI as well as at the respective add-ons used during the experiment.

Results and Discussion

Particle size distribution

Aerosol size measurements, released from the Spiriva Respimat inhaler (without mask), were compared under normal and humid conditions. Figure 4 shows the cumulative aerosol distribution (the value at the cut-off of 10 µm represents the mass fraction of all particles below 10 µm) for both conditions with their associated standard deviation displayed as error bars. As can be seen, larger amount of fine particles with diameters less than 4.7 microns (representing stages 3 to 7 in the Andersen Cascade Impactor, ACI) are obtained at the lower relative humidity. This shift in particle distribution, which was also observed by Ziegler and Wachtel,[15] and Martin and Finlay,[16] is due to evaporation or condensation where the particles gain or lose mass from their surface.[9] It is conjectured here that the droplet size distribution measured at 90% RH (relative humidity) closely resembles the distribution generated by the inhaler. For the 40-50% RH conditions, generated inhaler droplets will experience a different evaporation rate, thus changing the measured size distribution.

Table 2. Particle size distributions of aerosol from Spiriva Respimat inhaler under normal and humid conditions.

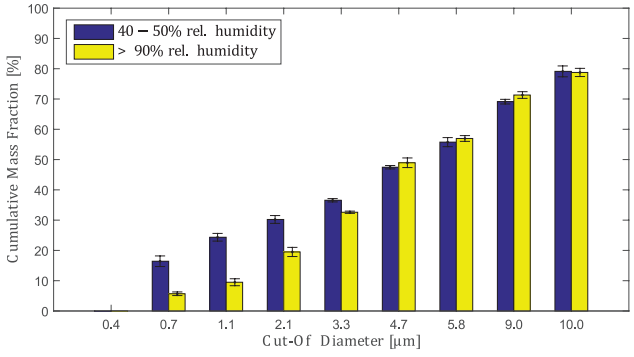
Condition	Relative Humidity [%]	MMAD [µm]	GSD [-]
Normal	40-50	5.0 ± 0.5	7.5 ± 0.5
Humid	>90	4.8 ± 0.2	2.8 ± 0.2

Table 2 summarizes the MMAD and GSD results for both normal and humid conditions, and their respective standard errors. Although there is a shift in the PSD due to the humidity effect, the difference in MMAD under normal (5.0 ± 0.5) and

humid condition (4.8 ± 0.2) was negligible (4.0%). In contrast, humidity had a greater impact on the GSD (7.5 ± 0.5 under normal condition compared to 2.8 ± 0.2 under humid condition) resulting in larger amount of fine particles, therefore, more drug was delivered to the alveoli.

Similarly, as can be observed in Figure 4, about 48% (48.9% for RH>90% and 47.5% for 40-50% RH) of the medication delivered by the Respimat SMI deposited in the tracheo-bronchial and alveolar regions (aerosol with diameters between 0.4 µm and 4.7 µm, ACI stages 3 to 7), which are sometimes referred to as the lung.[18] During the clinical study performed by Newman et al.,[11] on average 39.2% and 44.6% of fenoterol and flunisolide deposited in the lung, respectively. The slight difference in deposition obtained was mainly due to the steady inhalation rate (in addition to the usage of the induction port to simulate the medication losses on the actual mouth-throat-trachea geometry of patients) used in the current study as compared to the inhalation technique described in Ref.,[11] where the subjects inhaled slowly and deeply with a targeted rate of 30 L/min, and held their breath after inhalation for at least 10 seconds.

Figure 4. Aerodynamic particle size distribution under normal and humid conditions.



Aerosol deposition on ODAPT add-ons

To assess the effect on medication delivery when using the ODAPT add-ons, aerosol deposition measurements were conducted via the Spiriva Respimat SMI. Figure 5 shows the effect of the facemask as percentage deposition of tiotropium bromide monohydrate at an inspirational flow rate of 28.3 L/min for the normal (Figure 3(a)) and humid (Figure 3(b)) environments. Each test case was performed at least 5 times with the error bars representing ± one standard deviation (SD) of the experimental measurements. The aerosol depositions were measured at normal (40-50%) and humid (>90%) conditions, as shown in Figure 5(a) and Figure 5(b), respectively. As can be observed, the percent aerosol deposition on the walls of the ODAPT add-ons is about 23% and 20% of the medication delivered at the normal and humid conditions, respectively. However, when taking into account the decrease in aerosol deposition along the IP (simulated upper airway) walls, the medication loss was no more than 10% when using the ODAPT add-ons.

The amount of tiotropium bromide monohydrate deposited in the lungs (ACI stages 3 to 7 combined) is summarized in Table 3 as percent deposition (PD), where the relative percent loss was calculated with respect to the measurements without add-ons, given as $([PD_{nomask} - PD_{mask}] / PD_{nomask}) \times 100$. In spite of the medication losses on the walls of the add-ons, 44.1% and 38.8% of the medication was delivered to the lung (with mask) under the normal and humid conditions, respectively, which corresponds to previous studies.[8,11,12] Therefore, based on the lung deposition measurements, minimal therapeutic drug loss is achieved when using the ODAPT facemask and adapter. Furthermore, the addition of the ODAPT add-ons affected the inhaled drug delivery to the lungs by 7.0% under normal conditions and 20.7% under humid conditions when compared against the experiments without the mask (see again Table 3). Also, under normal conditions there was a greater percent deposition of medication in the stages 6 and 7 lung segments when using ODAPT at normal humidity conditions (see Figure 5(a)). The reason for the larger difference under humid conditions is due to the change in aerosol size distribution (same MMAD but different GSD, with more fine particles, $d_p < 4.7$ mm). This increases the chance of aerosol deposition on the ODAPT add-ons and thus lowering proportionally the deposition in the lungs.

Figure 5. Percent deposition of medication with and without add-ons at a constant temperature of 22 ± 2°C and relative humidity levels of (a) 40-50% and (b) >90%.

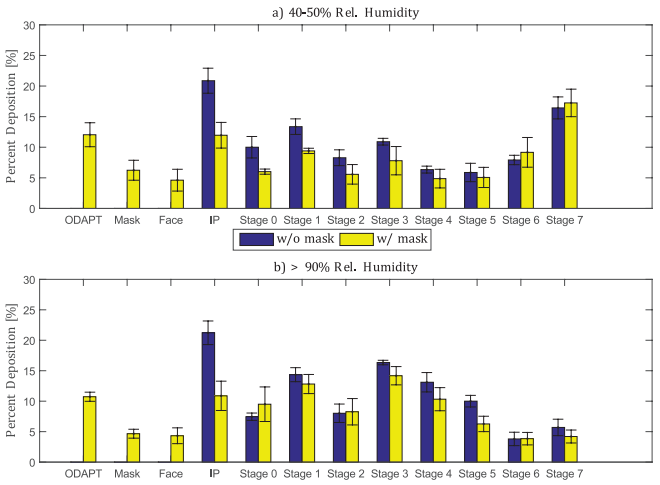


Table 3. Percent and mass deposition comparison with and without add-ons.

	No Mask	Mask	% loss
Percent deposition in lungs at relative humidity of 40-50% (SD) [%]	47.5 (4.0)	44.1 (3.2)	7.0
Percent deposition in lungs at relative humidity of >90% (SD) [%]	48.9 (2.0)	38.8 (3.5)	20.7

Conclusion

The current study showed a change in the Respimat SMI particle size distribution in a humid environment (>90% relative humidity, RH) when compared against normal conditions (indoors, air conditioned environment, 40 to 50% RH) due to droplet evaporation differences. The addition of the ODAPT adapter and facemask, to help deliver the medication to patients requiring a mask, was found to be effective under normal conditions (44.1% lung delivery with mask compared against 47.5% without mask). Increase in humidity levels (to >90% RH) will reduce lung delivery from 48.9% (without mask) to 38.8% (with mask). Nonetheless, 39-45% of the inhaled medication was delivered to the lungs, which is still quite significant when compared against common pressurized metered dose inhalers.

Acknowledgements
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Clinical and Technical Advances to the Forced Oscillatory Technique — a Long-Established Technique with a New, Novel Approach

Roberto "Roby" Perissin

Forced Oscillation Technique, the history and the advances today

FOT (Forced Oscillation technique) is a well-established, validated method originally appearing in the literature in the 1950's. The basic principle superimposes an oscillating pressure waveform, typically generated by a loudspeaker, during normal, tidal breathing. This gently "force" is transmitted on to the patient airway at different frequencies, with the lowest frequency reaching the small, peripheral airways, and the higher frequencies to larger, central airways.

The lung's structural and mechanical properties react to this external, oscillating, multi-frequency pressure allowing the device to measure the Impedance (Zrs) of the lung, which, much like spirometry, represents how air flows in and out of the lungs.

Figure 1. the Resmon Pro Full

The *Forced Oscillation Technique* (FOT) has evolved significantly and the culmination of innovation and the latest technological advances are incorporated in a new device, the Resmon PRO FULL (see figure 1). The popularity of this new, diagnostic device is reflected by numerous peer-reviewed publications. The Resmon PRO FULL is the result of more than a decade of research conducted by the Medical Engineering Department of the Politecnico University in Milan (Prof. Raffaele Dellaca' et al), alongside several clinical centers from Europe, the US and Australia.

Roberto "Roby" Perissin is the Vice President, Worldwide FOT and Asthma Management Business Development, MGC Diagnostics, St. Paul, MN.

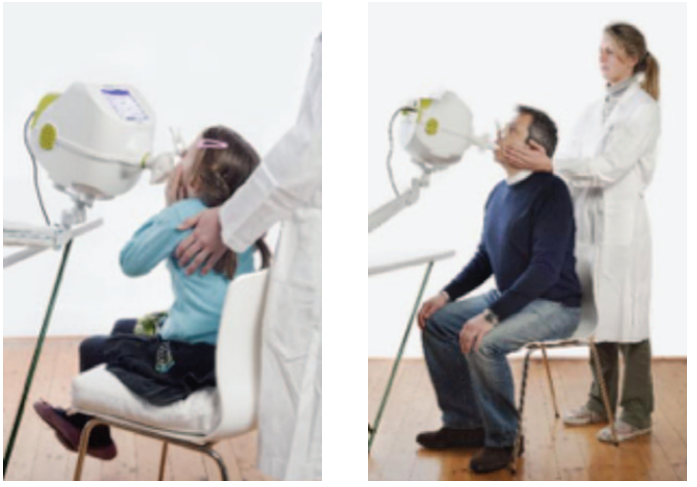

Figure 2. the Resmon Pro in use, tidal breathing testing

The Resmon™ Pro FULL system is founded on established, standardized methodologies while incorporating the latest technology and novel patented algorithms. Ease-of-Use and simplified data evaluation result in a quick & easy diagnostic test suitable for use in a diverse patient population from young children to the elderly.

This specialized device allows airway assessment via a unique 'within-breath' analysis of both inspiratory and expiratory parameters to determine:

- Location of airways obstruction.
- Expiratory Flow Limitation at rest.
- Quantitative assessement when compared to normative data.
- Reversibility of the airflow obstruction.
- Hypersensitivity of the airway.

What does Resmon PRO FULL measure:

Resmon Pro FULL features 3 modes of measurement to optimize the results according to the degree of obstruction of the patient.

- Single frequency modes suitable for very young children and severe COPD and Asthmatic adults with very high airways resistance,
- Specialized 5-11-19 Hz mode for all adults, with moderate to severe obstruction, and
- Traditional Pseudo-Random Noise mode

Resmon Pro FULL, measures the real-time Impedance (Zrs) and its components: Resistance (Rrs) and Reactance (Xrs). The device features a special algorithm, which identifies and discards

non-physiological breaths, so that only technically acceptable breaths, typically 10 accepted breaths, are sufficient to obtain a reliable measurement.

Central and Peripheral Components of Airway Obstruction:

Resistance (Rrs) provides information reflecting the degree of airway obstruction, comparable to FEV1, but measured at rest during normal, tidal breathing and similar to FEV1, Rrs reflects central airways obstruction. Rrs can be measured at different oscillating frequencies and if decreased at higher frequency ("frequency dependent"), is indicative of heterogeneous (mixed) obstruction.

Reactance (Xrs) enables the clinician to determine how effectively the deep lung is ventilated, or simply, how well air reaches the peripheral airways. Changes in peripheral obstruction and/or airway compliance may affect Xrs, and similar to FEF50-75, Xrs falls below predicted values at low oscillating frequencies in conditions such as peripheral obstruction, tidal expiratory flow limitation, alveolar gas trapping and chest wall restrictions (ie obesity, kyphoscoliosis, pregnancy, etc).

Resistance (Rrs) and Reactance (Xrs) are both measured by Resmon PRO FULL "within-breath" capabilities and are reported as inspiratory, expiratory and total components. The literature demonstrates that improvement in traditional FOT indices after bronchodilator may be variable, particularly true if a patient has expiratory flow limitation. Inspiratory resistance is the most sensitive and provides a sensitive measurement of obstruction.

Resmon Pro FULL measures and calculates Expiratory Flow Limitation Index at tidal breathing (EFLt) by Delta Reactance (ΔXrs) which is the difference between EXP and INSP reactance at 5Hz. If this difference is greater than 2.8 $cmH_2O/L/s$), the presence of EFL — expiratory flow limitation may exist. ΔXrs is a a patented index by the Politecnico di Milano and licensed exclusively to Restech Srl, (patents: US 7325545 B2 and US 8128575 B2)

Using these parameters the Resmon Pro allows a very easy test "evaluation" scheme, see Fig 3.

Clinical Applications of Resmon Pro FOT

The Resmon Pro, with its unique modes of data acquisition, high sample rate, sensitivity and ease of use may be used clinically in the following fields of application:

- **COPD** (all patients, especially those subjects that cannot easily perform a FVL)
  - » Early identification of functional impairment
  - » Evaluate pharmacological treatment
  - » Quantify functional improvement to rehabilitation sessions, secretion mobilization procedures and during recovery process from exacerbations
  - » Assessment of resting Expiratory Flow Limitation (EFL) in severe COPD patients
- **ASTHMA** (all patients, especially those subjects that cannot easily perform a FVL)
  - » Early identification of functional impairment
  - » Screening for asthma
  - » Quantify bronchodilator and broncho-provocation response
- **AIRWAY CLEARANCE EVALUATION** (Pulmonary and Neurological Rehabilitation, Cystic fibrosis)

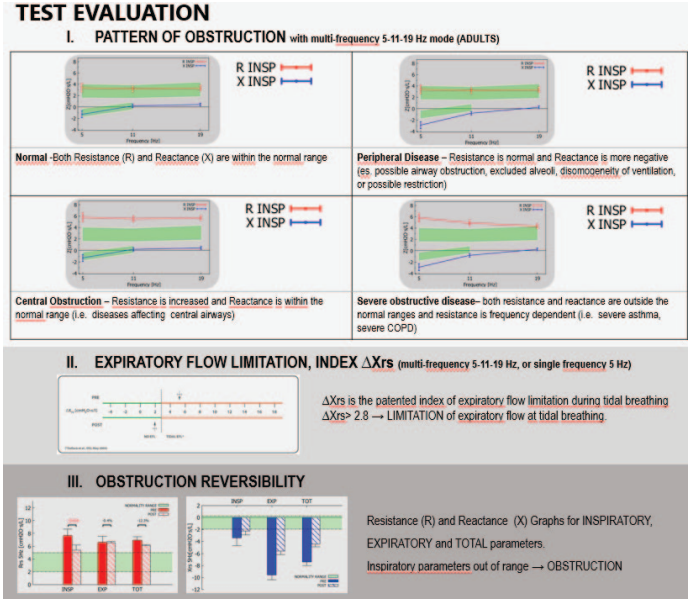

Figure 3. The Test Evaluation pathway of Resmon PRO

  - » Objectively quantifies lung functional improvement to rehabilitation sessions

Use with Spirometry

FOT does not replace forced spirometry, but both have advantages and disadvantages.
Forced Spirometry (FVL) vs. FOT can be compared

- Forced spirometry can classify severity (mild, moderate, severe) of disease with FEV1/FVC (GOLD, GINA guidelines and ATS/ERS statement). FOT has not been approved but clinical studies are underway.
- FVL cannot accurately estimate the site of airflow obstruction (large or small airways) and hence the presence and extent of small airways disease. FOT localizes the site of airflow limitation to large or small airways, assesses the extent of small airways disease, which may help the choice of inhaled medication, prescribed.
- In moderate to severe airflow obstruction, the FVL, due to the compression of the airways during the exhaled forced maneuver, does not give indication of possible restrictive processes; this is a shared concern with FOT. To confirm a diagnosis of restriction both require a Slow Vital Capacity or Lung Volumes test
- FVL requires repeated, forced, prolonged expiratory maneuvers, which may be difficult, particularly when ill. The Resmon Pro FOT needs only a 10 accepted breaths tidal breathing test and no deep inhalation.
- It is known that Forced Spirometry it is rather insensitive to mild disease and doesn't have optimal correlation with symptoms, FOT has been shown to be more sensitive than spirometry in detecting mild disease even when not present in FV loop.
- One of the major drawbacks of Forced spirometry is the operator and patient dependency.

Roberto "Roby" Perissin is the Vice President, Worldwide FOT and Asthma Management Business Development, MGC Diagnostics, St. Paul, MN, has been working in the field of pulmonary function testing since 1984, in the US first for 7 years then in Italy where he currently resides, and now works internationally.

He was trained in Respiratory Therapy and Pulmonary Function Technologies in the US and Italy in the 80's, is a renowned international expert in the field of respiratory diagnostics marketing and clinical applications as well as devices design and development, Roby consulted for the industry and contributed to the development of several commercial clinical devices and methods such as the Negative Expiratory Pressure (NEP), respiratory mechanics monitoring in ventilated patients, physical activity monitors, wearable armband for COPD etc. and other PFT devices, including now Forced Oscillatory Technique.

He currently travels and lectures worldwide on topics such as FOT in adults and pediatrics and Pulmonary Function testing, while maintaining contacts with many international Key Opinion Leaders in the adult and pediatric pulmonary field, asthma, COPD, rehabilitation.

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Preparing For Emergency Airway Management Outside the Operating Room

Chris Campbell

A hospital operating room offers optimal conditions for handling emergency airway situations — with plenty of space, staff and equipment to ensure a patient receives the best care possible.

But what happens when emergency airway management is needed after a patient leaves the operating room?

According to Lauren Berkow, MD, Associate Professor of Anesthesiology at the University of Florida College of Medicine in Gainesville, Florida, and President-Elect of the Society for Airway Management, the risks to patients and the challenges for anesthesiologists rise significantly once a patient leaves an operating room.

To help anesthesia providers better prepare when managing these patients, Berkow conducted a review that includes several recommendations on approaches facilities can use, including how to best mobilize resources and personnel.

Troubling Data

In the review, Berkow cites data from the American Society of Anesthesiologists (ASA) Closed Claims Project database and the 4th National Audit Project (NAP4) from the United Kingdom, which she says reveal a significant increase in incidence of airway-related complications associated with airway management outside the operating room and in the emergent setting.[1,2]

"The NAP4 report found that 61% of airway events in the ICU setting resulted in brain damage or death.[1] The ASA Closed Claims Project database analysis of adverse events outside the operating room found that respiratory-related events were twice as common in remote locations as in the operating room (44% vs 20%) and most often caused by inadequate oxygenation or ventilation.[2]"

Berkow writes in her review that most patients in need of emergent airway management are "critically ill, often with significant comorbidities that can affect hemodynamic stability and pulmonary reserve."

The challenge is that outside an operating room, many facilities lack consistent levels of available equipment and personnel, and often are limited in the space in which to provide airway management, Berkow writes.

"These factors should be considered when preparing for and providing airway management for these patients. The incidence of difficulty in airway management is significantly higher outside the operating room setting, and complications such as hypoxemia, aspiration, and cardiac arrest are much more common.[3,4]"

Ensuring Oxygenation

Berkow's review highlights the importance of maintaining oxygenation and ventilation.

However, for a critically ill patient who requires intubation, Berkow writes this "can be challenging, especially in patients who already require supplemental oxygen, continuous positive airway pressure (CPAP), or bi-level positive airway pressure (BiPAP). Reduced oxygen reserve may be due to a variety of factors: anemia, low cardiac output, ventilation/perfusion mismatch, cardiopulmonary pathology, obesity, or reduced respiratory effort.[5,6] A study by Mort demonstrated that critically ill patients do not tolerate interruptions in supplemental oxygen delivery and therefore are at high risk for hypoxemia during airway interventions.[7] Mort found that preoxygenation in this patient population for 4 to 8 minutes did not result in a significant increase in arterial oxygen concentration or prevent hypoxemia during airway management. Patients who cannot achieve oxygen saturation above 95% with preoxygenation have a high likelihood of desaturation during the period of apnea and intubation.[8]"

To ensure preoxygenation before airway management, Berkow writes that some routine methods in a spontaneously breathing patient include oxygen delivery via a nasal cannula or face mask with or without a reservoir bag ("non-rebreather"). The inspired oxygen delivered to the patient depends on the method employed. Positive airway pressure can be added either continuously (CPAP) or intermittently during inspiration (BiPAP) to relieve partial airway obstruction and increase the inspired oxygen, a technique often employed for patients with obstructive sleep apnea.

"Preoxygenation in the head-elevated position is recommended whenever possible,[9]" Berkow writes. "The addition of passive nasal oxygenation via a high-flow nasal cannula also has been reported to extend the period of safe apnea and prevent desaturation during intubation attempts.[9,10] Nonbreathing patients will require bag-valve-mask ventilation by the airway provider. If ventilation is difficult, adjuncts that can assist

Chris Campbell is the Senior Editor of Respiratory Therapy.

include nasal airways, oral airways, jaw thrust, or two-person mask ventilation (Figure 2). If these maneuvers fail, placement of a supraglottic airway device (SAD) can be lifesaving.[11]"

Available Devices for Oxygenation

Berkow writes about some "novel methods for oxygenation" that have come onto the market. "The Optiflow device (Fisher & Paykel Healthcare) delivers humidified high-flow nasal oxygen at a rate up to 30 L per minute, and can be applied to both the awake and sedated/apneic patient to deliver supplemental oxygen.[12,13] The SuperNO_2VA device (Revolutionary Medical Devices) delivers nasal positive-pressure and high-flow oxygen via a mask that fits over the nose. Both of these new devices can deliver nasal oxygen during airway management, unlike the traditional CPAP or BiPAP mask, and may potentially prolong apnea times in high-risk patients. The recently revised Difficult Airway Society guidelines for difficult airway management recommend the use of apneic oxygenation techniques for high-risk patients.[14]"

Planning and Backup Plans: Assessment, Equipment, and Personnel

When assessing a patient, Berkow writes, staff must gather as much information as possible, and ask some difficult questions. These include the stability of the patient, and time needed to prepare for intubation. Also, might mask ventilation, SAD placement, or intubation be difficult? These questions can help guide the creation of backup plans. Finally, what resources are necessary to manage the patient?

Aside from that is the need to predict difficulty, Berkow writes. "Many studies have examined the reliability of descriptive pre-operative airway assessments, but no single diagnostic test has been demonstrated to be highly specific or sensitive.[15,16] Some of the challenges of accurate prediction are lack of consensus for the definition of "difficult intubation" and the relatively low incidence of difficulty, even in high-risk populations. Research has found that the risk of preparing for a difficult intubation that turns out to be straightforward is low, but the risk of being unprepared for an unanticipated difficult intubation is high, so it is preferable to err on the side of caution.[15-19]"

Potential difficulty can be assessed not only with intubation but also with ventilation, as hypoxemia is a common complication in these patients. "The MACOCHA score (**M**allampati, **A**pnea syndrome, **C**ervical spine limitation, **O**pening mouth less than 3 cm, **C**oma, **H**ypoxia, **A**nesthesiologist untrained) has been described to predict difficult intubation in the ICU with 7 clinical factors.[20] Scores above 3 were associated with an increased incidence of difficult intubation, and this score has been used by nonanesthesiologists to predict difficulty in the ICU setting.[20,21]"

Stocking the Right Equipment

Berkow cites recommendations from the ASA Closed Claims Project database and NAP4 report on the use of airway carts near at-risk patients[11,22] Some of the recommended equipment includes supraglottic airway devices, flexible bronchoscope, video laryngoscope, and end-tidal carbon dioxide detectors.[22] "In addition, a portable airway bag or smaller cart that could be brought to remote locations can be useful, especially when the available space is too small to accommodate a large cart," Berkow writes. "Standardization of airway equipment (and personnel) has been demonstrated to reduce airway-related adverse events.[23] If a full complement of airway devices equivalent to what is available in the operating room is not possible due to limited resources, then SADs and a video laryngoscope, at a minimum, should be available when possible. SADs are recommended for rescue ventilation when intubation fails and play an important role in maintaining oxygenation.[11] Several studies have demonstrated increased first-pass success at intubation with a video laryngoscope in both the ICU and emergency department settings, as well as in the hands of less experienced airway managers.[24-26]"

Use of Algorithms

To create effective backup plans, Berkow writes that a variety of published algorithms exist that stress the importance of creating backup plans for airway management, including alternate methods for oxygenation, ventilation, and intubation.[11,14]

"It has been argued that in an emergency situation, these algorithms may be too complex or not readily accessible for use during emergent, stressful situations.[27,28] The Vortex Approach is a "high-acuity implementation tool" created for anesthesia providers during emergent airway management, recommended by the Australian and New Zealand College of Anaesthetists.[27,28] Unlike more comprehensive algorithms, the Vortex Approach is a graphic model that advises up to 3 best attempts at 3 nonsurgical techniques: face mask ventilation, SAD placement, or endotracheal intubation.

Staffing Recommendations

Additional personnel can assist with difficult ventilation and the implementation of backup plans, Berkow writes, so facilities should create multidisciplinary teams. "The inclusion of personnel from other specialties—such as surgery, otolaryngology, or emergency medicine—provides additional expertise as well as the ability to implement multiple backup plans, especially if a surgical airway is anticipated or necessary. Also, the collaboration and communication of a multidisciplinary airway team have been demonstrated to improve outcomes and reduce adverse airway events.[29,30]"

Conclusion

Berkow summed up her review by writing that "optimal attempts at preoxygenation, mobilization of additional resources and personnel, and availability of airway equipment are vital to ensure safe airway management in these patients. Newer and novel methods of oxygenation can be employed to maximize oxygen delivery during airway maneuvers. If available, a multidisciplinary approach is preferred. The creation of backup airway plans and use of algorithms and cognitive aids also are important steps. It is important to anticipate and prepare for difficulty to increase the chances of success and avoid complications."

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Using the Vivo 50: Reducing Hospital Re-admissions with NIV and End Tidal CO_2 in COPD Patients at Home

Wesley Arnold, RRT, and Michael Bowen, RRT

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is becoming an increasingly problematic healthcare issue in the United States. A study done in 2005 found COPD was causing 1.5 million emergency room admissions, 725,000 hospitalizations yearly, with estimated costs approaching $60 billion — which led to the decision by the US Centers for Medicare and Medicaid Services (CMS) to expand its Hospital Readmission Reduction Program (HRRP), part of the Affordable Care Act (Centers for Medicare & Medicaid Services), to include the COPD diagnosis (Feemster & Au, 2014). Today hospitals are being penalized by CMS for COPD readmissions occurring within 30 days of discharge via the HRRP. Hospitals stand to be penalized up to 3% of the irregular reimbursements for excess readmissions (Advisory Board, 2016). These penalties on hospitals have generated an increased demand for DME providers to become even more involved and concerned with therapies directed at meeting the clinical needs of the patient in the home.

Capnography (measurement of $EtCO_2$) is fairly new to the durable medical equipment industry and has been received with some scepticism as there are no billable codes for this modality. However, the potential benefits for capnography include a clinical perspective into the patient's condition which was not possible prior to the development and integration of $EtCO_2$ measuring modalities. With capnography monitoring in the home, clinicians have a chance to intervene in the patient's care prior to exacerbations occurring.

When clinicians utilize $EtCO_2$ in the home setting, less hospital re-admissions occur.

Per AARC Guidelines capnography may be indicated for evaluation of $EtCO_2$ gases, monitoring increases in severity of pulmonary disease, monitoring for patency of the airway and circuit (correct placement of trach, etc.), efficiency of the ventilator, and other indications (McArthur, 2003).

Non-invasive Mechanical Ventilation (NIMV) has been shown to decrease readmission rates in COPD patients (Murphy, PhD, et al., 2017). $EtCO_2$ monitoring of ventilator patients

has been proven to be an effective tool in monitoring hemodynamic changes in patients in acute-care settings. This paper aims to study how $EtCO_2$ monitoring, specifically with the Breas Vivo 50 ventilator, affects hospital readmission and clinical outcomes for patients in the home-setting.

Case presentation

Capnography is often done by nasal cannula sampling, mouthpiece sampling, or in-line with a ventilator circuit. All readings were collected via in-line sampling within the ventilator circuit. The test group was comprised of 15 patients who were placed on Breas Vivo 50 ventilators with integrated monitoring continuously for 30 days. Each of the 15 patients have the diagnoses of acute on chronic hypercapnic respiratory failure secondary to COPD. Each patient had more than two hospital admissions in the last 6 months. All patients were setup upon discharge from a hospital readmission. Each patient was setup in PSV (TgV) mode (pressure support ventilation with target volume). Each patient was instructed to use the Vivo ventilator for greater than 8 hours a day and document the $EtCO_2$ daily approximately the same time each day. Each patient was provided education regarding the $EtCO_2$ monitoring. Patients were instructed to call in if their $EtCO_2$ went 10 mmHg above their initial baseline reading. Alarms were set so the ventilator would alarm if the $EtCO_2$ went 10 mmHg above the initial baseline $EtCO_2$.

Patients from both groups were called 24-hours after set-up, had clinical visits 2-weeks and 4-weeks after set-up (Table 1).

For our control / comparison group, for 30 days we studied 25 patients with COPD and Chronic Hypercapnic Respiratory Failure discharged from hospital admissions that were setup on

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Table 1. $EtCO_2$ readings for 30 days in mmHg: Initial refers to the $EtCO_2$ reading at initial setup

$EtCO_2$	Initial	Lowest	Highest
A	45	40	47
B	44	36	50
c	53	44	52
D	42	31	44
E	34	33	40
F	42	33	44
G	47	45	47
H	55	47	54
I	51	47	51
J	54	46	52
K	54	52	55
L	40	35	48

the Breas Vivo 50 ventilator with PSV(TgV) mode, but without $EtCO_2$ monitoring. All education and equipment provided was along identical guidelines from the test group except for $EtCO_2$ monitoring. We were given clinical support via Dr. Rami Arfoosh who was available for consult before and during the process of our data collection.

Conclusion

From our control group (no $EtCO_2$ monitoring), 12 patients were readmitted with hypercapnic respiratory failure consequent to COPD exacerbation. Several of these patients were readmitted prior to the 2-week clinical visit while several made it past the 2-week visit, but none who were re-admitted made it past the 4-week visit. There were no patients from the test group admitted to the hospital for exacerbation of chronic respiratory failure consequent to COPD, or for any other issue. Patients with $EtCO_2$ monitoring were more engaged with their own care due to the diagnostic data they could utilize in their own care management. They were also more compliant, had higher daily usage, and demonstrated a more comprehensive understanding of the ventilator role in their care. Their caregivers (family, friends, and others involved in the patient's care) were more supportive of the use of the device due to the $EtCO_2$ giving them visual representation of the effectiveness of the ventilator. Our clinicians were given the opportunity to intervene in several instances which may or may not have contributed to the lack of readmissions.

There were two instances where the $EtCO_2$ alarm signalled, the patient called into our local branch, and with troubleshooting via phone our clinicians discovered the patient had been omitting their nebulizer medication therapies. Clinicians were able to re-educate those two patients on the importance of nebulized medication and likely prevent further harm. Each patient was contacted again after 48-hours and the hypercapnia (measured by the $EtCO_2$ monitor) was resolved back to normal levels. When clinicians utilize $EtCO_2$ monitoring in the home setting, less hospital re-admissions occur. We believe causality is most likely related to interventions brought about by clinician interpretation of $EtCO_2$ readings.

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Lung Protection Strategies – A Work in Progress

Edwin Coombs, MA, RRT, NPS, ACCS, FAARC

Lung Protective Ventilation – Advances in Understanding and Bedside Execution

The importance of utilizing a lung protective strategy during mechanical ventilation cannot be understated. Challenges to our understanding as to what is truly "protective" remains in the forefront of discussions and can only be answered by continued research and education. In time, through a high degree of collaboration, open dialogue, and evidence-based decision making this should lead to a standardization of clinical practice. Recently, the published variability of applications such as APRV, HFOV, and conventional ventilation highlights the need for additional research and education for clinicians to improve clinical outcomes of patients who have ARDS or who are at risk of developing ARDS.

ARDS

Acute Respiratory Distress Syndrome (ARDS) has a reported mortality of approximately 40%.[1] Despite the landmark ARDS Network (ARDSnet) study in 2000, where the standard of care was changed as a result of the study's ARDS mortality reduction by 9%[2]; the unchanged 40% mortality over the past 17-years should not be ignored. As clinicians we should constantly seek to challenge ways in which to improve patient outcomes, and in the absence of randomized controlled multi-center trials we must follow the best available evidence.

It is well known that delayed lung protective ventilation strategies and improper mechanical ventilation settings can exacerbate ARDS, leading to more severe progression of ARDS and increased morbidity and mortality. In fact, data has shown that ARDS is no longer a syndrome to be treated but a syndrome that can be prevented.[3,4,5,6]

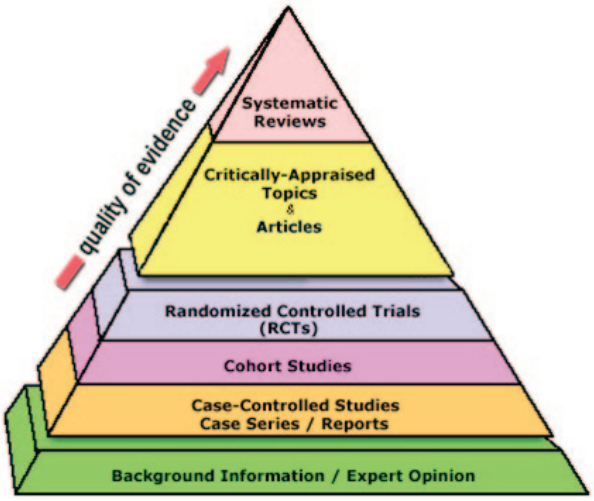
Latest Research and Information

As clinician's we are confronted with information every day. It is critically important to evaluate "evidence" based on the quality of that evidence as depicted in figure 1. This pyramid is an example of the quality and strength of facts being presented. Essential to understanding how to evaluate all of this information is key; however, there are many issues that arise which can include; out of date textbooks, experts may not have current information, traditional lectures may be ineffective, and research journals can be overwhelming at times. Given this, we tend to "fill in the blanks" with our clinical experiences which leads to our own bias or prejudice for method or approach that appears to be a best fit at the time.

Evidence-Based Approach

We often think of clinical practice as requiring a multi-center randomized control trial (RCT). While an RCT is a high quality level of evidence, these are very costly and exhaustive and may not be readily available. In addition, RCTs are simply statistical comparisons of outcome, they do not identify the mechanisms of injury or treatment. Evidence-based respiratory care is the conscientious, explicit, and judicious use of current best practice in making decisions regarding the care of individual patients. This is an integration of individual clinical experience, best available external evidence, and consistent with the patient's values and expectations. One must also remember that the best evidence will also change over time with additional research and education. It is important to remember that something that is unproven may not be wrong, but it also does not mean that it is correct either. As clinicians, we must critically evaluate the evidence as it exists and evaluate the science presented.

Rarely will one single study create a change in clinical practice, and one should not jump to immediate conclusions as most published studies can have flaws. It is advisable to find the evidence based on a multi-disciplinary systemic review that can sustain a critical appraisal and support answers to crucial questions. It is advisable to find the evidence based on a multi-disciplinary systemic review that can sustain a critical appraisal and support answers to crucial questions.



Edwin Coombs is the director of marketing at Draeger, Inc. The views expressed are that of his own and not necessarily Draeger, Inc.

Implementing Change / Execution of New Clincal Practice

While "one size does not fit all" in medicine, variability in practice can be detrimental. One should keep goal-directed therapies in mind. Having a fundamental understanding of the pathophysiology of ARDS and how to prevent or treat it should be the goal when instituting mechanical ventilation. Research breaking down the mechanical breath components and its impact on lung protection remains ongoing; however, the education and training component to execute non-traditional ventilation strategies is essential. Having this understanding would decrease the practice variability and potentially lead to a common approach that respects dynamic changes in individual patient pulmonary mechanics as severity of illness changes.

Proper training includes knowing the misconceptions and pitfalls associated with any mode of ventilation including APRV, high frequency oscillatory ventilation (HFOV), high frequency jet ventilation (HFJV), extracorporeal membrane oxygenation (ECMO), and conventional ventilation alike. Respiratory Therapists and Physicians should match the patient's pathophysiology and ventilation requirements to the modality most suited to meet the patient's needs. Further, clinical practice should remain consistent, applied and performed properly based on sound physiologic education, current evidence-based literature, and appropriateness of interventions.

Summary

Despite the lack of a randomized control trial, there is a myriad of laboratory studies and retrospective analysis available, which demonstrates APRV when applied with a time-controlled adaptive protocol can lead to improvements in the treatment or prevention of ARDS. While further study is required, this also gives us the opportunity to advance our understanding of the genesis and progression of ARDS. In parallel to this, advancing our training and educational efforts to enact change in a manner that results in the expected outcome is essential.

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Incidence of Bronchiectasis-Related Exacerbation Rates After High Frequency Chest Wall Oscillation (HFCWO) Treatment — A Longitudinal Outcome-Based Study

Chet E Sievert, Jr and Caroline A Beaner

Abstract

Background: Several recent studies have shown a significant reduction in exacerbation rates in non-cystic fibrosis bronchiectasis (NCFB) patients who received high-frequency chest wall oscillation (HFCWO) as an airway clearance therapy. Other studies have reported significant improvements in pulmonary function and quality of life in NCFB patients using HFCWO therapy. However, studies that evaluate the effectiveness of long-term HFCWO treatment in NCFB populations are more limited. The aim of this study was to investigate the effect of long-term HFCWO therapy on exacerbation rates of NCFB patients.

Methods: Thirty-nine patients with a confirmed bronchiectasis diagnosis, who were known to be compliant with their physicians prescribed HFCWO treatment regimen and meeting the inclusion/exclusion criteria, were enrolled in the study. The SmartVest Airway Clearance System (Electromed, New Prague, MN USA) was used by all patients. Exacerbations were defined as bronchiectasis-related antibiotic prescriptions, emergency department (ED) visits and hospitalization admissions. Bronchiectasis exacerbations were recorded by reviewing individual patient's medical records for one year prior to initiating HFCWO therapy and by repeated phone interview for 2.5 years after starting treatment. Each patient served as their own control. Exacerbations recorded in the first year prior to starting HFCWO treatment were compared to the 2.5 years after starting HFCWO treatment using descriptive statistics. P values were calculated by paired t-test.

Results: Bronchiectasis-related exacerbations were significantly reduced with HFCWO therapy; the incidence of hospitalizations was decreased by 42% (P=0.007), ED visits by 75% (P=0.008) and antibiotic prescriptions by 38% (P=0.0005). Sixty-eight percent of study participants reported, at will, a significant improvement in their quality of life and a reduction in the severity of their exacerbations.

Conclusions: Previous reports of significant decreases in exacerbation rates in short-term (1 year) HFCWO studies were reproduced with statistical significance in this longer-term (2.5 year) study. Longitudinal evidence, as demonstrated by this study, further supports using HFCWO in the treatment of NCFB patients to improve clinical outcomes and enhance quality of life.

Keywords: outcome, bronchiectasis, high frequency chest wall oscillation, HFCWO, exacerbation, quality of life

The authors are clinical researchers employed by Electromed Inc., 500 6th Ave NW, New Prague, MN 56071. The study was partially based on data located in Bronchiectasis Patient Registry sponsored by Electromed. The authors would like to thank Elizabeth Goodwin PhD for editorial support.

Introduction

Bronchiectasis is a chronic lung disease characterized by the presence of irreversible dilation and destruction of the bronchi due to chronic inflammation and recurrent infection.[1,2] The overall prevalence of non-cystic fibrosis bronchiectasis (NCFB) is about 52 per 100,000 adults and the mean age at diagnosis is 61 years.[3] The incidence of hospitalization due to NCFB is rising and is markedly increased for patients ≥50 years.[3,4] In 2005, the estimated costs for NCFB was $630 million annually in the United States.[3,5] The same study found that patients with NCFB averaged 2.0 additional days in the hospital, had 6.1 additional outpatient encounters, 27.2 more days of antibiotic therapy, and total excess medical expenditure of $5,681 (USD).[3,5]

Bronchiectasis is characterized by a repetitive vicious cycle of bronchial inflammation, tissue destruction and impaired mucus clearance resulting in bacterial infection that can permanently damage the respiratory epithelium causing a significant reduction in pulmonary function, greater dyspnea, increased hospitalizations, more antibiotic use and increased morbidity and mortality[4,6-9] People with NCFB commonly experience chronic cough and excessive sputum production. Diminished mucus clearance likely contributes to the initiation, progression and chronicity of NCFB.[10] The accumulation of mucus can lead to infection and inflammation by providing an environment for excessive microbial growth and colonization.[11] High levels of mucus in the airways are reportedly associated with increased bacterial load; in patients with NCFB, up to 64% are chronically infected with pathogenic bacteria.[12] Consequently, diminished mucus clearance can increase the risk of bronchiectasis-related exacerbations, which is directly associated with increased healthcare utilization and costs (hospitalizations, emergency department (ED) visits, antibiotics, and steroid use).[13,14]

The goals of bronchiectasis treatment are to minimize the number of exacerbations and improve a patient's quality of life by mobilizing airway secretions to enhance ventilation and reduce infection.[15,16] It is conjectured that efficient removal of retained secretions through airway clearance techniques breaks the viscous cycle of inflammation → structural tissue damage →

Table 1. Summary; incidence of exacerbations Pre and Post HFCWO therapy

	Pre-HFCWO (1 year) N=39	Post-HFCWO (2.5 years adjusted) N=39	Percent decrease	P value
Patients hospitalized	12 (30.8%)	7 (17.9%)	42%	0.007
Emergency department (ED) visits	4 (10.3%)	1 (2.6%)	75%	0.0002
Patients requiring antibiotics	29 (74.4%)	18 (46%)	38%	0.0005

Abbreviations: HFCWO, high frequency chest wall oscillations

mucus retention → infection → repeat and thereby slowing the rate of progressive respiratory deterioration.[3,17]

High-frequency chest wall oscillation (HFCWO) is an airway clearance method that creates high velocity, low amplitude oscillatory airflows through a pneumatic vest worn over the thorax, and is used for enhancing airway mucus clearance in several different diseases including cystic fibrosis, bronchiectasis, asthma, COPD, and a number of neuromuscular disorders.[18-21] A Cochrane review found HFCWO significantly improved health-related quality of life, lung function, ease of sputum expectoration, and reduced dyspnea and cough in patients with diminished mucus clearance.[22] HFCWO is approved by the FDA to "improve bronchial drainage and enhance mucus clearance in those patients who are mucociliary compromised." In addition, HFCWO is recommended by the American College of Chest Physicians (ACCP) as preventative treatment in patients with cystic fibrosis who have a similar viscous cycle of disease.[15]

A limited number of studies have evaluated the impact of HFCWO treatment outcomes in patients with NCFB.[14,23] A case review study evaluated the effectiveness of the SmartVest Airway Clearance HFCWO System (Electromed, New Prague, MN, USA) on exacerbation-related healthcare utilization and medication in subjects with NCFB after one year of therapy in a "real-world setting" without patient or treatment setting stratification.[14] The study found that one year of SmartVest therapy significantly reduced the incidence of bronchiectasis-related hospitalizations and ED visits. SmartVest was also associated with a significant reduction in the use of antibiotics and steroids. Here, we report longer-term findings using the same bronchiectasis patient registry, which include results after another 1.5 years of therapy to gain further insight into the effectiveness of long-term HFCWO therapy in reducing the incidence of bronchiectasis-related exacerbations.

Methods

This comparative, observational, retrospective, case review study included subjects with a radiographically confirmed diagnosis of NCFB who were being treated with HFCWO therapy. The study was performed in accordance with the Declaration of Helsinki and the Western Institutional Review Board which waved the necessity for review of the protocol and obtaining written informed consent from the subjects. However, all subjects were verbally asked for study participation prior to enrollment. All subjects had signed a HIPAA privacy agreement prior to the release of their medical records to the study Sponsor.

Study subjects

Included subjects had confirmed diagnosis of NCFB and had been using SmartVest for ≥2.5 years. Eligible patients also had medical records available for one year prior and 2.5 after start of SmartVest therapy and were compliant with their physician prescribed treatment regimen. Patients who had died or who were unable to be contacted by phone were excluded from the study. Compliance was determined by patient phone interviews, returned compliance report, and/or recorded clock hours in the SmartVest Airway Clearance generator.

Study design

A detailed description of the study methods has been previously published (see Sievert et al. [2016]).[14] In brief, the rate of bronchiectasis exacerbations for one year prior to the use of HFCWO were compared the exacerbation rate after 2.5 years of HFCWO therapy. Each patient served as their own control. Bronchiectasis-related exacerbations were defined as hospitalization admissions, ED visits, and antibiotic prescriptions. Exacerbations were ascertained by review of the subject's medical records for the one year prior to therapy and by repeated phone interview for the 2.5-year follow-up. Quality of life (QoL) was verbally reported at-will by the patient.

All data were summarized descriptively. The 2.5-year data were adjusted for comparison with the one-year data. A P-value of 0.05 or greater, as determined by the paired t-test, was considered significant.

Results

The initial study for evaluating exacerbation frequency following 1-year of HFCWO therapy included 59 patients; 39 of those were available for the additional 1.5-year follow-up. For these 39 patients, the use of HFCWO was associated with a reduction in the incidence of bronchiectasis-related exacerbations; after 2.5 years of HFCWO therapy the incidence of hospitalization decreased by 42% (P = 0.007), ED visits by 75% (P = 0.0002), and antibiotic use by 38% (P = 0.007) (see Table 1). Sixty-eight percent of the study participants reported, at-will, a substantial improvement in the QoL and a reduction in the number and severity of their exacerbations.

Discussion

Bronchiectasis has been previously underdiagnosed and overlooked although it is currently experiencing a surge in clinical interest. Numerous recent journal articles have described the importance of managing bronchiectasis-related exacerbations to improve patients' quality of life and reduce healthcare cost. The literature reports bronchiectasis patients are more likely to have:[32,33,34]

- More airway mucus clearance problems,
- Greater dyspnea (2nd most common symptom after productive purulent cough),
- More persistent symptoms with greater frequency (16% not recovered by 35 days),
- More pneumonia,
- Greater functional ability decline (which is an independent predictor of long-term mortality and exacerbation frequency),
- More severe exacerbations with a longer recovery time (longer hospital stays for pneumonia),

- And, most alarming, a significant potential for irreversible morbidity after an exacerbation (some patients never returning to baseline).

For these reasons, managing exacerbations can be vital to the health and well-being of NCFB patients.

The pathogenesis of bronchiectasis is well described as a vicious cycle of inflammation → airway tissue destruction → diminished mucus clearance → lung infection → repeat.[35] The authors go on to discuss the generally–accepted supposition of mucus "stasis" causing increased bacterial colonization and subsequent pneumonia. Hence, airway clearance has had a surge in interest clinically as a method of breaking the bronchiectasis vicious cycle.

This longitudinal study verifies that HFCWO airway clearance therapy significantly reduces bronchiectasis-related exacerbations including the need for antibiotics, ED visits and hospitalization admissions and that this effectiveness was maintained for 2.5 years after the initiation of treatment. The decrease in antibiotic use for pneumonia (ie, 41% ↓ in year 1 compared to 38% ↓ in year 2.5) was consistent and statistically comparable. Similarly, reductions in ED visits (ie, 63% ↓ in year 1 compared to 75% year ↓ in year 2.5) and hospital admissions (ie, 42% ↓ year 1 compared to 42% ↓ in year 2.5) were demonstrated by this study. Reductions in exacerbations and antibiotic use with HFCWO therapy has been found to greatly impact health-care costs; one study found the reduction in exacerbations translated into a 60% overall reduction in healthcare utilization and cost.[24] These findings indicate the long-term benefit of HFCWO therapy in patients with NCFB, and supports the clinical indication of HFCWO therapy as an FDA cleared treatment to improve bronchial drainage and enhance mucus clearance in those patients who are mucociliary compromised.

A randomized study by Nicolini et al. (2013) evaluated the effectiveness of HFCWO compared with traditional techniques of chest physiotherapy (CPT) in patients with non-cystic fibrosis bronchiectasis.[23] The study found that that use of HFCWO compared to CPT produced significant improvement in the inflammation parameter C-reactive protein (P<0.019), lung function (forced vital capacity [FVC] and forced expiratory volume in one second [FEV_1]; P values ≤0.006), and dyspnea. Both HFCWO and CPT were associated with significant improvements in QoL.

The benefit of HFCWO for airway clearance has also been observed in the treatment of patients with chronic obstructive pulmonary disease (COPD) or asthma. A randomized, controlled, cross-over study evaluated the effectiveness of SmartVest compared with conventional treatment in patients with moderate to severe COPD and mucus hypersecretion.[25] The study found that SmartVest therapy was associated with an improvement in sputum production (P = 0.06). An improvement in the St George's Respiratory Questionnaire including five-symptom scoring (ie, rating of cough, sputum, wheeze, shortness of breath, and exercise tolerance) was also seen.[25] In another randomized, multi-center, clinical trial HFCWO treatment within 24 hours of hospital admission in acute asthma or COPD resulted in significant improvement in dyspnea compared with the control (sham) group (70.8% control vs. 42.3% treatment).[26]

Antibiotic therapy plays a critical role in treating exacerbations of bronchiectasis once an infection has been diagnosed.[8, 27] The US Bronchiectasis Research Registry found that 41% of patients were treated with antibiotics during an exacerbation and 56% used suppressive antibiotics (oral or inhaled).[28]

The severity of bronchiectasis is associated with an increase in the use of antibiotics; one study found that radiologic severity of bronchiectasis was correlated with the number of antibiotic courses/year (P=0.002).[29] However, the use of antibiotics has major public health and therapeutic challenges, including the development of antibiotic resistance, antibiotic-related diarrhea (*C. difficile*), and toxicity.[27,30] In addition, bacterial biofilm growth can cause chronic inflammation of the airways, and makes eradication of respiratory infection by antibiotics impossible due to the inability of the drugs to penetrate bacterial biofilms.[31] Antibiotic use, particularly with systemically administered antibacterials and inhaled antibacterials, can cause bronchospasm in some patients.[30] It is clinically very important to consider, due to the lack of effectiveness data, that no antibiotic type or regimen is currently approved by the FDA for bronchiectasis-related exacerbations. Consequently, the Centers for Medicare & Medicaid Services (CMS) has not approved reimbursement for an antibiotic regimen which may result in significant economic burden to both the patient and the institution. Hence, a prophylactic therapy that would reduce the need for antibiotics would have great clinical utility for not only NCFB patients but the general population.

Although statistical significance was demonstrated, the current study is limited by its small sample size. While the healthcare and prescription medication use prior to SmartVest therapy was derived from the patients' medical chart information, the data through 2.5 years following initiation of treatment was captured by repeated individual phone interview, which was dependent upon subject recall, possibly confounding the findings. No clinical measurements were assessed, for example sputum production or lung function. We also did not collect information regarding prior airway clearance therapy, hospitalization length of stay, bronchiectasis-related outpatient visits, or changes in healthcare costs after start of SmartVest therapy.

In conclusion, this longitudinal (2.5 year) study found that the use of SmartVest continued to reduce bronchiectasis-related exacerbations with statistical significance in a non-stratified NCFB population. These findings contribute to the validation of the significant clinical utility and effectiveness of HFCWO airway clearance for the reduction of bronchiectasis-related exacerbations.

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A Multidisciplinary Approach in Reducing Pressure Injuries during the Utilization of Non-invasive Ventilation

Kenneth Miller MSRT MEd RRT-ACCS FAARC, Lucy Cascioli MSN RN ACNS-BC and Christine Hartner MSN RN

Background

The utilization of non-invasive ventilation (NIV) for both acute and chronic impaired gas exchange is a common clinical practice. While this type of therapy may help avoid more invasive treatment it is not without consequence. Non-invasive ventilation has been associated with the development of pressure injuries with rates in the literature ranging anywhere from 10 to 31%.[1] A pressure injury is defined as localized damage to the skin and/or underlying soft tissue usually over a bony prominence or related to a medical or other device. 6 Human skin is comprised of three layers; the epidermis, the dermis and the hypodermis also referred to as subcutaneous tissue. The significance of a pressure injury is based on the presentation and the depth of the injury within these layers. The depth and/or description of a pressure injury is based on definitions developed by the National Pressure Ulcer Advisory Panel (Figure 1). This staging system has been widely used in healthcare since 1989 and have recently been updated.[2]

Many factors contribute to the development of a pressure injury and these factors vary from patient to patient. In addition to direct pressure to the skin the presence of moisture and the forces of friction and shear have been linked to the development of a pressure injury.[3] A pressure injury associated with NIV is known as a medical device related pressure injury. The device, specifically the mask interface, creates the pressure which injures the skin. Moisture and heat develop on the surface of the skin between the mask and the skin which alters the skin surface and increases the potential for skin breakdown.[4] Repeated adjustment of the NIV mask in order to maintain adequate ventilation can contribute to friction and shear on the surface of the skin. The tolerance of soft tissue for friction and shear forces may also be affected by the patient's nutritional status, tissue perfusion, the presence of co-morbid conditions and the patient's overall state of health.[5]

The presence of a pressure injury can cause the patient both physical and emotional pain and it is often associated with increased morbidity and mortality.[7] Family members often share the burden of this event as they witness the patient's discomfort. The failure to prevent the development of a pressure ulcer may result in legal action on the part of the patient. Additionally, pressure injuries are considered a good indicator of the quality of care that is provided to a patient.[6] In 2008 The Centers for Medicare & Medicaid Services (CMS) announced that Medicare will no longer pay the extra cost of treating certain hospital acquired conditions including Stage 3 and Stage 4 pressure injuries.[3] Many hospitals are actively looking at ways to reduce the occurrence of pressure injuries, along with other hospital acquired conditions, to meet regulatory requirements.

The greatest risk for a NIV-related pressure injury is during the acute phase of therapy which requires continuous mask application to optimize gas exchange. The injury can occur at any point on the face where any part of the mask meets the surface of the skin. For our ICU's we most often experienced injury across the nasal bridge. The skin across the nasal bridge is different in that the third layer of skin, is absent, thus the depth from skin surface to bone is minimal and the risk for rapid injury evolution is significant.[2]

The clinical goal of NIV utilization should be both stabilization of gas exchange with the prevention of a pressure injury.[7] Preventing pressure injuries associated with NIV can be a daunting task because the population of patients that require NIV. Our patients often present with multi-comorbidities including one or more chronic diseases, medical frailty, and poor nutritional intake. Long-term steroid use is a common factor is also common in our patient population. Together these factors increase the risk for pressure injury development secondary to making the skin more fragile and prone to injury.[5]

Introduction

At our institution we noticed a significant increase in the number of pressure injuries associated with NIV from one fiscal year to the next. (24 occurrences in FY 16). To address this problem, a multidisciplinary team was formed with the goal of developing a plan to reduce the incidence of pressure injuries. The team was comprised of the following disciplines: providers who manage the patients who require NIV, critical care nurses including a member of the hospital's wound team, respiratory therapists whom manage NIV therapy and clinical educators from both nursing and respiratory. Together we performed a collaborative assessment of our current non-invasive ventilation practices.

Methods

The first step was to evaluate the current mask that was used for NIV. When evaluating other mask options we recognized the inherent limitations in mask design in that any mask designed for non-invasive ventilation would require continuous pressure against the skin. After looking all of our options the team chose

Kenneth Miller is a Clinical Educator, Dean of Wellness, Respiratory Care Services, Lehigh Valley Health Network, Allentown, Pa.

Figure 1. NPUAP Pressure Injury Stages

Stage 1 Pressure Injury	Intact skin with a localized area of non-blanchable erythema, which may appear differently in darkly pigmented skin.
Stage 2 Pressure Injury	Partial-thickness loss of skin with exposed dermis. The wound bed is viable, pink or red, moist, and may also present as an intact or ruptured serum-filled blister. Adipose (fat) is not visible and deeper tissues are not visible.
Stage 3 Pressure Injury	Full-thickness loss of skin, in which adipose (fat) is visible in the ulcer and granulation tissue and epibole (rolled wound edges) are often present. Slough and/or eschar may be visible. The depth of tissue damage varies by anatomical location.
Stage 4 Pressure Injury	Full-thickness skin and tissue loss with exposed or directly palpable fascia, muscle, tendon, ligament, cartilage or bone in the ulcer. Slough and/or eschar may be visible.
Unstageable Pressure Injury	Full-thickness skin and tissue loss in which the extent of tissue damage within the ulcer cannot be confirmed because it is obscured by slough or eschar.
Deep Tissue Pressure Injury	Intact or non-intact skin with localized area of persistent non-blanchable deep red, maroon, purple discoloration or epidermal separation revealing a dark wound bed or blood filled blister.
Medical Device Related Pressure Injury	Medical device related pressure injuries result from the use of devices designed and applied for diagnostic or therapeutic purposes. The resultant pressure injury generally conforms to the pattern or shape of the device. The injury should be staged using the staging system.
Mucosal Membrane Pressure Injury	Mucosal membrane pressure injury is found on mucous membranes with a history of a medical device in use at the location of the injury. Due to the anatomy of the tissue these ulcers cannot be staged.

NPAUP Staging Guidelines. (2018, January 19) Retrieved from http://www.npuap.org/resources/educational-and-clinical-resources/npuap-pressure-injury-stages/.

an oral-nasal mask that allowed for smoother placement on and off the patient's face. The respiratory therapists received individualized, hands-on education regarding proper fit of the mask. For patients who required NIV for longer than six hours we alternated the use of a full face mask with an oral/nasal mask in order to help redistribute the pressure across the skin surface of the face. This option was patient dependent as some patients could not tolerate the application of a full face mask. The respiratory therapist would be responsible to manage the schedule of mask rotation which would occur every four to six hours depending on the patient's clinical condition. Both the nurse and the respiratory therapist would be responsible to evaluate the skin surface when the mask is removed. The prevention of pressure injury is a complex process and requires constant vigilance to achieve success.[6]

Next, in conjunction with our skin expert, we looked at the skin barrier products that were available for use. We had experienced short term success a few years ago when we began using a lightweight foam dressing between the rim of the mask and the skin surface. However the success was short-lived. In the end we chose a gel-type of barrier which would be placed between the rim of the mask and the surface of the face. The barrier we chose offered the option of an individualized fit as it could be cut to fit each patient's facial features. The gel barrier would be applied to all NIV patients at start of therapy.

Perhaps the most important step in this process was the development of a NIV algorithmic protocol (Figure 2). We evaluated our clinical practice to assure that use of non-invasive ventilation was appropriate for the patient and that we were consistent in our practice. Developing an algorithmic protocol allowed us to guide the use of NIV across the network. Once the algorithm was developed we created an order set to match the algorithm. The new order set requires the provider to define specific clinical end-points when placing the order for NIV. These clinical end-points included the following: target SpO2 level, a maximum allowable respiratory and heart rate, and arterial pH and NIV liberation end-points (Figure 3). These defined end-points contributed to more appropriate NIV parameter adjustments with the end result of improvement in the overall clinical management of NIV. Daily rounding on the NIV patient population was conducted to ensure adherence to the algorithm and also provided opportunities for additional NIV education as needed.

After a trial period in the ICU the algorithm was moved other critical care units within the hospital. We followed the same process when providing education for all levels of caregivers who interact with patients who require NIV. Once again the education included correct mask sizing, mask application and removal techniques, review of the clinical management and specific clinical end-points for NIV failure and success, liberation criteria, and the roles and responsibilities of all the NIV team members.

Figure 2. NIV Protocol

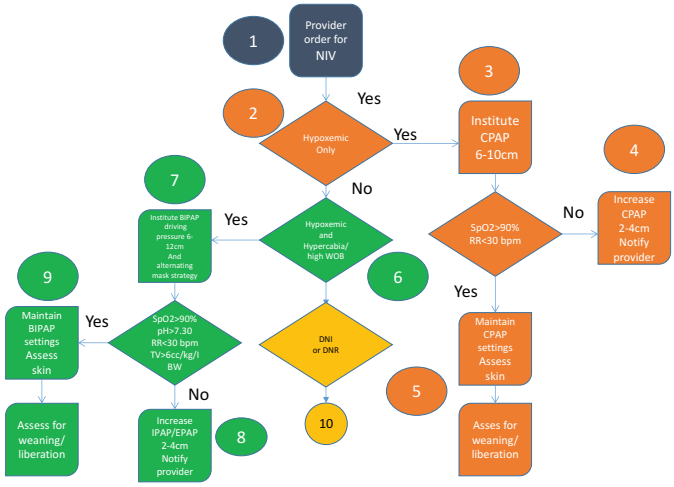
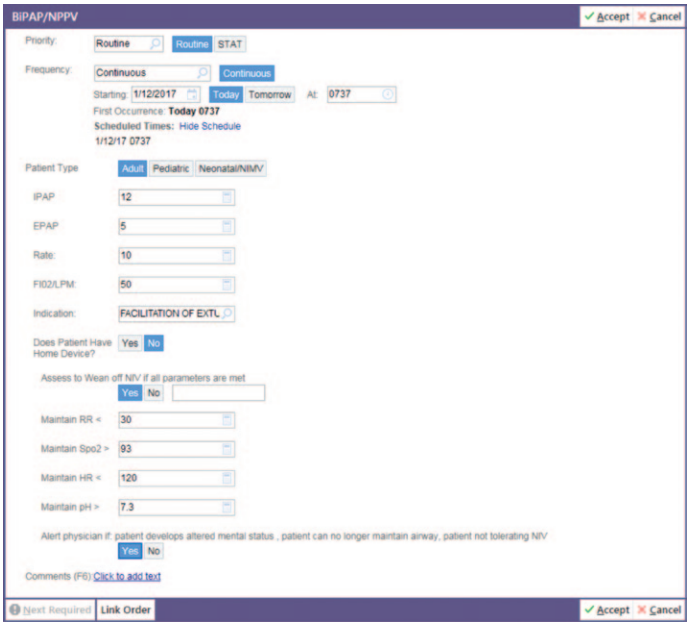


Table 1. Results - Reduce NIV Pressure Injuries

Site	FY'16 Number	GOAL	July	Aug	Sept	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	June	FY'17 Total
LVH-CC	24	16	2	2	Intervention 1	0	0	0	0	0	0	0	0	0	5
LVH-M	8	5	1	0	0	0	1	0	0	0	0	0	0	0	2

A reduction from a total of 32 injuries in FY16 to 7 during FY 17

Figure 3. Defined clinical endpoints



Results

In FY16 we reported 24 pressure injuries hospital-wide related to mask use during non-invasive ventilation. In FY17 the total number of NIV device related pressure injuries dropped to 5 (Table 1).

Discussion

What contributed most to our successful reduction in the occurrence of pressure injures? We knew from the start that there wasn't going to be a single action/intervention that would reduce our pressure injury rate. We approached the problem with three main goals; to find a mask with a better fit, to look for a more effective skin barrier and to critically evaluate how we provide non-invasive ventilation therapy to our patients. We strongly believe that involving all disciplines of care providers in the design of the protocol/algorithm was vital to its success. Each member of the team was able to contribute his or her expertise to improve the care of the patient receiving non-invasive ventilation. Thus all team members were engaged to achieve a successful outcome. Education of all members of the care team was imperative as it facilitated communication among the care team in the day to day management of the patient. Also, the development of specific NIV endpoints in terms of desired clinical outcomes was very beneficial. The endpoints became goals which, when met, would result in successful therapy for the patient. Future endeavors in this process include looking at the duration of non-invasive ventilation and its impact on ICU length of stay.

Conclusions

A pressure injury can be an undesirable side effect of NIV clinical management. All attempts should be made to minimize the occurrence of a pressure injury while the patient is receiving noninvasive ventilation. Based on our strategic process we were able to reduce the occurrence of pressure injuries significantly. As a result we advocate the implementation of a multi-disciplinary team to assess and evaluate current NIV practices and develop a strategic process to maximize patient outcomes and minimize pressure injuries.

Acknowledgement

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Recognition of Respiratory Compromise-Related Postoperative Respiratory Events with the Integrated Pulmonary Index (IPI) Algorithm

Suzanne Broens, MD, Albert Dahan, MD, PhD, and Monique van Velzen, PhD

Introduction

Respiratory compromise can be defined as a state in which there is a high likelihood of decompensation into respiratory insufficiency, respiratory failure or arrest when early identification and intervention may prevent further deterioration.[1] Respiratory compromise is a primary cause of postoperative complications, often leading to intensive care unit admission and an increased risk of brady- or tachyarrhythmias and cardio-respiratory arrest.[2] In addition to impaired central drive due to peri-operative opioid analgesia, certain patient comorbidities are associated with an increased risk of respiratory compromise.[3-5] These comorbidities include, but are not limited to: age ≥65 years, obstructive sleep apnea, chronic obstructive pulmonary disease, bronchoconstriction, idiopathic pulmonary fibrosis, pulmonary embolism, congestive heart failure, acute postoperative renal failure, diabetes, coronary artery disease and hypertension.[3-5]

Rapid recognition of respiratory events in the immediate postoperative period can reduce the risk or prevent the progression of respiratory compromise. However, spot checks of respiratory rate and peripheral capillary oxygen saturation (SpO_2) — a common care standard for monitoring patients — do not provide adequate clinical assessment of ventilatory status,[6] leaving the patient unmonitored over 95% of the time,[7] and recent literature on the incidence of postoperative respiratory events would appear to justify an enhanced patient monitoring protocol. For example, one study designed to quantify postoperative respiratory events (bradypnea and apnea) and the risk factors for these events in 68 patients ≥60 years showed that almost 80% of the patients experienced at least one bradypneic period during the 6-hour postoperative period, and almost 60% had at least one apnea event.[8] The occurrence of respiratory events in the post-anesthesia care unit (PACU) predicted a significantly higher rate of subsequent bradypneic and apneic episodes after transfer to the ward.[8] Patients with apnea had significantly larger neck circumferences than did those without apnea.[8] These results suggest that continuous respiratory monitoring of patients is warranted on the ward after transfer from the PACU, particularly for patients with risk factors such as opioid administration and a larger neck circumference.[8]

Continuous monitoring of oxygenation and ventilation using pulse oximetry and capnography, respectively, allows clinicians to identify trends in respiratory parameters not captured by intermittent monitoring and promotes timely medical intervention that may prevent respiratory arrest. The Integrated Pulmonary Index (TM) (IPI) algorithm utilizes an artificial intelligence algorithm that combines the real-time measures of four parameters (i.e., multiparametric) — end-tidal CO_2 ($etCO_2$); respiratory rate; pulse rate; and SpO_2 — into a single, easy-to-use 1-10 scale to provide an indication of changes in patients' ventilatory status.[9-10] Table 1 shows interpretive criteria. Lower numbers represent poorer respiratory status. Ten is considered normal; values between one and four reflect critical events that require intervention.

Table 1. IPI Patient Status Scale

	IPI	Patient status
	10	Normal
	8-9	Within normal range
	7	Close to normal range; requires attention
	5-6	Requires attention and may require intervention
	3-4	Requires intervention
	1-2	Requires immediate intervention

Capnography and the IPI algorithm are valuable tools for monitoring patients who may be at increased risk for respiratory compromise following surgery[11-16] and to increase the opportunity for treatment before cardio-respiratory arrest.[17] We conducted a study to evaluate the clinical utility of the IPI algorithm for detecting respiratory events in postoperative patients and to determine the incidence of respiratory events in these patients.

Patients and Methods

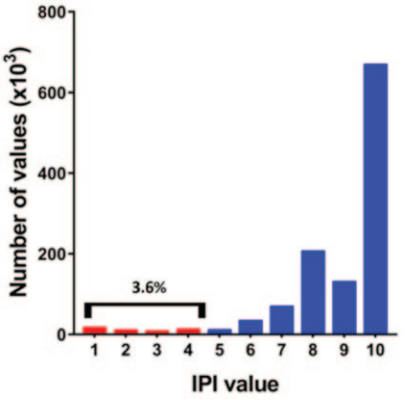
Following IRB approval and obtaining informed consent, 40 patients scheduled for elective surgery under general anesthesia were included in the study. Continuous IPI algorithm measurements (data storage frequency 0.5 Hz) using the Capnostream 20p patient monitor (Medtronic) began immediately after admission to the PACU and continued until 8 am of the first postoperative day. Known risk factors for respiratory compromise including sleep apnea and opioid administration were identified for each patient by history and chart review.

Results

Demographic data from the 40 patients are shown in Table 2.

The authors are with the Anaesthesia and Pain Research Unit, Department of Anaesthesia, Leiden University Medical Center, Leiden, The Netherlands.

Figure 1. Histogram of observed Integrated Pulmonary Index (IPI) algorithm values. IPI algorithm values were obtained at a 0.5 Hz interval and represent a data set of 1,153,427 observations collected from 40 patients. Critical IPI events, values 1-4, are labeled red.



One patient discontinued participation due to discomfort with the $etCO_2$ sampling cannula. The mean age was 57.2 years (range: 31.5 to 75.8), and the mean body mass index (BMI) was 26 kg/m^2 (range: 16.6 to 38.2). The large majority of patients received total intravenous anesthesia and opioid analgesia. The most common surgical procedure was post-mastectomy autologous fat graft.

Approximately 700 hours of postoperative IPI algorithm values were obtained, representing a data set of 1,153,427 observations with an average of 17 hours per patient (range: 13 to 22 hours); 5.8% of measurements were missing (e.g., sensor off). Thirty-nine of the 40 patients had at least one critical IPI event (defined as values between one and four), three patients displayed low IPI algorithm values during more than 15% of measurement time, and critical IPI events occurred in 3.6% of all measurements (Figure 1). These findings appeared unrelated to the presence of sleep apnea or opioid administration schedules. Although the critical IPI events likely required caregiver interventions, this was not recorded because the study was observational. Multivariate regression analysis was performed to predict the percentage of critical IPI events from age, gender, BMI and the duration of anesthesia (Figure 2). Age and BMI added significantly to the prediction. Figure 3 shows graphs of IPI algorithm recordings from three patients, demonstrating different IPI algorithm monitoring results. No serious adverse events occurred during the study.

Figure 2. Correlation plots of age (left panel) or BMI (right panel) and percentage of critical IPI events (range 1-4, as percentage of total recording period) per patient. Multivariate regression analysis was performed to predict the percentage of critical IPI events from age, gender, BMI and the duration of anesthesia. These variables predicted the occurrence of critical IPI events, $F(4,32)= 4.523$, $P = 0.005$. More specifically, age and BMI added significantly to the prediction ($P < 0.05$).

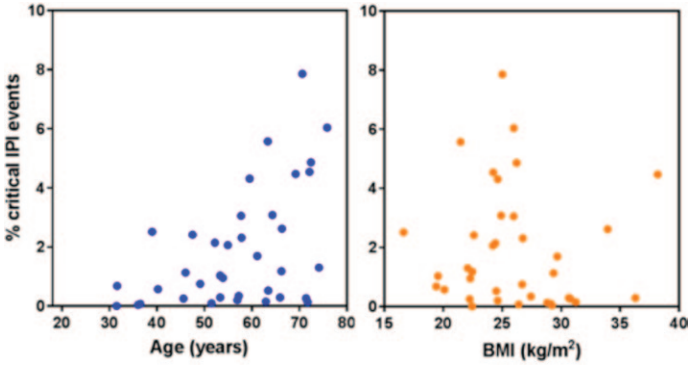
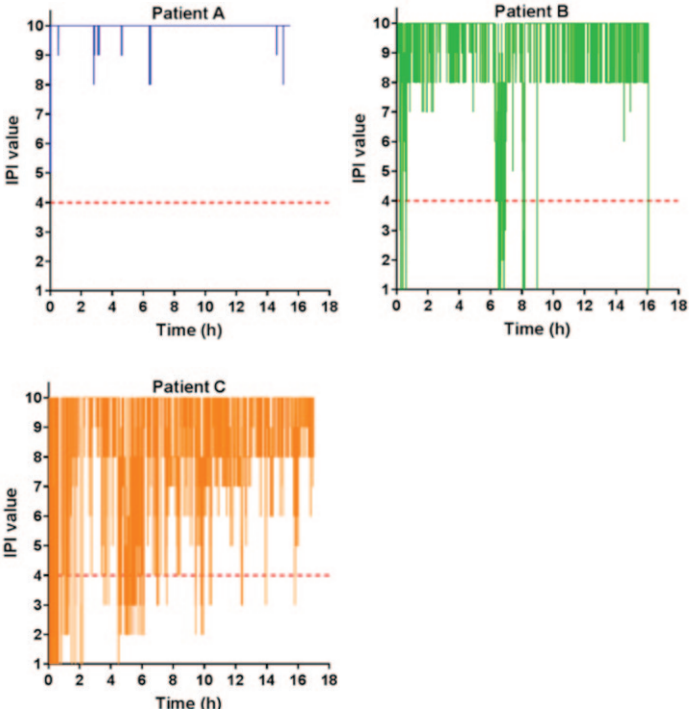


Table 2. Patient and Surgery Characteristics

Patient characteristics	
Number of patients analyzed	40
Gender (male/female)	22/18
Age (years)	57.2 ± 12.2 (range: 31.5-75.8)
Weight (kg)	80.9 ± 17.4 (range: 54.5-135)
Height (m)	1.76 ± 0.1 (range: 1.54-1.92)
BMI (kg/m^2)	26.0 ± 4.6 (range: 16.6-38.2)
Surgery characteristics	
Duration of anesthesia (min)	277 ± 146 (range: 48-659)
Type of surgery, n (%)	
General	
Nephrectomy	10 (25)
Post-mastectomy autologous	8 (20)
fat graft	13 (32.5)
Vascular	4 (10)
Other	5 (12.5)
Type of anesthesia	
Total intravenous	35 (87.5)
Balanced	5 (12.5)
Neuromuscular block reversal, n (%)	
None	30 (75)
Neostigmine	2 (5)
Sugammadex sodium	8 (20)
Postoperative pain relief, n (%)*	
None	11 (27.5)
Morphine	26 (65)
Methadone	5 (12.5)
Esketamine	1 (2.5)

*Total greater than 100% because some patients received more than one type of analgesia.

Figure 3. Example graphs of IPI algorithm recordings from three patients. (**A**) During the 17-hour recording period, no critical IPI events were observed. (**B**) Some critical IPI events were registered during the 17-hour study period. (**C**) Frequent and prolonged episodes of critical IPI events occurred during the 17-hour recording period. Critical IPI events are defined as values between 1-4; the cut-off is indicated in the graphs with a red dashed horizontal line.



Discussion

This study involved 40 patients with an average age of 57 and an average BMI of 26 kg/m^2 who were scheduled for elective surgery under general anesthesia. Following their respective procedures, most of the patients were provided pain relief with morphine, methadone or esketamine. They were monitored using the IPI algorithm in a postoperative setting for an average of 17 hours. Results from the study showed the IPI algorithm was easy to use, and almost all patients displayed at least one critical IPI event, likely requiring intervention. However, critical IPI events and low IPI values appeared to be unrelated to the presence of sleep apnea or opioid administration, which are known risk factors for respiratory compromise. In contrast, older age and higher BMI were particularly significant predictors of critical IPI events.

Conclusion

These results show that critical IPI events are common during the immediate postoperative period and demonstrate the clinical utility of the IPI values for detecting respiratory events in postoperative patients. Based on these results, interventional studies are planned to assess the performance of the IPI values as an early warning sign of respiratory compromise.

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Collecting Quality Spirometry at Home

Alex Stenzler

There is no doubt that healthcare is moving from the hospital to home. For patients with respiratory diseases, this is driven by both the need to discharge patients from hospitals as quickly as possible, and the recognition that "IF" quality spirometry data can be collected from the home, it might provide early detection of patients failing treatment, as well as provide more frequent monitoring, while lowering the institutional or physician office burden. It also would reduce the burden on patients who have to travel great distances for a test that could easily be done from home. That is a big "IF" that I believe we are on the cusp of being able to deliver on. There are many factors that can affect our ability to get quality spirometry data from the home and those of us managing patients at home might find these important to consider.

Selecting Devices

There are several critical areas that require our attention if we intend to get spirometric measurements at home that meet ATS/ERS criteria and provide data that can be interpreted and used in the treatment decision making process. As reported by McCarthy, it starts with selecting a spirometer that is capable of making measurements at home and if used correctly, will produce accurate data.[1,2]

It seems clear that to avoid the need for daily calibration, spirometers for home use should be limited to either ultrasonic or turbine based devices. These units have been demonstrated to retain their calibration for more than a year or two and still meet ATS/ERS performance criteria.[3,4] In addition, if FVC is an important parameter for identifying subjects who might be failing treatment or for diseases where FVC is an important parameter, only spirometers that meet the ATS/ERS low flow criteria should be selected.[2]

Alex Stenzler is the president of 12th Man Technologies, Inc. He was a Registered Pulmonary Function Technologist and has been working in the field of pulmonary function testing since 1968. He spent half of his career managing Respiratory Care Departments, COPD Clinics and Pulmonary Function Laboratories, or teaching pulmonary function technology as an Assistant Professor at the State University of New York at Stony Brook and twelve years at the Graduate School of Adelphi University. He has been the PI for two NIH and one DARPA grant and has extensive research experience. He has co-authored 16 peer-reviewed papers and one book chapter on pulmonary function testing. He holds 40 patents, most of which are related to pulmonary medicine.

Two other important characteristics to consider when selecting a spirometer for the home are:

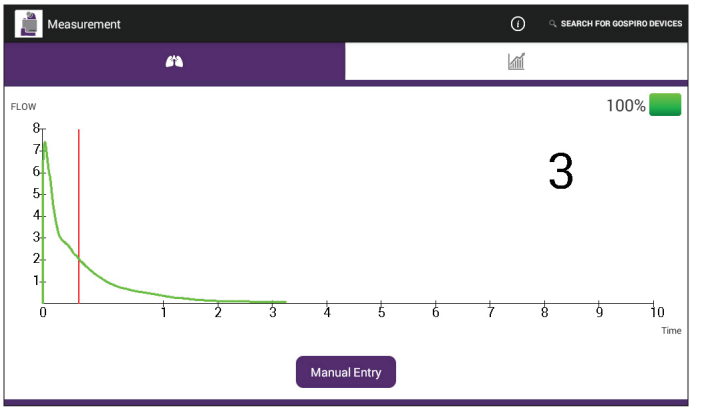
- Its having been tested and cleared specifically for home use; and
- It providing feedback to the patient as to the quality of their performance.

Not every spirometer gives the patient enough information about how they performed to correct bad efforts.[2]

Flow Time Presentation

When thinking about how to get the most reliable spirometric data from patients at home, we should give them the best tools to help them perform a good measurement. Most systems are designed for physicians and healthcare providers to interpret the output from the test, and therefore graphics are always presented as either a volume time curve or a flow volume loop. To the physician or healthcare provider, that is the presentation that they need to interpret the results and those graphs provide the visual information they need to understand the patient's disease. However, for the patient, those displays are nearly meaningless. If they see a flow volume loop, can they determine if they reached peak flow in less than 120 to 160 milliseconds? Can the patient tell if they've exhaled for at least 6 seconds? If they see a volume time curve, can they determine anything about their time to reach peak flow or know their back extrapolated volume? The two factors that a patient needs to focus on to perform a good spirometric measurement are:

Figure 1. Flow-Time trace displaying instantaneous flow versus time with countdown timer. Note the expanded time of the first second to provide the patient with the highest resolution where they need it the most. (Courtesy of Monitored Therapeutics, Inc.)



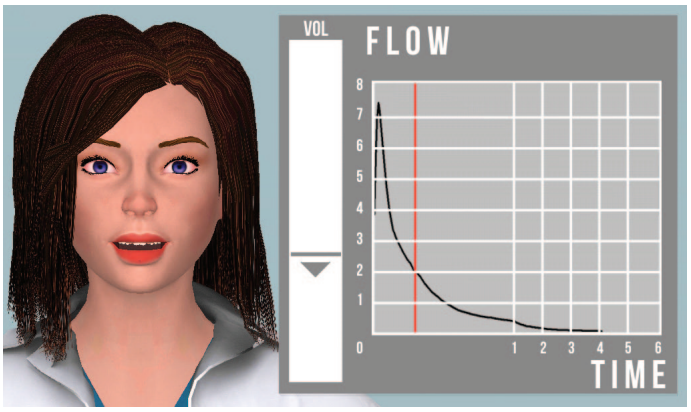
- They need to reach peak flow early; and
- They need to exhale for at least 6 seconds (or longer).

The graphical presentation to provide that information to patients therefore is not a flow volume loop or a volume time curve; it's a flow versus time curve (See Figure 1). Presenting the patient with instantaneous flow versus time, it becomes visually clear to the patient what the target for initial effort has to be to reach peak flow early in the forced exhalation. And with a time graph, it allows the patient to assure that they have exhaled for 6 seconds. In these days of digital data, it should not be necessary for physician and patients to only see the same data presentations. The flexibility of digital data can provide each with what means the most to them; flow volume curves for the physician and flow time curves for the patient.

Avatar Coaching

One recent area of interest is the use of avatars to coach patients through the spirometric maneuver. While gaming programs have been available for decades to get a patient to exhale for at least six seconds and primarily used for children, they don't provide direct, real-time verbal guidance to the patient. What we've now seen is a home spirometry system that uses a human-like avatar that talks the patient through each measurement. The availability of Bluetooth spirometers enables the avatar to watch the patient breathe on the spirometer and know exactly what the patient is doing instantaneously. This enables the avatar to coach the patient with quiet breathing and then have them take a maximum inhalation and then forcefully exhale for at least six seconds, encouraging at every point of their exhalation, just as would be done by a pulmonary technologist in a hospital laboratory (See Figure 2). The avatars know exactly where the patient is in the maneuver. The sophistication of the avatars has broadened to their ability to review how the patient performed the maneuver, telling them if they made a mistake, such as not exhaling forcefully enough or that they held their breath too long and offering feedback to improve their performance.

Figure 2. An avatar developed to coach the patient through the full spirometric maneuver in real time with posttest review and corrective action feedback. (Courtesy of Monitored Therapeutics, Inc.)



Minimizing the burden of testing

Even with measurement technology that is accurate and doesn't require patient calibration, and systems such as the described avatar to get the best efforts from the patients at home, if they don't perform the measurements, then all of these capabilities bring no value to home monitoring. To get test results, the burden to the patient needs to be as low as possible and the positive feedback as high as possible. What we know from the reported experience from several studies is that reminders work.[6,7] This is true for both medications that patients should take, as well as reminders for patients to perform tests. And the burden of the test should be low. When we think spirometry, we think "three reproducible measurements". That's because the ATS/ERS states that criteria for measurements performed in the laboratory. But patients don't go the PFT lab every day or even three times per week; they go once a year or perhaps once every three months. We need to disconnect our thinking of what is necessary for laboratory visits from what is really needed from patients at home. I believe that when you are collecting 2 to 7 measurements a week from a patient at home, as long as each measurement meets ATS/ERS criteria for a good maneuver, that a single measurement per session is sufficient. The variability of multiple measurements will sort themselves out within a few days if the changes are small and any large change can be addressed, particularly if the maneuver is good and the data immediately available for review with alarm triggers. Reducing the requirement from three forced maneuvers to one significantly reduces the time demand, but more importantly reduces the aversion to self-testing generated by the fatigue of the frequent three test requirement.

Experience with home spirometry collection

To evaluate how these technology interventions can impact the quality of home spirometry monitoring, we reviewed 2,100 spirometric measurements that were collected from 25 patients at home in a pilot self-testing program during a one year time frame. These patients averaged 84 measurements during that period. We used a GoSpiro turbine based spirometer with a Flow Time target scale for the patient to follow and an avatar to coach the patients through the maneuver. With only a single training session, we found that 82% of the measurements met ATS/ERS criteria for Forced Expiratory Time and 86% met the back extrapolated criteria for a good test as well. The time to peak flow criteria was met by the patients in 79% of measurements. Considering that previous reports have demonstrated that only 60% of spirometric studies collected in seventeen physician offices met the ATS/ERS criteria for good tests, the results from our evaluation demonstrated that home testing can outperform physician office testing.[5]

Conclusions

With more than 80% of self-administered spirometry tests by patients at home meeting ATS/ERS criteria for a good maneuver, it suggests that with use of the appropriate equipment and digital coaching technology with patient focused visual targets, high quality spirometry can be collected from patients at home that will provide meaningful and interpretable data. I believe that broader use of these technologies and further communication improvements and forecasting algorithms will realize the goal of enabling that transition from hospital to home.

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Value of Peripheral Blood Eosinophil Markers to Predict Severity of Asthma

Julian Casciano[1], Jerry A. Krishnan[2], Mary Buatti Small[3], Philip O. Buck[3], Gokul Gopalan[3], Chenghui Li[4], Robert Kemp[1] and Zenobia Dotiwala[1*]

Abstract

Background: Asthma represents a significant clinical and economic burden to the US healthcare system. Along with other clinical manifestations of the disease, elevated sputum and blood eosinophil levels are observed in patients experiencing asthma exacerbations. The aim of this study was to evaluate the association between blood eosinophil levels and asthma severity defined using Expert Panel Report 3 guidelines.

Methods: Patients with asthma diagnosis between 2004 and 2011 were extracted from the EMRClaims+ database (eMAX Health, White Plains, NY) containing electronic medical records linked to insurance claims for over 675,000 patients. The date of first asthma diagnosis was defined as the 'index date'. Patients were required to have at least 1 peripheral eosinophil test (elevated defined as ≥ 400 cells/μL) in the 12 month 'assessment' period following the index date. We classified patients as those with mild asthma and moderate-to-severe asthma based on the pattern of medication use, as recommended by the 2007 National Institutes of Health Expert Panel Report. Logistic regression models were used to determine if patients with moderate-to-severe asthma had increased likelihood of an elevated peripheral eosinophil count, after accounting for demographics and comorbidities.

Results: Among 1,144 patients with an asthma diagnosis, 60 % were classified as having moderate-to-severe asthma. Twenty four percent of patients with moderate-to-severe asthma and 19 % of patients with mild asthma had an elevated peripheral eosinophil count (p = 0.053). Logistic regression showed that moderate-to-severe asthma was associated with 38 % increased odds of elevated eosinophil level (OR 1.38, 95 % CI: 1.02 to 1.86, p = 0.04).

Conclusion: Patients with moderate-severe asthma are significantly more likely to have an elevated peripheral eosinophil count than patients with mild asthma.

Keywords: Asthma, Blood eosinophil, Elevated eosinophil, Asthma severity, EPR guidelines

[1]eMAX Health Systems, LLC, 445 Hamilton Avenue, 11th floor, White Plains, NY, USA. [2]Medicine and Public Health, Division of Pulmonary, Critical Care, Sleep, and Allergy, University of Illinois at Chicago, Chicago, IL, USA. [3]Teva, Frazer, PA, USA. [4]University of Arkansas for Medical Sciences, Little Rock, AR, USA.

Background

The American Lung Association has reported that nearly 26 million people (84.8 per 1000 people) in the US suffered from asthma in 2011, with children representing 27 % of them [1]. In terms of lifetime prevalence, asthma was reported in almost 40 million people in the US in 2011 (129 per 1000 people) [1]. Asthma attacks were recorded in 51 % of diagnosed patients, resulting in an attack rate as high 43.1 per 1000 [1].

The first Expert Panel Report (EPR) Guidelines [2] for asthma were established in 1991, focusing on patient education, environmental control to avoid asthma triggers, and assessment of asthma severity using lung function measures. Throughout the years, the EPR has been revised to reflect new research and novel treatment options; EPR-3 (2007) is the latest update [2]. Disease severity is central to EPR-3 guidance, with step-therapy recommended to address an escalating need for more drugs, at higher doses, with persistently uncontrolled disease. Asthma exacerbations undoubtedly increase the clinical and economic burden to patients and payers (emergency treatment being costlier than planned therapy), and are associated with substantial morbidity and mortality [3, 4].

Much progress has been made over the years in identifying external or environmental risk factors/triggers of asthma attacks such as allergens, pollutants, irritants, etc. [2, 5, 6]. Recently the focus has shifted to better understanding different patient phenotypes to manage risk and optimize outcomes. In order to prevent exacerbations and progression to more severe disease, it is essential to identify modifiable risk factors for asthma control specific to patient phenotypes. An emerging priority to standardize biological markers in clinical research in order to better evaluate patient outcomes with new and available therapeutic modalities is evidenced by the formation of an expert group by the National Institute of Health (NIH) to classify key biological outcome measures for federally sponsored asthma research. In the NIH Asthma Outcomes report, different biomarkers are grouped as "core", "supplemental", or "emerging". Core outcome biomarkers are required to be included in NIH funded asthma clinical trials and observational studies, whereas supplemental biomarkers are optional [7]. According to the NIH Asthma Outcomes report, multi-allergen screening of IgE against different allergens is considered the only core biomarker [7]. Blood eosinophils are a type of white blood cells that are a part of immune responses and also responsible for inflammatory effects when triggered by allergens. Blood eosinophil measurement is recommended as a supplemental

Table 1. Classification of patients by asthma severity adapted from EPR-3 step-treatment recommendations

Severity	EPR-3 Step-Treatment Recommendations
Mild	• Low dose ICS, or • Cromolyn, LTRA, Nedocromil, or Theophylline
Moderate-to-severe	• Low-dose ICS + LABA OR Medium-dose ICS OR Medium-dose ICS + LABA, or • Low-dose ICS + either LTRA, Theophylline, or Zileuton, or • Medium-dose ICS + either LTRA, Theophylline, or Zileuton • High-dose ICS + LABA OR High-dose ICS + LABA + oral corticosteroid,or • High-dose ICS + LABA + _Omalizumab, or High-dose ICS + LABA + oral corticosteroid + Omalizumab, or • Omalizumab

biomarker by the NIH asthma report [7], suggesting its optional use in NIH funded studies. Published studies evaluating its association with asthma exacerbation have reported significant association between blood eosinophil elevation and asthma exacerbations [8–10]]. Blood eosinophil measurement is inexpensive and widely collected as part of the Complete Blood Count (CBC) test. This study aimed to correlate asthma severity (based on EPR guideline step-therapy recommendations) and eosinophil elevation. In the absence of patient reported symptom classification, we explore the use of eosinophil biomarkers to identify patients who remain at risk for chronic exacerbation despite treatment.

Methods

Study design and data source

We conducted a retrospective data analysis of patients with asthma diagnosis, extracted from the EMRClaims+ integrated health services database (eMAX Health, White Plains NY) of patients located in the Midwest region of the United States. The database includes administrative insurance claims from approximately 675,000 lives linked to an overlapping healthcare provider database of over 20 million electronic medical records data (EMR), including laboratory values, and provider billing files.

Study population

The population was comprised of patients 12 years or older, who had at least two encounters (separated by at least 1 day) in the emergency room, outpatient or inpatient setting with a primary or secondary diagnosis of asthma (International Classification of Diseases-9- Clinical Modification [ICD-9-CM] code 493.xx) between January 2004 and July 2011 ("study period"). The date of the first asthma diagnosis in the study period was recorded as the index diagnosis date. The 12-month period following the index diagnosis was considered the 'assessment period'. Patients were also required to have at least 1 eosinophil test conducted during the assessment period. To account for the masking effect of systemic steroid use on eosinophil levels, patients only having eosinophil results under 400 cells/μL and all those eosinophil tests conducted while on systemic steroids (based on days of supply plus 14 days) were excluded. This approach minimizes misclassification of patients with lower eosinophil levels due to systemic steroid use. Patients with confounding diseases states of COPD, emphysema (ICD-9-CM codes: 491. xx-492.xx, 494.xx-496.xx), Churg Strauss syndrome/ Wegener's granulomatosis (ICD-9-CM code: 446.4), eosinophilia (ICD-9-CM code: 288.3), pulmonary fibrosis (ICD-9-CM code: 516.3), allergic bronchopulmonary aspergillosis (ICD-9-CM code: 518.6), cystic and pulmonary fibrosis (ICD-9-CM code: 277.x,515), and lung cancer (ICD-9-CM code: 162.x) in the assessment period, were excluded.

Table 2. Demographic and comorbidity distribution of patients by severity level

Patient characteristics	Asthma Severity		p-value
	Mild (n = 457) N (%)	Moderate-to-severe (n = 687) N (%)	
Gender			
Female	312 (68.27)	499 (72.63)	0.116
Race			
White	222 (48.58)	340 (49.49)	0.821
Black	59 (12.91)	81 (11.79)	
Hispanic	109 (23.85)	155 (22.56)	
Other/Unknown	67 (14.66)	111 (16.16)	
Age groups			
12–17 years	80 (17.51)	36 (5.24)	<0.0001
18–35 years	78 (17.07)	113 (16.45)	
36–64 years	232 (50.77)	401 (58.37)	
Greater than/equal to 65 years	67 (14.66)	137 (19.94)	
Top 5 Comorbidities			
Diabetes	53 (11.60)	107 (15.57)	0.057
Cancer/tumor	35 (7.66)	38 (5.33)	0.149
Congestive Heart Failure	23 (5.03)	45 (6.55)	0.288
Cerebrovascular disease	13 (2.84)	19 (2.77)	0.937
Renal disease	8 (1.75)	20 (2.91)	0.213
CCI Score Mean (SD)	1.49 (1.16)	1.52 (1.14)	0.701

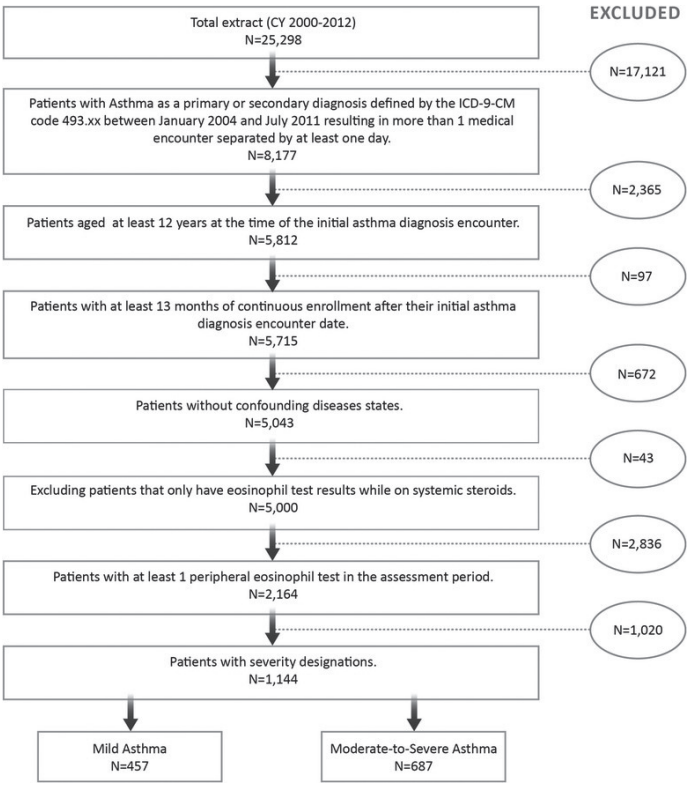
Study measures

Asthma severity was estimated using the medication use information reported in outpatient and/or inpatient pharmacy records during the assessment period using step-treatment recommendations for mild, moderate or severe disease by the EPR-3 criteria and adapted for use with retrospective data based on clinical guidance from asthma specialists (Table 1). Previous studies have defined elevated eosinophil levels at ≥ 400 cells/μL and have found very weak or no associations with severity at lower eosinophil cut-offs (≥200 cells/μL, ≥ 300 cells/μL) [8–10]. We also classified patients based on available eosinophil test results over the assessment period as "Elevated" if at least one test result during assessment period that was ≥400cells/μL, and 'Normal' if all available eosinophil test results were less than 400 cells/μL. Information on patient demographics (age, race, gender) was extracted. Comorbidities were captured and controlled for using the Charlson Comorbidity Index (CCI) score which was calculated for each patient. We also reported the top 5 comorbidities observed by the CCI.

Data analyses

Descriptive statistics were used to compare baseline characteristics between the different severity groups. Frequency distribution of patients with elevated eosinophils versus normal eosinophils were reported and cross tabulated with asthma severity level. Chi-square tests were used to compare the proportion of patients with elevated eosinophil between those

Figure 1. Study sample



that had mild and moderate-to-severe asthma. Logistic regression was used to determine the association between asthma severity (key factor) and eosinophil elevation, adjusting for patient demographics (age, race, gender), and comorbidity burden (the top comorbidities or CCI score, separately). To further assess the appropriate cut-off level for elevated eosinophils, we utilized cut-off levels adopted in other studies and conducted sensitivity analyses by defining elevated eosinophils as the cut off at ≥ 300 cells/μL and ≥ 140 cells/μL. All data management and analyses were conducted using SAS Enterprise Guide version 4.3 (SAS Institute Inc., Cary, NC).

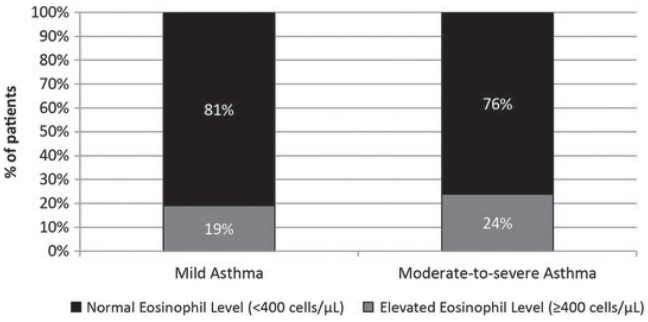
Results

The study identified 2,164 patients with at least one eosinophil test during the assessment period, of which 1,144 met our criteria for severity classification. Figure 1 provides a step-by-step breakdown of the study sample. Forty percent of patients were classified as having mild asthma and 60 % had moderate-to-severe asthma according to study definitions.

There was a greater proportion of women compared to men (Table 2), but the proportion was not significantly different between the severity groups (p = 0.116). Mean age of the overall sample was 47 years. Age distribution was significantly different between the two severity groups (P < 0.0001). Fifty-five percent of all asthmatics were in the 36–64 year age group; however, almost 17.5 % of patients with mild asthma were children between the ages of 12–17 years compared to 5 % in patients with moderate-to-severe asthma. Diabetes was a prominent comorbidity recorded in 14 % of asthmatic patients but the proportions of patients with diabetes were not significantly different among between the two severity groups (p = 0.057).

Overall, 22 % of subjects had at least one elevated eosinophil level (Fig. 2). Unadjusted Chi-square analysis showed that

Figure 2. Distribution of Subjects by Asthma Severity and Eosinophil level



proportions of subjects with elevated eosinophils were not significantly different between the two groups (Moderate-to-Severe 24 %, Mild 19 %, p = 0.053). However, logistic regression showed a 38 % increase in the odds (Odds ratio = 1.38, p = 0.040) of elevated eosinophils for moderate-to-severe asthma compared to mild asthma after adjusting for differences in demographic characteristics and comorbidities (Fig. 3). Males were also more likely to show elevated eosinophils.

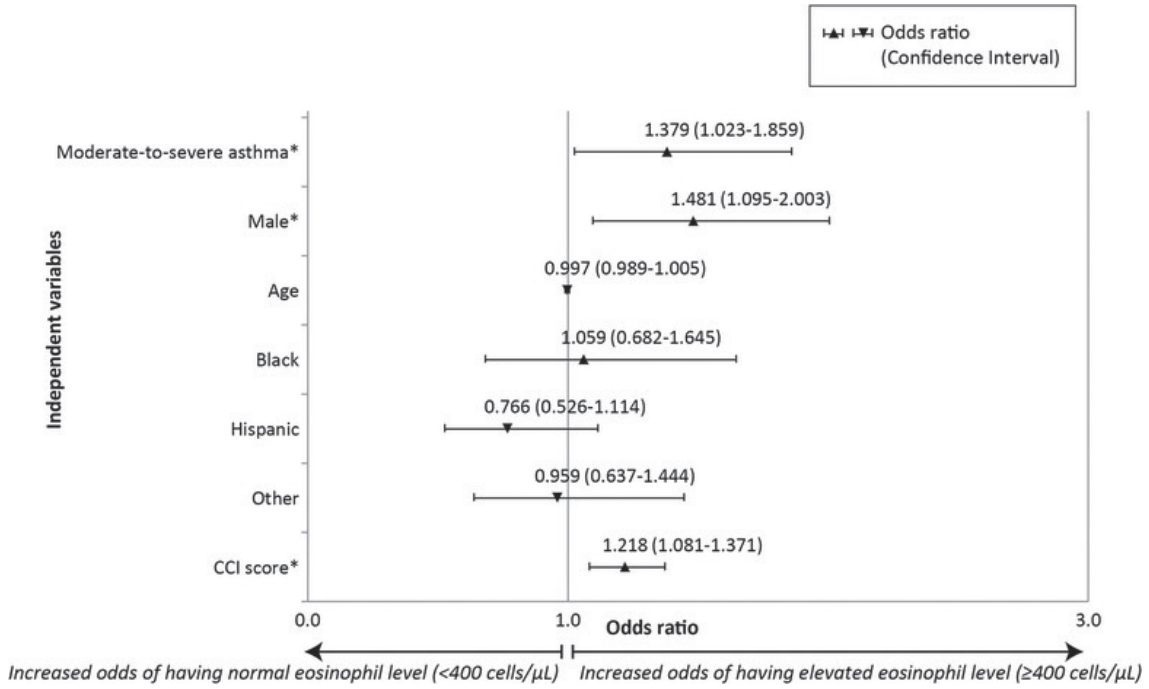
Sensitivity analyses

Results of sensitivity analyses conducted for elevated eosinophil level defined as ≥ 300 cells/μL showed that elevated blood eosinophils was not associated with moderate-to-severe asthma (OR: 1.07, 95 % CI: 0.83–1.38, p = 0.587. Similarly, elevated eosinophils at ≥ 140 cells/μL also showed no significant association with moderate-to-severe asthma (OR: 0.957, 95 % CI: 0.747–1.226, p = 0.728).

Discussion

In this sample of commercially insured asthma patients aged 12 years or older, we attempted to define asthma severity by adopting recommended medications described as step therapies, by EPR 3 guidelines. This study found a clear association between asthma severity and peripheral blood eosinophils, with moderate-to-severe asthma associated with increased likelihood of eosinophil elevation. The finding is consistent with previous literature showing correlation of sputum and blood eosinophil levels in asthmatic patients. Jatakanon and colleagues [11] followed a group of patients with asthma for a period of 8 weeks, and baseline comparisons showed a significantly greater sputum eosinophil count for the group that developed exacerbations versus those that did not. The same study, through step-wise forward regression, reported that increased sputum eosinophil was associated with decreased airway function in terms of decreased forced expiratory volume (FEV) [11]. While the literature supports the association of blood eosinophil elevation with severity or functional impairment generally, identification of a clinically meaningful threshold eosinophil value seems far less clear. Here we can only offer that our observed association between severity and eosinophil at ≥ 400 cell/ μL did not hold for levels ≥ 300 cells/μL or ≥ 140 cells/μL. While this does not provide evidence for the optimal threshold, it does suggest that these lower cut-points may be of limited value in assessing patient risk. The observed association between blood eosinophil levels at ≥ 400 cell/ μL and asthma severity supports the use of routine blood eosinophil screening practices to identify the sub-segment of patients with elevated eosinophil for more targeted treatment plans.

Fig. 3 Effect of covariates on odds of having elevated Eosinophils (Moderate-to-severe asthma versus Mild). Legend: * P < 0.05; Reference groups: Gender: Female; Race: White; Severity: Mild asthma



Our findings have significant implications for the medical management of asthma. Cost and resource use rises, and quality of life decreases with asthmatic exacerbation [12]. Emergency medical treatment for exacerbation in asthma is more costly than a managed regimen [3]; moderate-to-severe asthmatics with exacerbations result in 68–88 % greater annual all-cause healthcare expenditures compared to those without exacerbation [3, 4]. In light of these facts, proactive management of asthma (especially severe asthma) has the potential to reduce the frequency of and cost incurred by these patients. The observed association of elevated blood eosinophil with moderate-to-severe in this study supports the value, among competing tests, of using blood eosinophil markers to assess patient risk in order to promote more proactive management of this patient phenotype to reduce exacerbations.

Limitations

Requiring more than one asthma-related encounter may have resulted in over-representation of more severe patients; however, this criteria was implemented to reduce the selection of cases where a single diagnosis was assigned for suspected (but unconfirmed) asthma, a common approach when using retrospective claims data [13]. Asthma severity classification was based on medication use as opposed to observed exacerbation or impairment-based severity measures. While this classification technique may need to be validated against patient records or physician assessment, previous studies have defined asthma severity based on medication use (other than EPR-3 recommendations). Medication use serves as the best available technique in case of claims and administrative data. Lack of compliance with step-treatment recommendations may have misclassified patient asthma-severity level. We believe our classification approach is conservative, with potential misclassification which under represents the moderate-to-severe group, since poor compliance with step-treatment recommendations directionally is toward under-treatment of poorly controlled patients (as opposed to over treatment of well controlled patients). For some patients, eosinophil levels may have been defined using only one eosinophil test result over the one-year assessment period, but severity was defined based on medication use over the entire year; the temporal bias/relationship of these two variables was not assessed and should be considered as a limitation.

Conclusion

This study highlights the association between asthma severity, defined by using EPR guidelines, and eosinophil elevation. The probability of eosinophil elevation is increased for patients with greater asthma severity. Blood eosinophil level may represent an important characteristic of disease severity as new therapeutic alternatives emerge for this patient phenotype after exhausting less aggressive medication regimes. Further research correlating blood eosinophil level with risk-based severity and control measures (such as asthma exacerbations leading to ER visits and/or hospital admissions) is warranted to externally validate the presence of our observed association. Evidence of the association between blood eosinophil levels and asthma severity underscores the need for treatment options designed for asthma patients with elevated eosinophil.

Abbreviations

CCI, Charlson Comorbidity Index; CI, Confidence Interval; EMR, Electronic Medical Record; EOS, Eosinophil; EPR, Expert Panel Report; FEV, Forced Expiratory Volume; ICD-9-CM, International Classification of Diseases-9- Clinical Modification; ICS, Inhaled Corticosteroid; LABA, Long acting Beta agonist; NIH, National Institute of Health; OR, Odds Ratio; SAS, Statistical Analysis Software.

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Authors' contributions

All authors were involved in conceptualization, development and finalization of study design. JK and JC contributed significantly to core study design. ZD and CL were involved in conducting the analysis and interpreting results.

MS, RK, PB, GG contributed to manuscript text, content, and flow development. All authors were involved in developing the results into manuscript. All authors were involved in reviewing interim drafts to prepare a final version. All authors read and approved the final manuscript.

Competing interests

This study was funded by Teva Pharmaceuticals.

Ethics approval and consent to participate

The authors confirm that according to local legislation, ethics approval is not required for this retrospective study. The data used in this study has been recorded and presented in such a manner that subjects cannot be identified and consent to participate from the subjects is therefore not required.

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