Overdiagnosis of asthma in obese and nonobese Canadian adults
Shawn Aaron MD
Ottawa Health Research Institute, Ottawa, Ontario
saaaron@ohri.ca

BACKGROUND
It is unclear whether asthma is potentially overdiagnosed in Western countries, particularly among obese subjects who may experience more dyspnea.

METHODS
A longitudinal study of nonobese (body mass index 20 kg/m² to 25 kg/m²) and obese subjects (body mass index 30 kg/m² or greater) with physician-diagnosed asthma was conducted (1). Subjects were recruited via random-digit dialing from eight Canadian communities; they were assessed with asthma symptom questionnaires, spirometry and serial bronchial challenge tests while being tapered off asthma medications. A diagnosis of current asthma was excluded in subjects who did not have evidence of acute worsening of asthma symptoms, reversible airflow obstruction or bronchial hyper-responsiveness, despite being weaned off asthma medications. Asthma medications were stopped in those in whom a diagnosis of asthma was excluded and clinical outcomes were assessed.

RESULTS
Of 540 subjects with physician-diagnosed asthma who entered into the study, 496 (242 obese and 254 nonobese) could be conclusively assessed for a diagnosis of asthma. Obese patients were first diagnosed with asthma at an older age compared with nonobese subjects (27.9 versus 23.5 years, P=0.007). Obese subjects who self-identified as having physician-diagnosed asthma were also slightly older than nonobese subjects and were more likely to report wheeze and/or dyspnea within the past 12 months. Obese subjects had a higher prevalence of associated comorbidities including gastroesophageal reflux, diabetes and hypertension. Total Scores and Activity subscores on the Asthma Quality of Life Questionnaire were statistically lower in the obese cohort, but the differences in mean scores did not reach the clinically important threshold of 0.5. The diagnosis of asthma was ultimately excluded in 31.8% (95% CI 26.3% to 37.9%) of subjects in the obese group and in 28.7% (95% CI 23.5% to 34.6%) of subjects in the nonobese group. Obese subjects were not more likely to be overdiagnosed with asthma. Sixty-six percent of subjects in whom asthma was excluded did not restart asthma medications or require health care services for asthma symptoms during a 7.5 month follow-up period.

CONCLUSION
Approximately 30% of obese and nonobese Canadians with physician-diagnosed asthma did not have asthma when objectively assessed.
Asthma is likely overdiagnosed in Canadians; however, obese subjects are not at greater risk of overdiagnosis of asthma compared with non-obese subjects.

ACKNOWLEDGEMENTS: Dr Aaron is supported by funding from the Canadian Institutes of Health Research.

REFERENCES

Understanding the possible inflammatory pathophysiology of the fall asthma epidemic
Darryl J Adamko MD FRCP, Ramses Illaraza PhD, Yingqi Wu
Pediatric Pulmonology, Pulmonary Research Group, University of Alberta, Edmonton, Alberta
dadamko@ualberta.ca

Asthma exacerbation is a life-threatening event in which a person cannot breathe (1). Common cold viruses are the leading cause of asthma exacerbation (2,3). While most healthy adults are exposed to the same common viruses each year and have relatively mild symptoms, many asthma patients react with decreased lung function and severe shortness of breath. Why asthma patients respond so poorly to common colds is unclear. Understanding how airway virus infections can trigger such severe attacks in patients with asthma is an important but poorly understood area.

Prevention of asthma exacerbation has largely relied on inhaled corticosteroid therapy (4,5). While effective in most patients, the cellular target for inhaled corticosteroid therapy in the prevention of virus-induced exacerbations remains unclear. Being atopic is the major risk factor for hospitalization during virus infection (6,7). Experimental rhinovirus (RV) infection increases the recruitment of eosinophils to the airways after antigen challenge (8) and causes increased airway reactivity compared with nonallergic individuals (9). After intranasal infection with RV, biopsies of the lower airways of asthmatic adults contain increased levels of eosinophils that persist even into convalescence (10). During naturally acquired viral infection, children with asthma show significant increases in eosinophil major basic protein (MBP) in their nasal secretions (11). While experimental RV infection of the nose causes lower airway eosinophilia and airway hyper-reactivity in atopic asthmatics, it causes only mild lower airway narrowing and neutrophilia in nonatopic healthy subjects (12). In patients with asthma, the presence of airway eosinophils and their release products during periods of exacerbations is established (13-16). Patients with asthma have a baseline level of eosinophils in the airways before virus infection. Unlike neutrophils, the presence of eosinophil activity in the airways during virus-induced asthma exacerbation becomes a unique feature, which could explain why asthma patients do so poorly. Whether eosinophils are responsible for the asthma attacks and how they could be activated is unknown. Our laboratory believes that eosinophils are key effector cells that are activated by viruses to induce airway damage. The overall objective of our laboratory has been to determine the mechanisms by which airway viruses induce eosinophils to release their mediators both in vitro and in vivo.

There are major differences in the frequency of association between different airway viruses and the induction of asthma exacerbation. RV is by far most common (2). Whether this is due to intrinsic properties of RV and/or the frequency with which RV induces a host response is unknown. Given its importance, our laboratory focuses on RV compared with another airway virus, respiratory syncytial virus. We have published that eosinophils are activated by airway viruses in vitro, but only if the eosinophils are incubated with CD4+ T cells proliferating in response to antigen presenting cells (dendritic cells) (17). There remain many important questions for this model. We are determining whether eosinophils are responsible for the asthma attacks and how they release products during periods of exacerbations is established (13-16).

ACKNOWLEDGEMENTS: This work is supported by funding from the Canadian Institutes of Health Research and Merck-Frosst Canada.

REFERENCES
Complicated parapneumonic effusions in children

Mark Anselmo MD
Department of Respiratory Medicine, Montreal Children’s Hospital, McGill University, Montreal, Quebec
mark.anselmo@muhc.mcgill.ca

Although there has been a trend downward in the number of cases of pneumonia in children needing hospitalization in parts of Canada, there has been an increase in the percentage of complicated pleural effusions in children, especially the younger ones (1,2). While mortality in Canada is nonexistent for this problem, controversy exists as to the best care pathway for children with complicated parapneumonic effusions. Presently, we are faced with many options. Primary medical interventions include intravenous antibiotics alone, closed chest-tube drainage (CTD) and closed chest-tube drainage with intrapleural fibrinolytic therapy (IFT). Primary operative interventions include open thoracotomy (OT) and video-assisted thoracoscopic surgery (VATS). Until recently, there had been much controversy as to which interventional approach is superior in children due to many factors. First, there have been no large randomized controlled trials (RCTs) of one therapy against another in children. Second, small studies had not demonstrated a survival difference between the different approaches, and all approaches seem to achieve the same goals, resolution of symptoms and return to normal function. Third, the approach to many disorders seen in both adults and children tend to rely on patterns of practice established for adult patients, and this has held true for pediatric parapneumonic effusions. Initial expert panels such as the 2003 expert opinion on complicated parapneumonic effusions indicated that VATS was the definitive treatment for effusions in adults (3).

This opinion was echoed in an early meta-analysis of pediatric empyema. Avansino et al (4) systematically reviewed publications of primary operative approach (VATS/OT) versus medical therapy (CTD/IFT). While declaring operative therapy superior, the review acknowledged that the included studies were quite dissimilar and that no well-designed RCTs were available, diminishing the impact of this systematic review. A cohort review by Li and Gates (5) examined a large number of patients retrospectively and found primary operative management for pediatric empyema, there was no statistically significant difference between those treated with VATS versus IFT.

Sonnappa et al (6) performed the first RCT of VATS versus IFT in children. This study reported increased mortal risk of death and IFT in terms of LOS, days of procedure number, and morbidity, need for reintervention, LOS, duration of chest tube and antibiotics versus primary medical therapy in favor of VATS in children. Most recently, St Peter et al (8) performed a small RCT comparing primary VATS versus OT, and similar to the Sonnappa et al study, found no difference in the two approaches, except in cost (Table 1).

Table 1 (continued): Treatment options in pediatric parapneumonic effusions

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avansino et al (4)</td>
<td>Meta-analysis</td>
<td>Primary operative approach lowered LOS and cost and risk of transfer</td>
<td>Continued in next column</td>
</tr>
<tr>
<td>Li and Gates (5) cohort review</td>
<td>Retrospective</td>
<td>Primary operative approach lowered LOS and cost and risk of transfer</td>
<td>Significant in terms of OT/CTD; IFT vs VATS/OT trend toward VATS</td>
</tr>
<tr>
<td>Kurt et al (7) RCT</td>
<td>Primary VATS lowered LOS, procedure number, and days of tube drainage versus CTD</td>
<td>IFT only used after 24 h; small study size</td>
<td></td>
</tr>
<tr>
<td>Sonnappa et al (6) RCT</td>
<td>No difference between VATS and IFT in terms of LOS, days of CTD and procedure number. IFT less expensive</td>
<td>First VATS versus IFT RCT in children</td>
<td></td>
</tr>
<tr>
<td>St Peter et al (8) RCT</td>
<td>No difference between VATS and IFT in terms of LOS, febrile days and oxygen need</td>
<td>Smaller study than Sonnappa et al</td>
<td></td>
</tr>
<tr>
<td>CTD Chest-tube drainage; IFT Intrapleural fibrinolytic therapy; LOS Length of stay; OT Open thoracotomy; RCT Randomized controlled trial; VATS Video-assisted thoracoscopic surgery; vs Versus</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

After initial retrospective studies and small nonrandomized trials seemed to point toward VATS as being the primary choice for treatment of empyema in children, the most recent RCTs directly comparing IFT and VATS have only found VATS to be more costly, but no more effective. Currently, in cases of pediatric empyema, initial treatment with IFT seems reasonable and appropriate. Caveats must be kept in mind. First, a thorough initial assessment with proper history, examination and, if needed, diagnostic thoracentesis are necessary to establish the diagnosis before intervention. Second, in certain patients, VATS may be a reasonable initial choice. Finally, there are very little data regarding the third medical option – antibiotics alone without intervention – and we are presently left with patterns of practice from our adult colleagues suggesting that intervention in these children is necessary.

REFERENCES
Molecular mechanisms regulating ICU-acquired muscle dysfunction

Jane Batt MD PhD
Division of Respirology, University of Toronto, Toronto, Ontario
Jane.Batt@utoronto.ca

The molecular mechanisms underlying the development of intensive care unit (ICU)-acquired muscle dysfunction are being delineated through studies on rodent models of disease and humans. This presentation highlights three key phenomena now recognized to underpin the development of acute and persistent muscle dysfunction in the ICU survivor.

Skeletal muscle atrophy is a well-recognized phenomenon that occurs in multiple disease states including ICU-acquired muscle dysfunction. Loss of skeletal muscle mass results from an imbalance between protein synthesis and degradation, with increased muscle proteolysis relative to protein synthesis. Degradation of muscle protein is mediated via several intracellular signalling networks, but ubiquitin-dependent proteolysis is the predominant mechanism responsible for the development of muscle atrophy. Protein ubiquitination is a process whereby proteins to be degraded are tagged with chains of ubiquitin moieties, which serve as recognition markers, targeting proteins for cleavage by the 26S proteasome. Ubiquitin ligases are the critical enzymes that both link ubiquitin moieties to the target protein and confer specificity to the system by interacting directly with the target protein through well-defined protein-protein interaction domains. The ubiquitin ligation atrogin-1 and MuRF1 are key regulators of muscle atrophy.

Atrogin-1 and MuRF1 are increased in the muscle of multiple rodent models of skeletal muscle atrophy including the steroid-denervation (SD) and paralysis-ventilation models of ICU-acquired muscle dysfunction. Atrogin-1 and MuRF1 knockout mice are partially protected from skeletal muscle atrophy. Recently, we have identified a third ubiquitin ligase, Ned4H, that also appears to induce the development of muscle atrophy. It has been recently recognized that there is reciprocal signalling between pathways mediating muscle hypertrophy and atrophy, via regulation of expression of atrogin-1 and MuRF1, reiterating the important role these ligation play in the loss of muscle mass. Activation of the IGF1 receptor results in activation of AKT and subsequent downstream signalling, which induces protein synthesis/muscle hypertrophy and simultaneously inhibits transcription of atrogin-1 and MuRF1, thus shutting down muscle proteolysis.

Ubiquitin proteasome-mediated proteolysis is relevant to human disease. Increased 26S proteasome activity and increased atrogin-1, MuRF1 expression are evident in the atrophying skeletal muscle of individuals with diabetes mellitus, uremia, sepsis and chronic obstructive pulmonary disease. We have identified increased expression of Ned4H in the atrophied muscle of chronic obstructive pulmonary disease patients. Increased 26S proteasome activity is evident in the muscle of individuals with ICU-acquired muscle dysfunction. The expression of MuRF1 and atrogin-1, beyond the context of gene expression array analysis, which requires validation, has not yet been assessed in ICU patients.

What is the relevance clinically? Currently, there are no drugs that inhibit specific ubiquitin ligases. However, a 26S proteasome inhibitor, bortezomib, has recently become available and approved for the treatment of some cancers. In rodent models of denervation-induced, and congestive heart failure- or burn-associated skeletal muscle atrophy, bortezomib reduced the loss of muscle mass by a minimum of 50%. Bortezomib has not been assessed in rodent models of ICU-acquired muscle dysfunction, but this drug, and others like it, hold potential for treatment of this condition.

Muscle membrane inexcitability is a second phenomenon that contributes to the development of ICU-acquired muscle dysfunction. Investigations, conducted predominantly in the SD rodent model, reveal a ‘sodium channellopathy’ that leads to the loss of muscle excitability. There is an approximately twofold decrease in the density of sodium channels in SD muscle compared with control, which diminishes muscle excitability by reducing the number of sodium channels available to generate an action potential. The resting membrane potential of SD muscle is more depolarized than muscle from control rats. Depolarization of the resting membrane potential inactivates sodium channels so that they are unable to open and participate in generating muscle action potentials. Modulation of the voltage dependence of channel activity is also evident in SD muscle such that the sodium channels activate and inactivate at hyperpolarized membrane potentials in SD muscle. This alteration in sodium channel function is the primary failure that results in membrane inexcitability in the SD muscle. Ongoing investigation is necessary to determine whether the alterations in sodium channel function are relevant to the patient with ICU-acquired muscle dysfunction.

Hyperglycemia has been consistently associated with ICU-acquired muscle dysfunction, and normalization of blood sugars achieved with intensive insulin treatment is the only intervention shown to date to decrease neuromuscular dysfunction. The molecular mechanisms underlying this observation remain poorly understood. Current consensus is that hyperglycemia induces, in part, muscle mitochondrial dysfunction. Mitochondria are the main ATP-generating organelles, and it is speculated that a lower muscle mitochondrial content, and thus cellular energy status, results in increased muscle fatigability.

Treatment with insulin is effective because of the normalization of ‘toxic’ glucose levels. In addition, in rodent models, a neuroprotective effect is seen and insulin increases muscle mass by inhibiting atrogin-1/MuRF1 expression and muscle proteolysis, and increases muscle protein synthesis. These effects of insulin in patients with ICU-acquired muscle dysfunction have not been directly assessed.

REFERENCES

Using a chronic disease management model to improve patient care outcomes

Donna Bleakney
Chronic Disease Management and Renal Services, Saskatoon Health Region, Saskatoon, Saskatchewan
donna.bleakney@saskatoonhealthregion.ca

The burden of chronic obstructive pulmonary disease (COPD) and the impact on health care delivery is substantive and growing. The literature supports the concept that a comprehensive, interprofessional, patient-centred approach to managing chronic diseases is effective. Saskatoon Health Region (SHR) has established a COPD program (LiveWell COPD Program) that has proven to keep people out of the hospital and out of the intensive care unit, reduce
re-admission rates, and manage costs effectively. The components of the program: exercise, disease-specific management, and self-management are integral to establishing positive outcomes for the patient with COPD.

The LiveWell COPD program was established using a chronic disease management (CDM) model for care delivery. SHR adopted Wagner's Chronic Illness Care model as the CDM model to follow (1). The BC expanded chronic care model is an enhancement of the Chronic Illness Care model and is currently used in the SHR CDM programs (2). The global burden of chronic disease is significant because patients with chronic diseases account for a large proportion of the health care costs (more than 60%). Using a chronic disease management approach helps to target the population who traditionally have several admissions to the health care system each year, with many admissions having predictable and preventable complications. Scientific research has demonstrated that targeting COPD patients with optimal care leads to less shortness of breath, increased exercise capacity, better quality of life and reduced health care use (3).

PROGRAM DESIGN
An inter-professional team, including many community and health region partners, was developed to optimize the care provided to patients with a primary diagnosis of COPD. The program is centrally coordinated, with both urban and rural delivery. The LiveWell COPD program was designed from published, evidence-based research and the experience of others. Interventions used are guideline recommended or evidence-based. The program design and delivery is applicable to and appropriate for most chronic medical conditions – the greatest benefit would be realized for diseases with the highest burden. The program is designed with three pillars of care: exercise, disease-specific management and self-management (Figure 1).

<table>
<thead>
<tr>
<th>Group Exercise and Rehabilitation</th>
<th>Disease-Specific Management</th>
<th>Patient Self-Management Skills</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community-based exercise and rehabilitation programming</td>
<td>Inter-professional team working closely with the patient, family, family physicians and specialists</td>
<td>Individualized plan of action</td>
</tr>
<tr>
<td>Group education</td>
<td>Evidence-based optimal care delivery</td>
<td>Peer-led support</td>
</tr>
<tr>
<td>Group and social support</td>
<td>LiveWell with Chronic Conditions</td>
<td>Enhanced self-management skills</td>
</tr>
</tbody>
</table>

Figure 1) The LiveWell Chronic Disease Management Program

PROGRAM DELIVERY
Patients are referred to the LiveWell COPD program through inpatient identification during hospitalization or through outside referrals (eg, patient, physician, health care professional). All patients are assessed for eligibility in the program by using a standard eligibility criteria assessment form. The LiveWell COPD nurse clinician is the case manager and facilitates an appropriate plan of action in collaboration with the patient and their family physician. The LiveWell COPD health professional team are certified respiratory educators and have completed the Lung Association COPDTrec course. Patients receive education about their chronic disease as assessed in their individualized plan of action. The benefits of self-management and exercise for COPD patients are innumerable and well documented. Effective self-management skills are discussed, and patients are also referred to their local LiveWell program. Peer-led classes are based on the Stanford self-management program. All patients in the LiveWell COPD program are referred to a pulmonary rehabilitation program. Patients receive regular follow-up telephone calls. Program and patient outcomes are evaluated on a regular basis.

OUTCOMES
SHR LiveWell COPD program outcomes are evaluated on a regular basis (4). Significant improvements have been demonstrated by using a CDM approach for COPD management. Since 2005, system-wide COPD hospital readmission rates have decreased by 23%, hospital days by 22% and ICU days by 44%. Average length of stay days decreased from 11.0 to 7.9 days for patients with COPD.

Outcome measurement was also analyzed on the specific patients attending the comprehensive LiveWell COPD program. After one year of enrollment in the program, patient readmissions were reduced by 71%, hospital days by 62% and emergency department visits by 44%. After three years of enrollment in the comprehensive program, COPD readmissions were reduced by 64%, hospital days by 29% and ED visits by 30%. Patient quality of life has also been measured, using St George's Respiratory Questionnaire. After one year of program enrollment, St George's Respiratory Questionnaire scores were reduced (improved) by an average of 8.3 points (52.9 to 44.6). Patients also reported that they felt more in control of their chronic disease and were better able to manage their own care.

CONCLUSION
The SHR LiveWell COPD program outcomes demonstrate a comprehensive, interprofessional, patient-centred approach to managing chronic diseases is effective. Improved quality of life, reduced exacerbations and hospitalizations and reduced health care costs are possible when patients attend a COPD program that uses a chronic disease management model for care delivery.

REFERENCES

How obesity might predispose to the development of asthma
Louis-Philippe Boulet MD FCCP FRCPGC
Institut universitaire de cardiologie et de pneumologie de Québec, Québec City, Québec
lphoulet@med.ulaval.ca

Asthma and obesity are two frequently associated health problems (1,2). Although asthma may promote weight gain through increased sedentary lifestyle and/or systemic corticosteroids usage, this does not explain the association of asthma and obesity. Various mechanisms have been proposed to explain how obesity could promote the development of asthma (3-5) (Table 1). This article summarizes these possible etiological factors.

Table 1: How can obesity influence the development of asthma?

<table>
<thead>
<tr>
<th>Influence on lung mechanics/function</th>
<th>Reduced functional residual capacity and tidal volume</th>
<th>Breathing at lower lung volumes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proinflammatory cytokines (eg, tumour necrosis factor-alpha, interleukin 6)</td>
<td>Chemokines (eg, eotaxin)</td>
<td>Increased oxidative stress</td>
</tr>
<tr>
<td>Increased production of:</td>
<td>Increased leptin levels</td>
<td>Reduced adiponectin levels</td>
</tr>
</tbody>
</table>

Continued on next page
MECHANICAL CHANGES

Obesity induces numerous changes in lung mechanics and function (6). The most obvious change is a reduction of the expiratory reserve volume, the elastic properties of the chest wall being modified. Obese subjects breathe at lower lung volumes, near the airways closing volume. A restrictive pattern with a mild reduction in total lung capacity is occasionally observed, but only in some morbidly obese subjects. Furthermore, obese subjects show an altered pattern of breathing, with higher breathing frequencies and reduced tidal volumes, even when exercising. Obesity is associated with a reduction in respiratory system compliance, increased work of breathing and increased exertional dyspnea (6,7).

Breathing at low lung volumes may unload airway smooth muscle. Furthermore, a reduced airway distension during breathing can increase airway responsiveness, possibly from a change in airway smooth muscle plasticity (increased stiffness). Our observation that obese nonasthmatic subjects have lost the protective effect of a deep inspiration, as can be observed in nonobese nonasthmatic subjects, supports this hypothesis (8). However other mechanisms related to small airway closure may prevail to explain this observation, such as an influence of hypoxemia, particularly in the supine position, and airway edema. These changes may promote the development of airway hyperresponsiveness (AHR), although in human studies, increases in the prevalence of AHR in obese subjects have not been universally reported (9,10).

SYSTEMIC/AIRWAY INFLAMMATION

Adipocytes may store and release a variety of inflammatory agents, and obesity is considered to be a low-grade systemic inflammatory condition. Increased levels of various inflammatory cytokines and mediators such as tumour necrosis factor-alpha, interleukin-6, eotaxin, vascular endothelial growth factor, monocyte chemotactic protein, and markers of systemic inflammation such as C-reactive protein and serum fibrinogen have been observed in obese subjects (3,11). Furthermore, levels of markers of oxidative stress such as 8-isoprostane, are increased in the blood and the lungs of obese compared with nonobese subjects (12). Furthermore, the proinflammatory hormone leptin is found in increased quantities in adipose tissue, and markers of systemic inflammation such as C-reactive protein and serum fibrinogen have been observed in obese subjects (3,11). Furthermore, levels of markers of oxidative stress such as 8-isoprostane, are increased in the blood and the lungs of obese compared with nonobese subjects (12). Our group (13) and Todd et al (14) have, however, not found a significant difference in induced sputum differential cell counts in the obese compared to non-obese subjects globally although we and Van Veen et al (15) have found an inverse relationship between body mass index and sputum eosinophils.

ROLE OF COMORBIDITIES

Comorbid conditions such as gastroesophageal reflux, obstructive sleep apnea, diabetes, dyslipidemia and cardiovascular diseases are more prevalent in the obese and may possibly influence asthma expression, although a possible role in the development of the disease is less obvious (5). While obesity could theoretically be a risk factor for atopy, such a relationship has not been found convincingly.

DEVELOPMENTAL/GENETIC INFLUENCES AND OTHER FACTORS

The genes involved with asthma and obesity are closely related and it is possible that both conditions share a similar genetic predisposition (5,16). Finally, it is possible that common environmental, dietary or health-style influences act as common factors for both asthma and obesity, but this requires further evaluation.

ASTHMA CONTROL AND RESPONSE TO ASTHMA THERAPY

Asthma is usually more difficult to control in the obese patient (17). The first reason could be that it is not asthma and, as in the nonobese, respiratory symptoms may be due to another condition. In the case of obesity, weight gain can itself induce respiratory symptoms, but an increase in airway obstruction in the obese remains to be documented. Therefore, confirmation by objective measures showing reversible airway obstruction or AHR is absolutely needed. In a recent study, Aaron et al (18) showed that close to one-third of patients with or without obesity have an incorrect diagnosis of asthma.

Otherwise, poorer asthma control may be related to obesity-related comorbid conditions, or to an altered response to treatment. We and others have shown that obese patients respond less well to inhaled corticosteroids (19,20). Leukotriene receptor antagonists may be less affected by obesity but this remains to be confirmed (20).

EFFECTS OF WEIGHT LOSS ON ASTHMA

In the obese subject, even a modest weight loss is associated with a significant improvement of asthma and reduced medication needs (21). Weight reduction from diet and exercise can improve asthma symptoms, reduce peak expiratory flow variation and improve spirometric values, while bariatric surgery in the most severe forms of obesity brings the most remarkable results.

CONCLUSIONS – FUTURE RESEARCH

The recognition of the marked influences of obesity on asthma has led to an increasing number of studies on the relationships between these two entities. It has become obvious that obesity makes asthma more difficult to control, but how obesity contributes to the development of asthma remains to be studied. In most patients, this influence is probably multifactorial. Asthma in the obese is increasingly recognized as a specific phenotype but the clinical implications with respect to asthma management should be explored. Furthermore, the pattern of body fat distribution and its influence on airway function and responsiveness should be studied. Asthma diagnosis and control require objective measures of airway function in the obese particularly, and the effects of therapy should be carefully examined. In these patients, weight loss should be a priority and the patients should be supported in their efforts to achieve their ideal weight.

REFERENCES

Fluid redistribution: A unifying hypothesis for sleep apnea and cardiovascular disease

T Douglas Bradley MD
Toronto Rehabilitation Institute and Toronto General Hospital, Toronto, Ontario
douglas.bradley@utoronto.ca

Obstructive sleep apnea (OSA) is common and has significant morbidity. OSA is caused by repetitive collapse of the upper airway (UA) during sleep, but the cause of UA collapse is not completely understood. Although obesity is a risk factor for OSA, body weight and neck circumference only account for 30% of the variability in the frequency of apneas and hypopneas per hour of sleep (apnea-hypopnea index [AHI]) (1,2), and approximately 60% of patients with OSA in the community are not obese (3). Hence, factors other than obesity must contribute to UA obstruction in such patients. The observation that OSA is more prevalent in patients with edematous states, such as heart failure, than in the general population (4), suggests that fluid retention may increase the risk for OSA.

The upright posture of humans predisposes to dependent fluid accumulation in the legs. This is counteracted by contraction of the calf muscles during walking. However, modern living has increased the number of jobs requiring prolonged sitting, during which absence of contraction of the calf muscles leads to dependent fluid accumulation in the legs. Upon lying down at bedtime, the fluid retained in the legs is redistributed to the upper body (5). Therefore, some of this displaced fluid might reach the neck and peripharyngeal tissues, and predispose to UA obstruction. To test this general hypothesis, we embarked on a series of experiments to examine relationships between rostral fluid displacement from the legs, UA properties and severity of OSA.

In healthy nonobese adults, we displaced fluid from the legs by applying lower body positive pressure via inflatable trousers. This increased neck circumference, reduced UA calibre and increased UA resistance (6,7). We also examined UA collapsibility by determining the critical collapsing pressure in response to application of negative pressure to the UA during wakefulness. Critical collapsing pressure increased during lower body positive pressure in men but not in women (8,9). These findings suggested that the UA of young men becomes more susceptible to collapse in response to rostral fluid displacement than that of young women, and may be one factor accounting for the higher prevalence of OSA in men.

In 23 nonobese healthy men referred for sleep studies, we assessed the changes in leg fluid volume and in neck circumference before and after sleep, and the amount of time spent sitting the day of the sleep study (10). The overnight increase in neck circumference and the AHI correlated strongly with overnight reduction in leg fluid volume (r = 0.792, P < 0.001 and r = 0.802, P < 0.001, respectively). The overnight reduction in leg fluid volume was, in turn, related to the time spent sitting during the day (r = 0.588, P = 0.03), suggesting that greater fluid accumulation in the legs during the day led to greater movement of fluid out of the legs at night. Multivariate analysis revealed that the only independent correlates of the AHI were the overnight changes in leg fluid volume and neck circumference which, together, explained 68% of the variability in the AHI among subjects. These findings suggest that overnight rostral fluid displacement from the legs, related to prolonged sitting, may play a previously unrecognized role in the pathogenesis of OSA in nonobese men.

Our data imply that sedentary living and dependent fluid accumulation could be therapeutic targets for the management of some patients with OSA. Testing this hypothesis will require further studies to determine whether preventing leg fluid accumulation during the day, or rostral fluid shift overnight, reduces severity of OSA.

ACKNOWLEDGEMENTS: Dr Bradley is supported by funding from the Canadian Institutes of Health Research.

REFERENCES

Gender and asthma: An evolving understanding of the importance of sex

Anna Day MD FRCP C
Division of Respirology, University of Toronto, Toronto, Ontario
aday@utoronto.ca

There is an increasing body of evidence that suggests there are gender differences in both the prevalence and natural history of asthma. These gender differences are responsible for differences in asthma morbidity and outcome, and may have an impact on outcomes for other airway conditions including smoking-related pulmonary disease.
NATURAL HISTORY OF ASTHMA
The overall prevalence of asthma in childhood (16%) decreases by almost one-half in the adult Canadian population (8.5%) (1). However, when the data are disaggregated by gender, we find that boys have a significantly higher prevalence of asthma than girls (18% versus 12%). Following adolescence there is a marked decrease in the prevalence of asthma in adult men (7%) but only a small decrease in adult women (10%) and the prevalence of asthma is now greater in women than in men. These data and recent longitudinal studies following children to adulthood suggest that, while most boys outgrow their asthma by the end of their teenage years, women tend to have the onset of their asthma after puberty.

IMPACT OF ASTHMA BY GENDER
Mortality differences according to gender are small and unlikely to be significant because there are so few asthma-related deaths in Canada (1). However, there are differences in morbidity. Boys are hospitalized for asthma almost twice as often as girls. Adult women visit the emergency room and are hospitalized for asthma twice as often as men and have poorer outcomes in the community, despite better knowledge, greater reported use of inhaled steroids and satisfactory access to physicians (2). This suggests that gender differences in morbidity may be due to biological and environmental differences, rather than psychosocial etiologies.

AIRWAY RESPONSIVENESS AND GENDER
Increased airway responsiveness (AHR) is a hallmark of asthma and might be expected to parallel the gender differences in the natural history of asthma. However, despite the gender differences in morbidity for asthma in childhood, AHR is similar for asthmatic boys and girls (3). Following puberty, AHR improves only for boys and there is an increasing body of evidence that AHR is more prevalent in adult women than in men (4). In a recent study of athletes, males had close correlation of asthma symptoms, AHR and a diagnosis of asthma but females had twice the symptoms and three times the prevalence of AHR as the diagnosis of asthma (5). This suggests that AHR may not be the only factor in determining asthma morbidity.

BIOLOGICAL FACTORS IMPACTING ASTHMA MORBIDITY
Gender differences in asthma can be considered to be a result of biological determinants (physiological, immunological and hormonal) and psychosocial differences (environmental, social and psychological). We will address the biological factors in the present paper.

Morphometric and physiological studies of pulmonary structure and function have established the principle of dysanapsis, the variable relationship between airway size and lung size (6). Although males have larger lungs for size throughout life, boys have smaller airways in relation to lung size than girls, which may explain the increased morbidity for boys with asthma. At puberty, girls have proportional growth of airways in relation to parenchyma but boys have a disproportional increase in airway size relative to lung volume. The airways of men are 17% larger in diameter than the airways of women. The smaller size of women’s lungs and airways may contribute to increased breathlessness in women (7).

Immunological gender differences exist for allergy and atopy, and likely have an impact on the natural history of asthma. Boys are more likely than girls to have skin prick reactivity to common allergens, whereas women are more atopic than men. Serum immunoglobulin E is consistently lower in women. There is some suggestion that women with asthma have more immunological conditions and that women may handle inflammation differently than men (8).

Hormonal gender differences have an impact at multiple levels. Variation in hormones related to the menstrual cycle is clearly associated with asthma exacerbations. Some asthmatic women may have abnormalities in sex hormone regulation of the beta-adrenergic system. Other studies suggest that gender can affect the impact of genetic changes of the beta2 adrenoceptors (9).

WHY A GENDER APPROACH TO ASTHMA?
Biological gender differences may make women with or at risk for asthma more susceptible to the impact of environmental exposures including biomass fuels, air pollution, moulds and cigarette smoke, and result in greater asthma morbidity. Biological differences could impact the response to anti-inflammatory medications, particularly corticosteroids and bronchodilators. Increased AHR may result in a worse outcome for women who smoke, and may contribute to the increasing prevalence of chronic obstructive pulmonary disease we are seeing in women. The Lung Health Study demonstrated that women who smoke have a higher rate of AHR than men and that increased AHR is associated with faster decline in lung function for women but not for men (10). Airway size and increased AHR may in some way be related to the increasing incidence of lung cancer we are seeing in women who smoke. The significantly higher morbidity for boys with asthma and adult women with asthma requires investigation and appropriate intervention. It might even help Canada in the 2010 Olympics!

REFERENCES

Improving exercise function in patients with COPD: How do we get nonresponders to respond?

Neil D Eves PhD
Faculties of Kinesiology and of Medicine, University of Calgary, Calgary, Alberta
neves@ucalgary.ca

Pulmonary rehabilitation to improve exercise tolerance and quality of life in patients with chronic obstructive pulmonary disease (COPD) is well established (1). However, closer inspection of individual responses to rehabilitation identifies that a number of patients often fail to obtain clinically meaningful improvements in these important outcomes (2,3). Recently, Decramer (2) reported that in response to six months of pulmonary rehabilitation, only 47% of patients obtained a minimal clinically important improvement in 6 min walk distance of 50 m after both three and six months; 15%
were nonresponders after three months but became responders at six months, while 34% of patients were still unable to obtain a clinically meaningful improvement in 6 min walk distance even after six months. These findings highlight the heterogenous responses to rehabilitation in patients with COPD and clearly identify a subgroup of patients who struggle to benefit from a traditional pulmonary rehabilitation program.

Few studies have addressed why some patients may not respond to pulmonary rehabilitation. Eves et al (4) demonstrated a strong association between improvements in exercise tolerance and the volume (r=0.71, P<0.001) and intensity (r=0.70, P<0.001) of exercise performed by patients during pulmonary rehabilitation. Consequently, any factor that limits a patient’s capacity to perform exercise may reduce the benefits that can be obtained from a rehabilitation program. Figure 1 highlights a number of factors that affect exercise tolerance and may influence how a patient responds to rehabilitation. These include the severity of exertional symptoms, respiratory and skeletal muscle dysfunction, impaired cardiovascular function and the presence of comorbidities. Hypoxemia and the severity of systemic and skeletal muscle inflammation may also interfere with the normal adaptive processes in response to exercise. A further consideration is that a number of patients adhere poorly to pulmonary rehabilitation. Smoking status, lack of disease-specific social support, depression and social isolation have all been identified as factors associated with poor exercise adherence (5), and patients dealing with these issues present a unique challenge for rehabilitation programs.

The type and severity of exercise limitation may be a key factor in determining who responds to rehabilitation. Plankett et al (6) reported that ventilatory-limited patients achieved increases in peak oxygen consumption (VO2peak) following four weeks of pulmonary rehabilitation compared with those who demonstrated cardiovascular, mixed (cardiovascular and ventilatory) or no obvious cardiopulmonary limitation. Ventilatory limitation is commonly associated with dynamic hyperinflation, which has been closely linked with dyspnea severity and exercise intolerance in patients with COPD (7). As such, adjunct therapies that can reduce ventilatory limitation and/or respiratory muscle work and alleviate dyspnea may allow ventilatory limited patients to perform more exercise and gain greater benefits from pulmonary rehabilitation. Support for this postulate can be obtained from work performed in our laboratory, where patients were randomly assigned to six weeks of exercise breathing either air or helium-hyperoxia. Helium-hyperoxia attenuates dynamic hyperinflation by reducing ventilatory demand with hyperoxia, while additionally reducing expiratory flow limitation with helium (8). Patients who received helium-hyperoxia were able to exercise at a greater intensity on all days of rehabilitation, which resulted in a greater volume of exercise performed during rehabilitation. Following rehabilitation, those in the helium-hyperoxia group had significantly greater improvements in constant load exercise time (when breathing air) compared with those in the air group. Assessing individual responses in each of these groups, 53% of patients achieved a minimally clinically important improvement in exercise tolerance (9) with air, compared with 94% of patients with helium-hyperoxia. These findings highlight that if we can find ways to increase the volume of exercise that patients with COPD can perform during rehabilitation, we can potentially turn non-responders into responders and allow more patients to receive the known benefits of pulmonary rehabilitation.

REFERENCES

Alternatives to CPAP therapy
Kathleen A Ferguson BSc MD FRCP C
Division of Respiratory, Schulich School of Medicine, University of Western Ontario, London, Ontario kfergus@uwo.ca

Continuous positive airway pressure (CPAP) is the mainstay of treatment for obstructive sleep apnea (OSA). However, not all patients want or tolerate CPAP, so alternative therapies are required. The present paper briefly reviews the evidence for oral appliance therapy (OA) and upper airway surgery.

A systematic review of the evidence for OA was published in 2006 (1). Fifteen randomized controlled trials (RCTs) were reviewed. The authors concluded that OA reduced the apnea-hypopnea index (AHI) to less than five per hour in 40% of patients, to less than 10 per hour in 52%, and by at least 50% in 69% of patients. Many studies reported improvements in snoring, sleepiness and oxygenation. A recent RCT evaluated CPAP, conservative therapy and OA in 101 subjects with mild to moderate OSA (2). CPAP improved the AHI and sleepiness better than OA but both methods were more effective than conservative treatment (no benefit). Morning diastolic blood pressure decreased in both the OA and CPAP groups. CPAP was better at improving general health-related quality of life but was equal to OA in improving disease-specific quality of life.

Many RCTs have compared OA with CPAP (1). CPAP reduced the AHI to normal levels in all patients, whereas OA failed to do so in one-third or more. In patients with mild to moderate OSA (3), CPAP and OA improved sleepiness and other neurobehavioural outcomes.
There are several types of upper airway surgery performed for the treatment of OSA. One of the more common procedures is uvulopalatopharyngoplasty. A Cochrane review of uvulopalatopharyngoplasty concluded that approximately 50% of patients have a 50% improvement in apnea severity (5). A 2005 update reached a similar conclusion (6). However, clinical staging may improve success (7). In a study of consecutively treated patients, approximately one-third were successfully treated (50% reduction in respiratory disturbance index to less than 20 per hour). Thinner patients with larger tonsils and a high palate had the best outcomes while patients with low-lying palates and/or morbid obesity did poorly.

A systematic review and meta-analysis of the literature evaluated the efficacy of multilevel upper airway surgery in 49 studies that included almost 2000 patients (8). Surgery had to include procedures on at least two levels of airway obstruction. Surgery was successful in 66% of patients (AHI reduced by at least 50% to less than 20 per hour). Nasal obstruction is common in OSA but there are no RCTs of nasal surgery. Studies of nasal surgery have found minimal effects on AHI but one study found that CPAP pressures were lower postoperatively (9). Maxillofacial surgery may be performed in patients who have maxillary and/or mandibular insufficiency, or in patients with a normal facial skeleton if there is significant OSA and other treatments have failed. The surgery generally consists of a combined advancement of maxilla, mandible and chin. There are no published RCTs of maxillofacial surgery for OSA but there are many published case series using different combinations of surgical techniques, sometimes including nasal or palatal surgery. Case series in highly selected patients have found that most patients have a significant and often curative improvement in AHI (10).

CONCLUSIONS

CPAP remains the standard of care for patients with OSA. OAs are an effective option in some patients and represent an alternative to CPAP that is supported by evidence from well done RCTs. Upper airway surgery may play a role in the treatment of patients with OSA, particularly when noninvasive treatment options have failed. There are few controlled trials that support the use of most of the available procedures in unselected patients.

REFERENCES


The impact of technology on the diagnosis and treatment of lung cancer

Richard J Finley MD FRCS FACS
Division of Thoracic Surgery, Vancouver General Hospital, University of British Columbia, Vancouver, British Columbia
Richard.Finley@vch.org

In 2008, an estimated 23,900 Canadians will have been diagnosed with lung cancer, while 20,200 will die because of it. Lung cancer incidence and death rates continue to climb among women while decreasing among men. Lung cancer remains the leading cause of cancer death for both men and women, with 270,000 potential years of life lost. The purpose of the present abstract is to review the impact of the new technologies: low-dose computed tomography (CT) scanning for lung cancer screening, staging with CT/posterior emission tomography (PET) fusion imaging, and video-assisted thoracoscopic (VATS) lobectomy on the diagnosis, staging, treatment and survival of lung cancer.

The 15% decrease in mortality for colorectal, breast and prostate cancer seen in the past 20 years associated with early detection screening programs has stimulated new lung cancer screening programs, with the hope of improving survival by detecting and treating early stage disease. CT detection of small growing lung nodules can suggest early lung cancer. Unfortunately, confident distinction of benign from malignant small lung nodules (less than 15 mm) cannot be reliably achieved using only CT criteria, CT/PET scans or pathological diagnosis using CT-guided needle biopsy (1). VATS excision biopsy removes the entire nodule in one sitting and eliminates the sampling error associated with needle biopsy, making it appealing to physicians and patients. Suzuki et al (2), however, reported that failure to visualize or palpate the nodule at VATS, requiring conversion to thoracotomy, occurred in 63% of patients when the nodule was 10 mm or less in diameter and greater than 5 mm from the pleural surface. To reduce the incidence of open thoracotomy in our centre (3), 75 small nodules were marked preoperatively in the CT suite, where one end of an 80 mm long, 0.018 in diameter, fibre-coated microcoil was placed deep to small peripheral lung nodules, with the other end coiled in the pleural space. In the operating room, VATS excision of lung tissue, lesion and microcoil was performed successfully in 73 of 75 patients (97%) under fluoroscopic guidance. The preoperative treatment plan based on bronchoscope, needle biopsy and PET scan was changed in 19 of 69 patients (28%) following VATS excision.

The staging of lung cancer is continuously evolving, as technological advances combine with clinical advances to better stratify patients into treatment and prognostic categories and after preoperative investigation algorithms. The increasing use of CT/PET is increasingly identifying patients with additional lesions that could contraindicate surgical treatment, but which require pathological confirmation to exclude a false-positive result (4). Preoperative staging with PET/CT and cranial imaging of patients with early stage non-small cell lung cancer identifies more precisely those patients with mediastinal and extrathoracic disease, thereby sparing some patients from stage-inappropriate surgery when compared with conventional preoperative staging. CT/PET is not cost-effective if other investigations such as chest CT scans or brain imaging show non-resectable disease.

Over the past decade, VATS surgery has improved with better fibre-optic light transmission, better image processing techniques that magnify the image and share it with the operative team on a video screen, refinement of instruments and endostaplers, and the development of expertise in VATS pulmonary resections by thoracic surgeons. Compared with open thoracotomy, patients with VATS pulmonary resection experienced less pain and lower analgesic requirements up to postoperative day 7, but there was no significant difference in pain thereafter. In randomized controlled trials (5,6),
there were no significant differences in staging, complete resections, length of stay, costs, postoperative impairments of pulmonary function, operative morbidity and mortality, or in long-term survival. Although new technology has improved the diagnosis, staging and treatment of lung cancer, the cost of care has increased and mortality has not significantly changed.

ACKNOWLEDGEMENTS: Dr Finley is supported by funding from the British Columbia Lung Association.

REFERENCES

Knowledge translation: Moving knowledge to action in respiratory care
Ian D Graham PhD1,2, Jacqueline M Tetroe MA1
1Knowledge Translation Portfolio, Canadian Institutes of Health Research; 2School of Nursing, University of Ottawa, Ottawa, Ontario

Knowledge translation (KT) is about making users aware of knowledge or innovations and facilitating their use of it to improve health and health care systems. It is about moving knowledge into action. There are other terms in use to describe this concept, many of which are not operationally defined (1,2). The Canadian Institutes of Health Research has developed the following working definition: KT is a dynamic and iterative process that includes synthesis, dissemination, exchange and ethically sound application of knowledge to improve the health of Canadians, provide more effective health services and products and strengthen the health care system. This process takes place within a complex system of interactions between researchers and knowledge users that may vary in intensity, complexity and level of engagement depending on the nature of the research and the findings as well as the needs of the particular knowledge user. An examination of the meaning of the specific concepts in this definition allows a more in-depth understanding of what we mean by KT.

Synthesis means the contextualization and integration of research findings of individual research studies within the larger body of knowledge on the topic. A synthesis must be reproducible and transparent in its methods and can review qualitative or quantitative findings. Dissemination involves identifying the appropriate audience, and tailoring the message and medium to that audience. The exchange of knowledge refers to the interaction between the knowledge user and the researcher resulting in mutual learning through the process of planning, producing, disseminating, and applying existing or new knowledge. Ethically sound KT activities are those that are consistent with ethical principles and norms, social values as well as legal and other regulatory frameworks. The term application refers to the iterative process by which knowledge is put into practice or policy and has been illustrated in the action cycle of the knowledge to action process (Figure 1). Implicit in the Canadian Institutes of Health Research definition is the notion that evaluation and monitoring of KT initiatives, processes and activities are key components of KT.

Given the complexity of behaviour change and the multiple factors that can influence, there is growing recognition that application efforts should be guided by conceptual models or frameworks (3,4). The usefulness of conceptual models comes from the organization they provide for thinking, observation and interpreting what is seen. The Knowledge to Action Process was derived from a concept analysis of 31 planned change theories and models (5,6).

KT can be divided into three broad categories: KT Science – studying the determinants of knowledge use and effective methods of promoting the uptake of knowledge; end-of-grant KT – initiatives undertaken once the grant/research has been completed; and integrated KT – engaging users of research throughout the research process. End of grant KT refers to the standard KT activities of most researchers: KT to their peers and, when appropriate, tailoring the message and medium to audiences beyond the scientific community. Integrated KT represents a different approach and involves collaboration between researchers and research users in the research process starting with shaping of the research questions. This category of KT is similar to participatory research (7) or Gibbons’ Mode 2 knowledge production (8). Not every researcher should be involved in integrated KT. For many researchers, disseminating research findings to the appropriate audience (this includes other researchers) is usually sufficient. The intensity of knowledge translation should depend on factors such as the potential impact of using the findings; the strength of the evidence supporting the findings; the target audience(s); what is known about effective strategies to reach the audience(s); what is practical and feasible to do under the circumstances and considerations of who else should be involved in KT efforts.

Figure 1) The knowledge to action process. Reproduced with permission with modifications from ref 2, page 19, figure 1

REFERENCES

Acknowledgements: Dr Finley is supported by funding from the British Columbia Lung Association.

References
Nitric oxide
Hartmut Grasemann MD PhD
Division of Respiratory Medicine, The Hospital for Sick Children, Toronto, Ontario
hartmut.grasemann@sickkids.ca

Nitric oxide (NO) is enzymatically produced by NO synthases (NOS). There are three isoforms of NOS of which two, namely NOS1 (neuronal NOS) and NOS3 (endothelial NOS), are constitutively expressed and regulated predominantly by the calcium/calmodulin system, while the expression of NOS2 (inducible NOS) can be induced by certain proinflammatory cytokines. The NOS isoforms are expressed by a number of different cell types within the lung and NO is produced in the airways and can be measured in exhaled air. NO concentrations are highest in the nose and paranasal sinuses and lowest in the peripheral airways.

TECHNICAL ASPECTS OF EXHALED NO MEASUREMENTS
When measuring exhaled NO, published standardized techniques should be applied (1,2). In general, exhaled NO can be measured with on-line or off-line techniques, depending on availability of an NO analyzer in the patient area. The most commonly used technique is a single exhalation against a resistor. The pressure in the mouth will result in soft palate closure that allows for separation of the nasal and paranasal cavities from the lower airways. Single exhalations will typically be performed at a constant exhalation flow rate of 50 mL/s. Exhaled air obtained at higher flows, however, will represent more peripheral airways. Based on a two-compartment model (3), the exhaled NO concentration will depend on three flow-independent parameters: the maximum total volumetric flux of NO from the airway wall \((J_{NO})\), the diffusing capacity of NO in the airways, and the steady-state alveolar NO concentration. Using multiple constant flow exhalations at each expiratory flow, the NO output \((J_{NO})\) can be calculated as \(J_{NO} = \) expiratory flow \(\times\) the fraction of exhaled NO \((F_{NO})\). The slope of this regression line is the alveolar NO concentration and the intercept is the bronchial NO output \((J_{NO})\). Flow-independent NO parameters may help delineate diseases with involvement of different areas of the larynx or airways (3).

Different techniques are required to measure lower airway NO in children. While children five to 17 years of age will generally be able to follow the instructions to perform single-breath flow-controlled manoeuvres, the recommended techniques for preschool (two to five years of age) children are flow-controlled spontaneous breathing, where the operator changes resistance and thereby flow within a certain range while the child is breathing spontaneously, or uncontrolled flow methods. Uncontrolled tidal breathing techniques have also been described for children younger than two years of age, where single-breath forced exhalation manoeuvres are also used (2).

NASAL NO
The concentrations of NO in the nose are flow dependent, similar to \(F_{NO}\) from the lower airways. One technical difference is, however, that the flow through the nasal cavities is typically generated by the NO analyzer and equals the aspiration flow of the sample line. This flow needs to be held constant to make results comparable between different set-ups. At a constant aspiration flow rate, nasal NO concentrations will gradually increase during the measurement and eventually plateau. These plateaus are recorded and used for analyses.

CLINICAL INDICATIONS FOR NO MEASUREMENTS
The concentration of NO in the upper and lower airways has been found to be decreased in a number of diseases including primary ciliary dyskinesia (PCD) and cystic fibrosis. In contrast, eosinophilic airways inflammation has been shown to be associated with increased NO in exhaled air and increased \(F_{NO}\) is frequently found in asthma patients. The diagnosis of asthma is typically based on clinical history, reversible airway obstruction and presence of airways hyper-responsiveness. Direct assessment of airway inflammation is not part of conventional approaches used to diagnose or monitor control of asthma. Airway inflammation in asthma patients results in activation of NOS3 increased \(F_{NO}\) and decreases in response to anti-inflammatory treatment. Therefore, measurement of exhaled NO has been advertised as a noninvasive tool in the assessment of asthma airway inflammation.

Discussions about the usefulness of NO measurements in asthma management to date are controversial and studies in severe asthmatic patients are still lacking. In a recent randomized, double-blind, parallel-group, multicentre, 46-week treatment trial, the management of asthma based on \(F_{NO}\) in addition to guideline-based treatment showed no additional effect of NO measurements on asthma symptom control (4).

PCD is a disease that is characterized by chronic and recurrent respiratory symptoms including chronic cough, sinusitis, bronchitis, pneumonia and otitis media. Despite early onset of symptoms, the diagnosis of PCD is often missed early in life. Nasal NO is significantly decreased in patients with PCD and has been found to be diagnostic even in newborns with PCD and situs inversus (5). Nasal NO is therefore recommended as a noninvasive tool in the diagnosis of PCD (6).

SUMMARY
Airway NO can be measured by commercially available NO analyzers and published recommendations as to how to measure exhaled NO should be applied to make results comparable. Nasal NO can be used as a simple noninvasive screening tool for PCD. Repeated measurements of \(F_{NO}\) may be useful in titrating asthma therapy in individual patients. The usefulness of airway NO measurements for other clinical indications is, at this point in time, not clearly established.

REFERENCES
Knowledge translation: Breathing life into the knowledge-to-action cycle

Samir Gupta MD MSc,
Li Ka Shing Knowledge Institute of St Michael’s Hospital,
University of Toronto, Toronto, Ontario
Guptas@smh.toronto.on.ca

New medical knowledge and breakthroughs are the continuous product of an extensive global health research enterprise. However, evaluations of quality of care have consistently demonstrated gaps between existing knowledge and practice, across jurisdictions and disciplines. A growing recognition of both lost potential health gains and harms resulting from these gaps has spurred the science of knowledge translation (KT). Graham et al (1) termed the process of systematically bridging these gaps the “knowledge to action” (KTA) process and developed a framework describing its key elements, based on a review of planned-action theories and models. The resulting “action cycle” provides a step-by-step guide for would-be knowledge implementers. In this paper, I will operationalize the KTA process using a smoking cessation intervention as an example.

IDENTIFY THE PROBLEM

The process begins with identification of a problem that needs addressing. Smoking was the primary risk factor for the top three causes of death and was estimated to be responsible for 22% of all deaths in Canada (2). In chronic obstructive pulmonary disease (COPD), it accelerates lung function decline, leading to earlier morbidity and mortality (3). Despite this, 19% of Canadians aged 15 years and older (2) and 45.4% of Canadians with COPD smoke (4).

IDENTIFY, REVIEW AND SELECT KNOWLEDGE

We now turn to the knowledge creation funnel for existing knowledge on smoking cessation interventions. Randomized controlled trials have demonstrated that a brief physician smoking cessation intervention improves quit rates in all smokers and reduces all-cause mortality in COPD (3). A Cochrane review confirms that a brief intervention significantly increases the likelihood of quitting (5). The 2007 Canadian Thoracic Society COPD Guideline, a tailored knowledge product, states: “Minimal interventions, lasting less than 3 minutes, should systematically be offered to every smoker... (1A).” (6). Despite this, only 51% of Canadian smokers visiting a health care provider in the preceding 12 months were advised to reduce or quit smoking (7). This constitutes the KTA gap.

ADAPT THE KNOWLEDGE TO THE LOCAL CONTEXT

The highest-volume setting for a successful Canadian smoking cessation intervention is primary care, so the knowledge should be customized to this context. A simple and directed message for target practitioners would be: “A less than 3 min physician smoking cessation intervention significantly decreases smoking rates and improves health outcomes.”

ASSESS THE BARRIERS TO KNOWLEDGE USE

Identifying the barriers to local knowledge uptake is a prerequisite for designing successful interventions. Barriers to delivery of a smoking cessation intervention in primary care include attitudinal barriers such as concern about harming the doctor-patient relationship, a perceived lack of skills, and frustration owing to perceived low success rates; and external barriers, such as a lack of time (8,9).

SELECT, TAILOR AND IMPLEMENT INTERVENTIONS

Once barriers are identified, specific interventions should be developed accordingly. Literature reviews may provide a suite of previously applied KT interventions for consideration. Also, any previously studied KT interventions addressing the gap of interest, whether successful or not, should be studied for their applicability. Qualitative data on the effect of each intervention on recognized barriers may also be available. In this case, a literature review concluded that strategies combining physician education and training with practice-based approaches such as prompts and reminders were effective in increasing physician delivery of smoking cessation advice (9). In a unique study (10), an inexpensive chart stamp indicating the patient’s current smoking status was also effective. One might emulate some or all aspects of previous interventions, and/or may choose novel approaches.

MONITOR KNOWLEDGE USE

Knowledge use is a necessary but insufficient condition for achievement of the desired health outcome (in this case smoking cessation and resulting morbidity and mortality). Knowledge use should be measured at two levels: conceptual knowledge use, or changes in physician knowledge, attitudes, and beliefs regarding the benefits of smoking cessation advice delivery (which may or may not successfully change behaviour); and instrumental knowledge use, or the concrete application of this knowledge such that it actually increases the frequency of smoking cessation advice delivery (behaviour change). Although knowledge use is in itself an intermediate end point, when an intervention targets a behaviour for which there is strong evidence of health benefit, it may be appropriate to limit measurement to instrumental knowledge use alone.

EVALUATE THE OUTCOMES OF KNOWLEDGE USE

It is the impact of knowledge use that determines the ultimate success of a KT intervention. Generally, these outcomes may be measured at a patient, provider and/or a system level. In this case, relevant patient-level outcomes would include smoking cessation rates, rates and complications of smoking-related diseases, and mortality.

SUSTAIN KNOWLEDGE USE

Health systems are complex and ever-changing. As a result, while some barriers fall, others are erected, and previously designed interventions may become less effective. Barriers to sustainability may in themselves be distinct from barriers to initial adoption and behaviour change. Sustainability strategies are developed in the same way as initial interventions were, by cycling back through the steps in the KTA cycle, as such initiating a feedback loop.

Passive dissemination of research findings is an inadequate means to effect the behaviour change required to reap the health outcome benefits of new knowledge. Through the KTA cycle, Graham et al (1) have systematized the process of KT and provided a much-needed structured approach to implementation. As the respiratory community turns its attention to the science of implementation, areas of future inquiry may include exploration of certain cycle stages within the context of a particular problem, such as the magnitude of a particular care gap, or particular barriers to adoption. Ultimately, the action cycle can be used to address the many prevalent care gaps in respirology.

ACKNOWLEDGEMENTS: Dr Gupta is supported by funding from the Li Ka Shing Knowledge Institute of St Michael’s Hospital, Toronto, Ontario.

REFERENCES


A practical approach to formulating an exercise program for patients with COPD

Kylie Hill PhD
Department of Respiratory Medicine, West Park Healthcare Centre, and Department of Physical Therapy, University of Toronto, Toronto, Ontario
kyliehill73@hotmail.com

CURRENT RECOMMENDATIONS

Aerobic exercise that aims to condition the muscles of locomotion is a mandatory component of pulmonary rehabilitation (PR) (1,2). These exercises commonly involve walking and cycling, performed for 30 min, between three and five days a week, for six to 12 weeks. Although exercise training programs performed at low intensities are likely to yield benefits in clinical outcomes such as health-related quality of life, high-intensity training confers greater physiological benefit and should be encouraged to optimize gains in exercise capacity (2). The recommended initial training intensity is 60% to 80% of an individual’s maximum exercise capacity (3).

MEASUREMENT OF EXERCISE CAPACITY

In Canada, the 6 min walk test (6MWT) is used by approximately 90% of PR programs offered in the outpatient setting, making it a popular assessment protocol (4). In contrast, the incremental cycle ergometry test (ICET) is routinely performed by less than 50% of PR programs (4). Therefore, clinicians are likely only to have the results of a 6MWT on which to prescribe initial training intensities. An encouraged 6MWT and ICET elicit similar peak heart rates and rates of oxygen uptake in people with chronic obstructive pulmonary disease (5). This suggests that the 6MWT elicits maximum (or near-maximum) cardiac and oxidative demands in this population and its results can therefore be used to prescribe training intensities.

PRESCRIBING A HIGH-INTENSITY EXERCISE TRAINING PROGRAM

Walking

Previous studies have demonstrated that walking-based training at a speed equivalent to 80% of the average walking speed achieved during an encouraged 6MWT is feasible and effective (6). Table 1 provides an example of how to establish a high-intensity walking-based training program using the results of a 6MWT.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Measurement</th>
<th>Modality</th>
<th>Calculation</th>
<th>Prescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWD = 450 m</td>
<td>20 min corridor walk</td>
<td>(4.5 km/h×0.8)÷3</td>
<td>1.2 km in 20 min</td>
<td></td>
</tr>
<tr>
<td>6MWD = 450 m</td>
<td>Treadmill walking speed</td>
<td>4.5 km/h×0.8</td>
<td>3.6 km/h (2.24 miles/h)</td>
<td></td>
</tr>
</tbody>
</table>

Suggestions for prescribing a high-intensity walking program. 6MWD 6 min walk distance

Cycling

Training intensities equivalent to 60% of an individual’s peak work rate achieved during an ICET has been demonstrated to be effective (7). Because cycle-based training imposes a greater specific muscle load on the quadriceps, individuals with chronic obstructive pulmonary disease are often limited from tolerating higher initial loads due to local muscle fatigue and leg discomfort. The peak work rate achieved during an ICET can be estimated using the 6MWD (8). This enables clinicians to estimate cycle-based training work rates using the results of this field-based walking test.

Progression

Training volume should be increased in accordance with symptoms. Aiming for a score on the Borg category ratio scale of 4 is appropriate (1).

STRATEGIES TO OPTIMIZE TRAINING LOAD

Rollators may assist individuals who experience difficulty during walking-based exercise. Those with a baseline 6MWD of less than 300 m are most likely to benefit from this strategy (9). Interval-based training approaches, that intersperse work periods with regular rest periods, allow relief from intolerable symptoms and may also optimize the training load that can be tolerated (10).

REFERENCES


Rapid response teams: A successful type of ICU outreach

Rick Hodder MSc MD FRCP
Divisions of Pulmonary and Critical Care, the Ottawa Hospital, University of Ottawa, Ottawa, Ontario
rhodder@ottawahospital.on.ca

As our population ages, the demand for acute care hospital beds is rapidly rising and many hospitals regularly face overcrowding dilemmas, so that bed management issues have become a daily priority. Intensive care units (ICUs) are frequently full, and expanding patient numbers and strained resources have challenged us to find more effective ways of identifying deteriorating patients earlier so that we can institute pre-emptive rescue therapy to avert catastrophe and either prevent the need for ICU admission, or shorten the length of stay if
the use of a predetermined set of delegated acts, which the team nurse can initiate according to specific protocols without a physician’s order. Depending on the centre, such delegated acts might include starting an intravenous line and administering a fluid bolus or even a vasopressor for hypotension, or intravenous beta-blocker for extreme hypertension or certain dysrhythmias. In Ontario, many rapid response personnel have taken a CCRT course offered by the Canadian Resuscitation Institute and Critical Care Education Network (www.criedunet.ca) (9). Participants receive training in the skills of crisis resource and concurrent management, and become adept at communication, organized rapid patient assessment and institution of immediate therapy, followed by rapid reassessment and additional action if required.

Evaluation of rapid response teams has been limited in part because the models of critical care outreach and the systems to provide them vary nationally and internationally. However, in general, the evidence supporting their value has been positive. Most studies have used historical control data, but have consistently shown reductions in cardiac arrests (10-14), and some have shown increased hospital survival (11,12). The effect on ICU admissions has been variable, with some studies showing a decrease in number, while others have noted an increase in ICU admission rate but reduced ICU length of stay, suggesting benefits for earlier intervention. The results from the first two years’ experience with a rapid response team at The Ottawa Hospital are shown in Figure 1. Not only was there a reduction in the number of hospital cardiac arrests and a slight reduction in the need for ICU admissions from the wards, there was a significant reduction in the severity of patients requiring ICU admission based on the multiple organ dysfunction score, and a significant reduction in the number of readmissions to ICU within 48 h of ICU discharge (14). Similar data have been observed at the University Health Network in Toronto (S Reynolds, personal communication).

As a member of the Rapid Assessment of Critical Events team in Ottawa, I have observed another significant positive impact of the rapid response teams, namely, an improved sense of confidence in critical care assessment in the team members themselves and in the ward nurses of our hospital. I believe that this reflects the positive impact that rapid response teams can have on the education of health care professionals. During rapid response training, ICU nurses learn to be effective communicators and are given the opportunity to relearn the skills necessary for assessing patients who are not already fully trusted up with ICU technology such as indwelling arterial lines, mechanical ventilation and sophisticated monitoring equipment. Ward nurses also benefit from rapid response team calls by observing and participating in the acute assessment and therapy of their patients alongside their colleagues from the rapid response team. One of the most important empowering benefits of this experience is learning to recognize the patient who is on a downward spiral and gaining the

![Figure 1](image)

**Figure 1** Effect of institution of a rapid response team at The Ottawa Hospital, Ottawa, Canada (14). ICU Intensive care unit; MET Medical Emergency Team
Biologic agents in rheumatoid arthritis and pulmonary disease

Nader Khalidi MD FRCPC
Division of Rheumatology, McMaster University, Hamilton, Ontario naderkhalidi@sympatico.ca

Biologics are genetically engineered proteins derived from human genes. They are designed to inhibit specific components of the immune system that play pivotal roles in fueling inflammation, which is a central feature of several forms of arthritis. Biologics differ significantly from traditional drugs used to treat rheumatoid arthritis in that they target specific components of the immune system instead of broadly affecting many areas of the immune system. The biologic agents currently available include the anti-tumour necrosis factor agents infliximab, etanercept and adalimumab, the T-cell modulator abatacept, and B-cell modulator rituximab. There are many potential rare pulmonary side effects of these agents. Of the three anti-tumour necrosis factor agents, infliximab and etanercept have the greatest number reported in the literature, including acute diffuse interstitial lung disease, subacute diffuse interstitial pneumonia, pulmonary infiltrates with eosinophilia, irreversible pulmonary fibrosis and opportunistic infectious pneumonia. Abatacept use in chronic obstructive pulmonary disease has been associated with an increased risk of developing an acute exacerbation, and use of abatacept should be undertaken with caution. Interstitial lung disease or pulmonary fibrosis occurred in less than 0.5% of patients. There are rare descriptions of rituximab causing acute diffuse interstitial lung disease, subacute diffuse interstitial pneumonia, desquamative interstitial pneumonia, irreversible pulmonary fibrosis and diffuse alveolar hemorrhage. Strategies to reduce pulmonary toxicity include having knowledge of the drugs now being used by rheumatologists and working closely with them, and referring patients to a multidisciplinary rheumatology/respirology clinic with colleagues familiar with the use of these drugs (McMaster, McGill, Calgary and Vancouver have formal clinics, and Ottawa and Winnipeg have strong, close relationships).

AZATHIOPRINE AND TPMT

Azathioprine (AZA) is a drug that is commonly used as an immuno-suppressant by respirologists and rheumatologists (1). Thiopurine S-methyltransferase (TPMT) is the rate-limiting step in the conversion of thiopurine drugs including AZA to inactive metabolites. Heritable deficiency of TPMT activity increases risk of adverse events, most notably myelosuppression leading to leukopenia and neutropenic sepsis. In a series of 739 patients treated over a 27-year period (1964 to 1991) with 2 mg/kg per day of AZA, there was drug-attributable myelosuppression in 5%, including severe leukopenia in 1.2% of patients (2). Of these leukopenic patients, three had pancytopenia and two died. Thus, although rare, severe hematological toxicity can occur and can be fatal in approximately 0.3% (two of 739) patients. A recent Spanish study (3) detected abnormal liver enzyme levels in 15% and hepatotoxicity in 5% among 786 adult patients with inflammatory bowel disease who were prescribed AZA. Unlike myelosuppression, hepatotoxicity in AZA-prescribed patients was not correlated with TPMT deficiency in this and another United States study (3,4).

To date, at least 23 TPMT alleles have been classified, including TPMT*1 (wild-type allele), which encodes the enzyme with normal activity. Three variant alleles, TPMT*2, TPMT*3A and TPMT*3C, account for most intermediate or low activity cases, with allele frequencies of approximately 0.5%, 5% and 0.5%, respectively, in Caucasians. The main drawbacks of genotypic TPMT testing are lack of standardized testing and lack of knowledge of the phenotypic correlates of some of the rare TPMT mutations, in particular among non-Caucasians for whom less knowledge about the TPMT polymorphism is available. TPMT enzyme activity in the population is highly variable. Ninety per cent of individuals have high normal activity of more than 10 U/mL blood (reflecting two active alleles) and 10% have intermediate TPMT activity of between 5 U/mL and 10 U/mL blood (reflecting only one active allele); 0.3% (approximately one person in 300) have low/absent activity due to two inactive alleles. TPMT testing in leukocytes is technically difficult and, as such, erythrocyte TPMT activity is used as a surrogate for leukocyte TPMT activity. Many drugs such as methotrexate, furosemide and sulfasalazine can affect TPMT activity. TPMT enzyme levels may be increased in the case of blood transfusions from a homozygous wild-type person before the blood sample is taken for TPMT assay.

In the case of homozygous polymorphisms, the recommendation is not to give thiopurine or to reduce to 10% of standard starting dose. Dose is reduced to 50% of standard dose in heterozygotes, with some authors recommending an even safer initial dose reduction to 33%. If you start low and plan to increase, how long do you wait to reassess? The American College of Rheumatology guidelines, last updated in 1996 (6) recommend blood counts every two weeks until dosage is stable, then every one to three months.

TPMT testing, as sensitive and as cheap as it might become in the future, will never be able to identify in advance all patients who might suffer severe AZA-related adverse drug reactions, including severe
leukopenia. For these reasons, among others, TPMT testing alone cannot assure maximal safety for AZA- or 6-mercaptopurine-prescribed patients, and regular monitoring of blood counts and liver functions must be continued, even in patients who are found to be normal TPMT metabolizers (5). It is important to bear in mind that AZA-related adverse events are not necessarily the result of TMPT deficiency and may reflect drug interactions or variants of other metabolic enzymes that affect AZA metabolism.

In conclusion, heritable deficiency of TPMT activity increases risk for adverse events from thiopurines, most notably myelosuppression, but to levels not correlated with hepatotoxicity. It appears preferable to have phenotype testing and dose reduction in patients with heterozygous deficiency and intermediate activity. One should avoid thiopurines in patients with a homozygous deficient genotype and low activity.

REFERENCES

Lung cancer in women
Stephen Lam MD FRCP
British Columbia Cancer Agency and the University of British Columbia, Vancouver, British Columbia
Slam2@bccancer.bc.ca

EPIDEMIOLOGY
In Canada and the United States, lung cancer has surpassed breast cancer as the most common cause of cancer death in women. Women tend to have an earlier onset of lung cancer and have significantly higher risk for adenocarcinoma. While some studies suggest women may be more susceptible to lung cancer from smoking, the greater risk is thought to be related to misunderstandings about relative versus absolute risk. When incidence rates are compared, there is usually no significant difference between men and women smokers. However, self-reported smoking may not reflect the actual exposure. Women reporting smoking 20 cigarettes per day were found to have a serum cotinine level equivalent to men smoking 13 cigarettes per day (1). Whether the difference is due to over-reporting of cigarette consumption in women, under-reporting in men, or increased metabolism of nicotine due to over-expression of cytochrome P450 genes (which would also lead to production of more tobacco smoke carcinogens), the observation would imply women may sustain more damage from smoking the same or lower quantity of tobacco.

In never smokers, the National Institutes of Health AARP cohort study found 1.3 times as many women as men to have lung cancer (2). In Asia, 60% to 80% of lung cancers in never smokers are women (3). The gross gender imbalance could not be accounted for by exposure to known carcinogens such as environmental tobacco smoke, heated cooking oil, fumes from coal/wood burners/stoves or human papilloma virus infection.

BIOLOGICAL BASIS OF GENDER DIFFERENCES
Exposure to cigarette smoke in teenagers reduces lung function growth more severely in girls than in boys (4). This reduction in lung growth may have an impact in adult life. For the same decrease in forced expiratory volume in 1 s, adult women were found to be 2.6 times as likely to develop lung cancer as men (5). A recent study showed that early onset of chronic obstructive pulmonary disease in women is associated with an early onset of lung cancer (6). Female hormones such as 17β-estradiol up-regulate cycytrome P450 activity. Activation of estrogen receptors leads to increased cellular proliferation and tumour growth. In a xenograft model of adenocarcinoma, treatment with an estrogen receptor antagonist was found to reduce tumour growth (7).

Genetic alterations in tumours such as epidermal growth factor receptor mutations occur more often in women, especially never smokers of Asian origin (3). Polymorphism in the nicotinic acetylcholine receptor gene in chromosome 15q24-25.1 was found to be associated with relative risks for lung cancer of 2.5 in women and 1.37 in men (8). Nicotine and tobacco carcinogens such as NNK can activate the nicotinic acetylcholine receptor resulting in activation of a number of signalling pathways such as Akt, mitogen-activated protein kinase, cyclooxygenase-2 and epidermal growth factor receptor that can in turn lead to increase in cell proliferation, angiogenesis, inflammation and decrease apoptosis.

IMPLICATION OF GENDER DIFFERENCES
Gender differences have important implications in prevention and treatment of lung cancer. Removal of active and second-hand tobacco smoke exposure, modification of cooking practices and proper home ventilation can reduce lung cancer risk in women. In areas where human papillomavirus infection is prevalent, vaccination to prevent cervical cancer may have an added benefit of preventing lung cancer. Choice of systemic therapy needs to take gender into account in addition to histological cell type, smoking status and ethnicity. For example, response to erlotinib or gefitinib is better in women never smokers with adenocarcinoma.

SUMMARY
There is evidence suggesting that women may be more susceptible to lung cancer from exposure to tobacco smoke and other inhaled carcinogens. Lung cancer appears to be a different disease in women with predominant adenocarcinoma and a different molecular biology profile. Further prospective studies are needed to confirm whether the incidence rate is higher in women versus men never smokers, especially those in the premenopausal age group.

REFERENCES
Cystic fibrosis care as a model for general respiratory care

Larry C. Lands MD PhD
Department of Pediatrics, McGill University, Montreal, Quebec
larry.lands@muhc.mcgill.ca

The classical model of patient care has used a pyramidal structure, with instructions emanating from the doctor to nursing and allied health. Furthermore, the patient is viewed as an individual, out of context to their social situation. In reality, the patient lives in a complex social network involving spouses, parents, siblings, dependents and others, including work or education responsibilities. This network will impact the patient’s ability to cope with illness and manage symptoms and treatments. It is also important to differentiate disability or physiological impairment from handicap, or the consequences of this disability. Limited respiratory ability may result in a patient’s curtailment of pleasant or important social interactions or being unable to comfortably perform activities of daily living.

A more comprehensive approach can be achieved through patient- and family-centred care, with the patient and their family being the hub of a wheel, with the health care providers interacting with the patient, as well as interacting and supporting team members. A way to envision this management is a cilium seen in cross-section, with the patient and family at the centre, the team members circled around them connected by the radial spokes, and the dynein arms helping the other team members.

The team consists of various members, but is led by a tandem team of a respiratory and nurse-coordinator. In fact, the nurse-coordinator typically serves as a port of entry and coordinator of all needed services. Physiotherapists are important for instruction both in the clinic and at home to work on enhancing endurance, strength and mobility, as well as breath control. Respiratory therapists guarantee appropriate use of inhalation devices as well as performing pulmonary function and exercise testing. Nurses, social workers, psychologists and educators work to support the patient and family around the identification of barriers, gaps in education and stressors, including financial, that affect progress toward self-management. Motivational interviewing, discussed below, is now identified as a technique to help patients and families make sustained changes in behaviour by developing strategies that support short- and long-term attainment of personal goals.

Nutritionists are important team members providing both macro- and micronutrient advice, and help with the choice of adjuvant therapies, such as oral herbal supplements. As the mix of medications and other therapies becomes more complex, pharmacists can be very helpful in patient education, assisting with scheduling of therapies, avoiding interactions between medications and foods, and limiting the risk for adverse events.

Other physicians are also important team members. This can involve other subspecialists to deal with such problems as cardiovascular disease, diabetes and gastrointestinal disease impacting lung function or nutrition. The community physician is also an integral team member, allowing for continuity of care and maintaining the patient at home.

It is obvious that good communication is required among the team members and that a common approach to the patient is provided. Motivational interviewing is a “directive, client-centered counselling style for eliciting behaviour change by helping clients to explore and resolve ambivalence” (www.advancemed.org/839mi). In this process, change is elicited within the patient, where the patient identifies and resolves the barriers and ambivalence toward achieving goals set by the patient. The therapist’s and team’s role is to counsel and partner with the patient through this process. Readiness to change is dependent on the patient/team partnership, and will fluctuate over time.

Work completed through the United States Cystic Fibrosis Foundation has identified factors that can improve team function and outcome (available at www.cff.org/LivingWithCFQualityImprovement).

This includes involving patients and families in the organization and provision of care, anticipatory care, with attention to optimizing nutrition and preventing exacerbations, and early intervention when symptoms are worsening. The team also provides support and guidance surrounding transplantation and end-of-life decisions.

In summary, the team approach involves multiple medical, nursing, and allied health disciplines. The team requires good communication between members, respect of competencies, and living with shared responsibilities. This combined approach enhances results for patients and their families.

Is my ICU safe?

Denny P Laporta MD
Department of Adult Critical Care, Jewish General Hospital, McGill University, Montreal, Quebec
dlaporta@jgh.mcgill.ca

What would we say to our patients if they asked us how well we adhere to best accepted standards of practice in our intensive care unit (ICU)? Or, how often do patients experience harm during their ICU stay? Better stated, how often do we do what we should? Have we adequate documentation of our practices and outcomes to respond? The sooner we acknowledge that our ultimate goal of care is better patient outcomes and less harm, the sooner we realize that the issue is not “Is my ICU safe?” but rather, how are we making our ICU safer? It is about improvement.

The best starting point is the ICU staff. Ask them what are they most and least proud of and satisfied with in the care delivered; what is working and what is not; what could be done to improve care; and how they think the next patient will be harmed – and listen. Through their observations, perceptions and ideas, you will sense the overall climate of safety and identify common goals for improving it. This proactive approach shows ICU staff that they are supported in helping to improve safety, while cultivating individual accountability. It also promotes group interest and buy-in to improvement initiatives.

Physician engagement in safety improvement is as important as the care they provide. It starts with sharing common goals: improving patient outcomes as well as physicians’ personal sense of professional excellence. Simply ask, how can we save you time and make you safer? (1).

CREATE THE TEAM

The ICU safety improvement team should be mandated and supported by the hospital. Membership should include a chair, quality and safety manager, information technology, multidisciplinary clinical and secretarial support. The practice items chosen should be based on published evidence that will satisfy practitioners to change with an eye to expected outcomes. Regarding standardization, decide on what can be, should be and will be standardized. There are enough tasks in the ICU that would best be done without variation, that one need not attempt to standardize controversial practices. Start off by standardizing all aspects of simple high-volume practices (eg, heparin protocol, stress ulcer and venous thromboembolism prophylaxis). After successful change, consider moving to standardizing elements of more complex practices (eg, physiological goals in resuscitation, mechanical ventilation for hypoxemic respiratory failure).

MEASURE AND MONITOR

Safety improvement can only be evaluated by measuring its effect on patient care. Define the practice to be improved in terms of what you are trying to accomplish, how you will know that improvement has occurred, and what changes can be made that will result in improvement (2).

A few tips on measurement

Do not use the data until the improvement process is reliable. Remember that measurement is for improvement, not judgment. The primary concern being self-improvement, between-unit comparisons
should only be undertaken if associated with an improvement goal. Ask physicians and other team members what data they would like collected and that they would trust. ICU scorecards (3) are an example of a tool for aggregating a number of measurements that relate to domains of care: structure (how care is organized, eg, multidisciplinary clinical team with specific expertise, interest and time dedicated to the care of ICU patients), process (what is done by caregivers), outcome (the health care results achieved), and context and culture (collective attitudes and beliefs of local caregivers). There should be agreement among staff on what each measurement reflects, and how changes in the measurement could indicate an improvement. This can be gradually introduced during staff encounters (eg, morbidity and mortality rounds, service meetings) by regularly presenting a patient case with a safety issue, discussing ICU readmissions, unplanned extubations, reintubations, line infections, etc.

IMPLEMENTING CHANGE

Start with standard safety practices such as hand hygiene, respiratory etiquette and best practice bundles (prevention of nosocomial infections [4], nutritional support, etc). If adherence to the improvement process is problematic, the problem is more likely to be the process than the people. Fix it before attempting to improve compliance. Make the right thing easier to do than the status quo. Addressing barriers to change requires uncompromising commitment to honest interpersonal communication and willingness to improve patient care. Is my ICU safe? Yes, if ICU leaders and staff demonstrate an unrelenting commitment to improving the care of patients through individual and system competency and performance. “Engaging is not ‘their’ problem, but ‘our’ problem: it starts with us” (1). “The obstacles (to safe care) . . . are no longer technical . . . (but) lie in beliefs, intentions, cultures and choices . . . All of those can change . . . we will not become safe until we choose to become safe” (5).

REFERENCES

2. Safer Healthcare Now! The Canadian ICU Collaborative <www.saferhealthcarenow.ca/EN/about/WhoWeAre/ClinicalSupports/Pages/icu.aspx>

Knowledge translation: Barriers and facilitators to implementation

France Légaré MD PhD
Department of Family and Emergency Medicine, Université Laval, Montreal, Québec
France.legare@mfa.ulaval.ca

The effective transfer and exchange of knowledge in clinical practice is essential to ensure that Canadians have access to high-quality and safe care procedures. However, to date, there is a consensus among the implementation research community that most efforts in the translation and exchange of knowledge at the clinical level have met with very little success (1). Although each phase of the knowledge-to-action cycle is important for ensuring the effective translation and exchange of knowledge in clinical practice, the assessment of barriers and facilitators to knowledge use is a key stage for adapting knowledge to the target users’ context (2). In a recently published systematic review of 78 studies (3), factors most consistently associated with prediction of behaviour change in health care professionals were beliefs about capabilities; in other words, barriers and facilitators to knowledge use (3).

One of the most often cited conceptual frameworks regarding barriers to knowledge use in health care is the Clinical Practice Guidelines (CPG) Framework for Improvement (4). This framework was based on an extensive search of the literature regarding barriers to physician adherence to CPG and was organized according to knowledge, attitudes or behaviour of physicians (5). It proposes a well-defined taxonomy of barriers that can be used by those involved in transfer and exchange of knowledge in clinical practice. A total of 76 studies describing at least one barrier to adherence to CPG were included in this review. Taken together, the included studies reported on a total of 293 potential barriers to physician guideline adherence, including awareness of the existence of the guideline (ie, the ability to correctly acknowledge the existence of shared decision-making) (n=46), familiarity with the guideline recommendations (ie, the ability to correctly answer questions about the guideline content) (n=31), agreement with the recommendations (ie, consenting to the recommendations) (n=33), self-efficacy (ie, feeling one is able to carry out the recommendations) (n=19), outcome expectancy (ie, perception that one’s performance following the use of the recommendations will lead to improved patient outcome or process outcome) (n=8), ability to overcome the inertia of previous practice (ie, feeling one is able to modify his/her routine) (n=14) and absence of external barriers to following recommendations (ie, perception of factors external to oneself that would impede the use of the recommendations) (n=34) (4). In recent years, this framework has been used successfully in diverse clinical contexts and expanded to include new barriers as well as facilitators to knowledge use (6,7).

Based on the CPG Framework for Improvement, a tool to assess barriers to adherence to hand hygiene guidelines was developed and tested on a group of 21 infectious disease clinicians (8). The tool uses a six-point Likert scale and has two sections: attitudinal statements about practice guidelines in general, and specific statements regarding the Hand Hygiene Guideline. The survey was administered twice, at two-week intervals. The Attitudes Regarding Practice Guideline tool was found to have a test-retest reliability coefficient of 0.86 and a standardized Cronbach alpha of 0.80 (8). However, the authors concluded that their tool needed to undergo further testing and adaptation as a measure of potential barriers to adherence to CPG in general (8).

In summary, there is a need to standardize the reporting of barriers and facilitators to knowledge use for the effective transfer and exchange of knowledge in clinical practice. Those responsible for this important activity may want to consider using existing models and their taxonomy, such as the CPG Framework for Improvement, to conduct barriers and facilitators assessment studies (4). However, there remains a need for more research on how to choose the right intervention to address a specific barrier and/or a facilitator. Only then will the gap between research and practice be adequately addressed.

ACKNOWLEDGEMENTS: Dr Légaré holds the Canada Research Chair in Implementation of Shared Decision Making in Primary Care.

REFERENCES


Managing childhood asthma: New insights into the September epidemic

Piush J Mandhane MD PhD1, Neil W Johnston MSc2, Malcolm R Sears MB ChB2
1Department of Pediatrics, University of Alberta, Edmonton, Alberta;
2Division of Respirology, McMaster University, Hamilton, Ontario
mandhane@ualberta.ca

RELATIONSHIP BETWEEN ASTHMA EXACERBATIONS AND SCHOOL RETURN

Epidemics of asthma exacerbations requiring hospital treatment occur annually following school return after the summer vacation (1). In Canada, the peak of the epidemic in school-age children occurs consistently 18 days after Labour Day (week 38; Figure 1A) (1), with slightly later and attenuated peaks seen in preschool-aged children and adults. Between 20% and 25% of hospital admissions for asthma of children in Canada occur in the month of September.

POTENTIAL ETIOLOGY OF THE SEPTEMBER EPIDEMIC

The September epidemic is likely the result of a number of factors, including children not being on regular asthma controller therapy such as inhaled corticosteroids (ICS) over the summer (Figure 1B) (2); rhinovirus-associated respiratory tract infections (3); exposure to increased car pollution and allergens in the school (4); and increased stress associated with school return (5).

MANAGEMENT OF THE SEPTEMBER EPIDEMIC

Management of the September epidemic includes emphasizing that there are no holidays from asthma controller. Translation of this recommendation into practice may be difficult due to chaotic summer schedules for patients and practitioners in addition to challenges in providing timely asthma education programs effectively (6).

Pharmaceutical management has focused on adding asthma medication to the child’s usual therapy during or before the onset of the September epidemic. We recently demonstrated that children who started montelukast (a leukotriene-receptor antagonist) on September 1st for six weeks experienced over a 50% reduction in days with worse asthma symptoms compared with placebo (P<0.02) and a 78% reduction in unscheduled physician visits for asthma (P=0.011) (7). The benefit of montelukast was seen both in those using and not using regular ICS, and among those reporting and not reporting colds during the trial.

CONCLUSION

The September epidemic of asthma exacerbations is closely related to school return. Rhinovirus infection is common in September and an important reason for the epidemic. Lack of adequate controller medication may also fuel the epidemic. Short-term addition of effective asthma controller therapy provides the opportunity to attenuate the epidemic. Future research may include evaluating the utility of targeted asthma education around the September epidemic with strategies to improve compliance with ICS over the summer.

REFERENCES


What’s next for the National Lung Health Framework?

Darcy D Marciniuk MD FRCPCC1, Nora Sobolov2
1Division of Respirology, Critical Care and Sleep Medicine, Royal University Hospital, University of Saskatchewan, Saskatoon, Saskatchewan;
2President and CEO, Canadian Lung Association, Ottawa, Ontario
darcy.marciniuk@usask.ca

The National Lung Health Framework took a leap forward toward implementation with the welcome announcement by Health Minister Leona Aglukkaq on April 24, 2009, of 10 million dollars in initial funding over the next three years. The Framework was developed to address the growing and under-recognized burden of respiratory illness and disease in Canada. A coordinated plan and approach was required to enhance research intensiveness, to raise awareness of the benefits of improved respiratory health and the adverse consequences of disease, to focus attention both nationally and provincially on priority areas for action, and to enhance sharing
and implementation of best practices and existing knowledge.

The history of the National Lung Framework began in 2006 with an initial meeting of 40 interested stakeholders, including representatives of the Canadian Thoracic Society, the Canadian Respiratory Health Professionals and the Canadian Lung Association. Initial funding for the project was provided by the Public Health Agency of Canada and the Canadian Lung Association, which have continued to strongly support this important endeavor. An Interim Steering Committee was formed, and helped to plan a larger national forum held in April 2007, attended by more than 200 stakeholders and personally attended by Minister of Health Tony Clement, and Minister of the Environment John Baird. Following that successful meeting, forums were held in every province and territory in 2008, together with a number of expert advisory panel meetings. In total, more than 500 individuals participated in this process. In May 2008, an initial draft Framework document was presented to the Minister of Health, and received very strong support. The final document was released in fall 2008, and work then began on an action plan for implementation, priority- and goal-setting, monitoring and evaluation. To assist with this important task, an expanded Steering Committee was formed with the intent of guiding the process forward for the next five years.

The continuum of lung health as developed by the Framework is depicted in Figure 1. It recognizes that all individuals are at risk of lung disease, and the magnitude of that risk is dependent on a number of factors, including genetic, environmental, and other determinants of lung health. The Framework emphasizes the importance of:

1. Health promotion, awareness and disease prevention;
2. Disease detection and management;
3. Policy partnerships, and community/systems support; and
4. Research, surveillance and knowledge translation in the prevention, awareness, early detection, and optimal management of lung symptoms, disorders and diseases.

The goals of the National Lung Health Framework are excellent respiratory health for all in Canada. As the first ever health strategy that appreciates the close relationship between the environment and health, the starting point of the Framework was to develop a common strategic action plan for the respiratory health community, stakeholders and governments, so that we best use resources to improve the lung health of Canadians.

The announcement by Health Minister Aglukkaq represented an important leap in the process. Until now, we have taken a number of steps forward including markedly increasing awareness and profile of the problem with governments, increasing coordination and collaboration among partners, particularly the Public Health Agency of Canada. In addition, initial development of an online Knowledge Hub proceeded, and general consensus on the importance of priorities such as research funding, knowledge transfer, inadequate human resources, and the unique problems and needs of at-risk segments of the Canadian population was achieved.

While much has already been accomplished, there is more to be done. There is an opportunity for everyone to participate in the process, to share learnings and best practices with colleagues, and to listen to the successes of others. There is an opening to work with your member organizations to help with implementation and evaluation, and encourage those around you to do the same. The strong support of the federal government is both welcome and paramount, but that is only one piece to a very large puzzle. Without the engaged participation of all of us, we will not make progress. So much of what we need to do involves ensuring that we break down silos of excellence, share our knowledge and resources, and ensure that we continue to raise awareness of the impact of respiratory disease in Canada. To meet our goals and vision for our patients, we can do nothing less.

ACKNOWLEDGEMENTS: Dr Marciniuk is a Lung Association of Saskatchewan COPD Professor, and University of Saskatchewan/ Saskatchewan Health Research Foundation Airway Research Group Member.

Twenty-four hour noninvasive ventilation in neuromuscular disease: The Ottawa experience

Douglas A. McKirm MD FRCPC FCCP DABSM
Ottawa Hospital Sleep Centre and Respiratory Rehabilitation Services, University of Ottawa, Ottawa, Ontario
dmckirm@ottawahospital.on.ca

Noninvasive ventilation (NIV) has become a well established treatment in the management and survival of patients with neuromuscular diseases (NMD) (1-6). The benefits of NIV demonstrated in some populations include improved diurnal gas exchange, better sleep quality, better quality of life and increased survival. While NIV has been provided for more than 50 years with negative pressure ventilation, current devices are positive pressure, predominantly pressure-targeted bilevel ventilators with noninvasive mask interfaces. These are generally used overnight when gas exchange tends to be the most affected. As NMD progresses, the number of hours of required ventilatory support will also increase. In spite of a number of publications and extensive clinical experience (7,8), patients who require more than an arbitrary number of hours of NIV are often advised to undergo tracheostomy ventilation, the default means of provision of 24 h ventilatory support.

Since 1993, it has been common practice in Ottawa, as recommended by experts and international consensus (Bach [7], ATS DMD [9]), to offer all NMD patients with diurnal respiratory failure and sufficient bulbular function the opportunity to use 24 h NIV. As a result, not one permanent tracheostomy has been required or requested in any of our patients with Duchenne muscular dystrophy in 16 years (10). The benefits of 24 h NIV have also been applied to those with atypical lateral sclerosis (ALS), kyphoscoliosis, Becker’s muscular dystrophy, high-level spinal cord injury and others. Some patients with no measurable spontaneous lung function (maximal inspiratory and expiratory pressures = 0, vital capacity = 0) have managed adequate ventilation and survival for months without a tracheostomy and without hospitalization or intensive care unit admission.

Since well before 1953 (11), it has been recognized that polio patients, unable to breathe on their own, could achieve adequate ventilation outside their iron lungs with use of a pressurized mouth piece. Twenty-four hour NIV involves the use of a mouth piece which is attached to the end of a single-limb volume-targeted ventilator
(eg, LP10™, Legendaire™, Newport 50™) (12) or less commonly a double-limb portable ventilator (LTV 850™). The general principle is to allow an open system by providing sufficient airway (tubing) pressure to prevent initiation of the low-pressure alarm, providing an appropriate tidal volume and frequency for comfort and ventilation, and sufficient maximal pressures to permit the performance of lung volume recruitment (LVR) (13,14). This is achieved in a single-limb circuit by using a mouthpiece with adequate resistance or an in-line resistor, setting the low-pressure alarm to its lowest value (usually 2 cmH₂O) and determining appropriate tidal volumes, rate and inspiratory time. High-pressure alarms are usually set at 60 cmH₂O to 70 cmH₂O.

Figure 1) A patient with Duchenne muscular dystrophy with no ventilator-free breathing time using a chair-mounted, volume-targeted ventilator for mouthpiece ventilation

Most patients who are in a position of benefitting from mouthpiece ventilation (MPV) are power-wheelchair assisted. The ventilator can be mounted to the frame on the back of the chair to allow mobile ventilation. Volume-targeted ventilators with internal piston systems use little power and can last for hours with both internal and marine batteries. The ventilator tubing is provided to the patient through the mouth piece and fixed to the frame of the chair by a goose-neck clamp of similar fixation. It is critical that the individual be able to easily access the mouth piece for each required breath. Patients with limited or no ventilator-free breathing time must be accompanied because asphyxiation could occur if they were unable to access their mouth piece. Patients who chose this method, some for well over 10 years, understand and accept this unlikely risk rather than accept the risk and cost of a tracheostomy, particularly when a tracheostomy will likely prevent them from returning home. A minimal degree of oropharyngeal (bulbar) function is required to manage MPV, and those who cannot speak, swallow and protect their airway are not likely to be good candidates for this alternative. Patients with ALS, for example, tend to have difficulty with LVR and MPV if their bulbar component of the ALS Functional Rating Scale score (15) is less than 8 out of the total of 12. Such individuals who have elected not to pursue invasive tracheostomy ventilation (TV) would tend to use NIV via a mask for as long as tolerable while receiving palliation. Those who have chosen TV and cannot manage MPV and are requiring increasing hours of diurnal mask support will require elective tracheostomy. To date, we have found that approximately 25% of our patients with ALS who use NIV can subsequently utilize 24 h NIV/MPV. Almost all of our patients with Duchenne muscular dystrophy have been successful with MPV when required.

Most patients in our clinic at the Ottawa Hospital Rehabilitation Centre are trained to perform LVR effectively before any ventilatory requirement. These and other preventive airway clearance strategies can be continued during NIV and may contribute to the long-term success of NIV (16). Those individuals using MPV are encouraged to perform regular LVR, which they can do easily by stacking as many ventilator-delivered breaths as they can hold with their glottis. The MPV enables them to do this as often as they like, similar to a full sigh, which the able-bodied take for granted. The highest volume achieved with LVR is referred to as the maximum insufflation capacity (17). This can be more than a 400% increase over spontaneous vital capacity.

MPV can be an extremely valuable addition to the ventilatory care of patients with NMD who have sufficient bulbar function and a need for more than just nocturnal ventilation. It can safely provide support to patients with little or no respiratory function for extended periods of time. Essentially all of our (more than 40) patients have been managed entirely as outpatients. The arbitrary application of TV for such patients should be discouraged. In appropriate individuals, a trial of MPV is strongly recommended before committing patients and families to a potentially unnecessary, complex and costly tracheostomy.

REFERENCES


Chronic respiratory disease surveillance in Canada

Louise McRae
Public Health Agency of Canada, Chronic Disease Surveillance Division, Ottawa, Ontario
Louise_mcrae@phac-aspc.gc.ca

PUBLIC HEALTH SURVEILLANCE

The Public Health Agency of Canada’s Chronic Disease Surveillance Division defines public health surveillance as the tracking or forecasting of health events or health determinants through the regular collection of the best available data; the integration, analysis and interpretation of the data into surveillance products; and the dissemination of these data to those who need it, for a public health purpose or a policy objective (1).

COLLABORATION AND DEVELOPMENT FUNCTIONS

Within the Chronic Disease Surveillance Division, the work of the Collaboration and Development section includes four key functions.

1. Analysis, interpretation and use of existing data sources

Routine surveillance: Burden of respiratory disease in Canada: Existing data such as hospital morbidity, mortality and population survey databases are analyzed on an ongoing basis. Some highlights include:

- More than three million Canadians are affected by one of five serious respiratory diseases: asthma, chronic obstructive pulmonary disease (COPD), lung cancer, tuberculosis and cystic fibrosis (2).
- According to self-reported estimates from the Canadian Community Health Survey, COPD is now being reported more in women than in men younger than 75 years of age (2).
- Prevalence of self-reported asthma among children continues to increase; however, asthma prevalence among Canadians 12 years of age and over has stabilized (2).

Canadian Health Measures Survey (3): The Canadian Health Measures Survey is a new survey being conducted by Statistics Canada with both physical measures and questionnaire survey components. Data collection continues to Spring 2009 on a sample of approximately 5000 Canadians between the ages of six to 79 years, and data release is expected in Spring 2010. The variables of interest to respiratory disease surveillance are measured spirometry, self-reported diagnosed chronic conditions including asthma and COPD (including chronic bronchitis and emphysema), medications, and self-reported respiratory symptoms such as cough, phlegm, shortness of breath and persistent colds.

2. Reporting to key stakeholders

Life and Breath: Respiratory Disease in Canada (2): A surveillance report describing the burden of major respiratory diseases and their risk factors was released November 22, 2007, and has been widely disseminated.

Chronic Disease Infobase (4): Infobase is a free online data dissemination tool providing access to high-quality and up-to-date health data easily and quickly. Data available include demographics, hospital morbidity, length of stay, mortality, chronic disease risk factors and self-reported prevalence of selected chronic diseases. It is accessible through a web browser, allows one to develop custom queries of aggregated data and can provide data in map, graph or data table format with detailed sources and notes.

3. Expanding data sources

Canadian Community Health Survey (CCHS) (5) – Chronic Disease Prevention Theme: The prevention theme was conducted in 2007/2008, and data will be released in June 2009. The content focused on screening, prevention and awareness. PHAC was successful in adding a question on spirometry administered by a health professional.

Sleep Apnea Rapid Response Survey: The Public Health Agency of Canada developed and sponsored a 2 min supplement survey to Statistics Canada’s CCHS. Rapid response surveys collect data on a two-month survey sample of the main CCHS (approximately 10,000 respondents 12 years of age and over). In the case of sleep apnea, data collection was conducted from January to February 2009. The data will provide national level estimates of self-reported sleep apnea prevalence and prevalence of those at high risk for developing sleep apnea. Data are anticipated to be received at the Public Health Agency in the fall of 2009.

Provincial and Territorial Administrative Data: The Public Health Agency of Canada is expanding the National Diabetes Surveillance System (NDSS) (5) provincial/territorial administrative data platform to other chronic diseases. This platform uses three types of databases linked using a unique lifetime identifier: Physician Claims Files, Hospital Files, Health Insurance Registries. Preliminary pilot test results demonstrated the feasibility to generate comparable estimates of treated asthma and treated chronic obstructive pulmonary disease prevalence across provinces. Additional feasibility work is currently underway on revised case definitions and incidence. Recommendations will be presented to the NDSS Steering Committee in the winter of 2009/10.

Survey on Living with Chronic Disease in Canada (SLCDC) (6): The Public Health Agency of Canada has developed the SLCDC with Statistics Canada. The survey consists of a 20 min follow-up survey to the main CCHS survey focusing on specific chronic diseases. Survey content focuses on the following themes: symptoms/severity, self-management, clinical management, patient education, adherence, quality of life and risk factors. The first SLCDC was conducted in 2008/09 and consisted of surveys on hypertension and arthritis. In 2010/11 a survey on respiratory diseases will be conducted concurrently with a survey on diabetes. The respiratory survey will follow-up individuals who reported having asthma or chronic obstructive pulmonary disease (including chronic bronchitis and emphysema) in the main CCHS survey.

4. Coordination, planning and evaluation

Chronic Respiratory Disease Surveillance work at the Public Health Agency of Canada is not conducted in isolation. The input of our Chronic Respiratory Disease Surveillance Advisory Committee members and other project-specific working groups is instrumental to the success of this work.

REFERENCES

**State-of-the-art management of pulmonary hypertension**

Sanjay Mehta MD FRCPC FCCP

SW Ontario Pulmonary Hypertension Clinic, London Health Sciences Centre, University of Western Ontario, London, Ontario
Sanjay.mehta@lhsc.on.ca

Pulmonary hypertension (PH) is a serious and often fatal disease that is increasingly being recognized as neither rare nor uncommon. PH is defined hemodynamically by persistent elevation in mean pulmonary arterial pressure exceeding 25 mmHg at rest. Patients commonly experience dyspnea, and quickly become incapacitated due to progressive right ventricle (RV) failure. Untreated, the mean survival time in many PH patients is less than three years. There have been tremendous therapeutic advances over the past decade, as seven effective PH-specific medications are now approved and available for use. Appropriate use of novel PH medications depends on clinical recognition of PH, prompt and accurate diagnosis of the cause of PH, and institution of therapy in selected PH patients.

**DIAGNOSIS OF PH**

Patients with PH are usually diagnosed based on the clinical features of their disease (Figure 1). Dyspnea and exertion intolerance are common presenting complaints. Other symptoms include edema, chest pain, dizziness and syncope. Physical findings may be helpful in the identification of PH patients. The most sensitive sign is an accentuated pulmonic component (P2) of the second heart sound, best heard in the left second intercostal space. Other signs of PH include increased jugular venous pressure, pedal edema, palpable left parasternal right-ventricular heave, and a pansystolic murmur of tricuspid insufficiency. Many medical conditions are associated with a greater risk of PH, including cardiac disorders (eg, congenital heart disease), pulmonary disorders (eg, pulmonary fibrosis), pulmonary thromboembolic disease, connective tissue disorders, portal hypertension and HIV infection. In such patients, clinicians should be vigilant for any clinical or laboratory features that may suggest PH.

**REFERENCES**

The treatment traditionally recommended to patients with chronic obstructive pulmonary disease (COPD) has been based on drugs that were initially developed for the treatment of bronchial asthma. This anomalous situation was due to two causes. On one hand, investigations into the pathophysiology and pharmacology of COPD were scarce; on the other hand, there was an erroneous impression that all obstructive bronchial diseases followed the same pathogenic mechanisms. Fortunately, in recent years drugs have been developed according to the specific pathogenic mechanisms of COPD. Similarly, the Global Initiative for Obstructive Lung Disease (GOLD) guidelines adopted a stepwise approach for pharmacological treatment of COPD, similar to the approach in the Global Initiative for Asthma (GINA) guidelines for treatment of asthma.

One proposal for treatment of COPD according to the characteristics of the patients has recently been published (2). The following is a synthesis of these concepts.

1. The initial treatment of all patients with symptomatic COPD is based on the administration of a long-acting bronchodilator. Today, it is difficult to justify treatment with short-acting bronchodilators as the first option in symptomatic patients, even in mild cases.

2. Given that both the combination of salmeterol and formoterol with ipratropium has additive effects on lung function (3), if the initial response is not considered satisfactory, it seems reasonable to assume that the combination of tiotropium with any of these long-acting beta agonists (LABAs) may provide additive benefits similar to that observed with the combination of short-acting bronchodilators.

3. Theophylline is the next drug to add in the bronchodilator treatment of COPD. Theophylline has been shown to have additive effects on treatment with salmeterol (4). However, it is important to point out that the long-term effectiveness and, perhaps more important, the safety of this combination remain unknown.

4. In the most severe patients, the use of tiotropium plus the combination of inhaled corticosteroid (ICS) and LABA may be tested. A recent study (5) demonstrated that the addition of fluticasone/salmeterol to tiotropium treatment in severe patients was able to reduce all-cause and COPD-related hospital admissions, and also improved lung function and quality of life.

5. In patients who do not present with frequent exacerbations and do not have a significant bronchodilator response, despite the severity of their lung function (forced expiratory volume in 1 s less than 50% predicted), treatment with tiotropium plus salmeterol or formoterol may be sufficient. The last step of the treatment is the combination of all the therapeutic groups.

6. In any severity of disease, even in patients with mild to moderate COPD (forced expiratory volume in 1 s greater than 50% predicted) but with frequent exacerbations or characteristics similar to asthma, the use of ICS should be indicated (6-8), always in combination with a long-acting bronchodilator. The proportion of COPD patients that may benefit from treatment with ICS is not known. New studies such as Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) (9), aimed at identifying different subtypes and phenotypes of COPD, will provide new clues for selecting the most appropriate treatment for each patient with COPD.

The future trend in the treatment of COPD will undoubtedly be to use drugs in a single daily administration to ensure maximum compliance. It should be taken into account that most patients are elderly with multiple medications, and the treatment is indefinite in length. Long-acting bronchodilators alone or in different combinations will be the basis of the treatment (10), and the ICS are useful in the group of patients with well-defined characteristics. The latest studies indicate that the benefits of the ICS are limited in COPD and the risks are not insignificant. Therefore their use should remain limited to ‘responder’ patients and should always be administered in conjunction with LABA. There is no longer one treatment for COPD; rather, similar to other chronic diseases such as hypertension or diabetes, the different therapeutic options should be individualized based on the characteristics of each patient.

ACKNOWLEDGEMENTS: Boehringer Ingelheim and Pfizer Canada provided funding for Dr Miravitlles’ participation in the conference.

REFERENCES

The pharmacoeconomic evaluation of exacerbation of COPD

Marc Miravitlles MD
Fundación Clínic, Institut d’Investigacions Mèdiques August Pi i Sunyer (IDIBAPS), Hospital Clinic, Barcelona, Spain.
marcm@separ.es
The impact of obesity on dynamic respiratory mechanics, dyspnea and exercise tolerance in COPD

Denis E O’Donnell MD FRCPI FRCPC, Josuel Ora MD Respiratory Investigation Unit, Department of Medicine, Queen's University and Kingston General Hospital, Kingston, Ontario odonnell@queensu.ca

The prevalence of both chronic obstructive pulmonary disease (COPD) and obesity is increasing dramatically throughout the western world (1). Obesity is common in patients with COPD and population studies indicate that, paradoxically, its presence appears to convey a survival advantage (2). Although both of these common health problems have been studied extensively in isolation, the impact of their combination on respiratory pathophysiology and symptom intensity during activity is largely unknown.

RESPIRATORY CONSEQUENCES OF OBESITY

The mechanical derangements of simple obesity are well established and include reductions in chest wall, lung and total respiratory system compliance (3,4). Pulmonary function tests in obesity (excluding morbid obesity) show the following: little or no change in forced expiratory volume in 1 s (FEV₁) and forced vital capacity (FVC) with preserved or increased FEV₁/FVC ratio; reduction in expiratory reserve volume and functional residual capacity (FRC), with little or no change in total lung capacity (TLC), vital capacity and residual volume; increase in resting inspiratory capacity (IC); and increase in airway resistance (5,6). Respiratory muscle strength and endurance have been reported as either normal or reduced.

During activity, oxygen uptake (VO₂), carbon dioxide production (VCO₂) and ventilation (VE) are consistently higher at any given power output in obese people compared with normal weight subjects (7). Peak VO₂ is usually well preserved (adjusted for ideal body weight), but peak work rate is lower (8). Breathing pattern is more rapid and shallow, which is likely a compensatory strategy to minimize the increase in the elastic work of breathing.

Activity-related breathlessness is a common symptom in obesity, and dyspnea perception is higher during submaximal work loads in obese subjects compared with lean individuals. However, a recent study in obese adult women showed that during weight-supported cycle exercise, dyspnea/VE slopes were similar to those of normal

REFERENCES


weight controls (8). This was explained, at least in part, by the advantages of a reduced FRC and by recruitment of resting IC in the setting of a preserved TLC in obese individuals.

**EFFECTS OF OBESITY ON STATIC AND DYNAMIC LUNG MECHANICS IN COPD**

Despite the high prevalence of these two conditions, there are no studies to show the effects of obesity on respiratory system mechanics in COPD. Preliminary data from a population study (n=2267) in our laboratory indicated that among patients with similar FEV₁ (across Global Initiative for Obstructive Lung Disease [GOLD] stages I to IV), the FEV₁/FVC ratio was higher in the obese COPD group. Furthermore, indices of resting lung hyperinflation (FRC, TLC and residual volume) varied inversely with body mass index (BMI) (9).

To evaluate the consequences of these lower lung volumes in obese COPD patients, we compared dyspnea intensity ratings and ventilatory responses (breathing pattern and operating lung volumes) during symptom-limited incremental cycle exercise in well characterized groups of 18 obese (mean ± SD BMI=35±4 kg/m²) and 18 normal-weight (NW) (BMI=22±2 kg/m²) patients with moderate to severe COPD (10). The obese COPD group had a significantly smaller FRC, inspiratory reserve volume and TLC (expressed as % predicted) and the IC/TLC ratio was significantly larger compared with NW COPD. The dynamic end-expiratory and end-inspiratory lung volumes were lower at rest and throughout exercise in obese compared with NW COPD. Nevertheless, the magnitude of dynamic pulmonary hyperinflation during exercise was similar in both groups.

**IMPACT OF OBESITY ON DYSPNEA AND EXERCISE TOLERANCE**

At first glance, it would be reasonable to anticipate that when the derangements of dynamic ventilatory mechanics of COPD are coupled with the increased metabolic demands and mass loading effects of obesity, dyspnea and exercise intolerance should increase. In our study, obese COPD participants had a significantly greater V̇E and VO₂ at rest and throughout exercise compared with NW COPD controls. Despite these effects, the combination of obesity and COPD was not associated with diminished exercise capacity or greater dyspnea at any work rate compared with NW COPD. Moreover, in obese COPD, dyspnea intensity ratings were reduced at any given V̇E and VO₂ compared with NW COPD. We found a strong correlation (r=0.67, P<0.00001) between ratings of dyspnea intensity at a standardized ventilation and resting and dynamic end-expiratory lung volumes/TLC ratio in the whole group (n=36). We reasoned that the relatively reduced operating lung volumes at rest and throughout exercise (and the attendant advantages with respect to inspiratory muscle function), were the most likely contributory factors to reduced dyspnea intensity in obese COPD.

**SUMMARY**

In western countries, ‘the obese COPD patient’ has emerged as an increasingly common clinical phenotype. Obesity certainly has consistent effects on static and dynamic respiratory mechanics in COPD and this has important physiological and clinical implications. We were intrigued to find that the relatively reduced lung hyperinflation in obese COPD patients (compared with lean COPD patients matched for FEV₁) appeared to convey a mechanical advantage during cycle exercise. Of course, this does not mean that we should advocate excessive weight gain as the lung volume reduction intervention of choice in COPD! However, our results do justify further exploration of the impact of obesity on respiratory muscle function during rest and activity in patients with COPD.

**ACKNOWLEDGEMENTS:** This work was supported by the Ontario Ministry of Health and the Ontario Thoracic Society.

**REFERENCES**


**Assessment and treatment of pulmonary hypertension in COPD and other lung diseases**

Stevie Provencher MD MSc Centre de recherche de l’Institut Universitaire de Cardiologie et de Pneumologie de Québec, Université Laval, Montreal, Quebec,

Steve.Provencher@criucpq.ulaval.ca

Pulmonary hypertension (PH) is a frequent complication of chronic lung diseases (CLD), occurring in 15% to 95% of patients with severe chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (1,2). CLD also subsumes other interstitial lung diseases and diffuse parenchymal disorders that are often associated with clinically relevant PH. Nevertheless, the precise epidemiology of CLD-related PH remains unknown, because its prevalence depends on the population under study, the underlying disease severity, the definition applied (mean pulmonary artery [PA] pressure greater than 20 mmHg versus 25 mmHg), and the tools used to evaluate patients (echocardiography versus right heart catheterization).

The hemodynamic features of CLD-related PH significantly differ from those seen in pulmonary arterial hypertension (PAH). Although PAH may markedly worsen during exacerbations, the degree of PH is generally low to moderate in magnitude in stable CLD patients (mean PA pressure less than 35 mmHg), is slowly progressing (0.4-0.8 mmHg per year in COPD), and cardiac output is usually preserved (1,2). Nonetheless, a small proportion of patients display severe PH with mean PA pressure greater than 40 mmHg. Because these patients are frequently characterized by only moderate obstructive/restrictive disorders, severe hypoxemia, hyperventilation and a very low diffusing capacity (DLCO), it has been proposed that a subset of CLD patients with ‘out of proportion’ PH shares some clinical features with PAH. Disproportionate PH is also increasingly reported in patients with sarcoidosis (3), pulmonary Langerhans cell histiocytosis (4) and a combination of emphysema in the upper lung zones and pulmonary fibrosis in the lower lobes (5).

CLD-related PH has been traditionally attributed to pulmonary vasoconstriction related to alveolar hypoxia, vascular bed destruction and, less importantly, hypercapnia and hyperviscosity. There is, however, limited correlation between PH severity and markers of CLD severity (pulmonary function tests, blood gas analyses), suggesting that other mechanistic factors are involved in its pathophysiology (1,2).
PA pressure represents the sum of the driving pressure across the pulmonary circulation and of the pulmonary wedge pressure, both being influenced by intrathoracic and left heart pressures. More recently, pulmonary vascular remodelling and inflammatory changes, as well as endothelial dysfunction and genetic predisposition have also been shown to be involved in the pathophysiology of CLD-related PH. Pulmonary vascular infiltration by Langerhans cells (4) and sarcoid granulomas (3) have also been reported. PH thus results from the complex interactions among the pulmonary vasculature, intrathoracic pressures and left ventricular diastolic dysfunction commonly observed in CLD patients (6,7).

Numerous studies have confirmed the clinical relevance of even mild PH being one of the strongest predictors of mortality in many CLD including COPD, idiopathic pulmonary fibrosis, sarcoidosis and pulmonary Langerhans cell histiocytosis (1,2). PH is also independently related to exercise capacity in COPD (7). Whether PH influences prognosis and exercise capacity because it represents a surrogate marker of the CLD severity or because it relates to concomitant left heart abnormalities and intrinsic pulmonary vascular disorder remains unknown.

Dyspnea and fatigue are symptoms of both CLD and PH. Concomitant PH should be suspected when the symptoms or gas exchange abnormalities are more severe than one would expect from lung function data. Suspicion of PH should also be high if DLCO is disproportionally decreased, clinical deterioration is not matched by a decline in pulmonary function, or when signs of right heart failure develop. Echocardiography remains the screening tool of choice. PA pressure, however, is less likely to be measurable and is often inaccurate in CLD patients (8). Biomarkers such as brain natriuretic peptides lack specificity and sensitivity (8). Thus, right heart catheterization remains the standard for the diagnosis of PH, and is currently recommended when the presence of PH will likely affect patients’ management (8). Furthermore, an underlying CLD does not preclude a complete diagnostic work-up to exclude others causes of PH such as chronic thromboembolic PH, left heart diseases or a condition (eg, scleroderma) predisposing to PAH.

There is currently no specific therapy for CLD-related PH. The underlying CLD should be optimally treated according to relevant guidelines. Although PH was not an outcome of the pivotal trials on oxygen therapy in hypoxic COPD, long-term oxygen therapy was associated with either a stabilization (9) or a decrease in PA pressure (10). Long-term oxygen therapy is thus a logical treatment for hypoxic CLD patients. Nonspecific pulmonary vasodilators such as calcium channel blockers, urapidil and angiotensin-converting enzyme inhibitors were found to have no or even deleterious effects on pulmonary gas exchange.

Drugs with proven efficacy in PAH such as endothelin receptor antagonists, phosphodiesterase type 5 inhibitors and prostanoids are being increasingly used in CLD-related PH, despite the virtual absence of clinical trials supporting this approach. The only placebo-controlled randomized trials, evaluating bosentan in COPD with mild PH, resulted in no functional benefit and an increased pulmonary shunt. The few open-label trials also reported discordant results, suggesting that any pulmonary vasodilator has the potential to worsen gas exchange in patients with CLD. Whether patients with disproportionate PH, in which intrinsic vasculopathy may be a prominent pathophysiological feature, may benefit from these therapies remains unknown. It is noteworthy, however, that histological analysis of severe PH related to sarcoidosis (3), pulmonary Langerhans cell histiocytosis (4) and idiopathic pulmonary fibrosis (11) documented frequent pulmonary veno-occlusive-like lesions. Therefore, there is a theoretical risk of treatment-induced pulmonary edema with these therapies. All in all, much more evidence is needed before the use of PH-targeted therapy can be recommended for certain subpopulations of CLD. These patients should ideally be referred to specialized PH centres for inclusion in clinical trials (8).

PH is clearly a prevalent and clinically relevant complication of CLD. Its pathophysiology remains incompletely understood. The use of drugs approved for PAH is currently not recommended for the treatment of CLD-related PH until their safety and efficacy is clearly demonstrated. Patients with disproportionate PH should be ideally referred to specialized PH clinics for further evaluation and potential inclusion in clinical trials.

ACKNOWLEDGEMENTS: Dr Provencher is a clinical scientist of the Fonds de Recherche en Santé du Québec. He has received lecture fees from Actelion Pharmaceuticals Canada Inc, Enccysive Canada Inc, Pfizer Canada Inc, and received consultant fees from Actelion Pharmaceuticals Canada Inc, Eli Lilly Canada Inc, Enccysive Canada Inc, Glaxo-Smith-Kline Canada Inc and Pfizer Canada Inc.

REFERENCES

Controversies in pediatric ventilator-associated pneumonia
Pramod S Puligandla MD MSc FRCCSC FACS
Divisions of Paediatric Surgery and Paediatric Critical Care Medicine, Montreal Children’s Hospital, McGill University Health Centre, Montreal, Quebec
pramod.puligandla@mcgill.ca

Ventilator-associated pneumonia (VAP) is a pulmonary infection occurring in ventilated patients that is not present at the time of intubation. The true pathogenic mechanisms for the development of VAP are unknown. It is postulated that oropharyngeal colonization with noncommensal bacteria and distal spread to the airways represents a central event leading to VAP.

DIAGNOSTIC CRITERIA FOR VAP
The diagnostic criteria for VAP have been created by the National Nosocomial Infection Surveillance (NNIS) System (1). Furthermore,

32A

Can Respir J Vol 17 Suppl A January/February 2010
age-specific criteria have also been created to specifically address paediatric patients (2). These criteria comprise both clinical and radiological findings. Interestingly, the NNIS does not require microbiological confirmation of the diagnosis of VAP. However, several laboratory criteria have been described to support the clinical diagnosis of VAP (2).

**THE MANAGEMENT AND IMPACT OF VAP**

The treatment of VAP includes supportive measures as well as the early and judicious use of antibiotics. Empirical antibiotic regimens should cover all organisms associated with VAP, such as Staphylococcus aureus, Pseudomonas, and other Gram-negative species (Hemophilus, Enterobacter). Clinicians involved in the care of these patients must be aware of the local resistance patterns within their pediatric intensive care unit, hospital and community to provide effective treatment. Once an organism has been identified, therapy should be promptly de-escalated. The rates of pediatric VAP, as reported by the NNIS and National Healthcare Safety Network (NHSN), are 2.9 and 2.1 infections/1000 ventilator days, respectively (3). These rates represent a significant decrease from previously reported data (4), and may be the result of the use of a more stringent definition of VAP. However, one may question if VAP was previously over-diagnosed or that it is presently under-diagnosed.

The economic impact of VAP cannot be understated. Indeed, in adults, the cost of treatment of VAP in Ontario has been estimated at $11,450 per patient, with an overall excess cost approaching $46 million (5). Similar figures for pediatric intensive care units in Canada are more difficult to ascertain. However, in the United States, costs of over $30,000 per patient have been estimated for paediatric patients with VAP after controlling for age, illness severity, underlying disease and ventilator days (6).

**CONTROVERSIES IN PEDIATRIC VAP**

The controversies in pediatric VAP simply represent areas where further evaluation or study are required in paediatric patients. For instance, we currently lack a gold standard for the diagnosis of VAP. This has major implications because it makes evaluation of the literature difficult. Furthermore, the clinical and radiological criteria used by the NNIS and the NHSN are open to interpretation. For example, there are no objective indices for “worsening gas exchange”, (eg, increasing oxygenation index or decreasing PaO₂/FiO₂), or a “change in the character of secretions”. The latter is important because purulent tracheal secretions occur frequently in ventilated pediatric patients in the absence of pneumonia. Moreover, the discrimination of ‘atelectasis’ from ‘consolidation’ on chest radiographs may be plagued with significant interobserver variability (sensitivity 50% to 78% [7]). Indeed, focal persistent atelectasis is also a frequent finding in ventilated paediatric patients. What is really required is a determination of age-specific clinical and radiological criteria against a histopathological gold standard of VAP.

A second controversy relates to the use of invasive testing in children for the diagnosis of VAP (8). This is important because adult techniques such as bronchoalveolar lavage (BAL) or protected brush specimens (PBS) that have been shown to lead to faster de-escalation therapy for antibiotics, may not be applicable to pediatric patients. Only two studies evaluating these techniques have been performed in children. Gauvin et al (9) found that a bacterial index (sum of log of all bacterial species identified on BAL) was the best indicator of VAP in adults, the cost of treatment of VAP in Ontario has been estimated at $11,450 per patient, with an overall excess cost approaching $46 million (5). Similar figures for pediatric intensive care units in Canada are more difficult to ascertain. However, in the United States, costs of over $30,000 per patient have been estimated for paediatric patients with VAP after controlling for age, illness severity, underlying disease and ventilator days (6).

The pediatric VAP bundle is a collection of ‘evidence-based’ interventions that are meant to reduce the incidence of VAP (12). These interventions as a whole have led to some dramatic reductions in adult VAP in some institutional reports (12,13). Interestingly, an evaluation of the evidence behind the use of the specific elements of the bundle shows only a handful of studies that have been performed in children. For example, only two studies have evaluated the routine use of stress ulcer prophylaxis. Both studies failed to reveal any benefit to this practice with respect to the incidence of VAP (14,15). It seems evident that further pediatric-specific studies are required to ratify the individual elements of the bundle.

One of the most important aspects of VAP that is still unknown is its pathogenesis. Although oral colonization plays a central role in the development of VAP, a better understanding of those patients who do and do not develop VAP would certainly aid the development and implementation of both preventive and treatment strategies in these patients.

**CONCLUSION**

Paediatric VAP is an important problem with significant medical and economic implications. Better pediatric definitions for VAP, as well as the tests required to confirm its diagnosis, are required. Prevention seems to be a key element in the management of VAP but further pediatric-specific research is required to better understand its pathogenesis and treatment options.

**REFERENCES**


Cystic fibrosis: Pathophysiology and early intervention strategies
Felix Ratjen MD PhD FRCP(C)
Division of Respiratory Medicine, The Hospital for Sick Children, Toronto, Ontario felix.ratjen@sickkids.ca

PATHOPHYSIOLOGY
The cystic fibrosis (CF) gene defect leads to an absent or malfunctioning CF transmembrane regulator (CFTR) protein, which results in abnormal chloride conductance on the apical membrane of epithelial cells. More than 1500 different mutations have been described, but the majority of these mutations are rare: less than 10 mutations occur in different classes based on their functional consequences on CFTR within the cell. Until recently, the prognostic knowledge of the genetic mutation has been of limited clinical value, but new treatment approaches that address specific CFTR mutations are currently being tested. For instance, the most common mutation worldwide (DF508 CFTR) leads to a misfolded protein that is degraded intracellularly before reaching the plasma membrane. However, DF508 CFTR has functional activity and drugs that potentially correct the intracellular trafficking defect of DF508 CFTR are currently in development.

CFTR acts as a chloride channel in apical membranes, but possesses other important functions (2). CFTR has been described as a regulator of other membrane channels, to transport or regulate bicarbonate transport and to act as a channel for other proteins such as glutathione. In addition, interactions with many other intracellular proteins have been described. This may potentially be important for therapeutic interventions, because drugs that induce chloride secretion, but do not affect other CFTR functions, may not address all relevant aspects of CF pathophysiology.

Lack of CFTR activity causes less chloride secretion and, because ion transport also creates an osmotic gradient, less water transport into the epithelial surface layer. This results in airway surface liquid (ASL) depletion, and because ASL is essential to support ciliary stability and function, ciliary collapse and breakdown of mucociliary transport (3). The consequence of this is perpetuating a vicious cycle of mucus retention, infection and inflammation. However, mucociliary transport is not completely absent in CF and local mediators secreted into the ASL can induce both CFTR-dependent and -independent chloride secretion (4). For example, ATP mediates chloride secretion independently of CFTR by binding to P2Y receptors. Respiratory syncytial virus (RSV) has been shown to increase ATPase activity resulting in breakdown of ATP and loss of this compensatory mechanism, which may explain its negative impact on airway clearance in CF. ATP analogues are currently being tested as a treatment option for CF patients (5).

Lung infections with bacterial pathogens such as *Pseudomonas aeruginosa* and *Staphylococcus aureus* are a typical feature of CF lung disease. These bacteria are not unique for CF as other patient groups with poor mucociliary clearance show infections with these organisms. Most evidence would suggest that inhaled bacteria are trapped in the viscous mucus layer on respiratory epithelial cells that is not cleared effectively from the lower airways. It has also been shown that CF mucus lacks oxygen and these anaerobic conditions may be important to trigger a switch of *P. aeruginosa* from nonmucoid to mucoid cell types, the predominant phenotype in CF lungs. These mucoid strains form biofilms in CF airways, which are resistant to killing by the host defence system, resulting in chronic infection (3).

The cycle of mucus retention, infection and inflammation perpetuates itself, since inflammatory products released by neutrophils, such as elastase, stimulate mucus secretion. Whether inflammation is directly related to the CFTR defect is still disputed, but an exaggerated, sustained and prolonged inflammatory response to bacterial and viral pathogens is an accepted feature of CF lung disease (6).

**EARLY INTERVENTION STRATEGIES**

**Airway rehydration**
Because lack of airway surface liquid is an important step in the development of CF lung disease, increasing the airway fluid by inhalation of an osmotically active agent can potentially address the underlying abnormality in CF. Hypertonic saline was initially tested as an irritant to obtain sputum samples in patients with airway diseases, but smaller studies had also shown positive effects on mucociliary transport, and recent evidence suggests that hypertonic saline has a prolonged effect on ASL height in CF. Clinical efficacy of hypertonic saline was demonstrated in a multi-centre trial conducted in Australia that demonstrated a relatively modest improvement in lung function, but a more remarkable reduction in pulmonary exacerbations in treated patients (7). Studies in infants have shown tolerability in this age group as well, and a large trial in infants and young children is being conducted in North America (8). Mannitol is currently being tested as an alternative to hypertonic saline, but tolerability of this treatment varies among patients.

**P. aeruginosa eradication**
*P. aeruginosa* continues to be the major pathogen in CF lung disease. Most patients will eventually develop chronic infection with mucoid strains of *P. aeruginosa*, which cannot be eradicated even with intensive antibiotic therapy. However, there is increasing evidence that antibiotic therapy initiated early after the onset of infection has a much higher success rate (9). A recent, large, multicentre trial has demonstrated that a one-month course of inhaled tobramycin has both a high short- and long-term efficacy in clearing *P. aeruginosa* infection (10).

**REFERENCES**


**The current state of diaphragm pacing in spinal cord injured patients**

Jeremy Road MD1, John Yee MD2
1Division of Respiratory Medicine; 2Division of Thoracic Surgery, University of British Columbia, Vancouver, British Columbia jeremy.road@vch.ca

The diaphragm is considered to be the major muscle of inspiration. By contracting, force is exerted by the so-called insertional and appositional components of the diaphragm leading to expansion of the chest wall and, hence, lung inflation. Diaphragm shortening and function is very dependent on diaphragm length. When subjects with
Quadriplegia are tipped from the horizontal toward the upright position, diaphragmatic shortening and, hence, tidal volume decreases. Another aspect of diaphragm physiology is the implication of its continuous use. Recent data suggest that immobilization on mechanical ventilators can lead to quite rapid diaphragmatic atrophy and a change from slow-twitch oxidative to fast-twitch glycolytic fibres. The latter fibres are much more susceptible to fatigue.

Recently, the technique of stimulation of the diaphragm has been expanded to include placement of intramuscular electrodes within the diaphragm itself. Previously the diaphragm had been stimulated in patients with high-level quadriplegia via electrodes placed on the phrenic nerves. Placement of these electrodes is somewhat more problematic, as a thoracotomy has been traditionally used to place these electrodes and there is always concern regarding phrenic nerve injury. Diaphragm pacing stimulation (DPS) uses electrodes placed endoscopically at key points within the diaphragm. These points are determined by mapping areas of maximal activation of the diaphragm that lie close to the entrance of the phrenic nerve to the muscle. Thus the diaphragm is stimulated by activating the phrenic nerves within the muscle. Muscle stimulation without intact phrenic nerves requires excessive current and is not practical. Potential advantages of diaphragmatic stimulation as compared to mechanical ventilation are several, including the fact that spontaneous breathing is more closely simulated and, hence, there is less impact on cardiac output and less potential for barotrauma. The bases of the lungs are ventilated whereas when mechanical ventilation is used, the nondependent parts of the lung tend to be ventilated. Ventilators are also bulky, impeding mobility. Finally, there is improved taste and smell as well as speech with DPS.

The worldwide experience now is that 50 spinal cord injury patients have been instrumented with the DPS system (1). The average age is 36 years (range 18 to 74 years). The time since injury has varied from three months to 27 years. The average times the individuals were on mechanical ventilation before the DPS placement was 5.6 years. Needless to say, once the pacemaker is in place, the diaphragm has to be conditioned to sustain tidal volume potentially for 24 h a day, seven days a week. Initial attempts at stimulation reveal rapid fatigue. However, the diaphragm is readily conditioned. Control options on the pacing system include amplitude, frequency, rate, pulse, width and pulse modulation. The latter component allows a slow ramping stimulation that prevents aspiration while eating. The time for conditioning depends on the time from injury and the amount of training done per day.

Follow-up has been on average for two years (range 0.5 to eight years). There has been a 98% success rate in providing adequate tidal volumes and allowing patients to be removed from mechanical ventilators. Ninety-six per cent can use the pacer for more than 4 h. Ten patients have had cardiac pacemakers and there have been no device interactions. The main complication is capnorrhaphy, which occurred in 42% of patients and resolved without treatment. This complication occurs as a result of the CO₂ insufflation into the peritoneal cavity during the laparoscopic surgery and small leaks through the diaphragm into the pleural space. Wound infections occurred in two individuals. There have been five deaths, none of them related to pacemaker failures. Stimulated tidal volumes average 860 mL for men (range 540 mL to 1.5 L) and 528 mL for women (range 350 mL to 680 mL). These volumes were more than adequate to sustain the basal metabolic requirements. Patient questionnaires to evaluate efficacy have found 60% of individuals report a decrease in secretions and suctioning requirements. One hundred percent reported improved speech and improved independence.

Food and Drug Administration (United States) approval for the DPS system was obtained in June 2008. In Canada, Health Protection Branch approval has been applied for and is pending.

The DPS system is safe and effective. There have been no significant device-related adverse events. All patients have been able to utilize DPS for ventilation. No patients have stopped pacing and all would recommend it.

REFERENCES

The role of portable monitoring in the management of obstructive sleep apnea

C Frank Ryan MD
Division of Respiratory Medicine, University of British Columbia, Vancouver, British Columbia
fryan@interchange.ubc.ca

BACKGROUND
Polysomnography (PSG) is currently recommended for both the diagnosis of obstructive sleep apnea and the titration of optimal continuous positive airway pressure (CPAP) therapy (1-3). This approach to a common medical problem (approximately 5% of the adult population) inevitably leads to delays in diagnosis and treatment. Major disparities in the availability of PSG in Canada and internationally were recently highlighted (4). In 2006, the Institute of Medicine of the National Academies found that most American communities did not have adequate health care resources to meet the clinical demands to provide adequate prevention and management of sleep disorders (5). To increase diagnostic and therapeutic capacity, the report recognized the need to validate and develop existing and new technologies, especially portable technology.

THE EVIDENCE FOR PORTABLE MONITORING
In 2007, the Centre for Medicare and Medicaid Services undertook a critical appraisal of the evidence for portable monitoring, including an external technology assessment carried out by the Agency for Health Care Research and Quality (6). The main question addressed was whether there was adequate evidence to determine that diagnostic strategies other than facility-based PSG could accurately identify patients with obstructive sleep apnea who would benefit from CPAP treatment. The review found that facility-based PSG was not an error-free gold standard. The apnea-hypopnea index (AHI) or respiratory disturbance index measurements from portable monitors and facility-based PSG are not interchangeable, especially at the higher end of the AHI spectrum. Baseline AHI is only modestly associated with response to CPAP therapy or CPAP use among patients with a high probability of obstructive sleep apnea-hypopnea syndrome (OSAHS). Nevertheless, portable monitors may be able to predict an AHI suggestive of OSAHS with high positive likelihood ratios and low negative likelihood ratios. Limited evidence indicates that for high probability patients, PSG does not result in better outcomes compared with an ambulatory approach using portable monitoring (7). The increased accuracy in AHI estimation with facility-based PSG compared with a portable monitor did not translate into more accurate prediction of response to CPAP with respect to a quality of life outcome (7).

MODELLING DIFFERENT MANAGEMENT STRATEGIES
Because of the positive health outcomes associated with treating OSAHS, the optimal management strategy should maximize true positive diagnoses and reduce the time to diagnosis and treatment, while at the same time minimizing false positive diagnoses. The Agency for Health Care Research and Quality systematic review conducted a Markov process to model different simulated strategies among people with symptoms and signs suggestive of OSAHS (8). Polysomnography for both diagnosis and CPAP titration resulted in all patients with OSAHS being identified and offered CPAP therapy, whereas no patients without OSAHS were treated. The time to diagnosis was 13.6 weeks and the time to treatment was 27.3 weeks. Portable monitoring for diagnosis followed by home auto-CPAP titration for test-
positive patients and split night PSG for test-negative patients identified and offered CPAP to 99% of patients with OSAHS, but also 20% of patients without OSAHS. The ambulatory approach resulted in marked reductions in time to diagnosis (3.8 weeks), and treatment (6.2 weeks). The systematic review found no documented adverse health events in patients without OSAHS who received CPAP. Furthermore, patients without OSAHS were unlikely to improve with and adhere to CPAP. Nevertheless, false-positive diagnoses represent symptomatic patients who require further investigation and treatment. The Centers for Medicare and Medicaid Services (CMS) coverage decision published in March 2009 concluded that there was sufficient evidence to determine that portable monitoring tests could be used to diagnose OSAHS. Their use demonstrated improved health outcomes in patients who received appropriate treatment, and were reasonable and necessary tests. The recommendation excluded portable devices with less than three channels, such as oximetry. However, two recent randomized controlled trials that compared an ambulatory strategy using oximetry versus PSG showed at least equivalent outcomes in terms of CPAP adherence, sleepiness and quality of life (7,9).

IMPLICATIONS

These recent data and policy decisions recognize the limitations of both PSG and portable monitoring in predicting treatment outcomes. They place less emphasis on diagnostic accuracy and more emphasis on predicting favourable outcomes from treatment with CPAP. They also encourage a chronic disease management model for OSAHS. A simplified management strategy for OSAHS should include: knowledge of the pre-test probability of OSAHS; awareness of the limitations and pitfalls that can confound the diagnosis and treatment of OSAHS; and a back-up strategy for dealing with uncertainty. Strategies with high positive and low negative likelihood ratios for the diagnosis of OSAHS can be developed using baseline prevalence together with a clinical prediction rule and a suitable portable monitoring device. Factors that may confound diagnosis and treatment include co-morbid medical conditions and sleep disorders, technical limitations of portable monitors and auto-CPAP devices, and limited expertise among personnel using these strategies. A back-up strategy requires the expertise of a tertiary sleep program and the availability of polysomnography to deal with patients who do not meet the criteria of the ambulatory strategy, or who do not respond appropriately to treatment. Education, training and research may enable dissemination of these skills beyond the tertiary sleep program to include other physicians and health care workers, including those practicing in remote communities. Telehealth holds additional promise for the provision of timely care to patients with limited access to PSG.

REFERENCES


The Canadian Healthy Infant Longitudinal Development (CHILD) study

Malcolm R Sears MB ChB
Division of Respirology, McMaster University, Hamilton, Ontario
searsm@mcmaster.ca

Longitudinal studies of childhood asthma reveal considerable heterogeneity, but most cases of persistent asthma have their first symptoms in early life. Domestic animal exposure reduces risk of allergy (1), but breastfeeding may increase later childhood risks (2). Viral infections may be major pathogenetic factors (3). Patterns of asthma track from childhood into adult life, and loss of lung function may be established early. In the Dunedin Multidisciplinary Child Development Study, independent risk factors for persistence of childhood asthma included female sex, methacholine airway responsiveness, house dust mite allergy and personal smoking (4). Longitudinal assessment of lung function in those with persistent asthma indicated that lung function had tracked substantially lower than normal from age 9, suggesting the damage occurred in early childhood.

Many questions remain unanswered. What influences lung growth and development in infancy and early childhood? Is the development of asthma related primarily to nature or nurture? What role does environment play in the development of allergy and asthma? Do early childhood infections decrease or increase the risk of allergy and asthma? How do gene-environment interactions impact allergy and asthma?

To address these questions, a new longitudinal birth cohort study has been developed in conjunction with several interested groups, the Canadian Healthy Infant Longitudinal Development (CHILD) study. Researchers at McMaster University and the University of Toronto questioned whether children with persistent asthma are born with small airways, or whether the early environment (pollutants, infections, allergens) damages the airway. The Allergy, Genes and Environment (AllerGen) Network of Centres of Excellence (NCE) is seeking to determine the underlying causes of the major increase in allergic diseases, including asthma. The Canadian Institutes of Health Research (CIHR) expressed strong interest in the impact of the built environment on the health of the growing child, especially allergies and asthma. These groups came together to develop a proposal for a new longitudinal birth cohort study, funded jointly by AllerGen NCE and CIHR.

The primary hypothesis of CHILD is that exposure to indoor pollutants including chemical agents and microbiological agents, by interaction with host genetics, hormonal, metabolic, psychosocial, physiological, nutritional and immunological factors, increases the risk of allergy and asthma in infancy and early childhood. The study will recruit 5000 pregnant mothers in four major centres across Canada in 2009-2010, and follow the children until five years of age. The study will assess the home environment by questionnaire in pregnancy and at one, three and five years, and by direct inspection and sampling at three months; collect DNA at birth and five years; document infections in the first year of life; examine immune and inflammatory responses to pathogens and allergens; and correlate outcomes with markers of innate immune function. Lung function will be measured in infancy and at one, three and five years. Family data will be obtained by questionnaires, skin tests and lung function tests, together with parental genetics. The psychosocial environment will also be assessed, together with nutritional intake. Children will be seen at one, three...
and five years, with telephone contacts between visits. At five years, detailed questionnaires, clinical assessment, skin allergy tests, lung function tests and a final physician assessment will be undertaken.

The CHILD study team of more than 40 highly motivated skilled investigators has achieved CIHR and AllerGen funding after rigorous CIHR peer review, and has built excellent study teams at recruitment sites. Ethics approval has been obtained at all sites, and protocols and questionnaires developed and tested, using a multi-functional database built using HealthDiary. A pilot study was launched in late 2008, and the main study will commence in mid-2009.

Challenges facing the study include recruitment of a representative Canadian population avoiding biases in age, education, and socioeconomic status (to ensure diversity of environmental exposure), maintaining standardization of operational procedures within and across centres, quality assurance and control, administrative organization and communication, database management, long-term storage of biological samples, retention of the study families and ensuring sufficient funding.

Prospective studies such as CHILD, with multiple exposures carefully documented before outcome assessments, may allow determination of fundamental causes of diseases. Childhood studies may also become the base for lifelong studies of development of chronic diseases. Over the next six years, the CHILD study will gather a vast amount of data from Canadian children and their families, which will provide insights into the pathogenesis of allergy and asthma, and lead to improved health outcomes through appropriate interventions.

ACKNOWLEDGEMENTS: This work is supported by the CIHR and the AllerGen Network of Centres of Excellence.

REFERENCES

A sexual revolution in COPD
Don D Sin MD
The Providence Heart and Lung Institute & The James Hogg iCAPTURE Center for Cardiovascular and Pulmonary Research, St Paul’s Hospital, Vancouver, British Columbia
dsin@mrl.ubc.ca

Over the past 30 years, the age-adjusted mortality rate of chronic obstructive pulmonary disease (COPD) has more than doubled, whereas total mortality has decreased by one-third during the same period of time (1). The future looks even bleaker for COPD mortality, which is expected to increase by 50% over the next 15 years (2). Whereas the COPD mortality rates in men have plateaued in most western countries, the rates in women continue to increase (3). The exact reasons belying these gender differences are unknown. However, emerging epidemiological and animal studies are beginning to shed light on plausible mechanisms.

There is increasing evidence that female smokers are at increased risk of developing COPD compared with men. Kohansal et al (4) have shown that women smokers experience an accelerated decline in lung function compared with male smokers over an average follow-up of 23 years. In contrast, the rate of decline in lung function is similar between male and female never-smokers (4). This risk is modified by the number of cigarettes smoked per day and by the menopausal status of women. In the peri- and post-menopausal period, the risk of COPD is amplified among female smokers (5). Moreover, female smokers, in a dose-dependent manner, are at increased risk of total and COPD mortality compared with never smokers (6). The good news for female smokers is that if they stop smoking, they will recover more lung function than male smokers who quit smoking (7). The increased susceptibility of female smokers to COPD may be related to their smaller lung volumes, increased particle deposition of toxins in the airways, and enhanced generation of toxic metabolites of cigarette smoke from increased activity of cytochrome P450 enzymes (8).

While cigarette smoking is the leading risk factor for COPD in both men and women, it is notable that more women die from COPD than men despite the fact that there are fewer female than male smokers, suggesting that other factors are involved in the epidemic of COPD in women. This was well illustrated by a recent publication from China. Gu et al (6) found that the population attributable risk (i.e., the percentage of deaths that can be avoided by eliminating the risk factor from society) of cigarette smoking for COPD mortality in women was only 5.6%, whereas it was 12.1% for men. Similarly, the population attributable risk of smoking for lung cancer mortality, another disorder clearly linked with cigarette smoking, in women was only 14.8%, whereas it was 50.6% in men (6). These data raise the possibility that other risk factors such as gender differences in genetic susceptibility or exposure to other known environmental lung toxins (eg, biomass fuel, coal smoke and infections), may also play salient roles in enhancing the risk of COPD in women.

The role of sex hormones in COPD pathogenesis has not been fully elucidated. Animal models suggest that estrogens and progesterone may have proinflammatory effects in the lungs in response to aeroallergens, whereas they may have a protective effect against acute bacterial infections and acute lung injury by downregulating neutrophil accumulation in the lungs following acute injury (9). Interestingly, although in the premenopausal period estrogen and progesterone levels are markedly elevated in women than in men, postmenopausally, these female hormone levels may drop precipitously, and in some cases, below those levels in men. It is possible then that the withdrawal of the female hormonal milieu in the postmenopausal period may enhance the susceptibility of women toward lung injury from exposure to cigarette smoke and other environmental toxins. This theory will need to be tested in the future.

ACKNOWLEDGEMENTS: Dr Sin is supported by funding from ICEBERGS (Interdisciplinary Capacity Enhancement: Bridging Excellence in Respiratory disease and Gender Studies), which is funded by The Canadian Institutes of Health Research.

REFERENCES
5. Gan WQ, Man SE, Postma DS, Camp F, Sin DD. Female smokers beyond the perimenopausal period are at increased risk of chronic obstructive pulmonary disease: a systematic review and meta-analysis. Respir Res 2006;7:52.

**Physical activity behaviour in COPD: Implications for self-management interventions**

Judith Soicher PhD
Respiratory Epidemiology and Clinical Research Unit, McGill University Health Centre, Montreal, Quebec
judith.soicher@mcgill.ca

**PHYSICAL ACTIVITY IN CHRONIC DISEASE AND COPD**

Physical activity is a self-management behaviour with beneficial effects on survival (1) and quality of life (2). In a recent study of individuals meeting the diagnostic criteria for COPD (n=2386), those performing any level of physical activity had significantly lower risk of hospital admissions and all-cause mortality (3). Exercise is a type of physical activity, defined as planned and structured movement where the goal is to maintain or improve physical fitness (4). Pulmonary rehabilitation is the setting in which many patients with COPD adopt exercise; however, little is known about behavioural aspects of exercise. We undertook a longitudinal study to examine behavioural and disease-related aspects of exercise among individuals with COPD enrolled in rehabilitation.

**LONGITUDINAL STUDY OF PHYSICAL ACTIVITY IN COPD**

The longitudinal study was embedded within a randomized trial comparing the effectiveness of home-based versus outpatient hospital-based pulmonary rehabilitation (5). Subjects participated in four weeks of self-management education and eight weeks of either home- or hospital-based exercise training, comprising a three-month rehabilitation program.

In phase 1 of the longitudinal study (n=215), significant pre- to postrehabilitation improvements (P<0.05) were observed in exercise habits, self-efficacy for (confidence in ability to carry out) endurance and strength exercise, and barriers to exercise. There were no substantial pre- to postrehabilitation changes in the proportion of individuals reporting barriers related to time, schedule, cost or family.

In phase 2 (n=206), adherence to exercise was assessed at four, six, eight and 12 months using a one-week recall questionnaire, which uses the past week as a sample of an individual’s exercise over the past eight and 12 months using a one-week recall questionnaire, which uses the past month as a sample of an individual’s exercise over the past months. Adherence was operationally defined according to guidelines for older adults and individuals with chronic disease (6). At four months (one month after completing rehabilitation), 61% of subjects were adherent to endurance exercise (three or more days/week) and 54% to strength exercise (two or more days/week). These proportions declined to 46% and 37%, respectively, at 12 months. Longitudinal statistical modelling showed that adherence to endurance exercise from four to 12 months was significantly better in spring/summer (P=0.009) and among people who did any exercise before rehabilitation (P=0.018); adherence was worse among those with lower forced expiratory volume at 1 s (FEV1) at baseline (P=0.007) and who had a moderate or severe disease exacerbation during rehabilitation (P=0.045). Higher baseline self-efficacy for strength exercise significantly predicted better adherence to this type of exercise from four to 12 months (P=0.048). Exercise setting (home versus outpatient hospital) was not a significant predictor of subsequent adherence to either endurance or strength exercise.

**IMPLICATIONS FOR SELF-MANAGEMENT INTERVENTIONS**

To optimize longer-term adherence to exercise, variables that changed following rehabilitation (phase 1) or that predicted adherence (phase 2) should be targeted through educational and self-management interventions. In pulmonary rehabilitation, barriers to exercise should be identified with individual participants, and strategies to overcome or minimize barriers can then be developed jointly by the participant and health professionals. Group sessions can be used to discuss common barriers among participants and to share successful strategies.

Predictors of adherence to endurance exercise included disease-related variables (FEV1 at baseline, exacerbation during rehabilitation) and season. Although FEV1 is not modifiable, it can serve as an indicator to identify and monitor individuals who may have difficulty with exercise adherence. Exacerbations can be addressed through implementation of an action plan to recognize and treat early symptoms, and by highlighting to patients the detrimental effect of exacerbations and the need to resume exercise as soon as possible after the acute exacerbation has resolved. The finding that adherence was better in the spring and summer points to the need for patients to develop maintenance strategies, such as purchasing equipment for home use and/or attending organized exercise classes during the fall and winter. Future work is needed to study the effect on adherence of contextual factors related to program delivery and follow-up, and to examine qualitatively patient perceptions of personal and environmental factors that facilitate or hinder exercise.

**ACKNOWLEDGEMENTS:** Dr Soicher is supported by funding from the Canadian Institutes of Health Research, Fonds de la recherche en santé du Québec, and the Lung Association.

**REFERENCES**


**The Canadian Obstructive Lung Disease (COLD) initiative**

Wan C Tan MD1, Jean Bourbeau MD MSc2, Kenneth Chapman MD MSc3, Robert Cowie MB ChB MD MSc4, Paul Hernandez MD5, Mark FitzGerald MB MD1, Don Sin MD1
1University of British Columbia, Vancouver, British Columbia; 2McGill University, Montreal, Quebec; 3University of Toronto, Toronto, Ontario; 4University of Calgary, Calgary, Alberta; 5Dalhousie University, Halifax, Nova Scotia
wtan@mrl.ubc.ca

The prevalence of chronic obstructive pulmonary disease (COPD) in Canada is currently based on self-reported physician-diagnosed COPD, and ranges from 2.9% to 4.7% (1). It is widely recognized that...
an accurate diagnosis of COPD requires spirometric confirmation of chronic airflow limitation (2). There is a need for a population-based lung health study of COPD prevalence based on spirometry measurements in Canada.

**KEY FEATURES OF THE COLD INITIATIVE**
The Canadian Obstructive Lung Disease (COLD) initiative is a cross-sectional, multisite, nationwide, population-based, epidemiological study on lung health, initiated in Vancouver in August 2005. The initiative proposes to include nine study sites across the country and has been completed to date in five cities (Vancouver, Montreal, Toronto, Halifax and Calgary) in Canada. The primary aim of the initiative is to measure the prevalence of COPD and its risk factors in the Canadian population.

The COLD initiative is standardized by using the Burden of Obstructive Lung Disease (BOLD) protocol for all sites (3). The BOLD protocol includes standardized lung health questionnaires, standardized performance of spirometry and standardized conduct of the study. Details of the BOLD study protocol have been described in previous publications (3,4).

**COLD STUDY POPULATION AND DESIGN**
The target population consisted of adults 40 years of age and older who resided in each of five sampling frames of at least 250,000 people. These geographic areas are the health service delivery area for Vancouver; census subdivisions for Toronto, Montreal, and Calgary; and the Federal Electoral Districts for Halifax. The approximate population sizes of these sampling frames are 0.6 million (M) in Vancouver, 1.6M in Montreal, 2.5M in Toronto, 0.3M in Halifax and 1M in Calgary.

The minimal sample size per site in the COLD study was a random sample of 600 participants who complete the clinic visit, assuming a prevalence of chronic airflow limitation of 15% (3). Sampling was conducted in two stages, starting with random-digit-dialling to identify and recruit a random sample of at least 1000 individuals (4), followed by an invitation to complete the full protocol at the clinic. This consisted of interviewer-administered standardized questionnaires that included demographic details and questions about respiratory health and symptoms; smoking history of tobacco and marijuana; quality of life; health care use; cardiovascular comorbidities and other respiratory diseases; and the performance of spirometry before and after administration of 200 μg of albuterol/salbutamol, according to the American Thoracic Society acceptability and reproducibility criteria.

**DEFINITION OF COPD**
The presence of chronic airflow limitation in the COLD study is defined as postbronchodilator forced expiratory volume in 1 s (forced vital capacity of less than 0.70), while its severity is defined according to the Global Initiative for Obstructive Lung Disease (GOLD) severity classification, grades I to IV. Other spirometric definitions of COPD such as the lower limits of normal and the European Respiratory Society criteria will be used for comparison against the primary definition.

**RESULTS TO DATE**
The study has been completed in five sites. Preliminary results show similar sample characteristics and rates of usable spirometry data for the Vancouver and Montreal sites (Table 1). To date, a total of 3002 subjects have completed the full protocol, with 878 in Vancouver, 557 in Montreal, 546 in Toronto, 454 in Halifax and 567 in Calgary. Minimal telephone interview data on age, sex, smoking status, respiratory disorders and comorbidities, obtained from the random-digit-dialing recruitment process, are also available on 10,091 adults, with 878 in Vancouver, 1.6M in Montreal, 2.5M in Toronto, 0.3M in Halifax and 1M in Calgary.

**TABLE 1**

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Minimal telephone data</th>
<th>BOLD/COLD volunteers</th>
<th>BOLD/COLD data+spirometry with reversibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 to 39</td>
<td>180</td>
<td>240</td>
<td>240</td>
</tr>
</tbody>
</table>

**BOLD/COLD Study Completers Summary**

**ACKNOWLEDGEMENTS:** This work is supported by an unrestricted educational grant from AstraZeneca Canada, Boehringer Ingelheim Canada, GlaxoSmithKline Canada, and Pfizer Canada.

**REFERENCES**

**The pattern of health services use in children with asthma – a 10-year review of population-based data from Ontario**

Teresa To PhD
The Hospital for Sick Children, Toronto, Ontario
teresa.to@sickkids.ca

**OBJECTIVE**
Asthma is the most common chronic childhood illness in North America. The purpose of the present study was to measure the burden of childhood asthma in Ontario from 1996 to 2005, by reviewing the patterns of asthma incidence, prevalence and health services use.

**METHODS**
An asthma algorithm with 84% sensitivity and 89% specificity was applied to the Ontario health administrative data to identify children with asthma (1). Children (younger than 20 years) were considered to have physician-diagnosed asthma if they had one or more hospitalization for asthma and/or two or more physician visits for asthma within a period of two years. Three major Ontario health administrative databases were used for measuring health services use. They include the hospital discharge abstract database (collected by the Canadian Institute for Health Information), physicians’ billings (collected by the Ontario Health Insurance Plan) and the emergency room visit database (also collected by Canadian Institute for Health Information). Data were available from fiscal years 1996 to 2005. A fiscal year runs from April 1 to March 31 of the following year. From this 10-year period, the number of asthma prevalent cases in Ontario increased from slightly below 1 million to 1.67 million and 40% of them were in children aged 20 years or younger.
FINDINGS (TABLE 1)
Hospitalizations for asthma
There was a dramatic decline in hospitalization rates for asthma from 1996 to 2005 for all children from 2.7 to 1.3 per 100 asthma individual, representing a 52% relative reduction. However, the decline was much smaller in preschoolers aged zero to four years (5.4 to 4.0 per 100, 26% reduction).

Emergency room visits for asthma
Overall, in children younger than 20 years of age, there was a 37% decrease in emergency department (ED) visits for asthma (8.8 to 5.5 per 100) from 1996 to 2005. However, the ED visit rate for asthma remained highest in preschoolers. In the 10-year period of study, there was practically no change in the ED visit rates in this youngest group in our population (14.3 to 14.1 per 100).

Outpatient care for asthma
In 2005, there were nearly 900,000 Ontario Health Insurance Plan claims for asthma. About 40% of them were for children younger than 20 years. Over the 10-year observation period, there was a 40% decline in outpatient care for asthma in children from 1.8 to 0.6 asthma claims per individual with asthma. Again, in the very young; the rates showed a much smaller decline (1.6 to 1.4 claims per child with asthma, 12% decrease).

TABLE 1
Health services use for asthma in Ontario, 1996 and 2005

<table>
<thead>
<tr>
<th>Health services use for asthma</th>
<th>Year</th>
<th>Age groups, years</th>
<th>Total Ontario</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization (per 100)</td>
<td>1996</td>
<td>5.4</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td>2005</td>
<td>4.0</td>
<td>0.9</td>
</tr>
<tr>
<td>% change</td>
<td></td>
<td>−8.3</td>
<td>−75.3</td>
</tr>
<tr>
<td>ED visits (per 100)</td>
<td>1996</td>
<td>14.3</td>
<td>7.4</td>
</tr>
<tr>
<td></td>
<td>2005</td>
<td>14.1</td>
<td>3.6</td>
</tr>
<tr>
<td>% change</td>
<td></td>
<td>−1.5</td>
<td>−51.4</td>
</tr>
<tr>
<td>Outpatient care</td>
<td>1996</td>
<td>1.6</td>
<td>1.1</td>
</tr>
<tr>
<td>(per individual)</td>
<td>2005</td>
<td>1.4</td>
<td>0.6</td>
</tr>
<tr>
<td>% change</td>
<td></td>
<td>−12.2</td>
<td>−50.0</td>
</tr>
</tbody>
</table>

ED Emergency department

SUMMARY
While the 10-year review showed a stabilizing trend of asthma incidence in children, asthma still has a significant presence in children younger than 20 years of age, with 21.3% prevalence in 2005. The overall decrease in acute and primary health services for asthma is encouraging and may be explained by improvement in asthma control and management in the past decade. With proper management (use of appropriate medications, good control of symptoms, avoidance of triggers, etc), asthma exacerbations and the use of acute health services for that reason can be avoided. However, in children zero to four years of age, the use of both acute and primary health care for asthma remained substantial. While there is improvement in the level of use of health services for asthma, it is much less compared with older children and the rest of the population. Close monitoring of this most vulnerable age group is important to ensure their asthma is well managed and controlled.

ACKNOWLEDGEMENTS: Supported by funding from the Ontario Ministry of Health and Long-term Care and the Institute for Clinical Evaluative Sciences.

REFERENCES

Self-management: Motivational change to enhance behaviour modification
Margot Underwood
Education Consultant, Calgary COPD & Asthma Program,
University of Calgary, Calgary, Alberta
munderwo@ucalgary.ca

Self-management is an important strategy in chronic disease programs with the understanding that it can lead to improved health and quality of life. According to Lorig et al (1), self-management involves the person with the disease being actively involved in four key areas:

- engaging in activities that protect and promote health;
- monitoring and managing the symptoms and signs of illness;
- managing the impact of illness on functioning, emotions and interpersonal relationships; and
- adhering to treatment regimes.

Health care professionals such as respiratory physicians and Certified Respiratory Educators, who provide care and education in lung health programs, are interested in helping a patient gain the confidence to more effectively self-manage their asthma or chronic obstructive pulmonary disease. Translating this knowledge into practice (regarding self-management and self-efficacy) often necessitates health team members developing higher-level communication skills.

A key communication skill is that of motivational interviewing (MI), a directive counselling intervention that can enhance communication with patients and facilitate positive behaviour changes (2). A central MI concept is that the patient is responsible for their behaviour change, therefore their expertise and experience is always honoured.

Gaining experience in the use of MI helps the health provider to listen attentively, think reflectively, then provide empathetic, non-judgmental feedback. MI has been demonstrated to be especially useful in addressing ambivalence and resistance to change. Tools such as decisional balance worksheets can help an individual reflect on the pros and cons of a behaviour change and identify barriers that need to be addressed. Tracking cards and diaries will increase awareness of current behaviour or triggers in early stages and later will provide a means of tracking progress. Rating scales can be effectively integrated to help an individual identify their readiness to change, importance of the change and their personal confidence. It is also important to listen for change in language, such as, “I have been thinking about…” and consider how to integrate these statements when communicating back to the patient.

Listed below is a brief summary of the core MI strategies. Provided for each are examples of MI phrases that could be used in lung health education.

Support self-efficacy
Emphasize personal choice and control in behaviour change. Confidence and self-efficacy can be increased through incorporating past mastery experiences, integrating vicarious experiences and verbal persuasion (3).

- “What has worked for you in the past when you successfully quit smoking?”
- “You have identified, as have many others, that it helps to have a plan”.
- “It’s great that tracking your symptoms has helped you manage your asthma”.

Express empathy
Learn to listen reflectively and then let the person know that their concerns have been heard.

- “It sounds like you are finding it difficult to believe that you have COPD”.

Can Respir J Vol 17 Suppl A January/February 2010
In neutral tone and language, address the discrepancy between an individual's current behaviour and his/her stated values and interests. It can be helpful to listen for ambivalent statements such as "I want to..." and to provide reflective feedback to the individual.

- "So on one hand you find smoking pleasurable, but on the other hand you are worried about your increasing shortness of breath".
- "You want to have better asthma control, but are finding it hard to remember to use your inhaler".
- "Would you say that smoking is the only way for you to manage stress in your life?"

**Roll with resistance**

Avoid arguing and meet resistance with reflection. Reinforce that it is the patient's role to be the problem-solver.

- "I hear you. Right now you are not ready to quit smoking".
- "You don't like it when people pressure you to make changes".
- "It seems like this is a hard decision for you to make".

Motivational interviewing will help you to better understand a patient and their motives for changing a behaviour. Taking the time to attentively listen, use open-ended questions and provide thoughtful, empathetic reflections will help to build a bond with the individual. The information gained will then enable you to effectively assist the patient to develop and confidently use a tailored self-management plan.

More information on motivational interviewing and self-management can be found on these Web sites:

- Motivational Interviewing: www.motivationalinterviewing.org
- Stanford Patient Education Research Centre: www.patienteducation.stanford.edu
- Flinders Chronic Condition Management Program: www.flinders.edu.au
- Tobacco Reduction: www.smokingcessationrounds.ca

**REFERENCES**


**Chronic ventilatory support in patients with chronic obstructive pulmonary disease**

**Peter Jan Wijkstra MD PhD**
Department of Home Mechanical Ventilation / Pulmonary Diseases,
University Medical Centre, Groningen, The Netherlands
p.j.wijkstra@int.umcn.nl

International guidelines have advocated that patients with COPD admitted to hospital with acute respiratory failure (ARF) due to an exacerbation, should receive non-invasive ventilatory support along with standard medical therapy. There is no such consensus on chronic noninvasive positive pressure ventilation (NIPPV) as findings of studies have been conflicting (1,2). In the present short report we will discuss the various reasons why different outcomes might have been obtained.

**DISCUSSION**

Monitoring
One of the possible reasons for conflicting results is the lack of control of ventilation during the night. In contrast to many other negative studies, Meecham Jones et al (3) and Duiverman et al (4) did control ventilation by either transcutaneous partial pressure of arterial carbon dioxide (PaCO2) or arterial blood gases, and found an improved gas exchange and health-related quality of life.

**Number of hours on NIPPV**

While use of NIPPV 2 h daily for five days a week (5), and for 3 h daily for five days a week for three consecutive weeks (6) both showed significant benefits in clinical parameters, Duiverman et al (4) showed that increased number of hours on bilevel positive airway pressure was related to a decrease in PaCO2. As the optimal duration of ventilatory support is still unknown, different approaches are still being used.

**Patient selection**

The three studies that showed improvements in arterial blood gases after NIPPV included patients with a higher level of hypercapnia (3,6,7). Diaz et al (6) and Clini et al (7) selected only patients with a PaCO2 greater than 6.6 kPa (50 mmHg). Even though Meecham Jones et al (3) allowed a lower cut-off point, the lowest baseline PaCO2 actually seen in patients included was 6.9 kPa (52 mmHg). This suggests that the more hypercapnic patients benefit most.

**Mean inspiratory pressures**

When taking the levels of inspiratory pressure into account, it seems that the studies that targeted higher mean inspiratory pressure showed the greatest improvements in outcome measures, particularly in daytime blood gases (3,4). These findings correspond to two uncontrolled studies by Wndisch et al (8) and Budweiser et al (9), who both found significant reductions in daytime PaCO2 using high inspiratory pressures of 28 cmH2O and 21 cmH2O, respectively.

**Survival**

The two long-term trials lasting one and two years, respectively, did not find any differences in survival between the long-term oxygen therapy group and the NIPPV group (7,10). Because they used lower pressures of 12/4 and 14/2, respectively, the lack of benefit could have been due to insufficient ventilation. An uncontrolled study by Budweiser et al (9) compared long-term survival of 140 patients with severe persistent hypercapnic chronic obstructive pulmonary disease with or without NIPPV (9). Mean inspiratory pressure was 21 cmH2O. Significantly higher survival rates were reported in patients with NIPPV (87.7% and 71.8%) after one and two years, compared with those without (56.7% and 42.0%). It should be noted, however, that the control group comprised patients who refused NIPPV or could not tolerate it.

**Compliance**

Meecham Jones et al (3) and Clini et al (7) both showed improvements in several outcome measures and had good compliance, with mean total hours spent on ventilation of 9 h and 7 h per night, respectively. Similar positive results were reported by Duiverman et al (4), for patients using the ventilator for more than 7.5 h per night. Good compliance can be obtained by giving the patient sufficient time to become familiarized with NIPPV in an in-hospital setting, where experienced staff can adjust ventilation to optimal standards.

In conclusion, evidence is insufficient to recommend chronic NIPPV on a routine basis to stable severe chronic obstructive pulmonary disease patients. We do believe that it could be of benefit to certain patient groups, such as hypercapnic patients. Effective monitoring during the night and giving the patient sufficient time to become familiarized with NIPPV are crucial issues in obtaining effective ventilation.

**REFERENCES**

3. Meecham Jones DJ, Paul EA, Jones PW, Wedzicha JA. Nasal pressure support ventilation plus oxygen compared with oxygen
therapy alone in hypercapnic COPD. Am J Respir Crit Care Med 1995;152:538-44.

**Interstitial lung disease in scleroderma**

Pearce Wilcox MD
Respiratory Division, St Paul’s Hospital, University of British Columbia, Vancouver, British Columbia pwilcox@providencehealth.bc.ca

Interstitial lung disease (ILD) in systemic sclerosis (SSc) is highly prevalent, with clinically relevant disease occurring in 20% to 40% (1). Outcomes are worse in SSc patients who manifest ILD. Considerable pulmonary disease heterogeneity exists, however, and an ability to identify those most likely to progress would be valuable. Goh et al. (2) have developed a relatively simple clinical staging system and found that those with extensive lung disease based on a high-resolution computed tomography (HRCT) disease activity score of greater than 20%, or in indeterminate cases, forced vital capacity less than 70% predicted, are much more likely to progress. Earlier retrospective studies had suggested that an ‘active alveolitis’ based on bronchoalveolar lavage identified those more likely to worsen (3). However, in a recent large prospective SSc cohort, bronchoalveolar lavage parameters did not prove to be independent predictors of either disease progression or response to therapy (4).

Given this conflicting and limited information, we advocate incorporating composite measures including HRCT scores, lung function testing, serology, time from onset of diagnosis and, importantly, rate of progression when deciding whom to prioritize for therapy.

**THERAPY**

To date, the therapeutic literature for SSc has been most notable for the number of negative studies. Thus, the results of the Scleroderma Lung Study (SLS) (4), which sought to evaluate cyclophosphamide in a prospective placebo-controlled design, were anxious awaited. In this study, there was a statistically significant difference in favour of the cyclophosphamide group in the primary outcome parameter (vital capacity [VC]) and also in other secondary outcomes of total lung capacity, dyspnea score, quality of life and skin thickness scores. The clinical significance, however, has been correctly questioned given the very small differences in VC, and the fact that diffusing capacity did not differ. A decision has to be made on an individual basis, which incorporates the appreciable potential toxicity of cyclophosphamide (narrow suppression, bladder toxicity, infection risk, malignancy potential and gonadal suppression). One means of potentially reducing these risks is to use pulse intravenous dosing of cyclophosphamide (5).

Other data subsequently reported from the SLS help in understanding the longer term course of patients. In one further year of follow-up, in essence without therapy, there was a progressive improvement in VC seen in the former cyclophosphamide group up to 18 months; by 24 months, it had returned to the level of placebo patients (6). This has been interpreted as indicating that one year of cyclophosphamide does not modify the natural history of SSc ILD. If treatment is to be initiated, one year would seem insufficient in duration. Another interesting observation in this study was that the degree of ground glass HRCT changes had little predictive value, but that those with more fibrosis at baseline were more likely to respond to cyclophosphamide.

The very modest benefits of cyclophosphamide, when placed in the context of potential adverse effects, has driven the search for other therapies. Mycophenolate mofetil has biological plausibility, a reasonable safety profile, established efficacy in other disease states and a number of retrospective case series that have been promising in SSc ILD (7). Increased oxidant stress has been shown in SSc (8) and can drive disease progression in other ILD, providing rationale for further study in SSc ILD. Gastroesophageal reflux and aspiration is an almost invariable occurrence in SSc and can accelerate lung disease in idopathic ILD. Treatment can be problematic but attempts to at least minimize this complication should be a routine part of therapy. A number of other agents are attracting attention in SSc ILD such as novel antibiotics, biologics and even stem cell therapy, with a multi-centre North American study already underway.

**ILD AND PULMONARY HYPERTENSION**

Pulmonary hypertension (PH) is a well-recognized complication in SSc and one that has a high mortality (9). ILD itself can be a cause of PH; however, there exists a group of patients with ILD who have ‘disproportionate’ PH. The management of these individuals remains controversial, but evaluation for PH in ILD should be routine. It is notable that some in vitro data suggest that therapies used in PH, such as endothelin receptor antagonists, may have an antifibrotic effect.

**SUMMARY**

ILD in SSc is a common occurrence and an important cause of morbidity and mortality. The challenges remain not so much in its detection but in the decision of whom to treat with therapies that have limited potency and considerable potential adverse outcomes. Newer treatments are clearly required and a partnership among respiratory physicians, rheumatologists and PH specialists is necessary to properly evaluate and institute them.

**REFERENCES**


Can Respir J Vol 17 Suppl A January/February 2010

42A
**CONFLICTS OF INTEREST**

Dr Shawn Aaron: is supported by funding from the Canadian Institutes of Health Research; Dr Darryl J Adamko, Dr Ramses Illaraza, Yingqi Wu: this work is supported by funding from the Canadian Institutes of Health Research and Merck-Frosst Canada; Dr Mark Anselmo: none to report; Dr Jane Batt: none to report; Donna Bleakney: none to report; Dr Louis-Philippe Boulet: none to report; Dr T Douglas Bradley: is supported by funding from the Canadian Institutes of Health Research; Dr Anna Day: none to report; Dr Neil D Eves: none to report; Dr Kathleen A Ferguson: none to report; Dr Richard J Finley: is supported by funding from the British Columbia Lung Association; Dr Ian D Graham, Jacqueline M Tetroe: none to report; Dr Hartmut Grasemann: none to report; Dr Samir Gupta: is supported by funding from the Li Ka Shing Knowledge Institute of St Michael’s Hospital, Toronto, Ontario; Dr Kylie Hill: none to report; Dr Rick Hodder: none to report; Dr Nader Khalidi: none to report; Dr Stephen Lam: none to report; Dr Larry C Lands: none to report; Dr Denny P Laporta: none to report; Dr France Légaré: holds the Canada Research Chair in Implementation of Shared Decision Making in Primary Care; Dr Piush J Mandhane, Neil W Johnston, Malcolm R Sears: none to report; Dr Darcy D Marciniuk: is a Lung Association of Saskatchewan COPD Professor, and University of Saskatchewan/Saskatchewan Health Research Foundation Airway Research Group Member; Nora Sobolov: none to report; Dr Douglas A McKinn: none to report; Dr Sanjay Mehta: none to report; Dr Marc Miravitlles: Boehringer Ingelheim and Pfizer Canada provided funding for Dr Miravitlles’ participation in the conference; Dr Denis E O’Donnell, Dr Josuel Ora: this work was supported by the Ontario Ministry of Health and the Ontario Thoracic Society; Dr Steeve Provancher: is a clinical scientist of the Fonds de Recherche en Santé du Québec. He has received lecture fees from Actelion Pharmaceuticals Canada Inc, Encysive Canada Inc, Pfizer Canada Inc, and received consultant fees from Actelion Pharmaceuticals Canada Inc, Eli Lilly Canada Inc, Encysive Canada Inc, Glaxo-Smith-Kline Canada Inc and Pfizer Canada Inc; Dr Pramod S Puligandla: none to report; Dr Felix Ratjen: none to report; Dr Jeremy Road, Dr John Yee: none to report; Dr C Frank Ryan: none to report; Dr Malcolm R Sears: this work is supported by the CIHR and the AllerGen Network of Centres of Excellence; Dr Don D Sin: is supported by funding from ICEBERGS (Interdisciplinary Capacity Enhancement: Bridging Excellence in Respiratory disease and Gender Studies), which is funded by The Canadian Institutes of Health Research; Dr Judith Soicher: is supported by funding from the Canadian Institutes of Health Research, Fonds de la recherche en santé du Québec, and the Lung Association; Dr Wan C Tan, Dr Jean Bourbeau, Dr Kenneth Chapman, Dr Robert Cowie, Dr Paul Hernandez, Dr Mark FitzGerald, Dr Don Sin: this work is supported by an unrestricted educational grant from AstraZeneca Canada, Boehringer Ingelheim Canada, GlaxoSmithKline Canada, and Pfizer Canada; Dr Teresa To: supported by funding from the Ontario Ministry of Health and Long-term Care and the Institute for Clinical Evaluative Sciences; Margot Underwood: none to report; Dr Peter Jan Wijkstra: none to report; Dr Pearce Wilcox: none to report.