

## **Prevention and Management of Stress Ulcers in Critically ill Patients**

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### **ABSTRACT**

Stress ulcers or stress related mucosal damage (SRMD) is a term defining inflammation, erosion, and ulceration in the upper gastrointestinal tract complicating patients with critical illness. Stress ulcers occur because of imbalance between the aggressive factors in stomach (gastric acid, pepsin, and bile salt) and the defensive factors (mucous, bicarbonate, microcirculation, epithelial layer, and prostaglandin). The most common clinical feature of stress ulcers is upper gastrointestinal tract bleeding in which the incidence rate is 2.6% in critically ill patients. Stress ulcers commonly happen after a gastrointestinal mucosal break in 75–100% of intensive care unit (ICU) patients in the first 24 hours of admission. The classification of stress ulcers includes asymptomatic stress ulcers, stress ulcers with occult and overt bleeding, and stress ulcers with clinically significant gastrointestinal bleeding. The diagnosis of stress ulcers can be made by assumption only and do not need an endoscopy. Some cases of stress ulcers that need an endoscopy are patients with overt and clinically significant gastrointestinal bleeding stress ulcers. Thus, the treatment of stress ulcers is similar to upper gastrointestinal bleeding. Stress ulcers can be prevented by administering stress ulcers prophylaxis such as histamine H<sub>2</sub> receptor antagonist, proton pump inhibitor, cytoprotective agent (sucralfate), and usage of enteral feeding method.

**Keywords:** critical illness; intensive care unit; stress ulcers; stress ulcers prophylaxis; stress ulcers treatment

## INTRODUCTION

Stress ulcers or stress related mucosal damage (SRMD) is a term used to describe the inflammation, erosion, and ulceration of the upper gastrointestinal tract that often occurs in patients with critical illness.<sup>1</sup> Critical ill patient or patients with critical illness is defined as patients undergoing major surgery or serious illness, requiring intensive medical life support to support the function of vital organs for the patient is able to maintain his life.<sup>2</sup> Stress ulcers is the most frequent complication in critical ill patients in the intensive care unit (ICU).<sup>3</sup> According to Purnomo *et al.*, mucosal damage is found in 75-100% of ICU patients within the first 24 hours after hospital admission.<sup>1,4</sup> Moreover, stress ulcers also can cause further complications as gastrointestinal bleeding.<sup>1,3</sup> A study in 2013 – 2014 stated that around 2.5% of patients treated in the ICU experienced gastrointestinal bleeding.<sup>5</sup>

In general, stress ulcers occurs due to an imbalance condition of aggressive factors (gastric acid, pepsin, bile salts, etc.) with defensive factors (mucus, bicarbonate, state of mucosal microcirculation, epithelial lining, prostaglandins, etc.).<sup>6,7,10</sup> In critical ill, the pathogenesis that plays a major role is vasoconstriction and hypoperfusion of splanchnic. All kind of conditions that cause hypotension, hypovolemia, and decrease cardiac output (CO) can reduce splanchnic and mucosal perfusion. Thereby, reducing bicarbonate secretion, blood flow in the mucosa, and decreasing protective factors which result in deeper erosion and damage to the gastric mucosa. Deeper lesions will result in ulcers and gastrointestinal bleeding such as hematemesis and melena which can result in anemia and shock, making the

patient's condition become worse.<sup>6,7</sup> This condition is very risky in ICU patients who use a mechanical ventilator (>48 hours), have coagulopathy, extensive burns (>35% of body surface area), shock, sepsis, trauma and other conditions. Patients with those factors require prophylactic measures to avoid stress ulcers.<sup>8</sup>

Several methods like histamine H<sub>2</sub> receptor antagonists (H<sub>2</sub>blocker), proton pump inhibitors (PPIs), sucralfate, and enteral feeding. H<sub>2</sub>blocker are used as the first-line drug to reduce stress ulcers symptoms and accelerate healing by inhibiting the binding of histamine to the H receptor<sub>2</sub>, reducing concentration cyclic adenosine monophosphate (c-AMP), and reduces the secretion of hydrogen ions (H<sup>+</sup>) in parietal cells.<sup>8,9</sup> Meanwhile, PPIs work by suppressing stomach acid by deactivating the H enzyme<sup>+</sup>/K<sup>+</sup> ATPase on the secretory surface of parietal cells and inhibits H ion secretion<sup>+</sup>.<sup>9</sup> However, long-term use of these two drugs can pose a risk of enterocolitis by clostridium difficile. The next drug that can be used is sucralfate which works by attaching to the gastric mucosa, forming cytoprotective barrier thus protecting the gastric mucosa from the effects of acid and pepsin.<sup>9</sup> Another way to avoid stress ulcers by using enteral feeding or giving food through an enteral tube. It will help protect the critical ill patient from the risk of bleeding caused by stress ulcers.<sup>8</sup>

Handling patients who experience stress ulcer generally similar to upper GI bleeding (UGIB), by doing resuscitation, coagulopathy correction, bleeding control, and gastric protection. Resuscitation airway, breathing and circulation should be done immediately if the patient's condition is unstable.<sup>11</sup>

After successful resuscitation, gastric lavage was performed to remove clot and reduce gastric distension, while utilization of stomach acid suppressing drugs such as H<sub>2</sub>blocker, PPIs, and sucralfate are still given.<sup>10</sup>

According to Plummeret al., the majority of stress ulcers research which the current recommendations are based on were made more than 20 years ago.<sup>12</sup> As time goes by, research in prophylaxis and management of stress ulcers are needed in critical ill patients. Therefore, in this report we will discuss current prophylaxis and management of stress ulcers on critical ill patients.

### **STRESS ULCERS**

Stress ulcers or commonly called stress related mucosal damage (SMRD) is a broad term used to describe the spectrum of pathology associated with inflammation, erosion and ulcers for the upper gastrointestinal tract in patients with critical ill.<sup>1</sup> Generally, stress ulcers is detected in 75% of patients with endoscopy in the first 24 hours after ICU admission.<sup>2</sup> Stress ulcers is an asymptomatic superficial lesion discovered incidentally during endoscopy that causes gastrointestinal bleeding which also can lead to anemia.<sup>6,7</sup>

### **CRITICAL ILL**

Currently there is still no consensus regarding the definition of “critical ill” or “critical illness”. Kayambankadzanja, et al, analyzed and concluded that critical illness is a poor health condition with dysfunction of vital organs, which has a high risk of death and recurrence if appropriate treatment is not carried out.<sup>13</sup>

### **EPIDEMIOLOGY**

Incidence of stress ulcers is still unknown, but it is thought that stress ulcers almost always occur in severe acute illnesses. The most common description about stress ulcers is upper gastrointestinal (GI) bleeding. The incidence of GI bleeding secondary to stress ulcers ranges from 1.5-15% of cases, depending on whether the patient receives prophylaxis stress ulcers or not.<sup>14</sup>

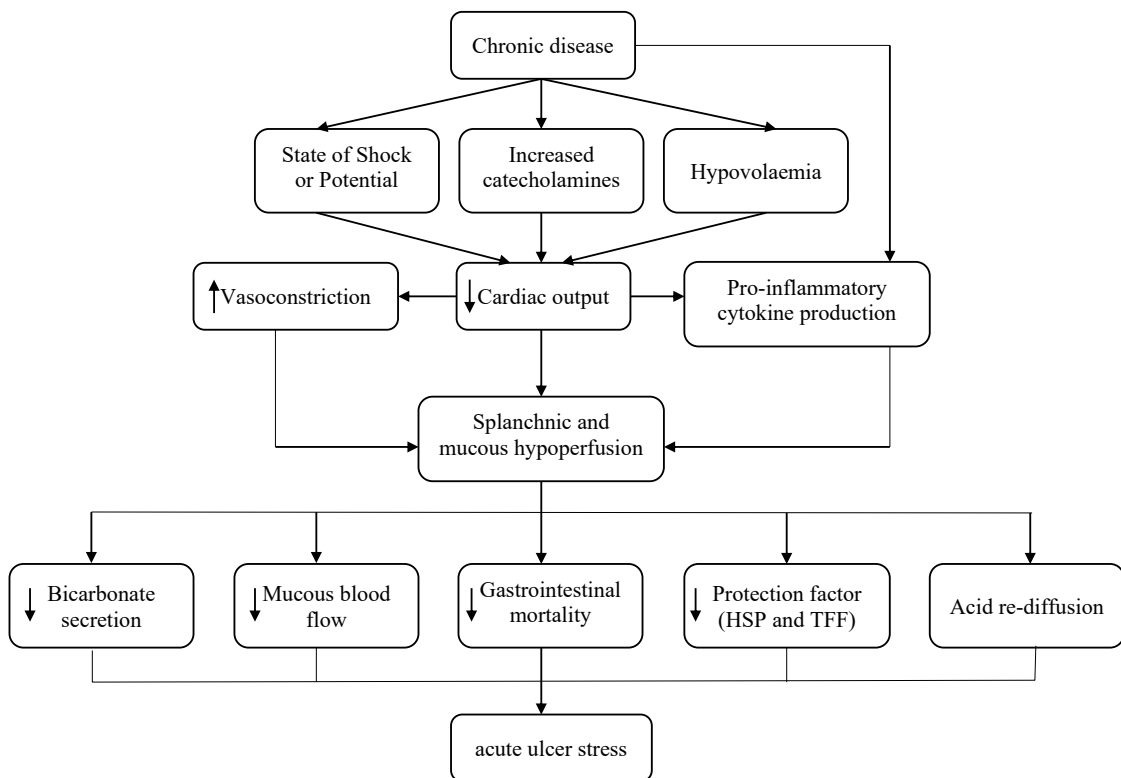
Stress ulcers bleeding occurs frequently in critically ill patients as a result of the underlying disease and therapeutic intervention, by increasing mortality and length of stay in the ICU. Mucosal damage is found in 75-100% of ICU patients within the first 24 hours after hospital admission.<sup>4</sup> An estimated of 4.4 million patients are treated in ICU each year. An international prevalence study reported that 27 of 1,034 critically ill patients (2.6%) experienced a significant gastrointestinal bleeding, and 49 of 1,034 critically ill patients (4.7%) experienced at least one event of overt gastrointestinal bleeding in the ICU. In previous studies, the fraction of ICU patients with GI bleeding associated with stress ulcers in patients without prophylaxis were reported at 17%, but now it has decreased to 1% or lower.<sup>3</sup>

### **PATHOGENESIS**

The stomach produces gastric acid to digest food and break down nutritional components into absorbable amino acids, carbohydrates, and fats. The stomach environment is a relatively acid, with a range of pH from 0.2 to 4.0 due to the presence of parietal cells, which secrete hydrogen ions, in the fundus and corpus.<sup>15</sup> Hydrogen ion secretion is stimulated by several things, such as histamine, gastrin, and acetylcholine.<sup>14,15</sup>

The stomach has the ability to protect itself from the acidic environment. The integrity of the gastric mucosa is maintained by protective mechanisms, namely by the production of prostaglandins, glycoproteins, bicarbonate, trefoil factor, phospholipids, and heat-shock protein (HSPs).<sup>6</sup> Prostaglandins stimulate mucosal blood flow, mucus and bicarbonate production which increasing the growth and repair of epithelial cells. Bicarbonate mucus protects it by becoming a barrier

between gastric acid and the gastric epithelium.<sup>6,7</sup> Apart from that, the stomach defense mechanism which plays a very important role is the high blood flow to the mucosa, which has been proven that 70-90% of the blood supply to the stomach is channeled to the mucosa.<sup>8</sup> Vasoconstriction and hypoperfusion of splanchnic which common found in critically ill patients can reduce blood flow to the gastric mucosa, causing interference with the defense system and damaging the gastric mucosa.<sup>6,7</sup>



**Figure 1.** Stress ulcers pathogenesis<sup>6</sup>

Critical ill or critical illnesses that require ICU care (such as trauma, severe shock, burns, sepsis) can cause splanchnic hypoperfusion which is the main cause of stress ulcer.<sup>6</sup> Critical ill often characterized by hypotension and hypovolemia, which directly contribute to gastric hypoperfusion. Apart from that, in critical conditions, an

inflammatory response often occurs and releases cytokines which also result in hypoperfusion. Despite good systemic circulation, significant reductions in visceral blood flow can still occur and conventional measurements of tissue oxygen levels do not reflect regional gastrointestinal (GI) oxygenation.<sup>7</sup>

The mechanical ventilation can also affect hemodynamics, especially ventilator, that have the potential to cause injuries such as high tidal volumes or high positive end-expiratory pressure (PEEP).<sup>7,14,16</sup> High PEEP can decrease venous return and reduce preload, resulting in decreased cardiac output (CO) and splanchnic hypoperfusion. PEEP also increases plasma-renin-angiotensin-aldosterone activity, as well as catecholamine release, which can also cause splanchnic hypoperfusion. In addition, mechanical ventilation with high tidal volumes and high end-expiratory pressure has been shown to increase pulmonary cytokine

release, which can enter the systemic circulation and result in splanchnic hypoperfusion.<sup>6,7</sup>

Drugs used for ICU patients can have adverse effects on GI function, especially when combined with the use of mechanical ventilation. The use of opiates and sedatives, such as benzodiazepines, can reduce intestinal motility and interfere with venous return. In theory, any drug that has a hypotensive effect, decreases heart rate, or CO can also decrease mesenteric blood flow causing the risk of formation stress ulcer.<sup>7</sup>

**Table 1.** Risk factors for stress ulcers<sup>8</sup>

Risk Factors of Stress Ulcer Bleeding	
Highest risk factor	Other high risk factors
1. Use of mechanical ventilation (>48 hours)	1. Shock
2. Coagulopathy - platelets < 50,000, or - INR > 1.5, or - PTT > 2x of control	2. Severe sepsis
3. Burns > 30% of body surface area	3. Multisystem trauma
	4. Traumatic brain injury and spinal cord injury
	5. Kidney failure
	6. Steroid therapy

**CLINICAL MANIFESTATIONS**

The clinical manifestation of stress ulcer can be erosion, GI bleeding, and a decrease in blood pressure. Luminal erosion is found in 75-100% of patients within 24 hours of ICU admission. Lesions that are deeper and involve the capillaries can cause GI bleeding. However, clinically significant bleeding (decrease in blood pressure and decrease in hemoglobin levels > 2g/dL) occurs in < 5% of ICU patients.<sup>8</sup>

Various signs can be found on physical examination, depending on the cause. However, the typical signs that can be found include: coffee ground vomitus, hematemesis, melena, abdominal pain, nausea and orthostatic problem.<sup>15</sup>

**CLASSIFICATION**

Stress ulcer can be classified as follows:<sup>17</sup>

**Table 2.** Classification of stress ulcers

Stress ulcer asymptomatic	Ulcer without bleeding
Stress ulcer with occult bleeding	Guaiac test was positive in gastric and fecal samples
Stress ulcer with overt bleeding	Hematemesis, coffee ground in nasogastric aspiration, and/or melena
Stress ulcer with clinically significant GI bleeding	Overt bleeding with the addition of one or more of the following: <ul style="list-style-type: none"> <li>● Systolic or diastolic decrease <math>\geq 20</math> mmHg in the 24 hours before or after bleeding</li> <li>● Orthostatic enhancement heart rate <math>\geq 20</math>/minute and systolic decrease <math>\geq 10</math> mmHg</li> <li>● Decreased hemoglobin level <math>&gt; 2</math> g/dL within 24 hours after bleeding begins</li> <li>● Use of vasopressors and/or invasive interventions</li> </ul>

**DIAGNOSIS**

In the case of occult bleeding, the diagnosis can only be made based on assumptions and usually no endoscopic examination is required. But it needs to be followed up furthermore to prove that the patient's condition has improved. After critical illness has been resolved, as long as the patient is in the period recovery and still shows signs of bleeding or other indications (such as upper GI symptoms, stool examination results that are still positive, or another screening) must be performed endoscopy.<sup>10,12</sup>

In patients who experience overt bleeding and/or clinically significant GI bleeding can be performed endoscopy if possible. Endoscopy is indicated if the results will influence decision making and/or there is a suspected lesion that requires further action. The diagnosis can be confirmed by finding erosion on the gastric mucosa. These lesions are usually shallow, well-defined, and affect the superficial layers. Although in some cases deeper ulcers can be found.<sup>10,12</sup>

**PREVENTION**

High mortality and morbidity results in stress ulcers bleeding causing various strategies to be designed to prevent such incidents.<sup>10</sup> Incident of stress ulcers and complications are known to decrease with active prophylactic methods.<sup>14</sup> Prophylactic purposes stress ulcers is to prevent clinically significant bleeding from the lesion. Prophylaxis is especially indicated for patients with the conditions listed in Table 2, especially for patients who are ventilator dependent for more than 48 hours, or have significant coagulopathy.<sup>8</sup>

The main methods of stress ulcers bleeding prophylaxis is by blocking the production of stomach acid using histamine H<sub>2</sub> receptor antagonists (H<sub>2</sub>blocker) proton pump inhibitors (PPIs), and maintaining a pH  $\geq 4$  in gastric aspiration. Another method of prophylaxis involves the use of cytoprotective agent (sucralfate) which protects damaged areas of the gastric mucosa without changing the acidity of the stomach.<sup>8</sup>

Optimal duration of stress ulcers prophylaxis in ICU patients is still unclear. Although most experts agree that prophylaxis should be used if risk factors are present, agreement on when to stop it is limited. The practical

approach is to evaluate the indicators associated with a high risk of stress ulcers occurrence. Once these stressors are mitigated, prophylaxis may be reduced.<sup>18</sup>

**Table 3.** Medication for bleeding stress ulcers prophylaxis<sup>8</sup>

Use of Drugs for Prophylaxis of Stress Ulcer Bleeding			
Drug	Type	Route	Dose
Famotidine	H <sub>2</sub> blocker	IV	20 mg every 12 hours <sup>2</sup>
Ranitidine <sup>1</sup>	H <sub>2</sub> blocker	IV	50 mg every 8 hours <sup>2</sup>
Lansoprazole	PPIs	of	30 mg once daily
Omeprazole	PPIs	of	20 mg once daily
Pantoprazole	PPIs	IV	40 mg once daily
Sucralfate	Protectant	of	1 gram every 6 hours

Information:

<sup>1</sup> The dose of gastric acid suppressant medication may need to be adjusted to maintain a pH ≥ 4 in gastric aspiration.

<sup>2</sup> Dose reduction may be necessary in renal failure.

Abbreviation: PPI=proton pump inhibitors; IV= intravenous; NG=nasogastric instillation.

**PHARMACOLOGICAL  
PROPHYLAXIS**

**Histamine H-2 receptor antagonists**

Histamine H-2 receptor antagonists (H<sub>2</sub>blocker) is a class of drugs used in prophylactic methods of stress ulcers and become the most popular for inhibiting gastric acid secretion. The main indication is to reduce symptoms and speed healing gastric ulcers.<sup>8,9</sup> Ranitidine and famotidine are the types of drugs most often used in this group. Both drugs are usually given via intravenous (IV) bolus at the doses (Table 3). Ranitidine is the most widely studied gastric acid suppressant drug for stress ulcers prophylaxis. Ranitidine given via IV bolus with a single dose of 50 mg will reduce gastric acidity levels (pH > 4) for 6 – 8 hours. Famotidine competitively inhibits histamine at H receptors of gastric parietal cells, thereby reducing gastric acid secretion, gastric volume, and hydrogen ion concentration.<sup>9</sup> Famotidine has a longer duration of action. A single dose of

famotidine 20 mg given via IV bolus will reduce gastric acidity (pH > 4) for 10 – 15 hours. IV famotidine and ranitidine are predominantly excreted in the urine. The accumulation of these drugs in renal failure can lead to a neurotoxic condition characterized by decreased consciousness, agitation, and even seizures. Therefore dose reduction is recommended in patients with renal insufficiency.<sup>8</sup>

H<sub>2</sub>blocker effectively reduces clinically significant GI bleeding as a consequence of stress ulcers. The use of H<sub>2</sub>blocker long term will be accompanied by a decrease in its ability to maintain a pH ≥4, but this does not affect its ability to prevent bleeding-related as a consequences of stress ulcers.<sup>8,9,10</sup>

The main risks associated with H<sub>2</sub>blocker associated with decreased gastric acidity, including an increased incidence of infectious gastroenteritis

(including enterocolitis clostridium difficile) and an increase in the incidence of pneumonia due to aspiration of gastric secretions that infect the respiratory tract.<sup>8</sup>

### **Proton pump inhibitors (PPIs)**

Proton pump inhibitors (PPIs) are drugs that potent to suppress stomach acid by binding to membrane proton pumps in gastric parietal cells and inhibiting the H enzyme system/K<sup>+</sup>-ATPase that catalyzes H exchange<sup>+</sup> and K<sup>+</sup>.<sup>9</sup> PPIs are drugs prodrug which must be converted into the active form in the parietal cells of the stomach. Once activated, the drug binds irreversibly to the membrane pump and results in complete inhibition of gastric acid secretion. PPIs are used for prophylaxis stress ulcers listed in Table 3.<sup>8</sup>

PPIs have several advantages over H<sub>2</sub>blocker. First, PPIs can produce a greater reduction in gastric acidity and have a longer duration of action. Second, the workability of PPIs does not decrease with continued use. Lastly, PPIs are metabolized in the liver and do not require dose adjustment in renal failure. Therefore, PPIs may gradually replace H<sub>2</sub>blocker as prophylaxis stress ulcers in inpatients.<sup>8</sup>

As stress ulcers bleeding prophylaxis, PPIs have not shown an advantage over H<sub>2</sub>blocker. Increased gastric acid suppression with PPIs may pose a greater risk of infection compared to H<sub>2</sub>blocker. This is supported by research showing that the use of PPIs compared to H<sub>2</sub>blocker increasing the incidence of pneumonia in hospitals as well as the incidence of enterocolitis clostridium difficile higher in outpatients.<sup>8,9</sup>

PPIs and antiplatelet agents (clopidogrel) are prodrug which is converted to the active form via the same pathway (cytochrome P-450) in the liver. Therefore, PPIs can inhibit clopidogrel activation in the liver (via competitive inhibition) and reduce its antiplatelet activity. This effect was proven by in vitro platelet aggregation assays, but the clinical significance of the interaction is unclear. The Food and Drugs Administration (FDA) recommends avoiding PPIs, if possible, in patients taking clopidogrel.<sup>8</sup>

### **Sucralfate**

Sucralfate is an aluminum salt of sucrose sulfate that adheres primarily to areas of damaged gastric mucosa, binds to positively charged proteins in the exudate, and forms a viscous fluid that protects the GI lining from luminal acid and pepsin proteolysis.<sup>9</sup> Sucralfate classified as protectant or cytoprotective agent, and has no effect on gastric acid secretion. Sucralfate improves healing of gastric and duodenal ulcers, and reduces the incidence of significant GI bleeding due to stress ulcers.<sup>8,9</sup>

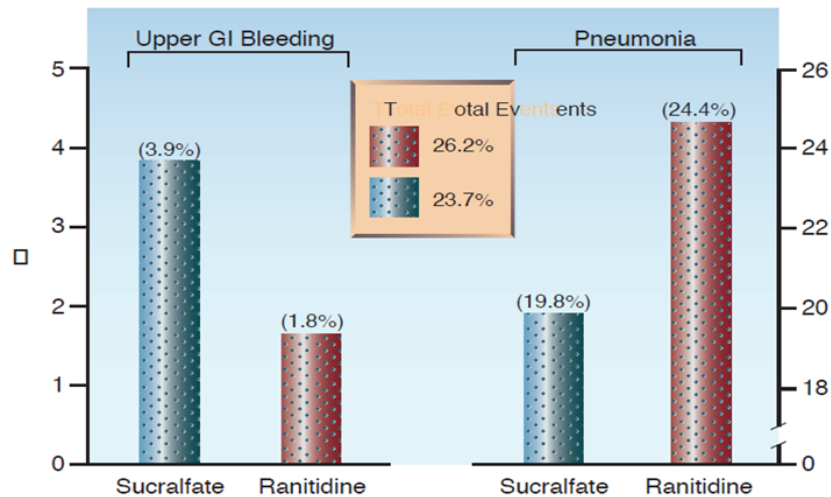
Sucralfate is available in tablet (1 gram per tablet) or suspension (1g/10 mL), and is most effective when given in suspension form. Sucralfate dose for stress ulcers prophylaxis (Table 3). Sucralfate will stick to the damaged gastric mucosa for about 6 hours, so it is recommended to administer doses at 6 hours intervals.<sup>8</sup>

Sucralfate is attractive because it does not alter gastric acidity, and does not pose the increased risk of infection that accompanies other gastric acid suppressing drugs. Several clinical trials have compared sucralfate with ranitidine as stress ulcers prophylaxis (Figure 2). In these clinical trials,



significant GI bleeding occurred less frequently with ranitidine use, whereas pneumonia occurred less in sucralfate use. When the incidence of bleeding and pneumonia were combined (as

shown in the middle box), adverse events occurred with use of less sucralfate. Although not shown, the death rate was the same for both drugs.<sup>8</sup>



**Figure 2.** Prophylactic effect of stress ulcers compared between ranitidine and sucralfate on the incidence of significant GI bleeding and pneumonia in ventilator-dependent patients.

There are two possible interpretations of the results (Figure 2), based on the desired outcome. If the desired outcome is fewer bleeding episodes, then ranitidine is better to be chosen rather than sucralfate. However, if the desired result is to have fewer side effects (bleeding and pneumonia), then sucralfate is better to be use rather than ranitidine.<sup>8</sup>

**PROPHYLAXIS  
NON-PHARMACOLOGICAL  
Enteral feeding**

Enteral tube feeding exerts a trophic effect on the GI mucosa that helps maintain the structural and functional integrity of the mucosal surface. Enteral feeding solutions also increase the pH in the gastric lumen. Both of these effects can protect patients from risk of stress ulcers bleeding. The combined results of three clinical studies demonstrate that the ability of H<sub>2</sub>blocker to reduce stress

ulcers bleeding disappeared when the patient received the regimen enteral feeding. These results indicate that patients who get enteral feeding does not require further prophylactic action toward stress ulcers bleeding.<sup>8</sup> This is also supported by a meta-analysis study showing that prophylaxis does not provide additional benefit in patients receiving enteral nutrition, as no statistically significant difference was found in the rate of GI bleeding. Early enteral nutrition is recommended because it improves intestinal integrity, reduces infectious morbidity, and may reduce the risk of death. There is no evidence of prospective randomized controlled trials regarding enteral nutrition as the only means of stress ulcers prophylaxis, then other prophylaxis should still be given to patients who have a very high risk of stress ulcers occurrence.<sup>18</sup>

## MANAGEMENT

Management of patients with stress ulcer or SRMD is generally similar to the upper GI bleeding (UGIB) case, which doing resuscitation, coagulopathy correction, bleeding control, and gastric protection.<sup>6,10</sup> Resuscitation airway, breathing and circulation also should be done immediately if the patient's condition is unstable.<sup>11</sup>

European non-variceal UGIB recommends prophylactic intubation only be performed in cases of severe hematemesis, agitation, and for patency airway.<sup>19</sup> Oxygen supplementation should also be given to maintain end organ oxygenation.<sup>11</sup> For resuscitation actions, it must be done with two venous accesses with a large cannula. However, if peripheral access is difficult to obtain, or fluids with high osmolarity are needed, central venous access is preferred.<sup>6,11</sup> It is recommended to administer 500 mL of crystalloid in less than 15 minutes in patients with unstable hemodynamics and a target systolic blood pressure of 90-100 mmHg.<sup>20</sup> For administering blood transfusions, a randomized controlled trial (RCT) showed that giving transfusions at hemoglobin levels <7 g/L (restrictive strategy) had a much lower risk of death within six weeks compared to giving transfusions at hemoglobin levels <9 g/L (liberal strategy).<sup>22</sup> Additionally, a meta-analysis concluded that restrictive transfusion strategies had lower mortality rates and reduced re-bleeding risk.<sup>21</sup>

After resuscitation, gastric lavage was performed using a measurement tube which is normally in saline room temperature to discard clot and reduce gastric distension with the aim of reducing the risk of aspiration.

By eliminating clot, gastric lavage also reduces local fibrinolytic activity. If bleeding persists, consider intravenous vasopressin or somatostatin. Giving somatostatin is preferred because the side effects are minimal. At the same time, H<sub>2</sub>blocker or PPI must be given to raise gastric pH above 5.0.<sup>10</sup> Administration of Vitamin K, vitamin-K-factor dependent or fibrinogen is also usually given as an anticoagulant.<sup>6</sup>

If possible, endoscopic hemostasis with electrocoagulation like argon plasma coagulation (APC) or by injection therapy can be performed. Selective angiographic catheterization of the left gastric artery can be performed with selective vasopressin infusion (48-72 hours) or embolization using gel foam, coil, or autologous clot for embolization of the left gastric artery. Regardless of the angiographic technique used, it is often unsuccessful due to the rich and extensive submucosal plexus and collateral circulation within the stomach.<sup>10</sup>

Surgical intervention is necessary if nonoperative therapy failed and blood loss continues. The goal of operative treatment is to control bleeding and reduce recurrent bleeding and death. In the event of life-threatening bleeding that cannot be controlled with endoscopy, gastric resection with or without vagotomy with reconstruction may be necessary.<sup>10</sup>

## COMPLICATIONS

### Complications of stress ulcer

The most common complications associated with stress ulcers are GI bleeding, perforation, penetration, and gastric outlet obstruction.<sup>23</sup> GI bleeding is the most common complication. Excessive amounts of bleeding can be life-threatening. Stress ulcers can

develop into a penetration which can then develop into a perforation and can progress to ulcers in adjacent organs such as the liver and pancreas. Perforation that occurs in stress ulcers often has bad consequences if left untreated. For example, Perforation of the gastrointestinal wall by stress ulcers causes the contents of the stomach or intestines to escape into the abdominal cavity, which can cause acute peritonitis which is preceded by chemical peritonitis and progresses to bacterial peritonitis. Meanwhile, another complication that may occur is gastric outlet obstruction, which can be defined as narrowing of the pyloric canal due to scar tissue and swelling of the antrum.<sup>6,23</sup>

#### **Complications caused by stress ulcer prophylaxis**

Patients with critical illness need to be re-evaluated during and after being treated in the ICU.<sup>3</sup> Buckley et al. showed that 14.4% of patients in the ICU received gastric acid suppressive therapy without appropriate indications, resulting in the risk of adverse side effects and increased costs.<sup>24</sup>

Patient identification and treatment stress ulcers will reduce complications, length of stay, and costs. However, to minimize potential complications due to pharmacological stress ulcers prophylaxis, routine use of such therapy should be limited to patients who have known risk factors for its stress ulcers occurrence.<sup>25</sup>

There is controversy surrounding the relationship between the use of stress ulcers prophylaxis and the development of infectious complications, especially ventilator-related complications (IVAC) and infections *Clostridium difficile*. Suppression of gastric acid production

and an increase in intragastric pH above the bactericidal threshold (intragastric pH <4) lead to increased colonization of pathogenic organisms.<sup>12</sup>

#### **Stress ulcers prophylaxis and complications related to ventilator use (IVAC)**

The mechanism that contributes to IVAC is contamination of the oropharyngeal area by reflux of gastric fluid, which is then followed by aspiration of oropharyngeal bacteria into the lower airway. Administration of drugs to increase gastric pH can facilitate colonization of gastric pathogenic organisms and predispose to respiratory tract infections.<sup>12</sup>

#### **Prophylaxis stress ulcers and clostridium difficile infection**

The use of stomach acid suppressing drugs carries a risk of enterocolitis caused by *clostridium difficile*. This happened because those drugs suppress stomach acidity, making the GI environment more alkaline. Meanwhile *clostridium difficile* cannot grow in acidic conditions and will grow well in alkaline conditions.<sup>12</sup> In outpatients and inpatients, an increase in enterocolitis C is often found greater in the use of PPI, compared to group H<sub>2</sub>blocker. There is a high probability of an increase in the incidence of enterocolitis *clostridium difficile* in hospitalized patients not caused by the use of antibiotics, but due to the use of stomach acid suppressant drugs for stress ulcers prophylaxis.<sup>8</sup>

#### **SUMMARY**

Stress ulcer is the most frequent complication in patients with critical illness in the ICU. This is caused by an imbalance of defensive and aggressive factors in the stomach. Patients with critical illness often run into vasoconstriction and hypoperfusion of

splanchnic, causing disruption of blood flow to the gastric mucosa and resulting in damage to the gastric mucosa. Cases that have the highest risk factors for stress ulcer occurrence including the use of mechanical ventilation (>48 hours), coagulopathy, and burns >30% of the body surface area. Meanwhile, other risk factors are shock, severe sepsis, multisystem trauma, brain injury, kidney failure and steroid therapy. Clinical manifestation of stress ulcer can range from erosion and ulcers to complications of GI bleeding, anemia, and decreased blood pressure.

Incidents of stress ulcers and complications are known to decrease with active prophylactic methods. Pharmacology that can be used as stress ulcers prevention are histamine H<sub>2</sub> receptor antagonists (H<sub>2</sub>blocker), proton pump inhibitors (PPIs), and sucralfate. H<sub>2</sub>blocker and PPIs have almost the same effect of prevention, but PPIs have a higher risk of pneumonia and clostridium difficile enterocolitis. Although sucralfate has less risk of infection, its effectiveness is lower than H<sub>2</sub>blocker. Duration of stress ulcers prophylaxis in ICU patients is still unclear. The practical approach is to evaluate the indicators associated with a high risk of stress ulcers occurrence. Once the cause has been mitigated, prophylaxis may be reduced. Apart from pharmacology, the main prevention strategy is administration enteral feeding. Although it is still controversial, several studies have concluded that patients who get enteral feeding do not require pharmacological prophylaxis. Therefore, further research should be carried out regarding effective enteral feeding without pharmacological administration as prophylaxis stress ulcers in critically ill.

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