YK Loke et al attempts to clarify the association of fracture risk with long term use of inhaled corticosteroids in COPD patients. They performed a meta-analysis reviewing both randomized-controlled trials, as well as, controlled observational studies that were at least of 24 weeks duration. None of the trials examined were designed to specifically evaluate fracture risk. A total of 16 RCTs and 7 observational studies were included in the meta-analysis. The inhaled corticosteroids used varied – RCTs used only budesonide or fluticasone, however, the observational studies also included beclamethasone and triamcinolone. Analysis of the RCTs demonstrated a significant increase in fractures (2.0% for ICS versus 1.7% in controls p=0.04) with a NNH of 83 over a 3 yr period. The authors felt that that their meta-analysis found consistent evidence of an increase risk of fractures with the use of long term ICS.

They argue that despite the barely significant data from the RCTs, similar findings in the observational studies support the overall findings of the RCTs.

There are many weaknesses to this study; the most glaring is that none of the studies analyzed focused on fractures as the primary end point. There is not consistent data regarding prior use of inhaled or systemic corticosteroids through all of the studies. Nor is there data regarding baseline bone density measurements throughout the studies. The studies also appear to have varied definitions of fractures with some looking at just vertebral versus any fracture versus non-vertebral. Finally, as the authors admit, a significant amount of the data originate from company reports which are not peer-reviewed.

In general, given the above concerns, I do not feel that this study sheds any significant additional light on this topic. As the authors point out at the conclusion of their article, the benefits and risks of ICS should be weighed for each individual patient and their underlying fracture risk. I think this study does highlight the need for a quality study that specifically looks at fracture risk in this patient population.

The August Issue of Thorax was reviewed by Kendra Hammond.
High Prevalence of Subclinical TB in HIV-1-infected persons without advanced immunodeficiency: implications for TB screening

Tuberculosis is the leading cause of mortality in HIV-infected patients. Current screening in high prevalence, limited resource areas are directed at symptomatic persons. Oni et al postulates that, perhaps, earlier detection of TB could lead to improved outcomes. They investigated the prevalence of asymptomatic, or subclinical, TB in HIV patients who have not yet met criteria to receive anti-retroviral therapy, i.e. without advanced immunodeficiency. Of note, in limited resource areas, CD4 counts of <200 are usually required before ART is begun, whereas, in contrast, ART is usually started at a CD4 count <350 in other areas.

The investigators recruited 274 persons, however, 61 patients could not produce sputum, and thus were excluded, leaving a total of 213 persons. These persons underwent a symptom screen for TB (cough, fever, nights sweats), received a tuberculin skin test, and had induced sputum collected. If the TST was positive, they underwent CXR and were started on INH if the CXR was clear. The collected induced sputum was used in smears, cultures, and spoligotyping (PCR method for detecting and typing TB). They state a TB case is defined as at least one positive culture; however, one of the 18 diagnosed with TB was diagnosed solely on CXR. As mentioned, 18 persons were diagnosed with TB, 8.5%. Ten of the fourteen persons who got a CXR had normal CXRs. Of the 18 persons diagnosed with TB, 16 had follow up. Of these, 9 (56%) developed symptoms - median 28 days after diagnosis. The authors then looked at CD4 counts in the asymptomatic groups (TB and no TB disease) compared with known symptomatic disease. As would be expected, the asymptomatic, no TB group had significantly higher CD4 counts (322) as compared with asymptomatic TB (249) and symptomatic TB (148). There were no significant risk factors found asymptomatic TB, however, positive PPD, longer history of HIV, and lower CD4 count showed a trend toward being predictive of TB.

In general, this article basically highlighted the increased prevalence of TB in HIV patients not yet receiving anti-retroviral therapies. It does offer some support for sputum culture screening for asymptomatic HIV+ patients, however, more detailed studies also looking at CD4 counts as a possible trigger for screening would likely be more helpful. Given the limited resources in the many areas this study would be most applicable, I doubt this will significantly change practice. However, it does highlight a population where improved screening will likely result in overall improved mortality.

Reviews worthy of attention

- Annals of Internal Medicine August 2: Review of Stable COPD done by ACP, ACCP, ATS, and ERS
- AJRCCM August 1: Update in Asthma 2010 by Shamzah Kazani and Elliot Israel
- Chest has a nice point-counterpoint with rebuttals in a Marini vs. McIntyre debate on pressure control vs. volume control in lung protective ventilation in patients with ARDS.
NEJM August 11

**Early vs. Late Parenteral Nutrition in Critically Ill Adults**

Looked at 4640 patients in Belgian hospitals over a 3 yr. period. 1/2 were randomized to starting parenteral nutrition on ICU day 4 (early), other half were started on ICU day 8 (late). Essentially comparing the European guidelines (early) vs. the US and Canada guidelines (late).

Parenteral nutrition was started when pts. were unable to meet their caloric needs through enteral nutrition alone. Results showed that the late nutrition group had a shorter length of ICU and hospital stay, had fewer infections, required HD and MV for fewer days. The late group also had higher CPK's which were used as a measure of inflammation. The article didn't really delve into why infections were higher in the early nutrition group and why the infections that were higher were mostly airway and wound infections as opposed to blood stream infections. They also didn't really talk about why they thought the results were favoring later nutrition.

NEJM August 25

**Azithromycin for Prevention of Exacerbations of COPD**

Looked at ~1200 COPDers for 1yr, half got 250mg azithromycin daily, other half got placebo. Looked at time to first exacerbation which was statistically significant for the azithro group. Looked at frequency of exacerbations which was s.s. for the azithro group. Subgroup analysis showed that Azithro was favored over placebo in:

a) -those who were on no long acting controllers as opposed to those who
b) were on ICS, LABA, and LAMA
c) -ex-smokers as opposed to current smokers
d) -not on O2 as opposed to on O2
e) -GOLD stage 2 or 3 as opposed to Stage 4
f) -Over 65 as opposed to Under 65

Discussion talked about possibly dosing less frequently than daily since no one gives azithro daily. Also discussed that in the Azithro group more macrolide resistant organisms were seen so it makes you wonder if we're winning the battle but losing the war by starting someone on Azithro. Also while both groups demonstrated a fair amount of hearing loss over the life of the study, the Azithro group had a statistically significant increase in hearing loss compared to the placebo.

AJRCCM August 1

**Continuous Positive Airway Pressure Reduces Postprandial Lipidemia in OSA**

OSA is a risk factor for cardiovascular disease and treatment of OSA with CPAP has been shown to decrease mortality related to MI, CVA and heart failure. This is likely due to lowering of blood pressure but some studies suggest that CPAP improves fasting total cholesterol. Recent studies found that post-prandial TG levels are strongly
associated with cardiovascular-related disease and death and others found that TG metabolism may be influenced by sleep and circadian rhythm so this study focused on whether treatment of OSA led to improved TG metabolism.

In this study, patients with moderate to severe OSA (who were not currently using CPAP) were randomized to receive 2 months of CPAP (at the pressure determined by a home auto-titrating CPAP to maintain AHI<10) or “sham-CPAP” (machine set at 0.5 cm H2O). After 2 months of treatment or placebo, the two groups crossed over after a 1-month “washout period” (patients in the treatment-CPAP arm now wore the sham-CPAP and vice versa for 2 months). During three days of the trial, patients spent the night at the laboratory and had lipid profiles drawn seven times during a 24-hour sleep/wake cycle (before each meal and 3 times during the night). Their 24-hr urine was also collected for catecholamine levels. These laboratory days occurred before the trial began, after the first two months of CPAP use and at the end of the trial (when the two groups crossed-over and had worn their CPAP for the 2nd two months.) The primary outcome, the area under the 24-hour TG concentration curve, was found to be lower after therapeutic CPAP than after placebo.

There were two peaks of TG during the 24 hrs, one during wake and one during sleep, and both peaks were significantly lower in the CPAP group when compared to placebo. Total cholesterol levels were also different between the two groups but there was no difference in free fatty acids or HDL levels. Urine noradrenaline levels were also lower in the CPAP group.

In summary, this study found that treatment of OSA with CPAP reduced TG peaks and thus may lead to decreased cardiovascular mortality. The authors note a few limitations: they did not repeat a baseline blood draw following the washout (prior to the cross-over); they found that compliance in the sham-placebo group was lower than in the therapeutic CPAP group; and the patient groups only included those with moderate to severe OSA (AHI>25) so it is not known how CPAP affects lipid levels in those with mild OSA. This paper focuses on “post-prandial TG levels” or 4-hour post-meal TG levels but according to the study design in Figure 1, it looks like all the blood draws were taken just before the meal. Also, the authors state that participants were served meals “representative of a standard western diet” but meals were served at odd times (9am, 3pm and 9pm) which may affect peak TG levels. Finally, in table 1, baseline levels of the patients’ lipid levels are listed and it appears that they are all within the normal range. Therefore, it is not clear how CPAP would affect someone with baseline elevated TG levels.
Observational Study of ICS on Outcomes for COPD patients with Pneumonia

The GOLD criteria recommend inhaled corticosteroids (ICS) for COPD patients with FEV1 <50% of predicted but prior studies suggest that ICS treatment is associated with increased risk of pneumonia and an increased 30-day mortality following hospitalization with pneumonia. This was a retrospective cohort study looking at hospitalized VA patients with a discharge diagnosis of pneumonia and a prior diagnosis of COPD who were on at least one type of respiratory medication (β-agonist, theophylline, tiotropium or ipratropium). They divided patients into two groups based on whether they had used ICS prior to admission (a “current user” was defined as a patient who had received a prescription within 90 days of the hospitalization.) Primary outcomes were 30- and 90-day mortality. The patients were well-matched though those who used ICS prior to admission were more likely to also be using LABA, tiotropium and theophylline. They found that patients who were using ICS prior to hospitalization had a lower 30- and 90-day mortality and were less likely to require mechanical ventilation (MV) during that hospitalization. They then looked at whether other respiratory medications affected mortality: when comparing short-acting beta-agonists (SABA) + ipratropium with or without ICS, those who used ICS had improved 90-day mortality and less need for mechanical ventilation. There was no difference in mortality or need for MV in patients on SABA + ipratropium + LABA with or without ICS. In summary, this study found that the use of ICS in COPD patients hospitalized with pneumonia was associated with decreased 30- and 90- day mortality and less need for mechanical ventilation. Prior studies showed that ICS use was associated with increased risk of pneumonia but this study did not look at that variable. Limitations of this study included the fact that the VA population is made up of mostly males so there are very few females in the study. Also, the definition of a current ICS user was one who had received a prescription for the medication in the previous 90 days; this did not guarantee that the pt was using it correctly or even using it at all.

Joanna Beros reviewed the August 15th issue of AJRCCM


A new weaning classification based on expert opinion from the multiple International Thoracic and Critical Care Societies was recently proposed at an International Conference in which patients are categorized into three groups: simple, difficult, and prolonged weaning. The authors’ objectives are to describe a cohort of mechanically ventilated patients based on this classification and analyze their risk of death. In a prospective study, patients were enrolled from 349 ICUs in 23 participating countries who had received a minimum of 12 hours of ventilation. The simple weaning group includes patients extubated on same day as their first attempt of withdrawal from ventilator. The difficult weaning group includes patients requiring up to 7 days from
their first attempt, and prolonged weaning includes patients requiring more than 7 days of weaning from their first attempt. The method of weaning tended to be with T-piece in the simple weaning group, while reduction in pressure support was preferred in the other two groups. Patients with COPD or pneumonia as the reason for ventilation were more likely to have a difficult or prolonged wean, while patients with postoperative respiratory failure were more likely to have a simple or easy wean. Also longer duration of ventilation prior to initiating weaning as well as high PEEP were also related to difficult or prolonged wean. In regards to outcome, the prolonged weaning group had a trend towards higher rates of reintubation and tracheostomy as well as a longer length of stay. The prolonged weaning group also had a higher mortality compared to the other two groups (OR 1.97 w/ 95% CI 1.17-3.31).

Comment: A simple (and even somewhat obvious) conclusion to draw from this is that patients who have a prolonged wean over 7 days are at increased risk of death. What is interesting is that the difficult and prolonged weaning groups tended to do more pressure support weaning, so perhaps this is contributing to longer duration of weaning. Perhaps spontaneous breathing trials are an underutilized approach to discontinuation from the ventilator.

Physical Activity Is the Strongest Predictor of All-Cause Mortality in Patients With COPD. A Prospective Cohort Study

Benjamin Waschki, MD; Anne Kirsten, MD; Olaf Holz, PhD; Kai-Christian Müller, PhD; Thorsten Meyer, PhD; Henrik Watz, MD; and Helgo Magnussen, MD.

There are prognosticators and then there is prognostic value. Physical activity/cardiovascular status in COPDers was compared to systemic markers of inflammation. 170 outpatients with stable COPD (mean FEV-1 56% predicted) underwent 6min walk test, actigraphy (multi-sensory armbands), echo, ankle-brachial index or ABI's, BNP, hs-CRP, IL-6 all measured. F/u was 2 years and all-cause mortality was the measured outcome. Compared to invasive measurements, 4 year survival as predicted by physical activity was associated with the highest relative risk for death. They used the C statistic of which this fellow is not at all familiar, though the authors say it's analogous to calculating the area under receiver-operator curve (like taking a bunch of correlated values and outcomes and seeing which one most specifically affects outcome). Even small incremental increases in physical activity lowered risk of death (hazard ratio 0.46 with p=0.001). They also mention some novel predictors of mortality - namely adiponectin, leptin; adiponectin and ABI's (less so), and physical activity (the most) on Cox regression were the best independent predictors of mortality. The editorial emphasizes how we do cardiopulm stress testing to get
our VO2’s but what might be perhaps equally important is daily physical activity - any movement no matter how small - may contribute to increasing conditioning. Although relatively small numbers recruited for this ‘survival study’, what’s notable is that actual accelerometer measurements rather than questionnaires as in prior studies were used.

**Bronchiolitis Obliterans Syndrome: The Final Frontier for Lung Transplantation**

Jamie L. Todd ; and Scott M . Palmer. CHEST 2011; 140( 2 ): 502 – 508

This is a nice review of the mechanisms of BO and possible translational research targets. Chronic allograft dysfunction is the inevitably doom long-term outcome of lung transplants. Airflow obstruction due to progressive intraluminal fibrosis not due to acute rejection (ACR) /infection/comorbidity. That BO does not occur in patients without transplants emphasizes the role of alloimmune Tcell function/regulation; the profibrotic inflammatory milieu that is the consequence of BO would suggest that T cell depletion is a preventative strategy. Unfortunately, despite what we consider intense immunosuppressants, it still happens eventually. Novel therapies like the monoclonal antibodies and other strategies (i.e., dispersing calcineurin inhibitor throughout the lung like in an aerosolized form) may help, but they still do not stabilize lung function or prevent BO. Thus there must be other pathways to BO. There is an evidence of HLA antibody activation; thus B-cell modulators are being used, like rituximab and IVIG (better in combination). The proteasome inhibitor Bortezomib specifically targets mature plasma cells and thus donor-specific antibodies. Finally autoimmune mechanisms that lead to BOS have recently been discovered. Injury/infection may expose self-antigens which are then targeted in the lung (ie, collagen type 5, tubulin); so inducing immune tolerance to these antigens is under investigation. Toll-like receptors which are in the innate pattern recognition receptor family - patients with polymorphisms and mice with knock-outs of TLR’s have dramatically less BO. Indeed, modulating TLR’s or downstream receptors is being studied in the treatment of sepsis as well. Basically, we ought to consider targeting more than just T cells - we have to address all aspects of immunity (B cells, innate and autoimmune adjuncts.) One example would be the lap Nissen’s we do for patients with GERD - it may reduce pathogen associated molecular patterns and has been shown to reduce BO.

**The value of positive end expiratory pressure and Fio2 criteria in the definition of the acute respiratory distress syndrome.**

Existing data from the 2,443 patients enrolled in four ARDS network clinical trials from 1996-2005 were reviewed. A frequency distribution of baseline PEEP was done; in order to characterize the relationship between baseline PEEP and FIO2 , the baseline FIO2 was divided into 10 subsets(with a range of FIO2 of 0.10). Tertiles of Pao2/Fio2 were created with ~ 770 pts. Three groups of baseline PEEP (<5, 6-10 & >11 cmhH20) and baseline Fio2 (<0.50, 0.50-0.69, & >0.70) within each Pa02/Fio2 tertile. Cochrane Armitage trend tests
were used to determine if the Pao2/Fio2 tertile predicted mortality and also to see if differences in PEEP and Fio2 within each tertile were associated with differences in mortality. To assess for effects of interventions (low tidal vol and vol. conservative strategies), pts. were separated to highest and lowest PaO2/Fio2 quartiles.

Among pts. with PaO2/Fio2 ratios < 200 (77%), mortality was ~ 31.4%. Remaining 23% of patients with PaO2/Fio2 ratio of >200 mortality was 21.9%. 1.3% of patients had their baseline PEEP set <5% and ~ 50% had their baseline PEEP >10cm H20. When the Fio2 was <50% most clinicians selected a PEEP of 5-8cm H20. When Fio2 was >50% most clinicians set PEEPs at 10cmH20. Overall there were few patients with a combination of high baseline PEEP and low baseline FiO2. Within each PEEP range (<5, 6-10 & >11 cmH20), mortality increased with decreasing Pao2/Fio2 but mortality did not increase within each PaO2 /Fio2 tertile with increasing PEEP. For FIO2, the contrary was the case, with each PaO2/Fio2 tertile there was increased mortality for significantly increasing FIO2. Interventions involving lower tidal vol and fluid conservation strategies did not have any significant effects on pts. in the mildest and most severe quartiles of baseline hypoxemia.

Overall TAKE HOME POINT of the study:

In single variable analyses, baseline PEEP and baseline PaO2/Fio2 ratio could predict mortality (of note PEEP was clinician dependent). However, after controlling for baseline Pao2/Fio2; increased FIO2 carried a more prognostic value (as seen by increased mortality) than increase in PEEP. This can help identify patients that are at higher risk of death in ARDS. Going forward, perhaps addition of Fio2 to the American European consensus criteria could be used to identify subsets of patients with high or low mortality.

Agreement in electrocardiogram interpretation in patients with Septic Shock

Arrhythmia and acute coronary syndromes are very common in critically ill/septic patients and the ability to read and interpreted EKG correctly not only enhances early intervention but could also carry prognostic values. This is a prospective, observational sub study from the Vasopressin in severe sepsis

Pts. 16 and above were recruited into the study (with SIRS, proven or suspected infection, new dysfunction of at least one organ and hypotension despite vol resuscitation). Pts. with unstable coronary syndrome, New york heart class III-IV were excluded. 25 initial EKGs were read to standardize interpretation by the reviewers. EKG was interpreted by two independent reviewers and intensivist and a cardiologist (each EKG was analyzed for rhythm, presence of Q waves, ST elevation, ST depression, and T wave inversion. The interpretation was done at baseline, 6hrs, 2 days and 4 days. Additional reviewers were asked for an overall assessment of whether the EKG was normal or abnormal or if there was ischemia or not.

There were total of 121 pts.
(similar to the VASST pop.) except that there were fewer females in this study. There was a significant change in the reads after they were unblinded to troponins. The blinded intra rater agreement for readers 1 & 2 showed that there was good correlation in the kappa values for myocardial ischemia, normal EKG and atrial fibrillation. When unblinded, there was a change in values for normal EKG and ischemia, but no significant difference was seen in atrial fibrillation, bundle branch block and ST elevation.

These results are not very different from daily practices in the MICU for critically ill patients. With the knowledge of troponins there is better inter reader correlation. Most readers do not seem to miss obvious arrhythmias (AFib) and ST elevation MIs. How does this help in practice? When not sure of the EKG read might be best to obtain troponin levels and trend it out or seek cardiology assistance.

**Impact of Hypoxic Hepatitis on Mortality in the Intensive Care Unit.**

Fuhrman et al.

Hypoxic Hepatitis (HH) or shock liver is a negative prognostic indicator in the ICU. In this single center study in Austria, the authors performed a prospective cohort study across three medical ICUs in order to quantify its incidence and effect on mortality. Inclusion criteria included a clinical setting of cardiac/circulatory/respiratory failure, with transient increase in aminotransferase levels of at least 20 times the upper limits of normal. Patients were excluded if known contributors of hepatic necrosis such as viral or drug induced hepatitis.

In this study, the authors noted 118 cases of HH (11%) out of 1066 ICU admissions. Most required mechanical ventilation and/or vasopressor therapy. ICU length of stay and mortality were increased in these patients, with an increased rate ratio of 4.91 if patient’s required vasopressor therapy. Overall, mortality in patients with HH was 57%. This study highlights the independent risk factor for HH in mortality in this population. Unfortunately, there is no directed therapy other than treatment of the underlying cause, though there is ongoing research in this direction. Limitations of this study include the heterogeneity of the patients in the study, as well as the fact that data were collected in a single center, which may limit broader conclusions. Larger studies across multiple centers may help to delineate these differences, and aid in understanding differences in a heterogeneous population.

**Intrapulmonary Percussive Ventilation Superimposed on Spontaneous Breathing: A Physiological Study in Patients at Risk for Extubation Failure.**

Intrapulmonary Percussive Ventilation (IPV) is a mode of ventilation that can be superimposed on spontaneous breathing. This mode of ventilation may unload respiratory muscles, improve gas exchange, and help mobilize secretions in patients at high risk of reintubation. It is generally well tolerated and can be administered without the challenges associated with synchronized breathing patterns seen with noninvasive ventilation (NIV). The authors performed a prospective trial involving 17 extubated patients and compared
the effects of IPV to NIV. Patients intubated for 48 hr or longer and had passed a spontaneous breathing trial were included if they also had two of the following (1 – age >65, 2 – underlying heart or respiratory failure, 3 – APACHE II >12 on day of extubation). Patient’s were excluded primarily if inability to provide NIV due to facial surgeries, or inability to place an esophageal balloon due to pathology or technical issues. Transdiaphragmatic and gastric pressures, ABGs, and vitals signs were measured post extubation, during and after IPV, and during and after NIV. Both treatments were well tolerated, and lead to a significant reduction in respiratory rate. PaCO2 decreased during NIV, but not during IPV. PTPdi/min (diaphragmatic work) decreased significantly to similar extents with NIV (35% reduction) and IPV (20% reduction) – the difference between the two was not statistically significant.

This study demonstrates the effective unloading of respiratory muscles post extubation with IPV. Only one setting of IPV was used in the study, and further unloading and ventilation improvements may be seen with different settings. Furthermore, the appropriate duration of IPV post extubation remains unknown. Although improved ventilation was not seen, IPV may have a role in the post extubation setting for those at high risk at reintubation, particularly in those patients who cannot tolerate NIV.