



# How to prevent and treat gastrointestinal bleeding in the critically ill patient: a pathophysiological approach

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**Abstract:** Stress ulceration and subsequent bleeding in critically ill patients shows an incidence of 2–6%. The pathophysiology is complex and begins with vasoconstriction. Mucosal ischemia ultimately leads to stress ulcer related bleeding (SURB). Upper gastrointestinal bleeding (UGIB) can also originate from other places, for instance reflux esophagitis, which has a different approach. Recently, it has become clear that acid suppression does not prevent UGIB or SURB. The meta-analyses on acid suppression are summarized in this review and show no clear effect on the incidence of UGIB or mortality. This knowledge urges us to reassess the pathophysiology of SURB. A conceptual model is presented based on pathophysiological studies. Insight in the pathophysiological process of SURB can lead to a multi-focused approach based on this conceptual model. In addition, a stepwise approach for the management of UGIB in critically ill patients is presented.

**Keywords:** Stress ulceration; upper gastrointestinal bleeding (UGIB); acid suppression; proton pump inhibitors (PPI); histamine receptor antagonists; critically ill

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## Introduction

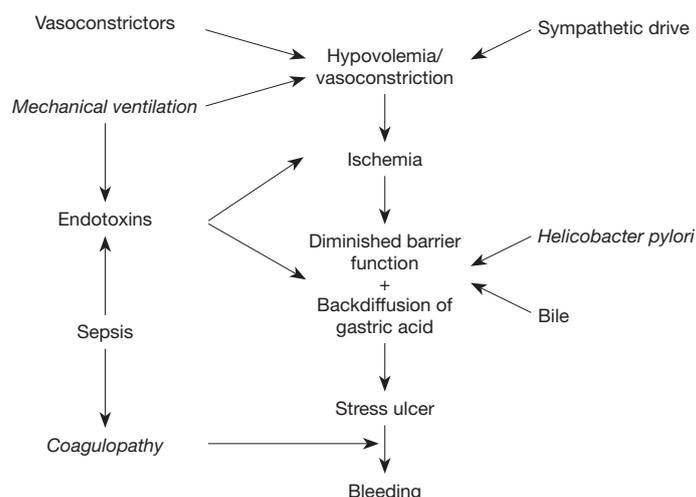
Critical care physicians are involved in the treatment of patients with gastrointestinal bleeding in several ways. First, patients outside the ICU suffering from gastrointestinal tract bleeding with hypovolemic shock may need ICU treatment. Second, patients can develop gastrointestinal bleeding as a complication during their treatment in the intensive care. In all cases, patients who are in a state of hypovolemic shock need appropriate shock treatment with fluids, blood- and plasma transfusions and if needed, vasopressors. In addition, specific causes such as oesophageal varices, gastric- or duodenal ulceration may need local treatment. This local treatment with e.g., endoscopic interventions, Sengstaken-Blakemore tube or coiling may be needed for some patients and at appropriate timing. Several scoring systems rate the severity of illness and their prognostication of patients who present with bleeding outside the ICU (1). A recent study showed that the AIMS65 and Glasgow-Blatchford scores performed

better than the pre-endoscopic Rockall score and pre-endoscopic Baylor score (1). The in-hospital mortality appeared to be around 10% (1).

The approach to patients who develop gastrointestinal bleeding during ICU treatment is different from the approach to patients who develop bleeding outside the ICU and is in a way more complex. This narrative review provides an overview of pathophysiology, prevention and treatment for patients who develop gastrointestinal bleeding during their ICU stay.

## Aetiology

The normal gastric mucosa is designed and highly matched to resist the acidic fluids in the gastric lumen. The integrity of the gastric mucosa is normally formed by the mucus layer, a phospholipid barrier, the tight junctions between epithelial cells, the regeneration capacity of the mucosa, prostaglandin production and the mucosa blood flow (2).



**Figure 1** The conceptual framework for stress ulcer related bleeding (SURB). Pathophysiology of stress ulcer formation and bleeding. In italics the known risk factors.

Loss of one or more of these barriers leads to a diminished integrity of the gastric mucosa. In critically ill patients, the inflammatory state and altered circulation of the splanchnic region can easily result in a reduction in one or more of these defence mechanisms. When disturbances in the integrity of the gastric mucosa occur, gastric acid is permitted to reach the deeper layers of the mucosa, which can lead to the formation of a gastric ulcer. Mucosal damage occurs in 75–100% of patients admitted to the ICU in shock (3,4). Also, the extreme physical stress with sympathetic drive and vasoconstriction in burn or neurosurgical patients lead to a high incidence of gastric ulcer in this group of patients (5). Probably the main reason for a disruption of the mucosal barrier function in any critically ill patient is a reduced mucosal circulation (2,6). A normally perfused mucosa recovers from injury within hours but an impaired splanchnic perfusion during an inflammatory state hampers recovery. Disturbed microcirculation and vasoconstriction in the splanchnic region occurs due to endotoxemia and hypovolemia in the acute phase of severe disease. This process enforces itself due to the increased translocation of endotoxins through the ischemic mucosa and subsequent endotoxic vasoconstriction (7). The reduced perfusion with ischemic mucosa leads to a loss of tight junctions. The concept of reduced integrity and increased permeability in critically ill patients was proven in at least two studies by measuring an increased absorption of sucrose (8,9). The damaged mucosa leads to acid back diffusion and consecutive ulcer formation occurs. In 1970 Skillman

published the results of his studies to the gastric mucosal barrier function and back-diffusion of acid (10). He concluded: “*These studies strongly suggest that disruption of the barrier function of the stomach, especially in the presence of poor vascular perfusion may be an important clue to the pathogenesis of the vexing and highly fatal problem of acute stress ulceration of the human stomach.*” However, many clinicians today still hold gastric acid responsible for stress ulceration in the stomach and choose their treatment according to that view instead of focussing on the improvement of splanchnic perfusion.

Above reasoning leads to a conceptual framework (Figure 1) that increases our insight in the pathophysiology of stress ulcer formation and prevention (11). Additional factors that add to the diminished gastric mucosa integrity are the presence of *H. pylori* and reflux of bile from the duodenum towards the stomach (4,12). Mechanical ventilation and coagulopathy were identified as independent risk factors and fit in the conceptual framework as shown (Figure 1) (13).

## Definition

The most frequent location of gastrointestinal bleeding is the stomach although all sites within the gastrointestinal tract may bleed. Bleeding may be occult or overt. Occult bleeding may happen unknown as many critically ill patients experience a decrease in haemoglobin level and many receive a transfusion at some point in their ICU stay. Occult bleeding can stop or develop into overt bleeding.

Overt bleeding is usually defined according to Cook and co-workers as hematemesis, gross blood or “coffee grounds” material in a nasogastric aspirate, hematochezia, or melena (13). Not every overt bleeding is severe enough to lead to clinical consequences such as shock. Cook used a detailed and complex definition of clinically important bleeding as overt bleeding complicated by a decrease in systolic blood pressure (20 mmHg), increase in heart rate (20 bpm), or a decrease in haemoglobin level within 24 hours after the onset of bleeding, in the absence of other causes (13). This definition is difficult to use at the bedside. In short, this definition describes that a clinically important bleeding is associated with hypotension and/or transfusion.

The location of the bleeding can be upper or lower gastrointestinal tract. The upper gastrointestinal tract is oesophagus, stomach and small bowel. Occasionally the bleeding originates from other locations such as the biliary tract (14). Often the location is initially unknown and bleeding from the upper gastrointestinal tract is then referred to as upper gastrointestinal bleeding (UGIB). It is important to realize that the source of the bleeding can be a reflux esophagitis, which has a completely different cause and treatment than stress ulcerations. In one study two or three out of 16 bleeds (12–18%) appeared to be caused by esophagitis (15). Bleeding that results from stress ulcerations is called stress ulcer related bleeding (SURB). This implies that an UGIB can only be called SURB after endoscopic investigation or, in retrospect, during autopsy. As a consequence, UGIB incidence is higher than the true SURB incidence (1.9% *vs.* 1.0% in one study) (15). This distinction is important when the literature on this subject is reviewed concerning incidence, prevention and treatment. The incidence of UGIB is variable in the literature as was shown in recent studies. Incidences of 1.96% (16) and as high as 6.1% were reported recently (17). However, a low incidence of 0.6% has been published before (18).

## Presentation

The clinical signs of gastrointestinal bleeding vary. Most patients with nasogastric tubes present with blood or coffee grounding in the gastric residual aspirations. Usually this is combined with signs of hypotension or a drop in haemoglobin and as such this may fit within the definition of clinically important bleeding (13). In case of esophagitis, in a minority of patients retrosternal pain is

expressed. Usually both esophagitis and stress ulceration are without signs of pain or discomfort, although in burn patients epigastric pain is associated with ulcer formation (5). Stress ulcerations are most often detected in the stomach but may be present throughout the complete gastrointestinal tract, from stomach to rectum. Bleeding in the upper gastrointestinal tract will usually lead to black, sticky and smelling faeces, melena. Bleeding from the lower gastrointestinal tract will appear as bloody stools, hematochezia. In that case, endoscopic studies are useful too as haemorrhoids will ask for a different approach than stress ulceration. Ulceration in the colon may be related to ischemia as ischemic colitis. The differentiation between ischemic colitis and stress ulceration in the colon is more or less semantic as both can be seen as a result of inadequate perfusion. A diffuse ischemia present in small or large bowel without obstruction in the arteries is called non-occlusive mesenteric ischemia (NOMI). In contrast, when occlusion is present, occlusive mesenteric ischemia is the case. It is important to differentiate between these two situations, as occlusive ischemia needs opening of the vessels were NOMI needs improvement of the (micro)circulation. The clinical presentation of NOMI is usually not bleeding but abdominal pain, distension of the bowel and inflammatory response (19). However, the clinical and laboratory signs are quite variable (19,20). It has become clear that no single or combined biochemical marker is precise and accurate enough to exclude or diagnose NOMI (20).

## Prevention

Clinically important bleeding adds to ICU mortality with a relative risk of 4 in a regression model, 1.0 in an adjusted regression model and 1.8 or 2.9 in matched cohort models (21). Another recent observational trial in patients with clinically important gastrointestinal bleeding, the adjusted odds ratio for 90-day mortality was not significantly higher (OR 1.7; 95% CI: 0.7–4.3) (22). One of these studies showed a significant longer length of stay of 4–8 days for patients with bleeding (21). Taken together, it is worthwhile to prevent stress ulceration and subsequent bleeding. Probably, over the years an improved treatment of the circulation, respiratory failure, optimization of feeding and early sepsis recognition and treatment has had its effect, leading to a lower incidence than in the 1970's. In those early years, many intensive care patients needed a laparotomy for gastric ulceration with bleeding and sometimes perforation. Most critically ill patients have stress ulcerations, although not

**Table 1** Reviews and meta-analyses performed since 2012 on stress ulcer prophylaxis

Author	Year	Method	Control	Medication	Endpoint	Result
Alhazzani (17)	2017	Meta-analysis	Placebo	PPI	UGIB	No significant differences
Alquraini (26)	2017	Meta-analysis	Sucralfate	H <sub>2</sub> RA	UGIB	No significant differences
Barletta (27)	2016	Concise Review	H <sub>2</sub> RA	PPI	Bleeding, complications	No significant differences
Alshamsi (28)	2016	Meta-analysis	H <sub>2</sub> RA	PPI	UGIB	PPI better than H <sub>2</sub> RA
Plummer (29)	2016	Review	H <sub>2</sub> RA	PPI	UGIB	No significant differences
Krag (30)	2014	Meta-analysis; TSA	Placebo or no prophylaxis	PPI or H <sub>2</sub> RA	Mortality; pneumonia; UGIB	No significant differences
Krag (31)	2013	Meta-analyse; TSA	H <sub>2</sub> RA none or Sucralfate	PPI H <sub>2</sub> RA	UGIB	PPI better than H <sub>2</sub> RA but not in TSA
Alhazzani (32)	2013	Meta-analysis	H <sub>2</sub> RA	PPI	UGIB	PPI better than H <sub>2</sub> RA
Pilkington (33)	2012	Review	H <sub>2</sub> RA	PPI	UGIB	No significant differences

PPI, proton pump inhibitors; H<sub>2</sub>RA, histamine receptor blocking agents; UGIB, upper gastrointestinal bleeding; TSA, trial sequence analysis.

many suffer from bleeding (3,4). In a setting with a combined strategy that focuses on most of the etiological factors, as reviewed in *Figure 1*, the incidence of UGIB appeared to be as low as 0.6% (18). In that study a combination of several approaches was used: early goal directed therapy, vasodilators to reduce vasoconstriction, selective decontamination of the digestive tract to reduce endotoxemia, *H. pylori* carriership and secondary sepsis, steroids to reduce inflammation, early use of prokinetics to reduce bile to regurgitate and protective mechanically ventilation strategies (18). Histamine receptor blocking agents (H<sub>2</sub>RA) and proton pump inhibitors (PPI) were not used at all. In contrast, acid reducing strategies are frequently used as a preventive strategy although acid is not the main cause of stress ulceration and bleeding (23). Moreover, acid suppression was for long a standard treatment for most intensive care patients according to guidelines that recommend its use routinely but the most recent guidelines restrict the use to patients at risk for SURB (24). In a survey of 97 ICUs, it was shown that all but one ICU routinely provided acid suppressive agents (23). The exact practice, however, varied considerably and PPI was most the frequently used agent (23). In another study it was shown that the adherence to the guideline concerning stress ulcer prophylaxis is low with both over- and underutilization (25). The available clinical research on the prevention of stress ulceration and associated bleeding also focuses on acid reducing interventions and is summarized in *Table 1*.

### *H<sub>2</sub>RA or PPI versus placebo*

Two meta-analyses reviewed the studies that compared acid suppressive agents, H<sub>2</sub>RA and PPI, with placebo. Both did not show any improvement in the incidence of UGIB and neither in mortality (*Table 1*). Alhazzani and co-workers found in around 600 patients that the odds ratio for clinically important UGIB was 0.96 (95% CI: 0.24–3.82) (17). Krag and co-workers found in 15 studies with the endpoint mortality a RR 1.00, 95 % CI 0.84–1.20. Neither PPI nor H<sub>2</sub>RA was associated with a mortality benefit when studied separately (30). For the outcome UGIB, in the included two studies using PPIs the RR was 1.04 with 95% CI 0.07–16.3. H<sub>2</sub>RA were associated with lesser UGIB in 20 studies with a RR 0.44, 95% CI 0.28–0.68. However, heterogeneity was large with 48%. The authors debated this finding themselves as a trial sequence analysis (TSA) showed that only 22% of the calculated number of needed patients were included in all studies together. As such, the evidence is in their conclusion not convincing yet (30). The same results were found in another earlier review by the same authors (31).

In addition, a new RCT that is not yet included in the meta-analyses yet, PPI compared to placebo suggest that primary prevention with PPIs is not per se needed for all intensive care patients (34). Moreover, the use of PPIs may even bear some risks in itself by increasing infection,

hypomagnesaemia and mortality (35).

### *H<sub>2</sub>RA versus PPI*

In five reviews and meta-analyses comparisons between H<sub>2</sub>RA and PPI have been reported (*Table 1*).

Compared to H<sub>2</sub>RA, PPIs lower the risk for bleeding in three of the reviews/meta-analysis. This was shown in the reviews from Alhazzani and Alshamsi and Krag (28,31,32). Although Krag found a RR of 0.44 (95% CI: 0.22–0.88 for PPI *vs.* H<sub>2</sub>RA), the trial sequence analysis was not significant (31). The reviews from Barletta, that from Plummer and an older review from Pilkington could not confirm the superior effect of PPI compared to H<sub>2</sub>RA (27,29,33). When this knowledge is regarded in relation to the absence of effect of H<sub>2</sub>RA or PPI compared to placebo, it is unlikely that PPI can have a significant effect compared to H<sub>2</sub>RA.

### *Other studies*

The use of sucralfate as a gastric mucosa-protecting agent was not more effective in preventing UGIB than H<sub>2</sub>RA but was associated with fewer ventilators associated pneumonia (VAP) (26).

For subgroups, neurocritical care patients were studied in a review of eight RCTs and over 800 patients. A significant effect was found for stress ulcer prophylaxis (H<sub>2</sub>RA or PPI combined) on both UGIB and mortality (36). As neurosurgical patients are subject to extreme sympathetic drive, which is probably associated with vasoconstriction and ulcer formation, acid reduction may have an effect in these patients.

The prophylactic use of acid suppressive agents has some potential drawbacks. It may be related to *Clostridium* colonization and consecutive infection (35). PPIs and H<sub>2</sub>RA interact with the local immune system and the neurological system, the enteric minibrain, in the gut (37,38). Also, PPIs are often continued after ICU discharge, even at hospital discharge and without clear indication (39). The prescription of acid suppressive medication in the ICU is inherently related to costs. In that respect, H<sub>2</sub>RA may be more cost efficient than PPI (40). Acid reducing medications have been studied for their effect on ventilator associated pneumonia incidence. A systematic review did not show any effect of PPI or H<sub>2</sub>RA on the incidence of VAP (30). A RCT compared sucralfate with PPI (pantoprazole) and found a significant lower incidence of VAP (41). The drawback

of this study is that this study is relatively small and the incidence in the PPI group is remarkably high (36%).

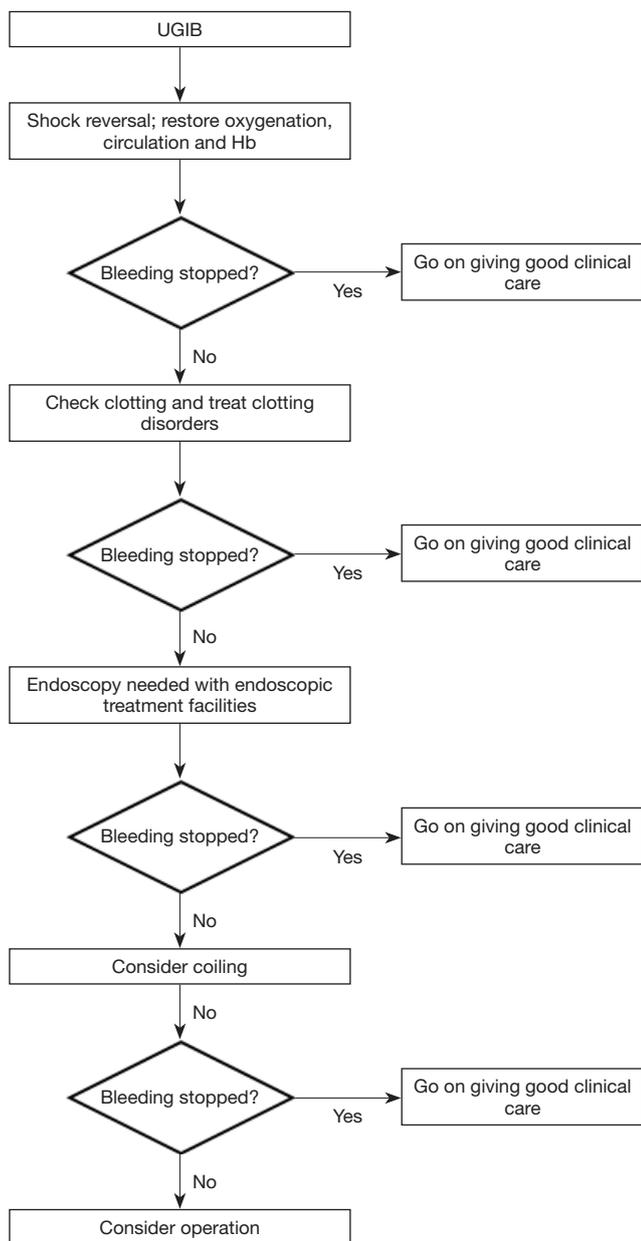
### **Treatment**

The cornerstone in the treatment of UGIB outside the ICU setting is acid suppression (42). Acid suppression provides an environment for the gastric mucosa to recover. Whether acid suppression in intensive care patients with UGIB leads to faster recovery has not been studied as such. Acid suppression therapy in critically ill patients can be questioned, as it is not evident that critically ill patients produce acid at all in a state of shock. Moreover, Skillman showed in 1970 that a 72% reduction of acid secretion occurred in hemorrhagic shock (10). When acid production is limited, then acid suppression will not have any effect on stress ulcer prevention or treatment. Based on the pathophysiological concept as explained previously, it is more logical to restore mucosal perfusion (11). Shock reversal using fluids, inotropes and vasopressors may all be useful in this respect. However, trials on vasodilator therapy for the splanchnic region have not been performed yet.

The cornerstone of the treatment of UGIB in intensive care patients is good clinical care: restore circulation, oxygenation and haemoglobin level. In addition, clotting disorders should be treated to enhance clot formation and haemostasis. Usually, these measures are sufficient to stop bleeding. When bleeding proceeds, the next step is to obtain an endoscopic examination with or without endoscopic treatment. Several options are available for local treatment, a discussion of which is outside the scope of this review. When bleeding persists, a coiling of the appropriate vessel is the next step to perform (22). With this sequential and step-up approach a surgical treatment is seldom needed (*Figure 2*).

### **Conclusions**

Stress ulceration and consecutive bleeding has a complex aetiology and ditto approach. We present a pathophysiological approach and propose a multifactorial preventive strategy that can reduce the incidence to less than 1%. Preventive treatment with acid reducing medications has not convincingly been proven effective and has potential side effects such as *Clostridium* infection. However, it may be effective in selected patients at high risk for UGIB such as neurosurgical and burn patients. Critically ill patients



**Figure 2** A stepwise approach for the management of UGIB in critically ill patients. UGIB, upper gastrointestinal bleeding.

with clinically important bleeding need appropriate shock treatment and additional local treatment in a stepwise approach.

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None.

### Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

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