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Critical Care [ALERT]

A monthly update of developments in critical care and intensive care medicine

SPECIAL FEATURE

Nutritional Support in the ICU

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Dr. Wall reports no financial relationships relevant to this field of study.

Nutritional support is an essential component of caring for critically ill patients. Historically, nutritional support in the critically ill patient was viewed as an adjunctive modality for supplying exogenous fuel to the patient during their illness. The goals were mostly to avoid malnutrition, immune suppression, and metabolic derangements. More recently, there has been a paradigm shift. Nutritional support is now considered a therapy, with goals of attenuating metabolic stress responses, preventing apoptosis (cell death), reducing oxidative stress in other organs, and modulating the body's immune response.

We often forget that the gut is the largest immune organ in the body. The gastrointestinal (GI) tract is an entry point to the external environment, and the presence (or absence) of nutrition has a direct effect on immune function. Systemic immunity is directly influenced by gut epithelial integrity, splanchnic blood flow, and bacterial flora colonizing the intestinal lumen. In this article, I will review general issues relating to nutritional support in ICU patients.

ENTERAL VS PARENTERAL

Enteral nutritional (EN) is the preferred route whenever feasible. EN maintains the functional and structural integrity of the intestinal epithelium by stimulating contractility and releasing trophic substances such as bile salts, gastrin, bombesin, and motilin.[1] Gut feeding releases secretory IgA, which coats bacteria and prevents them from adhering to the epithelial wall. The contractility from feeding subsequently sweeps bacteria downstream, thereby controlling bacterial numbers and reducing translocation. EN also stimulates blood flow to gut-associated lymphoid tissue (GALT), which in turn supports the education of naive CD4 helper lymphocytes that migrate to other organs such as the lungs, liver, and kidneys.

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Parenteral nutrition (PN) does not produce the same effects as EN. Critically ill patients without luminal nutrition lose both functional and structural integrity of the intestinal epithelium. Reduced contractility leads to bacterial overgrowth, emergence of virulent luminal organisms, and intestinal cell apoptosis. The apoptosis creates structural defects that allow bacterial products to aggravate the immune system. In turn, activated macrophages prime neutrophils, which then travel to distant organ sites and cause further oxidative stress. In other words, the absence of luminal food raises the overall systemic inflammatory response.

TIMING OF NUTRITION

Early EN can improve patient outcomes and reduce ICU length of stay. In a meta-analysis of 14 prospective, randomized controlled trials (RCTs), early EN started within 48 hours after admission was associated with a 24% reduction in infectious complications ($P = 0.04$) and a 32% reduction in mortality ($P = 0.06$), as compared with feedings delayed until after 48 hours.[2] Lewis et al conducted a meta-analysis of 12 RCTs in patients undergoing major elective surgery or needing surgical critical care.[3] Patients randomized on the operating table to early tube feedings had a 28% lower rate of infections and a nearly 1-day reduction in hospital length of stay ($P = 0.0001$), as compared to patients receiving no nutrition. Recent guidelines from the Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition suggest that enteral feeding routinely be started "early" (within 24-48 hours following admission).[4]

PATIENTS IN SHOCK

Many clinicians withhold EN if patients are hemodynamically unstable or on vasopressors. The rationale is that nutrient delivery to the gut in the setting of diminished cardiac output can cause intestinal ischemia and small bowel necrosis. In reality, ischemic bowel is a rare complication of EN, occurring in < 1% of cases. In addition, most cases of ischemic bowel were reported in the past with use of surgical jejunostomy tubes, not the more commonly used gastric tubes.

Guidelines now advise that EN be cautiously provided to patients who are adequately resuscitated and on stable low vasopressor doses. EN can be to either the stomach or small bowel.[4] EN infused directly into the small bowel, however, should be held until the patient is normotensive (mean arterial pressure > 60 mmHg). In general, when feeding a patient with recent hemodynamic instability, start with a low rate, progress slowly to goal, and use an isotonic non-fiber containing formula. Monitor for signs of intolerance that might indicate early gut ischemia (e.g., abdominal distension, increasing residual volumes, increasing metabolic acidosis and/or base deficit).

BOWEL SOUNDS AND FLATUS

In ICU patients, the presence of bowel sounds and passage of flatus or stool are not required to initiate EN. Bowel sounds only indicate contractility and do not necessarily reflect mucosal integrity, barrier function, or absorptive capacity. Studies describe success rates of reaching nutrition goals within the first 72 hours ranging from 30-85%, but when enteral feeding protocols are followed, success rates are typically 70-85%. Numerous studies, mostly in surgical patients, have reported feasibility and safety of early enteral feeding with the first 2 days. Bowel sounds and flatus were not strong factors in these high success rates.

GASTRIC VS POST-PYLORIC

EN can be achieved via either an oral or nasal enteric tube positioned in the stomach or small intestine. Gastric tubes are usually easier to place. Most institutions confirm correct position by portable radiograph. Other verification methods include auscultation and aspiration of gastric contents. However, studies have shown that auscultation alone is ineffective, and measuring pH of aspirated gastric contents is unreliable because of widespread use of acid-reducing

medications. In fact, no single non-radiographic method exists that can reliably differentiate between respiratory, esophageal, gastric, and small bowel placement of blindly inserted feeding tubes in the fed or unfed state.[5] Sometimes, a combination of non-radiographic techniques can be used successfully.

Numerous studies have evaluated gastric vs jejunal feeding in various ICU populations. Although there is probably less gastroesophageal reflux with small bowel feeding, studies have not consistently found that this translates to a reduction in ventilator-associated pneumonia (VAP). Of the three meta-analyses looking at this subject,[6-8] only one showed a significant reduction in VAP (RR = 0.76; 95% confidence interval, 0.59-0.99; $P = 0.04$).[8] Furthermore, this effect was driven largely by a single study, and when the study was removed from the meta-analysis, the difference was no longer significant. No study has ever shown a difference in mortality between gastric vs post-pyloric feeding.

ACHIEVING SUCCESS WITH ENTERAL NUTRITION

For various reasons, patients tend to receive only 50% of their target EN calories.[9] Providers tend to under-order calories, and feedings are held 20% of the day in the average ICU patient. Many of these stoppages are avoidable. Common reasons for cessation include "NPO after midnight" orders, elevated gastric residual volumes, and tube displacement.

Every ICU should have a formal protocol for ensuring adequate nutritional support, and daily ICU multidisciplinary rounds should include a registered dietician whenever possible. Evidence-based nutritional protocols increase the overall percentage of calories provided. Protocols standardize delivery of nutritional support, promote earlier initiation of feeding, improve patient tolerance, and minimize unnecessary stoppages. Numerous protocols are available online. A recent publication from Harborview Medical Center in Seattle outlines its current approach.[10]

Gastric residual volumes do not correlate well with gastric emptying, risk of aspiration, or incidence of pneumonia. Studies have showed that raising the gastric residual volume cutoff value from 50-150 mL up to 250-500 mL does not increase the risk for regurgitation, aspiration, or pneumonia.[11] Gastric residual volumes < 200 mL should rarely prompt cessation of feeds. Volumes of 200-500 mL should raise concern, but the feeds should not automatically stop if there are no other signs of intolerance. Rather, one should implement measures to reduce aspiration and continue to monitor closely. Unless contraindicated, all intubated patients receiving EN should have their head of bed elevated to 30-45 degrees regardless.

OTHER AGENTS

Prokinetic motility agents such as metoclopramide have been shown to improve gastric emptying and EN tolerance, but they have not changed other outcomes such as pneumonia or mortality. Other steps to decrease aspiration risk and pneumonia are probably more effective, including chlorhexidine mouthwash twice a day, minimizing sedation and analgesia when possible, minimizing transport out of the ICU for tests and procedures, and moving the patient to a unit with a lower patient:nurse ratio.

There are now a myriad of immune-modulating enteral formulations and supplements. Several meta-analyses suggest that the proper use of these formulations is associated with significant reductions in duration of mechanical ventilation, infectious complications, and hospital length of stay.[12] None of the studies have showed these products reduce mortality, however. In addition, the benefits are mainly apparent in postoperative and not medical ICU patients. In fact, the agents seem to have the greatest effect if given in the preoperative period.

Prior studies had suggested that patients with sepsis and acute lung injury (ALI) benefited from supplementation with omega-3 fatty acids. The recent OMEGA study, a double-blind, placebo-controlled RCT, seems to have tempered that excitement.[13] The study enrolled 272 patients within 48 hours of developing ALI, and randomized them to twice-daily placebo vs omega-3 fatty acids, gamma-linolenic acid, and antioxidants. The study was stopped early for futility because the patients receiving the supplements had fewer ventilator-free days (14 vs 17.2; $P = 0.02$) and fewer ICU-free days (14 vs 16.7; $P = 0.04$). Patients in the supplement group also had fewer non-pulmonary organ failure-free days and higher hospital mortality. The authors concluded that the supplements did not improve the measured outcomes. It remains unclear whether they were actually harmful.

PARENTERAL NUTRITION

A detailed discussion of PN is beyond the scope of this article, but I will offer a few thoughts. As mentioned above, the enteral route is always preferable to PN. If the gut works, use it. Several studies, including two meta-analyses,[14,15] have

shown a trend toward greater complications with PN as compared to EN. Explanations for this adverse signal include immune suppression and hyperglycemia associated with PN. Either way, most experts agree that PN should be conservatively withheld for at least 7-14 days while all enteral options are exhausted. There is one exception: patients with protein-calorie malnutrition on admission who are unable to receive or tolerate EN. In this group, early PN might be of benefit. In all other patients, the harms of early PN seem to outweigh the benefits.

CONCLUSION

In critically ill patients, nutritional support is no longer just about delivering calories but also an important therapeutic modality. Whenever possible, use of the enteral route is always preferable to the parenteral route. EN confers a variety of immune benefits that affect non-GI organs and it affects the body's systemic inflammatory response. Given the complexity of nutritional support, every ICU should include a registered dietician in the care team, and clinicians should care for their patients using formalized nutrition protocols and evidence-based guidelines. ■

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ABSTRACT & COMMENTARY

Rapid Response Teams: Evidence of a Broader Impact that Influences Morale and Nursing Workload

By Leslie A. Hoffman, RN, PhD

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SYNOPSIS: Advantages of a rapid response team extended beyond a reduction in codes to impact multiple endpoints, including positive effects on nurse morale and empowerment, unit workload, and education.

SOURCE: Benin AL, et al. Defining impact of a rapid response team: Qualitative study with nurses, physicians and hospital administrators. *BMJ Qual Saf* 2012;21:391-398.

In this study, the authors sought to elicit perceptions of the impact of a rapid response team (RRT) by interviewing care providers. The study was conducted at the Yale New Haven Hospital where the RRT covered 43 patient care units. The team was comprised of a rotating hospitalist physician, critical care nurse, and respiratory therapist. Those interviewed included 49 participants (16 physicians, 22 nurses, eight administrators, and three respiratory therapists). Nurses viewed the RRT as providing a sense of security and empowerment, resulting from knowing

they could summon help immediately. As noted by one nurse, "It's very comforting to have someone who can help assess the patient, determine if they are too sick to remain on the unit, and support us." Nurses valued being able to call the RRT if "something did not seem right," even if ill defined. Hospitalists had divergent opinions: some valued the opportunity to keep skills current through exposure to an unstable, decompensating patient, whereas others found the need to respond to calls "extremely disruptive" and a "huge stressor" that diverted time and attention from their caseload. One benefit was unexpected: Housestaff and nurses valued RRT calls as a means to realign their workload and give more attention to other assigned patients. As one nurse noted, "I'm focusing on one patient and hurting four other patients. I called in another nurse and now her four patients are also not seeing the care they need." Administrators viewed the RRT as a means to appropriately triage patients to the ICU, as well as a means to avert ICU transfers when appropriate, and to play an important role in nurse retention and improving nurse morale.

■ COMMENTARY

RRTs were introduced to provide a hospital-wide mechanism for bringing critical care expertise to patients who developed unexpected, potentially life-threatening clinical deterioration. Although initial studies showed a beneficial effect, subsequent studies failed to confirm these findings, leading to questions about the need for this resource. In these studies, "outcome" was typically evaluated by pre/post cardiac arrest and mortality data. Findings of this study suggest more subtle benefits that translate to all patients on the clinical unit where the call is placed. Nurses valued the ability to summon a highly experienced team, allowing the team to manage the unstable patient and thus redirect attention to other assigned patients they had neglected. Housestaff mentioned the same advantage, particularly on nights and weekends when faced with multiple admissions plus a highly unstable patient who required 1:1 attention. Administrators supported positive views, citing the RRT as a means to improve patient flow and nurse retention. There were also negative opinions that cited workload disruption, potential negative impact on housestaff education, and conflicts regarding how care should be provided. Findings of this study support the need to evaluate the impact of RRT in ways that extend beyond codes and mortality. ■

ABSTRACT & COMMENTARY

Threshold Vital Sign Abnormalities as Triggers for Rapid Response Activation

By David J. Pierson, MD, Editor

SYNOPSIS: This study shows that as hospitals adopt electronic workflows, automatic triggering of a rapid response system based solely on changes in vital signs could place a tremendous burden on the system.

SOURCE: Fagan K, et al. Vital sign abnormalities, rapid response, and adverse outcomes in hospitalized patients. *Am J Med Qual* 2012; Feb 28. [Epub ahead of print.]

Fagan and colleagues at Denver Health Medical Center examined electronic data collected on all adult patients who generated a medical surgical acute-care room charge during a recent 6-month period and remained on the ward for at least 24 hours. At the authors' institution, all vital signs are entered into an electronic database. Rapid-response activation (RRA) occurs whenever any of the following threshold vital sign abnormalities (TVSAs) is entered: respiratory rate < 8 or > 28 breaths/min, heart rate < 50 or > 120 beats/min, systolic blood pressure < 90 mmHg, diastolic blood pressure > 110 mmHg, oxygen saturation by pulse oximetry < 90% despite supplemental oxygen, or temperature > 39° C. The investigators examined data from patients for whom an RRA occurred, comparing them to non-RRA patients who had at least one TVSA and also to patients in whom neither of these occurred. Outcomes sought were in-hospital mortality, non-ICU cardiopulmonary arrest, and unexpected ICU transfer.

During the study period, there were 9074 adult patient discharges. A total of 2018 of these were non-index hospitalizations for those patients (only the first admission for a given patient during the study interval was used), and 728 admissions were for less than 24 hours. An additional 2485 admissions did not generate a

medical-surgical acute-care room charge, leaving 3843 hospitalizations (22,126 acute-care hospital days; 545,773 electronically documented vital signs) that constituted the study population. RRA occurred in 120 patients (3.1%), of whom 114 (95%) had a TVSA. An additional 1111 patients (29%) had at least one TVSA but no RRA, and 2612 patients (68%) had neither of these.

Patients for whom an RRA occurred were more likely to be female and have longer hospital lengths of stay than patients without an RRA. They were more likely to be transferred unexpectedly to the ICU (20.8% vs 7.3% for patients with TVSA but no RRA, and 1.7% for patients with neither; $P < 0.01$), and had a non-significant trend toward being more likely to experience a cardiopulmonary arrest during the hospitalization (1.7% vs 0.2% vs 0.3%, respectively; $P = 0.07$). Patients for whom an RRA occurred were more likely to have one or more of the sought-after adverse events than patients in either of the other groups. However, only 2.5% of TVSA recorded during the hospitalization triggered an RRA (120 RRAs for 4739 TVSAs), with a low systolic blood pressure and an elevated heart rate being the first and second most common TVSAs. Overall, one of every 20 recorded vital sign episodes contained a TSVA by the institution's threshold criteria, and about the same proportion of patient-days included at least two TVSAs in a single day.

Considering the entire patient population, the sensitivity of any TVSA for predicting an adverse event during hospitalization was 70%. However, the occurrence of any TVSA was the least specific of all characteristics examined (70%), with a positive predictive value (PPV) of only 9.2%. Four of the individual vital sign thresholds had PPVs < 10%, while an elevated respiratory rate had the highest PPV at 46%. The fact that only 120 RRAs were called, in the face of 4739 TVSAs that occurred during the same period, supports the assumption that the floor nurses exercised judgment and used additional clinical information in deciding whether the TVSA should trigger an RRA. The authors point out that if their institution were to automate the activation of their rapid response system based on their current thresholds, "we would immediately overwhelm our current resources to respond."

COMMENTARY

Although it is hard to argue with the concept that identifying, assessing, and intervening with non-ICU patients who experience acute clinical deterioration should improve both clinical and administrative outcomes, demonstration of this assumed benefit and the establishment of the right triggering mechanisms for rapid response have proven to be challenging. This study shows that electronically detecting vital sign changes by themselves is not the answer in terms of system efficiency and personnel costs. Ward patients whose vital signs were never recorded in the abnormal range that would qualify for a TVSA had an exceedingly low rate of adverse events. However, this study also demonstrates that if generally accepted vital sign abnormalities were used as the only criteria for triggering a rapid response system, the great majority of such calls would be false alarms and the logistics of responding to them all would be prohibitive. As hospitals become more reliant on electronic databases and automate more of their operations, the crucial importance of the bedside nurse's clinical skills in the operation of a rapid response system must not be left out of the equation. ■

ABSTRACT & COMMENTARY

Physicians' Own Beliefs on Goals of Care Strongly Influence Presentation of Comfort Care Option to Patient Surrogates

By Betty Tran, MD, MS

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Dr. Tran reports no financial relationships relevant to this field of study.

SYNOPSIS: During family discussions, physicians who believe more strongly that life support should be withdrawn are more likely to present the option of comfort care and describe its benefits.

SOURCE: Schenker Y, et al. Association between physicians' beliefs and the option of comfort care for critically ill patients. *Intensive Care Med* 2012;38:1607-1615.

This study conducted in five ICUs at two academic hospitals in San Francisco sought to describe how comfort care is presented to surrogates and if physicians' beliefs on whether life support should be withdrawn are associated with the option of comfort care being presented. One hundred and five physician-family conferences were identified through the ICU nurses, but only 72 were included in the final analysis after excluding conferences in which the physician and/or family declined participation. Each conference was audiotaped and subsequently transcribed verbatim for analysis. The study team coded whether comfort care was presented as an option by the physician, what risks and benefits of comfort care were presented, and what other treatment options (unlimited intensive care or limited intensive care) were offered. Demographic information was collected on patients, surrogates, and physicians. Physicians were also asked immediately after the conference to grade how strongly they believed life support should be withheld or withdrawn prior to the family conference on a scale of 0 (not strongly at all) to 10 (extremely strongly). Coders were blinded to all the participants' questionnaire responses.

The physician-family conferences occurred a mean of 10 days after ICU admission; on average, 60% of the ICU stay had elapsed at the time of the conference. Patients had a mean APACHE II score of 29 on the day of the conference, with the overall inpatient mortality rate being 72% (all due to withdrawal of life support). Comfort care was not presented as an option in 32 of 72 (44%) of the conferences; of these, 78% included only discussion of continued unlimited intensive care. In multivariate analyses, the only variable associated with the presentation of comfort care was the strength of the physicians' belief that life support should be withdrawn (odds ratio [OR] 1.38, 95% confidence interval [CI] 1.14-1.66; $P = 0.01$). In the 40 (56%) of 72 conferences in which comfort care was presented, there was an association between the strength of the physician's belief that life support should be withdrawn and the number of unique benefits of comfort care that were discussed (OR 1.12, 95% CI 1.01-1.25; $P = 0.04$).

COMMENTARY

In their clinical policy and consensus statements, the American College of Critical Care Medicine and American Thoracic Society support a shared decision-making model that includes surrogates, family members, and the health care team when the patient lacks full decision-making capacity. For example, for technical decisions regarding choice of antibiotics, surrogates overwhelmingly prefer physicians to make the final decision, but when it comes to life-sustaining treatment decisions, the extent to which the physician is involved is variable and can depend not only on surrogate preferences, but also the physician's own professional judgment and ethics.[1-3]

Thus, depending on the context, although the authors cite their findings as surprising, their results can be viewed as fairly predictable. Physicians may be more likely to present and promote comfort care as an option in cases where they believe no other medical treatment is available or for patients who have a dismal prognosis from a prior underlying condition, such as metastatic cancer or chronic lung disease. On the other hand, physicians may be less likely to present comfort care options in situations they perceive to be potentially reversible. Alternatively, if patients or surrogates have previously expressed their wishes to continue aggressive care, physicians may be more reluctant to raise the option of comfort care. In these situations, the omission of comfort care as an option is not necessarily an oversight on the part of the physician, but may be a conscientious decision based on the clinical scenario. As the authors duly note, the context surrounding the decision not to present comfort care as an option is an important area for future research.

Furthermore, although the authors rightly argue that failure to present comfort care as an option based purely on physicians' beliefs is problematic, the issue of how and when best to present this alternative to surrogates has yet to be answered. The notion that comfort care is "giving up" or "doing less" as opposed to "doing everything" will have to be quelled, and continual, open communication between physicians and surrogates will be necessary to foster trust in the families of critically ill patients and to understand their preferences in the decision-making process. These aims, in addition to improving clinician communication skills in discussing life-sustaining treatment decisions, will enhance the extent to which physicians can support and advise surrogates in the decision-making process. ■

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CME/CNE Questions

1. Which of the following is true about enteral nutrition in ICU patients?

a. A residual gastric volume of 250 mL is associated with a higher risk of aspiration pneumonia than a volume of 50 mL.
b. No study has ever shown a difference in mortality between gastric vs post-pyloric feeding.
c. Patients in shock should never receive enteral tube feedings.
d. Parenteral nutrition is always preferable to enteral nutrition, except in malnourished patients.
e. None of the above

2. Enteral feeding is preferable to parenteral feeding for critically ill patients in the ICU *except* in:

a. patients who have undergone major surgical procedures.
b. patients with severe sepsis or septic shock.
c. patients who are hypotensive.
d. patients with protein-calorie malnutrition on admission who are unable to receive or tolerate enteral nutrition.
e. All of the above

3. Interviews with nurses identified the following advantages of a rapid response team:

a. the ability to realign workload from one unstable patient to all assigned patients.
b. a means to ensure transfer of unstable patients off the unit to the ICU.
c. the ability to summon support when "something did not seem right."
d. a and c
e. All of the above

4. Administrators viewed the rapid response team as accomplishing all of the following *except*:

a. means to appropriately triage patients who need transfer to the ICU.
b. means to avert transfer to the ICU when not necessary.
c. having an important role in nurse retention.
d. having a positive influence on nurse morale.
e. negative impact for education of housestaff.

5. Which of the following statements is true about the use of vital sign data alone to automatically trigger a rapid response system?

a. It would save labor costs by taking the bedside nurse out of the equation.
b. It would reduce the total number of rapid-response activations.
c. Patients without vital sign abnormalities sufficient to trigger the system would still be at substantial risk for cardiopulmonary arrest.
d. An elevated respiratory rate has the lowest positive predictive value for the presence of a true medical emergency.
e. None of the above

6. Among adult medical-surgical patients on acute-care wards, approximately what proportion had a rapid response activation during their hospitalization?

a. 0.5%
b. 3%
c. 9%
d. 16%
e. 31%

7. In the study by Schenker et al, comfort care was presented as an option:

a. in physician-family conferences led by an attending physician only.
b. more often in physician-family conferences for patients who were more severely ill (i.e., higher APACHE II score).
c. more often in physician-family conferences involving elderly patients.
d. in roughly half of the physician-family conferences.
e. in the vast majority of physician-family conferences.

CME/CNE Objectives

Upon completion of this educational activity, participants should be able to:

- identify the particular clinical, legal, or scientific issues related to critical care;
- describe how those issues affect physicians, nurses, health care workers, hospitals, or the health care industry; and
- cite solutions to the problems associated with those issues.

[IN FUTURE ISSUES]

ICU organization and protocol use

PHARMACOLOGY WATCH

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

Zolpidem and Risk of Falls in Hospitalized Patients

In this issue: Zolpidem and risk of falls; AVR and anticoagulation; statins in cancer patients; and FDA actions.

Zolpidem and risk of falls

Zolpidem (Ambien) increases the risk of falls in inpatients, according to a new study from the Mayo Clinic. The records of hospitalized patients who were not in the intensive care unit were reviewed in this retrospective cohort study. The rate of falls was compared in those who were administered zolpidem vs those for whom it was prescribed but not administered. After controlling for age, gender, insomnia, delirium, dose of zolpidem, Charlson comorbidity index, Hendrich's fall risk score, length of stay, visual impairment, gait abnormality, dementia/cognitive impairment, and concomitantly administered meds, the rate of falls was four times higher in those administered zolpidem (n = 4962) vs those who were prescribed but did not receive zolpidem (adjusted odds ratio 4.37, 95% confidence interval [CI], 3.34-5.76; $P < 0.001$). The authors conclude that zolpidem was a strong, independent, and potentially modifiable risk factor for inpatient falls. The authors suggest that changing order sets so that zolpidem use is not encouraged could potentially reduce fall rates in hospitalized patients. They also suggest that there is limited evidence to recommend other hypnotic agents as safer alternatives (*J Hosp Med* published online Nov. 19, 2012. doi: 10.1002/jhm.1985). ■

Anticoagulation and AVR

Bioprosthetic valves are preferred to mechanical valves for aortic valve replacement (AVR) in the elderly because of lack of need for anticoagulation in the long-term, but short-term anticoagulation is required. The duration of anticoagulation after valve replacement has been unclear. Now, a new study from Denmark suggests 6 months is optimal. Using the Danish National Patient Registry, more than 4000 patients who had a bioprosthetic AVR between 1997 and 2009 were identified. Rates of stroke, thromboembolic events, cardiovascular death, and bleeding were assessed along with warfarin treatment duration. Rates of events per 100 person-years in patients not treated vs those treated with warfarin for 3 months were 7 vs 2.7 for stroke, 13 vs 4 for thromboembolic events, 11.7 vs 5.4 for bleeding, and 32 vs 3.8 for cardiovascular death. The rate of cardiovascular death was 6.5 vs 2.0, favoring warfarin from 90 days to 179 days. The authors conclude that stopping warfarin within 6 months of bioprosthetic AVR surgery was associated with increased cardiovascular death. These findings challenge the current guidelines that recommend 3 months of antithrombotic treatment after AVR surgery suggesting that "patients will gain from an additional 3 months of warfarin treatment in terms of reduced cardiovascular death without risking significant increase in bleeding events" (*JAMA* 2012;308:2118-2125). An accompanying editorial states that this study provides important information to help clinicians understand the benefits and risks of warfarin use after bioprosthetic aortic valve implantation, but it

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does not address the issue of adjunctive aspirin or the role of new novel oral anticoagulants (*JAMA* 2012;308:2147-2148). ■

Statins in patients with cancer

Patients taking a statin when diagnosed with cancer have a better prognosis than patients who are not taking statins, according to a new study. This study also used the Danish Registry in which all patients with a cancer diagnosis between 1995 and 2007 were evaluated. Roughly 19,000 patients were on a statin prior to diagnosis and 277,000 were not. Those taking statins were 15% less likely to die of any cause and 15% less likely to die of cancer (hazard ratio 0.85, 95% CI, 0.82-0.87 for cancer). The benefit was present regardless of statin dose or cancer type. The authors suggest that this is biologically plausible since cholesterol is needed for cell proliferation. They suggest "a need for trials of statins in patients with cancer" (*N Engl J Med* 2012;367:1792-1802). Previous studies have suggested reduced cancer mortality with statins in patients with prostate cancer and reduced recurrence rates in breast cancer patients. ■

FDA actions

The FDA has concluded a safety review of dabigatran (Pradaxa) and found that the drug is not associated with more serious bleeding events than warfarin. The review was done using insurance claims and data from the FDA's Sentinel Initiative. According to the FDA, the bleeding rates are consistent with the observations from large clinical trials, including RE-LY, which showed that bleeding rates in patients newly started on dabigatran were similar to rates associated with new use of warfarin. Therefore, the FDA has not changed its recommendation regarding dabigatran (FDA Drug Safety Communication, Nov. 2, 2012). The next day, *The New York Times* published an article reporting that dabigatran has been associated with more than 500 deaths in the United States since it was introduced. It also detailed several tragic cases of bleeding deaths associated with the drug. The article indicts the FDA stating "… the approval process was not sufficiently rigorous because it allowed a potentially dangerous drug to be sold without an option for reversing its effects." The article also mentions more than 100 lawsuits that have been filed in federal courts "…and thousands more are expected" (*The New York Times* Nov. 3, 2012:B1).

The FDA has expanded the approval of rivaroxaban (Xarelto) to include treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), both for acute treatment and prevention of recurrence. The drug is already approved for prevention of DVT and PE after knee and hip replacement surgery and for prevention of stroke in patients with non-valvular atrial fibrillation. It is the first oral drug approved to treat DVT and PE since warfarin was approved 60 years ago; but unlike warfarin, rivaroxaban can be used as monotherapy from diagnosis until treatment is discontinued. Approval was based on three studies of nearly 9500 patients with DVT or PE randomized to rivaroxaban, enoxaparin/vitamin K antagonist, or placebo. Rivaroxaban was equivalent to enoxaparin/vitamin K antagonist and superior to placebo for preventing recurrent DVT or PE.

The FDA has approved a new egg-free flu vaccine for adults. The vaccine is manufactured using cultured mammalian cells instead of fertilized chicken eggs. The manufacturer claims that the cell culture technology enables a rapid response to public health needs, such as a pandemic, since cell culture technology allows vaccines to be manufactured within weeks as opposed to traditional flu vaccines that depend on a large number of fertilized chicken eggs to grow the virus. Cell culture technology is used for several other vaccines including polio, rubella, and hepatitis A vaccines. Approval was based on a randomized, controlled clinical study of 7700 adults ages 18-49. The new vaccine was 83.8% effective in preventing influenza when compared to placebo. Injection site reactions are the most common side effects. The new vaccine is marketed as Flucelvax by Novartis.

The FDA has approved the first Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA). Tofacitinib, dosed orally twice a day, is approved for RA patients who have failed methotrexate. The drug will compete with the parenteral RA drugs adalimumab (Humira), etanercept (Enbrel), and infliximab (Remicade). Tofacitinib carries a boxed warning regarding the increased risk of opportunistic infections, tuberculosis, cancers, and lymphoma; increases in cholesterol and liver enzymes; and decreases in blood counts. Approval was based on seven clinical trials in which the drug showed improvements in clinical response and physical function compared to placebo in patients with moderate-to-severe RA. Tofacitinib will be marketed by Pfizer as Xeljanz. The cost is projected to be just over $2000 per month, similar to other non-methotrexate biologic treatment options. ■