Use of PPIs in noncritically ill patients—risk of gastrointestinal bleeding

Approximately 75% to 100% of critically ill patients have evidence of developing endoscopic gastrointestinal (GI) lesions. Critically ill patients are at risk for GI lesions after exposure to stressful or traumatic events—a result of a series of pathophysiologic events that increase the risk of GI bleeding. Ischemia and hypoperfusion can break down the mucosal protection barrier and can be accompanied by gastric hypersecretion and alterations in blood flow, all of which contribute to GI ulceration or lesions. Therefore, stress ulcer prophylaxis is recommended for patients who are critically ill. The American Society of Health-System Pharmacists, the EAST Trauma Group, and the International Surviving Sepsis Campaign guidelines recommend the use of antisecretory agents, either proton pump inhibitors (PPIs) or histamine (H₂) antagonists, for patients who are critically ill, including those patients with coagulopathy, mechanical ventilation, traumatic brain injury, major burn injuries, and/or sepsis, with no apparent preference for one antisecretory agent over another. The duration of stress ulcer prophylaxis should be individualized, with careful monitoring of patient risk factors.

Although use of stress ulcer prophylaxis is well-supported in critically ill patients, for noncritical patients, there is concern regarding the overuse of antisecretory agents, primarily the PPIs, for prophylaxis. In a retrospective study, Pham reported that the use of antisecretory agents among patients increased from 29% prior to admission to 71% after admission to a noncritical care general medicine service, with only a small percentage of patients meeting criteria for antisecretory use. Parente et al found that of 374 patients given acid suppression therapy in the hospital, 68% of orders were not appropriate. Of those given antisecretory agents unnecessarily, over half were discharged from the hospital on the agents, and many were continued on acid suppression therapy for more than 3 months after discharge. This inappropriate use of PPIs has been associated with potentially detrimental effects. Gulmez et al conducted a case control study on the use of PPIs and the risk of community acquired pneumonia (CAP) and found an association with increase risk of CAP in patients with current PPI use (odds ratio [OR] 1.5, 95% confidence interval [CI] 1.3-1.7). Eom and colleagues reported similar findings in a meta-analysis of 31 studies. Use of PPIs may also increase the risk of *Clostridium difficile* infections, possibly a result of suppression of gastric acid and an increase in GI bacterial growth. Linsky et al found a 42% increase in risk of *C difficile* with the use of daily PPIs (hazard ratio [HR] 1.42, 95% CI 1.11-1.82) compared with patients not receiving any antisecretory therapy. Another study evaluating the effects of PPI use and the efficacy of alendronate in fracture prevention found no risk reduction for hip fracture among patients on concurrent PPIs, suggesting an attenuation of the protective effects of alendronate. The mechanism of these effects are unknown but a decreased absorption of vitamin B12 and calcium has been suggested. Most recently, the Food and Drug Administration (FDA) has issued a safety announcement about the risk of hypomagnesemia with the chronic use of PPIs, based on published reports and data from the FDA's Adverse Event Reporting System. Because of the apparent overuse of PPIs in noncritical patients and the potential risks of unnecessary use of PPIs, studies have been conducted to investigate the true risk of GI bleeding among noncritical patients.

Risk of gastrointestinal bleeding in noncritical patients

In one of the largest trials, Herzig et al evaluated the risk of GI bleeding in hospitalized, noncritically ill patients. The authors examined medical records of 79,278 patients admitted to the hospital for more than 3 days and without an admitting diagnosis of GI bleeding. The primary outcome was the incidence of GI bleeding at 24 hours or more after hospital admission. Clinically significant nosocomial GI
bleeding was the secondary outcome.

During hospital stay, 59% of patients were exposed to antisecretory agents—81% were given PPIs and 29% received H$_2$ antagonists. A total of 1776 patients were identified as potentially having nosocomial GI bleeding. Of these, 224 (0.29%) met the criteria for nosocomial GI bleeding, and 176 (0.22%) were considered to have clinically significant bleeding. When those who received an antisecretory agent were compared to those untreated, the incidence of nosocomial bleeding was higher in the exposed group compared to the unexposed group (0.33% vs 0.22%; OR 1.5, 95% CI 1.15-2.03). The rate of clinically significant GI bleeding was also higher with treatment (0.26% vs 0.18%; OR 1.44, 95% CI 1.05-1.98). However, after adjustment for covariates and propensity scores, use of antisecretory agents was associated with a reduced risk of nosocomial GI bleeding (OR 0.63, 95% CI 0.42-0.93) and for clinically significant bleeding (OR 0.58, 95% CI 0.37-0.91) compared with no use. The calculated number needed to treat (NNT) was 770 for nosocomial GI bleeding and 834 for clinically significant GI bleeding. The authors concluded that, although antisecretory agents reduced the risk of nosocomial GI bleeding, the rate of nosocomial bleeding overall was low, supporting the recommendation against routine use of antisecretory agents in noncritically ill patients.

Qadeer et al conducted a similar trial to assess the incidence and risks of nosocomial GI bleeding. Of 17,707 patients admitted to the hospital during a 3-year period, 73 (0.43%) met the criteria for nosocomial GI bleeding. Use of PPIs prior to the bleeding episode did not decrease the risk of bleeding (OR 1.1, 95% CI 0.4-2.9). The biggest risk factor for nosocomial GI bleeding was the use of anticoagulants or antiplatelet agents. Similar to Herzig, the authors concluded that the risk of nosocomial GI bleeding in noncritically ill patients was low and routine stress ulcer prophylaxis was not needed for most patients.

Finally, Heidelbaugh et al conducted another retrospective review on the use and cost of stress ulcer prophylaxis in noncritical patients. During a 4-month period, the authors identified 391 patients (22% of admissions) as receiving inappropriate stress ulcer prophylaxis (primarily PPIs). Half of these patients were discharged home with an antisecretory agent. The cost of inappropriate stress ulcer prophylaxis for the 4-month period was $11,024. Combined with outpatient costs for antisecretory agents prescribed at hospital discharge, inappropriate use of stress ulcer prophylaxis cost an estimated $111,791 annually for the institution in the study.

**Summary**

Evidence has shown that the risk of nosocomial GI bleeding is low for noncritically ill patients, making the use of antisecretory agents for stress ulcer prophylaxis questionable in this patient group. Studies have suggested an increased risk of *Clostridium difficile* and CAP, and a reduced efficacy of bisphosphonates with these agents. Inappropriate use of antisecretory agents for stress ulcer prophylaxis may also be associated with a significant cost for health care institutions. Therefore, the use of antisecretory agents for stress ulcer prophylaxis in noncritical patients is not always necessary. The use of stress ulcer prophylaxis in noncritical patients should be limited to those with definite risk factors for nosocomial GI bleeding.

**Update on use of vitamin D—2011 Guidelines from the Endocrine Society**

Vitamin D deficiency is a growing health concern, with a significant portion of the US population having insufficient or deficient levels of vitamin D. There are a number of causes of vitamin D deficiency, with the major cause being inadequate exposure to the sun. Lack of vitamin D can result in decreases in the gastrointestinal absorption of both calcium and phosphorus from the diet, potentially causing release of bone calcium and possible decreases in bone mineral density. Severe vitamin D deficiency can manifest with muscle weakness or myopathy, muscle pain, and gait disturbances. Few foods are naturally high in vitamin D content, and some (eg, milk, yogurt, breakfast cereals) are fortified to provide up to 100 IU of vitamin D$_3$ per serving. However, vitamin D deficiency may occur despite use of fortified foods and vitamin D supplementation may be needed. In 2011, the Endocrine Society released updated guidelines on the evaluation and treatment of vitamin D deficiency.

**Screening for vitamin D deficiency**

The Endocrine Society recommends screening for vitamin D deficiency only for those individuals at risk, using circulating serum levels of 25-hydroxyvitamin D [25(OH) D]. Vitamin D deficiency is defined by the guidelines as a (25(OH)D) level less than 20 ng/mL; insufficiency as a level between 21 and 29 ng/mL; and sufficient vitamin D as 30 to 100 mg/mL. Those considered at risk for vitamin D deficiency include individuals with rickets, osteomalacia, or osteoporosis; renal or hepatic failure; certain malabsorption syndromes; hyperparathyroidism; African American or Hispanic individuals; older adults with a history of falls or nontraumatic fractures; and those with granuloma-forming disorders. Certain medications may also prompt screening for vitamin D deficiency, including antiseizure and human immunodeficiency virus infection medications, corticosteroids, antifungal agents, and cholestyramine.

**Vitamin D intake for individuals at risk**

The guidelines provide recommendations on vitamin D intake for those considered at risk for vitamin D deficiency. The recommendations are given as a minimum vitamin D intake to maintain bone and muscle health and a range needed for achieve a vitamin D level of at least 30 ng/mL. For example, adults require at least 600 IU (800 IU for >70 years) of vitamin D per day, with at least 1500 to 2000 IU needed to increase serum vitamin D levels above 30
ng/mL. Values are also provided for infants, children, adolescents, and pregnant/lactating women.

**Prevention and treatment of vitamin D deficiency**

Vitamin D$_2$ or vitamin D$_3$ are recommended to prevent as well as treat vitamin D deficiency, given either weekly or daily. The table below summarizes the guideline recommendations for vitamin D therapy for children, adolescents, and adults.

<table>
<thead>
<tr>
<th>Age</th>
<th>Treatment*</th>
<th>Duration</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 1 y</td>
<td>2000 IU/d</td>
<td>50,000 IU/wk</td>
<td>6 wks</td>
</tr>
<tr>
<td>1 to 18 y</td>
<td>2000 IU/d</td>
<td>50,000 IU/wk</td>
<td>6 wks</td>
</tr>
<tr>
<td>Adults</td>
<td>6000 IU/d</td>
<td>50,000 IU/wk</td>
<td>8 wks</td>
</tr>
<tr>
<td>For adults with obesity, malabsorption or medication affecting vitamin D: A higher dose is recommended (2 to 3x higher; at least 6000 to 10,000 IU/d)</td>
<td>At least 3000 to 6000 IU/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alternative for rapid correction in nursing home residents: Vitamin D$_3$ 50,000 IU 3x/wk</td>
<td>4 wks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Dose given either daily or weekly.

Vitamin D can be given as needed for individuals with primary hyperparathyroidism and vitamin D deficiency, with monitoring of serum calcium levels. The guidelines recommend against the use of vitamin D for non-calcemic benefits, with the exception of fall prevention.

**Summary**

Vitamin D deficiency is common among the US population, in part due to lifestyle changes that limit outdoor activities and exposure to direct sunlight. If severe, vitamin D deficiency can result in muscle weakness and increased risk of fracture in elderly individuals. These updated guidelines provide recommendations for prevention and treatment of vitamin D deficiency, along with a summary of the available evidence for the recommendation.

**Intravenous acetaminophen—use and efficacy in pediatric patients**

In 1998, the World Health Organization developed guidelines for the management of pain in pediatric patients with cancer. The basis of the approach is a stepwise analgesic “ladder”, in which each child receives the simplest treatment regimen to adequately manage their individual pain severity. In practice, these principles have been successfully applied to any child with pain. In 2004, the American Society of Anesthesiologists released practice guidelines suggesting that in the perioperative setting, use of non-steroidal anti-inflammatory agents (NSAIDs) or acetaminophen has a dose-sparing effect for systemic opioids in the management of acute pain. However, a barrier to this multimodal method has been the lack of available parenteral pain medications. Traditionally, the intravenous options for management of pain and/or fever have generally been limited to NSAIDs and opioids.

As a class, NSAIDs are known to possess analgesic, anti-inflammatory, and antipyretic effects. Ibuprofen (Caldolor) and ketorolac tromethamine (Toradol) are the only 2 parenteral NSAIDs approved for treatment of pain and/or fever in the United States. Ketorolac is only labeled for use in adult patients, although it has been studied in pediatric patients for treatment of postoperative pain with favorable safety and efficacy. The recommended duration of ketorolac use is restricted to a maximum of 5 days due to risk of gastrointestinal bleeding and irritation. Intravenous ibuprofen (Caldolor) was approved in 2009 for the management of pain and fever in adult patients. This product differs from ibuprofen lysine (Neoprofen), which, along with intravenous indomethacin, is only approved for closure of clinically significant patent ductus arteriosus and not as an analgesic. Both intravenous ketorolac and ibuprofen carry the NSAID class boxed warnings for cardiovascular thrombotic events and gastrointestinal adverse effects, as well as precautions for hypertension, renal toxicity, and fluid retention.

A wide range of natural and synthetic parenteral opioid analgesics are approved for use in pediatric patients. While these agents are effective, opioid use is generally reserved for episodes of moderate or severe acute pain because of the risk of associated adverse events, such as respiratory depression, constipation, altered mental status, sedation, and seizures.

Acetaminophen is a nonopioid, centrally-acting antipyretic and analgesic agent. Its unique mechanism of action allows its use as an alternative agent in the multimodal therapeutic approach to pain. The safety profile of acetaminophen is also unique from other analgesic agents. Acetaminophen does not increase the risk of bleeding, adversely affect renal function, or depress the respiratory drive, which may be advantageous perioperatively. Ofirmev (Cadence Pharmaceuticals) is the first intravenous acetaminophen product approved by the Food and Drug Administration. Ofirmev is indicated for the management of mild to moderate pain, management of moderate to severe pain with adjunctive opioid analgesics, and reduction of fever in patients ≥2 years of age.

**Pharmacokinetics of intravenous acetaminophen**

The peak blood concentration of intravenous acetaminophen occurs immediately following the end of the 15-minute infusion and is 70% higher versus an oral dose of acetaminophen. There is, however, no difference in overall exposure to acetaminophen between the 2 dosage forms, and no dose adjustment is needed when transitioning from intravenous to oral or from oral to intravenous routes.

Although not indicated for use in pediatric patients <2 years of age, data from pharmacokinetic studies are available for
this population. Exposure of children and adolescents to acetaminophen is similar to that of adults, but is higher in neonates and infants. Available information suggests a dose reduction of 33% in infants 1 month to <2 years of age and a 50% reduction for neonates up to 28 days of age, with a dosing interval of at least 6 hours.

Acetaminophen is primarily metabolized by the liver via the cytochrome P450 (CYP) enzyme pathway (primarily CYP2E1). Substances that induce CYP2E1 may increase the hepatotoxic effect of acetaminophen.

**Recommended dosing**

Dosing of intravenous acetaminophen is dependent on patient age and weight as described in Table 1.

<table>
<thead>
<tr>
<th>Age and weight</th>
<th>Dose</th>
<th>Maximum dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥13 y ≥50 kg</td>
<td>650 mg every 4 h 1000 mg every 6 h</td>
<td>1000 mg/dose 4000 mg/24 h</td>
</tr>
<tr>
<td>≥13 y &lt;50 kg</td>
<td>12.5 mg/kg every 4 h 15 mg/kg every 6 h</td>
<td>15 mg/kg/dose (up to 750 mg/dose) 75 mg/kg/24 h (up to 3750 mg/24 h)</td>
</tr>
<tr>
<td>≥2 to 12 y</td>
<td>12.5 mg/kg every 4 h 15 mg/kg every 6 h</td>
<td>75 mg/kg/24 h</td>
</tr>
</tbody>
</table>

**Administration and Stability**

Intravenous acetaminophen is commercially available in a 100-mL glass vial with 1000 mg acetaminophen (10 mg/mL). Doses should be infused over 15 minutes. If the calculated dose equals 1000 mg, the drug may be administered directly from the original vial using a vented intravenous set. However, for doses less than 1000 mg, the appropriate volume must be drawn out of the vial into a syringe for administration. According to the package insert, once the vacuum seal of the vial is compromised, the drug should be used within 6 hours. However, according to data on file with the manufacturer (Cadence Pharmaceuticals), the chemical stability of the medication remaining in the vial has been tested under conditions where the vial stopper was removed for up to 60 minutes and was found to be stable for 24 hours following stopper removal.

**Efficacy**

In the United States, data on efficacy of this new formulation for the management of pain and fever are largely derived from adult data. Internationally, there have been several studies on intravenous acetaminophen (known as paracetamol outside of the United States), as well as the prodrug propacetamol, in pediatric patients.

**Analgesic efficacy**

In 2006, Alhashemi and colleagues randomized 80 children (3 to 16 years) undergoing tonsillectomy to receive either intravenous acetaminophen 15 mg/kg or intramuscular meperidine 1 mg/kg intraoperatively after induction of anesthesia. All patients received a single dose of fentanyl during induction. No additional opioids or NSAIDs were given. Rescue analgesia with morphine was available during recovery. Postoperatively, patients were evaluated for objective pain scores, sedation scores, and time to recovery room discharge. Acetaminophen was found to be as efficacious as meperidine, with pain scores of 3.1 and 2.1, respectively (p=0.147). Also, acetaminophen was associated with less sedation 5 minutes after arrival to the recovery room (p=0.031) and a significantly shorter time to recovery room discharge (15 min vs. 25 min, p=0.005). More patients given acetaminophen required a single dose of rescue morphine compared with those given meperidine (p<0.001).

In 2008, Capici and colleagues compared intravenous and rectal acetaminophen for management of pain following adenotonsillectomy. Fifty children, aged 2 to 5 years, were randomized to receive either 15 mg/kg intravenous acetaminophen or 40 mg/kg rectal acetaminophen following induction of anesthesia. Postoperative pain and severity were assessed at regular intervals in the recovery room and on the floor. Rescue analgesia was available in the recovery room (fentanyl) and on the floor (rectal acetaminophen). The primary outcome was time to first rescue analgesia. Postoperative pain scores were also assessed. Although pain scores were similar between the 2 groups, the time to first rescue dose was longer in the children receiving rectal compared to intravenous acetaminophen (median 10 h vs. 7.6 h, p=0.01). The rate of adverse events was not discussed.

Hong and colleagues published 2 studies evaluating intravenous acetaminophen as an adjunct agent in the management of pain. In the first double-blind study, 63 children (6 to 24 months) scheduled for ureteroneocystostomy were randomized to receive postoperative analgesia with fentanyl with or without the addition of intravenous acetaminophen. The authors’ objective was to determine the fentanyl-sparing effects of intravenous acetaminophen. At the end of surgery, children received either a bolus dose of fentanyl plus intravenous acetaminophen 15 mg/kg or the same dose of fentanyl with saline placebo. Postoperatively, fentanyl/acetaminophen or fentanyl alone were given via intravenous patient- or nurse-controlled analgesia. The primary outcome was the postoperative total dose of fentanyl. Postoperative pain scores and adverse events were secondary outcomes. Total postoperative fentanyl doses were significantly lower in the fentanyl/acetaminophen group compared to the fentanyl only group on postoperative days 1 and 2 (p=0.021 and 0.042, respectively). No difference was seen on postoperative day 3. Postoperative pain scores were similar between both groups. Adverse events of vomiting (56% vs. 16%; p=0.011) and sedation (46.9% vs. 9.7%; p=0.019) were more common with fentanyl than with fentanyl/acetaminophen.

The authors also evaluated the opioid-sparing effect of...
intravenous acetaminophen when used in combination with intravenous ketorolac. A total of 55 children, aged 1 to 5 years, undergoing outpatient inguinal hernia repair were randomly assigned to treatment with either intravenous acetaminophen (20 mg/kg) plus ketorolac (1 mg/kg) or saline placebo at induction of anesthesia. All patients were given fentanyl 1 mcg/kg at the time of incision. The primary outcome was the need for and total rescue dose of fentanyl; adverse events were the secondary outcome. Patients in the treatment group experienced significantly better pain control than placebo, requiring fewer rescue doses of fentanyl (p<0.001) and reduced overall postoperative fentanyl use compared to the control group (0.54 mcg/kg vs. 1.37 mcg/kg; p=0.001). The placebo group also had significantly higher rates of sedation (55.6% vs. 25.0%) and vomiting (33.3% vs. 10.7%) compared with the acetaminophen/ketorolac group.

**Antipyretic efficacy**

In 2007, Duhamel and colleagues evaluated the efficacy of intravenous acetaminophen for the treatment of fever. Sixty-seven children (1 month to 12 years), with baseline rectal temperatures ranging from 38.5°C to 41°C, received a single dose of 15 mg/kg intravenous acetaminophen (paracetamol) or 30 mg/kg intravenous propacetamol. Reduction in temperature to ≤38°C was achieved in 79% of patients given acetaminophen compared to 75% with propacetamol. The median body temperature reduction in the intravenous acetaminophen group was 1.9°C compared to a reduction of 2.05°C in the propacetamol group. There was also a significantly higher incidence of infusion-site reactions with propacetamol compared to acetaminophen (28.1% vs. 5.7%, p=0.0134).

**Safety**

Prior to approval, pharmacokinetic and safety data were obtained from 355 pediatric patients treated with intravenous acetaminophen. In clinical studies, the most common adverse reactions (≥5%) differed between adult and pediatric patients. Adult patients most commonly experienced nausea, vomiting, headache, and insomnia. In addition to nausea and vomiting, pediatric patients more commonly experienced constipation, pruritus, agitation, and atelectasis compared to adults.

There is also a known safety concern with acetaminophen regarding the risk of hepatotoxicity, primarily when administering individual or total daily doses above the labeled recommendations, as well as with chronic use. Intravenous acetaminophen is contraindicated in patients with severe hepatic impairment or severe active liver disease. Additionally, use in patients with less severe hepatic disease, alcoholism, chronic malnutrition, severe hypovolemia, or severe renal impairment (creatinine clearance ≤30 mL/min) may necessitate longer dosing intervals and/or a reduced total daily dose. No specific dosage recommendations have been determined in these patient populations.

**Summary**

Approval of intravenous acetaminophen provides another treatment option for management of pain and/or fever in pediatric patients. Available studies have shown favorable efficacy when used as monotherapy or adjuvant therapy for pain. Intravenous acetaminophen has also demonstrated an opioid-sparing effect when added to fentanyl, resulting in similar analgesia and decreased sedation scores. When used at recommended doses, common side effects include nausea, vomiting, constipation, pruritus, agitation, and atelectasis. Similar to the oral dosage form, there is a risk of hepatotoxicity when given above the labeled dose or for prolonged periods of time, or to patients with severe hepatic impairment.

The primary limitation expected with intravenous acetaminophen is cost. The comparative costs of a single vial of intravenous acetaminophen, available parenteral NSAIDs, and acetaminophen suppositories are listed in Table 2. In addition to the wholesale price, the limited product stability of only 6 hours increases the potential cost associated with wasted product when drawing pediatric doses of intravenous acetaminophen. Intravenous acetaminophen (Ofirmev) has been added to the University of Illinois Hospital formulary, with its use restricted to perioperative use.

### Table 2. Average wholesale price of intravenous acetaminophen and other common nonopioid analgesics.

<table>
<thead>
<tr>
<th>Analgesic</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen (Ofirmev) 10 mg/mL 100-mL vial</td>
<td>$10.75</td>
</tr>
<tr>
<td>Ibuprofen (Caldolor) 100 mg/mL 4-mL vial</td>
<td>$9.20</td>
</tr>
<tr>
<td>Ketorolac 15 mg/mL 1-mL vial</td>
<td>$1.63</td>
</tr>
<tr>
<td>Acetaminophen suppository 325 mg</td>
<td>$0.65</td>
</tr>
</tbody>
</table>
P&T Committee Formulary Action

**Additions**
- Foscarnet injection - Use restricted to BMT and Infectious Disease Service
- Acetaminophen injection - Use restricted to perioperative areas (OR, PACU, Surgicenter)

**Line extensions**
- Lidocaine 5% topical patch
- Atorvastatin 40mg tablet

**Deletions**
- Cromolyn solution for inhalation
- Barium enema kit
- Ranitidine

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