

## Q: Do all hospitalized patients need stress ulcer prophylaxis?

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**A:** No. Based on current evidence and guidelines, routine acid-suppressive therapy to prevent stress ulcers has no benefit in hospitalized patients outside the critical-care setting. Only critically ill patients who meet specific criteria, as described in the guidelines of the American Society of Health System Pharmacists, should receive acid-suppressive therapy.

Unfortunately, routine stress ulcer prophylaxis is common in US hospitals, unnecessarily putting patients at risk of complications and adding costs.

### ■ STRESS ULCER AND CRITICAL ILLNESS

Stress ulcers—ulcerations of the upper part of the gastrointestinal (GI) mucosa in the setting of acute disease—usually involve the fundus and body of the stomach. The stomach is lined with a glycoprotein mucous layer rich in bicarbonates, forming a physiologic barrier to protect the gastric wall from acid insult by neutralizing hydrogen ions. Disruption of this protective layer can occur in critically ill patients (eg, those with shock or sepsis) through overproduction of uremic toxins, increased reflux of bile salts, compromised blood flow,

and increased stomach acidity through gastrin stimulation of parietal cells.

More than 75% of patients with major burns or cranial trauma develop endoscopic mucosal abnormalities within 72 hours of injury.<sup>1</sup> In critically ill patients, the risk of ulcer-related overt bleeding is estimated to be 5% to 25%. Furthermore, 1% to 5% of stress ulcers can be deep enough to erode into the submucosa, causing clinically significant GI bleeding, defined as bleeding complicated by hemodynamic compromise or a drop in hemoglobin that requires a blood transfusion.<sup>2</sup> In contrast, in inpatients who are not critically ill, the risk of overt bleeding from stress ulcers is less than 1%.<sup>3</sup>

### ■ ADDRESSING RISK

A multicenter prospective cohort study of 2,252 intensive care patients<sup>2</sup> reported two main risk factors for significant bleeding caused by stress ulcers: mechanical ventilation for more than 48 hours and coagulopathy, defined as a platelet count below  $50 \times 10^9/L$ , an international normalized ratio greater than 1.5, or a partial thromboplastin time more than twice the control value.<sup>4</sup> In hemodynamically stable patients receiving anticoagulation in a general medical or surgical ward, the risk of GI bleeding was low, and acid suppression failed to lower the rate of stress ulcer occurrence.<sup>3</sup>

Other risk factors include severe sepsis, shock, liver failure, kidney failure, burns over 35% of the total body surface, organ transplantation, cranial trauma, spinal cord trauma, history of peptic ulcer disease, and history of upper GI bleeding.<sup>3,5,6</sup> Steroid therapy is not considered a risk factor for stress ulcers unless it is used in the presence of another risk fac-

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tor such as use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs).<sup>2</sup>

### ■ INDICATIONS FOR PROPHYLAXIS

Prophylaxis with a proton pump inhibitor (PPI) is indicated in specific conditions—ie, peptic ulcer disease, gastroesophageal reflux disease, chronic NSAID therapy, and Zollinger-Ellison syndrome—and to eradicate *Helicobacter pylori* infection.<sup>7</sup> But in the United States, stress ulcer prophylaxis is overused in general-care floors despite the lack of supporting evidence.

The American Society of Health System Pharmacists guidelines recommend it in the intensive care unit for patients with any of the following: coagulopathy, prolonged mechanical ventilation (more than 48 hours), GI ulcer or bleeding within the past year, sepsis, a stay longer than 1 week in the intensive care unit, occult GI bleeding for 6 or more days, and steroid therapy with more than 250 mg of hydrocortisone daily.<sup>8</sup> Hemodynamically stable patients admitted to general-care floors should not receive stress ulcer prophylaxis, as it only negligibly decreases the rate of GI bleeding, from 0.33% to 0.22%.<sup>9</sup>

### ■ WHY ROUTINE ULCER PROPHYLAXIS IS NOT FOR ALL HOSPITALIZED PATIENTS

Although stress ulcer prophylaxis is often considered benign, its lack of proven benefit, additional cost, and risk of adverse effects, including interactions with foods and other drugs, preclude using it routinely for all hospitalized patients.<sup>10,11</sup> Chronic use of PPIs has been associated with complications, as discussed below.

#### Infection

Acid suppression may impair the destruction of ingested microorganisms, resulting in overgrowth of bacteria.<sup>12</sup> Overuse of PPIs may increase the risk of several infections:

- Diarrhea due to *Clostridium difficile*<sup>12</sup>
- Community-acquired pneumonia, from increased microaspiration of overgrown microorganisms into the lung.<sup>12</sup>
- Spontaneous bacterial peritonitis in patients with cirrhosis,<sup>13</sup> although the mech-

anism is not clear. (Small-bowel bacterial overgrowth is the hypothesized cause.)

#### Bone fracture

PPIs lower gastric acidity, and this can inhibit intestinal calcium absorption. Furthermore, PPIs may directly inhibit bone resorption by osteoclasts.<sup>14</sup>

#### Reduction in clopidogrel efficacy

PPIs may reduce the efficacy of clopidogrel as a result of competitive inhibition of cytochrome CYP2C19, which is necessary to metabolize clopidogrel to its active forms. Therefore, concomitant use of clopidogrel with omeprazole, esomeprazole, or other CYP2C19 inhibitors is not recommended.<sup>15</sup>

#### Nutritional deficiencies

The overgrown microorganisms consume cobalamin in the stomach, resulting in vitamin B<sub>12</sub> deficiency. Acid-suppressive therapy can also reduce the absorption of magnesium and iron.<sup>12</sup>

#### Unnecessary cost

Heidelbaugh and Inadomi<sup>16</sup> reviewed the non-evidence-based use of stress ulcer prophylaxis in patients admitted to a large university hospital and estimated that it entailed a cost to the hospital of \$111,791 over the course of a year.

### ■ WHICH ULCER PROPHYLAXIS SHOULD BE USED IN CRITICALLY ILL PATIENTS?

Studies have shown histamine-2 blockers to be superior to antacids and sucralfate in preventing stress ulcer and GI bleeding,<sup>8,15</sup> but no study has compared PPIs with sucralfate and antacids.

When indicated, an oral PPI is preferred over an oral histamine-2 blocker for GI prophylaxis.<sup>17</sup> This practice is considered cost-effective and is associated with lower rates of stress ulcer and GI bleeding. In intubated patients, however, an intravenous histamine-2 blocker is preferable to an intravenous PPI.<sup>3,8,11</sup> Interestingly, no difference was reported between PPIs and histamine-2 blockers in terms of mortality rate or reduction in the incidence of nosocomial pneumonia.<sup>17</sup>

Only critically ill patients who meet specific criteria should receive stress ulcer prophylaxis

## OUR RECOMMENDATION

Only critically ill patients who meet the specific criteria described here should receive stress ulcer prophylaxis. More effort is needed to educate residents, medical staff,

and pharmacists about current guidelines. Computerized ordering templates and reminders to discontinue prophylaxis at discharge or step-down may decrease overall use, reduce costs, and limit potential side effects.<sup>18</sup>

## REFERENCES

1. DePriest JL. Stress ulcer prophylaxis. Do critically ill patients need it? *Postgrad Med* 1995; 98:159–168.
2. Cook DJ, Fuller HD, Guyatt GH, et al. Risk factors for gastrointestinal bleeding in critically ill patients. Canadian Critical Care Trials Group. *N Engl J Med* 1994; 330:377–381.
3. Qadeer MA, Richter JE, Brotman DJ. Hospital-acquired gastrointestinal bleeding outside the critical care unit: risk factors, role of acid suppression, and endoscopy findings. *J Hosp Med* 2006; 1:13–20.
4. Shuman RB, Schuster DP, Zuckerman GR. Prophylactic therapy for stress ulcer bleeding: a reappraisal. *Ann Intern Med* 1987; 106:562–567.
5. Dellinger RP, Levy MM, Rhodes A, et al; Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013; 41:580–637.
6. Cook DJ, Reeve BK, Guyatt GH, et al. Stress ulcer prophylaxis in critically ill patients. Resolving discordant meta-analyses. *JAMA* 1996; 275:308–314.
7. Kahrilas PJ, Shaheen NJ, Vaezi MF, et al; American Gastroenterological Association. American Gastroenterological Association Medical Position Statement on the management of gastroesophageal reflux disease. *Gastroenterology* 2008; 135:1383–1391.e1–1391.e5.
8. Barkun AN, Bardou M, Pham CQ, Martel M. Proton pump inhibitors vs histamine 2 receptor antagonists for stress-related mucosal bleeding prophylaxis in critically ill patients: a meta-analysis. *Am J Gastroenterol* 2012; 107:507–520.
9. Herzig SJ, Vaughn BP, Howell MD, Ngo LH, Marcantonio ER. Acid-suppressive medication use and the risk for nosocomial gastrointestinal tract bleeding. *Arch Intern Med* 2011; 171:991–997.
10. Cook DJ. Stress ulcer prophylaxis: gastrointestinal bleeding and nosocomial pneumonia. Best evidence synthesis. *Scand J Gastroenterol Suppl* 1995; 210:48–52.
11. Messori A, Trippoli S, Vaiani M, Gorini M, Corrado A. Bleeding and pneumonia in intensive care patients given ranitidine and sucralfate for prevention of stress ulcer: meta-analysis of randomised controlled trials. *BMJ* 2000; 321:1103–1106.
12. Heidelbaugh JJ, Kim AH, Chang R, Walker PC. Overutilization of proton-pump inhibitors: what the clinician needs to know. *Therap Adv Gastroenterol* 2012; 5:219–232.
13. Deshpande A, Pasupuleti V, Thota P, et al. Acid-suppressive therapy is associated with spontaneous bacterial peritonitis in cirrhotic patients: a meta-analysis. *J Gastroenterol Hepatol* 2013; 28:235–242.
14. Farina C, Gagliardi S. Selective inhibition of osteoclast vacuolar H(+)–ATPase. *Curr Pharm Des* 2002; 8:2033–2048.
15. ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis. ASHP Commission on Therapeutics and approved by the ASHP Board of Directors on November 14, 1998. *Am J Health Syst Pharm* 1999; 56:347–379.
16. Heidelbaugh JJ, Inadomi JM. Magnitude and economic impact of inappropriate use of stress ulcer prophylaxis in non-ICU hospitalized patients. *Am J Gastroenterol* 2006; 101:2200–2205.
17. Alhazzani W, Alenezi F, Jaeschke RZ, Moayyedi P, Cook DJ. Proton pump inhibitors versus histamine 2 receptor antagonists for stress ulcer prophylaxis in critically ill patients: a systematic review and meta-analysis. *Crit Care Med* 2013; 41:693–705.
18. Liberman JD, Whelan CT. Brief report: reducing inappropriate usage of stress ulcer prophylaxis among internal medicine residents. A practice-based educational intervention. *J Gen Intern Med* 2006; 21:498–500.

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