
Tiotropium has been shown in the UPLIFT trial (NEJM. 2008; 359(15):1543-1554) to reduce mortality, reduce number of exacerbations, and increase lung function in patients with COPD. The authors of this study question whether this effect is seen in patients already on dual therapy with a LABA and ICS. They performed a retrospective cohort study using a COPD database in Scotland – TARDIS (Tayside Respiratory Disease Information System). Data from a 9 year period was reviewed – January 2001 to January 2010. They then used data from the National Health Service Scotland as well as Tayside Community Prescription database to determine hospital admissions due to COPD exacerbations (based on ICD 10 codes at discharge) and inhaler use, respectively. Patients with a history of malignancy were excluded. Patients were then divided into those using LABA + ICS and those using LABA+ICS+tiotropium. The total number of patients in the study was 2,853 – 1,857 on triple therapy and 996 on ICS + LABA. Hazard ratios were calculated using a Cox regression model. The baseline demographics of the two groups were well matched with the exception of the triple therapy group having a lower FEV1% (50.8 +/- 17.1) as compared to the ICS+LABA group (62.7 +/- 18.9).

The results of the analysis demonstrated a 35% reduction in all-cause mortality in favor of the triple therapy group. Subgroup analysis looking only at death related to respiratory disease demonstrated a hazard ratio of 0.70 (95% CI, 0.57-0.84). The number of COPD exacerbations (reflected by combination of steroid bursts and hospital admissions) was decreased by 29% in the triple therapy group, with 15% reduction seen in hospital admissions. They did not see any significant changes in lung function as measured by FEV1 and FVC data.

The results of this study are encouraging and offer additional support to the results from the aforementioned UPLIFT trial. That being said, there are many significant issues with this study. First, and most troublesome, is the retrospective nature of the study and the use of multiple databases to procure the data. The strength of the study lies in the strength of the databases, which may or may not confer an accurate picture. The use of the various inhalers was determined through a prescription registry, which lacks compliance information. It cannot be confirmed that these patients were actually taking these medications. Data may have been affected by different levels of compliance – the double therapy group may just have been much less compliant. In addition, as this was a
retrospective study, patient’s subjective feelings on dyspnea were not available. It would have been interesting to see if patient’s noticed a subjective improvement in dyspnea or if the above benefits were conveyed without subjective dyspnea improvement.

**Frequency of Undiagnosed Cystic Lung Disease in Patients with Sporadic Renal Angiomyolipomas.** Jay H. Ryu, Thomas E. Hartman, Vicente E. Torres, and Paul A. Decker.

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Renal angiomyolipomas are seen in about 50% of patients with sporadic lymphangioleiomyomatosis (LAM) and in up to 80% of LAM patients with tuberous sclerosis. This study considers those patients with renal angiomyolipomas seen on CT scan and asks how many of these patients have cystic lung disease suggestive of LAM. The study looked at 176 subjects who had been given the diagnosis of sporadic renal angiomyolipoma based on CT scan of either the abdomen or chest over a ten year period. A group of 176 age-, sex-, and smoking-matched subjects was used as a control. All of the CT scans were reviewed by two of the authors who were blinded to age, sex, past medical history, and smoking history. These authors identified cystic lung lesions with differences in interpretation decided by consensus.

The authors found that the majority of subjects with renal angiomyolipomas were women (81.8%) and most subjects had only a single tumor (79.5%). Lung cysts were found in 19 of the 176 renal angiomyolipoma subjects (10.8%) with 10 of those subjects having one to three cysts, three with four to nine cysts, and six with ten or more cysts. All of the subjects in the angiomyolipoma group with cysts were women. In the control group, only eight of the 176 had cysts, with six of these having only one cyst. The other two subjects with cysts had only two or three cysts. Two of the eight control subjects with cysts were men. Of the angiomyolipoma subjects with more than four cysts, there was no history of lung disease or prior pneumothorax. Interestingly, of the nine subjects with more than four cysts, the radiology reports only noted abnormalities in seven of the nine and these were described as “emphysematous changes”, “blebs”, “bullae”, or “cysts”. Additional follow up data on these subjects were very limited.

This study raises interesting questions regarding the prevalence of LAM in patients found to have sporadic renal angiomyolipomas. However, given the retrospective nature of the study, the conclusions we can draw from it are rather limited. It does appear that suspicious cystic lesions seen on imaging of the lungs are largely ignored and that increased awareness of the association of renal angiomyolipomas and LAM is needed. Ideally, findings of both renal angiomyolipomas and lung cysts should prompt at least dedicated lung imaging, if not already done, and depending on the extent of cystic changes, pulmonary function tests and pulmonary consultation.
High Doses of Vitamin D to Reduce Exacerbations in Chronic Obstructive Pulmonary Disease.


Vitamin D deficiency (serum 25-[OH]D levels<20ng/mL) is present in 60-75% of patients with severe COPD. Low serum vitamin D levels have also been associated with lower FEV1, respiratory tract infections and autoimmune diseases. Recent studies found that vitamin D supplementation did not decrease the incidence of pulmonary infections such as influenza and tuberculosis but the authors of this paper suggest that higher vitamin D levels are needed to see an effect. They therefore performed a single-center, double-blind, randomized, placebo-controlled trial looking at the safety and efficacy of high dose vitamin D supplementation in patients with COPD prone to exacerbations. They included any patient over the age of 50 with an FEV1 <80% of predicted who was admitted to their hospital with a COPD exacerbation. Of note, patients were excluded if they were taking azithromycin 3x per week because it would interfere with vitamin D dosing and exacerbation analysis. Patients were also excluded if they were receiving antibiotics and steroids for their exacerbation (unless they were already on maintenance steroids for their COPD). Patients were randomly assigned to receive either 100,000 IU vitamin D monthly or placebo. Primary endpoint was time to exacerbation. They found no difference in the number of exacerbations, time to exacerbation, annual rate of exacerbation, or number of exacerbations requiring hospitalization between the vitamin D and placebo groups. There was also no difference in survival, quality of life or FEV1 between the two groups. In a post-hoc analysis, it was noted that in a subgroup of patients with severe vitamin D deficiency (level <10ng/ml), there was a decrease in the rate of exacerbation in the vitamin D group. There were four cases of mild, asymptomatic hypercalcemia (Ca 10.5-11.0 mg/dl) in the vitamin D group (zero in the placebo group) that resolved despite continuing the study medication.

This study was limited by the fact that it was a single center study and it excluded a lot of COPD patients (those on TIW azithro or those on prednisone or antibiotics for their acute exacerbation) who possibly would have benefited from vitamin D supplementation.

Bottom line: High dose vitamin D supplementation does not reduce the number of COPD exacerbations but may have some effect in those with severe vitamin D deficiency.


It is well known that cigarette smoke leads to COPD and lung cancer but not much is known about the consequences of marijuana use over the years. This study used data from the CARDIA (Coronary Artery Development in Young Adults) study to determine whether marijuana use leads to a decline in lung function over time. CARDIA was a
longitudinal study that took place from 1985 to 2006 in order to determine risk factors for developing CAD in young healthy African American and white men and women. Participants were ages 18-30 and were healthy at the time of enrollment. Pulmonary function testing was performed at years 0, 2, 5, 10 and 20. Of the 5000 participants, 16% smoked marijuana only, 17% smoked tobacco only and 21% smoked both. They found that, not surprisingly, tobacco use was associated with a decline in both FEV1 and FVC with higher pack years leading to a steeper decline in lung function. However, marijuana use was actually associated with higher FVC and FEV1 and there was no evidence that increasing exposure to marijuana negatively affected pulmonary function.

The strengths of this study include its long follow-up (20 years) and sample size. It did however only follow patients to the age of 50 so the degree of pulmonary function decline from marijuana use may be underestimated.

**Bottom Line:** Marijuana use does not appear to have adverse effects on pulmonary function during a 20-year longitudinal study.

**Corticosteroid After Etomidate in Critically Ill Patients: A Randomized Controlled Trial**


Etomidate is by far the most common induction agent used for intubation in the critically ill. It is also well known that etomidate blocks cortisol synthesis and can result in primary adrenal insufficiency which can last for up to 48 hours. The authors of this French study, sought to evaluate the role of hydrocortisone (200mg/day) supplementation in overcoming this adrenal suppression in patients without septic shock.

Patients were randomly assigned to receive saline or hydrocortisone (HC). HC was given as a 50mg bolus, 6 hours after enrollment in the study and then as a continuous infusion until hour 48 (total 200mg). Cosyntropin stim test was performed 5 hours after enrollment, and serum cortisol and 11-beta-deoxycortisol levels were followed through the treatment period. The primary outcome was requirement of norepinephrine to treat shock, and secondary endpoints included 28 day mortality, duration of mechanical ventilation, ICU stay, and days with vasopressors support.

Interestingly, 88% of the enrolled patients (99 totals) fulfilled criteria for etomidate related adrenal insufficiency (as assessed by serum accumulation of 11 beta deoxycortisol and low response of serum cortisol to the cosyntropin stim test). There was no difference between the two groups in terms of the primary outcome or secondary outcomes except for a statistically significant decrease in NE dose at 24 and 48 hours. This latter effect was small, on the order of less than 0.02 ug/kg/min.

This study supports the safety of etomidate as an induction agent in the critically ill. Although this study did not include those with septic shock, the data does not demonstrate any clinically significant difference in any outcome despite confirmation of the

"Etomidate is safe in the critically ill!"
chemical effects of etomidate. We should have no concerns about adrenal suppression when using etomidate as an induction agent in the ICU.

**A Randomized Trial of Recombinant Human Granulocyte-Macrophage Colony Stimulating Factor for Patients with Acute Lung Injury.**


Protective ventilator strategies and conservative fluid management have demonstrated improved patient outcomes in patients with ALI/ARDS. Pharmacologic therapy has not proved to be as successful to date. GM-CSF plays an important role in alveolar macrophage maturation, surfactant clearance, and innate immunity. Increased levels of GM-CSF have been correlated with increased survival in patients with ALI/ARDS, and animal studies suggest that GM-CSF may help to limit epithelial cell injury.

The authors performed a multicenter randomized placebo controlled trial evaluating the impact of daily GM-CSF supplementation in patients with ALI/ARDS with a primary outcome of days free from ventilator, and secondary outcomes of 28 day mortality and duration of organ failure. The authors targeted 200 patients, but were only able to enroll 132 over a 5 year span. There was no difference between the placebo arm and treatment arm for any of the primary or secondary endpoints. Although WBC increased in the treatment arm, GM-CSF measured in the BAL of both groups was essentially the same. Likewise there was no difference in inflammatory biomarkers.

This study was underpowered, and thus, required a larger difference in outcome measures than would have otherwise been needed. Initiation of GM-CSF was also delayed until days 3-7 of ARDS diagnosis, the importance of which is unclear. In addition, it is unclear whether or not subjects were provided with doses of GM-CSF adequate enough to be expressed in the lungs (although similar doses had been noted to do so in animal models). Nevertheless, GM-CSF supplementation did not appear to cause harm, and suggests that further study is warranted if the above mentioned challenges are addressed.

**Results of a Phase IIa Study of VX-809, an Investigational CFTR Corrector Compound, in Subjects with Cystic Fibrosis Homozygous for the F508del-CFTR Mutation.** *Claney, J P, Steven Rowe et al. Thorax*

This article investigates the safety, tolerability, and pharmacokinetics of VX-809, an investigational CFTR corrector compound, for patients homozygous for the F508del-CFTR mutation. There are more than 1600 known mutations of the CFTR gene that are related to cystic fibrosis. F508del-CFTR results in the omission of phenylalanine at position 508. This results in an increased susceptibility to rapid degradation in the 26s proteosome. VX-809 restores F508-del CFTR processing and plasma membrane
localization in primary human bronchial epithelial airway cells isolated from patients homozygous for the F508del-CFTR mutation, achieving about 15% of wild-type CFTR levels as measured by the amount of chloride channel function.

This was a randomized, double blinded placebo controlled multiple dose multicenter phase IIa study. Patients were at least 18 years old, required to have homozygous F508del-CFTR mutations, and an FEV1 of at least 40% of predicted. Patients were enrolled into 2 cohorts, A and B. Group A was randomized to placebo, 25mg, or 50mg of study drug in 1:2:2 ratio. After 15 group A subjects completed 28 days of treatment, a safety review was done, and then enrollment in group B was initiated; patients were randomized to placebo, 100mg, or 200mg of study drug in a 1:2:2 ratio, study medication taken for 28 days. End points were safety and tolerability as well as CFTR activity measured by sweat chloride and nasal potential difference.

109 patients were screened; 89 were randomized. 1 patient was later found to be heterozygous for the F508del-CFTR but was included in the analysis. Baseline characteristics were matched, though there was a trend towards a higher FEV1 in the placebo and 25mg group. Adverse events were similar amongst the groups. There was no difference in incidence of physician diagnosed exacerbations between placebo and study groups (12% of placebo subjects vs. 17% of VX-809 subjects, p=0.62). 4 subjects discontinued study drug, one in each of the VX-809 dose groups. No placebo subjects withdrew from treatment.

Sweat chloride analysis showed a significant reduction at 28 days in the 100mg and 200mg treatment groups compared to placebo (-4.61 mmol/L in the 100mg group and -6.13 mmol/L in the 200mg group). Sweat chloride levels returned to baseline on follow-up post treatment. There was no difference in nasal potential difference or CFTR mature C-Band isolation in rectal biopsy samples between placebo and VX-809 dose groups. There was no significant change in lung function (FEV1, FVC, or FEF25-75%) in any of the dose groups.

This study demonstrates safety and tolerability of VX-809 in subjects homozygous for F508del-CFTR mutation. It also demonstrates a reduction in sweat chloride in the 100mg and 200mg dose groups, which may indicate increased CFTR function. There was no significant change in other markers of CFTR function, such as nasal potential difference; likewise there was no change in lung function. Further studies are warranted to evaluate the potential of VX-809 as a therapeutic regimen.
Vitamin D Levels and Risk of Acute Exacerbations of Chronic Obstructive Pulmonary Disease: A Prospective Cohort Study.

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This study investigates the relationship between low vitamin D 25(OH) levels and the risk of COPD exacerbation. The investigators are extrapolating from the association between low levels of vitamin D and increased risk of asthma exacerbation that there may also be a relationship between vitamin D levels and COPD exacerbation. Pts. with severe COPD are known to have a higher incidence of vitamin D deficiency. Also, vitamin D deficiency is associated with higher risk of respiratory infections. The relationship between vitamin D levels and acute exacerbation of COPD (AECOPD) was investigated by measuring plasma vitamin D 25(OH) at baseline in 973 participants on entry to a 1-year study that was originally designed to determine if daily azithromycin decreased the incidence of acute exacerbation of COPD. Relationships between baseline D 25(OH) and AECOPD over 1 year were analyzed with time to first AECOPD as the primary outcome and exacerbation rate as the secondary outcome. Pts. were placed in three categories; normal vitamin D level (>20ng/ml), low vitamin D level (<20ng/ml) and severely low vit D level (<10 ng/ml). In these patients with severe COPD (mean FEV1 of 1.12L) 33.1% of them were vitamin D deficient. In the primary analysis vitamin D level had no relationship to time to first COPD exacerbation; based on 10ng/ml increments in vitamin D level the estimated hazard ratio was 1.04 (95% confidence interval, 0.97-1.12) In the secondary statistical analysis the vitamin D level had no relationship to annual COPD exacerbation rates by Poisson (p=0.82) or negative binomial analyses (p=0.87. One limitation was the vitamin D level was not followed serially, only a one time baseline vitamin D level was obtained. The strength of this study is large sample size (973).

Neurogenic Changes in the Upper Airway of Patients with Obstructive Sleep Apnea


This study investigates the relationship between hypoglossal nerve dysfunction and obstructive sleep apnea. The investigators looked at motor unit potential (MUP) derived from electromyographic (EMG) signals in subjects with obstructive sleep apnea (OSA) vs. control subjects. The hypothesis is that there would be signs of neurogenic remodeling in the subjects with OSA. This hypothesis is derived from the observation that nerve damage can be caused by vibration. Patients with OSA have vibration through snoring and
this could cause changes in nerve and muscle function consistent with damage. It is known that Motor unit potential (MUP) durations are increased in neurogenic disorders and can be assessed by EMG. The increased MUP duration has been attributed to motor unit remodeling, collateral sprouting, and re-innervating. The investigators looked at Genioglossus EMG signals when subjects were awake, during supine eupneic breathing while wearing a nasal mask connected to a pneumotachograph. The investigators measured duration of MUP, peak-to-peak amplitude, area, area-to-amplitude ratio, and size index of OSA pts. vs. control. There were 17 subjects with OSA (AHI 55 +/- 6) and 16 control subjects (AHI 4 +/- 1) that gave a total of 1655 MUPs by EMG of the genioglossus muscle for analysis. MUP peak-to-peak amplitudes were not different from patients with OSA vs. control. However the MUPs from OSA subjects were longer in duration (11.5 +/- 0.1 vs. 10.3 +/- 0.1ms; p<0.001) and had a larger size index (4.09 +/- 0.02 vs. 3.92 +/- 0.1ms; p<0.001) compared with control subjects. This supports the hypothesis that patients with OSA have neurogenic changes of the genioglossus muscle suggesting that the peripheral axons have sprouted to adjust to the physiological requirements. The design of the study was unable to identify the causative nature of the remodeling, although the authors state that likely it is due to the mechanical strain induced by tissue vibration. The two arms of the study were matched by age, weight and sex; however the arms differed by BMI. Strengths of this study include the large number of subjects in both arms, the ultrasound guidance placement of EMG needle, and monitoring of subjects during eupneic breathing.