Among patients with obstructive sleep apnea treated with continuous positive airway pressure therapy, those with resistant hypertension may enjoy de-escalation or reduction in medical therapy.

**Background/Objective:** The relationship between obstructive sleep apnea (OSA) and hypertension has been confirmed by several studies, and has been attributed to effects of hypoxemia, hemodynamic effects, and/or disruption of sleep. Continuous positive airway pressure (CPAP) reduces sympathetic, radical, and inflammatory marker induction. In recent years, disagreement in clinical studies regarding blood pressure (BP) effects begged the question whether treating OSA with CPAP lowers BP in patients hypertensive despite medical therapy, and whether CPAP therapy affects antihypertensive treatment among patients who use CPAP for sleep-disordered breathing.

**Methods:** Polysomnograms with CPAP records were reviewed. Inclusion criteria were age ≥18 years, diagnosis of OSA, history of hypertension on drug therapy, and ≥3 documented daytime BP measurements obtained within 3 months of enrollment and every 3 months for 6 months and at 1 year from CPAP initiation. Resistant hypertension was defined as a daytime BP of ≥140 mm Hg systolic or ≥90 mm Hg diastolic, despite stable use of a combination of ≥3 antihypertensive medications. Patients with secondary causes of hypertension were excluded. There were 764 patients screened for entry into the study, and 98 were eligible. Of these, 42 patients had resistant hypertension. Mean difference in mean arterial pressure was -5.6 (95% CI, -2.0 to -8.7 mm Hg; \( P = 0.03 \)) in the resistant hypertension group, and -0.8 mm Hg (95% CI, -2.9 to 3.3 mm Hg; \( P = 0.53 \)) in patients with controlled BP at the end of the follow-up period. CPAP therapy led to stabilization of hypertension treatment in 71% of subjects with resistant hypertension, but did not significantly alter the antihypertensive regimen in the control group. Multivariate regression analysis showed that baseline BP (odds ratio [OR], 5.4; 95% CI, 2.3 to 8.9; \( P = 0.01 \)) and diuretic therapy (OR, 3.2; 95% CI, 1.8 to 6.1; \( P = 0.02 \)), but not apnea-hypopnea index or nightly hours of CPAP, were associated with a decrease in mean arterial pressure after 12 months of CPAP therapy. CPAP was associated with different effects on BP control in hypertensive patients with OSA. A beneficial response to CPAP therapy occurred in subjects with the most severe hypertension.

**Reviewer’s Comments:** CPAP therapy for OSA offers potential "2-for-1 special" benefits regarding ostensibly unrelated disease processes (gastroesophageal reflux disease, cardiovascular events, hypertension). Although this study has all the limitations of an observational study, and although more extensive measurements of BP (such as ambulatory monitoring) were not obtained, nevertheless long-term use of CPAP therapy was associated with improved BP control in patients with OSA and resistant hypertension, reflected by a reduction in mean arterial pressure as well as a decreased trend in use of antihypertensive therapy. Larger, randomized trials are needed to confirm these results. (Reviewer-A. Gray Bullard, MD).

© 2009, Oakstone Medical Publishing

**Keywords:** Obstructive Sleep Apnea, Hypertension, Continuous Positive Airway Pressure

**Print Tag:** Refer to original journal article
Asthma severity, gastroesophageal reflux disease, and use of an inhaled corticosteroid can predict obstructive sleep apnea risk in patients with asthma.

**Background/Objective:** In a longitudinal study, asthma was an independent risk factor for development of snoring. Since both obstructive sleep apnea (OSA) and asthma are common (approximately 4% and 8% of the U.S. population, respectively), the authors wished to assess factors associated with habitual snoring and OSA risk in patients with asthma. Their hypothesis was that asthma severity, coexistent disorders (gastroesophageal reflux disease [GERD], nasal diseases), and medications (corticosteroids) would be associated with OSA symptoms, aside from traditional OSA risk factors such as weight, age, and male gender.

**Methods:** The Sleep Apnea scale of the Sleep Disorders Questionnaire was used in patients with asthma surveyed in specialty clinics with questions about frequency of asthma symptoms, followed by medical record review. Logistic regression was used to model associations with habitual snoring and high OSA risk.

**Results:** Among 244 patients, 37% snored habitually and 40% demonstrated high OSA risk. Independent predictors of habitual snoring included GERD (odds ratio [OR], 2.9; 95% CI, 1.19 to 4.02) and use of an inhaled corticosteroid (OR, 2.66; 95% CI, 1.05 to 6.72). OSA risk was predicted by asthma severity, GERD, and inhaled corticosteroid use. A significant inverse relationship with FEV$_1$ percent predicted (OR, 0.98; 95% CI 0.97 to 0.99; $P=0.002$) was observed. Linear and dose-dependent relationships of inhaled corticosteroids with habitual snoring and high OSA risk were seen ($P=0.004$ and $P=0.0006$, respectively). Women were 2.1 times more likely to have high OSA risk when controlling for these factors.

**Conclusions:** Asthma severity, coexistent GERD, and use of an inhaled corticosteroid predict symptoms of OSA in asthmatics, in a dose-dependent fashion. Male-gender predominance for OSA symptoms is not apparent in these patients. Examining these relationships may help to explain the increased prevalence of OSA in asthma.

**Reviewer's Comments:** Perhaps the most striking question raised by these findings concerns women. In addition to confirming that symptoms of OSA in patients with asthma are predicted by asthma severity, coexistent GERD, and use of an inhaled corticosteroid in a dose-dependent pattern, these findings suggest the possibility that these factors may be at play in the reported female predominance of asthma morbidity and mortality. A drawback of the study, however, is that polysomnography was not used to confirm OSA, and certainly symptoms of asthma and OSA may overlap. Finally, the cross-sectional design restricts any ability to draw conclusions about causation. Nonetheless, the relationship between inhaled corticosteroids and OSA symptoms was robust. Additional study is required on these issues. In the meantime, clinicians might reasonably use this information to guide selection of certain asthma patients for OSA screening. (Reviewer-A. Gray Bullard, MD).
What Causes Early Death in COPD Exacerbations?

A Postmortem Analysis of Major Causes of Early Death in Patients Hospitalized With COPD Exacerbation.

Zvezdin B, Milutinov S, et al:

Chest 2009; 136 (August): 376-380

In acute exacerbations of chronic obstructive pulmonary disease, cardiac failure, pneumonia, and pulmonary thromboembolism must be considered as comorbidities.

**Objective:** To determine the actual cause of death in patients hospitalized for acute exacerbations of chronic obstructive pulmonary disease (COPD).

**Design/Methods:** Retrospective review of medical records and autopsy reports of patients admitted between January 1, 2005, and December 31, 2007, who died within 24 hours of admission for acute exacerbation of COPD. Autopsy reports were used to determine cause of death and other medical conditions. The cause of death was defined as that disease or organ dysfunction that led to the patient's demise. All clinical information was reviewed and considered in the final analysis. Exacerbation of COPD was defined as "acute worsening of the patient's baseline dyspnea, cough, and/or sputum production." Need for hospitalization was considered if the patient did not respond to emergency treatment, had persistent or worsening gas exchange and/or respiratory acidosis, had significant comorbidities, and/or was of older age.

**Results:** 43 patients met criteria for inclusion in the study; 72% were men. Median age was 70 years, and median duration of presence of COPD was 10 years. The main causes of death were cardiac failure (37%), pneumonia (28%), pulmonary thromboembolism (PTE; 21%), and respiratory failure (14%). Right heart failure was present in one third of heart failure patients. Of patients, 77% had 1 comorbidity, and 58% had ≥2 comorbidities. Six cancers were found at autopsy, 3 of which were of pulmonary origin. Of 6 patients found to have deep vein thrombosis, 4 died of PTE. Pneumonia patients tended to have productive cough. Tachycardia was common with PTE. Elevated creatinine was seen in pneumonia and PTE. Chest x-ray tended to be abnormal in those with cardiac failure and PTE. Atrial fibrillation was seen in some patients with PTE. All patients received treatment with bronchodilators and systemic steroids. Antibiotics and anticoagulants were used based on current practice. No patient was placed on mechanical ventilation.

**Conclusions:** When autopsy findings are used, it is clear that individuals admitted to the hospital with acute exacerbations of COPD more commonly die of cardiac failure, pneumonia, or PTE within the first 24 hours, as opposed to dying from COPD. Consideration and treatment of these diseases are important in trying to successfully treat these patients. Review of data obtained in evaluating these patients is extremely important in identifying significant comorbidities presenting with acute exacerbations of COPD.

**Reviewer's Comments:** This article is an excellent example of the importance of a complete history and physical exam and a review of all clinical data. One must remember that patients with COPD may, and probably do, have significant comorbidities that must be treated if acute exacerbations are to be reversed. (Reviewer-Allan R. Goldstein, MD).

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Keywords: Exacerbation, Postmortem Analysis, Cause of Death

Print Tag: Refer to original journal article
Tiotropium is safe and effective in the treatment of chronic obstructive pulmonary disease when used with long-acting beta-agonists plus inhaled corticosteroids.

**Objective:** To evaluate the effectiveness of tiotropium in various regimens of chronic obstructive pulmonary disease (COPD) treatment.

**Participants/Methods:** Patients from the VA were evaluated. The first cohort included patients with COPD treated between October 1, 2003, and September 31, 2004. Tiotropium was not available as primary care at the VA at that time. The second cohort included patients from October 1, 2004, through March 31, 2006. At that time, tiotropium was considered first-line treatment at the VA. The first cohort could receive tiotropium if seen by a pulmonologist in consultation. All patients in both cohorts had to be receiving a treatment regimen that included either tiotropium or long-acting beta-agonists (LABAs) plus inhaled corticosteroids (ICSs). Three outcomes were measured: (1) all-cause mortality, (2) COPD exacerbations, (3) and COPD hospitalizations. A 30-day immortal period was given to all patients. Exacerbations were defined according to ICD-9 codes and one of the following: (1) hospitalization, (2) emergency department visit, or (3) outpatient visit with either oral steroids or an antibiotic being prescribed within 5 days of the visit. Demographics, health care utilization, and comorbid conditions were recorded.

**Results:** A total of 135,422 cases were identified for inclusion. The base case included 42,090. A total of 38,850 were switched to an LABA + ICS regimen, whereas 3240 were switched to a tiotropium regimen. The most commonly used regimen was LABA + ICS + ipratropium. The most commonly used tiotropium regimen was in combination with LABA + ICS. Mortality rates were lowest for the tiotropium + LABA + ICS regimen. The incidence of exacerbations and hospitalizations was also least in this combination. Tiotropium in other regimens had a higher mortality and exacerbation/hospitalization rate. When ipratropium was added to the 3-drug regimen, the results were similar to those from LABA + ICS.

**Conclusions:** Tiotropium is safe and effective when added to a regimen of LABA + ICS. When added to other regimens, the effectiveness and outcome is not as positive. When LABA + ICS is unsuccessful, a new regimen that does not include tiotropium is much less likely to lead to a positive outcome.

**Reviewer’s Comments:** This article clearly points to the fact that not all patients with COPD on LABA + ICS will do well from the standpoint of exacerbation and hospitalization. In those patients, tiotropium is a safe and effective addition. Would those who require the addition of tiotropium do well on tiotropium only? That is for another study and another day. (Reviewer-Allan R. Goldstein, MD).

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Keywords: Tiotropium, Outcomes

Print Tag: Refer to original journal article
Milder degree of obstructive sleep apnea and lower body mass index have a better chance of responding to uvulopalatopharyngoplasty.

**Objective:** To assess the role of uvulopalatopharyngoplasty (UPPP) in the treatment of obstructive sleep apnea (OSA).

**Design/Methods:** Retrospective analysis of patients of patients aged ≥18 years who were diagnosed with OSA and treated with UPPP between January 1, 1988, and August 31, 2006. Patients included in this report had undergone polysomnography within 6 months before and after UPPP. Board-certified specialists in sleep disorders evaluated all cases. Hypopnea was defined as a 30% decrease in airflow for at least 10 seconds and a decrease in saturation of 2%. As of May 1, 2002, the desaturation criterion was changed to ≤4% to comply with the Centers for Medicare and Medicaid Services continuous positive airway pressure (CPAP) coverage requirements. OSA was defined as cessation of airflow for at least 10 seconds despite respiratory effort.

**Results:** 63 patients met study requirement criteria; 51 were men. Studies were done up to 97 days before and 122 days after UPPP. A mean reduction of 54.4% in the apnea-hypopnea index (AHI) was achieved, as well as a 38.4% decrease in mean arousal index with an improvement in time spent with an oxygen level <90%. Using the criteria of achieving a ≥50% decrease in AHI and/or an absolute AHI of ≤20 resulted in a 51% success rate. Using an AHI of ≤10 resulted in a success rate of 33%. Using an even more stringent criterion of an AHI of ≤5 resulted in a success rate of 23.8%. Four of 5 patients with a body mass index (BMI) of ≤25 achieved a post-UPPP AHI of ≤5. Ten of 17 patients with a BMI of ≤30 achieved an AHI of ≤5. However, only 5 of 46 patients with a BMI of >30 reached the ≤5 level. Of 48 patients who did not reach the ≤5 level, 13 chose weight reduction and positional therapy as opposed to CPAP; the other 35 accepted CPAP.

**Conclusions:** In an unselected group of patients with OSA, UPPP leads to a low rate of success if success is defined as a postoperative AHI of ≤5 or ≤10. Greater success is seen in those who have milder OSA and a BMI of ≤30.

**Reviewer’s Comments:** This study is of great importance if we are to look at “value” when treating patients with UPPP for OSA. Although outcome is the most important measure of success in any given patient, the likelihood of success must be ascertained before exposing a patient to the risk of surgery. Predictable poor outcome is not wise use of health care dollars. (Reviewer-Allan R. Goldstein, MD).
Coal dust is as strong a risk factor as cigarette smoking for development of emphysema.

Objective: To look at a subset of coal miners to determine contributions of smoking and dust exposure to emphysema.

Methods: The study unfortunately consists of 722 autopsy specimens. The majority of patients came from West Virginia, with a minority coming from Vermont. Patients all died prior to 1978. Smoking data were obtained from medical records. Individual dust exposure was estimated based on the job and conditions at the place of employment. The quality of assessment of exposure was estimated by investigators. Two different pathologists reviewed all material and evaluated at least 3 sections from the left lung. Emphysema was graded by distribution and severity. Lungs were also analyzed gravimetrically for lung dust.

Results: Interestingly, non-coal miners died at a younger age (56 years) compared to those were miners (66 years). However, the former group tended to smoke more but were also more likely to be never smokers. Mean emphysema severity index was significantly greater in miners when compared to non-miners. Emphysema incidence was also greater, as expected, in patients who smoked compared to those who never smoked. The largest difference in emphysema severity was between miners and non-miners who had never smoked. There was a high correlation between cumulative dust exposure and emphysema. After accounting for cigarette smoking and race, the correlation still persisted. It was estimated that, in whites, the mean cumulative dust exposure contributed 113 units to the emphysema severity index, whereas cigarette smoking contributed only 67 units.

Conclusions: Coal dust exposure or coal dust lung burden, cigarette smoking, age at death, and race have a statistically significant effect on the severity of emphysema. For the most part, coal dust and cigarette smoking had similar additive effects on emphysema severity.

Reviewer's Comments: The old thinking was that coal workers' pneumoconiosis (black lung disease) was not responsible for a large amount of lung injury, and it was the contribution of cigarette smoking that was prevalent among miners that was responsible for the injury. This article strongly suggests that this is not the case, at least for patients from the East Coast, where the coal is infiltrated with more silica than on the West Coast. The data here suggest that dust and cigarette smoking contribute just about equally to eventual severity of emphysema in a given patient. (Reviewer-Eric H. Gluck, MD, JD).

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Keywords: Emphysema, Coal Dust, Smoking, Miners

Print Tag: Refer to original journal article
Asthmatics Habituate to Dyspnea

Down-Regulation of Insular Cortex Response to Dyspnea and Pain in Asthma.

von Leupoldt A, Sommer T, et al:

Am J Respir Crit Care Med 2009; 180 (August 1): 232-238

There is a downregulation of the affect-related insular cortex activity by the PAG during the perception of dyspnea and pain in patients with asthma.

**Objective:** To establish a possible neural mechanism that might be responsible for varying degrees of dyspnea in asthmatic patients.

**Participants:** The patient group consisted of 14 subjects with mild-to-moderate asthma. They were matched by gender and age to 14 healthy individuals. All patients in both groups were free from major respiratory causes or difficulties for 4 weeks preceding the study.

**Methods:** Asthmatics were required to refrain from taking medication except for the inhaled steroids for 16 hours prior to the study. Dyspnea was created by breathing through an inspiratory flow resistance device. Standard respiratory parameters were measured during the testing. Dyspnea was measured using a Borg scale. After each measurement, the patients also rated the sensory intensity or pain associated with the resistive load using another horizontal scale. At this point in time, patients also underwent a functional brain scan using magnetic resonance.

**Results:** Except for lung function abnormalities, there were no differences between control subjects and test subjects. All subjects demonstrated an increase in perceived sensory intensity of both dyspnea and pain from the mild to the severe obstruction. However, the unpleasantness of the sensation of dyspnea was significantly reduced in the asthmatics when compared to the control subjects. Patients with asthma demonstrated reduced signal intensity in the insular cortex of the brain. This was associated with a greater increase than the controls in the periaqueductal gray area. Psychophysiological interaction analysis revealed that the increased periaqueductal gray (PAG) activation moderated the reduced insular activation in the asthmatic patients with increasing dyspnea.

**Conclusions:** There is a downregulation of the affect-related insular cortex activity by the PAG during the perception of dyspnea and pain in patients with asthma. The authors postulate that this might represent a habituation to reduce the unpleasantness of the often-felt dyspnea in patients with asthma similar to what happens in patients who have chronic pain.

**Reviewer’s Comments:** These data may help explain why we have such variability in patients presenting to the ED with symptoms of asthma. Some patients wait until the last possible moment, while others present significantly earlier. It may well be that habituation to symptoms of dyspnea in certain asthmatic patients may, in fact, be due to the detriment in the lack of perception of how sick they really are. This delay in seeking attention could result in significant morbidity as well as possible mortality. (Reviewer-Eric H. Gluck, MD, JD).

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**Keywords:** Symptoms, Dyspnea, Neural Mechanism

**Print Tag:** Refer to original journal article
Objective: To test the hypothesis that increased morbidity and mortality in African Americans with chronic obstructive pulmonary disease (COPD)/asthma is associated with an increase in utilization of health care resources when no difference in health insurance exists.


Methods: The study population was selected from the Maryland Medicaid Managed Care program. Patients were aged 40 to 64 years as of January 1, 2001, and had been followed for 360 days. Three cohorts were established: (1) COPD, (2) asthma, or (3) comorbid COPD/asthma. Health care and medical health services utilization was defined as all procedures, tests, and services performed inpatient, outpatient, or in the doctor's office.

Results: 9131 patients were studied; 52% were African American, 44% were Caucasian, and 4% were "other races." The asthma cohort was 33.6%, COPD was 37.8%, and the comorbid group was 28.5%. African Americans made up 63% of asthma cases, as well as 46% each of COPD and comorbid COPD/asthma groups. There were 2 separate groups by age: age 40 to 49 years (47%) and age 50 to 54 years (53%). Younger patients were more likely to be in the asthma group. In total, 70% were women. Women made up 83% of the asthma group, 54% of the COPD group, and 76% of the comorbid group. The older group used health services more often and had higher costs than did the younger group. Male and female patients used inpatient, emergency services, and physician services equally. The comorbid group had higher utilization and costs. The asthma cohort had the least utilization and cost. Caucasian patients used services more than did African Americans and other races. African Americans used 17% fewer services. As expected, older patients used services more often than did younger patients.

Conclusions: The hypothesis of the authors was disproved. In all cohorts and in both age groups, increased morbidity/mortality was related to underutilization and not to lack of insurance coverage or poor care. Decreased costs relative to other racial groups was found. The lack of utilization of physician/outpatient services did not lead to increased hospitalization in African Americans.

Reviewer's Comments: This important study clarifies, at least in this group, that increased morbidity/mortality is due to underutilization and that cost is not increased when services are not sought. The reasons people do not seek health care services need to be studied and defined. All patients should be educated as to why appropriate use of health care can improve quality and length of life. We also have to dispel the myth that care is dictated by race. (Reviewer-Allan R. Goldstein, MD).

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Keywords: Asthma, Available Services, Utilization, Outcomes

Print Tag: Refer to original journal article
Moxifloxacin Has Potent Anti-TB Properties

Substitution of Moxifloxacin for Isoniazid During Intensive Phase Treatment of Pulmonary Tuberculosis.

Dorman SE, Johnson JL:

Am J Respir Crit Care Med 2009; 180 (August 1): 273-280

Substituting moxifloxacin for isoniazid results in a small but statistically nonsignificant increase in week 8 culture negativity.

Objective: To do a follow-up to determine efficacy of moxifloxacin for initial treatment of tuberculosis (TB). Participants/Methods: Patients were enrolled in the study at 26 different sites including 22 in North America and 1 each from Brazil, South Africa, Spain, and Uganda. All patients who were adults and had acid-fast bacilli in the sputum were eligible for enrollment. Exclusion criteria included receiving antituberculosis medications within 6 months of identification, receiving a fluoroquinolone within the previous 3 months, pregnancy or breast-feeding, sputum negativity, a strain that was resistant to isoniazid, fluoroquinolones, rifampin, or pyrazinamide, or presence of HIV. Patients were randomly assigned to receive either isoniazid plus moxifloxacin placebo or moxifloxacin plus isoniazid placebo in addition to rifampin, pyrazinamide, and ethambutol. Treatment was administered following usual protocols. Standard laboratory data and sputum analysis were conducted every other week for the first 2 months of treatment. Results: 433 participants were enrolled in the study. About 20 patients from either group had to be removed from the study for various different study violations. There was a slight increase in the number of patients with cavitary disease in the isoniazid group. At the end of 8 weeks, culture negativity was achieved in 55% of patients with isoniazid versus 60% of patients with moxifloxacin. A post-hoc analysis did not demonstrate any major risk factor for moxifloxacin improvement, except for the fact that patients who had cavitary disease were not from Africa. Of patients, 10.0% discontinued the assigned treatment in the isoniazid group versus 14.5% in the moxifloxacin group. Nausea was more common among participants in the moxifloxacin arm; otherwise, other minor adverse effects were similar in both groups. Conclusions: Substituting moxifloxacin for isoniazid resulted in a small, nonsignificantly statistically speaking increase in week 8 culture negativity. Reviewer’s Comments: I guess the best that we can achieve from the study is that moxifloxacin is at least equivalent to isoniazid inefficacy. However, this does allow the addition of another drug to our regimen for tuberculosis, especially for those patients who might be isoniazid resistant. Side effects between groups were similar and, although there appeared to be slightly more gastrointestinal upset in the moxifloxacin group, this was not very significant. (Reviewer-Eric H. Gluck, MD, JD).

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Keywords: Treatment, Moxifloxacin, Isoniazid, Pulmonary Tuberculosis

Print Tag: Refer to original journal article
Objective: To assess health risks of exposure to coffee dust.

Design: Performance of an occupational medicine study of a company involved in transporting coffee, in a coffee silo, and in a decaffeinating company.

Participants/Methods: There were 24, 19, and 17 participants, respectively, all of whom were males, except for 4 in group 1. Investigations were done on Monday at the start and the end of the shift and at the following Friday at noon. Exposure symptoms, spirometry, and methacholine studies were used for evaluation. Air measurements for dust and germs were performed. Questionnaires were used to determine demographics and symptoms. IgE, total and specific, to green coffee beans and to castor beans was measured. Lung function was measured based on American Thoracic Society guidelines.

Results: (1) High coffee dust exposure was found with unloading coffee at the silo facilities. The dust exposure at the decaffeinating company was much lower. Gram-positive bacteria and several molds were also found. Mold was more often found in reference areas and not in the area exposed to coffee. (2) No demographic differences were found. Arabica coffee caused symptoms twice as frequently as Robusta coffee. Coffee from Brazil was more likely to cause symptoms. Rhinosinusitis, conjunctivitis, and sneezing were more common than symptoms of asthma. The diagnosis of asthma was not made in any participant based on no treatment for asthma being started. Work-exacerbated asthma occurred in 2 participants, both of whom had +IgE to coffee and castor beans in addition to high dust exposure. A diagnosis of chronic bronchitis was made in 3 workers. Post-shift and post-week symptom increases were in those with high coffee dust exposure. (3) Lung function parameters did not differ between smokers and non-smokers. Bronchial hyper-responsiveness and work-related symptoms were more common in the higher exposure group. Symptoms of asthma and rhinoconjunctivitis were noted in this group. (4) Allergologic findings revealed IgE antibodies to green coffee in 3, to castor beans in 4, and to both in 3; all had high exposure. Total IgE was elevated in 20 workers unrelated to exposure level. Symptoms occurred in 2 IgE+ coffee bean and 6 castor bean workers.

Conclusions: This study shows the potential for respiratory symptoms in workers exposed to high dust concentrations of green coffee beans. The problem with castor beans may be solved by using new type bags and containers free of castor bean dust. New exhaust systems will reduce dust levels, and therefore, symptoms.

Reviewer's Comments: This is a very nice study showing how to identify dusts that can cause respiratory symptoms. Once identified, action can be taken to reduce the dust burden, protect the worker, and have a safe place to work. (Reviewer-Allan R. Goldstein, MD).

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Keywords: Asthma, Coffee Dust

Print Tag: Refer to original journal article
The hormonal effect on lung function leads to asthma exacerbation in women.

**Objective:** To show that changes in gas transfer and the pulmonary vascular bed during the menstrual cycle cause worsening airflow obstruction.

**Participants/Methods:** 13 nonsmoking women with asthma and 10 healthy nonsmoking women were enrolled in the study. All subjects were followed up for 4 to 5 weeks with 1 visit per week. Menstrual cycle phases were verified by hormonal studies. Asthma was verified by reversible airflow obstruction or by methacholine challenge. All controls had normal spirometry. Other studies included fraction NO in exhaled air, diffusing capacity and all of its components, and angiogenesis markers, including circulating bone marrow-derived CD34+CD133+ cells, vascular endothelial growth factor (VEGF), and stem cell factor (SCF).

**Results:** (1) The pattern of airflow and exhaled NO was evaluated over the menstrual cycle, and no acute exacerbations occurred. Healthy women had no significant changes in function, and asthmatics showed some evidence of airflow obstruction. (2) Gas transfer in women with asthma showed a greater diffusing capacity. (3) With regard to angiogenesis factors in asthmatics, an increase in CD34+CD133+ circulating progenitor cells but not VEGF or SCF was found, with the greatest increase in week 1 of the menstrual cycle. Inhaled steroids had no effect on the findings. (4) The relationship of angiogenic factors to airflow and diffusion was evaluated. In asthmatics, circulating progenitor cells were directly related to diffusion and indirectly related to airflow. (5) Greater diffusion in asthma was directly related to alveolar capillary membrane diffusing capacity. (6) FEV\textsubscript{1} was directly related to diffusing capacity.

**Conclusions:** Cyclic changes in women with asthma modulate the function of the lungs and should be considered potential factors that lead to asthma exacerbations.

**Reviewer's Comments:** This study did not evaluate moderate to severe asthma cases, but the conclusions would be even more valid for those groups. How to treat this group is the question. Inhaled steroids do not seem to be the answer. Would diuretics or leukotrienes help? Guidelines surely don't. This is an issue for each treating physician to approach while more research is being done. (Reviewer-Allan R. Goldstein, MD).

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Keywords: Lung Function, Menstrual Cycle, Asthma Exacerbations

Print Tag: Refer to original journal article
Asymptomatic acid reflux is common in patients with asthma, but treatment with a PPI does not appear to improve respiratory symptoms.

**Background:** Studies of acid suppression in patients with asthma and symptomatic gastroesophageal reflux have been conflicting. However, current asthma guidelines recommend consideration of reflux treatment, especially with nocturnal symptoms. Given the prevalence of acid reflux, especially in patients with asthma, it has been postulated that relatively asymptomatic acid reflux may contribute to poor asthmatic control.

**Objective:** To determine if use of a proton pump inhibitor (PPI) would decrease symptoms in patients with poorly controlled asthma and limited acid symptoms.

**Design:** Randomized, double-blind placebo-controlled trial.

**Participants:** Patients aged ≥18 years with inadequately controlled asthma on appropriate doses of inhaled corticosteroids were evaluated. Asthma needed to be documented by spirometry, and poor control was determined using a standardized asthma questionnaire. Exclusion criteria included FEV\(_1\) <50% predicted, tobacco use, or frequent heartburn.

**Methods:** Patients were randomized to either esomeprazole 40 mg twice daily or matching placebo. They were then followed up for 24 weeks, tracking symptoms by diary and questionnaire along with spirometry every 4 weeks. Ambulatory pH monitoring was also used to objectively determine whether acid reflux was present or not. The primary outcome of interest was the rate of episodes of poor asthma control (decrease in peak flow by ≥30%, an urgent visit for asthma, or the need for systemic corticosteroid treatment).

**Results:** 412 patients with a mean age of 42 years were enrolled. Roughly 70% of patients were women. FEV\(_1\) was, on average, 76% to 78% of predicted, and 40% of patients had evidence of acid reflux by ambulatory pH monitoring. By the end of 24 weeks, 42% of patients had at least 1 episode of poor asthma control. However, no significant differences in the frequency of such episodes were seen between the PPI and control groups. In addition, there were no significant improvements in patients with nocturnal symptoms or those found to have reflux on objective testing.

**Conclusions:** In patients with inadequately controlled asthma, asymptomatic gastroesophageal reflux is common. However, the addition of a PPI does not appear to improve control, even in those with documented reflux.

**Reviewer’s Comments:** The idea that acid reflux, an enormously common problem, might be a factor in those with poorly controlled asthma has always been an attractive one. I have certainly found myself, at times, “trialling” acid suppression in some of these patients. Unfortunately, this study, by looking at both objective and subjective measures, convincingly shows that using medication to reduce asymptomatic reflux is unlikely to lead to improvement in asthma symptoms. For now, our attention should remain on more aggressive treatment of lung disease. (Reviewer-Mark E. Pasanen, MD).

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Keywords: Gastroesophageal Reflux, Proton Pump Inhibitors, Esomeprazole

Print Tag: Refer to original journal article
Simvastatin reduces lung and systemic inflammation in human volunteers in a lipopolysaccharide inhalation model of acute respiratory distress syndrome.

**Background:** Hydroxymethylglutaryl (HMG) CoA reductase inhibitors (statins) have pleiotropic anti-inflammatory and antimicrobial effects, leading some to speculate on their therapeutic potential in the ICU. Reports in several animal models of acute respiratory distress syndrome (ARDS) have indicated that statins reduce lung injury, while several retrospective studies in humans have shown that statins are associated with improved outcomes in pneumonia, sepsis, and bacteremia. To date, a single retrospective study of statins in ARDS patients was unable to find any effect of statins on outcomes, but prospective trials are underway.

**Objective:** To investigate in vivo if simvastatin modulates ARDS mechanisms in a model of lung inflammation induced by inhalation of lipopolysaccharide (LPS) in healthy human volunteers.

**Design:** Prospective double-blind placebo-controlled study.

**Participants:** 30 healthy adult subjects. **Intervention:** Subjects were randomized to receive placebo, 40 mg/day simvastatin, or 80 mg/day simvastatin for 4 days before LPS inhalation.

**Methods:** Measurements of inflammation were made in bronchoalveolar lavage fluid (BALF) 6 hours post-inhalation and in plasma 24 hours post-inhalation.

**Results:** Simvastatin pretreatment reduced LPS-induced BALF neutrophilia, myeloperoxidase, tumor necrosis factor-alpha, matrix metalloproteinases 7, 8, and 9, and C-reactive protein (CRP), as well as plasma CRP (all $P < 0.05$ vs placebo). There was no significant difference between the 40- and 80-mg doses. BALF from simvastatin-treated subjects was less inflammatory as assessed by its reduced activation of the inflammatory transcription factor NF-kappaB in cultured macrophages.

**Conclusions:** Simvastatin has anti-inflammatory effects in the airspace and serum in humans exposed to inhaled LPS, a model of ARDS.

**Reviewer's Comments:** Statins, originally developed for serum cholesterol reduction, have long been known also to attenuate pro-inflammatory cellular functions (eg, cytokine production, oxidant release, chemotaxis), leading to their progressive exploration in a variety of inflammatory conditions ranging from organ transplantation to Alzheimer's disease. Multiple studies in animals have demonstrated that statins are therapeutic in acute lung injury (ALI), liver injury, and sepsis, and retrospective studies in human sepsis and pneumonia have mostly found improved outcomes in statin-treated patients. Statins will next have to undergo prospective testing in critically ill patients. As there are presently at least 2 ongoing phase II clinical trials investigating the prevention and treatment of ALI with simvastatin, answers will be forthcoming. This paper is a landmark study, as it provides critical mechanistic evidence that simvastatin modulates several hallmark events in human ALI (neutrophil recruitment, cytokine induction) after only 4 days of pretreatment--a window that is pertinent to prevention/treatment of early ALI in patients. A recent report (Kruger et al, Intensive Care Med 2009) that septic patients are prone to supratherapeutic plasma levels of atorvastatin likely due to altered metabolism suggests that caution is, however, warranted as we explore statins in the ICU. (Reviewer-Michael B. Fessler, MD).

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**Keywords:** Statins, HMG CoA Reductase Inhibitors, Pulmonary Inflammation, Simvastatin

**Print Tag:** Refer to original journal article
New Adjunctive Treatment Available to Patients With Afib

*Dabigatran Versus Warfarin in Patients With Atrial Fibrillation.*
Connolly SJ, Ezekowitz MD, et al:


In patients taking dabigatran, a dose of 110 mg is associated with a similar rate of systemic embolization and stroke as that of patients receiving Coumadin and had lower rates of major hemorrhage.

**Background:** Coumadin has been used for stroke reduction in patients with a true percolation, but, unfortunately, it has a significant adverse effect of significant hemorrhage.

**Objective:** To evaluate dabigatran, a new oral direct thrombin inhibitor. The trial was set up to determine noninferiority.

**Participants/Methods:** >18,000 patients were randomly assigned to receive either dabigatran or Coumadin. Patients were followed up for 2 years. The primary outcome evaluated was distal embolization. Patients who received Coumadin had a 1.69% rate of systemic embolization versus 1.53% in those who received low-dose dabigatran and 1.11% in those who received high-dose dabigatran.

**Results:** A significant reduction in major bleeding was found in patients who received dabigatran (2.7% vs 3.36%). However, in this analysis, patients who received the higher dose of dabigatran actually had a statistically similar rate of bleeding as patients on Coumadin. The risk of hemorrhagic stroke in patients who received Coumadin was 0.38% per year versus only 0.12% per year for those who received a low dose of the active medication and 0.10% for those who received the higher dose. The overall mortality rate was 4.0% in the Coumadin group versus 3.75% for the low-dose dabigatran group (not statistically different) and 3.64% in the high-dose dabigatran group (which just barely did not achieve statistical significance with a *P* value of 0.05).

**Conclusions:** In patients with atrial fibrillation, a dose of 110 mg of dabigatran was associated with a similar rate of systemic embolization and stroke as seen in those who received Coumadin, with lower rates of major hemorrhage. A higher dose of dabigatran was associated with a similar rate of stroke and systemic embolization as Coumadin but also similar rates of major hemorrhage.

**Reviewer's Comments:** The authors conclude that, in patients on dabigatran, a dose of 110 mg was associated with a similar rate of systemic embolization and stroke as that of patients who received Coumadin and had lower rates of major hemorrhage. A higher dose of dabigatran was associated with a similar rate of stroke and systemic embolization as Coumadin, but also with similar rates of major hemorrhage. (Reviewer-Eric H. Gluck, MD, JD).

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Keywords: Atrial Fibrillation, Dabigatran, Warfarin

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The risk for ventilator-associated pneumonia increases with the duration of mechanical ventilation, achieving a risk at the end of the first week of 18 times baseline and a risk of 225 times baseline after 15 days.

**Objective:** To develop a scoring system to provide benchmarking for the rate of ventilator-associated pneumonia (VAP) based on case mix.

**Participants/Methods:** The study comprised almost 2000 patients from a database of ICU admission patients who required endotracheal intubation for mechanical ventilation for >48 hours. Patients were randomly assigned to either the training dataset or to the validation dataset area; standard statistical analysis was then used to determine appropriate coefficients for the scoring.

**Results:** The authors identified several independent risk factors for development of VAP that included the following: being of the male gender, which had a reference value of twice that of the general population; the Sequential Organ Failure Assessment score at the time of admission, with a reference value that increased progressively with the increase of the score; and lack of using parenteral nutrition and broad-spectrum antibiotics during the first 2 days of mechanical ventilation while the patient was in the ICU. The authors also found that the risk for VAP increased with the duration of mechanical ventilation, achieving a risk at the end of the first week of 18 times baseline and a risk of 225 times baseline after 15 days. They were able to achieve an area under the curve of 0.881 for these risk factors during the training set. The validation set demonstrated a similar area under the curve. Although the rate of VAP varied tremendously among ICUs (9.7 to 26.1 of 1000 mechanical ventilation days), the ratio of actual rates over theoretical VAP rates was only >1 in 2 ICUs.

**Conclusions:** VAP may be benchmarked to provide useful information from ICU to ICU when the case-mix is included in the analysis.

**Reviewer’s Comments:** Most studies that have looked at VAP for benchmarking purposes typically look at the incidence of VAP as a function of the ratio of mechanical ventilation. They do not include the other risk factors that were associated in this paper. These data will make it more reasonable to be able to compare one ICU to another for benchmarking. Obviously, these would not be necessary when looking at trends in an individual ICU. (Reviewer-Eric H. Gluck, MD, JD).

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Keywords: Nosocomial Pneumonia, Benchmarking, Critically Ill, Logistic Regression

Print Tag: Refer to original journal article
The cerebral cortex appears to have fully preserved flow, even during cardiogenic induced shock.

**Background:** Cardiogenic shock (CS) is associated with significant and persistent hypotension, reduced blood flow, and tissue perfusion.  

**Objective:** To determine whether cardiogenic shock can be identified and treated to prevent organ damage.  

**Design/Methods:** In this animal investigation, CS was induced in rats by banding of the aorta. The parietal lobe of the cerebral cortex was exposed in order to evaluate microcirculation as was the microcirculation of the buccal mucosa. Over a 4-hour interval, the animals were evaluated for hemodynamic function and then buccal and cerebral microcirculation. The study rats were then randomized to receive either sham operation or aortic banding.  

**Results:** Following the aortic surgery, there was a significant reduction in mean arterial blood pressure, ejection fraction, and cardiac output. The buccal mucosa demonstrated a significant reduction in perfusion. However, the cerebrovascular rate flow in the cerebral cortex was preserved.  

**Conclusions:** There was a significant disparity between hemodynamic parameters that demonstrated a significant reduction in cardiac output and blood pressure following ligation of the aorta, the buccal mucosa, which demonstrated a significant reduction in microcirculatory flow, and the cerebral cortex, which appears to have fully preserved flow even during cardiogenic induced shock. The authors suggest that this might help explain the disparity in studies that have demonstrated indifference to other circulations, the microcirculatory function of the cerebral cortex is preserved in cardiogenic shock in patients who have not undergone cardiac arrest.  

**Reviewer's Comments:** Protective measures appear to be invoked by the cerebral cortex that are unavailable to other circulatory systems in the body. Recent data have suggested that measurement of central venous oxygen saturation might be useful in predicting the adequacy of resuscitative efforts. These captures typically measure blood flow to the brain. Therefore, it is possible, based on these data, that one could have adequate cerebrovascular perfusion and oxygenation in the absence of adequate perfusion of other vital organs. Certainly when the brain is underperfused, we can assume that the rest of the body is also underperfused; however, the reverse may not be true. Further investigation of this phenomenon is critical to understanding the appropriate way to resuscitate. It would also appear that other measures besides blood pressure are necessary to understand adequacy of circulation into vital organs. (Reviewer-Eric H. Gluck, MD, JD).
This study is a verification that the new allocation system for lung transplantation has resulted in a fair dispersal of allograft material.

**Background:** In 2005, a new system for allocation of lung transplantation was created. This new system, the Lung Allocation Score (LAS), was based on several factors, including the patient's functional status, exercise capacity, lung function, hemodynamic data, and the need for oxygen or ventilatory support. Transplant benefit was determined based on medical urgency versus expected outcome. The purpose of LAS was to decrease waiting time and lower mortality rates.

**Objective:** To determine the impact of the LAS on transplantation for patients with pulmonary arterial hypertension (PAH).

**Methods:** The authors studied almost 8000 patients who were listed for lung transplantation between 2000 and 2008. The analysis was restricted, however, to only patients with idiopathic pulmonary fibrosis, idiopathic pulmonary hypertension, chronic obstructive pulmonary disease (COPD), and cystic fibrosis. The primary outcomes measured were waiting list mortality and transplant mortality before and after the implementation of the allocation system.

**Results:** The likelihood of a patient receiving a lung transplant after being placed on a waiting list increased for all diagnoses studied after implementation of the LAS when compared to a prior, similar time period. Waiting list mortality also decreased for every diagnosis except for idiopathic pulmonary hypertension, which did not demonstrate an increase or decrease; there was no change in the mortality rate after transplantation. The LAS system resulted in a reduction in the likelihood of patients with idiopathic pulmonary hypertension to be transplanted relative to patients with idiopathic pulmonary fibrosis. There was also an increased risk of death among patients on the waiting lists with pulmonary hypertension than with the diagnosis of COPD.

**Conclusions:** The new allocation system (the LAS) improves the likelihood of lung transplantation for patients with hepatic only arterial hypertension, but the mortality rates for those on the waiting list were still quite high when compared to other diagnoses.

**Reviewer's Comments:** This study is a verification that the new allocation system for lung transplantation has resulted in a fair dispersal of allograft material. The fact that certain diagnoses do better than others may represent just the rapidity at which the clinical status changes toward the end of the disease process. Obviously, the answer would be more lung transplant availability or some means of artificially maintaining gas exchange without requiring intubation. (Reviewer-Eric H. Gluck, MD, JD).

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Keywords: PAH, Transplantation, Lung Allocation Score

Print Tag: Refer to original journal article
Objective: To determine the incidence of cytomegalovirus (CMV) in the ICU. 

Design/Methods: Retrospective evaluation of the literature published up to October 2008; 13 studies qualified for evaluation (1258 patients).

Results: Among these studies, the prevalence of CMV was 17%, but this increased to 20% if the evaluation took place >5 days after ICU admission. Culture results for the virus resulted in less protection than did the DNA antigen test. In patients with unknown serology, presence of the virus was 7%, but it increased significantly in patients who had positive serology to 31%. Patients in the ICU who were most likely to develop the infection included those with severe sepsis. As disease severity increased, so did the prevalence of the CMV infection. The overall mortality rate associated with infection with the virus was almost 2 times as high as in patients who did not acquire the infection.

Conclusions: CMV is a frequent infection that occurs in the ICU in nonimmunocompromised individuals. Patients in the ICU >5 days, with high severity of illness and with severe sepsis, had a significantly higher rate of infection than other patients in the ICU. The authors also suggest that further evaluation in a more robust prospective study is in order to determine the true impact of this infection on mortality.

Reviewer's Comments: This is a well-done evaluation of the literature to date identifying a crude rate for the incidence of CMV superinfections in the ICU. Unfortunately, at the present time, there is no specific therapy for this virus that is generally agreed upon to be successful. Therefore, this evaluation tends to be more of a prognosticating exercise or at least an exercise in determining why any individual patient is not responding to the therapy that should have been successful. (Reviewer-Eric H. Gluck, MD, JD).

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Keywords: Nonimmunocompromised, Cytomegalovirus, Prevalence, Mortality

Print Tag: Refer to original journal article
Posterior penetration of the internal jugular vein occurs frequently, especially with inexperienced physicians.

**Objective:** To evaluate the frequency of posterior wall penetration during the placement of an internal jugular venous catheter.

**Design:** Prospective observational study.

**Participants/Methods:** All procedures were performed by residents who had undergone a 2-day course involving use of ultrasound as well as a didactic session for central venous catheter placement. Residents were required to place the catheter on any manikin. Without the knowledge of residents, researchers evaluated the frequency of penetration of the posterior wall and the final Neo location after the resident had assumed appropriate placement. All residents had previous experience with the catheter placement.

**Results:** 64% of residents penetrated the posterior wall during the cannula placement. The median number of posterior wall penetrations was 1 for all the residents. In 6 instances, the final resting place of the needle was posterior to the wall of the venous system, and there were 5 instances of carotid artery penetration. A significant amount of improvement was observed as the number of training exercises increased.

**Conclusions:** In a majority of cases, residents undergoing training for placement of central venous catheters actually penetrate the posterior wall. The authors suggest that ultrasound guidance is just a single tool for accurate placement of the catheter, and that additional guidance techniques, including visualization of the vein and the needle in the longitudinal axis, should be considered.

**Reviewer's Comments:** This is a short, but important, article regarding a routine procedure that is often taken for granted. Ultrasound has established ease at locating the venous and carotid artery, but, at least in a manikin setting, it does not appear to reduce posterior wall or carotid artery penetration to a lower level. However, this was a manikin and not a real-life individual. It is possible that under real-life circumstances, the results would be quite different. In 6 instances, the catheter was left in the posterior position. We have been placing internal jugular catheters using ultrasound in my ICU for 5 years now. I cannot recall a single instance where the catheter ended up posterior to the venous system. This may be due to the fact that further evaluation of the catheter is performed in a living breathing person, but cannot be accomplished in a manikin. Therefore, there are 2 take-home messages from this article, the first being that care is important in placing central venous catheters, even when using ultrasound. The second is that perhaps manikin-like devices are not sufficient for training residents on the placement of central venous catheters. (Reviewer-Eric H. Gluck, MD, JD).

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Keywords: Central Catheter Placement, Jugular Vein, Ultrasound, Posterior Vessel Wall Penetration

Print Tag: Refer to original journal article
Sputum analysis at the time of admission to the ICU results in a high specificity and likelihood ratio for identification of microorganisms that might be involved in early ventilator-associated pneumonia.

**Background:** We typically rely on sputum analysis despite reported poor correlation with actual invasive sampling in the literature. Unfortunately, delaying the onset of antibiotic therapy to recovering the appropriate specimen might result in poor outcome.

**Objective:** To evaluate use of sputum analysis for empiric therapy.

**Participants/Methods:** The study took place in a surgical ICU of a 700-bed hospital. Patients were enrolled if they had been on mechanical ventilation for at least 48 hours and had a suspicion of ventilator-associated pneumonia (VAP) occurring during the first 5 days. Sputum analysis was compared to the pulmonary plugged specimen. The authors compared the sensitivity, specificity, and the positive likelihood ratio.

**Results:** All 600 patients were enrolled; 48% had a positive pulmonary plugged specimen and received antibiotics. Of these, 92% had a positive upper airway sample at the time of ICU admission. For every identifiable organism in the study, the upper airway specimen demonstrated an 85% specificity. Except for the *Streptococcus* species, the likelihood ratio exceeded 64, ruling in the diagnosis.

**Conclusions:** Sputum analysis at the time of admission to the ICU results in a high specificity and likelihood ratio for identification of microorganisms that might be involved in early VAP.

**Reviewer's Comments:** In addition to providing information about which therapy might be appropriate in these patients, this study also suggests a potential pathophysiology of early VAP. If patients present with these organisms in their sputum and eventually develop VAP, it must be due to an increased microorganism production, or to a reduction in potential defenses against these organisms. Both of these concepts might be very useful in identifying and treating patients with early ventilator-associated pneumonia. (Reviewer-Eric H. Gluck, MD, JD).

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