

Supportive and Preventive Medicine

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Learning Objectives

1. Identify the importance of key components of intensive care medicine that can be applied to all critically ill patients.
2. Recommend therapeutic options to prevent stress-related mucosal disease.
3. Recommend therapeutic options to prevent venous thromboembolism in a critically ill patient.
4. Discuss therapeutic options for patients with heparin-induced thrombocytopenia.
5. Discuss medications that can be used to provide comfort to a critically ill patient at the end of life.

Abbreviations in This Chapter

aPTT	Activated partial thromboplastin time
CDI	<i>Clostridium difficile</i> infection
DVT	Deep venous thrombosis
ELISA	Enzyme-linked immunosorbent assay
H ₂ RA	Histamine-2 receptor antagonist
HIT	Heparin-induced thrombocytopenia
ICU	Intensive care unit
NGT	Nasogastric tube
PF4	Platelet factor-4
PPI	Proton pump inhibitor
SRMD	Stress-related mucosal disease
SUP	Stress ulcer prophylaxis
VTE	Venous thromboembolism

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. On rounds, you have a “checklist” of interventions that will benefit all critically ill patients in an intensive care unit (ICU). Which checklist would be most effective to implement?
 - A. Initiate stress ulcer prophylaxis (SUP) in patients who are admitted to the ICU, and if appropriate, discontinue sedation.
 - B. Initiate enteral nutrition when appropriate, and initiate mechanical venous thromboembolism (VTE) prophylaxis.
 - C. If appropriate, discontinue sedation, and ensure that the patient’s head is 30 degrees above the bed.
 - D. Assess the need for VTE prophylaxis in patients admitted to the ICU, and initiate an insulin infusion to maintain a blood glucose of 120 mg/dL.
2. Regarding pharmacologic prophylaxis for stress-related mucosal injury, which would be the most appropriate statement?
 - A. Sucralfate neutralizes gastric pH.
 - B. Proton pump inhibitors (PPIs) are superior to histamine-2 receptor antagonists (H₂RAs) in preventing clinically significant bleeding.
 - C. Tolerance will occur with continued administration of H₂RAs.
 - D. Antacids are effective when used up to three times daily.
3. A 66-year-old man is admitted to the ICU with abdominal pain, nausea, and altered mental status. He has a history of alcoholic cirrhosis, atrial fibrillation, and erosive esophagitis. He is intubated and stabilized on the ventilator. A nasogastric tube (NGT) is placed, and the patient is tolerating enteral tube feedings. Which would be best to recommend for preventing stress-related bleeding?
 - A. Pantoprazole 40 mg intravenously twice daily.
 - B. Ranitidine 50 mg intravenously three times daily.
 - C. Famotidine 20 mg twice daily by NGT.
 - D. Omeprazole suspension 20 mg once daily by NGT.
4. A 51-year-old woman is admitted to the ICU for hypovolemic shock secondary to severe dehydration. She reports a 5-day history of diarrhea and malaise. She has no recent history of illnesses or contact with health care personnel. Her medical history includes hypothyroidism and gastroesophageal reflux disease. Her medications include levothyroxine 25 mcg orally daily and famotidine 20 mg orally at bedtime. Recently, her primary care physician changed famotidine to omeprazole 20 mg orally at bedtime for increased gastroesophageal reflux disease symptoms. While she is in the ICU, testing for *Clostridium difficile* infection (CDI) comes back

- positive. Which would be the most appropriate statement regarding PPI use and CDI?
- PPIs are a potential risk factor for CDI by producing hypochlorhydria and increasing the host susceptibility to infections.
 - Prospective randomized controlled trials have shown that the risk of CDI is associated with PPI use.
 - Studies have shown that an increased risk of CDI is associated with daily PPI use compared with PPI administration more frequently.
 - Studies reporting on CDI and PPI use have used the same definition of CDI and implemented the same infection control practices.
5. A 50-year-old woman (weight 70 kg) is admitted to the ICU after having an acute myocardial infarction. She has a medical history significant for hypertension, tobacco use, and osteoporosis. The next morning, she is intubated and stabilized on a ventilator after an aspiration event. She has an NGT placed. Her current medications include piperacillin/tazobactam 4.5 g intravenously every 8 hours (she has normal renal function), famotidine 20 mg per NGT twice daily, metoprolol 50 mg per NGT every 8 hours, aspirin 325 mg per NGT daily, and atorvastatin 80 mg per NGT daily. Which would be the most appropriate VTE prophylaxis for this patient?
- Intermittent pneumatic compression devices.
 - Enoxaparin 40 mg subcutaneously daily.
 - Unfractionated heparin continuous infusion to maintain a therapeutic activated partial thromboplastin time (aPTT).
 - No VTE prophylaxis at this time.
6. A 34-year-old woman (weight 65 kg) is admitted to the ICU with several fractures, a closed-head injury, and a grade 4 liver laceration after sustaining a motor vehicle crash. Her medical history is not significant. She is admitted to the ICU on a ventilator after surgery. Current laboratory values are as follows: sodium 145 mEq/L, potassium 3.1 mEq/L, chloride 97 mEq/L, carbon dioxide 18 mEq/L, blood urea nitrogen (BUN) 70 mg/dL, and serum creatinine (SCr) 3.5 mg/dL. Which would be the most appropriate VTE prophylaxis for this patient?
- Intermittent pneumatic compression devices.
 - Dalteparin 5000 units subcutaneously daily.
 - Fondaparinux 2.5 mg subcutaneously daily.
 - No VTE prophylaxis is indicated at this time.
7. A 34-year-old man (weight 70 kg) is admitted to the surgical ICU for acute respiratory failure from pancreatitis. He has no pertinent medical history. His current medications include norepinephrine at 0.07 mcg/kg/minute, dexmedetomidine at 0.7 mcg/kg/minute, ampicillin/sulbactam 3 g intravenously every 6 hours, famotidine 20 mg intravenously twice daily, and heparin 5000 units subcutaneously three times daily. On day 3 of his ICU admission, the team suspects heparin-induced thrombocytopenia (HIT). The platelet count was 360,000/mm³ on admission, and today, it is 180,000/mm³. The 4T's score is used to determine the probability of HIT. The score is calculated as 3: low risk. The team would like to send the heparin–platelet factor 4 (PF4) immunoassay and initiate argatroban. Which is the most appropriate response?
- Discontinue all heparin products, but do not initiate argatroban.
 - Discontinue all heparin products, and initiate argatroban.
 - Send the heparin-PF4 immunoassay, and continue low-dose unfractionated heparin until the results come back.
 - Do not send the heparin-PF4 immunoassay, and do not discontinue low-dose unfractionated heparin.
8. Which would be the most important considerations in a critically ill patient approaching the end of life?
- Pain management, tight glucose management, and control of secretions.
 - Routine vital sign checks, discontinuation of unnecessary medications, and control of secretions.
 - Pain management, control of secretions, and discontinuation of unnecessary medications.
 - Discontinuation of unnecessary medications, insertion of a Foley catheter, and treatment of nausea and vomiting.

I. KEY ASPECTS IN THE GENERAL CARE OF ALL CRITICALLY ILL PATIENTS

- A. FAST-HUG is a mnemonic emphasizing important aspects of ICU medicine that can be applied at least daily to all critically ill patients to ensure safe, effective, and efficient care (Crit Care Med 2005;33:1225-9).

Table 1. Key Elements of the FAST-HUG Approach

Element	Importance	Considerations
F eeding	Malnutrition can lead to impaired immune function leading to increased susceptibility to infection, inadequate wound healing, bacterial overgrowth in the GI tract, and increased propensity for decubitus ulcers	<ul style="list-style-type: none"> Initiate oral or enteral feeding (preferred to parenteral feedings) as soon as possible, typically within the first 24–72 hours after stabilization
A nalgesia	Analgesic and sedative administration optimizes patient comfort and minimizes the acute stress response (hypermetabolism, increased oxygen consumption, hypercoagulability, and alterations in immune function)	<ul style="list-style-type: none"> Pain should be regularly assessed with a validated tool such as the Behavioral Pain Scale or the Critical-Care Pain Observation Tool Preemptive analgesia should be considered for invasive or potentially painful clinical procedures
S edation		<ul style="list-style-type: none"> Sedation should be assessed and reassessed with a validated tool such as the Richmond Agitation-Sedation Scale or the Sedation Agitation Scale Maintain light levels of sedation If appropriate, execute sedative interruption
T hromboembolic prophylaxis	Most ICU patients carry at least one risk factor for VTE	<ul style="list-style-type: none"> Initiate appropriate prophylaxis, considering VTE and bleeding risks Mechanical prophylaxis (graduated compression stockings or intermittent pneumatic compression devices) are alternative nonpharmacologic options in patients at high risk of bleeding
H ead of bed elevation	Elevating the head and thorax above bed to a 30–45 degree angle reduces the occurrence of GI reflux and nosocomial pneumonia in patients who are receiving mechanical ventilation	<ul style="list-style-type: none"> Ensure patient position periodically throughout the day, especially after procedures that require the patient to lie flat

Table 1. Key Elements of the FAST-HUG Approach (*continued*)

Element	Importance	Considerations
Stress <u>U</u> lcer prophylaxis	Critically ill patients develop stress-related mucosal damage, potentially leading to clinically significant bleeding	<ul style="list-style-type: none"> Consider discontinuing acid-suppressive medications when risk factors are no longer present
<u>G</u> lycemic control	Glycemic control is necessary in critically ill patients to decrease the incidence of complications such as decreased wound healing, increased infection risk, and increased risk of polyneuropathy	<ul style="list-style-type: none"> Continuous insulin infusions to maintain blood glucose between 140 and 180 mg/dL should be considered in the acutely ill patient when blood glucose levels are ³ 150 mg/dL or greater Transition to subcutaneous basal/bolus insulin once the patient is stabilized

GI = gastrointestinal; ICU = intensive care unit; VTE = venous thromboembolism.

B. Daily Checklists

- Checklists aim to provide a framework of standardization and regulation of interventions in a systematic manner, allowing individuals to assess the presence or absence of the items.
- Provides structure to important ICU-related interventions in an effort to reduce errors of omission and increase compliance with evidence-based practices to improve outcomes in the ICU patient population (N Engl J Med 2006;355:2725-32; N Engl J Med 2009;360:491-9)

Patient Case

- A 68-year-old man (weight 85 kg) is admitted to the ICU for management of severe hypoxemic respiratory failure associated with community-acquired pneumonia. He is endotracheally intubated and placed on mechanical ventilation. His medical history consists of Child-Pugh class B cirrhosis secondary to alcohol abuse, heart failure, and myocardial infarction. His laboratory values show a white blood cell count (WBC) of 15×10^3 cells/mm³, platelet count 75,000/mm³, BUN 15 mg/dL, SCr 1.1 mg/dL, potassium 4.5 mEq/L, international normalized ratio (INR) 1.0, aspartate aminotransferase (AST) 58 IU/mL, and alanine aminotransferase (ALT) 49 IU/mL. His current medications include ceftriaxone 1 g intravenously daily, vancomycin 1250 mg intravenously every 12 hours, heparin 5000 units subcutaneously every 8 hours, fentanyl drip at 50 mcg/hour, midazolam drip at 1 mg/hour titrated to a Richmond Agitation Sedation Scale (RASS) of 0 to -1, and a regular insulin drip at 1.5 units/hour titrated to maintain blood glucose 140–180 mg/dL. Currently, the patient's head is 30 degrees above the bed, his RASS is documented as -4, he is on minimal ventilator settings, and he has an NGT placed. As the clinical pharmacist rounding on this patient, you go through the FAST-HUG mnemonic. Which are the best recommendations to make to the team?
 - Initiate enteral nutrition by NGT, add SUP, and discontinue fentanyl and midazolam drips.
 - Initiate enteral nutrition by NGT, discontinue deep venous thrombosis (DVT) prophylaxis, and transition insulin drip to sliding scale.
 - Transition insulin drip to sliding scale, add SUP, and discontinue fentanyl and midazolam drips.
 - Discontinue fentanyl and midazolam drips, discontinue DVT prophylaxis, and add SUP.

II. STRESS ULCER PROPHYLAXIS

- A. Epidemiology of Stress-Related Mucosal Disease (SRMD)
1. Endoscopic evidence of superficial mucosal damage occurs in 75%–100% of patients within 1–2 days after ICU admission.
 2. Mortality from stress-related bleeding ranges from 50% to 70% in the critically ill, with a 20% mortality rate attributable to SRMD.
 3. Clinically significant stress-related bleeding has decreased during the past decade because of many factors, including early resuscitation and SUP.
- B. Characteristics of SRMD
1. Multiple superficial erosive lesions occurring early in the course of critical illness, potentially progressing to deep ulcers.
 2. Stress ulcers are diffuse in nature and are not amenable to endoscopic therapy; they generally heal over time, without intervention, as the patient's clinical status improves.

Table 2. Clinical Presentation of Stress vs. Peptic Ulcers

Stress Ulcers	Peptic Ulcers
Multiple superficial lesions at the proximal stomach bulb; involves superficial capillaries	Few deep lesions in the duodenum; typically involves a single vessel

- C. Pathophysiology of SRMD
1. Decreased splanchnic blood flow is the primary cause of stress ulcer-related bleeding.
 2. Reduced splanchnic blood flow is caused by mechanisms common to critical illness:
 - a. Hypovolemia
 - b. Reduced cardiac output
 - c. Proinflammatory mediator release
 - d. Increased catecholamine release
 - e. Visceral vasoconstriction
 3. Additional factors leading to stress ulcer-related bleeding:
 - a. Decreased gastric mucosal bicarbonate production
 - b. Decreased gastric emptying of irritants and acidic contents
 - c. Acid back-diffusion
 - d. Reperfusion injury that may occur following restoration of blood flow after prolonged periods of hypoperfusion

Table 3. Categories of Stress-Related Bleeding

Outcome	Incidence in ICU Patients	Definition
Endoscopically evident mucosal damage	75%–100%	Superficial lesions identified on endoscopy
Occult bleeding	15%–50%	Presence of guaiac-positive stools or nasogastric aspirate
Overt or clinically evident bleeding	5%–25%	Appearance of coffee grounds in nasogastric aspirate, hematemesis, melena, or hematochezia
Clinically significant bleeding	1%–5%	Bleeding with hemodynamic instability and/or blood transfusion

D. Risk Factors for Stress-Related Bleeding

1. Significant independent risk factors for SRMD and bleeding include respiratory failure requiring mechanical ventilation for 48 hours or longer OR coagulopathy (platelet count less than 50,000/mm³, INR greater than 1.5, or aPTT greater than 2 times the control) (N Engl J Med 1994;330:377-81).
 - a. Patients with at least one risk factor had a 3.7% incidence of bleeding compared with 0.1% if risk factors were absent.
 - b. Most of the 2252 patients enrolled in this study were cardiothoracic patients, potentially making extrapolations to other ICU settings inaccurate.
2. Other risk factors for SRMD and bleeding include:
 - a. Severe brain injury
 - b. Major surgery
 - c. Thermal injury affecting more than 20% total body surface area
 - d. Acute kidney injury
 - e. Acute hepatic failure
 - f. Severe sepsis
 - g. Hypotension
 - h. History of gastrointestinal (GI) bleed within the past year
 - i. Postoperative transplantation
 - j. Ulcerogenic medications (nonsteroidal anti-inflammatory drugs, aspirin, corticosteroids)
3. Risk factors associated with GI bleeding while receiving prophylaxis (all patients on mechanical ventilation):
 - a. Renal failure (Crit Care Med 1999;27:2812-7)
 - b. Age (50 years or older), male sex, diagnosis with acute respiratory failure or myocardial infarction, acute kidney injury, neurologic injury, sepsis, shock, acute or chronic hepatic failure, and coagulopathy (JAMA Intern Med 2014;174:564-74)

E. Pharmacologic Therapy for Preventing Stress Ulcers

1. Antacids
 - a. Dose-dependent neutralization of gastric acid
 - b. Not recommended for routine use because of frequency of administration (up to every hour), adverse effects (diarrhea, constipation, electrolyte abnormalities), and interactions (interferes with absorption of some drugs)

2. Sucralfate (Carafate)
 - a. Complexes with albumin and fibrinogen to form a viscous, adhesive substance that adheres to ulcers in the presence of a pH less than 4
 - b. Not recommended for routine use because of adverse effects (constipation, aluminum toxicity, hypophosphatemia) and interactions by chelation
 - c. Sucralfate is less efficacious than H₂RAs
3. Histamine-2 receptor antagonists
 - a. Competitive blockers of histamine subtype 2 receptor on the basolateral membrane of the parietal cells. In addition, H₂RAs inhibit gastrin secretion to reduce acid production; however, they do not reliably inhibit vagally induced acid secretion.
 - b. In animal models, H₂RAs may also attenuate reperfusion injury by decreasing interleukin-6 and neutrophil activation, reducing inflammation by enhancing cell-mediated immunity, and acting as a weak free radical scavenger.
 - c. Dose-dependent increase in gastric pH
 - d. Data against SRMD-related bleeding are primarily with the intravenous route of administration.
 - i. Previous studies used either continuous-infusion H₂RAs or combined H₂RAs with intermittent antacids to maintain pH greater than 4.
 - ii. Current practice is to use intermittent administration of H₂RAs without pH monitoring. May offer reduction in bacterial overgrowth and thereby less aspiration pneumonia and less tachyphylaxis
 - e. Adverse effects
 - i. Mental status changes such as confusion, hallucinations, agitation, and headaches (mainly associated with cimetidine)
 - ii. Thrombocytopenia (occurs over several days from hapten formation; may occur within hours if patient is sensitized)
 - iii. Rapid infusion-related hypotension
 - iv. Sinus bradycardia
 - v. Risk of nosocomial pneumonia
 - f. Drug interactions
 - i. Cimetidine inhibits cytochrome P450 (CYP) isoenzymes 3A4, 2D6, 2C9, 2C19, and 1A2.
 - ii. pH-dependent interactions

Table 4. Available H₂RAs

Drug Name	Dose ^a
Cimetidine ^b (Tagamet)	300 mg IV/PO every 6 hours or continuous infusion at 37.5–50 mg/hour
Famotidine (Pepcid)	20 mg IV/PO every 12 hours
Nizatidine (Axid)	150 mg PO every 12 hours
Ranitidine (Zantac)	150 mg PO every 12 hours or 50 mg IV every 8 hours

^aDose based on clinical data (cimetidine as a continuous infusion is the only H₂RA approved by the U.S. Food and Drug Administration for SUP). All H₂RAs are renally eliminated and require dose adjustments for renal dysfunction.

^bCompetitively inhibits tubular secretion of creatinine.

H₂RA = histamine-2 receptor antagonist; IV = intravenously; PO = oral.

4. Proton pump inhibitors
 - a. Prodrugs activated in the acidic environment of the parietal cell inhibiting both histamine-induced and vagally mediated gastric acid by binding and inhibiting active proton pumps
 - b. Dose-dependent increase in gastric pH, with maximal activity reached 3 days after initiation
 - c. Most trials had evaluated the effectiveness of enteral PPIs; however, they may be administered intravenously.
 - d. Despite short elimination half-lives, PPIs suppress acid secretion for 20 hours or more, permitting once-daily dosing without requiring gastric pH monitoring.
 - e. Tachyphylaxis does not occur with PPIs.
 - f. Rebound acid hypersecretion may occur after discontinuation; however, clinical relevance is unknown.
 - g. Adverse effects
 - i. GI such as diarrhea, abdominal pain, constipation, nausea
 - ii. Headaches
 - iii. Rash
 - iv. Interstitial nephritis
 - v. Hypomagnesemia (3 months or more of therapy)
 - vi. Neurologic effects with high-dose intravenous omeprazole (hearing and vision disturbances)
 - vii. Hypophosphatemia and metabolic alkalosis when administered with sodium bicarbonate
 - viii. Increased risk of fractures (hip, waist, and spine)
 - ix. *C. difficile* infection (definitive cause-effect relationship is not well established)
 - x. Risk of nosocomial pneumonia
 - h. Drug interactions
 - i. All agents are hepatically metabolized by CYP isoenzymes 3A4 and 2C19.
 - ii. Omeprazole is an inhibitor of 3A4, 2C19, 2C9, and 1A2.
 - iii. Lansoprazole may induce CYP1A2.
 - iv. pH-dependent interactions

Table 5. Available Proton Pump Inhibitors

Agent	Dose ^a	Alternative Routes of Administration (NGT/OGT)	Alternative Dosage Forms
Esomeprazole	40 mg daily	Intact capsule granules sprinkled on applesauce Suspend granules in a syringe with 50 mL of water; flush with 10 mL of water	Delayed-release oral suspension granules Intravenous
Lansoprazole	30 mg daily	Intact capsule granules sprinkled on applesauce, pudding, cottage cheese, or yogurt Suspend granules in a syringe with 40 mL of apple juice; flush with 20 mL of apple juice Dissolve granules in 10 mL of 8.4% sodium bicarbonate; flush with 10 mL of sodium bicarbonate or water (simplified lansoprazole suspension)	Packet for oral suspension Delayed-release orally disintegrating tablet Delayed-release suspension (xanthan gum will clog NGT or OGT)

Table 5. Available Proton Pump Inhibitors (*continued*)

Agent	Dose ^a	Alternative Routes of Administration (NGT/OGT)	Alternative Dosage Forms
Omeprazole	20 mg daily	Intact capsule granules sprinkled on applesauce Suspend granules in a syringe with 40 mL of apple juice; flush with 20 mL of apple juice Dissolve granules in 10 mL of 8.4% sodium bicarbonate; flush with 10 mL of sodium bicarbonate or water (simplified omeprazole suspension)	Powder for oral suspension
Pantoprazole	40 mg daily	Crush and dissolve enteric-coated tablet in 10 mL of 4.2% sodium bicarbonate and add 10 mL for a total volume of 20 mL; flush with 10 mL of sodium bicarbonate or water (pantoprazole suspended in sodium bicarbonate solution)	Packet for oral suspension Intravenous

^aDose based on clinical data (only omeprazole powder for oral suspension is approved by the U.S. Food and Drug Administration for SUP).

NGT = nasogastric tube; OGT = orogastric tube.

F. Clinically Significant Bleeding

1. Most trials define clinically significant bleeding as overt bleeding accompanied by one of the following:
 - a. Decrease in blood pressure of 20 mm Hg within 24 h of the first GI bleeding episode
 - b. Decrease in blood pressure of 10 mm Hg and an increase in heart rate of 20 beats/minute on orthostatic change
 - c. Decrease in hemoglobin of 2 g/dL and transfusion of 2 units of blood within 24 hours of bleeding OR failure of the hemoglobin concentration to increase after transfusion by at least the number of units transfused minus 2 g/dL
2. Antacids, sucralfate, H₂RAs, and PPIs have all reduced clinically significant SRMD-related bleeding compared with placebo.
3. Results of meta-analyses assist in providing a comparative estimate of treatment on bleeding rates.
4. Three meta-analyses favored PPIs to H₂RAs for GI bleeding; however, the studies that were included lacked methodological quality with unexpectedly high baseline bleeding rates, a disproportionate number of risk factors between patient groups, inconsistent definitions of bleeding, and different routes and dosing of agents.

Table 6. Results of Meta-analyses on Clinically Important Bleeding Rates^a

	Antacids vs. Sucralfate	H₂RAs vs. Antacids	H₂RAs vs. Sucralfate	PPIs vs. H₂RAs
Am J Med 1991;91:519-27	0.65 (0.16–2.49)	0.84 (0.45–1.56)	0.95 (0.06–15.40)	—
Infect Control Hosp Epidemiol 1994;15:437-42	1.39 (0.67–3.21)	0.84 (0.45–1.56)	1.05 (0.12–16.36)	—
JAMA 1996; 275:308-14	1.49 (0.42–5.27)	0.86 (0.46–1.59)	1.28 (0.27–6.11)	—
Crit Care Med 1991;19:942-9 ^b	0.87 (0.45–1.67)	—	0.53 (0.3–0.93) favoring sucralfate	—
Crit Care 2010;14:R194	—	—	0.87 (0.49–1.53)	—
Crit Care Med 2010;38:1197-1205	—	—	—	-0.04 (-0.09–0.01) favoring PPIs
Am J Gastroenterol 2012;107:507-20	—	—	—	0.30 (0.17–0.54) favoring PPIs
Crit Care Med 2013;41:693-705	—	—	—	0.36 (0.19–0.68) favoring PPIs

^aAll results reported as odds ratio or risk difference (95% confidence interval)

^bMacroscopic hemorrhages only; meta-analysis directly contradicts findings from a landmark study (N Engl J Med 1998;338:791-7) in which intermittent administration of intravenous ranitidine resulted in a lower rate of clinically significant bleeding compared with sucralfate.

H₂RA = histamine-2 receptor antagonist; PPI = proton pump inhibitor.

G. Infectious Complications

1. Increases in gastric pH promote bacterial overgrowth, potentially leading to infectious complications. Both H₂RAs and PPIs will cause changes in gastric pH; however, because tachyphylaxis occurs with H₂RAs, PPIs have a greater propensity to maintain a sustained higher pH.
2. Pneumonia
 - a. Meta-analyses showed lower pneumonia rates with sucralfate compared with H₂RAs alone or H₂RAs combined with antacids and no differences in pneumonia rates when H₂RAs were compared with PPIs. Many of the trials included in the analysis have variable definitions of pneumonia.
 - b. An observational study of cardiac surgical patients detected a higher rate of pneumonia with PPIs than with H₂RAs (relative risk [95% confidence interval {CI}] 1.19 [1.03–1.38] after propensity score adjustment (BMJ 2013;347:f5416).
3. *C. difficile* infection
 - a. A cohort study observed incremental increases in the risk of nosocomial CDI as the level of acid suppression increased. After adjustment, the CDI increased from an odds ratio of 1 (1 = reference of no acid suppression) to 1.53 (95% CI, 1.12–2.10) for H₂RA to 1.74 (1.39–2.18) with daily PPI use, and to 2.36 (1.79–3.11) for more frequent administration of PPI (Arch Intern Med 2010;170:784-90).

- b. There are no prospective trials evaluating the risk of CDI in ICU patients. Furthermore, many published trials have different definitions of CDI, unclear association of antisecretory therapy initiation and CDI diagnosis, and variable infection control practices.
- H. Duration of SUP: Continued as long as one or more risk factors are present
- I. Pharmacoeconomics
1. According to the landmark trial comparing H₂RAs with sucralfate, H₂RAs may be more cost-effective because of reduced incidence of bleeding without an increase in pneumonia rates.
 2. Cost-effectiveness models have compared H₂RAs with PPIs in relation to clinically important bleeding and adverse effects (ventilator-associated pneumonia [VAP] and CDI), yielding discordant results:
 - a. Use of PPI therapy for SUP resulted in a \$1250 net cost savings per patient compared with H₂RAs. Univariate sensitivity analysis showed that with changing the probability of VAP rates, PPI therapy would not be as cost-effective (Value Health 2013;16:14-22).
 - b. Use of H₂RA therapy for SUP resulted in a \$1095 net cost savings compared with PPIs. Univariate sensitivity analysis showed that assumptions of pneumonia and bleeding rates were the primary drivers of incremental costs (Crit Care Med 2014;42:809-15).
 3. Cost minimization is best practiced by initiating SUP in patients at risk and appropriately discontinuing SUP when a patient no longer possesses any of the risk factors for stress-induced bleeding.
- J. Guideline Recommendations: The Surviving Sepsis Guidelines published in 2012 recommend PPIs over H₂RAs for SUP (weak/low quality evidence) (Crit Care Med 2013;41:580-637).

Patient Cases

Questions 2–4 pertain to the following case.

A 72-year-old woman is admitted to the ICU for severe respiratory failure from community-acquired pneumonia. She is endotracheally intubated and placed on mechanical ventilation. An NGT is placed to begin enteral nutrition. She is currently receiving fluid boluses, norepinephrine and vasopressin infusions, and appropriate antimicrobial agents. Her WBC is 20×10^3 cells/mm³, platelet count 45,000/mm³, BUN 70 mg/dL, SCr 4.5 mg/dL (baseline 0.9 mg/dL), potassium 4.5 mEq/L, INR 1.4, AST 30 IU/mL, and ALT 46 IU/mL.

2. Which best reflects this patient's number of risk factors for stress-related bleeding?
 - A. One.
 - B. Two.
 - C. Four.
 - D. Five.
3. Which would be most appropriate for preventing stress-related bleeding?
 - A. Sucralfate 1 g four times daily by NGT.
 - B. Magnesium hydroxide 30 mL every 4 hours by NGT.
 - C. Pantoprazole 40 mg intravenously twice daily.
 - D. Famotidine 20 mg intravenously daily.

Patient Cases (*continued*)

4. One week later, the patient's respiratory status has greatly improved. She has been off sedation and vasopressors for the past 4 days, working with physical therapy, and is now extubated. Her only medications include ceftriaxone, heparin subcutaneously, and SUP from above. Her current laboratory values are as follows: WBC 6×10^3 cells/mm³, platelet count 256,000/mm³, BUN 10 mg/dL, SCr 1.1 mg/dL, potassium 4.0 mEq/L, INR 0.8, AST 15 IU/mL, and ALT 10 IU/mL. Which would be the most appropriate recommendation to make regarding this patient's SUP regimen?
- SUP should be continued until hospital discharge.
 - SUP should be continued until ICU discharge.
 - SUP should be discontinued now.
 - SUP should be discontinued once the patient is off antimicrobials.

III. PROPHYLAXIS AGAINST DEEP VEIN THROMBOSIS OR PULMONARY EMBOLISM**A. Risk Factors**

- Malignancy, previous VTE, immobility, known thrombophilia, recent (1 month or less) surgery or trauma, older age (70 years or older), heart or respiratory failure, sepsis, obesity (body mass index of 30 kg/m² or more), pregnancy, erythropoiesis-stimulating agents with hemoglobin 12 g/dL or more, hormonal therapy, recent transfusions of concentrated clotting factors, central venous lines, and long-distance travel.
- Additional VTE risk factors in critically ill patients:
 - Single-center prospective cohort (n=261) identified four independent risk factors for ICU-acquired VTE, including personal or family history of VTE (multivariate hazard ratio [HR] 4.0; 95% CI, 1.5–10.3; p=0.004), end-stage renal failure (HR 3.7; 95% CI, 1.2–11.1; p=0.02), platelet transfusion (HR 3.2; 95% CI, 1.2–8.4; p=0.02), and vasopressor use (HR 2.8; 95% CI, 1.1–7.2; p=0.03) (Crit Care Med 2005;33:1565-71).
 - In the critically ill patient population, there are no validated risk assessment models to estimate the risk of VTE.

B. Prevention of VTE in the General Critically Ill Patient Population – Summary of recommendations (Chest 2012;141:S195-226)

- Routine ultrasound screening is not recommended.
- Either low-dose unfractionated heparin or low-molecular-weight heparin should be initiated in a critically ill patient over no prophylaxis.
- Mechanical VTE prophylaxis should be used in a critically ill patient if bleeding or at high risk of bleeding. Once bleeding risk abates, initiate pharmacologic VTE prophylaxis.

Table 7. Randomized Trials of VTE Prophylaxis in Critically Ill Patients

Citation	Study Type	Population	Intervention	Screening Methods	VTE Rates	Major Bleeding Rates
Crit Care Med 1982;10:448-50	Single-center	119 medical-surgical ICU patients	LDUH 5000 units SC twice daily vs. placebo	Daily ¹²⁵ I-labeled fibrinogen leg scanning	13% in LDUH vs. 29% in placebo; p<0.05	Not reported
Am J Respir Crit Care Med 2000;161:1109-14	Multicenter, double-blind	221 MV patients with COPD	Nadroparin (weight based) SC daily vs. placebo	Weekly Doppler ultrasonography and day 21	15% in nadroparin group vs. 28% in placebo group; p=0.045	6% in nadroparin group and 3% in placebo group; p=0.28
Thromb Haemost 2009;101:139-44	Multicenter, double-blind	1935 patients with severe sepsis receiving drotrecogin alfa (activated)	LDUH 5000 units SC twice daily vs. enoxaparin 40 mg SC daily vs. placebo	Doppler ultrasonography between days 4 and 6	5.6% in LDUH group vs. 5.9% in enoxaparin group vs. 7.0% in placebo group; p=NS	Not reported
Blood Coagul Fibrinolysis 2010;21:57-61	Single-center, double-blind	156 surgical patients undergoing major elective surgery	LDUH 5000 units SC twice daily vs. enoxaparin 40 mg SC daily	Doppler ultrasonography 5–7 days after surgery and when clinically indicated	2.7% in LDUH group vs. 1.2% in enoxaparin group; p=0.51	2.7% in the LDUH group vs. 1.2% in enoxaparin group; p=0.48
N Engl J Med 2011;364:1305-14	Multicenter, double-blind	3746 medical-surgical ICU patients expected to remain in the ICU for ≥ 3 days (90% medical, 76% MV)	LDUH 5000 units SC twice daily vs. dalteparin 5000 international units SC daily	Doppler ultrasonography 2 days after admission, twice weekly, and as clinically indicated	9.9% in LDUH group vs. 8.2% in dalteparin group; p=0.24	5.6% in LDUH group vs. 5.5% in dalteparin group; p=0.98

ICU = intensive care unit; LDUH = low-dose unfractionated heparin; SC = subcutaneously; VTE = venous thromboembolism.

COPD = chronic obstructive pulmonary disease; ICU = intensive care unit; MV = mechanically ventilated; NS = not significant.

C. Prevention of VTE in the Non-Orthopedic Surgical Patient (Chest 2012;141:S227-77)

Table 8. VTE Prophylaxis Recommendations in Trauma Patients

Risk Level for VTE	Risk of Bleeding	Prophylaxis
Low-moderate	Low	LMWH, ^a LDUH, ^a or IPCD (all preferred to no prophylaxis)
High ^b	Low	LMWH ^a or LDUH ^a with elastic stockings or IPCD

^aIf LDUH or LMWH is contraindicated, mechanical prophylaxis with IPCD is preferred to no prophylaxis in the absence of lower extremity injury.

^bIncludes acute spinal cord injury, traumatic brain injury, and spinal surgery from trauma.

IPCD = intermittent pneumatic compression device; LDUH = low-dose unfractionated heparin; LMWH = low molecular weight heparin; VTE = venous thromboembolism.

LMWH = low molecular weight heparin; VTE = venous thromboembolism.

Table 9. VTE Prophylaxis Recommendations in the General and Abdominal-Pelvic Surgical Patient

Risk Level for VTE	Risk of Bleeding	Prophylaxis
Very low	Low	Early ambulation
Low	Low	IPCD
Moderate	Low	LMWH, LDUH, or IPCD
	High	IPCD
High	Low	LMWH or LDUH with elastic stockings or IPCD
	Low with contraindications to LMWH or LDUH	Low-dose aspirin, fondaparinux, or IPCD
	High	IPCD until risk of bleeding abates, then pharmacologic prophylaxis should be initiated

IPCD = intermittent pneumatic compression device; LDUH = low-dose unfractionated heparin; LMWH = low molecular weight heparin; VTE = venous thromboembolism.

Table 10. Available Agents and Dosing

	Dose in Patients with Normal Renal Function	Dose in Patients with Renal Impairment ^a
Enoxaparin	40 mg SC daily	30 mg SC daily
Dalteparin	5000 units SC daily	Specific dosage adjustments have not been recommended; accumulation was not observed in critically ill patients with severe renal insufficiency. No adjustment needed for CrCl ³ 20 mL/minute or greater. (Arch Intern Med 2008;168:1805-12)
LDUH	5000 units SC every 8–12 hours: choosing between every 8 and every 12 hours should be based on the patient's risk of thrombosis and bleeding	
Fondaparinux	2.5 mg once daily for patients weighing 50 kg or more	Contraindicated; however, doses of 2.5 mg SC every 48 hours have been used

^aEstimated CrCl 20–30 mL/minute.

CrCl = creatinine clearance; LDUH = low-dose unfractionated heparin; SC = subcutaneously.

D. Considerations for Critically Ill Patients

1. Inability to communicate symptoms (impaired consciousness) and altered physical examination (edema) makes diagnosis of symptomatic VTE challenging in the critically ill patient population. Routine screening for VTE with ultrasonography is not recommended.
2. Dosing frequency of low-dose unfractionated heparin (twice vs. thrice daily)
 - a. Large randomized controlled trials have only assessed twice-daily dosing, and no direct comparisons have been made in any population, including the critically ill.
 - b. Indirect comparisons from a meta-analysis suggest no difference in thrombosis or major bleeding rates with twice- compared with thrice-daily regimens (Chest 2011;140:374-81).
3. The bioavailability of subcutaneously administered drugs is reduced in critically ill patients with the concomitant use of vasoactive drugs or the presence of edema, thereby potentially providing a reduced effect.
4. Renal impairment
 - a. Critically ill patients (n=138) administered prophylactic subcutaneous dalteparin with an estimated creatinine clearance (CrCl) less than 30 mL/minute were evaluated in a prospective study.
 - b. No evidence of accumulation or an increased risk of bleeding (Arch Intern Med 2008;168:1805-12)
5. Bleeding
 - a. Bleeding rates in critically ill patients are variable, depending on the type of pharmacologic prophylaxis.
 - b. Patients at high risk of bleeding are often excluded from studies.
 - c. Patients at high risk of bleeding with a moderate to high risk of VTE may be considered for mechanical VTE prophylaxis; however, pharmacologic prophylaxis should be reassessed when bleeding risk is no longer present.

E. Novel Oral Anticoagulants for VTE Prophylaxis

1. No studies to date conducted in critically ill ICU patients.
2. Rivaroxaban has been shown to be noninferior to standard treatments in other settings such as orthopedic surgery.
3. Rivaroxaban 10 mg orally once daily (35-day regimen) was compared with enoxaparin 40 mg subcutaneously daily for 10 days, followed by placebo in acutely ill, hospitalized patients (N Engl J Med 2013;368:513-23).
 - a. Rates of composite end point (asymptomatic or symptomatic VTE, pulmonary embolism, or death):
 - i. Day 10: 2.7% in both the rivaroxaban and enoxaparin group, p=0.003; met criteria for noninferiority
 - ii. Day 35: 4.4% in the rivaroxaban group vs. 5.7% in the enoxaparin/placebo group, p=0.02; met criteria for superiority
 - b. Clinically relevant bleeding events
 - i. Day 10: 2.8% in the rivaroxaban group vs. 1.2% in the enoxaparin group, p<0.001
 - ii. Day 35: 4.1% in the rivaroxaban group vs. 1.7% in the enoxaparin/placebo group, p<0.001

F. Heparin-Induced Thrombocytopenia (Chest 2012;141(2 suppl):495S-530S)

1. HIT is a severe, immune-mediated reaction potentially leading to life-threatening complications such as myocardial infarction, skin necrosis, stroke, and VTE (around 50%–75% of patients with HIT develop symptomatic thrombosis).
2. A rare manifestation is delayed-onset HIT, affecting patients exposed to heparin in the recent past (prior 2 weeks) that present with new thrombosis and low platelet counts.

3. Frequency of HIT
 - a. Higher in patients receiving unfractionated heparin compared with low molecular weight heparin, occurring in 1%-5% of patients versus less than 1%, respectively.
 - b. Occurs in less than 1% of ICU patients
 - c. Higher risk in cardiac or orthopedic surgical patients receiving unfractionated heparin (1-5) than in medical patients (0.1-1)
4. Alternative causes of thrombocytopenia in critically ill patients include extracorporeal devices, intra-aortic balloon pumps, sepsis, disseminated intravascular coagulation, bleeding, and medications. Platelets may decrease post-cardiac bypass surgery and subsequently recover. A secondary drop in platelets may signal potential HIT.
5. The clinical diagnosis of HIT
 - a. Suspected when a patient has a decrease in absolute platelet count to less than 150,000/mm³ or a relative decrease of at least 50%, skin lesions at injection sites, or systemic reactions after intravenous boluses.
 - b. The typical onset is 5–10 days after heparin exposure, though it can be delayed and occur up to 3 weeks after cessation of therapy.
 - c. Recent heparin exposure may result in rapid-onset HIT, occurring within hours after rechallenge.
 - d. Patients with recent unfractionated heparin/low molecular weight heparin exposure and new thrombosis should have their platelet counts checked before starting anticoagulant therapy.
6. Probability of HIT
 - a. The 4T's pretest clinical scoring system has a high negative predictive value; however, it requires further investigation in ICU patients.
 - b. The HEP (HIT Expert Probability) score has not been assessed in ICU patients.
7. Laboratory testing
 - a. Platelet factor 4 (PF4): ELISA
 - b. Antibody present if sample from patient binds to the heparin-PF4-coated wells, leading to a color-producing reaction. A higher antibody concentration leads to more color production and a higher optical density reading. Optical density readings of 0.4 or greater are considered positive and indicate the presence of HIT antibodies.
 - c. High sensitivity (greater than 90%)
 - d. Low to moderate specificity
 - i. As low as 20%, depending on the patient population studied
 - ii. Clinically insignificant HIT antibodies are often detected among patients who have received heparin 5-100 days earlier.
 - iii. Detects a range of immunoglobulin (Ig) A and IgM antibodies that are not pathogenic
 - e. Heparin-induced platelet aggregation (HIPA) and C₁₄ serotonin release assay (SRA): Functional assays
 - i. Patient serum is mixed with washed platelets from healthy volunteers and low and high concentrations of heparin. In the presence of HIT antibodies, platelets are activated in low concentrations of heparin and detected using radioactive serotonin (SRA) or visually (HIPA).
 - ii. High sensitivity and specificity
 - iii. Technically challenging and not readily available
8. Treatment of HIT
 - a. Immediately discontinue all sources of heparin and initiate an alternative non-heparin anticoagulant.
 - b. Parenteral direct thrombin inhibitors are the agents of choice for anticoagulation in the setting of acute HIT because they have no cross-reactivity with heparin. Some studies support the use of the factor Xa inhibitor, fondaparinux for the treatment of HIT, although there are reports of fondaparinux-induced HIT.

- c. Parenteral direct thrombin inhibitors are associated with a higher rate of major bleeding complications compared with unfractionated heparin, and no antidote is available for excessive anticoagulation.
- d. Initiate warfarin once the platelet count has recovered and is within normal limits (at least $150,000/\text{mm}^3$) and after at least 5 days of therapy with an alternative anticoagulant. Alternatively, conservative warfarin dosing may begin once platelet count is recovering. If a patient is on warfarin at the time of HIT diagnosis, reversing with vitamin K is recommended.
- e. Argatroban dosing in the critically ill population (Crit Care 2010;14:R90; Ann Pharmacother 2007;41:749-54)
 - i. Mean dose in critically ill patients was $0.24 (\pm 0.16)$ mcg/kg/minute.
 - ii. Mean dose in critically ill patients with multiple organ dysfunction was $0.22 (\pm 0.15)$ mcg/kg/minute.
 - iii. Lower doses, 0.5 mcg/kg/min should be considered in severe liver impairment.
 - iv. Target aPTT is 1.5–3 times baseline.
- f. Bivalirudin dosing in the critically ill population (Pharmacotherapy 2006;26:452-60)
 - i. Dose reduced to 0.05–0.1 mg/kg/hour, depending on renal function and bleeding risks.
 - ii. Slightly higher doses may be necessary with continuous renal replacement therapy (0.07 mg/kg/hour).
 - iii. Target aPTT is 1.5–2.5 times baseline.

Table 11. Parenteral Agents for the Treatment of HIT

	Argatroban	Desirudin (Iprivask)	Bivalirudin (Angiomax)	Fondaparinux (Arixtra)
FDA approved for the treatment of HIT	Yes	No	Percutaneous coronary intervention with HIT	No
Mechanism of action	Direct thrombin inhibitor	Direct thrombin inhibitor	Direct thrombin inhibitor	Factor Xa inhibitor
Elimination half-life	40–50 minutes	120 minutes	25 minutes	17–20 hours
Elimination	Hepatobiliary	Renal	80% enzymatic; 20% renal	Renal
Dosing	2 mcg/kg/minute (see above for dosing in critically ill)	Unlabeled dose for HIT: 15–30 mg SC every 12 hours	Unlabeled dose for HIT: 0.15–0.2 mg/kg/hour (see above for dosing in critically ill)	Unlabeled dose for HIT: 5–10 mg SC daily (dependent on weight); 2.5 mg/day for prophylaxis
Monitoring	aPTT	aPTT	aPTT	Anti-factor Xa level
Effect on INR	Excessive	Minimal	Moderate	None

aPTT = activated partial thromboplastin time; FDA = U.S. Food and Drug Administration; HIT = heparin-induced thrombocytopenia; SC = subcutaneously.

Patient Cases

5. A 93-year-old bedbound man (weight 45 kg) is admitted from a nursing home with a chronic obstructive pulmonary disease exacerbation requiring mechanical ventilation. He has a history of diabetes mellitus and heart failure. His laboratory values are all within normal limits except for a BUN of 35 mg/dL and an SCr of 2.8 mg/dL (baseline 0.5). Which would be the most appropriate recommendation for VTE prophylaxis in this patient?
- A. Intermittent pneumatic compression devices.
 - B. Enoxaparin 30 mg subcutaneously once daily.
 - C. Heparin 5000 units subcutaneously twice daily.
 - D. Fondaparinux 2.5 mg subcutaneously daily.

Questions 6 and 7 pertain to the following case.

A 55-year-old man (weight 60 kg) with a medical history of diabetes mellitus, hyperlipidemia, and a DVT 2 months ago secondary to trauma to the lower extremity is admitted today to the ICU for acute respiratory failure from influenza virus. His current laboratory values are as follows, WBC 13.1×10^3 cells/mm³, platelet count 250,000/mm³, BUN 13 mg/dL, SCr 0.9 mg/dL, INR 1.2, AST 22 IU/mL, and ALT 11 IU/mL. His current medication regimen includes fentanyl and midazolam boluses for pain and agitation, piperacillin/tazobactam, vancomycin, regular insulin infusion, SUP, and a heparin drip. Five days later, the patient remains intubated on the same medications. At this time, it is noted that his platelet count has dropped to 112,000/mm³, and his BUN and SCr have increased to 45 mg/dL and 2.7 mg/dL, respectively. The team sends a heparin-PF4 immunoassay; however, the results will not come back for 48 hours.

6. Which would be the best course of action?
- A. Discontinue heparin drip, and initiate argatroban continuous infusion at 0.5 mcg/kg/minute.
 - B. Do nothing because the patient has several other reasons to be thrombocytopenic.
 - C. Discontinue heparin drip, and initiate fondaparinux at 10 mg subcutaneously daily.
 - D. Do nothing until the heparin-PF4 immunoassay results.
7. Three days later, both the heparin-PF4 immunoassay and the SRA (serotonin release assay) return positive, and the patient has a new DVT. The team would like to initiate warfarin. The patient's current platelet count is 130,000/mm³. Which would be the most appropriate response?
- A. Discontinue argatroban and initiate warfarin at 5 mg orally daily.
 - B. Discontinue argatroban and initiate warfarin at 10 mg orally daily.
 - C. Warfarin should never be used in patients with HIT.
 - D. Warfarin should not be initiated now.

IV. END-OF-LIFE CARE

- A. Clinicians commonly provide end-of-life and palliative care in ICUs.
- B. The World Health Organization describes palliative care as “an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual” (Global Atlas of Palliative Care at the End of Life).

C. Goals of Palliative Care

1. To improve the quality of life for individuals who have severe diseases.
2. To offer a diverse array of assistance and care to the patient.

D. Categories of Support

1. Pain management is of paramount importance for comfort and reduction of distress. Providers and families can collaborate to identify the sources of pain and relieve them with drugs and other forms of therapy.
2. Symptom management involves treating symptoms other than pain such as nausea, thirst, bowel and bladder problems, depression, anxiety, dyspnea, and secretions.
3. Emotional and spiritual support is important for both the patient and the family in dealing with the emotional demands of critical illness.

E. General Considerations

1. Minimization of uncomfortable or unnecessary procedures, tests, or treatments.
2. Minimizing or discontinuing routine vital sign checks, patient weights, cardiac or other electronic monitoring, fingersticks, and intermittent pneumatic compression devices.
3. Consider discontinuing routine blood draws, radiologic imaging, and other diagnostic procedures.
4. Consider discontinuing all medications not necessary for patient comfort.

F. Symptom Management

1. Pain

- a. Opioids are the mainstay of treatment for patients experiencing pain at the end of life.
- b. Administer opioid as an intravenous bolus dose and begin an intravenous continuous infusion, adjusting rates to maintain comfort; avoid using subcutaneous or enteral routes because the onset is delayed.
- c. No evidence that unconscious patients do not experience pain; therefore, opioid administration should be initiated or continued
- d. Bolus and titrate infusions to control labored respirations; specific dosages of medications are less important than the goal of symptom relief. Optimal dose is determined by assessing the patient and rapidly increasing it as needed until symptoms are no longer present. Dose determined by symptom relief and adverse effects (excessive sedation, respiratory depression [rare])
- e. Suggested goals include keeping the respiratory rate at or below 30 breaths/minute and eliminating grimacing and agitation.
- f. Never use neuromuscular blocking agents to treat pain.
- g. Morphine most commonly used; hydromorphone and fentanyl are alternatives.
- h. In addition, opiates will reduce dyspnea.
- i. Tolerance may develop over time.
- j. Evidence is good that pain can be improved with correct dosing and titration without causing respiratory depression or hastening death (JAMA 1992;267:949-53; Crit Care Med 2004;32:1141-8).

2. Anxiety/agitation/delirium

- a. Symptoms at the end of life can relate to acute or chronic anxiety, delirium, or terminal delirium.
- b. Nonpharmacologic treatments for agitation and anxiety can include frequent reorientation to the environment and reduction in noise and other bothersome or stimulating environmental factors.
- c. Intravenous haloperidol may be used without electrocardiographic (ECG) monitoring because the benefits outweigh the risks of prolonged QTc (corrected QT interval), given the goals of care.

- d. Benzodiazepines (midazolam and lorazepam)
 - i. Dose is determined by assessing the patient and increasing as needed until symptoms are no longer present if haloperidol fails to relieve significant agitation.
 - ii. Determining what would be perceived as an acceptable level of sedation with the patient and/or family or surrogate decision-maker is important before initiating sedatives.
 - iii. Tolerance may develop over time.
- 3. Fever
 - a. Acetaminophen is an effective therapy for improving comfort and decreasing the incidence of fever. If patient is unable to swallow, this agent may be administered per rectum.
 - b. A nonsteroidal anti-inflammatory drug may be used when acetaminophen is ineffective.
 - c. Dexamethasone, which is also known to have antipyretic properties, could be considered.
- 4. Nausea and vomiting
 - a. Underlying causes such as medications, uremia, ascites, gastroparesis, and intestinal or gastric obstruction should be treated or eliminated, if possible.
 - b. Agents to consider include haloperidol, metoclopramide, ondansetron, and dexamethasone.
 - c. Lorazepam can be considered as an adjunct, especially with anticipatory vomiting.
 - d. Use of more than one agent may be necessary for symptom relief.
- 5. Cough
 - a. Excessive coughing can lead to exacerbation of dyspnea, and spells of nausea and vomiting, in addition to disturbing sleep and exacerbating pain.
 - b. Non-opioid antitussives such as benzonatate and dextromethorphan may be considered.
 - c. All opioids have intrinsic antitussive action by inhibiting the brain stem cough center; however, if the patient is on an opioid for other reasons, adding another opioid has not shown additional benefit.
 - d. For refractory cough, consider nebulized lidocaine.
- 6. Secretions
 - a. Near the end of life, the ability to clear oral and tracheobronchial secretions diminishes.
 - b. Secretions are usually too low in the tracheobronchial tree for gentle oral suctioning to be of help, and suctioning can be disturbing.
 - c. The mainstay of treatment includes anticholinergic and antimuscarinic medications.
 - i. Scopolamine and atropine cross the blood-brain barrier and can be more sedating than glycopyrrolate.
 - ii. Glycopyrrolate (0.1 mg intravenously every 4 hours) or atropine (1% ophthalmic solution 2 drops sublingually every 4 hours as needed) should be used to manage acute symptoms.
 - iii. Scopolamine patch is more gradual in onset (12 hours).
 - iv. More than one scopolamine patch may be used for unrelieved symptoms.

Patient Case

8. An 88-year-old woman is admitted to the ICU for decompensated heart failure and acute kidney injury. This is her fourth admission to the ICU in the past 5 months. Speaking with the patient, you find that she wishes not to be resuscitated or intubated but only to be comfortable. In a meeting with the patient's family, all members agree that they do not want to see their loved one suffer any longer. It is decided to initiate a morphine drip at 2 mg/hour. Titration parameters include giving a bolus dose equivalent to the current rate and increasing the infusion by 25%. The nurse taking care of the patient believes that the titration parameters are too aggressive. Which would be the most appropriate change in titration parameters?
- A. Change the parameters to increase only the morphine drip when the patient shows signs of discomfort, such as an increase in blood pressure or heart rate.
 - B. Discontinue titration parameters, keeping the morphine infusion at the current rate.
 - C. Discontinue titration parameters, keeping the morphine infusion at the current rate and adding a midazolam infusion at 2 mg/hour.
 - D. Do not change the titration parameters at this time.

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End-of-Life Care

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ANSWERS AND EXPLANATIONS TO PATIENT CASES**1. Answer: A**

The mnemonic FAST-HUG stands for **F**eeding, **A**nalgesia, **S**edation, **T**hromboembolic prophylaxis, **H**ead of bed elevation, stress **U**lcer prophylaxis, and **G**lycemic control. Using this mnemonic as a “checklist” every day for each critically ill patient will assist in maximizing therapeutic interventions and promote patient safety. This patient would benefit from having enteral nutrition initiated (patient has an NGT already placed and has a working GI tract), a sedative interruption (current RASS [Richmond Agitation Sedation Scale] is above the designated goal), and the addition of SUP (risk factors include mechanical ventilation) (Answer A is correct). Critically ill patients with risk factors for VTE, should remain on VTE prophylaxis (Answers B and D are incorrect); moreover, sliding-scale insulin should be initiated when the patient is not critically ill, adding another reason why Answer B is incorrect, as well as making Answer C incorrect.

2. Answer: C

Two independent risk factors for SRMD include respiratory failure requiring mechanical ventilation for 48 hours or longer and coagulopathy (platelet count less than 50,000/mm³, INR greater than 1.5, or aPTT time greater than 2 times the control). This patient has both of these risk factors. In addition, this patient has severe sepsis, as evidenced by end-organ dysfunction and acute kidney injury (Answer C is correct). Answers A, B, and D are incorrect as this patient has four risk factors for SUP.

3. Answer: D

Antacids are not recommended for routine use because of their frequency of administration, adverse effects, and interactions (Answer B is incorrect). In a large randomized controlled trial, sucralfate was inferior to H₂RAs in preventing clinically significant bleeding from SRMD and is generally not recommended because of its adverse effect profile (Answer A is incorrect). Proton pump inhibitors are no better than H₂RAs in preventing SRMD and are associated with increased infectious complications, including pneumonia and CDI (Answer D is correct). Meta-analyses have favored PPIs to H₂RAs for GI bleeding; however, the individual trials included lacked methodological quality (Answer C is incorrect).

4. Answer: C

Once the risk factors are no longer present, SUP should promptly be discontinued (Answer C is correct). This patient no longer has risk factors (mechanical ventilation, coagulopathy acute kidney failure, and severe sepsis). In addition, there is no evidence that SUP should be continued until hospital or ICU discharge or when antimicrobial therapy is complete (Answers A, B, and D are incorrect).

5. Answer: C

The patient has several risk factors for VTE, including immobility and respiratory failure, making heparin 5000 units subcutaneously twice daily an appropriate choice for VTE prophylaxis (Answer C is correct). Neither enoxaparin nor fondaparinux is appropriate for this patient, who has acute kidney injury with an estimated CrCl of less than 20 mL/minute (Answers B and D are incorrect). Intermittent pneumatic compression would be insufficient in a patient with no contraindication to pharmacologic prophylaxis (Answer A is incorrect).

6. Answer: A

Diagnosing HIT is difficult in a critically ill patient because there are many alternative causes of thrombocytopenia. Clinical assessment is essential in diagnosing HIT because of the immediate need for treatment and the delay in laboratory testing (Answers B and D are incorrect). Clinically, this patient has a greater than 50% drop in platelet count within 5 days of receiving heparin. This patient had a DVT 2 months ago, when he was probably exposed to heparin products. The first step in managing suspected HIT is to ensure that all forms of heparin are discontinued, including flushes or heparin-coated catheters. The next step is to initiate an alternative form of anticoagulation. Direct thrombin inhibitors are the agents of choice for anticoagulation in the setting of acute HIT because they have no cross-reactivity with heparin (Answer A is correct). Factor Xa inhibitors have been used in the management of HIT; however, they would not be the best choice in this patient, who has acute kidney injury (Answer C is incorrect).

7. Answer: D

Warfarin can be initiated (Answer C is incorrect) once the platelet count has recovered to at least 150,000/mm³ and after at least 5 days of therapy with an alternative anticoagulant (Answer D is correct). Because this patient's platelet counts have not reached 150,000/mm³ and only 3 days of argatroban have been completed, warfarin therapy should not be initiated at this time (Answers A and B are incorrect). Argatroban should be continued, and warfarin may be considered at low doses (maximum 5 mg) as the platelet count continues to recover (Answer B is incorrect).

8. Answer: D

Up to 50% of seriously ill, hospitalized patients will experience moderate or severe pain. Opioids are the mainstay of treatment for patients experiencing pain and dyspnea at the end of life. Assessing pain in the ICU can be particularly challenging because many patients have impaired cognition and communication. The use of vital signs alone should not be used alone for pain assessment (Answer A is incorrect). Evidence suggests that pain can be improved with correct dosing and titration (Answers B and C are incorrect) without causing respiratory depression or hastening death (Answer D is correct).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS**1. Answer: C**

The FAST-HUG mnemonic can serve as a “checklist” for every patient admitted to the ICU. Every patient should be assessed for a sedation interruption in an effort to minimize sedative exposure and maintain a light level of sedation (Answer C correct). To decrease the risk of nosocomial pneumonia, each patient should have his or her head 30–45 degrees above the head of the bed (Answer C correct). Enteral nutrition should be initiated as soon as possible—typically, once the patient is stabilized; however thromboprophylaxis should be initiated in every patient, using pharmacologic agents preferentially to mechanical prophylaxis (Answer B is incorrect). Stress ulcer prophylaxis should be initiated only in patients who have risk factors present and should be discontinued when the risk factor does not exist (Answer A is incorrect). Insulin infusions should be initiated only if blood glucose readings are not within the range of 140–180 mg/dL (Answer D is incorrect).

2. Answer: C

Sucralfate forms a protective barrier over the surface of the stomach, reducing exposure to acidic gastric contents; therefore, sucralfate has no effect on gastric pH (Answer A is incorrect). Compared with H₂RAs, PPIs seem to be more effective in reducing gastric acidity, but no well-conducted trial has shown PPIs to be superior in preventing clinically significant bleeding (Answer B is incorrect). Tolerance to any H₂RA may occur, but not with PPIs (Answer C is correct). Antacids have some effect on reducing stress ulceration, provided the gastric pH is kept above 3.5, but frequent dosing (up to every 2 hours) is required to achieve this goal, making their use impractical (Answer D is incorrect).

3. Answer: D

The patient has an indication for SUP (mechanical ventilation). The patient has an NGT in place and is tolerating tube feedings, indicating a functioning gut; therefore, intravenous therapy is not required (Answers A and B are incorrect). The patient has erosive esophagitis, for which a PPI will be more effective than an H₂RA (Answer C is incorrect). Omeprazole suspension is effective in the prevention of SRMD; therefore, omeprazole suspension would be the most appropriate choice for this patient (Answer D is correct).

4. Answer: A

Proton pump inhibitors are potent inhibitors of gastric acid production and are the drug of choice for treatment of gastroesophageal reflux disease. To date, no prospective randomized controlled trials have evaluated the risk of CDI with PPI use (Answer B is incorrect). A cohort study showed an increased risk of CDI when PPIs were used more frequently than daily (Answer C is incorrect). All published trials assessing the risk of CDI with PPI use have been limited by the inconsistent definitions of CDI and the variable infection control practices (Answer D is incorrect). Gastric juice is strongly bactericidal for microorganisms. Proton pump inhibitors are commonly used to increase the gastric pH; therefore, they act as a potential risk factor for CDI (Answer A is correct).

5. Answer: B

Low-dose unfractionated heparin or low-molecular-weight heparin should be initiated for VTE prophylaxis in a critically ill patient over no prophylaxis (Answer D is incorrect). Intermittent pneumatic compression devices would be insufficient prophylaxis in a patient with several risk factors for VTE (Answer A is incorrect). A continuous infusion of heparin is inappropriate for the prevention of VTE (Answer C is incorrect). Enoxaparin may be used in a critically ill patient with stable renal function for VTE prophylaxis (Answer B is correct).

6. Answer: A

This patient sustained a closed-head injury, placing her at high risk of VTE (Answer D is incorrect). The patient is at high risk of having major bleeding and experiencing acute kidney injury; therefore, use of a low-molecular-weight heparin or a factor Xa inhibitor would not be the best option in this patient (Answers B and C are incorrect). Mechanical prophylaxis with intermittent pneumatic compression devices is preferred to no prophylaxis in the absence of lower extremity injury until the bleeding risk is no longer present (Answer A is correct).

7. Answer: D

Clinical assessment is essential in the diagnosis of HIT because of the immediate need for treatment and the delay in laboratory testing. Although this patient did experience a 50% decrease in his platelet count, the

characteristic onset of the platelet count fall in HIT is 5–10 days after heparin initiation. Clinical prediction rules to assist in determining the probability of HIT have been developed such as the 4T's score. Patients with a low 4T's score (0–3) have a very low probability of HIT (Answer D is correct). Direct thrombin inhibitors are the agents of choice for anticoagulation in the setting of acute HIT because they have no cross-reactivity with heparin. Initiating these agents in the setting of a low probability of HIT may lead to an unnecessary increase in bleeding risk (Answer B is incorrect). If HIT were highly suspected in this patient, the first step in the management of HIT would be to ensure the discontinuation of all forms of heparin, including flushes or heparin-coated catheters (Answer C is incorrect). The next step would be to initiate an alternative form of anticoagulation (Answer A is incorrect).

8. Answer: C

General considerations in the critically ill patient at the end of life include minimization of uncomfortable or unnecessary procedures, tests, or treatments, including fingersticks, Foley catheters, and routine vital signs (Answers A, B, and D are incorrect). Symptom management of pain and anxiety, fever, cough, secretions, nausea and vomiting, and delirium should be considered in the dying patient (Answer C is correct).