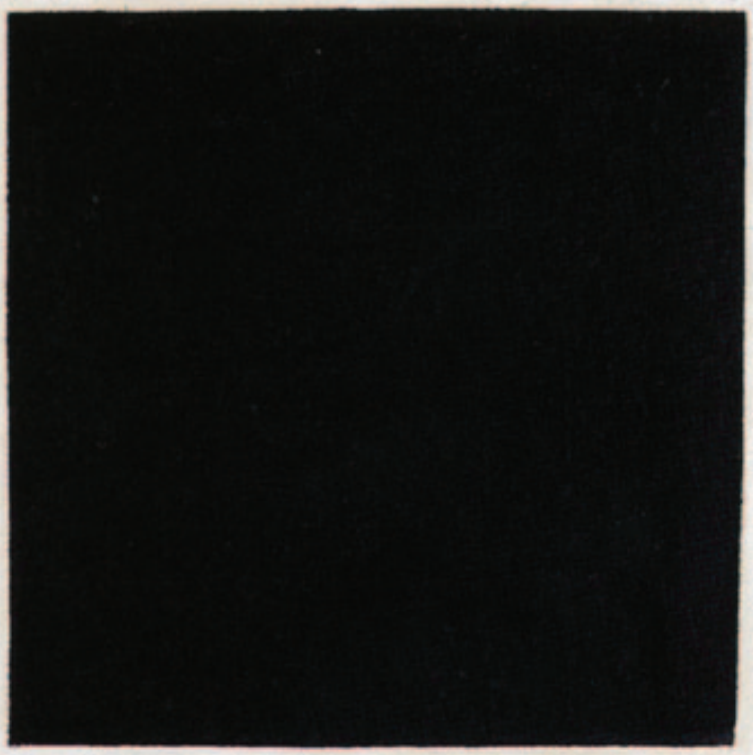
Volume 6 Number 2 April-May 2011

Respiratory Therapy™

The Journal of Pulmonary Technique



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The Journal of Pulmonary Technique

Vol. 6 No. 2
April-May 2011

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Editorial

Moral Judgments

"The secret of caring for the patient is caring for the patient." A compelling line, but what if you don't care for the patient? That's the theme of an article in the journal Philosophy, Ethics, and Humanities in Medicine. The piece doesn't try to come to a definite conclusion – how could it? But the information it provides is valuable.

What if a caregiver's reaction to the patient is negative, perhaps intensely so, driven by social and/or moral disapproval? As an example, a caregiver's patient with emphysema revealed during her intake history that she was an unrepentant Nazi anti-Semite who had supervised slave laborers during the war. The Jewish family physician struggled through her feelings and duties, noting: "I had decided that if she stayed with my practice, I could probably be a skilled and trustworthy physician to her. Intellectually, I had concluded that my job as a doctor was to take care of her, regardless of her history. I felt that I could achieve this. I could treat her emphysema and suppress or control my moral outrage. What I did not know was whether I could be compassionate."

The article says that moral emotions and judgments are active not just in such extreme cases, but in everyday clinical encounters: "Patients who fail to validate clinicians' sense of themselves as effective professionals, who threaten their control, and/or who create fruitless work are all subject to being labeled 'bad patients.'" Studies show that caregivers give more than routine care to higher status patients and less than routine care to those deemed unworthy. One study showed that staff will take moral judgments into account "unless discouraged from doing so by the organizational arrangements under which they work." A Kaiser study revealed that physicians liked their healthier patients more than their sick patients, and healthier patients liked their physicians more. One research study described the moral complexities faced by nurses on a gynecology unit devoted to failed pregnancies, abortions and cancer, where the nurses described a process of developing both task and emotional expertise over time, getting past their sometimes intense physical repugnance by focusing on details of the process at hand, and reported that the uniqueness of the challenges and expertise fostered group cohesion, which helped to sustain the nurses individually and to diminish the salience of moral issues.

Brain studies using fMRI have shown that automatic, stereotypical responses are mediated by negative emotions such as fear, anger, disgust, and contempt. Photos of homeless people and drug addicts, mixed in with other photos of people and objects triggered disgust and activated the amygdala and insula, thought to be associated with fear and disgust. Also, photos of homeless people, drug addicts, and inanimate objects failed to activate the medial prefrontal cortex, unlike all the other photos of people, thus offering a neuroscience model of dehumanization.

Neuroscientific arguments aside, there's some evidence that physicians serving poor communities are often troubled by what they perceive as their patients' inadequate motivation and dysfunctional behavioral characteristics. In a study of 12 urban hospitals, the factors predicting whether pediatric residents felt more anger and less empathy toward underserved families were whether their clinics were well-run and whether they themselves felt effective. In another study, patients with chronic low back pain or medically unexplained illness triggered negotiations that often led to unresolved contests of wills between physician and patient. Patients with problems and anxieties that could not be referred out or satisfactorily contained could trigger physician frustration and hostility. A study of unconscious defense mechanisms in nurses found that immature defenses, including passive aggression, correlated with emotional exhaustion and burnout.

The article goes on to say, "One might ask why truth-telling itself rises so infrequently as a moral issue in the minds of clinicians. In response to continual invasive

Continued on page 46…

Respiratory Therapy™
The Journal of Pulmonary Technique

ISSN 2152-355X
Published six times each year by
Goldstein and Associates, Inc.
10940 Wilshire Blvd., Suite 600
Los Angeles, CA 90024 USA
Tel: 310-443-4109 · Fax: 310-443-4110
E-mail: s.gold4@verizon.net
Website: www.respiratorytherapy.ca
Publisher Steve Goldstein
Editor Les Plesko
Senior Editor Carol Brass
Assistant Editor Laszlo Sandor
Design & Production http://accugraphics.net

Circulation, Coverage, Advertising Rates: Complete details regarding circulation, coverage, advertising rates, space sizes, and similar information are available to prospective advertisers. Closing date is 45 days preceding date of issue.

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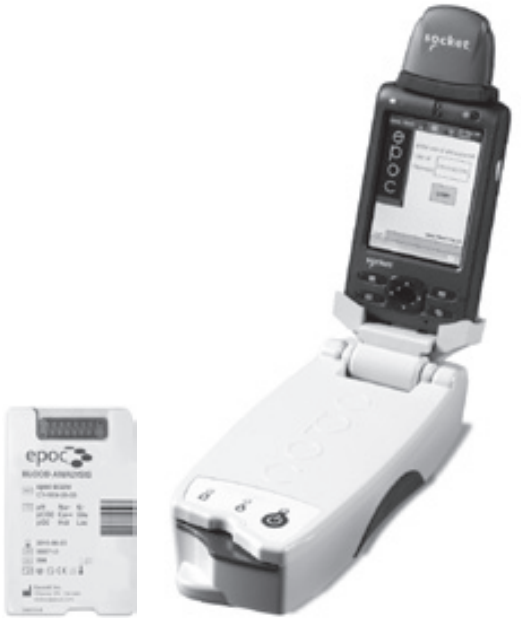

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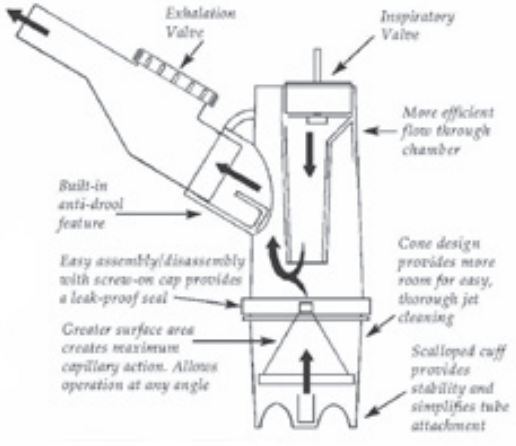

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News

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READY

A recent survey of 525 nurses from America's leading hospitals revealed that 93% were confident that hospitals were far better prepared to handle a potential pandemic than they were before the H1N1 outbreak. Additionally, 91% said their hospitals had fully incorporated flu outbreaks into their emergency preparedness systems. The H1N1 outbreak played a part in enhanced planning and awareness, as 82% said that the pandemic was "a humbling lesson from which we learned a lot." The survey was jointly conducted by Kimberly-Clark Health Care and Baylor Health Care System in cooperation with the American Nurses Credentialing Center (ANCC). Another part of the survey revealed that just 40% said the public is well informed about healthcare-associated infections.

HOME SWEET? HOME

Placebo Journal reported the announcement that Joint Commission is now going to accredit medical homes. The Journal responded: "How lovely. A third-party organization which everyone thinks works for the government is going to snoop around medical offices to see if they are pretending to make this medical home thing real. One happy horse***t organization watching over another… With more government involvement comes more regulations to follow which makes the Joint Commission feel even more self-important." See placebojournal.com.

BLOOD GAS E-BOOK

Respiratory Therapy has published its second full-length e-book, RESPIRATORY THERAPY BLOOD GAS. Our Blood Gas book is the second in a series of comprehensive knowledge resource books that will be published regularly. It is now available from Amazon for download onto Kindle, iPad, PCs and other compatible e-readers. BLOOD GAS includes dozens of up-to-date papers about blood gas from renowned clinicians, researchers and scientists. The articles in this electronic textbook have been carefully selected and culled by Respiratory Therapy's editors for relevance to the readers of this journal. BLOOD GAS 2011 is the premier edition in an ongoing series, and will be updated each year. Our other book also currently available is Respiratory Therapy Ventilation. The cost of this valuable educational and informational resource book is only $9.98. To order, go to Amazon.com and type "Respiratory Therapy Blood Gas 2011" (ASIN: B004KKZ3MG).

HOW IT'S DONE

The journal Pediatric and Developmental Pathology reports that researchers examined postmortem brain stem tissue from 17 fetuses and infants to locate the human retrotrapezoid nucleus (RTN), which serves as the critical central chemoreceptor. Mutations in the protein expression pattern of PHOX2B can lead to congenital central hypoventilation syndrome. This condition is responsible for loss of air hunger and complete sleep apnea. By applying immunohistochemical studies similar to those performed in rodent models, scientists sought to identify the RTN in the human brain. Reviews of autopsy records and stained slides from brain stem sections were conducted between 2001 and 2008. Selected cases were evaluated for PHOX2B immunoreactivity in parts of the caudal pons and medulla brain sections of these samples. In essence, researchers followed the PHOX2B pattern to locate the RTN. The predictions made from rodent models held true for human tissue. The authors report that the putative human RTN is located ventral to the facial nucleus and lateral to the superior olivary nucleus, where the two brain sections studied meet the pontomedullary junction. The authors describe this as a "valuable first step toward defining what is likely to be a key site of respiratory regulation."

FALLOUT

Patients suffering from COPD who are on long-term oxygen therapy face an increased risk of death from cardiovascular disease and other non-respiratory ailments. A study at Blekinge Hospital, Karlskrona, Sweden, suggests that physicians need to carefully monitor for these conditions and treat them to help decrease the risk of mortality. In Sweden, the mean age of patients starting LTOT increased from approximately 66 to 73 years between 1987 and 2000. The researchers wanted to find out if these changes had resulted in a shift in the causes of death for COPD patients with long-term oxygen therapy. They enrolled 7,628 adult patients who started LTOT for COPD between January 1987 and December 2004. Patients remained in the study until LTOT was suspended or until death. Study participants were followed for a median of 1.7 years. The researchers found that while the risk of death decreased annually for both respiratory disease (2.7%) and lung cancer (3.4%), there were annual increased risks of circulatory disease (2.8%) and digestive organ disease (7.8%). The overall risk of death also increased by 1.6% per year during the study period. In total, the risk of death for cardiovascular disease increased by 61.5%. The researchers noted that this supports the importance of optimized diagnostics and treatment of coexisting diseases and conditions to improve survival in severe COPD. The mechanism that underlies the increases in both overall mortality and mortality due to non-respiratory causes is that the patients have a progressively higher burden of coexisting diseases and conditions, and become more vulnerable with increasing age.

SLEEP BEFORE SLICE

Performing polysomnography prior to pediatric adenotonsillectomy may help identify children at a higher risk of developing postoperative respiratory complications, according to researchers at the George Washington University School of Medicine. Guidelines for adenotonsillectomy, established by the American Academy of Otolaryngology-Head and Neck Surgery, recommend that children should be healthy, have no evidence of obstructive sleep apnea-hypopnea syndrome, and be older than 3 years. To determine if polysomnography may potentially predict adverse outcomes following a pediatric adenotonsillectomy, the researchers examined the records of 1,131 children who underwent an adenotonsillectomy by two attending surgeons at an academic pediatric hospital. Preoperative polysomnography was performed on 151 patients, representing 13.4% of all those undergoing adenotonsillectomy. Of these, 23 (15.2%) experienced adverse respiratory events after surgery. Results of the polysomnography showed that patients who experienced respiratory complications had significantly higher apnea-hypopnea index, higher hypopnea index, and lower nadir oxygen

saturation. Additionally, the 23 individuals who experienced complications had a higher body mass index (BMI) compared with those who did not have complications, with 47.8% defined as obese, vs 29.7% in the non-complication subgroup. Overall, the patients who experienced adverse respiratory events spent an additional 22 days in the hospital beyond routine overnight observation for persons with obstructive sleep apnea-hypopnea syndrome.

BRUSH!

Maintaining periodontal health may contribute to a healthy respiratory system, according to research published in the Journal of Periodontology. A new study suggests that periodontal disease may increase the risk for respiratory infections such as COPD and pneumonia. The study included 200 participants between the ages of 20 and 60 with at least 20 natural teeth. Half of the participants were hospitalized patients with a respiratory disease such as pneumonia, COPD, or acute bronchitis, and the other half were healthy control subjects with no history of respiratory disease. Each participant underwent a comprehensive oral evaluation to measure periodontal health status. Patients with respiratory diseases had worse periodontal health than the control group, suggesting a relationship between respiratory disease and periodontal disease. Researchers suspect that the presence of oral pathogens associated with periodontal disease may increase a patient's risk of developing or exacerbating respiratory disease. However, the study authors noted that additional studies are needed to more conclusively understand this link. A related study at Sahlgrenska Academy noted that children with asthma have more caries and suffer more from gingivitis than people without asthma. The first study revealed that 3-year-olds who suffer from asthma have more caries than 3-year-olds without asthma. Researchers also compared the oral health of adolescents aged 12-16 years who had long-term moderate or severe asthma with that of adolescents of the same age without asthma. Only 1 out of 20 in the asthma group was caries-free, while 13 out of 20 were caries-free in the control group. One factor that may have influenced the development of caries is a somewhat lower level of saliva secretion, which was probably caused by the medication taken by those with asthma. An examination of the oral health of young adults aged 18-24 years, with and without asthma, had results that were nearly identical with those in the group of 12-16-year-olds.

RESTFUL NIGHTS

New research from the University of Toronto could provide some restful nights for sufferers from obstructive sleep apnea. In a recent study that appeared in the Journal of Neuroscience, scientists from the University demonstrated that repeated obstruction of the airways requires release of the brain chemical noradrenaline. The release of this chemical helps the brain learn to breathe more effectively and purposefully. "What we showed is that repeated disruption of normal lung activity – what happens during sleep apnea – triggers a form of learning that helps you breathe better. This type of brain plasticity could be harnessed to help overcome the breathing insufficiency that typifies sleep apnea," said Dr John Peever, Associate Professor of Neuroscience and lead author of the study. In order to mimic the experience of severe sleep apnea, scientists induced short 15-second apneas in sedated rats by repeatedly restricting airflow into the lungs. They found repeated apneas caused the brain to progressively trigger more forceful contraction of the respiratory muscles, which caused an increase in breathing. This increase in breathing lasted for over an hour. Peever said it seems the brain uses the unwanted side-effects of sleep

apnea to help it learn to prevent future apneas by increasing the depth of breathing. This study also pinpointed the brain chemical that allows this type of plasticity to occur. They found that noradrenaline is required in the case of repeated apneas to cause brain plasticity and enhance breathing. These findings were deemed important because they suggest that artificial manipulation with common drugs that affect noradrenaline levels in the brain could also help improve breathing in patients suffering from sleep apnea. This work could serve as the potential basis for developing the long sought after pill for sleep apnea.

CONSEQUENCES

Severe asthma in early childhood may lead to premature loss of lung function during adolescence and more serious disease during adulthood, according to researchers at Emory University School of Medicine. The researchers studied how airflow limitation changes throughout childhood and how this affects disease severity later in life. Although there are similarities between children and adults with severe asthma, recent research has shown that the limitation of airflow is not as significant in children as in adults. This raises questions about the course of severe asthma in childhood and the critical developmental time frame during which loss of lung function occurs. The authors used data from children with mild-to-moderate and severe asthma who were enrolled in a long-term National Heart, Lung, and Blood Institute Severe Asthma Research Program. The children were ages 8-11 years at the first evaluation and 11-14 years at the follow-up visit. Comparing measurements of symptoms, medication use and lung function, the researchers analyzed changes in the children's respiratory health over an average three-year period. The researchers found that children with severe asthma reported a higher frequency of daily symptoms and hospitalization during the previous year despite higher doses of ICS and controller medication, and that they had significantly lower lung function when compared to children with mild-to-moderate asthma. Additionally, they noted that daily asthma symptoms such as coughing and wheezing and sensitization to aeroallergens during the initial evaluation were strong predictors of declines in lung function of more than one percent per year. The authors concluded that children with severe asthma have a premature loss of lung function during the adolescent years that is associated with an increased frequency of wheezing and asthma symptoms and greater allergic sensitization during childhood.

THE NOSE KNOWS

A collaborative project between researchers at the Trudeau Institute and their colleagues at St Jude Children's Research Hospital in Memphis, TN examined the migration of white blood cells to the mucosal tissues of the nose in response to a viral infection. Researchers found that cells arrive early during the infection and persist at the site for months afterward, providing a first line of defense against a second infection with the virus. These cells are soldiers that guard nasal passages and combat viruses at their site of entry. The researchers said that in the future, a single application of vaccine by nasal spray or drops may be all that is needed for long-term protection against some serious respiratory virus infections.

SITTING AROUND

Up to 79% of Canadians with COPD avoid everyday activities, according to a survey by the Canadian Lung Association. The survey found that 17% of Canadians at risk for the disease don't believe COPD is as serious as other chronic illnesses like heart disease and diabetes, but it is the fourth leading cause of death in Canada. Lung attacks or COPD flare-ups are also the main cause of hospitalization for chronic medical conditions in Canada. Half of at-risk Canadians polled have already experienced one or more of the common symptoms of COPD, such as persistent cough, fatigue, phlegm and shortness of breath. In current smokers, 74% have experienced one or more symptoms. The survey also revealed that 39% of smokers avoid seeking medical advice for some of their COPD symptoms because they fear they are the consequence of smoking. Fifty-three per cent do not speak with their doctor about their COPD symptoms because they don't think it's anything serious; 27% of diagnosed and at risk Canadians who have not seen a doctor about their symptoms say they know their doctor is just going to tell them to stop smoking; and 17% of diagnosed and at risk Canadians who have not seen a doctor about their symptoms don't think there are serious consequences related to any of their COPD symptoms.

DRIVE, THEY SAID

You are six times more likely to end up at the doctors with an acute respiratory infection if you have recently used a bus or tram, but those who use buses or trams daily might be protected compared with more occasional users, according to a study at The University of Nottingham (thus, the tram). Research showed that bus or tram use within five days of symptom onset was associated with an almost six-fold increased risk of going to the doctor for ARI. The case control study ran during a local flu outbreak. One hundred and thirty eight patients (72 cases of ARI and 66 control patients) from a Nottingham GP practice were asked to fill in a questionnaire on bus or tram usages in the five days preceding the onset of their illness or the five days before consultation. The researchers found a statistically significant association between ARI and bus or tram use in the five days before symptom onset. The risk appeared greatest among occasional bus or tram users.

SURPRISING DEVELOPMENT

ALI and ARDS can develop in surprising ways that seem to have little relation to the lungs, from severe trauma and after severe burns, for instance. Researchers at the University of Colorado School of Medicine used animal models of ALI/ARDS to show that the aggressive inflammatory state of specific immune cells can be switched off to control such runaway inflammation. Studies of the neutrophils and macrophages that are responsible for ALI/ARDS have led to important ideas which offer hope for new concepts and options for treatment. For example, it is now known that the macrophage itself can exist in both an aggressive inflammatory state and in a more reparative state that can even help the lung to heal. The researchers said they'd like to see that if by switching the state of the macrophages to the more reparative state, the ongoing inflammation will be stopped and the capacity of the lung to repair itself will improve.

UNDER CONTROL

Scientists at Temple University have found a new therapeutic target for controlling dangerous inflammation in the lungs. Blocking the activation of the enzyme delta-protein kinase C (delta-PKC) could protect the lungs from neutrophil-mediated damage, which can result in out of control inflammation. In an animal model of acute respiratory distress syndrome (ARDS), inhibiting delta-PKC in the lungs showed dramatically reduced inflammation, thereby protecting the lungs from further

damage. Researchers used a rat model of severe inflammation or sepsis that produces lung injury. The animals that received the delta-PKC inhibitor had markedly reduced evidence of lung injury and distress. These results suggest that delta-PKC is an important regulator of inflammation in the lung and that targeted inhibition of this enzyme may protect the lungs from the damage associated with severe infection.

D-EFICIENCY

Vitamin D deficiency can be linked to the development and severity of autoimmune lung diseases, according to researchers at the University of Cincinnati. The researchers wanted to see if lack of sufficient vitamin D would also be seen in patients who are diagnosed with an autoimmune interstitial lung disease (ILD) and whether this was associated with reduced lung function. They evaluated 118 patients, 67 with connective tissue disease-related ILD and 51 with other causes of lung fibrosis, for serum 25-hydroxyvitamin D levels, and then evaluated associations between these serum levels and the patients' conditions. Those with connective tissue disease related ILD were 52% vs 20% more likely to have vitamin D deficiency. Vitamin D insufficiency was pegged at 52% vs 20%. Reduced serum 25-hydroxyvitamin D levels were strongly associated with reduced lung function. The findings suggest a high prevalence of vitamin D deficiency in patients with ILD, particularly those with connective tissue disease. Information is from Medical News Today, copyright Medical News Today.

CF AND EMPHYSEMA

Johns Hopkins Children's Center researchers have found the protein CFTR, involved in cystic fibrosis, also regulates inflammation and cell death in emphysema and may be responsible for other chronic lung diseases. In CF, the protein's chloride-carrying ability is absent due to genetic mutations, resulting in the buildup of thick sticky mucus in the lungs, which causes lung infections and breathing problems. The Johns Hopkins study indicates that CFTR is involved in immune regulation and immune response on a far wider scale than previously thought. Research on mice and human lung tissue showed that those with lung damage from emphysema had less CFTR on the cell surface and that changes in the level of CFTR corresponded directly to disease severity. Decreases in CFTR also corresponded to increased buildup of the fatty molecule ceramide, a trigger of inflammation and cell death. By regulating ceramide's inflammation-causing activity, CFTR appeared to be a "watchdog for inflammation and cell death." Researchers noted how CFTR causes ceramide to trigger lung-damaging inflammation by studying cell membranes using cytometry, which captures changes in inflammatory and protein markers. CFTR keeps a lid on the signaling activity of inflammatory receptors by preventing them from clustering, thus warding off inflammation and lung damage.

DON'T PANIC!

A new treatment program called CART can teach panic-disorder sufferers to calm down and control their breathing, according to researchers at Southern Methodist University in Dallas. Capnometry-Assisted Respiratory Training helps patients learn to breathe in a way that reverses hyperventilation, by doing simple breathing exercises twice a day. A portable capnometer supplies feedback during the exercises on a patient's CO_2 levels as the patient breathes more slowly and shallowly. In a study at the University, CART effectively reduced hyperventilation and proved effective by normalizing respiratory physiology. In a CART-CT study, 41 patients were assigned to complete either a CART or CT treatment program for panic disorder and agoraphobia. Both treatments worked, but CART physiologically altered panic symptoms by reversing hyperventilation. The above information is from Medical News Today, copyright Medical News Today.

PANT-PANT-PHEW!

Obese people are more likely to report exercise as a trigger for asthma, according to researchers at the Hospital of the Sacred Heart in Montreal. Of 673 people evaluated in the study, 71% reported exercise-induced asthma (ETA). The researchers found that every one-point increase in body mass index score was associated with a 9% increase in the probability of reporting exercise-induced asthma.

GOAL ACHIEVED

The DRIVE4COPD campaign announced that it achieved its goal of screening one million Americans to determine their risk for COPD in the campaign's first year. DRIVE4COPD aims to make a fundamental change in how COPD is addressed in the US, and an important part of this effort is to find the millions who may be at risk for COPD and do not know it. Nearly 20% of the people who have taken the screening scored high enough to indicate they may be at risk for COPD. The campaign asks those who identify as at-risk to share the results of the screen with their healthcare professional. All Americans age 35 or older who have smoked 100 cigarettes in their lifetime are encouraged to log onto drive4copd.com and be screened. A major corporate sponsor of the program is Boehringer Ingelheim Pharmaceuticals, Inc.

PRODUCTS

SAGE ACQUISITION

Royal Philips Electronics announced that it acquired the assets of medSage Technologies LLC, a provider of patient interaction and management applications ("medSage Technologies"). The acquisition will allow Philips to offer a web-based solution that enables homecare providers to manage ongoing compliance and replenishment services for individuals under treatment for obstructive sleep apnea, diabetes, respiratory and other conditions. The acquired business will become part of the Sleep business within Philips Home Healthcare Solutions. MedSage Technologies has developed a voice and email application that homecare providers can use to interact with patients. Contact philips.com.

BE ETHICAL

The book Medical Ethics for Dummies from Wiley offers an affordable course supplement for those studying medical ethics. It includes discussions of basic principles and common controversies, informed consent, distinctions between ethics and morality, ethical challenges, disclosing errors, and daily challenges. The authors are Jan Runzheimer, MD, a family physician and ethicist, and Linda Johnson Larsen, who has written 24 books on health. The book is $24.99, through Amazon or from Wiley Publishing.

NEW MANAGER

Respiratory Technology Corporation (Restech) announced the appointment of Madaline Woodard as Marketing Communications Manager, with responsibility for corporate communications and marketing. Ms Woodard manages all facets

of marketing operations including e-mail and print campaigns, campaign analytics, website maintenance, tradeshow exhibit coordination and promotions, and training-seminar and webinar promotions. She began her career producing non-fiction books for Thomson/Gale, then moved to the marketing side of the business at Plural Publishing, Inc. Contact restech-corp.com.

BIGGEST WINNERS

For the fifth consecutive season, Philips is supplying CPAP therapy devices for NBC's Biggest Loser finalists and contestants with CPAP equipment for sleep-disordered breathing. Through sleep testing with Philips Respironics' Alice 5 diagnostic equipment and treatment with REMstar auto titrating CPAP units, Philips Respironics equipment has been used by members of the Biggest Loser cast diagnosed with sleep apnea since season seven. Over the last five seasons, Philips Respironics has provided a variety of CPAP devices and masks for use in testing and treating the contestants. For season 11, the Philips Respironics System One sleep therapy platform, combined with the company's EasyLife dual-cushion mask, are being used. Contact philips.com.

TAKING FLIGHT

Flight Medical, developer of the Flight 60 and HT50 line of portable ventilators, announced a distribution agreement with SRC Medical of Northridge, CA to distribute the Flight 60 line of ventilators and ventilation monitoring in the western US. Flight 60 is a new line of portable ventilators featuring state of the art ventilation modes, with patient flow management, 12 hours of battery life, and hot-swap capabilities. Contact www.flight-medical.com.

INSPIRATIONAL

Inspire Medical Systems announced it has received approval from the FDA to begin its STAR pivotal clinical trial. The STAR trial (Stimulation Therapy for Apnea Reduction), is a multicenter study that will evaluate both the safety and effectiveness of Inspire Upper Airway Stimulation (UAS) therapy in patients with moderate to severe obstructive sleep apnea (OSA). The STAR trial will be conducted at leading medical centers across the United States and Europe. The results of this study will be the basis for a Pre-market Approval (PMA) application to the FDA. Inspire also announced that it has received CE Mark for Inspire Upper Airway Stimulation (UAS) therapy. Leading medical centers in Germany, Belgium and The Netherlands are currently approved to implant patients into the STAR trial. Inspire Medical Systems has already completed three independent feasibility studies in the US, Europe and Israel. While the OSA patient sleeps, Inspire therapy is designed to deliver physiologically timed, mild stimulation to the hypoglossal nerve on each breathing cycle. The stimulation is intended to restore tone to the muscles that control the base of tongue, preventing the tongue from collapsing and obstructing the airway. Patients control when the therapy is turned on and off via a handheld programmer. In contrast to other surgical procedures to treat sleep apnea, Inspire therapy does not require removing or permanently altering an OSA patient's facial or airway anatomy. [Investigational device, limited by US law to investigational use.] Contact InspireSleep.com.

EU APPROVAL

The European Commission (EC) approved InterMune's Esbriet (pirfenidone) as the first treatment for adults with mild to moderate idiopathic pulmonary fibrosis (IPF). The approval represents a major milestone in the treatment of IPF. Contact intermune.com.

SECOND TIME CHARM

Dräger has received the Zenith Award for continuing support of the respiratory care profession. This marks the second year that Dräger has received this top honor. The award, which is supported by the American Association for Respiratory Care, was announced during the 2010 International Respiratory Congress in Las Vegas. Dräger was one of five companies chosen for the prestigious industry award by the Association's more than 50,000 members. Selection was based on the quality of the company's equipment, accessibility and helpfulness of its sales personnel, overall responsiveness, service record, commitment to truth in advertising, and support of the respiratory care profession. Dräger continued to demonstrate its commitment to the respiratory care profession by launching two new ventilator platforms for critical and neonatal care, publishing several clinical booklets to support educational needs of respiratory therapists, introducing a resource website for neonatal practitioners and parents, creating a peer-reviewed document of shared best practices for protective lung ventilator, expanding its educational program with Intensive Care Online Network (ICON) to provide complimentary webinars, and developing a rental program. Contact draeger.com.

EXPANSION

OPTI Medical Systems is pleased to announce the expansion of the OPTI CCA-TS blood gas analyzer test menu to include lactate. The OPTI CCA-TS analyzer provides fast and accurate lactate and blood gas analysis results to assist in the early detection of sepsis. The OPTI CCA-TS measures lactate, pH, PCO_2, PO_2, tHb, and SO_2 in whole blood – perfect for quick diagnosis at the point of care. For more information visit optimedical.com.

ORAL RINSE + AWARD

Kimberly-Clark Health Care recently announced a significant new addition to its Kimberly-Clark KimVent 24-Hour Oral Care offering: CHG Oral Rinse. The CHG Oral Rise consists of 15 mL unit dose of CHG Oral Rinse, 0.12% and comes in single dosage cups for convenient dispensing. The cups also have barcode labeling for easy scanning and documentation; complying with hospital protocols. In other company news, Kimberly-Clark Health Care was awarded the 2010 American Association for Respiratory Care (AARC) Zenith Award. The award is based on quality, accessibility of sales personnel, responsiveness, service record, truth in advertising, and support of the respiratory care profession. Contact kchealthcare.com.

WONDERFUL WORLD OF COLOR

Rainbow Ties from Pepper Medical have added color, and now come in three different color schemes: variety, pastel, and bold. They also feature Orthowick, a new moisture wicking technology exclusively from Pepper Medical that pulls the moisture away from the child's skin, potentially aiding in the reduction of skin breakdown and infection. The Rainbow Ties feature soft Velcro tabs, with a plush backing that aids patient comfort. They're latex-free and are available in both one piece and two piece designs. Pepper Medical's Vent-Tie is a ventilator antidisconnect device with trach tube holder. It features 100% cotton flannel and open loop with moisture-wicking fabric and thicker foam padding. It is latex-free. The Vent-Tie's antidisconnect strap aids

in securing ventilator circuitry to the trach tube. It features a combination trach tie and ventilator antidisconnect device, and has a "no roping" effect with 100% cotton non-stretch fabric. Contact peppermedical.com.

ENVE-OUS

CareFusion launched the EnVe ventilator, a high-performance critical care ventilator that weighs 9.5 pounds-about 70-80 pounds lighter than other ventilators with similar functions. The EnVe ventilator has the capability to manage non-invasive or mask-ventilated patients to the most critically ill intubated patients in the ICU. The EnVe system's miniaturization and compact design allows patients to be easily transported throughout the hospital and other environments outside the hospital. Because the patient can remain on the ventilator, the clinician doesn't need to disconnect the breathing circuit, which helps reduce a patient's risk for infection. In addition, the ventilator's small size allows for it to be stored in a cabinet rather than on a typical ventilator stand, freeing up valuable space in some of the most crowded areas of a hospital. CareFusion first introduced the EnVe ventilator in Oct. 2009 in limited release and completed user preference evaluations at several U.S. hospitals this past year, including North Memorial Medical Center in Minneapolis. At the heart of the EnVe ventilator is the device's patented ActivCore technology, a gas delivery system that features unprecedented miniaturization and blower technology to provide high-end critical care ventilation while enabling independence from wall air systems. In addition, the ActivCore technology features a hot swappable four-hour battery for extended patient transport capabilities. The EnVe also incorporates a Spontaneous Breathing Trial which provides data that helps clinicians to make informed decisions about weaning patients from ventilation and features a pulse oximeter for transport. Contact carefusion.com.

SPOTLIGHT ON OXYGEN DELIVERY/ OXIMETRY

ON WATCH

Maxtec, Salt Lake City UT offers the all-new MD300C63 "**OxyWatch**" fingertip pulse oximeter by Choice Medical. This oximeter features a new, robust design and includes features not seen in any other fingertip unit. First, an all-new anti-slip design holds the finger in a strategically selected place that will not impede blood-flow. Next, the oximeter has been beefed up with an all-new microprocessor that will auto-compensate for changes in light through the finger. These new features provide for faster, more accurate readings even on patients with poor perfusion. Lastly, the OxyWatch features a bright OLED color display for easy viewing in light or dark environments and a locking battery door cover. This unit is backed by the Maxtec satisfaction guarantee. Contact (866) 4-maxtec, maxtecinc.com.

FULL SPECTRUM

From Smiths-Medical: **SPECTRO2 30** pulse oximeter: Dependable results, plus the flexibility to perform in virtually any clinical setting. Utilizing BCI patented technology, the SPECTRO2 30 pulse oximeter can be trusted for dependable readings on a wide range of patients in the most challenging situations. The SPECTRO2 30 pulse oximeter features multiple operating modes, audible and visual alarms, and the ability to transmit alerts to a remote nurse call system. The SPECTRO 30 oximeter enables caregivers to monitor the efficacy of respiratory treatments for: at risk patients, sleep screening, post anesthesia recovery, and analgesic monitoring. **SPECTRO2 20** pulse oximeter: Reliable results in challenging environments. Through the use of BCI patented serial autocorrelation technology, the SPECTRO2 20 pulse oximeter delivers reliable spot-check results – even in challenging clinical environments with the presence of low perfusion or motion. The SPECTRO2 20 oximeter aids caregivers in responding to a wide range of patient needs, including high acuity care and ambulatory situations, such as inter- and intra-hospital transport, triage, patient tremors, and unstable patients. **SPECTRO2 10** pulse oximeter: Affordable, dependable and easy to use. With the SPECTRO2 10 pulse oximeter, you don't have to sacrifice performance for cost. The SPECTRO2 10 oximeter delivers quick, reliable spotcheck results, meeting the needs of caregivers in primary care situations: routine patient care assessments, ongoing management of episodic conditions, and health wellness checks. Contact smiths-medical.com/bci.

NONINVASIVE HELP

Covidien announced that its INVOS Cerebral/Somatic Oximeter can provide a simple, noninvasive way to help cardiac surgeons assess patients at risk for poor outcomes prior to surgery. The new evidence, published in the journal Anesthesiology, showed that INVOS System cerebral regional oxygen saturation (rSO_2) values, which reflect brain oxygenation, measured prior to cardiac surgery, were independent predictors of 30-day and one-year morbidity and mortality. This is the first adult study to link decreased preoperative cerebral rSO_2 with postoperative morbidity and mortality. The study assessed cerebral rSO_2 readings from the INVOS System in 1,178 adult patients about to undergo on-pump cardiac surgery. The analysis showed that baseline cerebral rSO_2 values ≤50% were independent predictors of 30-day and one-year morbidity and mortality. The study also showed a statistically significant correlation between cerebral rSO_2 values and traditional measures of cardiopulmonary function such as left ventricular ejection fraction, pro-B natriuretic peptide and kidney filtration rate, among others. Other recent research found that cerebral rSO_2 monitoring provides a first alert to changes in oxygenation that could potentially lead to an adverse patient outcome. Cerebral oximetry data, such as that from the INVOS System, were registered from January 2008 through December 2009 in the Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Database, which is the gold standard for specialty outcomes databases. Initial findings were released in July 2010 and showed that in nearly one in four (23%) cardiac surgery procedures (n=36,548) "cerebral oximetry provided the first indication of a technical problem or physiologic change that could potentially lead to an adverse patient outcome." [rSO_2, and Sco_2 as used in the Heringlake study, both refer to cerebral regional oxygen saturation. Sources: 1. Heringlake M, Garbers C, Käbler JH, et al. Preoperative cerebral oxygen saturation and clinical outcomes in cardiac surgery. *Anesthesiology*. 2011;114(1):58-69. 2. Avery EG. INVOS Cerebral Oximeter Clinical White Paper Series. 2010;SMS1415(1).] Contact covidien.com.

OXIMETRY ROUNDTABLE

Maxtec

Tell us about your oximetry products currently available or in development.

Maxtec carries a wide range of pulse oximeters and pulse

oximeter probes for many major applications. Our pulse oximeters range from simple spot-check fingertip units to our High Resolution Pulsox-300i Monitor with recordable data. Our SpO_2 pulse oximetry probes offer a high quality alternative to costly OEM replacements and are covered by excellent warranties. Whether you're looking for reusable or disposable probes, we have a solution for every patient size from neonate to adult.

How can the use of oximetry potentially reduce costs while maintaining patient care?
The Maxtec line of pulse oximeters and pulse oximeter probes are quality assured and backed by the Maxtec satisfaction guarantee. Our pulse oximeter probes are Kevlar reinforced thus reducing wear and tear typically seen in other less expensive options. With Maxtec pulse oximetry products, a facility is guaranteed to reduce repair or replacement expenses. Our reusable probes are easy to clean, highly durable and covered by long warranties thus ultimately cutting expenses for a hospital that would normally purchase and replace one-time use probes.

Discuss the range of your oximetry product applications, and where your products can be used.
Maxtec's pulse oximetry product line is suitable for anyone in a home care, pre-hospital, hospital or even personal/recreational applications. Our MD300C2, MD300C63 and Pulsox-2 fingertip oximeters offer a quality solution for spot-checking blood-oxygen saturation and heart rate. Our Pulsox-300 and Pulsox-300i wrist-worn oximeters provide a High Resolution Pulse Oximetry (HRPO) option for monitoring and recording oxygen saturation and heart rate. In addition to the application areas mentioned above, the Pulsox-300 series is especially useful in the sleep specialty arena. We have a solution from neonate to adult size patients.

What type of training and customer assistance do you offer?
In addition to a satisfaction guarantee, Maxtec customer service is dedicated to providing only the best customer assistance. We have knowledgeable representatives available to answer questions and assist with training over the phone or even meet with you in your facility. We also offer detailed product information sheets available for download on our website, www.maxtecinc.com.

COMPANY PROFILE

Compumedics USA, Inc

Describe your products and their unique features.
Compumedics offers one of the most innovative and comprehensive lines of PSG and EEG diagnostic products on the market. Compumedics can address a range of both common and more unique needs in today's business environment. The new Grael High-Definition system for PSG and EEG applications produce the highest quality signals in the most demanding labs; the Siesta802 wireless amplifier system is used for both Ambulatory EEG and PSG studies and the SomtéPSG system provides full PSG studies virtually anywhere, while the simpler Somté HST system is a top performer. All these systems operate with our ProFusion software, an easy to use package that sets a new standard for functionality. The ubiquitous requirement to integrate the information from the Sleep and EEG labs into the Electronic Medical Record is managed handily by the neXus Lab Management System with HL7 connectivity and secure remote access.

Tell us about the latest advances in the area your products serve.
The sleep and neuro-diagnostic markets have been in flux these last few years and we see the primary requirements are flexibility, productivity and high value. Our engineering focus has been in producing new products that can do more, are even more reliable and can be used in a variety of business models from home testing to advanced clinical settings and research centers. The recent resurgence of interest in automatic signal analysis and event detection processes is another area that Compumedics has anticipated with its current products and ongoing R&D efforts.

Discuss your R&D process.
As stated above, we are constantly evolving our products to meet market needs. For instance, our just released ProFusion software extends on the popularity of our renowned diagnostic software by adding features that streamline the workflow in the lab, automate more mundane tasks and add tools that help with the latest lab accreditation requirements. A key part of our product development process is benchmarking to the best technologies and solutions from other markets that can be applied as solutions to the challenges of our customers. A perfect example of this is our unique ECGFree feature that removes ECG artifact from other high-frequency signals using a technology developed for removal of noise in data recorded in the MRI environment.

Discuss the education and training you offer for use of your product.
At Compumedics we believe that the systems can only reach their true potential excellence if the people using them feel competent and well trained on all aspects of the system. We provide a variety of solutions including on-site, custom tailored training courses per facility, regional courses and for the last few years we have offered a full range of online training for our users so that they can work one-on-one with our trainers in the comfort of their own lab. We don't believe in simply "dropping a system and letting the customer fend for themselves." Our customers can sign up for e-mail delivery of our ongoing ProFusion ProFiciency Tips which highlight the features that help our customers get the most out of our products.

What advances do you see in the future?
Compumedics has a full product development schedule to continue enhancing our current products, increasing value to the customer with added functions for clinical and research applications. The company will be expanding our Neuroscience product offering, complementing our strong position in the sleep diagnostics market and in the sleep market will be releasing new therapeutic sleep devices.

Nitrogen Wash Out — Conventional Approach to Non-Invasively Treat a Pneumothorax

Dave Swift, RRT

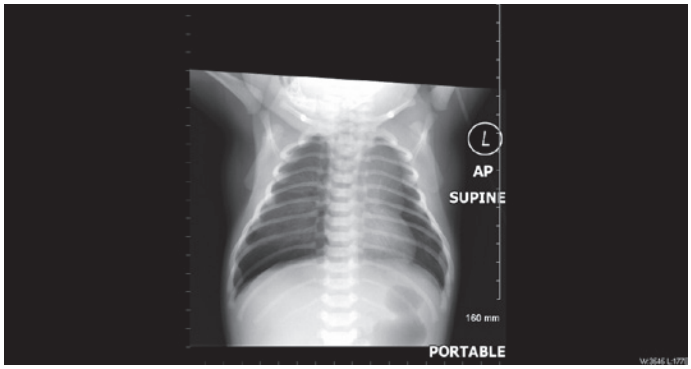
Conventional treatment for large pneumothorax (>50%) involves the invasive placement of a chest tube or needle thoracostomy to decompress the affected lung.[1,2] The risks and complications of these procedures are known.[3] The use of noninvasive treatment, using nitrogen washout, is demonstrated in the following case study.

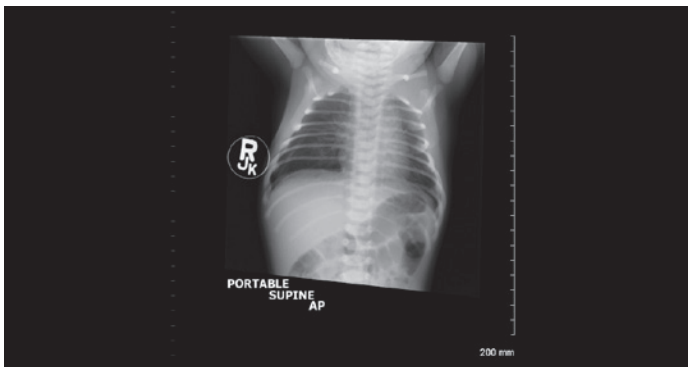
A term infant was delivered by emergency c-section after a drop in pulse was detected. The patient initially had an apgar score of 0. Rapid response by the resuscitation team quickly resestablished a pulse and placement of an endotracheal tube allowed for effective ventilation. The level of ventilatory support required was minimal, the patient was quickly weaned to room air and extubated. Over the next 20 minutes, the work of breathing was noted to be rapidly increasing (resp rate of 120 with moderate indrawing). An immediate chest x-ray was taken and revealed a 60% pneumothorax on the left and 40% on the right.

The patient was placed in an oxyhood with an FiO_2 of 1.00. Over the next 90 minutes the level of distress diminished (resp rate 80 with minimal indrawing) and the chest x-ray was repeated.

The effective treatment of a pneumothorax noninvasively demonstrates that there are effective noninvasive interventions available to non-physicians and physicians. In place of 100% oxygen, the use of a heliox mixture has also been described, as well, in the treatment of pneumothorax and offers the potential of further reduced work of breathing.

Nitrogen washout has been associated with atelectasis (alveolar collapse) in association with use of 100% oxygen. However, it also has a beneficial effect when used in a term or near term infant to reduce the size of a spontaneous pneumothorax.





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Moving Toward the Paradigm of Safe Delivery: Incentivizing Checklist Use

Carol Brass

Introduction

Since 1999, when the Institute of Medicine (IOM) released its seminal report, "To Err is Human," the growing patient safety movement has encouraged systemic change to ensure that medical interventions are delivered correctly.[1] Subsequent legislative responses enacted to protect patients and reduce medical error include the Patient Safety and Quality Improvement Act (PSQIA), mandatory and voluntary error reporting systems adopted by numerous states, and the Centers for Medicare and Medicaid Services' (CMS) "never-event" reimbursement rule.[2,3] However, these policies only indirectly attempt to reduce medical error, and perhaps as a result, they have achieved only limited success and have been subject to criticism by academics and practitioners. Critics observe that these policies simply reinforce existing incentives to avoid medical error and provide no insight into the policies that can be implemented to stem the commission of errors by individual providers. On the other hand, recent research indicates that medical checklists are one of the most promising emerging interventions to address medical error. An evidentiary privilege that bars admissibility of checklists in court would encourage healthcare institutions to experiment with new policies that incentivize providers to develop and use checklists and could have a significant positive impact on patient safety.

The PSQIA

The PSQIA creates an evidentiary privilege that protects information submitted to "patient safety organizations" (PSOs), which are specially defined groups (excluding health insurers) that compile information on medical errors. When providers—broadly defined to include hospitals, physicians, and others—create "patient safety work product" and submit it to a PSO, that work product is protected with an evidentiary privilege. The privilege therefore protects the reports created by a provider in the aftermath of an incident. However, the underlying facts of the incident are still open to discovery. The privilege is meant to encourage the creation of these after-incident analyses and reports.

While well-designed error reporting systems do represent a valuable means of gathering incident data so that policies can be formulated to combat medical error, the PSQIA fails to adequately address the most basic problem inherent in medical error reporting: that all self-reporting systems entail a degree of voluntarism in that they require the cooperation of the reporters. Removal of legal liability may encourage reporting in some instances, but there are still many other disincentives to reporting that the PSQIA—or, realistically, any legislation—cannot address. Thus, it is not clear that an evidentiary privilege in this context is sufficient to overcome the broad array of disincentives to self-reporting that providers face. They may worry that reporting an error will damage their reputations or job security, or will potentially prompt internal disciplinary actions.[4]

Given the presence of these additional disincentives to reporting, a significant amount of errors will go unreported so long as the expected costs of reporting exceed the expected benefits, which limits the efficacy of the privilege and its potential to substantially reduce medical error. Therefore, while the PSQIA does address providers' concerns about liability, it is significantly flawed in that it relies on providers to act against their perceived self-interest to ultimately reduce the rate of medical error.

State Error Reporting Systems

State error reporting systems may rely on either voluntary or mandatory error reporting by providers. Mandatory error reporting systems do not necessarily solve the problems that arise under voluntary reporting systems. Even when a system is mandatory, many errors will go unnoticed unless the provider steps forward to report them. In fact, it is not clear that making a system "mandatory" will better ensure that incidents are actually reported.[5] As the president of the American Hospital Association, Richard Davidson, explained, "[t]he idea that a mandatory reporting system is going to change behavior is naive at best. You need to focus on making a cultural change in hospitals, to promote open discussion of errors."[6]

Rather than promote a cultural change, error reporting systems require effort, paperwork, and self-implication of a provider in potentially tortious conduct. If the provider does not report the error, especially in situations where little or no injury occurs, it is unlikely that anyone will ever find out about the error. Moreover, even the best-designed reporting systems will by their very nature miss the entire class of medical errors consisting of those errors that providers do not notice.

Many other problems with error reporting systems exist.

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Hospitals often receive severely adverse publicity when a government entity publicly disseminates reports with aggregate medical error information, which may reduce public confidence in the medical system and possibly discourage some individuals from going to the hospital when they are ill.[6] There are also practical limits on the number of conditions for which a state or organization can feasibly gather and analyze data. Resource constraints in healthcare are notoriously tight, and gathering this data can be quite costly. Finally, publication of these reports may raise privacy concerns under HIPAA. The more detailed a report is, the more useful it is likely to be. However, the more detailed it is, the more likely it is to breach patient confidentiality rules. This paradox, along with the other problems plaguing reporting systems, limits the potential efficacy of these error reporting systems in substantially reducing medical errors.

The CMS Non-Reimbursement Rule

The Deficit Reduction Act of 2005 required the Secretary of Health and Human Services to select diagnosis codes that were either high cost or highly prevalent, and that "could reasonably be prevented through the application of evidence-based guidelines."[7] The "never-event" rule promulgated by CMS in response to the statutory mandate specifies that care for certain conditions known as "hospital-acquired conditions" is non-reimbursable by the government if the conditions were not present on admission to the hospital. Effective October 1, 2008, the categories of these conditions include: (1) foreign object retained after surgery, (2) air embolism, (3) blood incompatibility, (4) pressure ulcers (stages III and IV), (5) falls, (6) manifestations of poor glycemic control, (7) catheter-associated urinary tract infection, (8) vascular catheter-associated infection, (9) deep vein thrombosis, and (10) surgical site infection associated with certain specified procedures.[3]

The troubling aspect of the CMS non-reimbursement rule is that, although it purports to penalize only HACs that are fully preventable by adequate care, in reality a number of the enumerated conditions for which CMS denies payment are not always preventable by the hospital. For example, CMS itself acknowledges that catheter-associated urinary tract infections are not always preventable when a catheter is in place for more than three days; nevertheless, even though medical necessity sometimes requires long-term use of a catheter, such a condition is non-reimbursable under the rule.[8,9]

Another major criticism of the rule is that it assumes that hospitals and individual providers are not already motivated, both financially and otherwise, to avoid these conditions. The lack of financial incentives likely does not cause these conditions; rather, they occur because the current system fails to identify and implement successful and effective means of preventing them. One scholar observes, "[h]ospitals already have significant financial incentives to reduce preventable complications. What they lack, and urgently need, is proven models to implement the institutional change needed to consistently apply best treatment practices."[8] Because hospitals already absorb many of the costs associated with HACs, the CMS rule does not "create a new financial incentive for hospitals to prevent infections, but only [amplifies] an existing one."[8,10,11]

Rather than aligning incentives, the CMS rule creates an increased administrative workload by requiring hospitals to carefully code any conditions present on admission in order to ensure that they are reimbursed later for preexisting conditions. The rule increases unnecessary diagnostic testing at admission and discourages hospitals from treating the elderly and other patients who are at high-risk for certain HACs. If these conditions later develop the hospital will not be reimbursed regardless of whether or not it was at fault. Overall, the CMS reimbursement rule has only limited potential to reduce medical error rates because it does not successfully align incentives and may ultimately harm the patients that it seeks to protect by effectively rendering them uninsured for the cost of care stemming from medical errors.

First, Do No Harm: Moving Towards a Paradigm of Safe Delivery

The interventions undertaken in response to the IOM Report have not facilitated effective progress towards the Report's recommendation of the creation of "a 'culture of safety' in which systems are designed to keep patients safe from harm…"[8] Rather than moving toward a culture of safety, these interventions only address error through attenuated mechanisms and reinforce preexisting (and often misaligned) incentives. A culture of safety requires focusing on error prior to its commission, attempting to align incentives properly toward the common goal of patient safety, and making meaningful changes toward new systems that ensure that care is delivered properly in the first place. This requires direct intervention and a cultural shift in hospitals, instead of continued use of indirect interventions currently employed to reinforce the norms already in place.

In contrast to the uncertain results yielded by indirect mechanisms, direct interventions taken at the point of care can substantially reduce medical error. For example, the medical error rate at the VA Hospital in Topeka, Kansas dropped by 57% after the hospital began using bar-code technology to administer medications.[12] Until effective direct measures like this are identified and adopted as hospital policy, there will not be significant progress in reducing the rate of medical error.[13]

Another approach to error reduction utilizes direct action to prevent medical errors before they occur: the medical checklist. Rather than indirectly addressing medical errors by complex, attenuated, and mismatched incentive structures, checklists give providers a blueprint for preventing the commission of these errors. Unlike error reporting systems, checklists align incentives and deal with unrecognized error by improving recognition of improper care and would-be errors. Furthermore, unlike the CMS non-reimbursement rule, checklists provide an actual mechanism for reducing the number of medical errors at the level of the delivery of care. Checklists increase the likelihood that quality-optimizing precautions and procedures will be considered and followed by intervening in the delivery of care at the moment immediately preceding its improper provision.

Unlike the other policies that have been adopted in response to the IOM Report, the medical checklist bridges the gap between altering systems and altering individual behavior. Checklists are the ideal way to look at medical error on a broad-based, institutional level, to diagnose systematic problems, and to ensure that individual actors are incorporating the solutions into their everyday actions.

An Evidentiary Privilege to Encourage Use and Innovation

A major barrier to continued implementation and experimentation with checklist-use policies is that healthcare

institutions and providers are extremely sensitive to litigation concerns.[14] They shape their policies and actions according to the perceived risks of litigation.[15] They may not want to use checklists because in the event of a lawsuit, an incomplete checklist could be entered as evidence by a plaintiff and viewed as overwhelmingly persuasive by a jury, regardless of the context of the injury.[16] Perhaps as a result of these concerns, they have failed to take full advantage of this opportunity to improve care.[17,18]

An evidentiary privilege that protects against discovery and admissibility of medical checklists used during patient treatment should be created in order to incentivize healthcare institutions to establish policies that encourage their use. Given the potential patient safety improvements to be gained by more widespread use and development of checklists, failing to encourage their use by quelling liability fears is ultimately a disservice to patients and endangers their safety. An evidentiary privilege similar to that instituted for patient safety work product created after-the-fact of an incident under the PSQIA should be extended to medical checklists as well.

This privilege would prevent a person from entering a checklist into evidence to show whether a particular step was performed or not, or from testifying as to whether the checklist indicated that a particular step was performed or not. It is unlikely that plaintiffs would be seriously disadvantaged by this privilege. While a checklist is very valuable to healthcare providers and patients who receive care, its use in litigation is more attenuated and prejudicial than probative.[19] The reality of checklist use is that they are often used in chaotic, hectic, and stressful circumstances; in an emergency room or any surgical setting, providers are not (and should not be) focused on making tick-marks on a piece of paper. They may forget to make marks even though they have performed each item, or the patient may be in such a precarious condition that providers do not have the time to complete each item on the checklist. For example, one study found that, in a random sample of surgical checklists, a median of 80% of items per checklist were marked as completed.[20] Furthermore, due to the nature of many items on the checklist, admitting the checklist would typically be unnecessary to establish the cause of injury. Either the item would not be sufficient to establish causation of injury (ie, introducing each team member by name and role) or the item could be established by looking at the underlying facts of the incident. For example, entering a checklist as evidence would be unnecessary to establish that a patient had a sponge left inside his body after surgery; there would be far more compelling evidence than a checklist to show that the care provided was negligent.[21]

The Administrator-Provider Safety Partnership

Traditionally, hospital administrators have not regulated behavior that is considered to fall within the realm of clinical and safety measures.[22] However, hospitals are beginning to recognize that patient safety should be the foremost consideration of all hospital employees, not just those who actively deliver care.[18] Administrators and patient safety committees should work together to implement policies that encourage individual care providers to develop and use checklists tailored to their needs and institutional settings.

Various policies, some encouraging checklist use, and others requiring it, should be explored. In some situations, mandates may ultimately be counterproductive because they create a backlash from providers who feel that their autonomy is being infringed upon. In instances where third parties have mandated that physicians use checklists, doctors have not embraced the concept with considerable enthusiasm. "The checklist has arrived in our operating rooms mostly from the outside in and from the top down. It has come from finger-wagging health officials, who are regarded by surgeons as more or less the enemy, or from jug-eared hospital safety officers…".[18] Since "[j]ust ticking boxes is not the ultimate goal here" but rather "embracing a culture of teamwork and discipline[,]" rankling providers by mandating checklist use may sometimes not be the right way to proceed.[18] Individual institutions are best suited for determining whether and when mandating use of the checklist is preferable to encouraging it. That determination depends greatly on the personalities of providers and administrators at an institution. In either instance, however, a commitment by administrators to increasing the use of checklists and encouraging provider input in their development is critical.

Beyond their medical efficacy, checklists should also appeal to the cost sensitivity of hospital administrators.[22,23] Research demonstrates that checklist-use policies are inexpensive to adopt and save hospitals money.[24] Moreover, the existing financial disincentives to commit medical error will likely become even more pronounced once Medicare begins tracking hospital medical error rates as required by the Patient Protection and Affordable Care Act (PPACA).[25] Medical error is costly to patients in terms of their health and reduced economic productivity and to providers in terms of financial liability. Furthermore, estimates indicate that half of surgical complications alone are preventable.[18,26] Identifying and implementing effective methods of reducing preventable medical error can critically affect the assets of healthcare institutions and providers, particularly in the current era of Inpatient Prospective Payment System (IPPS) reductions, schedule-based fee reductions, and high medical malpractice payouts. Therefore, the adoption of policies that encourage the use of checklists achieves financial and administrative objectives in addition to patient safety goals.

The State's Role in Checklist Use

Under an alternative approach, state legislatures could mandate that healthcare providers use certain medical checklists as an element of the providers' standard of care. However, such an action would be inconsistent with the legislature's traditional stance of deference to the medical profession in setting the accepted medical standard of care. It would also impede medical professionals from developing and using checklists that uniquely suit each hospital's peculiar environment.

For example, in 2005 the United Kingdom's National Patient Safety Agency (NPSA) required hospitals to implement a specific set of guidelines in order to reduce the frequency of wrong-site surgeries. In 2010, the NPSA replaced the old guidelines with new ones adopting the WHO Surgical Safety standards.[27] In the interim, healthcare institutions were bound to the set of 2005 guidelines, which effectively prevented them from progressing to what is now largely recognized as a superior medical practice. Furthermore, new research indicates that a new surgical checklist, the SURPASS system, may replace the WHO standards at some point in the future. Development of new checklists is a constantly evolving and highly context-specific process. Unfortunately, experimental use of new checklists is stymied where use of one set of guidelines is mandated; under

such regimes, providers lack incentives to develop their own wrong-site checklists that would be more appropriate for the unique patient populations at their own hospitals because they are already bound to using a particular set of guidelines to reduce wrong-site surgeries. Accordingly, although checklists may potentially improve care in many areas, the absence of an evidentiary privilege dissuades hospitals from maintaining policies that encourage innovation with new checklist formulations and applications to determine which will optimally suit a particular hospital environment. If hospitals and healthcare providers are not given the freedom to experiment and innovate with new checklists, we will never realize the full potential that checklists have to offer.

In fact, checklists are most useful when they are developed by local healthcare providers to respond to local circumstances and problems. For example, Dr Atul Gawande describes the story of an emergency response team in a small Austrian town in the Alps. In a widely publicized case, a three-year-old girl was lost beneath the surface of an icy fishpond for thirty minutes. When authorities finally retrieved her, she had no blood pressure or pulse. Her brain appeared to have ceased functioning, and she was ostensibly dead. However, through a series of stunning medical interventions over a period of weeks, doctors slowly brought the girl back to life. Dr Markus Thalmann, a cardiac surgeon who operated on the girl, explained to Dr Gawande his understanding of why they were able to achieve this remarkable outcome:

> *[Dr. Thalmann] had been working in Klagenfurt for six years when the girl came in. She had not been the first person whom he and his colleagues had tried to revive from cardiac arrest after hypothermia and suffocation. His hospital received between three and five such patients a year, he estimated… For a long time, he said, no matter how hard the hospital's medical staff tried, they had no survivors. Most of the victims had been without a pulse and oxygen for too long when they were found. But some, he was convinced, still had a flicker of viability in them, yet he and his colleagues had always failed to sustain it. He took a close look at the case records. Preparation, he determined, was the chief difficulty. Success required having an array of people and equipment at the ready… Almost routinely, someone or something was missing. He tried the usual surgical approach to remedy this—yelling at everyone to get their act together. But still they had no saves. So he and a couple of colleagues decided to try something new. They made a checklist. They gave the checklist to the people with the least power in the whole process—the rescue squads and the hospital telephone operator—and walked them through the details. In cases like these, the checklist said, rescue teams were to tell the hospital to prepare for possible cardiac bypass and rewarming. They were to call, when possible, even before they arrived on the scene, as the preparation time would be significant. The telephone operator would then work down a list of people to notify them to have everything set up and standing by. With the checklist in place, the team had its first success—the rescue of the three-year old girl.*[18]

The team has had two other such rescues, even after Dr Thalmann's departure to a different hospital. This story illustrates the adaptability of checklists to a wide array of situations and the importance of providers' freedom to develop new uses for checklists. No legislator in a state capitol would be able to identify the need for a checklist in this circumstance and create one perfectly suited to it; the innovative role of providers should be preserved and encouraged, not minimized by implementation of rigid, centralized checklist policies. Other instances of checklists developed within institutions to meet particular institutional needs abound. For example, in one hospital, the director of surgical administration (who also happened to be a pilot) decided to utilize the aviation approach to checklists by designing a whiteboard to be placed in each operating room that would provide check boxes for nurses to verbally confirm with the team that they had the correct patient and correct surgery site. He also designed a special tent to be set over the scalpel that could only be removed by the nurse once the checklist was completed. Another institution devised a broader, twenty-one-item list to catch a span of potential errors. This checklist was implemented alongside a mandatory team briefing prior to surgery. A Johns Hopkins surgeon devised an eighteen-item checklist that he and eleven surgeons implemented at their institution. A group of Kaiser hospitals in Southern California adopted a thirty-item checklist also premised on aviation checklist principles. The considerable diversity of institutional checklists indicates the need to ensure institutional autonomy in their development. Further, outside of the operating room, "there are hundreds, perhaps thousands, of things doctors do that are as dangerous and prone to error as surgery… All involve risk, uncertainty, and complexity—and therefore steps that are worth committing to a checklist and testing in routine care. Good checklists could become as important for doctors and nurses as good stethoscopes."[18] By incentivizing their production with an evidentiary privilege, the potential for such safety gains is enormous.

Conclusion

Medical error is a serious problem in hospitals and the eighth-leading cause of death in the United States.[1] Checklists may be a significant part of the solution to this problem. One study found that the use of a surgical checklist caused complications from surgery to fall by more than a third and the rates of surgical site infections and post-surgical deaths to roughly halve.[29,30] In a different hospital setting, researchers found that "simply having the doctors and nurses in the ICU create their own checklists for what they thought should be done each day improved the consistency of care to the point that the average length of patient stay in intensive care dropped by half."[18] An evidentiary privilege that bars admissibility of checklists in court would encourage healthcare institutions to experiment with new policies that incentivize providers to develop and use checklists. Such a privilege would increase the willingness of providers to pool their knowledge to develop and use institutional checklists, thereby increasing the quality of patient care. Given that a similar evidentiary privilege has been instituted to protect the after-error data created in response to incidents that have already occurred, an evidentiary privilege is certainly warranted to protect data tools that are used to prevent those incidents in the first place.

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Outcome of Children with Life-Threatening Asthma Necessitating Pediatric Intensive Care

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Abstract

Objective: To report the outcome of children with life-threatening asthma (LTA) admitted to a university Pediatric Intensive Care Unit (PICU).

Methods: Retrospective study between October 2002 and May 2010 was carried out. Every child with LTA and bronchospasm was included.

Results: 30 admissions of 28 patients (13 M, 17 F) were identified which accounted for 3% of total PICU admissions (n = 1033) over the study period. The majority of patients were toddlers (median age 3.1 years). Few had past history of prematurity, lung diseases, or neuro-developmental conditions. Approximately half had previous admissions for asthma and one-forth with history of non-compliance to recommended treatment for asthma. One patient had parainfluenza virus and one had rhinovirus isolated. None of these factors were associated with need for mechanical ventilation (n = 6 admissions). Comparing with patients who did not receive mechanical ventilation, ventilated children had significantly higher PIM2 score (1.65 versus 0.4, $p < 0.001$), higher PCO_2 levels (9.3 kPa versus 5.1 kPa, $p = 0.01$) and longer PICU stay (median 2.5 days versus 2 days, $p = 0.03$) The majority of patients received systemic corticosteroids, intravenous or inhaled bronchodilators. There was one pneumothorax but no death in this series.

Conclusions: LTA accounted for a small percentage of PICU admissions. Previous hospital admissions for asthma and history of non-compliance were common. Approximately one quarters required ventilatory supports. Regardless of the need for mechanical ventilation, all patients survived with prompt treatment.

Introduction

Asthma is a very common childhood condition worldwide and in Hong Kong. Acute asthmatic attacks cause significant morbidity and account for a significant number of emergency department consultations and hospital admissions.[1-4] Most children admitted to the hospital because of acute asthma do not require intensive care treatment. Nevertheless, a small percentage of children with life-threatening asthma (LTA) would develop progressive respiratory failure refractory to treatment and require admission to the pediatric intensive care unit (PICU).[5-7] In those who are admitted to the ICU, approximately 10 to 33% need intubation and mechanical ventilation, with a risk of worsening bronchospasm and hyperinflation, barotrauma, and cardiovascular depression.[8,9] If not promptly managed, severe asthmatic attacks may occasionally result in death.[1-10] The purpose of this study was to report the clinical pattern and outcome of all children with LTA and severe bronchospasm admitted to the PICU.

Methods

We retrospectively reviewed the medical records and analyzed data from all children with LTA admitted to the PICU of a tertiary care university hospital (Prince of Wales Hospital) in Hong Kong during the period October 2002 and May 2010. LTA was defined as all children with asthma who required ICU admission and care. The initial diagnosis was made clinically by the admitting physicians. Final diagnosis was confirmed on chart review and subsequent evaluations. The hospital provides PICU care to a catchment population of approximately 1.1 million. The following data were collected: age, sex, duration of admission, treatment of the LTA, clinical condition, blood gases, the incidence of barotrauma, and outcome. Respiratory viruses and bacterial pathogens were routinely screened for by standard examination of nasopharyngeal aspirate and cultures. The Pediatric Index of Mortality 2 (PIM2) score based on admission data was used as severity score.[11] Numerical data were compared with Mann Whitney U test and categorical data with χ^2 or Fisher exact test. All comparisons were made two-tailed, and p-values less than 0.05 considered statistically significant.

Results

There were 30 admissions (13 boys and 17 girls; median age, 3.1 years; IQR 2.0 - 6.8 years; Table 1) with LTA which accounted for 3% of total PICU admissions (n = 1033) over a study period of 7 years and 8 months. Two male patients were admitted twice because of a recurrent episode of LTA. Indications for admission to the PICU were severe dyspnea, worsening or failure to improve on nebulized bronchodilators, and need for administration of intravenous salbutamol or mechanical ventilation. The decision for PICU admission was determined clinically together with blood gas as well as pulse oximetry parameters by the admitting physicians.

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Table 1: Clinical data of children with status asthmaticus admitted to PICU

Case	Total (n = 30)	Ventilated (n = 6)	Non-ventilated (n = 24)	P*
Male (%)	13 (0)	5 (75)	8 (40)	0.06
Median age (IQR), yr	3.1 (2.0-5.4)	3.3 (2.0-5.5)	3.1 (1.9-6.8)	0.84
Median (IQR) PIM2, %	0.50 (0.30-1.00)	1.65 (1.45-1.95)	0.4 (0.3-0.5)	< 0.001
Relevant risk factors				
Family history of atopy	12	1	11	0.36
Prematurity < 36 weeks (%)	4 (14)	0 (12)	4 (15)	0.57
History of chronic lung disease, bronchiolitis, pneumonia, or pneumothorax (%)	7 (17)	0 (0)	7 (25)	0.29
Neurodevelopmental delay (mental retardation, cerebral palsy, neuromuscular disease) (%)	2 (14)	0 (25)	2 (10)	1.00
Previous asthma admission (%)	16 (50)	4 (62)	12 (45)	0.66
Maintenance inhaled CS (%)	12 (35)	3 (37)	9 (35)	0.66
Non-compliance (%)	7 (25)	2 (25)	5 (25)	0.60
1st $PaCO_2$ in PICU, kPa	5.5 (4.3-7.9)	9.3 (6.4-10.9)	5.1 (4.3-5.9)	0.01
1st PaO_2 in PICU, kPa	9.9 (7.8-13.2)	10.1 (9.4-13.5)	9.3 (7.5-13.3)	0.40
Viral isolation (%)	2 (3)	0 (0)	2 (5)	1.00
Treatment at PICU				
Systemic CS (%)	30 (100)	6 (100)	24 (100)	N/A
Inhaled salbutamol (%)	22 (73)	5 (83)	17 (71)	1.00
Inhaled ipratropium (%)	7 (23)	0 (0)	7 (29)	0.29
Inhaled adrenaline (%)	2 (7)	1 (17)	1 (4)	0.37
Intravenous salbutamol (%)	22 (73)	5 (83)	17 (71)	1.00
Intravenous magnesium sulphate (%)	4 (13)	2 (33)	2 (8)	0.17
Systemic antibiotics (%)	19 (63)	5 (83)	14 (58)	0.37
Outcome				
Median (IQR) PICU stay, day	2.0 (1.0-2.5)	2.5 (2.0-4.5)	2.0 (1.0-2.0)	0.03
Median (IQR) hospital stay, day	5.0 (3.0-7.5)	6.5 (3.0-20.0)	5.0 (3.0-6.8)	0.27
Pneumothorax (%)	1 (3)	0 (0)	1 (4)	1.00
Died in PICU	0	0	0	N/A

CS: corticosteroid; IQR, interquartile range; N/A, not applicable.
* Analyzed between ventilated and non-ventilated patients by Fisher exact test or Pearson χ^2 for categorical variables and Mann-Whitney U test for numerical variables.

In terms of risk factors, 'smoker(s) at home' were present in 5 of the admissions, 'history of atopy in 1 st degree relative' in 11 admissions, and 'personal history of atopy' in 20 admissions. Few had past history of prematurity (n = 4 admissions), lung diseases (1 neonatal pneumothorax, 1 pneumonia, 1 chronic lung disease, and 4 recurrent bronchiolitis), neuro-developmental condition (Rasmussen's encephalitis plus epilepsy × 2 admissions). Half had previous admissions for asthma and one-fourth with history of non-compliance to recommended treatment for asthma. In the ventilated group, three patients were on inhaled corticosteroid but compliance to corticosteroid was reportedly poor in two. In the non-ventilated group, 9 patients were on inhaled corticosteroid. One patient also received oral montelukast. Poor-compliance to asthma management was reported in 5 patients. One patient had parainfluenza virus and one had rhinovirus isolated. None of these factors were associated with need for mechanical ventilation which was required in 6 patients. Ventilator modes included Synchronized Intermittent Mandatory Ventilation (SIMV) or Pressure Regulated Volume Control mode (PRVC), with low Positive End-Expiratory Pressure (PEEP) and low inspiratory to expiratory (I:E) ratios. Comparing with patients who did not receive mechanical ventilation, ventilated children had significantly higher PIM2 score (1.65 versus 0.4, $p < 0.001$), higher first $PaCO_2$ levels measured at PICU (9.3 kPa versus 5.1 kpa, $p = 0.01$) and longer PICU stay (median 2.5 days versus 2 days, $p = 0.03$) but no differences in other factors evaluated in Table 1. These patients received systemic corticosteroids and intravenous or inhaled bronchodilators. Some received intravenous magnesium sulphate. There was one pneumothorax but no death in this series. A 7-year-old girl with asthma but no previous asthma hospitalization, presented with sudden dyspnoea following a 2-day history of blocked nose and cough. Her private practitioner prescribed inhaled and oral bronchodilators. However, dyspnoea was not relieved and chest radiograph at the emergency department revealed left apical pneumothorax, which was drained with a chest

Table 2: The incidence of PICU admissions for LTA during the study period

Year	PICU admissions	PICU for LTA (%)
2002 (partial data)	33	1 (3)
2003	122	7 (6)
2004	155	3 (2)
2005	111	2 (2)
2006	127	3 (2)
2007	144	5 (3)
2008	138	3 (2)
2009	140	3 (2)
2010 (partial data)	63	3 (5)

Median of 2% of annual PICU admissions were due to LTA (average absolute deviation from Median = 1.0%)

drain. CT scan of the thorax showed subcutaneous emphysema, pneumomediastinum, and pneumothorax. Her symptoms resolved at the PICU following corticosteroid and inhaled salbutamol. Mechanical ventilation was not required. The chest drain was removed three days later. Regardless of mechanical ventilation, all had very brief PICU stays (median 2 days; range, 1 to 7 days). Furthermore, there did not appear to be any increase in incidence of PICU admissions for LTA between 2003-2009 (median 2% of PICU admissions; Table 2).

Discussion

Incidence of PICU admissions: Asthma is a common disease and its frequency of occurrence sometimes detracts from its potential seriousness.[12] Severe asthma in children is a frequent cause of hospital and pediatric ICU admissions in reported series.[12-14] Globally, morbidity and mortality associated with asthma have increased over the last 2 decades.[1,2,4] This increase is attributed to increasing urbanization and undertreatment of asthma especially among the high risk pediatric population with low-socio-economic class.[15] Despite advancements in our understanding of asthma and the development of new therapeutic strategies, the morbidity and mortality rates due to asthma reportedly increased between 1980 and 1995.[2,4,13] In the United States, the mortality rate due to asthma has increased in all age, race, and sex strata. From 1975-1993, the number of deaths nearly doubled in people aged 5-14 years.[2] In Hong Kong, data about severe asthma hospitalizations are lacking. In a previous study, we reported that asthma accounts for approximately 10% of general pediatric admissions.[3] In the present study, the admission rate was only 3% of PICU admissions. It appears that LTA is a relative uncommon cause of PICU admission in our locality. The reason for this is unknown. It might reflect that treatment received at the emergency department is prompt and effective to halt PICU admission.[6]

PICU treatment: Status asthmaticus is severe asthma that does not respond well to immediate care and is a life-threatening medical emergency.[5] Ensuing respiratory failure results in hypoxia, carbon dioxide retention and acidosis.[16] Patients require aggressive treatment with oxygen, bronchodilators, and corticosteroids.[5,17-19] Rapid reversal of airflow obstruction is achieved by using repeated or continuous administration of an inhaled beta2-agonist. Early administration of systemic corticosteroids (oral or intravenous) is indicated in children with LTA.[5,19] In severe cases, alveolar hypoventilation requires mechanically assisted ventilation.[1,5,8,16] In our study, the only significant difference between ventilated and non-ventilated group is the presence of CO_2 retention. LTA can be associated with metabolic acidosis, which reduces the effectiveness of ß-agonists.[9] In a prospective randomized trial, continuous nebulization of albuterol is safe and results in more rapid clinical improvement than intermittent nebulization in children with impending respiratory failure due to status asthmaticus.[20] In severe LTA attacks, intravenous salbutamol was found to be a safe and effective bronchodilator capable of reversing severe bronchospasm in most children who would otherwise require mechanical ventilation.[21] Mechanical ventilation compromises active expiration with increased air trapping and hypercapnia, and should therefore be delayed as long as possible by using medical therapy.[1] Noninvasive positive pressure has also been advocated but further evaluation of its efficacy is required.[22]

Co-infections: One of the clinical problems facing pediatric intensivists is the differentiation between viral and bacterial infections when an acutely ill child with LTA is admitted. Empirical course of antibiotics were often used in the initial management in order to avoid missing any treatable bacterial co-infections. Rapid diagnosis of respiratory viral infections in children is important because prompt diagnosis may result in significantly reduced antibiotic use and unnecessary strict isolation for respiratory viruses. In this study, there was no bacterial isolation and viral co-infection was only found in two cases (parainfluenza and rhinovirus).

Complications and morbidity: Status asthmaticus is one of the most common causes of admission to a pediatric intensive care unit (PICU). There have been published data examining the complications associated with the treatment of status asthmaticus in children in the PICU. In one study of children admitted to PICU, there was a 22% complication rate, increased by intubation.[14] The risk of death is increased where there is delay in getting treatment, particularly time to starting steroids. Another retrospective review showed 8% of children admitted to the ICU with status asthmaticus experienced one or more complications during their treatment. The most common complications were aspiration pneumonia, ventilator-associated pneumonia, pneumomediastinum, pneumothorax, and rhabdomyolysis.[23] Intubated children were significantly more likely than non-intubated children to experience a complication (RR 15.3; 95% CI 6.7-35). Intubated children experiencing a complication also had significantly longer duration of mechanical ventilation, ICU length of stay, and hospital charges than intubated children not experiencing a complication, suggesting that intubation and mechanical ventilation itself may increase the risk of developing a complication in this population.[7,14] Asthma patients have variable resolution of airway obstruction during mechanical ventilation and controlled hypoventilation can be a safe therapy for the patients with more severe obstruction.[8] Prompt treatment with corticosteroid, bronchodilator (intravenous route if needed), magnesium sulphate, permissive hypercarbia, and the avoidance of mechanic ventilation together might have accounted for the satisfactory outcome seen in our patients. Indeed mechanical ventilation has not been needed for the past 3 years in our unit.

Conclusions

Near-fatal asthma continues to be a significant problem despite the decline in overall asthma mortality. Two distinctive

phenotypes of near-fatal asthma have been identified: one with eosinophilic inflammation associated with a gradual onset and a slow response to therapy and a second phenotype with neutrophilic inflammation that has a rapid onset and rapid response to therapy. In stable condition, near-fatal asthma frequently cannot be distinguished from mild asthma. Diminished perception of dyspnea plays a relevant role in treatment delay, near-fatal events, and death in patients with severe asthma. Reduced compliance with anti-inflammatory therapy has also been associated with fatal or near-fatal asthma.[24] The sudden-onset patients were older and they more commonly presented to the emergency department between midnight and 8:00 am with severe exacerbations that required intubation and intensive care unit admission. Nevertheless, this sudden-onset group was discharged from the hospital earlier.[25] The preventable factors included inadequate assessment or therapy of prior asthma, poor compliance with therapy, and delay in seeking help.[10] In our series, history of previous asthma admissions and noncompliance were also relevant factors. Nevertheless, we report no fatality and the majority required brief PICU stay regardless of need for mechanical ventilation.

Approximately one third of patients were on maintenance inhaled corticosteroid; many of these patients were on inhaled salbutamol on a prn-basis and had been asymptomatic for a number of months, but some were non-compliant to prescribed therapy. The limitation of this study is the small sample size and there was high chance of type II error with regard to different parameters studied.

In conclusion, LTA and bronchospasm accounted for a small percentage of PICU admissions following initial stabilization at the emergency department. Approximately 20% required ventilatory supports. Ventilated patients appeared to have higher PIM2 severity score, higher PCO_2 and longer PICU stays. Regardless of the need for mechanical ventilation, all patients survived with prompt treatment, and only required brief PICU stays.

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NCPAP Improves Myocardial Perfusion Reserve and Endothelial-Dependent Vasodilation in Patients with OSA

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Abstract

Background: Obstructive sleep apnea (OSA) has been associated with cardiovascular disease (CVD), but whether OSA is an independent risk factor for CVD is controversial. The purpose of this study is to determine if patients with OSA have subclinical cardiovascular disease that is detectable by multi-modality cardiovascular imaging and whether these abnormalities improve after nasal continuous positive airway pressure (nCPAP).

Results: Of the 35 consecutive subjects with newly diagnosed moderate to severe OSA recruited from the Stanford Sleep Disorders Clinic, 20 patients were randomized to active vs sham nCPAP. Active nCPAP was titrated to pressures that would prevent sleep disordered breathing based on inpatient polysomnography. OSA patients had baseline vascular function abnormalities including decreased myocardial perfusion reserve (MPR), brachial flow mediated dilation (FMD) and nitroglycerin-induced coronary vasodilation. Patients randomized to active nCPAP had improvement of MPR (1.5 ± 0.5 vs 3.0 ± 1.3, p = 0.02) and brachial FMD (2.5% ± 5.7% vs 9.0% ± 6.5%, p = 0.03) after treatment, but those randomized to sham nCPAP showed no significant improvement. There were no significant changes seen in chamber sizes, systolic and diastolic function, valvular function and coronary vasodilation to nitroglycerin.

Conclusions: Patients with moderate to severe OSA had decreased MPR and brachial FMD that improved after 3 months of nCPAP. These findings suggest that relief of apnea in OSA may improve microvascular disease and endothelial dysfunction, which may prevent the development of overt cardiovascular disease. Further study in a larger patient population may be warranted.

Background

Obstructive sleep apnea (OSA) has been associated with an increased incidence of cardiovascular disease (CVD) and these patients are, thus, likely to have a high burden of subclinical disease.[1,2] However, the extent of subclinical CVD has not been systematically evaluated. Previous studies have used single measures of subclinical disease.[3-7] In addition, whether OSA plays an independent role in the development of CVD remains controversial since most previous studies are cross sectional and not randomized, and, thus, may not adequately control for confounding factors.

We use multi-modality cardiovascular imaging (CVI) to evaluate subclinical CVD in patients with OSA before and after randomization to active or sham nasal continuous positive airway pressure (nCPAP). We will (1) determine the frequency of subclinical CVD using multi-modality imaging in adults with newly diagnosed moderate to severe OSA and (2) test the hypothesis that nCPAP therapy, the standard treatment for OSA, improves these abnormalities.

Methods

Subjects: A total of 35 consecutive patients were recruited from the patient population seen at the Stanford Sleep Disorders Clinic. The inclusion criteria include: 1) newly diagnosed moderate to severe OSA as defined by the American Academy of Sleep Medicine,[8] 2) RDI ≥ 15 events per hour by inpatient polysomnography, and 3) Epworth Sleepiness Scale score > 10. The exclusion criteria include: 1) prior treatment for OSA, 2) an oxygen saturation < 75% for > 10% of the diagnostic sleep study or < 75% for > 25% of the first 4 hours of the diagnostic sleep study, 3) clinical symptoms or diagnosis of coronary artery disease, congestive heart failure, cardiac rhythm disturbance, Raynaud's disease (which is a contraindication for flow mediated dilation), respiratory disease, diabetes, chronic neurological disorders, cancer not in remission, and renal failure, 4) metal objects, devices or implants in or on the body including pacemakers, aneurysm clips, prostheses, bullets, buckshot, shrapnel, and any metal fragments from working around metal (which are contraindications for cardiovascular magnetic resonance imaging) and 5) contraindications to adenosine or nitroglycerin. Seven participants failed the initial screening for eligibility, and 8 withdrew prior to randomization. The Stanford Institutional Review Board approved the study. All subjects gave written informed consent.

Recruitment, Randomization and Blinding: Subjects were identified for recruitment after undergoing a standard overnight inpatient respiratory polysomnographic sleep study. The

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Table 1 Demographics and Clinical Characteristics

	Sub therapeutic nCPAP (n = 10)	Therapeutic nCPAP (n = 10)	All Patients (n = 20)	p value
Age, years	53.9 ± 10.8	52.9 ± 11.6	53.4 ± 11.2	0.85
Male	10/10	8/10	18/20	0.47
Caucasian	6/10	6/10	12/20	1.00
BMI, kg/m^2	29.6 ± 5.6	30.1 ± 4.7	29.8 ± 5.2	0.85
Smoking	0/10	1/10	1/20	1.00
HTN	10/10	10/10	20/20	1.00
DM	1/10	0/10	1/20	1.00
Dyslipidemia	5/10	4/10	9/20	1.00
# Awakenings During Night	1.35 ± 0.98	2.1 ± 0.6	1.7 ± 0.9	0.07
# Hours of Sleep on Weekday Nights	7.15 ± 1.32	7.53 ± 0.81	7.34 ± 1.11	0.48
# Hours of Sleep on Weekend Nights	6.93 ± 2.43	7.7 ± 1.12	7.34 ± 1.11	0.40
# Naps ≥ 5 minutes Per Week*	1.7 ± 2.25	1.1 ± 1.46	1..4 ± 1.92	0.51
Feels Unrested During Day*	1.8 ± 1.2	1.2 ± 0.87	1.15 ± 1.2	0.25
Feel Excessively Sleepy During Day*	1.8 ± 0.87	1.3 ± 0.64	1.56 ± 0.80	0.18
Do Not Get Enough Sleep*	2.4 ± 0.8	2.0 ± 0.89	2.2 ± 0.87	0.33
Feel Excessively Fatigued During Day*	2.3 ± 1.27	1.6 ± 0.92	1.95 ± 1.16	0.20
# Caffeinated Beverages Per Week	1.9 ± 1.5	1.05 ± 0.57	1.5 ± 1.2	0.13
# Alcoholic Beverages Per Week	4.3 ± 5.2	2.1 ± 5.01	3.2 ± 5.2	0.37

p values reflect differences in scores between Post nCPAP minus Baseline for the Active vs. Sham Groups

* 0 = never; 1 = rare (1/month or less); 2 = sometimes (2-4/month); 3 = often (5 - 15/month); 4 = almost always (16-30/month)

BMI: body mass index, HTN: hypertension, DM: diabetes

diagnostic polysomnogram served as the baseline measure. Patients also completed a standard questionnaire to evaluate the degree of sleepiness and underwent baseline echocardiography, cardiac magnetic resonance imaging, and vascular ultrasound. After baseline assessments, subjects were randomized to either active (therapeutic) or sham (sub therapeutic) nCPAP and then admitted for a second night of polysomnography for nCPAP titration. During the nCPAP titration night, if patients were randomized to active nCPAP, pressures were varied throughout the night to control the patients' sleep disordered breathing. For those on sham nCPAP, pressures fluctuated slightly but no more than 0.5 cm H_2O pressure, which was achieved by inserting a flow restricting connector at the machine outlet and six extra 4 mm holes in the collar of the main tubing at the end of the mask to allow air to escape and to prevent re-breathing of carbon monoxide. A certified technician reviewed the polysomnograms the next day to determine the optimal therapeutic pressure to control snoring and sleep apnea for patients in the active nCPAP group. Patients assigned to sham nCPAP received a similar nCPAP device but the machine delivered air pressure insufficient to prevent sleep disordered breathing. In all other ways, the nCPAP machines were similar. The patients, technicians conducting the titration studies and investigators assessing the imaging studies were not aware of treatment group assignments. Thus, the study was effectively double-blind.

Within 7 days after the assessment, the patients were given their nCPAP machines and instructed how to use the machines at home. Study staff contacted patients monthly to assess adherence to the devices. Patients returned after three months for repeat polysomnogram and multi-modality CVI studies. Information on compliance was downloaded from the assigned nCPAP machines at the end of the study.

Polysomnography: Overnight respiratory polysomnographic sleep studies were performed at baseline, for nCPAP titration, and after treatment. An obstructed breathing event consisted of an obstructive apnea, hypopnea, or respiratory effort-related arousals.[9] Moderate or severe apnea was defined as a respiratory disturbance index > 15 events per hour of sleep.

Table 2 Clinical Parameters Before and After Treatment

	Baseline			Treatment			Before vs. After Treatment Pairwise Comparison (p value)	
	Active	Sham	p	Active	Sham	p	Active	Sham
Average SBP, mmHg	121.0 ± 11.6 (10/10)	127 ± 10.3 (10/10)	0.26	126.0 ± 15.8 (10/10)	130.4 ± 14.2 (10/10)	0.54	0.55	0.33
Average DBP, mmHg	75.2 ± 11.1 (10/10)	78.9 ± 11.4 (10/10)	0.11	83.9 ± 10.6 (10/10)	78.7 ± 11.2 (10/10)	0.97	0.34	0.06
Fasting glucose	99.5 ± 17.1 (10/10)	91.1 ± 13.9 (9/10)	0.27	101.6 ± 18.7 (10/10)	91.6 ± 19.3 (9/10)	0.28	0.96	0.92
2 hour Fasting Glucose	142.3 ± 64.3 (10/10)	109.1 ± 58.6 (9/10)	0.26	140.5 ± 38.4 (10/10)	120.0 ± 55.6 (9/10)	0.39	0.89	0.58
LDL, mg/dl	105.3 ± 16.7 (9/10)	109.4 ± 30.4 (8/10)	0.75	114.6 ± 34.3 (9/10)	107.1 ± 40.0 (8/10)	0.89	0.45	0.75
HDL	47.1 ± 18.5 (10/10)	42.2 ± 15.0 (10/10)	0.56	42.0 ± 15.9 (10/10)	40.1 ± 9.0 (10/10)	0.78	0.04	0.86
Cholesterol/HDL	4.1 ± 1.3 (10/10)	5.0 ± 2.4 (10/10)	0.31	4.9 ± 1.8 (10/10)	4.6 ± 1.7 (10/10)	0.86	0.12	0.15
Triglycerides	148.0 ± 128.4 (10/10)	172.9 ± 200.4 (10/10)	0.76	145.8 ± 86.0 (10/10)	173.9 ± 206.8 (10/10)	0.71	0.96	0.92

SBP: systolic blood pressure, DBP: diastolic blood pressure, LDL: low density lipoprotein, HDL: high density lipoprotein

Table 3 Polysomnography Before and After Treatment

	Baseline			Treatment			Before and After Treatment Pairwise Comparison (p value)	
	Active	Sham	p	Active	Sham	p	Active	Sham
RDI	37.7 ± 19.4	36.2 ± 17.0	0.87	2.2 ± 1.5	37.4 ± 23.3	0.0003	0.0004	0.91
Obstructive events	84.4 ± 89	35.3 ± 29.7	0.13	0.8 ± 1.6	71.2 ± 115	0.08	0.02	0.4
OEI	13.6 ± 15.2	7.4 ± 5.9	0.21	0.11 ± 0.22	10.6 ± 16.4	0.07	0.03	0.59
AHI	38.8 ± 21.38	31.6 ± 11.14	0.79	2.2 ± 1.5	37.4 ± 23.3	0.0003	0.0004	0.89
Sleep Efficiency	80.2 ± 8.6	73.8 ± 13.1	0.23	87.4 ± 6.8	86.7 ± 7.6	0.84	0.02	0.002
Sleep Latency (min)	17.2 ± 19.6	16.7 ± 17.0	0.77	8.3 ± 9.5	9.54 ± 6.6	0.89	0.1	0.03
Total Sleep Time, min	379.2 ± 48.8	291 ± 81.5	0.01	408.2 ± 51.3	377.9 ± 66.7	0.27	0.18	0.04
NREM I, % of TST	10.84 ± 8.0	12.5 ± 10.9	0.65	9.5 ± 5.0	3.2 ± 0.6	0.6	0.50	0.20
NREM II, % TST	67.0 ± 11.3	58.2 ± 27.4	0.35	69.6 ± 6.3	70.8 ± 4.5	0.62	0.60	0.80
NREM III, % TST	2.7 ± 5.8	0.94 ± 1.9	0.39	1.6 ± 1.9	2.0 ± 0.8	0.74	0.62	0.16
NREM, IV, % TST	0.05 ± 0.15	0.71 ± 1.4	0.17	0.9 ± 1.7	0.2 ± 0.1	0.14	0.17	0.37
REM, % of TST	18.9 ± 7.4	14.1 ± 7.3	0.18	17.7 ± 5.1	2.8 ± 0.4	0.40	0.70	0.38
Minimal nocturnal SaO_2	82.3 ± 5.5	83.8 ± 11.5	0.17	93.4 ± 2.3	86.1 ± 7.8	0.01	0.13	0.28
SaO2 < 90%, % of TST	8.0 ± 14.4	4.1 ± 0.3	0.28	0.07 ± 0.2	5.7 ± 7.4	0.03	0.0003	0.05

RDI: respiratory disturbance index defined as the number of events that distrupt sleep divided by the sleep duration in hours;
OEI: obstructive events index defined as the number of obstructive events divided by the sleep duration in hours.
AHI: apnea-hypopnea index defined as the number of apnea-hypopnea events divided by the sleep duration in hours.

Echocardiography: Echocardiographic images were obtained in standard views by the same experienced sonographer (Hewlett Packard, Sonos, 5500). Left ventricular diastolic function and pulmonary arterial pressure was assessed by Doppler echocardiography in accordance with the American Society of Echocardiography recommendations.[10]

Cardiovascular magnetic resonance: Cardiovascular magnetic resonance (CMR) included an assessment of structure and function, adenosine stress myocardial perfusion, and coronary artery vasodilation to nitroglycerin (NTG). Imaging analysis was performed using Report Card, the GE software. Scans were performed using a 1.5T Signa MR scanner (GE Healthcare,

Table 4 Diastolic Function and Pulmonary Arterial Pressure by Echocardiography Before and After Treatment

	Baseline		Treatment		Before vs. After Treatment: Pair-wise Comparison (p value)	
	Active	Sham	Active	Sham	Active	Sham
E wave, cm/s						
≤ 1 cm/s	90% (9/10)	100%(10/10)	90% (9/10)	80% (8/10)		
> 1 cm/s	10% (1/10)	0% (0/10)	10% (1/10)	20% (2/10)		
p value	1.0		1.0		1.0	0.25
E/A ratio						
≤ 0.75	40% (4/10)	10% (1/10)	0% (0/10)	20%(2/10)		
> 0.75 & < 1.5	30% (3/10)	90%(9/10)	90%(9/10)	60%(6/10)		
≥1.5	30%(3/10)	0%(0/0)	10% (1/10)	20%(2/10)		
p value	1.0		1.0		0.03	0.25
DT						
< 140 ms	0 (0/10)	0 (0/10)	0 (0/10)	0 (0/10)		
140-240 ms	60% (6/10)	80% (8/10)	90% (9/10)	70%(7/10)		
> 240 ms	40% (4/10)	20% (2/10)	10%(1/10)	30%(3/10)		
p value	0.62		0.33		1.00	1.00
E′						
≤ 8 cm/s	11% (1/9)	20%(2/10)	11% (1/9)	40% (4/10)		
> 8 cm/s	89% (8/9)	80%(8/10)	89%(8/9)	60%(6/10)		
p value	0.92		0.30		1.00	0.25
E/e′						
< 8	66.7% (6/9)	50% (5/10)	44% (4/9)	60% (6/10)		
8-15	33.3%(3/9)	50%(5/10)	56%(5/9)	40%(4/10)		
> 15	0% (0/10)	0% (0/10)	0% (0/10)	0% (0/10)		
p value	0.90		0.66		0.5	0.5
S/D ratio						
S > D	50%(4/8)	40% (2/5)	5/8 (50%)	40% (2/5)		
S = D	50%(4/8)	60% (3/5)	3/8(30%)	60% (3/5)		
S < D	0% (0/8)	0 (0/5)	0 (0/8)	0 (0/5)		
p value	1.00		0.59		1.00	1.00

E: peak velocity associated with early mitral filling, A: peak velocity associated with the atrial kick, DT: deceleration time, E′: E prime by tissue doppler, S: peak systolic velocity associated with the pulmonary vein flow, D: peak diastolic veolicty associated with pulmonary vein flow

Table 5 Cardiac Structure and Function, Myocardial Perfusion Reserve and Coronary Artery Vasoreactivity by Magnetic Resonance Imaging

	Baseline			Treatment			Before vs. After Treatment Pairwise Comparison (p value)	
	Active	Sham	p	Active	Sham	p	Active	Sham
LV Mass	106.1 ± 28.9	108.3 ± 23.6	0.86	111.34 ± 39.8	118.4 ± 25.0	0.66	0.36	0.18
LV Mass/BSA	52.2 ± 11.4	49.3 ± 7.9	0.54	56.6 ± 18.4	69.9 ± 32.2	0.98	0.38	0.15
RVEDV	161.1 ± 28.6	171.8 ± 35.4	0.49	165.8 ± 38.1	181.6 ± 54.2	0.48	0.40	0.40
RVEDV/BSA	79.7 ± 13.0	79.1 ± 15.8	0.93	81.7 ± 79.4	82.6 ± 22.5	0.92	0.45	0.53
LVEDV	148.3 ± 32	158.3 ± 31.1	0.51	151.1 ± 30.5	163.4 ± 38.7	0.46	0.63	0.39
LVEDV/BSA	73.0 ± 13.5	72.3 ± 9.6	0.88	74.7 ± 13.4	74.4 ± 14.2	0.96	0.47	0.57
RV EF	58.9 ± 6.9	56.7 ± 9.0	0.57	55.5 ± 5.7	54.0 ± 11.4	0.80	0.26	0.43
LV EF	68.9 ± 7.1	67.4 ± 8.2	0.69	71.5 ± 4.6	65.1 ± 7.5	0.04	0.34	0.31
MPR	1.5 ± 0.5	2.0 ± 1.2	0.38	3.0 ± 1.3	2.5 ± 1.1	0.49	0.02	0.38
Change in CSA RCA, %	14+8	20 ± 10	0.16	18 ± 15	15 ± 8	0.58	0.46	0.23

LV: left ventricle, BSA: body surface area, RV: right ventricle, EDV: end diastolic volume, EF: ejection fraction, MPR: myocardial perfusion reserve, CSA: cross sectional area, RCA: right coronary artery

Milwaukee, WI) equipped with high-performance gradients (40 mT/m, 150 mT/m/ms). A commercial 4-channel cardiac phased-array surface coil provided signal reception (GE Healthcare, Milwaukee, WI). A real-time interactive system (iDrive, GE Healthcare, Milwaukee, WI) was used for localization. Assessment of cardiac function was obtained using an ECG-triggered retrospectively gated cine SSFP sequence (20 phases per cardiac cycle, TR = 3.6 ms, TE = 1.6 ms, FOV = 280 to 390 mm and flip angle = 40°). First-pass myocardial perfusion imaging was performed using a segmented echo-planar imaging pulse sequence with a notched saturation pulse.[11] For stress imaging, adenosine was administered intravenously at a rate of 140 mcg/kg/min for 4 minutes, followed by first-pass myocardial perfusion imaging during intravenous injection of 0.1 mmol/kg gadolinium-DPTA at a rate of 5 ml/s. Rest perfusion images were acquired approximately 10 minutes after stress images. The following perfusion pulse sequence parameters were used: TR = 2.4 ms, TE = 1.2 ms, inversion time = 158 to 211 ms, echo train length = 4 to 8 ms, FOV = 34 to 37 × 25 to 27 cm, matrix = 128×128, flip angle = 25°, and slice thickness = 10 mm. The rest perfusion images were generally acquired with the same graphic prescription used for the stress images. For analysis of myocardial perfusion, signal intensity was determined for each of the three contiguous slices representing the base, mid and apex of the left ventricle. The signal intensity before contrast agent administration was subtracted, and the upslope of the resulting signal intensity time curve was determined. A perfusion score was generated by adding the upslope of each of the three slices. The myocardial perfusion reserve (MPR) was calculated as the ratio between the myocardial perfusion score at stress divided by the myocardial perfusion score at rest.

NTG-induced coronary vasodilation was then performed. Using a real-time interactive system, in-plane views of the right coronary artery (RCA) were prescribed. A cross-sectional view of the most linear portion of the proximal to mid RCA was prescribed. Multi-slice high-resolution spiral coronary magnetic resonance angiography was performed with cardiac gating, breath-holding, and acquisition during diastole (FOV = 22 cm, in-plane spatial resolution = 0.7 mm, slice thickness = 5 mm, 3 slices, TR = 1 heart beat, TE = 2.5 ms, 18 interleaves, and flip angle 60°). Cross-sectional spiral high-resolution coronary magnetic resonance angiography images[12] were acquired before and 5 minutes after administration of 0.4 mg sublingual NTG while the patient was inside the magnet.

Using the cross-sectional RCA images, the most circular and corresponding slices were identified on the pre- and post-NTG images. These images were all pooled and then randomized, with neither patient nor NTG information provided on the images. We used a custom designed software program to analyze the cross sectional images. Images were magnified two-fold, and an ovoid region of interest tool was used to trace around the RCA, yielding the cross-sectional area.

Vascular Ultrasound: Endothelial function was assessed non-invasively using vascular ultrasound to measure brachial artery flow mediated dilation (FMD) following reactive hyperemia in accordance with published guidelines.[13] Studies were performed by one of two trained operators. Studies were performed at the same time of day and in the fasting state. Vasoactive medications were held 24 hours prior to the study.

Brachial artery diameters were measured using an automated software system to detect near and far wall edges and measure vessel diameter for each frame in the 10-second loop (Vascular Analysis Tools, Medical Imaging Applications, Iowa, USA). All analyses were performed by one of two trained operators. Previous reproducibility studies indicate high operator agreement.

Sample Size Calculation: The sample size was estimated based on a previous randomized study comparing FMD in patients with moderate to severe OSA randomized to 3 months of nCPAP and

Table 6 Brachial Artery Reactivity by Vascular Ultrasound at Baseline and On Treatment

	Baseline			Treatment			Before vs. After Treatment Pairwise Comparison (p value)	
	Active	Sham	p	Active	Sham	p	Active	Sham
% Brachial FMD	2.5 ± 5.7	4.0 ± 2.4	0.53	9.0 ± 6.5	2.7 ± 2.4	0.01	0.03	0.24
% NTG induced vasodilation	7.0 ± 5.0	9.0 ± 5.0	0.38	9.0 ± 7.0	7.0 ± 5.0	0.47	0.47	0.38

FMD: flow mediated dilation; NTG: nitroglycerin

no nCPAP.[14] FMD was significantly lower in patients randomized to nCPAP (nCPAP 8.9 ± 1.9%, no nCPAP 5.0 ± 0.7%, p = 0.02). Using a two tailed $\alpha = 0.01$ and power of 0.90, an attrition rate of 20%, the estimated sample size is 10 subjects per each group (total number of subjects is 20).

Statistical Analysis: Continuous variables were reported as means with standard deviations. Categorical variables were reported as frequencies and counts. Standard thresholds for abnormal values were used for all parameters. An MPR < 2.5 was considered abnormal. This cut off value is chosen based on a review of studies by Koch, which showed that arteries with significant narrowing (> 70%) had a flow reserve less than 2.5.[15] An MPR of < 2.5 was, therefore, selected for the most significant flow impairment. A global MPR < 2.5 was also used as the cutoff in the Multi-Ethnic Study of Atherosclerosis (MESA), a population-based prospective cohort study of subclinical cardiovascular disease and its progression.[16] A change of < 9% and < 15% in the brachial artery diameter after FMD and in the coronary artery cross sectional area after NTG were considered abnormal, respectively. These cutoff values were chosen based on a study in 228 non diabetic subjects who were matched for age and gender. The study showed that flow mediated dilation (8.5% ± 5.3% versus 11.7% ± 6.3%, p < 0.001) and NTG-mediated vasodilation (14.9% ± 6.0% vs. 18.5% ± 7.8%, p = 0.003) were both impaired in hypertensive compared to normotensive individuals.[17]

The differences between clinical characteristics and compliance between patients receiving active and sham nCPAP were assessed by unpaired Student's t test and Chi square test for continuous and categorical variables, respectively. Multi-modality imaging parameters were compared before and after treatment using paired Student's t test and McNemar's test for continuous and categorical variables, respectively. For the analysis of diastolic function parameters using the McNemar's test, categories were collapsed into normal and abnormal. Specifically, the following were considered normal: E/A > 0.75 and < 1.5, DT = 140 - 240 ms, E prime < 8 cm/s and a pulmonary vein pattern that was not diastolic predominant. Other values were considered abnormal. Linear regression analysis was performed to determine the relationship between the RDI and the following variables measured at baseline: 1) MPR, 2) NTG-induced coronary vasodilation, and 3) FMD. A two-tailed p value < 0.05 was considered statistically significant. Statistical analyses were performed with SPSS software version 13.0 (SPSS, Inc Chicago, IL).

Results

Demographic and Clinical Characteristics: There were no significant differences between baseline characteristics between the two groups (Table 1). The average age of subjects was 53.4 ± 11.2 years. The majority of patients were Caucasian males who were overweight and nonsmokers with hypertension. There were no significant differences between patients randomized to active vs sham nCPAP in the RDI (37.7 ± 19.4 vs 36.2 ± 17.0, p = 0.87) and apnea hypopnea index (38.8 ± 21.38 vs 31.6 ± 11.14, p = 0.79). There was no significant difference after adjustment for sleep duration in patients randomized to active vs. sham nCPAP for obstructive apneas (84.4 ± 89.0 vs 35.3 ± 29.7, p = 0.12), total apneas (85.1 ± 89.5 vs 39.8 ± 28.8, p = 0.17) and total hypopneas (149.2 ± 33.8 vs 130.0 ± 63.2, p = 0.41), respectively. Except for changes in high density lipoprotein levels, there were no significant differences between the two groups before and after nCPAP (Table 2).

Polysomnography: Compliance with nCPAP was equivalent in both groups with the average use per night of 5.1 ± 1.9 hours and 4.9 ± 2.3 hours in the active and sham groups, respectively (p = 0.9). Changes in polysomnography measurements before and after treatment are shown in Table 3.

Echocardiography: Echocardiography assessment was performed successfully in 20/20 patients, respectively. Seven patients with OSA had at least one diastolic parameter that was suggestive of diastolic dysfunction. Four patients had significant valvular abnormalities including 3 patients with significant aortic regurgitation and one patient with significant mitral regurgitation. Most patients had inadequate tricuspid regurgitation to estimate right ventricular systolic pressures, but of those with measurable values, all (8/8) had normal pulmonary pressures. Patients randomized to active nCPAP had significant improvement in the E/A ratio after treatment; whereas, those randomized to sham nCPAP did not. Changes in echocardiographic parameters before and after nCPAP are shown in Table 4.

Cardiovascular Magnetic Resonance: Assessment of cardiac structure and function was successfully performed in 20/20 patients with no significant differences in cardiac structure and function between the two groups (Table 5). Except for LV ejection fraction, there was no significant change in chamber sizes, end diastolic volumes, right ventricular ejection fraction, and LV mass after 3 months of therapy.

Adenosine stress perfusion CMR was successfully performed in 16/20 patients. No patients had adverse cardiovascular events during adenosine stress study. No regional myocardial perfusion defects were noted by qualitative visual assessment in either group.

Baseline MPR was abnormal in patients with sleep apnea with no significant differences between subjects randomized to active and sham. There was no significant correlation between baseline RDI and MPR (r = 0.32, p = 0.24). Three months after randomization, the MPR increased significantly in patients randomized to active nCPAP (1.5 ± 0.5 vs 3.0 ± 1.3, p = 0.02); however, it did not change significantly in patients randomized to sham nCPAP (2.0 ± 1.2 vs 2.5 ± 1.1, p = 0.38 (Table 5).

NTG Coronary Vasodilation: At baseline, the mean percent vasodilation to NTG was abnormal, but did not significantly differ between the two groups (Table 5). There was no significant correlation between baseline RDI and NTG coronary vasodilation (r = -0.14, p = 0.64). There was no significant difference in coronary vasodilation after 3 months of therapy in either the active or sham groups.

Vascular Ultrasound: Assessment of brachial artery FMD by vascular ultrasound was successfully performed in 18/20 patients. Patients with OSA had impaired FMD with no significant differences in brachial artery FMD at baseline in the active vs. sham groups (Table 6). There was no significant correlation between baseline RDI and FMD (r = 0.08, p = 0.78). Three months after randomization, FMD increased significantly and even normalized in the active group (2.5 ± 5.7 vs 9.0 ± 6.5, p = 0.03); however, there was no significant improvement in the sham group (4.0 ± 2.4 vs 2.7 ± 2.4, p = 0.47). No significant difference was detected in either group in NTG induced vasodilatation of the brachial artery following 3 months of therapy.

Discussion

This is the first study to provide a comprehensive evaluation of subclinical CVD using multi-modality CVI in patients with OSA. As expected in asymptomatic patients with moderate to severe OSA and no known cardiovascular disease, most patients did not have significant abnormalities of cardiac structure and contractility. Patients with OSA, however, had abnormal MPR and brachial FMD, suggesting these patients have microvascular disease and endothelial dysfunction, respectively. These abnormalities improved after 3 months of active nCPAP, providing further evidence that OSA may contribute to the development of CVD.

Preserved Cardiac Structure and Function: Previous studies have shown that OSA adversely affects the structure and systolic function of the left[18-20] and right ventricle.[19,21] Patients with OSA have recurrent increases in left ventricular (LV) afterload during sleep that results from large negative intra-thoracic pressure swings, hypoxemia and arousals from sleep. Recurrent LV strain over several hours of apneas may result in chronic LV dysfunction. Increased sympathetic activity and hypoxemia also contribute to LV dysfunction. Improvement has been reported after nCPAP and may be related to a reduction in nocturnal afterload. LV dysfunction, however, appears to be a late complication and was observed in < 10% of cases in a previous study[18] and was not observed in this study.

Other abnormalities have been reported in patients with OSA including an increase in LV mass[22,23] and diastolic dysfunction.[23] However, a recent report[23] has shown that these abnormalities did not correlate with the apnea hypopnea index (AHI) or with oxygen saturation but were associated with age, hypertension and obesity. Consistent with these findings, most patients in our study whose average age was 55 years old and who were not obese (average body mass index < 30) had normal LV mass and diastolic function. Although all patients had a history of hypertension, the average blood pressure was normal and the majority of patients had good control of their blood pressure with prescribed medications.

Similarly, RV dysfunction may be a result of chronic intermittent hypoxia and hypercapnia during apneic episodes. RV dysfunction may also be secondary to left ventricular dysfunction as a result of increased afterload and sympathetic activity, which causes secondary hypertension. RV dysfunction[21] and elevated RVSP,[24] however, is an uncommon finding in patients with sleep apnea and was not found in our study.

Estimates of ejection fraction, however, may not be sensitive enough to detect early changes related to obstructive sleep apnea. Previous studies[19] have shown impairment of the left and right ventricular myocardial performance index, which is derived by measurement of the isovolumic contraction and relaxation times and valvular ejection times. Improvement correlated well with AHI, independent of confounders. Reduced systolic and diastolic velocities[25] of the left and right ventricle have also been observed in patients with OSA and were noted to improve after six months of CPAP. Future studies are needed to determine the clinical utility of these measures in the assessment of patients with sleep apnea.

Microvascular Disease and Endothelial Dysfunction in Patients with OSA: Microvascular disease and endothelial dysfunction are the earliest manifestations of coronary heart disease and can be found in patients without obstructive coronary artery disease (CAD) or myocardial disease. Coronary microvascular dysfunction has been previously described in patients with risk factors for CAD. In a previous study, coronary flow reserve was reduced by 21% in smokers and normalized with vitamin C administration, an anti-oxidant.[26] Impairment in coronary flow reserve has also been shown in asymptomatic subjects with hypercholesterolemia[27] and angiographically normal coronary arteries with demonstrated reversibility with cholesterol lowering strategies.[28] Similarly, in our study, patients with OSA with no documented obstructive CAD and no myocardial disease had impaired MPR. MPR improved in patients randomized to active but not sham nCPAP, suggesting that the presence of microvascular disease is due to OSA and not to the presence of cardiovascular risk factors in these patients. To our knowledge, this is the first study to show that patients with OSA have microvascular disease measurable by CMR MPR, which improves with therapeutic nCPAP.

Similarly, endothelial dysfunction has been described in patient with coronary risk factors as well as those with OSA. Previous studies have shown that patients with OSA have impaired brachial artery dilation to acetylcholine, an endothelial-dependent stimulus, compared with control subjects.[29,30] A recent study showed that endothelial function in OSA patients improved after 3 months of nCPAP.[31] This study also demonstrated that resting nitric oxide (NO) production was higher after CPAP. Other studies have confirmed improvement in peripheral endothelial function as early as two weeks after CPAP and increases in plasma levels of NO have been observed as early as one night after nCPAP.[32,33] Our study confirms these findings. In this study, patients with OSA had decreased brachial FMD. Patients randomized to active nCPAP showed improvement in brachial FMD; whereas, those randomized to sham nCPAP showed no significant change. At baseline and at 3 months, there were no significant changes in cardiac risk factors except for high density lipoprotein, which decreased in both groups. The significance of which is unclear but may be related to inactivity secondary to nCPAP usage. This study supports that relief of apneic events by nCPAP in patients with sleep apnea improves endothelial function.

Several mechanisms[34] have been suggested to explain the relationship between OSA and vascular dysfunction. Evidence suggests that recurrent apnea-hypopnea events in OSA patients are associated with repetitive hypoxemia and reoxygenation, resulting in increased production of reactive oxygen species. This leads to increased intra and extra cellular oxidative stress and breakdown of NO, resulting in vascular dysfunction. The relationship between apnea and vascular dysfunction was further supported in a recent study,[35] which showed that regional myocardial perfusion defects were present during periods of apnea in patients with OSA without obstructive CAD but were not present during daytime scintigraphy. In addition, the presence of cardiac risk factors in OSA patients, including insulin resistance, hypertension, and hyperlipidemia adversely, impairs vascular function. Cardiac risk factors are associated with increased oxidative stress.[36] Recruitment and differentiation of endothelial progenitor cells is also impaired by cardiovascular risk factors, preventing endothelial cell repair.[37] Finally, cardiac risk factors have been associated with increased asymmetric dimethylarginine,[38] an endogenous eNOS inhibitor produced by increased methylation of L arginine, which decreases synthesis of NO, increases oxidative stress and inhibits endothelial cell repair.

Study Limitations: A limitation of the study is the relatively small sample size, which may decrease the power to detect abnormalities in all clinical and imaging parameters. However, with the small sample size, we were able to detect the presence of microvascular disease and endothelial-dependent function, suggesting that these abnormalities are the most significant and earliest manifestation of CVD in patients with OSA. Further study in a larger population is warranted to confirm these findings. Furthermore, we may not be applying the most sensitive measures. Future studies, for example, could measure myocardial performance index, a more sensitive measure of ventricular function. In addition, 3 months of nCPAP may be inadequate to detect a significant change in some cardiovascular outcomes such as left ventricular mass, diastolic dysfunction, and pulmonary HTN. However, it may not be ethical to withhold nCPAP for a longer duration in this population. Future studies with a longer therapeutic duration could be performed in non-sleepy patients to determine if nCPAP is effective to improve these parameters. Another limitation of the study is that the duration of OSA may affect the results of CVI studies. Although we recruit only patients who are newly diagnosed, the duration that they had undiagnosed OSA is unknown. The final limitation of the study is that we are using imaging measurements as surrogate measurements for outcome. Findings from this initial study, however, may be applied to design a large, prospective randomized trial of nCPAP vs. sham CPAP to determine if nCPAP improves cardiovascular outcomes.

Conclusions

Our findings indicate that nCPAP therapy improves coronary microvascular and endothelial function in OSA patients. These findings suggest that nCPAP therapy may prevent the development and progression of subclinical atherosclerosis, and, thus, significantly reduce cardiovascular morbidity and mortality in OSA patients. Larger, well-designed, multi-center prospective studies are needed to evaluate the impact of nCPAP therapy on various cardiovascular outcomes in OSA patients.

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Factors Associated with Motivation and Hesitation to Work Among Health Professionals During a Public Crisis

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Abstract

Background: The professionalism of hospital workers in Japan was challenged by the pandemic (H1N1) 2009. To maintain hospital function under critical situations such as a pandemic, it is important to understand the factors that increase and decrease the willingness to work. Previous hospital-based studies have examined this question using hypothetical events, but so far it has not been examined in an actual pandemic. Here, we surveyed the factors that influenced the motivation and hesitation of hospital workers to work in Japan soon after the pandemic (H1N1) 2009.

Methods: Self-administered anonymous questionnaires about demographic character and stress factors were distributed to all 3,635 employees at three core hospitals in Kobe city, Japan and were collected from June to July, 2009, about one month after the pandemic (H1N1) in Japan.

Results: Of a total of 3,635 questionnaires distributed, 1,693 (46.7%) valid questionnaires were received. 28.4% (N = 481) of workers had strong motivation and 14.7% (N = 249) had strong hesitation to work. Demographic characters and stress-related questions were categorised into four types according to the odds ratios (OR) of motivation and hesitation to work: some factors increased motivation and lowered hesitation; others increased motivation only; others increased hesitation only and others increased both motivation and hesitation. The strong feeling of being supported by the national and local governments (Multivariate OR: motivation; 3.5; CI 2.2-5.4, hesitation; 0.2; CI 0.1-0.6) and being protected by hospital (Multivariate OR: motivation; 2.8; CI 2.2-3.7, hesitation; 0.5; CI 0.3-0.7) were related to higher motivation and lower hesitation. Here, protection included taking precautions to prevent illness among workers and their families, providing for the care of those who do become ill, reducing malpractice threats, and financial support for families of workers who die on duty. But 94.1% of the respondents answered protection by the national and local government was weak and 79.7% answered protection by the hospital was weak.

Conclusions: Some factors have conflicting effects because they increase both motivation and hesitation. Giving workers the feeling that they are being protected by the national and local government and hospital is especially valuable because it increases their motivation and lowers their hesitation to work.

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Background

The professionalism of hospital workers was challenged by the pandemic (H1N1) 2009. To maintain the function of hospitals under high risk conditions in the future, it is important to clarify the factors that promote or hinder a professional attitude in actual situations.

Historically, the professionalism of medical workers has been tested by various events such as HIV, Ebola hemorrhagic fever, the Tokyo sarin gas attack, SARS and so on. Among these events, SARS raised the question of how professionals should respond in public emergencies. SARS spread to 26 countries, where it infected 8096 people and killed 774 (mortality rate: 9.6%). Most hospitals continued to serve the public, but at least one hospital in China ceased to function because of mass absence of its workers.[1] Many people in the public were afraid of what would happen if infections like SARS occurred on a pandemic scale.

After the SARS crisis, various studies were carried out, in which hospital workers were asked how they would respond to a hypothetical pandemic infection. In Germany, 28% of nurses, doctors, medical students and hospital officials answered that they might be absent from work during a pandemic to protect themselves and their families.[2] In the United States, 46.2% of local public health workers reported that they would probably not work during a future influenza pandemic[3] and 21.7% of health care employees would be unwilling to work during a SARS pandemic.[4] In Singapore, 27.7% of primary care physicians would not look after patients infected with avian influenza.[5] In Canada, 21% of family physicians indicated that they would be unwilling to help in a pandemic infection if their help was requested by the public health department.[6] Overall around 20 or 30% of health care-related workers showed a hesitation to work during a future infection pandemic regardless of their culture.

On June 11, 2009, WHO declared the H1N1 influenza infection a pandemic. On May 16, our hospital admitted the first patient that had been domestically infected with the H1N1 influenza virus in Japan. In the following two weeks, 1687 people who suspected that they had H1N1 influenza infection came to our hospitals and were released as outpatients and an additional 144 patients who

Table 1 Demographic characteristics of the study population and likelihood of reporting hesitation and motivation to work

		High		Likelihood of reporting			
				Hesitation to work		Motivation to work	
Characteristic	n(%)	Hesitation n (%)	Motivation n (%)	Bivariate OR (95%CI)	Multivariate+ OR (95%CI)	Bivariate OR (95%CI)	Multivariate+ OR (95%CI)
Age							
20-30	623 (36.8)	112 (18.0)	111 (17.8)	Reference	Reference	Reference	Reference
30-40	466 (27.5)	86 (18.5)	125 (26.8)	1.0 (0.8-1.4)	1.1 (0.8-1.5)	1.7 (1.3-2.3)	1.6 (1.2-2.1)
40-50	326 (19.3)	29 (8.9)	117 (35.9)	0.4 (0.3-0.7)	0.4 (0.3-0.7)	2.6 (1.9-3.5)	2.3 (1.7-3.2)
50-60	239 (14.1)	20 (8.4)	114 (47.7)	0.4 (0.3-0.7)	0.5 (0.3-0.8)	4.2 (3.0-5.8)	3.4 (2.4-4.8)
60-70	39 (2.3)	2 (5.1)	14 (35.9)	0.2 (0.1-1.0)	0.3 (0.1-1.2)	2.6 (1.3-5.1)	1.8 (0.9-3.7)
Gender							
Male	411 (24.3)	38 (9.2)	174 (42.3)	Reference	Reference	Reference	Reference
Female	1282 (75.7)	211 (16.5)	307 (23.9)	1.9 (1.3-2.8)	1.7 (1.2-2.6)	0.4 (0.3-0.5)	0.6 (0.5-0.8)
Job Classification							
Clinical staff	1114 (65.8)	180 (16.2)	265 (23.8)	Reference	Reference	Reference	Reference
Clinical technical/Support staff	181 (10.7)	13 (7.2)	81 (44.8)	0.4 (0.2-0.7)	0.6 (0.3-1.0)	2.6 (1.9-3.6)	1.7 (1.2-2.5)
Non-clinical support staff	398 (23.5)	56 (14.1)	135 (33.9)	0.9 (0.6-1.2)	1.2 (0.8-1.7)	1.6 (1.3-2.1)	1.2 (0.9-1.6)
Working at high risk environment							
No	1157 (68.3)	169 (14.6)	286 (24.7)	Reference	Reference	Reference	Reference
Yes	536 (31.7)	80 (14.9)	195 (36.4)	1.0 (0.8-1.4)	1.2 (0.9-1.7)	1.7 (1.4-2.2)	1.6 (1.2-2.0)

+ Adjusted for Age, Gender, Job classification, Working place.

we suspected as having H1N1 were admitted. Of these, 49 were diagnosed as having an H1N1 influenza infection after they were admitted. Kobe City Medical Center General Hospital had 122 admissions who were suspected to be H1N1-positive, including 31 patients who were subsequently diagnosed with H1N1. Kobe City Medical Center West Hospital had 22 admissions including 18 patients diagnosed with H1N1 afterward. The peak was May 17 and the number of patients coming to our outpatient unit for H1N1 infection on that day was 211. On May 27, the mayor of Kobe city declared the emergency had subsided. On June 3, the outpatient unit for H1N1 infection was closed.

To the best of our knowledge, no studies have evaluated hospital workers' willingness to work and the factors that influence their decisions in a real pandemic.

Individuals interacting within a social setting are known to be subject to intrinsic and extrinsic motivation, and are often manipulated or managed to strategically meet societal and/or organizational goals.[7,8] Professionals, who are traditionally granted a high degree of autonomy, may be particularly sensitive to incentives and disincentives, of whatever nature.[9] A hospital-based study suggested that the willingness of workers to respond to an influenza pandemic is powerfully influenced by their perceptions of threat and efficacy.[10] Professional conduct of physicians is affected by incentives and disincentives.[11-16] From these points of view, the willingness to work is thought to be a function of the conflicting factors of motivation (incentives), and hesitation (disincentives). To maintain willingness of hospital workers and improve hospital function in critical situations, it is important to understand the factors that motivate hospital workers to work and that discourage them from working. After our experience with the H1N1 influenza pandemic, we investigated the attitudes of workers in Kobe area hospitals about willingness to work in a pandemic and the factors that influence them by using questionnaire.

Methods

This survey was approved by the Kobe City Medical Center General Hospital Ethical Review Board. Participation in this survey was voluntary. We conducted the study at Kobe City Medical Center General Hospital (912 beds), Kobe City Medical Center West Hospital (358 beds) and Nishi-Kobe Medical Center (500beds), which compose Kobe City Hospital Organization and are tertiary teaching hospitals in Kobe city. All three hospitals accepted H1N1 influenza patients starting March 16, 2009, when the first domestically infected patient visited Kobe City Medical Center General Hospital. Paper-based self-administered anonymous questionnaires were personally handed to all employees or placed in their mail boxes from June 22, 2009 and were collected from collecting boxes in the participating hospitals till July 31, 2009, which is about one month after the peak of the H1N1 outbreak in Kobe city. When this survey was conducted, the level of the pandemic was phase 6 in the world

Table 2 Associations of stress factors and likelihood of reporting hesitation and motivation to work

			Among the strong		Likelihood of reporting			
					Hesitation to work		Motivation to work	
	Weak n(%)	Strong n(%)	High Hesitation n (%)	High Motivation n (%)	Bivariate OR (95%CI)	Multivariate+ OR (95%CI)	Bivariate OR (95%CI)	Multivariate +OR (95%CI)
Risk for infection								
Anxiety about being infected	709 (41.9)	981 (57.9)	212 (21.6)	291 (29.7)	5.2 (3.6-7.4)	4.8 (3.3-7.0)	1.2 (0.9-1.4)	1.3 (1.1-1.7)
Anxiety about infecting family	733 (43.3)	950 (56.1)	191 (20.1)	301 (31.7)	3.0 (2.2-4.0)	2.8 (2.1-3.9)	1.5 (1.2-1.8)	1.6 (1.3-2.0)
Anxiety of being infected during commuting	905 (53.5)	781 (46.1)	169 (21.6)	235 (30.1)	2.9 (2.2-3.9)	2.8 (2.1-3.8)	1.2 (0.9-1.4)	1.5 (1.2-1.8)
Knowledge and measurement								
Lack of knowledge about infectiosity and virulence	1017 (60.1)	666 (39.3)	132 (19.8)	214 (32.1)	1.9 (1.5-2.5)	1.8 (1.4-2.4)	1.4 (1.1-1.7)	1.5 (1.2-1.9)
Lack of knowledge about prevention and protection	1337 (79.0)	348 (20.6)	88 (25.3)	107 (30.7)	2.5 (1.9-3.3)	2.3 (1.7-3.1)	1.1 (0.9-1.5)	1.3 (1.0-1.7)
Protection								
Feeling of being protected by country and local government	1593 (94.1)	96 (5.7)	3 (3.1)	56 (58.3)	0.2 (0.1-0.5)	0.2 (0.1-0.6)	3.9 (2.5-5.9)	3.5 (2.2-5.4)
Feeling of being protected by hospital	1349 (79.7)	338 (20.0)	26 (7.7)	168 (49.7)	0.4 (0.3-0.6)	0.5 (0.3-0.7)	3.3 (2.6-4.2)	2.8 (2.2-3.7)
Anxiety about compensation	906 (53.5)	780 (46.1)	183 (23.5)	240 (30.8)	3.9 (2.9-5.3)	3.6 (2.7-4.9)	1.2 (1.0-1.5)	1.4 (1.1-1.8)
Condition								
Burden of increase quantity of work	1098 (64.9)	589 (34.8)	107 (18.2)	192 (32.6)	1.5 (1.1-2.0)	1.6 (1.2-2.1)	1.4 (1.1-1.7)	1.2 (0.9-1.5)
Burden of change of quality of work	1096 (64.7)	592 (35.0)	101 (17.1)	201 (34.0)	1.4 (1.0-1.8)	1.4 (1.0-1.9)	1.5 (1.2-1.9)	1.4 (1.1-1.8)
Physical exhaustion	1151 (68.0)	541 (32.0)	124 (22.9)	187 (34.6)	2.4 (1.9-3.2)	2.5 (1.8-3.3)	1.5 (1.2-1.9)	1.5 (1.2-1.9)
Mental exhaustion	1122 (66.3)	565 (33.4)	134 (23.7)	202 (35.8)	2.7 (2.1-3.6)	2.7 (2.1-3.6)	1.7 (1.4-2.1)	1.8 (1.4-2.3)
Insomnia	1618 (95.6)	73 (4.3)	22 (30.1)	38 (52.1)	2.6 (1.6-4.4)	2.9 (1.7-5.0)	2.9 (1.8-4.6)	2.6 (1.6-4.2)
Elevated mood	1505 (88.9)	185 (10.9)	35 (18.9)	115 (62.2)	1.4 (0.9-2.1)	1.6 (1.0-2.4)	5.1 (3.7-7.1)	4.6 (3.3-6.5)
Isolation								
Feeling of being avoided by others	1495 (88.3)	192 (11.3)	56 (29.2)	44 (22.9)	2.8 (2.0-4.0)	2.4 (1.7-3.4)	0.7 (0.5-1.0)	0.9 (0.6-1.3)
Feeling of being isolated	1588 (93.8)	104 (6.1)	42 (40.4)	38 (36.5)	4.5 (3.0-6.9)	4.7 (3.0-7.2)	1.5 (1.0-2.3)	1.6 (1.0-2.5)
Others								
Feeling of having no choice but to work due to obligation	604 (35.7)	1081 (63.9)	186 (17.2)	330 (30.5)	1.9 (1.4-2.6)	1.7 (1.3-2.4)	1.4 (1.1-1.7)	1.6 (1.2-2.0)
Burden of child care including lack of nursery	380 (22.4)	221 (13.1)	56 (25.3)	74 (33.5)	3.0 (1.9-4.7)	2.7 (1.6-4.5)	1.0 (0.7-1.4)	1.3 (0.9-1.9)

+ Adjusted for Age, Gender, Job classification, Working place.

and the number of patients in Japan was growing, but the alert to the infection was downgraded as information accumulated that the virulence was not strong. By June 8, 2009, our hospitals returned to their normal practice.

Survey content: The questionnaire explained its purpose and stated that the results would be published, and respondents would remain anonymous. The first item asked for approval to use the responses in the survey. Answers without this approval were omitted from the analysis. The questionnaire contained 20 items that addressed sociodemographic characteristics, perceived stress associated with the H1N1 event, and motivation and hesitation to work during the event.

The personal characteristics included gender, age, job and working place (the ward for H1N1, the outpatient department for H1N1, emergency outpatient unit, headquarter and others). The stress-related questions were as follows: anxiety about being infected; anxiety about infecting family; anxiety of being infected during commuting; lack of knowledge about infectiosity and virulence; lack of knowledge about prevention and protection; feeling of being protected by national and local government; feeling of being protected by hospital (the protection include taking all reasonable precautions to prevent illness, providing for the care of those who do become ill, reducing malpractice threats for those working in high-risk emergency situations and providing reliable compensation for the families of those

who die while fulfilling this duty and attenuating the duty of hospital workers not to become a patient him or herself and so on); anxiety about compensations; burden of increase quantity of work; burden of change of quality of work; physical exhaustion; mental exhaustion; insomnia; elevated mood; feeling of being avoided by others; feeling of being isolated; feeling of having no choice but to work due to obligation; burden of child care including lack of nursery. These are the essential items from previous studies on SARS[17,18] and hypothetical infection pandemics[2,3,5,19] and hypothetical symptoms during crises. The respondents used a 4-point Likert scale (0; "never", 1; "rarely", 2; "sometimes", 3; "always") to respond to the questions about how often they felt about the 18 items. The responses of how often they felt motivation and hesitation to work were also scored by a 4-point Likert scale as above.

The jobs of hospital workers were classified into three categories: (1) clinical staff (doctors and nurses); (2) clinical technical/ support staff (radiological technologists, clinical laboratory technicians, pharmacists, dieticians, social workers, physical therapists, occupational therapists and speech therapists); and (3) non-clinical staff (office workers, clinical clerks, guards, janitors and others). Working places were categorised into the high-risk places (the ward and the outpatient department for H1N1 influenza infection, emergency outpatient unit and headquarter) and the low-risk places (others). We were unable to determine how many workers in high risk places actually came in contact with H1N1 patients, but all such workers could have come in contact with H1N1 patients and they recognized this.

Data analysis: Responses to the stress-related questions and motivation and hesitation to work were dichotomized into responses with a score two or less (weak) and all other (strong) responses. Bivariate and multivariate logistic regression models (adjusted for age, gender, job and working place) were used to compute odds ratios (OR) to evaluate the association of personal characteristics variables and stress-related items with self-described motivation and hesitation to work. SPSS (17.0J: Tokyo) was used for data capturing and analysis.

Results

We sent out a total of 3,635 questionnaires. We received a total of valid 1,995 questionnaires (54.9%). The breakdown of the responses is as follows: we received 1081 out of 1625 (66.5%) from Kobe City Medical Center General Hospital, 313 out of 775 (40.4%) from Kobe City Medical Center West Hospital and 601 out of 1235 (48.7%) from Nishi-Kobe Medical Center. Of the 1,995 responses, 302 were excluded because of missing personal characteristics or items of motivation and hesitation, leaving 1,693 (46.7%) questionnaires for analysis. As compared with the distribution of survey respondents key characteristics shown in Table 1, the total staffs of three hospitals had similar proportional distribution, with 73.7% females (compared with 75.7%), 64.2% clinical staffs and 10.3% clinical support/technical staffs (compared with 65.8% and 10.7%), 42.1% 20-30 years old, 27.3% 30-40 years old, 15.6% 40-50 years old and 12.6% 50-60 years old (compared with 36.8%, 27.5%, 19.3%, 14.1%).

Among these 1,693 responses, 481 (28.4%) said they were strongly motivated to work and 249 (14.7%) said they were very hesitant to work.

According to the personal characteristics and OR, compared with workers in their 20s, workers in their 30s had higher motivation (Multivariate OR: 1.6; CI 1.2-2.1) without any significant difference in hesitation. Workers in their 40s and 50s had higher motivation (Multivariate OR: 40s; 2.3; CI 1.7-3.2, 50s; 3.4; CI 2.4-4.8) and lower hesitation (Multivariate OR: 40's; 0.4; CI 0.3-0.7, 50's; 0.5; CI 0.3-0.8). Females showed lower motivation (Multivariate OR: 0.6; CI 0.5-0.8) and higher hesitation (Multivariate OR: 1.7; CI 1.2-2.6) than males. Clinical technical/ support staff had higher motivation (Multivariate OR: 1.7; CI 1.2-2.5) than clinical staff without any significant difference in hesitation. Working at a high-risk facility was related to higher motivation than working at a low-risk facility (Multivariate OR: 1.6; CI 1.2-2.0) without any significant difference in hesitation (Table 1). The associations between stress-related questions and OR are shown in Table 2. Among the items with significant difference between the responses to the stress-related questions with strong scores and those with weak scores, ORs that are over 2.5 or under 0.4 are indicated as follows; "Being protected by the national or local government" (Multivariate OR: motivation; 3.5; CI 2.2-5.4, hesitation; 0.2; CI 0.1-0.6) and "being protected by hospital" (Multivariate OR: motivation; 2.8; CI 2.2-3.7, hesitation; 0.5; CI 0.3-0.7) were associated with higher motivation and lower hesitation. 94.1% responded that the protection from the national and local governments was weak and 79.7% responded that the protection provided by their hospital was weak. "Elevated mood" was associated with higher motivation without any significant difference in hesitation (Multivariate OR: 4.6; CI 3.3-6.5). The items with higher motivation without any significant difference in hesitation were "burden of child care including lack of nursery" (Multivariate OR: 2.7; CI 1.6-4.5). The items with higher motivation and hesitation were "anxiety about being infected" (Multivariate OR: motivation; 1.3; CI 1.1-1.7, hesitation; 4.8; CI 3.3-7.0), "anxiety about infecting family" (Multivariate OR: motivation; 1.6; CI 1.3-2.0, hesitation; 2.8; CI 2.1-3.8), "anxiety of being infected during commuting" (Multivariate OR: motivation; 1.5; CI 1.2-1.8, hesitation; 2.8; CI 2.1-3.8), "anxiety about compensation" (Multivariate OR: motivation; 1.4; CI 1.1-1.8, hesitation; 3.6; CI 2.7-4.9), "physical exhaustion" (Multivariate OR: motivation; 1.8; CI 1.4-2.3, hesitation; 2.7; CI 2.1-3.6), "mental exhaustion" (Multivariate OR: motivation; 2.6; CI 1.6-4.2, hesitation; 2.7; CI 2.1-3.6), "insomnia" (Multivariate OR: motivation; 2.6; CI 1.6-4.2, hesitation; 2.9; CI 1.7-5.0),and "being isolated" (Multivariate OR: motivation; 1.6; CI 1.0-2.5, hesitation; 4.7; CI 3.0-7.2). The percentage of workers that considered childcare to be a burden was significantly higher among females (43.2%) than males (21.3%).

Discussion

Although some studies have examined professionalism or willingness to work in a hypothetical pandemic or high-risk infection and one study examined the hospital absentee rate during an actual H1N1 pandemic,[20] as far as we know, our survey is the only one that evaluated hospital workers' willingness to work and the influencing factors following an actual pandemic infection. Our study was focused on the factors associated with willingness. The results show that willingness has conflicting aspects. That is, factors that raise motivation do not necessarily lower hesitation: some factors raise both motivation and hesitation.

We found factors were categorized into four types according to their influence on the OR of motivation and hesitation to work. That is, some factors increased the OR of motivation and lowered the OR of hesitation, other factors increased the OR of motivation only, other factors increased the OR of hesitation

only, and others increased the OR of both motivation and hesitation. This is important because understanding factors that cause or reduce conflict is necessary to find ways to support professionalism of hospital workers in a high-risk environment.

A limitation of our study is the non-response bias as a result of the 46.7% response rate. However, the total number of subjects was large and their demographics to the population as a whole that did not make noticeable difference.

The most important factors are ones that resolve conflicting emotions and promote willingness, that is, increase motivation and lower hesitation. Above all, the various types of protection that workers receive from the national and local governments and from their hospitals (eg. protecting them from getting sick and from malpractice suits) needs improvement. The physicians, nurses and others in the ward for H1N1 and the outpatient department for H1N1were provided with protection suits, N95 masks, goggles and antiviral prophylaxes but many of them felt that they were not strongly protected by the national and local government and hospitals. There were no plans about what they should do or how they would be reimbursed in case they became infected and the governments provided no encouraging words to the hospitals. In a study of the use of the antiviral oseltamivir as a prophylactic,[21] 274 employees who worked in high risk places at Kobe City Medical Center General Hospital (KCGH) took oseltamivir from May 16 to May 25, 2009. Only 37% took the medicine for the full ten days. The others stopped taking it for a variety of reasons, including side effects, anxiety about the drug, failure to remember taking it, or because the virulence of H1N1 seemed weak.

The fact that governmental and hospital protection increased motivation and lowered hesitation suggests that positive intervention in these fields will have the strongest impact on reducing non-illness-related absenteeism. Therefore, the protection of hospital workers by governments and hospitals should be emphasized.[22-24] Samuel et al.[25] suggested that two major factors are involved in instilling employees sense of ethical obligations to treat patients during a crisis. First is an expectation of some reciprocal social obligations. For example, in preparation for epidemics, communities or employers should take all reasonable precautions to prevent illness among health care workers and their families, provide for the care of those who do become ill, reduce or eliminate malpractice threats for those working in high-risk emergency situations and provide reliable compensation for the families of those who die while fulfilling this duty. Second, the duty of physicians should be attenuated but not eliminated, by his or her responsibility in order to prevent them from becoming patients.[25] Work can be attenuated by reducing working time, by restricting the number of patients, by assigning physician to a place with lower workload or by shifting them to jobs with lower risk. In order for workers to fulfil their duties, they need to feel safe. The feeling of safety will be strong when the safety is provided by their organizations. But, in addition to these measurements, there is a need for frequent communication between individual workers and their organization or governments. Encouragement from organizations or governments would also support workers mentally.

In the present study, increased motivation and less hesitation was noted in middle-aged and male workers. Age and gender were also examined in two studies that presented hospital workers with a hypothetical influenza pandemic in the United States[3] and a hypothetical SARS pandemic in Singapore.[26] These studies found no age or gender difference in the willingness to work, which is inconsistent with our results. This discrepancy may be partly because people in management positions have a strong sense of responsibility, and in our hospitals, many of the management positions are held by males in their 40s and 50s. Another reason for the discrepancy is that our study was based on a real pandemic and the others were based on hypothetical pandemics. As for gender, studies of physicians' burnout have indicated that females feel more stress than males in the workplace.[27,28] As a result, extra measures should be taken to alleviate the stress of female workers during stressful events, such as by providing childcare services.

Factors that increase motivation only may not always be good because they could result in overfatigue in the long run. Paradoxically, we found that working in a place of high risk and demands for unaccustomed work increased motivation. A Canadian study of senior practitioners with reputations for resilience indicated that making a unique contribution, and receiving privileges and rewards are central to building resilience, although the burden of increased workload was found to lower the level of satisfaction.[29] In view of these results, working in a place of high risk with new work may be considered as a special contribution by hospital workers. Technical/support staffs were especially motivated, perhaps because, in addition to the above reason, they usually had little direct contact with patients and thus had lower perceived levels of risk.

Reducing the factors that cause hesitation only will reduce the barrier to work in high-risk situations. Such stress factors include a lack of knowledge about prevention and protection, the burden of increased quantity of work, the feeling of being avoided by others, and the burden of childcare without childcare facilities. Examples of such measures include work sharing or rotation of duty. Sharing of duties and increasing the number of people who work in high-risk places will provide workers with more concrete knowledge about prevention and protection, lighten their workload, promote a sense of unity and reduce the sense of isolation.

Reducing factors that increase both motivation and hesitation should be given high priority, as these factors can result in the conflict among hospital workers in the long term, although in the short term they may cancel each other out. In the present study, many of the respondents had strong fears of being infected (57.9% of respondents), infecting family (56.1%), feeling of having no choice but to work due to obligation (63.9%) and anxiety about compensation in case of being infected (53.5%). During an infection pandemic, it is to some degree inevitable to feel exhausted and isolated and to worry about becoming infected. But a study said that mitigation strategies that include options for preferential access to either antiviral therapy, protective equipment, or both for the employee as well as his or her immediate family will have the greatest impact.[30] Our hospitals provided all protective measurements listed above to the employee but not to his or her immediate family. The measurement should include protection of employees' family, which might support their motivation and reduce hesitation. In addition, government and hospital managers should develop plans to compensate and treat workers that become infected and to help workers meet their obligations. This would also increase the feeling of protection given by the hospital and the

various levels of government. Although our survey was related to an influenza pandemic, most of the questions used here have generalizability to other high-risk situations. Further studies are needed to test the external validity of our results.

Conclusions

We found that there are factors which influence motivation and hesitation to work in an influenza pandemic. Some factors have conflicting effects that increase both motivation and hesitation. Giving workers the feeling that they are being protected by the national and local governments and by their hospital is especially valuable because it increases their motivation and lowers their hesitation to work. This can be achieved by not only providing protective materials and compensation but also by frequently communicating with and encouraging workers.

We should prepare for severer and longer infection pandemic as soon as possible.

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Eosinophilic Infiltrate in a Patient with Severe Legionella Pneumonia as a Levofloxacin-Related Complication

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Abstract

Introduction: Legionella pneumonia can appear with different levels of severity and it can often present with complications such as acute respiratory distress syndrome.

Case presentation: We report the case of a 44-year-old Caucasian man with Legionella pneumonia with successive development of severe acute respiratory distress syndrome. During his stay in intensive care the clinical and radiological situation of the previously observed acute respiratory distress syndrome unexpectedly worsened due to acute pulmonary eosinophilic infiltrate of iatrogenic origin.

Conclusion: Levofloxacin treatment caused the occurrence of acute eosinophilic infiltrate. Diagnosis was possible following bronchoscopic examination using bronchoaspirate and transbronchial biopsy.

Introduction

Since the pneumonia epidemic that struck the delegates of the American Legion Convention in Philadelphia in 1976, Legionella spp. has become a relatively frequent cause of community acquired pneumonia.[1]

Legionella may appear in different forms, from subclinical presentations to Legionnaires' disease, which has a mortality rate as high as 30 to 50% in cases of hospital infections and in cases of complications such as acute respiratory distress syndrome (ARDS). The fatality rate is 5 to 25% even in patients who are immunocompetent.[2]

Other complications are rare, although a significant number of drugs used in the treatment of Legionella pneumonia can be associated with the appearance of pulmonary eosinophilic infiltrates, especially non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics.[3] The diagnosis is mainly based on the temporal correlation between the administration of drugs and the appearance of the clinical condition, but it is often not easy to determine the etiologic agent with certainty.

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This report concerns the case of a man with Legionella pneumonia that evolved into ARDS and then became complicated with eosinophilic infiltration as an effect of treatment with levofloxacin. Usually this drug is safe, though in some cases can cause eosinophilic pneumonia.[4]

Case Presentation

A 44-year-old Caucasian man presented to our hospital for hyperpyrexia (over 39°C) for about a week, with general weakness and strong headaches; he had been treated by his general practitioner with amoxicillin and clavulanate administrated orally with no improvement. His case history revealed that he was a smoker (20 packs/year). No other pathologies or trips abroad had been registered in the last 6 months. On admission, he had hyperpyrexia (38.9°C), headache, dry cough, diarrhea, general weakness and sinus tachycardia (100 beats/minute); his oxygen saturation was 95% (no oxygen supplement). The results of a physical examination of his chest were reduced vesicular respiration and crackling in the median axillary line to the left and in front; a chest X-ray showed extensive inconsistent parenchymal consolidation at the fissure of the left upper lobe (Figure 1A).

The results of initial laboratory examinations revealed his white blood cell count was 2020 cells/mm^3, total bilirubin level was (1.6 mg/dL), he had reduced albuminemia (2.7 g/dL), increased alkaline phosphatase (382 U/L), γ-glutamyl transferase (69 U/L) and creatine phosphokinase (422 U/L). His serology test results were negative for Hepatitis B virus, Hepatitis C virus and HIV. His initial blood culture test results were negative for aerobic and anaerobic germs and mycetes.

Our patient began treatment with intravenous piperacillin and tazobactam (13.5 g/day) and clarithromycin orally (1 g/day). On the third day the results of his urinary antigen test were found to be positive for Legionella serogroup 1, so clarithromycin was suspended and substituted with intravenous levofloxacin (750 mg/day). We maintained the piperacillin and tazobactam treatment to help prevent secondary infection from other Gram-positive and Gram-negative bacteria.

On the sixth day, his clinical condition worsened. After consultation with an infectious disease specialist, we added rifampicin (900 mg/day) to support the levofloxacin action against Legionella pneumonia.

On the ninth day he showed respiratory distress (40 breaths/

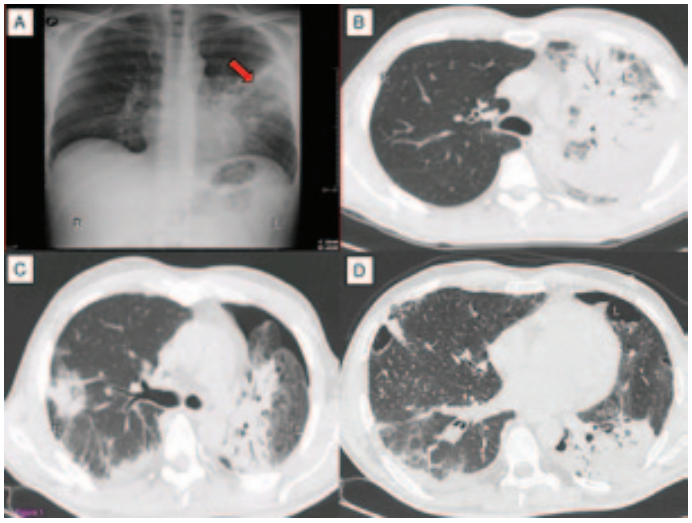

Figure 1. Chest X-ray and computed tomography (CT) images. A) A chest X-ray taken on admission: extensive pulmonary consolidation can be seen in the upper left lobe (arrow). There was an absence of pleural effusion and no cardiomegaly. B) A chest CT scan taken on the ninth day: consolidation areas can be seen on the whole superior left lobe, mixed with ground-glass areas and air bronchogram. There was an absence of pleural effusion. C,D) A CT scan taken on the 21st day: on the left there is parenchymal consolidation with air bronchogram and pneumothorax, and several areas of parenchymal consolidation on the right superior lobe. There was an absence of pleural effusion.

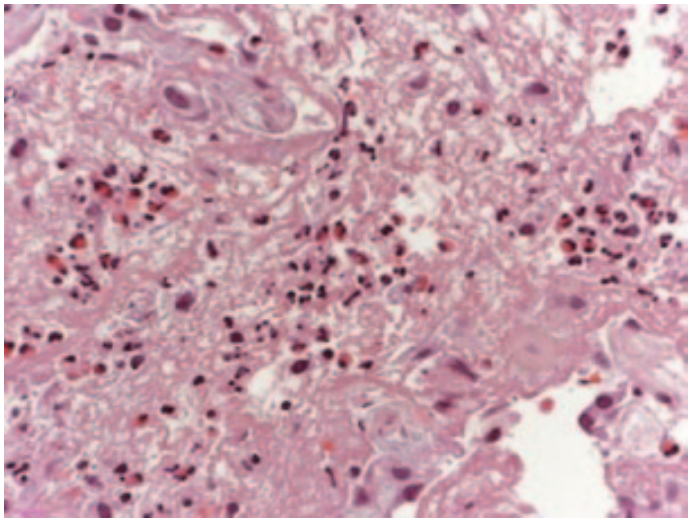

Figure 2. Histological images. Transbronchial biopsies showed several eosinophils associated with fibrin (hematoxylin and eosin stain, 200×).

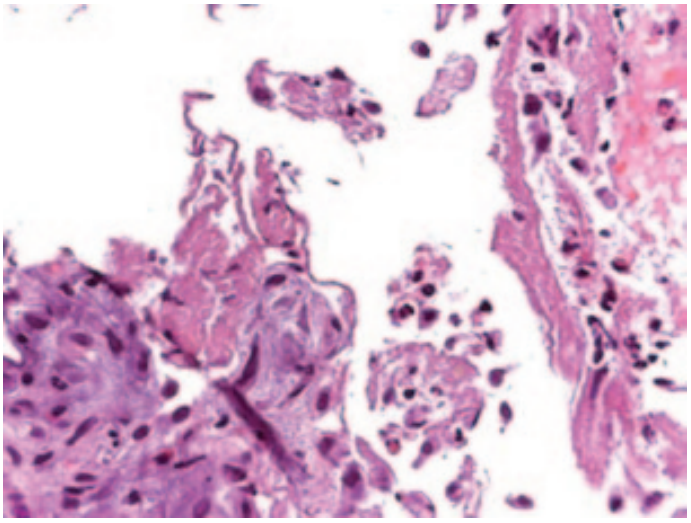

Figure 3. Histological images. Focally, hyaline membranes were present (hematoxylin and eosin stain, 200×).

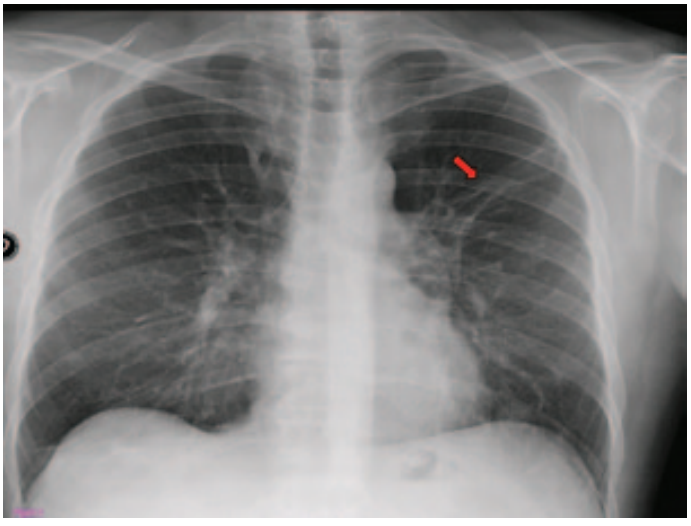

Figure 4. Chest X-ray. Thickening areas and parenchymal distortion can be seen on the left upper lobe. Diffuse thickening can be seen on medial and lower lobes (arrow).

minute). An Arterial Blood Gas analysis in room air gave the following results: partial O_2 pressure (pO_2) of 50 mmHg, partial CO_2 pressure (pCO_2) of 30 mmHg, pH 7.50 and oxygen saturation (SaO_2) of 86%.

A computed tomography (CT) scan of his chest revealed multiple areas of parenchymal consolidation in the entire upper left pulmonary lobe, mixed with ground-glass areas and abundant pleural effusion. In the right lung, in the dorsal and basal regions, there were ground-glass areas mixed with consolidation areas (Figure 1B).

On the 10th day PaO_2/fraction of inspired O_2 (FiO_2) ratio was 101 and he was moved to our intensive care unit. Here he was placed on a ventilator on continuous positive airway pressure modality, with noticeable improvement of the respiratory parameters (PaO_2/FiO_2 ratio of 254). On the 17th day, levofloxacin was suspended in order to allow wash-out and taking of further blood cultures. On the 19th day levofloxacin was resumed; after advice from an infectious diseases specialist intravenous levofloxacin 1500 mg per day together with intravenous fluconazole 800 mg per day were given

On the 21st day, after an initial improvement, he showed respiratory distress. A CT scan showed increased parenchymal consolidation with left pneumothorax (Figure 1C, D). On the 22nd day, because of the unexpected occurrence of muscular exhaustion, orotracheal intubation was performed and he was placed on a mechanical ventilator in synchronized intermittent mandatory ventilation mode associated with appropriate kinetic therapy on a reclining bed. A fibrobronchoscopy study, carried out with bronchoalveolar lavage (BAL) for bacteriological reasons and in order to define the cytological profile, revealed the presence of numerous macrophages (32%), lymphocytes

(26%; CD4/CD8 ratio 0.8), neutrophilic granulocytes (40%) and some eosinophilic granulocytes (2%). Protozoa, fungus and neoplastic cells were absent.

On the 23rd day, methylprednisolone (120 mg/day intravenously) was added to the therapy. On the 26th day, he underwent another bronchoscopy, with BAL and transbronchial biopsy in the basal segments of the lower right lobe, which revealed a histological condition compatible with acute eosinophilic pneumonia (Figures 2 and 3). The BAL confirmed the presence of eosinophils 28%, macrophages 57%, lymphocytes 15%, neutrophilic granulocytes 2% and a CD4/CD8 ratio of 1. Incidental findings showed masses of finely pigmented macrophages (due to our patient's smoking habit). Serum levels of total IgE were within normal limits, and the specific IgE antibody results for allergens (food, pollen, fungal) were also negative. Fecal and serological test results were negative for parasites.

On the 27th day, his steroid therapy was increased (methylprednisolone 1 g/day) while levofloxacin was suspended. His response to steroid therapy was rapid, with a general improvement starting from the fifth day of treatment (the 32nd day overall), associated with accompanying improvement of respiratory exchange and subsequent return to spontaneous breathing on the 41st day (PaO_2/FiO_2 ratio of 357). On the 51st day, a chest X-ray showed that the pneumonia bilateral consolidation had completely resolved (Figure 4).

Discussion

ARDS is a common medical emergency and is usually a complication of a previous illness, which is the etiological cause.[5] In our patient, the unusual fact was the overlapping of acute eosinophilic infiltrate in legionellosis.

Eosinophilic pneumonias include a wide range of pulmonary pathologies, characterized by alveolar and peripheral blood eosinophilia. Peripheral eosinophilia may be absent, in particular in the early stages of acute idiopathic eosinophilia pneumonia or in patients taking systemic corticosteroids. It may occur with extremely variable forms of seriousness, from asymptomatic pulmonary infiltrates to acute respiratory distress syndrome associated with respiratory insufficiency. The possible causes, such as drugs or parasitic infections, have been widely studied, but are, in most cases, idiopathic.[6] In our opinion, in accordance with the findings of other authors,[7] early low-dose steroid therapy leads to a better outcome of pneumonia with severe respiratory distress; however it could determine a delayed onset of eosinophilic pneumonia.

In our patient, we are inclined to consider it as having an iatrogenic etiopathogenesis. Other causes were excluded by laboratory tests for differential diagnosis options (serum total and specific IgE, fecal and serologic examinations for parasite infections).

Eosinophilic pneumonia has been linked to more than 80 drugs, although only 20 of these (for the most part NSAIDs and antibiotics) can be considered as common causes of this pathology.[6] All the drugs administered in the weeks prior to the appearance of eosinophilic infiltrate should be suspected as a possible cause of the pathology. Iatrogenic eosinophilic infiltrates usually develop progressively, with dyspnea, cough and fever in subjects who have taken certain drugs for weeks or months.

The diagnosis of drug-induced eosinophilic pneumonia is mainly based on a detailed history of drug exposure, evidence of eosinophil accumulation in the lung and exclusion of other causes. Numerous methods have been studied in order to demonstrate sensitivity to one or more drugs. One of the most commonly applied methods is the lymphocyte stimulation test (LST), which measures the proliferation of T lymphocytes in response to a drug in vitro, in order to diagnose a previous reaction in vivo. This concept was confirmed by the finding of drug-specific T lymphocyte clones that can interact with cellular receptors without being metabolized and without bonding to protein carriers.[8]

We did not consider it necessary to carry out the LST with our patient because this method is not specific and sensitive, and it has the major drawback of being difficult to interpret.[8] With regard to the challenge test in vivo, this was not performed because of the serious clinical condition of our patient, who in any case did not give his consent. However, voluntary challenge may cause life-threatening adverse reactions and it should be limited to rare situations.[9]

Among the possible causes we considered, the first was levofloxacin. There are some reports in the literature regarding the possibility of development of eosinophilic pneumonia during the course of levofloxacin therapy;[4] moreover, it was the drug administered to our patient for the greatest number of days (21 in total). Other points can be taken into account: (1) the drug was suspended for four days in order to allow for wash-out and subsequent blood culture; afterwards, the same drug was resumed. At the same time, the clinical radiological findings became worse, with an unintentional challenge effect. (2) The BAL on the 22nd day, as some other authors have reported, still showed compatibility with ARDS Legionella,[10] while the following BAL showed eosinophilia (28%) compatible with an acute eosinophilic pneumonia,[6] which histological exams confirmed (Figure 3).

With regard to the other drugs administered, there are reports of isolated cases of eosinophilia associated with parenchymal infiltrates as a consequence of rifampicin therapy.[11] There is only one reported case where clarithromycin may have led to eosinophilic pneumonia,[12] but our patient was only treated with this drug for two days. Moreover, it is possible that eosinophilic pneumonia could be an adverse reaction to smoking in predisposed subjects: this sometimes happens to patients who have recently started smoking or who have modified their 'way' of smoking (for example, increasing or changing type of smoking). Our patient, however, did not report any changes, either in quantity or in quality, in his smoking habits, so this would seem to exclude any relation to smoking.[13]

However, it is plausible that smoking could have acted as a cofactor (together with the drugs) in triggering the clinical condition, because it is a known fact that acute eosinophilic infiltrates are often frequent in smokers.[14]

Conclusion

In conclusion, levofloxacin may be the most probable cause of the occurrence of acute eosinophilic infiltrate in this patient. It is important to emphasize that we decided to change the diagnostic and therapeutic approach only when the presence of eosinophilic infiltrate was proven by transbronchial biopsy. Published studies dealing with risks of invasive endoscopic

procedures in a patient who was critically ill on mechanical ventilation showed a higher incidence of complications such as hemorrhage and pneumothorax. Correlating the endoscopic risk to the percentage of correctly carried out diagnoses, which varies from 33% to 76%, with consequent change in therapeutic strategy, it may be stated that the risk/benefit ratio of the endoscopic procedure in terms of therapeutic response is surely in its favor and it is, therefore, recommended.[15]

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Editorial…continued from page 4

questioning, patients routinely withhold, distort, and otherwise injure the truth, either consciously or not, and yet within the clinical relationship and its contextual frame, such violations usually do not merit moral notice and do not trigger moral appraisals… Within the healthcare setting, patients remain moral agents and retain accountability, so their behavior in this setting is also subject to legitimate moral judgments. Patients' violent or racist behavior within healthcare facilities, for instance, arouses clinicians' legitimate disapproval and triggers sanction."

The article concludes: "Improvements in the empirical research base will inform clinicians' efforts to minimize stereotyping and stigma, honor their own moral feelings and beliefs, and stay engaged with the patients they find morally troubling." The key to dealing with moral judgments was that normative behavior can be motivated by a combination of high social consensus, as evidenced in organizational and professional norms that encourage non-judgment, together with the caregivers' acquired self-image as moral individuals.

Les Plesko, Editor

Information for the above editorial, and quotes and paraphrases, are from BioMed Central, from the article: How clinicians make (or avoid) moral judgments of patients. Terry E. Hill, BioMed Central, Philosophy, Ethics, and Humanities in Medicine, 2010, 5:11.

Pharmacotherapy and the Risk for Community-Acquired Pneumonia: a case-control study of hospitalized older adults

Jen-Tzer Gau, Utkarsh Acharya, Salman Khan, Victor Heh, Lona Mody, Tzu-Cheg Kao

Abstract

Background: Some forms of pharmacotherapy are shown to increase the risk of community-acquired pneumonia (CAP). The purpose of this study is to investigate whether pharmacotherapy with proton pump inhibitors (PPI), inhaled corticosteroids, and atypical antipsychotics was associated with the increased risk for CAP in hospitalized older adults with the adjustment of known risk factors (such as smoking status and serum albumin levels).

Methods: A retrospective case-control study of adults aged 65 years or older at a rural community hospital during 2004 and 2006 was conducted. Cases (N=194) were those with radiographic evidence of pneumonia on admission. The controls were patients without the discharge diagnosis of pneumonia or acute exacerbation of chronic obstructive pulmonary disease (COPD) (N=952). Patients with gastric tube feeding, ventilator support, requiring hemodialysis, metastatic diseases or active lung cancers were excluded.

Results: Multiple logistic regression analysis revealed that the current use of inhaled corticosteroids (adjusted odds ratio [AOR]= 2.89, 95% confidence interval [CI]=1.56-5.35) and atypical antipsychotics (AOR= 2.26, 95% CI=1.23-4.15) was an independent risk factor for CAP after adjusting for confounders, including age, serum albumin levels, sex, smoking status, a history of congestive heart failure, coronary artery disease, and COPD, the current use of PPI, β2 agonist and anticholinergic bronchodilators, antibiotic(s), iron supplement, narcotics, and non-steroidal anti-inflammatory drugs. The crude OR and the AOR of PPI use for CAP was 1.41 [95% CI = 1.03 - 1.93] and 1.18 [95% CI= 0.80 - 1.74] after adjusting for the above confounders, respectively. Lower serum albumin levels independently increased the risk of CAP 1.89- fold by decreasing a gram per deciliter (AOR=2.89, 95% CI = 2.01 – 4.16).

Conclusion: Our study reaffirmed that the use of inhaled corticosteroids and atypical antipsychotics was both associated with an increased risk for CAP in hospitalized older adults of a rural community. No association was found between current PPI use and the risk for CAP in this patient population of our study.

Background

Community-acquired pneumonia (CAP) is one of the major leading causes of death in older adults.[1-2] In 2006, adults aged 65 years or older accounted for approximately 57% of the total number of pneumonia discharges from hospitals in the US.[3] Identifying risk factors and implementing strategies in reducing the exposure to modifiable conditions may decrease mortality and morbidity. Risk factors that are associated with CAP include age,[4-5] chronic obstructive pulmonary disease (COPD),[5] asthma, diabetes mellitus, congestive heart failure,[4-6] smoking,[4-9] malnutrition,[10-13] and aspiration. More studies reveal that some forms of pharmacotherapy may increase the risk of CAP. Current use of atypical antipsychotic drugs is shown to increase the risk of pneumonia in the elderly patients by 2.1 folds in a nested case-control study.[14] The use of proton pump inhibitors (PPI) significantly increases the risk of CAP by 50% to 89%[15-17] and hospital-acquired pneumonia by 30%,[18] particularly in those patients with a recent initiation of PPI therapy.[15-16,19] However, a conflicting result was reported with the use of long-term PPI therapy in a study of approximately 880,000 patients by using the UK General Practice Research Database.[19] Subsequently, a meta-analysis study of clinical trials failed to show a definite conclusion.[20] While COPD is increasingly common in older adults, the use of inhaled corticosteroids is shown to significantly increase the risk of pneumonia by 34% as shown by a meta-analysis study (ranges of odds ratio: 0.67-3.16 among the studies cited).[21-25]

Malnutrition contributes to the increasing risks for CAP as demonstrated by several studies.[10-13] Results of previous pharmacotherapy studies that demonstrated the increased risk for CAP were mainly from large data bases, and there was no adjustment for nutritional status among those studies. Because older adults often suffer from malnutrition and therefore, are susceptible to CAP, it is important to include nutritional status

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in analyzing the association between risk factors and CAP in this age population.

The purpose of this study is to investigate whether the association between pharmacotherapy with PPI, inhaled corticosteroids, and atypical antipsychotics and the increased risk for CAP also holds true among hospitalized older adults of a rural community with the consideration of known risk factors (such as smoking status and serum albumin levels).

Methods

Setting: Data were retrieved from 2004 and 2006 medical records of a community hospital by trained research assistants. Medical records from 2005 were not available during the study period (being sent out for microfilm storage). All data were recorded on standardized paper forms and all medical records under study were reviewed and verified by the principal investigator for accuracy. This hospital is the major one in the Athens county community of the State of Ohio that provides 62,000 residents first-line access to an emergency department (ED) and/or hospitalizations. This study was approved by the Ohio University Institutional Review Board.

Identification and ascertainment of cases and control subjects: Adults aged 65 years or older who were hospitalized during 2004 and 2006 were identified by the assistance of medical record department staff. Patients with the following diagnosis or conditions were excluded from our study: clinically-evident aspiration pneumonia or pneumonitis (N=47) due to documented dysphagia or with gastro-duodenal tube feeding (N= 7) as patients with aspiration pneumonia differ in the pathophysiology and risk factors;[19] documented known active lung cancer or metastatic disease (including leukemia; N=32) as they have underlying conditions that predispose to airway obstruction and pneumonia; being on ventilator therapy (N= 14) as they have a high risk for ventilatorassociated and nosocomial pneumonia; death during hospital stay; requiring hemodialysis as those patients were transferred to tertiary care centers; and others (incomplete records or charts not available for review [n=25]; patients who could not recall medication use [n=3]).

Cases of CAP were identified initially by the discharge diagnosis and further confirmed by the report of the radiographic findings (a new infiltrate or consolidation) suggestive of pneumonia. Patients with "atypical" clinical presentation (such as mental status changes, increasing lethargy, or accidental falls without the classic symptoms such as productive cough, dyspnea, or fever; N=17) were included in the final data analysis.

Hospital-acquired pneumonia (N=5) were not included in our study. Patients from nursing homes with pneumonia were included in our data analysis. Only the medical records of the first occurrence of hospitalizations with pneumonia episode during that year were reviewed. Total 194 cases were identified and included in the final data analysis.

The control group was selected as follows: all hospitalized patients aged 65 or older were initially identified by all diagnostic codes (from 0 to 9999). After excluding those with the primary discharge diagnosis of pneumonia, acute and chronic respiratory failure on ventilator therapy, and the conditions previously mentioned in the case group (ie, death during hospital stay, active lung cancers or metastatic cancers), the first admission medical record was reviewed and data were recorded. Because

Table 1: Characteristics of Cases with Community-Acquired Pneumonia and Control Subjects

Variables* N (%)	Cases N=194	Control N=952	P value§
Mean age (yr) (SD)	80.3 (8.5)	79.8 (8.1)	.486
Female	119 (61)	641 (67)	.108
White	194 (100)	941 (98.8)	.133
Ex-smoker†	60/191 (31)	151/949 (16)	<.001
Current smoker†	28/191 (15)	73/949 (8)	.002
Past Medical History			
Congestive heart failure	63 (32)	201 (21)	<.001
Coronary artery disease	77 (40)	299 (31)	.025
COPD	91 (47)	178 (19)	<.001
Prior pneumonia	38 (20)	43 (5)	<.001
Diabetes mellitus	52 (27)	277 (29)	.520
Atrial fibrillation	35 (18)	136 (14)	.181
Stroke	34 (18)	148 (16)	.492
Cognitive impairment	40 (21)	152 (16)	.114
Depression	58 (30)	243 (26)	.207
Psychiatric illness	7 (4)	24 (3)	.395
GERD	56 (29)	233 (24)	.199
Medication			
Atypical antipsychotics	25 (13)	63 (7)	.003
Proton pump inhibitor	86 (44)	343 (36)	.030
H2 receptor antagonist	7 (4)	46 (5)	.460
Antihistamine	29 (15)	129 (14)	.607
β2 agonist bronchodilator	72 (37)	109 (11)	<.001
Inhaled corticosteroid	49 (25)	47 (5)	<.001
Anticholinergic bronchodilator	44 (23)	63 (7)	<.001
Antibiotic use prior to admission	44 (23)	88 (9)	<.001
NSAIDs	27 (14)	115 (12)	.479
Narcotics	60 (31)	224 (24)	.030
Iron supplement	37 (19)	82 (9)	<.001
Admission laboratory results			
Serum albumin (gm/dL)	2.9 (0.5) (N=167)	3.2 (0.5) (N=807)	<.001
White cell count (K/μL) (mmol/L)	13.6 (6.0) (N= 194)	9.3 (4.0) (N=948)	<.001
Discharge diagnoses			
Congestive heart failure	46 (24)	107 (11)	<.001
Any GI-related illness	18 (9)	269 (28)	<.001
Upper GI illness‡	8 (4)	100 (11)	.006
Lower GI illness¶	10 (5)	140 (15)	<.001
C. difficile associated diarrhea	7 (4)	27 (3)	.564

* Data were presented by number (percent) or mean (SD).

† Smoking status was unknown in 3 patients of cases and in 3 patients of controls.

‡ Including esophageal, stomach, duodenum, and small intestine diagnoses.

¶ Including large colon and rectal diagnoses, but not *C. difficile* associated diarrhea.

§ Obtained using chi-square or two-sample-t test.

Abbreviations: SD= standard deviation; *C. difficile= Clostridium difficile*; COPD= chronic obstructive pulmonary disease; GERD= gastro-esophageal reflux disease; GI= gastro-intestinal; NSAIDs= non-steroidal anti-inflammatory drugs.

acute exacerbation of chronic obstructive pulmonary disease (AECOPD) may overlap with pneumonia in clinical presentation, patients with the discharge diagnosis of AECOPD (N= 111) were excluded from both the case and the control groups.

All cases were reviewed by the principal investigator and further efforts were made (based on the documented x-ray findings on admission) to classify each case into an appropriate category (cases vs. controls). The approximate 1:5 ratio of the cases to the controls was not intentional but co-incident. A total of 952 patients were included in the control group.

Measurement: Age, sex, demographic data, smoking status, past medical history, medication use prior to admission, admission and discharge diagnosis, admission laboratory test results (ie, white cell count, serum albumin level, and electrolytes) obtained at ED or the first set of blood tests on admission were recorded. Medication use prior to admission was based on the documentation on the medication reconciliation forms or physician's notes (current use vs. non-use). Nursing home residents almost had medication administration records available for review.

PPI is the group of medications that include omeprazole, lansoprazole, pantoprzaole, rabeprazole and esomeprazole. β2 agonist bronchodilator is the group of inhalation medications of short or long-acting effects. Atypical antipsychotic drugs include clozapine, olanzapine, quetiapine, aripiprazole, ziprasidone, and risperidone. Because very few study patients used typical antipsychotic drugs prior to admission, such category of medication was not reported. Systemic corticosteroids were not included in the data analysis as very few patients received such a treatment in our study. Further information on the duration of medication use was not available. Smoking status was based on the documented ex-smoker vs current smoker from physicians' notes. Co-morbidity (such as congestive heart failure, coronary artery disease, diabetes, COPD, prior pneumonia, and atrial fibrillation), which is common in the elderly, was the documented previous event or existing condition prior to the study period, and it was recorded as ever vs never event.

Missing data were encountered in the smoking history and laboratory results. Patients without documented data were excluded from the data analysis. Data analysis: Mean, standard deviation (SD), and percentage with frequency were used to report continuous and discrete variables. Chi-square test and two-sample t-tests (two-sided) were used to assess if there was a significant association between two groups. Multiple logistic regression with odds ratio (OR) with a 95% confidence interval (CI) was used to measure the association between a risk factor and the occurrence of CAP after adjusting for other variables in the model.

Potential confounders used in the multiple logistic regression model analysis included age, serum albumin levels (gram per deciliter), sex, smoking status (ex- and current smoker), a past

Table 2: Odds Ratio for the Risk Factors Associated with Community-Acquired Pneumonia in the Multiple Logistic Regression Model* (N=969)

Variables†	Cases (Yes/No)‡	Control (Yes/No)‡	Crude OR [95% CI]	Adjusted OR [95% CI]
Age (yr)	--	--	1.01 [0.99-1.03]	1.01 [0.99 – 1.04]
Number of serum albumin level below 4 gm/deciliter¶	--	--	3.23 [2.34 – 4.47]	2.89 [2.01 – 4.16]
Sex (female=1/ male=0)	119/75	641/311	0.77 [0.56 - 1.06]	1.01 [0.66 - 1.53]
Ex-smoker	60/131	151/797	2.42 [1.70 - 3.44]	1.88 [1.15 – 3.06]
Current smoker	28/163	73/876	2.06 [1.29 – 3.29]	2.34 [1.22 – 4.50]
Past Medical History				
Congestive heart failure	63/131	201/751	1.80 [1.28 - 2.52]	1.60 [1.04 – 2.46]
Coronary artery disease	77/117	299/653	1.44 [1.05 – 1.98]	1.40 [0.94 – 2.08]
COPD	91/103	178/774	3.84 [2.77 – 5.32]	1.82 [1.17 – 2.82]
Medication				
Atypical antipsychotics	25/169	63/889	2.09 [1.28 - 3.41]	2.26 [1.23 – 4.15]
Proton pump Inhibitor	86/108	343/609	1.41 [1.03 - 1.93]	1.18 [0.80 - 1.74]
β2 agonist bronchodilator	72/122	109/843	4.56 [3.21 - 6.50]	1.29 [0.69 - 2.40]
Anticholinergic bronchodilator	44/150	63/889	4.14 [2.71 – 6.31]	1.16 [0.59 – 2.26]
Inhaled corticosteroid	49/145	47/905	6.51 [4.20 - 10.07]	2.89 [1.56 - 5.35]
Antibiotic use prior to admission	44/150	88/864	2.88 [1.93 - 4.30]	1.81 [1.09 – 3.02]
Iron supplement	37/157	82/870	2.50 [1.64 - 3.82]	1.58 [0.94 - 2.67]
Narcotics	60/134	224/728	1.46 [1.04 - 2.04]	1.01 [0.66 – 1.56]
NSAIDs	27/167	115/837	1.18 [0.75 - 1.85]	1.25 [0.70 – 2.23]

* Hosmer and Lemeshow goodness-of-fit test: chi square= 16.43, df= 8, p= .037.

† Variables were dichotomized as 1=yes, 0=no, unless stated otherwise.

‡ indicated the number of the presence (yes) and the absence (no) of the medical condition or exposed (yes) vs. unexposed (no) to medication use for the variable of interest.

¶ Which is equal to the number of 4 minus patient's serum level.

Abbreviations: CI= confidence interval; COPD= chronic obstructive pulmonary disease; NSAIDs= non-steroidal anti-inflammatory drugs; OR= odds ratio.

medical history of congestive heart failure, coronary artery disease, and COPD, and the use of the following medications: atypical antipsychotic drugs, β2 agonist and anticholinergic bronchodilators, inhaled corticosteroids, and prescribed antibiotic(s) prior to admission, iron supplement, narcotics, and non-steroidal anti-inflammatory drugs (NSAIDs). A history of COPD and medication used for the treatment of COPD were both included in the adjustment in order to analyze whether the treatment is an independent risk factor for CAP in addition to the presence of disease.

Regression diagnostics showed no colinearity among the risk factors and no noticeable outlier or influential observations in the model. Hosmer and Lemeshow goodness-of-fit test was used to assess the fit of the model to data. Statistical significance level was set at a level of .05. Statistical software package, PC SAS version 9.1 (SAS Institute, Inc., Cary, NC) was used to perform the statistical analyses.

Results

As shown in Table 1, case patients had a significantly different clinical profile compared to the control group. Case patients were more likely to be ex- or current smokers and had a significant medical history of congestive heart failure, coronary artery disease, pneumonia and COPD than the controls. Case patients were more likely to receive atypical antipsychotic drugs, PPI, β2 agonist and anticholinergic bronchodilators, inhaled corticosteroids, prescribed antibiotic(s) prior to admission, narcotics and iron supplements (all p values < 0.05). On the admission blood test results, the case group had a significantly lower mean serum albumin level (2.9 ± 0.5 vs. 3.2 ± 0.5 gm/dL, $p < 0.001$) and a higher mean white blood cell count (13.6 ± 6.0 vs. 9.3 ± 4.0 K/μL, $p < 0.001$) than the control group.

Discharge diagnoses among study patients are shown in Table 1. There was no difference in the proportions of upper and lower gastro-intestinal (GI) illness, and hepato-biliary-pancreatic diseases between PPI users and non-users (except in the pneumonia diagnosis). While acute congestive heart failure was more often seen in the case group, GI-related diagnoses were more common in the controls (Table 1). As shown in Table 2, lower serum albumin level, ex- and current smoker, a history of congestive heart failure and COPD, and the use of atypical antipsychotic drugs (adjusted OR= 2.26, 95% CI= 1.23 – 4.15), inhaled corticosteroids (adjusted OR= 2.89, 95% CI= 1.56 – 5.35), and prescribed antibiotic(s) prior to admission (adjusted OR= 1.81, 95% CI= 1.09 – 3.02) was significantly associated with an increased risk for CAP after adjusting for the potential confounders as listed in the table 2. The unadjusted OR of PPI exposure for CAP was 1.41 with 95% CI=1.03 - 1.93; the association became weaker and not significant after adjusting for all other confounders (adjusted OR= 1.18, 95% CI= 0.80 – 1.74). Our study revealed that lower serum albumin levels independently increased the risk of CAP by 189% by decreasing the concentration of one gram per deciliter (AOR=2.89, 95% CI = 2.01 – 4.16).

Discussion

This case-control study reaffirmed that the use of inhaled corticosteroids and atypical antipsychotic drugs was independently associated with an increased risk for CAP among hospitalized older adults of a rural community with the adjustment of nutritional status based on serum albumin levels and other risk factors. However, the association between current PPI exposure and the risk for CAP was not observed in our study. Our study also demonstrated that by decreasing serum albumin level by one gram per deciliter, the risk for CAP can be increased by 1.89- fold in older adults.

COPD has been demonstrated as a major risk factor for CAP. Inhaled corticosteroids, often prescribed for the treatments of COPD and/or asthma, were also identified as an independent risk factor by our study and others.[20-24] Although inhaled corticosteroid therapy may improve the quality of life,[26] inappropriate prescriptions of these medications may be highly prevalent among stable COPD patients.[27] Reevaluating the need for a long-term corticosteroid therapy or using it at a minimally effective dose is warranted.

Our study also demonstrated that atypical antipsychotic drug use independently increased the risk of CAP, which was consistent with the report by Knol et al.[14] Their study included all types of pneumonia in the cases and demonstrated a 2.1-fold increase in the risk for CAP among those taking atypical antipsychotic drugs. With the exclusion of aspiration pneumonia in the case group, our study still revealed a similar result with a modest risk (AOR= 2.26, 95% CI=1.23-4.15). Effects of atypical antipsychotic drugs on the gastrointestinal system and particularly on the esophageal dysfunction were described.[28] Though it is highly possible that the intrinsically sedative and anticholinergic side effects of this group medication could increase the risk of aspirations by decreasing peristalsis, the exact mechanism of increasing the risk for CAP is not clear.

Our study did not find an association between current PPI therapy and the risk for CAP after the adjustment for confounders. The result was consistent with a recent report of a large nested, case-control study by using the UK General Practice Research Database by Sarkar et al.,[19] in which patients with the diagnosis of aspiration pneumonia were excluded in the data analysis as we did in our study. Please note that the study by Sarkar et al. included cancers in the full adjustment when reporting the adjusted OR, while our study excluded active lung cancers and metastatic diseases in the final data analysis. Compared to previous studies that reported the association between PPI use and the risk for CAP (but not hospital-acquired pneumonia),[15-17] the exclusion of aspiration pneumonia was not explicitly mentioned in their studies, which could be one of the possible explanations for the discrepancy of reported findings between ours and other studies.

Our studied patients had a higher prevalence rate of co-morbidities, and a higher percentage of patients received PPI therapy compared to other studies.[15-17] This finding was expected as aging older adults have more co-morbidity and increasingly use pharmacotherapy for chronic illness, especially among hospitalized patients. As the most potent acid-suppression drugs, PPIs have substantially replaced H2 receptor antagonists for the treatment of acid-related gastroesophageal diseases. Evidence suggests that patients with multiple co-morbid conditions are most likely to receive PPI therapy,[29] and it is also this group of patients who are most vulnerable to lower respiratory tract infections. Evidence also suggests that hypoalbuminemia and malnutrition are associated with CAP in older adults,[10-12] which is also demonstrated by our study. However, PPI users and non-users had no difference in average serum albumin levels among hospitalized older patients as demonstrated in our previous study.[30]

Despite PPI therapy drastically reduces gastric acid secretion it does not prevent or inhibit the gastro-esophageal reflux episodes. Clinical observations suggest that reflux of gastric contents into the upper and lower airway may precipitate acute asthma attacks, or acute exacerbation of COPD though there is no strong evidence from clinical studies.[31-32] It is quite possible that PPI therapy could also be prescribed for the early symptoms that are associated with lower respiratory tract infections or gastro-esophageal reflux disease (GERD) (ie, protopathic bias). This may partially explain why PPI therapy started within the past 7 to 14 days of pneumonia diagnosis was found to be associated with an increased risk for pneumonia in some studies.[15-16,19]

Another possible explanation for the different result observed between our and other studies[15-16] was the categorization of exposure history. Other studies[15-16] had data available (based on prescriptions of PPIs) that employed three categories: current, recent, and past use; ours only included current use vs. non-use. Furthermore, our study was hospital-based, case-control. One may suggest that a Berkson's bias, a phenomenon in which the relationship between exposure and disease becomes indistinct in hospital-based studies, may occur in our study. Although we could not exclude the possibility, this current study also demonstrated the association between the use of inhaled corticosteroids and atypical antipsychotic drugs and the increased risk for CAP in our studied patients. Because of the small sample size compared to those population-based studies, the issue of statistical power could be one of the explanations for the lack of the association. However, other investigators[19] of a large study also reported a finding similar to ours in the relationship between overall PPI use and the risk for CAP. Therefore, we do not believe that increasing the sample size will change the conclusions drawn from our study.

Whether age could be an explanation for the discrepancy between our study and the others[15-17] is an interesting question. In the study by Gulmez et al,[16] the association between current use of PPI and CAP became weaker in the age group of older than 60 years (adjusted OR 1.5, 95% CI= 1.3 - 1.7) when compared to the age group of less than 40 years (adjusted OR 2.3, 95% CI= 1.3 - 4.0). We speculate that the association between PPI use and the risk for CAP may become non-significant in the advanced aged group. As demonstrated by Sarkar et al,[19] their paper also reported no association between PPI use and the risk for CAP in persons aged 60 years or older.

As gastric acid production decreases with aging and there is a high prevalence rate of chronic gastritis in people aged older than 70 years, there may be a high prevalence rate of bacterial colonization in the upper gastro-esophageal tract of older adults at baseline even in those older people not receiving PPI therapy. If this is true, use of PPI therapy may not further increase the prevalence rate of bacterial colonization in older adults, by which is the mechanism thought to be responsible for the increased risk for CAP by PPI therapy.

There is no information in how PPI therapy affecting the rate of bacterial colonization in older adults compared to young adults in the literature. One of the strengths in our study was to demonstrate that patients with CAP had a significantly higher mean white blood cell count on admission compared to the control patients (Table 1). Though we could not exclude the possible use of systemic corticosteroid treatment prior to the blood tests obtained in the ED or on admission as the cause of leukocytosis, the exclusion of acute exacerbation of COPD, respiratory failure requiring a ventilator therapy and leukemia cases from our data analysis, as well as very few patients receiving oral systemic steroid therapy, should minimize such a possibility.

Our study also demonstrated that lower serum albumin levels independently increased the risk for CAP 1.89-fold in older adults. This is the first of such a report to the best of our knowledge.

The limitations of our study included the lack of diversity as the study subjects were a predominately white population. Therefore, the findings may not apply to other ethnic groups. Furthermore, our data collection resources could not confirm whether patients were compliant with medication use nor the duration as the data collection was based on medical records and physician's notes. Dosage information will provide more insights into the association between a drug therapy and the risk for CAP. Another limitation was unmeasured or residual confounding. Examples are the use of NSAIDs, as readily available over-the-counter, and co-morbidity that may not be completely documented by health-care providers. Certain medical conditions that may be under- assessed and underdocumented, such as cognitive impairment or dementia, lack of standardized criteria for making a diagnosis of diseases, as well as the lack of data on cognitive functions prior to and during hospital stay, in which potential limitations are all inherent to a retrospective study design.

Conclusion

This case-control study of a rural community reaffirmed that the use of inhaled corticosteroids and atypical antipsychotic drugs was an independent risk factor for CAP in hospitalized older adults after adjusting for known risk factors, including serum albumin levels. Current PPI use did not increase the risk for CAP in this hospitalized older population. Our study may imply that other factor(s), such as malnutrition or other pharmacotherapy, may play a greater role than PPI therapy in developing CAP in this population.

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Effect of Oral Beta-Blocker on Short and Long-Term Mortality in Patients with Acute Respiratory Failure

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Abstract

Introduction: Acute respiratory failure (ARF) is responsible for about one-third of intensive care unit (ICU) admissions and is associated with adverse outcomes. Predictors of short- and long-term outcomes in unselected ICU-patients with ARF are ill-defined. The purpose of this analysis was to determine predictors of in-hospital and one-year mortality and assess the effects of oral beta-blockers in unselected ICU patients with ARF included in the BASEL-II-ICU study.

Methods: The BASEL II-ICU study was a prospective, multicenter, randomized, single-blinded, controlled trial of 314 (mean age 70 (62 to 79) years) ICU patients with ARF evaluating impact of a B-type natriuretic peptide- (BNP) guided management strategy on short-term outcomes.

Results

In-hospital mortality was 16% (51 patients) and one-year mortality 41% (128 patients). Multivariate analysis assessed that oral beta-blockers at admission were associated with a lower risk of both in-hospital (HR 0.33 (0.14 to 0.74) P = 0.007) and one-year mortality (HR 0.29 (0.16 to 0.51) P = 0.0003). Kaplan-Meier analysis confirmed the lower mortality in ARF patients when admitted with oral beta-blocker and further shows that the beneficial effect of oral beta-blockers at admission holds true in the two subgroups of patients with ARF related to cardiac or non-cardiac causes. Kaplan-Meier analysis also shows that administration of oral beta-blockers before hospital discharge gives striking additional beneficial effects on one-year mortality.

Conclusions: Established beta-blocker therapy appears to be associated with a reduced mortality in ICU patients with acute respiratory failure. Cessation of established therapy appears to be hazardous. Initiation of therapy prior to discharge appears to confer benefit. This finding was seen regardless of the cardiac or non-cardiac etiology of respiratory failure.

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Introduction

Acute respiratory failure (ARF) is responsible for about 30% of intensive care unit (ICU) admissions and is a major complication in patients already treated in the ICU. This serious condition was shown to be associated with high morbidity and mortality rates. Acute decompensated heart failure (ADHF), community acquired pneumonia (CAP), acute exacerbation of chronic obstructive pulmonary disease (AECOPD), pulmonary embolism (PE) and asthma are responsible for the vast majority of ICU hospitalization due to respiratory failure. In-hospital mortality in ICU patients with respiratory failure is more than twice the mortality related to other ICU admissions.

Although mortality rates have been described in specific patient groups admitted for heart failure, severe AECOPD or severe CAP, data concerning mortality rates and predictors of outcome in ICU patients with acute respiratory failure regardless of causal etiology are scarce. This is important for the reason that respiratory failure in one-third of ICU patients is multi-causal.

Accordingly, the aim of the present study was to assess in-hospital and one-year mortality in a cohort of consecutive ICU patients with acute respiratory failure indifferent of underlying etiology. We specifically determined the independent predictors of in-hospital and one-year mortality and assessed the impact of beta-blocker at admission and/or at discharge on outcome.

Materials and Methods

Setting and study population: This report is a sub-study of the B-type natriuretic peptide (BNP) for Acute Shortness of Breath Evaluation (BASEL) II-ICU trial. The goal of the BASEL II-ICU trial was to evaluate impact of a BNP-guided management strategy on outcome (hospital length of stay and costs) in ICU patients with acute respiratory failure. The BASEL II-ICU trial was a prospective, randomized, controlled, single-blinded multicenter study. Patients were enrolled in seven ICUs (one medical and one surgical ICU of a primary

Baseline characteristics of study population.

	All studied patients (n = 314)	In-hospital survivors (n = 263)	In-hospital non-survivors (n = 51)	p-value	One-year survivors (n=183)	One-year non-survivors (n=128)	p-value
Demography/Scores							
Gender (male) - n (%)	181 (58)	147 (56)	34 (68)	0.15	100 (55)	78 (61)	0.27
Age (year)	70[62-78.75]	70[61-79]	73[63-76]	0.013	69[60-77]	74[64-80]	0.003
BMI[a]	25.8[22.6-30.8]	25.85[22.6-30.8]	25.8[22.5-28.4]	0.06	26.15[23.4-31.1]	25.3[21.2-29.1]	0.008
SAPS[b] II score	32[26-46]	32[24-45]	36 [31-46]	0.12	32[24-45]	44[30-44]	0.07
Hemodynamic parameters							
Heart rate (bpm)	98[84-116]	97.5[83.75-115]	105[85-123]	0.16	98[83-116]	100[84-115.25]	0.8
Systolic blood pressure (mmHg)	127[111-148]	128[111-148]	127[111-139]	0.34	129.5[111-150]	126[112-143]	0.19
Diastolic blood pressure (mmHg)	67[56-80]	67[57-80]	64[53-78]	0.17	70[59-82]	62[53-74.5]	0.006
Mean arterial pressure (mmHg)	85[73-100]	87[74-101]	85[73-96]	0.15	89[76.25-103]	83[71.5-95]	0.04
Left ventricular ejection fraction (%)[c]	55[35-60]	50[35-60]	60[35-65]	0.35	50[35-60]	60[43.5-63.75]	0.26
Atrial fibrillation- n (%)	50 (16)	37 (14)	13 (26)	0.04	22 (12)	28 (22)	0.02
Respiratory/metabolic parameters							
Mechanical ventilation- n (%)	42 (13)	34 (13)	8 (16)	0.59	26 (14)	16 (13)	0.66
Non invasive ventilation- n (%)	158 (50)	131 (59)	27 (53)	0.68	87 (48)	70 (55)	0.21
Breathing frequency (cpm)	24[19-30]	24[19-30]	25[20-30]	0.75	24[18-30]	25[20-30]	0.38
PaO2/FiO2	161[101-240]	169[101-239]	144 [92-216]	0.20	169 [99-248]	152[100-228]	0.41
PaCO2 (kPa)	5.9[4.9-7.8]	5.9[5-7.8]	5.8[4.8-8.2]	0.33	5.9[5-7.5]	6.05[4.8-8.4]	0.34
Laboratory parameters							
Hemoglobin (g/l)	118[101-141]	120[102-142]	108[97-128]	0.04	121[101-145]	114[100-134]	0.013
Uric acid (µmol/l)	381[275.5-502]	370[274-494.5]	412[311-521]	0.31	362[278-470.5]	397[273-557]	0.10
eGFR MDRD[d] (mL/min/1.73 m^2)	69[46-99]	71.5[46-102]	56[45-88]	0.04	72[49-102.75]	60.5[41.75-95]	0.08
Blood urea nitrogen (mg/dl)	21[13-33]	19[12-31]	26[18-38]	0.04	19[12-28]	24[14-39.5]	0.01
Comorbidities - n (%)							
History of heart failure	85 (27)	71 (27)	14 (28)	0.94	48 (26)	37 (29)	0.60
History of coronary artery disease	119 (38)	95 (36)	24 (47)	0.14	61 (33)	58 (45)	0.03*
Hystory of hypertension	165 (53)	114 (55)	21 (41)	0.075	99 (54)	65 (51)	0.56
Hystory of COPD[e]	123 (39)	105 (40)	18 (35)	0.53	69 (38)	54 (42)	0.42
History of malignancy	61 (19)	41 (16)	20 (39)	< 0.0001	21 (12)	39 (31)	< 0.0001
Etiology of respiratoy failure- n (%)							
Heart failure (HF) alone	101 (32)	86 (33)	15 (30)	0.64	67 (37)	34 (27)	0.06
HF + any additional diagnosis	75 (24)	61 (23)	14 (28)	0.51	40 (22)	35 (27)	0.26
HF + pneumonia	42 (14)	32 (12)	10 (20)	0.15	16 (9)	26 (20)	0.003
HF + AECOPD[f]	20 (6)	18 (7)	2 (4)	0.44	17 (9)	3 (2)	0.014
HF + other diagnosis	13 (4)	11 (4)	2 (4)	0.93	7 (3)	6 (5)	0.71[25]
Pneumonia	50 (16)	38 (15)	12 (24)	0.11	27 (15)	22 (17)	0.57
AECOPD	30 (10)	26 (10)	4 (8)	0.66	15 (8)	15 (12)	0.31
Pneumonia + AECOPD	11 (3.5)	10 (4)	1 (2)	0.52	5 (3)	6 (5)	0.36
Pulmonary embolism	15 (5)	14 (5)	1 (2)	0.31	8 (4)	6 (5)	0.90
Unknown cause	4 (1)	4 (1.5)	0 (0)	0.38	1 (1)	2 (1)	0.37
Other cause	28 (9)	24 (9)	4 (8)	0.77	20 (11)	8 (6)	0.16
Admission medication - n (%)							
Diuretics	135 (52)	117 (53)	18 (47)	0.52	84 (56)	49 (46)	0.12
Nitrates	29 (11)	27 (12)	2 (5)	0.19	22 (15)	7 (7)	0.04
ACEi/ARB[g]	144 (46)	126 (48)	18 (35)	0.09	91 (50)	50 (39)	0.06
Beta-blocker	101 (32)	94 (36)	7 (14)	0.001	81 (44)	20 (16)	< 0.0001
Statins	80 (31)	67 (30)	13 (33)	0.69	54 (36)	26 (24)	0.05
Aspirin/Clopidogrel	102 (39)	86 (39)	16 (41)	0.80	67 (44)	35 (33)	0.07
Calcium-antagonists	43 (17)	36 (16)	7 (18)	0.79	25 (17)	18 (17)	0.92
Coumarines	86 (33)	77 (35)	9 (23)	0.15	46 (31)	39 (37)	0.31
Beta-mimetics	94 (36)	78 (35)	16 (41)	0.48	49 (33)	44 (41)	0.15
Oral steroids	45 (17)	38 (17)	7 (18)	0.89	28 (19)	16 (15)	0.45
Discharge medication – n (%)							
Diuretics	130 (41)	-	-	-	86 (47)	44 (34)	0.12
Nitrates	39 (13)	-	-	-	23 (13)	16 (13)	0.966
ACEi/ARB	160 (51)	-	-	-	121 (66)	38 (30)	0.010
Beta-blocker	119 (38)	-	-	-	84 (46)	34 (27)	< 0.001
Statins	77 (25)	-	-	-	56 (31)	20 (16)	0.001
Aspirin/Clopidogrel	91 (29)	-	-	-	61 (33)	29 (23)	0.024
Calcium-antagonists	30 (10)	-	-	-	22 (12)	8 (6)	0.057
Coumarines	104 (33)	-	-	-	67 (37)	36 (28)	0.075
Beta-mimetics	89 (28)	-	-	-	55 (30)	32 (25)	0.272
Oral steroids	41 (13)	-	-	-	20 (11)	21 (16)	0.156

[a] BMI= body mass index [mass (kg)/height $(m)^2$]; [b] SAPS 2 = Simplified Acute Physiology Score [45]; [c] measured by echocardiography in 128 patients; [d] estimated glomerular filtration rate using Modification of Diet in Renal Disease (MDRD) formula [46]; [e] COPD = chronic obstructive pulmonary disease; [f] AECOPD = acute exacerbation of COPD; [g] ACEi = angiotensin-converting enzyme inhibitors. ARB = angiotensin receptor blocker

Values are displayed as median [interquartile range] or number of patients (%).

care facility and five interdisciplinary ICUs of tertiary referral hospitals) in Switzerland from December 2004 to March 2007. The study was carried out according to the principles of the Declaration of Helsinki and approved by the ethical committee responsible for each hospital. Written informed consent was obtained from patients or their surrogate. Details regarding study design has been published elsewhere. In brief, patients presenting with acute respiratory failure severe enough to require ICU monitoring and treatment were randomized into one of two different diagnostic strategy groups. One of these groups included admission BNP value in addition to standard diagnostic workup (BNP group), while the other group did not have BNP values (control group).

Important exclusion criteria of the BASEL II-ICU trial were an obvious trauma, a BNP measurement within the preceding six hours, severe renal disease (serum creatinine >250 µmol/L), more than 12 hours since the eligibility criteria in the ICU were met, sepsis, cardiopulmonary resuscitation within 12 hours or shock.

Final discharge diagnoses of studied patients.

Characteristic	(n=314)
Heart failure (HF)	101 (32)
HF + any additional diagnosis	75 (24)
HF + pneumonia	42 (13)
HF + obstructive pulmonary disease	20 (6)
HF + other diagnosis	13 (4)
Pneumonia	50 (16)
Obstructive pulmonary disease	30 (10)
Pneumonia + obstructive pulmonary disease	11 (3)
Pulmonary embolism	15 (5)
Unknown cause	4 (1)
Other cause[a]	28 (9)

[a]Including aspiration, anaemia, atelectasis, pneumothorax, oversedation, interstitial lung disease, obesity hypoventilation syndrome and pleural effusion.
Values are displayed as number of patients (%).

Predictors of one-year mortality by univariate analysis (n=314)

	HR [95%CI]	p-value
Age	1,03 [1.01 – 1.06]	0.0012
Diastolic blood pressure	0.98 [0.97 – 0.99]	0.0025
BMody mass index	0.96 [0.92 – 0.98]	0.031
History of malignancy	1.99 [1.18 – 3.32]	0.0093
Atrial fibrillation	1.86 [1.06 – 3.33]	0.033
Creatinin levels at admission	1.00 [1 – 1.01]	0.048
Blood urea nitrogen levels at admission	1.01 [1 – 1.02]	0.02
Uric acid levels at admission	1.00 [1 – 1]	0.048
Beta-blockers at admission	0.32 [0.18 – 0.52]	<0.0001
Statines at admission	0.51 [0.28 – 0.94]	0.03
Aspirine/Clopidogrel at admission	0.56 [0.33 – 0.95]	0.03
ACEi/ARB at discharge	0.56 [0.36 – 0.88]	0.011
Oral steroides at discharge	2.34 [1.37 – 4.01]	0.0019

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; CI, confidence interval; HR, hazard ratio.

The adjudicated diagnosis, used in the present study, was performed by two ICU specialists on the basis of all available medical records, the response to therapy and autopsy results in those patients who died in the hospital. Adjudicated diagnosis was performed by choosing one or more diagnoses from a pre-specified list that included the following items: HF, pneumonia, AECOPD/Asthma, pulmonary embolism (PE), atelectasis, mechanical airway obstruction, pneumothorax, other or unknown. The study protocol of the BASEL II-ICU study had no influence on mechanical ventilation or non-invasive ventilation (NIV) therapy. The decision about medical treatment including NIV or mechanical intubation was made solely by the ICU staff in charge following the current guidelines of the respective hospital.

The study included 314 ICU patients with acute respiratory failure. A one-year follow-up, assessed by telephone interview of the patients, their family or the referring physician, was completed in 311 (99.3%) of patients representing our study population.

Statistical analysis: The statistical analyses were performed with the use of the SPSS/PC software package (version 15.0, SPSS Inc., Chicago, IL, USA). Comparisons were made using the t-test, Mann-Whitney U test, Fisher's exact test and chi-square test as appropriate. Mortality risk was estimated using the Kaplan-Meier method. All prognostic relevant characteristics were identified using univariate Cox-regression analysis. The model for in-hospital mortality included the following characteristics: age, systolic and diastolic blood pressure, heart rate, breathing frequency, Glasgow coma scale, body temperature, body mass index (BMI), history of malignancy, history of congestive heart failure (CHF), history of coronary artery disease (CAD), left ventricular ejection fraction, atrial fibrillation, admission pH, HCO3, base excess, PO2/FiO2 ratio, sodium, potassium, C-reactive protein, hemoglobin, white blood count (WBC), partial thromboplastin time (PTT), creatinine, blood urea nitrogen

Independent predictors of in-hospital and one-year mortality by multivariate analysis.

	In-hospital mortality (n=51) HR [95%CI]	p-value	One-year overall mortality (n=128) HR [95%CI]	p-value
Beta-blockers at admission	0.33 [0.14- 0.74]	0.007	0.29 [0.16 -0.51]	0.0003
History of malignancy	2.7 [1.5- 4.9]	0.0012	2.75 [1.70- 4.43]	0.0003
History of coronary artery disease	-	-	1.81 [1.15- 2.82]	0.009

CI, indicates confidence interval; HR, hazard ratio.

Different agents and mean dosages of beta-blocker administered at presentation, at 24 hours and at discharge.

Beta-blocker	Hospital admission n (%)	mean dosage (mg)	24-hours n (%)	mean dosage (mg)	Hospital discharge n (%)	mean dosage (mg)
Metoprolol	36 (36)	100 [50-125]	30 (36)	100 [50-125	51 (43)	100 [50-125
Carvedilol	18 (18)	12.5 [6.25-25]	16 (19)	12.5 [6.25-25]	20 (17)	12.5 [7.81-25]
Bisoprolol	16 (16)	5 [5-8.75]	13 (16)	5 [5-5]	19 (16)	5 [5-5]
Nebivolol	22 (22)	5 [3.75-7.5]	19 (24)	5 [2.5-7.5]	26 (22)	5 [2.5-7.5]
Atenolol	4 (4)	62 [50-94]	2 (2.5)	75 [50-100]	1 (1)	100
Sotalol	3 (3)	160	0	-	0	-
Celiproplol	2 (2)	200	2 (2.5)	150 [100-200]	1 (1)	200

Values are displayed as number of patients (%) and mean [quartiles] dosage in mg .

(BUN) and uric acid levels, need for mechanical intubation, need for non-invasive ventilation, need for catecholamine and admission medical treatment (diuretics, nitrates, angiotensin converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB), beta-blockers, statins, aspirin (ASS)/clopidogrel, calcium antagonists, coumarines, beta-mimetics, steroids). For the one-year mortality model, discharge medication was added to all variables included in the in-hospital mortality model. All variables of the in-hospital and one-year mortality model with a univariate P-value ≤ 0.05 were each included in the two multivariate Cox-proportional hazard models.

Results

Patient characteristics and mortality: A total of 314 ICU patients (median age 70 IQR (62 to 79) years) with acute respiratory failure were analyzed in the present study. ICU median (range) length of stay (LOS) was 3 (2 to 4) days and median in-hospital LOS 14 (9 to 22) days. Overall in-hospital mortality was 16% (51 patients), 30-day mortality was 20% (61 patients) and one-year mortality was 41% (128 patients).

Risk factors of one-year and in-hospital mortality: Univariate analysis demonstrates that age, a history of CAD or malignancy, BMI, diastolic blood pressure, atrial fibrillation, creatinine, blood urea nitrogen (BUN) or uric acid levels as well as treatment with oral steroids at discharge were associated with an increased risk of one-year mortality. By contrast, treatment with oral beta-blockers, statins, aspirin and/or clopidogrel at admission, as well as ACEi/ARB at discharge was associated with a lower risk for one-year mortality. Multivariate analysis shows that history of CAD or history of malignancy was associated with an increased risk and oral beta-blocker treatment prior to admission with a decreased risk of one-year mortality.

Univariate analysis shows that a history of malignancy, BMI, atrial fibrillation and creatinine levels on admission were associated with an increased risk of in-hospital mortality. By contrast, treatment with oral beta-blockers prior to admission was associated with a lower risk of in-hospital mortality. Multivariate analysis shows that history of malignancy was associated with an increased risk and oral beta-blocker treatment prior to admission with a decreased risk of in-hospital mortality in ICU patients with acute respiratory failure.

Impact of oral beta-blockers on short and long term outcome: Table 5 displays the different beta-blocker agents and the mean dosage administered during hospitalization. Kaplan-Meier analysis confirmed a lower in-hospital and one-year mortality in ARF patients admitted with than without oral beta-blockers ($P = 0.001$ for in-hospital and $P < 0.001$ for one-year mortality respectively). The beneficial effect of oral beta-blockers at admission on one-year mortality holds true in the two subgroups of ARF related to cardiac or non-cardiac causes.

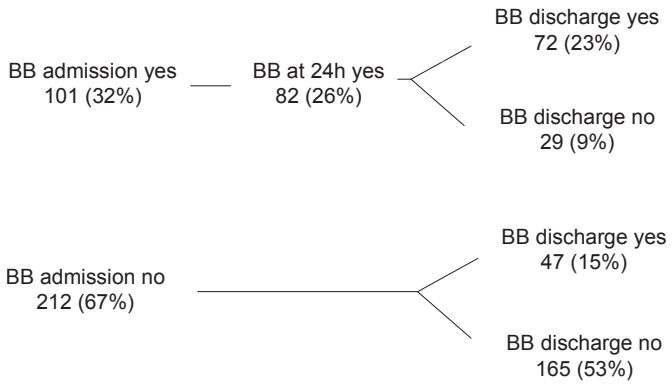
We further explored whether oral beta-blockers at discharge would give an additional beneficial effect on long term outcome. Kaplan-Meier analysis shows that administration of oral beta-blockers before hospital discharge gives striking additional beneficial effects on one-year mortality in our ARF patients. A beneficial effect of oral beta-blockers at discharge is seen regardless of the cardiac or non-cardiac origin of ARF.

Discussion

The present study focuses on the predictors of in-hospital and one-year mortality in ICU patients with acute respiratory failure. Our study confirms the negative impact of renal dysfunction on in-hospital survival and of malignancy and history of CAD on one-year survival. Further, a positive impact on one-year overall survival was seen in patients given beta-blockers prior to admission. Discontinuation of beta-blocker therapy in patients admitted on beta-blockers was associated with higher mortality.

Short and long-term mortality has been studied in some surveys and trials involving ICU patients with a primary diagnosis of ADHF, AECOPD or acute pneumonia. However, data describing mortality in ICU patients admitted for acute respiratory failure indifferent to underlying etiology are rare. In the present study, in-hospital mortality was 16% and 30-day mortality 20%. This suggests that most of the initial deaths occurred during the initial hospitalization with only a few deaths occurring shortly after discharge. One-year mortality in our ICU patients was 41%, in line with mortality rates previously described in selected ICU patients hospitalized for ADHF, AECOPD or severe pneumonia (14).

Our study shows for the first time that ICU patients with acute respiratory failure treated by oral beta-blockers prior to hospital admission experienced lower in-hospital and one-year mortality. The positive impact of being treated with oral beta-blockers at the time of respiratory failure in ICU patients was unknown. Exact mechanisms of a better short term and long-term survival in patients being treated with oral beta-blockers at the time of respiratory failure remained to be explored. One assumable explication may be the relevant co-morbidities found in our patients including history of CAD in 38%, history of CHF in 27%, arterial hypertension in 53% and COPD in 39% and the positive effect of beta-blocker therapy in these different diseases. This may include an adequate control of the sympathetic nervous system in patients with CAD, CHF or arterial hypertension as well as a possible improvement of bronchodilator responsiveness and effectiveness of inhaled β_2-sympathicomimetics in patients with AECOPD.



More importantly, we could demonstrate that discontinuation of beta-blocker therapy during hospitalization is associated with higher mortality rates, suggesting a protective effect of beta-blocker therapy in our acute respiratory failure patients. Discontinuation of beta-blocker therapy is indeed associated with a "withdrawal syndrome", a transient sympathetic hyper-response caused by hypersensitivity of cardiac β-receptors. Patients in whom beta-blockers were discontinued complained of transient palpitations, tremor, sweating, headache and general malaise. A significant increase in blood pressure and heart rate could also be demonstrated 24 h after beta-blocker withdrawal. A survival benefit of continuation of beta-blocker therapy in patients with ADHF was demonstrated by Butler et al. and recently confirmed by Fonarow et al., Jondeau et al and Orso et al. There is, furthermore, evidence that patients admitted with AECOPD may also benefit from continuation of beta-blocker therapy. The observed positive association of beta-blocker continuation with lower mortality may be explained by the prevention of malignant ventricular arrhythmias, protection against myocardial infarction or acute negative mechanical remodeling, which may initiate the development of fatal pump failure.

In our study, treatment with beta-blockers at discharge was associated with lower one-year mortality. There is solid evidence showing that oral treatment with beta-blockers improves long-term survival in various cardiovascular diseases including CHF, CAD or arterial hypertension. A recently published, large observational cohort study demonstrated that treatment with beta-blockers also reduce risk of exacerbations and improve survival in patients with COPD. Interestingly, this effect was shown to be independent of cardiovascular co-morbidities. Beta-blockers are known to temper the sympathetic nervous system, including the reduction of heart rate. Therefore, negative systemic effects in the disease progression of cardiovascular disease including CAD, CHF or arterial hypertension, as well as COPD could be diminished. Heart rate reduction itself may be an important mechanism of the benefit of beta-blockers. Large epidemiological studies have shown that resting heart rate was an independent predictor of all-cause mortality in individuals with and without cardiovascular disease.

Angiotensin converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARB) and beta-blockers build the mainstay of therapy in patients with CHF and/or CAD with impaired left ventricular function. In our study, treatment with ACEi/ARB was also associated with improved one-year survival. Importantly, lower in-hospital and one-year mortality benefits of beta-blocker therapy demonstrated in our study was independent of concomitant ACEi/ARB treatment.

Interestingly, the present study shows that the beneficial effect of beta-blockers on survival was consistently present regardless of a cardiac or non-cardiac etiology of respiratory failure. The

beneficial effect of beta-blockers in the non-cardiac respiratory failure group might seem to be a paradox. However, again the high incidence of relevant cardiovascular co-morbidities known to benefit from beta-blocker treatment may explain this finding. Beta-blocker treatment has been shown to reduce mortality in patients with COPD and arterial hypertension compared with other antihypertensive agents and to reduce cardiac toxicity of short-acting beta-agonists.

Our study corroborates and extends this finding to ICU patients with respiratory failure. While early diagnosis is often difficult to perform in ICU patients presenting with acute respiratory failure, this finding may be of major clinical importance. Roughly one-third of our patients were treated with beta-blockers at admission suggesting frequent uncertainty in ICU physicians regarding the question of whether beta-blocker therapy should be continued or not. Our data advocate for a continuation of beta-blocker therapy in this patient group, although study design and power were not conceived for analysis of this issue.

In our study elevated uric acid levels were associated with increased one-year mortality in univariate analysis. In patients admitted with acute dyspnea at the emergency department, uric acid levels were demonstrated to be higher in dyspnea due to ADHF compared to other etiologies. In this study uric acid levels also independently predicted two-year all-cause mortality. Our study expands these findings to ICU patients with acute respiratory failure. Uric acid is known to be associated with most cardiovascular risk factors and components of the metabolic syndrome including arterial hypertension, hyperlipidemia, or diabetes mellitus. Uric acid levels reflect the degree of circulating xanthine oxidase activity which is stimulated by various cardiovascular diseases and is an important source of free radicals. Accordingly, levels of uric acid might reflect a composite of cardiovascular risk factors.

Another important predictor of one-year mortality in our study was a low BMI. Previous studies demonstrated that a low BMI is associated with adverse outcome. This finding was recently confirmed in a large ICU database including 41,011 patients. In this study low BMI also prolonged ICU and hospital length of stay. These findings were regardless of severity of illness quantified by SAPS II score.

A more intriguing finding of our study was the association of a low diastolic blood pressure with increased one-year mortality, even when only found in univariate analysis. At the same time, beta-blocker treatment which lowers diastolic blood pressure improved outcome. Low diastolic blood pressure is known to affect microcirculation particularly in the coronary bed, and was previously demonstrated to be associated with higher mortality in older patients. Patients with severe forms of hypertension and overt coronary ischemia especially show a J-shaped relation between diastolic blood pressure during treatment and myocardial infarction. The J-curve seems to be independent of treatment, pulse pressure, and the degree of decrease in diastolic blood pressure, and is unlikely to be caused by poor left ventricular function. The most probable explanation is that subjects who have severe coronary artery disease and concomitant arterial hypertension may have a poor coronary flow reserve, which makes the myocardium vulnerable to coronary perfusion pressures that are tolerated by patients without ischemia, particularly at high heart rates. The most suitable explanation for this conflicting finding in our study is that patients with acute coronary syndrome as well as patients with shock were excluded due to study protocol. Patients included in our study had diastolic blood pressures that were still in a normal range (mean 62; 95%CI (53 to 74.5) mmHg).

Study limitations: There are limitations to our study design and conclusions, related to the post hoc nature of the analyses. Patients were not randomized into the study according to the beta-blocker status at baseline. However, patients currently being treated with oral beta-blockers at the time of acute respiratory failure had consistently lower in-hospital and one-year overall mortality. Accordingly, the impact of beta-blocker therapy on in-hospital and one-year survival merits further confirmation by an appropriate trial. Also, data regarding duration of beta-blocker therapy prior to admission, as well as percentage of beta-blocker therapy at one-year follow-up cannot be provided. Due to the exclusion of patients with sepsis or shock our findings cannot be generalized to these subgroups of ICU patients. No adjustment for APACHE or SAPS II score has been performed in our linear regression model. The most relevant variables of both severity scores have, however, been considered.

Conclusions

In our analysis established beta-blocker therapy appears to be associated with reduced mortality in patients admitted to the intensive care unit with acute respiratory failure. Cessation of established therapy appears to be hazardous. Initiation of therapy prior to discharge appears to confer benefit. This finding was seen regardless of the cardiac or non-cardiac etiology of respiratory failure. This observation should be confirmed by a large study that is adequately powered.

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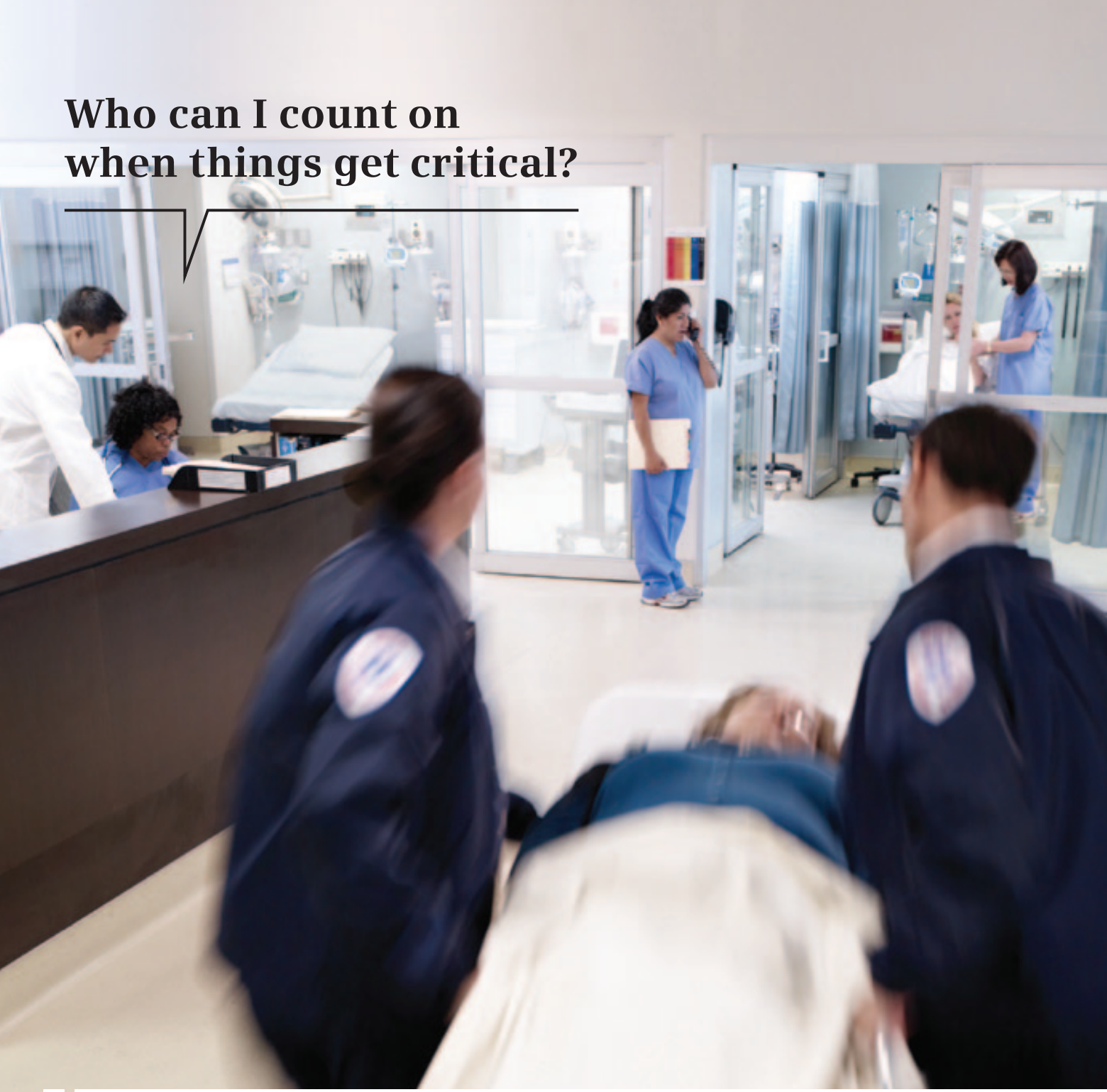

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