

Volume 6 Number 3 June-July 2011

Respiratory Therapy™

The Journal of Pulmonary Technique

SLEEP SPECIAL REPORT
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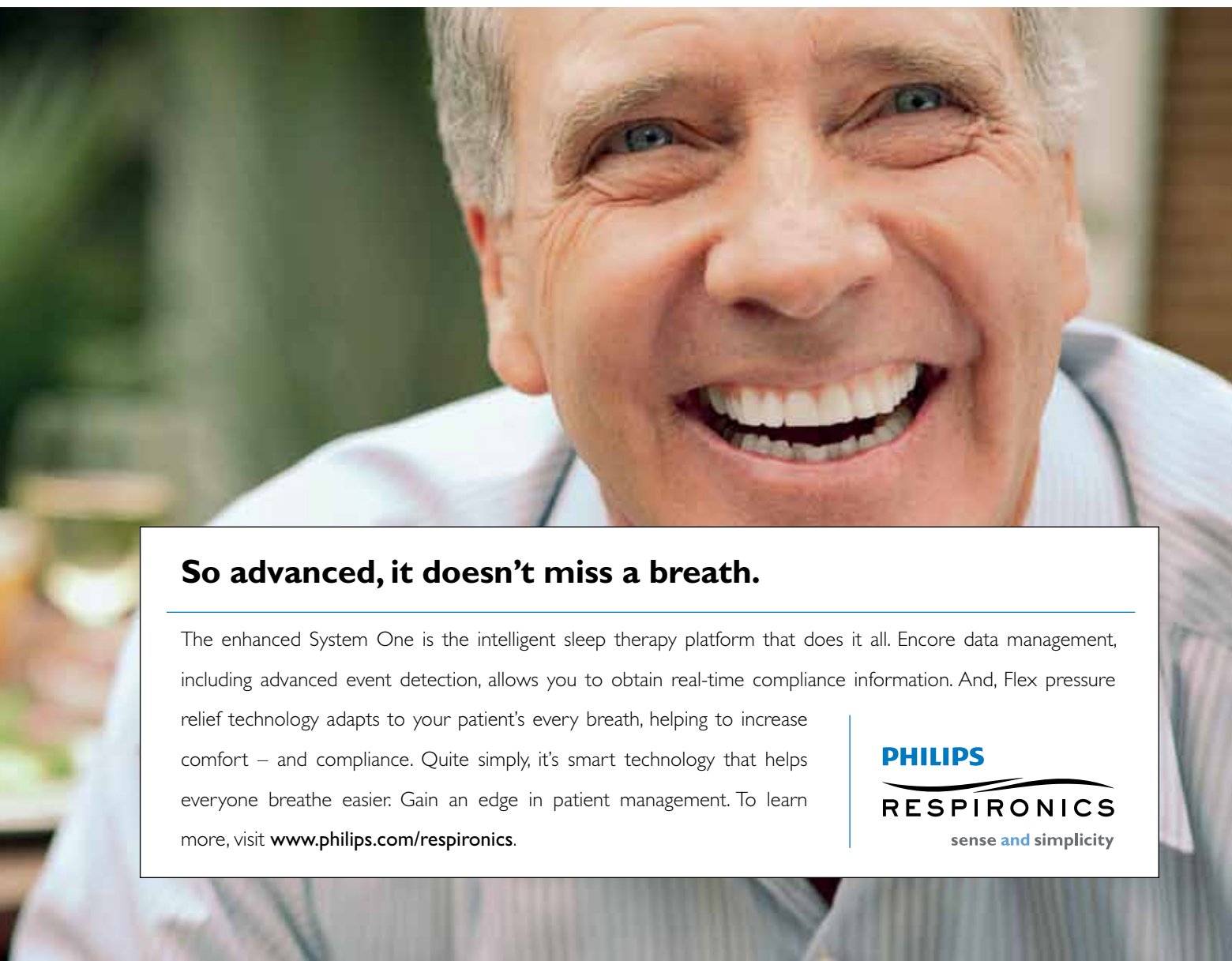


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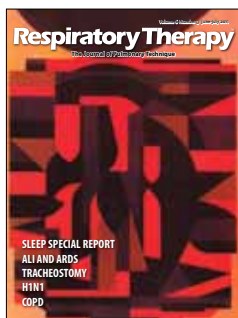
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The Journal of Pulmonary Technique

Vol. 6 No. 3
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Editorial

Losing Sleep

It's coming up: the new credentialing exam from AASM, shortly on the heels of the new BRPT sleep credentialing program. The inaugural exam is slated for November. RPSGT credentialisers will be grandfathered in. The idea, apparently, is that the field needs more certified sleep techs, and that the AASM's test is easier to pass.*

The two groups have been arguing over who has the more thorough test, "professionalism," and other issues, such as whether the AASM is basically a tool of physicians. The AASM said its goal is to offer an exam based on day-to-day professional responsibilities of sleep technicians. The BRPT wonders why the AASM is stepping all over its toes.

In related news the website Sleep Scholar asked its readers to weigh in on this issue and on the AASM's supporting a routine 3:1 ratio of patient to tech. Some responses: "More money-driven decisions are being made by the AASM, an organization run by physicians." "Sounds to me like a continuation of lowering of standards." "I believe sleep studies should be a 1 on 1 experience. A 3 to 1 ratio makes it all about money, not patient care." "It's just another cost cutting measure by those who have no idea what occurs during a 12-hour shift in a sleep center." "Why the sudden interest in trying to 'dummy down' the profession?" But here's an opposing view: "What's the fuss? How many patients is an RN or RRT responsible for in the ICU? Three to one is fine but another healthcare professional should be available to offer support."

As far as the dustup between the BRPT and AASM, one respondent noted, "Sleep has no clear leadership right now. The BRPT is run by an outside managing company. The AASM is run by the bigwig docs... both are in it for the revenue." Finally, a respondent noted, "Why in the world would you negate all the people who are already credentialed and why would you make an opening for Respiratory Therapy to come back again and say, see, we know what we are doing and there is all this infighting in the field; let us handle it."

Les Plesko, Editor

PS: Please see our special report on sleep, which begins on page 39.

*AASM is the American Academy of Sleep Medicine; BRPT is the Board of Registered Polysomnographic Technologists; RPSGT is the designation for Registered Polysomnographic Technologists.



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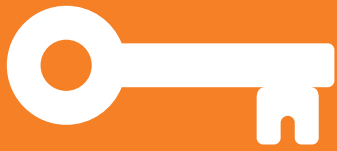


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□ June-July 2011

STAY OFF THE ROAD

Lung transplant patients have double the risk of organ rejection and death within five years of the procedure if they live near a main road, according to researchers in Belgium who tracked the health of 281 patients who had undergone a lung transplant or retransplant. Half of all patients who undergo a lung transplant develop bronchiolitis obliterans syndrome within five years of having the procedure. During the study, 117 patients developed the syndrome and 61 died. Those who lived within a 171 meter radius of a main road were twice as likely to develop the syndrome and more than twice as likely to die as their peers who lived further away. For every 10-fold increase in distance from a main road, patients were 43% less likely to develop the syndrome and 28% less likely to die. Lung lavages and blood samples taken from 207 lung transplant recipients also showed that levels of inflammatory markers were associated with distance from a main road: the greater the distance from a main road, the lower they were. One in four cases of bronchiolitis obliterans syndrome and almost 30% of deaths in lung transplant recipients across the country could be attributed to living near a major road. The findings were reported in *Thorax*, "The impact of traffic air pollution appears to constitute a serious risk..."

CONTRACEPTIVE OKAY

Oral contraceptives with progesterone do not influence fetal respiratory and immune development, according to researchers in Norway. Researchers looked at associations between the type of OCP used by the mother before pregnancy and lower respiratory tract infections in 60,225 children followed to 6 months old, lower respiratory tract infections and wheezing in 42,520 children followed to 18 months old and asthma in 24,472 children followed to 36 months old. The use of estrogen-progestin combined pills before pregnancy was not associated with lower respiratory tract infections, wheezing or asthma in the children followed in the study. Progestin-only pill use in the year before pregnancy had a small positive association with wheezing in children at 6 to 8 months but the researchers noted that very few women used this type of pill. The use of OCPs was not associated with adverse respiratory outcomes in the offspring.

STEROIDS AND PNEUMONIA

Patients admitted to a hospital with major trauma and treated with hydrocortisone were less likely to be diagnosed with hospital-acquired pneumonia than patients who received a placebo, according to researchers at the University of Nantes, France. The researchers found that corticosteroid use may decrease the occurrence and severity of nosocomial pneumonia in patients treated in ICUs. They conducted a randomized trial with 150 patients with severe trauma from 7 ICUs in France. Patients were randomly assigned to a continuous intravenous infusion of either hydrocortisone (200 mg/d for 5 days, followed by 100 mg on day 6 and 50 mg on day 7) or

placebo. Twenty-six of 73 patients treated with hydrocortisone and 39 of 76 patients treated with placebo developed hospital-acquired pneumonia at day 28 of hospitalization. Twenty of 56 patients with corticosteroid insufficiency who were treated with hydrocortisone and 31 of 57 patients receiving placebo developed hospital-acquired pneumonia at day 28. The average duration of mechanical ventilation-free days was 16 days in the hydrocortisone group and 12 days in the placebo group. Three of 73 patients in the hydrocortisone group and 11 of 76 patients in the placebo group developed acute lung injury or ARDS. The average length of ICU stay was 18 days in the hydrocortisone group and 24 days in the placebo group. Seven of 76 patients in the placebo group and none of the 73 in the hydrocortisone group developed hyponatremia. For the entire study population, 6 of 73 patients died in the hydrocortisone group and 4 of 76 died in the placebo group.

PROTEIN MAKES CHANGES

Changes that occur in the airways of asthma patients are in part caused by interleukin-13, which stimulates invasion of fibroblasts, according to a study conducted by researchers at Duke University. Researchers said they showed for the first time that fibroblasts from asthma patients, stimulated with IL-13, invade in significantly greater numbers than those isolated from normal control subjects. IL-13 acts in combination with other mediators produced by cells in the airways, transforming growth factor- β 1 (TGF- β 1), which causes cellular changes, and matrix metalloproteinases (MMPs), which act to break down proteins. These agents cause cellular changes that lead to loss of lung function in asthma patients. Many of the fibroblast responses that occur in airway remodeling are comparable to the interaction between cancer cells and stromal fibroblasts. Researchers enrolled 37 subjects, including 20 men and women with mild asthma who were not taking inhaled corticosteroids, and 17 healthy controls. All asthmatic subjects had been diagnosed with asthma for at least one year prior to study enrollment. Airway cells were collected from all patients using bronchoscopy and studied in a laboratory setting. After application of IL-13, invading cells were counted using microscopy. The addition of IL-13 resulted in a significant increase in airway fibroblast invasion in asthma as compared to normal controls. In addition, airway fibroblasts of asthmatic subjects invaded in greater numbers than those of control subjects.

TB OR NOT TB

The CDC has published 2010 tuberculosis surveillance data for the nation. TB in the US is at an all-time low. In 2010, a total of 11,181 cases were reported, with a rate of 3.6 cases per 100,000 population. Racial/ethnic minorities and foreign-born individuals continue to be disproportionately affected by TB. The TB rate for foreign-born individuals is 11 times higher than the rate for those born in the U.S. Nearly 9% of people with TB were also infected with HIV. Those living with HIV are at high-risk for rapid progression to active TB once infected and are more likely to die during treatment. Multi-drug resistant and extensively-drug resistant TB – remains a serious threat to our ability to treat and control TB. The Partners in Health and Treatment Action Group called on action to speed up treatment for drug-resistant tuberculosis (M/XDR-TB) reflected in a recent World Health report. Globally, only 6% or 30,000 of the estimated 500,000 MDR-TB cases were detected in 2009. Of these, only 11,000 patients were in defined quality-assured treatment programs. Almost a million people with drug-resistant TB are untreated, or poorly

treated. Countries with fast-growing economies such as India and China have failed to commit more than 10% of the funds needed to implement their MDR-TB control programs in 2011. In 2010, drug stock-outs still occurred worldwide, including the US, for second-line TB drugs. Over the past decade, the price of some second-line TB drugs actually quadrupled.

HOW IT WORKS

The following note appeared in the latest issue of The Placebo Journal (placebojournal.com). The editor wrote: I have for some years written that society has broken its compact with physicians and in so doing has altered their actual role. The utter consumption of medicine by the third-party payer mentality, and the expectation of perfect care to be enforced by lawyer-threats made physicians largely a commodity; once patients were granted healthcare as a right by their elected officials, that finished the transformation. Through the onerous sanctioning of state, federal, and quasi-governmental institutions, the work of doctors has become largely the property of the state; hence, doctors have become government agents increasingly more akin to the drones at the DMV.

BIOMED CENTRAL

To further promote Open Data and data sharing, BMC Research Notes has launched a series of articles on data standardization, sharing and publication edited by Dr Bill Hooker and Prof David Shotton. BioMed Central is looking for contributions from all fields of biology and medicine. The timely launch of this collection coincides with a themed issue in Science exploring data sharing for biomedical and clinical research that highlights articles from Trials and BMC Bioinformatics. The Scientist magazine also recently emphasized the importance of data

standards... The publishing company Springer acquired 12 open access journals from Hindawi Publishing Corporation, including the International Journal of Pediatric Endocrinology (IJPE). The journals acquired include seven titles published in cooperation with the European Association for Signal Processing (EURASIP) and four mathematics journals. Matthew Cockerill, Managing Director of BioMed Central, said, "These journal acquisitions confirm the strategic importance of open access at Springer, and strengthen the BioMed Central and SpringerOpen portfolios. BioMed Central's expertise and services will help the International Journal of Pediatric Endocrinology (IJPE) to further establish itself as a leading journal in its field." Contact biomedcentral.com.

NEW WEBSITE

In India, respiratory therapy and chest physical therapy are often ignored. Even the budding physiotherapists and students shows less interest towards these specialties. There are numerous scientific rationale to support the benefits of respiratory therapy and chest physical therapy. There are a limited number of websites available on chest physical therapy and treatment updates. At this juncture a new website has been launched: chestphysio.in, to enable physiotherapists around the world to make use of this URL and update themselves. Viewers of the site can look into the treatment innovations and clinical updates regarding chest physical therapy and respiratory therapy. Contact www.chestphysio.in.

EMR ERROR?

The Placebo Journal reports on an article in the Wall Street Journal, "Getting Docs to Use PCs." The Placebo Journal notes: "They are just talking about EMRs or electronic medical

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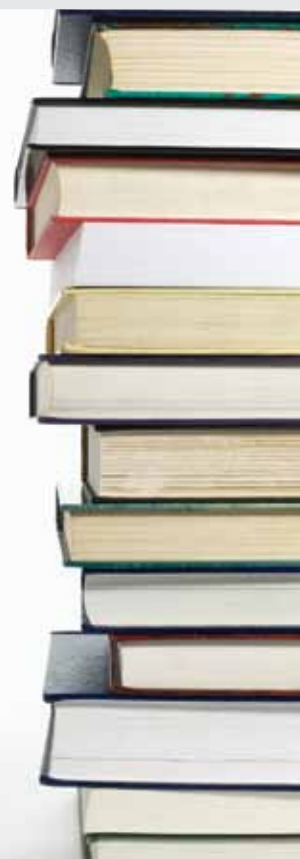
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records. The piece explains how hard the hospitals are pushing to get doctors trained in this area. As much as they try, however, there is still some resistance by physicians. It seems some docs don't want to look like idiots during the training sessions but the real story is when they explain why the EMR is so important. Hospitals are 'aiming to get a slice of the government's \$27 billion in incentives.' Training docs is 'crucial to get federal incentive payments, which require that care providers 'meaningfully use' the systems. Nowhere does it say that EMRs are there to help patients. Nowhere is that proven. This... is being done only for money." Placebo's editor Doug Farrago commented, "I use an EMR. I like it. I now am trapped in a whirlpool of numbers where the clicks never end and the measurements never stop. I have been duped. The EMR in its basic form is good but it has become a Trojan Horse to let hospitals, insurers and the government spy on my work without proof that what they are measuring does any good. The tail is wagging the dog. Doctors are just pawns in this and are unable to fight back because we just want to treat patients and because we are wussies. As the last line in the article says, the attitude from computer trained docs to newbies was to "Buck up! We did it." In other words, resistance is futile. This, my friends, is called learned indifference and we physicians deserve what we get for being so passive."

PEEP PLUS

Pediatric Research recently published a paper on increasing PEEP to recruit alveoli during HFJV, hypothesizing that high PEEP would recruit alveoli and reduce lung injury but compromise pulmonary blood flow. The study was carried out using preterm lambs delivered after instillation of surfactant. The lambs either remained on constant PEEP of 5 cm H₂O or adjusted stepwise to 12 cm, then back to 8cm over an hour-long period. Pressure volume deflation curves were recorded postmortem and tissue assessed for inflammation. Lambs receiving increased pressure had lower pressure amplitude, fractional inspired oxygen concentration and PBF and more compliant lungs. Inflammatory markers were also lower. The study concluded that "adjusted PEEP during HFJV improves oxygenation and lung compliance and reduces ventilator requirements despite reducing pulmonary perfusion." The paper noted: "The current strategy recommended for treatment of RDS with HFJV is to commence HFJV early in the disease process with a PIP just below that being used during CMV (Bunnell Inc, HOW to use the LifePulse HFV: Seven Steps to Success)." Bunnell supplied the high frequency ventilators for the study. For the complete study, see High Positive End-Expiratory Pressure During High-Frequency Jet Ventilation Improves Oxygenation and Ventilation in Preterm Lambs, Pediatric Research, Vol 69 No 4, pages 319-324. Information above was provided by Bunnell.

PRODUCTS

HOME WORK

CareFusion has introduced a portable ventilator for adults and children who require mechanical ventilation at home. The CareFusion LTV 1100 ventilator is designed to significantly enhance the mobility of patients with spinal injuries or neuromuscular diseases who require continuous ventilation to breathe. The LTV1100 ventilator offers features common to ventilators used in hospital intensive care units, but in a small, easy-to-use, durable package for patient and caregivers. The system enables all-day portability for active, ambulatory patients in vehicles, wheelchairs, walkers or scooters, or can be attached to a wall,

bedside table or patient gurney. For patients with chronic ventilatory failure, the LTV 1100 ventilator enables non-invasive positive pressure ventilation, an approach reported to reduce the risk of respiratory infection, improve voice function and enhance quality of life. The LTV 1100 ventilator also features a spontaneous breathing trial (SBT) mode, which uses a rapid shallow breathing index to evaluate a patient's readiness to be weaned off of the ventilator. Clinicians can customize the SBT setting to individual patients, ensuring optimal levels of support as patients are tested on their required level of breathing support. Contact www.carefusion.com.

SEAL OF APPROVAL

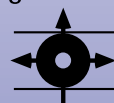
WHAT: The Sami the Seal pediatric compressor nebulizer system incorporates a child-friendly design to help support aerosol compliance. The compressor is paired with Philips Respironics' highly efficient SideStream nebulizers and Tucker the Turtle pediatric mask to provide fast and friendly treatment to pediatric patients in the home. The product is the company's first compressor nebulizer system designed specifically for children. **WHY:** Sami the Seal can be used with commonly prescribed respiratory medications and is designed for use with SideStream disposable and reusable nebulizers. Both nebulizers feature venturi technology that provides air flow in addition to that supplied by the compressor, resulting in faster drug delivery and shorter treatment times. Lightweight at only 3.5 pounds, Sami is durable, easy to use and easy to maintain. The Tucker the Turtle pediatric character mask is made of soft, flexible material that contours to the face for comfort and fit. It also incorporates a vent design that directs medication away from the eyes, reducing undesirable aerosol eye deposition. Contact philips.com.



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MANLY PILLOW

Philips announced its Philips Respironics GoLife for Men nasal pillows mask, to be used in the treatment of obstructive sleep apnea (OSA). The product is the company's first sleep therapy mask built exclusively for men. Designed to be the most stable nasal pillows mask available, GoLife for Men has facial contour arms that conform to and hug the patient's face to maintain a secure seal and stability, even when moving during sleep. The mask features straightforward, preformed headgear and self-adjusting, optimally angled nasal pillows for a one-step fit. It is engineered for stability, designed for simplicity, and built for men. In the near future, Philips will release its GoLife for Women mask, which will offer the same customized features designed for a female patient's face. GoLife has few parts, comes in a FitPack with all sizes (petite, small, medium, and large), and is easy to size and fit. Used together with Philips Respironics System One Resistance Control, the mask helps to deliver optimum PAP therapy and comfort. Contact philips.com.

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Hamilton Medical's ventilation systems have earned the top User Satisfaction Ratings in all categories in MD Buyline's Quarterly User Satisfaction Report. Hamilton Medical, Inc is entering its third year holding the top composite score in ventilation as rated by the clinical members of MD Buyline. Hamilton Medical, Inc continues to stand behind the quality of its ventilation technology products and it is passing its commitment to continued superior performance along to our customers. Beginning January 2011, all new ventilation systems purchased from Hamilton Medical, Inc will have a one year labor and three year parts warranty included standard on every system. Hamilton Medical also announced that Annette Dusek has been named Marketing Manager, with the responsibility for corporate communications and marketing. She will manage all areas of marketing operations within the United States. Ms Dusek began with Hamilton as customer service representative in 1993. Contact www.hamiltonmedical.com, (800) 426-6331.

PRODUCT LAUNCH

Pharmaxis announced the commercial launch of ARIDOL (mannitol inhalation powder) Bronchial Challenge Test Kit, the first new bronchial challenge test in more than two decades and the company's first product launch in the US. ARIDOL is used to assess bronchial hyperresponsiveness in patients six years of age and older who do not have clinically apparent asthma. ARIDOL is a single-use, indirect test that takes about 20 minutes to administer, requires minimal preparation time and a 15% reduction in lung function from baseline for a positive test. The ARIDOL test requires patients to inhale increasing doses of dry powder mannitol from a simple, hand-held device, which causes airways to narrow and contract when airway inflammation is present. The doses are contained in capsules that are administered at one-minute intervals until a positive response is achieved or until all the capsules have been inhaled, indicating a negative result. A positive response is indicated when there is a 15% reduction in lung function from baseline compared to a 20% fall required by a methacholine challenge test. The safety and efficacy of ARIDOL as a bronchial challenge test were verified in two global Phase III clinical trials. Contact www.pharmaxis.com.

CASE REPORT

Linda Dean, RRT, Clinical Specialist, Passy-Muir, Inc, reports the following in the company's newsletter: Charlotte Mills, 54 years old, arrived in the emergency room quite ill. She was

admitted to the ICU with a diagnosis of urosepsis that quickly progressed to respiratory failure, secondary to an acute onset of Adult Respiratory Distress Syndrome (ARDS). Charlotte required emergency intubation, and was quite unstable for many days. Extubation was unsuccessful twice, so after two weeks the decision was made to perform a tracheotomy. Shortly after the tracheotomy, the speech-language pathologist and the respiratory therapist evaluated Charlotte and placed the Passy-Muir Valve. The staff and the Mills family began to see a rapid turnaround in her condition. After 21 days in the ICU, Charlotte could once again communicate effectively with everyone, and participate in her rehabilitation. She confessed that the ability to talk enabled her to orient herself to time and place. She stated, "I could finally speak and have a say in my care. The Passy-Muir Valve let me communicate my needs and express my desire to move as quickly as possible through rehab and get home. My children were so emotional, so glad to hear my voice, and amazed at how natural and real it was to my original voice." Her husband said, "Once the Passy-Muir Valve was placed, we began to see a real change. It was a turning point in the healing process to hear her voice again, especially for the children. I got to hear her voice and it brings you back to who that person is." He further expressed, "It was as significant for the family as it was for Charlotte to be able to speak again." Approximately 29 days after her admission, Charlotte was discharged to home without a tracheostomy tube and without need for supplemental oxygen or medications, and was eating a regular diet. Contact passy-muir.com.

FACT FROM FICTION

A long-term oxygen therapy symposium was recently organized by Tufts University and Ganesco. The day and a half symposium presented clinical evidence on LTOT, and weighed the evidence to separate the "fact" from the "fiction" in the transitional process of patient care from the hospital to the homecare environment. The symposium focused on lectures and hands-on workshops with oxygen delivery devices used in the homecare environment to identify and address the underlying clinical problems which create pitfalls for prescribing LTOT. Recently, there is new thought which suggest that clinical factors can be linked in a more efficient way to reimbursement by examining the impact on re-hospitalizations and the initiation of a collaborative care model. These potential new models of chronic care delivery are funded in healthcare reform law. The symposium focused on the reimbursement opportunities and the clinical evidence. Contact ganesco.com.

TO MARKET

InterMune, Inc announced that the European Commission (EC) has granted marketing authorization for Esbriet (pirfenidone). Esbriet is indicated in adults for the treatment of mild to moderate idiopathic pulmonary fibrosis (IPF). The approval authorizes marketing of Esbriet in all 27 EU member states. Based on anticipated EU country reimbursement timelines, InterMune currently plans to launch Esbriet in Germany in September of 2011; France, Spain and Italy in the first half of 2012 and in the United Kingdom in mid-2012. InterMune also plans to launch Esbriet in all or substantially all of the 10 most important pharmaceutical markets in the EU by approximately mid-2012. Esbriet has been granted Orphan Drug designation in Europe, which provides 10 years of marketing exclusivity lasting until 2021. In addition, InterMune has a number of granted, allowed and pending patent applications in Europe relating to Esbriet's formulation and use in IPF patients, particularly related to the safe and efficacious usage of the product. This collection

of patents is currently expected to provide patent protection in Europe until 2030. Pirfenidone has also been granted Orphan Drug designation in the United States. InterMune will conduct a drug-drug interaction study to determine the impact of the antibiotic ciprofloxacin, a moderate CYP1A2 inhibitor, on the pharmacokinetics and safety of Esbriet in 25 healthy subjects. Esbriet is an orally active, small molecule drug that inhibits the synthesis of TGF-beta, a chemical mediator that controls many cell functions including proliferation and differentiation, and plays a key role in fibrosis. It also inhibits the synthesis of TNF-alpha, a cytokine that is known to have an active role in inflammation. Contact intermune.com.

PLAY MISTY FOR ME

MyPurMist is a patented Over-The-Counter device that delivers adjustable warm vapor for sinus therapy. It uses the same Capillary Force Vaporizer (CFV) device that is used to humidify hospital ventilator circuits and high-flow oxygen systems. The technology is now available for the home in a portable and convenient product that is completely safe for children and adults. MyPurMist has no risk of scalding (even when the product is tipped) and creates a germ-free, warm vapor that is directed and concentrated to provide soothing sinus therapy for children and adults. The product is portable, safe and easy to use, it can be used nearly anywhere, anytime and by any age. Contact MyPurMist.com.

CONSERVATION

CHAD Therapeutics announced the launch of its new electronic oxygen conserver, the EVOLUTION. The newest in the line of CHAD products, the EVOLUTION is able to provide a minimum of two years operation using just two AA alkaline batteries. With a sensitive triggering mechanism, fast delivery, and conserve settings up to 7 LPM, the EVOLUTION can accommodate a broad range of patients and conditions. The single-lumen design provides a 5:1 savings ratio at all settings. Features also include, a uniform volume of oxygen with each pulse ranging from 14-40 breathes per minute and operation between 200 and 3000 PSI. Contact (800) 423-8870, chadtherapeutics.com.

ON THE BUS

The Kimberly-Clark Education bus was created to help promote education and awareness of healthcare-associated infections. This year's bus tour is underway, and there are some new additions to the "ride." The bus now includes new environments, including learning and demo areas. It has a one-of-a-kind mobile classroom that offers accredited CE and CME education on HAIs to clinicians on-site. The bus also has a new three-year commitment to be on the road. Kimberly-Clark's Education Bus provides cutting-edge healthcare worker education around HAI prevention. Last year, the bus visited 79 locations in the US and Canada, including stops at tradeshow and conferences. The stops occurred in 60 cities in 25 states and one Canadian province. In addition, an average of 29 CE credits were awarded per bus visit. The highest attended stop was at the VA Hospital in Houston, with over 200 attendees (average of 54/day).

COMPANY PROFILES

IngMar Medical

Describe your products and their unique features.

IngMar Medical offers a wide variety of respiratory simulation products including the world's most sophisticated breathing simulator, the ASL 5000. For nearly 20 years IngMar Medical has focused on providing innovative breathing simulators, lung models, and test lungs for training, testing, research, product development, and sales support. Our flagship product, the **ASL 5000 Adult/Neonatal Breathing Simulator**, is able to simulate almost any respiratory patient with breath-by-breath control; offering clinicians, educators and device manufacturers a clinical "flight simulator" with the highest level of fidelity. The new **RespiSim-PVI Option** for the ASL 5000 Breathing Simulator is a groundbreaking tool for interactive ventilator management training. The RespiSim-PVI Option leverages our FiRST system (Fully Interactive Respiratory Simulation Technology) and provides an advanced interface for instructor and student displaying both ventilator and "patient" parameters in real time on the same screen. The immediate feedback provided by the RespiSim-PVI, coupled with the fidelity of the ASL 5000 Breathing Simulator, serve to enhance and accelerate training. One of the most powerful features of RespiSim-PVI is the accompanying teaching modules on such topics as waveform interpretation, understanding ventilation modes, and ventilator management for specific disease states. These "plug and play" modules aim to significantly decrease instructor workload. IngMar Medical's product line also includes: **RespiTrainer Advance**, an airway management and manual ventilation skills trainer, which provides real-time feedback on ventilation parameters, allowing for skills training and competency testing. Infant version also available; **QuickLung**, a compact, precision test lung for ventilator testing and training. No other test lung performs at this level of precision and versatility at this price; **Breather Option** for the QuickLung, a cost-effective tool to represent a spontaneously breathing patient; creating new opportunities to demonstrate and test ventilator triggering and important modes of ventilation such as SIMV, Pressure Support and PAV; **NeoLung**, a versatile tool to simulate neonatal patients; **Linear Test Lung**, a bag-style test lung with a predictable linear compliance curve; **Adult/Pediatric Lung Model**, a two-bellows lung simulator with easy control of compliance, resistance and leak settings.

Tell us about the latest advances in the area your product serves.

The use of simulation in medical training has been growing rapidly in recent years. Attendance at the annual International Meeting on Simulation in Healthcare (IMSH) has increased nearly 50% from 1,840 attendees in 2010 to 2,730 in 2011. Additionally, the American Association for Respiratory Care (AARC) has recently established a Simulation Roundtable as a forum for those involved in respiratory simulation. With new tools to complement a proven line of respiratory simulation devices, our goal is to incorporate Fully Interactive Respiratory Simulation Technology, or FiRST, to assist trainers as they advance from sequential, instructor-driven training to simultaneous, experience-driven training with the benefits of enhanced learning with less instructor workload.

Discuss your R&D process, including clinical user input.

Clinical user input has been instrumental in the research and development of IngMar Medical's line of simulation products. User requests for customization have been a valuable source of new product ideas. The initial idea of the RespiSim-PVI, ie simultaneously displaying ventilator and "patient" data, was born from discussions with leading respiratory therapists and current users of the ASL 5000 Breathing Simulator. Rob Chatburn, Cleveland Clinic; and Teresa Volsko, Youngstown State University, have played an integral role in the development of the training modules for the RespiSim-PVI.

Discuss the educational services you offer for use of your product.

A key component of the new RespiSim-PVI are the training modules for a respiratory care curriculum. These "plug and play" modules aim to significantly decrease instructor workload. IngMar Medical also offers live, online support for ASL 5000 customers via webconferencing software. This software allows our technical assistance experts to remotely operate the ASL 5000 to quickly help users with technical issues. Additionally, IngMar Medical has just launched a user forum to enable users to enhance their simulation experiences and gain valuable insight into the full capability of their devices. The User Forum is also designed to facilitate discussion that will advance the fields of respiratory simulation and respiratory care generally.

What new technology do you see as having the greatest impact on your area of expertise?

Key developments in medical technology include the integration of wireless, handheld devices and electronic charting. IngMar Medical has embraced these developments, utilizing electronic charting technology to enable real-time data capture from the ventilator to be displayed alongside patient simulator data in the new RespiSim-PVI Option for the ASL 5000 Breathing Simulator. Ventilators are among the most complex and sophisticated pieces of patient treatment equipment. Technology that supports and sustains life is always advancing, demanding continual (re)training of clinicians, for example for new modes of spontaneous breathing support and ventilator graphics. The technology present in RespiSim-PVI, coupled with the sophistication of the ASL 5000 Breathing Simulator, brings ventilator management training to a new level with a fully immersive simulation environment and complete, real-time analysis of patient ventilator interaction (PVI).

SeQual Technologies

Describe your products and their unique features.

SeQual Technologies focuses primarily on the design and development of oxygen delivery devices used in homecare, emergency and industrial applications. We have engineered leading edge products in the field of gas separation which have been recognized as industry standards such as the Advanced Technology Fractionation system, Rotary Valve designs, auto servo regulation of components to derive consistent delivery of oxygen in the most demanding conditions.

Tell us about the latest advances in the area your product serves.

We have been focused on a couple of key areas over the past few years which should prove to set new bench marks in the

field of long term oxygen care as well as emergency applications. We typically have been investing 8-9% of our revenues into research and development for the past 5 years, which in turn will yield some technologies that will leapfrog today's standards in care. Our work with the military along with leading medical researchers has provided us with new insights that have led to developing oxygen systems that will better match with patients clinical as well as lifestyle needs.

Discuss your R&D process, including clinical user input.

Our processes related to R&D are very disciplined and also based in over 15 years of direct experience with end users across a spectrum of oxygen applications. We consider our company as one that balances art with science when it comes to oxygen products. Much of what we have accomplished has come about by focusing on being the best in this space and to date no company has surpassed the performance of our Eclipse portable oxygen systems. Clinically we have been co-developing the products with input from patients, key pulmonary physicians and home care providers and by approaching the market with an open mind we can gather data in a non biased manner and in turn via trial and experimentation execute quickly on features and benefits that first and foremost produce better outcomes and are efficacious. Basics always count in medicine so the product must be capable of meeting the demands of the patient and provide positive results or they simply won't comply with their therapy.

Discuss the educational services you offer for use of your product.

We pride ourselves in being clinically driven not marketing driven with our product designs. Marketing plays a key role in our company but the marketplace determines what we actually design. Many of the new features for instance in the new Eclipse 3 product are crossover modes being used on portable home care ventilators. We have designed the first portable oxygen concentrator that can be upgraded with software, adjustable rise times in pulse mode, a battery conservation mode to extend travel times and increased the bolus size in our pulse mode to 192 ml in order to address the clinical needs on a wider range of patients. Our clinical support staff consists of RTs with extensive experience in hospital and home care settings and we offer CEUs on many aspects of care for LTOT topics.

What new technology do you see as having the greatest impact on your area of expertise?

Again speaking to the needs of our patients and clinicians we have been tasked to produce an equally powerful platform of oxygen systems that produce high levels of oxygen but in an even lighter weight and at lower costs. Reimbursement will continue to play a role in our decisions as well as the providers as to what technologies they adopt for their patients and business models but overall the trends look favorable towards portable oxygen generators. We are always looking at new battery options as well as adsorbents which are more efficient and at telemedicine components that can be coupled with our products to create better formulas for medicine. I think as we have seen in other sectors of the medical world, oxygen devices will become smaller – lighter and be able to provide better therapy for LTOT patients which in turn will increase adherence and reduce overall health care costs related to a disease which is the 4th leading cause of death in the world.

BLOOD GAS ROUNDTABLE

OPTI Medical Systems

Please describe your blood gas products.

OPTI Medical Systems manufactures the OPTI line of analyzers for measuring time sensitive diagnostic assays including blood gas, electrolytes, ionized calcium, measured SO₂, tHb, glucose, and lactate. OPTI Medical offers the portable **OPTI CCA-TS** blood gas analyzer, the **OPTI R** blood gas analyzer with Auto QC, and the **OPTI LION** electrolytes and ionized calcium analyzer. Each analyzer provides fast, lab-accurate results, simple intuitive operation, and can be integrated with any HIS/LIS. The patented optical fluorescent and reflectance technology used in the OPTI analyzers virtually eliminates maintenance costs, test delays, and down time. OPTI Medical also offers the **PrismPOC** data management system which makes managing blood gas results easy and efficient. The web-based system includes advanced QC reports with statistical analysis and patient data history/trending. Visit optimedical.com or call (800) 490-6784.

Tell us about your current R&D efforts.

OPTI Medical has recently released two new cassette styles for the OPTI CCA-TS analyzer. The **OPTI B-Lac** cassette is for the measurement of lactate, pH, PCO₂, PO₂, tHb, and SO₂ in whole blood – perfect for quick diagnosis and to assist in early detection of sepsis at the point of care. The **OPTI B60** cassette offers accurate blood gas analysis with only a few drops of blood. pH, pCO₂ and PO₂ can now be measured using only 60 µl of blood.

How has point of care testing improved clinical decision-making?

Point of care testing has allowed clinicians to obtain accurate results at the point of care without having to wait for longer lab turnaround times. This can lead to faster diagnosis in critical care situations with improved patient outcomes. With the OPTI CCA-TS, obtaining accurate blood gas results at the point of care is fast, easy, and convenient. It is easy-to-use with excellent reliability. Its optical fluorescence and reflectance technology eliminates electrodes, minimizing maintenance and operational costs making it ideal for near patient and point-of-care testing.

How does your product provide for accuracy in measurement?

The OPTI CCA-TS and OPTI R analyzers have a variety of internal controls that are performed with each measurement to ensure the functionality of the system and the integrity of the results. To ensure no sample loss, the OPTI CCA-TS analyzer calibrates every test cassette using precision buffers and gas mixes before the patient sample is introduced. The OPTI R analyzer has an internal quality monitoring system that continually checks the performance of each test sensor and executes corrective actions if needed. Both analyzers automatically aspirate the patient sample and have automatic clot, short sample, and bubble detection to ensure the reliability of the results. The OPTI CCA-TS comes with easy-to-use electronic controls and the OPTI R automatically tests 3 levels of aqueous controls to monitor measurement accuracy.

What type of training and customer assistance/support programs do you have in place?

OPTI Medical is dedicated to providing the highest quality of

customer care. Our Technical Support team is available via phone and e-mail 24 hours a day 7 days a week. OPTI Medical offers various training solutions both online and on-site which can be specifically tailored to fit user needs.

Roche Diagnostics

Please describe your current blood gas products.

As a world leader in diagnostic testing, the Roche **cobas b 221** blood gas system was uniquely designed to help provide virtually uninterrupted performance. One way of doing this is by resolving blockages often caused by blood clots. Blood clots are commonplace for most blood gas analyzers and it can be time consuming to return the analyzer to reliable performance. If a clot enters the cobas b 221 blood gas system, a powerful fluidic system that includes both peristaltic pump and vacuum pump mechanics can remove the source of trouble and help minimize downtime. The cobas b 221 configurable menu has options for blood gas (pO₂, pCO₂, and pH), electrolytes (Na⁺, K⁺, Cl⁻, Ca²⁺, Hematocrit), metabolites (glucose, lactate, BUN), and Co-oximetry (O₂Hb, HHb, COHb, MetHb, tHb, Bilirubin). The cobas b 221 blood gas system was the first FDA 510(k) cleared for testing pleural fluid pH. With the ability to trend patient data and automated acid-base mapping trending, the cobas b 221 system provides actionable information and simplifies regulatory compliance. The cobas b 221 blood gas system coupled with cobas bge link Instrument Manager software enables monitoring and control of decentralized system from one location. Cobas bge link enhances operational efficiency of all connected systems through screen sharing to provide immediate real-time performance status, maintenance updates, and remote access for administrative management.

How has your company pursued R&D efforts to improve blood gas technology?

Roche Diagnostics is committed to continuous research and development in blood gas systems. Roche has a new point of care blood gas system in development. This product is currently in development/research stage only and is not available for sale in the US.

How has point of care testing improved clinical decision making?

The cobas b 221 blood gas system can help improve point of care clinical decision making by delivering results in 60 seconds for fast turnaround time and enhanced workflow efficiency. The speed to results combined with the low blood sample volume (88 µl), required by the cobas b 221, helps healthcare professionals get blood gas test results faster and reduces the time for physicians to make critical medical decisions that impact patient outcomes. In addition, the cobas b 221 offers direct interfacing options to the hospital HIS/LIS which allows the respiratory therapist to run the sample and enable the physician to interpret the results in another part of the hospital or remotely. The automated acid-base mapping on the cobas b 221 system can help clinicians rapidly identify metabolic and respiratory acid-base disturbances without the need for a calculator and help differentiate between acute and chronic patient conditions in complex environments such as the ED or ICU.

How does your product provide for accuracy in measurement?

The cobas b 221 system maintains accuracy through calibrations

with NIST calibration solutions and an AutoQC module. The cobas b 221 can be programmed to run a 1-point calibrations every 30 minutes or 1 hour, 2-point calibration every 4, 8, or 12 hours, and a 2-point system calibration every 8, 12, or 24 hours. The AutoQC module utilizes a 120 ampoule based system that can be programmed to perform individual QC sampling at the times and frequency programmed by the user. A sample can only be run after a valid calibration has been completed. If a calibration error is detected, the cobas b 221 system automatically reruns the calibration. The AutoQC system can also be set to rerun and lock out future samples should they fail in order to assist with regulatory compliance. In the critical care setting, spectrophotometer analysis of hemoglobin and its derivatives (co-oximetry), in combination with blood gas analysis, provides immediate actionable information about oxygen transport in human blood. The accuracy of the hemoglobin and bilirubin results depends on the performance of the co-oximetry technology. The co-oximetry module of the cobas b 221 blood gas system measures both hemoglobin derivatives and bilirubin spectrophotometrically in the visible spectrum (460nm to 660nm). Absorbance of the sample is measured at a total of 512 discrete wavelengths. The concentration of hemoglobin, hemoglobin derivatives and bilirubin are determined by applying an accepted mathematical algorithm. This enables the cobas b 221 systems' co-oximetry technology to detect the presence of light-absorbing substances necessary to prevent the reporting of incorrect values due to interfering substances. This advanced co-oximetry design helps improve the accuracy of patient test results, while demonstrating a high correlation with results from accepted clinical chemistry methods.

What type of training and customer assistance/support programs do you have in place?

Roche Diagnostics provides a variety of educational materials to help healthcare professionals operate the cobas b 221 system properly and help maintain operator certification. These educational materials include: • Onboard video tutorials and a customer-based training CD-ROM along with Instruction manuals that provide detailed descriptions to help operators avoid errors using the equipment. • Roche offers a two-day training programs at its Indianapolis headquarters for two operators as well as on-site training at the customer facility. • Roche offers extensive on-line support through MyLabOnline, which gives users web-based access to all current documentation such as MSDS sheets, package inserts, customer bulletins and manuals. • Online CEU courses are available for staff members to help maintain their lab and/or Respiratory Therapy accreditation. • Roche's Indianapolis-based Tech Support team provides telephone support for immediate, real-time troubleshooting which may help reduce downtime and the need for a service visit.

Siemens Healthcare Diagnostics

Please describe your blood gas products

Siemens Healthcare Diagnostics has a comprehensive critical care portfolio used for monitoring and analysis of blood gas results in many areas of the hospital, including the ICU, NICU, operating room, emergency department, laboratory, and respiratory therapy areas. The portfolio provides rapid, reliable blood gas information and a connectivity solution for

secure facility-wide communication. Siemens most recently introduced the neonatal total bilirubin parameter on the **RAPIDLab 1200** blood gas analyzers. Additionally, updated versions of the **RAPIDPoint 400/405** and **RAPIDLab 1200** blood gas analyzers were introduced allowing laboratory managers to view the instrument display from a remote location using the **RAPIDComm** system.

Tell us about your current R&D efforts.

Siemens Healthcare Diagnostics dedicates more than 9% of revenue to R&D spending and has more than 45 years of blood gas experience. With a continued commitment to meeting future customer demands, the company uses customer surveys as a guide towards developing new point-of-care products, improvements, and educational programs. The company's overall focus for developing new products includes addressing today's challenges in the laboratory environment: cost pressures, labor shortage, lack of space, turnaround time, and improving patient outcomes.

How has point-of-care testing improved clinical decision making?

Point-of-care testing has accelerated the availability of critical care testing information to help clinicians diagnose and treat patients faster. Today's point-of-care instruments and data management systems improve workflow efficiencies, quality of care, and patient outcomes.

How does our product provide for accuracy in measurement?

Siemens Healthcare Diagnostics blood gas instruments have industry-proven accuracy and reliability through long-life **Ready Sensor** electrode technology. Lab-quality results and regulatory compliance are also ensured through on-board automatic quality control cartridges requiring no operator intervention during the 28-day cartridge life.

What type of training and customer assistance programs do we have in place?

Siemens Healthcare Diagnostics partners with respiratory care professionals to improve skills when caring for the critically and chronically ill. Siemens developed seminars accredited by the AARC/PACE for up to six CEU credits for respiratory therapists, respiratory care directors, lab managers, and supervisors, to help meet requirements for continuing education credits. The seminars use practical, evidenced-based articles and case studies to emphasize patient focus. Siemens also partners with laboratory customers and offers a comprehensive portfolio of online educational courses focused on point-of-care testing. These courses help to expand industry-related knowledge while avoiding excessive time or travel. Siemens online courses offer a variety of accredited modules that reflect all experience levels to meet the needs of staff. Siemens also has an extensive training program providing point-of-care customers with dedicated and highly specialized support and training services unmatched in the industry. Siemens customer education specialists and network support specialists will ensure customers are properly trained to operate products, manage data, and provide the best care for patients while being inspection-ready at a moment's notice. The Siemens network support specialists also work closely with hospital IT departments to ensure seamless integration with LIS systems and Siemens **RAPIDComm** Data Management System. Visit usa.siemens.com/bloodgases.

ALI and ARDS

Jeff Borrink, BS, RRT

Anti-platelet Therapy May Reduce the Incidence of Acute Lung Injury

Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS) can be difficult to treat and potentially fatal. Accepted ventilation strategy includes treatment with low tidal volumes of 4 to 6cc/kg of Ideal Body Weight and low plateau pressures of < 28-30cmH₂O. However, there are many components to the pathophysiology of ALI/ARDS. Platelet activation is one key component, and therefore may offer an opportunity to help prevent the development of ALI/ARDS in susceptible patients.

A study by Jason Erlich MD et al, published by the American College of Chest Physicians showed that pre-hospitalization anti-platelet therapy was associated with a reduced incidence of ALI/ARDS. One hundred and sixty-one patients in Olmsted County Minnesota with an ICU admission in 2006 were evaluated. Patients with at least one risk factor for ALI were included in the study. Seventy-nine (49%) of the patients were receiving anti-platelet therapy at the time of admission. Thirty-three patients (21%) developed ALI/ARDS. Patients receiving anti-platelet therapy had a reduced incidence of ALI/ARDS (12.7% vs 28%) and this association remained significant after adjusting for confounding variables. The authors concluded that if these results can be confirmed in a more diverse patient population, the results would support the use of anti-platelet agents in an ALI prevention trial. [Reference: Jason M. Erlich, MD, Daniel S. Talmor, MD, MPH, Rodrigo Cartin-Ceba, MD et al. Pre-hospitalization anti-platelet therapy is associated with a reduced incidence of acute lung injury: A population-based cohort study. *Chest*. 2010 Aug 5.]

Higher vs Lower Positive End-Expiratory Pressure in Patients with ALI and ARDS

It is well documented that mechanical ventilation can cause Ventilator Induced Lung Injury (VILI) from volutrauma, or lung over-distention at end-inspiration. Lung protective ventilation utilizing low tidal volumes and low end-inspiratory plateau pressures help mitigate VILI, and are beneficial in treating patients with Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS). Therefore, the critical care community has generally embraced this approach to ventilation and it has become the standard of care for these patients.

VILI can also be caused by atelectrauma, or the cyclic closing and reopening of alveoli. Attempts have been made to mitigate this type of VILI by manipulating the Positive End-Expiratory Pressure (PEEP), but the optimal level of PEEP remains unestablished,¹⁻² and best approach to apply the optimal level of PEEP remains controversial and uncertain. Some studies have found no survival advantage from managing ARDS with higher PEEP settings.³⁻⁵

However, one systematic review and meta-analysis of individual patient data from multiple studies on higher PEEP vs. lower PEEP settings published in the *Journal of the American Medical Association (JAMA)* supports higher PEEP levels in patients with ARDS.

The objective of the study by Briel M. et al was to evaluate the association of higher vs lower PEEP with patient important outcomes in adults with ALI or ARDS who were receiving ventilation with low tidal volumes, and to investigate whether these associations differed across pre-specified subgroups.⁶

In order to evaluate this association, the authors searched studies from 1996-2010 and conference proceedings from 2004-2010. Data was then extracted from three clinical trials and included 2299 patients that met their eligibility criteria. The three clinical trials consisted of the Assessment of Low Tidal Volume and Elevated End-Expiratory Pressure to Obviate Lung Injury study (ALVEOLI), the Lung Open Ventilation to Decrease Mortality in the Acute Respiratory Distress Syndrome study (LOVS), and the Expiratory Pressure study (EXPRESS).² Mean tidal volumes were close to 6ml/kg of predicted body weight in the control group and the experimental group in all three clinical trials.

Results of the analysis for patients with ARDS at baseline showed that higher levels of PEEP were associated with a relative mortality reduction of 10%, and patients in the higher PEEP group were more likely to achieve un-assisted breathing earlier.⁶ In contrast, patients with ALI but without ARDS may not benefit, or may actually experience harm from higher PEEP levels.⁶ This study provides some preliminary support for those looking for evidence based medicine to support the concept of the need for higher PEEP levels in patients with ARDS.

Of interest is the fact that 45% of patients in both the low and high PEEP groups received paralytics, presumably to control excess respiratory drive, asynchrony, and/or transpulmonary pressures when indicated.

Jeff Borrink is Clinical Specialist, Hamilton Medical, Inc. These two reports are from Hamilton Medical's newsletter.

The analysis does not support any specific method for determining the need for higher PEEP, but as in the ALVEOLI study, patients not only suffered no harm from higher PEEP levels, but had improved outcomes.

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Reducing PPRs (Potentially Preventable Readmissions): Tracheostomy Management Services Averts Readmissions

Joann Miller

It is critical for health care to develop an organized, proactive, multidisciplinary approach to manage chronic tracheostomy associated complications. Instilling personal self-management skills prior to patient transitioning will not only create compliant patients resulting in reduced readmissions but will also reduce hospital costs.

Presently, comprehensive guidance of tracheostomy management services does not universally exist nor do patient self-management plans. Patient self-management plans are not routinely used and do not exist at all in many markets.

“Too often patients are sent home without proper instructions on how to care for themselves. A patient with congestive heart failure, left guessing about what to do, is more likely to be readmitted. Just one averted readmission through better patient instruction can save \$5,000 or more.”¹ For tracheostomy patients the savings nearly triple that of non-trached patients. Just one averted readmission of a tracheostomy patient through better patient instruction can save on average \$14,500.

Inconsistent levels of knowledge and variations in clinical practice represent a patient safety threat throughout all disciplines of tracheostomy patient care. Tracheostomy care re-admittance due to nosocomial infections or airway complications can result in prolonged re-hospitalization and even death.

“The top ten procedures associated with the most costly stays in hospitals, with the mean charges for the hospital stay, according to 2003 statistics from 17 selected states are:

- 1 Organ transplantation, including transplants of the lung, heart, spleen, intestine, liver and pancreas and excluding kidney, bone, corneal and bone marrow transplants — \$275,621
- 2 Tracheostomy — \$240,010
- 3 Bone marrow transplant — \$207,622
- 4 Destruction of lesion of retina — \$197,169
- 5 Ileostomy and enterostomy — \$129,499
- 6 Heart valve procedures — \$125,545

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- 7 Kidney transplant — \$115,023
- 8 Swan-Ganz catheterization — \$105,421
- 9 Extracorporeal circulation auxiliary — \$99,057
- 10 Gastronomy — \$98,772

CCS Principal Procedure statistics as of 2008, show 3% of patients requiring a tracheostomy were admissions from Long Term Care (LTC) facilities with 10% from other hospitals, 62% from emergency departments and 25% primary/acute care patients within the current facility, with an average length of stay of 30 days at a total cost of \$252,110.²

With tracheostomy second to organ transplantation it is not only the second most expensive hospital stay, it is among the longest length of stay (LOS). Tracheostomy procedures are not in themselves costly but are associated with critical illness and expensive ICU stays.

Standard tracheostomy care is no longer acceptable. “A dispiriting truism of modern medicine is that clinicians routinely do not provide treatments proven to reduce complications and save lives... Respiratory care is not immune to this problem: multiple published studies demonstrate deficits in the quality of care for patients with severe respiratory disease. Unfortunately, lagging behind our understanding of the evidence gap is our understanding of how to bridge that gap... as governments, payers, and patients demand more accountability in healthcare, it is increasingly important that all healthcare practitioners be familiar with its tenets.”³

The Agency for Health Care Research and Quality (AHRQ) has, through a grant opportunity, titled, Researching Implementation and Change while Improving Quality (R18). AHRQ underlined the importance of implementation of quality improvement strategy, “...There is increasing evidence that success in achieving quality improvement goals is at least partially attributable to implementation processes and contexts and not just to the nature of the quality improvement strategy...”⁴

Tracheostomy patients are among the most fragile of patients, and among the most likely to require readmission due to complications and infections of their dramatically altered and vulnerable upper respiratory system. “...readmission rates of these patients is higher than non-tracheostomized patients (4–10% 2). This higher readmission rate may be the reflection of the degree of compromise of these patients leading in fact to the need of tracheostomy. The already established ICU readmission

predictors of non tracheostomized patients did not apply to tracheostomized patients...)⁵

Respiratory care practitioners must create a New Standard throughout respiratory care disciplines from initial patient admission to transition and after care whether the transition is home care or LTC.

Further, patients requiring a tracheostomy as a principal procedure are readmitted to hospitals and emergency departments at an average cost of \$14,500. Historically, adult tracheostomy patients average two re-hospitalizations annually due mainly to Potentially Preventable Complications (PPCs) brought on by being sent home without proper instructions on how to care for themselves. Pediatric readmissions surpass that of adult readmissions in all statistical data currently available.

Humidification of the sinus, oral and nasal cavities and trachea must be included in the New Standard in patient self-management skills prior to patient transitioning from acute care to home or LTC. The Wright Face & Tracheostomy Nebulizing Mask Delivery System, is easily adopted into patients' self-management plans.

Initially invented for patients readmitted due to humidification treatment non-compliance, the Wright Mask is a convenient delivery system which turns non-compliant patients into compliant comfortable patients, able to enjoy an improved quality of life both at home or in LTC.

When included in discharge plans, outpatient humidification with the Wright Mask Delivery System complements and improves standard treatment in tracheostomy care management goals just as inpatient humidification does.

The ultimate goal of the Wright Mask Delivery System is to reduce the need for readmission due to PPCs such as tracheostomy associated pneumonia, mucous plugs or trachea infection. Through proper and regular use within Patient Self-Management Plans, the Wright Mask stands to reduce healthcare costs and possibly reduce mortality rates caused by PPCs.

"...Good discharge plans can help reduce the rate of unplanned readmissions by giving patients the care instructions they need after a hospital stay and by helping patients recognize symptoms that may require immediate medical attention."⁶

"Reducing readmissions is a priority among the medical community, researchers and policymakers who are focused on identifying the causes of readmissions and implementing evidence-based strategies to reduce those that are preventable. One national study found that almost one-fifth of Medicare patients are readmitted within 30 days of discharge and a third are re-hospitalized within 90 days."⁷ "As such, examining readmission rates is important from both a quality of care and cost standpoint. While not all readmissions can be prevented, high-quality care may lessen the need for subsequent hospitalizations."⁸

Can Outcomes of Intensive Care Unit Patients Undergoing Tracheostomy Be Predicted?

Reasons for Readmission of 15 Patients to the Intensive Care Unit

Diagnosis/Organ Dysfunction	
Necessitating Readmission	n
Respiratory	9
Cardiac	3
Sepsis	0
Gastrointestinal bleeding	2
Unknown	1

The above identifies a small sample of reasons for readmission to ICU of tracheostomy patients. The authors of this study "...undertook this retrospective review of data from patients who underwent tracheostomy in our ICU to determine if specific diagnostic factors could be identified in this population, with the thought that identification of any such factors might lead to changes in clinical management strategies or patient-safety initiatives."⁹

CMS tracking of readmission rates for certain high-volume or high-cost conditions is scheduled to begin in 2012; the need for each and every clinician to do what one can to prevent re-hospitalization of this patient population is now more than ever in the hands of all disciplines of tracheostomy patient care.

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Ventilatory and ECMO Treatment of H1N1-Induced Severe Respiratory Failure

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Abstract

Background: Since the first outbreak of a respiratory illness caused by H1N1 virus in Mexico, several reports have described the need of intensive care or extracorporeal membrane oxygenation (ECMO) assistance in young and often healthy patients. Here we describe our experience in H1N1-induced ARDS using both ventilation strategy and ECMO assistance.

Methods: Following Italian Ministry of Health instructions, an Emergency Service was established at the Careggi Teaching Hospital (Florence, Italy) for the novel pandemic influenza. From Sept 09 to Jan 10, all patients admitted to our Intensive Care Unit (ICU) of the Emergency Department with ARDS due to H1N1 infection were studied. All ECMO treatments were veno-venous. H1N1 infection was confirmed by PCR assayed on pharyngeal swab, subglottic aspiration and bronchoalveolar lavage. Lung pathology was evaluated daily by lung ultrasound (LUS) examination.

Results: A total of 12 patients were studied: 7 underwent ECMO treatment, and 5 responded to protective mechanical ventilation. Two patients had co-infection by Legionella Pneumophila. One woman was pregnant. In our series, PCR from bronchoalveolar lavage had a 100% sensitivity compared to 75% from pharyngeal swab samples. The routine use of LUS limited the number of chest X-ray examinations and decreased transportation to radiology for CT-scan, increasing patient safety and avoiding the transitory disconnection from ventilator. No major complications occurred during ECMO treatments. In three cases, bleeding from vascular access sites due to heparin infusion required blood transfusions. Overall mortality rate was 8.3%.

Conclusions: In our experience, early ECMO assistance resulted safe and feasible, considering the life threatening condition, in

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H1N1-induced ARDS. Lung ultrasound is an effective mean for daily assessment of ARDS patients.

Background

Since the first outbreak of a respiratory illness caused by Influenza A (H1N1) virus in Mexico,¹ several reports have described the need of intensive care²⁻⁴ or extracorporeal membrane oxygenation (ECMO) assistance⁵ in young and often healthy patients. Beginning August 2009, the Italian Ministry of Health and the Tuscany Ministry of Health issued instructions to identify and establish referral centers able to care for the more severely ill influenza patients. Therefore, several referral centers were identified throughout the national territory among the hospitals already experienced in extracorporeal respiratory support techniques. The referral ECMO centres, in addition to being capable of guaranteeing the most advanced treatment in influenza related respiratory failure, were also entrusted with providing support to the nearby hospitals and assuring safe transportation.

In the present investigation we report our experience, as an ECMO referral center, in H1N1-induced acute respiratory distress syndrome (ARDS) and we present the critical care service planning in response to the H1N1 pandemic.

Methods

Following the instructions of the Italian Ministry of Health and Tuscany Regional Ministry of Health, an Emergency Medical

Table 1 Italian Ministry of Health criteria to discuss the need of ECMO

Acute respiratory failure with one of the following condition:

1. SaO₂ < 85% for at least 1 hour
2. Oxygenation Index >25 for at least 6 hours after ventilation optimisation
3. PaO₂/FiO₂ < 100 with PEEP ≥ 10cmH₂O for at least 6 hours after ventilation's optimization
4. Hypercapnia with pH < 7.25
5. SvO₂ < 65% with hematocrit >30 and under vasoactive drugs infusion

The parameter are referred to a condition of lung protective ventilation (tidal volume:4-6 ml/Kg of predicted body weight; plateau pressure ≤ 30 cmH₂O; PEEP >lower inflection point of the curve pressure-volume).

PEEP: positive end-expiratory pressure; PaO₂: arterial oxygen partial pressure; FiO₂: inspired oxygen fraction; RR: respiratory rate; SaO₂: peripheral oxygen saturation; SvO₂: central venous oxygen saturation.

Oxygenation Index: Mean airway pressure (cmH₂O) * FiO₂ * 100/PaO₂;

Table 2 baseline and clinical characteristics of H1N1-pneumonia patients

Number	12
Male sex, N (%)	8 (66.7%)
Age (years)	44.5 (36.8-48.8)
BMI	27 (23.8-31)
SAPS II	36 (27.75-44.75)
Patients with comorbidities, N (%)	5 (41.7%)
Patients with proved coinfection, N (%)	2 (16.7%)
Days from onset to ICU admission	7 (6-8.25)
§ PaO ₂ (mmHg)/FiO ₂	92 (53.5-119.5)
§ PaCO ₂ (mmHg)	65 (39.9-83)
§ pH	7.37 (7.32-7.50)
§ Respiratory rate (N/min)	8.62 (6.87-11.3)
§ White cells count (N*1000/ml)	8.620 (6.870-11.300)
§ Platelets count (N*1000/ml)	158.5 (102-217.3)
§ Lactate dehydrogenase (U/l)	617 (391.2-919.8)
§ Creatine kinase (U/l)	611 (402.5-893.8)
§ Aspartate aminotransferase (U/l)	53.5 (39.8-121.3)
§ Alanine aminotransferase (U/l)	37.5 (27.3-43.5)
§ C-reactive protein (mg/dl)	80.5 (35.9-132.4)
§ Serum creatinine (mg/dl)	0.87 (0.69-1.26)
§ Procalcitonin (ng/ml)	3.2 (1.1-4.3)
Chest radiographs (mean per patient)	7.3
Chest CT-scan (mean per patient)	1.25
Tracheostomy, N (%)	5 (41.7%)
ECMO, N (%)	7 (58.3%)
CVVH, N (%)	2 (16.7%)
Duration of mechanical ventilation (days)	13.5 (10.8-21.5)
ICU length of stay (days)	16.5 (10.5-25.5)
Mortality, N (%)	1 (8.3%)

Data are referred to first assessment at ICU admission. Continuous data are represented as medians with 25th to 75th interquartile range (IQR). Percent data are referred to the total population of each group.

BMI: body mass index; CVVH: continuous veno-venous hemofiltration; ECMO: extracorporeal membrane oxygenation; SAPS: simplified acute physiology score.

§ values at ICU admission

Service was established in the Careggi Hospital in Florence Italy for the novel pandemic influenza.

The Careggi Hospital ECMO Team is composed of: an intensivist, a cardiac surgeon, a cardiologist, a nurse, and a perfusionist. All of the members of the team are properly trained in ECMO treatment. An ambulance and a car are equipped with an ECMO circuit, a transport ventilator and all of the materials needed to initiate extracorporeal support in the peripheral hospitals, and permit safe transportation while on extracorporeal circulation to our referral hospital.

The requirement of ECMO was decided based on the Italian Ministry of Health criteria (Table 1).

From September 2009 to January 2010, all patients admitted to our ICU with severe respiratory failure due to H1N1 infection were included in this study. Patient demographics and clinical characteristics were collected from institutional ICU database (FileMaker Pro, FileMaker, Inc, USA), from Italian Group for the

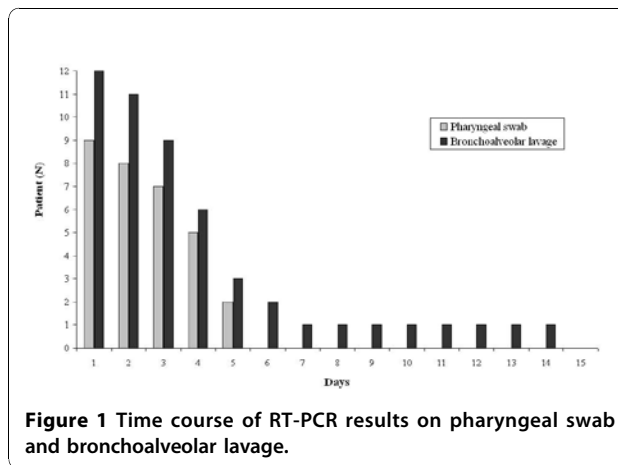


Figure 1 Time course of RT-PCR results on pharyngeal swab and bronchoalveolar lavage.

Evaluation of Interventions in Intensive Care Medicine database (GIVI Margherita Project, Istituto Mario Negri, Bergamo, Italy) and from ECMO national network database. Discrete variables are expressed as counts and percentages, whereas continuous variables are reported as medians with 25th to 75th interquartile range (IQR). The Internal Review Board approved this retrospective study and informed consent for data publication was obtained from the patients or relatives.

Ventilation strategy: Pressure volume curves were calculated with ventilator's built in application (Draeger Evita XL, Draeger Medical AG, Lubeck Germany) starting from a PEEP level of 5 cm H₂O, with a pressure limit of 40. Ventilation parameters were set on the basis of this calculation, with a PEEP of 2 cmH₂O above the lower inflection point of the pressure-volume curve, and a peak pressure below the upper inflection point. In all cases, pressure plateau was limited to 30 cmH₂O and the tidal volume was kept below 6 ml/Kg.⁶ Recruitment manoeuvres (40 sec at 40 cmH₂O) were performed twice a day, if needed, to improve pulmonary gas exchange.

ECMO: All ECMO treatments were veno-venous (Maquet Rotaflow Centrifugal Pumps with Quadrox-D oxygenators, Maquet, Rastatt, Germany) and biocoated circuits were used. Two types of cannulation were used. Initially a venous withdrawal cannula was inserted via femoral vein (Edwards Lifesciences Femoral Venous Cannula 22-24 Fr, Edwards Lifescience, Irvine, CA or Maquet HLS Venous Cannula 21-25 Fr, Maquet Cardiopulmonary AG, Hirrlingen-Germany) and an infusion cannula in the right jugular vein (Edwards Lifesciences Fem-Flex II Cannula 20 Fr., Edwards Lifescience, Irvine, CA-USA or Maquet HLS Arterial Cannula 23 Fr, Maquet Cardiopulmonary AG, Hirrlingen-Germany) were adopted. During the period study Avalon double lumen cannulas (Avalon Elite Bi-Caval Dual Lumen Catheter 27-31 Fr, Avalon Laboratories, Rancho Dominguez, CA) become available and were inserted through internal right jugular vein in 2 patients. Cannulation was conducted percutaneously with Seldinger technique in all cases, and cannulas position was confirmed by transesophageal echocardiography. Heparin infusion during extracorporeal lung assistance was monitored every two hours by bedside aPTT measurement (Hemochron Jr Signature plus, ITC Europe, Milan, IT), which was maintained between 50 and 80 seconds. In case of renal replacement therapy requirement in ECMO patients, a continuous veno-venous hemodiafiltration circuit was assembled on the ECMO circuit (aspiration on pre-pump line, restitution on pre-oxygenation line). ECMO patients were ventilated with

Table 3 differences between ECMO and ventilated patients

	ECMO patients	Non-ECMO patients
Number (%)	7	5
Male sex, N (%)	6 (85.7%)	2 (40%)
Age (years)	45 (37-46.5)	42 (39-51)
BMI	27 (23.5-36.5)	27 (25-29)
SAPS II	44 (39-50.5)	28 (27-28)
Patients with comorbidities, N (%)	5 (71.4%)	2 (40%)
Patients with proved coinfection, N (%)	2 (28.6%)	0
Days from onset to ICU admission	6 (6-7.5)	7 (7-9)
§ PaO ₂ (mmHg)/FiO ₂	48.7 (46.8-58)	116 (107-141)
§ PaCO ₂ (mmHg)	81.6 (60.6-88)	57 (55.8-63)
§ pH	7.25 (7.20-7.30)	7.33 (7.28-7.34)
§ Respiratory rate (N/min)	10 (8.5-15)	20 (18-22)
§ PEEP (cmH ₂ O)	14 (11-15)	14 (11-15)
§ Static compliance(ml/cmH ₂ O)	34 (30-38)	32 (23-38)
§ White cells count (N*1000/ml)	11 (9.1-13.3)	7.03 (6.7-8.6)
§ Platelets count (N*1000/ml)	151 (115.5-218.5)	158.5 (125.3-182.5)
§ Lactate dehydrogenase (U/l)	445 (372.5-920.5)	627 (607-632)
§ Creatine kinase (U/l)	477 (189-890.3)	435 (281.5-695)
§ Aspartate aminotransferase (U/l)	54 (42-121.5)	53 (42-78)
§ Alanine aminotransferase (U/l)	38 (25.5-41)	37 (29-45)
§ C-reactive protein (mg/dl)	83.5 (77.5-315.7)	127.5 (96.3-158.8)
§ Serum creatinine (mg/dl)	1.02 (0.79-1.72)	0.81 (0.55-0.85)
§ Procalcitonin (ng/ml)	4.3 (2.7-29.4)	1.9 (0.2-2.6)
CVVH, N (%)	2 (28.6%)	0
Chest radiographs (mean per patient)	9.6	4.2
Chest CT-scan (mean per patient)	1.6	0.8
Duration of mechanical ventilation (days)	19 (12-36)	9 (5-11)
ICU length of stay (days)	23 (17.5-38)	11 (8-14)
Packed Red Blood Cells Units, N	4 (1-6)	1 (0-3)
Mortality, N (%)	1 (14.3%)	0 (0%)

Data on airway pressures and respiratory rate are referred after intubation and recruitment. Continuous data are represented as medians with 25th to 75th interquartile range (IQR). Percent data are referred to the total population of each group.

BMI: body mass index; CVVH: continuous veno-venous hemofiltration; ECMO: extracorporeal membrane oxygenation; SAPS: simplified acute physiology score.

§ Values at ICU admission

protective parameters, and respiratory rate and ECMO flow were adjusted to achieve normocarbia and oxygen saturation above 92%.

Infection control: H1N1 infection was confirmed by real-time reverse transcriptase-polymerase-chain-reaction (RT-PCR) assayed on pharyngeal swab, subglottic aspiration and bronchoalveolar lavage in accordance with published guidelines.⁷ Bronchoalveolar specimens were obtained with a mini-invasive system (Kimberly-Clark BAL Cath, Kimberly-Klark NV Zaventem - Belgium), or by bronchoscopy.

Patients were isolated in negative pressure atmosphere rooms, and staff wore full protective garments (including FFP3 respirators, 3 M Italia SpA, Segrate, Italy), until 2 consecutive tests were confirmed negative. During the study period only one case of suspected transmission of influenza to a nurse occurred.

Antiviral therapy consisted in oral oseltamivir (75 mg twice daily) and inhaled zanamivir (10 mg twice daily).

Blood and urinary cultures, tracheal aspirate, and pharyngeal swab were obtained upon patient admission. Empiric antimicrobial regimen at ICU admission was initiated with levofloxacin and amoxicillin/clavulanate; eventually specific antimicrobial therapy was varied or ended on the basis of microbiological results. Steroids were administered at low dosage (20 mg metilprednisolon twice per day) to prevent lung fibrosis. Diuretics were administered at different dosages, depending on clinical judgment and the patient's renal function.

Lung ultrasound examination: Lung ultra sound (LUS) examinations were daily performed by the attending physician, with a multi-frequency convex probe (3.5-5 MHz, Mylab TM 30CV, ESAOTE, Genova, IT). With the patient in semirecumbent position, lateral and anterior views were obtained from base to apex of the chest. Posterior axillary line was followed during lateral transversal examinations. Chest quadrants defined by the intercostal spaces and the parasternal, mid-clavicular, and anterior axillary lines were scanned on the anterior chest wall.⁸ The occurrence and extension of parenchymal consolidations,

Table 4 main ventilation and ECMO data of patients treated with ECMO

Patient	Age (years)	Comorbidity	Pre-ECMO parameters							In-ECMO parameters (Day 1)							
			Peak Pressure	PEEP	tV	RR	PaO ₂ *	CO ₂	pH	Ventilation days before ECMO	Peak Pressure	PEEP	tV	RR	Pump Flow	Days on ECMO	Ventilation days after ECMO
1	15	Asthma	30	14	350	14	50	52	7.18	1	18	10	300	10	5.2	6	3
2	58	-	30	14	400	16	66	76	7.14	2	22	14	300	7	5.0	6	5
3 [§]	44	Obesity	33	15	240	20	60	89	7.27	2	28	15	200	9	6.1	15 [^]	12
4 [§]	48	Cigarette smoke	40	10	700	18	58	54	7.29	1	24	14	270	7	5.9	8	10 [^]
5 [§]	30	Asthma, obesity, cigarette smoke	35	15	700	22	48	55	7.22	2	24	14	400	6	5.3	6	3
6 [§]	45	Psychiatric disorder, emphysema bulla	45	18	250	20	54	73	7.22	6	28	17	160	8	5.7	37 [#]	-
7	45	-	35	15	410	32	73	84	7.17	7	25	15	300	20	5.0	18	21 [^]

PEEP: positive end expiratory pressure; RR: respiratory rate; tV: tidal volume.

* Measured with FiO₂ = 1

§ Patient referred from another hospital

Dead on ECMO

^ patient tracheostomized during ECMO

alveolar interstitial syndrome (measured by the number of B-lines), and morphology of pleural line were evaluated.^{9,11} Pleural effusions were estimated by using Balik's formula.^{12,13} In order to ensure a uniform record, and allow to follow the evolution of the findings over time, all exams were recorded in an electronic form, in which the description of the main LUS features was predetermined.¹⁴

Results

Overall patients: During the study period, 12 patients requiring invasive ventilation treatment and/or ECMO were admitted or transferred to our ICU. Baseline and clinical characteristics of patients admitted for H1N1-induced severe respiratory failure are summarized in Table 2.

The median time between initial, non specific, symptoms and respiratory failure was 7 days (IQR 6-8.25), and severe hypoxia, unresponsiveness to non-invasive ventilation, was the main clinical feature. Our patients were young, median age 44.5 years, none of them older than 58 years, and eight (80%) younger than 50. Two patients were severely obese (BMI > 40), one woman was pregnant (18 weeks), two patients had a history of chronic obstructive respiratory disease (COPD), and one had diabetes. Two patients had Legionella Pneumophila coinfection at admission, and one young patient (16 years old) with suspect viral myocarditis and heart failure. At admission the patients, with the exception of the two coinfecting, presented low leukocyte and platelet count and low plasma procalcitonin levels, significant levels of lactate dehydrogenase (LDH), creatine kinase (CK), and C-reactive protein (Table 2). Median duration of mechanical ventilation (days) was 11.5 (IQR 9.8-16.3) and median ICU length of stay (days) was 14 (IQR 12-16.5). The pregnant woman continued the pregnancy without significant complications.

In ICU infection rate was low with two ventilator associated pneumonia and two asymptomatic positive blood cultures in two ECMO patients. One ECMO patient died due to a systemic secondary infection by Aspergillus: this patient was the only non-

surviving patient (overall mortality rate 8.3%).

H1N1 infection monitoring and therapy: RT-PCRs from bronchoalveolar lavage samples were positive in all patients included in this study. On the contrary, RT-PCR dosed on pharyngeal swab resulted positive in less than 70% of patients at ICU admission, and in 90% of patients in the second day (Figure 1). Also efficacy of antiviral therapy was reliably followed through RT-PCR from bronchoalveolar samples, since analysis on pharyngeal swabs became negative quite early. Finally, no RT-PCR significant for H1N1 infection from subglottic aspirate sample was found.

In one patient, intravenous administration of zanamivir was needed, since the patient remained positive to viral infection after two weeks of therapy. Intravenous formulation of zanamivir is still subjected to pre-phase 4 clinical trial investigation, even if some reports on its safety profile are already available in literature. Therefore, local Ethical Committee approval was requested and the manufacturer provided the drug for use. Zanamivir was administered intravenously for five days (600 mg twice daily), as indicated by the producer. The patient's respiratory function improved and RT-PCR became negative after the third day. No adverse reaction was noted.

Lung ultrasound (LUS) examination in H1N1-induced ARDS: A total of 156 LUS have been performed. During every LUS, the following parameters were considered: pleural line aspect and motility, presence of consolidations, occurrence and severity of Alveolar Interstitial Syndrome (based on the number of B-lines), presence of pleural effusion and occurrence of pneumothorax. Pleural thickness was described in 100% of cases and mostly bilaterally. Lung base was always involved. Lung gliding was present in 70% of LUS, even if decreased (20%). Pathological Lung Pulse was found in 20% of LUS, often in proximity to large parenchyma consolidations. Pleural effusion occurred in 7 patients. Two spontaneous pneumothorax have been detected with LUS during ICU treatment.

Alveolar Interstitial Syndrome was present in all ultrasound examinations, with the presence of normal lung pattern (spared areas). In 90% of cases, B-Lines were described as moderate/many. At lung recovery, residual B-Lines patterns were found mostly at both bases. White lung feature occurred in about 15% of LUS performed, mostly in the anterior and lateral scans. White lung was never uniformly distributed, but it was alternated to spared areas, or areas with a limited number of B-Lines.

Consolidations were found in 100% of cases. Most of them were multiple (65%), and lung bases were always involved. Contiguous subpleural consolidations were also present, increasing the pleural thickness laterally, mostly at the base and the apical part. Aerial bronchograms were always found within the consolidation pattern.

The routine use of LUS limited the number of conventional radiology examinations (Table 3). In ECMO patients group, the higher number of chest X-ray examinations was needed to verify the correct cannulae positioning. In both groups, bedside LUS limited the transportation to the CT-scan room, increasing patient safety and avoiding the transitory disconnection of the patient from the ventilator.

ECMO patients: ECMO was needed in 7 patients (Table 3). In 4 cases, the ECMO Team was alerted and extracorporeal oxygenation was implanted directly at peripheral ICUs. No major transportation related problems were faced, even in the case of a long distance journey (400 Km). Median duration of ECMO support was 8 days (IQR 6-16.5), with a median duration of mechanical ventilation (days) of 19 (IQR 12-36).

Main clinical features and ventilatory and ECMO parameters of patients treated with ECMO are presented in Table 4. Bleeding was the most important complication. In three cases, bleeding from vascular access sites due to heparin infusion required blood transfusions. Three patients presented prolonged oropharyngeal bleeding and transfusions were required. Among them, one needed electrical coagulation of a palatine injury, probably related to nursing manoeuvres. Two patients presented severe intra-bronchial bleeding, and several flexible bronchoscopy examinations and clot suction were required. In one of these patients, bleeding from the lower airways during the weaning phase from ECMO, and ECMO removal has been hastened. Table 3 summarizes the main differences between patients who underwent to ECMO treatment and patients only ventilated. Despite the small sample, ECMO patients clearly showed a higher critical illness score (SAPS II), and worst pulmonary gas exchange compared to patients who did not required extracorporeal lung assistance. Coinfection and comorbidities at admission were present only in ECMO patients.

Discussion

Our study population is young, comprising mainly healthy subjects, as previously reported.^{1,2,15} Risk factors are similar to other studies, such as obesity, diabetes and pregnancy. In the present case series, bacterial infection rate at presentation was low. Previous reports showed incidence of secondary superinfection by *Streptococcus Pneumoniae*, *Staphylococcus Aureus*, *Pseudomonas Aeruginosa*, *Acinetobacter Baumannii*, *Escherichia coli*.^{1,3,2} In our experience, we found two cases (16.7%) of co-infection with *Legionella Pneumophila*, which is, to the best of our knowledge, a new epidemiological data, since no other case has been reported in literature. It is questionable

whether *Legionella Pneumophila* infection occurred before or after H1N1 pneumonia. However, it could be that H1N1 pneumonia was associated with a lower reactivity of the immune system, as suggested by the low leucocytes count reported in our sample and by other authors.^{3,2,1}

One young patient presented heart failure, and viral myocarditis was suspected. The association of influenza with myocarditis is debated,¹⁶ and H1N1 related myocarditis, has rarely been reported.¹⁷ Furthermore, in our patient prolonged pre-hospital hypoxia was present and myocardial hypoxemia damage might have been involved. The patient required inotrope/vasoactive support for several days and eventually recovered fully with normal heart function.

Our observations confirm the responsiveness of this infection to antiviral therapy. We adopted a two-modality administration, both oral and inhaled. Our choice was made in consideration of the decrease in gut motility and adsorption usually observed in critically ill patients.

The World Health Organization (WHO) has questioned the sensibility of RT-PCR analysis for H1N1 in pharyngeal swab sample, encouraging analysis on samples from the lower respiratory tract. We routinely monitor H1N1 infection on three compartments: pharyngeal swab, subglottic aspiration, and bronchoalveolar lavage. In our experience, bronchoalveolar lavage at admission was positive in all patients while pharyngeal swab resulted positive in only 75% of cases.

As shown in Figure 1, RT-PCR from pharyngeal swab at ICU admission failed to demonstrate the viral infection in 3 patients. Similarly, the time course showed that RT-PCR from pharyngeal swab resulted negative in an average time of 3 days after therapy start. Conversely RT-PCRs from bronchoalveolar lavage remained positive for a longer period and resulted more reliable for infection monitoring and assessment of the efficacy of administered therapy.

Based on our experience, RT-PCR from bronchoalveolar lavage resulted to be the most reliable method to diagnose and monitor H1N1 infection, since pharyngeal swab does not offer enough sensibility, neither for antiviral therapy initiation nor for antiviral therapy management. As subglottic aspiration resulted persistently negative, we do not recommend this sampling for diagnosis and monitoring of H1N1 infection.

Despite the severe clinical pictures, we experienced a very low mortality rate: only one patient out of 12 died (8,3%). One of the surviving patients presented a lung cavern for a past pulmonary infection, and deceased for a secondary superinfection by *Aspergillus*, probably already colonizing lung parenchyma before the onset of viral infection.

Our mortality rate is surprisingly low in comparison to a larger series of H1N1 patients, even when extracorporeal support technique were employed.^{5,18} Our finding can be related to the small number of patients included the study and definitive comparison with larger studies could be misleading. However, despite the severity of symptoms and the rapid progression to ARDS, H1N1 respiratory failure presents a relatively benign course when adequately treated, if compared to non-H1N1 induced ARDS, reported to have a mortality rate from 37% to 43%.^{19,22} Several factors may account for the favourable outcome

in our series. All patients received protective ventilation. In particular, ECMO support permitted the maintenance of patients under a protective tidal volume with a respiratory rate below 12 per min, and a FiO_2 below 60%, compared with non-ECMO patients who needed a higher respiratory rate and FiO_2 to maintain an acceptable pulmonary gas exchange.

The availability of easily accessible tools for pulmonary mechanics evaluations on modern ventilators allowed an individualized and appropriate setting of ventilation pressure within the thresholds of so called "protective ventilation".²³ Furthermore, early access to ECMO resource allowed the maintenance of protective ventilation even in more severe patients (Table 4). In this regard, lactate dehydrogenase is commonly considered a marker of lung damage, and in H1N1 pneumonia is reported as high.¹ In our ECMO patients, lactate dehydrogenase values presented lower levels than in non-ECMO patients (445 U/L vs 627 IU/L, respectively), suggesting that in ECMO patients the reduced need of pulmonary ventilation could reduce lung ventilatory stress and enhance healing, regardless of the more impaired lung condition.

However, it is possible that, since the technique has gained popularity and experience gathered to demonstrate its feasibility, we used ECMO also in patients who might previously have been successfully treated conventionally, and this may have influenced mortality. Moreover, more than half of our ECMO patients needed to be land-transported from other hospitals in an advanced stage of respiratory failure. This may have further encouraged an early treatment with ECMO to ensure the safest transport.

Bleeding is commonly reported during ECMO treatment,²⁴ and either anticoagulation or platelet and coagulation cascade activation through oxygenator and pump is involved.²⁵ In our population bleeding also occurred more frequently in ECMO patients, and they required more transfusions compared to non-ECMO patients. Nevertheless, in our experience, bleeding from cannulas insertion site or from upper airways, despite requiring transfusion, were not life threatening, and could be managed. In only two cases did severe bleeding occur in the lower respiratory tract. Fortunately in one case it occurred during weaning from ECMO, and it ceased after extracorporeal support removal. The other patient died from pulmonary aspergillosis and the haemorrhage could be also related to parenchyma disruption caused by the fungus.

Monitoring heparin regimen is extremely important during extracorporeal circulation, and activated clotted time is commonly measured bedside. Some debate exists regarding the optimal range and the accuracy of point-of-care measuring devices.²⁶⁻²⁸ In our protocol, we usually measured aPTT every two hours with Hemochron Jr. in order to closely monitor heparin administration in the low range of dosage.

In our clinical practice, lung recovery and response to treatment are daily assessed by LUS examination, following several recent reports which underline the reliability of LUS in the evaluation and management of chest disorders.^{10,29} Despite CT-scan is the reference technique for evaluating lung lesions, it requires a transitory disconnection of the patient from the ventilator to permit the transportation radiology suite with potential risk of alveolar de-recruitment and worsening of oxygenation. Moreover, severe complications have been reported in intra-hospital transportation of critically ill patients.^{30,31} As we recently

reported,¹³ the routine use of bedside LUS has significantly reduce of the number of CT-scan and chest X-ray examinations in critical patients. The potential clinical benefit of reducing in-hospital transport for diagnostic radiology, it can be particularly relevant in patients with ECMO. In these patients, in fact, transportation requires time and a significant commitment of resources, although it was proved feasible both for in-hospital^{32,33} and for inter-hospital long distance transportations.³⁴⁻³⁵

Another advantage of LUS is the ability to evaluate the effectiveness of alveolar recruitment manoeuvres with the possibility to visualize real-time imagines of lung parenchyma re-aeration.^{8,10,29} Finally, pleural effusions can be accurately diagnosed and monitored with LUS and in case of need for treatment an ultra-sound guided technique is recommended.^{36,13} This option seems to be particularly appropriate ECMO patients, where bleeding for conventional chest tube placement can occur in consideration of the need of heparin infusion.

Conclusions

The present case series comprises a small number of patients, and naturally, it cannot be considered a high grade of evidence trial. However, our experience might be helpful for intensivists challenging H1N1-induced ARDS. For H1N1 infection monitoring (or diagnosis, if patient was intubated before) bronchoalveolar lavage can be more reliable than pharyngeal swab in order of the higher sensitivity. In our clinical practice, ECMO therapy resulted safe and feasible in the context of a life threatening condition, and it might be taken into consideration as a therapeutic choice rather than a rescue solution in experienced centers.

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Are There Any Differences in Clinical and Laboratory Findings on Admission Between H1N1 Positive and Negative Patients with Flu-like Symptoms?

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Abstract

Background: The World Health Organization alert for the H1N1 influenza pandemic led to the implementation of certain measures regarding admission of patients with flu-like symptoms. All these instructions were adopted by the Greek National Health System. The aim of this study was to retrospectively examine the characteristics of all subjects admitted to the Unit of Infectious Diseases with symptoms indicating H1N1 infection, and to identify any differences between H1N1 positive or negative patients. Patients from the ED (emergency department) with flu-like symptoms (sore throat, cough, rhinorhea, or nasal congestion) and fever $>37.5^{\circ}\text{C}$ were admitted in the Unit of Infectious diseases and gave pharyngeal or nasopharyngeal swabs. Swabs were tested with real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR).

Findings: Patients were divided into two groups. Group A comprised 33 H1N1 positive patients and Group B (control group) comprised of 27 H1N1 negative patients. The two groups did not differ in terms of patient age, co-morbidities, length of hospitalization, temperature elevation, hypoxemia, as well as renal and liver function. There were also no significant differences in severity on admission. C-reactive protein (CRP) (mean 12.8 vs 5.74) and white blood count (WBC) (mean 10.528 vs 7.114) were significantly higher in group B than in group A upon admission. Obesity was noted in 8 patients of Group A (mean 31.67) and 14 patients of Group B (mean 37.78). Body mass index (BMI) was lower in H1N1 positive than in H1N1 negative patients (mean 31.67 vs 37.78, respectively; $p=0.009$).

Conclusions: The majority of patients in both groups were young male adults. CRP, WBC and BMI were higher among H1N1 negative patients. Finally, clinical course of patients in both groups was mild and uneventful.

Findings

Background: In June 2009, the World Health Organization signaled that a novel H1N1 flu pandemic was underway.¹⁻⁵ The

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H1N1 virus is a triple-reassortant influenza virus containing genes from human, swine, and avian influenza viruses. This is a case control study. Patients were selected from the influenza special clinic (emergency flu department) according to their attendance. Control group were patients with flu symptoms and signs with negative serological test. Most patients with H1N1 infection present flu-like symptoms with a benign course.⁶ Patients with co-morbidities may have a serious clinical presentation with hypoxemia. The main cause of death is acute respiratory distress syndrome (ARDS).⁷⁻¹⁰ The first case of influenza A (H1N1) virus infection in the area of Thrace, Greece was documented in the University Hospital of Alexandroupolis on 10th August 2009. The purpose of this study was to investigate the potential differences on admission between H1N1 positive and negative patients with flu-like symptoms.

Patients and Method: The University Hospital of Alexandroupolis is a report center of the H1N1 virus for the region of Thrace in Greece. The hospital consists of more than fifty departments, one of which is the Unit of Infectious Diseases. During the influenza epidemic a special department for flu was established in which all patients with flu symptoms and/ or signs were referred. Patients with positive flu test were transferred in an 8 bed unit with negative pressure especially designed to quarantine and isolate patients with airborne transmitted viral infections.

From 10th August until 31st December 2009, 33 cases of confirmed H1N1 influenza A virus were hospitalized and quarantined in the Unit of Infectious Diseases. All patients with flu-like symptoms (sore throat, cough, rhino rhea, or nasal congestion) and fever $>37.5^{\circ}\text{C}$ were admitted in the Unit of Infectious diseases and gave pharyngeal or nasopharyngeal swabs. The swabs were tested with real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) as in previous reported studies.¹¹⁻¹³ It should also be mentioned that although RT-PCR is the most sensitive and specific test for the diagnosis of influenza virus infection, upper respiratory tract specimens are not as specific (~80%) as lower respiratory tract specimens (~100%).¹⁴ All results were given in a period of time from 8 to 48 hours, and all patients remained under quarantine and isolation in negative pressure chambers according to WHO guidelines.¹⁵ Our department prefers to use the Pneumonia Severity Index in order to evaluate the severity of the disease. However, this score was not different between the two groups. The Pneumonia Score Index was calculated for patients in both groups and the Class range was between II-IV.¹⁶ We repeated HINI test 7 days

Table 1. Characteristics, underlying medical conditions and outcomes.

Characteristic	H1N1(+) Range (±SD)			H1N1(-) Range (±SD)			P Value
Age (years)							
Mean	33.46	14-65	(14.7)	43.48	16-86	(22.7)	0.057
Male/Female	23/10 (69.69% / 30.3%)			17/10 (62.96% / 37%)			NS
Smoke	7/33 (21.2%)			7/27 (25.9%)			NS
BMI							
Mean	31.67	20-45	(9.15)	37.78	20-45	(8.0)	0.009
No.pts with obesity	18/33 (54.5%)			24/27 (88.8%)			
Coexisting conditions							
Asthma	8/33 (24.2%)			7/27 (25.9%)			NS
COPD	2/33 (6%)			0 (0%)			NS
IPF	1/33 (3%)			0 (0%)			NS
Lymphoma	5/33 (15%)			1/27 (3.7%)			NS
Diabetes	3/33 (9%)			5/27 (18.5%)			NS
Coronary Heart Disease	6/33 (18%)			5/27 (18.5%)			NS
Outcomes-days							
Duration of fever							
Mean	2.57	1-6	(1.0)	2.22	1-5	(1.0)	0.227
Days of Hospitalization							
Mean	6.11	2-18	(3.2)	5.85	2-12	(2.6)	0.750
Days under oseltamivir regimen							
Mean	5.8	5-18	(2.7)	1.93	1-5	(1.2)	NS

after admission and no patient negative in the initial test became positive.

In total, 60 patients were admitted in a four month period, of whom 33 were H1N1 positive (group A) and 27 negative (group B). The 33 H1N1 positive patients remained under quarantine and isolation, while the 27 negative patients were moved to the Department of Internal Medicine. Patients were monitored until discharge, with symptoms and signs recorded daily. Return to normal body temperature was defined as a temperature of less than 37°C for 1 day after withdrawal of antipyretic treatment.¹⁷ The criteria for discharge were absence of hypoxemia, normal chest x-ray and temperature <37°C for 1 day without antipyretic treatment.

Upon admission procalcitonin (PCT) evaluation was performed in 51 patients (25 group A/26 group B), for nine patients this exam was not available due to lack in reagents in our laboratory. Also urine antigen for Legionella and Streptococcus pneumoniae was tested upon admission in all patients but they were negative. Upon admission sputum stain was given in 12/33 patients in group A and 15/27 in group B. The rest of the patients did not produce enough sputum quantity for staining or did not cooperate in giving sputum. Finally blood cultures were collected in 49/60 patients when the body temperature exceeded 38°C, but no results came positive.

Statistical Analysis: Continuous variables were summarized as mean (±SD) or median (with interquartile ranges). For

categorical variables, the percentages of patients in each category were calculated. Unpaired t test was used in normal distribution parameters comparing the mean values of the parameters of the two groups. A p value of less than 0.05 was considered to indicate statistical significance. Characteristics of the groups and clinical laboratory parameters were compared between the two groups (A, B). All analyses were carried out with the use of SPSS statistical software package.

Clinical Characteristics of Patients: The majority of H1N1 positive patients (group A) were Caucasian male (23/33) with mean age 33.46 years and H1N1 negative patients (group B) were Caucasian male (17/27) with mean age 43.48 years. (Table 1.) Coexisting conditions were present in 25/33 patients in group A and 18/27 patients in group B (asthma: 24.2% vs. 25.9%, chronic obstructive disease: 6% vs. 0%, idiopathic pulmonary fibrosis: 3% vs 0%, lymphoma: 15% vs. 3.7%, diabetes: 9% vs 18.5%, coronary heart disease: 18% vs 18.5%) as in previous reported studies.^{12,18} (Table 1.) Only 2 patients in group A and 1 in group B had acute asthma exacerbation and none of the females in this study was pregnant. All female patients who were sexually active (8/33 group A) had negative pregnancy tests. All patients were treated with oseltamivir regimen (mean time 5.8 days in group A vs 1.93 days in group B). In 7 patients of group A, additional treatment with azithromycin/moxifloxacin or ceftriaxone was added at the time of admission, due to local patchy shadowing on the chest x-Rays and fever >37.5°C. In 7/33 patients of group A and 10/27 of group B the second chest film was positive for pneumonia infiltrates. The patient's chest x-ray status upon admission is presented in table 2.

In 6 out of 12 patients of group A from whom sputum culture was received, a pathognomonic isolation (>106 CFU) of bacteria was achieved (3 Streptococcus pneumonia species, 2 Mycoplasma species and 1 Moraxella catarrhalis). On the other hand from group B only in 8 out of 15 patients a pathognomonic isolation was achieved (5 Streptococcus pneumoniae species and 3 Mycoplasma species).

In group B, all patients were treated with double antibiotic regimen amoxicillin-clavulanic acid+azithromycin or ceftriaxone+moxifloxacin/ciprofloxacin (mean time of hospitalization was 5.85 days). Empiric antibiotic treatment was added upon admission based on elevated values of CRP, WBC and chest x-ray findings and since early antibiotic treatment prevents progression of the disease and these markers are known to be elevated in infection diseases.¹⁹⁻²¹ Reiquelme et al²² also initiated early antiviral and antibiotic treatment in order to prevent further progress and co-infection of the clinical status. Patients in our study were discharged when their chest radiograph became normal and their temperature <37°C for 1 day. Seven patients of group A and 6 patients of group B had severe hypoxemia upon admission (PO₂ ≤ 60mmHg) on room air. (Table 1.) Hypoxemia was defined as decreased partial pressure of oxygen in blood ≤60mmHg.²³ There was no difference between the two groups for smoking (A: n=7/33 vs. B: n=7/27). (Table 1.) Obesity was observed higher in patients from group B (mean 37.78) and a small number in group A (mean 31.67) (p value=0.009). (Table 1.) According to WHO global database on Body Mass Index a patient is considered obese when BMI is ≥ 30.²⁴

Laboratory Findings: Leucopenia grade 1 (≥2,500 to <4,000/mm³) was observed in 2/5 patients diagnosed with lymphoma in

Table 2 . Radiographic findings in the two groups, according to H1N1 status.

	H1N1(+)	H1N1(-)
Abnormalities on chest radiograph		
Local patchy shadowing	7/33 (21.2%)	10/27 (37.7%)
Ground-glass opacities	2/33 (6%)	7/27 (25.9%)
Interstitial abnormality	1/33 (3%)	0/27 (0%)

group A. (Table 1.) In group B, only 1 patient had lymphoma and presented pneumonia. On admission, abnormal liver function (elevated levels of serum liver enzymes or bilirubin) was found in 4/33 patients in group A vs. 2/27 patients group B. (Table 1.) These patients were under no treatment. Moreover, there was no platelet abnormality in any patient of the two groups. C-reactive protein (CRP normal laboratory values <0.50mg/dL) and white blood count (WBC) were elevated in group B in comparison to group A (mean 12.8 vs 5.74). Among the white blood count (WBC) subgroups there were no significant differences observed. The white blood count (WBC) returned to normal in 9/33 patients of group A and in 17/27 of group B between 6-12 days of hospitalization. C-reactive protein (CRP) returned to normal in 7/33 patients of group A and 27/27 of group B. Also in 4/33 patients in group A and 2/27 in group B elevated levels of serum liver enzymes or bilirubin returned to normal after 4-6 days. It should be mentioned that none of the patients received medications that affected their white blood count WBC (e.g. corticosteroids). (Table 3.)

None of the patients had acute renal failure and none of the patients in the Unit of Infectious diseases had to be intubated and admitted to the ICU in comparison to other studies.^{7,25} Also all patients were asked if they had vaccination for H1N1, but none of them had been vaccinated, even for seasonal influenza. There was no difference in mean saturation among the two groups. (Table 3.) Only 2/33 patients in group A with hypoxemia had to be hospitalized for 12 days and 18 days. The one of these 2 patients was recently diagnosed with idiopathic pulmonary fibrosis, while the other had no co-morbidities. No significant differences were observed for mean temperature, saturation and partial O₂ between the two groups. (Table 3.)

Discussion and Conclusions

We described a case series of sixty patients who were hospitalized in the Unit of Infectious diseases from 10th August to 31st December 2009 with flu-like symptoms and were tested with RT-PCR for H1N1 virus. Of these, 33 patients were positive for H1N1, while the remaining 27 were negative. The main differences between these two groups and corresponding clinical messages are summarized underneath.

In this case control study we included all patients with influenza symptoms admitted to the emergency flu department according to their attendance. Limitations of the study include that our data represent the experience of a single center, that procalcitonin test was given only in 51/60 patients and also Erythrocyte Sedimentation Rate (ESR) was sporadically collected during the follow up of the patients and so was not evaluated. Bacterial pneumoniae in association with influenza has been considered a important factor leading to poor patients outcomes in prior pandemics.²⁶ Even though none of the blood cultures were positive, we were unable to evaluate the effect of bacterial

co-infection on patient outcomes, since blood cultures were obtained in only 17% of the study population (when fever $\geq 38^{\circ}\text{C}$) and workup for atypical pathogens was not performed. Although bacterial co-infection was not documented, the majority of the study population was treated with antibiotics. Prior publications failed to demonstrate any significant involvement of bacterial pathogens in hospitalized patients with 2009 H1N1 virus pneumonia.^{3,27-29} During the initial evaluation in 4/27 patients of group B and 6/33 of group A an antibiotic treatment was prescribed by a General Practitioner and none of these patients had a sputum culture at that time. Furthermore, we did not receive cultivable sputum samples from all patients. We supposed that false negative culture in pneumonia patients is mainly due to mixed microbial flora or the natural colonization admixture of the upper airway. The subgroup of patients with pneumonia in both groups is so small that any statistical analysis is impossible and the power of the sample is quite small. Future studies are necessary to define the best treatment of 2009 H1N1 virus pneumonia and the role of combination antiviral therapy.

The lack of significant differences in the percentages of patients with hypoxemia between the two groups is probably due to the proximal number of patients with local patchy shadowing observed in group B and group A. (Table 2.)

Obesity is known to be associated with influenza A (H1N1) viral infection, but in this cohort we observed that in group B there was a larger number of obese patients in opposition to group A (88.8% vs 54.5%) ($p=0.009$). We were unable to explain the reason that the majority of H1N1 patients were not obese in our study as in previous reported studies.^{9,25} Obesity is not a risk factor for poor outcomes in patients with seasonal influenza, but obesity has been suggested as a risk factor for poor outcomes in patients with 2009 H1N1 influenza infection in the USA.³⁰

In our case control study a large number patients suffering from lymphoma were observed, because these patients received chemotherapy regimen making them vulnerable to respiratory infections. Patients in group B had elevated C-reactive protein (mean 12.8 vs 5.74) and white blood count WBC in comparison to group A (mean 10.528 vs 7.114) suggesting a microbial infection already upon admission.¹⁹⁻²¹ These elevated values (C-reactive protein and WBC) are known to be associated with bacterial infection and early antibiotic treatment prevents progression of the disease as reported in previous studies.¹⁹⁻²¹

Symptoms from oseltamivir were mainly observed in group A (nausea 4.5% vs 1.5%, diarrhea 4.5% vs 1.5%, vomiting 1.4 vs 0.5%) probably because of the larger dose and prolonged treatment with oseltamivir (5.8 vs. 1.93) as previously reported.^{18,31-33} However, it was difficult to distinguish the pharmaceutical side effects of oseltamivir (tamiflu) from influenza symptoms in patients receiving antiviral treatment for less than 5 days.²³ Oseltamivir should be given until proof of negative RT-PCR result, since if a patient is positive, it prevents progression of the disease as shown in previous observational studies.^{17,34,35}

Moreover, mean duration of hospital stay was 5.85 in group B vs 6.11 days in group A, because of the time needed for normalization of chest radiographs. Nevertheless, there were no significant differences between the two groups and the days of hospitalization were limited due to early oseltamivir for group A and antibiotic treatment for group B as previously explained.

Table 3. Clinical features of infection, according to H1N1 status: symptoms, signs and laboratory tests upon admission.

	H1N1(+) Range		(±SD)	H1N1(-) Range		(±SD)	P Value
Adverse events							
Abnormal liver function	4/33 (12%)			2/27 (7.4%)			NS
Nausea, Diarrhea	4.5%			1.5%			NS
Vomiting	1.4%			0.5%			NS
Hypoxemia	7/33 (21.2%)			6/27 (22.2%)			NS
CRP							
Mean	5.74	0.26-17.38	(4.75)	12.8	0.14-43.98	(11.56)	0.004
WBC							
Mean	7.114	3.340-10.950	(2172.160)	10.528	2.660-23.050	(5506.19)	0.004
Fever							
Mean	38.99	36.60-40	(0.79)	38.6	36.50-40.80	(1.01)	0.122
CR							
Mean	0.9	0.5-1.30	(0.18)	0.85	0.20-1.60	(0.25)	0.392
UR							
Mean	26.5	11-41	(7.9)	32.2	17-72	(11.8)	0.038
SpO₂							
Mean	95.3	89-99	(2.7)	95.2	89-100	(2.4)	0.809
PO₂ (FiO₂21%)							
Mean	77.54	54-113	(14.6)	74.22	56-108	(13.0)	0.381

Lastly the mean young age of the patients in both groups, and the small number of comorbidities observed in our sample of patients, possibly were also responsible for having overall mild clinical course. In conclusion: All the patients in general, had a mild clinical course and none of the patients had to be admitted in the ICU.

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Level of Daily Physical Activity in Individuals with COPD Compared with Healthy Controls

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Abstract

Background: Persons with Chronic Obstructive Pulmonary Disease (COPD), performing some level of regular physical activity, have a lower risk of both COPD-related hospital admissions and mortality. COPD patients of all stages seem to benefit from exercise training programs, thereby improving with respect to both exercise tolerance and symptoms of dyspnea and fatigue. Physical inactivity, which becomes more severe with increasing age, is a point of concern in healthy older adults. COPD might worsen this scenario, but it is unclear to what degree. This literature review aims to present the extent of the impact of COPD on objectively-measured daily physical activity (DPA). The focus is on the extent of the impact that COPD has on duration, intensity, and counts of DPA, as well as whether the severity of the disease has an additional influence on DPA.

Results: A literature review was performed in the databases PubMed [MEDLINE], Picarta, PEDRO, ISI Web of Knowledge and Google scholar. After screening, 11 studies were identified as being relevant for comparison between COPD patients and healthy controls with respect to duration, intensity, and counts of DPA. Four more studies were found to be relevant to address the subject of the influence the severity of the disease may have on DPA. The average percentage of DPA of COPD patients vs. healthy control subjects for duration was 57%, for intensity 75%, and for activity counts 56%. Correlations of DPA and severity of the disease were low and/or not significant.

Conclusions: From the results of this review, it appears that patients with COPD have a significantly reduced duration, intensity, and counts of DPA when compared to healthy control subjects. The intensity of DPA seems to be less affected by COPD than duration and counts. Judging from the results, it seems that severity of COPD is not strongly correlated with level of DPA. Future research should focus in more detail on the relation between COPD and duration, intensity, and counts of DPA, as well as the effect of disease severity on DPA, so that

these relations become more understandable.

Background

Chronic Obstructive Pulmonary Disease (COPD) is a disabling airway disease with variable extrapulmonary effects that may contribute to disease severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases. The characteristic symptoms of COPD are cough, sputum production, and dyspnea upon exertion.¹

Persons with COPD, who perform some level of regular physical activity, have a lower risk of both COPD-related hospital admissions and mortality.^{2,3} COPD patients at all stages of the disease seem to benefit from exercise training programs, showing improvement with respect to both exercise tolerance and symptoms of dyspnea and fatigue.⁴ Inactivity contributes to a further worsening of the physical condition of the subject and to even more dyspnea. This, in turn, contributes to a downward spiral of inactivity, deconditioning, and dyspnea.^{5,6} COPD is a disease that mainly affects persons of older age. It develops over several decades of exposure to inhaled particulates, and, generally, becomes visible starting at the age of 40. In a global study, Buist et al.⁷ found that the prevalence of COPD increases steadily with age for both men and women. The overall pooled Odds Ratio for COPD stage II or over was 1.94 (1.8-2.1) per 10-year age increment.

The American College of Sports Medicine and the American Heart Association provide physical activity recommendations for healthy older adults.⁸ They recommend that each week older adults should do at least 30 minutes of moderate physical activity for 5 days or 20 minutes of vigorous physical activity for 3 days; 8-10 strength exercises for 2 days; and flexibility exercises for at least 10 minutes for 2 days. Many older adults do not meet these recommendations.⁹ Caspersen et al.¹⁰ studied the changes in physical activity patterns in the United States by sex and cross-sectional age. They found that both men and women reported more physical inactivity with greater age, with an increase between the 65-74-yr and >75-yr groups. After the age of 74, the prevalence of regular, sustained activity began to decline substantially for both sexes. Thus, physical inactivity, which becomes more serious with increasing age, is already a point of concern in healthy older adults. COPD might worsen this scenario, but it is unclear to what extent. There are various

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Table 1. Study characteristics of included trials.

Reference	N (P/C)	Mean Age (yrs±SD, P;C)	Gender (Male/Female) (P/C)	Variation in GOLD stage	Measurement device	Duration of study (days)
Coronado (2003)	25 (15/10)	67±9; 57±5	13:2; 4:6	1-4	Uni-axial accelerometer	1
Hernandes (2009)	70 (40/30)	66±8; 64±7	18:22; 14:16	2-4	Tri-axial accelerometer	2
Lores (2006)	35 (23/12)	62±7; 59±7	20:3; 9:3	2-4	Tri-axial accelerometer	3
Pitta (2005)	75 (50/25)	64±7; 66±5	36:14; 17:8	1-4	Tri-axial accelerometer	2
Pitta (2008)	40	68±7	21:19	1-4	Multisensor armband	2
Sandland (2005)	20 (10/10)	nd	nd	3	Uni-axial accelerometer	7
Schönhofer (1997)	50 (25/25)	56±12; 53±14	14:11; 14:11	2-3	Pedometer	7
Singh (2001)	20 (11/9)	66±9; 59±4	7:4; 5:4	3	Uni-axial accelerometer	2
Steele (2000)	47	66±8	44:3	1-4	Tri-axial accelerometer	3
Steele (2003)	63	nd	nd	nd	Accelerometer	3
Troosters (2010)	100 (70/30)	66±9; 65±7	58:12; 19:11	1-4	Multisensor armband	6-8
Walker (2008)	51 (33/18)	67±8; 70±6	17:16; 8:10	3	Uni-axial accelerometer	3
Watz (2008)	170	64±6.6	128:42	1-4	Multisensor armband	5-6

studies that examine the level of daily physical activities (DPA) in COPD patients. However, as of now, there is no overview of the literature that combines these studies to see to what extent the DPA of COPD patients differs from healthy individuals.

This literature review aims to present the extent of the impact of COPD on the DPA. The focus is on the extent of the impact that COPD has on duration, intensity, and counts of DPA, as well as whether the severity of the disease has an additional influence on DPA.

Methods

Potentially relevant literature was identified through computerized searches. PubMed [MEDLINE], Picarta, PEDRO, ISI web of knowledge, and Google scholar were searched for articles. DPA was defined as: “the totality of voluntary movement produced by skeletal muscles during every day functioning.”⁵ For this literature review we used the GOLD guidelines¹ to define disease severity. The severity of COPD is classified in four stages (mild to very severe) by postbronchodilator forced expiratory volume in 1 second (FEV1) value% predicted. The search was performed for the years 1966 to 2010 using the MeSH headings: “Pulmonary Disease, Chronic Obstructive”, “Activities of Daily Living”, “Motor Activity” and “Monitoring, Physiologic”.

1. “Pulmonary Disease, Chronic Obstructive”[MeSH terms] AND “Activities of Daily Living”[MeSH terms] AND “Motor Activity”[MeSH terms] AND “Monitoring, Physiologic”[MeSH terms]/(8); 2. “Pulmonary Disease, Chronic Obstructive”[MeSH terms] AND “Activities of Daily Living”[MeSH terms] AND “Motor Activity”[MeSH terms]/(36); 3. “Pulmonary Disease, Chronic Obstructive”[MeSH terms] AND “Activities of Daily Living”[MeSH terms] AND “Monitoring, Physiologic”[MeSH terms]/(16); 4. “Pulmonary Disease, Chronic Obstructive”[MeSH terms] AND pedometer[All Fields]/(8); 5. “Pulmonary Disease, Chronic Obstructive”[MeSH terms] AND accelerometer[All Fields]/(20); 6. “Pulmonary Disease, Chronic Obstructive”[MeSH terms] AND activity[All Fields] AND monitors[All Fields]/(8); 7. “Pulmonary Disease, Chronic Obstructive”[MeSH terms] AND monitors[All Fields]/(14). Inclusion criteria were as follows: 1) patients were diagnosed with COPD. 2) The study included a control group consisting of age-matched healthy subjects. 3) DPA was measured with an objective tool. 4) There was at least one whole day of measurements to be able to draw conclusions about daily physical activity.

Exclusion criteria were as follows: 1) DPA measured by questionnaires or diaries. 2) Measures on exercise capacity (for

instance six minute walk test). These measures reflect one’s capacity to perform physical activity in daily living, but give no information on the degree of DPA that is actually performed. 3) Measures on energy expenditure. Energy expenditure does not provide a direct measure of DPA. This is especially true in COPD patients because they exhibit an increased total daily energy expenditure while their daily physical activity level is reduced in comparison with healthy subjects.¹¹

Inclusion criterion 2 was not used in the search for articles on the effect of the severity of COPD on DPA. Articles were selected on the basis of title and abstract. References of obtained articles were verified whether they yielded any potentially relevant literature. After selection of the articles, full-text versions were obtained and read in their entirety after which, articles were either included or excluded based on the in- and exclusion criteria formulated above.

Results

With the combinations of the keywords used, there were a number of 110 hits in total, 92 abstracts of which were screened. After screening, 11 studies were included based on the in- and exclusion criteria for comparison between COPD patients and healthy controls with respect to duration, intensity and counts of DPA. Two^{12,13} were excluded because they measured DPA with questionnaires instead of objective measurements, resulting in 9 studies¹⁴⁻²² used for data-extraction. Initially, the objective was to perform a meta-analysis with the data from all studies using the software package RevMan 5. Subgroup analyses with age, gender and disease severity were planned. Unfortunately, three studies were based on non-parametric data, and one study did not provide means and standard deviations.¹⁸ This would leave 5 studies for analysis, which was decided to be too limited a basis to perform a meta-analysis. Instead, a descriptive review was written with 9 studies. In addition, four more studies^{3,23-25} were included in this review as they address the subject of the influence the severity of the disease may have on DPA. These additional studies did not compare the COPD patients with healthy control subjects.

The total number of subjects in all studies was 766; 597 COPD patients and 169 healthy controls. Although different outcome measures were used in the various studies, they all represented an objective measure of DPA. The results were expressed in percentage of time of total recording time of DPA spent in various intensities,^{14,23} vector magnitude units (VMU) (sum of the three axes of the accelerometer),^{16,24,25} walking time in minutes,^{15,17} mean number of movements per day,¹⁹ steps per

Table 1. Results of included studies.

Reference	Duration of DPA			Intensity of DPA			Counts of DPA		
	P	C	P/C ×100%	P	C	P/C ×100%	P	C	P/C ×100%
Coronado (2003)	17% of recording time active	33%	52%						
Hernandes (2009)	55 ± 33 min/day walking	80 ± 28	69%	1.9 ± 0.4 m/s ²	2.3 ± 0.6	83%			
Lores (2006)							184 ± 99 counts/3 days	314 ± 75	59%
Pitta (2005)	44 ± 26 min/day walking	81 ± 26	54%	1.8 ± 0.3 m/s ²	2.4 ± 0.5	75%			
Schönhofer (1997)							3781 ± 2320 movements/day	8590 ± 4060	44%
Singh (2001)	136.1 min/2 days walking	386.2	35%				14.838 ± 7115 counts/2 days	24.028 ± 12399	62%
Troosters (2010)	106 min/ day active	232	46%				5584 ± 3360 steps/day	9372 ± 3574	60%
Walker (2008)	50.8% ± 15.4% of recording time mobile	61.4% ± 11.2%	83%	156 ± 63 ×10 ³ counts/h	232 ± 90	67%	82 ± 49 ×10 ³ counts/h	143 ± 61	57%
Average			57%			75%			56%

DPA= daily physical activity, P=patients, C=controls, P/C×100%=percentage DPA patients perform in comparison to healthy controls, value after ± is the standard deviation.

day,^{3,21} mean activity count,¹⁸ total activity count,²⁰ and mean activity (×10³ counts/h).²² Study characteristics are shown in Table 1. This Table shows all 13 studies included for this review. The four studies analyzed with respect to disease severity display solely patient characteristics since these did not include healthy controls. Results of the individual studies are shown in Table 2.

The effects of COPD on duration, intensity, and counts of daily physical activity: To make a comparison between the studies with respect to the effect of COPD on duration, intensity and counts of DPA, the activity outcomes of COPD patients are given as a percentage of control values (Table 2). For example, in the study of Pitta et al.,¹⁷ the COPD patients walked for 44 minutes per day compared to 81 minutes of the healthy controls; 44 was then divided by 81 to come to a DPA percentage of 54 of COPD patients versus their healthy controls.

Duration of DPA: Coronado et al.¹⁴ showed in their study that the COPD patients were physically active for significantly less time of the day than healthy control subjects in low intensity activity (13% ± 4% vs 22% ± 7%; p = 0.0001), and medium intensity activity (4% ± 4% vs 11% ± 9%; p = 0.01). Hernandes et al¹⁵ evaluated the characteristics of physical activities in daily life in COPD patients in Brazil for 12 hours on two consecutive days. Mean walking time per day was shorter for COPD patients than for the controls (55 ± 33 vs 80 ± 28 minutes per day; p = 0.001). In the study of Pitta et al¹⁷ patients also showed lower walking time than controls (44 ± 26 vs 81 ± 26 minutes per day; p < 0.0001). Walker et al²² determined that patients spent significantly less time of the day being mobile than the controls (50.8% ± 15.4% vs 61.4% ± 11.2% of recording time). Singh et al²⁰ examined the discriminatory properties of an activity monitor by looking at the overall level of activity generated over two days by patients with COPD and healthy subjects. Patients completed a mean of 36.1 ± 17.1 minutes of brisk walking over the 48 hour period, whereas the healthy group completed 29.6 ± 41.4 minutes (p < 0.05).

Patients, furthermore, performed 100 ± 64.3 minutes of slow or intermittent walking, whereas healthy subjects achieved a mean of 356.6 ± 219 minutes (p < 0.05). Troosters et al²¹ investigated DPA in patients with COPD and controls. Subjects were instructed to wear a multisensor armband device able to assess physical activity continuously (day and night) for six to eight days. The time spent in activities with mild (80 ± 69 minutes vs. 160 ± 89 minutes, p < 0.0001), moderate (24 ± 29 minutes vs 65 ± 70 minutes; p < 0.0036), and high intensity (2 ± 5 minutes per day vs 7 ± 9 minutes per day; P = 0.01) was significantly reduced in patients compared to controls. Table 2 shows the values of duration of DPA for the studies that include results on this parameter. Some studies reporting on the duration of DPA distinguish between various intensities at which activities were carried out. These are summarized in Table 2 to provide a single value of duration of DPA over a certain period of time. The ratio of duration of being active for healthy controls vs. patients with COPD is 1:0.57.

Intensity of DPA: Hernandes et al²⁶ showed that movement intensity was lower in patients vs. controls (1.9 ± 0.4 vs 2.3 ± 0.6 m/s²; p = 0.004). In the study of Pitta et al¹⁷ patients showed lower movement intensity during walking (1.8 ± 0.3 vs 2.4 ± 0.5 m/s²; p < 0.0001). Walker et al²² determined the relationship between lower limb activity and total DPA and related DPA to laboratory assessments before and after rehabilitation. The patients had a lower intensity of activity score (156 ± 63 vs 232 ± 90 × 10³ counts/h) than the healthy volunteers. The study of Coronado et al¹⁴ assessed the usefulness of an accelerometer to characterize walking activity during a 3-week rehabilitation program. They recorded patients as well as healthy subjects with an uni-axial accelerometer on the first and last days of a rehabilitation program. The results of the first day showed that the COPD patients studied showed significantly less time spent in low and medium intensity activity. The values for high-intensity activity were negligible in all subjects

and thus not reported. Specific values for intensity of DPA were not mentioned, only the percentage of time spent in a certain intensity of DPA (see previous paragraph). The same representation of results on intensity is seen in Troosters et al²¹ and Singh et al²⁰. The first study shows similar results to Coronado et al¹⁴. In the study of Singh et al²⁰ patients spent more time on brisk walking, but substantially less on slow or intermittent walking (see previous paragraph). The ratio of intensity of DPA for healthy controls versus patients with COPD is 1:0.75 (Table 2).

Activity counts: Lores et al¹⁶ assessed the agreement between different measurements of mean DPA. All subjects wore a tri-axial accelerometer for 8 days. Activity counts in COPD patients were significantly lower than those of controls (184 ± 99 vs. 314 ± 75 ; $p < 0.01$). The mean number of movements per day for patients and controls in the study of Schönhofer et al¹⁹ was 3781 ± 2320 and 8590 ± 4060 , respectively ($p < 0.0001$). They concluded that COPD patients had DPA levels much lower than the average DPA level recorded in age- and gender-matched healthy individuals. Also, the range of DPA was much greater in healthy subjects than in COPD patients. Sandland et al¹⁸ explored the regular level DPA in patients with COPD and healthy subjects during a 7-day study with accelerometers. Their results showed that there was a significant difference ($p < 0.001$) in the level of DPA between healthy controls and COPD patients. Exact numbers, however, were not mentioned in the article. They do mention that the activity counts in COPD patients compared to those in the healthy group were reduced by 49%. The total activity count for COPD patients in the study of Singh et al²⁰ was significantly lower than the total activity count in healthy subjects ($14,838 \pm 7115$ vs $24,028 \pm 12399$; $p < 0.05$). Troosters et al²¹ showed that patients took significantly less steps per day (5584 ± 3360) compared to controls (9372 ± 3574 ; $p < 0.0001$). Walker et al²² also reported that patients had a lower activity count compared to healthy volunteers (82 ± 49 vs. 143 ± 61 ; $P = 0.001$). The ratio of counts of DPA for healthy controls versus patients with COPD is 1:0.56 (Table 2).

Disease severity and daily physical activity: The study of Pitta et al¹⁷ looked at the relation between disease severity and level of DPA in their patients. They found that there was no significant difference between walking time in patients with GOLD stages I and II when compared to patients with GOLD stage III ($P = 0.10$) and GOLD stage IV ($P = 0.19$). Standing time was significantly lower in patients with GOLD stages III and IV. They concluded that it appears that the correlation between disease severity and physical activity in daily life is not strong. A different study by Pitta et al²³ measured DPA for two days using a multisensor armband device in 40 COPD patients. They correlated FEV1 with sedentary activities ($r = -0.26$), moderate activities ($r = 0.29$) and vigorous activities ($r = 0.31$; $P = 0.05$). Only the correlation with vigorous activities proved to be significant.

Hernandes et al¹⁵ found that walking time per day was not significantly correlated with FEV1% predicted ($r = 0.17$). The time spent standing per day correlated positively with FEV1% predicted ($r = 0.41$; $p < 0.01$).

Steele et al²⁴ recorded walking and DPA in a sample of GOLD stage III COPD patients. They found that the accelerometers' output (vibrations in m/s^2) correlated positively with FEV1% predicted ($r = 0.62$; $p < 0.001$). A different study by Steele et al²⁵ measured 63 outpatients with COPD for three days and found a

significant correlation between accelerometer measured daily activity and FEV1% predicted ($r = 0.37$; $p < 0.01$)

In the study of Schönhofer et al¹⁹ patients with stable non-hypercapnic COPD, patients with respiratory failure, and healthy subjects were measured. For the COPD patients the number of movements per day was positively correlated with the FEV1% predicted ($r = 0.54$, $p = 0.006$).

In the study of Singh et al,²⁰ total activity count was moderately correlated with FEV1% predicted when measured with an activity monitor ($r = 0.41$) but not statistically significant.

Walker et al²² found a correlation of $r = 0.57$ ($P < 0.01$) between mean activity of the legs and FEV1. Percentage of time spent mobile compared with FEV1 showed a correlation of $r = 0.51$ ($p < 0.01$).

In the study of Troosters et al,²¹ the number of steps reached 87% \pm 34%, 71% \pm 32%, 49% \pm 34% and 29% \pm 20% of control values in GOLD-stages I to IV, respectively. The time spent in activities at moderate intensity was 53% \pm 47%, 41% \pm 45%, 31% \pm 47% and 22% \pm 34% of the values obtained in controls, respectively, with increasing GOLD-stage. These differences were statistically significant as of GOLD stage II ($p < 0.05$). The authors concluded that physical activity is reduced early in the disease progression (as of GOLD-stage II), and that reductions in physical activities at moderate intensity seem to precede the reduction in the amount of physical activities at lower intensity.

Watz et al³ measured DPA for five to six consecutive days using a multisensor armband device in 170 stable COPD outpatients. Steps per day diminished with increasing GOLD level (I:7990 \pm 3370, II:7160 \pm 3284, III:5126 \pm 3692, IV:2377 \pm 1897; $p < 0.001$). The same pattern was seen for mean physical activity level (I:1.63 \pm 0.25, II:1.62 \pm 0.27, III:1.45 \pm 0.25, IV:1.27 \pm 0.17; $p < 0.001$).

Discussion

First, the reason for excluding the two studies that measured DPA with questionnaires will be elucidated. Studies that measured DPA by questionnaires or diaries were excluded because these measures represent subjective DPA. COPD patients significantly overestimate time spent walking and underestimate time spent standing,^{5,24,27} which makes results obtained via this method unreliable. The study of Gosker et al¹² assessed DPA administering the Physical Activity Scale for Elderly (PASE) questionnaire. They found that the 25 COPD patients scored significantly lower ($p < 0.001$) than the 36 healthy gender- and age-matched controls; a lower score indicating a lower level of physical activity. Inal-Ince et al¹³ used the Activities of Daily Living Questionnaire (ADL-Q) in 30 COPD patients and 30 healthy controls. The ADL-Q scores were significantly higher in COPD patients ($p < 0.0001$), indicating a more pronounced inability to perform activities of daily living. The two excluded studies are in line with the results of this review, thereby lowering the chances of selection bias.

The effect of COPD on daily physical activity: Table 2 shows similar results for all studies: COPD patients have lower levels of duration, intensity, and counts of DPA compared to healthy subjects. The average of the percentage of DPA of COPD patients vs. controls for duration was 57%, for intensity, 75%, and for activity counts, 56%. This shows that DPA is significantly affected

by COPD. When converting the results of the studies to these percentages, it has to be taken into account that the values used in this calculation are mean values with large standard deviations for the COPD patients as well as for the healthy controls. It seems that the large differences between persons in level of DPA is not caused by the disease but merely by individual differences.

Next to a shorter duration of activity, the included studies also reported longer durations of inactivity. The COPD patients tended to spend more time seated than controls (294 ± 114 vs 246 ± 122 min/day, $p = 0.08$) in Hernandez' study¹⁵ as well as in Pitta's (374 ± 139 vs. 306 ± 108 minutes/day; $p = 0.04$).¹⁷ This latter study also reported a higher lying time (87 ± 97 vs 29 ± 33 min/day; $p = 0.004$). Furthermore, they reported a lower standing time (191 ± 99 vs 295 ± 109 min/day; $p < 0.0001$). The study of Coronado et al¹⁴ showed that the COPD patients studied were significantly physically inactive for longer periods of time than the healthy control subjects (82% of recording time vs. 68% for controls).

It might be expected that having COPD would cause one to achieve the same duration of DPA, albeit at a lower intensity. Interestingly, intensity of DPA seems to be less affected by COPD than duration and counts. This trend is also evident in the study of Singh et al.²⁰ The patients performed less physical activity overall, but interestingly enough, they completed more minutes of brisk walking than the healthy controls. It could be that the patients are trying to perform activities as fast as possible so as to alleviate the unease caused by physical activity. This puts a lot of strain on their bodies, which are already weaker as a result of the disease. The longer duration of inactivity seen in the studies of Hernandez et al¹⁵ and Pitta et al¹⁷ could be a result of this behavior. If trained to perform activities at a lower intensity, they might be able to improve their overall duration and count of DPA.

Disease severity and daily physical activity: Overall there seems to be a relation between DPA and severity of the disease, but this correlation is moderate at most and certainly not strong. Aliverti and Macklem²⁸ mention that shortness of breath is not necessarily the primary factor that limits exercise. They hypothesize that that both respiratory muscles and skeletal muscles do not receive sufficient oxygen to continue metabolizing aerobically. The fact that some individuals terminate exercising because of dyspnea, whereas others stop because of leg fatigue, suggests that sometimes the legs receive more oxygen and other times, the respiratory muscles. This would explain this moderate correlation between the severity of COPD based on the GOLD classification and DPA.

There has been some discussion about whether FEV1% predicted is a good variable to classify disease severity in COPD. It does not correlate well with important outcomes such as symptoms, quality of life, survival, exacerbation frequency, and exercise tolerance.²⁹⁻³¹ A different classification model might better correlate disease severity with DPA. In the study of Sandland et al,¹⁸ there was a significant reduction in the level of DPA in the group of COPD patients with long term oxygen therapy (LTOT) compared with the group without LTOT. The two groups had the same level of disease severity according to the GOLD staging system. The difference between the two groups was the LTOT, which indicates that the group with LTOT had more severe hypoxemia and thus more symptoms. Here, the increase in severity of symptoms independent of disease severity according

to the GOLD classification seems to further worsen the level of DPA. It seems important that when prescribing exercise training to a COPD patient, one takes into account that a more severely afflicted patient does not necessarily need a less physically demanding program. The patient might be able to perform on a higher level than one might think judging by their disease severity measured by FEV1 (% predicted).

Limitations: The selection of patients and controls varied between the studies, which may constitute an important source of bias. Patients who were recruited were either participating in an inpatient rehabilitation program,^{14,15,18,22} an outpatient rehabilitation program,^{16,19,21} just graduated from a rehabilitation program,²⁰ or recruitment of patients was not clearly stated.¹⁷ Patients referred to rehabilitation programs may be more likely to be inactive than the general population of COPD patients. This latter group may prevent themselves from entering a period of rehabilitation because they are more physically active and thereby maintain a better health status. The selection of the healthy controls was not always clearly described. Coronado et al.¹⁴ included subjects, who participated on a voluntary basis from a senior group practicing fitness. Pitta et al¹⁷ recruited relatives and friends from the researchers and patients. Hernandez et al¹⁵ and Troosters et al²¹ recruited relatives of students of the university. A random sample of healthy persons may be more inactive than volunteers, which would diminish the difference between COPD patients and their healthy controls.

It was decided that too few studies were available in order to perform a meta-analysis. This is due to limited research that is specifically directed at the relation between COPD and duration, intensity, and counts of DPA, as well as the effect of disease severity on DPA. Future research should focus in more detail on this subject so that these relations become more understandable.

Apart from the fact that there were too few studies for a meta-analysis, another difficulty in the comparison of the studies was that there was a great variety in the instruments used to obtain an objective measure of daily level of physical activity. When comparing studies with different kinds of pedometers and accelerometers, this can lead to some variation in the outcome that is not attributable to the subjects but rather to the different measurement devices. The methods of the studies also differed considerably in measurement time. However, since the difference in daily physical activity between COPD patients and healthy controls was so large in the included studies, the effect of various methodologies is probably negligible.

Conclusion

Even though there was a great variation between the studies in terms of measurement devices and measurement time, the large differences between the healthy subject group and the COPD patient group allow us to draw conclusions. From the results of this review, it appears that patients with COPD have a significantly reduced duration, intensity, and counts of DPA when compared with healthy control subjects. Intensity of DPA seems less affected by COPD than duration and counts. Judging from the results, it seems that severity of COPD is not strongly correlated with level of DPA. Future research should focus in more detail on the relation between COPD and duration, intensity, and counts of DPA, as well as the effect of disease severity on DPA, so that these relations become more understandable.

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SLEEP SPECIAL REPORT

A surreal painting of a person with a tree for a head. The person's face is a pale, almost white color, with closed eyes and a serene expression. They are wearing a green long-sleeved shirt and yellow pants. A large, gnarled tree with a thick trunk grows out of the top of their head. The tree's branches are dark brown and spread out across the upper half of the image. The leaves are a mix of green and yellow, and there are small white flowers scattered throughout. The background is a soft, hazy landscape with a purple and pink sky, suggesting a sunset or sunrise. The overall style is painterly and dreamlike.

NEWS AND PRODUCTS
SARS AND SLEEP
CHRONIC COUGH AND OSA

Sleep News

□ June-July 2011

TO PEE OR...

Men with enlarged prostates may not be getting up to pee in the night, but could have obstructive sleep apnea instead, according to researchers at Ben-Gurion University of the Negev. Their study compared men between the ages of 55 and 75 years-old, who were randomly sampled from primary care clinics, diagnosed with BPE and reported nocturia at least once nightly. More than half of patients with enlarged prostates may in fact have the sleep disorder, according to the researchers.

HYPED ON HOPE

Making decisions while sleep-deprived results in optimism, according to researchers at Duke University. Using MRI, they noted that a night of sleep deprivation leads to increased brain activity in brain regions that assess positive outcomes, while this deprivation leads to decreased activation in the brain areas that process negative outcomes. Sleep-deprived individuals tended to make choices that emphasized monetary gain, and were less likely to make choices that reduced loss. This is the first study to show that sleep deprivation can change the way the brain assesses economic value, independent of its effects on vigilant attention. The study also demonstrates that sleep deprivation increases sensitivity to positive rewards while diminishing sensitivity to negative consequences. The researchers tested 29 healthy adult volunteers with an average age of 22 years, who had to perform a series of economic decision-making tasks twice, once at 8 in the morning after a normal night of sleep and once at 6 after a night of sleep deprivation. To evaluate neural sensitivity to rewards, participants passively watched as gambling outcomes were sorted as positive or negative. The researchers noted that late-night gamblers at casinos are fighting a sleep-deprived brain's tendency to implicitly seek gains while discounting the impact of potential losses, and noted that countermeasures to combat fatigue and improve alertness may be inadequate for overcoming these decision biases.

AKA THE VAPORS

The circadian system is a contributor to fainting, according to researchers at Brigham and Women's Hospital, who offer evidence that the system may contribute to the daily pattern of VVS via its influences on physiological responses to changes in body posture. In their study, repeated tilt-table tests were used to determine the susceptibility to VVS across the day and night in twelve healthy participants who stayed in a controlled laboratory environment for 2 weeks. To measure the influence of the internal body clock on VVS while controlling for other factors including the sleep/wake cycle, meals and the environment, the researchers scheduled all behaviors of participants while they lived on a recurring 20-hour "day" (with 6.7 hours scheduled for sleep and 13.3 hours for wake). The study was performed in dim light so that the internal body clock still oscillated with an approximate 24-hour period. Core body temperature was measured throughout to indicate the times of the internal body

clock. To stop the participants from actually fainting, signs of imminent VVS (presyncope) were closely monitored and tilt-table tests were immediately aborted whenever there were notable symptoms of nausea, dry mouth, dizziness, or low blood pressure or rapidly falling blood pressure. The researchers found that the vulnerability to presyncope has a strong connection to the internal body clock, with susceptibility nine times higher at the circadian times between 10:30 at night and 10:30 in the morning, compared to the opposite. The highest risk for presyncope occurred at the circadian time corresponding to 4:30 AM, which has implications for night shift workers and others awake at this time who have already been awake all night.

SLEEP IN THE USA

The 2011 Sleep in America poll released by the National Sleep Foundation offers tons of comprehensive info about the state of sleep in the USA. Forty-three percent of Americans say they're not getting enough sleep and 60% say they have sleep problems. They say they need 7½ hours but aren't getting it. Ninety-five percent of the respondents say these use some kind of electronics in the hour before going to bed, and researchers say this is part of the problem, because artificial light exposure at night suppresses the release of melatonin. Six in ten respondents said they used laptops or computers in the hour before sleep and almost half of young people said they surfed the internet almost every night before going to – or trying to – go to sleep. Younger people also used cellphones to talk or text more. So maybe it's no surprise that 13 to 18 year olds reported being sleepest during the day, or perhaps that's from heavy partying. Or natural laziness or slackerism. Americans cope with sleepiness by drinking caffeine and taking regular naps. The average person on a weekday drinks about three 12 ounce caffeinated beverages, and about half in all categories take a little nap. Two-thirds of adults polled said lack of sleep affected their sex lives. Kids weren't asked this question, which is too bad; it would have made for an interesting comparison.

NO KIDDING

The employed and self-employed sleep better than those out of work, according to a study by the University of Surrey. Also, those who don't like their jobs sleep worse than those who like them. The study followed 40,000 UK households. Here's more results: Women have more problems getting to sleep quickly. Young people under 25 have trouble falling asleep three or more nights a week. This figure declines with age for men, but increases for women. Older men have more trouble sleeping than younger guys. One in ten people take sleep medicine three or more nights a week; people who work long hours, and managers, sleep less.

GET MOVING

The American Thoracic Society has recommended incorporating ambulatory management of adults with OSA into healthcare systems. The report identifies barriers preventing incorporation of portable monitor testing into clinical management pathways. and recommends research and development needed to address those barriers. PSG is generally performed at special healthcare facilities, resulting in limited accessibility to patients, specifically in rural areas. PSG is expensive and patients have limited access to this specialized testing. In recent years, the use of less expensive, more accessible portable home monitoring to diagnose and manage patients with OSA has gained favor, but studies regarding its use and patient outcomes are lacking, according to the ATS, which noted: "We need to understand

the significant clinical limitations of PSG and work to further standardize the sensors, signal processing and protocols used in this 'gold-standard' test... Similar efforts are needed to further standardize portable monitors, especially to allow study results to be compared across monitors."

A WORLD OF SLEEP

Royal Philips Electronics was part of a global partnership with the World Association of Sleep Medicine (WASM), as official sponsor of World Sleep Day 2011, which was held on March 18. At the same time, Philips, together with leading Australian sleep researcher Dr Sarah Blunden and the WASM, announced the launch of a new educational module on sleep for children around the world, as part of the SimplyHealthy@Schools program.

Available online at simplyhealthyatschools.com, the program aims to support teachers in educating children between the ages of 8 and 12 years, on the importance of sleep. The Philips Index for Health and Well-being report - a massive consumer research study conducted across 23 countries and involving more than 31,000 people, revealed that 35% of people do not feel they get enough sleep. Philips also offers a self-assessed Sleep Quiz to determine if they suffer from OSA, at Philips.com/sleepapnoea.

SLEEP-DISORDERED

Philips introduced BiPAP autoSV Advanced-System One as its newest innovation in treating the most complex sleep-disordered breathing patients. The Philips Respiroics BiPAP autoSV Advanced-System One combines the company's proven SV Advanced algorithm with Philips Respiroics' premiere System One platform. BiPAP autoSV Advanced-System One was

specifically designed and clinically validated to treat complicated sleep-disordered breathing patients. By combining the proven autoSV Advanced algorithm with the System One platform, the product treats the most complex sleep-disordered breathing patients and incorporates the state-of-the-art Encore patient data management and reporting system, giving clinicians the ability to access real time patient compliance data including detailed patient and usage information, AHI, leak, and periodic breathing data, and detailed patient-flow waveform data. BiPAP autoSV Advanced features cellular modem data transfer to Encore Anywhere and incorporates the same advanced System One humidification system that is in the System One product line. Contact philips.com.

SLEEP ROUNDTABLE

ActiGraph

Tell us about the sleep products your company offers.

ActiGraph's **ActiSleep** home monitoring system is an actigraphy-based sleep assessment tool used by healthcare providers and sleep researchers to determine patient sleep quality, identify sleep/wake patterns and screen for potential sleep disorders in the home environment. The ActiSleep home monitoring system, composed of the wrist-worn ActiSleep monitor and the **ActiLife** analysis software, delivers sleep measurements including total sleep time (TST), sleep latency, wake after onset (WASO), sleep efficiency and ambient light levels. The ActiSleep home

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monitoring system is a cost effective and noninvasive alternative to PSG and provides a level of objectivity and accuracy that cannot be achieved through self-report. Visit actisleep.com to learn more.

CleveMed

What sleep products do you offer?

CleveMed's current sleep product offerings include complete wireless **PSG systems**, the 14-channel **Crystal Monitor 20-S** and 20-B and the 22-channel **Sapphire PSG**. The **SleepScout** is a 9-channel type III monitor for home sleep testing. All four systems include Crystal PSG software, a sophisticated software package for data acquisition, scoring and reporting.

What are the latest developments in sleep testing and diagnostics?

Our latest product, **SleepView** is the smallest, lightest home sleep monitor following AASM guidelines for portable monitoring. It is ergonomically designed for patients to perform a self test at home. SleepView works hand in hand with the eCrystal PSG Web Portal, where sleep studies are uploaded for review and scoring by sleep technologists and interpreted by a board certified sleep physician. This practical and efficient patient monitoring system, allows physicians to provide a continuum of care.

How does your product enhance patient compliance and ease of use?

The SleepScout and SleepView can be used to monitor patients during treatment at home. This allows the provider to monitor effectiveness of treatment and re-titrate if needed. Ensuring that the treatment option is effective for the patient enhances compliance by improving the patient's condition.

What training and education do you offer in the use of your product for healthcare providers?

The purchase of a system includes initial training on the product. Webex is used for follow up training and for customer support.

Compumedics USA Inc

Tell us about the sleep products your company offers.

Compumedics has a full diagnostic sleep product line from products for home sleep testing to basic in-lab PSG to extended PSGs for neurologic disorders, pediatric sleep and advanced research applications. The **SomtéPSG** system can be used for Full PSG Anywhere; in-lab (Type I) and ambulatory/home (Type II) sleep studies with wireless Bluetooth communication to a monitoring computer and full-disclosure storage built-in. The Compumedics **GraeI PSG** system raised the bar once again for advanced diagnostic sleep centers – the world's first HD-PSG system.

How does your product enhance patient compliance and ease of use?

Ease of use for technicians and physicians is a significant factor when Compumedics develops its products. The features of our digital amplifiers include built-in high-definition oximeters, pressure sensors, RIP signals, and support for up to 16 external device signals. The **ProFusion** software on our systems is designed to be efficient and flexible, yet full-featured.

What training and education do you offer in the use of your product for healthcare providers?

Training for our in-lab systems is provided onsite by our credentialed clinical training staff. Refresher training or training on specific topics can be arranged through professional online training modules. Compumedics is one of only a few companies that offer AAST-recognized Continuing Education Credits for its training courses.

Discuss any issues relevant to cost-control/reimbursement.

Insurance reimbursement adjustments require that lab managers assess the total cost of providing their diagnostic sleep services, regardless of the type of business they operate. Compumedics systems are known for their durability and long life in the most demanding testing environments so ongoing support costs are predictable and reasonable. Many sleep labs will be evaluating an adjusting patient to technician ratios from the common 2:1 to a lower cost 3:1 ratio. This requires a sleep system that allows for easy operation of multiple beds, something our systems are designed to handle with ease. Supply costs for sleep studies are always a concern. Compumedics systems are designed to support either disposable or reusable sensors and electrodes, so managers can follow whichever protocol produces the lowest total cost for their operation. Just as important is operational efficiency. With the Compumedics **neXus Lab Management** system our clients enjoy improvements in workflow and sleep testing operations, providing a real return on investment through better patient, study and document management – accomplishing more with fewer resources.

Fisher & Paykel Healthcare

Tell us about the sleep products your company offers.

At Fisher & Paykel Healthcare we believe everyone should enjoy a good night's sleep. We've based our business on this belief. For those who suffer from Obstructive Sleep Apnea (OSA) and those who provide treatment for them, we bring a family of unique solutions. Our comprehensive range of continuous positive airway pressure (CPAP) devices, masks and humidifiers deliver the best in sleep performance for an energized lifestyle. They are the results of our dedication to 24 hour wellness. **Mask Solutions:** Only Fisher & Paykel Healthcare offers a mask in all delivery categories. There are four different delivery categories which should be considered when choosing a mask. Our range of masks and their inherent performance features delivers greater flexibility, because they are designed to meet the needs of every sleeper. Our range offers a unique combination of features and technologies that allow for simple fitting and maintenance such as **FlexiFit** technology for auto contouring, the **Glider Strap**, which compensates for movement during the night, and the **FlexiFoam Cushion** that conforms naturally to a patient's face. **CPAP & Humidifier Solutions:** The **F&P ICON** has been designed from the outside-in to answer the CPAP user's strong call for a compact, stylish CPAP that blends seamlessly into any bedroom environment. The F&P ICON is stylish on the outside and smart on the inside so CPAP users can feel at ease knowing they are being taken care of by a range of the world's leading clinical technologies for treating sleep apnea. The F&P ICON has a range of useful features such as integrated heated humidifier, clinically proven **ThermoSmart** Technology for optimal delivery of humidification without condensation, and **SensAwake** technology which senses irregular breathing indicative of

wakefulness and reduces the pressure to aid the transition back to sleep.

How does your product enhance patient compliance and ease of use?

Appealing and effective CPAP therapy: Patient adherence to therapy is an area of strength for Fisher & Paykel Healthcare. Research has shown that providing positive user experiences with products, including qualities such as aesthetics and user-friendliness and incorporating technological advances, may encourage adherence to CPAP therapy. Based on this philosophy, we have developed the new F&P ICON family of CPAPs which is a comfortable yet visually appealing system, designed to enhance patient adaptation to CPAP therapy. We also believe that patient adherence requires a total solution. This solution must be focused on the primary areas that create challenges for the patient, including psychological barriers related to the acceptance of the device, interface fit and comfort, humidification, pressure relief and most importantly ease of use. Our Interfaces offer 3 primary market differentiators: 1. Patient ease of use: No need for complicated adjustments to adjust the T-piece to relieve pressure on the bridge of the nose or prevent leaks. Instead, by utilizing FlexiFit auto-contouring technology, available in all of our nasal and full face masks, we provide one-step ease of fitting and an optimized seal for the patient. 2. Patient freedom of movement: By offering the unique Glider Strap, patients can rotate their heads side to side while maintaining the mask seal and minimizing the occurrence of leaks. 3. Simplicity: All of our masks come assembled and ready to use with less parts to deal with. These characteristics simplify the fitting and cleaning and maintenance for patients. **Optimal humidification:** Patient comfort is improved when adverse effects of therapy are reduced. Evidence suggests that improving patient comfort with CPAP by providing heated humidification increases patients' CPAP acceptance and adherence. Fisher & Paykel Healthcare's innovative ThermoSmart technology, available in our F&P ICON Family, offers a unique system that allows for the delivery of higher levels of humidity throughout the night, while preventing condensation in the tubing. ThermoSmart technology clears the way for optimal therapy success and greater levels of patient comfort. **Pressure Relief:** Clinical evidence has shown that patients commonly arouse from sleep (~10/hr) which can sometimes lead to full awakenings. During these awake states, patients can be intolerant of the pressure and patient comfort is critical for the patient to return to sleep. Our unique SensAwake technology, available in the F&P ICON Auto, detects when a patient is transitioning to a wakeful state and promptly lowers the pressure to aid the transition back to sleep. The result is a more personalized therapy during sleep and awake states. **Measuring Outcomes:** In today's market measuring compliance has more importance than ever before. Keeping it simple is the hard part. The **SmartStick** is our compliance measurement solution that is very simple. The SmartStick uses a USB port to download patient data.

What training and education do you offer in the use of your product for healthcare providers?

In addition to an intensive new hire training program, all Fisher & Paykel Healthcare sales and clinical staff are trained periodically throughout the year. Today our customers have access to multiple CEU courses provided at no cost, as well as new and existing product in-services on demand. We also offer our customers and patients training, education, and support through websites (vigor8.com and fpicon.com). These sites include instructional streaming videos on our product line,

literature reviews, and clinical pathways. We are also looking to further improve our employee and customer training utilizing the latest online technologies available.

Discuss any issues relevant to cost-control/reimbursement.

Given the current economic environment, solutions to reduce costs associated with inventory management and augmenting existing revenues while improving staff efficiencies remain critical. We have taken several steps to help provide solutions for our customers such as offering masks with greater fit across the normal population (Zest Nasal Mask) or masks with multiple sizes in one package (Forma Full Face Mask). This type of solution will allow our customers to manage their inventory more efficiently while ensuring a great fit for their patients. We also provide training to assist non-credentialed staff to assist with patient follow up to address the common questions or concerns about CPAP or F&P equipment which are easily-overcome. This process allows for an immediate response to be offered to a patient by the call-center personnel, allowing the therapist to focus on revenue-generating activities. The therapist only need become involved only when an escalation path is identified. We always strive to work with our customers to provide them with effective and cost efficient solutions and technology that creates market differentiation.

Inspire Medical Systems

Tell us about the sleep products your company offers.

Inspire Medical Systems is the world's leading developer of innovative, implantable neurostimulation technologies to treat Obstructive Sleep Apnea (OSA). Utilizing well-established technologies from the fields of cardiac pacing and neurostimulation, Inspire has developed a proprietary Upper Airway Stimulation (UAS) therapy for patients who suffer from obstructive sleep apnea.

How does your product enhance patient compliance and ease of use?

Treatments for OSA include weight loss, CPAP, oral appliances, and surgeries. CPAP (Continuous Positive Air Pressure) applied through a nasal mask is the current standard of treatment for OSA. However several recent studies show that CPAP compliance can be as low as 50 percent because of the nasal mask constriction, discomfort and inconvenience. **Inspire Upper Airway Stimulation (UAS) therapy** works with the body's physiology to prevent airway obstruction during sleep. Many people suffering from OSA experience decreased muscle tone in their airway during sleep. When this occurs, the tongue and other soft tissues can relax, obstruct the airway, and cause apnea events. Inspire therapy is designed to deliver mild stimulation to the hypoglossal nerve on each breathing cycle while the OSA patient sleeps. This stimulation intends to help keep the airway open during sleep. Patients control when the therapy is turned on and off via a handheld programmer. While Inspire therapy does require a surgical procedure, in contrast to other surgical options to treat sleep apnea, Inspire therapy does not require removing or permanently altering an OSA patient's facial or airway anatomy. As such, the procedure is less invasive and may result in a shorter recovery time.

Discuss any issues relevant to cost-control/reimbursement.

The Inspire Upper Airway Stimulation (UAS) therapy is currently undergoing a pivotal clinical trial called the STAR Trial. The STAR trial is a global, multi-center clinical trial which will assess the safety and effectiveness of Inspire Upper Airway Stimulation (UAS) therapy in patients who suffer from moderate to severe obstructive sleep apnea (OSA). The results of this study will be the basis for a Pre-market approval (PMA) application to the FDA. For more information on The STAR trial, visit TheStarTrial.com.

Nihon Kohden

What sleep products do you offer?

Nihon Kohden offers several platforms for both in lab and home sleep testing. In lab testing devices come in two platforms; dedicated PSG and Combination EEG/PSG. **Dedicated PSG Platforms: Polysleep 921** – Total 40 Channels (32 AC, 8 DC) available internal mainstream EtCO₂; **Polysleep 912** – Total 37 Channels (27 AC, 10 DC). **Combination Platforms: EEG-1200 EEG/PSG** is available in 27, 32, 64, 128, 192 AC channel platforms. Up to 16 DC channels. **Home Sleep Testing: Track-it Ambulatory** Type II recorders for EEG or PSG available in 18+8 channels, 24 Channels, 32 Channels. Built-in SpO₂ available; **Track-it Sleepwalker** dedicated type II recorder; **Nomad Type III** recorder 11 channels. **Polysmith** Sleep acquisition and analysis software; Polysmith DMS (Data Management Software).

How does your product enhance patient compliance and ease of use?

Our products are mainly diagnostic and require professional intervention to operate. The exception is the Home Sleep Testing devices. We have created easy to follow patient videos that instruct patients how to set up home sleep testing devices for ease of use.

What training and education do you offer in the use of your product for healthcare providers?

Nihon Kohden offers advanced training courses for the operation of our polysomnographic equipment as well as for the Home Sleep Testing devices. Further we offer clinical training classes for preparation for the RPSGT exam. We have advanced support contracts that provide webinar training on various subjects throughout the year.

Discuss any issues relevant to cost-control/reimbursement.

Nihon Kohden is continually developing software to allow our customers to lower their cost of providing services. Our Polysmith DMS database allows users to store and manage data related to lab management efficiency giving them the ability to keep their finger on the pulse of their clinical operations and business. Creating tools to allow users to lower scoring and review time as well as turn-around time is a priority in being competitive in the ever changing sleep services market.

Philips Respironics

Tell us about the sleep products your company offers.

Philips Respironics offers a complete range of sleep diagnostic and therapy products, services and programs that support sleep

labs and homecare providers in treating patients across the care continuum. Our products help to facilitate the identification, diagnosis, titration, treatment, and compliance management for sleep disorders. We are focused on building these solutions with our customers. Our products are designed to meet their varying needs and the needs of the patients they serve. We are working together with our customers to increase the number of patients who are comfortable with and adhere to their PAP therapy over the long term. The evolution in comfort of CPAP includes improvements in both masks and devices. Finding the right mask for the patient is critical to therapy success. For a more comfortable mask experience, materials and design are the biggest factors. Gel mask features are soft and flexible and conform to a patient's facial structure. These features enable the mask to be more comfortable on the face and create a better seal so that mask leaks can be minimized. Over the past few years a new category of minimal contact masks including pillows and direct seal cushions has been introduced, to remove the bulk and claustrophobic feeling patients may experience with other styles of masks. The newest addition to our range of nasal, pillows and full-face masks is **GoLife for Men**. When designing GoLife for Men, we listened to what sleep therapy providers, clinicians, and male patients told us they wanted in a nasal pillows mask, and that was stability and simplicity. As a result, GoLife for Men takes the complexity out of achieving successful nasal pillow therapy for male patients. And soon, a GoLife for Women mask will offer the same customized features designed for a female patient's face. Both masks are designed so that used together with Philips Respironics **System One Resistance Control**, they help to deliver improved PAP therapy and comfort. Like our mask portfolio, our PAP systems also have improved over time. Enhancements include the delivery of humidification, flexibility with expiratory pressure, smart ramps that detect flow changes and other comfort features. The enhanced System One device now provides dramatically quieter, intelligent sleep therapy. System One matches the patient's breathing cycle for increased comfort, due to the patented, flow-based Flex technology. With advanced detection, it continuously monitors activity to recognize when therapy needs are changing. It also provides higher target relative humidity levels. The humidity control minimizes the nuisance side effect of rainout. New technologies such as System One Resistance Control enhance the way the device and a specific mask deliver comfortable therapy. This is an excellent example of how we're building solutions with our customers. As further support for therapy success, Philips Respironics offers a 30-day **Mask Satisfaction Promise Program** to help get patients fitted with the mask that will work best for them. All of our products are backed by industry-leading after-sales support and customer service.

How do your products enhance patient compliance and ease of use?

We are entering a new era in sleep therapy. Technology is enabling a higher level of care for patients while helping to streamline business operations that benefit the clinician. The most recent developments in CPAP treatment help improve compliance by giving providers and care team members faster and easier access to patient therapy data so that they can intervene more quickly and effectively. Data can be transferred automatically via a modem into a web-based system, such as EncoreAnywhere, where providers, labs and physicians can view data, communicate to other members of the care team and make pressure adjustments remotely. With this faster flow of information, enhanced and more efficient protocols are being

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implemented to enable a higher level of care for more patients, which ultimately leads to better compliance.

What training and education do you offer in the use of your product for healthcare providers?

Philips Respironics offers a variety of education and training resources for clinicians to help patients achieve positive treatment outcomes. Resources include self-directed written and web-based tutorials or face-to-face instruction. Clinicians learn key concepts and practical applications in the area of sleep medicine that they can apply to their daily activities or to the care of their patients. Clinicians can earn continuing education credits as required by their states to maintain credentials. As in most life-impacting disease management situations, caregivers play an important role in helping patients get the most out of their sleep apnea treatments. Philips Respironics provides extensive materials in written, audio/video and web-based formats to help educate the patient, caregiver and family on the condition and treatment, including tips for use and the need for regular replacement of accessories to maintain comfort and performance of therapy. The materials are available for distribution to caregivers or people using Philips Respironics equipment. Co-morbidities such as heart disease, diabetes, hypertension, stroke and post-operative care continue to be an area of focus for sleep researchers. Education is critical. There are studies that show positive trends in conventional management of these co-morbidities when OSA is effectively treated. We believe that efforts to educate physicians and patients on the need to treat OSA should extend to the medical specialties where co-morbid conditions exist.

Discuss any issues relevant to cost-control/reimbursement.

The combination of our products, technology and programs helps to ensure that patients are compliant with sleep therapy and that providers are equipped with the tools they need to address the challenges of cost-control and reimbursement. We place a great value on understanding the challenges facing clinicians and patients, and we work to provide tools and solutions to help them deal with these challenges. For example, enhancements to our System One sleep therapy platform, coupled with our web-based patient data management system, EncoreAnywhere, and our wireless modems for monitoring, have been very well received in the market. In the last decade, we've gone from looking at data on the machine to a web-based system, where the device stays in the patient's home, and information is bi-directionally transferred daily for easy access and intervention anytime, anywhere by the entire care team.

Ventus Medical

Tell us about the sleep products your company offers.

Provent Sleep Apnea Therapy is a prescription device indicated for the treatment of obstructive sleep apnea. It is an easy-to-use, disposable treatment that works across mild, moderate and severe OSA. Provent Therapy is cleared by the US Food and Drug Administration (FDA) and numerous peer-reviewed published studies have demonstrated that Provent Therapy improves sleep apnea and oxygenation. The device works through a proprietary **MicroValve** technology that uses the patient's own breathing to create expiratory positive airway pressure (EPAP) to keep the airway open during sleep. The Provent devices attach over the nostrils with a hypoallergenic

adhesive. Provent Sleep Apnea Therapy is clinically proven to reduce AHI, ODI, improves daytime sleepiness and is a good option for sleep apnea sufferers looking for an alternative treatment to CPAP.

How does your product enhance patient compliance and ease of use?

Most patients with OSA are prescribed a CPAP machine. CPAP is extremely effective at treating OSA if worn as directed. However, more than half of all patients stop treatment with CPAP due to its cumbersome nature. Provent Therapy was developed to help patients who do not use CPAP regularly and who can benefit from a non-invasive and clinically effective treatment alternative. Provent Therapy offers a good treatment option for patients who refuse, fail or are not compliant with CPAP therapy. Most patients find Provent Therapy easy to use. Provent Therapy requires no mask, tubes, or machine; just a pair of two small devices worn over the nostrils. The product is available in a 10-night trial pack as well as 30-night supply for ongoing use. The devices are small, disposable and portable, making it easy for every night use as well as travel. In a 30 day at-home clinical study, subjects reported using the device all night during 94% of possible nights. In a market research study with current Provent Therapy users, satisfaction and intent to continue therapy was very high. Nearly 8 in 10 current Provent Therapy users were highly satisfied, and 9 in 10 current Provent users claimed they planned to continue therapy.

What training and education do you offer in the use of your product for healthcare providers?

Patient education is important to adherence and compliance with Provent Therapy, and many educational and support materials are provided to healthcare providers and suppliers:

- Detailed patient information is included in each Provent Therapy package. This includes steps and visuals on how to apply Provent Therapy, what to expect, and tips to acclimate.
- A comprehensive training video that provides application instructions instructs patients on the proper application method, expectations and acclimation tips.
- Comprehensive information is available at the Provent Therapy website, proventtherapy.com, including a detailed patient video, downloadable tip sheet and instructions.
- A Provent Therapy product specialist is available through a toll-free number to patients who have questions about how to apply and get adjusted to using Provent.
- A patient acclimation guide is provided to physicians and Provent Therapy suppliers. This acclimation guide contains steps and tips for successful acclimation to Provent Therapy and is a helpful at-home resource.
- Ventus Medical provides education and training to its DME suppliers through "Provent University", an online training program.

Discuss any issues relevant to cost-control/reimbursement.

As Provent Therapy is relatively new, it may not be covered by insurance plans or prescription programs. In many cases, tax-free, flexible spending accounts may be used to cover the cost of Provent Therapy.

Chronic Widespread Musculoskeletal Pain, Fatigue, Depression and Disordered Sleep in chronic post-SARS Syndrome

Harvey Moldofsky, John Patcai

Abstract

Background: The long term adverse effects of Severe Acute Respiratory Syndrome (SARS), a viral disease, are poorly understood.

Methods: Sleep physiology, somatic and mood symptoms of 22 Toronto subjects, 21 of whom were healthcare workers, (19 females, 3 males, mean age 46.29 yrs. \pm 11.02) who remained unable to return to their former occupation (mean 19.8 months, range: 13 to 36 months following SARS) were compared to 7 healthy female subjects. Because of their clinical similarities to patients with fibromyalgia syndrome (FMS) these post-SARS subjects were similarly compared to 21 drug free female patients, (mean age 42.4 \pm 11.8 yrs.) who fulfilled criteria for fibromyalgia.

Results: Chronic post-SARS is characterized by persistent fatigue, diffuse myalgia, weakness, depression, and nonrestorative sleep with associated REM-related apneas/hypopneas, an elevated sleep EEG cyclical alternating pattern, and alpha EEG sleep anomaly. Post-SARS patients had symptoms of pre and post-sleep fatigue and post sleep sleepiness that were similar to the symptoms of patients with FMS, and similar to symptoms of patients with chronic fatigue syndrome. Both post-SARS and FMS groups had sleep instability as indicated by the high sleep EEG cyclical alternating pattern rate. The post-SARS group had a lower rating of the alpha EEG sleep anomaly as compared to the FMS patients. The post-SARS group also reported less pre-sleep and post-sleep musculoskeletal pain symptoms.

Conclusions: The clinical and sleep features of chronic post-SARS form a syndrome of chronic fatigue, pain, weakness, depression and sleep disturbance, which overlaps with the clinical and sleep features of FMS and chronic fatigue syndrome.

Harvey Moldofsky is with the Sleep Disorders Clinic of the Centre for Sleep and Chronobiology, Toronto. Patcai is with St John's Rehab Hospital and the Department of Medicine, University of Toronto. The authors wish to thank the assistance of the technical and administrative staff of the Sleep Disorders Clinic of the Centre for Sleep and Chronobiology and St John's Rehabilitation Hospital. Most particularly, they wish to thank all the post-SARS patients who, despite their ongoing personal difficulties, gave permission to use their data. Reprinted from BioMed Central, BMC Neurology, © 2011 Moldofsky and Patcai; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License.

Background

In light of public health concerns about the adverse effects of the recent H1N1 pandemic viral infection, it is noted that the long-term effects on survivors of those who survive severe illness are unknown. In this paper we report the results of our study of the long term adverse effects of Severe Acute Respiratory Syndrome (SARS) that emerged from South East Asia in early 2003 as the first contemporary novel severe acute infectious global health problem. In North America, Toronto experienced the bulk of cases that largely affected health care workers.¹ The Ontario health authorities alerted health care personnel on March 14, 2003 about 4 family members with atypical pneumonia that resulted in two deaths. A province-wide emergency was declared on March 26, 2003 when it became evident that these cases were the epidemiological link to SARS. The government and health care providers took steps to contain the spread of SARS by enacting infection control procedures, screening and isolating those people who were exposed, and admitting affected personnel, many of whom were health care workers, to special hospital SARS units. The public health precautions proved effective enough that by June 12, 2003 there were no more new cases. During those 3 months 273 people were identified as being confirmed SARS² cases. 44³ died. Because identification of victims and containment were the orders of the time, medical attention focused upon the features of the acute phase of the illness. They were identified as having new onset of fever, documented elevated temperature, and were likely to have nonproductive cough, myalgia, and dyspnea. Such individuals may have been exposed to patients who had traveled to a location known to harbor such cases, ie, South China, South East Asia, or may have acquired these symptoms as the result of direct contact or exposure.^{1,4} Subsequently a novel coronavirus was identified as the cause of the acute outbreak.⁵⁻⁷

Although the epidemic in Toronto was considered controlled because no new cases appeared after June 2003 with no one remaining in quarantine^{1,8} one year later when life in the hospitals and city had returned to normal, a cohort of post-SARS patients remained disabled and unable to return to their work. They complained of persisting debilitating physical symptoms including variable musculoskeletal pain, profound weakness, easy fatigability, shortness of breath that accompanied psychological distress and major sleep problems. Because of the possibility of persistence of sleep-related respiratory dysfunction and arousal disturbances in the sleep EEG that could affect daytime fatigue and mood disturbances in the patients with the greatest clinical sleep disturbances, we examined their sleep

physiology and coincident somatic and psychological symptoms. This is the first report of the long-term adverse effects of SARS on sleep and somatic symptoms.

Methods

The University Health Network human research ethics board approved the retrospective study of clinically necessary sleep studies, and signed informed consent forms were obtained from all patients. 19 females (mean age 46.29 ± 11.02 y., BMI = 28.26 ± 6.88) and 3 males, (all except one being health care workers) were assessed about 19.8 months after onset of the acute SARS illness (range: 13 to 36 months) with hospitalization and/or quarantine for SARS. They were part of a cohort of 50 post-SARS patients who had come under the care of the Ontario Workers' Safety and Insurance Board (WSIB) because of persistent impaired health that interfered with their hospital work capabilities. They had been sent by WSIB for a complex, intense, interdisciplinary clinical program of physical and psychological restorative rehabilitation. This post-SARS group was compared to a small group of younger healthy 8 females (mean age 30 ± 6.7 y., $p = 0.0002$), but with a similar BMI (24.8 ± 6.1 , $p = .242$) by employing standard self-ratings of physical symptoms [the Wahler Physical Symptom Inventory (WPSI)],⁹ of depression [Beck Depression Inventory (BDI)],^{10,11} of self rated symptoms of post traumatic stress disorder (PTSD) because of their exposure to the threat of death as the result of their exposure to the SARS virus [PTSD check list civilian version {PCL-C}],¹² and of sleep symptoms [the Sleep Assessment Questionnaire^c (SAQ^c)].¹³ The SAQ is a 17-item questionnaire that has been found to be useful for identifying sleep disorders related to chronic fatigue. One overnight polysomnography was employed in order to objectively evaluate sleep physiology. The procedures included electroencephalogram (EEG C3, C4) electro-oculogram, submental and bilateral anterior tibialis electromyogram, single anterior lead electrocardiogram, measures of respiration comprising measures of airflow with oral-nasal thermistors and respiratory impedance plethysmography, and pulse oximetry. An experienced registered polysomnographic technologist completed blind ratings of sleep physiological indices¹⁴ and standardized ratings (1 to 5) of the presence of a measure of arousal in the non rapid eye movement sleep EEG (NonREM sleep), known as the alpha frequency anomaly¹⁵ where 1 was the percentage of alpha EEG in Non REM sleep (7.5 Hz to 12Hz) less than 20% and where 5 was more than 80% of alpha EEG in Non REM sleep. In order to evaluate daytime lethargy the overnight sleep study was followed by the multiple sleep latency test (MSLT) comprising of at least four 20 minute nap opportunities at 2 hour interval beginning 2 hours after morning awakening.¹⁶ Self ratings of symptoms pre-sleep and post sleep consisted of standard measures of total regional musculoskeletal pain severity (0-24), of fatigue (1-7),¹⁷ and sleepiness¹⁸ that had been used in previous studies of patients with fibromyalgia syndrome (FMS) and chronic fatigue syndrome (CFS). Because clinically the post-SARS patients described many of the features seen in patients with FMS we also compared the self ratings of pain, fatigue and sleepiness symptoms and objective indices of overnight sleep physiology to an aged matched population of 21 drug free female patients, (mean age 42.4 ± 11.8 yrs.) who fulfilled criteria for fibromyalgia.¹⁹ They had participated in a double blind placebo- controlled drug trial, to which they had provided their ethics approved signed consent. Only the initial overnight pre- treatment sleep study was employed for the purposes of comparison with this post-SARS chronically ill patient population. In addition to the standard sleep

Table 1. Sleep in SARS vs. Healthy Controls.

Sleep Parameter	SARS	Healthy Controls	Significance
	Mean (SD)	Mean(SD)	P
Sleep onset latency (min.)	24.13 (21.63)	29.34(31.48)	n.s.
Total sleep time (min)	370.83 (83.84)	343.43(38.47)	n.s.
Sleep Efficiency %	77.44 (13.56)	83.23(12.36)	n.s.
Stage 1 %	9.11 (4.13)	6.60(4.61)	n.s.
Stage 2 %	60.22 (9.95)	49.77(6.53)	$p=0.006$
Stage 3 %	7.83 (6.36)	4.84(2.11)	n.s.
Stage 4 %	6.27 (5.80)	9.70 (2.84)	$p=0.051$.
REM onset Latency (min.)	136.79 (63.72)	87.23 (38.47)	$p=0.004$
REM %	16.57 (5.94)	17.27 (5.35)	n.s.
Apnea/Apnea-Hypopneas Index (no. per hr. of sleep)	4.70 (5.53)	2.73 (2.08)	n.s.
REM Apnea-Hypopnea Index (no. per hr. of REM sleep)	14.33 (15.41)	N/A	N/A
NREM O2 saturation (max/min)	99.13 (0.68) 92.09 (3.61)	N/A	N/A
REM O2 saturation (max/min)	98.69 (0.93) 92.24 (4.60)	N/A	N/A
		96.50 (0.71)	N/A

physiological indices described above we analyzed another sleep EEG anomaly known as a high frequency of cyclical alternating pattern (CAP). The CAP rate has been found to be a quantified measure of EEG sleep stability where frequent periodic EEG arousal disturbances indicate sleep instability or poor quality sleep. This high frequency of CAP has been related to less efficient sleep and the severity of symptoms of patients with FMS.^{20,21} Objective ratings of CAP rate was assessed using a validated, computerized automatic detection methodology (Somnologica).^{22,23} Statistical analyses were completed between group 2 tail t-tests for behavioural self-ratings, sleep physiological indices, and pre-post sleep ratings of current symptoms. Bonferroni corrections were performed on the multiple t tests.

Results

In comparison to healthy subjects, post-SARS subjects reported more physical symptoms on the WPSI (mean 10.6 ± 5.0 vs. 0.4 ± 0.5 , $p < .0001$). On most days they complained of tiredness, difficulty sleeping, myalgia and muscular weakness. They had more mild to moderate depressive symptoms (BDI mean = 13.3 ± 8 vs. 0.86 ± 1.5 , $p < .0001$), more sleep disturbances on the SAQ^c (mean total score = 30.9 ± 5 vs. 10.9 ± 3.4 , $p < .0001$), more fatigue post-sleep ($p < .05$), and more myalgia pre- and post-sleep ($p < .01$). See Table 1. For the 21 patients that completed the PCL-C, the mean score was 40.75 ± 10.26 . Two patients had scores of 50 or more that would be suggestive of the symptoms seen in patients with PTSD.²⁴

The overnight sleep physiology in the post-SARS group showed more arousal disturbances and the alpha EEG sleep disorder which consists of the anomalous appearance of the EEG alpha frequency (7.5-12 Hz) in approximately 50% of sleep. There was more stage 2 NonREM sleep and a delay in onset to REM sleep, but no other significant differences in measures of sleep EEG. See Table 1.

In measures of sleep-related respiratory disturbances, 5 post-SARS subjects who snored had variable daytime sleepiness on the MSLT (defined as rapid onset to sleep in less than 8 min on at least one of the 4 or 5 nap opportunities, range from 3-8 min). Two of these Post-SARS subjects (ages 63 yrs., BMI = 28, and 49 yrs, BMI = 32) who were being treated for hypertension had moderate and mild sleep hypopnea/apnea disorder (with a respiratory distress index (RDI) = 18.8 and 8.4 respectively) and arterial oxygen desaturation (minimum of 81.2% and 83% respectively). The only other person (age 57 yrs, BMI 25.5)

Table 2. Sleep, Pain and Fatigue in SARS vs. FMS Subjects.

Sleep Parameter	SARS (n=22)	Fibromyalgia (n=21)	Significance
	Mean (SD)	Mean (SD)	
Sleep onset latency (min.)	24.13 (21.63)	18.37 (35.39)	n.s.
Total sleep time (min)	370.83 (83.84)	338.54 (76.26)	n.s.
Sleep Efficiency %	77.44 (13.56)	79.34 (15.63)	n.s.
Stage 1 %	9.11 (4.13)	9.76 (3.66)	n.s.
Stage 2 %	60.22 (9.95)	54.61(5.41)	0.031
Stage 3 %	7.83 (6.36)	7.35 (3.08)	n.s.
Stage 4 %	6.27 (5.80)	9.53 (6.18)	n.s.
REM onset Latency (min.)	136.79 (63.72)	87.26 (35.78)	0.004
REM %	16.57 (5.94)	18.77 (4.81)	n.s.
Apnea/Hypopneas Index (no. per hr.of sleep)	4.70 (5.53)	3.29 (2.37)	n.s.
Periodic leg movements (no.per hr of sleep)	2.03 (5.64)	2.38 (3.81)	n.s.
Arousals per hr of sleep	14.01 (7.59)	11.31 (5.31)	n.s.
CAP rate per hr of sleep	71.64 (14.25)	70.39 (15.64)	n.s.
Alpha EEG sleep (1-5)	3.00 (0.63)	3.50(0.61)	0.014
Presleep Pain	6.24 (4.01)	10.95 (5.74)	0.005
Presleep Fatigue (1-7)	4.57 (1.57)	4.30 (1.08)	n.s.
Presleep Sleepiness (1-7)	2.76 (1.14)	4.30 (1.08)	0.0001
Post Sleep Pain (0-24)	7.10 (3.81)	11.75 (6.45)	0.009
Post Sleep Fatigue (1-7)	4.30 (1.87)	4.60 (1.23)	n.s.
Post Sleep Sleepiness (1-7)	3.45 (1.57)	3.90 (1.12)	n.s.

being treated for hypertension had very mild elevation of RDI (7.5) but no snoring, no significant sleep-related arterial oxygen desaturations or daytime sleepiness. The others had no specific disturbances in sleep-related respiration. The limited number of healthy subjects and their incomplete detailed data on REM and NonRem arterial blood oxygen saturations did not permit proper comparison with such data from the post-SARS group.

Although most complained of being depressed only two were receiving antidepressants (citalopram), one of which had sleep apnea. All patients were seen by clinical psychologists unless they declined to do so, and psychiatric consultation was available to all if requested by the patient or other team members.

In the comparison between the post-SARS & FMS patients there were no clinically significant sleep related breathing disturbances or periodic leg movements during sleep. Both groups had a similarly elevated measure of sleep instability as indicated by the high cyclical alternating pattern rate,^{22,23} compared to the published norms as reported by Parrino²⁵ et al. These are also comparable to the findings of Rizzi et al in their study of CAP in FM patients.

FMS patients, however, showed a significantly higher rating of the alpha EEG sleep anomaly than did the post-SARS patients. Other than there being more NonREM stage 2 sleep and a relative delay in onset to the initial REM sleep episode there were no other differences in their stages of sleep EEG. In their ratings of somatic symptoms post-SARS patients reported pre and post sleep fatigue and sleepiness similar to that reported by patients with FMS. Unlike the FMS patients they complained of less pre sleep and post sleep musculoskeletal pain symptoms (see table 2). See Table 2.

Discussion

This is the first report of the long-term adverse effects of widespread chronic pain, fatigue, psychological distress and disturbed sleep after acute SARS that contributed to the failure to return to productive work of a small cohort of health care professionals at least one year after their acute illness.

After their initial SARS symptoms of severe respiratory distress, fever with evidence for infiltrates in their lungs had remitted so that they were considered to be no longer in need of special quarantine and acute treatment measures, a constellation of symptoms persisted that interfered with their ability to function in their occupations. This was then a potentially biased selection process of 22 patients who were members of a group of 50 chronically ill survivors of SARS. A larger study of 107 patients from Toronto, with a more widely selected population²⁶ had shown that, at the one year mark some continued to describe problems with pain, reduced vitality, physical, mental, and social functioning. Only 14 (13%) were asymptomatic, leaving 93 patients (87%) symptomatic, where 18 (17%) had not returned to work, and 10 (9%) had returned to modified work. If one presumes that the asymptomatic group was most likely to return to unmodified work, then of the 79 patients returning to unmodified work, only 14 were asymptomatic.

This leads to the arithmetic conclusion that 65 (82%) of their patients who returned to unmodified work were nevertheless continuing to work despite ongoing symptoms.

Furthermore, 5 of our 22 subjects showed variable daytime sleepiness, which was associated with snoring indicative of sleep disordered breathing, but not necessarily overt sleep apnea. While sleep-related breathing disturbances have been reported in some patients with FMS/CFS²⁷⁻²⁹ only three post-SARS subjects exhibited mild to moderate sleep apnea/hypopneas. However, they may have had this sleep disorder before SARS because they were being treated for hypertension, a common causal risk for untreated sleep apnea.³⁰ Nevertheless, these sleep-related respiratory disturbances together with the alpha EEG sleep disorder may have contributed to their unrefreshing sleep and daytime symptoms.

Our single overnight study showed sleep physiological changes in stage 2 and REM onset latency that may have been influenced by being a feature of the potential adverse effect on sleep of the procedures employed in the study, known as the first night effect. The groups, however, were compared under similar circumstances although the SARS healthcare subjects may have been more sensitive to being tested in the sleep laboratory, and being more depressed. The two who were receiving antidepressant medications (citalopram) did not differ in any of the sleep parameters from the others who were equally depressed and not receiving such medications.

In our cohort, their disabling chronic fatigue, variable nonspecific myalgia, depression and sleep disturbances are similar to those experienced by patients with post-febrile Chronic Fatigue Syndrome (CFS)³¹ and Fibromyalgia Syndrome (FMS).³² Indeed, physiological changes in their sleep EEG, ie, the alpha EEG sleep anomaly is a common feature in such patients who commonly complain of unrefreshing sleep, fatigue, musculoskeletal pain, impaired cognitive functioning, and emotional distress.^{21,23,33-36} In the comparison of the post-SARS patients to the FMS subjects we noted similar sleep EEG elevated cyclical alternating pattern rate as previously reported by ourselves and others.^{22,23} However, in this study both the

Table 3. Published Studies.

re Patients Post-SARS (re Sleep)		
Location	Followup Time	Outcomes
Toronto	Acute illness (Retrospective)	no discussion sleep [2]
	21 day	no discussion of sleep [1]
	3 weeks post discharge	Appears to be 100% prevalence insomnia (two cases were severe) [4]
	One year	complaints of sleep disturbance averaging 47% prevalence [26]
Asia	"peak of outbreak"	Sleep problems noted, no incidence given [50]
	6 months	No discussion sleep [51]
	Summary 2005	No discussion sleep [52]
	Summary 2006	No discussion sleep [53]
re Health Care Workers Not Ill With SARS (re Sleep)		
Toronto	4 weeks	No prevalence given, but "sleep may be the first casualty"[54]
	~ 5 months	"Stigma, fear, frustration" but no discussion sleep [55]
	26 months	Negative psychological effects but no discussion sleep [56]
Asia	5 weeks	No discussion sleep [57]
	April, May 2003	No discussion sleep [58]
	3 months	Sleep "poor", improved by prevention program [37]
	30 months	"Mental health catastrophe" but no discussion sleep [59]

alpha EEG sleep ratings and the pain ratings were greater in FMS disorder than the post-SARS patients. Indeed the post-SARS patients seem to be similar to CFS patients where their focus is on fatigue symptoms rather than the pain.

Some contribution to the post-SARS persistent sleep, pain, fatigue, and depressive symptoms may have occurred as the result of the psychologically traumatic effects of their acute infectious illness. That is, these symptoms may have arisen as the result of their isolation from family and friends, uncertain outcome and threat of death. While as a group the post-SARS patients did rate themselves as having psychological distress only 2 patients described features on the PCL-C rating scale that are attributed to those with PTSD.¹² Such distressing experiences together with their acute SARS may have contributed to their alpha EEG arousal disturbances in sleep, recurrent nightmares and their inability to obtain restful sleep. Sleep difficulties have been reported in health care workers who did not have SARS themselves, but who did care for patients with SARS.³⁷ Indeed, similar unrefreshing sleep, fatigue and musculoskeletal pain symptoms occur in healthy people who have been experimentally exposed to several nights of frequent noise induced disruption of slow wave sleep, which artificially produces the periods of the alpha EEG sleep.³⁸

In addition there is the possibility that the sleep disorder, fatigue and behavioral symptoms may have occurred as the result of the Coronavirus A directly; this virus is known to invade the central nervous system and peripheral tissues.^{39,40} Viral particles and viral genome sequences were isolated from the cytoplasm of neurons more commonly in the hypothalamus and the cortex.^{41,42} Although the evidence indicates that the virus crosses the blood-brain barrier into the brain, the route of infection in humans remains unknown.⁴³ In mice that are transgenic for the SARS-CoV receptor (human angiotensin-converting enzyme 2) the virus enters the brain primarily via the olfactory bulb. Thereafter the infection spreads rapidly via neurons throughout the brain.⁴⁴ The virus may have resulted in chronic post-inflammatory CNS pathology that adversely affects sleep, pain sensitivity, and energy. In previous studies of chronic post-viral fatigue, both severity of the initial illness⁴⁵ and symptom-attributional style

and physician behaviour⁴⁶ have been associated with such outcomes.

The literature regarding SARS has documented many physical and psychological sequelae of the illness in both the short and the long term. Many studies did not note sleep disturbances, most likely on the basis that the focus of the study was elsewhere, even when one would expect sleep disturbances - such as when reporting incidence of post traumatic stress disorder (PTSD). In the studies where questions were asked about sleep, sleep disturbances were noted, although prevalence numbers are hard to find (table 3).

Conclusions

Chronic post-SARS is characterized by persistent fatigue, diffuse myalgia, weakness, depression, and nonrestorative sleep with associated REM-related apneas/hypopneas and alpha EEG sleep disorder. These clinical and sleep features of chronic post-SARS are similar to those features which may be found in patients with chronic fatigue syndrome/fibromyalgia. This report of the possible contribution of the coronaviral SARS to the emergence of chronic fatigue, unrefreshing sleep fatigue and widespread musculoskeletal pain symptoms also raises the question of the specificity the infectious retrovirus, XMRV, in blood cells that was recently reported⁴⁷ but is now a source of controversy as to its significance and specificity for patients with chronic fatigue syndrome.^{48,49} A longer term, large scale study is needed to establish the contribution of epidemic and pandemic viral disease to the disordered sleep, chronic fatigue and somatic symptoms of chronic fatigue/fibromyalgia syndrome.

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Chronic Cough and Obstructive Sleep Apnea in a Community-Based Pulmonary Practice

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Abstract

Background: Recent reports suggest an association between unexplained chronic cough and obstructive sleep apnea (OSA). Current guidelines provide an empiric integrative approach to the management of chronic cough, particularly for etiologies of gastroesophageal reflux (GERD), upper airway cough syndrome (UACS) and cough variant asthma (CVA) but do not provide any recommendations regarding testing for OSA. This study was done to evaluate the prevalence of OSA in patients referred for chronic cough and examine the impact of treating OSA in resolution of chronic cough.

Methods: A retrospective review of chronic cough patients seen over a four-year period in a community-based pulmonary practice was done. Patients with abnormal chest radiographs, abnormal pulmonary function tests, history of known parenchymal lung disease, and inadequate followup were excluded. Clinical data, treatments provided and degree of resolution of cough was evaluated based on chart review. Specifically, diagnostic testing for OSA and impact of management of OSA on chronic cough was assessed.

Results: 75 patients with isolated chronic cough were identified. 44/75 had single etiologies for cough (GERD 37%, UACS 12%, CVA 8%). 31/75 had multiple etiologies for their chronic cough (GERD-UACS 31%, GERD-CVA 5%, UACS-CVA 3%, GERD-UACS-CVA 3%). 31% patients underwent further diagnostic testing to evaluate for UACS, GERD and CVA. Specific testing for OSA was carried out in 38/75 (51%) patients and 33/75 (44%) were found to have obstructive sleep apnea. 93% of the patients that had interventions to optimize their sleep-disordered breathing had improvement in their cough.

Conclusions: OSA is a common finding in patients with chronic cough, even when another cause of cough has been identified. CPAP therapy in combination with other specific therapy for cough leads to a reduction in cough severity. Sleep apnea evaluation and therapy needs to be considered early during the

management of chronic cough and as a part of the diagnostic workup for chronic cough.

Background

The revised ACCP guidelines provide a step-wise approach for managing patients with chronic cough.¹ These guidelines recommend basing the etiology of chronic cough upon clinical opinions derived from historical information and therapeutic interventions.¹ Considerable variations therefore result in the management of chronic cough. Variations in management also stem from the diagnostic workup used to ascertain the cause of cough² and also from the occurrences of multiple etiologies of chronic cough.³ Recent reports have suggested an association between chronic cough and obstructive sleep apnea (OSA).⁴ There is also evidence that treatment of sleep apnea can improve chronic cough.⁵ Despite the lack of any specific guidelines on testing for OSA in patients with chronic cough,^{6,7} the impact of treatment of OSA is being noted in community-based pulmonary practices where chronic cough is most frequently encountered.

This study was undertaken to evaluate current strategies in approaches to chronic cough in non-smokers without known parenchymal lung disease in a large community-based pulmonary clinic. Besides evaluating treatment regimens and diagnostic testing, the impact of diagnosis and treatment of sleep apnea on the course of chronic cough was also assessed.

Methods

A retrospective review of medical records of patients seen in the Utah Valley Pulmonary Clinics in Provo and American Fork between 2005 and 2009 was done. Charts with diagnoses of "cough" and "bronchitis" were reviewed for cough lasting longer than 8 weeks. Since this study was confined to the evaluation of chronic cough in non-smokers without parenchymal lung disease, patients with abnormal chest X-rays, any prior smoking history, history of asthma requiring maintenance therapy, history of chronic parenchymal lung disease were excluded. Also patients that were not compliant with follow-up visits were excluded. Patients with only "normal" spirometry were included. Pulmonary function tests were conducted and interpreted based on the Intermountain Thoracic Society standards.⁸

Following above exclusions, 75 patient records were identified and reviewed for clinical data, diagnostic workup and therapeutic interventions. Clinical data obtained included demographic information, cough duration, comorbidities, etiologies for chronic cough, treatments provided and ancillary

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Table 1: Patient demographics, comorbidities and etiology of chronic cough. (Abbreviations: BMI - Body mass index, ACE-I – Angiotensin converting enzyme inhibitors.)

Patient characteristics	N = 75
Age in years (mean ± SD)	57 (± 14)
Female:Male ratio	1.5
BMI kg/m ² (mean ± SD)	
Overall	32 (± 8)
Male	31 (± 5)
Female	33 (± 9)
Duration of cough in weeks (mean ± SD)	
Overall	127 (± 274)
Male	55 (± 101)
Female	175 (± 337)
Comorbidities	
Hypertension	25 (33%)
Diabetes mellitus	9 (12%)
Rheumatoid arthritis	1 (1%)
Known sleep apnea	13 (17%)
Coronary artery disease	1 (1%)
ACE-I therapy	10 (13%)
Single diagnoses for cough	43/75 (57%)
GERD	28 (37%)
UACS	9 (12%)
CVA	6 (8%)
Multiple diagnoses for cough	31/75 (41%)
GERD & UACS	23 (31%)
UACS & CVA	2 (3%)
GERD & CVA	4 (5%)
UACS, GERD & CVA	2 (2%)

laboratory, radiological, and physiological workup. Patient records were specifically reviewed for mention of details regarding concomitant or pre-existing evaluation for OSA. Details regarding sleep history, physical exam pertinent to sleep apnea (pharyngeal crowding, neck circumference more than 17” in males and 16” in females, moderate to morbid obesity) were looked for.

Polysomnography was done based upon pulmonologist’s decision to pursue testing for OSA based upon findings of sleep history, physical exam consistent with a possibility of sleep disordered breathing and results of overnight oximetry. For patients undergoing polysomnography, the severity of sleep apnea was estimated based on the calculated apnea-hypopnea index.⁹ Treatments and effects of therapy for chronic cough at the initial and following visits were reviewed. Improvements in cough were ascertained based on self-reported assessments of cough during followup visits. Waiver of consent for the study was obtained from the Intermountain Office of Research. Part of the study findings were presented in an abstract form during CHEST 2009, San Diego, USA.¹⁰

Results

Patient records were reviewed from 8 different American Board certified pulmonologists. The number of included patients varied from 1 to 23 patients per provider, with a mean of 9. Patient characteristics, duration of cough, body mass index and co-morbidities are as shown in Table 1. Out of 75 patients, 44 patients had a single diagnosis for chronic cough at the time of the first visit with gastro-esophageal reflux disease (GERD) being the most common etiology (37%) followed by upper airway cough syndrome (UACS) (12%) and cough variant asthma

Table 2: Investigative workup for etiology of chronic cough and sleep-apnea specific workup in patients with chronic cough (Abbreviations: OSA - Obstructive sleep apnea; AHI – Apnea hypopnea index. * Bravo pH capsule with delivery system (Medtronic, Inc. Minneapolis, MN, USA))

INVESTIGATIONS PERFORMED	N (%)
Pulmonary Function Tests	
Spirometry	70/75 (93%)
Diffusion capacity	60/75 (80%)
Lung volumes	44/75 (59%)
Methacholine challenge testing	2/75 (3%)
Six-minute walk test	1/75 (1%)
Radiologic studies	
Chest X-ray	54/75 (72%)
Chest CT scan	10/75 (13%)
Sinus imaging	10/75 (13%)
Endoscopic studies	
Bronchoscopy	0/75
Upper GI endoscopy	2/75 (3%)
24 hour pH monitoring (Bravo* pH probe)	1/75 (1%)
Laboratory studies	5/75 (7%)
SLEEP APNEA RELATED WORKUP	
Sleep history obtained	41/75 (55%)
Abnormal	36/75 (48%)
Screening overnight oximetry	6/75 (8%)
Abnormal	6/75 (8%)
Polysomnography	38/75 (51%)
Sleep disordered breathing	33/75 (44%)
No OSA (AHI < 5)	4/75 (5%)
Mild OSA (AHI 6-15)	6/75 (8%)
Moderate OSA (AHI 16-30)	6/75 (8%)
Severe OSA (AHI >31)	14/75 (19%)
Periodic limb movement disorder	1/75 (1%)
Sleep efficiency (mean)	89%
Arousal index (mean)	17
Oxygen saturation (mean)	91%
Lowest oxygen saturation (mean)	78%

(CVA) (8%) (Table 1). One patient was diagnosed and treated only for OSA. 31/75 (41%) patients had multiple diagnoses for chronic cough with the combination of GERD-UACS being the commonest followed by GERD-CVA and UACS-CVA (Table 1). Two patients received therapy for all three causes - UACS, GERD and CVA at first visit.

GERD was the commonest etiology for chronic cough (irrespective of whether diagnosis was made as part of single or multiple etiologies) followed by UACS and then CVA. Proportion of patients with diagnoses of GERD, UACS and CVA (single or multiple diagnoses of cough) were 76%, 48% and 19% respectively. In 39% of patients, there was a history of an upper or lower respiratory tract infection at the onset of cough although this occurred more than 8 weeks before the patient presented to the pulmonary clinic. 5/75 patients had stoppage of angiotensin-converting enzyme inhibitors as a part of their management of chronic cough.

The investigative workup for these patients is detailed in Table 2. Two patients underwent methacholine challenge testing with one test demonstrating bronchial hyperreactivity. All chest CT scans performed were normal. Sinus radiographs or CT scans were ordered in 10 patients with 3 showing evidence of sinusitis (Table 2). ENT referrals were made in 4 patients. Two

Table 3: Characteristics of patients diagnosed with OSA. (Abbreviations: OSA - Obstructive sleep apnea; BMI - Body mass index; ACE-I - Angiotensin converting enzyme inhibitors.)

Patient characteristic	N = 33
Age (mean ± SD)	57 (± 13)
Female:Male ratio	1.3
BMI kg/m ² (mean ± SD)	
Overall	35 (± 7)
Male	33(± 4)
Female	36 (± 8)
Duration of cough in weeks (mean ± SD)	
Overall	88 (± 262)
Male	23 (± 26)
Female	136 (± 341)
Comorbidities	
Hypertension	12 (37%)
Diabetes mellitus	7 (21%)
Known sleep apnea	12 (37%)
Coronary artery disease	1 (3%)
ACE-I therapy	6 (18%)
Single diagnoses for cough	
GERD	17/33 (52%)
UACS	2/33 (9%)
CVA	0
Multiple diagnoses for cough	
GERD & UACS	10/33 (30%)
UACS & CVA	0
GERD & CVA	1/33 (3%)
UACS, GERD & CVA	2/33 (6%)

patients underwent upper gastrointestinal endoscopy with one undergoing 24 hour pH monitoring (Table 2).

67 patients in this study came as referrals from primary care providers (5 patients were self-referred to clinic). Two patients were referred from an ENT specialist and 1 from a gastroenterologist. Most if not all had been tried on multiple previous therapies including those for GERD, CVA and UACS. Despite this all patients were tried on therapeutic interventions based on the clinical impression of the treating pulmonologist. No patient underwent additional workup beyond chest X-rays and PFTs at the time of the initial visit. Initial and subsequent therapies were guided entirely by pulmonologist's empiric diagnosis of etiology of cough and therapeutic responses to rendered therapies. Although this approach broadly followed the outlines of the pathway for the management of chronic cough in the ACCP guidelines, there were variations from this pathway based on intention to pursue therapy based upon the perceived etiology. Percentage of improvement with different initial therapies for GERD, UACS and CVA was 82%, 56%, 83% respectively. In the groups with multiple diagnoses, initial therapies were successful in 78% of the UACS-GERD group, 50% of the GERD-CVA group and 100% of the UACS-GERD-CVA and UACS-CVA groups. Inhaled steroid therapy was done in 19% of patients and oral steroids were given in 4% of patients. 12 patients received empiric macrolide therapy in conjunction with other therapies that improved cough in 7 patients. Significant variations were noted in the proportion of patients treated for GERD, UACS and CVA between different providers.

A sleep history was elicited in 55% of the patients (Table 2). This included history of duration of sleep, sleep quality, daytime somnolence, history of snoring and apneic spells.

The decision to elicit history pertinent to the diagnosis of OSA varied amongst providers. A sleep history was consistently elicited in pulmonologists who were American Board certified in Sleep Medicine as well. Similarly details regarding historical aspects pertaining to OSA were variable. All six patients that underwent screening oximetry had abnormal studies. 12 patients had previously known OSA that was inadequately treated out of which 3 patients were not on any CPAP due to non-compliance with previously tried CPAP therapy. 34/38 patients had abnormal polysomnographies with 33 being diagnostic for OSA. Out of these 33 patients, 16 patients had initiation of CPAP therapy and 11 patients had retitration of their CPAP therapy. Improvement in cough was noted in 25/27 (93%) patients that had initiation of new CPAP therapy or re-titration to optimal CPAP pressures. CPAP therapy was initiated or re-titrated in 18/27 of patients following the first visit, 6/27 following the second visit and 3/27 of patients thereafter. Patient characteristics, duration of cough, concomitant diagnoses, and comorbidities of patients who were diagnosed with OSA during evaluation for chronic cough is shown in Table 3.

Discussion

The development of guidelines for evaluation and management of chronic cough represents a major milestone in the history of treatment of this common health problem.¹ Chronic cough accounts for 3.6% of outpatient physician visits in the US and is the commonest complaint for which medical attention is sought in the US.¹¹

Current guidelines emphasize empirical management of GERD, UACS and CVA depending on historical information gathered in favor of these diagnoses. This is based on the fact that a number of studies have consistently shown that UACS, GERD and CVA account for the majority of cases of chronic cough in the nonsmoker.^{12,13} However, there is no understanding of the pathobiologic mechanisms by which these conditions lead to cough. Neither is there a defined pathological substrate that triggers cough from these conditions. This has led to difficulty in associating the results of investigative testing for UACS, GERD and CVA with the occurrence of cough. In addition, the common occurrence of these predisposing conditions in chronic cough patients and the lack of reliable tests to link GERD and UACS to cough results in therapeutic interventions being the mainstay for the diagnosis and resolution of the cough.

This study explores current approaches towards chronic cough in community-based pulmonologists from a single center in the United States. There has been a paucity of studies from North America on chronic cough evaluating current diagnostic and therapeutic trends over the last decade. This retrospective study evaluates management patterns of chronic cough over a time period overlapping and following the revised ACCP guidelines. Not surprisingly, it continues to show the same preponderance of etiologic diagnoses, namely GERD, UACS and CVA in patients with chronic cough and a tendency towards treating multiple etiological diagnoses during the initial visit. As reflected in the guidelines, the etiological diagnoses for chronic cough were based on therapeutic interventions despite the fact that a number of these referred patients underwent similar therapeutic interventions prior to evaluation by the pulmonologist.

The extent of therapeutic testing for chronic cough has been debated upon.¹⁴ In this study, invasive testing for GERD, non-acid reflux disease, abnormal esophageal motility and testing

for sputum eosinophilia was limited or lacking. The lack of a standardized protocol for evaluating sputum eosinophilia resulted in empiric therapy for CVA in a number of patients. Testing for OSA in patients with chronic cough has been recently recommended.⁵ OSA is a common condition increasing in prevalence with age and body mass index¹⁵ and therefore, likely to occur in a significant proportion of patients with chronic cough. Even though chronic cough has been reported to be a presenting symptom of OSA, no large prospective studies evaluating for OSA in chronic cough patients exist.

A major finding of this retrospective study was the impact of concomitant evaluation and treatment for OSA. OSA has been reported in prior case reports of chronic cough and one case series of four patients that resolved their cough with treatment for OSA.^{16,17} In our current study, 44% patients with chronic cough were found to have OSA and following optimization of nocturnal positive pressure therapy, improvement or resolution of cough was noted in 93% of the patients. Since therapy for OSA was done in conjunction with other therapies for chronic cough in all but one patient, it is not clear to what degree the treatment for OSA had impact on the resolution of chronic cough. Despite this, the evaluation for OSA in the management of chronic cough requires important consideration given the increasing number of reports reporting improvement in cough with treatment of OSA. OSA can lead to or has been associated with GERD, asthma symptoms and upper respiratory complaints, all of which underlie the "pathogenic triad" leading to more than 95% of chronic cough.¹⁸ OSA has been shown to be associated with airway inflammation that can contribute to chronic cough. In a study performed in Sweden, the number of patients with chronic bronchitic symptoms that were found to have sleep-disordered breathing was up to 14-29%.¹⁹ Other studies on patients with OSA have shown an increase in exhaled nitric oxide values and other markers of inflammation on sputum analyses.^{20,21} A number of OSA patients can present with bronchitic symptoms and demonstrate bronchial hyperreactivity.^{22,23} Treatment of OSA has been shown to improve other known disorders of airway inflammation, especially asthma and COPD. Whether this is as a result of lessening gastroesophageal reflux that is common with OSA²⁴ or due to improvement in airway inflammation is unknown.

As compared to other series, the diagnosis of unexplained cough was not given to any of our patients. A significant incidence of unexplained cough has been noted in different series.²⁵ Interestingly the profile of patients reported for unexplained cough patients fits in with those patients in our series that improved with specific therapy for OSA.²⁵ A number of these patients start out with a post-infectious cough that fails to resolve despite multiple therapies directed at GERD, UACS or CVA. Whether OSA can perpetuate cough by impairing resolution in patients with acute bronchitis needs to be evaluated in future studies. OSA can potentially contribute to abnormal esophageal motility²⁶ and an enhanced cough reflex,¹⁶ both of which have been shown to contribute to or perpetuate cough.

This study is limited by a retrospective design, non-standardized protocol and data collection with only 55% of subjects being screened for OSA. Despite this a significant number of patients were found to have OSA. Whether this high prevalence of OSA in our chronic cough population is due to some kind of referral bias or due to a higher body mass index of patients is not clear. The majority of cough patients came from primary providers

who considered possible etiologies for chronic cough as outlined in the ACCP guidelines but failed to ascribe any relationship between the possibility of sleep-disordered breathing and the cough. Henceforth a number of these patients were not evaluated for possibility of sleep-disordered breathing or if they had known OSA, the possibility of inadequately treated OSA contributing to cough was not entertained. Although only half the patients underwent workup for OSA and this was expected to reduce the estimate of OSA-cough in this population, the prevalence of OSA encountered in this study is nevertheless very high (44%). The majority of patients undergoing sleep apnea-related workup had an elevated BMI that makes obesity a confounding factor in this study purporting a link between OSA and chronic cough. Ascribing a relationship between chronic cough and OSA in obese subjects may also carry an overlap bias given the common occurrence of these problems and the linear relationship between obesity and OSA. However, the majority of obese patients in this study improved their cough following CPAP therapy and since resolution of cough remains the sine qua non for the diagnosis of the etiology of cough,⁶ further prospective studies researching the link between chronic cough and OSA will have to be designed factoring in the contribution of obesity. In addition, treatment for OSA can improve the contribution from multiple etiologies especially GERD that improves with the treatment of OSA. This study was also confined to the evaluation of cough in non-smokers without parenchymal lung disease. A number of recent studies have shown a high prevalence of OSA in patients with interstitial or airway lung disease.^{27,28} Treating OSA early on in patients with parenchymal lung disease may not only offer the potential of impacting the course of the underlying lung disease but also the potential for amelioration of the cough seen in these disorders.²⁹

A small number of patients in this study received macrolides that were effective in 70% of those treated. Azithromycin used for up to 12 days improved cough in subsets of patients that also received PPIs. Macrolides have been shown to have beneficial effects on lower respiratory tract inflammation in a number of diseases ranging from asthma to post-transplant bronchiolitis.³⁰ Whether resolution in cough following macrolide therapy is due to its salutary effects on lower-respiratory tract inflammation or due to effects on sinus inflammation needs to be proven.

Conclusions

This retrospective evaluation of management of patients with chronic cough in nonsmokers found that GERD, UACS and CVA continued to be the commonest etiologies for chronic cough. A significant proportion of patients had multiple etiologies for their chronic cough and specific diagnostic workup was limited. Clinicians primarily relied on the results of therapeutic interventions in cases with single or multiple etiologies for chronic cough. A number of patients improved with therapy of OSA that was given in conjunction with other therapies for chronic cough. The impact of OSA in occurrence and perpetuation of chronic cough needs to be evaluated prospectively in future studies of chronic cough.

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One Disease?

BioMed Central recently published a paper making the case that EDD (eosinophilic digestive disease) and allergic bronchial asthma are clinical expressions of one disease in two systems. The abstract of the paper, by Mostafa Yakoot, in the Italian Journal of Pediatrics, states: Eosinophilic digestive disease (EDD) includes a broad spectrum of clinical presentations due to eosinophilic inflammation involving anywhere from the esophagus to the rectum. The heterogeneity in the clinical presentations of EDD is determined by the site and depth of eosinophilic infiltration. The sites of inflammation determine the nomenclature for EDD. The most well characterized of these, eosinophilic esophagitis (EE), eosinophilic gastroenteritis (EG), and eosinophilic colitis or enterocolitis. While the depth of eosinophilic infiltration through the three main layers (mucosa, musculosa and serosa) determines the prominent clinical manifestation. The recent advances in gastrointestinal endoscopy and the increasing awareness and diagnosis of EDD, in my viewpoint, can be of help to add to our understanding of the heterogeneous clinical syndrome under the broad title bronchial asthma. Here I present my viewpoint that EDD and the allergic bronchial asthma can be regarded as two clinical expressions of one disease in two different but related anatomical systems.

The paper continues: The rationale behind this lies in our “unpublished observations” in 2 cases presenting with a full picture of EDD with abdominal pain, protein wasting, ascites with eosinophilia detected in peripheral blood, ascitic fluid as well as in biopsy tissues from lower endoscopy. The offending cause in these cases had been found to be parasitic infection by fascioliasis in the early migratory hepatic phase. The dramatic response to a course of systemic corticosteroids after the persistence of manifestations in spite of the treatment of fascioliasis, plus the typical picture of a multilayer eosinophilic enterocolitis, and the associated history of other atopic diseases have urged us to consider the term “intrinsic” rather than “secondary” EDD which hints to more heterogeneous pathogenetic factors for eosinophilia. The recent advances in gastrointestinal endoscopy and the increasing awareness and diagnosis of EDD, in our mind, can be of help to add to our understanding of the heterogeneous clinical syndrome under the broad title bronchial asthma, which remains a genuine medical mystery. There is a need for more differentiation of cases on the basis of more homogeneous pathogenesis and pathology rather than the current definitions which are based mainly on the clinical manifestations leading to the inclusion of highly heterogeneous groups with many differing phenotypes, endotypes and response to treatment under

one diagnosis. There is no reason in my opinion, so far, to consider the allergic bronchial asthma or (the eosinophilic phenotype), and the eosinophilic bronchitis as two separate entities but we would rather explain this as in case of EDD on basis of the depth of eosinophilic and mast cell infiltration in the layers of the bronchial tissue whether to the layer of smooth muscle leading to asthma or just in mucosa and submucosa manifested as bronchitis. Likewise the allergic rhinitis and allergic bronchial asthma can be regarded as one disease manifested in one system but in two different sites. Furthermore with this view, the EDD and the allergic bronchial asthma can be regarded as two clinical expressions of one disease in two different but related anatomical systems, adding the fact that the embryological origin of the lower airway is a budding from the endoderm of the foregut.

It is obvious that the smooth muscle spasm leading to bronchoconstriction, wheezes and air flow limitation in the respiratory system is manifested in the gastrointestinal tract as dysphagia when it affects the smooth muscle layer in the esophagus, or colic and intestinal obstruction when affecting the small intestine. Even more, the circular strictures and longitudinal furrows seen in the endoscopic picture of the EE are much reminding us of the picture of bronchial smooth muscle spasm. Also, the mucosal irritation with cough and sputum in the respiratory system is manifested in the EG by diarrhea with malabsorption and protein losing. The documented association of the clinical picture of GERD with asthma and vice versa can be explained at least partly in some cases on basis of undiagnosed atopic EE associated with atopic asthma.

The treatment of EDD, so far is similar to that of allergic bronchial asthma which includes avoidance of suspected allergens and systemic corticosteroids. Leukotriene modifiers, and oral cromones had also been tried with some reports of success.

With regard to this apparent strong interrelation between EDD and allergic bronchial asthma, not only in terms of similarity in pathogenesis, pathology and origin in embryology but also in drug therapy; might we be justified to simplify matters to use terms like allergic esophageal asthma or enteral asthma?



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