What Fellows Are Reading in Other Journals

Recommended Reading from the University of Chicago Pulmonary and Critical Care Fellows

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A Comparison of Obese and Nonobese People with Asthma: Exploring an Asthma-Obesity Interaction. *Chest* (1)

Reviewed by Karen Patterson, M.D.

Several large-scale epidemiologic studies demonstrate an increased risk of new-onset asthma in obese patients (2). These studies, however, relied on patient-reported asthma, and some have argued that respiratory symptoms in obese subjects are often incorrectly attributed to asthma (3). In a previous study using a rigorous diagnostic algorithm, this group found that nearly one-third of patients were misdiagnosed with asthma and that misdiagnosis was not more common in obese patients compared with nonobese patients (4). The current study evaluated the clinical characteristics associated with the misdiagnosis of asthma in obese and nonobese patients. In a cross-sectional design, 496 subjects with physician-diagnosed asthma were randomly identified from eight Canadian cities. Demonstration of reversible obstruction (improvement in FEV₁ by 15% and ≥ 200 ml after using a short-acting bronchodilator) or bronchial hyperresponsiveness following a step down in asthma therapy (decrease in FEV₁ of 20% with ≤ 8 mg/ml of methacholine) was used to confirm a diagnosis of asthma.

Although a misdiagnosis of asthma was not higher among obese individuals compared with nonobese individuals, recent use of urgent care services for respiratory symptoms by obese subjects was associated with a fourfold increase in asthma misdiagnosis when compared with nonobese individuals. Older subjects, men, and subjects with higher FEV₁ were also more likely to be misdiagnosed with asthma. One major limitation of the study is the lack of ancestral diversity (>94% were white), which raises the question of applicability in other populations. This study also excluded individuals with a BMI of 25 to 30. By not evaluating weight as a continuous variable, some of the contribution of body habitus to asthma prevalence and/or severity may have been missed.

Nevertheless, these conclusions suggest that objective evidence of reversible airflow obstruction (response to β -agonists) or bronchial hyperresponsiveness should be sought when a new diagnosis of asthma is considered in older adult patients, especially those with normal spirometry or those at risk for heart failure, which can mimic asthma.

Effect of Azithromycin on Pulmonary Function in Patients with Cystic Fibrosis Uninfected with *Pseudomonas aeruginosa*: a Randomized Controlled Trial. *JAMA* (5)

Reviewed by P. J. McShane, M.D.

Azithromycin has been shown to improve FEV₁ in patients with cystic fibrosis (CF) chronically infected with *Pseudomonas aeruginosa* (6), but it is not known if azithromycin has a role in the management of patients with CF without *Pseudomonas* infection.

This large, multicenter, randomized, double-blind, placebo-controlled trial sought to determine the impact of azithromycin on lung function in children and adolescents with CF uninfected with *Pseudomonas*. The 168-day study included 260 patients with mostly mild obstruction. Azithromycin was dosed on a weight basis (either 250 mg or 500 mg) and given thrice weekly. At study completion, lung function was not statistically different between the two groups, but patients treated with azithromycin had a higher BMI, fewer exacerbations, and less use of oral antibiotics than those in the placebo group. Nausea and diarrhea occurred with similar frequency in both groups. The only macrolide-resistant organisms that emerged at study completion were *Staphylococcus aureus* and *Haemophilus influenzae*, and these organisms were present in both treatment groups. No participants in either group developed nontuberculous mycobacteria during the study.

This was a negative study with regard to the primary end point, improvement in FEV₁. However, the limitation of this study is that this end point is not realistic in patients with already normal baseline lung function (mean FEV₁ = 97.7 % predicted, SD = 16.40), particularly when the observation period is short. In future studies, a longer observation period would be better able to determine if azithromycin prevents lung function decline over time. Longer-term studies have already shown that height and weight have a positive correlation with lung function (7) and that many children fail to recover to baseline FEV₁ months after an exacerbation (8). This study did show that azithromycin reduced the number of exacerbations and increased BMI. As such, azithromycin may, over an extended period of time, protect lung function in patients with CF uninfected with *Pseudomonas*.

Comparison of Dopamine and Norepinephrine in the Treatment of Shock. *NEJM* (9)

Reviewed by Matthew M. Churpek, M.D., M.P.H.

The optimal initial vasopressor for the management of shock remains unclear due to the paucity of high-quality prospective randomized trials. Both dopamine and norepinephrine are recommended as first-line agents for patients with shock, although observational data have suggested that dopamine is associated with inferior outcomes.

This multicenter trial randomized 1,679 patients with signs of tissue hypoperfusion and a mean arterial pressure less than 70 mm Hg or systolic blood pressure less than 100 mm Hg despite a fluid challenge to dopamine or norepinephrine (9). The primary endpoint was the rate of death at 28 days.

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There was no significant difference in mortality at 28 days between the two groups. Significantly more arrhythmias (mostly atrial) occurred in the dopamine group (24.1 vs. 12.4%, $P < 0.001$). A subgroup analysis showed that dopamine was associated with an increased risk of death at 28 days in 280 patients with cardiogenic shock ($P = 0.03$), but no difference was seen in the patients with septic or hypovolemic shock.

This large prospective, multicenter, randomized trial provides high-quality evidence in an area in which such data have been previously lacking. Additionally, the trial enrolled patients with different types of shock and had few exclusion criteria, increasing its generalizability. Limitations of the study include the small amount of fluid administration necessary for study enrollment (1,000 ml of crystalloids or 500 ml of colloids), especially considering that 78% of the patients had septic or hypovolemic shock. Also, data regarding specific interventions shown to be effective in the treatment of septic and cardiogenic shock, such as early antibiotic therapy, coronary revascularization, and early goal-directed therapy, were not reported.

Current evidence does not support the use of dopamine as the initial vasopressor in patients with undifferentiated shock, and norepinephrine should be considered the drug of choice. Also, in patients with cardiogenic shock, norepinephrine may be superior to dopamine as the initial vasopressor, at least in part due to the decreased risk of arrhythmias. Further studies are necessary to determine if dopamine increases the risk of death in this subset of patients when compared with norepinephrine.

A Protocol of No Sedation for Critically Ill Patients Receiving Mechanical Ventilation: a Randomised Trial. *Lancet* (10)

Reviewed by Philip A. Verhoef, M.D., Ph.D.

A great deal of research over the last 15 years has revealed that minimizing the use of sedative medications (especially benzodiazepines) and providing daily interruptions of sedation leads to improved morbidity and mortality in the intensive care unit (ICU). A single institution in Denmark has used a standard no-sedation protocol in their ICU since 1999 and researchers therefore designed a trial comparing this protocol to one involving daily interruption of sedation (10, 11).

One hundred forty critically ill, intubated patients in a closed medical-surgical ICU were assigned either to a control group (daily sedation interruption) or an intervention group, wherein the patients were given only as-needed bolus doses of morphine and no sedation. The control group received 48 hours of sedation with propofol, followed by transition to midazolam infusion for sedation (titrated to Ramsay score of 3–4) in addition to receiving as-needed bolus doses of morphine. Patients in the intervention group had significantly more ventilator-free days (which was the primary outcome measure) of 13.8 versus 9.6, ($P = 0.0191$), shorter ICU stays (13.1 vs. 22.8 d, $P = 0.0316$), and shorter hospital stays (34 vs. 58 d, $P = 0.0039$). However, there was an increased incidence of delirium (20 vs. 7%) and subsequent use of haloperidol in the intervention group.

This study was well designed and this particular institution was uniquely well-equipped to conduct research of this nature, given that the standard of care in this ICU is a protocol that does not routinely use sedation. These results have significant implications for improving the quality of ICU care as well as

reducing health-care costs. However, several additional factors weaken the study or limit its generalizability. Patient-to-nurse ratios were 1:1, and patients who became delirious were assigned an additional provider to verbally comfort them; these interventions would not be conceivable in most institutions in the United States where staffing shortages and limited resources are perpetual problems. Patients also received midazolam infusions after 48 hours of propofol, which is not the practice in our ICU; it remains possible that the change in sedating medication further contributed to the noted differences. This was a single-institution study as well, raising the possibility that this effect may not be noted with other populations or in different institutions.

Regardless, this research indicates that our approach to sedation in the ICU must continue to evolve, and further multicenter prospective trials should explore protocols that avoid or minimize use of sedative medications.

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