

TABLE OF CONTENTS

| | |
|---|-----|
| • Acetaminophen: recommendations from the FDA Advisory Committee | 1 |
| • Recombinant human erythropoiesis-stimulating agents and mortality in cancer patients | 1-2 |
| • Hospital-acquired pneumonia: risks with acid suppression therapies | 2-3 |
| • Updated guidelines for nutrition support in the adult critically ill patient: SCCM and A.S.P.E.N. | 3-4 |
| • P&T Committee Formulary Action | 5 |

Acetaminophen—recommendations from the Food and Drug Administration Advisory Committee

On June 30, an Food and Drug Administration (FDA) advisory panel released recommendations regarding the use of acetaminophen, following an FDA report describing severe liver damage and death due to use of the pain reliever. The panel discussed both prescription and nonprescription dosage forms of acetaminophen and submitted the following to the FDA for consideration:

- A ban on prescription acetaminophen/opiate combinations (eg, Vicodin and Percocet) by a vote of 20-17.
- Lowering the maximum daily dose of acetaminophen, from the current 4 g/day limit by a vote of 21-16; however, a new maximum daily dose was not included in the recommendations.
- Lowering the maximum single dose of acetaminophen to 650 mg, from the current 1 g/dose limit by a vote of 24-13.
- Changing the 1 g/dose of acetaminophen to prescription only status by a vote of 26-11.

Which, if any, of the advisory panel recommendations the FDA will put into place is pending.

Recombinant human erythropoiesis-stimulating agents and mortality in cancer—results of a recent meta-analysis

Erythropoiesis-stimulating agents (ESAs) have been used for the treatment of anemia in patients with non-myeloid malignancies undergoing chemotherapy to

reduce the need for blood transfusions and potentially improve quality of life. However, labeling for available ESAs was revised in 2008 with the addition of a boxed warning for increased mortality and/or tumor progression associated with the use of these agents in patients with certain types of cancers. This warning was mandated by the Food and Drug Administration (FDA) and was based on the results of 8 clinical trials where an ESA was used in patients with cancer (metastatic or early breast cancer, lymphoid malignancy, head/neck cancer, non-small cell lung cancer, or non-myeloid malignancy) to achieve a target hemoglobin of 12 to 14 g/dL or greater. Results of these studies reported a decreased overall survival, a decreased progression-free survival or locoregional disease control, and/or a decreased relapse-free survival. Currently, ESAs are not indicated for use in the treatment of cancer patients receiving myelosuppressive therapy when a cure is anticipated, for anemia due to nonchemotherapy causes (eg, iron or folate deficiencies, hemolysis, or gastrointestinal bleeding), nor to improve quality of life. The most recent guidelines on the use of ESAs from the American Society of Clinical Oncology limit the use of ESAs for patients with chemotherapy-associated anemia when hemoglobin levels approach 10 g/dL or less, primarily due to the risk of thromboembolic events.

Meta-analyses of ESAs in cancer

Several meta-analyses have evaluated the effects of ESAs in the treatment of anemia in cancer patients (see Table). Although results regarding the effects of ESAs on survival have been mixed, the risk of thromboembolic events was generally seen to be increased in those analyses reporting this outcome.

| Table. Summary of meta-analyses of ESA use in cancer patients. | | | | |
|---|-------------------------------------|---|---|--|
| Reference | No. patients | ESA | Outcomes assessed and results (95% CI) | Summary |
| Bennett 2008 | 13,611 (51 phase 3 clinical trials) | Epoetin alfa Epoetin beta Darbepoetin | Survival (as mortality): HR 1.10 (1.01-1.20) VTE events: HR 1.57 (1.31-1.87) | Increased risk of mortality and VTE |
| Aapro 2008 | 2297 (12 RCTs) | Epoetin beta | Survival: HR 1.13 (0.87-1.46) Tumor progression: HR 0.85 (0.72-1.01) VTE events: 1.62 (1.13-2.31) | No effect on survival or tumor progression; increased risk of VTE |
| Aapro 2006 | 1413 (9 clinical trials) | Epoetin beta | Mortality: RR 0.97 (0.69-1.36) Tumor progression: RR 0.78 (0.62-0.99) | No increase in mortality; decreased risk of tumor progression |
| Bohlius 2006 | 9353 (57 RCTs) | Epoetin Darbepoetin | Survival: HR 1.09 (0.99-1.18) VTE events: 1.67 (1.35-2.06) | No change in survival; increased risk of VTE |
| Bohlius 2005 | 3287 (27 RCTs) | Epoetin alfa Epoetin beta | Red blood cell transfusions: RR 0.67 (0.62-0.73) VTE events: RR 1.58 (0.94-2.66) Survival: HR 0.81 (0.67-0.99 [adjusted]) | Reduced risk of transfusion; no increase in VTE; improved overall survival |

CI=confidence interval; ESA=erythropoiesis-stimulating agents; HR=hazard ratio; RCT=randomized controlled trial; RR=relative risk; VTE=venous thromboembolic event.

In the most recent investigation, Bohlius and colleagues conducted a meta-analysis using individual patient data from 53 randomized controlled trials involving 13,933 patients with cancer given an ESA (epoetin or darbepoetin). The primary outcome assessed was mortality, both during the active treatment period (from randomization until 28 days after treatment ended) and overall (from randomization until last follow-up). Breast and lung tumors were the most common type of cancer, followed by hematologic and gynecologic cancers; over half of the patients had advanced or metastatic disease. Baseline hemoglobin levels ranged from 10.6 to 10.8 g/dL.

After treatment with an ESA, the median hemoglobin ranged from ≥ 15 g/dL in 2 studies, ≥ 14 g/dL in 4 studies, and < 14 g/dL in the remaining trials. For overall mortality, the hazard ratio (HR) was 1.06 (95% confidence interval [CI], 1.00-1.12; $p=0.046$) for ESAs versus controls (no use of an ESA). The HR for mortality for all patients with cancer during active treatment was 1.17 (95% CI, 1.06-1.30; $p=0.003$), for ESA versus controls. However, when mortality outcomes were stratified by study characteristics—type of treatment, planned ESA duration, planned ESA frequency, target hemoglobin concentration, placebo-controlled, mortality as primary or secondary endpoint, or last year of randomization, only the planned frequency of ESA administration showed a significant effect modification. Once weekly ESA treatment was associated with a higher rate of mortality (HR 1.4 [1.18-1.66]) compared to doses given 3 times or more per week or less than every second week. Stratification by patient characteristics (ie, baseline hemoglobin and hematocrit, ECOG [Eastern Cooperative Oncology Group] performance status, history of thromboembolism, tumor type, and tumor state) found an increase in risk of mortality only for a low baseline hematocrit ($p=0.01$). Number needed to harm

(NNH) was also calculated, using 3 different underlying survival probabilities for cancer. For a 95% underlying survival probability, the NNH was 121 (95% CI, 69-343). For an 80% probability, the NNH was 34 (95% CI, 19-94), and for a 70% survival probability, the NNH was 24 (95% CI, 14-67), indicating that ESA use may cause more harm among patients who are less likely to survive the cancer. The authors concluded that use of ESAs in patients with cancer may increase the risk of mortality by 17% among those receiving chemotherapy; for all patients evaluated, a 6% increase in mortality risk was seen.

Summary

Although data are conflicting, results of 8 clinical trials and 2 meta-analyses indicate an increased risk in mortality, tumor progression, and/or thromboembolic events among patients with cancer. Labeling for ESAs and guidelines for their use in patients with cancer have been revised to reflect these findings. The exact mechanism of increased risk with ESAs in cancer patients has not been fully explained. However, one recent study found a decrease in locoregional progression-free survival in patients given ESAs in the presence of head and neck cancers positive for erythropoietin receptor expression.

Hospital-acquired pneumonia—risks with acid suppression therapies

Hospital-acquired pneumonia (HAP) is a serious complication of hospitalization. According to the most recent guidelines from the Infectious Disease Society of America and the American Thoracic Society, HAP is associated with an increase in hospital stay of 7 to 9 days, an additional cost of \$40,000 per patient, and an estimated

33 to 50% mortality. Several risk factors for HAP have been identified, including prior antimicrobial therapy, 5 or more days of hospitalization, antimicrobial resistance, and immunosuppressive disease or therapy. In addition, recent studies have suggested that use of acid suppressive therapies may increase the risk of HAP. Acid suppression therapy is widely used in the inpatient setting. Over 50% of hospitalized patients have been reported to be prescribed an acid suppressant therapy—primarily histamine-2 (H2) receptor antagonists (62%). However, as many as 65% of those patients prescribed did not have an indication for use. And, among those patients continued on acid suppression therapy at discharge, use was considered unnecessary in 67%. To assess the risk of acid suppression therapy on the development of HAP, Herzig and colleagues conducted a pharmacoepidemiologic cohort study in hospitalized patients.

The cohort consisted of patients admitted to a large, urban academic medical center over a 3-year period, who had length of stay of 3 or more days, and who were not admitted to an intensive care unit. Acid suppression therapy was defined as either H2 receptor antagonists or proton pump inhibitors. The primary outcome assessed was the occurrence of any HAP; secondary outcomes were the occurrence of either of 2 subcategories of HAP—aspiration pneumonia and nonaspiration pneumonia. Of 136,529 patients admitted to the hospital during the study period, 63,878 met the inclusion criteria; 52% were given acid suppressive therapy (83% as proton pump inhibitors and 23% as H2 receptor antagonists). Among those given acid suppression therapy, HAP occurred in 4.9%, as compared to 2.0% in those patients not given acid suppression therapy. The unadjusted odds ratio (OR) was calculated as 2.6 (95% confidence interval [CI], 2.3-2.8), indicating a significant increase in the risk of HAP when acid suppressive therapy was used. This risk remained significant (OR 1.3 [95% CI, 1.1-1.4]) after the outcomes were adjusted for covariates such as age, sex, race, type of admission, length of hospital stay, season, gastrointestinal bleeding, and certain medication use. Exposure to acid suppressive therapy also increased the risk of secondary outcomes of aspiration and nonaspiration pneumonia compared to no use. The risk for aspiration pneumonia was slightly higher (OR 3.1 vs. OR 2.4) compared with nonaspiration pneumonia. Both secondary outcomes remained significant after adjustment for covariates. Risk of HAP for specific acid suppressive therapy was also assessed. For patients given proton pump inhibitors, an OR for HAP of 2.8 (95% CI, 2.5-3.1) was found; this remained significant after adjustment for covariates. However, although the unadjusted OR for H2 receptor antagonists indicated an increased risk of HAP (1.6 [95% CI, 1.3-1.9]), when adjusted for covariates, no significant difference in risk of HAP was seen with H2 receptor antagonists compared with no use (1.2 [95% CI, 0.98-1.4]). The authors did note that the study was

not powered for this subgroup analysis.

Summary

Results of studies suggest that unnecessary use of acid suppressive therapies may increase the risk of HAP in hospitalized patients, potentially as much as 30%. Accepted uses of acid suppressive therapy include peptic ulcer disease, esophagitis and gastritis, gastroesophageal reflux, gastrointestinal bleeding, and stress ulcer prophylaxis. For stress ulcer prophylaxis, practice management guidelines from the Eastern Association for the Surgery of Trauma (EAST) recommend prophylaxis for select patients, such as those on mechanical ventilation, or with coagulopathies, multiple trauma, major burn injuries, or sepsis. Institutions should review use of acid suppressive therapies initiated at patient admission to assure appropriate use of these agents and to avoid increasing the risk of HAP.

Updated guidelines for the nutrition support in the adult critically ill patient: SCCM and A.S.P.E.N.

Introduction

It is well documented and understood in the hospital setting, particularly the critical care arena, the importance and necessity of nutrition support. Traditionally, nutrition support was considered adjunctive care. However, the new goals of nutrition support are therapeutic and more focused, attempting to attenuate the metabolic pathways associated with stress response, prevent oxidative cellular injury, and improve the immune response. Delivering early nutrition, particularly enteral nutrition (EN), is seen as a therapeutic strategy to attain these new goals, as well as to reduce disease severity and complications, decrease length of stay in the intensive care unit (ICU), and favorably impact patient outcome. In May 2009, the Society of Critical Care Medicine (SCCM) and American Society of Parenteral and Enteral Nutrition (A.S.P.E.N.) collaborated and released guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient. This summary provides an overview of these guidelines, with a focus on when and how to initiate EN and parenteral nutrition (PN). The guidelines contain information for special patient populations including patients with pulmonary conditions, renal failure, hepatic failure, acute pancreatitis, obesity, and those at the end of life.

Guideline summary

Assessment and initiation of nutrition

Evaluation of weight loss, disease severity, comorbid conditions, gastrointestinal (GI) tract function, and preadmission nutrient intake is recommended for assessment of nutrition status in ICU patients in place of traditional assessment tools (ie, markers of protein such as albumin, prealbumin, and transferrin). These traditional markers have been shown to be a reflection of the acute phase response and do not accurately represent nutrition status in the ICU. Enteral nutrition is recommended when nutrition support is initiated in ICU patients and is the preferred route over PN.

Enteral nutrition supports the functional and structural integrity of the gut and has been shown in prospective randomized control trials to have beneficial effects when compared to PN in critical illness including trauma, burns, head injury, major surgery, and acute pancreatitis. The most consistent effect from EN is reduction of infectious morbidity, especially for pneumonia, central line infections, and abdominal infections in trauma patients. Other significant benefits of EN include reduction in length of ICU stay, reduced cost of nutrition therapy, and return of cognitive function (for head trauma patients). The use of enteral feeding protocols has been shown to increase the overall percentages of goal calories provided and should be implemented.

It is recommended that EN be started within 24 to 48 hours following admission to the ICU once fluid resuscitation and hemodynamic stability have been reached. Feedings can be advanced over the following 48 to 72 hours to goal. If early EN is not feasible or available during the first 7 days following admission to the ICU in previously adequately nourished patients, no nutrition support should be provided. If EN is still unfeasible after the first 7 days, PN can then be initiated.

However, if protein-calorie malnutrition (>10 to 15% recent weight loss or weight <90% of ideal body weight) is present at admission, and EN is not available, PN should be initiated as soon as possible. Parenteral nutrition can also be initiated in patients scheduled to undergo major upper GI surgery, if EN is not available. The following table summarizes the indications for PN.

| Table. Indications for PN |
|---|
| <ul style="list-style-type: none"> • Well nourished prior to admission, >7 days ICU, and EN unfeasible. • Malnourished at ICU admission and EN unfeasible. • Surgical necessity (major upper GI surgery) with EN unfeasible: <ul style="list-style-type: none"> ○ 5-7 days preoperatively and continued postoperative for malnourished patients. ○ Do not initiate PN immediately postoperatively (due to increase risk of complications); if needed, hold initiation until postoperative day 5 to 7. ○ Initiate PN only if expected duration is ≥7 days; shorter durations do not provide benefits and may increase risks. |

EN=enteral nutrition; GI=gastrointestinal; ICU=intensive care unit; PN=parenteral nutrition.

Dosing of nutrition

The target goal of EN (defined by energy requirements) should be determined and clearly identified at the time of initiation of nutrition support. Predictive equations may not be as accurate as indirect calorimetry, especially in obese patients. For EN, providing >50 to 65% of goal calories is recommended for clinical benefits for critically ill patients (eg, burn and bone marrow transplant patients, head injury patients). If energy requirements (100%) are not met after the first 7 to 10 days, supplemental PN can be considered. Parenteral nutrition is not recommended earlier in patients

already receiving EN since it may increase cost, with no additional benefit.

If PN is to be used as indicated above, steps to maximize the safety and efficacy of PN should be initiated. Underfeeding should occur initially in critically ill patients and is defined as 80% of energy requirements. This strategy has been shown to reduce the incidence of hyperglycemia, infections, ICU and hospital length of stay, and duration of mechanical ventilation. After clinical stabilization of the patient, increases toward 100% of energy requirements may occur. Other strategies to maximize safety and efficacy of PN include: protocol placement for strict control of serum glucose (potentially in range of 110 to 150 mg/dL [though controversial]), glutamine supplementation (shown to decrease incidence of infections and mortality), and termination of PN when EN reaches >60% of target energy requirements. Overall, EN is preferred unless criteria for PN are met and steps are taken to ensure the safe and efficacious delivery of PN.

Enteral formulations

In selection of appropriate enteral formulations for the critically ill patient, the clinician must determine first if a patient is a candidate for immune modulating enteral nutrition (IMEN). Immune modulating enteral nutrition is supplemented with arginine, glutamine, nucleic acid, omega-3 fatty acids, or antioxidants. Those patients that have been shown to have significant benefit from IMEN include:

- Those undergoing major elective GI surgery.
- Trauma patients (abdominal trauma score >20).
- Those with burns (>30% total body surface area).
- Patients with head and neck cancer.
- Critically ill patients on mechanical ventilation who are not severely septic.

No data support the use of IMEN in other subgroups. Patients with acute respiratory distress syndrome (ARDS) and severe acute lung injury (ALI) should be placed on enteral formulations with an anti-inflammatory lipid profile (ie, fortified with omega-3 fish oils or borage oil) and antioxidants. The addition of glutamine to enteral formulas has shown benefit compared to formulas in which glutamine was not already present. The additional of trace elements (zinc, copper, and selenium) has also been shown to be beneficial. Therefore, the addition of glutamine, antioxidant vitamins, and trace elements to enteral formulas (if not already fortified) should be considered for critically ill patients.

Conclusions

The new SCCM and A.S.P.E.N. guidelines give practitioners evidence-based recommendations for providing nutrition to critically ill patients. The guidelines emphasize the provision of nutrition therapy versus nutrition support. Enteral nutrition is the preferred route

of feeding while no nutrition is recommended over PN for patients who are well nourished and cannot eat for 7 days or less. When PN is used, it should be done carefully to maximize efficacy and minimize complications.

P&T Committee Formulary Action

Additions

- None

Line extensions

- Tetracaine 0.5% Ophthalmic, 5mL

Deletions

- None

Authors: Scott Benken, PharmD; Joan Stachnik, PharmD; Jamie Paek, PharmD

Editor:

Joan Stachnik, PharmD, BCPS