Risk Factors and Outcome of Changes in Adrenal Response to ACTH in the Course of Critical Illness
Margriet Fleur Charlotte de Jong, et al.

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Single center longitudinal retrospective cohort study of patients admitted to an ICU over a 3-year period in Holland. The purpose of the study was to further assess CIRCI (critical illness related corticosteroid insufficiency). The authors suggest that there is currently a large amount of conflicting literature regarding Cortisol and ACTH stimulation tests both in their use and their usefulness. The authors of this paper felt that if the results of ACTH stim tests were looked at longitudinally in individual patients it might shed light on the value of the ACTH stim. They hypothesized that a decrease in the response to ACTH stim tests over time would be associated with increased risk factors for CIRCI and increased mortality.

They included all admissions to their 28 bed ICU over a 3 year period who had 2 or more ACTH stim tests with at least 24hrs in between them. In patients who underwent 3 tests the 2nd and 3rd tests were used. Patients with known abnormalities of the hypothalamic-pituitary-adrenal axis were excluded. ACTH testing was done on all patients who were hypotensive (SBP <100) for greater than 6hrs who were requiring fluid challenges and/or vasopressors. Cortisol levels were measured at 0,30min, 60min after giving 250micrograms of synthetic ACTH. The higher of the 30 and 60 minute levels was used to indicate response. Both change from baseline and % change from baseline were assessed. Their “normal values” were a baseline cortisol of 165nmol/L, peak response to ACTH up to 500-550 nmol/L, and increases from baseline of 200-250 nmol/L.

The patients were divided into two groups: those whose delta cortisol increased from test 1 to test 2 and those whose delta cortisol decreased. If delta cortisol was unchanged the patients were included in the increased group.

The study showed that delta cortisol changes inversely related to changes in SAPS II and SOFA scores. Decrease in delta cortisol carried a mortality of 19% compared to 0% for increased delta cortisol. Also ICU and hospital mortality were higher in patients w/ a persistent or fall in delta cortisol to <100 nmol/L.

It seems like this article could be used as evidence for “change in ACTH stim test response” to be incorporated as an outcome predictor. However, in my experience we don’t routinely do ACTH stim tests at Loyola/Hines and as the article points out their use in general has been called into question. I don’t think the data in the paper is strong enough to warrant a change in management.
Initial Trophic vs. Full Enteral Feeding in Patients With Acute Lung Injury: The EDEN Randomized Trial

The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network


The authors of this study seek to address the question of how best to provide nutrition in patients with acute lung injury. Enteral nutrition, when possible, providing full caloric needs has been the practice rather than parenteral nutrition. Recent studies, however, have suggested that permissive underfeeding may result in decreased duration of mechanical ventilation as well as improved mortality. To help clarify the issue of full caloric support versus underfeeding, the authors performed this prospective randomized controlled, open-label, multicenter trial. Study participants were adult ICU patients who were within 48 hours of acute lung injury diagnosis and had received less than 72 hours of mechanical ventilation. Exclusion criteria included chronic lung disease, refractory shock, intracranial hemorrhage, severe malnutrition, and severe neuromuscular disease. A total of 1000 patients were enrolled. Of note, the first 272 patients were also enrolled in a separate study involving omega 3 fatty acid supplementation. The patients were randomized to receive either trophic feeds at 20 kcal/hr (the initial 242 patients randomized received 10 ml/hr instead) or feeding beginning at 25 ml/hr and then advanced to goal rate as quickly as possible using a predetermined protocol. After 6 days, the trophic feeding group had their feeding advanced to goal rates using the same rate advancement protocol. The primary outcome was ventilator free days through day 28. Secondary end points included daily percentage of goal enteral feeding, frequency of GI intolerance, 60-day mortality, ICU free days, and new infections. The authors hypothesized that the study would demonstrate an increase in ventilator free days due to decreased incidence of GI side effects.

The results revealed that there was no significant difference noted between the two groups with regards to ventilator free days – the primary outcome. There were significant differences noted with regards to GI intolerance – less vomiting, constipation, and elevated gastric residual volumes (>400cc). Other secondary end points such as 60 day mortality, ICU free days, and infections were the same for both groups. As would be expected, the authors did find that mean plasma glucose and insulin usage was increased in the full feeding group, as was overall fluid intake at day 7 – 2.1 liters in the full feeding group versus 0.4 liters in the trophic feeding group.

In general, this study was well designed and had the benefit of having a large number of participants. The results are believable, but the population they pertain to are rather limited – only patients with ALI without chronic lung disease or malnutrition. This narrow population is one of the weaknesses of the study as well as making application of the results more difficult. That being said, the study does not really support making any current changes to our current practice. Overall, a good study, but it won’t impact clinical practice as it basically supports current methods.
End-of-Life Care Discussions Among Patients With Advanced Cancer: A Cohort Study

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Current national guidelines recommend that patients with an incurable cancer and less than a one year life-expectancy have discussions regarding end of life care with their physicians. As critical care physicians, we know that this does not always happen. Previous studies have shown that this occurs in less than 40% of cases. JW Mack et al attempted to delve further into this issue by looking at patients with stage IV lung or colorectal cancer. They performed a prospective cohort study recruiting patients from the Cancer Outcomes Research and Surveillance Consortium (CanCORS) which is a multiregional, population- and health system- based cohort study including 10,000 patients with lung and colorectal cancer. Patients with newly diagnosed stage IV lung or colorectal cancer were interviewed approximately 4 to 6 months following diagnosis. A baseline interview was conducted as well as a follow up interview at 15 months from diagnosis. Medical records of the included patients were also reviewed for documentation of end of life discussions beginning from 3 months prior to diagnosis to 15 months following diagnosis. If patients were unable to tolerate the full interview, a brief interview was given. If patients were too ill for any type of interview or if the patient had died prior to the baseline interview, a surrogate interview was performed. A total of 1535 lung cancer and 620 colorectal cancer patients were interviewed. In the lung cancer group, a majority of the baseline interviews were with surrogates, while a majority of the colorectal cancer patient baseline interviews were the full patient interview.

The results of the study demonstrated at 73% of patients had evidence of end of life discussions prior to death – 81% reported through interviews and 69% documented in the medical record. Interestingly, of these discussions 82% included the topic of hospice and only 46% included the topic of resuscitation. Of the discussions recorded in the medical records and thus timing, location, and provider information was available, 55% occurred in the inpatient setting. Of the discussions that included provider type, oncologist were the participating provider 49% of the time, which was the most common, followed by general medical physicians with 36%. However, medical oncologist documented end of life discussion with only 27% of their patients. When looking at those patients who died during the study period, initial end of life discussions occurred a median of 33 days before death. However, inpatients who lived more than 12 months, median time before death for first end of life discussion was 69 days.

Although this study has many flaws including the substantial use of surrogate interviews, it does highlight the fact that end of life discussions are not happening as they should – well before death and in the outpatient setting with the added emotional stresses that can be seen in the inpatient environment. This study can serve as an impetus for improvement in our own clinics with our newly diagnosed high stage lung cancer patients as well as our patients with terminal lung diseases.
Metabolic Syndrome Biomarkers Predict Lung Function Impairment

A nested Case-Control Study

Previous cross sectional studies have suggested associations of impaired lung function with metabolic syndrome and coexistence of metabolic syndrome with COPD. Air flow obstruction from particulate matter (PM) and smoke induced inflammation is poorly understood. Bushra Naveed et al investigated if metabolic syndrome biomarkers (Glucose, HDL, Triglycerides, BMI, leptin, amylin, heart rate) can predict future loss of lung function in a cohort with exposure to World Trade Center (WTC) dust.

In this longitudinal study, 801 New York personnel with normal pre September 11th 2001 FEV1 (FEV1 >75% predicted, never smoker) who presented for a subspecialty pulmonary evaluation (SPE) before March 2008 were included. Correlation was made between metabolic syndrome biomarkers obtained within 6 months of WTC dust exposure and subsequent FEV1. Among 801 participants, study sub-cohort (case cohort) had 109 participant with FEV1 Less than LLN (lower limit of normal), with metabolic syndrome biomarkers available in 71 participants. Control cohort had 218 participants had FEV1 greater or equal to LLN with biomarkers available in 166 participants. Comparison was made between control cohort that had FEV1 and metabolic biomarkers less than LLN. There was no statistical significant difference in baseline characteristics of participants such as age, race, years of service at 9/11, WTC arrival time, 9/11 event to evaluation time except BMI which was higher in participants with lower FEV1. Results showed that cases cohort had lower FEV1 % predicted than control cohort all across the board with pre 9/11, MME (Medical Monitoring Entry), and SPE with p value <0.001 for all evaluation. Among metabolic biomarkers, case cohort groups had higher glucose (93 vs. 90 with P= 0.03) and higher heart rate (71 vs. 66 with P= 0.02) than control cohort. Among metabolic protein markers, Case cohort had higher levels of leptin than control (8035 vs. 5370 pg/ml, p = <0.001), lower level of amylin (54.8 Vs. 59.2 pg/ml, p= <0.01) and lower level of pancreatic polypeptide (108.5 vs. 151.5 pg/ml, p =0.05). When compared metabolic syndrome biomarkers with lung function, using logistic regression models adjusted for BMI, age on 9/11, race and WTC arrival time, the odds of being a case (decrease in FEV1 below LLN) increased in participants with dyslipidemia (OR , 3.03; 95% CI, 1.39-6.16) , elevated heart rate (HR equal or greater than 66 with OR 2.20; 95%
CI, 1.14-4.24) and elevated leptin (OR 3.00; 95% CI, 1.35-6.66).
Elevated amylin decreasing the odds (OR 0.16; 95% CI, 0.06-0.43) of being a case (FEV1 less than LLN) by 84%. This test had a sensitivity of 41% and specificity of 86%.

Main points:

1. Non smokers with normal FEV1 pre 9/11, dyslipidemia, elevated Heart rate and leptin greater than 10,300pg/ml had increased risk of developing abnormal lung function over 6 years

2. Elevated amylin prevent decline in lung function

Limitations:

1. Single cohort study that looked at particular population segment that does not represent wide patient population
2. Low sensitivity of the test
3. Metabolic biomarkers measured within 6 months of 9/11, sampling bias could not be discounted.

This study needs further validation with a randomized control trial that incorporates wider patient population.

CSF measured in the BAL of both groups was essentially the same.

Heart Rate Recovery Predicts Clinical Worsening in Patients with Pulmonary Arterial Hypertension

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Cardiopulmonary exercise testing has been used to predict survival in patients with IPAH. 6MWD has a strong correlation with cardiopulmonary exercise testing and has been shown to be a strong predictor of survival in Idiopathic Pulmonary Arterial Hypertension (IPAH). Recent studies have reported the presence of autonomic dysfunction and its possible association with survival in patient with PAH. Abnormal heart rate recovery during the first minute after graded exercise is a powerful predictor of overall mortality in patients CHF/COPD and IPF. It has not been examined in patients with IPAH.

In this article, Omar A. et al evaluated the relationship between heart rate recovery at 1 minute (HRR1) of rest (defined as difference in heart rate at the end of 6MW test and at 1 minute after completion of the 6MW test) after 6 minute walk test (6MW) and clinical worsening in patients with IPAH. This study came about when several previous studies on prognostic indicators lacked reproducibility and clinical relevance. The study was
Conducted between August 2009 and March 2010 in 75 patients with IPAH. Only patients with PAH diagnosed with right heart catheterization and without evidence of secondary cause of PAH were enrolled in the study. 6MW test was conducted after patient has been seated for 10 minutes, pulse ox and heart rate were measured under baseline home oxygen. Heart rate recovery in 1 minute of rest was measured. Clinical worsening was defined as any of the four end points: death, lung transplantation, hospitalization from worsening of IPAH, and escalation of pulmonary hypertension therapy was measured. Time to Clinical Worsening (TCW) was defined at the time from the date of 6MW test to the first clinical worsening. Abnormal HRR1 cut off value was identified to be less than 16 beats at 1 minute. This value was determined by finding the maximum value of the log-rank chi-square statistics for all possible cut-off points for abnormal HRR1 between the 10th and 90th percentile in the study sample. Out of 75 patients, 45 had HRR1 > 16 beats at 1 minute and 30 had HRR1 <16 beats at 1 minute. Patients who had HRR1 < 16 beats in 1 minute had overall worsening clinical events (death, lung transplant, hospitalization due to PH exacerbation, escalation of PH therapy) 60% Vs 13% on patients with HRR1>16 with P value <0.001. Individual clinical events were significant only in escalation therapy in patients with HRR1 <16 with 37 % vs. 2% in patients with HRR >16, p value <0.001. TCW was evaluated by using univariable and multivariable cox proportional hazard analysis which showed that the best predictor of clinical worsening were HRR1 less than 16 (HR 5.2, P= 0.002) and mean pulmonary arterial pressure (HR 1.04; P =0.02). Excluding those on Beta blocker therapy (n=12) the median TCW for HRR1 greater or equal to 16 group was 8.4 months and the median TCW for the HRR1 less than 16 group was 13 months with P value of 0.0003. HRR1 less than 16 also identified a greater proportion of World Health Organization Functional Class 2 (WHO FC 2) and Class 3 patients with clinical worsening compared with 6MWD less than 335 meter and BNP <100. By using logistic regression model and C statistics, they found HRR1 less than 16 was a better predictor of clinical worsening compared with 6 MWD (6 minute walk distance) alone. The best predictor of HRR1 less than 16 by multivariate logistic regression were BNP and baseline WHO FC. HRR1 significantly had a negative correlation with age, renal function, BNP, and mean right atrial pressure. HRR1 had a significant positive correlation with % predicted FVC, % predicted FEV1, 6MWD and peak heart rate during 6MW test. Patients with HRR1 less than 16 were also more likely to require supplemental oxygen during 6MWT, belong to WHO FC 4, have BNP >100 pg/ml, have sodium less than or equal to 36 and pericardial effusion on Doppler study.

Summary points:

1. HRR1 can highly predict clinical worsening and TCW in patients with IPAH
2. HRR1 less than 16 highly correlated with poor prognosis in patients with IPAH.

It is a retrospective study that used data of RHC done previously. Not certain when RHC was done and how long patients were treated for IPAH before this study was conducted and if previous treatment for IPAH had any implication to this study outcome. This study would need prospective validation.
Efficacy of Aclidinium Bromide 400 μg Twice Daily Compared with Placebo and Tiotropium in Patients with Moderate to Severe COPD.

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Aclidinium bromide is a novel, long acting, muscarinic antagonist. It is currently under review with the US FDA and European Medicines Agency for the bid maintenance treatment of COPD. COPD is characterized by increased cholinergic tone and daily tiotropium is currently the only available long acting anticholinergic drug.

This study assessed the bronchodilator efficacy and safety of inhaled aclidinium 400 μg bid vs. a morning dosing regimen of tiotropium 18 μg and placebo in patients with moderate to severe COPD.

The study was a phase 2A randomized, two-center, double-blind, placebo and active controlled crossover clinical study with three 15-day treatment periods, separated by a 9 to 15 day washout, and a follow up visit or phone call 4 to 6 days after each patient’s last dose of study drug. Patients with moderate to severe COPD were equally randomized to one of six treatment sequences. Each treatment sequence consisted of 3 double-dummy treatments: aclidinium bromide 400 μg bid, tiotropium 18μg daily and placebo. Patients >= 40 years with FEV1/FVC ratio of < 70% and FEV1 of >= 30% and <80% predicted 10 to 15 min post-salbutamol 400μg who were current or ex-smokers with a smoking history of >=10 pack years were included in the study. Subjects with a known contraindication to anticholinergics, clinically relevant EKG abnormalities, or cardiovascular conditions such as MI in the 6 months prior to screening were excluded.

Spirometric assessments were performed in triplicate at 1 hr. and immediately before the morning dose and at 0.5,1,2,3,4,6,8,10,11,12 h(pre-evening dose) and 2.5,13,14,15,16,19,22,23 and 24 h post morning dose. The primary efficacy variable was mean change from baseline in FEV1 AUC 0-12/12h at day 15 of treatment. Secondary efficacy end points included changes from baseline in AUC 0-12/12h of FEV1 (day 1 only) and also changes in daily COPD symptom scores and in average daily use of relief medication after 2 weeks of treatment.

A total of 30 patients with COPD were randomized and 27 completed the study. Out of the subjects, 63.3% were current smokers, with a mean age of 58.4 years and a mean baseline post-bronchodilator FEV1 of 58.5% predicted.

The results of the analysis demonstrated that treatment with aclidinium was superior to placebo and led to a significant treatment difference of 221 ml at day 15(95% CI,136-306 ml; P<.0001) and tiotropium also resulted in a significant treatment difference vs placebo of 244 ml (95% CI, 159-330 ml; P<.0001). Also, aclidinium bid provided improvements in morning pre-dose FEV1, which were above the suggested minimal clinically important difference and comparable to those of tiotropium. Furthermore, improvements from baseline in normalized FEV1 and FVC were significantly
greater for aclidinium vs. tiotropium over last 12h of both days 1 and 15. Greater improvements in bronchodilation with aclidinium vs tiotropium at nighttime can be attributed to its evening dose. The significant differences between two agents observed as early as day 1 may be due to variations in their P.kinetic and P.dynamic properties.(PK steady state of aclidinium is achieved by 2 days post dose vs 14-21 days for tiotropium, suggesting that PD steady state may be achieved earlier as well).

This study also revealed that there was significant improvement in nighttime symptoms (as reported by the patients) with bid aclidinium vs. placebo, and these were not observed with tiotropium.

Aclidinium was a safe drug and well tolerated in patients with COPD. Larger phase 3 clinical trials of aclidinium 200μg daily suggested that efficacy achieved with this dose may not be optimal and that a higher daily dose, different dosing regimen(bid), or both may be necessary(like 400μg bid used in this study).

The results of this study are encouraging. It is the first clinical trial to investigate the effect of bid aclidinium on lung function and nighttime symptoms compared with tiotropium. Twice daily aclidinium may, therefore provide a new effective treatment option for COPD in the future.

However, there are limitations of this study including small population, short study duration, and use of non-validated questionnaire to assess nighttime symptoms.

Proteasomal inhibition after injury prevents fibrosis by modulating TGF-b1 signaling. Budinger et al.

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Can the systemic administration of the proteasomal inhibitor bortezomib prevent the development of lung fibrosis after injury is established?

Hot off the breath of the PANTHER trial, investigations into other treatments for pulmonary fibrosis are underway. Our colleagues at Northwestern have further examined what has previously been shown: namely, that proteasomal inhibition may prevent lung and skin fibrosis after injury.

Bortezomib has for years now been used as a treatment for mantle cell lymphoma, multiple myeloma, and more recently investigationally for myelodysplastic syndrome (in which this author participated in clinical trial research when the drug was known as PS-341). In prior animal models, bortezomib's antifibrotic mechanism in intrahepatic/renal/cardiac tissues is proposed to work through activating NF-KB or matrix metalloproteinases, which does not fully account for its widespread activity in a variety of tissue-types. It now known that injury and subsequent activation of the fibrosing cascade requires transcription...
growth factor beta-1; its inhibition has shown to prevent the fibrosis in the liver, kidney, and bone marrow.

Bleomycin was used in mice to induce intratracheal and intradermal fibrosis. A week later, bortezomib was given systemically and the lung and skin fibroblasts were examined a few weeks later. Interestingly, if the drug was given with or before bleomycin, more than 70% of mice died. Another drug in a previous study, imatinib, was shown to decrease fibrosis similarly through modulating TGF-β1—but the drug showed almost no activity when given in the context of bleomycin.

Human lung and skin fibroblasts from both normal patients and those with IPF and scleroderma were also treated with the drug. There is an extensive methods section also available in the online supplement and techniques such RT-qPCR, immuno-blotting/fluorescence/assay, histology, and transfection of vector for specifically targeting the PPAR-gamma in cell membranes (and used as controls).

The authors show that bortezomib works on TGF-β1-mediated target gene expression by inhibiting transcription induced by activated Smads (intracellular signal transducing proteins). This led to a buildup of the the nuclear hormone receptor PPAR-gamma, a repressor of Smad-mediated transcription. PPAR-gamma is essential for normal adipogenesis/glucose regulation that can be activated by endogenous lipids/eicosanoids or drugs like the thiazolidinedione rosiglitazone. The drug in this study, bortezomib, both increases the transcriptional activity and half-life of PPAR-gamma and is most effective when given once weekly, as is how it is usually given in many hematologic malignancies. So why not just use the diabetes drugs? Because, the authors argue, the antifibrotic effects with bortezomib are almost complete whereas with rosiglitazone it is a moderate decrease in fibrosis.

Bortezomib, a medication in widespread clinical use, may offer a therapeutic alternative for patients with lung fibrosis. It would be particularly interesting to see if there are specific PPAR-gamma agonists available to be used and studied alone or in combination with bortezomib. These are encouraging results, but need more rigorous testing and demonstration, especially in the wake of the PANTHER trial.


Is there an occupational exposure association with organic dust and lung cancer risk in the general population? Organic dust is known to contain viruses, mold/fungal forms, plant matter, and endotoxins from gram-negative bacteria. These are all known to cause asthma/COPD/hypersensitivity pneumonitis and other respiratory ailments. It has previously been reported that agricultural workers actually had a negative association between lung cancer risk and occupation (cotton mills and other agricultural workers), presumably due to macrophage stimulation from endotoxins and overall immune activation. However, these meta-analyses did not control for tobacco smoking history/exposure.

Olsson et al recently described a population of people with occupational carcinogen exposures in North America and Europe. Known as the SYNERGY...
project, it is a pooled analysis of case-control studies, and was key to this study. The project provided pooled information on lifetime working and smoking from 13 300 lung cancer cases and 16 273 controls from 11 case-control studies conducted in Europe and Canada. The population had no prior COPD, the mean age was 62, 81% men, and the cancer subtypes for those who were unfortunately diagnosed were mostly squamous (41%), then adeno (26%), then small cell (7%).

A newly developed general population job-exposure matrix (an extension of the previously described DOM-JEM) assigning no, low or high exposure to organic dust, endotoxin, and contact with animals/fresh animal products was applied to determine level of exposure. The authors independently assigned ordinal intensity scores to rate degrees of exposures (besides 70% concordance for endotoxins, there was above 90% concordance for organic dust and contact with animals). Odds ratios for lung cancer were estimated by logistic regression, adjusted for age, sex, study, cigarette pack-years, time since quitting smoking, and ever employment in occupations with established lung cancer risk.

The results included 2nd – 4th quartile of cumulative exposure (which could vary from months to decades, based off author’s intensity-rating) showed significant risk estimates ranging from 1.12 to 1.24 in a dose-dependent manner (p<0.001). Even in those subjects without COPD/asthma (potential risks for lung CA) and excluding those without prior exposure to dust or tobacco smoke (i.e., never smokers), the risk remained the same. No association was observed between lung cancer and exposure to endotoxin or contact with animals or animal products. In the subgroup of those exposed to endotoxin, there was no protective effect for those who were also exposed to organic dust. Further analysis is warranted of subtypes of exposures, occupations, and mechanisms of exposure leading to the association of lung CA, and whether this is preventable with commonly used masks/filters.

Effects of methylprednisolone infusion on markers of inflammation, coagulation, and angiogenesis in early acute respiratory distress syndrome.

The purpose of this study was investigate the role of methylprednisolone treatment on inflammation as well as coagulation and angiogenesis in ARDS. This study was part of a larger study that was investigating outcome when methylprednisolone was given in addition to standard therapy for ARDS. 79 patients had plasma samples taken at enrollment, day 3, and day 7. Samples were analyzed for TNF-alpha, IL-6, VEG-F, Protein C, procalcitonin, and proadrenomedullin. 79 patients had all required samples (63 in the methylprednisolone arm and 28 in the standard therapy arm). Dose of methylprednisolone was 1 mg/kg/day. Baseline characteristics were the same between groups, including age, APACHE III score, and P/F ratio. At study entry, TNF-alpha, VEG-F, Protein C,
proadrenomedullin, and procalcitonin levels were similar between groups; IL-6 was higher in the standard therapy group (558 pg/mL standard therapy vs. 264 pg/mL methylpred group, p=0.03). Methylprednisolone was associated with a greater decline in IL-6 when compared to standard therapy on day 3 (p < .0001) and day 7 (p=.002). This effect was persistent when patients were broken down into both infectious and noninfectious causes of ARDS. There also was a greater increase in protein C in the methylprednisolone group when compared to standard therapy at both day 3 and day 7. Though not the primary outcome, ICU survival was improved in the methylprednisolone group (80% vs. 58%, p=.05).

The authors conclude that methylprednisolone is associated with lowered markers of inflammation (IL-6) as well as an increase in protein C. They postulate that the improvement in protein C may be responsible for the reduction in inflammation, though there is no way to prove with this study whether the improvement in protein C is a cause or effect of the decreased inflammation. Their conclusion does not really comment on the improvement in ICU mortality, though this is a little difficult to believe given prior studies that have not shown improvement.