Volume 4 Number 2 April-May 2009

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April-May 2009

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Editorial

Conflict of Interest

While respiratory care practitioners don't rely on pharmaceuticals as extensively as other medical care providers, they are at least as dependent on the, shall we say, largesse, of corporate donors in order to carry out clinical studies, make decisions about medication and equipment, and try out new modes of care. Thus I thought you might be interested in an article that appeared in The New York Review of Books, "Drug Companies & Doctors: A Story of Corruption." The story was written by Marcia Angell, Senior Lecturer in Social Medicine at Harvard Medical School and former Editor in Chief of The New England Journal of Medicine.

Angell writes, "No one knows the total amount provided by drug companies to physicians, but I estimate from the annual reports of the top nine US drug companies that it comes to tens of billions of dollars a year. By such means, the pharmaceutical industry has gained enormous control over how doctors evaluate and use its own products. Its extensive ties to physicians, particularly senior faculty at prestigious medical schools, affect the results of research, the way medicine is practiced, and even the definition of what constitutes a disease.

"Consider the clinical trials by which drugs are tested in human subjects. A few decades ago, medical schools did not have extensive financial dealings with industry, and faculty investigators who carried out industry-sponsored research generally did not have other ties to their sponsors. But schools now have their own manifold deals with industry and are hardly in a moral position to object to their faculty behaving in the same way. A recent survey found that about two thirds of academic medical centers hold equity interest in companies that sponsor research within the same institution. A study of medical school department chairs found that two thirds received departmental income from drug companies and three fifths received personal income. In the 1980s medical schools began to issue guidelines governing faculty conflicts of interest but they are highly variable, generally quite permissive, and loosely enforced.

"Because drug companies insist as a condition of providing funding that they be intimately involved in all aspects of the research they sponsor, they can easily introduce bias in order to make their drugs look better and safer than they are. In view of this control and the conflicts of interest that permeate the enterprise, it is not surprising that industry-sponsored trials published in medical journals consistently favor sponsors' drugs—largely because negative results are not published, positive results are repeatedly published in slightly different forms, and a positive spin is put on even negative results. Many drugs that are assumed to be effective are probably little better than placebos.

"Clinical trials are also biased through designs for research that are chosen to yield favorable results for sponsors. For example, the sponsor's drug may be compared with another drug administered at a dose so low that the sponsor's drug looks more powerful. A common form of bias stems from the standard practice of comparing a new drug with a placebo, when the relevant question is how it compares with an existing drug. In short, it is often possible to make clinical trials come out pretty much any way you want, which is why it's so important that investigators be truly disinterested in the outcome of their work.

"Conflicts of interest affect more than research. In a survey of two hundred expert panels that issued practice guidelines, one third of the panel members acknowledged that they had some financial interest in the drugs they considered. Many members of the standing committees of experts that advise the FDA on drug approvals also have financial ties to the pharmaceutical industry. Conflicts of interest and biases exist in virtually every field of medicine, particularly those that rely heavily on drugs or

Continued on page 28…

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E-mail: s.gold4@verizon.net
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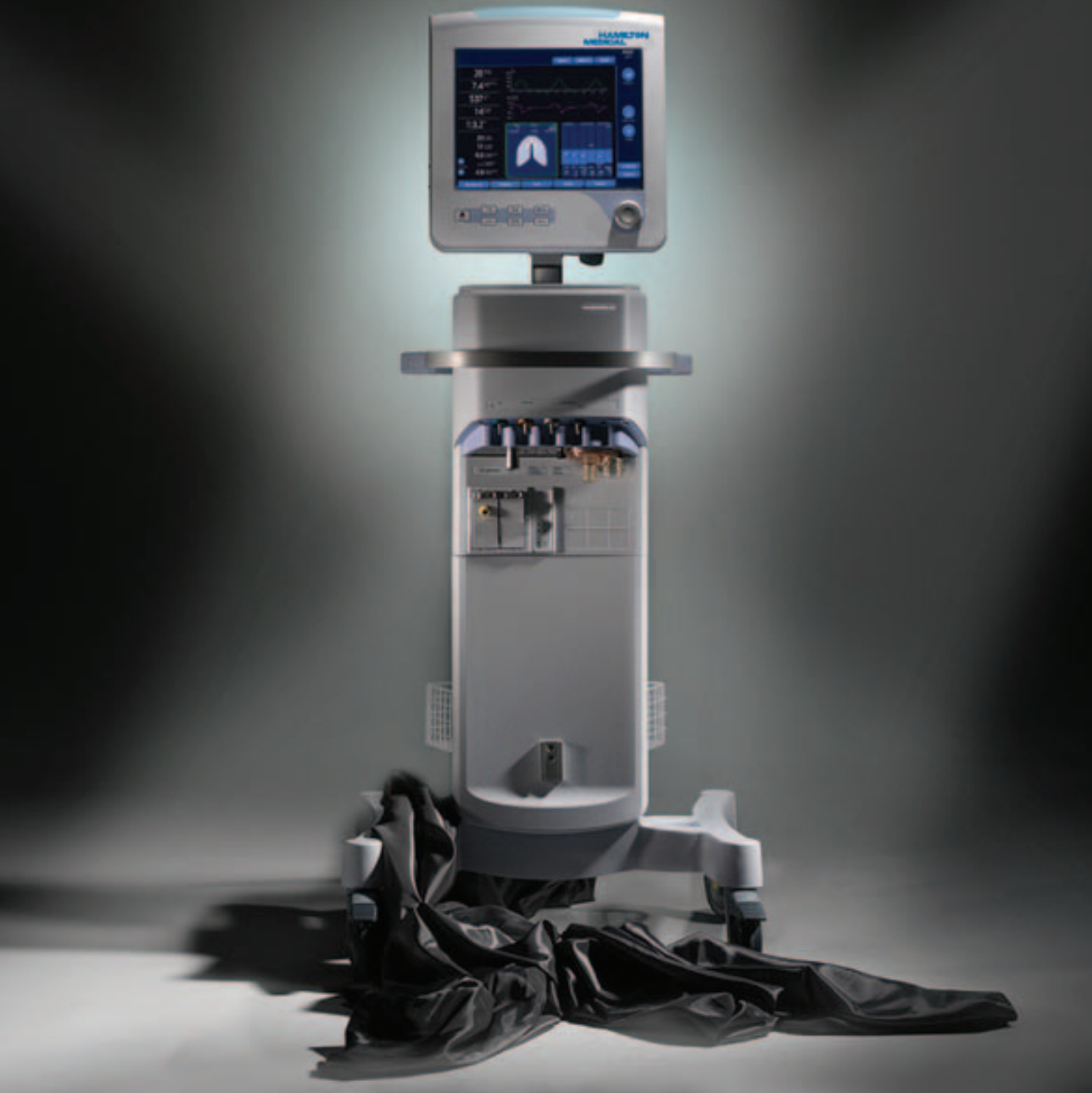

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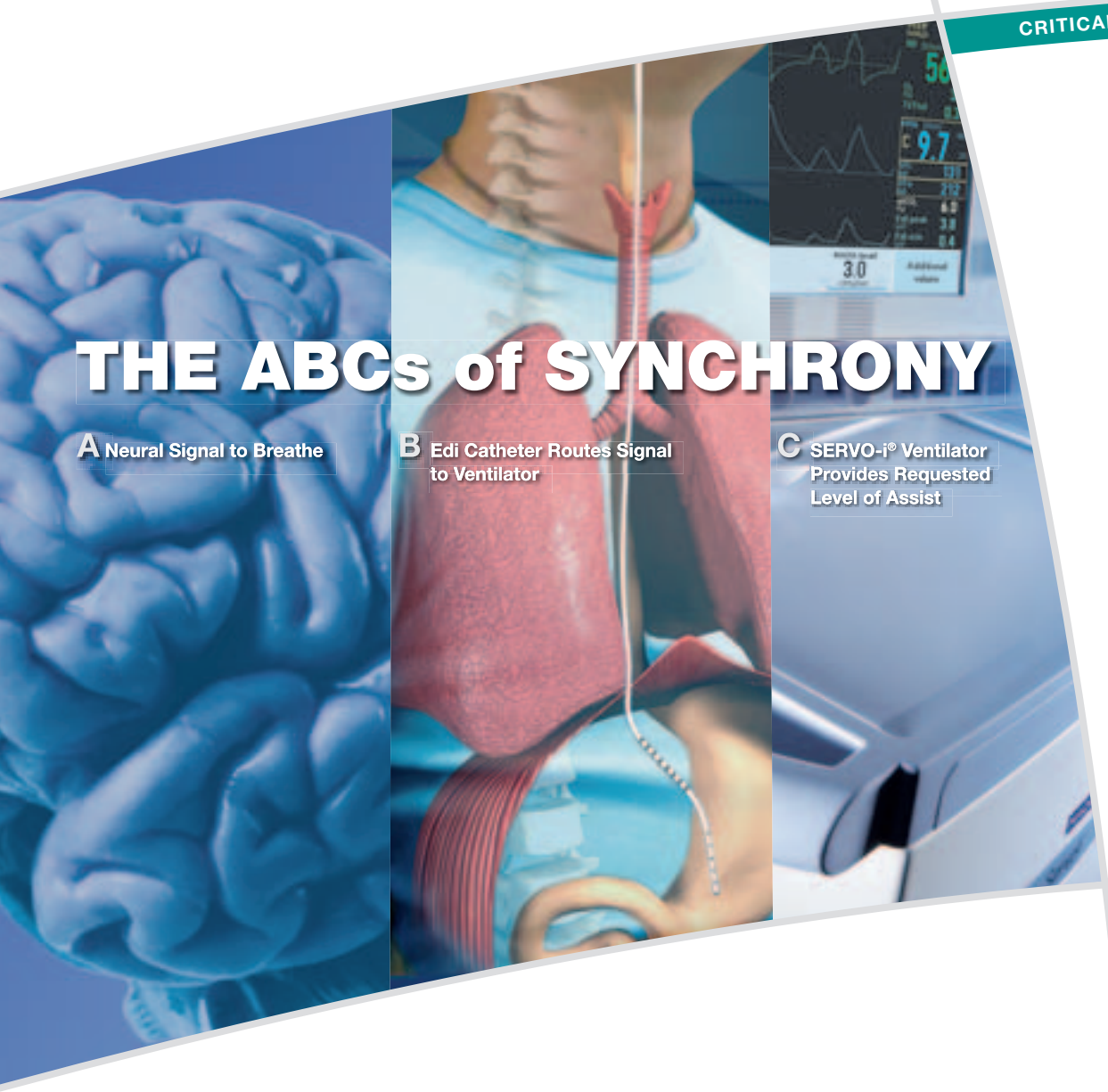

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* See, for example: Thille, A; Rodriguez, P; Cabello, B; Lellouche, F; Brochard, L; "Patient-ventilator asynchrony during assisted mechanical ventilation," Intensive care med., (226), 32:1515-1522, DOI 10. 1007/s00134-006-0301-8

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News

☐ April-May 2009

INDEPENDENCE

BioMed Central has further expanded its portfolio of Independent Journals with Journal of Biomedical Science and Genetics Selection Evolution having transferred to its open access publishing platform. A growing number of journals joining BioMed Central are established publications, often supported by affiliated scientific societies, research institutions or governmental agencies. Its first journal to launch in 2009 was Genetics Selection Evolution, which enters its 41st year of publication and offers a forum for research on all aspects of animal genetics. Supported by the National Science Council of Taiwan, Journal of Biomedical Science serves as an international forum for interdisciplinary discussions of all fundamental and molecular aspects of basic medical sciences. In related BioMed news, the University of Calgary established an Open Access Central Fund. There are now several institutions leading the way and establishing central funds to allow authors to benefit when publishing in open access journals. BioMed's online journal, Silence, is now accepting submissions. The journal covers all aspects of genetic and epigenetic control mediated by RNA. Head & Neck Oncology joins the independent journals portfolio as a new publication encompassing all aspects of clinical practice, basic and translational research relating to tumors of the head and neck. New supplements on BioMed Central are Malaria Journals' major collection of review articles. Breast Cancer Journal has published a collection of short communications from Controversies in Breast Cancer 2008, a conference held in Edinburgh. For more type BioMed Central into any search engine.

SALT IN THE WOUND

Paul Garbarini, MS, RRT, reports: "The traditional instillation of saline during suctioning of mechanically ventilated patients has received considerable bad press in the past few years. The lack of demonstrated benefit along with studies showing adverse affects on oxygenation and the potential to "dislodge" bacteria from the endotracheal tube biofilm have been cited as reasons not to routinely instill saline. Now a recent article in Critical Care Medicine throws a wrench at those of us who've poo-pooed saline instillation. My position has been that if saline instillation promotes an effective cough that actually mobilizes secretions then it may be worth doing. This study evaluated the effect of saline instillation on ventilator-associated pneumonia (VAP). One group of patients was instilled with 8cc of saline during suctioning while the other received no saline. The study population was ventilated oncology patients on mechanical ventilation greater than 72 hrs. The probability of developing VAP was double in those patients who did not receive saline lavage. The authors noted that previous studies demonstrating increased bacteria transmission with lavage were invitro models vs this invivo study. They suggest that facilitated secretion removal may have been the reason for decreased VAP rates

in the saline group. The accompanying editorial suggests further research in this area is needed. As the patients with microbiological confirmed VAP had double ICU length of stay and increased mortality, this simple intervention bears further investigation." From Hamilton Medical's newsletter.

SMOKING & ASTHMA

A recent study in New Eng J Med (2008;359:1) studied the effect of 17q21 variants and smoking exposure in early-onset asthma. In the study by Bouzigon et al, genetic, medical and demographic data from 1,511 subjects were examined for correlations with time of asthma onset. Of the 36 single-nucleotide polymorphisms (SNPs) analyzed, 11 were associated with asthma ($p<0.01$) and 3 were strongly associated ($p<0.001$). There was almost a 3-fold increase in risk of early-onset (≤4 yr of age) asthma, with the strongest effect in subjects exposed to environmental tobacco smoke. There was no association with late-onset asthma. The fact that chromosome variants can affect early-onset but not late-onset asthma suggested a difference in the pathogenesis of the two disease types.

GOING VIRAL

Reuters reports that researchers have found out what made the 1918 flu pandemic so deadly: a group of three genes that lets the virus invade the lungs and cause pneumonia. University of Wisconsin and University of Kobe researchers mixed samples of the 1918 influenza strain with modern seasonal flu viruses to find the three genes. They said the discovery might point to mutations that could turn ordinary flu into a dangerous pandemic strain. The researchers used ferrets, which develop flu much like humans. During pandemics, such as in 1918, a new and more dangerous flu strain emerges. The influenza pandemic of 1918 caused 50 million deaths. It killed 2.5 percent of its victims. To find out why it killed so many, the researchers substituted single genes from the 1918 virus into modern flu viruses and, one after another, they acted like garden-variety flu, infecting only the upper respiratory tract. But a complex of three genes helped to make the virus live and reproduce deep in the lungs. The genes, PA, PB1, and PB2, along with a 1918 version of the nucleoprotein or NP gene, made modern seasonal flu kill ferrets in much the same way as the original 1918 flu. Researchers noted that the next influenza pandemic will likely be from the avian influenza virus, H5N1, which is currently circulating in Asia, Europe and parts of Africa, and has killed a majority of the people it has infected since 2003. It is surmised that a few mutations could make it into a strain that would kill millions within a few months. (Based on a report by Reuters, by Maggie Fox, edited by Will Dunham and John O'Callaghan.)

GROW OUT OF IT

Adolescents often outgrow asthma and appear to be symptom-free as young adults, but may later redevelop the disease, according to the study Sputum Eosinophilia, Airway Hyperresponsiveness and Airway Narrowing in Young Adults With Former Asthma (Hara J, et al, Allergology Internatl 2008; 57:211.) The question posed by the study was whether those in remission are really disease free. A group of 326 adults (age 21-34) were screened for asthma history and categorized according to those with current physician-diagnosed asthma, those with former asthma and those with no history of asthma. Participants who had been free of symptoms and taken no asthma medication for at least 10 years prior to the study were tested for FEV_1, PC_2O, maximal mid-expiratory flow (MMF) and sputum eosinophilia. The results showed that former asthma patients in remission had significantly lower FEV_1, PC_2O and MMF and greater eosinophilia than subjects with no history of asthma. In addition, 18% of those with no history of asthma also showed decreased FEV_1 and PC_2O. The long-term prognosis of these subjects needs to be examined. The investigation brought up the question of whether treatment of symptom-free former asthmatics might prevent the reappearance of asthma.

THIS OLD HOSPITAL

A famous old respiratory hospital in Los Angeles is undergoing some major changes, with a major renovation in the works. Barlow Respiratory Hospital was launched 106 years ago in the Elysian Park section of Los Angeles, near Dodger Stadium. Barlow Respiratory Hospital was launched largely to serve tuberculosis patients; its founder, a New York physician, was himself a patient, prompting his move to California for the warm, dry air, the chief remedy at the time. Patients lived in the hospital's cottages, sometimes for years, once they were well enough to leave the central sanatorium. According to an article in the Los Angeles Times, "the hospital has always felt timeless, partly because it looks like a borscht belt summer camp and partly because its central mission, helping people breathe, has always been so fundamental. Lately, the hospital has taken on another fundamental mission – survival."

The facility is building a new hospital and redeveloping 25 acres of private land two miles north of downtown LA. Two dozen architects, engineers and other specialists will participate. The hospital has been under a mandate to comply with new seismic regulations since the 1994 Northridge earthquake, when 11 hospitals were closed due to damage. Barlow has 49 beds and treats complex cases. Its typical patient has at least one chronic disease in addition to an acute medical problem such as pneumonia. The average patient stay is 30 days, 10 times longer than the average at many larger, general hospitals. If the hospital didn't figure out a way to rebuild before 2013, it could have been forced to close. Hospital administrators determined quickly that retrofitting the hospital's main infirmary would be impossible. Barlow is a famously quirky and dated facility, with narrow hallways and nursing stations that are "crowded on the best days, and unworkable on the worst," the Times article noted. Five years ago, Barlow decided to sell some of its property to raise enough money to build a replacement hospital. It was a mess from the start. Prospective buyers declined to tell Barlow what they planned to do with the land. The site abuts neighborhoods that were emptied to make way for Dodger Stadium, and many nearby residents are fiercely insular and protective. Further complicating the deal, prospective buyers wanted all of the land. Barlow would have had to move. Administrators looked for a place to build for two and a half years. The cost of rebuilding, meanwhile, continued to climb, up to $100 million. Barlow made a decision: it would rebuild on one corner of the property, and it would take on a new role. Instead of selling the land, Barlow would become its own developer. The new three-story facility will bump the bed count to 56. The new design is expected to cut nurse walking time by half, insofar as nurses currently walk five miles per day to secure paperwork and supplies, without necessarily seeing a patient. Every room will be private and every patient will have a sight line to Barlow's main campus. The new hospital has been designed with a secondary front door that residents can use to walk inside for community meetings, so they won't have to pass through the main treatment areas, and the hospital will try to maintain its historic buildings. A recent tour of an old cottage revealed

empty packs of cigarettes and graffiti: "DRUNK BUMS." Another cottage held documents from slip-and-fall lawsuits and a room full of chest X-rays that no one had looked at in 25 years.

The hospital, 25 years ago, is on the far left.

NEWS FEATURE

pH PROBE

Respiratory Technology Corporation (dba Restech) announced that the Restech Dx-pH Measurement System played a key role in a study by Dr David J. Malis, MD, FACS, FAAP, of Melbourne, FL, to accurately measure reflux in children. The study, entitled A New pH Probe for the Detection of Laryngopharyngeal Reflux (LPR) in Children, was presented at the 2008 Annual Meeting of the American Society of Pediatric Otolaryngology (ASPO) as a podium presentation. The study of 100 pediatric patients helped differentiate baseline pH and potential etiology for various upper airway symptoms believed to be caused by acid reflux. "Until recently, a definitive diagnosis has been challenging, and traditional test procedures, including dual lumen pH probe, are coming under scrutiny as to their effectiveness. LPR exists and accurate diagnosis is crucial to proper diagnosis and treatment of our smallest patients," said Dr Malis. "This study demonstrates that accurate diagnoses can be performed easily and comfortably using the Restech Dx–pH Measurement System." An alarming increase in the incidence of gastroesophageal reflux disease (GERD) and laryngopharyngeal reflux disease (LPRD) in Americans has led to the need for accurate diagnosis of extraesophageal acid reflux as provided by the Restech Dx–pH Measurement System. In determining the etiology of conditions such as chronic cough, recurrent laryngitis, sinusitis and asthma, it is important for physicians to be able to rule reflux in or out as a possible contributing factor. Instead of treating 'in the blind' with a medication based on symptoms alone, physicians will be able to prescribe treatment based on definitive quantification of acidic reflux in the upper airway. Current diagnostic techniques available to pediatric otolaryngologists include panendoscopy with biopsy, lipid-laden macrophages score and histology, the Bravo capsule, an esophagram / barium swallow, or an empiric therapeutic trial with H_2 blockers or PPIs. In contrast, the Restech Dx–pH Measurement System is a preferred method of testing as its highly sensitive Dx–pH Probe is specifically developed to detect aerosolized reflux. This provides more objective data, enabling physicians to determine a more accurate diagnosis and a more effective treatment plan. Manifestations of LPR in children are protean. The most commonly attributed symptoms are nasal stertor, recurrent croup, stridor, hoarseness, chronic cough, medically refractory reactive airway disease (asthma), dysphagia and failure to thrive. Less commonly attributed symptoms are sleep disordered breathing (both central and obstructive apneas), Eustachian tube dysfunction, and recurrent sinusitis. **Materials and Methods:** One hundred pediatric patients (presenting with symptoms consistent with LPR) were tested in a community-based private pediatric otolaryngology practice in Melbourne, Florida. Ten compelling cases were selected from the 100 patients. Patients received follow up six to ten months from initial presentation. The main outcome measure was the ability to correlate patients with suspected LPR by testing with the new Restech pH probe. The secondary outcome measure was resolution of presenting symptoms after 12 weeks of medications and objective improvement by repeat Restech pH probe testing. **Conclusion:** Laryngopharyngeal Reflux (LPR) in children may be more common than previously appreciated. Preliminary experience with the Restech Dx-System is encouraging in identifying children with LPR. Additional prospective studies are warranted to develop normative data and clinical guidelines in children. **Product info:** The Restech Dx–pH Measurement System is a revolutionary system that comfortably measures pH in the airway. Gastric reflux in the upper airway, or laryngopharyngeal reflux, commonly takes a gaseous form that cannot easily be measured using conventional technology. The miniaturized pH sensor at the tip of the Dx–pH Probe is unique in its ability to measure pH in a non-liquid environment, such as the pharynx. By monitoring the pH levels in the pharynx, the Dx–System enables physicians to determine the presence of laryngopharyngeal reflux, and its role in their patients' symptoms. The Dx–pH Probe has a 1.5mm, tear-drop shaped tip which houses the pH sensor. The tip rests comfortably in the throat, just behind the soft palate. pH testing before the development of the Restech Dx–System was done using trans-nasal esophageal catheters that were cumbersome, uncomfortable and interfered with a patient's ability to perform normal, everyday activities. The smaller shape and less-invasive position of the Restech Dx–pH Probe allows patients to more easily carry on normal, everyday behavior including eating, exercise, work, bathing, and sleeping with less disruption. The measurements taken by the pH sensor are sent wirelessly to a recording device which the patient carries throughout the test period. Upon completion of the test period (usually 24 hours), the patient returns to the physician's office where the study data is downloaded and analyzed using Restech's custom Dx–pH DataView software. The above information was provided by Restech. Contact (800) 352-1512 or restech-corp.com.

Does Successful SBT Mean Successful Extubation?

Melissa Turner, BA, RRT

This article is from Hamilton Medical's newsletter.

In addition to other assessment skills, respiratory therapists must also be able to make assessments regarding a patient's readiness to breathe without assistance before performing extubation. This important decision is made only after a patient has tolerated a spontaneous breathing trial (SBT). Although a patient tolerates the SBT, that alone does not predict a successful extubation. There are other factors and parameters to look to in order to make a safer prediction about the success of an extubation.

According to Mokhlesi et al, 10-20% of extubations are failures. Extubation failures are also associated with worse outcomes. Some of the known extubation predictor factors include endotracheal secretions, strength of cough, mental status, and pre-extubation $PaCO_2$. A closer look at endotracheal secretions has shown that patients with moderate to large amounts of secretions are 3-8 times more likely to fail extubation than those with little to no secretions. It is also known that patients who develop hypercapnea ($PaCO_2$ greater or equal to 45torr) during a successful SBT have a higher mortality rate due to respiratory failure than those who do not. Let's take a look at the recent Mokhlesi study which found factors that related to successful extubation.

The study was conducted over a 15 month period and included patients receiving mechanical ventilation for at least 2 or more days. It did not include patients with tracheostomies or patients that required withdrawal of support. The patients in the study were considered for an SBT once the underlying cause of respiratory failure improved or resolved. Other requirements for the SBT were adequate gas exchange, hemodynamic stability without vaso-active medications, and an adequate cough during suction. The SBT was stopped if the patient had any of the following occur:

- Respiratory Rate greater than 35
- SpO_2 less than 90%
- Heart rate greater than 140, or sustained 20% increase or decrease
- Systolic blood pressure greater than 180 or less than 90torr
- Agitation
- Diaphoresis
- Anxiety

Patients were considered for extubation once they tolerated an SBT for 120 minutes on PEEP 5 cmH_2O, Pressure Support (PS) of 5-7 cmH_2O. Once the patients were extubated, they were followed for 48 hours and the following variables were obtained:

- APACHE II score (acute physiology and chronic health evaluation)
- Duration of mechanical ventilation
- Hemoglobin and blood chemistries
- ABG values at 1 hour into SBT and time of extubation
- Use of paralytics or systemic corticosteroids
- Negative Inspiratory Pressure (NIP) before SBT initiation
- Secretions
- Mental status (GCS score)
- $PaCO_2$

For this particular study, the outcome of interest is extubation failure, which is defined as re-intubation within 48 hours of extubation.

Out of 673 mechanically ventilated patients, 122 were eligible for this study after tolerating a 2 hour SBT. Of those 122 patients, 76 were in medical ICU, 23 in surgical ICU, 16 in neurosurgical ICU, and 7 in coronary care unit. Primary indications for mechanical ventilation were as follows:

Pneumonia or ARDS.....40 patients
Upper airway edema or need for airway protection.....22 patients
Heart failure or cardiac arrest.....18 patients
Post operative respiratory failure.....17 patients
Exacerbation of obstructive airway disease.....12 patients
Other causes.....13 patients

Methods for weaning in this study included gradual decrease of PS which accounted for 57% of participants, SIMV for 39% (primarily surgical and neurosurgical ICU patients), and daily SBT via T-piece for the remaining 4%.

The re-intubation rate for this study was 10.5% for patients in medical ICU, 14% in coronary care unit, 22% in surgical ICU, and 12.5% in neurosurgical ICU. In all, 16 patients required re-intubation within 48 hours. The reasons for the re-intubations were as follows:

Secretions.....3 patients
Progression of underlying process.....3 patients
Upper airway edema.....2 patients
Depressed mental status.....2 patients
Respiratory muscle fatigue.....2 patients
Pulmonary edema.....2 patients
Atelectasis.....1 patient
Unclear reasons.....1 patient

There were 5 variables in the study that were found to be different between extubation failures and successes. Those variables are hemoglobin, $PaCO_2$, endotracheal secretions, GCS score, and duration of mechanical ventilation. There were 3 specific variables that predicted re-intubation within 48 hours. Those three variables are moderate or copious secretions, GCS score of less than 10, and pre-extubation hypercapnea greater or equal to a $PaCO_2$ of 44torr.

According to this study, the best model to use as a predictor of extubation success is first to assess the pre-extubation $PaCO_2$ to see if hypercapnea exists. Second, to assess whether there are minimal to no secretions with a GCS score of greater than 10 versus moderate or copious secretions with a GCS score of 10 or less. If the patient is found to have hypercapnea and moderate to copious secretions or GCS less than or equal to 10, then the extubation failure rate is 69%. If all 3 risk factors are absent, the failure rate is only 2%. Any other combinations of risk factors produce a moderate risk factor of 7%.

As shown by Mokhlesi et al[1], the decision to extubate requires the respiratory therapist to weigh the potential benefits of early extubation with the potential harm and costs of failed extubations. It is critically important to assess the 3 variables, which are secretions, mental status, and pre-extubation $PaCO_2$ in order make better predictions of extubation success or failure for mechanically ventilated patients. Successful extubation requires a patent airway and adequate ventilation. A patent airway is evaluated through secretions and mental status.

Editorial note: Although there have been many studies on weaning predictors, few predictors have been shown to be entirely reliable. A given predictor such as minute volume may be highly predictive of which patients will successful extubate (is a highly sensitive test), yet at the same time may exclude patients from being extubated who would actually do ok if extubated. (In this case the predicator has low specificity, or doesn't do well at identifying patients who would be successfully extubated).

This study is one of few that have looked at secretions, mental

status and $PaCO_2$ which are not typically included in wean assessments. In fact, recent reviews on weaning suggest that traditional 'weaning parameters' or pre-spontaneous breathing trial predictors may not be needed at all. On the other hand, most bedside RTs and MDs empirically know these factors indeed play a role in extubation success.

Reference: 1. Mokhlesi B, Tulaimat A, Gluckman TJ, Wang Y, Evans AT, Corbridge TC. Predicting extubation failure after successful completion of a spontaneous breathing trial. Respiratory Care 2007; 52(12): 1710-1717.

PRODUCTS AND COMPANIES

Please note: it is Respiratory Therapy's policy not to publish trademarks or registration marks, or names of companies in all caps unless they are abbreviations.

FRESH AIRE

AvalonAire Inc, a division of Pepper Medical, has created a new Breath-EZ series of CPAP headgear and chinstraps for the sleep apnea market. These products are offered at price levels to save you money. We offer the following products currently with additional styles coming soon: AvalonAire BreathEZ-4 Headgear (Product # AA- 4PT) is a 4 point universal black headgear with four adjustable Velcro tabs (no clips) to engage through the 4 mask slots for perfect, snug fit. For use with Respironics and similar products. AvalonAire BreathEZ-3 Headgear (Product # AA-3PT) is a 3 point universal black headgear with three adjustable Velcro tabs (no clips) to engage through the mask 3 (one on top) slots for perfect, snug fit. AvalonAire BreathEZ-Adjustable Chinstrap (Product # AA-09ADJ) is an adjustable, chinstrap with a deep chin cup and Velcro tabs for a snug, comfortable fit, similar to the Tiara Topaz and Ruby chinstraps. AvalonAire BreathEZ-SuperDeluxe Chinstrap (Product # AA-08) is an adjustable, chinstrap with a deep chin cup and Velcro tabs for a snug, comfortable fit, similar to Respironics. For more information or samples please contact peppermintmedical.com, avalonaire.com, (800) 647-0172.

HAPPY ANNIVERSARY

Instrumentation Laboratory (IL), the worldwide developer, manufacturer and distributor of in vitro diagnostic instruments, related reagents and services, recently celebrated the anniversary date of its founding, fifty years ago. The company launched its "50 and Forward" celebration in 2008 and will continue the program through its anniversary year with events that reflect on IL's 50 years of historic achievements, as well as its plans for continued innovation in the future. The company's first instrument, the IL 113, launched a new era of automation in the industry, and set the stage for IL's constant innovation for half a century. From the IL 113 blood gas analyzer, to the IL 143 flame photometer, to the invention of CO-Oximetry, IL launched products that replaced time-consuming manual techniques, setting new standards in hospitals worldwide. The cornerstone of IL's 50th anniversary celebration is the "Passion and Results" Award for customers. Three laboratorians, respiratory therapists, physicians or nurses who have demonstrated passion and dedication resulting in enhanced patient care will receive an award and an educational grant to their institution. Industry professionals are invited to submit an inspiring story of patient care – about themselves or another person – by completing IL's Passion and Results nomination form available through an IL sales representative or online at ilus.com/50forward. Submissions are being accepted through June 1, and are open to all worldwide customers. Winners will be honored in July, 2009. IL's leadership in the development of diagnostic instruments is largely due to its many renowned thought leaders. Members of the 50 and Forward ILeader Panel of esteemed experts in a variety of diagnostics-related areas are available to contribute to the betterment of diagnostics through forums, webcasts, roundtables, seminars and press comments throughout IL's 50th anniversary celebration year. Persons and publications interested in securing the ILeader Panel's services should contact IL's Sally McCraven at 781-861-4577, smccraven@ilww.com. Instrumentation Laboratory, founded in 1959, is a worldwide developer, manufacturer and distributor of in vitro diagnostic instruments, related reagents and controls for use primarily in hospitals and independent clinical laboratories. The company's product lines include critical care systems, hemostasis systems and information management systems. IL's GEM product offerings, part of the critical care line, include the new GEM Premier 4000 analyzer with Intelligent Quality Management (iQM), GEM Premier 3000 analyzer, GEM OPL, a portable whole blood CO-Oximeter and the GEM PCL Plus, a portable coagulation analyzer. IL's hemostasis portfolio includes the ACL TOP Family of Hemostasis Testing Systems, fully automated, high-productivity analyzers, including the ACL TOP and the new ACL TOP 500 CTS. IL also offers the ACL ELITE and ELITE PRO, other hemostasis analyzers and the HemosIL line of reagents. As the world's leading developer of hemostasis testing systems, IL began 2009 with the launch of another innovative addition to its ACL family of hemostasis testing instruments,

that use chemiluminescence technology to automate specialty assays. The AcuStar is the first fully automated random-access chemiluminescence analyzer dedicated to specialty assays in hemostasis.

GET THE RED IN

Leister Technologies, LLC, announced today that its infrared (IR) sources are ideally suited for capnography and anesthesia monitoring instruments. Leister Technologies infrared sources are micro-machined, electrically modulated thermal infrared emitters featuring true black body radiation characteristics, low power consumption, high emissivity and a long lifetime. The patented design is based on a resistive heating element integrated onto a thin dielectric membrane, which is suspended on a micro-machined silicon structure. Leister's IR sources are packaged in compact TO-39 cans and are available with protective cap or with reflector. They can be fitted with Sapphire, Germanium, CaF2, or BaF2 windows. Leister Technologies' infrared sources were specifically designed for applications with requirements for high accuracy, fast measurement response, low power consumption and long lifetime. Since 1999, the Microsystems division of Leister Process Technologies has leveraged its MEMS (microelectromechanical systems) foundry to create OEM solutions in micro-optics, infrared sources, and thermal mass flow sensing. The Leister engineering and manufacturing team combines broad experience in design, simulation, fabrication and characterization, from chip level to complex integrated electronic modules. Contact leisterlaser.com.

WHAT'S THE FREQUENCY?

Dymedso offers The Frequencer. The Frequencer is a digitally controlled electro-acoustical airway clearance device manufactured by Dymedso. Consisting of two parts, a control unit and a transducer, the Frequencer along with airway clearance The Frequencer greatly reduces mucus viscosity by applying low-energy resonant vibrations. The transducer provides both mechanical and acoustical stimulation at an adjustable forcing frequency usually between 30Hz and 70Hz, depending on the patient's needs. The Frequencer is easy to use; requiring no special training or breathing techniques it is priced competitively and is well suited for treating young children. The Frequencer is ideal for inpatient and outpatient settings. It is currently in use at pediatric hospitals, adult facilities, as well as long term care facilities. Dymedso will train staff and provide biomedical services if needed. Contact dymedso.com.

CONTINUING CARE

Nonin Medical, Inc announced the first Continua Certified product. The Nonin 2500 PalmSAT handheld pulse oximeter with USB is the first product to be certified to meet the Continua design guidelines. With the award-winning Bluetooth Onyx II, Model 9560 currently in the process of certification, Nonin Medical plans to offer Continua compliant tools across its product lines. Nonin has been a key contributor in the architecture of interoperable standards, including ISO/IEEE 11073, USB Personal Healthcare Device Class (PHDC) and Bluetooth Health Device Profile (HDP), all part of the Continua Alliance Certification requirements. Dedicated to developing cross-industry standards to reduce the cost of healthcare, Nonin is working with a wide array of Continua partners to achieve this goal. Nonin's physiological monitoring products for telemedicine are the prevailing standard for vital sign assessment of a wide range of chronic disease conditions, such as COPD, CHF and asthma. Contact nonin.com.

MEET THE NEW

Hamilton Medical, Inc announced that it has recently expanded its sales staff with the addition of six direct sales representatives. David Tucker, Tim Lynch, Rick Daniel, Chris Stannard, Mike Bresson and Phil Szunyog are the new contacts for Intelligent Ventilation solutions. The recent additions to the sales staff were the first step in Hamilton Medical's US expansion. The company expects strong demand for the newest products to require the continued addition of sales and clinical staff over the next several years. If you have not yet met your new representative, please call our Sales Coordinator, John Nadolny, at (800) 426-6331, Ext 208 to locate your direct sales representative. Contact hamilton-medical.com.

MD WEBSITE

B&B Medical Technologies has launched a new clinician- and product-focused website that gives users every resource needed to access the company's complete line of specialty airway management products. Designed for functionality and with busy people in mind, the new BandB-Medical.com delivers A World of Products for Better Breathing^{S} on the web. Intuitive to navigate and fast to load, the new site includes downloadable training modules and videos, instructions for use, easy-to-customize policies and procedures, catalog sheets, evaluation forms and ordering information. A comprehensive All Products page puts all those resources in a quick, clickable format. B&B Medical Technologies is the leading designer of specialty airway management devices and Heliox nebulizers, providing products that are safe, versatile, cost-effective and convenient.

APPROVED

Respiratory Technology Corporation (Restech) announced today that its revolutionary Dx-pH Measurement System has received CE Mark approval, allowing introduction to the European Union and all countries recognizing the CE Mark. This approval from the European Union certifies Restech has met EU health, safety and environmental requirements that ensure consumer safety. With the CE Mark approval, the Dx-pH Measurement System is available to physicians throughout Europe who have recognized a need for this technology for several years especially after an alarming increase in the incidence of GERD and LPRD over the last two decades. Contact restech-corp.com.

VESTED INTEREST

Hill-Rom offers The Vest Airway Clearance System. When you need a way to clear airway secretions that can complicate patient recovery and you want to reduce the time needed to deliver therapy, The Vest Airway Clearance System is the solution. The Vest Airway Clearance System represents the 5th generation technology from the innovators of High Frequency Chest Wall Oscillation (HFCWO). This therapy utilizes a device that generates increased airflow velocities that create cough-like shear forces and decreases secretion viscosity. Both serve to assist patients in moving retained secretions from smaller airways to larger airways where they can more easily be removed by coughing. Hill-Rom provides educational programs on The Vest Airway Clearance System to assist in educating healthcare professionals. Designed with the Acute Care Respiratory Care Department in mind, The Vest Airway Clearance System, Model 205 is: safe, easy and effective. Hill-Rom received the 2008 Therapy Times Most Valuable Products award in Respiratory Therapy for the Wrap SPU Vest and The Vest System. The Wrap SPU Vest is a single patient use disposable product designed to minimize the risk of cross contamination and to ease product

placement and removal for patients in acute and long-term care settings. The Vest Airway Clearance System, Model 205 was also the winner of the 2007 Medical Design Excellence Award. Contact hill-rom.com.

PRODUCT FEATURE

Vapotherm

In its recent newsletter, Vapotherm reports on: Proper Sizing of the Nasal Cannula. The company notes: For safe and effective application of HFT, an open system should be maintained. Appropriate cannula size is selected by the anatomy of the nare. We recommend that fifty percent of the nare should be available for exhalation and maintaining an open system. Vapotherm neonatal cannulas have an inside diameter of less than 2mm.

The company refers RTs and neonatologists to the article: Heated Humidified High-Flow Nasal Cannula: Use and a Neonatal Early Extubation Protocol, by Holleman-Duray, D., Kaupie, D., and Weiss, MG. Holleman-Duray describe how the use of High Flow Therapy (HFT; Vapotherm 2000i) supports infants post extubation. The patient data, compared to historical control where CPAP was used prior to their adoption of HFT, resulted in extubation from higher ventilator rates and fewer days on ventilators. This data supports Vapotherm's proposed mechanisms of action for HFT with respect to CO_2 elimination and improved alveolar oxygen concentrations. In addition, this study showed that incidence of ventilator-associated pneumonia was reduced and infants were discharged with greater weights despite similar lengths of stay and time to full feeds. The decrease in pneumonia is likely associated with reduction in ventilator time, while the greater discharge weights may be indicative of a reduced respiratory work effort (caloric consumption).

Vapotherm wants to know: Is Your Department Using HFT? Vapotherm invites you to share best practices related to High Flow Therapy. Each newsletter highlights one standout hospital, department or clinician on topics including clinical best practices, research or education. Contact Rachael.Osberger@vtherm.com.

New Year, New CEUs for 2009: The online courses listed here are available free of charge and have been approved by the American Association for Respiratory Care for 1 (CEU) credit hour each. 1) Advances in Respiratory Care: High Flow Therapy Review & Assessment; 2) Neonatal Respiratory Care Curriculum: High Flow Therapy in the NICU; 3) High Flow Therapy: Mechanisms of Action. For more, log in at the Vapotherm Education Center and click on the Continuing Education Courses for Medical and Allied Health Professionals link.

EXECUTIVE PROFILES: FOCUS ON FACILITIES

We asked respondents to answer the following questions: 1. describe the product(s) you offer for use in a hospital setting; 2. what education and training do you offer hospital staff and administrators?; 3. discuss end-user input by hospital staff and administrators; 4. discuss technical support you offer for

hospitals using your products; 5. what new technologies do you anticipate for hospital use of your product?; 6. please tell us which major hospitals are currently using your products, and which products.

OPTIMedical

Information provided by Chris Southerland, VP of Sales and Marketing, OPTIMedical.

PRODUCTS FOR HOSPITALS: OPTIMedical is focused on manufacturing and marketing portable analyzers for the measurement of time sensitive diagnostics tests such as blood gas, electrolyte and metabolite analysis. These products include: OPTI R Automated Blood Gas Analyzer; OPTI CCA-TS Blood Gas Analyzer; OPTI LION Stat Electrolyte Analyzer, ComfortSampler Arterial Blood Gas Collection Kit

EDUCATION: OPTI Medical provides on-site training for all operators of OPTI instruments. OPTI Medical also provides remote, web based training with competency exams.

END-USER INPUT: All OPTI instruments allow the entry of full patient demographics as well as information such as ventilator settings and operator comments.

TECHNICAL SUPPORT: OPTI Medical provides telephone technical support 24/7/365 including holidays.

NEW TECHNOLOGIES: Data Management utilizing customized patient and QC reports

CURRENT APPLICATIONS: OPTI Medical references are available upon request.

Aerogen

PRODUCTS FOR HOSPITALS: Aerogen supplies highly efficient micropump nebulizers, the autoclavable Aeroneb Pro and the single patient use nebulizer, Aeroneb Solo. The Aeroneb Pro Nebulizer is specifically developed for acute care patients receiving mechanical ventilation, it offers caregivers the option for improving drug delivery efficiency and reducing drug and personnel costs associated with respiratory care in the hospital setting. The Aeroneb Pro adds no pressure or volume to ventilator circuits and minimizes drug waste by nebulizing virtually all medication. The Aeroneb Pro produces a fine particle, low velocity aerosol optimized for deep lung drug deposition. This autoclavable nebulizer enables multi-patient use in-line with mechanical ventilators or in hand-held mode with a standard mouthpiece or aerosol mask. The product is cleared for use with infants through to adults and with all nebulizer solutions approved for use with a general-purpose nebulizer. The Aeroneb Solo nebulizer offers all the advantages of the Aeroneb Pro, but in a single patient use format. It has the added dual functionality of intermittent and continuous nebulization. The Aeroneb Solo can be left in line with the same patient for up to 7 days continuously and up to 28 days intermittently. Caregivers can change between intermittent and continuous nebulization without removing the nebulizer or changing the settings of the ventilator.

EDUCATION: Our website, aerogen.com, has a broad offering of publications on our technology and posters presented by RT staff across the US. Aerogen provides onsite demonstrations and training of our nebulizers to staff. Our team are always on hand to answer any questions hospital staff may have.

END-USER INPUT: Feedback from critical care providers is crucial for product development and design processes. Although manufacturers are the experts in medical devices they are not the experts in patient therapy, manufacturers must rely on critical care providers to help ensure products meet their clinical needs and expectations. We design our nebulizers to ensure user convenience in terms of set-up, operation and disposal. An example of this was when clinicians requested a continuous nebulizer for use with the ventilator, but were inconvenienced by the collection of condensate in the nebulizer over time. These concerns resulted in the development of our Aeroneb Solo nebulizer which is inserted above the breathing circuit whereby the medication reservoir is separated from the circuit, and therefore will not collect condensate.

TECHNICAL SUPPORT: Technical support on our products is available directly from Aerogen by calling (866) 423-7643, or by contacting us via e-mail at info@aerogen.com. Our distribution partners also provide comprehensive technical support and in-house demonstrations on the use of our technology.

NEW TECHNOLOGIES: For the next 3 to 5 years Aerogen will continue to focus on broadening the use of its unique technology, enabling aerosol respiratory treatment of a wider range of drugs to be delivered with a much greater efficiency in the ICU and across the acute care setting. Our current R&D focus is involved in exciting new applications of our aerosol technology and we will be announcing details of these developments in due course.

Dräger

Information provided by Ed Coombs, MA, RRT, Associate Director of Marketing – Respiratory Care Systems.

PRODUCTS FOR HOSPITALS: Dräger offers a wide range of ventilation products for the hospital setting. Our flagship product is the Evita XL ventilator which offers a comprehensive array of features such as non-invasive modes, neonatal capability, lung protective methodologies, automated weaning protocols and most recently, proportional pressure support. Additionally, for neonatal specific areas, Dräger offers the Babylog 8000+ which provides pressure and volume ventilation specifically designed for neonatal patients. For chronic care or non-invasive ventilation, Dräger offers the Carina ventilator which can provide both invasive and non-invasive ventilatory support. The "Synch-Plus" technology of the Carina continuously monitors the interface leakage and adjusts the pressure accordingly. Transport in and out of the hospital environment for mechanically ventilated patients (pediatric and adult) can be a challenge. To meet this specialized need, Dräger offers the Oxylog 3000 which is lightweight, portable, and relatively easy to use for a variety of practitioners.

EDUCATION: Dräger has a team of 26 dedicated RRTs that serve as clinical applications specialists as well as 21 ventilation sales executives, most of whom are also RRTs. Dräger offers on-site education which is approved by the American

Association of Respiratory Care to provide CRCEs. Training at all levels including nursing and physician training is available. Additionally, all Evita, Savina, and Babylog customers can take advantage of ICON (Intensive Care Online) support which provides clinical support and education 24 hours a day, seven days a week.

END-USER INPUT: Dräger is committed to continuing its R&D efforts to improve our products. Throughout the year, Dräger conducts voice-of-the-customer meetings and focus groups to understand the challenges that our customers are seeing and to understand current trends in respiratory care. These interactions help Dräger understand marketplace requirements which allows us to continue to bring new products to our customers. Many of Dräger's new field staff are diligently working to reconnect with their area customers and to meet many of their colleagues through active engagement, site visits, educational symposia, and supporting their local Respiratory Care Society. Dräger's executive management team always welcomes customer feedback and will take the time to listen to their needs and concerns.

TECHNICAL SUPPORT: Our technical call center is staffed by trained professionals and calls are tracked for later follow-up if repeat contact is necessary. Whether for parts orders, technical advisement, or general questions, the triage center is available to support both RT and biomedical staffs. Dräger employs approximately 85 field service technicians to support its products and maximize your ventilator uptime.

NEW TECHNOLOGIES: Generally speaking, our customers are concerned with a patient's length of stay on a ventilator, rapid weaning, and the prevention of ventilator associated pneumonias. Dräger has focused its effort on addressing those through improvements in its non-invasive modes and its development of Smartcare/PS – the automated ventilator weaning technology. Dräger also now has FDA 510(k) clearance for Proportional Pressure Support – which will improve patient-ventilator synchrony and adapt the pressure support necessary for spontaneously breathing patients who have variable support requirements.

Vortran Medical Technology 1, Inc.

Information provided by Jody McCarthy, Vice President of Sales and Marketing.

PRODUCTS FOR HOSPITALS: Vortran Medical Technology 1, Inc is the innovator and manufacturer of the advanced Pulmonary Modulation Technology (PMT). We offer a unique line of low cost, single patient, fully automatic disposable respiratory devices for treating patients with pulmonary diseases in the hospital and alternate site market segments (EMS, post-acute, homecare).

EDUCATION: Vortran Medical continues to enhance its website by providing up-to-date clinical research and outcomes, our product brochure, and a user guide in PDF format. We also offer an interactive CDROM, which contains a multi-media presentation on a PC platform, including an instructional video, brochure and user guide for all Vortran products. Educational Module Sponsorship programs are also available for online continuing education units (CEU) at no charge to medical professionals.

END-USER INPUT: We appreciate the end-user input that we receive from hospital staff and administrators because they provide key communication links to improving our products. The users of our VAR (Vortran Automatic Resuscitator) gave us very valuable input about the alarm, which we subsequently redesigned according to the requirements specified in the AARC 2006 "Guidelines for Acquisition of Ventilators to Meet Demands for Pandemic Flu and Mass Casualty Incidents." The new VAR-Monitor works with all current VAR models, is easy to set up and use, operates with a standard 9 volt battery, and is financially practical for all existing VAR users to stockpile.

TECHNICAL SUPPORT: We provide technical support to end-users through a 24 hour toll free number. Customers are placed in contact with our technical or clinical staff, who will assist customers in troubleshooting our devices.

NEW TECHNOLOGIES: Because Vortran Medical is truly a business whose future depends upon the quality of our product offerings and the satisfaction of our customers, we continue to invest in R&D resources in order to develop our next generation of designs. We believe this moves us towards being the worldwide leader of fully automatic, disposable, superior quality respiratory medical devices that provide cost-effective treatments for patients with pulmonary diseases. Expect to see many new and exciting products from Vortran Medical.

Hamilton Medical

Information provided by Paul Garbarini, MS, RRT, Clinical Applications Manager and Steve Chaucer, RRT, National Sales Manager.

PRODUCTS FOR HOSPITALS: Hamilton G5, GALILEO GOLD and RAPHAEL XTC Ventilators • Booster, HMEs.

EDUCATION: Hamilton Medical's Clinical Application team, comprised of experienced RT's, provides direct on-site clinical support for RTs, RNs and MDs. Resources include: • Lectures and hands-on training; • CRCE workshops and "super-user" training; • Computer based ventilation simulators; • User guides and "pocket" reference guides and protocols; • PowerPoint presentations and competencies; • Web based multimedia presentations (streaming and/or downloadable); • "WebEx" Internet training with document sharing, teleconferencing and/or video; • 24/7 on-call clinical support; • Monthly "Enews" clinical newsletter.

END-USER INPUT: Our Sales, Clinical, Technical and Customer service teams solicit end-user feedback via: • Direct contact with hospital; • Educational program evaluation forms; • Independent data from marketing firm satisfaction surveys and MDBuyline ratings; • Periodic focus group meetings with both users and non-users to help identify user needs and provide direction for product enhancements; • Research protocols to provide valuable data regarding utility and effectiveness of both current and future products.

TECHNICAL SUPPORT: Experienced technical staff provides on-site installation and repair services • Service training is provided

several times a year for hospital biomedical staff • 24/7 on-call Technical Support.

NEW TECHNOLOGIES: Hamilton Medical pioneered and continues to develop "Intelligent Ventilation." Design objectives for the end user include: • Increased simplicity to reduce potential errors and minimize the need for manipulation of modes and controls; • Automated compliance with evidence based medicine goals for protective lung ventilation and weaning; • Interfaces that reduce training requirements and facilitate rapid clinical assessments; • Technology applicable to a wide patient population, including non-invasive and increased efficiency over prior or alternative technology. Currently, users of Hamilton ventilators have adopted several new technologies: • The Ventilation Cockpit integrates complex data into intuitive graphics which allow the user to rapidly assess lung condition, ventilatory status, and weaning status. • ASV (closed-loop control) provides automated lung protection and weaning. • Ventilates virtually all intubated patients. • Adapts to pt pathology and activity. • Fewer user interactions and alarms. • Facilitates shorter ventilation times. • The automated P/V Tools use a simple and repeatable method to find best PEEP, based on respiratory mechanics. It also enables automated lung recruitment maneuvers and therapy assessment. Future technology will provide more comprehensive closed loop control ventilation, integrating user friendly but data rich displays to increase simplicity. These technology innovations reduce task oriented work for clinicians and allow the clinician to focus on patient clinical assessments and outcomes.

CURRENT APPLICATIONS: Hamilton Medical ventilators are available worldwide and are installed at major hospitals as well as small rural hospitals. User Reports can be located at hamilton-medical.com or to request a specific reference list, please contact Annette.dusek@hamiltonmedical.net.

Medical Graphics Corporation

PRODUCTS FOR HOSPITALS: Medical Graphics Corporation designs, manufactures and distributes innovative cardiorespiratory systems that noninvasively analyze breathing and other physiologic parameters. The Medgraphics name is synonymous with easy-to-use, cost effective assessment of lung function with the award winning Elite Series Plethysmographs and the UltimaPF Pulmonary Function System. Medgraphics' reputation for quality breath-by-breath metabolic measurements is embodied in a complete line of gas exchange systems including the Ultima CPX, Ultima CardiO2 and the VO2000 which is portable, inexpensive and simple to use. The latest addition to the product line is the CCM Express for nutritional assessment. All Medgraphics products use our patented preVent flow sensor, which is unparalleled for patient comfort, and eliminates the need for bulky hoses and bacterial filters while effectively addressing concerns over infection control. Medgraphics systems are used worldwide for the prevention, early detection and cost-effective management of heart and lung disease. The Platinum Elite Plethysmograph provides state of the art technology for complete assessment of pulmonary function. The plethysmograph has become the system of choice compared to standard pulmonary function systems because it not only decreases test time, but also increases accuracy of test results. The plethysmograph adds two testing capabilities, Thoracic Gas Volume and Airway Resistance, which are not available on standard PF systems. Airways Resistance increases sensitivity to identify lung diseases. It allows for fast, easy testing of all patients, from pediatric through adult and becomes a powerful diagnostic tool for the physician. The main purpose of the plethysmograph is to determine the presence of lung disease and the extent of abnormalities. With this information you can determine the course and response of therapy and measure the progression. By making an early diagnosis of respiratory disease, the clinician can begin treatment to reverse, stop or slow down the progression of the disease. The Ultima Series is the most comprehensive stress testing system on the market. The Ultima can perform complete cardiopulmonary exercise tests, with or without integrated ECG. It also has the versatility of expanding your testing capabilities by adding nutritional assessments or complete pulmonary function. This allows the facility to grow their system as their practice or patient size increases. The Ultima offers true breath-by-breath analysis for exercise testing and nutritional assessment. The system allows you to fully integrate the 12-lead ECG onto dual monitors, or simply interface to an existing ECG system. The newest addition to the Medgraphics family of products is the CCM Express. This small compact unit is designed for mobile nutritional assessment for spontaneously breathing patients as well as patients on ventilators in the critical care unit. The patented DirectConnect Flow Sensor is unique in that it interfaces between the ET tube and the ventilator circuit; thereby having the ability to test patients in all standard ventilator modes. By measuring the actual nutritional needs of the patient, you can take the guess work out of determining what to feed your patient. Giving the patient the correct nutritional intake can decrease ventilator days and ultimately save the hospital money.

EDUCATION: All of our systems offer one on one or group training to maximize the use of the equipment. These training classes are usually held at the factory, but arrangements can be made for training at the hospital or clinic. In addition to formal classes, each system comes with PowerPoint presentations for the operator to review at a later time. Also, Medical Graphics Corporation sponsors a yearly Cardiopulmonary Diagnostics Seminar with experts in the field of pulmonary function testing, cardiopulmonary exercise testing and nutritional assessment. This three day seminar allows the participants to learn from experts in their field, ask questions, and see live demonstrations of each test. Participants of the operator training as well as the diagnostic seminar are given CRCE credits from the American Association for Respiratory Care.

END-USER INPUT: Customer feedback is one of the most important aspects of any company. You cannot survive if you do not meet the needs of the customer. To that end, Medical Graphics has a formal process of documenting comments and suggestions from our customers, reviewing them and implementing those that are beneficial to the end user. There are multiple contact points within our system which include the sales rep, trainer, field service and technical support. All of these employees have direct contact with the customer and can relay their suggestions back to the company.

TECHNICAL SUPPORT: Medical Graphics has an excellent team of technical support personnel to handle everything from clinical to technical inquiries. Most of the questions are handled through our technical call center which is staffed by highly trained individuals which include technicians, respiratory therapists and exercise physiologists. We also have the ability to provide tele/

video conferencing as well as support by directly linking up to the customers' computer. Field Service personnel are stationed throughout the US and are available for questions or on-site service.

CURRENT APPLICATIONS: Medical Graphics products are used worldwide in all types of clinical settings from major universities and teaching hospitals, to a single physician office.

Ohio Medical

Information provided by Scott Hippensteel, Vice President of Marketing.

PRODUCTS FOR HOSPITALS: • Continuous/Intermittent Suction Regulators; • Air/Oxygen Flowmeters; • Air/Oxygen Blenders; • Portable Suction equipment; • Gas Fittings & Adapters; • Central Vacuum and Air Systems; • Medgas Pipeline equipment

EDUCATION: We have a fully trained sales force that can provide remote or in hospital training where required on our products. We also offer Instructions-For-Use manuals and videos that supplement this training.

END-USER INPUT: We use focus groups and Clinical Advisory Panels for product input and development of new product concepts.

TECHNICAL SUPPORT: We have an in-house engineering staff along with customer service to answer technical issues. We also offer service manuals with technical specifications for biomedical departments and engineers.

NEW TECHNOLOGIES: Currently we have three new products recently launched with a fourth product expected in Q2 of 2009: • New Digital Push-To-Set Suction Regulators (Domestic/International); • New 7700 Series Air/Oxygen Flowmeters (Domestic/International); • New line of Air/Oxygen Blenders which includes a Neonatal version (NEO_2 Blend), equipped with a unique gas saving bleed switch with two flowmeters pre-attached. (Domestic/International); • (Coming Soon) Portable Suction Pump (Homecare/Domestic/International).

Cardinal Health (Cardinal/ VIASYS)

PRODUCTS FOR HOSPITALS: The tremendous resources of Cardinal Health allow us to provide total solutions for hospitals respiratory care needs. Starting with our diagnostic products, we offer everything from simple hand held spirometry through full PFT systems, including three gas analyzers and metabolic measurement systems. Our ventilator portfolio encompasses every area of respiratory support from non-invasive through sub-acute, acute care as well at transport and homecare products. Additionally our specialty product offerings address specific needs such as infant non invasive or High Frequency ventilation. Strongly linked to our capital products are our consumables and accessory products, from humidifiers to cannulas Cardinal health can provide everything your department needs. And finally our sleep diagnostic and therapeutic products provide the diagnostic tools and treatment devices needed to treat this growing patient care population.

NEW TECHNOLOGIES: The most significant advancements of care will come from the integration of comprehensive patient data. This will allow continuous monitoring and correlation of patient information providing direct feedback to clinicians alerting them of any change in patient condition far in advance of current systems. These predictive systems will ultimately lay the foundation for more closed loop control in critical care equipment. Additionally, we will see a major evolution of user interfaces. This new focus on human factors will target enhanced safety and reduce "information overload" of the clinician allowing them to focus on the patient and not the medical devices. All of these technologies are focused on reducing workloads and increasing patient safety.

EDUCATION: We have staffed, developed and fielded a large number of Clinical Educators to address this need. Our Clinical Educator and Clinical Support Specialists provide a comprehensive array of educational programs, even offering Continuing Education Credits to our customers. In addition we offer full biomedical training on our products as well as in factory advanced training programs.

END-USER INPUT: User satisfaction is at the foundation of everything we do at Cardinal Health. We constantly obtain feedback from customers on our existing products as well as current information on key research and challenges facing medical practitioners and their patients. Key to this process is our Clinical Advisory Boards and Center of Excellence Program. These programs bring together diverse populations of clinicians, administrators and support staff to provide direct input into future product development. This information drives our R&D and sustaining efforts and the subsequent feedback provides confirmation that we are indeed moving the practice of medicine and quality of care forward.

TECHNICAL SUPPORT: Our Customer Care Team is staffed by experienced, highly trained Biomedical Technicians and Clinicians who provide real time 24 hours support to our global customers. This team is further enhanced by our Field Service Organization which is available to repair and maintain all of our product lines ensuring quality and timeliness to the service process. The Customer Care Team also provides our factory biomedical training classes for customers who choose to maintain their own equipment.

CURRENT APPLICATIONS: Cardinal Health is a global manufacturer and distributor of pharmaceuticals and medical supplies. Ninety percent of hospitals and fifty percent of all surgeries in the US use Cardinal Health products or services. More than 50,000 deliveries are made each day to approximately 40,000 customer sites including hospitals, pharmacies and other points of care.

Instrumentation Laboratory

Information provided by Sally McCraven, Manager, Marketing Communications, Instrumentation Laboratory.

PRODUCTS FOR HOSPITALS: The GEM Premier 4000 and the new GEM Premier 3500 critical care analyzers measure pH, blood gases, CO-Oximetry (integrated on the GEM Premier 4000), electrolytes, metabolites and more from a single sample of whole blood. They are exceptionally easy-to-use, allowing

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Please contact your IL sales representative, at **1.800.955.9525**, or visit **www.ilus.com**.

Werfen Group | Instrumentation Laboratory

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users to perform time-sensitive diagnostic tests efficiently and accurately, in the central laboratory or at the point of care. Both analyzers feature IL's patented Intelligent Quality Management (iQM), a real-time, automated, quality assurance system that continuously detects, corrects and documents potential errors, to assure quality results and regulatory compliance 24/7, regardless of operator or testing location. iQM, coupled with the GEM disposable cartridge technology and ease of use, allows the GEM Premier 4000 to provide consistent, accurate, lab-quality results throughout the hospital. GEMweb Plus software enables remote access to any networked analyzer for real-time status updates and supervision of remote locations. IL also offers GEM OPL, a portable whole blood CO-Oximeter and the GEM PCL Plus, a portable coagulation analyzer for point-of-care testing.

EDUCATION & TRAINING: A Training Guide and Training Video accompany each installation of the GEM Premier 4000. Onsite, IL dedicated technical field representatives perform a comprehensive training program to ensure that end-users are not only comfortable running the system, but are fully competent in running different types of samples (from capillary tubes to syringes) by addressing both analytical testing and pre-analytical sample handling. These field-based technical representatives provide on-going and on-site training and support. IL also conducts educational seminars throughout the year at customer hospitals and at national conferences in which experts in the field of diagnostics and quality control discuss the key components of a quality point-of-care testing program. These seminars provide Continuing Education Units (CEU) for attendees. More information is available at ilus.com.

END-USER INPUT: IL's critical care products make an impact on point-of-care and laboratory testing every day by helping healthcare professionals provide the very best patient care. Lynn Pompa, RCP, Supervisor, Respiratory Care and Pulmonary Diagnostics at Albert Einstein Medical Center, Philadelphia, PA represents just one of the many satisfied GEM Premier customers. Pompa says, "…the GEM Premier 3000 analyzer represents the best of both the 'point-of-care' and 'benchtop' analysis worlds—on-board QC and password lockout make it safe in any environment, putting it light-years ahead of the i-Stat products we have used—yet it has the stability and trackability of a benchtop analyzer—and to each and every staff member, the GEM Premier 3000 is a welcome change from the electrode-based systems of the past." Rick Plunk, Director of Respiratory Care Services, Medical City Dallas, Dallas, TX describes his partnership with IL as a GEM Premier 4000 customer: "Purchasing the GEM Premier 4000 as our analyzer in Medical City Dallas, has been a good decision… I've been blown-away by the responsiveness of the IL…they have listened to all of my concerns…and when I have an issue, they are right there.... it is important that I am not just a customer, but I'm a partner with the company that I do business with. With IL, I truly feel like I have a vote and an ear, and if things need to be turned left or turned right, I can get those things done. So, I'm very happy to be a partner with IL."

TECHNICAL SUPPORT: IL's GEM Premier 4000 and new GEM Premier 3500 analyzers feature the only single-component, multi-use cartridge analyzers on the market today. Since all components for critical care testing are contained in the cartridge itself, there is virtually no need for maintenance or technical support. A "back up" cartridge, which can be stored at room temperature at any testing site, is simply installed when needed. However, we do provide our customers with specialists in the areas of Data Management, Product Line Support and Technical Support to ensure optimal product performance and customer satisfaction. Our experienced sales and support organization in the field provide training, data management support and service and preventative maintenance for our instruments. Additionally, our technical support group is just a toll-free phone call away, 24 hours a day, 7 days a week, via our toll-free phone number.

NEW TECHNOLOGIES: In January 2009, IL launched the GEM Premier 3500 critical care analyzer. Building on the unprecedented testing simplicity, flexibility and reliability of the GEM Premier 3000, the GEM Premier 3500 offers new capabilities, such as wireless communication to the LIS/HIS, in an enhanced system adaptable to the needs—and volume–of any hospital and lab. IL's flagship product, the GEM Premier 4000, will be expanding its test menu to include BUN*, Creat*, Total Bili*, HCO_3^-*, further enhancing its applications in critical care testing. Additionally, new features will be added to GEMweb Plus, IL's revolutionary integrated information management platform that allows complete, real-time, system control throughout the hospital, such as: onboard user training, certificates and new interfacing capabilities [*in development].

CURRENT APPLICATIONS: IL currently holds contracts with most major Group Purchasing Groups (GPOs) in the US for our critical care portfolio including: MedAssets, Broadlane, Amerinet, Health Trust, Premier, and GSA. IL's products can be found in hundreds of hospitals around the world, including some of the most prestigious teaching institutions in the US and abroad.

RespirTech

Information provided by K. James Ehlen, MD, CEO, RespirTech.

PRODUCTS FOR HOSPITALS: RespirTech offers a suite of single patient use jackets and wraps marketed under the ClearChest label. The products utilize a new proprietary polymer system specifically engineered for use in patient-contact medical supplies. ClearChest jackets and wraps, used together with the inCourage system high frequency chest compression device, are available in three models to manage the full spectrum of airway clearance needs in both critical care and general medicine settings. RespirTech also offers a sleek, easy to maneuver cart.

EDUCATION AND TRAINING: RespirTech provides a variety of accredited CEU programs for AARC and CMSA members. It also offers presentations and seminars on HFCC technology, supporting research and clinical applications tailored to meet the in-house continuing education needs of healthcare team members including physicians, nurses, respiratory care providers and case managers/discharge planners. ClearChest products, like RespirTech's reusable jackets, have the patented QuickFit feature to assure optimally individualized fit. Additionally, RespirTech staff are happy to schedule inCourage™ system in-service sessions at any time.

END-USER INPUT: Intensivist/hospitalist physicians and respiratory care team leaders have reported notable clinical outcomes associated with inCourage system therapy in the critical care/long-term acute care setting. Observations include

enhanced ventilatory weaning, rapid resolution of atelectasis and accelerated recovery from hospital-acquired or ventilator–associated pneumonia. End users comment favorably on product ease-of-use, tolerance and acceptance.

TECHNICAL SUPPORT: In addition to providing comprehensive in-service training for clinical staff, RespirTech's team is available for technical support 24/7.

ROUNDTABLE PREVIEW: EMERGENCY PLANNING

Vortran Medical

Vortran Medical manufactures and markets a patented line of fully automatic disposable respiratory devices for patients in the hospital and other market segments (EMS, post acute and home care). Our latest advances in product development and applications have provided for efficient gas consumption, Positive End Expiratory Pressure (PEEP) valve and an intrinsic alarm system for the Vortran Automatic Resuscitator (VAR). Vortran is able to help an area stricken by disaster or in an emergency situation by marketing our products to emergency service agencies and critical care providers. The VAR and E-vent Case products provide an inexpensive ventilation solution for any Mass Casualty Incident (MCI), whether man-made, natural or bioteroorism-type disasters. The VAR being single patient and disposable, eliminates cross-infectivity, contamination and equipment sterilization issues. The E-vent case is organized for rapid deployment and provides ventilatory support for seven patients simultaneously with the 7-port manifold. Connecting the manifold to a single gas source such as wall connection, "H" tank, or even medical grade air compressors provides maximum clinical performance during an initial emergency medical response. Vortran's contingency plans for boosting production of our VAR and E-vent Case has remained the same since the 911 terrorist disaster situation. We continually monitor our raw materials, finished goods, stocking levels of our dealers and follow up with pending business. With this daily plan, we have been able to meet the demand and be prepared for future production. Because of the interest and widespread use of our (VAR), for disaster preparedness and pandemic influenza, we have recognized the need for education and training. The 3 types of education and training we provide relevant to emergency services or disaster planning, is the interactive CD-ROM which contains a multi-medias presentation for PC platform, includes instructional video, brochure and user guide in a pdf format for all Vortran products. Second, is an online Educational Module Sponsorship for free CEU. The program provides online continuing education 1 contract hour (CEU) at no charge to medical professionals at accessce.com/courses.aspx. Third is the Vortran website, vortran.com. More information about Vortran's emergency preparedness programs will be presented in Respiratory Therapy's June/July issue featuring its Emergency Preparedness Roundtable.

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devices. It is simply no longer possible to believe much of the clinical research that is published, or to rely on the judgment of trusted physicians or authoritative medical guidelines. I take no pleasure in this conclusion, which I reached slowly and reluctantly over my two decades as an editor of The New England Journal of Medicine.

"Physicians, medical schools, and professional organizations have no excuse, since their only fiduciary responsibility is to patients. The mission of medical schools and teaching hospitals—and what justifies their tax-exempt status—is to educate the next generation of physicians, carry out scientifically important research, and care for the sickest members of society. It is not to enter into lucrative commercial alliances with the pharmaceutical industry. As reprehensible as many industry practices are, I believe the behavior of much of the medical profession is even more culpable. Drug companies are not charities; they expect something in return for the money they spend, and they evidently get it or they wouldn't keep paying.

"So many reforms would be necessary to restore integrity to clinical research and medical practice that they cannot be summarized briefly. Many would involve congressional legislation and changes in the FDA, including its drug approval process. But there is clearly also a need for the medical profession to wean itself from industry money almost entirely… There is seldom a legitimate reason for physicians to accept gifts from drug companies, even small ones, and they should pay for their own meetings and continuing education. If the medical profession does not put an end to this corruption voluntarily, it will lose the confidence of the public, and the government will step in and impose regulation. No one in medicine wants that."

Newborn Diagnosis of Cystic Fibrosis: A Window of Opportunity to Prevent Bronchiectasis?

Jane Braverman, PhD

Preventing or delaying the onset of bronchiectasis in cystic fibrosis is a fundamental treatment goal. Recent studies of infants diagnosed by newborn screening show that CF lung disease begins very early in life, presenting a unique "window of opportunity" to alter the natural history of the disease. Implementation of effective anti-inflammatory, antibiotic and airway clearance therapies may prevent or arrest lung damage before symptoms are overt. Because few safety and efficacy studies of treatments used widely in older individuals include very young patients, research to guide clinical risk/benefit judgments are urgently needed. Until such data are available, judicious use of therapies with strong histories of safety and efficacy in older patients may be warranted.

When cystic fibrosis (CF) was first described nearly seventy years ago, affected infants and children lived brief lives diminished by respiratory crises and relentless decline.[1] Today, the outlook is dramatically different. Although still life-shortening, CF is quite well understood, highly treatable, and potentially curable. Since CF was first described in 1940, median life expectancies have increased steadily from barely one year to more than 37 years.[2] Lifespans for children diagnosed and treated early are now projected to extend into at least the fifth decade.[3] Despite such progress, however, people with CF continue to live with debilitating, costly chronic illness; approximately 90% eventually die of complications resulting from lung infection.[4]

Recent implementation of newborn screening (NBS) for CF, now standard practice in at least 40 states, has provided a unique opportunity to investigate the first appearance of pulmonary abnormalities.[5] Among important new insights, progressive lung damage in CF is now known to begin in early infancy. There appears to be a "window of opportunity" to use targeted interventions to maintain normal lung function indefinitely, raising the prospects for longer and healthier lives to an entirely new level.[6-8]

Lung health studies

The "pristine" lungs of CF newborns remain structurally and functionally healthy for only a brief period of time.[9, 10] Although most CF infants appear to be relatively healthy, subtle pathophysiological changes quickly set the stage for progressive deterioration. Key findings now show: 1) infection and/or inflammation is present in the first months of life [9-10] 2) CF lungs lack specific intrinsic defense mechanisms necessary to clear infection;[11] 3) lung function deficits occur early and;[7,10, 12] 4) airway remodeling and bronchiectatic changes appear far sooner than previously thought. [6, 10, 12-14.]

Inflammation/infection

In CF lungs, well understood metabolic abnormalities result in production of large quantities of physically and chemically abnormal mucus. In symptomatic patients, hypersecretion of infected, viscous and sticky secretions, in combination with mucosal and peripheral airway inflammation, bronchoconstriction, mucus plugging and progressive tissue damage, initiate and accelerate obstructive lung disease.

CF lungs are structurally normal at birth.[9] Infection and inflammation are early markers of CF pathology. Examinations of lung fluid obtained by bronchioalveolar lavage (BAL) demonstrate the frequent presence of inflammation and/or infection within the first several weeks of life.[9,10] Whether inflammation precedes exposure to bacteria or vice versa is a topic of controversy, but the key finding is that significant airway inflammation is present in many CF infants shortly after birth.[9, 10, 15] Although infection and inflammation occur intermittently in infants with CF, deleterious effects on the airways may be permanent.[9,16,17] With disease progression, byproducts of chronic inflammation, especially those derived from neutrophils, precipitate bacterial colonization, accelerated decline of lung function and, ultimately, initiate bronchiectasis.[6,8,11]

Lung defense defects

There is no systemic immune defect in CF.[11] Although inflammation may occur in any mucus-producing organ, including the pancreas, bowel and liver, only the lungs are highly susceptible to infection. In healthy individuals, lungs remain sterile despite constant exposure to inhaled pathogens. Small quantities of bacteria are routinely cleared without triggering an inflammatory response. In CF lungs, inherent abnormalities in chloride ion channeling induce hyperproduction of mucus with low moisture content, promoting adherence to airway walls. As a consequence, clearance mechanisms are impaired. Cilia are physically disabled by an excess load of thick, sticky secretions and cough force is insufficient to shear mucus from the airways.

Complex interactions of other physical and chemical factors encourage the survival, adaptation and colonization of mucus-entrapped organisms.[11] The corrosive effects of chronic, exuberant inflammation simultaneously damage lung tissue until frank bronchiectasis is established. Once such damage has occurred, the ability to clear infection without therapeutic intervention is effectively lost.

Lung function deficits

Increasingly sophisticated methods of assessing lung function in CF newborns permit accurate assessment of baseline lung function and lung function trends over time. Data obtained with forced expiration techniques including raised—volume rapid thoraco abdominal compression have shown lung function to diminish progressively with age in CF infants and toddlers despite good nutrition and routine care in specialist centers.[18] Importantly, data show that asymptomatic infants less than six months old have lung function comparable to healthy non—CF controls, but those older than six months, even in the absence of evidence of infection or inflammation, demonstrate progressive, statistically significant deficits. [7, 9.17]

Airway remodeling and bronchiectatic changes

Emerging tools in radiographic imaging techniques, most notably low-dose computed tomography (CT) scanning, have opened entirely new territory in the assessment and scoring of early morphological functional abnormalities. It is now possible not only to safely quantify air trapping in infant airways, but also to assess atelectasis, mucus plugging, bronchial wall thickening and, critically, the onset of bronchiectasis.[13-17, 19, 20] Alarmingly, bronchiectatic changes have been identified in a significant proportion of children over the age of three years.[6, 14]

Weighing the evidence: benefit/risk judgments

New insights into the early appearance of lung abnormalities in infants with CF oblige consideration and study of targeted treatment strategies.[6, 7, 9,10,13,15] The production and retention of abnormal, infected airway mucus is both a cause and effect of CF disease-related pathology. Management of airway secretions, together with associated inflammation and infection, before lung disease is established and irreversible, is a rational objective. However, identification and implementation of new treatments is not a simple matter. On the one hand evidence for early treatment of asymptomatic CF infants diagnosed by NBS is compelling. On the other, few or no studies have investigated the safety and efficacy of those therapies prescribed routinely for older children and adults.

As in all medical decision-making, clinicians must weigh available evidence to make risk/benefit judgments before initiating new treatments. Pharmacological interventions, by their nature, pose risks for drug interactions, adverse side-effects and indiosyncratic responses. Physical/mechanical treatments, including chest physiotherapy (CPT) and high-frequency chest compression (HFCC), carry few of the risks inherent in drug therapy, but may present different risks and challenges.

Potential therapies: pros and cons

Anti-inflammatory therapy: Inflammation, with or without overt infection, triggers an exaggerated host response in CF and promotes tissue damage leading to bronchiectasis. Theoretically, anti-inflammatory therapy begun in the first few months has potential for long-term benefit.[6] In clinical practice with older CF patients, modulation of airway inflammation is unequivocally beneficial, but deleterious side-effects are also recognized.[21] Long-term use of corticosteroids is especially concerning. Decision-making is complicated by a paucity of data from studies including infants and very young children.

Antibiotic Therapy: Before the age of one year, between 40-65% of CF infants identified by NBS and participating in BAL fluid analysis show colonization with at least one pathogen.[6,22,23] The common CF pathogen, Pseudomonas aeruginosa, is strongly associated with intensification of inflammation and worse outcomes.[6] The emergence of resistant strains of the organism merits further concern. Unfortunately, studies of P aeruginosa suppression or eradication in children under six, as well as of other organisms, are scarce. In existing studies, certain known adverse effects of inhaled tobramycin, including growth of resistant strains, fungal infections and tintinitis, underscore the need for age-appropriate studies.[6, 24]

Airway clearance therapy: The effects of secretion retention are recognized as a fundamental component of pulmonary morbidity in CF. Daily airway clearance therapy (ACT) is a universally applied element of CF care and considered medically necessary throughout life regardless of disease severity.[15] In clinical practice, ACT is usually prescribed at the first appearance of symptoms.[15,25,26] There is general agreement that the benefits of airway clearance therapy are greatly diminished if treatment is deferred until the development of significant lung disease.[27] With new evidence of nascent lung disease in NBS CF infants, presymptomatic initiation of ACT may confer prophylactic benefit. Approaches include mucolytic/mucokinetic drugs and mechanical methods. The use of pharmacologic agents, most popularly recombinant human DNase [pulmozyme], is a topic of ongoing debate among clinicians owing to its variable, indiosyncratic effects on long term lung function.[28, 29] Although apparently well-tolerated in older children, this drug has not been studied in children under the age of two years.[29, 30] Only two forms of physical/mechanical ACT – CPT and HFCC- are practical for infants and young children. Each have advantages and disadvantages. Few studies exist that address inherent differences between infants and more mature children with respect to mechanical/physical aspects of CPT and HFCC therapy. These include 1) differences in respiratory mechanics that may increase risk for airway obstruction and atelectasis; 2) increased compliance of airway walls; 3) lower functional residual capacity; 4) smaller airway diameter; 5) fewer alveolar collateral channels; 6) risk for gastroesophageal reflux and; 7) risk for aspiration.[31]

Chest Physiotherapy (CPT)

In the early 1960's, twice or more daily CPT became a standard component of the CF care approach.[1] In a short time, pulmonary and general health, as well as median life expectancy, began to improve steadily. Although it is difficult to distinguish its precise contribution from the effects of other novel or improved therapies, CPT was soon established as the "cornerstone" of disease management.[1, 15]

- Treatment Barriers: CPT, a highly technique and effort-dependent therapy, is based on the premise that a combination of strategic pulmonary percussion and positioning can enlist gravity to drain loosed secretions from smaller to larger airways. Effective therapy requires five-minute percussion treatments of each lung segment followed by serially positioning the patient in 9-12 drainage postures. For obvious

reasons, CPT is generally incompatible with the demands of modern life and has been largely replaced by less labor-intensive, more practical forms of ACT.[32,33] Until recently, however, because infants are unable to cooperate with alternative methods, CPT has been the only ACT available to them.[31] Although studies of CPT in infants are few, its safety in this population has been generally assumed. A growing body of evidence suggests otherwise.

- Gastroesophageal: Several studies have associated CPT with worsened pulmonary health in infants and young children. Gastroesophageal reflux (GER) can cause upper respiratory symptoms, chronic lung inflammation and accelerated lung deterioration.[34-37] CPT requires positioning the patient's head and lungs downward, below the lower esophageal sphincter (Trendelenburg position), thus triggering episodes of reflux. Most CF patients and virtually all CF infants are prone to GER.[34-41] Refluxed gastric contents are a significant cofactor in pulmonary deterioration.[15,42-43] In a five-year study including 20 asymptomatic infants diagnosed by newborn screening and randomized to receive either standard CPT or a modified regimen omitting the head down positions, the "head down" group had significantly more days with upper respiratory infections and longer courses of antibiotics at one year, significantly worse chest X-ray scores at 2.5 years, and worse pulmonary function (FEC and FEV_1) at 5-6 years of age.[42]

- Additional adverse effects: CPT requires the use of substantial force. Serious neurologic injury and rib fractures following CPT have been reported in neonatal ICU patients.[44,45] Other, less common adverse effects include oxygen desaturation and discomfort or pain.[46, 47]

High-Frequency Chest Compression (HFCC)

HFCC therapy is administered by means of an inflatable jacket fitted over the patient's chest and connected by hoses to an air-pulse generator. The rhythmic inflation and deflation of the jacket against the patient's chest produces oscillatory effects within the airways shown to loosen, thin and mobilize bronchial secretions from peripheral to central airways for clearance by coughing, swallowing or suctioning.[50] Treatments are usually administered with the patient in a sitting position, thus reducing the risk for of GER associated with CPT.

- Safety and efficacy research: Second to CPT, HFCC is the most thoroughly studied ACT.[51-52] To date, more than 80 basic and clinical studies have been completed; several additional studies are in progress or in planning. Laboratory studies have elucidated the mechanisms of action and physiological effects of HFCC.[53-59] Clinical trials show that HFCC provides secretion clearance superior or equivalent to comparator modalities, including CPT.[58, 60-63] Numerous studies confirm the short-term and long-term impact of HFCC therapy on pulmonary functions.[62, 64-70] No studies have demonstrated significant short or long-term adverse effects.

- Children under two years of age: Formal studies of safety and efficacy of HFCC in patients under the age of 2 years are lacking. Eleven clinical trials and reports show safety and/or efficacy in children between the ages of 2-12.[61, 66, 67, 71-77] Based on a presumption of safety, HFCC—like CPT—has been prescribed for many very young children and used without known incidents. HFCC applies significantly less pressure to the thorax than that applied by thoracoabdominal methods used to obtain infant pulmonary function data.[78-81] However, because infants have distinct skeletal and physiological characteristics, the risk for potential adverse events remains unknown.

Summary

Compelling new evidence supports the concept that early intervention to moderate or prevent development of CF bronchiectasis in infants identified by NBS. However, treatment decisions in infants are hampered by a lack of quality studies of standard treatments. Physicians face a dilemma. They must weigh the likely consequences of delaying treatment against possible risk for harm. The need for expertly conducted clinical trials is critical to address unanswered questions. Until definitive data are available, close monitoring of therapeutic tolerance and outcomes must inform treatment choices. Judicious use of therapies with strong histories of safety and efficacy in older patients is likely to advance long-term health in newly diagnosed CF infants.

References

1 Carl F. Doershuk, Editor. Cystic Fibrosis in the 20th Century: People, Events, and Progress. Cleveland Ohio, 2001 AM Publishing Ltd., 417 pp.
2 Cystic Fibrosis Patient Registry Data, 2008, cff.org.
3 Ratjien F. Recent advances in cystic fibrosis. Paediatr Respir Rev 2008; 9 (2) 144-148.
4 Sibley CD, Rabin H, Surette MG. Cystic fibrosis: a polymicrobial infectious disease. Future Microbiol 2006; 1: 53-61.
5 National Newborn Screening Status Report. Feb 2008. National Newborn Screening and Genetics Resource Center, Austin Texas.
6 Stick SM. Clinical trials in infants with cystic fibrosis detected following newborn screening. Paediatr Respir Rev 2008; 9: 176-180.
7 Linnane BM, Hall GL, Nolan G. Lung function in infants with cystic fibrosis diagnosed by newborn screening. Am J Respir Crit Care Med 2008; 178: 1238-1244.
8 Boucher RC, New concepts in the pathogenesis of cystic fibrosis lung disease. Eur Respir J 2004; 23 (1): 146-158.
9 Armstrong DS, Hook SM, Jamsen KS, et al. Lower airway inflammation in infants with cystic fibrosis detected by newborn screening. Pediatr Pulmonol 40: 500-510.
10 Nixon GM, Armstrong DS, Carzino R. Early airway infection, inflammation, and lung function in cystic fibrosis. Arch Dis Child 2002; 87: 306-311.
11 Chmiel JF, Davis PB. State of the art; why do the lungs of patients with cystic fibrosis become infected and why can't they clear infection? Respir Res. 2003; 4: 8-20.
12 Farrell PM, Li Z, Kosorok MR. Longitudinal evaluation of bronchopulmonary disease in children with cystic fibrosis. Pediatr Pulmonol 2003; 36: 230-240.
13 Robinson TE. Computed tomography scanning techniques for the evaluation of cystic fibrosis lung disease. Proc Am Thorac Soc 2007; 4: 310-315.
14 Long FR, Williams RS, Castile RG. Structural airway abnormalities in infants and young children with 15Cystic fibrosis. J Pediatr 2004; 144: 154-161.
15 Lannefors L, Button BM, McIlwaine M. Physiotherapy in infants and young children with cystic fibrosis; current practice and future developments. J Roy Soc Med 2004; 44 (97): 8-25.
16 Hilliard TN, Regamcy N Shute, et al. Airway remodeling in

children with cystic fibrosis. Thorax 2007; 62: 1074-1080.
17 Martinez TM, Llapur CJ, Williams TH, et al. High-resolution computed tomography imaging of airway disease in infants with cystic fibrosis. Am J Respir Crit Care Med 2005; 172: 1133-1138.
18 Ranganathan SC, Stocks J, Dezateux C, et al. The evolution of airway function in early childhood following clinical diagnosis of cystic fibrosis. Am J Respir Crit Care Med 2004; 169: 928-933.
19 Brennan S, Stick S, Douglas T, et al. HRCT correlates with inflammation and symptoms in young children with cystic fibrosis. Respirol 2007; 12 (Suppl) A22.
20 Stick 2007 Orenstein DM, Rosenstein BJ, Stern RC. Cystic fibrosis Medical Care. Pediatr Pulmonol (Lippincott, Williams & Wilkins, Philadelphia PA, 2000).
21 Balfour-Lynn IM. Anti-inflammatory approaches to cystic fibrosis airway disease. Curr Opin Pulm Med. 2007; 13: 522-528.
22 Rosenfield M, Gibson RL, McNamara S, et al. Early pulmonary infection, inflammation and clinical outcomes in infants with cystic fibrosis. Pediatr Pulmonol 2001; 32: 356-366.
23 Armstrong DS, Grimwood K, Carlin JB, et al. Bronchoalveolar lavage or oropharyngeal cultures to identify lower respiratory pathogens in infants with cystic fibrosis. Pediatr Pulmonol 1996; 21: 267-275.
24 Cheer SM, Waugh J, Nobel S. Inhaled tobramycin (TOBI): a review of use in the management of Pseudomonas aeruginosa infections in patients with cystic fibrosis. Drugs 2003; 63: 2501-2520.
25 Dankert-Roelse JE, te Meerman GJ. Screening for cystic fibrosis-time to change our position? [Editorial] New Engl J Med 1997; 337(14): 997-999.
26 McCoy KS, Stokes D, Dubroff M, Hoffman A, Mischler NE, Erickson S. Managed care and the CF patient. Curr Opin Pulm Med 1997; 3(6): 425-429.
27 Weiser G, Kerem E. Early intervention in CF: how to monitor the effect. Pediatr Pulmonol 2007; 42 (11): 1002-1007.
28 Suri R. The use of human deoxyribonuclease (rhDNase) in the management of cystic fibrosis. BioDrugs 2005; 119 (30: 135-144.
29 Nasr SZ, Kuhns LR, Brown RW, et al., Use of computerized tomography and chest x-rays in evaluating the efficacy of aerosolized recombinant human Dnase in cystic fibrosis patients younger than age five years a preliminary study. Pediatr Pulmonol 2001; 377-382.
30 McKenzie SG, Chowdhury S, Strandvik B, Hodson ME. Dornase alpha is well tolerated: Data from the epidemiologic registry of cystic fibrosis. Pediatr Pulmonol 2007; 42: 928-937.
31 Zach MS, Oberwalder B. Pediatric mucus clearance by chest physiotherapy: principles and practice. Chapter 18; 471-502. In: Rubin BK, van der Schans CP, Eds: Therapy for Mucus-Clearance Disorders. Lung Biology in Health and Disease [Executive editor: Claude Lenfant] Vol 188; Marcel Dekker, Inc. New York 2004.
32 Lapin CD. Conventional postural drainage and percussion: is this still the gold standard? Pediatr Pulmonol 1994; 10: 87-88. (Suppl)
33 Sutton PP. Chest physiotherapy: time for reappraisal. Br J Dis Chest 1988; 82: 127-137.
34 Bendig DW, Seilheimer DK, Wagner ML, Ferry GD, Barrison GM. Complications of gastroesophageal reflux in adult cystic fibrosis patients. J R Soc Med 1998; 91 (1): 7-9.
35 Malfroot A, Dab I. New insights on gastro-oesophageal reflux in cystic fibrosis by longitudinal follow up. Arch Dis Child 1991; 66: 1339-1345.
36 Yellon RF. The spectrum of reflux-associated otolaryngological problems in infants and children. Am J Med 1997; 103: 125-129.
37 Vinocur CD, Marmon L, Shildlow DV, Weintraub WH. Gastroesophageal reflux in the infant with cystic fibrosis. Am J Surg 1985; 149: 182-186.
38 Taylor CJ, Threlfall D. Postural drainage and gastro-oesophageal reflux in cystic fibrosis. Lancet 1997; 349 (9065): 1567-1568.
39 Button BM, Heine RG, Catto-Smith AG, Phelen PD, Olinsky A. Postural drainage and gastro-oesophageal reflux in infants with cystic fibrosis. Arch Dis Child 1997; 76(2): 148-150.
40 Button BM, Heine RG, Catto-Smith AG, Phelen PD. Postural drainage in cystic fibrosis: is there a link with gastro-oesophageal reflux? J Paediatr Child Health 1998; 34:330-334.
41 Ledson MJ, Tran J, Walshaw MJ. Prevalence and mechanisms of gastro-oesophageal reflux in adult cystic fibrosis patients. J R Soc Med 1998; 91(1): 7-9.
42 Button B. Catto-Smith AG, et al. Chest physiotherapy in infants with cystic fibrosis: to tip or not to tip. Pediatr Pulmonol 2003; 35: 208-213.
43 Orenstein DM. Heads up! Clear those airways! Pediatr Pulmonol 2003; 35: 160-161.
44 Harding JE, Miles FK, Becroft DM, et al. Chest physiotherapy may be associated with brain damage in extremely premature infants. J Pediatr 1998; 132 (3 pt 1): 440-444.
45 Chalumeau M, Foix-L'Helias L, Scheinmann P. Rib fractures after chest physiotherapy for bronchiolitis of pneumonia in infants. Pediatr Radiol 2002; 32 (9): 644-647.
46 McDonnell T, McNichols WT, FitzGerald MX. Hypoxia during chest physiotherapy in patients with cystic fibrosis. Ir J Med Sci 1986; 1986; 155: 345-348.
47 Webber BA, Hodson ME. Effect of chest physiotherapy on oxygen saturation in patients with cystic fibrosis. Thorax 1990; 45: 77.
48 Prasad SA, Main E, Dodd ME. Finding consensus on the physiotherapy management of asymptomatic infants with cystic fibrosis. Pediatr Pulmonol 2008; 43: 236-244.
49 Kozlowska WJ, Bush A, Wade A, et al., Lung function from infancy to the preschool years after clinical diagnosis of cystic fibrosis. Am J Respir Crit Care Med 2008; 178: 42-49.
50 Braverman J, Nozzarella MJ. High-frequency chest compression: advanced therapy for obstructive lung disease. Respir Therp 2007; 2(2): 48-51.
51 Fink JB, Mahlmeister MJ. High-frequency oscillation of the airway and chest wall. Respir Care 2002; 47; 797-807.
52 Annotated Bibliography: High Frequency Chest Compression. www.respirtech.com
53 King, M, Phillips DM, Gross D, Vartian V, Chang HK, Zidulka A. Enhanced tracheal mucus clearance with high frequency chest wall compression. Am Rev Respir Dis 1983; 128 (3): 511-515.
54 King M, Phillips DM, Wight D, Gross D, Chang HK. Tracheal mucus clearance in high frequency oscillation: effect of peak flow rate bias. Eur Respir J 1990; 3 (1): 6-13.
55 Gross RJ, Zidulka A, O'Brian C, Wight D, Fraser R, Rosenthal L, King M, Peripheral mucociliary clearance with high-frequency chest wall compression. J Appl Physiol 1985; 58 (4); 1157-1163.
56 Tomkiewicz RP, Biviji A, King M. Effects of oscillating air flow on the rheological properties and clearability of mucous gel simulants. Biorheology 1994; 31 (5): 511-520.

57 Chang HK, Weber ME, King M. Mucus transport by high-frequency nonsymmetrical oscillatory airflow. J Appl Physiol 1988; 65(3): 1203-1209.
58 Hansen L, Warwick W. High-frequency chest compression system to aid in clearance of mucus from the lung. Biomed Instru & Tech 1990; 24: 289-294.
59 Hansen LG, Warwick WJ, Hansen K. Mucus transport mechanisms in relation to the effect of high-frequency chest compression on mucus cleaning. Pediatr Pulmonol 1994; 17: 113-118.
60 Arens R, Gozal D, Omlin K, Vega J, Boyd K, Keens T, Woo M. Comparison of high-frequency chest compressions and conventional chest physiotherapy in hospitalized patients with cystic fibrosis. Am J Respir Crit Care Med 1994; 150; 1154-1157.
61 Kluft J, Beker L, Castagnino M, Gaiser J, Chaney H, Fink R. A comparison of bronchial drainage treatments in cystic fibrosis. Pediatr Pulmonol 1996; 22: 271-274.
62 Braggion, C. Cappelletti L, Cornacchia M, Zanolla L, Mastella G. Short-term effects of three chest physiotherapy regimens in patients hospitalized for pulmonary exacerbations of cystic fibrosis: a crossover randomized study. Pediatr Pulmonol 1995; 19: 16-22.
63 Scherer TA, Barandun J, Martinez E, Wanner A, Rubin EM. Effect of high-frequency oral airway and chest wall oscillation and conventional chest physical therapy on expectoration in patients with stable cystic fibrosis. Chest 1998; 113(4): 1019-1027.
64 Warwick WJ, Hansen LG. The long-term therapy effect of high frequency chest wall compression therapy on complications of cystic fibrosis. Pediatr Pulmonol. 1991: 11: 265-271.
65 Wilenski CL, Warwick WJ. Change in pulmonary function over a 30-month period for high-frequency vest users vs. Non-users in a cystic fibrosis population. Am J Respir Crit Care Med 1996; 153; A71.
66 Clayton Sr, RG, Donahue M. ThAIRapy use in 6-12 year old children with cystic fibrosis. Pediatr Pulmonol 1998; Suppl 17: 345, A 496.
67 Anbar RD, Powell KN, Iannuzzi DM. Short-term effect of ThAIRapy Vest on pulmonary function of cystic fibrosis patients. Am J Respir Crit Med 1998; 157 (Suppl 3): A 130.
68 Butler S, O'Neill B. High-frequency chest compression therapy: a case study. Pediatr Pulmonol 1995; 19: 56-59.
69 Burnett M, Takis C, Hoffmeyer B, Patil S, Pichuko B. Comparative efficacy of manual chest physiotherapy and a high-frequency chest compression vest in inpatient treatment of cystic fibrosis. Am Rev Respir Dis 1993; Suppl 147: A30.
70 Hull KK, Warren RH. ThAIRapy Vest vs conventional chest physical therapy (CPT): case report. Respir Care 1991; 36 (11): 1266-1267.
71 Anbar RD. Compliance with use of ThAIRapy® Vest by patients with cystic fibrosis. Pediatr Pulmonol 1998 ;(suppl 17): 346, A497.
72 D'Angelo S, Craigmyle L, Kanga J. How are patients using alternating pressure vests for chest physiotherapy? Pediatr Pulmonol 1994 ;(suppl 10): 266, A314.
73 D'Angelo S, McClendon T, Kanga J. Using objective data to monitor and increase use of chest physiotherapy (CPT) in patient education. Pediatr Pulmonol 1997 ;(suppl 14): 327-328, A448.
74 Landon C, Goldie W, and Evans JR. Airway clearance therapy utilizing high-frequency chest wall oscillation for medically fragile children. Unpublished clinical study data, 2001.
75 McColley SA, Schulz C, Qualter N, Boas SR, Jain M, Goodman DM. Participation in an observational study of airway clearance in cystic fibrosis does not affect patient adherence. Pediatr Pulmonol 1999; (Suppl 19): 331- A 581.
76 McColley SA, Harris CV, Qualter N, O'Malley C, Boas SR, Jain M. Predictors of adherence to an airway clearance technique in cystic fibrosis. Pediatr Pulmonol 1999 ;(suppl 19): 332, A582.
77 Plioplys AV, S Lewis, and I Kasnicka. Pulmonary Vest Therapy in Pediatric Long-Term Care. Journal of American Medical Directors Association 2002; 3: 318-321.
78 Maynard R, Mammel MC, Holloman KK. Effect of thoracic compressions on the cerebral blood flow-velocity patterns of small infants. Pediatr Pulmonol 1992; 13 (4): 235-238.
79 Hammer J, Newth CJL. Effect of lung volume on forced expiratory flows during rapid thoracoabdominal compression in infants. J Appl Physiol 1995; 78 (5): 1993-1997.
80 Lum S, Hoo AF, Stocks J. Effect of airway inflation pressure on forced expiratory maneuvers from raised lung volume in infants. Pediatr Pulmonol 2002; 33: 130-134.
81 Lum S, Hoo AF, Stocks J. Influence of jacket tightness and pressures on raised lung volume forced expiratory maneuvers in infants. Pediatr Pulmonol 2002; 34: 361-368.

Prolonged Mechanical Ventilation in the US

Gene Gantt, RRT

Introduction

Advances in life-prolonging and life-saving interventions over the last 30 years have lead to a rapidly growing subgroup of patients who aren't liberated from mechanical ventilation as quickly as expected. These patients often are referred to as ventilator-dependent individuals who are receiving prolonged mechanical ventilation (PMV).

The plight of these patients is often very difficult as there are limited resources and a lack of access to post acute continued care. Acute care hospitals struggle with placement in post acute care venues. Published studies have proven that with extended time some 50-60% of these ventilated patients can still be liberated from mechanical ventilation. In areas without subacute venues and continued weaning capabilities these patients are simply discharged home to live out there lives on the ventilator.

What is PMV?

The Centers for Medicare & Medicaid Services defines PMV as at least six hours per day of mechanical ventilation for 21 consecutive days.

Mechanical ventilation in short-term acute care hospital intensive care units generally have an average LOS of about 8-10 days. However those who fail to wean have an average acute care LOS of around 30 days. Following the acute care stay patients who remain on mechanical ventilation will begin the often difficult journey through the various sites of care available to them in hopes of eventual liberation from the ventilator.

The sites of care, involve transfers to either Long Term Acute Care Hospitals (LTAC) with an average LOS of somewhere around 30 days or to Skilled Nursing Facilities with subacute capabilities. Additionally some patients will then transition to home where they are cared for by family with often limited professional support.

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This article was provided by Linde, linde-rss.com.

How Many Patients Require PMV?

Studies have demonstrated that approximately 20 percent of patients supported with mechanical ventilation won't wean successfully in the acute care setting.

Based on this published data and information from MedPar database (made up of only Medicare beneficiaries) for 2001 the estimated population is between 47,000 and 65,000 patients requiring PMV.

Pediatric patients, home care patients, Medicaid patients and privately insured patients remain a poorly studied group, and there are no known systematic estimates of the size of these patient populations. Therefore, a reasonable estimate of the annual incidence of PMV is perhaps 50,000 to 70,000.

Patient Settings

The vast majority of patients receiving PMV are cared for in traditional ICUs of acute care hospitals. Many of them are in the ICU solely due to the presence of the ventilator. A portion of these patients are stable compared to the traditional ICU patient and don't require the minute-to-minute or hour-to-hour assessment and interventions typical of an ICU. This in turn consumes vast ICU resources and results in a high cost of care. Acute care hospitals are already financially burdened and this issue certainly has a negative impact on the hospitals bottom line.

Beginning in the mid-1980s, long-term acute care (LTAC) hospitals have developed as acute care level hospitals focusing on the patient requiring a prolonged hospital stay (greater than 25 days on average). Many of these patients require prolonged mechanical ventilation. By almost any definition, patients undergoing mechanical ventilation in LTAC hospitals are PMV patients. As a result of extremely rapid growth and spending in this segment of health care the Medicare Payment Advisory Commission (MedPAC advises congress and CMS on Medicare payment issues) and CMS have begun to impose new regulations on the LTACs in an effort to address the rapid growth. LTACs like the acute care counterparts are not able to keep patients whose prolonged ventilator use becomes more chronic in nature. They too must find acceptable discharge plans for those patients.

A small number of skilled nursing facilities (SNF) have developed specialized units suitable for PMV patients. Reimbursement changes in Medicare in 1998 seriously limited the financial feasibility of these units for elderly patients. Additionally the state to state variation in Medicaid reimbursement is an issue in the SNF setting. This core reimbursement is more likely the reason for poor access across the country. A stable ventilated patient that requires long-term weaning is very well suited for these SNF subacute centers.

Lastly, home ventilation remains an option for the stable nonweanable patient who has a very dedicated caretaker team. Home ventilation is a very difficult task for families. Unfortunately these patients frequently rebound to acute care resulting in a high cost of care overall.

High Costs

PMV is associated with some of the highest costs in medical care. Depending on the care setting and the patient's co-morbidities, a daily cost of $600 in the SNF to several thousand dollars per day in acute care is typical. The care of ventilator patients accounts for approximately 37% of all ICU cases and utilizes vast resources through clinical care needs and from the standpoint of case management resources.

Medicare pays about $98,000 per admission for each of the roughly 65,000 PMV patients. Costs to acute care hospitals for PMV patients almost always are paid through the high cost outlier payment policy (more than the standard DRG payments) and materially exceed the Medicare payment. This amounts to a daily equivalent of 1500 to 2000 per patient day.

SNF ventilator care is a fraction of the cost of acute care. This will range from 900 per day in some states to 500 in others. Unfortunately all states do not have a Medicaid funded chronic ventilator program. So patients who reside there have little to no access for care. They are forced to move to other states who do offer such services. Usually they are far from their families in strange surroundings with little hope of returning home.

Clinical Outcomes

A growing consensus is that successful weaning in the PMV setting might best be defined as freedom from mechanical ventilation for seven days.

As a poorly studied group, PMV patient outcomes aren't well-described. Depending on the patient population and definition of PMV hospital survival for adult PMV patients in acute care hospitals range from 39 percent to 75 percent.

Weaning success is approximately 50 percent, influenced by both patient selection criteria and the quality of the weaning program. Acute care ICUs typically define a successful wean at 48 to 72 hours post extubation.

Weaning success rates for subacute centers has been documented at somewhere between 30% and 60%. Some facilities depending on screening criteria are reporting as high as 75%. This is accomplished at a fraction of the cost of acute care.

What We Have Done

Following drastic reimbursement changes in 1998 nearly all SNFs in the US closed their subacute programs creating a huge void in post acute placement options.

At the request of many acute care contacts we revisited the issue of long term ventilator care in the SNF arena. In early 2001 in partnership with an SNF we opened our first ventilator rehabilitation and weaning unit. It quickly became clear that we could wean many of the cases and return them to home, ventilator free. This dramatically reduced the cost of care for these patients.

Since then we have opened several more centers all of similar size and utilizing a consistent model. Our goal was to create centers of excellence for this population of difficult to wean patients. Additionally we wanted to build a model that would set the standards of ventilator care delivery. We also created a resource website ventweaning.com to help families and clinicians better understand the role of the ventilator.

In 2008 we joined the Linde Group in a global initiative to provide state-of- the art complex ventilator care across the world. Our ventilator program is called REMEO (Latin for "I return Home"), our growth is fueled by success in the liberation of mechanically ventilated patients and our ability to design programs in various reimbursement models. For those who cannot wean we provide an enhanced quality of life and excellence in daily care.

Conclusion

PMV is a large and growing clinical, financial and psychosocial problem. PMV involves 50,000 to 70,000 patients per year at an annual cost of $6 billion to $7 billion to Medicare alone.

A number of sites are suitable for patients with PMV depending on their clinical stability, weanability and intensity of required services. SNF ventilator rehabilitation can be very successful and cost effective.

State controlled Medicaid funding is the core issue in access to SNF based ventilator care. With improved coverage access would be available for the vast majority of these patients.

A national coverage policy for patients requiring PMV as well as national standards of care should be developed for this rapidly growing population of patients.

A Predictive Model for Respiratory Syncytial Virus (RSV) Hospitalization Of Premature Infants Born At 33-35 Weeks Of Gestational Age, based on data from the Spanish FLIP study

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Abstract

Background: The aim of this study, conducted in Europe, was to develop a validated risk factor based model to predict RSV-related hospitalization in premature infants born 33-35 weeks' gestational age. Methods: The predictive model was developed using risk factors captured in the Spanish FLIP dataset, a case-control study of 183 premature infants born between 33-35 weeks' GA who were hospitalized with RSV, and 371 age-matched controls. The model was validated internally by 100-fold bootstrapping. Discriminant function analysis was used to analyse combinations of risk factors to predict RSV hospitalisation. Successive models were chosen that had the highest probability for discriminating between hospitalised and non-hospitalised infants. Receiver operating characteristic (ROC) curves were plotted.

Results: An initial 15 variable model was produced with a discriminant function of 72% and an area under the ROC curve of 0.795. A step-wise reduction exercise, alongside recalculations of some variables, produced a final model consisting of 7 variables: birth ±10 weeks of start of season, birth weight, breast feeding for ≤2 months, siblings ≥2 years, family members with atopy, family members with wheeze, and gender. The discrimination of this model was 71% and the area under the ROC curve was 0.791. At the 0.75 sensitivity intercept, the false positive fraction was 0.33. The 100-fold bootstrapping resulted in a mean discriminant function of 72% (standard deviation: 2.18) and a median area under the ROC curve of 0.785 (range: 0.768-0.790), indicating a good internal validation. The calculated NNT for intervention to treat all at risk patients with a 75% level of protection was 11.7 (95% confidence interval: 9.5-13.6).

Conclusions: A robust model based on seven risk factors was developed, which is able to predict which premature infants born between 33-35 weeks' GA are at highest risk of hospitalization from RSV. The model could be used to optimize prophylaxis with palivizumab across Europe.

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Background

Respiratory syncytial virus (RSV) causes a severe lower respiratory tract disease that results in substantial morbidity in premature infants.[1,2] Infants born up to 35 weeks' gestational age (wGA) lack the necessary pulmonary and immunologic development and function essential to combating infection.[3,4,5] It is estimated that 1-3% of previously healthy infants are hospitalized because of RSV infection,[6] whereas the RSV-hospitalisation rate ranges between 3.75% and 9.8% for infants born between 33-35 wGA.[1,7,8] Studies suggest that infants born between 33-35 wGA are at risk of developing severe RSV infection that can result in morbidity and health care resource utilization similar to infants born ≤32 wGA.[9,10] Additionally, RSV-related hospitalization in 32-35 wGA infants causes significant morbidity and healthcare utilization in the subsequent years.[11]

Palivizumab, a humanized monoclonal antibody, has been proven a safe and efficacious option to significantly reduce RSV disease in prematurely born infants up to and including 35 wGA.[12,13,14] Based on the findings of the pivotal Phase III trial (IMpact RSV Study),[12] palivizumab received European approval in 1999 for use in infants up to and including 35 wGA.[15] Despite the clinical evidence, only a few countries in Europe make passive immunoprophylaxis available to at-risk 33-35 wGA infants, as reflected in current national guideline and reimbursement policies.[16,17,18] Passive immunoprophylaxis for all infants born at 33-35 wGA is not financially viable. However, based on risk profile and a higher rate of RSV-related hospitalisation, a certain proportion of these infants may be legitimate candidates for prophylaxis.

Table 1. A comparison of the risk factors for RSV hospitalised and non hospitalised infants in the FLIP and Munich studies†

	FLIP [9]				Munich [8]			
	Hospitalised (n=186)	Non-hospitalised (n=367)	Odds Ratio (CI 95%)	P-value*	Hospitalised (n=20)	Non-hospitalised (n=357)	Odds Ratio (CI 95%)	P-value*
Birth ± 10 weeks of start of season	*136 (73.1%)*	*145 (39.5%)*	*4.16 (2.78-6.23)*	***<0.0001***	*12 (60.0%)*	*148 (41.5%)*	*2.12 (0.77-6.12)*	*0.1101*
Birth weight, kg[a]	*2.20 (0.38)*	*2.12 (0.42)*	-	***0.0419***	*2.14 (0.38)*	*2.11 (0.39)*	-	*0.7526*
Breast fed ≤ 2 months or not[§]	*146 (78.5%)*	*206 (56.1%)*	*2.85 (1.87-4.40)*	***<0.0001***	*18 (90.0%)*	*286 (80.1%)*	*2.23 (0.51-20.3)*	*0.3887*
Number of siblings ≥2 years	*1 (0-1)*	*0 (0-1)*	-	***<0.0001***	*1 (0-2)*	*0 (0-1)*	-	***0.0172***
Number of family with atopy[§]	*0 (0-0)*	*0 (0-0)*	-	***0.0117***	*12 (60.0%)*	*175 (49.0%)*	*1.56 (0.57-4.51)*	*0.3671*
Male gender	*117 (62.9%)*	*199 (54.2%)*	*1.43 (0.98-2.09)*	*0.0513*	*18 (90.0%)*	*177 (49.6%)*	*9.15 (2.13-82.14)*	***0.0003***
Number of family with wheeze	*0 (0-1)*	*0 (0-0)*	-	***0.0004***	-	-	-	-
Gestational age								
33 weeks	49 (26.3%)	77 (21.0%)	1.34 (0.87-2.07)	0.1554	4 (20.0%)	119 (33.3%)	0.50 (0.12-1.60)	0.3265
34 weeks	60 (32.3%)	139 (37.9%)	0.78 (0.53-1.15)	0.1935	11 (55.0%)	172 (48.2%)	1.31 (0.48-3.68)	0.648
35 weeks	77 (41.4%)	151 (41.1%)	1.01 (0.69-1.47)	0.9544	5 (25.0%)	66 (18.5%)	1.47 (0.40-4.44)	0.5544
Number of regular carers	2 (1-2)	2 (1-2)	-	**0.0377**	-	-	-	-
Furred pets at home	46 (24.7%)	68 (18.5%)	1.44 (0.92-2.25)	0.0885	-	-	-	-
Educational level of parents								
No school	7 (3.8%)	4 (1.1%)	3.54 (0.89-16.71)	0.0711	-	-	-	-
Primary	53 (28.5%)	84 (22.9%)	1.34 (0.88-2.04)	0.1491	-	-	-	-
High school	78 (41.9%)	156 (42.5%)	0.98 (0.67-1.42)	0.8978	-	-	-	-
University	48 (25.8%)	123 (33.5%)	0.69 (0.45-1.04)	0.0639	-	-	-	-
Number of births in delivery	1 (1-2)	1 (1-2)	-	0.531	1 (1-1)	1 (1-2)	-	0.1675
Smoking during pregnancy[b]	56 (30.3%)	79 (21.5%)	1.58 (1.03-2.40)	**0.0241**	-	-	-	-
Number of smokers around infant[c]	1 (0-2)	1 (0-2)	-	0.062	0 (0-1)	0 (0-1)	-	0.9479
Number of family with asthma	0 (0-0)	0 (0-0)	-	0.1114	-	-	-	-

The 8 variables used in the final model are shown in italics. All variables were used in the initial 15 variable model
† Mean (standard deviation), median (P25-P75), number (%)
* Student's *t* test, Mann-Whitney *U* test, χ^2 test
§ Recorded as breast fed yes/no and atopy yes/no for Munich
a 2 missing values for FLIP, 5 missing values for Munich
b 1 missing value for FLIP
c 2 missing values for Munich

A comprehensive review of the literature revealed environmental and demographic risk factors that predispose infants to developing severe RSV leading to hospitalization.[19] Subsequent prospective studies in Spain,[9] Canada,[7] and Germany[20] examined those risk factors in infants born 33-35 wGA. The risk factors identified include: chronological age, number of siblings/ contacts, history of atopy, absence/duration of breastfeeding, postnatal cigarette smoke exposure, male sex, and day care attendance.[7,9,20] Despite these data, no predictive tool that can identify infants most at risk of RSV-hospitalization has been developed. We have developed an objective, evidence-based model to assist clinicians to predict the likelihood of RSV hospitalisation in European infants born 33-35wGA. Such a model would facilitate the effective and responsible application of passive immunoprophylaxis in this population.

Methods

Population used for modeling: The predictive model was derived from the Spanish FLIP dataset,[9] a prospective, case-control study, which aimed to identify those risk factors most likely to lead to the development of RSV-related hospitalization among premature infants born at 33-35 wGA. The dataset comprises 186 cases and 371 age-matched controls recruited from 50 centres across Spain during the 2002/2003 RSV season (Oct. 2002-Apr. 2003).

Criteria for inclusion as a case included: GA between 33-35 weeks, discharge during the RSV season (or age ≤6 months at the start of the RSV season), and proven RSVrelated hospitalisation. Controls were selected from premature infants born or discharged from the same hospital, during the same time period, and within the same GA limits as cases, but who had not been previously hospitalized for any acute respiratory illness during the RSV season. Additionally, although not a criterion for study exclusion, no infant had chronic lung disease.

Statistical methodology: Discriminant function analysis[21] was used to build the predictive model. Univariate analyses included the Student's t test, the χ^2 test, the Mann-Whitney's U test, and the calculation of odds ratios (with 95% confidence intervals). The model was internally validated using bootstrapping methods.[22] All data were analyzed by SPSS software (version 10).[23] Records with missing values for one or more of the predictor variables were excluded from the analyses.

Development of a model to predict RSV-related hospitalisation of infants 33-35 wGA: All the available risk factors collected in the FLIP study were included in the discriminant analysis. The discriminant analysis established how well the presence or absence of certain risk factors was able to separate infants in the hospitalized group from those in the non-hospitalized group (generating a discriminant function).

Following the development of an initial model, backward selection was used to remove the variables that contributed least to the discriminant function. The elimination of a variable from the analysis was based on a comparison of the discriminant power of the function derived with and without the variable. At each stage, the functions for each reanalysis were compared to identify the most discriminatory.

Table 2. Analyses of the predictive accuracy of the various models.

	True Positive	False Positive	False Negative	True Negative	Sensitivity	Specificity	PPV %	NPV %	LR	Diagnostic Accuracy %
FLIP 15 variable model[§]	130	102	53	265	0.71	0.72	56	83	2.56	72
FLIP Final 7 variable model[¤]	139	113	45	254	0.76	0.69	55	85	2.45	71
Munich 6 variable model[†]	14	106	4	247	0.78	0.70	12	98	2.59	70

[§] Records for 550 infants were included within the analysis. Seven records were dropped from the analysis due to missing data for one or more of the predictor variables
[¤] Records for 549 infants were included within the analysis. 8 records were dropped from the analysis due to missing data for one or more of the predictor variables
[†] Records for 370 infants were included within the analysis. Three records were dropped from the analysis due to missing data for one or more of the predictor variables. Two records for hospitalised cases were removed from the analysis, as they each had one negative RSV test
PPV = positive predictive value
NPV = negative predictive value
LR = likelihood ratio of a positive test; for information about likelihood ratios see reference 25
Standardised canonical discriminant function coefficients for the FLIP final 7 variable model: birth ± 10 weeks of start of season=0.678, birth weight, kg=0.184, breast fed ≤ 2 months or not=0.511, number of siblings ≥2 years=0.489, number of family with atopy=0.151, female sex=-0.113, number of family with wheeze=0.125

Receiver operator characteristic (ROC) curves were constructed by plotting the sensitivity against 1- the specificity. The area under the curve was calculated for each ROC plot, with areas closer to 1 representing better predictive accuracy. To explore diagnostic accuracy, positive predictive values (PPV), negative predictive values (NPV), and likelihood ratios were generated.[24,25] Additionally, example numbers needed to treat (NNT) were calculated.

Validation of the predictive model: The FLIP dataset was subject to 100-fold bootstrapping validation.[22] For each of the 100 samples, coefficients for each predictor variable were calculated. The 100 coefficient sets were then used to derive predictor functions on 100 replicates of the original data. The correct prediction of RSV-related hospitalization was calculated and ROC curves were plotted for each of the 100 outputs. The distribution of correct prediction rates and areas under the ROC curve were then assessed. To test for normality in the distribution of correct prediction rates and areas under the ROC curve, the Kolmogorov-Smirnov test was used.[26] The results were also tested for skewness.

Test of the predictive model against an external dataset: Despite extensive investigation, there were no suitable European datasets available against which the model could be fully externally validated. Therefore, to gain a measure of the applicability of the model to other European populations, the model was tested against data from the Munich RSV study.[8] The Munich RSV study, a population based cohort study, examined the incidence and risk factors for RSVrelated hospitalisation of premature infants born ≤35 wGA. Questionnaires were sent to all parents of infants discharged from primary neonatal care to determine the event of rehospitalization for acute respiratory infections. A total of 717 infants were studied, 375 of whom were born between 33-35 wGA and were used in the validation.

There were 37 RSV-related hospitalisations (5.2%) overall and 20 amongst the 375 preterms of 33-35 wGA (5.3%). Of the 20 RSV-related hospitalisations, six had a confirmed diagnosis of RSV, with the remaining 14 cases being classified as having a clinical suspicion of RSV, although two had a negative RSV test on one occasion. The two infants with a negative RSV test were excluded from the analysis.

The predictive function derived from the FLIP dataset was tested in two ways against data from the Munich RSV study. Firstly, the predictive variables identified from the FLIP dataset were used to generate a discriminant function from the data of the Munich RSV study itself. Secondly, the non-normalised coefficients (derived from unadjusted variable data) generated from the FLIP dataset were applied to the Munich data.

Prior to testing, the final model had to be adjusted to account for differences in the data captured within the FLIP study and that which were captured within the Munich RSV study. The variable, "number of family members with wheeze" had to be removed, as this was not available in the Munich dataset, the variable "breast fed for ≤2 months or not" had to be modified to "breast fed Yes/No," and the variable "number of family members with atopy" had to be changed to a categorical "family member with atopy Yes/No."

Test of the predictive model against the Spanish Guidelines recommendations for prophylaxis of 32-35 wGA infants: To put the clinical usefulness of the model into perspective, its predictive ability was compared to that based on the Spanish Neonatal Society Guidelines[16] recommendations for prophylaxis of infants born 32-35 wGA. The Spanish Guidelines[16] recommend that premature infants born 32-35 wGA who are ≤6 months old when the RSV season starts and have two risk factors (less than 10 weeks when RSV season starts, tobacco smoke at home, daycare assistance, no breastfeeding, family history of wheezing, school age siblings, and crowded homes [≥4 residents and/or visitors at home, excluding school age siblings and the subject him/herself]) receive prophylaxis with palivizumab. Using these criteria, a discriminant function was generated from the FLIP dataset, a ROC curve plotted, and diagnostic accuracy tested. The results from this analysis were then compared to the results for the model.

Results

Development of the predictive model: The 15 variables in the

Table 3. Final seven variable model number needed to treat analyses*

ROC AUC plus confidence limits	True Positive Fraction	True positives treated	False Positive Fraction	False positives treated	NNT	NNT (80% efficacy)
0.791 (mid point)	0.75	75	0.33	627	9.4	11.7
0.751 (lower limit)	0.75	75	0.39	741	10.9	13.6
0.830 (upper limit)	0.75	75	0.26	494	7.6	9.5

*Number needed to treat (NNT) to prevent hospitalisation of 75% of at risk infants, assuming a 5% hospitalisation rate and 80% treatment efficacy (n=2,000)

Table 4 100-fold bootstrap statistics on the FLIP dataset

	Percentages correctly predicted	Areas under ROC curves (AUC)
Mean	72.00	0.784
Median	72.20	0.785
Standard deviation	2.18	0.004
Minimum	66.20	0.768
Maximum	77.40	0.790
Kolmogorov-Smirnov Z	0.56 (P=0.910†)	1.22 (P=0.101†)
Skewness statistic	0.19 (0.48§)	-1.20 (0.48§)

n= valid: 100, missing: 0
† Asymptotic significance (2-tailed)
§ 2 standard error of skewness

FLIP study are compared in the hospitalized and nonhospitalized infants in Table 1. In a univariate analysis of the FLIP data, hospitalized infants were significantly more likely to be born within 10 weeks of the start of the RSV season, be heavier at birth, have more family members with atopy or who wheezed, had more carers at home, had mothers who smoked during pregnancy, had more siblings ≥2 years of age, and were breast fed for ≤2 months or not at all.

The initial analysis of the FLIP dataset produced a function based on 15 risk factors, which could discriminate significantly between hospitalised and nonhospitalised infants. This function could correctly classify whether a child was hospitalized or not in 72% of cases (table 2). Importantly, the correct classification of hospitalised infants was 71%. The area under the ROC curve was 0.795 (Figure 1A).

The variable reduction exercise resulted in a final model of seven variables (table 1), with an area under the ROC curve very similar to that of the 15 variable model (Figure 1B). Discrimination also remained similar at 71%, with 76% of hospitalizations classified correctly (table 2). At the 0.75 sensitivity intercept, the specificity was 0.67, with the false positive fraction (FPF) being 0.33. The NNT to prevent hospitalization of 75% of at risk infants was calculated to be 11.7, assuming a 5% hospitalization rate (consensus of European RSV Risk Factor Study Group based on a review of the available data[1,7,8]) and 80%[12] treatment efficacy (table 3). At the point of maximum sensitivity/specificity the NNT was 10.7, again assuming a 5% hospitalization rate and 80% treatment efficacy (Figure 1). The likelihood ratio for this model was 2.45 and the PPV and NPV were 55% and 85%, respectively.

Contribution of individual variables: A variable reduction exercise on the 7 variable model showed that, although some variables were more important than others, removing any variable produces a decrease in discrimination and/or area under the ROC curve. For example, removing "sex" reduced the area under the ROC curve to 0.789 (Figure 1D). On this basis, no clear case could be made for removing any of the constituent seven variables. Thus, the final seven variable model includes: birth within 10 weeks of the start of season, birthweight, breast-fed for ≤2 months or not, number of siblings ≥2 years, number of family members with atopy, male sex, and number of family members with wheeze.

Validation: The bootstrapping analysis resulted in a tight symmetrical distribution of results for the 100 calculations of percentage correctly predicted and area under the ROC curve (table 4). The mean percentage of cases predicted correctly was 72% (standard deviation [SD]: 2.18) and the median area under the ROC curve was 0.785 (range 0.768-0.790). The Kolmogorov-Smirnov test indicated that the distribution of results for the correct prediction of outcomes (asymptotic significance: P=0.910) and for the ROC curves (asymptotic significance: P=0.101) is assumed to be normal for the purposes of calculation. Calculation of the skewness statistic found no indication of skewness in the distribution of results for the correct prediction of outcomes (0.19, two standard errors of skewness [SES]: 0.48), but did find significant skewness in the area under the ROC curve results (-1.20, 2xSES: 0.48). However, a Q-Q plot for the areas under the ROC curve suggests that the deviation from normality was symmetrical (figure not shown). In summary, this means that two SDs for the correct prediction of hospitalization (2x2.18 = 4.36) can be take as the 95% CI for the results ie 72% ± 4.36.

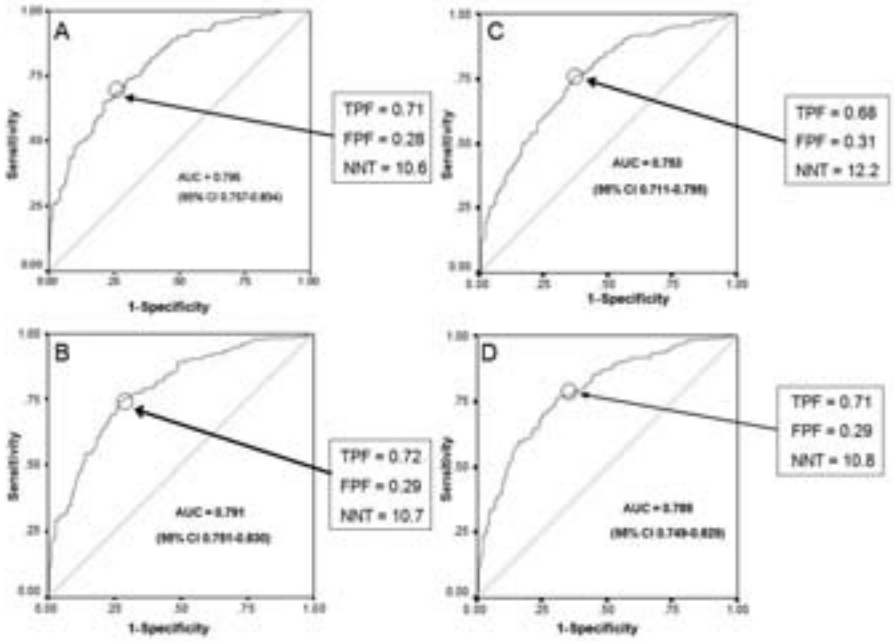

Figure 1. Receiver operating characteristic (ROC) curves for 15 variable model (A), final 7 variable model (B), 6 variable model for Munich test (C), and 6 variable model with sex removed (D).

The number needed to treat (NNT) at the point of maximum sensitivity/specificity is based on a hospitalisation rate of 5% and a treatment efficacy of 80%. Each point on the ROC curve represents a case being either a true positive or a false positive, based on their discriminant score. CI = confidence interval; TPF = true positive fraction; FPF = false positive fraction.

External Test: The Munich dataset did not include numbers of family members with wheeze, so coefficients obtained for the remaining six variables of the seven variable model were used. The recalculated six variable model was somewhat weaker than the seven variable model defined earlier. However, its power, derived by running the model on the FLIP data, was adequate for running the validation tests (correct classification: 68%; area under ROC curve 0.753 (Figure 1C).

When we used the six variables identified in the FLIP study to derive coefficients from the Munich dataset, the function derived solely from the Munich data was comparable to that obtained with the FLIP dataset (correct classification: 70% [table 2]; area under ROC curve 0.812, 95% CI 0.737-0.887). Applying the FLIP derived coefficients (from the seven variable model) to the Munich data produced a function that could correctly classify 64% of cases, with an area under the ROC curve of 0.677 (95% CI 0.551-0.804).

Spanish Guidelines Test: The discriminant function based on the guidelines recommendations could correctly classify 38% of cases, which is no better then chance, and had an area under the ROC curve of 0.520 (95% CI 0.468-0.573). The PPV was 36%, the NPV 100%, and the likelihood ratio 1.04. (It is worth remembering that a completely nondiscriminatory test that selects all patients for treatment except one, would have a NPV of 100% if this patient were truly negative.) Based on a 5% hospitalization rate and 80% efficacy, the NNT to prevent hospitalization of 75% of at risk infants was calculated to be 24.7.

Discussion

We have developed and validated a robust European predictive model to identify the risk of RSV-related hospitalization in infants born between 33-35 wGA. The FLIP 7-variable model correctly classifies over 70% of cases, which, to put into context, compares to a figure of 38% when using the Spanish Guidelines[16] for prophylaxis. The predictive ability of the model was confirmed through validation. The tight symmetrical distributions for both the correct predictions of hospitalization and area under the ROC curve results and the mostly convex nature of the ROC curve demonstrate that the model is not skewed by outliers in the FLIP dataset and is, therefore, highly reproducible however the data may be sampled. This lends a high degree of confidence to the model derived from the FLIP dataset.

The seven variables used in the final model were: birth within 10 weeks of the start of season, birth weight, breastfed for ≤2 months or not, number of siblings ≥2 years, number of family members with atopy, male sex, and number of family members with wheeze. All of these variables have been documented as risk factors for RSV-related hospitalization.[7,19,20,27] Indeed, a critical evaluation of the literature concluded that "male sex" and "crowding/siblings" were significant risk factors for severe RSV lower respiratory tract infection.[19] However, the same review also reported that a lack of breast feeding did not appear to increase the risk of severe RSV lower respiratory tract infection or RSV-related hospitalization.[19] A recently published nested case-control study supports that familial atopy and wheezing are strong determinants of RSV-related hospitalization.[27]

The strength and utility of the FLIP 7-variable model was highlighted by an examination of NNT. Assuming a 5% hospitalization rate and 80% treatment efficacy, the calculated NNT to prevent hospitalization of 75% of at-risk patients was 11 (range 10-14). A NNT of 11 is better than half the result if infants are prophylaxed based on the Spanish Guidelines recommendations[16] (25) and is considerably lower than the 17 obtained from using the raw numbers of the IMpact-RSV trial.[12]

Although various analytical approaches were considered, it

was decided to develop the model using discriminant function analysis. This approach produced similar results to logistic regression, but was arguably more applicable in the manipulation involved in validation, such as handling missing values and continuous data. Further, models derived from discriminant function analysis can benefit from the inclusion of variables that are not independently significant, but which contribute to the overall predictive ability of the model. Indeed, the discriminatory power of such models is always greater than that afforded by the simple sum of its component parts. To exemplify this, one of the seven variables in the final model was not independently significant (male sex), but is a well known risk factor.[19] The model also has good flexibility, as the sensitivity and specificity along the ROC curve can easily be varied such that different cutoff points can be selected and NNTs calculated according to the needs of the individual European country.

As is the case whenever developing such a model, limitations were imposed by what and how data were captured within the base dataset. Although the FLIP study[9] contained a great deal of information on risk factors and hospitalization rates for children born between 33-35 weeks' GA, it was limited by being a case-control study. Since RSV infection had to be proven and these were likely to have been the most severe cases, this might have lead to selection and, therefore, bias in the dataset. Further, allowance had to be made for the variability in admission criteria for the various hospitals across Spain. Finally, since day care attendance is not commonly practiced in Spain, there were limited data on this variable and it was not included in the final analyses.

External validation of the model presented a challenge as there were no suitable databases in Europe that were available for such a purpose. As a surrogate, the model was tested against data from the Munich RSV study. Allowances have to be made for the differences in how the study was conducted and what data were captured compared with FLIP. For example, no data were captured on wheeze in the Munich study. Perhaps most significantly, data were available for only 20 hospitalized infants within the Munich study. Further, only six of the hospitalized infants had a confirmed diagnosis of RSV, as testing is not routine in Germany. Taking these differences into consideration, the test can be considered a worse case scenario, as it would be not be expected for the model to validate particularly well against the Munich data. However, despite these significant limitations, the FLIP model tested very well against the Munich data. Nevertheless, rigorous external validations of the model are planned when suitable prospective data become available within Europe over the next couple of years.

A recently published Dutch model,[28] which estimated the monthly risk of hospitalization, reported that gender, GA, birth weight, presence of bronchopulmonary dysplasia, age, and seasonal monthly RSV pattern were significant predictors and could potentially be used to discriminate between high and low risk children. The Dutch model included only risk factors that were reported as independently significant in the published literature. In comparison, all risk factors available within the FLIP dataset were included within our modelling, regardless of their individual significance. In addition, the Dutch model does not specifically address the group we are trying to predict RSV-related hospitalisation within, namely, those infants born 33-35 wGA without CLD. Finally, the Dutch model imputed missing values, whereas in the development of the FLIP model, patients with incomplete records were excluded from the analyses. Several other studies have proposed using identified risk factors to predict RSV hospitalization in premature infants;[7,20,29] however, as far as the authors are aware, no other models or scoring systems have been formally published.

Importantly, although the significance of the individual risk factors may vary between countries, the validation and testing process indicates that the model may be applicable for widespread use across Europe. Moreover, the model appears flexible yet robust enough that, if necessary, individual variable parameters can be modified to suit the needs and of individual countries. Further, although the model is suitable for adoption as it stands, countries could use their own data, either existing or prospectively collected, to refine a predictive tool. When considering intervention levels within a predictive tool, variation in hospitalization rates for RSV across different countries would not affect the performance of the model in terms of prediction, as this is not factored into the analysis.

The model could be realized as a working tool in a variety of formats to optimize its applicability to an individual country, or, indeed, an individual unit. Formats could potentially include a bespoke software application, a website, a simple spreadsheet, or even a paper-based form or nomogram. The big advantage of a software application or website is that either could prospectively capture risk factors and outcomes data, which could be used to further refine and validate the model and justify its continuing use. The tool itself would be used in daily practice to predict the risk of RSV-related hospitalization for individual infants. Chronic conditions such as CLD, congenital heart disease, and severe neurological diseases may further increase the risk of RSV-related hospitalisation, and, therefore, should always be taken into consideration when using the tool.

Conclusions

By using data from the Spanish FLIP study[9] and carrying out validation, we have produced an evidence-based model which is applicable for adaptation and use in different countries across Europe. The model has the potential to improve standards of care by better identifying high risk infants and, thus, optimizing prophylaxis. It may also be used to inform guidance and to help clarify the justification of funding and reimbursement for palivizumab within health services. Finally, this study has led to a better understanding of the risk factors and their interrelationships for infants born between 33-35 weeks' GA.

References

1 Simoes EAF: Immunoprophylaxis of respiratory syncytial virus: global experience. Respir Res 2002;3(Suppl 1):S26-S33.
2 Law BJ, MacDonald N, Langley J, Mitchell I, Stephens D, Wang EEL, Robinson J, Boucher F, McDonald J, Dobson S: Severe respiratory syncytial virus infection among otherwise healthy prematurely born infants: what are we trying to prevent? Paediatr Child Health 1998;3:402-404.
3 Yeung CY, Hobbs JR: Serum-gamma-G-globulin levels in normal premature, post-mature, and "small-for-dates" newborn babies. Lancet 1968;7553:1167-1170.
4 Langston C, Kida K, Reed M, Thurlbeck WM: Human lung growth in late gestation and in the neonate. Am Rev Respir Dis 1984;129:607-613.
5 de Sierra TM, Kumar ML, Wasser TE, Murphy BR, Subbarao EK: Respiratory syncytial virus-specific immunoglobulins in preterm infants. J Pediatr 1993;122:787-791.

6 Simoes EA: Respiratory syncytial virus infection. Lancet 1999;354(9181):847-852.
7 Law BJ, Langley JM, Allen U, Paes B, Lee DS, Mitchell I, Sampalis J, Walti H, Robinson J, O'Brien K, Majaesic C, Caoette G, Frenette L, Le Saux N, Simmons B, Moisiuk S, Sankaran K, Ojah C, Singh AJ, Lebel MH, Bacheyie GS, Onyett H, Michaliszyn A, Manzi P, Parison D: The pediatric investigators collaborative network on infections in Canada study of predictors of hospitalization for respiratory syncytial virus infection for infants born at 33 through 35 completed weeks of gestation. Pediatr Infect Dis J 2004;23:806-814.
8 Liese JG, Grill E, Fischer B, Roeckl-Wiedmann I, Carr D, Belohradsky BH: Incidence and risk factors of respiratory syncytial virus-related hospitalizations in premature infants in Germany. Eur J Pediatr 2003;162:230-236.
9 Figueras-Aloy J, Carbonell-Estrany X, Quero J, IRIS Study Group: Case-control study of the risk factors linked to respiratory syncytial virus infection requiring hospitalisation in premature infants born at a gestational age of 33-35 weeks in Spain. Pediatr Infect Dis J 2004;23(9):815-820.
10 Horn SD, Smout RJ: Effect of prematurity on respiratory syncytial virus hospital resource use and outcomes. J Pediatrics 2003;143(5 Suppl):S133-141.
11 Sampalis JS: Morbidity and mortality after RSV-associated hospitalizations among premature Canadian infants. J Pediatr 2003;143:S150-S156.
12 IMpact-RSV Study Group: Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. Pediatrics 1998;102:53-537.
13 Feltes TF, Cabalka AK, Meissner C, Piazza FM, Carlin DA, Top FH jr, Connor EM, Sondheimer HM, Cardiac Synagis Study Group: Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. J Pediatr 2003;143:532-540.
14 Pedraz C, Carbonell-Estrany X, Figueras-Aloy J, Quero J, IRIS Study Group: Effectiveness of palivizumab prophylaxis in decreasing syncytial virus hospitalizations in premature infants. Pediatr Infect Dis J 2003;22:823-827.
15 European Medicine Agency. Synagis European Authorisation. [http://www.emea.europa.eu/humandocs/Humans/EPAR/synagis/synagis.htm] Accessed 17/09/08.
16 Figueras AJ, Quero J, Domenech E, Comite de Estandares de la Sociedad Espanola de Neonatologia.: [Recommendations for the prevention of respiratory syncytial virus infection]. An Pediatr (Barc) 2005;63:357-362.
17 Rondini G, Macagno F, Barberi I: Raccomandazioni della Società Italiana di Neonatologia per la prevenzione delle malattie da virus respiratorio sinciziale (VRS). Acta Neonantologica 2004;1:1-11.
18 Deutsche Gesellschaft für Pädiatrische Infektiologie (DGPI). Stellungnahme zur Prophylaxe von schweren RSV-Erkrankungen bei Risikokindern mit Palivizumab. [http://www.dgpi.de/pdf/Leitlinie_Palivizumab_27Okt2006.pdf.] Accessed 04/12/07.
19 Simoes EAF: Environmental and demographic risk factors for respiratory syncytial virus lower respiratory tract disease. J Pediatr 2003;143:S118-S126.
20 Doering G, Gusenleitner W, Belohradsky BH, Burdach S, Resch B, Liese JG: The risk of respiratory syncytial virus-related hospitalizations in preterm infants of 29 to 35 weeks gestational age. Pediatr Infect Dis J 2006;25:1188-1190.
21 Fisher RA: The Use of Multiple Measurements in Taxonomic Problems. Annals of Eugenics 1936;7:179-188.
22 Efron B, Tibshirani RJ: An introduction to the bootstrap. Chapman and Hall, London. 1993.
23 SPSS Inc. 444 N. Michigan Avenue, Chicago, IL 60611.
24 Altman DG, Bland JM: Diagnostic tests 2: predictive values. Statistical Notes. BMJ 1994;309:102.
25 Deeks JJ, Altman DG: Diagnostic tests 4: likelihood ratios. Statistical Notes. BMJ 2004;329:168-169.
26 Chakravarti IM, Laha RG, Roy J: Handbook of Methods of Applied Statistics. Volume I. John Wiley and Sons, New York, pp. 392-394. 1967.
27 Stensballe LG, Kristensen K, Simoes EA, Jensen H, Nielsen J, Benn CS, Aaby P, the Danish RSV data Network: Atopic disposition, wheezing, and subsequent respiratory syncytial virus hospitalization in Danish children younger than 18 months: a nested case-control study. Pediatrics 2006;118(5):e1360-1368.
28 Rietveld E, Vergouwe Y, Steyerberg EW, Huysman MWA, de Groot R, Moll HA, the RSV Study Group Southwest Netherlands: Hospitalization for respiratory syncytial virus infection in young children: development of a clinical prediction rule. Pediatric Infectious Disease Journal 2006;23(3):201-207.
29 Rossi GA, Medici MC, Arcangeletti MC Lanari M, Merolla R, Paparatti UD, Silvestri M, Pistorio A, Chezzi C, Osservatorio RSV Study Group: Risk factors for severe RSV-induced lower respiratory tract infection over four consecutive epidemics. Eur J Pediatr 2007;166(12):1267-1272.

Prevalence of Latent Tuberculosis Infection Among Health Care Workers in a Hospital for Pulmonary Diseases

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Abstract

Background: Little is known about the prevalence of latent tuberculosis infections (LTBI) in health care workers (HCW) in low-incidence countries especially in hospitals for pulmonary diseases. With Interferon-gamma release assays (IGRA), a new method for diagnosis of LTBI is available which is more specific than the tuberculin skin test (TST).

Objectives: The study was designed to estimate prevalence of LTBI among 270 HCW in a Hospital of Pulmonary Diseases routinely screened for TB.

Methods: LTBI was assessed by the QuantiFERON-Gold In Tube (QFT-IT). Information on gender, age, workplace, job title, BCG vaccination and history of both TB and TST were collected using a standardized questionnaire. Adjusted odds ratios for potential risk factors for LTBI were calculated.

Results: The prevalence of LTBI was 7.2%. In HCW younger than 30 years LTBI prevalence was 3.5% and in those older than 50 years 22%. Physicians and nurses showed a higher prevalence rate than other professions (10.8% to 4.5%). The putative risk factors for LTBI were age (>50 year OR 9.3, 95% CI 2.5-33.7), working as physicians/nurses (OR 3.6, 95%CI 1.2-10.4) and no previous TST in medical history (OR 4.4, 95% CI 1.01-18.9) when compared to those with a negative TST.

Conclusions: Prevalence of LTBI assessed by QFT-IT is low, this indicates a low infection risk even in hospitals for pulmonary diseases. No statement can be made regarding the occupational risk as compared to the general population because there are no LTBI prevalence data from Germany available. The higher LTBI prevalence rate in older HCWs might be due to the cohort effect or the longer time at risk.

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Background

Germany is a country that developed from a high tuberculosis incidence country to a low incidence country during the last 50 years. Since the 1950s, the number of new tuberculosis (TB) cases in Germany decreased from 9.064 newly diagnosed TB cases in the year 2000 (Federal Department of Statistics, 2000) to 5.402 in 2006.

The introduction of effective control and preventive measures against tuberculosis transmission, the advent of an effective treatment for tuberculosis and the concurrent long-term downwards trend of tuberculosis incidence substantially decreased the occupational risk among healthcare workers. Currently, in industrialized countries such as Germany, occupational tuberculosis among HCWs is re-emerging as an important public health issue, because of the resurgence of tuberculosis epidemic in former Soviet Union (NIS) states, the emergence of multidrug-resistant strains of mycobacteria especially in these countries and increasing migration from exactly these countries. Furthermore, the occurrence of TB as a co-infection to HIV especially in the US has resulted in a flare-up of the discussions about this work related infection risk and in the initiating of a large number of related epidemiological studies. In addition, molecular epidemiological studies have shown that even in countries with a low TB incidence, 30 to 40% of all cases are cases of "newly transmitted TB."

In high-income countries (HIC) relatively few LTBI prevalence surveys have been published since 1990. Findings were consistent with earlier surveys in that the median prevalence of positive TST was 24% with a range from 4% to 46. So far, these conventional studies on prevalence of LTBI in HCW used the TST and were thus hampered by the low specificity of the TST and its cross-reactivity with BCG and nontuberculous mycobacteria (NTM) infections.

The M tuberculosis-specific interferon-gamma (IFN-y)-based diagnostic tests may improve this situation. Two IGRAs, Quantiferon-TB and the T-spot TB are now commercially available. The third generation of the Quantiferon test (Quantiferon®TB Gold In-Tube, QFT-IT) measures in vitro IFN-y production by the Tcells during in vitro stimulation with peptides of the M. tuberculosis-specific antigens of the region of

Table 1: Description of the Study Population

Variable		N	%
Gender	Female	196	74
	Male	69	26
Age*	< 30 years	115	43.4
	30 - < 40 years	41	15.5
	40 - < 50 years	68	25.7
	50 - 67 years	41	15.5
Country of birth	Germany	214	80.8
	foreign country	51	19.2
BCG-vaccination	No	125	47.2
	Yes	140	52.8
TST history	No TST in medical history	33	12.5
	Negative TST in history	151	57
	Positive TST in history	81	30.6
Job category	Nurse	94	35.5
	Physician	17	6.4
	Other professions	154	58.1
QFT-IT	Negative	246	92.8
	Positive	19	7.2
	Admission ward	18	6.8
Workplace	Infection ward	110	41.5
	Other	137	51.7
Reason for testing	Serial examination	246	92,8
	Contact tracing	19	7,2
Total		265	100

* mean age 34.7, standard deviation 12.6

difference (RD-1) ESAT-6, CFP-10 and TB7. These antigens are not shared by any of the BCG vaccine strains nor by the more common species of NTM (e.g. M. avium). Available evidence reviewed elsewhere suggests that these Interferon-y release assays have higher specificity and at least equal sensitivity as the TST and are unaffected by previous BCG vaccination and most NTM. Therefore this test reduces the risk of LTBI overestimation due to crossreactions with BCG vaccination or exposure to environmental mycobacteria.

So far only few studies have investigated the prevalence of LTBI in HCWs in low incidence countries with the new in-vitro tests. These prevalence rates are much lower than those assumed for German HCW so far.

Employees in hospitals for pulmonary diseases are among those individuals who are routinely screened for TB as stipulated by German OSH legislation. It is assumed that this occupational field bears an increased risk of M. tuberculosis infection for the employees because their institutions frequently treat TB patients.

Out of 247 hospital workers of a German Hospital for Pulmonary Diseases in Großhansdorf on average 1 TB case per year occurred in the 30 years from 1950 to 1079. Most TB-cases appeared at medically technical professions (31.3%) followed by doctors (23%), nurses (13.6%) and other non-medical professions. While for the general German population a sharp decrease in TB incidence was observed in this time period there was no significant decrease in TB incidence in the hospital staff. According to the authors this indicated a "strong, flowing source of infection." This hospital is still the referral center for TB treatment in Hamburg. Therefore we analyzed the prevalence of LTBi in the staff of this hospital with the QFT-IT in order to assess the strength of the "source of infection" more than 25 years later.

Methods

We conducted a cross-sectional study in a hospital for pulmonary disease in the northern part of Germany. The clinic has three wards specialized in pneumology, pneumology/oncology, and thoracic surgery, with a total capacity of 213 beds. About 8,500 in-patients and 4,500 out-patients from all over Northern Germany are treated each year. The clinic has 350 staff members (40 physicians, 150 nurses, 80 employees in the areas of radiology, pulmonary function, laboratory etc. plus 20 in anesthesia/surgery. One of the treatment foci is tuberculosis. 60 TB patients are treated per year, 95% of them presenting with infectious pulmonary TB. Up to 10% of these TB-cases were drug resistant, particularly MDR, and up to 3 cases were multi drug resistant (XDR). 75% of the TB patients treated per year are referred without a diagnosis or suspicion of TB. Only 25% of the patients were already diagnosed or referred with the suspicion of TB. These patients were isolated on arrival. The clinic has a special TB-ward but no engineering controls such as ventilation and UN light. The study population consisted of HCWs tested between December 2005 and January 2008, either in the course of a contact tracing or in serial testing of TB high risk groups following German OSH legislation (Biostoffverordnung). A total of 270 HCW were enrolled in the study. There were no exclusion criteria for study participants.

For the IGRA, the QuantiFERON-TB Gold In-Tube test was used (Cellestis Limited, Carnegie, Australia). This whole-blood assay uses overlapping peptides corresponding to ESAT-6, CFP-10, and a portion of tuberculosis antigen TB7. (Rv2654). Stimulation of the antigenic mixture occurs within the tube used to collect the blood. Tubes were incubated at 37 C overnight before centrifugation, and INF-y release was measured by ELISA following the protocol of the manufacturer. All the assays performed met the manufacturer's quality control standards. The test was considered positive if INF-y was ≥0.35 UI/ml after correction for the negative control.

Information on the following variables was collected using a standardized questionnaire: age, gender, reason for testing, occupational exposure to TB, time of occupation in health care sector, reason for testing, family history of TB, BCG vaccination, place of birth, prior TST, job title, workplace and chest radiographic findings. BCG vaccination was verified by scars or vaccination records.

The study protocol was approved by the ethics committee of the Hamburg Medical Council. All persons gave their written informed consent prior to their inclusion in the study.

Data analysis was performed using SPSS, Version 14 (SPSS Inc, Chicago, IL). The study population comprises 270 HCWs, which means that more than two thirds of the hospital staff were examined. Due to indeterminate QFT-IT result 5 HCWs (1.9%) were excluded from the analysis. Adjusted Odds ratios for QFT-IT depending on different putative predictive variables were calculated using logistic regression. Model building was performed backwards using the chance criteria for variable selection.

Results

The mean age of the participants was 24.7 ± 12.6 years. The majority of the participating HCWs (74%) were female and the mean age was 24.7 years (SD ± 12.6). A history of BCG vaccination was recorded for 52.8% of the participants. 19.2%

of the study population were born outside Germany or had a history of migration and 80.2% of the study population were born in Germany (table 1). Most of the foreign-born participants came from Turkey, former Soviet Union (NIS) states and Eastern Europe, e.g. Poland and Bulgaria. 25.5% of the employees with a history of migration were physicians or nurses. The vast majority worked in non-medical areas, for example as cleaner (56.9%). None of the foreign-born physicians/nurses was QFT-IT positive. 35.35% of the total study population were nurses, 6.4% physicians and 58.1% were professions in health care sector or non-medical staff including cleaners, transportation service staff, physiotherapists, interns, radiology staff, conscientious objectors, apprentices and administrative staff. In the subgroup other professions only two persons with direct patient contact (one physiotherapist and one radiology staff member) are included. These two persons were positive by QFT-IT but either 5 cleaners and administrative staff members were QFT-IT positive (data not shown). 92.8% (n=246) of the HWCs were investigated because of serial examinations of high risk groups following the German OSH legislation (Biostoffverordnung) and 19 (7.2%) of these participants were positive by QFT-IT. 19 HCWs were investigated in course of contract tracing but nobody in these group was positive by QFT-IT (table 1).

A positive QFT-IT result was observed in 19 (7.2%) participants and 81 participants reported a positive previous TST (table 1). Out of 33 participants with no TST in their medical history, 4 persons (12.1%) were now positive by QFT-IT (TB-antigen-Nil range from 0,44 to 1,50). Of the 81 participants positive in a previous TST, 10 (12.3%) were confirmed by the IGRA (TB-antigen-Nil range from 0,46 to 270,2) (no table). The prevalence of LTBI assessed by QFT-IT correlated with age. In the subgroup with participants under 30 years old, LTBI prevalence was 3.5%. In the subgroup with participants between 50-67 years the prevalence increased to 22%. LTBI prevalence was higher in physicians and nurses (10.8%) than in other areas of occupation (4.5%) within the hospital. In the wards of pulmonology/ infectious diseases, QFT-IT was less often positive than in the admission ward (3.6 versus 11%). However, the differences were not statistically significant.

The putative risk factors for a positive QFT-IT were age (>50 year OR 7.7, 95% CI 2.1-28.2) and working as a physician/nurse (OR 3.2, 95%CI 1.1-9.0). Using the subgroup with a negative TST in history as comparison group, the odds ratio for those with no previous TST in medical history was elevated (OR 4.4, 95% CI 1.01-18.9). The latter statistically significant association was observed after adjustment for age and job category, it did not show in the crude data. No statistically significant association was observed for gender, BCG vaccination, workplace and migration. All participants with a positive QFT-IT were offered a clinical and radiologic examination to rule out active TB. None of them showed any clinical or radiological sign of active TB disease and hence no further action was taken.

Discussion

In this study, we have found that the prevalence of LTBI assessed by QFT-IT is low and it is considerably lower than assumed in the past. With the IGRA we have, for the first time, a test that allows for valid statements regarding the LTBI prevalence, infection risk and disease probability.

Only few studies in low-incidence countries have so far employed the IGRA as a screening instrument in health care workers. In accordance with the literature, Nienhaus et al investigated 261 HCWs from different types of hospitals who are routinely screened for TB as stipulated b German OSH legislation using QFT-IT and TST following the German Guidelines with a cut off >5 mm. LTBI prevalence assessed by QFT-IT was 9.6% compared to 24.1% with TST. Furthermore, Soborg and colleagues used QFT-Gold TB to test 139 HCWs at two departments for infectious diseases in Copenhagen. 105 HCW had direct patients contact and 34 HCW were employed with office work and had no daily patient contact. They found an LTBI prevalence rate of only 1% (n=2) as compared to 34% (n=47) with the TST (cut off >12mm); and this rate was much lower than the estimated prevalence (7.2%) in our study. Stebler et al also studied the prevalence of LTBI among hospital employees at the University Hospital of Berne using the IGRA. A total of 777 HCWs were investigated. A positive IGRA was found for 59 (7.6%). In addition Harada et al investigated the performance of the QFT-G for detecting LTBI by testing 332 HCWs in a Japanese general hospital and suggested a prevalence of LTBI of 9.9%. Kobashi and colleagues found a prevalence of LTBI of 3% among 109 HCWs who were examined during contact investigations. In the study among 95 HCWs working in departments of radiology, Barsegian et al observed a prevalence of LTBi of 1% using the T-SPOT in 95 German radiologists.

The relatively low rate of positive QFT-IT we found in HCWs in a German hospital for pulmonary diseases indicates a low infection risk even in this occupational area. Especially in working fields with an increased risk of TB exposure, effective control measures are an important tool to reduce TB transmission. Because TB treatment is one of the focus areas of hospitals for pulmonary diseases, it can be assumed that physicians and nurses are familiar with the appropriate protective measures. As patients are referred to the clinic after some clinical evaluation elsewhere, TB cases may be identified early or even before referral and effective control measures may be taken.

In this study, we found no indication for a “strong, flowing source of infection.” From 1950 to 1979 a total of 29 employees of the Pulmonary Hospital of Gro hansdorf developed active TB while the overall TB incidence in the general population was decreasing. The authors concluded that he staff of this hospital was exposed to a greater risk than the population of Germany or other industrialized countries. In the scope of the present examination, none of the employees developed active TB in the observation time of 1 year. Only 7.2% of the employees were QFT-IT positive. This may indicate further improvement of the TB control measures.

In contrast to our findings, three molecular biological studies have found a job-related exposure to TB for HCWs. First, a molecular biological fingerprint study from Hamburg/Germany (n=848) has shown that the risk of active TB for HCWs is not increased as compared to the general population. However when disease occurred, the infection is most probably due to job-related exposure. In the Hamburg fingerprint study, a total of 10 HCWs developed TB; a job-related infection was established in 8 of them (80%). Second, Ong et al failed to detect an increased TB rate among HCWs in San Francisco in their fingerprint study (n=2510). The proportion of clustered cases in HCWs (32%) was similar to that observed in the community (36%). In at least 10 (32%) of the HCWs, there was genotyping and/or epidemiological evidence of job-related transmission. Third, the objective of the

Table 2: Frequency and Adjusted Odds ratios (OR) and 95% Confidence Interval (95%CI) for Covariates associated with QFT-IT Results.
QFT-IT

Characteristics		negative N (%)	positive N (%)	Odds Ratio	95% CI
Gender**	female	182 (92.9%)	14 (7.1)	1	
	male	64 (92.8)	5 (7.2)	1.3	0.4-4.2
Age*	>30 years	111 (96.5)	4 (3.5)	1	
	30-40 years	39 (95.1)	2 (4.9)	1.2	0.2-7.0
	40-50 years	64 (94.1)	4 (5.9)	1.5	0.4-6.5
	50-67 years	32 (78.0)	9 (22.0)	7.7	2.1-28.2
Country of birth**	Germany	198 (92.5)	16 (7.5)	1	
	foreign born	48 (94.1)	3 (5.9)	0.9	0,2-3,3
Job Category*	other professions	147 (95.5)	7 (4.5)	1	
	physician/nurse	99 (89.2)	12 (10.8)	3.2*	1.1-9.0
BCG vaccination**	no	114 (91.2)	11 (8.8)	1	
	yes	132 (94.3)	8 (5.7)	0.5	0.2-1.3
TST history*	negative TST in history	146 (96.7)	5 (3.3)	1	
	no TST in medical history	29 (87.9)	4 (12.1)	4.4	1.01-18.9
	positive TST in history	71 (87.7)	10 (12.3)	3.0	0.95-9.6
Workplace**	other	124 (90.5)	13 (9.5)	1	
	admission ward	16 (88.9)	2 (11.1)	1,4	0.3-79.2
	infection ward/pulmology	106 (96.4)	4 (3.6)	0,4	0.1-1.3

* the final multivariate logistic regression model contains the variable age, job category and TST history
** adjusted Odds ratio for age, job category and TST history

epidemiological and microbiological study of de Bries et al was to determine which TB cases among HCWs in the Netherlands were infected during work. Of a total of 101 TB cases, the infection pathways of 67 cases could be established; 42% (28 out of 67) were due to infection at work.

In our study a positive QFT-IT result was associated with age (>30 years 3.5%, 50-67 years 22%), no previous TST in the medical history and occupation as a physician or nurse. The higher prevalence rate in older HCWs might be due to a cohort effect or the longer time at risk. HCWs without a previous TST in their history had an increased OR compared to those with a negative TST in history even after controlling for risk of infection. A clear explanation to this was not found. Probably those with a negative TST once in history might be genetically protected against infection. HCWs with an earlier positive TST also had an increased OR which was, however, not statistically significant. This may be due to the small size of the group. A booster phenomenon when IGRA are applied after TST can be excluded because the QFT-IT was carried out in front of the TST.

In the recent review from Menzies et al occupational risk factors were associated with work in internal or respiratory medicine, years of work in healthcare, more direct indicators of TB exposure, including TB admission or the percentage of patients with TB or HIV cared for. Another reason for transmission in healthcare settings was the delayed diagnosis of the index case, especially in elderly patients. In the HCW study by De Vries et al 44% of the index patients were older than 60 years. Delayed diagnosis in older patients was the main cause of patient-to-HCW transmission in the Netherlands.

So far the occupational LTBI infection risk of nurses has been investigated in several conventional studies. Most studies showed a statistically significant increase of >2 in relative risk. The infection risk of physicians was examined in various studies of varying quality. Because of the inadequate data, it is difficult to evaluate the tuberculosis risk in different medical specialties. The results are contradictory and all in all do not indicate an increased infection risk for physicians. Pathologists have an increased risk of infection but no pathologists were included in this study. Several studies also identified a statistically clearly increased TB infection risk of the staff of wards where TB patients are treated; thus the increased infection risk of HCWs in areas with TB patients is epidemiologically ascertained.

The IGRAs proves to be a more important screening instrument for LTBI diagnosis in low-incidence countries as it allows valid statements on the prevalence and incidence of LTBI. The IGRA can help to identify at-risk groups and reduce the indication of preventive chemotherapy. The use of IGRAs in serial testing of health care workers is still not very well studied and the influence of the role of potential dynamic of IGRA responses still needs to be clarified. Most of the serial testing studies have been done in high-incidence countries and show inconsistent results. Very few studies so far have been done on disease progression. The data indicate that a positive IGRA correlate with a high progression rate but the number of cases is still small and these results need to be interpreted with care. The recent study from Diel et al (2008) on disease probability after positive IGRA showed that, out of 41 participants with a positive IGRA result, 14.6% developed TB within the 103 weeks of observation. The progression rate for TST-positives was only 2.3%. Thus the progression rate estimated by IGRA was higher than the one estimated by WHO for lifetime after positive TST (5 to 10%).

As changes with time cannot be considered in a cross-sectional study, the OR can provide evidence for factors influencing the results, but only restricted conclusions about the causality of these correlations are possible. To allow for a comparison between professions under risk we created a variable with the groups Nurse, Physician and other professions (reference group). It was known, that in the unexposed group might also be employees with contact to patients (e.g. physiotherapist and radiology staff), but there was only two cases of QFT-IT positive. This may limit the generalizability of our results.

Conclusion

In summary, the prevalence of LTBI assessed by QFT-IT in a hospital for pulmonary diseases is rather low. Other than in the years before 1980, we found no indication for a "strong, flowing source of infection." No statement can be made regarding the occupational risk as compared to the general population because there are no data from Germany available for comparison. It is important, especially in high-risk settings, to follow the current guidelines for the prevention of tuberculosis in the workplace, including appropriate patient risk assessment, active hospital tuberculosis case surveillance and development of an effective institutional infection control plan to reduce the transmission rate of tuberculosis in healthcare settings. Disease probability in HCWs tested positive by serial testing should be investigated in longitudinal studies.

Evaluation of the Safety of High-Frequency Chest Wall Oscillation (HFCWO) Therapy in Blunt Thoracic Trauma Patients

Casandra A. Anderson, Cassandra A. Palmer, Arthur L. Ney, Brian Becker, Steven D. Schaffel, Robert R. Quickel

Background: Airway clearance is frequently needed by patients suffering from blunt chest wall trauma. High Frequency Chest Wall Oscillation (HFCWO) has been shown to be effective in helping to clear secretions from the lungs of patients with cystic fibrosis, bronchiectasis, asthma, primary ciliary dyskinesia, emphysema, COPD, and many others. Chest wall trauma patients are at increased risk for development of pulmonary complications related to airway clearance. These patients frequently have chest tubes, drains, catheters, etc. which could become dislodged during HFCWO. This prospective observational study was conducted to determine if HFCWO treatment, as provided by The Vest Airway Clearance System (Hill-Rom, Saint Paul, MN), was safe and well tolerated by these patients.

Methods: Twenty-five blunt thoracic trauma patients were entered into the study. These patients were consented. Each patient was prescribed 2, 15 minute HFCWO treatments per day using The Vest Airway Clearance System (Hill-Rom, Inc, St Paul, MN). The Vest system was set to a frequency of 10–12 Hz and a pressure of 2–3 (arbitrary unit). Physiological parameters were measured before, during, and after treatment. Patients were free to refuse or terminate a treatment early for any reason.

Results: No chest tubes, lines, drains or catheters were dislodged as a result of treatment. One patient with flail chest had a chest tube placed after one treatment due to increasing serous effusion. No treatments were missed and continued without further incident. Post treatment survey showed 76% experienced mild or no pain and more productive cough. Thirty days after discharge there were no deaths or hospital re-admissions.

Conclusion: This study suggests that HFCWO treatment is safe for trauma patients with lung and chest wall injuries. These findings support further work to demonstrate the airway clearance benefits of HFCWO treatment.

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Background

Blunt thoracic trauma can result in a variety of bony and non-bony injuries.[1] These patients are often cared for in the intensive care unit (ICU), and frequently require some form of pulmonary support. Mechanical ventilation carries with it risk for additional complications such as atelectasis and ventilator associated pneumonia (VAP). Patients requiring intubation often require longer ICU stays.[2] Avoiding mechanical ventilatory support of patients who don't absolutely require it results in a better outcome for these patients.[3] Blunt thoracic trauma patients and patients with flail chest have been treated effectively with bilevel positive pressure (BiPAP), continuous positive airway pressure (CPAP), or intermittent positive pressure ventilation (IPPV), with improved outcomes resulting from BiPAP and CPAP.[2,4] A recent study of mucociliary clearance in ICU patients demonstrated a significant deficit in clearance ability that correlated to patient acuity.[5] Effective mucociliary clearance is an essential first line of defence to maintaining respiratory health[6] and impairment of this clearance may contribute to the risk for pulmonary complications during an ICU stay.

There are different methods which have been employed to facilitate pulmonary clearance. Conventional chest pulmonary therapy (CPT), which consists of manual percussion and or positioning techniques (postural drainage) to help mobilize and clear mucus is one. Continuous Lateral Rotational Therapy (CLRT), which consists of alternatively elevating one lung over the other around the patient's long axis has been shown to help mucus transport.[7]

High frequency chest wall oscillation (HFCWO) uses a pressurized vest to transmit high frequency oscillations to the chest. This mobilizes secretions which are then cleared by cough or by suction in the case of intubated patients. Early trials of HFCWO demonstrated mucus clearance in dogs.[8] Studies in humans found that HFCWO helps tracheal mucus clearance.[9] This clearance decreases pulmonary complications in patients with chronic pulmonary diseases.[10,11] A comparison of clearance in hospitalized patients demonstrated equivalent efficacy of CPT and HFCWO.[12,13] Figure 1 shows an intubated patient being prepared for HFCWO treatment.

Since it was shown that airway clearance would be advantageous for thoracic trauma patients, HFCWO had been shown to be equivalent to CPT in patients with other clearance needs, and CPT was tolerated by blunt thoracic trauma patients, we hypothesized that: Treatment with HFCWO therapy will result in no significant changes in physiological parameters in patients with chest wall injuries (CWI). There will be no increase in the number of adverse outcomes related to treatment with HFCWO in patients with CWI.

Methods

This study was approved by the institution's Institutional Review Board. Patients (18 years or older) with chest wall injury (blunt or penetrating) admitted to the Hennepin County Medical Center trauma service (Minneapolis, Minnesota) with one or more of the following: a) Two or more rib fractures (unilateral or bilateral); b) Pulmonary contusion as the result of direct force applied to the lung documented as an area of increased density or consolidation by chest x-ray; c) Sternal fracture; d) Clavicular or scapular fracture; e) Spinal cord injury patients (T5 and above) deemed stable by the neurological staff; f) Hemothorax; or g) Pneumothorax requiring one or more chest tubes were recruited into the study after informed consent. These criteria were documented with chest radiograph (CXR), or by chest or neck computerized tomography (CT) scan. In addition, patients had to have been admitted within the previous 48 hours. See figure 2 for a flow diagram.

Since this was a safety study and not a controlled comparison, power calculations were not performed. The selection of 25 patients was empirical. Only the actual number of patients enrolled was recorded. The total number screened was not documented.

The first twenty-five eligible patients to consent were enrolled in the study over approximately 10 months. Each patient was prescribed 2, 15 minute HFCWO treatments per day using The Vest Airway Clearance System (Hill-Rom, Inc, St Paul, MN). The Vest system was set to a frequency of 10–12 Hz and a pressure of 2–3 (arbitrary unit). Physiological parameters were measured before, during, and after treatment. These parameters were: incentive spirometry; heart rate; heart rhythm; respiratory rate; mean arterial pressure calculated from systolic and diastolic blood pressure; O_2 saturation (SpO_2); and in selected cases, intra-cranial pressure. For those patients receiving mechanical ventilation, the following ventilator settings were documented: ventilation mode; ventilation rate; PEEP; pressure support level; delivered tidal volume; FiO_2; peak pressure. All treatments were offered to the patients, but some were skipped according to the patient's wishes (16 total treatments skipped due to pain, 7 treatments due to nausea) or early discharge (25 treatments). Because of inconsistencies in recording the "during treatment" parameters, only the before and after treatment parameters were compared. Student's t-test for paired values was used and values were considered significant at a p value of 0.05. All patients were followed-up after 30 days to determine: subject health status, number of hospital days required, number of ICU days required,

Figure 1. Intubated patient being fitted for HFCWO treatment. The vest type being fitted is the "wrap type" of vest. This allows for positioning of the vest so it does not interfere with chest tubes or lines.

Table 1: Patient demographics, diagnoses, and adjunctive equipment present during HFCWO therapy

Patient #	Age	Gender	Injuries	Adjunct equipment
01	39	M	rib fract, scapular fract, pneumothorax, h	None
02	68	M	rib fract, clavicle fract, stab spinal cord fract, pneumothorax	chest tube
04	40	F	pulm contusion	other line
05	48	M	rib fract	other line
06	18	F	rib fract, pulm contusion, clavicle fract, scapular fract, pneumothorax	other line
07	19	M	rib fract, pulm contusion, clavicle fract, pneumothorax	chest tube, DS, other line
09	62	M	pneumothorax	chest tube, other line
10	44	F	rib fract	other line
11	26	M	rib fract, pneumothorax	chest tube, other line
12	39	M	rib fract, sternal fracture, pneumothorax	chest tube, other line
13	68	M	rib fract, liver laceration, kidney laceration, pneumothorax	other line
14	70	M	rib fract, pneumothorax	chest tube, other line
15	44	F	rib fract, pulm contusion, pneumothorax	other line
16	49	F	rib fract, pulm contusion, pneumothorax	chest tube, other line
19	44	M	rib fract, pulm contusion	other line
20	21	M	rib fract, clavicle fract, stab spinal cord fract	other line
21	59	M	rib fract, pneumothorax, intraperitoneal hemorrhage	other line
22	42	F	rib fract, pulm contusion, hemothorax, pneumothorax	other line
23	51	M	pulm contusion, hemothorax	chest tube, other line
24	70	M	rib fract, pulm contusion, pneumothorax	chest tube, other line
25	44	F	rib fract, hemothorax, pneumothorax, kidney laceration	chest tube, other line

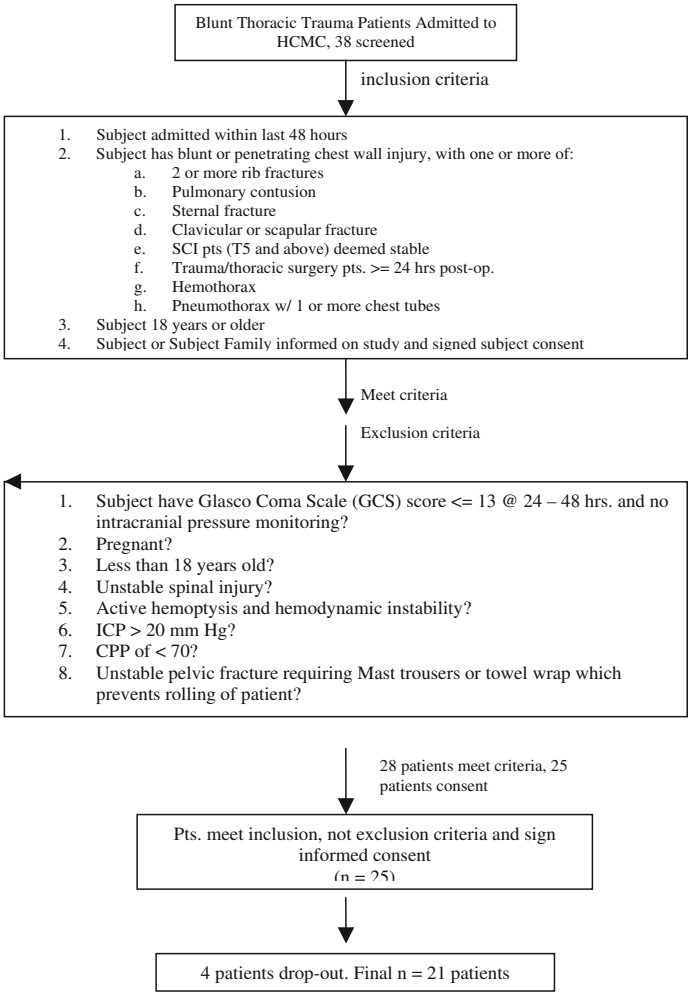

Figure 2. Flow Chart showing patient selection and exclusion. A total of 38 patients were screened. Of these, 28 patients met criteria. Twenty-five patients consented but four did not complete the therapy course. Twenty one patients were evaluated and followed-up for evaluation of HFCWO treatment. As an observational pilot safety study, power calculations for the number of patients to be enrolled were not done. The target of 25 patients was arbitrary.

number of days on mechanical ventilation (if applicable), incidence of re-intubation (if applicable), hospital re-admissions for pulmonary complications, and subject assessment of HFCWO therapy (comfort/tolerance).

Results

Twenty-five patients were initially enrolled. Four withdrew prior to the completion of the study. None withdrew as a result of adverse effects of the HFCWO treatment. Table 1 presents the age and sex of the patients who remained in the study, the type of trauma injuries and the adjunct equipment at the time of HFCWO treatment. None of the equipment was dislodged or compromised in function by the HFCWO treatment. The majority of trauma was the result of motor vehicle accidents but also included 3 falls, 1 industrial accident, and 1 gunshot wound to the chest.

Seven patients initially admitted with small pneumothoraces were treated conservatively; none of these patients required tube thoracostomy after HFCWO. In patients with chest tubes (n = 11), mean chest tube output during treatment and the 30 minutes following was 10 cc (range 0–50 cc). One patient with flail chest and a large pleural effusion required chest tube placement after the first HFCWO treatment due to increasing serous pleural fluid; treatments were continued without further incident. None of the ten patients with solid organ injury being managed non-operatively required transfusion or operative management. Use of HFCWO did not result in increased bleeding or need for surgical treatment of solid organ injury in those subjects that were not scheduled for surgery.

Table 2 presents the results of physiologic parameters measured before and after HFCWO treatment. Heart rhythm is not included as there were no remarkable changes pre and post treatment. Mean arterial pressure was measured for some time points for some of the patients (data not shown). None were significantly different than the pre- or post-treatment values. The mean number of treatments each patient received was 7.7.

The 30 day follow-up survey revealed no deaths or hospital re-admissions. Two patients required re-intubation. One of them was diagnosed with pneumonia. Patient 24 was intubated and heavily sedated during the HFCWO treatment and did not remember the therapy. The other patients were asked about their experience with the Vest. Their responses are shown in Table 3. Seventy-five percent experienced mild or no pain due to the Vest therapy itself. Seventy percent felt the therapy made their breathing better. Seventy-five percent felt the treatment improved their cough and seventy percent would recommend this therapy.

Discussion

This study was undertaken to see if HFCWO would be safe and tolerated by patients with blunt chest wall trauma. Studies have shown that HFCWO can aid in the process of airway clearance for hospitalized patients with or without ventilator support.[12,13] The patients in this study tolerated the therapy well and typically did not require additional medication for pain management, despite the severity of their injuries. There were no lines, chest tubes, drains or epidural/ventriculostomy catheters dislodged.

Maintaining pulmonary function in the compromised critically ill patient is challenging. Patients with thoracic trauma are compromised mechanically so that ancillary methods such as mechanical ventilation are often required. However, numerous studies have shown that ventilator-associated pneumonia (VAP) rates can be as high as 65%.[14] Pulmonary clearance is important to prevent VAP, but critical illness impairs the function of the normal mechanisms.[5] Bacterial infections both disrupt the ciliary beat frequency[15] and induce the release of inflammatory components which in turn causes mucus production.[16-20] It is well documented that HFCWO is efficacious for pulmonary clearance in CF patients[21,22] so it is reasonable to try HFCWO for clearance in other conditions.

The overall care of the thoracic trauma ICU patient may be improved by the addition of airway clearance modalities. However, the safety of the device when used by the blunt trauma patient had not been previously demonstrated. The thirty day follow up was an arbitrary time. The intention was to query the patients after significant healing in order to get a more objective opinion of their response to the therapy.

One of the limitations of the study is the lack of documentation of the conditions of the patients who did not participate. It is possible that they represented an overall more seriously injured group which would not find the treatment as tolerable as the

Table 2: Physiological parameters measured before and after HFCWO (Vest) treatment

Parameter	Before Tx Mean (SD) (95% CI)	After Tx Mean (SD) (95% CI)	P value
Incentive Spirometry (cc)	1330.8 (582.0) (166.8 – 2502.8)	1349.8 (544.7) (260.4 – 2439.2)	0.81
Respiratory Rate (bpm)	18.1 (4.0) (10.1 – 26.1)	18.1 (3.9) (10.3 – 25.9)	0.95
Heart Rate (bpm)	91.4 (16.6) (58.2 – 124.6)	91.0 (15.9) (59.2 – 122.8)	0.80
Systolic BP (mm Hg)	131.1 (16.9) (97.3 – 164.9)	128.9 (16.7) (95.5 – 162.3)	0.24
Diastolic BP (mm Hg)	70.1 (12.5) (45.1 – 95.1)	68.3 (12.9) (42.4 – 94.1)	0.21
MAP	90.4 (12.5) (65.4 – 115.4)	88.6 (12.7) (63.2 – 114)	0.20
SaO2 (%)	95.9 (2.7) (90.5 – 101.3)	95.9 (2.7) 90.5 – 101.3)	0.85

Table 3: Patient survey results

	Describe the pain you experienced during Vest therapy				How do you feel overall this therapy made your breathing?			Did the vest therapy improve your cough?			Would you recommend this therapy?		
ID	None	Mild	Moderate	Severe	Better	Worse	No Change	Yes	No	No Change	Yes	No	Unsure
0001		X			X			X			X		
0002			X		X				X		X		
0004		X					X	X				X	
0005		X			X			X			X		
0006	X				X			X			X		
0007			X		X			X					X
0009		X					X		X				X
0010		X			X			X			X		
0011			X				X	X			X		
0012		X			X			X			X		
0013	X				X			X			X		
0014		X			X			X			X		
0015		X					X			X			X
0016			X				X		X			X	
0019		X			X			X			X		
0021		X			X			X			X		
0022	X						X	X					X
0023	X				X			X			X		
0025			X		X			X			X		
Sum	4	10	5		14	0	6	15	3	2	14	2	4
%	20	50	25	0	70	0	30	75	15	10	70	10	20

included patients. Another limitation is the lack of randomization to conventional CPT or HFCWO therapy. It is not known if the results would be weighted toward one method or the other. However, we felt it was crucial to know that the Vest treatment would be tolerated and as safe as CPT.

The results presented here demonstrate that HFCWO therapy is well tolerated by patients with blunt thoracic trauma and support additional studies to see if the airway clearance capabilities of HFCWO add to the successful treatment of thoracic trauma patients. If so, this method will add another tool to free-up the provider of manual CPT for other patients. It will also add a consistent, technique independent therapy which can be modified (pressure, frequency, and duration) to best accommodate a patients needs.

Conclusion

This study suggests that HFCWO treatment is safe for trauma patients with lung and chest wall injuries. These findings support further work to demonstrate the airway clearance benefits of HFCWO treatment.

References

1 Schorr RM, Crittenden M, Indeck M, Hartunian S, Rodriguez A: Blunt thoracic trauma, analysis of 515 patients. Ann Surg 1987, 206:200-205.

2 Xirouchaki N, Kondoudaki E, et al.: Noninvasive bilevel positive pressure ventilation in patients with blunt thoracic

trauma. Respiration 2005, 72:517-522.
3 Richardson JD, Adams L, Flint LM: Selective management of flail chest and pulmonary contusion. Ann Surg 1982, 196:481-486.
4 Gunduz M, Unlugenc H, Ozalevli M, Inanoglu K, Akman H: A comparative study of continuous positive airway pressure (CPAP) and intermittent positive pressure ventilation (IPPV) in patients with flail chest. Emerg Med J 2005, 22:325-329.
5 Nakagawa NK, Franchini ML, Driusso P, de Oliveira LR, Saldiva PHN, Lorenzi-Filho G: Mucociliary clearance is impaired in acutely ill patients. CHEST 2005, 128:2772-2777.
6 Randell SH, Boucher RC: Effective mucus clearance is essential for respiratory health. Am J Respir Cell Mol Biol 2006, 35:20-28.
7 Dolovich M, Rushbrook J, Churchill E, Mazza M, Powles AC: Effect of continuous lateral rotational therapy on lung mucus transport in mechanically ventilated patients. J Crit Care 1998, 13:119-125.
8 King M, Phillips D, Gross D, Vartian V, Chang HK, Zidulka A: Enhanced tracheal mucus clearance with high frequency chest wall compression. Am Rev Respir Dis 1983, 128:511-515.
9 King M, Phillips D, Zidulka A, Chang HK: Tracheal mucus clearance in high-frequency oscillation: chest wall versus mouth oscillation. Am Rev Respir Dis 1984, 130:703-706.
10 Chiapetta A, Mendendez A, Gozal D, Kiernan M: High-frequency chest wall oscillation in hospitalized non-cystic fibrosis patients. Am J Respir Crit Care Med 1996, 153:A56.
11 Hansen L, Warwick W: High-frequency chest compression system to aid in clearance of mucus from the lung. Biomed Instrum Technol 1990, 24:289-294.
12 Whitman J, Van Beusekom R, Olson S, Worm M, Indihar F: Preliminary evaluation of high-frequency chest compression for secretion clearance in mechanically ventilated patients. Respir Care 1993, 38:1081-1087.
13 Arens R, Gozal D, Omlin KJ, Vega J, Boyd KP, Keens TG, Woo MS: Comparison of high-frequency chest compression and conventional chest physiotherapy in hospitalized patients with cystic fibrosis. Am J Respir Crit Care Med 1994, 150:1154-1157.
14 Evans B: VAP prevention. Nursing Management 2005, 36(12):10-16.
15 Steinfort C, Wilson R, Mitchell T, Feldman C, Rutman A, Todd H, Sykes D, Walker J, Saunders K, Andrew PW, Boulnois GJ, Cole PJ: Effect of Streptococcus pneumoniae on Human Respiratory Epithelium In Vitro. Infect Immun 1989, 57(7):2006-2013.
16 Park JA, He F, Martin LD, Yuehua L, Chorley BN, Adler KB: Human Neutrophil Elastase Induces Hypersecretion of Mucin from Well-Differentiated Human Bronchial Epithelial Cells in Vitro via a Protein Kinase C -Mediated Mechanism. American Journal of Pathology 2005, 167:651.
17 Wilson R, Dowling RB, Jackson AD: The biology of bacterial colonization and invasion of the respiratory mucosa. Eur Respir J 1996, 9(7):1523-1530.
18 Dohrman A, Miyata S, Gallup M, Li JD, Coste A, Escudier E, Nadel J, Basbaum C: Mucin gene (MUC 2 and MUC 5AC) upregulation by Gram-positive and Gram-negative bacteria. Biochim Biophys Acta 1998, 1406:251-259.
19 McNamara N, Basbaum C: Signaling networks controlling mucin production in response to Gram-positive and Gramnegative bacteria. Glycoconj J 2001, 18:715-722.
20 Basbaum C, Li D, Gensch E, Gallup M, Lemjabbar H: Mechanisms by which Gram-positive bacteria and tobacco smoke stimulate mucin induction through the epidermal growth factor receptor (EGFR). Novartis Found Symp 2002, 248:171-180.
21 Tecklin JS, Clayton RG, Scanlin TF: High frequency chest wall oscillation vs. traditional chest physical therapy in CF – a large, one-year, controlled study. Pediatr Pulmonol 2000:459.
22 Darbee JC, Kanga JF, Ohtake PJ: Physiological evidence for highfrequency chest wall oscillation and positive expiratory pressure breathing in hospitalized subjects with cystic fibrosis. Physical Therapy 2005, 85:1278-1289.

Identification and Management of Adults with Asthma Prone to Exacerbations: Can We Do Better?

Neil C. Thomson, Rekha Chaudhuri

Abstract

Exacerbations are a major cause of morbidity in asthma and generate high health costs. Identification and management of adults with asthma who are prone to exacerbations is of considerable importance as by this means it should be possible to reduce the number of patients who currently experience inadequately controlled disease. Exacerbations occur most frequently in individuals with severe disease. Other risk factors include a history of a recent exacerbation, comorbidities such as a raised body mass index and psychological problems as well as current smoking and lower socioeconomic status. A low FEV_1, particularly if combined with the additional information from questionnaires helps predict exacerbations. Despite the association between these risk factors and exacerbations it remains difficult to accurately predict in an individual patient with asthma whether they will go on to develop an exacerbation in the future. A major aim of international guidelines on the management of asthma is to prevent future risks of exacerbations, but some patients, particularly those with severe disease, respond poorly to current therapies and continue to experience recurrent exacerbations.

There is an unmet need for improved management strategies and drugs targeted at preventing asthma exacerbations. Monitoring induced sputum esinophil cell counts is helpful in preventing exacerbations in some patient with severe asthma. Future developments are likely to include the identification of better biomarkers to predict exacerbations or the cause of exacerbations, augmentation of the immunological response to viruses at the time of the exacerbation, the use of telemonitoring in patients with severe asthma and the development of improved therapies targeted at reducing exacerbations.

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Background

A major goal of international guidelines on the management of asthma is to achieve control of current symptoms, lung function and reliever inhaler use and to prevent future risks of exacerbations and decline in lung function. Despite the widespread dissemination of asthma guidelines many patients have inadequately controlled disease and experience frequent exacerbations of asthma. Exacerbations are associated with an accelerated decline in lung function, generate high health costs and are the main cause of mortality in asthma. The identification and appropriate management of adults with asthma who are prone to exacerbations is of considerable importance as by this means it should be possible to reduce the large number of patients who currently experience uncontrolled disease.

Definition and risk factors for exacerbations: Severe exacerbations, defined as the need for courses of high dose corticosteroids or hospitalization because of asthma, occur most commonly in patients with severe asthma. This group can experience exacerbation rates ranging from 1.5 to over 4 exacerbations per year. Information on previous asthma control, comorbidities and demographic factors as well as physiological and inflammatory biomarkers may help identify some individuals prone to exacerbations. These factors are often associated with severe asthma. A history of a recent exacerbation within the last 3 months is associated with a considerably increased risk of a future exacerbation [relative risk (RR) 3.7]. Several co-morbidities in patients with difficult-to-treat asthma are associated with recurrent exacerbations including severe nasal sinus disease [adjusted odds ratio (OR) 3.7], gastroesophageal reflux (OR 4.9), recurrent respiratory infections (OR 6.9), psychological problems (OR 10.8) and obstructive sleep apnea (OR 3.4). Current smokers with asthma are more likely to experience exacerbations compared to non-smokers with asthma. A raised body mass index is also a risk factor for exacerbations [RR 1.7 (1.2–2.3)] and hospitalization because of asthma. Hospital admission rates for asthma in the US are associated with lower socioeconomic status and are higher in black and Hispanic patients with asthma compared to whites. A low pre-bronchodilator FEV_1 of 60 to 80% of predicted gives a 2.4-fold increased risk of an exacerbation, which rises to 4.6-fold increased risk when the pre-bronchodilator FEV_1 is < 60% of predicted. Addition of information gained from questionnaires,

including a history of pet ownership, increases the likelihood of identifying exacerbations over the next 30 months to a medium risk (RR 3.0) or high risk (RR 11).

The categorisation of patients with severe asthma by cluster analyses into different phenotypes termed early onset atopic asthma, obese non-eosinophilic asthma, early symptoms predominant asthma and inflammation predominant asthma found that exacerbation rates were high in each of the distinct categories, but that no subgroup was more prone to exacerbations. Thus despite the association between known risk factors and exacerbations it remains difficult to accurately predict in an individual patient with asthma whether they will go on to develop an exacerbation in the future.

Management of patients prone to exacerbations: Several pharmacological and non-pharmacological management approaches are likely to be effective in preventing exacerbations. Current drugs therapies for asthma, particularly inhaled corticosteroids alone or in combination with long-acting $beta_2$ agonists, but also leukotriene modifiers and omalizumab all reduce the rate of asthma exacerbations. Different ways of using currently available medication may reduce exacerbation rates. The SMART approach, which involves using both budesonide and formoterol given as needed, reduces the frequency of severe exacerbations in patients receiving regular combination therapy, although the value of this approach in patients with severe asthma is less clear. The heterogeneity of the therapeutic response to corticosteroids and to other drug therapies for asthma means that some patients respond poorly to current treatments and continue to experience recurrent exacerbations, probably due to a combination of genetic and environmental factors as well as poor adherence to drug therapy. Written individualized management plans, when combined with regular review, improve asthma control including reduced hospitalization and attendance at emergency rooms for exacerbations.

The effect of treating comorbidities associated with severe asthma, targeting smokers with asthma to quit smoking or patients with a high BMI to lose weight, may result in improvements in indices of current asthma control. Future studies are needed to assess whether these interventions reduce exacerbation rates. Avoidance of trigger factors such as allergens, non-steroidal anti-inflammatory agents or occupational agents in sensitive individuals, as well as exposure to environmental irritants such as passive smoke, is likely to prevent some exacerbations.

Can we do better?

Taken together, there is considerable evidence to indicate a need for improved methods both to identify adults with asthma who are prone to exacerbations and also to identify the early development and cause of an exacerbation. There is also a need for better management strategies and drugs targeted at treating and preventing exacerbations.

Monitoring biomarkers of airway inflammation may have a role in reducing exacerbation rates in selected patients. Treatment based on serial sputum eosinophil count measurements, prevents exacerbations in patients with severe asthma. Serial exhaled nitric oxide measurements however, does not decrease exacerbation rates in 12–20 year olds or in adults followed up for one year.

In the future, it may be possible to use genetic markers to identify exacerbators. For example, in children and young adults with asthma the risk of asthma exacerbations is associated with filagrin null mutations and IL-10 polymorphisms. The complex and fluctuating interaction between environmental, immunological and mechanical factors on the risk of future exacerbations may require the use of sophisticated analytical methods to assess risk. The majority of asthma exacerbations are caused by respiratory rhinovirus infections. Recent studies have demonstrated that patients with asthma are more susceptible to the clinical and inflammatory adverse effects of respiratory viruses due to augmented Th2 or impaired Th1 or IL-10 immunity. These findings suggest that one approach in the future to the management of exacerbation may be through immunological augmentation with interferons at the time of the exacerbation or by the use of specific anti-viral therapies. Telemonitoring of patients with severe asthma may be an advance that could identify worsening asthma control at an earlier stage, but evidence for this is still awaited. In the future, biological therapies, such as anti-IL13, current drugs, such as macrolides, or novel treatments, such as bronchial thermoplasty may prove useful approaches in reducing exacerbations in some patients with severe asthma. Hopefully future research in asthma exacerbations will translate into improved levels of asthma control within the population.

Multidrug Resistant Tuberculosis Co-existing with Aspergilloma and Invasive Aspergillosis in a 50 Year Old Diabetic Woman: A Case Report

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Abstract

Aspergilloma and invasive aspergillosis coexisting with multidrug resistant Mycobacterium tuberculosis (MDR-TB) in the same patient is a rare entity. We report a 50 year old South Indian woman, a diabetic, who presented to us with complaints of productive cough and hemoptysis for the past 2 months. She was diagnosed to have pulmonary tuberculosis 2 years ago for which she took irregular treatment. Lung imaging showed features of a thick walled cavity in the right upper lobe with an indwelling aspergilloma. She underwent a right lung upper lobe resection. Biopsy and culture of the resected specimen showed the coexistence of Aspergillus fumigatus and multi-drug resistant Mycobacterium tuberculosis. Two blood cultures grew Aspergillus fumigatus. She was successfully treated with Voriconazole and anti tuberculous therapy against MDRTB.

Background: Pulmonary tuberculosis is the most commonly associated disease in cases of secondary aspergilloma.[1] Generally aspergilloma is seen residing in an old tuberculous cavity. In this case report we present a rare case of an aspergilloma co-existing with multidrug resistant mycobacterium tuberculous in an old cavity. This patient also had invasive aspergillosis. This combination is uncommon and to the best of our knowledge is not reported in literature.

Case presentation

A 50 year old South Indian woman presented to the outpatient department of our tertiary care hospital with complaints of productive cough with hemoptysis for the past 2 months. She was a house wife and was from a low socio economic class. She was diagnosed to have pulmonary tuberculosis 2 years ago and was started on anti-tuberculous therapy consisting of Isoniazid (300 mg), Rifampicin (600 mg), Ethambutol (1200 mg), and Pyrazinamide (1500) mg. But within just 3 weeks she had discontinued treatment on her own. She suffered from diabetes mellitus with peripheral neuropathy for the past 8 years and was taking oral hypoglycemic agents for the same. There was no history of hypothyroidism, coronary artery, disease, hepatic disease or renal disease. No history of relevant family diagnosis of parents, siblings, or children was elicited. She is now a known smoker or alcoholic. She is married and currently postmenopausal for the past 5 years. She weighed 53 kgs and was 156 cms tall with a body mass index 22kg/m2. General physical examination was unremarkable. Respiratory system exam revealed bronchial breath sounds in the right infraclavicular area. Admission baseline investigations showed anemia. Renal and liver functions were within normal limits (Table 1). Computed tomogram of the thorax revealed a thick walled cavity in the right lung upper lobe with an indwelling aspergilloma (Figure 1). Three sputum samples were tested positive for acid fast bacilli by Ziehl Neelsen's staining technique. Conventional method of culture on Lowenstein Jensen's medium yielded growth of M. tuberculosis in 6 weeks time. The anti-tuberculosis drug susceptibility performed by resistance ratio method using Lowenstein Jensen's medium showed resistance to Isoniazid, Rifampicin but sensitive to Ehambutol, Pyrazinamide and Streptomycin in their critical concentrations of 2 ug, 50 ug and 4 ug respectively as given by Lee and Heifet.[8] Consequently in view of hemoptysis and presence of an aspergilloma a right upper lobectomy was performed (after anemia correction with 3 units of packed red cell transfusion). Biopsy of the resected specimen showed caseous necrosis and granuloma formation (Figure 2) and septate fungal elements suggestive of Aspergillus species (Figure 3). A fungal culture of the resected specimen in Sabouraud's dextrose agar grew dirty green colonies, with lactophenol cotton blue slide mount showed fungal elements characteristic of Aspergillus fumigatus.[2] Blood culture inoculated in Sabouraud's dextrose agar also grew Aspeergillus fumigatus. In view of invasive Aspergillosis patient was given an oral loading dose of Voriconazole 400 mg 12th hourly for 2 doses which was followed by an oral maintenance dose of 200 mg 12th hourly was continued for 6 weeks. Initially before AFB culture reports were ready, the patient was initiated empirically on a daily dose of Isoniazid (300 mg), Ethambutol (1200 mg), Pyrazinamide (1500 mg) and Streptomycin 1g. Rifampicin due to its interactions with Voriconazole was not included in the treatment regimen.[2] After culture demonstrated MDR-TB, Isoniazid was stopped and oral Levofloxacin 750 mg once a

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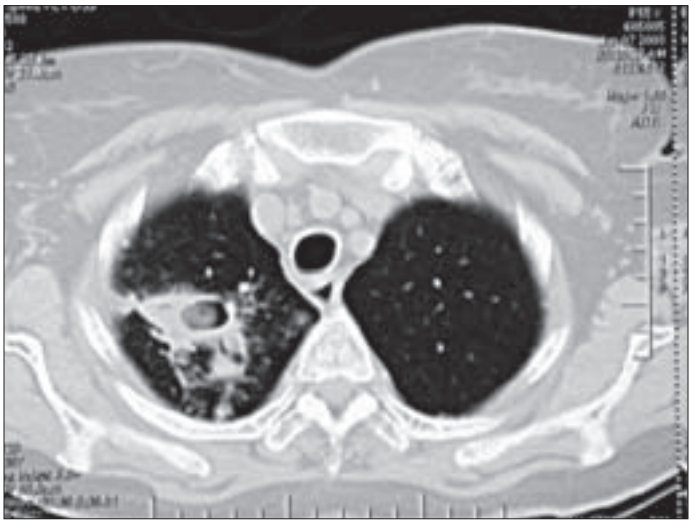

Figure 1: Computed tomogram of the thorax. Thick walled cavity in the right lung upper lobe with an indwelling aspergilloma.

Table 1. Laboratory investigations

Hemoglobin	7 g / dl	
Total count	4,500 cells / mm3	
Differential count	Poly morphs:	73 %
	Lymphocytes:	24 %
	Eosinophils:	3 %
Platelet count	3,25,000 cells / mm3	
Serum creatinine	0.9 mg / dl	
Total serum bilirubin	1.1 mg / dl	
Direct bilirubin	0.6 mg / dl	
Random blood sugar	231 mg / dl	
ELISA for HIV 1 and 2	non – reactive	
Sputum AFB (3 samples)	Positive	
Sputum culture	Mycobacterium tuberculosis (MDR-TB)	
Blood culture (2 samples)	Aspergillus fumigatus	

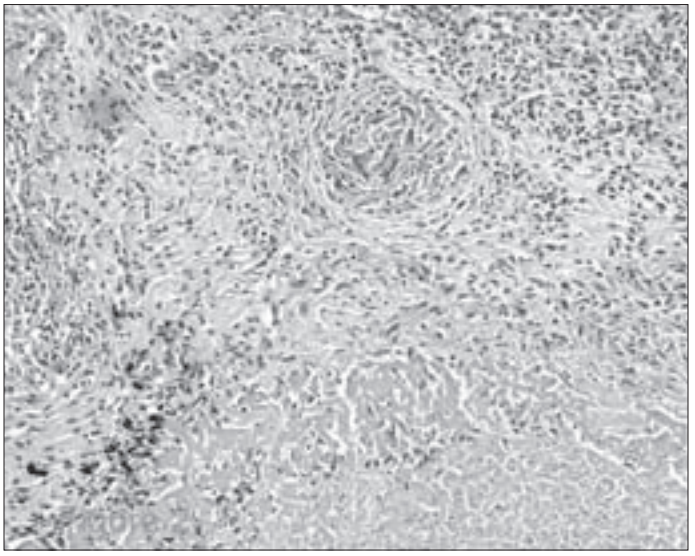

Figure 2: Caseating granuloma suggestive of Tubercular infection. Histology picture showing Langhan's giant cells, epitheloid cells with surrounding necrosis (H and E X 100).

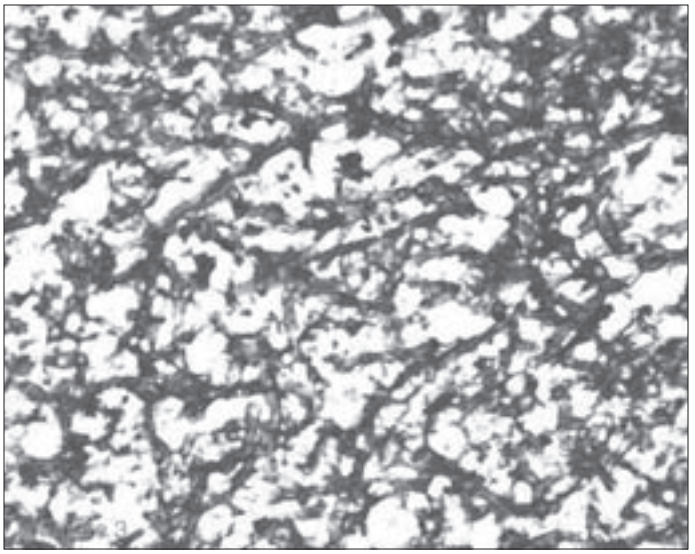

Figure 3: Aspergillus species. Histology picture showing fungal hyphae of Aspergillus (Periodic Acid Schiff- G stain X 400)

day and Ethionamide 250 mg 12th hourly were included as per WHO protocol for MDR-TB.[3] Hemoptysis completely resolved after lobectomy. Within a week of initiating Voriconazole blood became sterile for fungal elements. After 3 weeks sputum became negative for acid fast bacilli. Currently patient is in the 4th month of treatment and is doing well.

Discussion

TB is principally a disease of poverty, with 95% of cases and 98% of deaths occurring in developing countries. Of these, more than half the cases occur in five South-East Asian countries.[4] Globally, about 3% of all newly diagnosed patients have MDR-TB.[5] Definition of multi-drug resistance refers to isolates resistant to both Isoniazid and Rifampicin with or without resistance to other drugs.[5] Three common forms of pulmonary disease associated with Aspergillus infection has been described, namely, allergic aspergillosis, colonizing aspergillosis, and invasive aspergillosis. A study showed that aspergilloma was commonly associated with pulmonary tuberculosis and affected the upper lobes in 94% of the cases.[6] Our patient also had pulmonary tuberculosis and aspergilloma had affected the right upper lobe. The uniqueness of our case report is that this association between MDR-TB, aspergilloma and invasive aspergillosis in the same patient is rare and to the best of our knowledge has not been reported in the literature before.

The natural history of aspergilloma is variable. Hemoptysis is the commonest mode of presentation, with an incidence of around 80%, which is life threatening in 30%.[7] In the majority of cases, the lesion remains stable, however, in approximately 10% of cases, it may decrease in size or resolve spontaneously without treatment.[8] Rarely, the aspergilloma increases in size.[9] Predicted mortality due to aspergilloma is reported at a rate of 6% per annum.[10] Surgery not only offers symptomatic control but also confers survival advantage.[11] Hemoptysis completely resolved in our patient after right lung upper lobe resection. Invasive aspergillosis is commonly seen in immunocompromised patients. Except for the poorly controlled diabetes, we could not identify any other risk factor for invasive fungal infection in our patient.

Conclusion

Aspergilloma, invasive aspergillosis, and MDR-TB can coexist

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Why Aren't We Practicing Homogenized Medicine?

Mervyn Singer

Abstract

Why is the practice of intensive care so heterogenous? Uncertainty as to "best practice," conservatism, and complacency may all contribute to our divergent management strategies. The need for further generalizable research, anonymized audit, external peer review and open access databases is discussed.

Commentary

Lauralyn McIntyre and colleagues have neatly used a septic shock scenario-based survey to highlight considerable variations within Canadian critical care practice.[1] They acknowledge the potential pitfalls of translating survey results into real life; however, my own experience of the diversities within UK practice suggest this would be representative of at least one other industrialized country, albeit with some variation in the detail (for example, use of gelatin as a plasma expander is much commoner in Europe).

They found decisions regarding treatment strategy (choice of fluid, use of inotropes and transfusion triggers) to be highly variable. However, they did demonstrate consistency in a continuing reliance on basic monitoring (blood pressure, heart rate, central venous pressure, urine output, pulse oximetry). This was to the relative exclusion of other, more sophisticated techniques (cardiac output, central venous saturation) whose use has been linked with outcome improvements in specific situations, such as the scenario on which their survey was based.

Is this heterogeneity a triumph of uncertainty and/or natural conservatism and/or arrogance and/or sloth over heavily promoted, multiple Society-endorsed guidelines [2] based primarily on the important yet limited Rivers study?[2,3] Why aren't we all practicing homogenized medicine? What does it take to standardize our approach to care of the critically ill?

Uncertainty does exert a considerable effect. The Institute of Healthcare Improvement's Surviving Sepsis Campaign website boldly states that a bundle – a group of interventions related to a disease process – "when executed together will result in better outcomes than when implemented individually" and that "the science behind the elements of a bundle is so well-established (my italics) that their implementation should be considered a generally accepted practice."[4] Yet three of the major planks upon which the two sepsis bundles are based, namely the use of corticosteroids, activated protein C and early goal-directed therapy are currently being questioned via, respectively, the CORTICUS study findings, the European Agency for the Evaluation of Medicinal Products (EMEA), and the National Institutes of Health (through their recent $8.4 million funding of the ProCESS study). These new challenges will, I believe, serve to increase uncertainty still further in the short-term and, thus, affect participation in an approach that is worthy but, in my opinion, critically flawed through a lack of prospective validation.[5]

Medics are a naturally conservative bunch – the avid uptake of new technologies by a rapid responder minority is rarely translated into standard practice, often because the initial enthusiasm for a drug, device or strategy fails to pass muster when more rigorously scrutinized or trialed. Too many bandwagons have lost their wheels and this has nurtured an understandable cynicism. It was not that many years ago that we were being exhorted to use high doses of dobutamine to achieve "supranormal" cardiorespiratory goals in the critically ill, as an extrapolation of findings from a high-risk surgical patient cohort.[6] When subsequent randomized trials made it painfully clear that the intensive care unit (ICU) patient outcomes did not match up to expectation,[7,8] the concept was generally discarded, even from the surgical patient population in whom the benefit was repeatedly seen.[9,10]

What about complacency? I've yet to meet a self-confessed mediocre intensivist so we all need to take a critical and regular look at our own individual performance. We do require a healthy degree of self-confidence to support our decision-making ability, but are we ready to accept that our ICU is perhaps offering an inferior level of care to the hospital down the road? Or if we do acknowledge poor performance, is this from someone/everyone/anyone else but me? Anonymized audit should, in a non-threatening manner, facilitate recognition and, hopefully,

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correction of our shortcomings. The Dutch offer external peer review "visitations" that can be initiated either by the ICU or their hospital administration. How widespread is this practice?

Finally, it is also a deficiency of ourselves as a community that we still cannot answer many fundamental questions. For an individual patient, what constitutes optimal targets, for example, for blood pressure and tissue perfusion, or 'best' treatment, such as the optimal duration of a course of antibiotics? Altruistic, multi-centre, generalizable research addressing simple questions is evolving. The Canadians and Australasians have clearly led the way while European and other countries are catching up. Perhaps these studies could (should) be better coordinated to complement each other. Perhaps this spirit of cooperation could (should) also be extended to open access, anonymized patient databases as a means of comparing models of care and for future hypothesis generation.

References

1 McIntyre LA, He'bert PC, Fergusson D, Cook DJ, Aziz A, for the Canadian Critical Care Trials Group: A survey of Canadian intensivists' resuscitation practices in early septic shock. Crit Care 2007, 11:R74.

2 Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM, for the Surviving Sepsis Campaign Management Guidelines Committee, et al.: Surviving Sepsis Campaign Guidelines for management of severe sepsis and septic shock. Crit Care Med 2004, 32:858-873.

3 Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M, Early Goal-Directed Therapy Collaborative Group: Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001, 345:1368-1377. PubMed Abstract | Publisher Full Text

4 Institute for Healthcare Improvement: Surviving Sepsis Campaign.

5 Singer M: The Surviving Sepsis guidelines: evidence-based ... or evidence-biased? Crit Care Resusc 2006, 8:244-245.

6 Shoemaker WC, Appel PL, Kram HB, Waxman K, Lee TS: Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. Chest 1988, 94:1176-1186. PubMed Abstract | Publisher Full Text

7 Gattinoni L, Brazzi L, Pelosi P, Latini R, Tognoni G, Pesenti A, Fumagalli R: A trial of goal-oriented hemodynamic therapy in critically ill patients. N Engl J Med 1995, 333:1025-1032.

8 Hayes MA, Timmins AC, Yau EH, Palazzo M, Hinds CJ, Watson D: Elevation of systemic oxygen delivery in the treatment of critically ill patients. N Engl J Med 1994, 330:1717-1722.

9 Boyd O, Grounds RM, Bennett ED: A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. JAMA 1993, 270:2699-2707.

10 Wilson J, Woods I, Fawcett J, Whall R, Dibb W, Morris C, McManus E: Reducing the risk of major elective surgery: randomised controlled trial of preoperative optimisation of oxygen delivery.
BMJ 1999, 318:1099-1103.

Multidrug…continued from page 55

in the same patient. Hence patients who have a recurrence of tuberculosis, and who were previous defaulters of antitubercular therapy, an AFB culture should be performed in order to identify MDRTB. Surgery often gives good results in the treatment of aspergilloma. Systemic antifungals should be administered against invasive fungal infections.

Patient's perspective: I have realized my mistake of stopping the TB medicines. Now the treatment is prolonged and the injection is painful. I could have spread these resistant bacteria to many people. Henceforth I will be careful and follow my doctor's instructions. I have learnt my lesson for sure but in a hard way.

References

1 Sugar AM, Olek EA. Diagnosis of Aspergilloma. In: Fishman AP, Elisa JA, Eds. Fishman's Pulmonary Diseases and Disorders. 3rd Ed. USA. McGraw Hill Companies; 1998: 2272-78.

2 Geist MJ, Egerer G, Burhenne J, Riedel KD, Mikus G. Induction of voriconazole metabolism by rifampin in a patient with acute myeloid leukemia: importance of interdisciplinary communication to prevent treatment errors with complex medications. Antimicrob Agents Chemothere. 2007 Sept;51(9):3455-6. Epub 2007 Jul 2.

3 World Health Organization. Treatment for tuberculosis. Guidelines for national programmes, 3rd ed. Geneva: World Health Organization, 2003 (WHO/CDS/TB/2003.313).

4 Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. Consensus statement. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring project. JAMA 1999; 282: 677-86.

5 S.K. Sharma, A. Mohan Multi-drug resistant tuberculosis. Review article. Indian J Med Res 120, October 2004, pp 354-376.

6 Garrós Garay J, Ruiz de Gordejuela E, Vara Quadrado F. Pulmonary aspergillomas. Analysis of 31 patients. Arch Bronceoneumol. 1994 Nov; 30(9):424-32.

7 Vaideeswar P, Prasad S, Deshpande JR, Pandit SP. Invasive pulmonary aspergillosis: A study of 39 cases at autopsy. J Postgrad Med 2004;50:21-6.

8 Gefter, WB. The spectrum of pulmonary aspergillosis. J Thorac Imaging 1992; 7,56-74.

9 British Tuberculosis Association. Aspergillus in persistent lung cavities after tuberculosis: a report from the Research Committee of the British Tuberculosis Association. Tuberecle 1968; 49,1-11.

10 British Thoracic and Tuberculosis Association. Aspergilloma and residual tuberculous cavities: the results of re-survey. Tubercle 1970; 51:227-45.

11 Ueda H, Okabayashi K, Ondo K, Motohiro A. Analysis of various treatment for pulmonary aspergillomas. Surg Today 2001; 31: 768-73.

What Determines Subjective Health Status in Patients with COPD: Importance of Symptoms in Subjective Health Status

Signe Berit Bentsen, Anne Hildur Henriksen, Tore Wentzel-Larsen, Berit Rokne Hanestad, Astrid Klopstad Wahl

Background: Subjective health status is the result of an interaction between physiological and psychosical factors in patients with chronic obstructive pulmonary disease (COPD). However, there is little understanding of multivariate explanations of subjective health status in COPD. The purpose of this study was to explore what determines subjective health status in COPD by evaluating the relationships between background variables such as age and sex, predicated FEV_1%, oxygen saturation, breathlessness, anxiety and depression, exercise capacity, and physical and mental health.

Methods: This study had a cross-sectional design, and included 100 COPD patients (51% men, mean age 66.1 years). Lung function was assessed by predicted FEV_1%, oxygen saturation by transcutaneous pulse oximeter, symptoms with the St George Respiratory Questionnaire and the Hospital Anxiety and Depression Scale, physical function with the Incremental Shuttle Walking Test, and subjective health status with the SF-36 health survey. Linear regression analysis was used.

Results: Older patients reported less breathlessness and women reported more anxiety ($p < 0.050$). Women, older patients, those with lower predicted FEV_1%, and those with greater depression had lower physical function ($p < 0.050$). Patients with higher predicted FEV_1%, those with more breathlessness, and those with more anxiety or depression reported lower subjective health status ($p < 0.050$). Symptoms explained the greatest variance in subjective health status (35%–51%).

Conclusion: Symptoms are more important for the subjective health status of patients with COPD than demographics, physiological variables, or physical function. These findings should be considered in the treatment and care of these patients.

Background

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease characterized by impairment of lung function with airway obstruction, which is most frequently the result of tobacco smoke. COPD is one of the major causes of morbidity and mortality worldwide. Many people suffer from this disease for years and die from it or its complications. Hoogendoorn et al estimated that the prevalence of diagnosed COPD, the number of deaths, and the associated health costs will increase during the next decade. In addition to the social strain, COPD also influences the patients' symptoms, function, and subjective health status.

An important issue in understanding the complexity of COPD as an illness and thereby its management, is what determines the subjective health status of these patients. Wilson and Cleary suggested a model that clarified the relationships between biological and physiological variables, symptoms, function, general health perception, and overall quality of life, and the impact of the characteristics on individuals and their environments. This model indicated that biological and physiological processes affect the perception of symptoms, which in turn affects function, general health perception, and overall quality of life. However, these authors point out that this main causal direction in their model does not imply that there are not reciprocal relationships.

Several studies of COPD patients have examined different associations between physiological variables, symptoms, physical function, and subjective health status. For example, de Torres et al investigated differences in physiological factors and sex, and reported that women have better oxygen saturation than men. In terms of symptoms, studies of COPD patients have shown that higher oxygen consumption is associated with improved mood, and lower predicted FEV_1% is associated with

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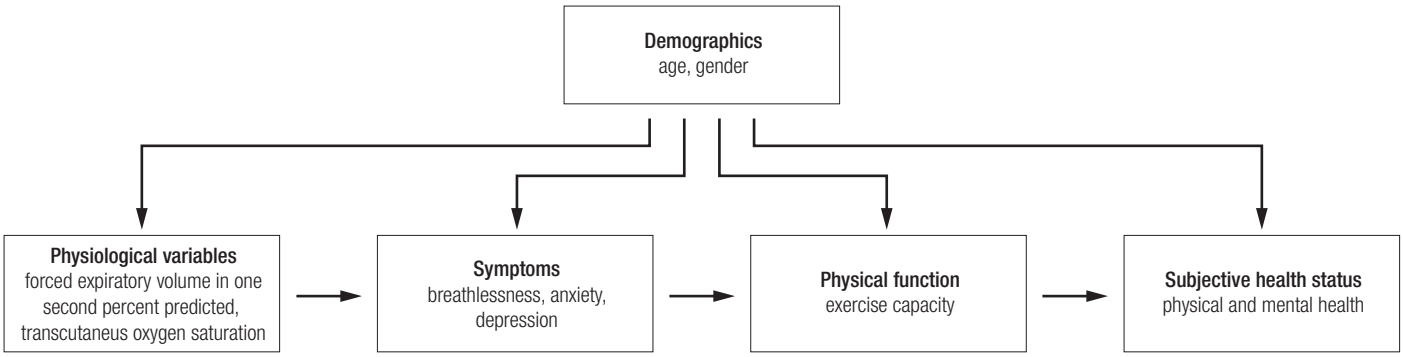

Figure 1. A proposed model for the relationships between demographics, physiological variables, symptoms, physical function and subjective health status.

more breathlessness. Furthermore Cleland et al found that older COPD patients report less anxiety and depression than younger. Anderson found that greater depression is associated with lower physical function. With regard to subjective health status, studies have reported that women suffering from COPD and older COPD patients report worse physical health. Other studies have reported that lower predicted FEV_1% and functional exercise capacity and greater anxiety and depression are associated with lower subjective health status.

The abovementioned studies mainly investigated bivariate relationships between demographics, physiological variables, symptoms, physical function, and subjective health status, but lack a multivariate perspective on subjective health status in COPD. According to the biopsychosocial perspective, subjective health status cannot be explained by biological and physiological factors alone. Instead, subjective health status is the result of an interaction between physiological and psychosocial factors. COPD is a chronic disease, which must be managed rather than cured. Therefore, knowledge about what determines subjective health status in this group of patients is relevant for the treatment of COPD, and for the care and rehabilitation of patients. To this end, the aim of the present study was to explore the determinants of subjective health status in COPD by evaluating the relationships between background variables such as age and sex, predicted FEV_1%, oxygen saturation, breathlessness, anxiety and depression, exercise capacity, and physical and mental health. Based on previous studies in COPD patients and the conceptual model of Wilson and Cleary, the following conceptual model is postulated.

Methods

This study had a cross-sectional design, and included 136 patients with COPD recruited from the outpatient clinic at a medium-sized hospital between August 2005 and August 2007. The patients were referred to the out-patient clinic to attend a rehabilitation programme designed for COPD patients. Those who fulfilled the criteria listed below were invited to participate in this study.

Inclusion criteria: Age > 35 years; Diagnosed with COPD by a respiratory physician; Symptoms such as breathlessness, chronic cough, and sputum production; FEV_1/FVC < 70% and FEV1 < 80% predicted; Able to read and write Norwegian. Exclusion criteria: Using long-term oxygen treatment; Unstable heart disease. Patients were given verbal and written information about the study, an informed consent form giving their permission to take part in the study, and a questionnaire with a hand-signed cover letter and a pre-stamped envelope when they underwent the examination at the out-patient clinic. Each patient's respiratory symptoms and physical health were assessed by a physician, nurse, and physiotherapist, all specialized in pulmonary disease. All patients underwent height and weight measurements, spirometry, an Incremental Shuttle Walking Test (ISWT), and electrocardiogram. Those who had not returned the questionnaire within two weeks were sent a reminder. This study was performed according to the Declaration of Helsinki and was approved by the hospital unit, the Regional Committee for Medical Research Ethics, and the Norwegian Social Science Data Services.

The following measurements described below were used to examine demographics, physiological variables, symptoms, physical function, and subjective health status:

A) Demographics – The patients completed a questionnaire consisting of the following variables: age (continuous variable, in years) and sex.

B) Physiological variables – Data on lung function and transcutaneous oxygen saturation were collected during the visit at the out-patient clinic. Pulmonary function tests: Spirometry was performed with a Vitalograph Alpha spirometer, according to international guidelines. Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were measured and the predicted values calculated according to a Norwegian reference population. FEV1/FVC% was calculated and a value < 0.7 together with FEV_1 < 80% predicted was used as a diagnostic criterion for COPD. FEV_1 (litre) and FEV_1 as a percentage of the predicted value (predicted FEV1%) were used as a measure of lung function. Transcutaneous oxygen saturation (SaO_2%) was measured with a Konica Minolta PulsOx-3i Pulse Oximeter. SaO_2% was measured immediately before the incremental shuttle walking test.

C) Symptoms – To measure their symptoms, the patients filled out a questionnaire on breathlessness, anxiety, and depression.

Breathlessness was measured with the St George's Respiratory Questionnaire (SGRQ). The SGRQ is a disease-specific instrument for patients suffering from pulmonary disease. The questionnaire consists of 76 items divided into three components: 1) symptoms, 2) activity, and 3) impact. A sum is calculated for each component. Each of the scores ranges from 0 to 100, the lower scores indicating better health status. The SGRQ has been translated into different languages and used in several studies of COPD patients, including in Norway. The questionnaire has been tested for reliability and validity in different studies and the results showed satisfactory reliability and validity in COPD patients. Only the symptom component,

Table 1: Characteristics of the Responders (N=100)

		N	(%)	Mean	(SD)	Range
Age (years)				66.1	(8.3)	42-82
Gender	Male	51	(51)			
	Female	49	(49)			
Spirometry	FEV1(litre)[a]			1.31	(0.50)	0.42-2.54
	FEV1% predicted[a]			46.0	(15.0)	16.79
	FEV1/FVC%[a]			51.6	(12.5)	28-69
Transcutaneus oxygen saturation (SaO2%)[a]				96.0	(1.9)	88-99
Breathlessness (SGRQ)[b] (0-100)				49.8	(27.8)	0.0-97.5
Anxiety (HADS-A)[b] (0-21)				5.9	(3.9)	0.0-17.0
Depression (HADS-D)[b] (0-21)				4.5	(3.7)	0.0-19.0
Exercise capacity (ISWT)[a] (metre)				336.7	(163.9)	57.0-770.0
Physical health summary scale (SF-36)[a]				38.4	(9.9)	14.7-58.2
Mental health summary scale(SF-36)[a]				48.6	(10.4)	20.8-68.3

[a]Higher score indicate better lung function, oxygen saturation, exercise capacity and physical and mental health.
[b]Higher score indicate more breathlessness, anxiety and depression.

which measures breathlessness in terms of frequency and distress, was used in this study. The symptom component consists of 8 items including frequencies and distress of breathlessness in term of phlegm/sputum, shortness of breath, wheezing and chest trouble.

Anxiety and depression were measured with the Hospital Anxiety and Depression Scale (HADS). HADS is a questionnaire developed to measure anxiety and depression in nonpsychiatric patients treated at hospital clinics. The questionnaire consists of 14 items. Seven items measure anxiety (HADS–A) and seven items measure depression (HADS–D). The items are scored on a four-step scale ranging from 0 (not at all) to 3 (very much). One anxiety and one depression scale are scored by summing the patient's responses. The scores range from 0–21, with higher scores indicating higher anxiety and depression. HADS has been thoroughly tested for psychometric properties and has been used in patients suffering from COPD and the general population in Norway.

D) Physical function – Data on physical function were collected during the examination at the out-patient clinic.

Exercise capacity was measured with the ISWT. The ISWT is a standardized progressive walking test used to measure functional exercise capacity in patients with cardiorespiratory conditions. The test requires patients to walk at increasing speeds up and down a 10-metre course. The speed of walking increases every minute and is controlled by audio signals played on a DVD. The distance walked is reported in metres and greater distances indicate better exercise capacity. The ISWT has shown satisfactory reliability and validity in COPD patients.

E) Subjective health status – Physical and mental health.

The Short Form 36 health survey (SF-36) was used to measure physical and mental health. SF-36 is one of several generic questionnaires developed in the United States by the Medical Outcomes Study to assess subjective health status. The questionnaire consists of 36 questions that measure eight conceptual components: physical functioning, physical role limitations, bodily pain, self-reported general health, vitality, social function, emotional role limitations, and mental health. The scores in each component and the total scores are transformed onto 0–100 scales. Higher scores indicate better subjective health status. One physical health summary score and one mental health summary score were computed from the eight dimension scores. The physical health summary score is mainly based on the physical health, physical role limitations, bodily pain, and general health components, whereas the mental health summary score is mainly based on the vitality, social function, emotional role limitations, and mental health components. In this study, we used the physical and mental health summary scores. The questionnaire has shown satisfactory reliability and validity in COPD patients, and has been thoroughly tested for psychometric properties in several countries, including Norway.

The data were analysed with SPSS for Windows version 15.0 (SPSS Inc, Chicago, IL). Missing data for the SF-36 and SGRQ were accommodated according to the user manuals. For the HADS, missing data were accommodated for individuals who had responded to five or more of the seven items of HADS–A or HADS–D. Descriptive analyses (mean, standard deviation [SD], range) were used. Simple and multiple linear regression analyses were used to investigate the relationships between demographics, physiological variables, symptoms, physical function, and subjective health status. In the multiple linear regressions, the analysis demographics were entered as independent variables. Physiological variables, symptoms, and physical function values were used as both independent and dependent variables, and subjective health status was entered as a dependent variable according to the model shown in Figure 1. In the present study, $p < 0.05$ was considered statistically significant.

Results

The sample consisted of 100 (response rate, 74%) patients suffering from COPD and awaiting participation in an outpatient pulmonary rehabilitation program. The characteristics of the responders are shown in Table 1. In the bivariate analysis, age (regression coefficient = –0.75, p = 0.025) and predicted FEV1% (regression coefficient = –0.42, p = 0.024) showed a significant relationship to breathlessness, and sex (difference = –1.86, p = 0.017) to anxiety (level 0). When both demographic and physiological variables were entered in the analysis, age (regression coefficient = –0.84, p = 0.019) and sex (difference = –2.21, p = 0.011) still showed a significant relationship to breathlessness and anxiety (level 2). Age (regression coefficient = –7.12, p = 0.001), predicted FEV_1% (regression coefficient = 2.97, p = 0.015), anxiety (regression coefficient = –9.22, p =

0.041), and depression (regression coefficient = –16.26, $p < 0.001$) showed significant bivariate relationships to exercise capacity (level 0). When all the variables were entered into the regression analysis, age (regression coefficient = –7.45, $p < 0.001$), sex (difference = 76.41, $p = 0.022$), predicted FEV1% (regression coefficient = 2.71, $p = 0.020$), and depression (regression coefficient = –14.22, $p = 0.009$) showed significant relationships to exercise capacity (level 3). In the bivariate analysis, predicted FEV_1% (regression coefficient = 0.19, $p = 0.007$), breathlessness (regression coefficient = –0.17, $p < 0.001$), anxiety (regression coefficient = –1.04, $p < 0.001$), depression (regression coefficient = –1.54, $p < 0.001$), and exercise capacity (regression coefficient = 0.02, $p = 0.021$) were significantly associated with physical health (level 0). When demographics, physiological variables, symptoms, and physical function were entered into the analysis, only breathlessness (regression coefficient = –0.09, $p = 0.027$) and depression (regression coefficient = –0.88, $p = 0.015$) were significantly associated with physical health (level 4).

Our results also showed significant bivariate relationships between anxiety (regression coefficient = –1.74, $p < 0.001$), depression (regression coefficient = –1.80, $p < 0.001$), exercise capacity (regression coefficient = 0.02, $p = 0.031$), and mental health (level 0). When all the variables were entered into the regression analysis, predicted FEV1% (regression coefficient = –0.14, $p = 0.043$), anxiety (regression coefficient = –0.85, $p = 0.004$), and depression (regression coefficient = –1.31, $p < 0.001$) showed significant relationships to mental health (level 4).

Age and sex account for only –1% and 1%, respectively, of the adjusted R2 for physical and mental health. When the physiological variables were entered into the model, the adjusted R2 increased to 1% for physical health and 2% for mental health. When symptoms were added, the explained variance increased to 36% for physical health and 53% for mental health, whereas physical function added no substantial variance. When all the variables were entered into the regression analysis, the explained variance was 37% for the physical health component and 53% for the mental health component (levels 1–4).

In this study, Cronbach's alpha was 0.86, 0.85, and 0.87 for the symptom, activity, and impact components, respectively, and 0.93 for the total score of the SGRQ. With regard to HADS, Cronbach's alpha was 0.85 for anxiety and 0.84 for depression. Cronbach's alpha ranged from 0.77 to 0.90 for SF-36 subscales. The lowest value was observed for the general health component (0.77) and the highest value for the bodily pain component (0.90).

Discussion

The results of this study show that patients with more breathlessness and depression reported lower physical health. Moreover, those with better lung function but more anxiety and depression reported lower mental health. These results also show that symptoms explain a greater proportion of the variance in subjective health status than do demographics, physiological variables, or physical function. According to the biopsychosocial model, no one single factor explains the subjective health status. Instead, it reflects the complexity of the associations between biological and psychosocial factors, progresses of symptoms, to clusters of symptoms, to syndromes, and finally to diseases with specific pathogeneses and pathology.

This is the first study to explore a multivariate perspective on subjective health status in COPD patients based on Wilson and Cleary's conceptual model of biopsychosocial relationships to subjective health status. In this study, a conceptual model was established based on Wilson and Cleary's framework and previous COPD-specific studies. In the model, there is a unidirectional relationship between the biological and physiological variables, symptoms, and physical function, which leads to the subjective health status (Figure 1). According to Osoba, there is a reasonably strong correlation between the proximal components of Wilson and Cleary's model (such as symptoms and physical function) and a weaker correlation between the more distant components (such as the physiological variables and subjective health status). There may also be a bidirectional relationship between some components. There is not necessarily a strong association between the objective physiological indicators of the disease and the patients' subjective experience of their health status. In this respect, studies of COPD patients have found weak associations between objective measures of disease, symptoms, physical function, and subjective health status.

The results of this study show insignificant associations between age, sex, and oxygen saturation. Conflicting results have been found in previous studies. De Torres et al. found that women suffering from COPD tended to have better oxygen saturation than men. Conversely, Di Marco et al found an insignificant association between sex and oxygen saturation. Insignificant associations between age, sex, and oxygen saturation suggest that the women and men studied were at the same stage of COPD.

The observation that older COPD patients report less breathlessness than younger is in contrast to Stavem et al who not find any such association. This finding may be due to response shift. Patients adapt over time in relation to goals, expectations and values, and their perceptions of symptoms may therefore change. Furthermore, the process of learning to cope with health problems is well-known in chronically ill patients. Older COPD patients may have suffered longer from COPD and anticipate illness as part of growing old. Moreover, health- related stressors may not produce the same reactions in elderly. Although older patients may have difficulties due to breathlessness, they may see physical and functional disability as result in growing older. The fact that women tend to report more anxiety than men is not surprising because there is ample evidence of a higher prevalence of anxiety among woman than among men. That women report more anxiety than men is also consistent with previous studies of COPD patients. In this study, small and insignificant associations were identified between physiological variables and symptoms. These results are in accordance with previous studies of COPD patients, which found small and insignificant associations between physiological measurements and breathlessness, anxiety, and depression.

Patients with less breathlessness and depression reported better physical health, and those with less anxiety and depression reported better mental health, which is consistent with previous studies of COPD patients. However, it is surprising that lung function was not associated with physical health and that better lung function was associated with worse mental health. The same trend was observed in other studies of COPD patients, although the association was not statistically significant.
The results of our study show that the association between symptoms and subjective health status was stronger than the

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Extrathoracic Airway Hyperresponsiveness as a Mechanism of Post Infectious Cough: Case Report

Nicole M. Ryan, Peter G. Gibson

Post-infectious cough is a common diagnosis in people with chronic cough. However, the specific infectious aetiology and cough mechanisms are seldom identified.

We report a case of chronic cough after Mycoplasma pneumoniae lower respiratory tract infection with extrathoracic airway hyperresponsiveness as the cough mechanism. Extrathoracic airway hyperresponsiveness may be a common mechanism in post-infectious cough, which may be useful both diagnostically and therapeutically since chronic cough with extrathoracic airway hyperresponsiveness responds to speech pathology treatment.

Background

Post-infectious cough is a common diagnosis, especially in primary care settings, although a specific infectious aetiology is rarely confirmed. Aside from pertussis, the role of other infectious agents in chronic cough is poorly understood. In specialist clinics chronic cough occurs in association with asthma, rhinitis, gastro-oesophageal reflux (GERD), and ACE inhibitor use.[1] However, even in these settings, a respiratory infection is often reported at the onset of chronic cough. Extrathoracic airway hyperresponsiveness (EAHR) represents variable extrathoracic airflow obstruction following inhalation provocation testing.[2-6] It manifests as a fall in inspiratory airflow during challenge with histamine, exercise, or hypertonic saline. EAHR is a feature of cough due to ACE inhibitor use,[2] rhinosinusitis[3,4] and GERD,[5] and possibly asthma.[6] The mechanism of post-infectious cough is not known, however, upper airway sensory hyperresponsiveness might be one important mechanism in driving cough in some entities of CC[7] and this current case suggests that EAHR may be a useful objective marker and relevant mechanism in post infectious cough.

Case Presentation

A 60 year old non-smoking male presented to the Emergency Department with a non-productive cough and cold symptoms. For the past week he had been confined to bed and reported severe bodily pain, a troublesome cough and shortness of breath when showering and toileting. His temperature was 38.6°C. Physical examination of the chest was unremarkable and chest radiograph showed increased bronchial markings centrally. Arterial blood gas results breathing room air were: pH 7.46, pCO_2 4.6 kPa, pO_2 6.9 kPa. He was commenced on oral roxithromycin 150 mg bd, inhaled salbutamol 100 ug 2 puffs qid, and analgesia, and continued pre-existing carbamazepine 300 mg bd for controlled epilepsy (a recent onset condition) and thyroxine 50/100 mcg on alternative days for hypothyroidism which had developed five years prior. He was subsequently changed to oral azithromycin 500 mg, improved and was discharged on day 5. Acute and convalescent serology confirmed recent infection with Mycoplasma pneumoniae (antibody titre 1:1280 (ref range < 1:40).

At a seven week follow-up visit he described persistent cough, inspiratory dyspnea, voice changes (characteristics common to paradoxical vocal cord movement (PVCM) and EAHR disorders) and fatigue. Hypertonic saline provocation test was requested and conducted 2 months later.

Spirometry was FEV_1 84% predicted, FVC 86% predicted, FEV_1/FVC 78%; and $FIF_{50\%}$ 5.22 L/sec. Hypertonic (4.5%) saline provocation challenge identified EAHR with attenuation of the inspiratory flow curve. The $FIF_{50\%}$ decreased by 39% to 3.20 L/s at a cumulative saline dose of 10.59 mL (figure 1, solid line). The fall in FEV_1 (12%) was within normal limits. A trial of fluticasone/salmeterol and nedocromil sodium was commenced.

The patient's cough and dyspnea had greatly improved by three months. One year later the cough had resolved completely and an inspiratory/expiratory flow volume curve was normal. There was no EAHR or bronchial hyperresponsiveness after repeat hypertonic saline challenge (figure 1, dotted line), fall in FEV_1 remained within normal limits (8%) and laryngoscopy showed no posterior chinking during inspiration and no paradoxical vocal cord movement (PVCM).

Discussion

This case report describes Mycoplasma pneumoniae respiratory tract infection as a cause of persistent cough, occurring in association with EAHR. EAHR was demonstrated by a 39% fall in inspiratory flow during hypertonic saline challenge. The cough resolved as the EAHR resolved. Extrathoracic airway sensory hyperresponsiveness might be an important mechanism in

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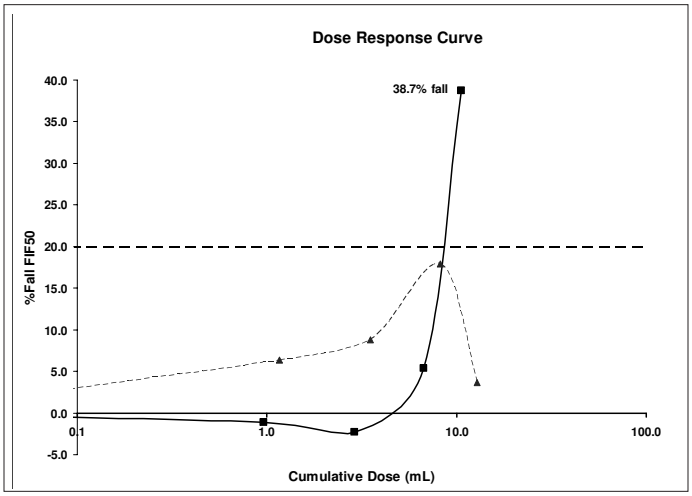

Figure 1. Hypertonic saline provocation dose response curve for FIF50% prior to treatment (demonstrating extrathoracic airway hyperresponsiveness) and after treatment. Solid line = pre treatment. Dotted line = post treatment.

driving cough in some entities of chronic cough (CC).[7] This case report extends these data to show that transient EAHR can occur with post infectious cough.

It has previously been proposed[8] that some patients with CC sustain vagal injury from respiratory infection and that airway hyperresponsiveness may persist beyond resolution of the acute upper respiratory tract infection (URTI). This hyperresponsiveness could decrease the cough threshold to irritating stimuli resulting in higher susceptibility to chemical or mechanical stimulation of the cough reflex. Transient post-infectious bronchial (intrathoracic) hyperresponsiveness is well recognised.[9] This case report identifies transient EAHR as an additional relevant mechanism associated with post infectious cough.

These observations have implications for the treatment of post infectious cough. There may be a role for inhibition of neuropeptide release, by cromoglycate, nedocromil, or specific neuropeptide antagonists in post infectious cough. Fontana et al[10] evaluated the effects of nedocromil sodium administration on cough threshold in a placebo-controlled study of healthy subjects. They found a significant increase in cough threshold values after nedocromil and an unaffected result after placebo suggesting that nedocromil sodium administration may be useful for treating cough, especially when the use of centrally acting antitussive drugs should be avoided. These agents are also of benefit in ACE Inhibitor cough, which is associated with EAHR. Also, given the similarity between PVCM and EAHR,[11] adapting techniques used by speech language therapists that were developed for PVCM maybe of benefit for post infectious cough with EAHR. In PVCM the vocal cords adduct episodically and involuntarily during inspiration. This phenomenon leads to reduced inspiratory airflow associated with signs of stridor and a perception of dyspnea characterized by the inability to inspire sufficient air.[12] EAHR is thought to be the primary underlying pathophysiology of PVCM.[13] Speech language therapy has been shown to be a successful treatment in chronic persistent cough. Vertigan et al[14] conducted a randomised placebo-controlled trial in 87 patients with CC persisting despite medical treatment. Half of these patients had EAHR and symptoms of PVCM. Patients were randomly assigned to receive either a specifically designed speech pathology intervention or placebo intervention. Participants in the treatment group were found to have a significant reduction in cough with 88% having a successful outcome compared to 14% in the placebo group. In a comprehensive literature review, Gallivan et al[15] presented cases of episodic paroxysmal laryngospasm with definitive diagnosis by videolaryngoscopy of paradoxical vocal cord adduction during inspiration and extrathoracic airway obstruction by attenuation of the inspiratory portion of the flow volume curve. Prior to this, Christopher et al[16] identified 5 patients with a functional disorder of the vocal cords that mimicked attacks of bronchial asthma, that is paroxysms of wheezing and dyspnoea refractory to standard asthma therapy. During episodes of wheezing, the maximal expiratory and inspiratory flow-volume relationship was consistent with variable extrathoracic obstruction. Laryngoscopy confirmed adduction of the true vocal and false vocal cords. While during asymptomatic periods the maximal flow-volume relationship and laryngoscopic examination were normal. Patients were not aware of the vocal-cord dysfunction, which uniformly and dramatically responded to speech language therapy where they were taught to focus attention away from the larynx and the inspiratory phase of breathing during episodes of wheeze and dyspnea.[16] EAHR may be a useful objective assessment measure to characterize laryngeal dysfunction in chronic cough.

EAHR can be assessed during inhalational provocation challenge. We prefer the use of hypertonic saline to assess EAHR as it is known to provoke neuropeptide release from nonadrenergic-noncholinergic nerves, which are prevalent in the larynx. Inhaled histamine to assess EAHR has been successfully used before[6] where the histamine concentration causing a 25% fall in mid-inspiratory flow was used as the respective threshold of EAHR. It was found that patients presenting with cough as the sole symptom had significantly greater probability of having EAHR. Histamine can however cause edema of the vocal cords furthering our preference for hypertonic saline stimulus. Methacholine challenge appears to be a less sensitive stimulus for EAHR. This is likely because of its specific action on cholinergic receptors in airway smooth muscle, and unproven action on laryngeal responses. Exercise can also be used to assess EAHR, although quantification of the stimulus may be more difficult.

Our male patient had preexisting hypothyroidism which has been associated with idiopathic chronic cough and airway inflammation.[17] This is unlikely to be the primary cause of cough in the patient as the cough developed after a well-documented Mycoplasma pneumoniae lower respiratory tract infection that occurred some 5 years after the onset of hypothyroidism. Further there is a female predominance in cases of idiopathic CC and its association with mild chronic lymphocytic airway inflammation.[18] It is however possible that a preexisting autoimmune lymphocytic bronchitis had a permissive effect on the occurrence of post-Mycoplasma chronic cough. Prospective studies would be helpful in evaluating this possibility.

Conclusion

Post infectious cough can occur with EAHR. There are opportunities to further investigate the frequency and treatment of EAHR as a mechanism of post-infectious cough with speech pathology.

References

1 Morice AH: The diagnosis and management of chronic cough.

European Respiratory Journal 2004, 24:481-492.
2 Bucca C, Rolla G, Pinna G, Oliva A, Bugiani M: Hyperresponsiveness of the extrathoracic airway in patients with captopril induced cough. Chest 1990, 98:1133-1137.
3 Bucca C, Rolla G, Scappaticci E, Chiampo F, Bugiani M, Magnano M, D'Alberto M: Extrathoracic and intrathoracic airway responsiveness in sinusitis. Journal of Allergy and Clinical Immunology 1995, 95:52-59.
4 Rolla G, Colagrande P, Scappaticci E, Bottomicca F, Magnano M, Brussino L, Dutto L, Bucca C: Damage of the pharyngeal mucosa and hyperresponsiveness of airway in sinusitis. Journal of Allergy and Clinical Immunology 1997, 100:52-57.
5 Rolla G, Colagrande P, Magnano M, Debermardi V, Dutto L, Delpiano L, Cassolino P, Bucca C: Extrathoracic airway dysfunction in cough associated with gastroesophageal reflux. Journal of Allergy and Clinical Immunology 1998, 102:204-209.
6 Bucca C, Rolla G, Brussino L, De Rose V, Bugiani M: Are asthmalike symptoms due to bronchial or extrathoracic airway dysfunction? Lancet 1995, 346:791-795.
7 Cho YS, Lee CK, Yoo B, Moon HB: Cough sensitivity and extrathoracic airway responsivenesss to inhaled capsaicin in chronic cough patients. Journal of Korean Medical Science 2002, 17:616-620.
8 Altman KW, Simpson CB, Amin MR, Abaza M, Balkissoon R, Casiano RR: Cough and paradoxical vocal fold motion. Otolaryngol Head and Neck Surgery 2002, 127:501-511.
9 Braman SS: Postinfectious Cough: ACCP Evidence-Based Clinical Practice Guidelines. Chest 2006, 129:138S-146.
10 Fontana GA, Lavorini F, Pistoloesi M: Water Aerosols and Cough. Pulm Pharmacol & Ther 2002, 15:205-211.
11 Vertigan AE, Theodoros DG, Gibson PG, Winkworth AL: The relationship between chronic cough and paradoxical vocal fold movement: A review of the literature. Journal of Voice 2006, 20:466-480.
12 Jamilla F, Stevens D, Szidon P: Vocal cord dysfunction. Clin Pulmonary Med 2000, 7:111-119.
13 Brugman SM: What's this thing called vocal cord dysfunction? In Chest Online www.chestnet.org/education/online/pccu/vol20/ lessons25_27 ; 2006.
14 Vertigan AE, Theodoros DG, Gibson PG, Winkworth AL: Efficacy of speech pathology management for chronic cough: a randomised placebo controlled trial of treatment efficacy. Thorax 2006, 61:1065-1069.
15 Gallivan GJ, Hoffman L, Gallivan KH: Episodic paroxysmal laryngospasm: voice and pulmonary function assessment and mangement. Journal of Voice 1996, 10:93-105.
16 Christopher K, Wood R, Eckert R, Blager F, Raney R, al. : Vocal cord dysfunction presenting as asthma. N Engl J Med 1983, 308:1566-1570.
17 Birring SS, Brightling CE, Symon FA, Barlow SG, Wardlaw AJ, Pavord ID: Idiopathic chronic cough: association with organ specific autoimmune disease and bronchoalveolar lymphocytosis. Thorax 2003, 58:1066-1070.
18 Birring SS, Murphy AC, Scullion JE, Brightling CE, Browning M, Pavord ID: Idiopathic chronic cough and organ specific autoimmune diseases: a case control study. Respir Med 2004, 98:242-246.

What Determines…continued from page 61
association between physiological variables and subjective health status, and this supports the multidimensional impact of COPD on subjective health status. Furthermore, the fact that subjective health status represents something other than physiological and pathological factors is useful information for consideration in the treatment and care of COPD patients.

In this study, age, sex, lung function, oxygen saturation, breathlessness, anxiety, depression, and exercise capacity influenced subjective health status. However, according to previous studies of COPD patients, body mass index, education, social status, sleeping habits, and comorbidity could be important supplementary factors affecting subjective health status in this sample. This study is limited to some degree. The sample size was quite small, which restricts the number of factors included in the multivariate testing of subjective health status. Because of the cross-sectional design, no absolute conclusions can be drawn about causality or the directions of the relationships between many of the variables. The patients included in this study were awaiting participation in a pulmonary rehabilitation programme, and were thus not a representative sample of all COPD patients. The strength of this study is its multivariate approach to explaining subjective health status. According to the biopsychosocial model, subjective health status is associated with physiological factors as well as symptoms and psychosocial factors.

The results of this study indicate that symptoms are very important to patients' subjective health status, which in turn supports the view that a pulmonary rehabilitation programme focusing on the management of symptoms, such as breathlessness, anxiety, and depression, is required to alleviate symptoms and increase subjective health status. A model that explains the relationships between different outcomes is important in clinical practice to correctly interpret the results of outcome assessments. For example, if subjective health status is determined by symptoms and physical function, then symptoms and physical function should be treated. In COPD, symptoms such as breathlessness, anxiety, and depression are usually evident before there is a reduction in subjective health status. However, it is more difficult to determine the causal direction between breathlessness, anxiety, depression, and physical function, and as breathlessness, anxiety, and depression may be caused by a decrease in function.

Conclusion

When controlled for all variables, more breathlessness and depression were associated with lower physical health, and better lung function, and greater anxiety and depression were associated with a lower mental health, with symptoms explaining the greatest variance. These findings highlight the importance of rehabilitation programs that focus on the management of symptoms in relation to COPD.

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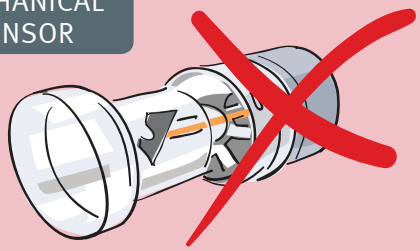

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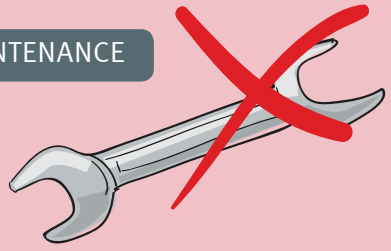

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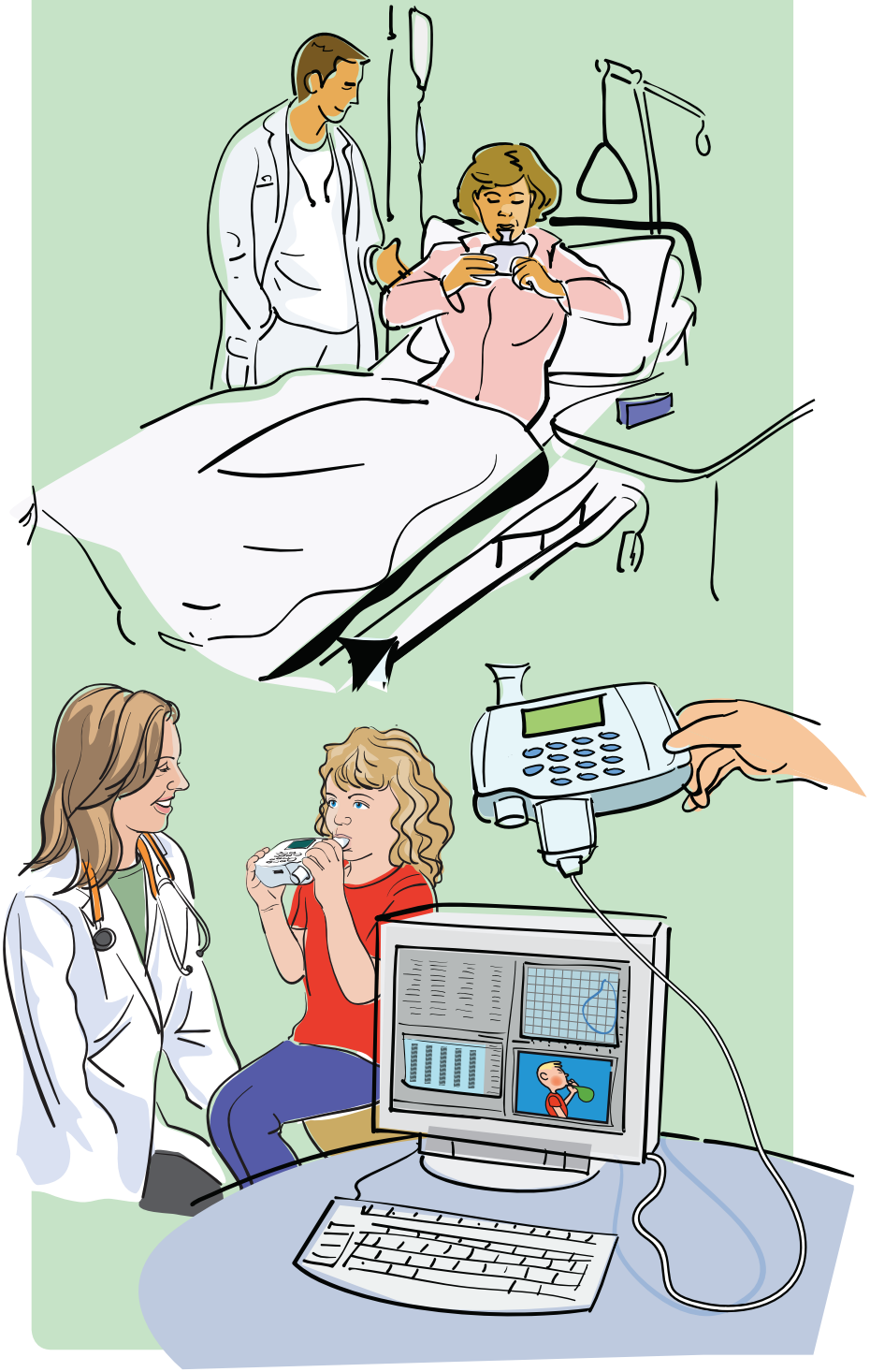

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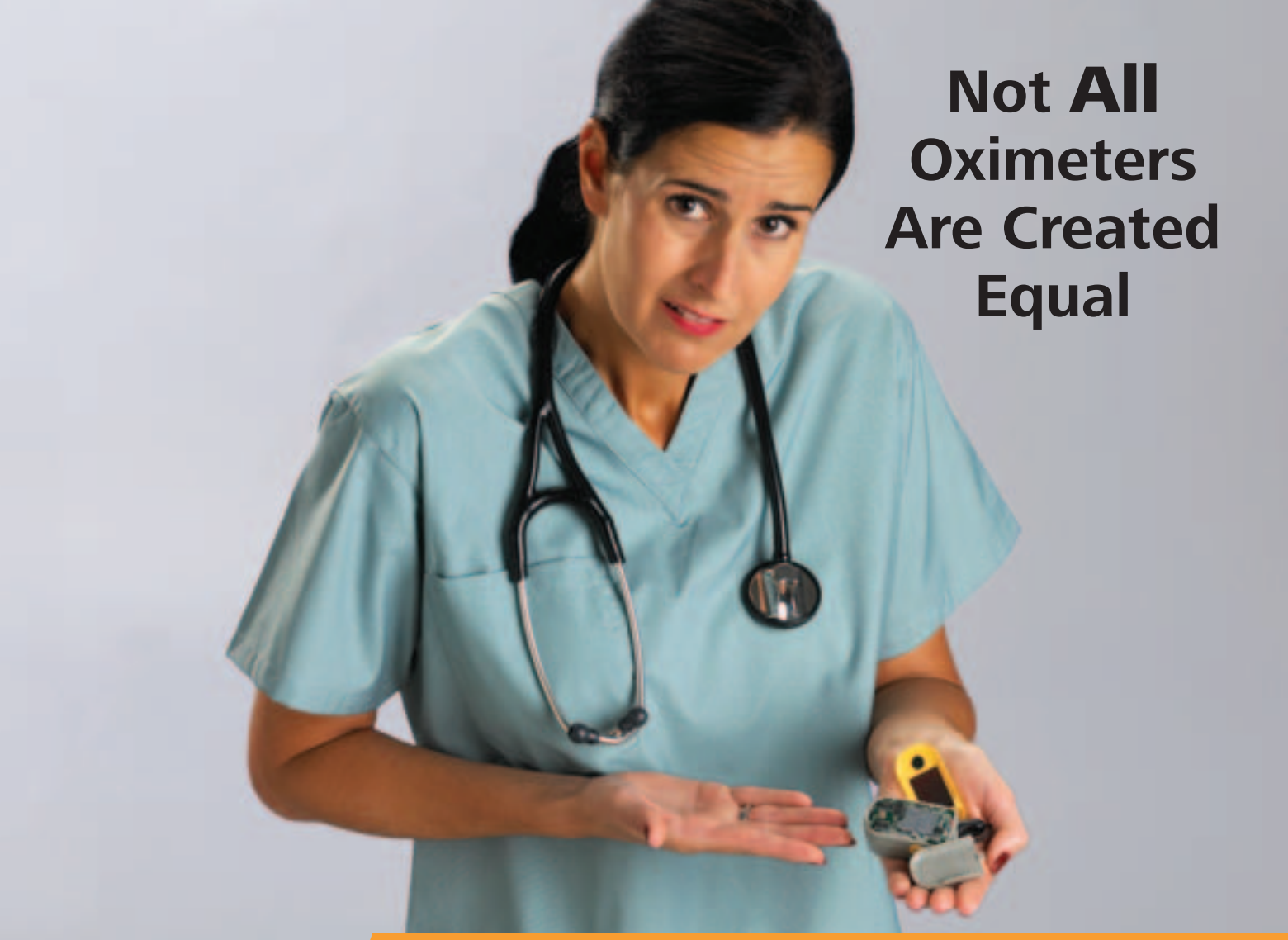

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