



Consensus and Guideline

Guidelines for the prevention and treatment of stress ulcers in critically ill patients (2026)[☆]Guideline Working Group of the Chinese Society of Critical Care Medicine[#], Yan Kang^{1,*}, Xiangdong Guan^{2,*}, Dechang Chen^{3,*}¹ Department of Critical Care Medicine, West China Hospital, Sichuan University, Chengdu 610044, China² Department of Critical Care Medicine, the First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, China³ Department of Critical Care Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China

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ABSTRACT

Stress ulcers is a common complication in critically ill patients, associated with increased mortality risk and prolonged intensive care unit stay. In recent years, several large-scale clinical studies on risk factors, prevention, and treatment of stress ulcers have provided new evidence for guideline development. Moreover, the lack of standardized protocols for the prevention and treatment of stress ulcers in clinical practice underscores the urgent need for authoritative guidelines to address inconsistent management strategies. Accordingly, the Chinese Society of Critical Care Medicine established a multidisciplinary expert panel to develop the “*Guidelines for the Prevention and Treatment of Stress Ulcers in Critically Ill Patients (2026)*”. Following the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology, the guideline formulation process involved proposing clinical questions, literature retrieval and screening, meta-analysis and evidence synthesis, initial formation of recommendation items, panel reviews, three rounds of remote meetings, four rounds of face-to-face meetings, manuscript revisions, and final approval by the Standing Committee of the Society. The guidelines were finalized in the form of 23 evidence-based recommendations. These guidelines cover key aspects of stress ulcer management, including risk factors, prevention, treatment, and adverse effects of acid-suppressive drugs. The aim is to provide evidence-based guidance for healthcare professionals and promote standardized clinical management of stress ulcers in adults.

Introduction

Stress ulcers, characterized by acute gastrointestinal mucosal erosion, ulceration, and secondary bleeding, is induced by stressors. Evidence indicates that 75%–100% of patients undergoing endoscopic examination within 72 h of onset exhibit gastric mucosal lesions, with 1%–17% progressing to stress ulcers accompanied by bleeding.^[1] While prophylactic acid-suppressive therapy may mitigate the risk of stress ulcers and severe gastrointestinal bleeding, it is associated with an increased risk of *Clostridium difficile* infection and ventilator-

associated pneumonia.^[2–4] Furthermore, considerable heterogeneity exists in clinical practices regarding the selection of acid-suppressive agents and the duration of treatment for stress ulcer prophylaxis.^[5,6] Therefore, the Expert Working Group of the Chinese Society of Critical Care Medicine (Beijing, China) formulated guidelines to standardize the clinical management of stress ulcers in critically ill patients. By integrating the latest evidence and expert consensus, the objective of these guidelines is to provide evidence-based recommendations for the diagnosis, prevention, and treatment of stress ulcers in critically ill patients across clinical specialties.

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* Corresponding authors: Dechang Chen, Department of Critical Care Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China; Xiangdong Guan, Department of Critical Care Medicine, the First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, China; Yan Kang, Department of Critical Care Medicine, West China Hospital, Sichuan University, Chengdu 610044, China.

E-mail addresses: kangyan@scu.edu.cn (Y. Kang), guanxd@mail.sysu.edu.cn (X. Guan), 18918520002@189.cn (D. Chen).

[#] All the members of the “Guideline Working Group of the Chinese Society of Critical Care Medicine” are given in the section “Expert Working Group for Guideline Development”.

Methodology

Working group and development process

The process was initiated by the Chinese Society of Critical Care Medicine, and these guidelines were collaboratively developed by 22 multidisciplinary experts specializing in critical care medicine, health statistics, evidence-based medicine, and medical informatics. The working group, established in March 2023, formulated the “Guidelines for the Prevention and Treatment of Stress Ulcers in Critically Ill Patients”. The guidelines were registered on the International Practice Guidelines Registry and Transparency Platform (Registration No.: PREPARE-2024CN873). The final version was rigorously developed through sequential phases: kick-off meetings; clinical question formulation; comprehensive literature search and screening; meta-analysis and evidence synthesis; preliminary recommendation drafting; iterative peer review by the working group; three virtual and four face-to-face meetings; draft revisions; and culminating in a formal vote by standing committee members of the Society.

Formulation of clinical questions

The working group identified high-priority clinical questions by reviewing recent advances in domestic and international literature, relevant guidelines, consensus statements, and clinical practices. Key domains encompassed the definition, epidemiology, pathogenesis, risk factors, prevention, and treatment of stress ulcers, alongside adverse effects of acid-suppressive drugs. All clinical questions were structured using the PICO framework, specifying: Participants (Populations), Interventions (Interventions), Comparisons (Controls), and Outcomes (Outcomes). This methodology established explicit inclusion/exclusion criteria for literature retrieval and guided the selection of clinical studies for evidence synthesis.

Systematic review and meta-analysis

Working group members systematically searched English databases (PubMed, Cochrane Library, Embase, Web of Science) and Chinese databases (Wanfang, China National Knowledge Infrastructure [CNKI], VIP [also known as Chinese Scientific Journal Database]) in accordance with PICO principles. The search period spanned from January 1973 to March 2024. Search terms included abbreviations and full nomenclature for “stress ulcer”, “acute gastric mucosal lesions”, “acute gastric mucosal erosion”, “acute gastric mucosa injury”, “stress-related mucosal disease”, “upper gastrointestinal bleeding (UGIB)”, “gastrointestinal bleeding”, and “gastrointestinal hemorrhage”. Literature retrieval adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, with identification, screening, and inclusion processes following the PRISMA flowchart. Systematic reviews, clinical trials, and retrospective cohort studies were prioritized, whereas case series and case reports were excluded. Three independent working group members screened articles for relevance. Eligible full texts were assessed using predefined inclusion and exclusion criteria. Studies exclusively involving adult patients (aged ≥18 years) were included. Studies failing to report

Table 1
GRADE framework for assessing the quality of evidence.

Assessment domain	Criteria
Methodology	• High: randomized controlled trials (RCTs), observational studies with an upgraded quality of 2 levels • Moderate: RCTs with a downgrading quality of 1 level or observational studies with an upgrading quality of 1 level • Low: RCTs with a downgrading quality of 2 levels or observational studies. • Very low: RCTs with a downgrading quality of 3 levels, observational studies with a downgrading quality of 1 level, case series, expert opinions, or others
Downgrading factors	• RCTs with a high possibility of bias • Inconsistent results, including subgroup analyses • Indirect evidence (different populations, interventions, controls, outcomes, comparisons) • Inaccurate results • High possibility of reporting bias
Upgrading factors	• Large effects with an upgrading quality of 1 level (direct evidence, relative risk >2 with no suspected confounding factors) • Larger effects with an upgrading quality of 2 levels (direct evidence, relative risk >5 and no confounding factors affecting validity) • Dose–response relationship

GRADE, Grading of Recommendations Assessment; Development, and Evaluation; RCT, Randomized controlled trial.

intensive care unit (ICU) admission status, therapeutic interventions, or mortality data were excluded. As the working group focused on critically ill adults, pediatric populations were excluded. Consequently, recommendations apply solely to critically ill adults; extension to pediatric populations necessitates dedicated literature searches and evidence evaluation. Given the dynamic nature of evidence on stress ulcers diagnosis, prevention, and treatment, these guidelines maintain a validity period of 5 years.

Formulation of recommendations

The strength of recommendations is determined based on the quality of evidence, assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework. This system classifies evidence certainty from high to very low (Tables 1 and 2).

Evidence grading

The GRADE methodology evaluates the certainty of evidence according to five key criteria: (1) risk of bias; (2) inconsistency; (3) indirectness; (4) imprecision; and (5) publication bias. The GRADE evidence certainty classification is detailed in Table 1. High-certainty evidence derived from randomized controlled trials (RCTs) may be subject to downgrading based on factors outlined in Table 1. Conversely, low-certainty evidence originating from observational studies can be elevated through the upgrading factors specified in Table 1.

Recommendation levels

The GRADE methodology classifies recommendations into Strong or Weak, with factors influencing this determination de-

Table 2
Determinants of recommendation levels.

Considered questions	Recommendation process
High or moderate quality evidence	Higher evidence quality increases the likelihood of a strong recommendation.
Certainty of risk/benefit and burden	Greater difference between the intervention and control groups denotes greater certainty of the difference and increases the likelihood of a strong recommendation. Smaller net benefit indicates less certainty of the benefit and increases the likelihood of a weak recommendation.
Certainty and similarity of effects	Greater certainty or similarity of effects increases the likelihood of a strong recommendation.
Cost of expected benefit	Lower cost in the intervention group compared with the control group (i.e., fewer resources consumed) increases the likelihood of a strong recommendation.

Table 3
Good Practice Statement criteria.

Index	Criteria
1	Is this statement clear and performable?
2	Is this recommendation necessary?
3	Is the net benefit (or harm) explicit?
4	Is it difficult to collect and summarize evidence?
5	Is the recommended reason explicit?
6	Is it better than the GRADE method?

tailed in [Table 2](#). The working group assigns recommendation levels based on the quality of the evidence, the risk/benefit ratio of the intervention, the certainty of the outcomes, resource availability, and the feasibility and acceptability of the intervention. An intervention demonstrating a clear preponderance of benefits over harms warrants a Strong Recommendation. Conversely, an intervention where benefits likely outweigh harms, but substantial uncertainty exists (e.g., due to low-quality evidence) is classified as a Weak Recommendation. In instances where the evidence on benefits or risks cannot be adequately synthesized or assessed using the GRADE framework, the working group formulates and presents Good Practice Statements (GPS). The criteria for formulating GPS are described in [Table 3](#).

Expert voting

The working group formulated draft recommendations following discussion via remote or in-person meetings. Subsequently, all members participated in an anonymous vote via questionnaire to indicate approval, opposition, or abstention. A recommendation was accepted only if it achieved a minimum participation rate of 75% and secured at least 80% support. In case consensus was not reached after three voting rounds, participants submitted written feedback. The working group considered this feedback to determine whether the recommendation warrants revision or rejection.

Overview of Stress Ulcers

Definition, classification, and epidemiology of stress ulcers

Stress related mucosal disease (SRMD)/Stress ulcer (SU)

Stress ulcer, also clinically termed SRMD, refers to a series of acute gastrointestinal mucosal lesions—including erosions, ulcerations, and hemorrhage—that occur under condi-

tions of severe physiological stress, such as major trauma, complex surgery, or critical illness. Endoscopically, these manifestations may present as acute gastric mucosal lesions, acute erosive gastritis, acute hemorrhagic gastritis, or peptic ulcers.^[7]

Stress ulcer bleeding (SUB)

SUB refers to gastrointestinal hemorrhage resulting from erosion of submucosal vessels by the aforementioned mucosal lesions. It typically manifests clinically as hematemesis, melena, or bloody stools and represents a severe complication of SRMD/stress ulcer. Stress ulcer bleeding can be categorized into three types: stress ulcer with covert bleeding, stress ulcer with overt gastrointestinal bleeding, and stress ulcer with severe gastrointestinal bleeding. The incidence of covert bleeding is approximately 15%–50%, overt bleeding manifested as hematemesis or melena occurs in about 1.5%–8.5% of cases, while severe gastrointestinal bleeding requiring vasopressor support or endoscopic intervention has an incidence of approximately 1%–3%.^[7] The classification and incidence of stress ulcer bleeding in critically ill patients are summarized in [Table 4](#).

Stress ulcer with perforation

Stress ulcer with perforation, the most severe mechanical complication of stress ulcer, refers to the progression of ulcer depth penetrating the entire wall of the stomach or duodenum, leading to the leakage of gastrointestinal contents into the peritoneal cavity. Clinically, it presents as sudden severe abdominal pain, board-like rigidity, and signs of acute peritonitis and septic shock. Although less common than bleeding, this condition is extremely critical and can rapidly exacerbate systemic infection and multiple organ failure, with a mortality rate as high as 20%.^[8]

Stress ulcer and its complications pose a significant threat to the overall outcomes of critically ill patients and serve as an important marker of poor clinical prognosis. Stress ulcer is associated with increased mortality risk and prolonged ICU stays in critically ill populations.^[9] Patients experiencing clinically significant gastrointestinal bleeding within the ICU exhibit substantially higher mortality compared with non-bleeding counterparts (49% vs. 9%, respectively).^[10] A multinational study including 1034 critically ill patients across 97 ICUs in 11 countries demonstrated clinically significant gastrointestinal bleeding in 2.6% of subjects, with an unadjusted mortality odds ratio (OR) of 3.7 (95% confidence interval [CI]: 1.7–8.0) and an adjusted OR of 1.7 (95% CI: 0.7–4.3).^[11] The classification and incidence of stress ulcers in critically ill patients are listed in [Table 4](#).

Pathogenesis of stress ulcers

The pathogenesis of stress ulcers is illustrated in [Figure 1](#).^[12] Pathogenesis is attributed to augmentation of mucosal injury factors; activation of the sympathetic nervous system elevates catecholamine release, inducing vasoconstriction, hypovolemia, and reduced cardiac output. Concurrently, impaired synthesis of pro-inflammatory cytokines and nitric oxide diminishes gastric mucosal perfusion. This visceral hypoperfusion compromises gastrointestinal motility, delaying the clearance of acidic contents and other luminal irritants. Prolonged exposure to gastric acid consequently increases the risk of ulcer-

Table 4
Classification and incidence of stress ulceration in critically ill patients.

Classification	Definition	Incidence
Stress ulcer with covert bleeding	Fecal occult blood test positivity	15%–50%
Stress ulcer with clinically significant gastrointestinal bleeding	Vomiting blood, black stools, or bloody fluid from gastrointestinal decompression	1.5%–8.5%
Stress ulcer with massive gastrointestinal bleeding	Clinically significant gastrointestinal bleeding within 24 h with one or more of the following: • Decrease in systolic blood pressure, mean arterial pressure, or diastolic blood pressure >20 mmHg • Orthostatic hypotension (change in systolic blood pressure of >10 mmHg) or orthostatic tachycardia (increase in pulse rate by 20 beats/min) • Decrease in hemoglobin level >2 g/dL • More than two units of red blood cell transfusion • Requiring vasopressors or invasive interventions (e.g., endoscopic procedures)	1%–3%

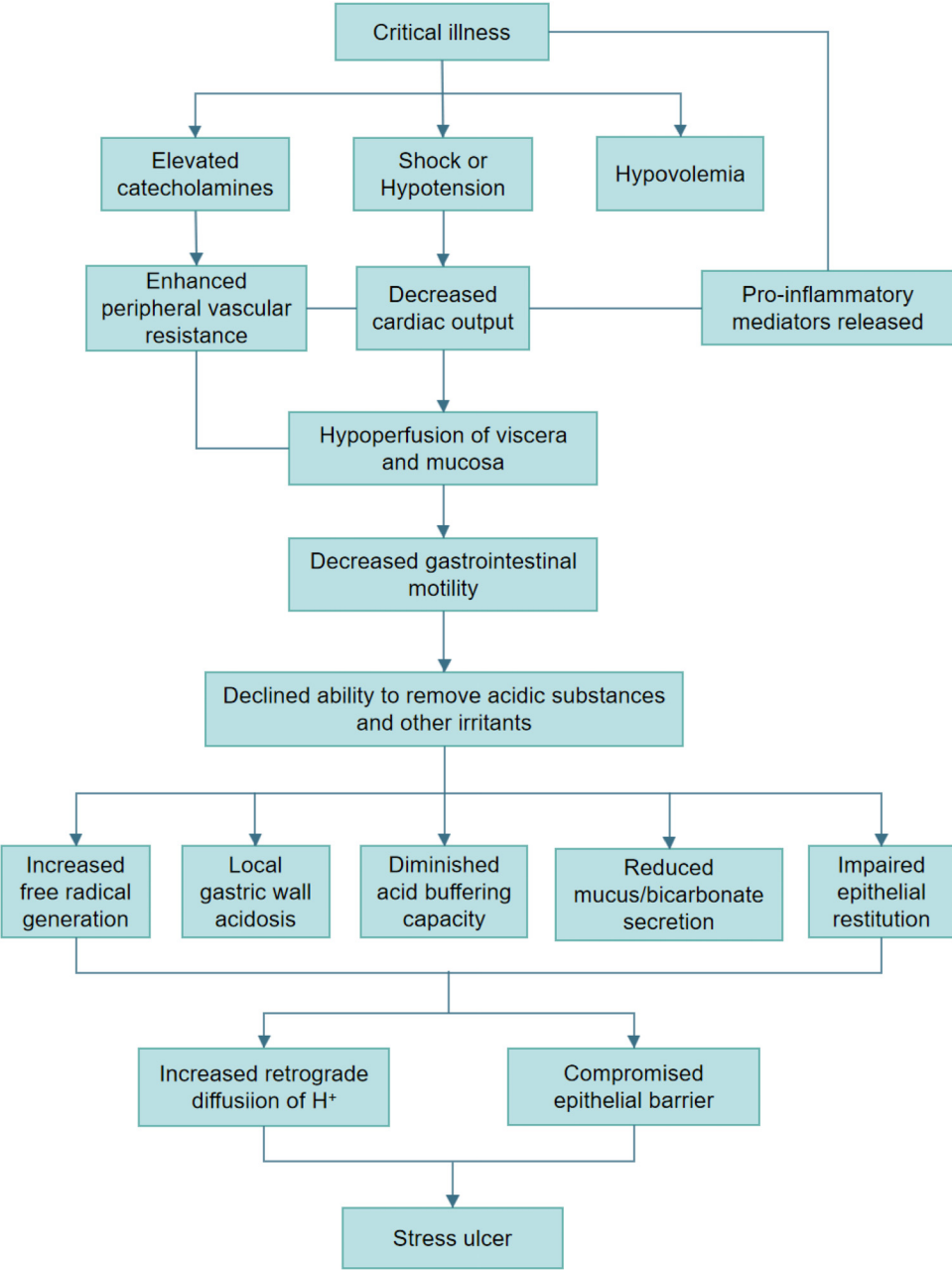


Figure 1. Pathogenesis of stress ulcers.

ation. In addition, the pathogenesis of stress ulcers is associated with impairment of mucosal defense layers; gastric mucosal integrity is maintained by protective elements including prostaglandins, the mucin glycoprotein layer, bicarbonate ions, trefoil factor family (TFF) peptides, phospholipids, and heat shock proteins (HSPs, notably HSP70). Prostaglandins enhance mucosal blood flow while stimulating mucus and bicarbonate secretion, thereby promoting epithelial proliferation and repair. The mucin glycoprotein layer functions as a physical barrier to hydrogen ion diffusion and retains bicarbonate, locally neutralizing gastric acid. In critical illness, shock, severe infection, bile reflux, or toxin exposure, this protective mucin-bicarbonate barrier is disrupted. Resultant local gastric wall acidosis, increased free radical generation, diminished acid buffering capacity, reduced mucus/bicarbonate secretion, and impaired epithelial restitution collectively facilitate increased retrograde diffusion of H^+ ions. This process culminates in structural compromise of the epithelial barrier and gastric mucosal injury.

Risk Factors for Stress Ulcers

Question 1: Which patient-related factors are associated with stress ulcer (or bleeding) in critically ill patients?

Recommendation: High-risk factors for stress ulcer (or bleeding) in critically ill patients include male sex, coagulation dysfunction, shock, and acute coronary syndrome, as well as higher Simplified Acute Physiology Score II (SAPS II) and Sequential Organ Failure Assessment (SOFA) scores (Weak recommendation, low-quality evidence).

Rationale: Critically ill patients frequently present with multiple risk factors for stress ulcers. From a preventive perspective, patients admitted to the ICU should undergo early identification of these factors, and appropriate measures should be implemented following a comprehensive evaluation to mitigate the risk of stress ulcers.

Evidence summary: A systematic review identified 15 studies reporting risk factors for stress ulcer (or bleeding) in critically ill patients.^[11,13–26] Meta-analysis of 9 studies indicated a significantly higher risk in male patients (OR: 1.18, 95% CI: 1.07–1.30).^[11,13–20] Meta-analysis of 7 studies demonstrated that coagulation disorders substantially increase the risk (OR: 2.13, 95% CI: 1.45–3.11).^[5,17,18,21–24] Meta-analysis of 6 studies identified shock as an additional high-risk factor (OR: 1.61, 95% CI: 1.07–2.41).^[15,18,22,24–26] Other significant risk factors included acute coronary syndrome (OR: 1.65, 95% CI: 1.41–1.93)^[17,18], higher SAPS II score (OR: 1.02, 95% CI: 1.01–1.03),^[14,15] and higher SOFA score (OR: 1.23, 95% CI: 1.02–1.49).^[11,15] In summary, established high-risk factors comprise male sex, coagulation disorders, shock, acute coronary syndrome, SAPS II score, and SOFA score.

Question 2: Which non-pharmacological risk factors are associated with stress ulcer (or bleeding) in critically ill patients?

Recommendation: We suggest intensive monitoring for stress ulcer (or bleeding) in critically ill patients receiving renal replacement therapy (RRT) or mechanical ventilation (Weak recommendation, low-quality evidence).

Rationale: Iatrogenic interventions during ICU admission may elevate the risk of stress ulcer in critically ill patients.

Clinical practice should prioritize minimizing the duration of such interventions whenever feasible. Early implementation of protective measures, tailored to the condition of the patient, is warranted to reduce the risk of stress ulcer (or bleeding).

Evidence summary: A recent RCT and its secondary analysis confirmed RRT as a risk factor for stress ulcer (or bleeding) in critically ill patients.^[11,15] Meta-analysis of relevant literature further substantiated RRT as a significant risk factor (OR: 3.36, 95% CI: 1.88–6.04).^[11,14,15] Prolonged ICU stay has been associated with increased risk in retrospective analyses.^[27–29] Three studies found no association between parenteral nutrition and gastrointestinal ulcer or bleeding risk (OR: 1.22, 95% CI: 0.92–1.64)^[17,18,22]. In contrast, a retrospective study conducted by Cook et al.^[30] identified enteral nutrition as a protective factor against gastrointestinal bleeding (OR: 0.30, 95% CI: 0.13–0.67). Meta-analysis of 12 studies revealed no significant association between mechanical ventilation and stress ulcers or clinically important bleeding; however, the evidence level remains low due to substantial risk of bias.^[11,14–17,22–24,31–34] Notably, A meta-analysis of 14 studies showed that, compared with no prophylaxis or prophylaxis with histamine-2 receptor antagonists (H2RAs), prophylactic use of proton pump inhibitors (PPIs) significantly reduced the incidence of gastrointestinal bleeding in mechanically ventilated patients (OR: 0.44, 95% CI: 0.19–1.00).^[18,35–47] Consequently, intensive monitoring is advised for critically ill patients undergoing mechanical ventilation.

Question 3: Which pharmacological risk factors for stress ulcer (or bleeding) should be prioritized in critically ill patients?

Recommendation: We suggest intensive monitoring for stress ulcer (or bleeding) in critically ill patients receiving glucocorticoids, anticoagulants, antiplatelet agents, or nonsteroidal anti-inflammatory drugs (NSAIDs) (Weak recommendation, low-quality evidence).

Rationale: Certain pharmacotherapies may elevate the risk of stress ulcer (or bleeding) in critically ill patients experiencing physiological stress. For instance, systemic glucocorticoid therapy increases gastric acid and pepsin secretion,^[48] potentially exacerbating impairment of the mucosal barrier. NSAIDs may compromise host defense mechanisms by inhibiting prostaglandin synthesis, thereby reducing mucus and bicarbonate secretion and increasing mucosal vulnerability. Furthermore, anticoagulants or antiplatelet agents may promote clot dissolution and inhibit platelet aggregation.

Evidence summary: A meta-analysis of 9 studies examining glucocorticoid use and stress ulcer (or bleeding) risk in critically ill patients revealed that glucocorticoid administration (>200 mg/day hydrocortisone or equivalent) constituted a significant risk factor (pooled OR: 2.02, 95% CI: 1.44–2.84).^[21,49–56] An investigation identified long-term NSAID use as an independent risk factor for gastrointestinal stress ulcer following hip fracture surgery (OR: 4.321, 95% CI: 1.196–15.597; $P=0.025$).^[57] A multicenter prospective study evaluating 12 potential risk factors determined that anticoagulant use (heparin or warfarin) increased the incidence of stress ulcer (or bleeding) (OR: 3.3).^[21] A multicenter retrospective study of patients with severe traumatic brain injury demonstrated that the incidence of UGIB was 25.3% (49/194) in those

receiving anticoagulants and 10.9% (133/1222) in those receiving antiplatelet agents; use of these medications was significantly associated with stress-related ulcer bleeding (OR: 0.458, 95% CI: 0.327–0.643).^[32] A retrospective multicenter study reported gastrointestinal bleeding in 7.2% (50/695) of critically ill patients with coronavirus disease-2019 receiving anticoagulants, constituting the most frequent hemorrhagic complication.^[58]

Prevention of Stress Ulcers

Question 4: Should acid-suppressive drugs be used for the prevention of stress ulcers or UGIB in critically ill patients?

Recommendation: For critically ill patients exhibiting high-risk factors for stress ulcers, we suggest using acid-suppressive drugs for the prevention of stress ulcers or UGIB, in conjunction with active management of the underlying disease and stressors (Weak recommendation, moderate-quality evidence).

Rationale: Critically ill patients frequently present with high-risk factors for stress ulcers, including shock, trauma, surgical procedures, and severe infections. These stressors affect the central nervous system and gastrointestinal tract, potentially precipitating excessive gastric acid secretion, acute thrombosis of the gastrointestinal mucosal vasculature, and mucosal ischemic necrosis. These pathological alterations may culminate in stress ulcers and UGIB. PPIs, such as omeprazole and lansoprazole, inhibit gastric acid secretion at the level of the parietal cell.^[59] Histamine-2 receptor antagonists (H2RAs), such as ranitidine and famotidine, suppress gastric acid secretion induced by gastrin and M-receptor agonists. Both mechanisms effectively attenuate gastric acid production, thereby reducing the risk of stress ulcers in critically ill patients.

Evidence summary: A meta-analysis encompassing 36 studies demonstrated that prophylactic administration of PPIs or H2RAs in critically ill patients significantly reduced the risk of stress ulcer or UGIB (OR: 0.43, 95% CI: 0.32–0.56).^[41,42,60–93] However, prophylactic use did not reduce the risk of all-cause mortality (OR: 1.05, 95% CI: 0.94–1.16).^[63,68,71–73,85,86,90,92–97] Pooled results from 15 RCTs indicated that prophylactic administration of PPIs or H2RAs did not increase the risk of pneumonia (OR: 1.13, 95% CI: 0.98–1.29) or *Clostridium difficile* infection (OR: 0.94, 95% CI: 0.57–1.55) in critically ill patients.^[41,61,63,66,69–74,90–92,94,98]

Question 5: Which acid-suppressive drugs should be used for the prevention of stress ulcers and UGIB in critically ill patients?

Recommendation: We suggest using PPIs for the prevention of stress ulcers or UGIB in critically ill patients (Weak recommendation, moderate-quality evidence).

Rationale: PPIs specifically target the H⁺/K⁺-ATPase enzyme on the membrane of intracellular vesicles within gastric parietal cells, irreversibly binding to the proton pump and rendering it inactive. This mechanism ensures more complete, potent, and prolonged acid suppression. H2RAs, which inhibit H₂ receptors on gastric mucosal parietal cells, confer a shorter duration of acid suppression (4–8 h) and exhibit weaker efficacy compared with PPIs. For stress ulcer prophylaxis, PPIs are asso-

ciated with a lower risk of clinically significant gastrointestinal bleeding compared with H2RAs.

Evidence summary: A meta-analysis of 52 studies showed that, compared with H2RAs, prophylactic administration of PPIs significantly reduced the risk of stress ulcer or UGIB in critically ill patients (OR: 0.52, 95% CI: 0.37–0.74);^[2,18,40,43,61,69,73,96,99–142] however, it did not reduce the risk of all-cause mortality (OR: 1.02, 95% CI: 0.82–1.26)^[96,102,105,111,115,124,131,132,137,140,141] and pneumonia in critically ill patients compared with H2RAs (OR: 1.05, 95% CI: 0.80–1.38).^[18,61,69,96,99,101,103,105,106,111,122,124,131,133,134,136,142]

Question 6: Does enteral nutrition reduce the risk of stress ulcers and UGIB in critically ill patients?

Recommendation: We suggest using enteral nutrition to reduce the risk of stress ulcers and UGIB in critically ill patients without contraindications (Weak recommendation, low-quality evidence).

Rationale: Early enteral nutrition provides essential nutritional support for critically ill patients and preserves gastrointestinal mucosal integrity, thereby enhancing mucosal barrier function. This intervention may exert a preventive effect against stress ulcers and gastrointestinal bleeding. Consequently, enteral nutrition should be initiated expeditiously when the clinical condition of the patient permits.

Evidence summary: A meta-analysis incorporating 15 studies demonstrated that enteral nutrition, compared with parenteral nutrition, significantly reduced the risk of stress ulcer or UGIB in critically ill patients without contraindications (OR: 0.36, 95% CI: 0.17–0.76).^[143–157] Nevertheless, enteral nutrition failed to result in a significant reduction in the risk of all-cause mortality among critically ill patients (OR: 0.62, 95% CI: 0.27–1.41).^[143,145,147,152,153,155–157]

Endoscopic Examination for Stress Ulcers

Question 7: Is early endoscopic examination recommended for diagnosing stress ulcers in critically ill patients?

Recommendation: We recommend against routine endoscopic examinations for the sole purpose of confirming the presence of stress ulcers in critically ill patients. However, endoscopy should be performed to identify the etiology and provide endoscopic therapy for massive gastrointestinal bleeding refractory to medical management (GPS).

Rationale: Current evidence-based research confirms endoscopy as the gold standard for diagnosing acute UGIB. Clinical guidelines for non-variceal upper gastrointestinal bleeding uniformly recommend performing endoscopic procedures within 24 h of bleeding onset in hemodynamically stable patients without contraindications when feasible. However, this guidance applies to critically ill patients, whose unique clinical status presents significant challenges for early endoscopic diagnosis of stress ulcers. Firstly, critically ill patients with stress ulcers frequently exhibit severe comorbidities and poor tolerance for endoscopy, substantially increasing procedural risk. Secondly, stress ulcers may be clinically suspected or diagnosed based on medical history, established risk factors, and clinical manifestations.^[158,159] Critically, these ulcers typically manifest as mucosal erosions with self-limited bleeding amenable to pharmacologic management. Consequently, major Chinese clin-

ical guidelines do not classify endoscopy as a diagnostic necessity for stress ulcers,^[158–160] emphasizing instead its therapeutic role; specifically, endoscopic hemostasis is indicated when pharmacotherapy fails to control bleeding. Performing gastroscopy solely for diagnostic confirmation of stress ulcers elevates patient risk and contradicts the prevailing clinical consensus. Endoscopic intervention should be reserved for cases of refractory massive gastrointestinal bleeding, enabling definitive etiologic diagnosis and targeted hemostatic therapy.

Evidence summary: Limited literature exists regarding the endoscopic diagnosis of stress ulcers. A retrospective study evaluating the management of 32 patients with stress ulcer-related major bleeding demonstrated that emergency endoscopy, performed alongside aggressive medical therapy, clarifies lesion characteristics and guides therapeutic planning.^[161]

Management of Stress Ulcers

Question 8: Should gastrointestinal decompression and fasting be recommended for the management of stress ulcers and UGIB in critically ill patients?

Recommendation 8.1: We suggest performing gastrointestinal decompression as appropriate in critically ill patients with suspected or confirmed stress ulcers and UGIB (Weak recommendation, low-quality evidence).

Recommendation 8.2: We suggest fasting in critically ill patients with suspected or confirmed stress ulcers and active UGIB. The duration of fasting should be determined based on clinical assessment, with early resumption of oral feeding considered for low-risk patients (Weak recommendation, low-quality evidence).

Rationale: Gastrointestinal decompression is typically indicated for critically ill patients with stress ulcers and UGIB. This intervention reduces intraluminal pressure, thereby mitigating risks of emesis, gastric distension, and gastroesophageal reflux. Monitoring effluent volume and characteristics provides essential data for assessing disease progression. Fasting reduces mechanical and chemical irritation of the gastrointestinal mucosa and decreases intestinal motility. This approach alleviates gastrointestinal burden, prevents bleeding exacerbation, and facilitates mucosal recovery.

Evidence summary: Regarding gastrointestinal decompression, one RCT demonstrated that continuous decompression combined with nasogastric feeding effectively monitored bleeding activity, reduced rebleeding risk, and significantly improved therapeutic outcomes in UGIB.^[162] However, high-quality clinical research evidence regarding the optimal range for specific negative pressure settings in gastrointestinal decompression is currently lacking. Based on clinical principles and pathophysiological mechanisms, it is generally accepted that the negative pressure should not be set too high, in order to prevent the gastric mucosa from being drawn into and adhering to the tube opening due to excessive suction force. This precaution helps avoid mechanical injury and microvascular rupture, thereby reducing the risk of exacerbating bleeding or causing poor drainage. A meta-analysis indicated that, compared with prolonged fasting, initiating oral intake within 24 h post hemostasis in acute non-variceal UGIB did not increase rebleeding rates (OR: 0.87, 95% CI: 0.47–1.647) or mortality (OR:

0.46, 95% CI: 0.19–1.08), while significantly reducing hospital length of stay (mean difference [MD]: –2.40 days, 95% CI: –2.43 to –0.12).^[163] A recent large observational study further supported the finding that fasting durations ≤24 h in acute non-variceal bleeding were not associated with increased rebleeding risk, and shorter fasting durations correlated with reduced hospitalization duration and costs.^[164] However, the current evidence base is limited by low methodological quality and small sample sizes. High-quality, large-scale, multicenter RCTs are warranted to further validate the efficacy and safety of early oral feeding.

Question 9: Should gastric mucosal protectants be recommended for the treatment of stress ulcers and UGIB in critically ill patients?

Recommendation: Current evidence is insufficient to support the routine recommendation of gastric mucosal protectants for critically ill patients with suspected or confirmed stress ulcers and UGIB (GPS).

Rationale: Gastric mucosal protectants enhance mucosal defense by strengthening the cellular barrier of the stomach and duodenum and the mucus-bicarbonate barrier. This is achieved through binding to pepsin to inhibit its activity, stimulating prostaglandin E2 synthesis, and forming a protective layer over ulcerated surfaces, thereby promoting epithelial regeneration. Additionally, these agents reduce hydrogen ion back-diffusion into the mucosa, protecting it from damage by gastric acid and pepsin. Factors such as epidermal growth factor and basic fibroblast growth factor further contribute to ulcer healing. Nevertheless, robust clinical evidence supporting their efficacy specifically for stress ulcer and UGIB in critically ill patients remains limited.

Evidence summary: While gastric mucosal protectants are clinically employed for gastric and duodenal ulcer management, evidence regarding their effectiveness for stress ulcers and UGIB in critically ill populations is lacking.

Question 10: Should PPIs be recommended for the treatment of stress ulcers and UGIB in critically ill patients?

Recommendation: We recommend using PPIs in critically ill patients with suspected or confirmed stress ulcers and UGIB (Strong recommendation, high-quality evidence).

Rationale: PPIs act by irreversibly inhibiting the H⁺/K⁺-ATPase (proton pump) in gastric parietal cells. Physiological acid secretion is regulated through neurocrine (neurotransmitters), endocrine (gastrin), and paracrine (histamine, somatostatin, prostaglandins) pathways, all converging to stimulate the proton pump. By blocking this final common pathway, PPIs achieve potent and sustained acid suppression while reducing pepsin output. This mechanism renders PPIs particularly effective for patients at high risk of rebleeding, such as those with active endoscopic bleeding, visible vessels, or ulcers with adherent clots, and those with perforation.

Evidence summary: A meta-analysis demonstrated that therapy with PPIs significantly reduces the risks of rebleeding (OR: 0.57, 95% CI: 0.44–0.73), blood transfusion (requirement (OR: 0.67, 95% CI: 0.52–0.85), need for endoscopic therapy (OR: 0.56, 95% CI: 0.42–0.75), and surgical intervention (OR: 0.62, 95% CI: 0.45–0.84) in patients with acute UGIB.^[165] Furthermore, a Cochrane Systematic Review indicated that initiat-

ing treatment with PPIs before endoscopic examination reduces the requirement for endoscopic hemostasis (OR: 0.68, 95% CI: 0.50–0.93).^[166]

Question 11: Should H2RAs be recommended for the management of stress ulcers and UGIB in critically ill patients?

Recommendation: We recommend against the routine administration of H2RAs in critically ill patients with suspected or confirmed stress ulcers and UGIB. H2RAs may be considered as an alternative in settings where PPIs are unavailable or inaccessible (Weak recommendation, low-quality evidence).

Rationale: H2RAs exert a significant inhibitory effect on basal and nocturnal gastric acid secretion in patients with ulcers, as well as acid secretion stimulated by pentagastrin, histamine, and food intake, through competitive blockade of histamine H2 receptors. Additionally, they demonstrate inhibitory effects on pepsinogen secretion and confer protective benefits against gastric mucosal injury and acute ulcer formation.

Evidence summary: A meta-analysis demonstrated that H2RAs did not reduce the risk of rebleeding, need for blood transfusion, surgical intervention, or all-cause mortality in patients with acute UGIB.^[165]

Question 12: Should somatostatin and its analogues be recommended for the management of stress ulcers and UGIB in critically ill patients?

Recommendation: We recommend against the routine use of somatostatin and its analogues in critically ill patients with suspected or confirmed stress ulcers and UGIB (Weak recommendation, low-quality evidence).

Rationale: Somatostatin and its analogues inhibit the secretion of gastrin, gastric acid, and pepsin, potentially offering therapeutic benefits in the context of stress ulcer and gastrointestinal bleeding.

Evidence summary: A RCT found no statistically significant differences in mortality, rebleeding rate, transfusion requirements, length of hospital stay, or need for surgery between patients with acute nonvariceal UGIB receiving octreotide (a somatostatin analogue) and those receiving placebo.^[167]

Question 13: Should tranexamic acid, thrombin, hemostatic powder (TC-325), or topical norepinephrine be recommended for the management of stress ulcer and UGIB in critically ill patients?

Recommendation 13.1: We suggest using tranexamic acid as appropriate for the management of stress ulcer and UGIB in critically ill patients who are not at high thrombotic risk (Weak recommendation, moderate-quality evidence).

Recommendation 13.2: We suggest using thrombin, hemostatic powder (TC-325), or topical norepinephrine in critically ill patients with SUB refractory to conventional therapy (Weak recommendation, low-quality evidence).

Rationale: Tranexamic acid, a synthetic lysine derivative, functions as an antifibrinolytic agent. It competitively binds to lysine-binding sites on plasminogen, thereby inhibiting fibrin degradation, reducing fibrinolytic activity, and achieving hemostasis. Thrombin catalyzes the conversion of fibrinogen to fibrin, facilitating clot formation. This agent is primarily indicated for achieving hemostasis in small vessels, capillaries, and solid parenchymal organs, as well as in UGIB. Hemostatic powder

(TC-325) is an adsorbent-based agent that forms a mechanical barrier and concentrates serum components, promoting coagulation factor aggregation and activating the coagulation cascade. It has been applied in the management of gastrointestinal bleeding from various etiologies. Norepinephrine, acting as an α -adrenergic receptor agonist, induces potent vasoconstriction in hemorrhagic arterioles, effectively achieving hemostasis.

Evidence summary: A meta-analysis encompassing 14 RCTs demonstrated that tranexamic acid significantly reduced the rates of persistent bleeding (RR: 0.59, 95% CI: 0.45–0.78) and rebleeding (RR: 0.88, 95% CI: 0.79–0.98) in patients with gastrointestinal bleeding compared with controls, without increasing the risk of thromboembolism (RR: 1.15, 95% CI: 0.86–1.54).^[168–181] Subgroup analysis by administration route indicated that topical tranexamic acid application significantly reduced rebleeding rates (RR: 0.60, 95% CI: 0.39–0.91), whereas intravenous administration did not induce a significant effect (RR: 0.78, 95% CI: 0.48–1.25). Two studies evaluated the hemostatic efficacy of thrombin for stress ulcers in critically ill patients. Results indicated that thrombin reduced time to hemostasis, shortened hospital length of stay, and decreased complication rates. No nausea, vomiting, significant alterations in hepatic or renal function, or other adverse reactions were reported during treatment.^[182,183] A meta-analysis of 5 RCTs found that, compared with standard endoscopic therapy, endoscopic application of hemostatic powder (TC-325) for non-variceal gastrointestinal bleeding did not lead to greater rates of initial hemostasis or lower failure rates; moreover, there were no significant differences in hospitalization duration or the risk of recurrent bleeding [Low methodological credibility as assessed by AMSTAR-2 (A Measurement Tool to Assess Systematic Reviews, version 2)].^[184] Three studies indicated that norepinephrine combined with omeprazole was more effective than omeprazole monotherapy for SUB.^[185–187] Furthermore, 6 studies suggested that endoscopic injection of norepinephrine, compared with endoscopic spraying, more effectively reduced bleeding duration, hospital length of stay, and blood loss while minimizing complications.^[188–193] Currently, the efficacy of these agents for SUB in critically ill patients remains inadequately validated, with the utility of some agents subject to ongoing debate. Therefore, they are not recommended as first-line therapies.

Question 14: Should NSAIDs, glucocorticoids, and anticoagulants/antiplatelet agents be discontinued in critically ill patients experiencing stress ulcer-related bleeding?

Recommendation: We suggest discontinuing treatment with NSAIDs, glucocorticoids, and anticoagulants/antiplatelet agents in critically ill patients with active SUB. For patients receiving warfarin, we suggest discontinuation and administration of specific reversal agents. If cessation of these medications is not feasible, we suggest concomitant administration of PPIs (GPS).

Rationale: In critically ill patients subjected to physiological stressors, certain pharmacotherapies may increase susceptibility to SUB. Systemic glucocorticoid therapy enhances gastric acid and pepsin secretion, potentially exacerbating damage to the mucosal barrier. NSAIDs compromise mucosal defense mechanisms by inhibiting prostaglandin synthesis, thereby reducing mucus and bicarbonate secretion and increasing mucosal vulnerability, which may elevate the incidence of stress ulcers. Furthermore, anticoagulant and antiplatelet agents can promote

clot dissolution and inhibit platelet aggregation, potentially exacerbating hemorrhage.

Evidence summary: Meta-analytic evidence indicated that NSAIDs (e.g., ibuprofen, diclofenac, indomethacin) are associated with an increased risk of UGIB (Low methodological credibility as assessed by AMSTAR-2).^[194] Glucocorticoids may aggravate pre-existing ulcers by increasing gastric acid secretion and impairing protective factors in the gastric mucosa.^[195] A meta-analysis encompassing 25 studies demonstrated that corticosteroid therapy was associated with a modest increase in gastrointestinal bleeding incidence (OR: 1.26, 95% CI: 1.01–1.57); nonetheless, it was not linked to increased bleeding severity (OR: 1.10, 95% CI: 0.92–1.32; High methodological credibility as assessed by AMSTAR-2).^[196] Evidence further indicates that anticoagulation therapy constitutes a significant risk factor for gastrointestinal bleeding.^[197] However, Wolf et al.^[198] reported that mild to moderate anticoagulation did not increase the risk of rebleeding in patients undergoing endoscopic hemostasis for bleeding ulcers. In patients with non-variceal UGIB, a retrospective analysis found that continuation of anticoagulants, antiplatelet agents, and NSAIDs did not significantly impact hospital length of stay, transfusion requirements, or rebleeding rates.^[199] Another retrospective study demonstrated a 75% higher 30-day mortality risk in patients who discontinued aspirin therapy compared with those who resumed it.^[200] A third retrospective study revealed that use of warfarin was significantly associated with UGIB;^[201] prompt discontinuation of treatment with warfarin and reversal are recommended in such scenarios.^[202,203] However, data indicate that rapid reversal of anticoagulation may elevate the risk of thrombosis.^[203,204] Concurrently, Lanas et al.^[205] demonstrated that PPI co-therapy can mitigate the risk of ulcer bleeding associated with anticoagulants, antiplatelet agents, and NSAIDs. Robust evidence directly evaluating the discontinuation of these specific agents in critically ill patients with active SUB is lacking. Based on the pathophysiological risks and available indirect evidence, these guidelines recommend discontinuation where feasible during active hemorrhage. Furthermore, for patients with cardiovascular indications, anticoagulant and antiplatelet therapy should be reinstated as soon as clinically appropriate following hemostasis. If discontinuation is contraindicated, PPI therapy should be administered.

Question 15: When should endoscopic intervention be performed for SUB in critically ill patients?

Recommendation: We suggest performing endoscopic examination expeditiously to identify the bleeding site and initiate endoscopic local hemostasis when conventional medical therapy fails to control SUB in critically ill patients (GPS).

Rationale: Endoscopy constitutes the cornerstone for the diagnosis and management of UGIB.^[206] It enables identification of the bleeding source and prognostic assessment, and facilitates therapeutic hemostasis when indicated.^[207] Most stress ulcer manifestations involve mucosal erosions with minor bleeding and minimal active hemorrhage. Conservative medical management typically achieves spontaneous resolution, rarely necessitating endoscopic intervention. However, when pharmacotherapy fails to control persistent or significant bleeding resulting in hemodynamic instability, emergency endoscopy should be performed to identify the source and achieve hemostasis, provided

that aggressive controlled fluid resuscitation and airway protection are implemented.

Evidence summary: A literature search identified no studies specifically addressing endoscopic treatment for stress ulcers. A systematic review and meta-analysis were conducted on 38 studies comparing endoscopic therapy versus conservative medical management for non-variceal UGIB.^[208–245] Pooled analysis of six studies demonstrated significantly lower mortality in the endoscopic therapy group (OR: 0.31, 95% CI: 0.17–0.58).^[208,221,241–244] In addition, pooled analysis of eight studies indicated a significant reduction in complications associated with endoscopic management (OR: 0.38, 95% CI: 0.18–0.78).^[210,218,220,221,223,230,231,235] Moreover, analysis of 32 studies revealed a significantly higher rate of hemostatic success with endoscopic therapy compared with non-endoscopic management (OR: 1.22, 95% CI: 1.17–1.27).^[209–212,214–223,225–241,245] Furthermore, pooled results from 24 studies demonstrated that endoscopic hemostasis significantly reduced the risk of rebleeding (OR: 0.26, 95% CI: 0.20–0.35).^[208,209,212–214,216–219,222,224,228,230–232,235,237–243,245] Finally, analysis of 27 studies demonstrated that the endoscopic group exhibited a significantly shorter hospital stay (MD: –4.67 days, 95% CI: –5.57 to –3.78).^[208,209,211–219,221,222,224–231,233,234,237–243,245]

Question 16: How should patients with SUB be managed following unsuccessful endoscopic intervention?

Recommendation: We suggest considering endovascular or surgical intervention for patients with SUB refractory to endoscopic hemostasis (Weak recommendation, low-quality evidence).

Rationale: Advances in endoscopic hemostatic techniques have substantially improved the initial success rate of bleeding control. While endoscopic management achieves initial hemostasis in >90% of UGIB cases, a minority of patients experience persistent or recurrent hemorrhage, necessitating consideration of surgical or endovascular approaches. Endovascular intervention is characterized by minimal invasiveness and diverse embolic materials. This intervention has been increasingly applied in clinical practice as the technique matures, emerging as a complementary or alternative strategy to surgery. Although angiography exhibits high specificity for identifying obscure bleeding sources, its sensitivity remains relatively low.^[246] This limits its utility primarily to active arterial bleeding where the hemorrhage rate meets specific thresholds (≥ 0.5 mL/min) during the procedure for reliable detection.^[247] However, rebleeding rates following endovascular intervention are generally higher than those observed with surgery,^[207,248–250] and potential complications include access site hemorrhage, thrombosis, contrast agent allergy, and post-embolization ischemic injury. Historically regarded as the gold standard for definitive hemostasis with a low rebleeding rate, surgical intervention entails significant risks, including substantial trauma and a high incidence of complications. Associated mortality rates range from 14% to 33%,^[251–253] escalating to approximately 50% in high-risk patients (e.g., APACHE II score ≥ 16.5).^[254] The choice between surgical and endovascular interventions fundamentally involves balancing the risks of rebleeding against those of surgical morbidity. For critically ill patients—often elderly individuals with significant comorbidities, poor surgical tolerance, and/or inde-

terminate bleeding sites—endovascular treatment is generally preferred. Surgical intervention may be considered if both endoscopic and endovascular modalities fail to achieve adequate hemostasis.

Evidence summary: Currently, no RCTs directly compare the efficacy of endovascular intervention *versus* surgery specifically for SUB. Available evidence primarily derives from retrospective analyses focusing on non-variceal UGIB, rather than exclusively on stress ulcers. A literature search identified 15 comparative studies evaluating outcomes of interventional therapy *versus* surgery.^[248–262] Systematic review and meta-analysis indicated that the rebleeding rate was significantly higher in the interventional group compared with the surgical group (OR: 2.37, 95% CI: 1.78–3.16) and the requirement for further intervention was also increased (OR: 2.25, 95% CI: 1.56–3.25). Nevertheless, the interventional group demonstrated significantly lower complication rates (OR: 0.38, 95% CI: 0.27–0.54) and a reduced mortality risk (OR: 0.77, 95% CI: 0.61–0.98). Notably, two retrospective studies reported that although patients in the interventional group were older and presented with more severe illness, their mortality rates were comparable to or lower than those observed in the surgical group.^[251,254]

Question 17: What should be the initial blood pressure target during resuscitation in patients with shock caused by stress ulcer and massive gastrointestinal bleeding?

Recommendation: We suggest that the initial resuscitation goal for patients with shock secondary to stress ulcer and massive gastrointestinal bleeding should be hemodynamic stabilization and the maintenance of adequate tissue perfusion. Following fluid resuscitation, the mean arterial pressure (MAP) should be targeted at ≥ 65 mmHg, with continuous dynamic assessment of vital organ perfusion status (GPS).

Rationale: Aggressive resuscitation is imperative in stress ulcers complicated by massive gastrointestinal bleeding. Targeting an initially elevated blood pressure necessitates substantial fluid and vasoactive agent administration, thereby increasing the risk of persistent bleeding, volume overload, and pulmonary complications. Conversely, sustaining a hypotensive state risks inadequate perfusion of vital organs and tissues, potentially leading to adverse outcomes. Thus, clinicians face a challenging balance between these two competing risks. Currently, there is a lack of direct clinical studies specifically addressing the initial blood pressure target for shock resuscitation in patients with stress ulcer-associated bleeding. However, the underlying pathophysiology of hemodynamic resuscitation to sustain tissue perfusion parallels that of other shock etiologies. A review of 19 studies^[263–281] indicated substantial heterogeneity in target blood pressure ranges across different research protocols. A meta-analysis demonstrated that a resuscitation strategy targeting a MAP > 65 mmHg was associated with lower all-cause mortality compared with targeting a MAP < 65 mmHg. However, this conclusion is limited by the heterogeneity in target populations and distinct research methodologies among the included studies. Further investigation is warranted to validate these findings.

Evidence summary: Impact of different MAP levels during the early phase of shock resuscitation on in-hospital all-cause mortality. Five studies^[263,264,266,280,281] targeted a MAP < 65 mmHg during resuscitation, reporting an all-cause mortal-

ity rate of 36.16% (95% CI: 14.28–58.06%), indicating considerable uncertainty. Twelve studies^[263–267,269,270,273,276,277,280,281] targeted a MAP > 65 mmHg during the early resuscitation phase, reporting an all-cause mortality rate of 34.92% (95% CI: 25.07–44.76).

Question 18: What are the indications for red blood cell (RBC) transfusion in patients with stress ulcers and massive gastrointestinal bleeding?

Recommendation 18.1: For patients with stress ulcer and massive gastrointestinal bleeding in the absence of specific comorbidities (e.g., cardiovascular, cerebrovascular, or pulmonary diseases), a hemoglobin level < 7 g/dL may constitute an indication for packed RBC transfusion (GPS).

Recommendation 18.2: For patients with stress ulcer and massive gastrointestinal bleeding who have comorbidities sensitive to hypoxia (such as cardiovascular, cerebrovascular, or pulmonary diseases), the transfusion threshold should be individualized based on clinical circumstances and multidisciplinary consultation with relevant specialists, aiming to maintain a relatively higher hemoglobin level (GPS).

Rationale: RBC transfusion is indicated in stress ulcers complicated by gastrointestinal bleeding to augment tissue oxygenation. However, large-volume RBC transfusion carries risks of fluid overload and increased transfusion-related complications. Given the physiological similarities between bleeding from stress ulcers and other causes of gastrointestinal bleeding, the established RBC transfusion thresholds for conventional bleeding should be used as a reference.

Evidence summary: A systematic literature review identified 7 studies investigating clinical outcomes associated with varying RBC transfusion indications for gastrointestinal bleeding of other causes.^[282–288] Due to inconsistent definitions of transfusion indications across studies, a subgroup analysis was performed to assess optimal outcomes under different hemoglobin thresholds. The results indicated that, among patients with acute gastrointestinal bleeding, transfusion initiated at a hemoglobin threshold of 7 g/dL did not lead to significant difference in re-bleeding rate, mean hemoglobin units transfused, 28-day complication rate, or total length of hospital stay compared with thresholds of 8 g/dL or 9 g/dL (95% CI for all comparisons included 1.0).

Question 19: When should enteral nutrition be reinitiated after SUB?

Recommendation: We suggest that enteral nutrition should be initiated early and advanced gradually in critically ill patients following the cessation of SUB, provided there is no severe hemodynamic instability (norepinephrine equivalent dose < 0.5 $\mu\text{g}/(\text{kg}\cdot\text{min})$) or evidence of inadequate tissue perfusion (GPS).

Rationale: Conventional fasting practices after SUB aim to enhance gastric pH regulation, stabilize thrombi, and mitigate the risk of re-bleeding, as nutrient ingestion stimulates gastric acid secretion. Conversely, enteral nutrition confers potential benefits, including direct nourishment of gastric tissue, stimulation of mucus and bicarbonate secretion by mucosal epithelia and glands, maintenance of the gastric mucosal barrier, physiological activation of the parasympathetic nervous system, and enhanced perfusion to injured tissues—collectively promoting

ulcer healing.^[289] However, enteral nutrition may precipitate serious gastrointestinal complications in the context of severe hemodynamic instability or inadequate tissue perfusion.^[290] Furthermore, bleeding typically resolves spontaneously upon elimination of precipitating risk factors, supporting the clinical rationale for early enteral nutrition initiation post-bleeding.

Evidence summary: A RCT of patients with UGIB secondary to peptic ulcer who received early oral diet (day 1) and delayed oral feeding (day 3) showed no difference in the rate of re-bleeding between the two groups (8% vs. 10%, respectively).^[291] In another study, patients with non-variceal UGIB were randomly assigned into two groups.^[292] The intervention group received a clinical pathway protocol including an early feeding strategy within 24 h, while the control group received routine treatment. The average time to initiate feeding was 21.3 h and 43.9 h, respectively, with no significant differences in re-bleeding rates or transfusion needs. However, shortened hospitalization time and reduced costs were noted in the intervention group. A study investigated patients with severe head injuries and SUB in the upper gastrointestinal tract who received enteral nutrition or traditional fasting treatment.^[293] In the traditional fasting treatment group, patients received a standard nasogastric tube for gastrointestinal decompression following hemorrhage, with restriction of oral intake and administration of antacids and hemostatic agents. After improvement of bleeding, nasogastric feeding resumed with gradual administration of rice water, mixed liquid formula, and blenderized diet. In the enteral nutrition group, nasogastric feeding was discontinued until hemostasis was achieved, after which the feeding process was repeated as described. In the observation group, patients were managed with enteral nutrition combined with local hemostatic therapy. The data revealed that initiating enteral nutrition after the gastric juice color significantly light-

ened on the second day significantly shortened bleeding time ($[2.0 \pm 0.5]$ days vs. $[6.0 \pm 1.0]$ days, respectively) and prevented re-bleeding compared with traditional fasting treatment. Additionally, the enteral nutrition was fully initiated earlier in the enteral nutrition group ($[8 \pm 2]$ days vs. $[40 \pm 3]$ days, respectively). In another study,^[294] patients with severe burns and SUB were randomly assigned into an experimental group and a control group. The experimental group was given a three-lumen feeding tube after bleeding and received enteral nutrition during gastrointestinal decompression, while the control group received parenteral nutrition after the shock phase. The experimental group had a shorter time to normalize blood-tinged gastric juice drainage ($[13.5 \pm 2.7]$ days vs. $[16.8 \pm 3.2]$ days, respectively) and better nutritional status.

In summary, the clinical management of stress ulcers and massive gastrointestinal bleeding is illustrated in Figure 2.

Drug Adverse Reactions

Question 20: Should the risk of renal adverse events be considered when using PPIs?

Recommendation: We suggest paying attention to the increased risk of renal adverse events and closely monitoring renal function when using PPIs. (Weak recommendation, moderate-quality evidence)

Rationale: PPIs and their metabolites accumulate within renal tubules and interstitial tissues. These compounds may act as haptens or directly stimulate T-cell expression, thereby initiating immune responses. Moreover, activated macrophages in the renal interstitium may further damage the tubular basement membrane by releasing proteolytic enzymes, reactive oxygen species, reactive nitrogen species, and inducible nitric oxide

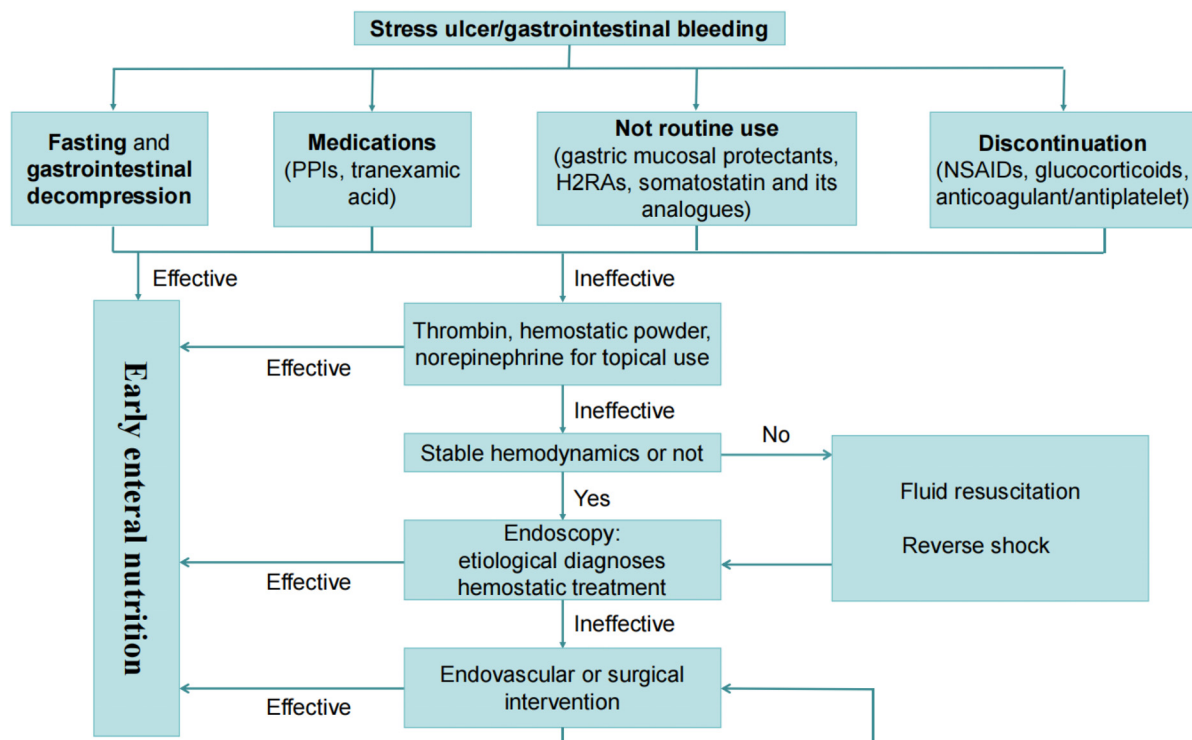


Figure 2. Flowchart of clinical management for stress ulcer/gastrointestinal bleeding.

synthase, ultimately leading to acute interstitial nephropathy or acute kidney injury (AKI).^[295] Compared with PPIs, H2RAs are associated with a significantly lower incidence of renal adverse events. However, due to their inferior therapeutic efficacy, H2RAs are not recommended for routine use.

Evidence summary: A systematic review of 16 studies compared the incidence of renal adverse events with PPIs or H2RAs for the treatment of stress ulcers.^[296–311] The results showed that, compared with no acid-suppressive drugs, PPIs increased the risk of AKI in six studies (OR: 1.86, 95% CI: 1.09–3.16),^[296,299,301,307,308,310] acute interstitial nephropathy in four studies (OR: 2.38, 95% CI: 1.84–3.08),^[303,306,308,310] and end-stage renal disease in three studies (OR: 1.51, 95% CI: 0.99–2.30).^[296,302,309] All differences were statistically significant. Three studies showed an increased risk of chronic kidney disease (CKD) (OR: 2.17, 95% CI: 0.67–7.05);^[296,302,309] however, the differences were not statistically significant. Data from a medical insurance database in Taiwan (China) showed that the cumulative dosage and duration of PPIs were associated with the occurrence of AKI and CKD. For almost all major types of PPIs, the risk of CKD increased by 1.02 (95% CI: 1.01–1.02) for every month of cumulative use, and the risk increased by 1.23 (95% CI: 1.19–1.28) for every 1 g of cumulative dosage.^[305] A cohort study with propensity score matching involving adults who underwent major cardiac surgery showed that administration of PPIs within 3 weeks prior to surgery was significantly associated with the occurrence of AKI (OR: 1.21, 95% CI: 1.03–1.42) and dialysis-requiring AKI (OR: 1.74, 95% CI: 1.15–2.63).^[312] Importantly, preoperative discontinuation of treatment with PPIs was associated with a lower incidence of AKI.

Compared with H2RAs, PPIs were associated with a significantly increased risk of AKI (OR: 1.25, 95% CI: 1.14–1.37) and CKD (OR: 1.28, 95% CI: 1.24–1.33) in three retrospective controlled studies,^[296,298,300] as well as end-stage renal disease (OR: 2.02, 95% CI: 1.29–3.15) in two retrospective studies.^[298,311] Compared with no acid-suppressive drugs, H2RAs were not associated with a significantly increased risk of AKI (OR: 1.00, 95% CI: 0.92–1.08) and CKD (OR: 0.96, 95% CI: 0.91–1.00) in two retrospective studies.^[296,307]

Based on systematic Meta-analyses addressing several key clinical questions, this guideline has formulated 23 recommendations for the prevention, diagnosis, and treatment of stress-related ulcers in critically ill patients, integrating the latest evidence-based medicine. It comprehensively covers aspects such as risk factor identification, preventive strategies, indications for endoscopy, pharmacological therapy, and interventional or surgical management, aiming to provide standardized, high-quality evidence-based guidance for clinical practice.

In clinical application, individualized prevention and treatment should be implemented based on the patient's specific condition and available medical resources, with an emphasis on multidisciplinary collaboration. Further research focusing on diverse populations of critically ill patients is encouraged to inform the continuous updates of this guideline.

Expert Working Group for Guideline Development

Chairman

Dechang Chen, Department of Critical Care Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine

Yan Kang, Department of Critical Care Medicine, West China Hospital, Sichuan University

Xiangdong Guan, Department of Critical Care Medicine, the First Affiliated Hospital, Sun Yat-sen University

Secretaries

Sheng Zhang, Department of Critical Care Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine

Yuetian Yu, Department of Critical Care Medicine, Renji Hospital, Shanghai Jiao Tong University School of Medicine

Working Group Members

Ye Gong, Department of Critical Care Medicine, Huashan Hospital, Fudan University

Bo Hu, Department of Critical Care Medicine, Zhongnan Hospital, Wuhan University

Chen Li, Department of Critical Care Medicine, Qilu Hospital, Shandong University

Xuelian Liao, Department of Critical Care Medicine, West China Tianfu Hospital, Sichuan University

Fen Liu, Department of Critical Care Medicine, The First Affiliated Hospital of Nanchang University

Jiao Liu, Department of Critical Care Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine

Ling Liu, Department of Critical Care Medicine, Zhongda Hospital, Southeast University

Bin Ouyang, Department of Critical Care Medicine, The First Affiliated Hospital of Sun Yat-sen University

Aijun Pan, Department of Critical Care Medicine, The First Affiliated Hospital of China University of Science and Technology

Mi Tian, Department of Critical Care Medicine, Huashan Hospital, Fudan University
Changsong Wang, Department of Critical Care Medicine, The First Affiliated Hospital, Harbin Medical University

Zhixiong Wu, Department of Critical Care Medicine, East China Hospital, Fudan University

Hui Xie, Department of Critical Care Medicine, Shanghai First People's Hospital

Yuan Xu, Department of Critical Care Medicine, Beijing Tsinghua Changgung Hospital

Xianghong Yang, Department of Critical Care Medicine, Zhejiang Provincial People's Hospital

Xiaofei Ye, Department of Health Statistics, Naval Medical University

Haiyan Yin, Department of Critical Care Medicine, The First Affiliated Hospital of Jinan University

Yuetian Yu, Department of Critical Care Medicine, Renji Hospital, Shanghai Jiao Tong University School of Medicine

Sheng Zhang, Department of Critical Care Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine

Dong Zhang, Department of Critical Care Medicine, Bethune First Hospital, Jilin University

Xiangrong Zuo, Department of Critical Care Medicine, The First Affiliated Hospital of Nanjing Medical University

Steering Expert Panel Members

Youzhong An (Department of Critical Care Medicine, Peking University People's Hospital), Dechang Chen (Department of Critical Care Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine), Bin Du (Department of Critical Care Medicine, Peking Union Medical College Hospital), Xiangdong Guan (Department of Critical Care Medicine, First Af-

filiated Hospital, Sun Yat-sen University), Yuan Gao (Department of Critical Care Medicine, Renji Hospital, Shanghai Jiao Tong University School of Medicine), Yan Kang (Department of Critical Care Medicine, West China Hospital, Sichuan University), Weiqin Li (Department of Critical Care Medicine, General Hospital of the Eastern Theater Command), Wenxiong Li (Department of Critical Care Medicine, Beijing Chaoyang Hospital Affiliated to Capital Medical University), Hong Liu (Department of Critical Care Medicine, First Hospital of Shanxi Medical University), Penglin Ma (Department of Critical Care Medicine, Guiqian International General Hospital), Xiaochun Ma (Department of Critical Care Medicine, First Hospital Affiliated to China Medical University), Zhiyong Peng (Department of Critical Care Medicine, Zhongnan Hospital, Wuhan University), Chuanyun Qian (Department of Critical Care Medicine, First Affiliated Hospital of Kunming Medical University), Haibo Qiu (Department of Critical Care Medicine, Zhongda Hospital Affiliated to Southeast University), Bingyu Qin (Department of Critical Care Medicine, Henan Provincial People's Hospital), Songjing Shi (Department of Critical Care Medicine, Fujian Provincial Hospital), Wang Chunting (Department of Critical Care Medicine, Shandong Provincial Hospital), Hongliang Wang (Department of Critical Care Medicine, Second Affiliated Hospital of Harbin Medical University), Jianfeng Wu (Department of Critical Care Medicine, First Hospital Affiliated, Sun Yat-sen University), Lei Xu (Tianjin Third Central Hospital), Jing Yan (Department of Critical Care Medicine, Zhejiang Hospital), Yi Yang (Department of Critical Care Medicine, Zhongda Hospital, Southeast University), Kaijiang Yu (Department of Critical Care Medicine, First Affiliated Hospital, Harbin Medical University), Xiangyou Yu (Department of Critical Care Medicine, First Affiliated Hospital, Xinjiang Medical University), Lina Zhang (Department of Critical Care Medicine, Xiangya Hospital, Central South University), Xijing Zhang (Department of Critical Care Medicine, Xijing Hospital, Air Force Medical University, Mingyan Zhao (Department of Critical Care Medicine, The First Affiliated Hospital, Harbin Medical University), Fachun Zhou (Department of Critical Care Medicine, First Affiliated Hospital, Chongqing Medical University), Feihu Zhou (Department of Critical Care Medicine, First Medical Center of PLA General Hospital), Jianxin Zhou (Department of Critical Care Medicine, Beijing Shijitan Hospital, Capital Medical University),

CRedit Authorship Contribution Statement

Yan Kang: Project administration, Writing – original draft, Writing – review & editing. **Xiangdong Guan:** Project administration. **Dechang Chen:** Project administration.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The author is an Editorial Board Member/Editor-in-Chief/Associate Editor/Guest Editor for this journal and was not involved in the editorial review or the decision to publish this article.

Data Availability

The evidence-based data referenced in this guideline are derived from publicly available clinical research literature published in Chinese and English. Unpublished meta-analysis data conducted by the working group may be reasonably shared upon request. It is important to note that unpublished data are intended solely for academic research and clinical practice reference and shall not be used for commercial purposes.

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