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INSIDE

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Delayed Transfer to the ICU Increases Length of Stay and Mortality

ABSTRACT & COMMENTARY

By Leslie A. Hoffman, PhD, RN

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Dr. Hoffman reports no financial relationship to this field of study.

Synopsis: *Critically ill emergency department patients with a ≥6 hour delay in ICU transfer had an increased hospital length of stay and higher ICU and hospital mortality.*

Source: Chalfin DB, et al. *Crit Care Med.* 2007;35:1477-1483.

This study examined outcomes in 50,322 patients admitted to the emergency department and later transferred to the ICU during the period from 2000-2003. Study data were obtained from Project IMPACT, a voluntary database that includes a nationwide sample of 120 adult ICUs in 90 hospitals. Patients admitted from the emergency department to the ICU were divided into two groups: those remaining in the emergency department ≥ 6 hours (delayed) and those remaining < 6 hours (non-delayed).

Patients whose admission to the ICU was delayed (n = 1,036) or non-delayed (n = 49,286) were similar in age, gender, and do-not-resuscitate status as well as APACHE II score (p = NS). Among hospital survivors, the median hospital length of stay was 7.0 days (delayed) vs 6.0 days (non-delayed) (p < .001). ICU mortality was 10.7% (delayed) vs 8.4% (non delayed) (p <.01). In-hospital mortality was 17.4% (delayed) vs 12.9% (non-delayed) (p <.001). A diagnosis of sepsis was more common in the delayed group (p <.001), whereas multiple trauma (p <.01), coronary artery disease (p <.001) and respiratory diagnostic categories (p <.01) were more common in the non-delayed group. When examined using logistic regression, delayed admission, advancing age, higher APACHE II score, male gender, and a diagnosis of either trauma, intracerebral hemorrhage, or neuro-

logic disease were associated with lower hospital survival (odds ratio for delayed admission, 0.79; 95% confidence interval, 0.561-0.895).

COMMENTARY

Today our emergency care system faces an epidemic of crowded emergency departments, patients experiencing long waits to be seen and admitted, and ambulance diversions. Hospitals are faced with the difficulty of simultaneously meeting the needs of patients who require urgent and lifesaving care and providing non urgent care for the uninsured who use the emergency department as a safety net. The Institute of Medicine reports that 40% of hospitals experience crowding on a daily basis in their emergency department.[1] More than one-third report using diversion (closure to ambulance traffic) within the past year as a consequence of a lack of critical care beds.

In this study, critically ill patients whose admission to the ICU was delayed had a longer hospital stay and an increase in ICU and hospital mortality. As might be expected, there was considerable overlap in the APACHE II diagnostic categories between delayed and non-delayed patients. Among delayed patients, those with sepsis were significantly more likely to be delayed. In patients with septic shock, mortality can be significantly reduced if goal-directed therapy is instituted as soon as the diagnosis is made. Categories of patients diagnosed with other "time-sensitive" conditions, such as coronary artery disease or trauma, did not experience delays, suggesting that the time-sensitive nature of sepsis management may not be fully appreciated.

A second concern relates to the availability of critical care beds as a cause of the delay. Boarding of critically ill patients in the emergency department while waiting for an available bed is a common occurrence. Noting this, the Institute of Medicine recently identified emergency department boarding as a major public health concern,[1] a conclusion supported by study findings.

There were several limitations to this study. It used retrospective data and therefore could not identify the cause of the observed delays. The database did not include information about institutional characteristics, physician or nurse staffing or other variables, such as board certification or eligibility, or the availability of specialists, which might have influenced outcomes. Further studies are necessary to identify the specific factors that led to a prolonged emergency department stay and ways to modify them. ■

Reference

1. The future of emergency care in the United States health system: Institute of Medicine, 2006. Available at: http://www.iom.edu.

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Predicting Poor Outcome from Acute Upper Gastrointestinal Hemorrhage

ABSTRACT & COMMENTARY

By James E. McFeely, MD

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Dr. McFeely reports no financial relationship to this field of study.

Synopsis: *In this study of male veterans with acute upper GI bleeding, those with an APACHE II score of 11 or more, esophageal varices, or stigmata of recent hemorrhage, or some combination of these, had a 6-fold higher likelihood of a poor outcome.*

Source: Imperiale TF, et al. *Arch Intern Med.* 2007;167(12):1291-1296.

Upper gastrointestinal hemorrhage results in 250,000 hospitalizations and between 15,000

and 30,000 deaths per year in the United States. There is considerable variability in how patients with upper gastrointestinal hemorrhage are managed, as well as in resource use, both within and between various institutions. A variety of clinical prediction rules for risk stratification have been published; however, none have achieved widespread use. Reasons for poor implementation include limited clinical applicability, complexity of use and relatively weak validation sets underlying the developed rules themselves.

Investigators at three VA hospitals defined two *a priori outcomes*: a composite GI hemorrhage-specific variable including re-bleeding and need for surgery or an advanced technique to control hemorrhage (Outcome 1); and a more comprehensive outcome variable that includes Outcome 1 plus worsening of any additional co-morbidities (Outcome 2). A total of 391 patients were enrolled in the trial, 244 in the derivation set, 147 in the validation set. Demographic variables were typical for a VA population: 99% of the patients were men with a mean age of 63 years, and 35% of the patients were older than 70.

Eight percent of the patients experienced major re-bleeding; 22% experienced major re-bleeding or had worsening of a co-morbid condition. Three variables were identified as significant in multiple logistic regression analysis. These were stigmata of recent hemorrhage, APACHE II score greater than 11, or esophageal varices. Unstable co-morbidity at the time of hospital admission was also identified as a variable for the more broadly encompassing Outcome 2.

Only two of 138 patients (1.4%) who had none of these risk factors developed any adverse outcomes. Seven of 149 (4.6%) patients with one risk factor had significant re-bleeding.

COMMENTARY

The authors of the above study have identified a relatively straightforward clinical prediction rule that appears to work well for elderly white male VA patients. Patients who present with this typical VA profile and have none of the three identified risk factors are at relatively low risk for significant re-bleeding or development of worsening co-morbidities. This prediction rule may be useful in decision-making regarding length of stay and location of admission within the hospital. What is unclear from the study is whether this can be generalized to women or to different, non-VA-type populations.

Given that these rules seem easy to track and are relatively robust in describing the risks in this subset of patients, they can probably begin to be used when a typical VA-type patient comes to your hospital. Hopefully these prediction rules can be validated soon for other subsets of patients and implemented more broadly at that time. ■

Special Feature

Pressures, Volumes, Outcomes, and Physiology in Mechanical Ventilation

By Dean R. Hess, PhD RRT

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Dr. Hess reports no financial relationship to this field of study.

THERE IS LITTLE DEBATE THAT TIDAL VOLUME (V_T) should be lowered in patients with acute lung injury (ALI) or the acute respiratory distress syndrome (ARDS). The pivotal trial of more than 800 patients conducted by the ARDS Network[1] reported significantly lower mortality for a V_T target of 6 mL/kg predicted body weight (range 4-8 mL/kg) compared to a V_T of 12 mL/kg. Translated to evidence-based medicine terms, the number-needed-to-treat from this trial was 12 patients: for every 12 mechanically ventilated patients with ALI/ARDS treated with a V_T of 6 mL/kg rather 12 mL/kg, 1 additional life is saved. Mechanical ventilation, a life-support technology, can increase the risk of death if set improperly or, if set properly, can increase the likelihood of survival.

The ARDS Network protocol[1] also calls for monitoring of plateau pressure (PPLAT). PPLAT is measured using an end-inspiratory breath-hold maneuver. This is easily accomplished on modern ventilators with the press of a button, which closes both the inspiratory and expiratory valves, allowing pressure in the lungs to equilibrate with proximal airway pressure. In this way, pressure measured at the proximal airway estimates the alveolar pressure at end-inhalation. Thus, PPLAT is an estimation of peak alveolar pressure. The ARDS Network protocol targeted PPLAT ≤ 30 cm H_2O. If PPLAT > 30 cm H_2O, the protocol calls for a reduction in V_T to as low as 4 mL/kg. If severe acidosis or patient-ventilator dys-synchrony occurs, the protocol allows V_T to be increased to as much as 8 mL/kg provided that PPLAT remains ≤ 30 cm H_2O.

When Might We be Fooled by the PPLAT?

Alveolar injury is likely the result of excessive trans-pulmonary pressure (PTP) rather than V_T or alveolar pressure *per se*. PTP is the difference between the pressure in the alveolus (PPLAT) and the pressure outside the alveolus. The pressure outside the alveolus is pleural pressure (PPL). During passive positive pressure ventilation (ie, no spontaneous inspiratory efforts by the patient), PPL is determined by V_T and chest wall compliance. During active breathing efforts, PPL is determined by the magnitude of the inspiratory efforts by the patient.

Imagine the scenario in **Figure 1** (below). In this case, the chest wall compliance is reduced, as might occur with abdominal compartment syndrome or chest wall burns. When the lungs are passively inflated to an alveolar pressure (PPLAT) of 30 cm H^2O, the pleural pressure increases by 15 cm H_2O. In this case, the PTP is only 15 cm H_2O. One might argue that there is reduced risk of ventilator-induced lung injury (VILI) in this case and that a higher PPLAT might be safe. In fact, the restrictive effects of a stiff chest wall may be protective against VILI, as has been shown in experimental animal models.[2]

Imagine now the scenario in which the ventilator is set for pressure-controlled ventilation of 20 cm H_2O and PEEP of 10 cm H_2O **(Figure 1)**. Thus, the ventilator will target an alveolar pressure (PPLAT) of 30 cm H_2O. If the patient makes an active inspiratory effort, the ventilator will deliver more flow (and volume) to maintain the PPLAT constant. If the inspiratory effort of the patient decreases the pleural pressure by 15 cm H_2O, note that the PTP is 45 cm H_2O, which might be sufficiently high to produce VILI. In animal models, VILI resulted from either high positive pressure applied inside the lungs or high negative pressure applied outside the lungs.[2]

Evaluation of PPLAT demands consideration of the pleural pressure because PTP is determined not only by PPLAT but also by PPL as well. Although it has been argued to focus on PPLAT rather than V_T in the context of preventing VILI,(3)[3] it might not be so simple. A lower PPLAT does not necessarily decrease the risk of VILI. Imagine the case in which the alveolar pressure is 30 cm H_2O and the PPL is 5 cm H_2O. In another case, the alveolar pressure is 15 cm H_2O during pressure-controlled (or pressure support) ventilation and the PPL decreases by 10 cm H_2O as the result of the inspiratory effort of the patient. One can argue that the PTP and V_T are the same in both scenarios.

How Can We Estimate PPL at the Bedside?

The traditional approach to assessing PPL is the use of an esophageal balloon, which consists of a

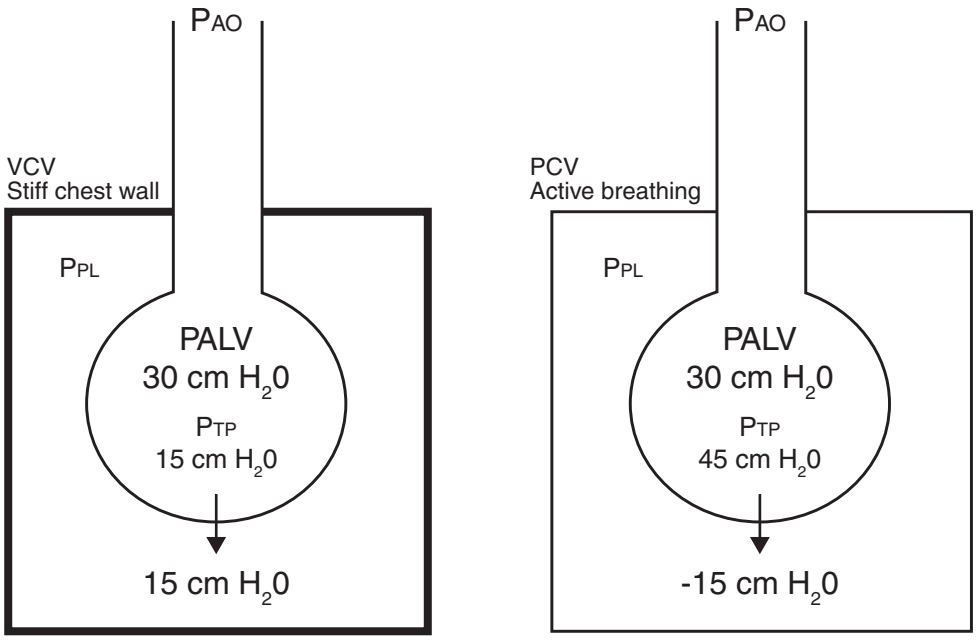

Figure 1. The effects, on trans-pulmonary pressure, of a stiff chest wall during volume-controlled ventilation (on the the left) and of active breathing during pressure-controlled ventilation (on the right). PAO: pressure at the airway opening, PPL: pleural pressure, PALV: alveolar pressure, PTP: transpulmonary pressure, VCV: volume-controlled ventilation, PCV: pressure-controlled ventilation.

thin catheter with multiple small holes in the distal 5-7 cm of its length.[4] A 10-cm balloon is placed over the distal end of the catheter to prevent the holes in the catheter from being occluded by esophageal tissue, and the balloon is inflated with a small amount of air (0.5-1 mL). The proximal end of the catheter is attached to a pressure transducer. The proximity of the esophagus to the pleural space allows use of esophageal pressure (PES) as an estimate of PPL. However, PES accurately reflects PPL only if the pressure measured in the balloon is an accurate measure of the pressure in the esophagus, the transmural pressure of the esophagus is zero, there is no compression of the esophagus by the heart or other intrathoracic structures, and the pressure in the mediastinum surrounding the esophagus is equal to PPL.

PES may be affected by measurement artifacts such as the elastic recoil of the balloon (worsened by balloon over-inflation), elastic recoil of the esophagus, active esophageal contraction, or pressure transmitted from surrounding structures. Moreover, PES varies with lung volume and body position. Upright-to-supine differences in PPL are attributed to artifact caused by direct compression of the esophagus by mediastinal contents such as the heart. It follows that absolute values of PES are unpredictable and of questionable value for clinical purposes.[5] However, changes in PES closely reflect changes in PPL and hence changes in PES are useful when assessing respiratory system mechanics.

Measurement of PES is invasive, requires special equipment, and is not commonly available for the care of mechanically ventilated patients. While PES is the standard method of estimating PPL, PPL changes during lung inflation are transmitted to other structures in the mediastinum. In 1965, Comroe suggested that an intra-thoracic vein with its thin wall is capable of transmitting PPL and might therefore be an acceptable alternative to the esophagus for PPL measurement.[6] Respiratory variation in central venous pressure is easily detected at the bedside during mechanical ventilation and varies from a positive deflection when the respiratory muscles are completely inactive to negative swings during large inspiratory efforts. Chieveley-Williams et al[7] compared ΔPES to changes in central venous pressure (ΔPCVP) and reported that useful information can be obtained from ΔPCVP during mechanical ventilation. In an experimental model, Valenza et al[8] recently reported that ΔPCVP was similar to ΔPES.

Talmor et al[9] used PES to estimate the influence of the chest wall on PPL and PTP in patients with acute respiratory failure. They subtracted 5 cm H_2O from each value of PES to correct for artifacts attributable to body position and balloon pressure and then calculated PTP from the difference between airway opening pressure (PAO) and corrected PES:

$$P_{TP} = P_{AO} - P_{ES} + 5 \text{ cm } H_2O$$

They reported a wide range of calculated PTP at all values of PAO, supporting the concern that PAO is influenced by chest wall mechanics. They suggested that, by using this approach, ventilator settings could be more appropriately customized to accommodate inter-individual variations in lung and chest wall mechanics. Although this approach is attractive, it is potentially flawed by the assumption that corrected PES accurately reflects PPL. The approach suggested by Talmor and associates[9] cannot be recommended without further confirmation and evidence that this results in improved patient outcomes.[5]

Volume-controlled vs Pressure-controlled Ventilation

An area of some debate is whether a lung-protective ventilatory strategy can be achieved using pressure-controlled ventilation rather than volume-controlled ventilation as used by the ARDS Network protocol. This question can be addressed by examination of the equation of motion for the respiratory system:

$$P_{VENT} = V_T / C + \dot{V} \times R - P_{MUS}$$

where P_{VENT} is the pressure applied by the ventilator, V_T is tidal volume, C is respiratory system compliance, $\dot{V}$ is flow, R is airways resistance, and P_{MUS} is the pressure generated by the respiratory muscles.

During volume-controlled ventilation, the ventilator controls $\dot{V}$ and V_T. Thus, an active inspiratory effort of the patient (PMUS) results in a decrease in alveolar and proximal airway pressure. The result is the characteristic scooped-out appearance of the airway pressure graphic during active breathing efforts during volume-controlled ventilation. Because V_T and $\dot{V}$ are fixed, the equation of motion predicts that PPLAT and PPL should be reduced by equivalent amounts with active inspiratory efforts. In other words, PTP is not affected. Although this may be uncomfortable for the patient, volume-controlled ventilation protects the patient from increases in PTP

in the presence of active inspiratory efforts.

During pressure-controlled ventilation, the ventilator controls P_{VENT}. In this case, an active inspiratory effort of the patient (P_{MUS}) results in an increase in $\dot{V}$ and V_T. The increase in P_{MUS} increases PTP and V_T, both of which are a potential source of VILI. Note that this applies to all pressure-controlled modes, including airway pressure-release ventilation (APRV). Theoretically, vigorous inspiratory efforts may result in large PTP swings during the high pressure phase of APRV.

How Low Can We Go?

Another controversial issue is whether a PPLAT of ≤ 30 cm H_2O is sufficient or whether lower levels are better. In other words, should the V_T be lowered even if PPLAT is ≤ 30 cm H_2O?[3] This was addressed by a secondary analysis of the data from the ARDS Network, in which mortality was lower with a lower PPLAT. That would suggest that mortality is reduced by a reduction in PPLAT, even if PPLAT ≤ 30 cm H_2O.[10] On day 1 of enrollment in the original ARDS Network trial, patients in the lowest quartile of PPLAT randomized to a V_T of 12 mL/kg had a PPLAT of 16-26 cm H_2O and a mortality of 34%. However, patients in the lowest quartile of PPLAT who were randomized to a V_T of 6 mL/kg had a PPLAT of 10 to 20 cm H_2O and a mortality of only 23%. A recent study by Terragni et al[11] reported alveolar overdistention in two-thirds of patients with PPLAT < 30 on 6 mL/kg V_T.

A Lower PPLAT for Everyone?

If lower PPLAT is associated with improved survival in ALI/ARDS, and if a lower PPLAT is achieved with use of smaller V_T, should V_T and PPLAT be decreased in all mechanically ventilated patients, whether or not ALI/ARDS is present? Although no randomized controlled trial has addressed this question, lower levels of evidence are accumulating to support that a lower V_T and PPLAT should be considered in all mechanically ventilated patients. Several studies have shown that higher V_T is associated with a greater risk of developing ALI/ARDS in patients whose lungs are essentially normal at the time of intubation.[12-14] Another study showed a lower risk of ALI/ARDS following implementation of a protocol to limit V_T to a maximum 10 mL/kg predicted body weight in all patients and a recommendation to use 6-8 mL/kg PBW for patients at any risk of ALI/ARDS.[15] In patients with severe brain injury, the use of high V_T was recently reported as a predictor of ALI.[16]

Shultz et al[17] recently addressed the question, "What Tidal Volumes Should Be Used in Patients without Acute Lung Injury?", and recommend that the use of lower V_T should be considered in all mechanically ventilated patients whether they have ALI or not. Prospective studies should be performed to evaluate optimal ventilator management strategies for patients without ALI.

Concluding Comments

Evidence is clear that V_T and PPLAT should be targeted to 6 mL/kg predicted body weight and ≤ 30 cm H_2O, respectively, in patients with ALI/ARDS. Evidence is also suggestive of a benefit with a lower V_T and PPLAT, suggesting that the lowest possible V_T and PPLAT should be targeted in patients with ALI/ARDS. Accumulating evidence suggests that lower V_T and PPLAT should also be targeted in patients who do not have ALI/ARDS. The message to the bedside clinician is that we should be treating the lungs as gently as possible during positive pressure ventilation. ■

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36. Delayed admission from the emergency department to the ICU was associated with which of the following?
a. transfer from a community hospital.
b. diagnosis of adult respiratory distress syndrome
c. diagnosis of sepsis
d. admission on nights and weekends.
e. all of the above.

37. According to the Institute of Medicine, what proportion of US hospitals report experiencing emergency department crowding on a daily basis?
a. 10%
b. 20%
c. 30%
d. 40%
e. 60%

38. In the VA-based study to determine risk factors for recurrent upper gastrointestinal hemorrhage, what percent of patients were men?
a. 50%
b. 75%
c. 85%
d. 95%
e. 99%

39. In the VA-based study to determine risk factors for recurrent upper gastrointestinal hemorrhage, what percent of patients who had none of the 3 identified risk variables developed an adverse outcome?
a. 1.4%
b. 2.8%
c. 5.6%
d. 8.4%
e. None of the above

40. Randomized controlled trials have reported a survival benefit for the use of smaller tidal volumes during mechanical ventilation in which of the following groups?
a. Acute respiratory distress syndrome
b. Chronic obstructive pulmonary disease
c. Acute neurologic injury
d. Neuromuscular disease
e. All of the above

41. An increase in chest wall stiffness, as in abdominal compartment syndrome, would be most likely to have which of the following effects during volume-control ventilation?
a. higher plateau pressure, increased trans-pulmonary pressure
b. higher plateau pressure, decreased trans-pulmonary pressure
c). higher plateau pressure, no change in trans-pulmonary pressure
d. no change in plateau pressure, increased trans-pulmonary pressure
e. no change in either plateau or trans-pulmonary pressure

Answers: 36 (c); 37 (d); 38 (e); 39 (a); 40 (a) 41 (c)

CME / CE Objectives

After reading each issue of *Critical Care Alert*, readers will be able to do the following:

- Identify the particular clinical, legal, or scientific issues related to critical care.
- Describe how those issues affect nurses, health care workers, hospitals, or the health care industry in general.
- Cite solutions to the problems associated with those issues.

In Future Issues:

Should We Continue using Erythropoietin in the ICU?

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

Are Thiazolidinediones (TZDs) Safe?

In this issue: *Are thiazolidinediones safe? New study shows Zometa reduces risk of hip fractures and improves survival; Merck HIV vaccine proven ineffective in clinical trials; no causal association found between exposure to mercury from thimerosal; and FDA approvals.*

There's no hotter topic in medicine right now than the safety of the thiazolidinediones (TZDs) rosiglitazone (Avandia) and pioglitazone (Actos). Several meta-analysis have pooled data from multiple clinical trials and come to different conclusions regarding the safety of the drugs. The September 12 issue of *JAMA* contained two papers, both meta-analysis, the of first which suggests that pioglitazone is associated with a significantly lower risk of death, myocardial infarction, or stroke among a diverse population of patients with diabetes. An increase in heart failure was noted, although no increase in mortality (*JAMA* 2007; 298:1180-1188).

The second paper looked at rosiglitazone and noted that in patients with impaired glucose tolerance or type 2 diabetes, use of rosiglitazone for at least 12 months was associated with a significantly increased risk of myocardial infarction and heart failure, again without a significant increase risk of cardiovascular mortality (*JAMA* 2007; 298:1189-1195). This followed on conflicting meta-analysis regarding the risk of rosiglitazone published in the *New England Journal of Medicine* in June and July, the first of which suggested the rosiglitazone was associated with an increase risk of myocardial infarction and increased risk of death from cardiovascular causes (*NEJM* 2007; 356:2457-2471), while the second showed an increased risk of heart failure but no increased risk of myocardial infarction or death from cardiovascular causes (*NEJM* 2007;357:28-38). The studies led to congressional hearings, multiple editorials in medical journals and eventually led the FDA to recommend black box warnings regarding the risk of heart failure for both drugs in July. But despite cries from consumer groups suggesting that this was the Cox-2 debacle redux, the FDA stopped short of taking rosiglitazone off the market. The most recent entry into the fray is a new meta-analysis from the Lahey Clinic in Boston. This review analyzed over 3000 studies of which 7 were used for the analysis—all randomized double-blind clinical trials of drug-related congestive heart failure in prediabetic or diabetic patients given either rosiglitazone or pioglitazone. In over 20,000 patients, 360 had congestive heart failure, 214 on TZDs and 146 on comparators. As with other studies there was an increase risk of heart failure associated with both drugs (relative risk 1.72, 95% CI 1.21-2.24, P= 0.002), but again no increase in cardiovascular death was noted with either drug (RR 0.93). The authors suggest that TZDs cause worsening heart failure, but are not associated with progressive systolic or diastolic dysfunction of the left ventricle that leads to death. They also suggest that more studies are needed (*Lancet* 2007;370:1129-1136). The take home message from all the studies is to use caution in TZDs in patients with diabetes and heart failure (NYHA I and II), and to carefully monitor patients for worsening signs and symptoms including weight gain and edema. Initiation of these drugs in patients with established NYHA Class III or IV heart failure is contraindicated.

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5413. E-mail: iris.young@ahcmedia.com.

Zometa and hip fractures

A single 5 mg infusion of zoledronic acid (Zometa) within 90 days of a hip fracture reduced the risk of new fractures and improved survival according to new study. Zoledronic acid is a long acting bisphosphonate that is approved for once yearly treatment of postmenopausal osteoporosis. The drug is effective at reducing vertebral, hip, and non-vertebral fractures in women with osteoporosis. In this current study, 1065 men and women with hip fractures were assigned to receive yearly intravenous zoledronic acid 5 mg IV or placebo, the infusions were administered within 90 days of surgical repair of a hip fracture. All patients received vitamin D and calcium. Mean age was 74.5 years, with approximately 75% women. The rate of new clinical fracture was 8.6% in the zoledronic acid group and 13.9% in the placebo group (35% risk reduction, $P = 0.001$). The respective rates of new clinical vertebral fractures were 1.7% vs 3.8% ($P = 0.02$) and for non-vertebral fractures 7.6% vs 10.7% ($P = 0.03$). The death rate was 28% less in the zoledronic acid group (101 of 1054 [9.6%] vs 141 of 1057 [13.3%], $P= 0.01$). No cases of osteonecrosis of the jaw were reported and no adverse effects of healing fractures were noted. The authors conclude that an annual infusion of zoledronic acid within 90 days of a low trauma hip fracture was associated with reduced rate of new fractures and improved survival (published early at www.NEJM.org September 17, 2007).

Merck HIV Vaccine Ineffective in Clinical Trial

After years of development and clinical trials Merck has announced that their HIV vaccine is ineffective in a large clinical trial, and the company has halted further test vaccinations. Other HIV vaccines have also failed but many had hoped that the Merck vaccine, which worked by stimulating T cells, might be more effective. The trial, which was begun in 2004 vaccinated 3000 uninfected volunteers in the US and Latin America. Among 741 patients who received a least one dose of the vaccine, 24 new HIV infections were identified, compared to 21 infections in 762 patients who received placebo. Work continues on other HIV vaccines, currently 30 worldwide are in clinical trials, but the failure of the Merck vaccine is seen is a major setback for HIV researchers.

Thimerosal and Mercury Exposure

Thimerosal has been the subject of intense scrutiny for years regarding its potential link to various neuropsychological deficits in children. Thimerosal has been used as a preservative in vaccines and gamma globulin for decades, although it is rarely used now because it is metabolized to mercury and thiosalicylate, potentially leading to high mercury levels in children. In a new study from the CDC and several large HMOs, 1047 children between ages of seven and 10 years were enrolled and tested for 42 neuropsychological outcomes, then the medical records were examined for history of exposure to mercury from thimerosal. Prenatal mercury exposure from thimerosal was associated with better performance on one measure of language and poor performance on one measure of attention and executive functioning. Exposure in infancy up to seven months old was associated with better performance in one measure, fine motor coordination, and on one measure of attention and executive functioning. Increasing mercury exposure from birth to 28 days was associated with poorer performance on one measure of speech articulation and better performance on one measure of fine motor coordination. The authors conclude that they could not find a causal association between early exposure to mercury from thimerosal and deficits in neuropsychological functioning at age 7 to 10 years (*NEJM* 2007; 357: 1281-1292).

FDA Actions

Eli Lilly has received approval from the FDA to market raloxifene (Evista) for the indication of reducing the risk of breast cancer in postmenopausal women with osteoporosis and postmenopausal women who are at high risk for invasive breast cancer. Raloxifene is a selective estrogen receptor modulator (SERM) that is already approved for prevention and treatment of osteoporosis in postmenopausal women. The drug was recently required to add labeling regarding an increased risk of fatal strokes in women taking the drug. It also carries a black box warning regarding risk of thromboembolism in women who are at high risk (those with an active or past history or thromboembolism).

Just in time for the winter flu season, the FDA has approved nasal influenza vaccine (FluMist) for use in children between the ages of 2 and 5. Previously the vaccine was only approved for children 5 years old and older and adults up to age 49. The CDC is recommending all children between the ages of 6 months to 59 months receive a flu vaccine. Children ages 2-8 who have never received a flu vaccine will initially require two doses of fluMist at least one month apart.

The FDA has approved a new oral granules form of terbinafine for the treatment of tinea capitis (ringworm) in children. The preparation may be sprinkled on food, allowing easier administration to children who may not otherwise take medicine over the two weeks required to treat tinea. Terbinafine granules are indicated for the treatment of tinea capitis in children age 4 years and older. It is marketed by Novartis AG as Lamisil Oral Granules. ■