

Volume 1 Number 3 April/May 2006

Respiratory Therapy™

The Journal of Pulmonary Technique



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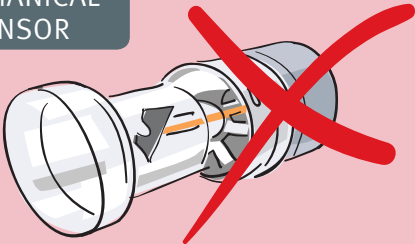
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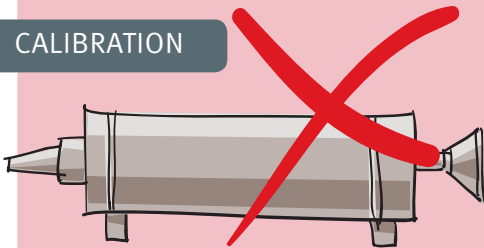
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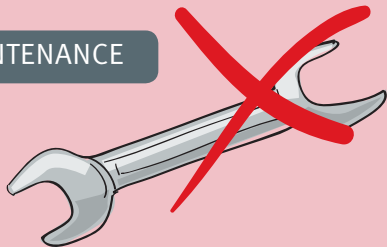
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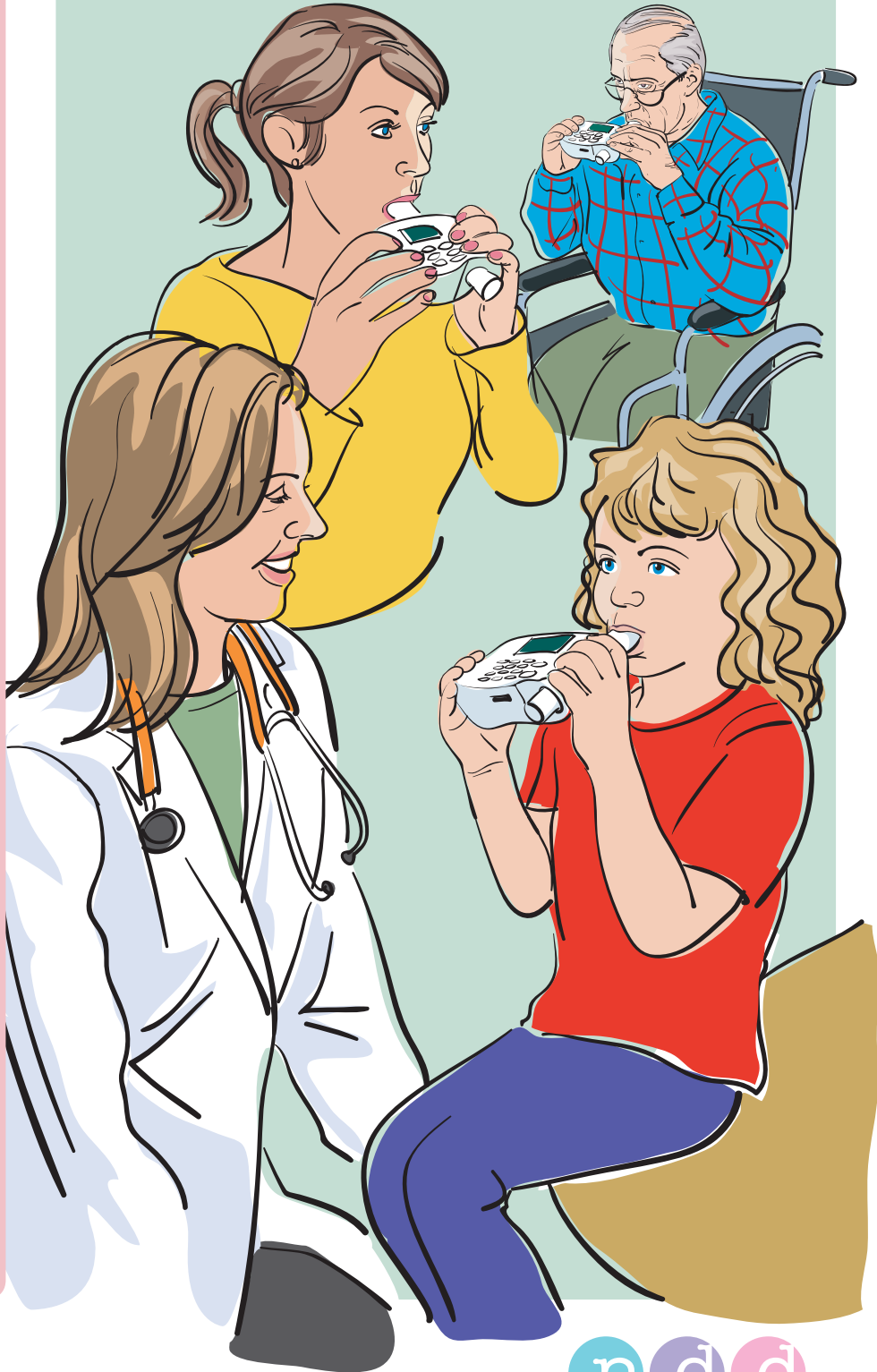
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Zemaira® is indicated for chronic augmentation and maintenance therapy in adults with alpha₁-proteinase inhibitor (A₁-PI) deficiency and clinical evidence of emphysema. Clinical data demonstrating the long-term effects of chronic augmentation therapy with Zemaira® are not available.

As with other Alpha-1 therapies, Zemaira® may not be appropriate for the following adult individuals as they may experience severe reactions, including anaphylaxis: individuals with a known hypersensitivity and/or history of anaphylaxis or severe systemic reaction to A₁-PI products or their components and individuals with selective IgA deficiencies who have known antibodies against IgA.

In clinical studies, the following treatment-related adverse events were reported in 1% of subjects: asthenia, injection-site pain, dizziness, headache, paresthesia, and pruritus.

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Please see brief summary of full prescribing information on the back of this page.

Zemaira®
alpha₁-proteinase inhibitor (Human)

www.Zemaira.com

Reference: 1. American Thoracic Society. American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with Alpha-1 antitrypsin deficiency. *Am J Respir Crit Care Med.* 2003;168:818-900.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

Alpha₁-Proteinase Inhibitor (Human)

Zemaira®

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Rx only

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INDICATIONS AND USAGE

Alpha₁-Proteinase Inhibitor (Human), Zemaira®, is indicated for chronic augmentation and maintenance therapy in individuals with alpha₁-proteinase inhibitor (A₁-PI) deficiency and clinical evidence of emphysema.

Zemaira® increases antigenic and functional (ANEC) serum levels and lung epithelial lining fluid levels of A₁-PI.

Clinical data demonstrating the long-term effects of chronic augmentation therapy of individuals with Zemaira® are not available.

Safety and effectiveness in pediatric patients have not been established.

Zemaira® is not indicated as therapy for lung disease patients in whom severe congenital A₁-PI deficiency has not been established.

CONTRAINDICATIONS

Zemaira® is contraindicated in individuals with a known hypersensitivity to any of its components. Zemaira® is also contraindicated in individuals with a history of anaphylaxis or severe systemic response to A₁-PI products.

Individuals with selective IgA deficiencies who have known antibodies against IgA (anti-IgA antibodies) should not receive Zemaira®, since these patients may experience severe reactions, including anaphylaxis, to IgA that may be present in Zemaira®.

WARNINGS

Zemaira® is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. Because Zemaira® is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically the Creutzfeldt-Jakob disease (CJD) agent. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses during manufacture. (See **DESCRIPTION** section of full prescribing information for viral reduction measures.) The manufacturing procedure for Zemaira® includes processing steps designed to reduce further the risk of viral transmission. Stringent procedures utilized at plasma collection centers, plasma testing laboratories, and fractionation facilities are designed to reduce the risk of viral transmission. The primary viral reduction steps of the Zemaira® manufacturing process are pasteurization (60°C for 10 hours) and two sequential ultrafiltration steps. Additional purification procedures used in the manufacture of Zemaira® also potentially provide viral reduction. Despite these measures, such products may still potentially contain human pathogenic agents, including those not yet known or identified. Thus, the risk of transmission of infectious agents can not be totally eliminated. Any infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to ZLB Behring at 800-504-5434. The physician should discuss the risks and benefits of this product with the patient.

Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections (see **Information For Patients**).

During clinical studies, no cases of hepatitis A, B, C, or HIV viral infections were reported with the use of Zemaira®.

PRECAUTIONS

General – Infusion rates and the patient's clinical state should be monitored closely during infusion. The patient should be observed for signs of infusion-related reactions.

As with any colloid solution, there may be an increase in plasma volume following intravenous administration of Zemaira®. Caution should therefore be used in patients at risk for circulatory overload.

Information For Patients – Patients should be informed of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, dyspnea, wheezing, faintness, hypotension, and anaphylaxis. Patients should be advised to discontinue use of the product and contact their physician and/or seek immediate emergency care, depending on the severity of the reaction, if these symptoms occur.

As with all plasma-derived products, some viruses, such as parvovirus B19, are particularly difficult to remove or inactivate at this time. Parvovirus B19 may most seriously affect pregnant women and immune-compromised individuals. Symptoms of parvovirus B19 include fever, drowsiness, chills, and runny nose followed two weeks later by a rash and joint pain. Patients should be encouraged to consult their physician if such symptoms occur.

Pregnancy Category C – Animal reproduction studies have not been conducted with Alpha₁-Proteinase Inhibitor (Human), Zemaira®. It is also not known whether Zemaira® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Zemaira® should be given to a pregnant woman only if clearly needed.

Nursing Mothers – It is not known whether Zemaira® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Zemaira® is administered to a nursing woman.

Pediatric Use – Safety and effectiveness in the pediatric population have not been established.

Geriatric Use – Clinical studies of Zemaira® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. As for all patients, dosing for geriatric patients should be appropriate to their overall situation.

ADVERSE REACTIONS

Intravenous administration of Zemaira®, 60 mg/kg weekly, has been shown to be generally well tolerated. In clinical studies, the following treatment-related adverse reactions were reported: asthenia, injection site pain, dizziness, headache, paresthesia, and pruritus. Each of these related adverse events was observed in 1 of 89 subjects (1%). The adverse reactions were mild.

Should evidence of an acute hypersensitivity reaction be observed, the infusion should be stopped promptly and appropriate countermeasures and supportive therapy should be administered.

Table 3 summarizes the adverse event data obtained with single and multiple doses during clinical trials with Zemaira® and Prolastin®. No clinically significant differences were detected between the two treatment groups.

Table 3: Summary of Adverse Events

	Zemaira®	Prolastin®
No. of subjects treated	89	32
No. of subjects with adverse events regardless of causality (%)	69 (78%)	20 (63%)
No. of subjects with related adverse events (%)	5 (6%)	4 (13%)
No. of subjects with related serious adverse events	0	0
No. of infusions	1296	160
No. of adverse events regardless of causality (rates per infusion)	298 (0.230)	83 (0.519)
No. of related adverse events (rates per infusion)	6 (0.005)	5 (0.031)

The frequencies of adverse events per infusion that were ≥0.4% in Zemaira®-treated subjects, regardless of causality, were: headache (33 events per 1296 infusions, 2.5%), upper respiratory infection (1.6%), sinusitis (1.5%), injection site hemorrhage (0.9%), sore throat (0.9%), bronchitis (0.8%), asthenia (0.6%), fever (0.6%), pain (0.5%), rhinitis (0.5%), bronchospasm (0.5%), chest pain (0.5%), increased cough (0.4%), rash (0.4%), and infection (0.4%).

The following adverse events, regardless of causality, occurred at a rate of 0.2% to <0.4% per infusion: abdominal pain, diarrhea, dizziness, ecchymosis, myalgia, pruritus, vasodilation, accidental injury, back pain, dyspepsia, dyspnea, hemorrhage, injection site reaction, lung disorder, migraine, nausea, and paresthesia.

Diffuse interstitial lung disease was noted on a routine chest x-ray of one subject at Week 24. Causality could not be determined.

In a retrospective analysis, during the 10-week blinded portion of the 24-week clinical study, 6 subjects (20%) of the 30 treated with Zemaira® had a total of 7 exacerbations of their chronic obstructive pulmonary disease (COPD). Nine subjects (64%) of the 14 treated with Prolastin® had a total of 11 exacerbations of their COPD. The observed difference between groups was 44% (95% confidence interval from 8% to 70%). Over the entire 24-week treatment period, of the 30 subjects in the Zemaira® treatment group, 7 subjects (23%) had a total of 11 exacerbations of their COPD.

HOW SUPPLIED

Zemaira® is supplied in a single use vial containing the labeled amount of functionally active A₁-PI, as stated on the label. Each product package (NDC 0053-7201-02) contains one single use vial of Zemaira®, one 20 mL vial of Sterile Water for Injection, USP (diluent), one vented transfer device, and one large volume 5 micron conical filter.

STORAGE

When stored up to 25°C (77°F), Zemaira® is stable for the period indicated by the expiration date on its label. Avoid freezing which may damage container for the diluent.

Prolastin® is a registered trademark of Bayer Corporation.

Adapted from 19131-03
Revised: August 2004

READ IT AND DON'T WEEP

Medical journals have received a lot of bad press lately, much of it from the nation's "consumer" publications – there's an irony hiding in there – those paragons of unbiased information. In looking back at past issues of this and some of our other titles, I've noticed we've done some on the fly journal bashing ourselves. Needless to say, the bashees, as it were, have not been blameless, printing specious articles about cloning, fake articles planted by tricksters, and so forth. And we've received some not so kind words ourselves about being a non-peer-reviewed journal.

For the other side of the coin, Thomas Stossel asks, in a recent edition of the Wall Street Journal: why are scientific journals regarded with such reverence? Why are they asked to be perfect, to cover every side of an issue, to be some kind of final arbiters of truth? Stossel notes, "In a [recent] article in the New England Journal of Medicine, I reported that no systematic evidence exists that corporate sponsorship of academic research contributes to misconduct, bias, public mistrust or poor research quality." For the historical record, Stossel notes that until the volume of scientific research exploded, "no peer review restricted publication. Once restrictions arose, human competitiveness established a journal prestige pecking order that grew in importance as research became more prevalent and complex... The journals at the top got there because of herd behavior by researchers, not because they are better than lower-tier journals at vetting research quality." He notes that many journals can "afford to maintain their prestige by rejecting, not publishing, many high quality papers. That's brand creation – not science. Most of their editorial effort goes into deciding which submitted papers are sufficiently newsworthy. Anonymous peer review has its merits, but it has a tendency to select for fashionable if relatively unoriginal and inoffensive papers. Top medical journals compete for papers describing large clinical trials reporting small effects of treatments for diseases affecting many people, although these reports often do not substantively advance scientific knowledge, and many subsequently are invalidated." Stossel adds that if journals had to vet papers with the stringency of, say, the FDA [sic], "academic biomedical research would come to a screeching halt." He notes, "If reporters understood that journals are magazines, not holy scripture, we might not be witnessing ever more onerous regulations inhibiting interactions between academic and industry science." He concludes, "prestigious biomedical journals are good for our health – provided they stick to their core business of facilitating imperfect communication between researchers."

While I'm not so blithely cavalier about brushing off evidence of collusion between journals, medical corporations, and researchers, I'm also aware that the main goal of a professional journal should be, as Stossel says, to provide open channels for researchers to say what they want to say. Journals can't afford to be some kind of quasi-moral Maginot line for scientific truthfulness. (Isn't this the actual researchers' mandate?) Like I've said here before, I would hopefully, safely assume that our readers aren't idiots, that they can make judgments about the validity of published information by considering the source. If they disagree, they're certainly welcome to put it in writing, and we'll publish it.

Les Plesko
Editor



Respiratory Therapy™

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News

□ April-May 2006

CORRECTION

Two articles from the previous issue, Neonatal-Pediatric Application of Transcutaneous pO₂/pCO₂ Monitoring, and Transcutaneous Monitoring: Back to the Future – An Important Adjunct to Care During High Frequency Oscillatory Ventilation should have had the notice: “Reprinted with permission from bloodgas.org, a knowledge site maintained by Radiometer.” We apologize for the error.

MORE BREASTFEEDING, LESS WHEEZING

New research from a study conducted at UC Davis Children’s Hospital, the University of Rochester, and the American Academy of Pediatrics is being used to support the AAP’s recommendation that babies be breastfed until the age of six months. According to lead author Dr. Caroline Chantry, “We found that babies who received an additional two months of full breastfeeding were over four times less likely to contract pneumonia and half as likely to suffer recurrent ear infections.” The study looked at a total of 2,277 children nationally represented aged 6 to 24 months. They were split into five groups: only formula-fed, full breastfeeding (use of formula on less than a daily basis) for less than 1 month, from 1 to 4

months, from 4 to 6 months, and for 6 months or more. Even when adjusted for factors such as age, birth weight, and ethnicity, the results showed lesser occurrences of pneumonia, wheezing, and recurrent colds or ear infections among the children breastfed for 6 months. Chantry emphasizes the importance of helping to enable women, especially those in the workplace, to breastfeed their children.

ASTHMA AND ATOPY

Arch Dis Child reports on a University Hospital of North Staffordshire, United Kingdom study about the relationship between asthma severity and atopy. The authors say many studies have failed to show significant relationships between clinical severity or lung function and markers of atopic sensitization. The study aimed to determine whether increasing asthma severity is related to atopic sensitization in a population of children with asthma. Four hundred children (7-18 years) with asthma were recruited as part of a multicenter study of the genetics of asthma. Detailed phenotypic data were collected on all participants. Associations between measures of asthma severity and atopic sensitization were sought using multilevel models allowing variation at the individual and family level. Children recruited to the study had a range of asthma severities, with just over a third having mild-persistent asthma. Increasing skin prick test reactivity to a panel of 7 aeroallergens was associated with increased risk of hospital admission, use of an inhaled steroid and airways obstruction. The study concludes that in children with asthma, increasing atopy is associated with increasing asthma severity. However, the relationships between asthma severity and skin prick tests, and asthma severity and total serum IgE values, appear subtly different.



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CATCHING SOME ACETAZZZZZZ'S

A new study of sleep apnea found that taking acetazolamide helps to improve blood oxygen levels. Acetazolamide, a mild diuretic and respiratory stimulant, has otherwise been used to treat breathing irregularities and sleep apneas occurring at high altitude. This study, funded by the National Heart, Lung and Blood Institute, focused on the relationship between sleep apnea and blood pressure. The double-blind study followed 12 patients with stable heart failure who were randomly assigned to either take acetazolamide or placebo an hour before going to sleep. Compared to placebo, patients perceived a significant improvement in their sleep quality and woke up more refreshed. The study says that "with long-term drug therapy, as sleep-related breathing disorders improve, it may be reflected in an improvement in cardiac function that will further improve periodic breathing, resulting in a positive feedback cycle. Improvement in sleep apnea may assist cardiac function by a variety of mechanisms such as improved oxygenation." It also notes that long-term studies will be necessary to supplement the short-term findings.

GOT UNIVERSAL HEALTHCARE?


The Executive Summary reports that an overwhelming majority of 1,104 surveyed adults agree that "fundamental changes" need to occur in the US healthcare system. Specific problems cited were increases in cost and decreases in quality. As for universal health care, after the survey presented arguments from both the pro and con sides of the debate, 84% supported universal health care in principle, while 52% continued to support it if consequences included increases in both taxes and government role in healthcare.

IT'S NOT FISHY

The December issue of CHEST published a study in which Japanese researchers looked at the effects of omega-3 fatty acids in the diet. Found in fish, canola oil, and walnuts, omega-3 is known for its anti-inflammatory properties and for helping facilitate exercise for chronic obstructive pulmonary (COPD) patients. Sixty-four COPD patients were evenly split into two groups, one which consumed a diet rich in omega-3 fatty acids and one which did not. Every 3 months over the course of 3 years, dyspnea scores, exercise capacity, and levels of inflammatory mediators were measured. Dyspnea scores and exercise capacity increased, while inflammatory mediator levels decreased at a significant level only in the group which consumed omega-3 fatty acids, while the group which did not consume them did not experience any significant changes.

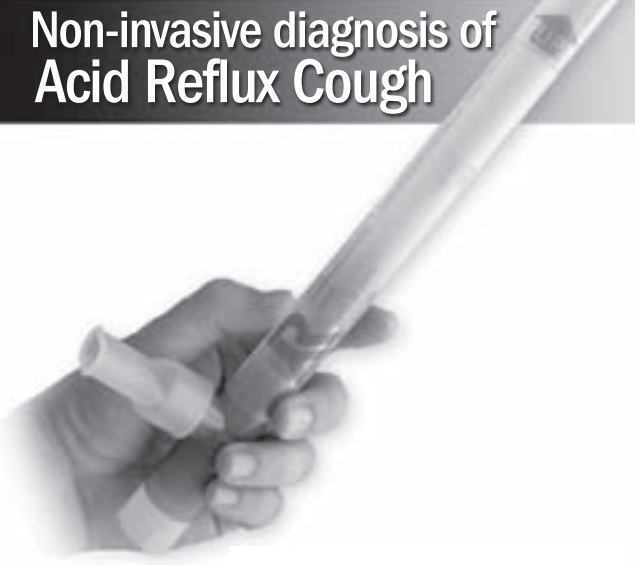
THEY SQUEAKED RIGHT BY

Japanese researchers at the Juntendo University School of Medicine conducted a study in which a control group of mice was compared to a group of tomato juice-fed mice. All the mice were then exposed to 1.5% tobacco smoke for 30 minutes each day for five weeks, but only the control group mice developed emphysema. The researchers believe that emphysema was prevented by the presence of lycopene, a strong antioxidant, in the tomato juice. However, because the mice were fed tomato juice but not pure lycopene, they concede that it is still possible that "other ingredients contained in tomato juice affected the results." The FDA approved (highly-qualified) labels last year linking consumption of tomato products to reduced occurrence of prostate cancer.



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VENGO A ESTUDIO

Clarion University–Venango Campus is offering an associate of science degree in respiratory care through the university's School of Nursing and Allied Health. The 24-month respiratory care program will include science and liberal arts courses at Clarion University–Venango Campus and a 14-month course of technical education in respiratory care at affiliated clinical sites. Upon successful completion of the respiratory care program, students are awarded the Associate of Science in Respiratory Care degree from Clarion University and are eligible to sit for the Written Registry Examination and Clinical Simulation Examination administered by the National Board for Respiratory Care. Contact clarion.edu.

BUT WILL THERE BE LONG LINES?

Sionex corporation's microDMx sensor, currently used at airports to detect explosives, may have a new use: diagnosing lung disease. At the University of Manchester, Dr Paul Thomas is heading a team of researchers who hope that they can utilize the technology in the sensor, which is able to very accurately identify molecules, to create a simple device to detect lung cancer. By simply breathing into the device, according to Dr. Thomas, the microDMx would be able to sense molecules associated with diseases such as cancer and asthma and "identify a spectrum of [medical] conditions." Dr. Thomas hopes that it would also aid in determining correct dosages of medication. "For instance, if a patient is taking steroids for asthma, we would be able to determine whether they were being given the right amount of steroids from the molecules in their breath." Pharmaceutical companies have already lined up to fund further research.

THEY SURE HAVE MOXIE

Dr Antonio Anzueto of The University of Texas Health Science Center led a study comparing two medications used to treat community-acquired pneumonia (CAP) in elderly patients. CAP, which is the fifth-leading cause of death in senior citizens, has generally been treated with the medication levofloxacin. However, after looking at the recovery rates of 281 patients from 47 different centers, Anzueto found that the medication Moxifloxacin HCl was related to higher rates of recovery. Levofloxacin treated patients recovered at a rate of 90 percent, while Moxifloxacin HCl patients recovered at a rate of 97.9 percent. Dr. Anzueto notes that both treatments were determined to be safe, but believes that the use of Moxifloxacin should help reduce the occurrence of "incapacitating long-term effects."

NOT SUE ENOUGH

Medical malpractice claims in the US likely will decrease by 1% next year, after "years of soaring liability" for physicians and hospitals, according to a recent study by Aon. However, the study found that the average size of malpractice claims likely will increase by 7.5%. The study examined about 60 healthcare organizations, or 10% of the \$10 billion hospital liability market and 15% of the alternative insurance market. Four states are expected to lead the expected decrease – California, Florida, Pennsylvania and Texas, all states that have enacted legislation to limit malpractice claims, such as caps on damages, restrictions on expert witnesses and rules about where patients can file claims.

A TALE OF TWO FETUSES

A new study from the Yale School of Medicine looked at the

effect a fetus's sex can have on its mother's breathing. After monitoring 702 pregnant asthmatics, researchers found that female fetuses were associated with harsher asthma symptoms than male fetuses. Data taken at 10-day intervals during the pregnancies showed that women carrying male fetuses had a 10% better lung function. The senior author of the study, Michael Bracken, suggested that this might have to do with the testosterone secreted by the male fetuses, which can help inhibit the mother's response to histamines. In most women, breathing difficulties were the worst until 30 weeks gestation, and then improved. He also noted that lung function is highly influenced by medical treatment and smoking patterns.

ASBESTOS HAS NOT LEFT THE BUILDING

Linda Reinstein, co-founder of the Asbestos Disease Awareness Organization (ADAO), says that many Americans are not aware that asbestos is still present in over 30 million homes and schools. Recently interviewed in *CancerWire*, she discusses the dangers of asbestos exposure. "Asbestos can cause or contribute to cancers such as mesothelioma, lung, larynx, esophageal, and stomach cancer and many non-malignant diseases. . . Ten thousand lives are lost every year to all asbestos-related disease." She points out that asbestos is still legally allowed "in certain concentrations. For example, under OSHA, an employee cannot be exposed to more than 0.1 asbestos fibers per cubic centimeter of air for an average eight hour work day." However, she believes that these regulations may not help because of EPA guidelines stipulating that the only safe level of asbestos exposure is no exposure at all.

COME HEAR ALL ABOUT IT

On April 21-22, 2006, Lund, Sweden will be hosting the 1st European Conference on Scientific Publishing in Biomedicine and Medicine. Titled "Researchers and Open Access - the new scientific publishing environment," the conference features speakers who are some of the most prestigious names in the field. They include: Dr Eugene Garfield, Founder & Chairman Emeritus, Institute for Scientific Information, who will be lecturing on "Identifying Nobel Class Scientists and the Vagaries of Research Assessment", and BioMed Central's Marketing and Sales Director Natasha Robshow who will be giving a lecture titled "Open Access: Moving into the mainstream." Additional information, including lectures and workshops at the conference, is available at www.ecspbiomed.net, or email.

GROWTH SUPPRESSION

Researchers from Cyprus and Greece evaluated impairment of growth of asthmatic children treated with inhaled corticosteroids. Low dose synacthen test was performed in 72 asthmatic children on long-term treatment (6-84 months) with low to moderate doses of inhaled budesonide. Changes in height standard deviation scores (HSDS) at the time of testing and height velocity SDS (HVSDS) in the preceding year were also calculated. Adrenal suppression was demonstrated in 15 asthmatic children (20.8%) but this was only a biochemical finding, since none of these children presented symptoms of adrenal insufficiency. There were no differences in HSDS and HVSDS between children with and without adrenal suppression. There was no correlation between adrenal response and dose or duration of treatment. However, a positive relation between HVSDS and duration of treatment was noted. The study team concludes that long-term treatment of asthmatic children with low to moderate doses of inhaled budesonide may result in mild adrenal suppression that cannot be predicted by growth

deceleration. An idiosyncratic sensitivity of some children to ICSs may exist. The full study was reported in ERJ.

SHORT BUT BREATHING

While both inhaled corticosteroids (ICS) and leukotriene receptor antagonists (LTRA) have been proven to help control mild-to-moderate persistent asthma in school-age children, a new study shows ICS may be the more effective treatment. A 16-week study was conducted as a multi-center, double-masked, 2-sequence crossover trial by the National Heart, Lung and Blood Institute (NHLBI) Childhood Research and Education (CARE) Network. Researchers, led by Robert S. Zeiger, MD, PhD, from the University of California San Diego Department of Pediatrics, administered an ICS (fluticasone propionate) twice daily or an LTRA (montelukast) nightly to more than 100 children ages 6 to 17 who had mild-to-moderate persistent asthma. Researchers found both fluticasone and montelukast led to significant improvements in many measures of asthma control. However, similar to earlier research, they found strong evidence of greater mean improvements after 8 weeks of therapy with an ICS compared with a LTRA across many other outcomes.

SOUNDS OF SNORING

Snoring is a frequent problem in marriage, says Rosalind Cartwright, PhD. "Couples who struggle with sleep apnea have a high-divorce rate. Can we save marriages by treating sleep apnea?" Cartwright, founder of the Sleep Disorders Center, is running a study following 10 men diagnosed with sleep apnea and the effect it has on their spouses. The couples each filled out surveys relating to their sleep patterns and marital satisfaction and then spent a night in a lab. In the lab, scientists monitored various indicators of sleep quality. "Our early results are showing that the wife's sleep is indeed deprived due to the husband's noisy nights. . . The lack of sleep for both partners puts a strain on the marriage and creates a hostile and tense situation," says Cartwright. In one couple, following the husband's treatment for sleep apnea (using continuous positive airway pressure) the wife's marital satisfaction score improved from 3 to 5.8. Cartwright hopes this research may even help save marriages.

STAYING STABLE

A recent study by St Joseph's Healthcare and McMaster University in Canada by Pizzichini, et al, Stable COPD: predicting benefit from high dose inhaled corticosteroid treatment, delineates the role of inhaled corticosteroids in the management of chronic obstructive pulmonary disease. According to the abstract, COPD remains controversial. The purpose of the study was to evaluate whether sputum eosinophilia ($\geq 3\%$) predicts clinical benefit from inhaled corticosteroid treatment in patients with stable moderate-severe smokers COPD. Forty consecutive patients with effort dyspnea were enrolled. Subjects were treated with inhaled placebo followed by inhaled budesonide, given for 4 weeks. While the treatment was single-blind (subject level), sputum cell counts before and after treatment interventions were double-blind, thus removing bias. Outcome variables included spirometry, quality of life assessment and 6-minute walk test. Sputum eosinophilia was present in 38% of subjects. In these, budesonide treatment normalized the eosinophil counts and, in comparison to placebo treatment, resulted in clinically significant improvement in the dyspnea domain of the disease specific chronic respiratory questionnaire and a small but statistically significant improvement in post-bronchodilator spirometry. The researchers concluded that sputum eosinophilia predicts short-

term clinical benefit from high dose inhaled corticosteroid treatment in patients with stable moderate-severe COPD.

GO BACK TO SLEEP!

Full-night sleep studies and echocardiography may need to be incorporated into routine assessments of patients. Those who are resistant to treatment and who are found to have sleep apnea may benefit from mineralocorticoid receptor antagonists. CPAP should be encouraged, based on results of a study funded by the National Heart, Lung and Blood Institute and presented last month at the American Heart Association annual meeting. Researchers found a direct relationship between the severity of sleep apnea and cardiovascular changes associated with high blood pressure. Since sleep apnea is associated with patients who take a single dose of acetazolamide before going to bed they exhibit less sleep apnea, improved blood oxygen levels and fewer daytime symptoms of sleepiness.

A double-blind, placebo-controlled trial studied 12 male patients who had more than 15 episodes per hour each night of sleep apnea. The patients with stable heart failure were randomized to a double-blind cross-over protocol with either acetazolamide or placebo, taken one hour before bedtime over the course of six nights. There was a two-week washout period between the two study segments—acetazolamide and placebo. An important finding of the double-blind study was the significant improvement in patient perception of improved sleep quality, waking up more refreshed, with less daytime fatigue and sleepiness while taking acetazolamide, compared with placebo.

OFF OUR BACKS

Researchers at The University of Texas Medical School at Houston have discovered that babies with sleep apnea experience more respiratory disturbances when they sleep on their backs than in other positions. The findings contradict earlier studies on the subject. The children underwent polysomnography (PSG, the continuous recording of physiologic variables during sleep) to evaluate OSAS, and later had their tonsils and adenoid tissue removed. The PSGs were analyzed for data on the respiratory disturbance index (RDI, an index measuring respiratory events that disturb sleep), time spent in each body position during sleep, the number of apnea events in each position, oxygen saturation, and time spent in each stage of sleep. The mean RDI rose when more than 50 percent of the time was spent in supine (face upwards) sleep and there was a greater increase when supine sleep comprised 75 percent of the total sleep time.

The study indicated that supine sleep correlates with an increase in RDI as well as with OSAS in patients younger than four.

UNMASKED

Some face masks commonly used to help young children inhale asthma medicine are not effective, according to a new study by researchers from Wake Forest University School of Medicine. "With some masks, the amount of medicine available to the youngest children is severely decreased because of mask size, stiffness, and poor fit on the face," said Bruce Rubin, MD, a professor of pediatrics and biomedical engineering in the Wake Forest-Virginia Tech Biomedical Engineering & Sciences. Researchers studied seven masks used in combination with pressurized metered-dose inhalers and found that some masks don't fit well or have too much dead space volume. The seven masks evaluated were those used with the Aerochamber, Optichamber, Easivent, BreatheRite, Ace, Pocket Chamber and

Vortex inhalers. The investigators measured mask volume by filling them with water after sealing the outlet end. Then, using an infant-sized mannequin head that is used to teach cardiopulmonary resuscitation, they measured the dead space volume of the masks. They also measured how well the mask fit on the face by analyzing digital photographs to determine if there was any leak. Dead space volume ranged from 20 mL to 100 mL – with the higher number meaning that less medicine gets to the lungs. Only the Aerochamber, Optichamber and the Vortex had dead space volume that was low enough for the mask to be emptied with the normal breathing of a six-month-old infant. The poorest fit and biggest leak was with the Vortex, Pocket Chamber and BreatheRite masks. In fact, the Pocket Chamber was too stiff to seal at any force. The group didn't study the drug delivery, which is the ultimate test of effectiveness. This summer, they plan to do studies in children to evaluate how effectively medication is getting to the lungs.

PRODUCTS

VIASYS Healthcare was awarded the prestigious Zenith Award from the AARC at this year's International Congress in San Antonio. The Zenith Award recognizes five companies out of more than 400 chosen by over 38,000 members of the AARC, that exemplify the utmost standards in excellence in the respiratory care industry. Also at the 2005 AARC, VIASYS was able to raise over \$4,000 for the ARCF through its "Riverwalkin' For Respiratory Care" promotion. Visitors to the VIASYS booth received a free pedometer and a mileage card. They were invited to track their mileage while in San Antonio and return to the VIASYS booth prior to the close of the show. For every mile walked, the company donated ten cents to the ARCF.

News from Masimo

Masimo reported that a new study, presented at the 2005 American Society of Anesthesiology (ASA) Annual Meeting in Atlanta, demonstrates the value of its highly accurate monitoring technology in caring for infants with congenital heart disease. Accurate monitoring of blood oxygen levels is especially important in the care of critically ill infants. Pulse oximeters, developed in the 1980's to allow continuous monitoring of patients' blood oxygen levels, have posed significant challenges for clinicians especially in neonatal care. With conventional pulse oximetry technologies, patient motion and low blood circulation in feet or hands can produce inaccurate monitoring results. Infants and children with cyanotic (insufficient oxygen in their bloodstream) heart disease have been extremely difficult to monitor accurately.

At the recent ASA conference, an independent research team from Texas Children's Hospital at Baylor College of Medicine presented study results on the Masimo SET LNOP Blue Sensor, which is the first device of its kind specifically designed - and cleared by the FDA - for accurately monitoring blood oxygen levels in cyanotic infants. The study, "Substantial Improvement in Accuracy," compared the performance of the Masimo SET Blue Sensor, attached to a Masimo SET Radical Pulse Oximeter, with that of the OxiMax Max-I sensor attached to Nellcor's N-595 pulse oximeter in patients with cyanotic heart disease. Comparing the monitoring performance of both technologies with blood test results, investigators found that the Masimo technology was significantly more accurate. The Masimo SET Radical and Blue Sensor exhibited a bias of 0.17 % compared with a bias of 5.63% for the Nellcor device. Masimo's precision was also significantly better, 2.51% compared to 5.24 % for the Nellcor N-595. In an abstract of their study presentation at ASA,

researchers stated that Masimo technology "represents a significant advance in the care of this complicated group of patients". Gina Whitney MD, one of the researchers, commented on the study presented at ASA, "Our research found that the Masimo SET Radical and the Blue Sensor provided a substantial improvement in accurately monitoring children with cyanotic congenital heart disease." Dr. Whitney, currently Assistant Professor of Pediatrics and Anesthesia at Vanderbilt Children's Hospital, conducted the study while working in the division of Pediatric Intensive Care at Texas Children's Hospital in Houston Texas. "The other cardiac intensive care physicians were so impressed with the performance that they began 'borrowing' the study for use in other critically ill patients who were not enrolled," said Dr. Whitney. "Accuracy and reliability in monitoring oxygen levels is especially important in these fragile patients," said Maribeth P. Sayre MD, Director of Medical Affairs at Masimo. "Developing technology specifically designed to help clinicians provide optimal care for these children has been a top priority for Masimo. We are delighted that independent clinical research shows that we are succeeding."

Comparison Studies Also Document Superior Masimo Performance with Adults. Other studies presented at ASA compared Masimo with "new generation" pulse oximeters from Nonin and Philips. A research team at Long Beach VAHS & University of California at Irvine Medical Center, led by Nitin Shah, MD, examined the performance, accuracy, failure rate and recover time of the Masimo Radical (rev 4.3), the Nonin 9700 (2004) and the Philips CMS (FAST rev C.1) oximeters. Volunteers were tested in a cooled room (16-18 degrees Centigrade), an environment that lowered blood circulation in feet and hands. The study participants were connected to all three pulse oximeters, which were compared to control oximeters. During different types of motion, low perfusion (blood circulation) and hypoxia (low blood oxygen levels), researchers measured differences from the control devices. The Masimo SET Radical pulse oximeter performed significantly better than both the Philips and the Nonin technologies during all parts of the test, and the Masimo SET Radical was the only device that did not zero out (fail to report readings) during any test. "Masimo SET technology has been repeatedly tested against competitive technologies, worldwide. Time after time, in neonatal, pediatric or adult care, research proves that no other oximetry technology matches the performance of Masimo SET," said Mike Petterson, Masimo Vice President of Clinical Research. Contact masimo.com.

RAPHAEL from Hamilton

The US Food and Drug Administration has granted **Hamilton Medical** a 510(k) clearance to market a new version of its RAPHAEL Color ventilator, complete with noninvasive ventilation (NIV) and tube resistance compensation (TRC). The NIV mode is an adaptation of pressure support ventilation designed to compensate leaks and to minimize leak-related nuisance alarms. Provided through a mask or mouthpiece, noninvasive ventilation can decrease the need for intubation and promote early extubation. Reduced mortality in COPD patients, reduced ventilation time in COPD and ARF patients, and reduced complication rates of ventilator-associated pneumonias have been clearly demonstrated. The new RAPHAEL Color also features tube resistance compensation (TRC). To reduce the patient's work of breathing while on the RAPHAEL, TRC offsets the flow resistance imposed by the endotracheal (ET) or tracheostomy tube. The RAPHAEL Color is a compact biphasic ventilator designed to help pediatric and adult patients breathe

more freely in all modes and phases. Small enough to fit into almost any ICU environment and competitively priced, it covers the full range of clinical requirements: invasive and noninvasive ventilation, from intubation to weaning. The RAPHAEL Color is designed for use in the ICU, in the recovery room, and in transit between them. It is the ideal solution for smaller community and rural hospitals, special care areas including ICUs, cardiac surgery recovery, step-down units, subacute care units, and long-term care (LTC) centers. Contact hamilton-medical.com.

MAQUET Update

The company is sponsoring a two-day respiratory conference during which experts will explore paradigm shifts in mechanical ventilation. World-renowned pulmonary experts will discuss today's paradigm shifts in mechanical ventilation at a two-day symposium at the New York City Marriott Marquis, August 28 to 29, sponsored by **MAQUET** Critical Care. The event will focus on the latest developments in mechanisms and therapy related to ventilator-induced lung injury (VILI) and will discuss recent research on patient-ventilator synchrony. Covering the theme from multiple perspectives, VILI topics will include the impact of alveolar geometry on lung injury distribution; quantitative endpoints for lung recruitment; the role of microvasculature; differences among open-lung protective ventilation with pressure control ventilation, high-frequency oscillation and NIH protocol, and the use of positive end-expiratory pressure after a recruitment maneuver. Among the pre-eminent speakers will be Arthur Slutsky, MD, University of Toronto, St. Michael's Hospital; Gary F. Nieman, PhD, SUNY Upstate Medical University; John Marini, MD, Regions Hospital; Fernando Suarez Sipmann, MD, Fundacion Jimenez Diaz, and Robert M. Kacmarek, PhD, RRT, Massachusetts General Hospital. A special focus of the symposium will be the current research involving neurally adjusted ventilatory assist (NAVA), the emerging technologies that support the new paradigm and how NAVA is expected to influence clinical practice in the future. Specific presentations will include a physiologic approach to patient-ventilator interaction; utilization of cerebral signaling for feedback in mechanical ventilation. Christer Sinderby, PhD, University of Toronto, St. Michael's Hospital, and other major contributors in this growing area of interest will lead the presentations. "MAQUET has long supported research and development of new technologies related to ventilation," said Douglas Smith, vice president for MAQUET Critical Care. "We are pleased to sponsor this seminar which features some of the field's pre-eminent experts and cutting-edge topics. Through events such as this, MAQUET hopes to support the efforts of the dedicated clinicians who bring a high level of skill and commitment to respiratory care as well as to foster an educational dialogue among these specialists." For more information and registration, visit MAQUET at <https://programs.regweb.com/meridian/maquet2006/> or email us at worldclass.conference@maquet.com.

MAQUET manufactures and markets SERVO ventilators, combining advanced technology and high performance with versatility and ease-of-use. SERVO-i ventilators provide a stable, customizable platform for a full range of ventilator applications. They can easily and cost effectively be upgraded to keep abreast of advancing technologies and to meet a hospital's evolving needs and patient populations, from neonatal to pediatric and adult. MAQUET Critical Care is a division of MAQUET, a subsidiary of Getinge AB, based in Sweden, which employs some 6,600 employees worldwide with over \$1.5 billion in sales in 2004. For more information, visit maquet.com or email us at

customer.support@maquet-inc.com. For more marketing information, please contact Ed Coombs, MA, RRT, Director of Marketing & Product Management, 1-888-MAQUET 3 (ext. 2313).

News from Dolphin

The **Dolphin** 2000/3000 sensor line provides a full range of reusable and disposable pulse oximetry sensors, including Nellcor-compatible sensors. Dolphin Medical has developed more than 150 oximetry sensors, including high volume, low cost disposable sensors, high performance reusable sensors, specialty niche products and proprietary high performance products like Dolphin ONE and ESIX. All Dolphin compatible sensors have regulatory approval and meet or exceed manufacturer specifications for accuracy and are certified to be "device" compatible. The Dolphin ONE oximeters use a light to frequency converter in the sensor, creating a digital signal at the source. Conventional pulse oximeters digitize the signal remotely. The Dolphin ONE features advanced Digital Signal Processing, making it extraordinarily sensitive in low perfusion cases without compromising exceptional noise and motion immunity. Dolphin ONE products include the Pocket PC-based Dolphin Voyager, the Dolphin 2150 hand-held oximeter, and the Dolphin 2100 full feature bedside pulse oximeter. Contact dolphinmedical.com.

Transtracheal Systems Inc

Transtracheal Systems Inc manufactures and markets a complete line of products designed to improve oxygenation, ambulation, and quality of life for patients requiring continuous supplemental oxygen. Currently celebrating our 20th year of continuous operation, our core products are based primarily on the SCOOP line of transtracheal oxygen catheters. The catheter is easily introduced into the trachea by otolaryngologists utilizing the specially designed instruments found in the Fast Tract Procedure Pack. The procedure takes about 45 minutes, and is performed in the operating room using local and conscious sedation anesthesia. The Fast Tract procedure most closely resembles a mini-trach with the creation of skin flaps. The skin flaps are used to fashion an epithelialized tract down to the anterior wall of the trachea. A custom punch and stenting device have been developed to ensure uniformity of the tracheal opening, as well as patient comfort and safety during the overnight stenting period. The Fast Tract Starter Pack contains everything necessary for the surgeon to a Fast Tract procedure, and the first 90 days of supplies required by the patient to insure a smooth transition to transtracheal oxygen therapy. Advanced applications of transtracheal oxygen therapy include augmented ventilation (TTAV), alternative treatment of OSA, and weaning long term patients from mechanical ventilation. Information regarding reimbursement, on-site inservice, as well as video and CD-ROM descriptions of the Fast Tract procedure are available on request from tto2.com.

Online Education

Radiometer has selected HealthStream, Inc to develop and deliver Radiometer's online blood gas education program. The program is being delivered through a new education portal, Radiometer University, at www.radiometeruniversity.com. Radiometer is distributing its accredited and product-focused courses through HospitalDirect, a software tool that provides a gateway to HealthStream's 1,100-hospital network.

EXECUTIVE PROFILES

All information for Executive Profiles is provided by the manufacturers or their representatives. Information may have been edited for length, clarity and appropriateness for our audience of RT caregivers. It is the policy of Respiratory Therapy not to print registration marks or trademarks (®, ™). Products in this section are assumed to be the registered trademarks or products of the company featured, unless otherwise noted.

Event Medical Ltd.

Stephen Tunnell, RRT

Stephen Tunnell is CEO and President of eVent Medical.

Thank you for the opportunity to describe our company and products, but more importantly to talk about what sets eVent Medical and the Inspiration Ventilator System apart from others in our field. eVent Medical was founded by clinicians who had worked in the field of respiratory therapy and medical manufacturing. Many of us, myself included, lived through the days of converting fee for service institutions into cost centers. The DRGs made a lasting impact on the health care system and as a respiratory manager I was asked to do more with less. Medical manufacturers I like to say live down stream of the hospital pressures and therefore need to be focused on the needs of their customers to survive. When I worked for Puritan Bennett on the release and growth of the 7200 ventilator platform in the 80's, we knew it was important to assist our customers to be more effective at their jobs. We took it personally to make waveform analysis during mechanical ventilation easy to access. We believed that providing mode choices allowed customers an opportunity to practice in a way they wanted. Not in a way the manufacturer told them was best. Today at eVent Medical we make our customers' needs our top priority and we are embodying their feedback in everything we do. It doesn't hurt to also have walked in their shoes. However now that we are not in their shoes we are certainly in their lives asking them for guidance and input so we can understand what they value today.

The Inspiration Ventilator Platform offers customers a powerful Proportional Solenoid based breath delivery system with an actively controlled exhalation valve. This makes our product a true ICU ventilator with sophisticated algorithms and low work of breathing. The features and configurability of the Inspiration makes it one of the most flexible products in today's market. Our patented internal compressor and battery backup systems have already made our customers happy in the tornado belt. Unique features like our mini-web and patented lung recruitment technology allow clinicians the ability to embody the latest practice patterns of lung protective strategy while monitoring the ventilator from within their hospital intranet. Virtual reporting is possible by viewing ventilated patients real-time from within or outside the hospital. In situations where isolation is employed this tool allows the caregivers to monitor and trend their vent patients from outside the room. The unique patented design of the Inspiration ventilator system allows for variable gas sources and high pressure wall outlets are not necessarily a requirement. When you can free yourself from

cumbersome gas sources transporting your patient becomes easier. Where most ventilators become troublesome the Inspiration becomes easier to use. For example helium is now a gas used by many clinicians because of the lower gas density. It serves as a terrific carrier gas and because of its inert nature it is safe. The lower density of heliox mixtures is ideal for high resistance patients. Most ICU quality ventilators that employ hot film sensors go crazy in the presence of heliox. The Inspiration patented gas sensing technology does well and our design avoids wasting this expensive gas because we don't employ bleeding regulators. The overall size of our technology is small and many people are amazed we can do so much with such a small product.

We believe customer feedback and input has helped us offer terrific value and come so far in such a short period of time. We will never lose sight of the fact that a ventilator is a life support device that must be reliable and robust. We've put our money where our mouth is with a standard 5 year parts warranty in the USA. Biomedical training and user training is a key so we have offered those items free to our customers in the USA. It is not uncommon to find more customers at our facility in San Diego than employees. We provide 7-24 service and clinical lines with real people answering the phones. We love to partner with a community and involve ourselves in presenting materials at their professional meetings; materials not simply about us but about the emerging scientific trends. We actively sell in over 35 countries and promote the field of respiratory medicine whenever and wherever we can. With manufacturing located in Ireland, R&D in San Diego and Switzerland, sales, assembly and service all over the world we have a terrific opportunity to spread the good news. We are excited about the future products and services our company will add to our community, so don't hesitate to pick up the phone and call us. We will be sure to listen!

ZLB Behring

Paul Perreault

Paul Perreault is Executive VP of Worldwide Commercial Operations for ZLB Behring.

ZLB Behring is one of the world's leading pharmaceutical companies specializing in the manufacture of plasma products. Our comprehensive line of therapies includes treatment for hemophilia and other coagulation disorders, immunoglobulins for the prevention and treatment of immune disorders, treatments that inhibit the formation of blood clots, wound-healing agents used during major surgical procedures, and plasma expanders for the treatment of a variety of conditions such as shock, burns and circulatory disorders. Additionally, ZLB Behring operates one of the world's largest, fully-owned plasma collection networks.

ZLB Behring continues to invest heavily to ensure that we bring highly-safe, highly-pure products to market. One of ZLB Behring's premiere products, Zemaira [alpha-1 proteinase inhibitor (human)], is the only augmentation therapy for alpha1 antitrypsin (AAT) deficiency that is FDA-approved as "highly purified." Further, Zemaira provides a similar level of lung protection compared with other augmentation therapies.

Interestingly, a retrospective analysis of the pivotal clinical trial revealed that Zemaira is associated with 44% fewer COPD exacerbations compared to Prolastin. With that said, it should be noted that Zemaira, and all of the other AAT augmentation therapies, is a plasma-derived product, and therefore the risk of transmission of infectious agents, included viruses and, theoretically, the Creutzfeldt-Jakob Disease (CJD) agent, cannot be completely eliminated. Moreover, as with any pharmaceutical, the physician should weigh the risks and benefits of administration and discuss them with the patient prior to initiating therapy.

In addition to ensuring that patients receive a highly pure and convenient product, ZLB Behring has developed a unique and comprehensive patient care program for alpha patients. We have brought together the expertise, services and programs of AlphaNet and our exclusive distributor, Accredo, to help ensure that patients receive the highest quality care possible. ZLB Behring also serves the alpha-1 patient community by sponsoring monthly patient education days and support group meetings in collaboration with Alpha-1 Foundation.

IMPROVEMENTS AND PATIENT CARE

Top priorities at ZLB Behring center on providing safe, effective and innovative products and services to patients around the world. Zemaira is a good example since it was developed to offer Alpha-1 patients the next generation in convenience, safety, purity and efficacy.

R&D, NEW FEATURES, PRODUCT INPUT

ZLB Behring employs a collaborative approach to developing and marketing innovative therapies that meet patients' needs. All functional areas of the business are aligned with a single objective: providing safe, effective, innovative therapies for patients around the world. To that end, we continually incorporate our learning from the communities we serve into our strategic planning, which occurs at regular intervals throughout the year. Our long-standing relationships with individual patients, their families and with patient groups around the world are critical to this process, as well. Our product portfolio, one of the most robust in the industry, reflects this collaborative approach to R&D at ZLB Behring.

SERVICE FOR EDUCATION

ZLB Behring is committed to the detection of AAT deficiency among a largely undiagnosed population. Of the millions of patients with emphysema in the United States, it is estimated that as many as 100,000 have AAT deficiency. However, only 3,000 to 4,000 individuals have been diagnosed to date. By educating healthcare professionals, we hope to close this gap and ensure that every individual living with AAT deficiency is properly identified and properly treated.

ZLB Behring offers a comprehensive suite of health management services for patients and healthcare professionals who rely on our products, including product and disease-state educational materials, reimbursement support, and patient advocacy. Specifically, ZLB Behring's Making A Clear Diagnosis AAT detection program offers physicians all of the necessary tools to test their COPD patients. Another important medium for communicating information to patients and physicians is the internet. In fact, the product website recently won the silver award for "Best Overall Pharmaceutical Website" as ranked by e-Healthcare Leadership. Other programs include the ZLB

Behring Personal Inventory Management System that helps ensure patients a personal allocation of Zemaira in its full prescribed dose and at the prescribed dosing interval for a minimum of 52 weeks. Lastly, the ZLB Behring Assurance program allows eligible patients who rely on Zemaira to continue receiving treatment – even if they experience a lapse in their third-party, private health insurance. We believe strongly that these programs provide value to the alpha-1 community. These are just a sampling of the many services we offer to our healthcare and patient customers.

THE ROLE OF CLINICIANS

ZLB Behring views clinicians as extremely valuable partners in caring for patients with Alpha 1 and other conditions. At each step along the pathway of research and clinical development, and then on to launching and marketing a new product, healthcare professionals offer ZLB Behring their expertise, personal insights, and professional experience as guidance. ZLB Behring incorporates much of that guidance into our strategic planning.

NEW TECHNOLOGY

ZLB Behring is committed to innovation at every level of its business, including the area of manufacturing. For example, at present ZLB Behring is completing the licensure process for a state-of-the-art expansion of our manufacturing facility located in Illinois, which serves as the site for the production of Zemaira. Once this site is up and running, ZLB Behring's ability to manufacture Zemaira will be dramatically increased. This in turn will help ensure that all Alpha patients will have access to proper treatment.

INTERNATIONAL COMMUNITY AND MARKETPLACE

Because ZLB Behring is a global company, international marketplace dynamics play an important role in how we manage our business. No single product can effectively serve all patients around the world, as disease states vary from region to region depending on a host of factors over the course of time. Therefore, lifecycle management of products is a key theme in our global business strategy. We must ensure that introduction of a given product into a marketplace is planned so that patients have access to the therapy when they need it.

CONFERENCES, FORUMS, SEMINARS

These events are excellent opportunities to share and promote clinical education and learning within patient and medical communities. Recent studies, clinical data, and smart approaches to serving patients are all important to examine whenever possible. We must all work together to expand the body of knowledge about how best to prevent and treat disease.

Feasibility and preliminary safety study of a physiologically based solution for airway care in the neonatal intensive care unit

Daniel D. Woodhead, RRT; Diane K. Lambert, RN; Gorgi D. Rigby, RRT; Scott H. Scoffield, RPH; Susan E. Wiedmeier, MD; Gregory Snow, PhD; Vickie L. Baer, RN; and Robert D. Christensen, MD

ABSTRACT

Objective: Sterile saline is sometimes instilled into the endotracheal (ET) tube as part of ET suctioning. It is also sometimes instilled into the nasal passages of neonates on nasal CPAP, or used to moisten the mouth of a neonate who cannot oppose the lips. However, recent studies indicate that saline can inactivate important natural antimicrobial peptides in airway secretions. Thus, we produced a low-sodium, sterile solution for airway care, based on the electrolyte constituents of normal neonatal saliva. As a step toward determining the risks and benefits of using this new solution *vs.* 0.9% saline for airway care, we performed an open-label feasibility and preliminary safety trial.

Study Design: The feasibility of using the new airway solution was subjectively assessed by respiratory therapists and bedside nurses who used the solution for all airway care on 10 intubated neonates. Their responses were recorded on a specific bedside checklist. In addition, the immediate short-term intolerance of the solution was monitored by vital signs and oxyhemoglobin saturation. Potential systemic toxicity of the new solution was monitored by renal, hematological, and hepatic function tests, contrasting values among the ten study subjects with those of a cohort of 497 intubated neonates who received airway care with 0.9% saline.

Results: The new airway care solution was used, instead of 0.9% saline, in ten intubated neonates. These ten were intubated for mechanical ventilation for 2 to 55 days. No problems with

feasibility or immediate intolerance of the new solution were observed in any of the subjects. No significant adverse effects on vital signs or oxyhemoglobin saturation were observed and no new rashes were observed. No systemic adverse effects were seen; specifically the renal, hematological, and hepatic laboratory tests of the ten test subjects did not differ from the ranges predicted by the 497 patient cohort.

Conclusions: It was feasible to administer the new airway care solution as planned. The solution was well tolerated with no observed short-term adverse effects or systemic toxicity. On the basis of this pilot study we judge that a phase II, randomized, controlled trial can occur, comparing the risks and benefits of the new airway care solution, head-to-head with 0.9% saline, for the airway care of intubated neonates.

INTRODUCTION

Small amounts of sterile normal saline (0.9% sodium chloride) are sometimes instilled into the ET tube as part of the periodic care of intubated patients.¹ Instilling saline before suctioning through the ET tube is thought to help mobilize secretions and avoid occlusion or narrowing of the internal tube diameter by secretions. Sterile normal saline is also sometimes used to periodically clean the nasal passages of neonates on nasal CPAP or nasal cannula oxygen, and it is occasionally used to moisten the mouth of a neonate who cannot appose the lips because of an ET tube. Although these practices are routine in many neonatal centers, the risks and benefits of periodically instilling saline into the airways are debated.¹⁻³

A new potential problem derived from instilling saline into the airways came to light with a recent series of studies showing that saline inactivates the human beta-defensins and LL-37, substances that provide innate immunity in tracheal effluent, nasal secretions, and saliva.⁴⁻⁷ Thus, periodically instilling saline into the airways might impair airway antimicrobial defenses. Perhaps the practice of periodically instilling saline into the airways unwittingly reduces local innate immunity and contributes to the high incidence of airway and systemic infections in the NICU.^{8,9}

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To avoid this problem, we designed a new low-sodium solution for airway care, with a composition based on the constituents of unstimulated neonatal saliva. The present study was undertaken as a first step toward determining whether this new solution performs better than saline for airway care of intubated neonates. We reasoned that before a head-to-head trial with saline could be designed, a pilot study was needed to assess the feasibility and preliminary safety of the new airway care solution. Therefore we undertook an open-labeled, two centered, non-randomized trial, aimed at assessing the feasibility and tolerance of using this new solution for airway care of intubated neonates.

METHODS

Constituents of the airway care solution – The test solution was produced in the Research Pharmacy Department of Intermountain Healthcare, using the following reagents; sodium chloride, potassium chloride, calcium chloride, magnesium sulfate, potassium phosphate, human albumin, and sterile water. The specific concentrations of each constituent in the final solution are given in Table 1. The airway care solution was stored in the pharmacy department's refrigerated research cabinet at 36 to 46°F for up to four weeks per batch. In preliminary studies, aliquots of the stored solution were periodically sampled for bacterial culture (plating on Enriched Thioglycollate Medium), refractive index measurement (refractometer), and pH determination (Bristol-Myers Squibb Company). These tests were done weekly for four consecutive weeks. In no case was bacterial growth, change in refractive index, or change in pH (6.5) observed.

Study design – Ten newborn infants, on the first day of life, with an ET in place, constituted the study group. In each of these ten patients the new airway care solution was used instead of the standard 0.9% NaCl solution for all airway care. Patients were deemed eligible to participate if they were delivered at McKay-Dee Hospital or LDS Hospital and had an ET tube inserted for the purpose of mechanical ventilation. The new airway care solution was to be instilled at intervals determined by the respiratory therapist and bedside nurse, in a manner in keeping with their usual practice for neonates with an ET tube in place. A protocol was followed for the instillation and suctioning maneuvers. The protocol involved assessing the need for suctioning, rather than using a set-time schedule for suctioning. Briefly, a Ballard inline suction catheter was used with suction pressure between 80 and 100 cmH₂O. The suction depth was 0.5 cm past the ET tube tip for infants <1000 grams and 1.0 cm past the tip for those >1000 grams. The volume of airway care solution to be instilled was set at approximately 0.5 mL. Once the catheter was in place, suction was applied for 2 seconds and then the catheter was withdrawn with suction applied. Preoxygenation and reoxygenation were used as indicated. For each subject, the study was concluded when the patient was extubated, but data on possible systemic effects were tabulated through discharge to home.

Feasibility assessment – At the end of every 12 hr shift, each respiratory therapist and bedside nurse who had administered the new airway care solution was asked to carefully consider, and recorded on a checklist, specific issues relating to feasibility of using the new airway care solution.

Signs of immediate intolerance – Respiratory therapists and bedside nurses who administered the airway care solution were

asked to observe, and report on a checklist, possible signs of immediate intolerance of the solution. The specific immediate intolerances sought were coughing, oxyhemoglobin desaturation, bradycardia, tachycardia, hypotension, hypertension, or appearance of a cutaneous rash.

Signs of systemic toxicity – Laboratory tests of renal, hematologic, and hepatic function, from the ten study subjects, were compared with values from the historic cohort comparison group, who all received airway care using 0.9% saline. The cohort was comprised of all patients with an ET tube, with a date of birth from January 1, 2003 through December 31, 2004, cared for in the McKay-Dee NICU. All such infants received airway care with normal saline. Information on the comparison cohort was obtained as a de-identified limited data set from the electronic medical record. The program used for data collection and extraction is a modified subsystem of "clinical workstation." The 3M Company (Minneapolis, MN) approved the structure and definitions of all data points for use within the program. Data were collected from the electronic medical record, case mix, pharmacy, and laboratory systems. Trained and designated clinical personnel enter additional data, and data were managed and accessed by authorized data analysts. For tabulation of the number of days an ET tube was in place, calendar days (not actual hours) were used, as listed in the electronic medical record. The Intermountain Healthcare Institutional Review Board approved the study protocol and parents of the study patients provided written informed consent.

RESULTS

Study subjects and cohort – Between February and September of 2005, 13 families of neonates newly admitted to the NICU, with an ET tube in place, were approached with the invitation to learn about the airway care solution study. These families were approached because their neonate qualified for this study and was not already enrolled on another research study protocol. Ten families consented to have their neonate participate in this study. All ten of the consented patients received the new airway care solution, rather than sterile 0.9% saline. All ten finished the study, receiving the new solution for all airway care until endotracheal extubation.

Feasibility and signs of immediate intolerance – In each of the ten study subjects, every instillation of the airway care solution was given as planned, and subjectively judged and feasible by those who administered the solution. No instillations of the new airway care solution were held or aborted because of apparent intolerance of the solution. In every case where the airway care solution was instilled, the respiratory therapist or bedside nurse judged that the solution was well tolerated. No instillations were aborted because of oxyhemoglobin desaturation, bradycardia, tachycardia, hypotension, or hypertension. No new cutaneous rashes were reported.

Signs of systemic toxicity – Four hundred seventy-nine neonates served as a cohort for comparing whether the study solution might have resulted in systemic abnormalities; specifically abnormalities of renal, hematological, or hepatic function. These 479 were born in the period January 1, 2003 through December 31, 2004, and all received endotracheal intubation for mechanical ventilation, and all received airway care with sterile 0.9% saline. Sixty-five percent of these (310/479) were intubated for three days or less, but the range

Table 1. The constituents of the airway care solution are compared with 0.9% NaCl and with normal unstimulated neonatal saliva (mean±SD, [22]).

	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)	Ca (mEq/L)	Mg (mEq/L)	PO ₄ (mEq/L)	Protein (mg/dL)
0.9% NaCl	154	0	154	0	0	0	0
Neonatal Saliva	8±3	22±4	34±8	3.6±1.0	1.2±0.2	3±1	194±120
Airway Care Solution	8	24	36	3.7	1.2	3	194

Table 2. Demographic features of the study subjects and the historic cohort.

Patient #	Birth weight (g)	Gestational age (w.d)	Gender	Race/Ethnicity	Days on Ventilator
1	1062	27.1	M	White	42
2	1026	30.2	M	White	2
3	3779	36.6	M	White	2
4	3280	37.3	M	White	3
5	2832	36.6	M	White	3
6	600	26.4	M	Hispanic	21
7	1459	29.5	F	White	2
8	550	25.0	F	Black	55
9	2423	35.1	F	White	3
10	1198	28.4	M	White	8
Study (n=10)	1329 550-3779 (median, range)	31.1± 4.5 (mean, SD)			3 (2-55) (median, range)
Cohort (n=479)	2111±203 (mean, SD)	33.1±4.0 (mean, SD)	60% M	84% White 12.5% Hispanic 0.5% Black 0.5% American Indian 0.5% Pacific Island 1% Asian 1% Other	3 (1-88) (median, range)

g=grams; w.d=weeks.days; M=male; F= female; SD = standard deviation.

Table 3. Laboratory tests among the study subjects and the historic cohort.

Patient #	Creat >1.5 mg/dL	Platelets <100,000 /μL	ANC <1,000 /μL	Total bili >10 mg/dL	Total bili >15 mg/dL	Direct bili >2.0 mg/dL	ALT >45	AST >60
1	No	No	No	No	No	Yes	No	No
2	No	No	No	No	No	No	No	No
3	No	No	No	No	No	No	No	No
4	No	No	No	No	No	No	No	No
5	No	No	No	No	No	No	No	No
6	No	Yes	No	No	No	No	No	No
7	No	No	No	No	No	No	No	Yes
8	No	Yes	No	No	No	No	No	No
9	No	No	No	Yes	No	No	No	Yes
10	No	No	No	No	No	Yes	No	Yes
Study (n=10)	(0%)	(20%)	(0%)	(10%)	(0%)	(20%)	(0%)	(30%)
Cohort (n=497)	(2.2%) 11/497	(11.3%) 56/497	(8.5%) 42/497	(60.4%) 300/497	(20.1%) 100/497	(5.2%) 26/497	(7.6%) 38/497	(59.8%) 297/497

23. Creat, creatinine; ANC, absolute neutrophil count; bili, bilirubin; ALT, alanine amino transferase; AST, aspartate amino transferase.

was from one to 88 days. Ninety-eight percent (469/479) of the cohort and all 10 of the study subjects survived to be discharged home. Demographic features of the airway care solution recipients and the cohort controls are given in Table 2. Table 3 lists laboratory findings during the entire hospitalization among the ten study subjects and the cohort patients. The table lists whether an elevated creatinine, a low platelet or neutrophil count, or an elevated total or direct bilirubin, ALT or AST were observed during the hospitalization. Compared with the cohort, the study subjects did not have a higher than anticipated occurrence of abnormalities of these laboratory values.

DISCUSSION

Tracheal secretions, nasal secretions, and saliva contain potent salt-sensitive cationic antimicrobial peptides.^{4,7, 10-14} These antimicrobials include LL-37, β -defensin-1, and β -defensin-2. Each of these undergoes rapid and complete inactivation of their microbial killing properties when NaCl concentrations exceed about 80 meq/L.¹⁴⁻¹⁸ In fact, the high sodium and chloride content of saliva and airway surface liquid in patients with cystic fibrosis inactivates these salt-sensitive antimicrobials in the saliva and airway liquid, thus partly explaining the high incidence of airway infections in these patients.¹⁴⁻¹⁶

Small and ill neonates with an ET tube in place have a very high rate of nosocomial infections.^{8,9} Many such infections are with organisms of low virulence in healthy adults, such as *Candida albicans* and *Staphylococcus epidermidis*. Low IgG concentrations are one factor predisposing preterm neonates to these infections,^{8,9} but poor immunologic barrier function in the mouth and trachea, caused by the presence of an ET tube, likely also contributes to this predisposition. In addition, the recent studies on salt-sensitive antimicrobial peptides in the airways suggest that caregivers might further weaken the innate defenses of these neonates by the repeated instillation of 0.9% sodium chloride into the trachea, nose, or mouth.

Normal human saliva inhibits colonization of the oral cavity by *Candida albicans*.¹⁹ In ill neonates, oral candidiasis may be a step in the pathogenesis of systemic candidiasis, a condition with a high mortality rate.²⁰ A Cochran Library Review by Austin and Darlow indicates that there is insufficient evidence to support the use of prophylactic oral antifungal agents in very low birth weight infants to reduce oral candida. They state that reducing oral candida among ill neonates is indeed worthwhile, but new ways of doing this are needed.²¹ Taken together, these observations raise the possibility that the practice of periodically instilling 0.9% saline into the ET tube, nose, or mouth, weaken the airway antimicrobial defenses.¹⁻³ Certainly the damaging effects of saline instillation on airway immunity need more study.

We developed a new low-sodium solution for airway care, the makeup of which is based on physiologically relevant constituents.²² We postulated that if a sterile liquid is wanted to assist in suctioning the ET tube, nose, or mouth, this new solution would be better than the 0.9% saline used currently. Specifically, we postulated that the new airway care solution would not induce saline-inactivation of β -defensins and LL-37 in the airway, as occurs when saline is instilled. We postulated further that patients receiving the new airway care solution would have less predisposition to developing pathogenic organisms and inflammatory cells in their tracheal aspirates. However, we reasoned that before studies could be done to test

those postulates, a pilot study was needed to examine feasibility and preliminary safety. Therefore, we conducted this ten-patient open-labeled trial. The pilot study had three goals; to assess feasibility, short-term tolerance, and adverse systemic toxicity of the new airway care solution.

The feasibility of using this new airway care solution was assessed by asking experienced respiratory therapists and bedside NICU nurses who used the new solution to pay careful attention to whether it could be given as planned, in a manner identical to the way sterile saline is used. The short-term intolerance of the solution was assessed by asking the respiratory therapists and bedside nurses to attend specifically to coughing, desaturations, bradycardia, tachycardia, hypotension, hypertension, and appearance of new rashes after using the new solution. Systemic toxicity of the new solution was assessed by comparing renal, hematological, and hepatic function tests of the ten recipients with those of 479 intubated historic controls who received airway care with 0.9% saline. From these pilot observations, we judge that the new airway care solution is feasible to administer, and that it has no dominant short-term intolerance or short-term systemic toxicity. Clearly, much additional investigative work remains to be accomplished before the benefits and risks of this new airway care solution are known. However, based on the outcome of the present pilot study, we maintain that a phase II, randomized, head-to-head comparison study with 0.9% saline can now be undertaken.

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The Transplantation of Bone Marrow-Derived Stem Cells and the Treatment of Emphysema

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INTRODUCTION

Harboring the potential to restore human health and improve an overall quality of life, stem cell research has become a source of both promise and controversy for millions of individuals. Since the first isolation and culturing of human stem cells in 1998, scientists have been attempting to differentiate these cells into the more specialized types needed for transplantation into ailing patients. Known as regenerative medicine, this field of study holds significant promise in treating numerous diseases involved in the dysfunction or necrosis of specific cell types.

Recently, the transplantation of bone marrow-derived stem cells in patients with emphysema has become a topic of interest. The biological intricacy and inadequate proliferation of the lung, however, leave this area of study vaguely understood.¹ This paper provides an overview of the complexities of pulmonary stem cells, a description of the clinical presentation of emphysema, and a discussion on the potential benefits of bone marrow-derived stem cell transplantation in the treatment of emphysema.

PROPERTIES OF STEM CELLS

The primary purpose of regenerative medicine is to culture and nurture cells in an attempt to correct injuries in various tissues of the body. Stem cells, the most primitive of all cells, possess the following three distinct characteristics that make this possible:

- Stem cells are unspecialized
- Stem cells give rise to specialized cells
- Stem cells are capable of long-term self-renewal¹

Stem cells are unique in that they are unspecialized. With no tissue specific structures, these cells cannot assist in distinct functions like gas exchange or the transmission of nerve impulses.¹ Through differentiation, however, they can give rise to specialized cells that are able to carry out these functions.

Stem cells are classified according to the degree to which they can differentiate. Totipotent stem cells have the ability to give rise to any cell in the body, including extraembryonic tissues.² Formed at the beginning stages of human development, a totipotent cell remains unspecialized for several cellular divisions and produces additional totipotent cells. Approximately four days after fertilization, the totipotent cells begin to specialize and become pluripotent.²

Pluripotent stem cells give rise to many of the tissues necessary for human development. These cells have the ability to form the ectoderm, mesoderm, and endoderm of a growing embryo.³ They are unable to form a fully functioning individual, however. As pluripotent cells continue to divide, they specialize into multipotent or unipotent cells.

Multipotent cells become the progenitors, or originators, of specific cell lines. For example, a multipotent blood stem cell can further differentiate into an erythrocyte or leukocyte.² After a series of divisions, these cells become permanently differentiated and committed to a specific function.

Another key component to the reparative quality of stem cells is their ability to proliferate. Proliferation is a rapid succession of cellular divisions. This long-term self-renewal provides researchers with a renewable source of cells for experimental purposes. In addition, it protects the lung following trauma through the production of the telomerase enzyme. Telomerase resets the cells' biological clocks, thus preventing apoptosis. Most recently, human cells treated with the gene for telomerase have been living for several hundred proliferative cycles. Consequently, these treated sources are void of signs of aging and transformation.

LOCALLY DERIVED STEM CELLS OF THE LUNG

The lungs of an average adult are comprised of 70 square meters of diffusible surface.⁴ To aid in the process of gas exchange, some portions of this surface are remarkably thin. This makes the lung a constant target for injury and disease. For this reason, systems of tissue renewal are a necessity. Studies have

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shown that stem cells serve as one of these systems.

The lung provides an intricate arrangement of stem cells according to the changing anatomy of the airway. Basal cells in the proximal airways serve as regenerative cells. Studies have shown that these basal cells accumulate at the site of injury and that their transitional makeup is similar to that of goblet cells.⁴ One additional study showed that these cells produced various cellular phenotypes following tracheal injury, thus correcting the injury.⁴ Mucous secreting cells in the trachea and bronchi have demonstrated similar effects.

Certain Clara cells influence regeneration in the respiratory and terminal bronchials. Normal Clara cells contain cytochrome P-450, the microsomal membrane protein responsible for cleaving and activating the majority of toxic compounds.⁵ Researchers recently found that a subset of these cells containing Clara cell secretory protein (CCSP) exhibits resistance to several airway toxins.⁴ This finding suggests that the cells containing CCSP have stem cell like properties, or mutations in the P450 gene, that contribute to airway homeostasis through proliferation and differentiation.

On an alveolar level, type II pneumocytes possess proliferate properties. Studies have shown that these cells are capable of restoring epithelial tissue following damage by environmental toxins and other predecessors of lung injury.⁴ Such a response is stimulated by the destruction of type I pneumocytes and by inflammatory responses to particle inhalation.⁴

Stem cells as an intrinsic form of protection are beneficial in repairing minor pulmonary injuries. Complications arise, however, when the lung faces more traumatic injuries such as emphysema.

CLINICAL PRESENTATION OF EMPHYSEMA

Emphysema is the permanent enlargement of the airways accompanied by the degradation of respiratory tissue. This causes alveolar tissue to lose its ability to stretch and recoil, resulting in the entrapment of air and the development of pulmonary hyperinflation. The destroyed air sacs become incapable of exchanging oxygen and carbon dioxide, which serves as a precursor of airway obstruction and collapse.⁶

The most common cause of emphysema is cigarette smoking. Recent studies contribute 80-90% of COPD related deaths to smoking.⁷ Cigarettes and other environmental pollutants cause the release of chemicals from within the lungs that damage the alveolar walls.⁷ This occurs through the destruction of the lung structural protein, elastin. For example, smoking stimulates macrophages and neutrophils to accumulate in the lung. This accumulation of inflammatory cells promotes the production of the enzyme elastase, which destroys elastin.

Another cause of emphysema involves a deficiency of alpha 1-antitrypsin (AAT). AAT inhibits the activity of elastase generated by neutrophils in the lung resulting in alveolar destruction.⁷ Approximately 100,000 Americans develop emphysema as a result of this deficiency and another 25 million Americans carry a single deficient gene that may pass to their children.⁷

Symptoms of emphysema include shortness of breath, chronic cough (with or without sputum production), wheezing, and a limited exercise tolerance. Radiographic findings show a

lowered diaphragm, increased angles of the costophrenic sinuses, an enlarged retrosternal space, and a decrease of the heart width on a PA film. Following the progression of the disease, additional symptoms may include weight loss, anxiety, and fatigue.⁸ Emphysema and chronic bronchitis often co-exist to comprise chronic obstructive pulmonary disease (COPD).⁸

As emphysema progresses over time, the degree of tissue injury continues to increase which compromises the lung's ability to repair itself through stem cell proliferation. To account for this loss in protective ability, researchers are attempting to repair damaged portions of the lung through extraneous stem cell transplantation.

SOURCES FOR STEM CELL TRANSPLANTATION

Stem cells for transplantation can be harvested from both adult and embryonic sources. Embryonic stem cells form the inner portion of a blastocyst, or early embryo, that is fertilized *in vitro*.¹ Under careful observation, embryonic stem cells are separated and grown under conditions in which they remain undifferentiated. This cell source has the potential to become any cell type in the body. In a process known as direct differentiation, scientists can target these cells into more specific types.¹ Although embryonic stem cells are a plentiful and purified source for transplantation, their use in many studies has been delayed due to moral arguments.

Adult stem cells are derived from bone marrow, blood, skin, etc. Although the adult source is more difficult to isolate and culture, these cells are harvested harmlessly from live donors, thus circumventing ethical concerns. In the past, researchers believed that adult stem cells could only produce a particular cell type. Recent studies, however, have demonstrated that adult stem cells are capable of transdifferentiation. Transdifferentiation enables a cell to form a new cell distinct from its specific function.⁹

These new and somewhat controversial findings have widespread implications in regenerative respiratory medicine. For instance, a group of researchers from the Laboratory of Molecular Cardiology in Bethesda, Maryland¹⁰ have been able to induce the differentiation of murine skeletal muscle cells into active, beating cardiomyocytes. These cells are responsible for the pumping work of the heart and are known to cease dividing soon after birth. When these labeled neo-cardiomyocytes were injected *in vivo* into cardiac compromised mice they localized in the heart within two days and became fully functioning within three months. Although these cells did not differentiate into lung tissue, these results merely suggest that the possibility of transdifferentiation from one cell type to another may have broader applications. For example, the fact that this mechanism is productive in the heart supports the hypothesis that a similar mechanism would be productive if properly implemented in the lungs.

TRANSPLANTATION OF BONE MARROW-DERIVED STEM CELLS

Researchers have had great success following the transplantation of bone marrow-derived stem cells. In a study by Suratt and co-workers,¹¹ a group of six female participants received allogeneic, bone marrow-derived stem cell transplants from a random group of male donors. Tissue samples from these female patients were examined 50 to 463 days following transplantation. Following lung biopsy, the slides were stained

and observed for the presence of male donor cells. In the same study, additional staining with platelet endothelial cell adhesion molecule (PECAM) and cytokeratin showed a particular alveolar dominance of stem cells. This suggests that the most regenerative airways are the most distal. These results also show that regeneration can take place following stem cell transplantation and that these transplanted cells can play a therapeutic role in the restoration of disease-damaged lung tissue.

Kotton, Sumner, and Fine¹² transplanted single marrow stem cells from male donors into a group of marrow-ablated female mice. Upon observation, the transplanted cells were identified by the co-presence of the Y-chromosome and specific epithelial markers. After 11 months, the incidence of transplanted cells had reached 20%. Later studies using CD34(+)Lin(-) cells showed that proliferation of alveolar type II cells was apparent five days after transplantation and abundant within two months.¹² With a theoretically limitless ability to divide and a low risk of immune system rejection, this source serves as an innate mechanism of repair for the body.

THERAPEUTIC BENEFITS FOR EMPHYSEMA PATIENTS

Bone marrow-derived stem cells have proven to aid in the reparative function of lung specific cells and to promote the local production of stem cells. Recently, Halleux, *et al*¹³ demonstrated that bone marrow-derived mesenchymal cells have the ability to undergo regenerative doubling (up to twenty passages) and multi-lineage differentiation, two of the essential characteristics of any stem cell.

In a study conducted by Yamada and associates¹⁴ at the Tohoku University School of Medicine, lung injury was induced on a group of bone marrow-suppressed mice. Following the injection of lipopolysaccharide (LPS), a component in gram-negative bacteria cell walls, the mice experienced emphysema-like tissue damage. The mice were then transplanted with green fluorescent protein (GFP)-positive bone marrow. Results showed a significant decrease in the presence of emphysematous lesions in the lungs. This suggests that bone marrow-derived stem cells are useful for repairing the epithelial and endothelial damage caused by emphysema.

CHALLENGES OF STEM CELL TRANSPLANTATION

The field of regenerative medicine is continuously evolving and encountering new challenges. A greater understanding of the pathological timing of emphysema is needed to introduce transplanted stem cells successfully.¹ Researchers must also be able to maintain a plentiful and relevant source of stem cells that are appropriate to the diversity of airway structures. The cellular intricacy of the lung makes this especially difficult.

A more comprehensive knowledge of lung morphogenesis is also necessary. In patients with emphysema and other chronic lung diseases, the anatomical "blueprint" of the lung is destroyed. Therefore, researchers depend on the fact that transplanted stem cells "know" where to go in order to restore the complex architecture of the lung.¹ To clarify the mechanics of this process, thorough research is currently being conducted to determine how pulmonary tissue differentiates during development.

CONCLUSION

The basis of regenerative medicine lies in the fact that stem cells possess several unique properties. Furthermore, locally derived stem cells of the lung differ according to the anatomic structure of the lung and serve as a defense mechanism against pulmonary injury. The trauma associated with emphysema disables this defense mechanism. The hope for therapeutic success lies in the evidence that bone marrow-derived stem cells are capable of proliferation once transplanted in the lung and that their transplantation is beneficial in the treatment of pulmonary injury. Although several laboratory studies have proven successful, a greater understanding of the clinical outcomes of this subject is necessary. With future attention, however, it is hopeful that additional efforts will bring to light a more solid relationship between the lungs and regenerative medicine.

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Daily Practice With SmartCare in a Difficult to Wean Patient

J.C. Lewejohann

BIOTRAUMA AND GOALS FOR WEANING

The advances in critical care medicine have resulted in more patients surviving calamitous diseases. A considerable amount of these patients require mechanical ventilation for extended periods. Patients requiring respiratory support more than fifty days are still not a rarity, even today, in our ICU.

Weaning procedures continue to gain more importance in the Intensive Care Unit, combined with increasing knowledge about the detrimental effects of mechanical ventilation and iatrogenic lung injury resulting in a so-called biotrauma. Apart from the pulmonary effects of ventilator induced lung injury, the systemic effects, eventually resulting in multiorgan dysfunction syndrome, become more and more evident today. The trend, therefore, in modern respiratory therapy, is increasingly moving towards assisted forms of mechanical ventilation.

The main goal for treatment of patients with respiratory failure and the necessity for ventilatory support is to minimize the potential lung injury induced by ventilation itself. Therefore, as the saying goes, weaning begins with intubation. It's a training process for respiratory muscles, much like athletes do in training to improve their performance. If you rest the weaning of your patient he or she will become lazy.

In consideration of the current pathophysiologic understanding of the acute lung injury, spontaneous breathing modes should be used as much as possible in the course of critical illness.

Adjusting the ventilator settings frequently, according to the changing demands and needs of the patient, is a major problem in the daily routine of almost every ICU.

WHAT IS "SMARTCARE?"

With SmartCare, Dräger Medical introduced a new weaning technique integrated into their EvitaXL ventilator, developed from a knowledge-based weaning system resulting from a protocol developed by Brochard and coworkers. This approach

includes a special innovation of a derived pressure support mode that lets the ventilator react to the patient's demand for an adjusted ventilatory support every two to five minutes. It's the first ventilator with an integrated circuit that includes the patient and his ventilator. SmartCare is not only a computer system but, also, a reliable bedside-tested clinical protocol for weaning that aims for comfortable recovery from respiratory failure.

WEANING BEFORE KNOWLEDGE-BASED WEANING AT OUR SICU

Our previous weaning technique was based on periodical clinical judgments of the patient's respiratory status, reduction of sedoanalgesics, early use of pressure support ventilation, CPAP and ventilator independence, including spontaneous breathing trials with a T-piece.

The main problem today with the consuming weaning technique is very obvious: the requirement for considerable staff in a frequently understaffed ICU environment. Nevertheless, our surgical ICU is comparatively well staffed, in contrast to many other Intensive Care Units, especially in smaller sized hospitals.

Therefore, like other ICU teams we appreciate a knowledge-based weaning system, like SmartCare, for daily clinical use.

A CHALLENGE TO WEAN THE PATIENT

This report outlines the application of SmartCare in a difficult to wean patient:

A 50 year old man, suffering from severe protracted ARDS, which resulted from aspiration of gastric secretion and subsequent pneumonia. The aspiration occurred after esophageal perforation, following dilation and stenting of a stenosis, resulting from an achalasia.

The clinical course of the patient was complicated by recurrent phases of a severe candida and staphylococcus sepsis despite the use of adequate antifungal and antibiotic therapy with periodic microbiological testing at regular intervals. He was ventilator dependant with high PEEP-levels and high FiO₂,

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Specifications											
Time	0:00	2:00	5:00	8:50	9:10	10:30	11:45	13:30	18:00	21:20	23:40
Setting	BP 12	BP 12	BP 10	BP 10	BP 12	BP 14	SC	SC	SC	SC	BP 12
FO ₂	35	35	30	30	45	40	40	40	40	40	40
p _{max}	24	24	24	23	25	25	30	36	36	36	28
PEEP	5	5	5	5	5	5	5	5	5	5	5
f	40	37	44	40	40	47	34	35	32	36	27
I:E	1:2	1:2	1:2	1:2	1:2	1:2					
MV		17.6	19.3			12.3	18.5	21.3	22.9	17.2	12.3
V _t		0.65	0.6			0.65	0.78	0.6	0.57	0.75	0.65
PaO ₂	101	101	77.1	50.4	65.9	103	112	126	122	127	144
PaO ₂ /FO ₂	288.6	288.6	257.0	168.0	146.4	257.5	68.0	315.0	305.0	317.5	360.0
PaCO ₂	39.6	38.7	37.5	36.4	36.0	38.1	38.0	38.0	36.0	33.0	36.4
pH	7.4	7.4	7.44	7.44	7.44	7.4	7.44	7.39	7.44	7.46	7.42
SaO ₂	98.6	98.5	96.7	88.3	94.3	98.6	99.1	99.3	97.6	99.6	99.7
HCO ₃ ⁻	24.1	24.2	25	24.5	24.8	24.62	24.5	23.3	24.6	24.2	25
BE	-0.1	0.1	1.2	0.9	0.4	-0.8	0.9	-1.3	-0.1	-0.3	-0.7

Table 1: Patient ventilator settings and results of blood gases in the course of a day with SmartCare (BP=BIPAP; SC=SmartCare)

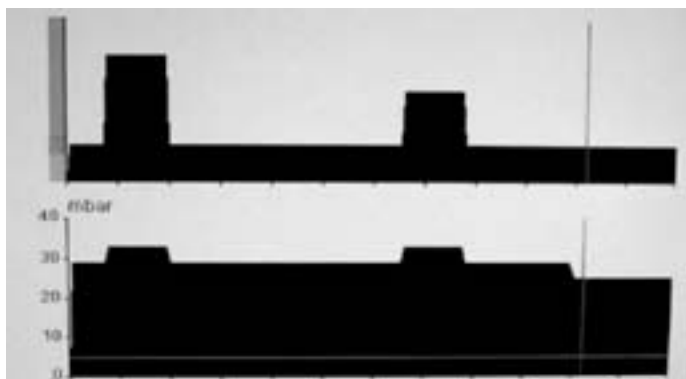


Fig. 1: The challenge to wean a patient in the comfort zone (lower left, shaded portion).

requiring positioning therapy using the prone position and kinetic therapy over a period of about 60 days.

Frequent dramatic deteriorations of his respiratory situation with repeated phases of septic shock combined with a multiple organ dysfunction syndrome and the need for catecholamines, renal replacement therapy and liver dialysis prolonged his ICU stay considerably.

First attempts to wean the patient were commenced after 60 days of invasive ventilation. The patient had comparatively high respiratory rates starting the weaning process resulting from respiratory muscle weakness. Nevertheless, during the SmartCare period, the respiratory rates varied in the range of those with BIPAP ventilation, with a slight trend to lower frequencies.

Tidal volumes stayed within the same range after the change and paCO₂ remained nearly unchanged. Despite of the change from BIPAP to SmartCare there seemed to be no relevant increase of respiratory workload for the patient. We even saw a slight increase of the oxygenation index during the SmartCare period. While using SmartCare, the patient remained breathing, for the most part, in the so-called “respiratory zone of comfort” (Fig. 1).

In summary, it can be said that in this patient, who previously needed a long time interval of mechanical ventilation with strong ventilator settings, SmartCare appeared to work without any detrimental effect on oxygenation and paCO₂. Also, the respiratory workload of the patient seemed not to increase. Furthermore, the patient remained in the “respiratory zone of comfort” for a long time.

OUR IMPRESSIONS ABOUT SMARTCARE

Weaning should be considered a process in which the goals are to promote ventilator independence under preservation of the functional status. The choice of weaning technique is an important decision in the convalescence of the respiratory muscles and reconditioning.

Traditional methods of weaning, like progressive reductions in the number of fully supported breaths [SIMV], continuous positive airway pressure [CPAP] or spontaneous breathing trials [SBT] lack the continuous feedback of the ventilator to the patient's needs – they are mechanical and not adjustable to the patient.

From our experience, SmartCare seems to meet all requirements for a knowledge-based weaning system, even in long-term ventilated patients. It saves considerable time in the strenuous weaning process. The outstanding advantage of this ventilator-integrated weaning system is its demand for fewer ICU staff. Even if the staff of an ICU makes every endeavor possible to wean a patient from the ventilator, the respiratory therapist cannot be at the patient's bedside every minute of the day as SmartCare can.

Therefore, SmartCare can minimize the momentous consequences of mechanical ventilation to the lung and contribute to the reduction of systemic effects of ventilator induced lung injury and, thus, the biotrauma.

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The Influences of Positive End Expiratory Pressure (PEEP) Associated With Physiotherapy Intervention in Phase I Cardiac Rehabilitation

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ABSTRACT

Purpose: To evaluate the effects of positive end expiratory pressure and physiotherapy intervention during Phase I of cardiac rehabilitation on the behavior of pulmonary function and inspiratory muscle strength in postoperative cardiac surgery.

Methods: A prospective randomized study, in which 24 patients were divided in 2 groups: a group that performed respiratory exercises with positive airway expiratory pressure associated with physiotherapy intervention (GEP, n = 8) and a group that received only the physiotherapy intervention (GPI, n = 16). Pulmonary function was evaluated by spirometry on the preoperative and on the fifth postoperative days; inspiratory muscle strength was measured by maximal inspiratory pressure on the same days.

Results: Spirometric variables were significantly reduced from the preoperative to the fifth postoperative day for the GPI, while the GEP had a significant reduction only for vital capacity ($P < .05$). When the treatments were compared, smaller values were observed in the GPI for peak flow on the fifth postoperative day. Significant reductions of maximal inspiratory pressure from preoperative to the first postoperative day were found in both groups. However, the reduction in maximal inspiratory pressure from the preoperative to the fifth postoperative day was significant only in the GPI ($P < .05$).

Conclusions: These data suggest that cardiac surgery produces a reduction in inspiratory muscle strength, pulmonary volume, and flow. The association of positive expiratory pressure with physiotherapy intervention was more efficient in minimizing these changes, in comparison to the physiotherapy intervention alone. However, in both groups, the pulmonary volumes were

not completely reestablished by the fifth postoperative day, and it was necessary to continue the treatment after hospital convalescence.

Cardiac surgery reverts symptoms for individuals with specific cardiopathologies and measurably increases their chances of survival and quality of life.¹⁻³ However, pulmonary complications are quite frequent and represent an important cause of morbidity and mortality for patients undergoing cardiac surgery with cardiopulmonary bypass.^{2,4-6}

These patients can develop various degrees of a systemic inflammatory response syndrome due to factors such as surgical trauma, contact of blood with nonendothelial surfaces of the bypass circuit, and alterations known as reperfusion post-cardiopulmonary bypass lesions, mainly affecting the cardiac and pulmonary regions.^{2,4-6}

In the pulmonary region, there is an increase in extravascular water with alveolar filling caused by inflammatory cells, which leads to the inactivation of the pulmonary surfactant and collapse of some areas, modifying the pulmonary ventilation/perfusion relationship, with resultant increases in the respiratory effort during the postoperative (PO) period.^{7,8}

In spite of modernization of procedures, cardiac surgery can damage pulmonary function, with decreases of respiratory muscle strength and spirometric measurements occurring postoperatively, in addition to the occurrence of atelectasis in more than 90% of the patients.⁹

Reduction in oxygenation,¹⁰ pulmonary function,^{11,12,13,14} and respiratory muscle strength,^{4,5,9,12} as well as radiological changes such as atelectasis^{8,12,15} have been cited as common alterations in postoperative cardiac surgery. The reduction of respiratory muscle strength, resulting from direct or indirect lesion of respiratory muscles during surgery and the secondary diaphragmatic dysfunction due to phrenic nerve lesion, has also been related to reduced pulmonary function tests, worsened gas exchange, and increase in the rate of pulmonary

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complications.^{4,5,9,12} Considering this, some authors^{8,15-19} have investigated the application of different physiotherapeutic treatment techniques in an attempt to minimize the alterations in the respiratory and cardiovascular system and thereby reduce the incidence of complications.

Physiotherapy intervention in phase I of cardiac rehabilitation (PPI) is routinely performed with patients who have undergone cardiac surgery.^{11,13,18,19} The application of deep breathing exercises, cough stimulation, thumping and vibration of the rib cage, and continuous positive airway pressure may prevent further deterioration in pulmonary function and reduce the incidence of pulmonary complications.¹⁸ However, Jenkins et al¹⁹ observed that deep breathing exercises, thumping and vibration of the rib cages, and cough stimulation did not result in significant increases in spirometric measurements when compared to the control group.

With the identification of communication between the respiratory bronchioles in human lungs, some authors have concluded that collateral ventilation is important in normal pulmonary function¹⁷ and thereby confirm that the application of positive end-expiratory airway pressure (PEEP) can promote a more homogenous distribution of pulmonary ventilation through interbronchial collateral channels and prevent expiratory collapse.¹⁷ Thus, PPI associated with the application of PEEP through a circuit of expiratory positive airway pressure (EPAP) using a face mask coupled to a PEEP valve could be effective in minimizing complications that occur postoperatively after cardiac surgery.

Campbell et al²⁰ found that PEEP assists with the removal of secretions from the main bronchi, which can be expectorated, in those hypersecretive patients who undergo upper abdominal surgery. In a study by Larsen et al,¹⁵ the tendency for reduced complications was observed in a group that was administered PPI associated with PEEP, when compared to a group treated only with PPI. However, in another study, the prophylactic application of PEEP did not present benefits when compared to PPI in patients who had undergone thoracic surgery.¹⁶

In view of the conflicting results of these studies, the objective of this study was to investigate the efficacy of the association of PEEP with a protocol of physiotherapy intervention in Phase I of cardiac rehabilitation, through the evaluation of pulmonary function and inspiratory muscle strength in patients who had undergone elective cardiac surgery.

MATERIALS AND METHODS

Thirty patients were recruited for participation, but only 24 patients concluded the study. The patients included in this study

presented coronary insufficiency diagnosed by coronary angiography. These patients underwent elective cardiac surgery with cardiopulmonary bypass, and the surgical incision utilized was sternotomy. All patients received medical prescriptions for the physiotherapy procedures. Patients who presented hemodynamic instability, associated neurological sequelae, or difficulty in comprehension or adherence to the procedures performed in this study were excluded.

Patients were randomly distributed into 2 groups in a 1:2 proportion, as follows: 1. a group in which EPAP associated with PPI was performed after cardiac surgery (GEP, n = 8) and 2. a group receiving physiotherapy intervention only (GPI, n = 16) The anthropometrical, clinical, and surgical characteristics of the groups are presented in Table 1.

Experimental Procedure

In the preoperative period, all the patients underwent a standardized evaluation that consisted of personal data, anthropometrics, medical diagnosis, vital signs, and personal antecedents. The body mass index (BMI) was calculated as: BMI = body weight (kg)/[height(cm)]².

Postoperative length of hospitalization, total duration of the surgical procedure, duration of ischemia, and cardiopulmonary bypass surgery time were recorded. Heart rate (HR) and peripheral saturation of oxygen (SpO₂) were monitored and recorded during the procedures with a portable pulse oximeter (Nonin 8500A, Plymouth, MN, USA).

After an initial evaluation, all patients were informed of the proposed protocol, surgical procedure, tracheal intubation, course of treatment, and the importance of physiotherapy for recovery during hospitalization. This was followed by pulmonary function and respiratory muscle strength evaluations.

Pulmonary function test spirometry was performed using the Vitalograph Pulmonary Hand-Held 2120 spirometer (Ennis, Ireland). During the pulmonary function tests, patients remained in the sitting position, with the nostrils occluded by a noseclip, while the maneuvers of vital capacity (VC) and forced vital capacity (FVC) were performed. The technical procedures, acceptable criteria, and reproducibility followed American Thoracic Society guidelines.²¹ Measurements for VC, FVC, PF, and FEF25-75% were obtained, and these values were analyzed as percentages of predicted values. Reference values from Knudson et al²² were used. The results obtained were expressed in BTPS (liters at body temperature and pressure saturated with water vapor).

Table 1 - Anthropometrics, clinical, and surgical characteristics of the population studied (mean ± SD)

	GEP (n = 8)	GPI (n = 16)	P value
Age (years)	59.9 ± 9.8	55.9 ± 11.9	.24
Weight (kg)	70.2 ± 12.3	64.5 ± 10.1	.14
Height (m)	1.7 ± 0.1	1.6 ± 0.1	.09
Body mass index (BMI) (kg/m ²)	24.7 ± 3.0	24.1 ± 3.0	.30
Surgery time (min)	170.7 ± 32.1	188.7 ± 43.9	.19
Cardiopulmonary bypass time (min)	70.1 ± 17.7	89.2 ± 25.9	.06
Duration of ischemia (min)	64.1 ± 28.9	56.2 ± 20.7	.44
Hospitalization (days)	6.6 ± 1.0	8.0 ± 2.1	.09

Table 2 - Spirometric variables in the preoperative and postoperative treatment (5th PO) with statistical results for intra- and inter-groups (mean ± SD)

	Preoperative	GEP 5 th PO	P value	Preoperative	GPI 5 th PO	P value
VC (%)	84.7 ± 21.2	57.6 ± 16.8	.0078*	71.5 ± 21.6	53.6 ± 19.4	.0006*
FEV ₁ (%)	73.6 ± 23.8	57.4 ± 14.1	.1094	70.5 ± 19.3	46.3 ± 28.2	.0001*
FEF ₂₅₋₇₅ (%)	57.1 ± 37.1	34.0 ± 21.0	.1563	54.3 ± 17.8	38.3 ± 20.8	.0015*
FVC (%)	83.1 ± 24.4	67.4 ± 23.8	.1094	83.0 ± 38.0	49.3 ± 16.0	.0004*
PF (%)	69.1 ± 37.9	62.8 ± 13.2	.4063	64.0 ± 26.0	40.5 ± 21.9	.0020*.0189†

*: Differences between conditions; †: Differences between groups; %: predicted; VC: vital capacity; FEV₁: forced expiratory volume in one second; FEF₂₅₋₇₅: forced expiratory flow from 25 to 75 percent of FVC; FVC: forced vital capacity; PF: peak flow

To measure IMS, Inspiratory Muscle Strength, a Monavacuometer, GER-AR (SP-Brazil) was used, with a scale varying from 0 to 150 cm H₂O, according to the methodology proposed by Black & Hyatt.²³ The maximal respiratory pressures were assessed by maximal inspiratory pressure (MIP) at residual volume. Using a noseclip, patients were asked to produce maximal efforts against an obstructed mouthpiece with a small leak to prevent patients from closing their glottis during the maneuver. Patients sustained maximal effort for 1 second, and the best of 3 consecutive attempts was used.

The 2 groups were reevaluated regarding pulmonary function on the fifth postoperative day (5th PO) and regarding the inspiratory muscle strength at the 1st PO and 5th PO. The evaluations described above were performed by the same professional, with the patient in the sitting position.

Proposed Treatments

Physiotherapy intervention in Phase I of cardiac rehabilitation (PPI): The patients underwent 2 physiotherapeutic interventions daily each lasting approximately 40 minutes, from the immediate postoperative day (IPO) until hospital discharge. The physiotherapeutic sessions carried out were elaborated according to the following protocol: IPO: Weaning from mechanical ventilation assistance, thumping and vibrating patients' rib cages (airway clearance maneuvers), endotracheal tube aspiration and extubation, which occurred at a maximum of 12 hours after surgery.

1st PO: Airway clearance maneuvers in the prone position; cough assist with the head of bed inclined at 45° (approximately 10 min), respiratory diaphragmatic exercises (3 series of 20 repetitions), inspiration in three stages (2 series of 20 repetitions) of room air, assisted active exercises of the extremities (ankles and wrists, 3 series of 10 repetitions).

2nd PO: Airway clearance maneuvers in prone and semilateral positions and cough assist in a sitting position (approximately 10 min); respiratory diaphragmatic exercises (3 series of 20 repetitions) and inspiration in three stages (2 series of 20 repetitions) in a sitting position. In addition, the following assisted active exercises of upper and lower limbs associated with respiration were performed: 1) flexion-extension of the elbow and elevation of the arms, respecting the articular amplitude range and pain tolerance (2 series of 10 repetitions for each exercise); 2) flexion-extension of the knee, respecting articular amplitude and pain tolerance (2 series of 10 repetitions for each exercise);

3rd PO: Airway clearance maneuvers in a semilateral position

(approximately 10 minutes), cough assist in a sitting position, and the respiratory exercises described for the 2nd PO. The following active free exercises of upper and lower limbs of items 1 and 2 associated with respiration were performed; maintaining an orthostatic position and walking in place for a 5-minute period.

4th PO: Airway clearance maneuvers when necessary and cough assist (approximately 10 min); respiratory exercises, exercises of the upper and lower limbs (as in the protocol for the 2nd PO). During this phase, all the patients were in the medical ward, and walking was performed in the corridor for 10 minutes.

5th PO: The protocol for the 4th PO. Walking in the hospital corridor for 10 minutes, and walking up and down 1 flight of stairs.

Expiratory Positive Pressure in Airways (EPAP): The application of PEEP was performed through an EPAP circuit using a facial mask coupled to a unidirectional valve containing, at its extremity, a PEEP valve of 10 cm H₂O^{15,24} for all patients in the GEP. This group performed 60 repetitions of respiratory exercises divided into 3 series of 20 respirations in 2 daily sessions until discharge from the hospital. The patient inhaled room air through the mask, without additional oxygen, and exhaled against the referred resistance. The patients in this group also went through the PPI protocol after the EPAP exercises, in accordance with the standard hospital physiotherapy treatment routine.

DATA ANALYSIS

Based on the means and standard deviations of data for the spirometric variables, a power size calculation was performed with Graphpad StatMate version 1.01, 1998. This revealed that a power of 80% and a significance level of 5% would be obtained. To verify the data distribution, data was plotted on a gaussian curve and did not distribute according to a normal distribution. Therefore, for matched-pair comparisons, the nonparametric Wilcoxon test and the Friedman test for matched variables (MIP) were used; the Dunn test was used for differentiation between conditions. For comparison between groups, the Mann-Whitney test was used. The level of significance was set at $P < .05$.

RESULTS

From a total of 30 eligible patients, only 24 patients constituted the final research study population of 15 men (62.5%) and 9 women (37.5%), aged 57 ± 11 years. Of the 6 patients excluded from the study, 2 presented hemodynamic instability and were

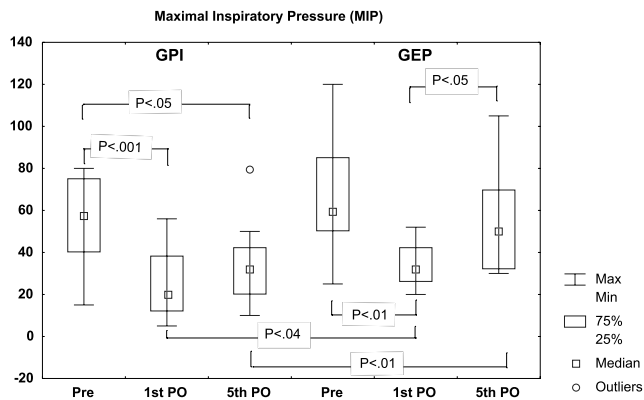


Figure 1 - Maximal inspiratory pressure (MIP) at preoperative (pre), 1st postoperative (1st PO) and 5th postoperative (5th PO) day for the groups studied. (* $P < .05$)

not released by the medical team for spirometric and respiratory strength measurement, 1 presented neurological sequelae, 2 presented difficulties in performing the spirometric test and exhibited a comprehension deficit, and 1 refused to continue the treatment. Table 1 shows the age, weight, height, IMC, duration of surgery, hospitalization, and perfusion of the patients included in this study. No significant differences were found in the anthropometric parameters, clinical, or surgical aspects between the groups analyzed.

Concerning angina, in the GEP, 25% were functional class III and 75% were functional class IV; for the GPI, 31.2% were functional class III and 68.8% were class IV, according to Campeau.²⁵ Concerning drains, 87.5% of the GEP patients and 81.2% of the GPI patients used the subxiphoid drain, in addition to the mediastinal drain applied to all patients in the postoperative recovery. Of the total grafts, 85% were performed with the left internal thoracic artery plus saphenous vein, and 15% with the radial arteries plus saphenous vein or only the saphenous vein.

The spirometric results obtained in preoperative and 5th PO are presented in Table 2. No differences were found between preoperative spirometric variable values for the groups studied. However, it can be observed that for all spirometric values, previous values for the GPI were not reestablished by the 5th postoperative day, while for the GEP, only VC did not return to its preoperative values ($P < .05$). Intergroup analysis revealed a significant difference only in PF, with greater values for the GEP when compared to the GPI postoperatively.

Inspiratory muscle strength, evaluated through MIP values, was significantly reduced on the 1st PO for both groups studied, with MIP increasing from the 1st PO to 5th PO only in the GEP. However, in the GPI, significant reductions are observed when comparing preoperative to 5th PO values. In relation to intergroup analysis, greater values of MIP were found on the 1st PO and 5th PO for the GEP compared to the GPI ($P < .05$). Figure 1 illustrates the behavior of this variable for inspiratory muscular strength.

DISCUSSION

Patients undergoing cardiac surgery with cardiopulmonary bypass were studied to determine the effects of a physiotherapy intervention in phase I of cardiovascular rehabilitation,

associated or not with the application of PEEP on pulmonary and inspiratory muscular strength.

Alterations in pulmonary function can be associated with various factors such as the type of surgical incision,²⁶ the anesthetic modality employed, diaphragmatic dysfunction,²⁷ postoperative pain,²⁶ and the positioning of the pleural drain.¹¹ In the present study, all the patients were operated through a sternotomy with the thoracic drain positioned in the subxiphoid (pleural and/or mediastinal) region, which minimized the possible differences that might result from the procedure.

Additionally, some authors have demonstrated that a large number of patients who undergo cardiac surgery with cardiopulmonary bypass present alterations in pulmonary functions in postoperative evaluations.^{10,12} Therefore, the performance of procedures to improve their recovery becomes necessary in an effort to minimize the deleterious effects on pulmonary function and on immobility.

Alterations in pulmonary function after cardiac surgery were observed in this study, in agreement with other findings, which supports that a reduction in functional residual capacity (FRC),²⁷ VC,^{13,14,23,28,29} and expiratory flows^{11, 13,14} occurs following cardiac surgery. According to published studies, the FVC presents a general reduction for a minimum period of 10 to 14 days.^{28,30} In the present study, the FVC was analyzed until the 5th day PO, and no difference was found between the preoperative level and that for 5th PO in the GEP, indicating this variable had returned to previous values. However, in the GPI, in which only PPI was performed to the 5th PO, the FVC was not reestablished. These results corroborate those reported by Guizilini et al¹¹ in patients who underwent cardiac surgery without cardiopulmonary bypass.

Westerdahl et al¹³ evaluated pulmonary function up to 4 months after cardiac surgery in patients who did PPI and found that VC and FEV1 were still significantly reduced when compared to preoperative values. In the present study, the only preoperative measurements reestablished by the 5th postoperative day occurred for the GEP that is, when EPAP was associated with PPI.

The importance of a postoperative physiotherapeutic intervention protocol for cardiac surgery has been justified by some authors in that it can lower the incidence of pulmonary complications brought on by reductions in spirometric measurements.^{13,18} Additionally, the application of PEEP has been shown to be effective in increasing the return to pulmonary volumes and the resolution of atelectasis.¹⁷

Differing from findings in our study, Larsen et al¹⁵ found no difference between the group treated with PPI plus EPAP and the group treated with PPI alone. However, a tendency for the reduction of complications was observed in the group that received PEEP. Ricksten et al²⁹ concluded that the administration of EPAP or continuous positive airway pressure was superior to PPI regarding gas exchange, the preservation of pulmonary volumes, and the prevention of atelectasis, in accordance with the findings of the present study, although those findings were from postoperative abdominal surgery patients.

In another study, the application of PEEP did not confer

additional prophylactic benefits regarding atelectasis and the reduction of hypoxemia, when compared to physiotherapy intervention.¹⁶ The FVC was not improved postoperatively in patients receiving EPAP compared to those receiving incentive spirometry or physiotherapeutic interventions.³⁰ In contrast, our results show superiority for the variables analyzed after the application of EPAP associated with PPI in comparison to isolated physiotherapeutic intervention. As in this study, other authors^{20,29} have also concluded that the application of PEEP should be used as an adjuvant in the routine physiotherapeutic intervention for surgical patients.

Reduced pulmonary function, worsening of gas exchange, and higher rates of pulmonary complications have been associated with the reduction of IMS.^{4, 5,9,12} In this study, the values of MIP showed significant reductions from preoperative to 1st PO measurements for the groups studied, and the reestablishment of this variable was found only for the GEP. These results suggest an additional effect by EPAP regarding an earlier reversion of IMS when compared to isolated physiotherapeutic intervention, since significantly higher values were found for MIP on the 1st and 5th PO for the GEP than for the GPI.

The improvement of MIP in the postoperative period was confirmed by Elias et al.,⁹ even without training directed towards inspiration muscles, in agreement with our results in that no specific muscle training had been done. This increase can be related to a possible improvement in the mechanics of thoracic-abdominal movement and consequently an increase in the amplitude of respiratory movements,⁹ which were not measured in this study.

This study presents some limitations such as the absence of a group with only EPAP application without PPI, which would meet the objective of verifying whether patients who underwent this treatment would present higher pulmonary function values and inspiratory muscle strength, when compared to patients who underwent physiotherapeutic intervention. However, in our study, all patients followed a routine established by the hospital's physiotherapeutic section.

Another important aspect was the limited number of EPAP kits available, which kept the sample size small. While some additional benefits were observed with the use of PEEP in this study, it is necessary to consider the cost/benefit ratio of using this equipment in addition to the proposed physiotherapeutic treatment.

In conclusion, patients who underwent elective cardiac surgery with cardiopulmonary bypass exhibited reductions in postoperative pulmonary function and muscle strength. Physiotherapeutic intervention associated with the application of positive end-expiratory pressure improved the recovery of these patients in comparison to physiotherapeutic intervention alone. However the pulmonary volumes were not completely reestablished until the 5th PO, suggesting the need to continue treatment after the period of hospital convalescence. Due to the small sample size in this study, the performance of new studies to better establish the results obtained in this study is suggested.

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Impact of Long-Term Ventilation on Patients' Health Status

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Therapy and rehabilitation of common causes of respiratory-induced disability are directed towards a reduction of exacerbations, minimization of symptom severity, and improvement, or at least maintenance, of the patient's health. Unfortunately, these diseases are frequently complicated by chronic respiratory failure (CRF), which determines a rapid increase in the impact of the disease on the patient's daily life and well-being. Under such circumstances, the effect of therapy on a patient's health status and well-being represents the most important subjective outcome of treatment. An adequate assessment of patient's quality of life can only be obtained from the patients themselves; that is, it requires direct measurement through the use of valid and reliable questionnaires, whether generic or disease-specific. The St George's Respiratory Questionnaire and the Mageri Foundation Respiratory Failure Questionnaire have been shown to be applicable and reliable in patients on long-term ventilation.

Key words: chronic respiratory failure; COPD; health status; kyphoscoliosis; quality of life

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INTRODUCTION

Chronic respiratory diseases affect the lungs, but also have effects in other organs. These secondary effects must be addressed if the patient's quality of life (QoL) is to be improved. This applies especially when the disease interferes with daily activities such as washing, dressing and cooking.

Chronic obstructive pulmonary disease (COPD) is the commonest cause of respiratory-induced disability. Like most chronic respiratory causes it is incurable, but unlike them it is also usually progressive. Therapy and rehabilitation are directed towards a reduction of exacerbations, minimization of symptom severity, and improvement, or at least maintenance, of the

patients' health. Restrictive diseases such as kyphoscoliosis can also have a severe impact on patients' health status.

Unfortunately, these diseases are frequently complicated by chronic respiratory failure (CRF). When CRF sets in, there is a rapid increase in the impact of the disease on the patient's daily life and well-being. A significant reduction in daily activities is one of the main consequences.¹

It has been demonstrated that long-term oxygen therapy (LTOT) improves these patients' survival,^{2,3} adding approximately three to five years of life.⁴ However, survival is worse if a high level of disability is present when oxygen therapy is started.⁴ Patients affected by kyphoscoliosis yield better results.⁵

When long-term ventilation is needed, patients have problems in performing the simplest activities of daily life (for example, washing, dressing, cooking). Consequently, they bear a very important physical and psychological handicap, determining a high social cost in treatment, nursing, and economic terms. Under such circumstances, the effect of therapy on patients' health status and well-being represents the most important subjective outcome of treatment.

DIFFERENCES BETWEEN QUALITY OF LIFE, HEALTH-RELATED QUALITY OF LIFE, AND HEALTH STATUS

A number of different terms are applied to the measurements used to quantify the impact of COPD on a patient's daily life and well-being. For instance, the terms quality of life and health status measurement are too often used interchangeably, but they represent different concepts.⁶ This can lead to confusion through overlap and differences of interpretation and definition between authors.

Quality of life (QoL) is a general term that applies to all individuals, whether diseased or healthy. It can be broadly defined as the gap between what is desired in life and the degree to which this desire is achieved, that is, the gap between wishes and achievements. It can be influenced by many factors including financial status, housing conditions, spirituality, family and social support, and health.

Within the context of medicine the focus is more upon the effects of disease. For this reason, the term "health-related quality of life" (HRQoL) has been proposed to signify the effect of disease on the gap between desires and the degree to which

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they are achievable. Both QoL and HRQoL should be thought of as being indicators of how individuals rate their lives.

Measurement requires standardization, so questionnaires designed to measure HRQoL must be applicable to all patients with the disease. In other words they treat each patient as if he or she were a typical patient. They rarely permit any individuality. For this reason we prefer to draw a distinction between HRQoL, which applies to individuals, and health status, which applies to populations. Health status questionnaires are made up of a set of items that are appropriate and common to all subjects with the disease in question. Inevitably this means that they tend to address essential activities and functions of daily living specifically, and examine social and recreational matters in a more general manner. While this might seem to be a limitation, standardization does permit health status scores to be used in the same way as any other standardized measure, for example, spirometry. An easy-to-understand definition of health status measurement may be: "quantification of the impact of disease on daily life and well-being in a formal and standardized manner."⁷

HEALTH STATUS (QUALITY OF LIFE) IN VENTILATED PATIENTS

Health status (quality of life) (HS-QoL) measurements are aimed to: define the health of groups of patients; measure changes over time in the health of groups of patients; predict future health resource allocation; and assess the impact of disease and treatment on an individual basis.

However, all the measurements commonly used as an index of functional damage and/or improvement correlate poorly with reported impairment of physical function or overall QoL, and therefore provide an incomplete picture of impaired health.⁷ In particular, although there is a clear negative relationship between spirometric mean values from different patient populations and health status – QoL, it is known that within a given study population the correlation emerges as very low, regardless of the questionnaire used.⁷⁻⁹

It is clear from the foregoing that there is a need to provide a global estimate of health in patients on long-term home mechanical ventilation (HMV), and that health status cannot be inferred from indirect and surrogate measures. An adequate assessment of QoL can only be obtained from the patients themselves; that is, it requires direct measurement through the use of valid and reliable questionnaires, whether generic or disease-specific.

Health status questionnaires used in COPD fall into two main classes: generic questionnaires, such as the Medical Outcomes Study Short-Form Health Survey (SF36),^{10, 11} Sickness Impact Profile (SIP),¹² EuroQoL,¹³ and disease-specific questionnaires. Among the latter are the Chronic Respiratory Questionnaire (CRQ),¹⁴ Mageri Respiratory Failure Questionnaire (MRF-28),¹⁵ Quality-of-Life for Respiratory Illness Questionnaire (QOL-RIQ)¹⁶ and St George's Respiratory Questionnaire (SGRQ).¹⁷ These all meet criteria for validity, reliability and responsiveness. The disease-specific questionnaires have both discriminative properties (ability to detect differences in health status among patients at a given moment), and evaluative properties (ability to detect changes in health status within the same group), but only the MRF-28 and SGRQ were designed specifically to have both discriminative and evaluative

properties. It was necessary for these two questionnaires to have good performance in both of these functions, because they were intended for long-term studies over years as well as over much shorter time periods. All of the questionnaires listed above are complex and relatively time consuming.

IMPACT OF CHRONIC MECHANICAL VENTILATION ON HEALTH STATUS

Among generic questionnaires, only the SF36 has been used in patients on long-term ventilation. For example, using the SF36, it was shown that patients on overnight nasal intermittent positive pressure ventilation (NIPPV) had a significantly higher impairment in physical function compared to patients with other chronic diseases.¹⁸

With the same questionnaire, it was demonstrated that hypoxemic COPD patients on NIPPV have better health status scores in comparison to hypoxemic COPD patients who, for one reason or another, used neither LTOT nor NIPPV.¹⁹

The SF36 was administered also to a group of patients with severe respiratory failure one year after successful discharge from an intensive care unit.²⁰ All these patients had an acute or acute onset chronic respiratory failure following a chronic pulmonary disease, neuromuscular disorder, chest wall deformity or sleep apnea with difficult weaning from mechanical ventilation. Although patients had very low scores for general health, physical function and role limitation due to physical problems, which can be expected as they were extremely physically disabled, the scores for emotional role limitation, mental health, vitality and pain were not so dissimilar from those of the general population.

Unfortunately, for many dimensions the SF36 is too insensitive as it cannot differentiate between patients on mechanical ventilation and other conditions. To increase the level of sensitivity to health status impairment, disease-specific questionnaires have been designed.

In hypercapnic ventilated COPD, the SGRQ was also shown to be sensitive to changes following ventilatory treatment.²¹ In this randomized, crossover study, the effects of the combination of nasal pressure support ventilation (NPSV) and LTOT were compared to those of LTOT alone in hypercapnic COPD. QoL with oxygen plus NPSV was significantly better than with oxygen alone. During the LTOT alone period there was a significant deterioration in impact and total scores. Conversely, during the NPSV plus LTOT study period there were significant improvements in symptoms, impact and total scores over LTOT alone. The symptom score was also significantly improved over the run-in. Data from this study show that in severely impaired COPD patients the combination of LTOT and NPSV determines significant improvements in patients' perceived QoL. The reason for this is not clear since the greatest benefit was seen in the Symptoms component of the SGRQ rather than in the Activity component or the Impacts component, which includes factors such as sleep and mood. However, it is worth noting that the difference in total score between LTOT alone and LTOT plus NPSV was nearly 10 units, almost double the minimum difference that is considered clinically significant (that is, 4 units).²²

The SGRQ was also used to measure the effects of domiciliary NIPPV in hypercapnic COPD patients.²³ Data obtained in 14

Name of Questionnaire:	Quality-of-Life for Respiratory Illness Questionnaire (QOL-RIQ)					
Description:	Disease-specific quality of life measure designed for patients with reversible and fixed airway obstruction. Patients are asked how much of a problem each item has been during the past year.					
Developer:	A. Maille, A. Kaptein, C. Koning, A. Zwinderman					
Address:	A. Maille Department of Psychiatry University of Leiden, P.O. Box 1251 2340 BG Oegstgeest The Netherlands					
E-mail:						
Cost & availability:	Contact A Maille for permission for use.					
Administration:	Self					
Time to complete:	Not reported.					
Number of items:	55					
Domains & categories (#):	7 domains					
Name of domains & categories:	Domains: breathing problems (9 items); physical problems (9 items); emotions (9 items); situations triggering or enhancing breathing problems (7 items); daily and domestic activities (10 items); social activities, relationships and sexuality (7 items); general activities (4 items)					
Scaling of items:	7-point Likert-type					
Scoring:	Domain and total scale scores					
Reliability:	<table border="1"> <tr> <td>a. Test-retest/reproducibility:</td> <td>Not reported</td> </tr> <tr> <td>b. Internal consistency:</td> <td>Reported 1</td> </tr> </table>		a. Test-retest/reproducibility:	Not reported	b. Internal consistency:	Reported 1
a. Test-retest/reproducibility:	Not reported					
b. Internal consistency:	Reported 1					
Validity:	Reported; clinical indices of disease severity (dyspnea, frequency of attacks, severity, general practitioner visits, absence from work) 1, 2					
Responsiveness:	Not reported					
Minimally important difference:	Not determined.					
Research use:	Not reported					
Clinical use:	Not reported					
Languages:	English, Dutch					
References:	<p>Maille AR, Koning CJM, Kaptein AA. Developing a quality-of-life questionnaire for patients with respiratory illness. <i>Monaldi Arch Chest Dis</i> 1994;49:76-8.</p> <p>2 Maille AR, Koning CJM, Zwinderman AH, Willems LNA, Dijkman JH, Kaptein AA. The development of the Quality-of-Life for Respiratory Illness Questionnaire (QOL-RIQ): a disease-specific quality-of-life questionnaire for patients with mild to moderate chronic non-specific lung disease. <i>Respiratory Med</i> 1997;91:297-309.</p>					

An assessment of the CRQ and the SGRQ was made by Nick Anthonisen, editor in chief of the Canadian Respiratory Journal. The questionnaires were translated and administered to two groups of COPD patients. Anthonisen noted, in an editorial: One group had stable COPD and was tested twice with a two-week period between tests to examine test-retest reproducibility. The second group consisted of patients who either had an exacerbation of their COPD or who underwent rehabilitation for their disease. Both situations are associated with improvements in quality of life that should be detectable by the questionnaires. These results were compared with a third standard quality of life questionnaire. The results were very good. The questionnaire results met expectations: they were reproducible in stable patients and showed when patients improved. In psychometric terms, they were reliable and valid. I recommend the paper to people who are interested in developing and testing such instruments, both for the knowledge displayed by the authors and for the clarity of their presentation. Questionnaires are really the only way to assess that elusive property "quality of life," which is an extremely important item, especially in chronic disease. The CRQ, which is of Canadian origin, and the SGRQ are designed to measure the symptoms of chronic respiratory disease and their impact on the patient (ie, they are disease-specific). More general quality of life measures assess broader domains, such as the quality of one's spousal relationship, and are less useful in the setting of chronic respiratory disease. While the CRQ was designed specifically for use in COPD, the SGRQ was designed for use in both COPD and asthma (although its use in asthma has been limited because there are simpler questionnaires that probably work as well in this disease). COPD presents a special problem. Although the hallmark of the disease is a decrease in forced expiratory volume in 1 s (FEV₁), and decline in FEV₁ is the best marker of disease progression, changes in FEV₁ (or other lung function measures) are tricky in patients with very

advanced disease. It is very common in my clinic for patients to complain of increasing dyspnea and decreasing quality of life while their FEV₁, which is low, does not change. Indeed, many of them are so sick, they could not sustain a measurable decrease in FEV₁ and remain alive. This is the conundrum faced by workers trying to assess whether a particular treatment 'works' in clinic-based COPD populations; many treatments are unlikely to significantly change the FEV₁, but they may offer real benefit, which is often best assessed in terms of quality of life. The shining example of such a therapy is pulmonary rehabilitation, which has substantial positive effects on quality of life in COPD (3), but which does not improve lung function. I believe that there are cogent arguments for the approval of drugs that improve quality of life in severe COPD in the absence of substantial changes in lung function. I am not the only person to hold this belief, and many commercially sponsored trials measure disease-specific quality of life. However, these measurements are at least as complex and difficult as measuring FEV₁, and are seldom done as well. Peculiar, counterintuitive results, such as major improvements in the placebo arm of a trial, are not infrequent in regard to changes in life quality in COPD. Although observed more frequently with tests other than the CRQ and SGRQ, they do occur even when these standards are employed. This is almost certainly because the questionnaires were not administered in a standard, consistent fashion. For example, in a long-term COPD trial, one would never dream of measuring the FEV₁ during or immediately after an exacerbation of COPD because one is interested in the stable state, but this simple proviso has not been established for quality of life assessments. Just as there are many rules regarding lung function measurements, there needs to be specific protocols for the administration of instruments such as the CRQ and SGRQ.

patients during a four-week run-in period were compared with measurements at the end of the six-month study period. Mean baseline scores were very high; that is, health status was highly impaired: activity, 69%; impact, 58%; symptoms, 68%; total, 68%. During the NIPPV period, patients' QoL as measured by the SGRQ improved. This improvement was more evident in impact (-9 units) and in total (-10 units) scores, where it was statistically significant ($P=0.04$). In regard to the total score, the improvement was also clinically significant, that is, well above the threshold for clinical significance.

Even more interesting are the data from a two-year multicenter Italian study that compared NIPPV plus LTOT to LTOT alone in 122 COPD patients.²⁴ In that study, the SGRQ did not show any difference between the two groups, but the MRF-28 appeared to be more specific and sensitive. At the end of the two years of follow-up, patients on LTOT alone showed slightly worsened health status scores, measured using the MRF-28, whereas patients who received LTOT and NIPPV had improved scores. This study is important because it suggests that for the most severe patients with respiratory failure, a condition-specific questionnaire such as the MRF-28 (developed specifically for use in such patients) may be more appropriate than a disease-specific questionnaire such as the SGRQ, it being more discriminative.

CONCLUSION

The interest shown towards the measurement of health status or 'quality of life' in patients with respiratory diseases has progressively increased over the last decade, but only recently has it been applied also to more severe patients, that is, patients with chronic respiratory failure on LTOT or NIPPV.

The impact of chronic respiratory failure on the daily life and well-being of patients may be measured in a number of different ways. However, there is evidence that it is not possible to predict patients' health from surrogate measures, for example, spirometry or exercise performance, and that the size of the health gain following treatments or interventions cannot be predicted from changes in physiological measurements. Adequate assessments of health status can only be measured directly through the use of valid and reliable QoL questionnaires.

A range of different instruments are available in the literature. The St George's Respiratory Questionnaire (SGRQ) and the Mageri Foundation Respiratory Failure Questionnaire (MRF-28) have been shown to be applicable and reliable in patients on long-term ventilation.

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Using Back Up Rates During Non-Invasive Ventilation In Premature Infant

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ABSTRACT

Objective: To evaluate the efficacy of back up rates during non-invasive ventilation (NIV) in premature infants with moderate respiratory distress.

Methods: All premature newborn infants with gestational age of or below 34 weeks with clinical and laboratory evidence of moderate to severe respiratory distress were provided with back up rates during NIV. Infants were continued to receive NIV as per the protocol till improvement or failure. The failure criteria were set forth in the protocol: $PCO_2 > 60$ mm of Hg, $FiO_2 > 60\%$ to keep saturation $> 90\%$ and /or recurrent serious episodes of apneas or need for intubation for any other reason.

Results: A total of 14 premature neonates less than 34 weeks of gestation received NIV. Out of these 14 infants, 10 (71%) had success with the NIV while 4 (29%) failed the trial. The mean duration of NIV was 43 hours (< 2 days).

Conclusions: Back up rates during NIV are advantageous and its usage with NIV decreases the need for unnecessary intubation. It is less expensive and less labor intensive. It may also be beneficial in reducing the intubation related complication in the premature infants.

INTRODUCTION

Non-invasive ventilation (NIV) has been gaining reputation in intensive care units as an effective alternative to intubation. The mode in addition to being non-invasive is less expensive and less labor intensive. Also, the potential complications of NIV are less as compared to intubation. In neonatal medicine, the use of NIV has so far been confined to preventing post-extubation failure and apnea in premature neonates.^{1,2} The early use of NIV

in premature infants with respiratory distress however has been viewed critically. In a quality assurance survey, a high rate for elective intubations was observed for infants < 34 weeks with respiratory distress. In view of the potential complications of unnecessary intubations and low threshold of tolerance for respiratory distress among neonatal physicians, we developed a 'early non-invasive ventilation with back up rate' protocol at our institution. To test the success or failure of the protocol, we conducted this study.

MATERIALS AND METHODS

A prospective study was carried out using the early NIV protocol (Figure 1) at Neonatal Intensive Care Unit (NICU) at Royal Hospital, Muscat, which has 30 beds and provides level III-IV care for all high-risk neonates including general and cardiac surgery. All premature newborn infants with gestational age of or below 34 weeks (based on the antenatal ultrasound reports) with clinical and laboratory evidence of moderate to severe respiratory distress were given the trial. Inclusion, exclusion, failure and exit criteria were set forth and discussed with the neonatal staff. The study protocol was approved by the local ethic committee and parental consent was taken for the trial.

The NIV was given through the Dragër ventilator (Babylog 8000) selecting IPPV mode of ventilation. Sterile nasal prongs (Argyle, Sherwood Medical Co, St. Louis, MO) were used to provide NIV. Blood gas analyses were performed using the automatic analyzer (Ciba-Corning 850, MA, USA) before and after NIV administration. Infants were continued to receive NIV as per the protocol till improvement or failure. The failure criteria were set forth in the protocol : $PCO_2 > 60$ mm of Hg, $FiO_2 > 60\%$ to keep saturation $> 90\%$ and /or recurrent serious episodes of apneas or need for intubation for any other reason. The initial ventilator settings were established in the protocol as: PIP = 18, PEEP = 4, Rate = 25, FiO_2 50%, Flow = 8-10 L/min, where PIP is peak inspiratory pressure, PEEP is positive end expiratory pressure. The settings were decreased based on clinical improvement and post NIV blood gas. The increase in requirement of ventilatory settings resulted in the exit of the infant from the trial. During

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Table 1: Comparison between the successful and failed group

Variable	Successful group (n =10)	Failed group (n = 4)	P value
Age at entry (hours)	0.76 ± 1.84	0.16 ± 0.0	0.53
Apgar Score at 1 minute	6.5 ± 1.5	3.2 ± 2.2	0.009*
Apgar Score at 5 minute	8.4 ± 0.9	8 ± 0.1	0.43
Birth weight (grams)	1911 ± 517	1422 ± 386	0.11
Gestational age (weeks)	32 ± 1.07	31 ± 1.4	0.03*
Duration of NIPPV (hours)	43 ± 36	0.54 ± 0.34	0.03*

Values expressed as mean ± standard deviation

* P < 0.05 taken as statistically significant

NIV infants were cared for in high dependency area of the NICU with 24-hour monitoring of vital signs, saturations and signs of clinical improvement or deterioration in the respiratory status. Big bore orogastric tube was inserted in all infants to deter the unwanted effect of abdominal distension during NIV. Infants were fed through the same tube kept in burp position.

The baseline data including the medical record number, birth weight, gestational age, sex, type of delivery, Apgar score, mode of resuscitation, age at entry, duration of NIV and pre and post NIV blood gas (arterial or capillary) were entered into the data collection proforma sheets. Infants with congenital anomalies, those requiring intubation and needing rescue surfactant replacement therapy were excluded from the study. The pilot study was conducted over a period of three months, August 1, 2003 to October 31, 2003. Statistical Package for Social Science (SPSS) version 7.5 was used for statistical analyses.

RESULTS

During the study period, a total of 14 premature neonates less than 34 weeks of gestation received NIV. Out of these 14 infants, 10 (71%) had success with the NIV while 4 (29%) failed the trial. The mean duration of NIV was 43 hours (< 2 days). There were no major differences in the failed and successful group (Table 1). The NIV failed infants were significantly depressed at birth (low 1 minute Apgar Score) and were smaller than the successful group.

DISCUSSION

In the present study, we were able to demonstrate that back up rate during NIV enhances the chance of success and results in reducing the unnecessary intubations. The addition of back up rates was based on previous studies³⁻⁵. Physiologically, the nasal continuous positive airway pressure (NCPAP) provides only a single level of airway pressure, which is maintained above the atmospheric pressure throughout the entire respiratory cycle. NIV with rates, on the other hand, provides an inspiratory positive pressure for ventilatory assistance and lung recruitment and an expiratory positive pressure to help recruit lung volume and adequate lung expansion. The other expected advantage of

NIV with rates over NCPAP is the elimination of PCO₂ by providing rates.

Being a pilot study with small sample size some limitations were expected. The comparison between groups with small numbers may not depict the accuracy. Similarly, we only looked at the short-term outcome, the success or failure of NIV. Long term outcome such as incidence of chronic lung disease, cost of care, length of hospital stay was not looked at.

CONCLUSIONS

The findings of our study suggest that use of early NIV with back up rates could be used successfully and safely in premature infants with respiratory distress as an effective alternative to intubation. The major advantage of this strategy is its non-invasive mechanics. It is less expensive and less labor intensive. Early intervention with NIV may result in preventing undue intubation and risk associated with it. However, further randomized control trials with larger sample size are warranted to confirm our findings.

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Figure 1

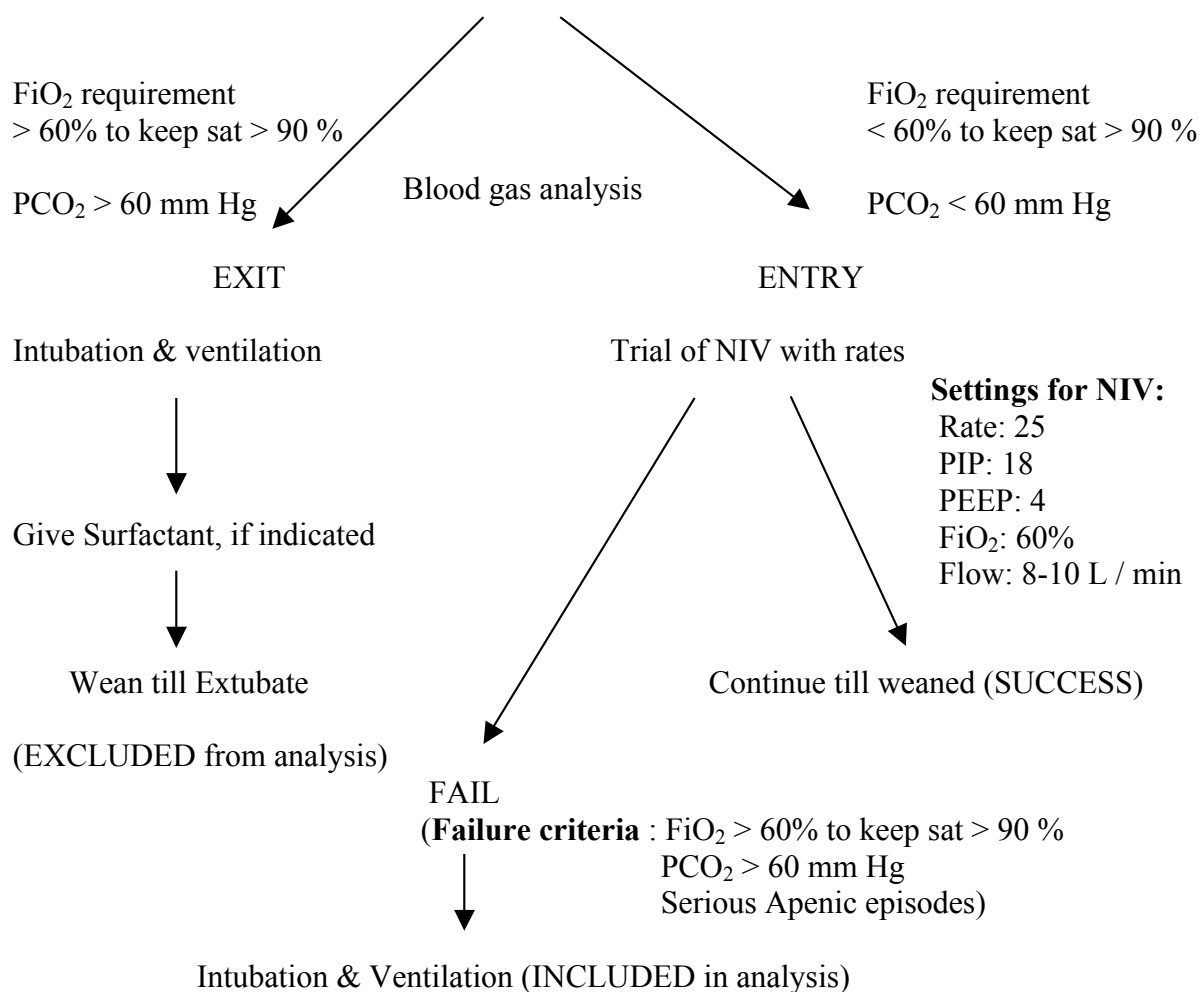
Protocol for non-invasive ventilation (NIV) with back up rates in premature infants

Inclusion criteria: Gestational age of = or < 34 weeks, respiratory distress after birth (tachypnea with respiratory rate of > 60/ min, grunting, nasal flaring, subcostal or/ and intercostal recessions).

Exclusion criteria: Lethal anomalies, admitted to NICU already intubated from delivery suite/ operation theater.

General procedure:

Newborns of gestational age = or < 34 weeks with signs of respiratory distress



SARS and Hospital Priority Setting: A Qualitative Case Study and Evaluation

Jennifer A.H. Bell, Sylvia Hyland, Tania De Pellegrin, Ross E.G. Upshur, Mark Bernstein, Douglas K. Martin

BACKGROUND

As of August 12, 2003 there were 438 probable and suspected cases of Severe Acute Respiratory Syndrome (SARS) in Canada — the majority located in Toronto. In Toronto there were forty-four SARS related deaths and over 100 health care workers contracted SARS, placing intense pressure on Toronto's public health and hospital system.¹

Due to both the importance of hospitals in any health system and the difficulties they face, improving priority setting (also known as rationing or resource allocation) within hospitals is crucial. Priority setting is one of the most difficult issues facing hospitals because of funding restrictions and changing patient need. A deadly communicable disease outbreak, such as SARS in Toronto in 2003, amplifies the difficulties of hospital priority setting.

Key goals of priority setting in any context are legitimacy and fairness. "Accountability for reasonableness" is an explicit ethical framework for legitimate and fair priority setting in health care.² It is internationally recognized as a framework that can guide priority setting in health systems and their institutions.³⁻⁵ According to "accountability for reasonableness," an institution's priority setting may be considered fair if four conditions are met: relevance, publicity, appeals and enforcement (see Table 1).

In 2003, the outbreak of SARS further challenged priority setting decision-makers in Toronto hospitals, creating decision-making

difficulties in relation to both SARS and non-SARS patients. To what extent should the need for containment over-ride other important needs? To what extent should the need for quick decisions over-ride the need for legitimate and fair decision-making?

Only a few studies have directly examined priority setting in hospitals — two focused on technology acquisition,^{6,7} one on strategic planning,⁸ one on a hospital drug formulary,⁹ and two on hospital ICUs.^{10,11} The latter four studies used "accountability for reasonableness" as the study framework. To our knowledge there have been no studies of hospital priority setting during an emergency response to a communicable disease outbreak.

The purpose of this study was to describe priority setting in a hospital in response to SARS and evaluate it using "accountability for reasonableness."

METHODS

Design: To describe priority setting we used qualitative case study methods. A case study is "an empirical inquiry that investigates a contemporary phenomenon within its real-life context."¹² This is an appropriate method because priority setting in hospitals is complex, context-dependent, and involves social processes. To evaluate the description we used the four conditions of "accountability for reasonableness" (described in Table 1).

Setting: This case study was conducted at a large tertiary hospital in Toronto, Canada.

Sample: We sampled key documents and people. We used theoretical sampling to determine which people and documents were "key." Included among the individuals sampled were senior administrators, managers, physicians, nurses, patients, and family members.

Data Collection: There were two sources of data: (1) over two hundred key documents (eg emails, minutes of meetings), and (2) 35 interviews with key informants (senior administrators (6),

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physicians (10), managers (5), nurses (5), a patient (1), family members (2), and other staff (6)). Interviews were audiotaped and transcribed. Interview participants were asked to describe priority setting decisions in relation to SARS and their thoughts about it. We developed an interview guide based on previous research and improved it through pilot interviews with personnel from other hospitals. As is traditional with qualitative studies, the interview guide was modified during the study to explore emerging themes.

Data analysis: The data were analyzed concurrent with collection using a modified thematic approach in three phases: open coding, axial coding, and evaluation. In open coding, the data were fractured by identifying chunks of data that relate to a concept or idea. In axial coding, the concepts were organized under overarching themes (ie the four conditions of “accountability for reasonableness”). In evaluation, the descriptive data were compared with the conditions of “accountability for reasonableness” — correspondence with the framework was considered “good practice”; instances where the conditions are not met were considered “opportunities for improvement.” Concepts were formalized and made explicit through the writing of the findings.¹³

The validity of the interpretations was enhanced in four ways.¹⁴ First, the coding was conducted in collaboration between two researchers, thus limiting the influence of any one person’s biases. Second, the coding was reviewed and modified by an interdisciplinary team who provided challenges that were resolved through consensus. Third, the findings were presented to participants who verified the findings—traditionally called a “member check.” Finally, all research activities were rigorously documented to permit a critical appraisal of the methods.¹⁵

Research ethics: Approval for this project was obtained from the participating hospital’s Research Ethics Board. Written informed consent was obtained from each individual before being interviewed. All data were kept confidential and viewed only by the research team. No individuals have been identified without their explicit agreement.

Results: In this section we describe one hospital’s priority setting in response to SARS by focusing on the types of decisions, the decision-making process, and the supportive reasoning. We then evaluate our findings using the four conditions of “accountability for reasonableness.” We have also included verbatim quotes from participants to illustrate key points.

I. Description of priority setting

Types of priority setting decisions: There were two distinct phases of priority setting at the hospital during the SARS outbreak. First, during the initial days of the outbreak, decisions were made in order to contain the spread of the virus. The Ontario Ministry of Health and Long-Term Care (MOHLTC) directed Toronto acute care hospitals to establish or maintain as necessary a SARS isolation area, restrict patient visits, limit visitors and suspend selected patient transfers. Second, after the initial weeks of the outbreak, was a “ramp up” phase during which the hospital gradually increased its level of activity. Throughout both phases, priority setting decisions can be organized according to four specific types: decisions relating to staff and patients, beds/rooms, clinical activity, and visitors.

- Staff safety
- Infection control
- Patient safety
- Medical need
- Surgeon activity
- Operational need
- Compassion
- Screening capability
- Squeaky wheel
- Fear of unknown
- Duty to care

Figure 1
Reasons justifying priority setting decisions

1) Staff and patients: Staff were allocated for SARS patients in the SARS unit and ICU, screening at the doors, manning the site command centre, or helping out in occupational health; pregnant and immunosuppressed staff were either redeployed to low-risk activities or sent home; staff deemed non-essential were sent home with pay; students were sent home and educational rounds were cancelled. General medicine patients were transferred to other medical units to maintain the SARS isolation unit; outpatients who had been waiting for non-emergency surgery or clinic appointments were told to wait indefinitely.

2) Beds/rooms: The SARS isolation unit required negative pressure beds. The hospital created these spaces in a specific isolation unit on a general medicine floor, and in the ICU and Emergency. Admissions to negative pressure beds were decided case-by-case and were based on the assessment of the referring physician, the hospital’s infectious disease representative, and the hospital intensivist.

3) Clinical activity: All non-emergency surgery and ambulatory care were cancelled during the initial 7-10 days of SARS. During the ramp up phase, clinical activity volumes increased in percentages allowing for urgent cases to be seen as determined by physicians. Operating room time was allotted by division—each individual surgeon reported to their division head the cases they considered urgent. This activity was coordinated by the hospital’s command center.

4) Visitors: A “no visitors” policy was enforced during the initial stages of SARS except for compassionate grounds as determined by the nurse manager or nurse in charge of the particular unit, in consultation with the attending physician and the hospital command centre. During the ramp up phase, the hospital relaxed the no visitor policy according to changing directives from the MOHLTC and the human resources available for screening at the doors.

Decision making process: Priority setting decisions were made across all levels of the institution. We identified four groups of key decision makers: Corporate Command, Hospital Command, Department Management/Chiefs, and Individual Clinicians. MOHLTC directives were interpreted by a team of senior

Table 1: The four conditions of 'accountability for reasonableness'

Relevance	Rationales for priority setting decisions must rest on reasons (evidence and principles) that 'fair-minded' people can agree are relevant in the context. 'Fair-minded people seek to cooperate according to terms they can justify to each other – this narrows, though does not eliminate, the scope of controversy, which is further narrowed by specifying that reasons must be relevant to the specific priority setting context.
Publicity	Priority setting decisions and their rationales must be publicly accessible.
Revision/Appeals	There must be a mechanism for challenge, including the opportunity for revising decisions in light of considerations that stakeholders may raise.
Enforcement	There is either voluntary or public regulation of the process to ensure that the first three conditions are met.

administrators (corporate command) and then communicated to the hospital's command center. The hospital's command center implemented the recommendations from the corporate command in accordance with patient population requirements and physical logistics. Department managers and clinical staff also participated in allocating human resources and determining patient care priorities. The corporate command was in constant communication with the hospital's command center who maintained communication with the managers and other leaders through teleconferencing and email.

Priority setting reasoning: Throughout each stage of the SARS outbreak, safety was the primary rationale underpinning priority setting. During the early stages of SARS, decisions were made for infection control focused on protecting staff. During the ramp up phase, decisions were based more on a duty to care for patients, emphasizing the hospital's role in the community. However, in addition, there were several other reasons used in support of each decision (See Figure 1).

During the ramp up phase the reasoning shifted to address patient need. Leaders recognized that the hospital could not operate under the shut down conditions for very long; urgent cases were quickly becoming emergent. Thus, though staff and patient safety remained a primary concern, very few of the decisions can be linked solely to safety; rather, decisions involved clusters of reasons. Table 2 describes decisions made, the reasons used, and the level at which they were made.

II. Evaluation of priority setting using "accountability for reasonableness"

1) Relevance: Many participants confirmed that staff and patient safety was, appropriately, the primary criterion used in the decision-making process.

"I think due to the fact that this was so communicable, and I think, certainly felt, most people felt this was all being done in our best interest."

Some expressed concern about the relevance of the reasoning used in the allocation of OR time and in the visitor policy. For example, one surgeon commented that the OR schedule was allocated by division as opposed to being allocated by patient need. Similarly, the visitor policy was appreciated by family members of patients on an abstract level but some still could not understand why exceptions to the policy could not be made in certain instances.

Many participants found it difficult to evaluate the relevance of

the reasons underlying many of the MOHLTC directives because the directives did not explicitly describe the reasoning involved.

2) Publicity: Priority setting decisions and the reasons behind them were readily accessible to those directly involved in making the decisions. However, even though decisions and reasons were regularly distributed via email, or posted on the hospital intranet and worldwide web, many felt that communication beyond the core group of decision makers was incomplete. At the height of the crisis, MOHLTC directives were changing almost hourly, and this made real-time communications to the front lines difficult. It was generally felt that communication was excellent, with room for improvement.

"Even though we have a very good communications team you know some people are still left out of the loop—they don't read the paper, they don't listen to the radio, they don't read their emails, or they don't have email. So there are still small pockets of lack of or miscommunication, so communication is always something that we need to improve."

3) Revision/appeals: There was no revisions/appeals mechanism. Instead the hospital CEO felt it was important to address all disagreements personally. Many participants thought there were ample opportunities for informal discussion and debate in meetings and email communication. However, one participant commented that without formal appeals mechanisms, some stakeholders participated unfairly by using a "squeaky wheel" approach.

"[B]y appealing the process, the sickly squeaky wheel method of appeal, we just begged, pleaded, ranted, raved, called back, and called back."

4) Enforcement: Overwhelmingly, participants thought the process was as fair as it could have been given the time constraints and the knowledge base at the particular time. The hospital leadership made an effort to meeting the conditions of "accountability for reasonableness." However, some felt that the decision-making was not ideal.

"At a moment of crisis, which I think that SARS was, there's not always opportunity for full and open and even decision making.

Some stated that more support and accountability implementing decisions could have occurred—that there was a gap between the decisions that were made in high level administration and the implementation of those decisions at the front lines.

"Most of us felt, you know the decisions were made, up there,

Table 2: List of decisions, reasons, and decision level

Decisions: Staff and Patients	Reasons	Decision Level
Determine which staff to deploy to help with screening at the doors	Operational need; Screening capability; Infection control; Medical need	Hospital Command
Determine urgent patients and care for those first	Medical need	Individual Clinicians
The hospital as a whole determined few hospital workers unessential	Operational need; Screening capability; Infection Control	Hospital Command
Redeploy staff from screening back to clinical areas	Medical need; Duty to care; Operational need	Hospital Command
Hire screeners	Medical need; Operational need; Infection control	Hospital Command
Remove pregnant staff from the clinical environment	Staff safety	Corporate Command; Hospital Command
Decant staff and inpatients (25) from 8 th floor general medicine to make room for SARS unit and potential SARS patients	Operational need; Medical need	Hospital Command; Department Managers/Chiefs
Separate staff entrance from visitor and patient entrance	Operational need; Infection control	Corporate Command; Hospital Command
Send staff home	Infection control	Department Managers/Chiefs
Decisions: Beds	Reasons	Level Made At
Accept SARS patient transfers from other hospitals	Duty to care	Corporate Command; Individual Clinicians
Each GTA and Simcoe County hospital to establish a SARS specific isolation unit.	Infection control	MOHLTC
Hospitals greater than 500 beds will be expected to provide a 30 bed unit each. (Mar 27)		
Create SARS unit physical space on 8B with negative pressure capabilities	Directive; Infection control; Medical need; Operational need; Duty to care	Hospital Command; Department Managers/Chiefs; Individual Clinicians
Decisions: Clinical Activity	Reasons	Decision Level
Maintain emergency based activity during initial days of outbreak	Duty to care; Medical need	Corporate Command; Hospital Command
Ramp up clinical activity	Duty to care; Medical need	Corporate Command
Allocate OR time by division	Medical need; Surgeon activity	Department Managers/Chiefs
Determine which patient needed urgent OR care this could be listed second	Medical need	Individual Clinicians
SARS II – the decision not to cancel surgery again	Medical need; Duty to care	Corporate Command
Treat some 'elective cases' in the OR as being urgent	Medical need; Surgeon activity; Duty to care; Squeaky wheel	Individual Clinicians; Department Managers/Chiefs
Determine what/who is emergent and urgent in terms of clinical volumes in family medicine	Screening capability; Medical need; Squeaky wheel	Department Managers/Chiefs; Individual Clinicians
Family Medicine did not go out into the community to provide care in the initial stages of SARS (care to detox centres, shelters)	Infection control; Screening capability	Corporate Command; Department Managers/Chiefs
Decisions: Visitors	Reasons	Decision Level
No Visitor Policy except for compassionate grounds (such as palliative care, critically ill children or visiting a patient whose death may be imminent)	Infection control	MOHLTC
Restrict visitors for certain hours (5–9 pm)	Screening capability	Hospital Command
Lift visiting restrictions on case-by-case basis	Compassion; Squeaky wheel; Medical need	Department Managers/Chiefs
Hospitals must restrict access to each hospital site. Ideally, access should be restricted to one staff and one public entrance for each building	Infection control	MOHLTC

and we could understand them, we could agree with them, but we were the ones who had to live with them. And there was nobody who really came and asked us what that was like. There was some, it wasn't that there was nothing—but there wasn't a sense of being listened to the way that we needed to be listened to, the way that we needed to be supported.”

Some participants expressed concern that many staff started relying on senior management to make many of the decisions for them.

“When you go into another mode that commands and controls,

doesn't take too long until you understand how comfortable and actually how easy that is. It is way easier to do what you're told.”

CONCLUSIONS

This study examined priority setting at one Toronto hospital as it responded to the 2003 SARS crisis. Even though the crisis created safety concerns and time constraints that impinged upon decision-making, this hospital endeavored to meet the four conditions of “accountability for reasonableness.”

By describing and evaluating priority setting using the four

conditions of “accountability for reasonableness,” we are able to identify examples of “good practices” that other hospital should emulate, and “opportunities for improvement” that this and other hospitals should consider.

We identified the following good practices: 1) staff and patient safety was the primary criterion in decision making, but each decision was based on a cluster of relevant reasons—decision maker’s use of clusters of relevant reasons has been identified and discussed in the previous study,¹⁶ 2) decisions were regularly accessible on hospital email, intranet, and the world-wide web; 3) challenges were addressed directly by the CEO; 4) hospital leadership made a concerted effort to meet the conditions of “accountability for reasonableness.” We also identified the following opportunities for improvement: 1) patients and families did not have access to the reasons for many decisions, including the visitation policy and ramp-up of clinical activities; 2) a formal revision/appeals mechanism could help improve the quality of decision making and alleviate the unfair reliance on the “squeaky wheel” phenomenon; 3) OR time was allocated by division, rather than by patient need, and those decisions should be discussed more fully; 4) institutional leaders should maintain two-way contact with front-line staff who are implementing priority setting decisions—this will provide support and enhance accountability for decision making by staff.

“Accountability for reasonableness” is a framework that can be used to guide legitimate and fair priority setting in health care organizations, such as hospitals. It assumes that the time and effort required for meeting the conditions of fairness is justified for two reasons: First, it is important to act ethically and be perceived to be acting ethically—in this case, fairly. Second, acting ethically can help an organization achieve “goodwill” benefits including, but not limited to, increased trust and satisfaction and decreased complaints. However, it is clear from this scope of decisions examined in this study that time constraints imposed on a health care organization by a highly communicable and potentially fatal infectious disease creates significant priority setting difficulties. It may appear that the conditions of “accountability for reasonableness” are too demanding to implement in the time constraints—that perhaps containment should take precedence over procedural requirements. We disagree. During the SARS outbreak the hospital’s leadership developed and implemented several sophisticated processes to help with their crisis management. Tailoring those processes to meet the four conditions of “accountability for reasonableness” is not any more difficult or demanding. Moreover, we argue, and some of the participants also that in the midst of a crisis where guidance is incomplete, consequences uncertain, and information constantly changing, where hour-by-hour decisions involve life and death, fairness is more important rather than less.

Our findings are limited in that they may not be generalizable to other hospitals. However, generalizability is not the goal of qualitative studies like this. We expect that other hospitals may benefit from the insights provided in the study. For example, this was the first time that “accountability for reasonableness” has been used to evaluate priority setting in response to an infectious disease outbreak. Other hospitals in similar crises can use “accountability for reasonableness” to help evaluate and enhance the fairness of their priority setting.¹⁷

The best assurance of fair priority setting in a crisis is fair priority setting everyday. A healthcare organization that incorporates legitimate and fair decision making everyday, where the decision making culture of the organization is permeated with the conditions of “accountability for reasonableness,” will be primed to meet the challenges of fair priority setting in a crisis. This may be the most important lesson to take from this study.

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The Asthma Epidemic and Our Artificial Habitats

Wasim Maziak

ABSTRACT

Background: The recent increase in childhood asthma has been a puzzling one. Recent views focus on the role of infection in the education of the immune system of young children. However, this so called hygiene hypothesis fails to answer some important questions about the current trends in asthma or to account for environmental influences that bear little relation to infection.

Discussion: The multi-factorial nature of asthma, reflecting the different ways we tend to interact with our environment, mandates that we look at the asthma epidemic from a broader perspective. Seemingly modern affluent lifestyles are placing us increasingly in static, artificial microenvironments very different from the conditions that prevailed for most part of our evolution and shaped our organisms. Changes that occurred during the second half of the 20th century in industrialized nations with the spread of central heating/air conditioning, building insulation, hygiene, TV/PC/games, manufactured food, indoor entertainment, cars, medical care, and sedentary lifestyles all seem to be depriving our children from the essential inputs needed to develop normal airway function (resistance). Asthma according to this view is a manifestation of our respiratory maladaptation to modern lifestyles, or in other words to our increasingly artificial habitats. The basis of the artificial habitat notion may lie in reduced exposure of innate immunity to a variety of environmental stimuli, infectious and non-infectious, leading to reduced formulation of regulatory cells/cytokines as well as inscribed regulatory pathways. This could contribute to a faulty checking mechanism of non-functional Th2 (and likely Th1) responses, resulting in asthma and other immunodysregulation disorders.

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Summary: In this piece I discuss the artificial habitat concept, its correspondence with epidemiological data of asthma and allergy, and provide possible immunological underpinning for it from an evolutionary perspective of health and disease.

BACKGROUND

Asthma is a major health problem that has reached alarming proportions in the past two decades in western societies.¹ What lies behind the recent increase in asthma in affluent societies is still an area of lively debate, but its rapid changing patterns and huge variation across populations favor environmental explanations.¹⁻³ While assessment of different old and new exposures is continuing, a unifying paradigm remains elusive, so as a guiding principle for prevention. The simultaneous increase of all forms of allergic disease, on the other hand, argues for a change in host susceptibility/resistance.⁴

The apparent association between asthma and western lifestyle has led to numerous studies trying to link novel or increased exposures associated with westernization-modernization, especially those occurring during childhood, to asthma. For example, exposure to gas cooking, tobacco smoke, trans fatty acids, domestic animals, and allergens were found to influence respiratory health, but did not provide a conclusive answer to the current trends in asthma.⁵⁻¹⁰ While it is early to discard the role of these and other factors, a major contribution of asthma research during the past two decades lies in the elucidation of its heterogeneous and multi-factorial nature, where different exposures have different roles and relevance depending on the target population, setting, and disease course.

DISCUSSION

1 - The hygiene hypothesis and asthma

Since its introduction in the nineties, the hygiene hypothesis (HH) continues to generate enthusiasm among asthma researchers as the most comprehensive theoretical framework, by which the relation between suspected environmental factors and allergy can be tested.¹¹⁻¹³ This hypothesis originated from the coupling of observations on the allergy-protective effect of sibship size/birth-order with the emerging concept of helper T

cell polarization into two counter-regulatory subsets; pro-infection Th1, and pro-allergy Th2.^{14, 15} Backed by some experimental and clinical evidence,¹⁶⁻¹⁸ the hygiene hypothesis suggests that the recent rise in allergic disease among children in affluent societies is due to the preferential programming of the T cell repertoire towards pro-allergy Th2 responses, brought by the decline in infections (increased hygiene, immunization, decreased sibship size, antibiotic use).¹³⁻¹⁵ With the increasing recognition of the role of T regulatory cells (Tregs) and cytokines in the pathogenesis of allergic inflammation, the hygiene paradigm has been extended recently integrating infection's role in generating such cells and mediators.¹⁹⁻²¹

Asthma trends, however, did not fit well with the hygiene model, which failed to explain the urban predominance of asthma, the increase in non-allergic asthma, the disparity between atopy and allergy in some populations, and the asthma inducing properties of some infections.²²⁻²⁷ Specifically, studies looking at the infection-asthma relationship failed to yield a consistent pattern so far,²⁸⁻³⁴ prompting David Strachan, the father of the hygiene hypothesis, to conclude that "the totality of current evidence from cross sectional and longitudinal studies of common specific and non-specific infectious illnesses in infancy and childhood offers no support for the hygiene hypothesis."¹¹ Other studies doubted even the fundamentals of the HH showing that the effect of siblings is not universal, or could have been programmed in utero rather than being a marker of childhood infection.^{35, 36} Perhaps the hygiene model's major shortcoming lies in its concentration on only one aspect (infection) of the drastic change that touched upon every detail of life in western societies in the past few decades. It also adopted a mechanistic approach for the study of adaptive immune responses and the relation between exposure-outcome, where an array of potential interactions are reduced to a single level; Th1-Th2 counter-regulation, siblings-infection, daycare attendance-infection, dog ownership-endotoxin, farming-endotoxin, etc. In brief, the search for a holy grail in the asthma epidemic may need to be replaced by the conceptualization of a more generalizing notion that allows for the consideration of a multitude of factors within an ever-changing environment.

2 - Asthma and our artificial habitats

The hygiene model on the other hand, involved an evolutionary logic alerting us to the negative potential of sudden elimination of exposures that have shaped throughout the ages our organs and systems.³⁷ Health from such a perspective is not about abstract assessment of the relation between exposure and outcome, or eliminating harmful exposures, but about seeing the whole dynamics of our interaction with our novel habitats.³⁸ Because of the slowness of adaptive evolutionary machinery, of particular interest according to this perspective are lifestyle factors that either witnessed a rapid change in recent times or represent an obvious departure from the conditions that prevailed for most part of our evolution, i.e. factors likely to exemplify the discordance between our "Stone Age" genes and "Space Age" living conditions.^{37, 38}

General trends of asthma show that populations who conserved elements of ancient lifestyles have low levels of asthma. The north-south, urban rural, gradients in asthma occurrence have been extensively documented.^{24, 37, 39-43} In addition, studies in Africa show that some populations seem to be protected from asthma regardless of atopic predisposition or parasitic infection (both are Th2-related).^{20, 22, 44-46} This indicates that some

environmental influences associated with more traditional lifestyles are conferring respiratory resistance to stimuli that could have led otherwise to clinically relevant airway inflammation. Within western societies furthermore, lower levels of asthma were found in families with traditional lifestyles^{47, 48} and higher levels of asthma were found among obese or less physically fit children and adults.⁴⁹⁻⁵¹ Because not all these observations can be explained by variability in infection, or any other single factor for that matter, a broader concept seems more plausible.

Modern life is increasingly placing us in static, artificial, micro-niches optimized for our convenience, but which bear little resemblance to the dynamic inputs provided by the environments that nurtured our evolution. In other words, we are increasingly living within an array of artificial habitats designed to handle us very well, but we may well not be equipped to handle them. Asthma according to this view, becomes a manifestation of our respiratory maladaptation to modern lifestyles. Changes that occurred during the second half of the 20th century in industrialized countries with the spread of central heating/conditioning, building insulation, hygiene, TV/PC/games, manufactured food, indoor entertainment, cars, medical care, and sedentary lifestyles all seem to be depriving our children from the essential inputs needed to develop normal airway function (resistance).

3 - Epidemiology of asthma from a new perspective

The suggested view - called here the artificial habitat (AH) - can provide alternative interpretations to existing data starting with the protective effect of sibship size/birth-order, which is one of the landmark observations of the HH that has been ascribed to increased exposure to infection.⁵² It can be postulated that the mechanism of protection of siblings (especially older males) is related to their importance to the child's level of physical activity as well as ability to spend more time outdoors (i.e. in a more dynamic environment). This is particularly relevant to children living in dangerous neighborhoods, such as inner cities in the US, where the spread of asthma represents one of the main challenges to the hygiene paradigm.⁵³ Indeed, Andrew-Aligne and colleagues found that the higher prevalence of asthma among inner city black children is not due to race or low income per se, but to their living in an urban setting.⁵⁴ Additional intriguing support to the AH notion comes from the two largest studies looking at the effect of siblings on the occurrence of allergy, whereby a stronger protective effect was observed for brothers than for sisters.^{55, 56} While exposure to infection cannot be expected to be related to sibling's gender, activity and outdoor time may well be influenced by this factor. By the same token, birth order can determine, among other things (e.g. social development, healthy food availability), the child's level of activity (how many playmates the child has) and ability to spend time outdoors. As new evidence emerging against the HH's assumption considering the infection-related effect of the sibship size/birth-order, by showing for example that the role of birth order is independent of sibship size,⁵⁷ and that in the same population sibship size can protect against asthma while infection predisposes to it,^{31, 58} the AH concept seems to offer an alternative explanation.

Another important observation of the hygiene paradigm concerns the protective effect of early daycare attendance on later development of asthma, which is ascribed to increased exposure of infection.²⁸ Alternatively, it can be argued that the

daily routine at a daycare center would be different in many aspects from home, in addition to exposure to infection. Reducing potential differences in activity, exposure, socio-behavioral development, and parental attitudes between those who do and don't attend daycare to mere infection seems oversimplistic. The AH concept looks at this observation from a broader angle involving a mixture of lifestyle and developmental factors. Related to this issue is the argued window of opportunity in early infancy for the protective effect of daycare attendance/infection,^{59, 60} which is connected to a critical period of immune education.¹³ By its own nature in contrast, the AH view is consistent with the notion that environmental signals throughout the lifespan can affect the risk as well as the course of asthma and allergy.

On a different juncture of asthma research, a multitude of recently published reports show lower rates of asthma and atopy in children raised on a farm.⁶¹⁻⁶⁸ Heavily influenced by the HH, these observations were largely attributed to increased exposure to bacterial components found in barns or farm milk (endotoxin in particular),⁶⁷⁻⁶⁹ forgoing that children raised on a farm have very different lifestyles from children growing in inner cities in the US for example, where infection is also commonplace.⁷⁰ For example, one of the landmark farming studies has shown that endotoxin levels in children's mattresses were inversely associated with the occurrence of hay fever and atopic asthma.⁶⁷ However, leukocytes of children exposed to high levels of endotoxin produce less Th2 suppressing cytokines (mainly interleukin 10), arguing against the endotoxin-hygiene paradigm.^{67, 71, 72} From the AH perspective however, a farm is the closest we can get in today's western societies to conditions that prevailed for most part of our evolution. Such an environment can provide ample opportunities of behaviors and exposures different from those of modern urban life.

The AH perspective is consistent with the assumption that time spent outdoors and level of physical activity should be protective against the development of asthma. A recent study by McConnell and colleagues however, has shown just the opposite, where the risk of developing asthma was positively associated with number of sports played and time spent outdoors.⁷³ However, when participating communities were separated according to their level of atmospheric ozone, this association was only seen in the high ozone levels communities, while number of sports played and time spent outdoors seem to be protective in the low ozone communities.⁷³ On the other hand, twins in the Odense study who participated in conditioning exercise had a decreased risk of asthma compared to the more sedentary co-twins.⁵¹ The psychological underpinning of the effect of activity on asthma can be partly elucidated by the work of Feldberg and colleagues and Togias and colleagues, who showed that disruption of dynamic breathing (static breathing without deep breaths or sighing) can lead to bronchial hyper-responsiveness (BHR), the pathophysiological hallmark of asthma.^{74, 75} Furthermore, recent evidence shows that obesity and weight gain are associated with increased risk of BHR,⁷⁶ providing more insight on possible ways by which sedentary life factors can co-interact to predispose to asthma.

Finally, the AH concept can offer an explanation for some puzzling observations, such as the protective effect of dog ownership on asthma.^{77, 78} While the HH proponents looked for explanation in endotoxin levels associated with dog ownership,

but with conflicting results so far,⁷⁹ one can argue that the change in lifestyle (of children particularly) associated with dog ownership can be responsible (more playing, more time out, emotional interaction, as well as exposure to dog's constituents). Generally, families who opt to have a dog may be different from those who don't in being more active and outgoing. The focus here on activity and outdoor time is because these factors are clearly envisioned. Other aspects of traditional lifestyles may be just as important, such as household air exchange (eg affecting allergens, pollutants, humidity), nutritional habits (eg breast feeding), as well as behavioral adaptations.

4 - An innate control of asthma and allergy

Now how can the AH view be related to what we know about the immunopathology of asthma and allergy? Asthma is an immunological disorder with a predominant Th2 inflammatory response in the airways. This Th2 response is thought to be a remnant of our ability to expel parasites abundant in the cradle of human evolution, the tropical savannah.⁸⁰ Indeed, evidence exist showing that Th2 pro-inflammatory genetic alleles are more prevalent in populations with a tropical origin than those with a temperate one.⁸¹ It is possible that the need to deal with a wide variety of pathogens may have meant that the activation threshold of Th2 responses has to be set low, leading to many false alarms to non-pathogenic particles and giving rise to asthma. Evolutionary logic indicates however, that a trait with a potential to endanger air passage into our vital respiratory organs would not have been selected, had some regulatory mechanisms not been in place. Studies on the initial phase of allergic sensitization show that a transient low-level IgE (the atopic antibody) response to inhaled antigen occurs in normal children, with those who do not develop allergy down-regulate it in the first years of life.⁸²⁻⁸⁴ Asthma in this regard, becomes a manifestation of breakdown of regulatory mechanisms at respiratory mucosal surfaces.

But let's take one step back to look at another recent puzzling trend; the increase of Th1 autoimmune disorders such as type-1 diabetes and multiple sclerosis in western societies.²¹ Recent evidence suggests that the two groups (Th1 and Th2 mediated diseases) can be associated in individuals,⁸⁵⁻⁸⁸ arguing against the Th1-Th2 counter-suppression of the HH, and favoring a common ground of faulty regulation. Such developments were picked up by proponents of the HH to suggest that hygiene can work through depriving the immune system from signals necessary for the development of regulatory pathways/cells capable of dampening both Th1 and Th2 responses.^{89, 90} While this can be true, the focus on infection yet again is a reductionistic view likely to suffer the same shortcomings of the original Th1-Th2 counter-regulation of the HH. At the same time, advances made in immunology were unraveling the central role of the innate immune system in orchestrating immune responses.⁹¹ In particular, antigen presenting cells, such as dendritic cells (DCs), can engage infectious components with their Toll-like receptors (TLRs) (a group of ancient immune recognition molecules) leading to activation of adaptive immune responses and induction of regulatory cells and mediators.^{92, 93} In their turn, T regulatory cells (Tregs), which are induced naturally or by elements of innate immunity are able to regulate all types of adaptive immune responses as well as influence DCs activation and regulation.^{94, 95} Interestingly, it looks that none of the Th1, Th2, or Treg-inducing functions of DCs is an intrinsic attribute that is not sensitive to instructions from the

surrounding environment.^{96, 97} Without getting into the details of this fascinating and still unfolding field, the move from the see/saw mechanistic counter-regulation of adaptive Th1-Th2 responses to elements of innate immunity offers an evolutionary sound and possibly robust checking mechanism (break) against inappropriate responses (eg, Th2 responses to non-pathogenic elements) at our vital airways. The ability of DCs to be activated in response to danger signals induced by stress, damage, or necrotic cell death,⁹⁸ and the role of DCs at the gastrointestinal tract in the development of mucosal tolerance,⁹⁹ broadens their possible range of involvement with different environmental stimuli and thus their contribution to immune homeostasis at the respiratory surface. For example, heat-shock proteins (hsps, which are highly conserved cellular proteins that can be produced by thermal stimuli, physical activity, or other stresses) can activate DCs as well as contribute to T cell regulation of inflammatory responses.^{100, 101}

Taken together, it can be suggested according to the AH concept that dynamic/traditional lifestyles with associated exposures can ensure constant challenge of DCs and other elements of innate immunity giving rise to immune responses, but at the same time maintaining adequate turnover of regulatory cells and cytokines and inscribed regulatory pathways. This ongoing activation of regulatory pathways can help maintain healthy control of non-functional Th2 responses at the respiratory surface. The DC-orchestrated dynamic balance between Th2 responses and regulatory mechanisms is likely to influence all phases (initiation, effector) or inflammation in the airways, and throughout the lifespan of the individual.

SUMMARY

While it offers no specific explanation to different asthma trends and variations, the suggested AH notion provides a generalizing scheme for the study of asthma, and provides novel insights for existing epidemiological observations. According to this perspective there is no single answer to the asthma epidemic, but different factors have different relevance depending on the population and environment in focus. In addition to being free from the HH one-dimensional approach for the relation between exposure-outcome, this view is evolutionary-driven allowing us to place the asthma epidemic within the wider perspective of increasing discordance between us and our dramatically changing environments. Sedentary lifestyles, static indoor microenvironments, and automation of the food chain are apparently not only predisposing us to obesity and cardiovascular disease but also depriving our respiratory system from many stimuli necessary for the development of normal airway resistance. The immunological basis of the AH notion can lie in the centrality of innate immunity and its ability to respond to different types of environmental stimuli, insuring adequate turnover of regulatory cells and mediators. The evolutionary tenet “the more we change the world the more we stay the same” probably lacks accuracy. Newer environments, constantly confront us with new adaptive challenges that should be looked upon, as in the case of asthma, within the evolutionary context of health and disease.

ABBREVIATIONS

HH	hygiene hypothesis
AH	artificial habitat
DCs	dendritic cells
BHR	bronchial hyper-responsiveness
IL10	interleukin 10
hsps	heat shock proteins
Th1	T helper cell type 1
Th2	T helper cell type 2
Tregs	regulatory T cells
IgE	immunoglobuline E
TLRs	Toll-like receptors

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Why Most Published Research Findings Are False

John P. A. Ioannidis

SUMMARY

There is increasing concern that most current published research findings are false. The probability that a research claim is true may depend on study power and bias, the number of other studies on the same question, and, importantly, the ratio of true to no relationships among the relationships probed in each scientific field. In this framework, a research finding is less likely to be true when the studies conducted in a field are smaller; when effect sizes are smaller; when there is a greater number and lesser preselection of tested relationships; where there is greater flexibility in designs, definitions, outcomes, and analytical modes; when there is greater financial and other interest and prejudice; and when more teams are involved in a scientific field in chase of statistical significance. Simulations show that for most study designs and settings, it is more likely for a research claim to be false than true. Moreover, for many current scientific fields, claimed research findings may often be simply accurate measures of the prevailing bias. In this essay, I discuss the implications of these problems for the conduct and interpretation of research.

Published research findings are sometimes refuted by subsequent evidence, with ensuing confusion and disappointment. Refutation and controversy is seen across the range of research designs, from clinical trials and traditional epidemiological studies to the most modern molecular research. There is increasing concern that in modern research, false findings may be the majority or even the vast majority of published research claims. However, this should not be surprising. It can be proven that most claimed research findings

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are false. Here I will examine the key factors that influence this problem and some corollaries thereof.

MODELING THE FRAMEWORK FOR FALSE POSITIVE FINDINGS

Several methodologists have pointed out that the high rate of nonreplication (lack of confirmation) of research discoveries is a consequence of the convenient, yet ill-founded strategy of claiming conclusive research findings solely on the basis of a single study assessed by formal statistical significance, typically for a p-value less than 0.05. Research is not most appropriately represented and summarized by p-values, but, unfortunately, there is a widespread notion that medical research articles should be interpreted based only on p-values. Research findings are defined here as any relationship reaching formal statistical significance, eg, effective interventions, informative predictors, risk factors, or associations. “Negative” research is also very useful. “Negative” is actually a misnomer, and the misinterpretation is widespread. However, here we will target relationships that investigators claim exist, rather than null findings.

IT CAN BE PROVEN THAT MOST CLAIMED RESEARCH FINDINGS ARE FALSE

As has been shown previously, the probability that a research finding is indeed true depends on the prior probability of it being true (before doing the study), the statistical power of the study, and the level of statistical significance. Consider a 2×2 table in which research findings are compared against the gold standard of true relationships in a scientific field. In a research field both true and false hypotheses can be made about the presence of relationships. Let R be the ratio of the number of “true relationships” to “no relationships” among those tested in the field. R is characteristic of the field and can vary a lot depending on whether the field targets highly likely relationships or searches for only one or a few true relationships among thousands and millions of hypotheses that may be postulated. Let us also consider, for computational simplicity, circumscribed fields where either there is only one true relationship (among many that can be hypothesized) or the

Table 1. Research Findings and True Relationships

Research Finding	True Relationship		Total
	Yes	No	
Yes	$c(1 - \beta)R/(R + 1)$	$c\alpha/(R + 1)$	$c(R + \alpha - \beta R)/(R + 1)$
No	$c\beta R/(R + 1)$	$c(1 - \alpha)/(R + 1)$	$c(1 - \alpha + \beta R)/(R + 1)$
Total	$cR/(R + 1)$	$c/(R + 1)$	c

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Table 2. Research Findings and True Relationships in the Presence of Bias

Research Finding	True Relationship		Total
	Yes	No	
Yes	$(c[1 - \beta]R + uc\beta R)/(R + 1)$	$c\alpha + uc(1 - \alpha)/(R + 1)$	$c(R + \alpha - \beta R + u - u\alpha + u\beta R)/(R + 1)$
No	$(1 - u)c\beta R/(R + 1)$	$(1 - u)c(1 - \alpha)/(R + 1)$	$c(1 - u)(1 - \alpha + \beta R)/(R + 1)$
Total	$cR/(R + 1)$	$c/(R + 1)$	c

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Table 3. Research Findings and True Relationships in the Presence of Multiple Studies

Research Finding	True Relationship		Total
	Yes	No	
Yes	$cR(1 - \beta^n)/(R + 1)$	$c(1 - [1 - \alpha]^n)/(R + 1)$	$c(R + 1 - [1 - \alpha]^n - R\beta^n)/(R + 1)$
No	$cR\beta^n/(R + 1)$	$c(1 - \alpha)^n/(R + 1)$	$c([1 - \alpha]^n + R\beta^n)/(R + 1)$
Total	$cR/(R + 1)$	$c/(R + 1)$	c

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Table 4. PPV of Research Findings for Various Combinations of Power ($1 - \beta$), Ratio of True to Not-True Relationships (R), and Bias (u)

$1 - \beta$	R	u	Practical Example	PPV
0.80	1:1	0.10	Adequately powered RCT with little bias and 1:1 pre-study odds	0.85
0.95	2:1	0.30	Confirmatory meta-analysis of good-quality RCTs	0.85
0.80	1:3	0.40	Meta-analysis of small inconclusive studies	0.41
0.20	1:5	0.20	Underpowered, but well-performed phase I/II RCT	0.23
0.20	1:5	0.80	Underpowered, poorly performed phase I/II RCT	0.17
0.80	1:10	0.30	Adequately powered exploratory epidemiological study	0.20
0.20	1:10	0.30	Underpowered exploratory epidemiological study	0.12
0.20	1:1,000	0.80	Discovery-oriented exploratory research with massive testing	0.0010
0.20	1:1,000	0.20	As in previous example, but with more limited bias (more standardized)	0.0015

The estimated PPVs (positive predictive values) are derived assuming $\alpha = 0.05$ for a single study. RCT, randomized controlled trial.

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power is similar to find any of the several existing true relationships. The pre-study probability of a relationship being true is $R/(R + 1)$. The probability of a study finding a true relationship reflects the power $1 - \beta$ (one minus the Type II error rate). The probability of claiming a relationship when none truly exists reflects the Type I error rate, α . After a research finding has been claimed based on achieving formal statistical significance, the post-study probability that it is true is the positive predictive value, PPV. The PPV is also the complementary probability of what Wacholder et al. have called the false positive report probability. According to the 2×2 table, one gets $PPV = (1 - \beta)R/(R - \beta R + \alpha)$. A research finding is thus more likely true than false if $(1 - \beta)R > \alpha$. Since usually the vast majority of investigators depend on $\alpha = 0.05$, this means that a research finding is more likely true than false if $(1 - \beta)R > 0.05$. What is less well appreciated is that bias and the extent of repeated independent testing by different teams of investigators around the globe may further distort this picture and may lead to even smaller probabilities of the research findings being indeed true.

BIAS

First, let us define bias as the combination of various design, data, analysis, and presentation factors that tend to produce research findings when they should not be produced. Let u be the proportion of probed analyses that would not have been “research findings,” but nevertheless end up presented and reported as such, because of bias. Bias should not be confused with chance variability that causes some findings to be false by chance even though the study design, data, analysis, and presentation are perfect. Bias can entail manipulation in the analysis or reporting of findings. Selective or distorted reporting is a typical form of such bias. We may assume that u does not depend on whether a true relationship exists or not. This is not an unreasonable assumption, since typically it is impossible to know which relationships are indeed true. With increasing bias, the chances that a research finding is true diminish considerably.

Conversely, true research findings may occasionally be annulled because of reverse bias. For example, with large measurement errors relationships are lost in noise, or investigators use data inefficiently or fail to notice statistically significant relationships, or there may be conflicts of interest that tend to “bury” significant findings. There is no good large-scale empirical evidence on how frequently such reverse bias may occur across diverse research fields. However, it is probably fair to say that reverse bias is not as common. Moreover measurement errors and inefficient use of data are probably becoming less frequent problems, since measurement error has decreased with technological advances in the molecular era and investigators are becoming increasingly sophisticated about their data. Regardless, reverse bias may be modeled in the same way as bias above. Also reverse bias should not be confused with chance variability that may lead to missing a true relationship because of chance.

TESTING BY SEVERAL INDEPENDENT TEAMS

Several independent teams may be addressing the same sets of research questions. As research efforts are globalized, it is practically the rule that several research teams, often dozens of them, may probe the same or similar questions. Unfortunately, in some areas, the prevailing mentality until now has been to focus on isolated discoveries by single teams and interpret

research experiments in isolation. An increasing number of questions have at least one study claiming a research finding, and this receives unilateral attention. The probability that at least one study, among several done on the same question, claims a statistically significant research finding is easy to estimate.

COROLLARIES

A practical example is shown in Box 1. Based on the above considerations, one may deduce several interesting corollaries about the probability that a research finding is indeed true.

Corollary 1: The smaller the studies conducted in a scientific field, the less likely the research findings are to be true.

Small sample size means smaller power and, for all functions above, the PPV for a true research finding decreases as power decreases towards $1 - \beta = 0.05$. Thus, other factors being equal, research findings are more likely true in scientific fields that undertake large studies, such as randomized controlled trials in cardiology (several thousand subjects randomized) than in scientific fields with small studies, such as most research of molecular predictors (sample sizes 100-fold smaller).

Corollary 2: The smaller the effect sizes in a scientific field, the less likely the research findings are to be true.

Power is also related to the effect size. Thus research findings are more likely true in scientific fields with large effects, such as the impact of smoking on cancer or cardiovascular disease (relative risks 3–20), than in scientific fields where postulated effects are small, such as genetic risk factors for multigenetic diseases (relative risks 1.1–1.5). Modern epidemiology is increasingly obliged to target smaller effect sizes. Consequently, the proportion of true research findings is expected to decrease. In the same line of thinking, if the true effect sizes are very small in a scientific field, this field is likely to be plagued by almost ubiquitous false positive claims. For example, if the majority of true genetic or nutritional determinants of complex diseases confer relative risks less than 1.05, genetic or nutritional epidemiology would be largely utopian endeavors.

Corollary 3: The greater the number and the lesser the selection of tested relationships in a scientific field, the less likely the research findings are to be true.

As shown above, the post-study probability that a finding is true (PPV) depends a lot on the pre-study odds (R). Thus, research findings are more likely true in confirmatory designs, such as large phase III randomized controlled trials, or meta-analyses thereof, than in hypothesis-generating experiments. Fields considered highly informative and creative given the wealth of the assembled and tested information, such as microarrays and other high-throughput discovery-oriented research, should have extremely low PPV.

Corollary 4: The greater the flexibility in designs, definitions, outcomes, and analytical modes in a scientific field, the less likely the research findings are to be true.

Flexibility increases the potential for transforming what would be “negative” results into “positive” results, i.e., bias, u . For several research designs, eg, randomized controlled trials or meta-analyses, there have been efforts to standardize their conduct and reporting. Adherence to common standards is likely to increase the proportion of true findings. The same applies to outcomes. True findings may be more common when outcomes are unequivocal and universally agreed (eg, death)

rather than when multifarious outcomes are devised (e.g., scales for schizophrenia outcomes). Similarly, fields that use commonly agreed, stereotyped analytical methods (eg, Kaplan-Meier plots and the log-rank test) may yield a larger proportion of true findings than fields where analytical methods are still under experimentation (eg, artificial intelligence methods) and only “best” results are reported. Regardless, even in the most stringent research designs, bias seems to be a major problem. For example, there is strong evidence that selective outcome reporting, with manipulation of the outcomes and analyses reported, is a common problem even for randomized trials. Simply abolishing selective publication would not make this problem go away.

Corollary 5: The greater the financial and other interests and prejudices in a scientific field, the less likely the research findings are to be true. Conflicts of interest and prejudice may increase bias, *u*. Conflicts of interest are very common in biomedical research, and typically they are inadequately and sparsely reported. Prejudice may not necessarily have financial roots. Scientists in a given field may be prejudiced purely because of their belief in a scientific theory or commitment to their own findings. Many otherwise seemingly independent, university-based studies may be conducted for no other reason than to give physicians and researchers qualifications for promotion or tenure. Such nonfinancial conflicts may also lead to distorted reported results and interpretations. Prestigious investigators may suppress via the peer review process the appearance and dissemination of findings that refute their findings, thus condemning their field to perpetuate false dogma. Empirical evidence on expert opinion shows that it is extremely unreliable.

Corollary 6: The hotter a scientific field (with more scientific teams involved), the less likely the research findings are to be true. This seemingly paradoxical corollary follows because, as stated above, the PPV of isolated findings decreases when many teams of investigators are involved in the same field. This may explain why we occasionally see major excitement followed rapidly by severe disappointments in fields that draw wide attention. With many teams working on the same field and with massive experimental data being produced, timing is of the essence in beating competition. Thus, each team may prioritize on pursuing and disseminating its most impressive “positive” results. “Negative” results may become attractive for dissemination only if some other team has found a “positive” association on the same question. In that case, it may be attractive to refute a claim made in some prestigious journal. The term Proteus phenomenon has been coined to describe this phenomenon of rapidly alternating extreme research claims and extremely opposite refutations. Empirical evidence suggests that this sequence of extreme opposites is very common in molecular genetics.

These corollaries consider each factor separately, but these factors often influence each other. For example, investigators working in fields where true effect sizes are perceived to be small may be more likely to perform large studies than investigators working in fields where true effect sizes are perceived to be large. Or prejudice may prevail in a hot scientific field, further undermining the predictive value of its research findings. Highly prejudiced stakeholders may even create a barrier that aborts efforts at obtaining and

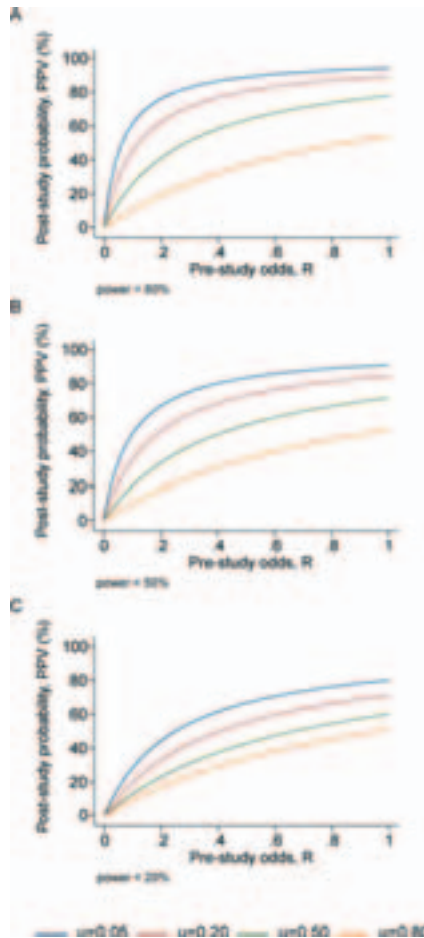
disseminating opposing results. Conversely, the fact that a field is hot or has strong invested interests may sometimes promote larger studies and improved standards of research, enhancing the predictive value of its research findings. Or massive discovery-oriented testing may result in such a large yield of significant relationships that investigators have enough to report and search further and thus refrain from data dredging and manipulation.

MOST RESEARCH FINDINGS ARE FALSE FOR MOST RESEARCH DESIGNS AND FOR MOST FIELDS

In the described framework, a PPV exceeding 50% is quite difficult to get. A finding from a well-conducted, adequately powered randomized controlled trial starting with a 50% pre-study chance that the intervention is effective is eventually true about 85% of the time. A fairly similar performance is expected of a confirmatory meta-analysis of good-quality randomized trials: potential bias probably increases, but power and pre-test chances are higher compared to a single randomized trial. Conversely, a meta-analytic finding from inconclusive studies where pooling is used to “correct” the low power of single studies, is probably false if $R \leq 1:3$. Research findings from underpowered, early-phase clinical trials would be true about one in four times, or even less frequently if bias is present. Epidemiological studies of an exploratory nature perform even worse, especially when underpowered, but even well-powered epidemiological studies may have only a one in five chance being true, if $R = 1:10$. Finally, in discovery-oriented research with massive testing, where tested relationships exceed true ones 1,000-fold (e.g., 30,000 genes tested, of which 30 may be the true culprits), PPV for each claimed relationship is extremely low, even with considerable standardization of laboratory and statistical methods, outcomes, and reporting thereof to minimize bias.

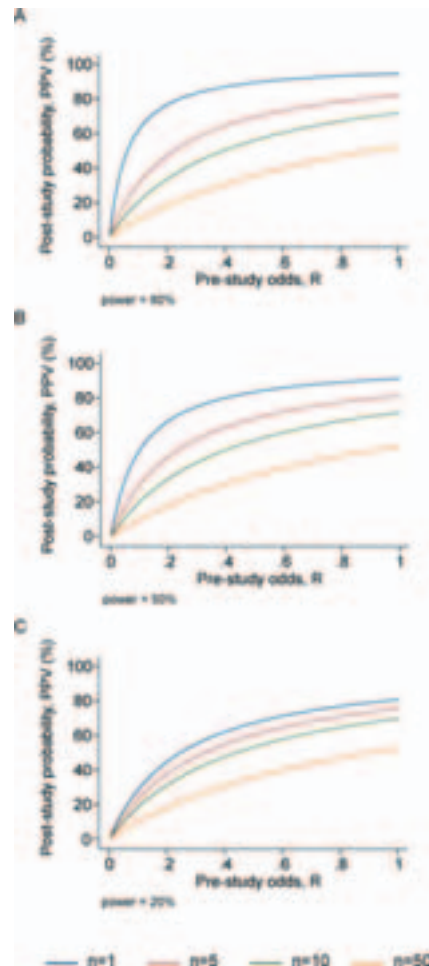
Claimed research findings may often be simply accurate measures of the prevailing bias. The majority of modern biomedical research is operating in areas with very low pre- and post-study probability for true findings. Let us suppose that in a research field there are no true findings at all to be discovered. History of science teaches us that scientific endeavor has often in the past wasted effort in fields with absolutely no yield of true scientific information, at least based on our current understanding. In such a “null field,” one would ideally expect all observed effect sizes to vary by chance around the null in the absence of bias. The extent that observed findings deviate from what is expected by chance alone would be simply a pure measure of the prevailing bias.

For example, let us suppose that no nutrients or dietary patterns are actually important determinants for the risk of developing a specific tumor. Let us also suppose that the scientific literature has examined 60 nutrients and claims all of them to be related to the risk of developing this tumor with relative risks in the range of 1.2 to 1.4 for the comparison of the upper to lower intake tertiles. Then the claimed effect sizes are simply measuring nothing else but the net bias that has been involved in the generation of this scientific literature. Claimed effect sizes are in fact the most accurate estimates of the net bias. It even follows that between “null fields,” the fields that claim stronger effects (often with accompanying claims of medical or public health importance) are simply those that have sustained the worst biases.



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Figure 1. PPV (Probability That a Research Finding Is True) as a Function of the Pre-Study Odds for Various Levels of Bias, u
Panels correspond to power of 0.20, 0.50, and 0.80.



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Figure 2. PPV (Probability That a Research Finding Is True) as a Function of the Pre-Study Odds for Various Numbers of Conducted Studies, n
Panels correspond to power of 0.20, 0.50, and 0.80.

For fields with very low PPV, the few true relationships would not distort this overall picture much. Even if a few relationships are true, the shape of the distribution of the biases involved in the field. This concept totally reverses the way we view scientific results. Traditionally, investigators have viewed large and highly significant effects with excitement, as signs of important discoveries. Too large and too highly significant effects may actually be more likely to be signs of large bias in most fields of modern research. They should lead investigators to careful critical thinking about what might have gone wrong with their data, analyses, and results.

Of course, investigators working in any field are likely to resist accepting that the whole field in which they have spent their careers is a “null field.” However, other lines of evidence, or advances in technology and experimentation, may lead eventually to the dismantling of a scientific field. Obtaining measures of the net bias in one field may also be useful for obtaining insight into what might be the range of bias operating in other fields where similar analytical methods, technologies, and conflicts may be operating.

HOW CAN WE IMPROVE THE SITUATION?

Is it unavoidable that most research findings are false, or can we improve the situation? A major problem is that it is impossible to know with 100% certainty what the truth is in any research question. In this regard, the pure “gold” standard is unattainable. However, there are several approaches to improve the post-study probability.

Better powered evidence, eg, large studies or low-bias meta-analyses, may help, as it comes closer to the unknown “gold” standard. However, large studies may still have biases and these should be acknowledged and avoided. Moreover, large-scale evidence is impossible to obtain for all of the millions and trillions of research questions posed in current research. Large-scale evidence should be targeted for research questions where the pre-study probability is already considerably high, so that a significant research finding will lead to a post-test probability that would be considered quite definitive. Large-scale evidence is also particularly indicated when it can test major concepts rather than narrow, specific questions. A negative finding can then refute not only a specific proposed claim, but a whole field or considerable portion thereof. Selecting the performance of

large-scale studies based on narrow-minded criteria, such as the marketing promotion of a specific drug, is largely wasted research. Moreover, one should be cautious that extremely large studies may be more likely to find a formally statistical significant difference for a trivial effect that is not really meaningfully different from the null.

Second, most research questions are addressed by many teams, and it is misleading to emphasize the statistically significant findings of any single team. What matters is the totality of the evidence. Diminishing bias through enhanced research standards and curtailing of prejudices may also help. However, this may require a change in scientific mentality that might be difficult to achieve. In some research designs, efforts may also be more successful with upfront registration of studies, e.g., randomized trials. Registration would pose a challenge for hypothesis-generating research. Some kind of registration or networking of data collections or investigators within fields may

be more feasible than registration of each and every hypothesis-generating experiment. Regardless, even if we do not see a great deal of progress with registration of studies in other fields, the principles of developing and adhering to a protocol could be more widely borrowed from randomized controlled trials.

Finally, instead of chasing statistical significance, we should improve our understanding of the range of R values—the pre-study odds—where research efforts operate. Before running an experiment, investigators should consider what they believe the chances are that they are testing a true rather than a non-true relationship. Speculated high R values may sometimes then be ascertained. As described above, whenever ethically acceptable, large studies with minimal bias should be performed on research findings that are considered relatively established, to see how often they are indeed confirmed. I suspect several established “classics” will fail the test.

Nevertheless, most new discoveries will continue to stem from hypothesis-generating research with low or very low pre-study odds. We should then acknowledge that statistical significance testing in the report of a single study gives only a partial picture, without knowing how much testing has been done outside the report and in the relevant field at large. Despite a large statistical literature for multiple testing corrections, usually it is impossible to decipher how much data dredging by the reporting authors or other research teams has preceded a reported research finding. Even if determining this were feasible, this would not inform us about the pre-study odds. Thus, it is unavoidable that one should make approximate assumptions on how many relationships are expected to be true among those probed across the relevant research fields and research designs. The wider field may yield some guidance for estimating this probability for the isolated research project. Experiences from biases detected in other neighboring fields would also be useful to draw upon. Even though these assumptions would be considerably subjective, they would still be very useful in interpreting research claims and putting them in context.

An Example: Science at Low Pre-Study Odds

Let us assume that a team of investigators performs a whole genome association study to test whether any of 100,000 gene polymorphisms are associated with susceptibility to schizophrenia. Based on what we know about the extent of heritability of the disease, it is reasonable to expect that probably around ten gene polymorphisms among those tested would be truly associated with schizophrenia, with relatively similar odds ratios around 1.3 for the ten or so polymorphisms and with a fairly similar power to identify any of them. Then $R = 10/100,000 = 10^{-4}$, and the pre-study probability for any polymorphism to be associated with schizophrenia is also $R/(R + 1) = 10^{-4}$. Let us also suppose that the study has 60% power to find an association with an odds ratio of 1.3 at $\alpha = 0.05$. Then it can be estimated that if a statistically significant association is found with the p-value barely crossing the 0.05 threshold, the post-study probability that this is true increases about 12-fold compared with the pre-study probability, but it is still only 12×10^{-4} .

Now let us suppose that the investigators manipulate their design, analyses, and reporting so as to make more relationships cross the $p = 0.05$ threshold even though this would not have been crossed with a perfectly adhered to design and analysis and with perfect comprehensive reporting of the results, strictly according to the original study plan. Such manipulation could be done, for example, with serendipitous inclusion or exclusion of certain patients or controls, post hoc subgroup analyses, investigation of genetic contrasts that were not originally specified, changes in the disease or control definitions, and various combinations of selective or distorted reporting of the results. Commercially available “data mining” packages actually are proud of their ability to yield statistically significant results through data dredging. In the presence of bias with $u = 0.10$, the post-study probability that a research finding is true is only 4.4×10^{-4} . Furthermore, even in the absence of any bias, when ten independent research teams perform similar experiments around the world, if one of them finds a formally statistically significant association, the probability that the research finding is true is only 1.5×10^{-4} , hardly any higher than the probability we had before any of this extensive research was undertaken!

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¹Brian Tiep, MD. High flow nasal vs high flow mask oxygen delivery: Tracheal gas concentrations through a head extension airway model. *Respiratory Care* 2002; Vol 47 No 9. ²Shyan Sun, MD. Safety and efficacy of the Vapotherm 2000i in the neonatal population. *Respiratory Care* 2004; Vol 49 No 11. ³Jorge Rojas, MD. The use of Vapotherm in an NICU. Effects on respiratory support and cost. *Respiratory Care* 2005; Vol 50 No 11.



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