Commentary

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What's New in Preventing Pediatric Gastrointestinal Bleeding in Critically Ill Patients?

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Bleeding from stress-related gastrointestinal mucosa disease in critical patients remains a major clinical management problem in the intensive care unit in both adults and pediatrics. Although the incidence is low (1%-6%), a substantial proportion presents clinical risk factors (such as mechanical ventilation greater than 48 hours and coagulopathies) that predict an increased risk of bleeding. In addition, we can find lesions of the gastrointestinal mucosa in up to 75 to 100% of patients in the ICU. Although rare, stress ulcer bleeding is a serious complication with an estimated high mortality of 40 to 50%, mainly due to decompensation of an underlying condition or multi-organ failure. Although the majority of ICU patients receive stress ulcer prophylaxis, mainly with IBP, there is some controversy surrounding its efficacy and safety. Indeed, no individual trial has shown that stress ulcer prophylaxis reduces mortality. Some reports suggest that the use of IBP increases the risk of nosocomial infections. However, several meta-analyzes and cost-effectiveness studies suggest that IBP are clinically more effective and cost-effective than histamine-2 receptor antagonists (H2RA), without considerable increases in nosocomial pneumonia [1]. In pediatrics gastrointestinal hemorrhages are described in up to 10% of the complications in patients with critical illness of these 1.6% are significant hemorrhages, of these are associated with risk factors such as respiratory failure, coagulopathy or PRISM score>10, with incidences probably even older in neonatal ICUs [2].

The pathophysiology is complex and begins with vasoconstriction, mucosal ischemia eventually leads Bleeding that results from stress ulcerations is called stress ulcer related bleeding (SURB). Upper Gastrointestinal Bleeding (UGIB) can also originate in other places, for example, reflux esophagitis, which has a different approach. Recently, it has become clear that acid suppression does not prevent UGIB or SURB. It is believed that stress ulcers are caused by decreased mucosal blood flow, ischemia and reperfusion injury, and therefore are less related to acid secretion than peptic ulcers. However, the pathophysiology has not been fully clarified [3].

Patients in critical condition may have an alteration in gastric mucosa from the first 24 hours of admission resulting from erosion, ulcers and even significant bleeding causing hemodynamic instability. To prevent mucosal damage caused by acid produced by gastric cells several pharmacological options as sucralfate whose main function is used is to inhibit acid secretion, this adheres to epithelial cells to cover the gastric mucosa and create a thin protective layer between the mucosa and the gastric acid in the stomach lumen; receptor antagonists Histamine-2 are also used being an antagonist of H2 receptors and proton-pump inhibitor which inhibits this the adenosine triphosphatase H^+/K^+ resulting in reducing the production of acid by the parietal cells [4].

The normal gastric mucosa is designed and highly adapted to resist acid fluids in gastric light. The integrity of the gastric mucosa is normally formed by the mucus layer, a phospholipid barrier, the tight junctions between the epithelial cells, the ability to regenerate the mucosa, the production of prostaglandins and the blood flow of the mucosa. Loss of one or more of these barriers leads to decreased integrity of the gastric mucosa. In critical patients, inflammatory status and altered circulation of the splanchnic region may result in a reduction of one or more of these defense mechanisms. When alterations in the integrity of the gastric mucosa occur, gastric acid is allowed to reach the deeper layers of the mucosa, which can lead to the formation of a gastric ulcer. Mucosal damage occurs in 75% to 100% of patients admitted to the ICU in shock. Probably, the main reason for a disruption of the mucosal barrier function in any critical patient is a reduction in mucosal circulation. A perfused mucosa normally recovers from the lesion in a matter of hours, but a damaged splanchnic perfusion during an inflammatory state makes recovery difficult **(Figure 1)** [4].

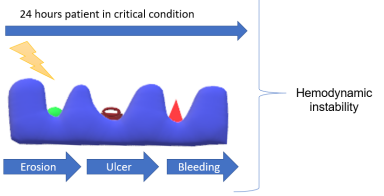

Figure 1: Natural history of gastric mucosal injury in a critical patient.

The altered microcirculation and vasoconstriction in the splanchnic region occur due to endotoxemia and hypovolemia in the acute phase of severe disease. This process happens in the increase of the translocation of endotoxins through the ischemic mucosa and the subsequent endotoxic vasoconstriction. Reduced perfusion with ischemic mucosa leads to a loss of tight junctions. The concept of reduced integrity and increased permeability in critical patients was demonstrated in at least two studies measuring increased sucrose absorption. The damaged mucosa leads to the diffusion of acid and produces the formation of consecutive ulcers. In 1970, Skillman published the results of his studies on the gastric mucosal barrier function and acid backscattering. Concluding: "These studies strongly suggest that disruption of the stomach barrier function, especially in the presence of poor vascular perfusion, may be an important clue to the pathogenesis of the irritating and highly fatal problem of the acute stomach ulcer of the human stomach." However, many doctors today still consider the gastric acid responsible for the stomach ulcer for which the treatment is chosen according to that point of view instead of focusing on the improvement of splanchnic perfusion. Additional factors that add to the decrease in the integrity of the gastric mucosa are the presence of H. pylori and bile reflux from the duodenum into the stomach, mechanical ventilation and coagulopathy were identified as independent risk factors and fit into the conceptual framework as shown in **(Figure 2)**[4].

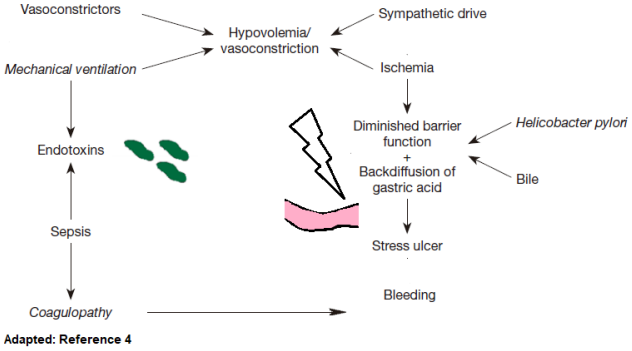

Figure 2: Mechanisms of the pathophysiology of stress ulcer formation and bleeding.

Reveiz et al. performed a systematic review which compared two groups and found to be more effective for the prevention of significant bleeding treatment group compared to where no administration of prophylaxis (RR 0.41, 95% CI, 0 is performed, 19-91; I=12%). When ranitidine compared vs. not mechanically ventilated children handling a significant difference for preventing this medication (RR 3.53, confidence interval 95%, 1.34 to 9.29) found [5-7].

Moreover, a meta-analysis studies included 57 patients which included 7293 showing results show that the proton-pump inhibitor prevents gastrointestinal bleeding developed significantly (OR) 0.38; This confidence interval 95% (95%) but is related to increase risk of developing pneumonia compared with sucralfate (OR 1.65, 95% CI 1.20, 2.27) **(Table 1)** [4]. The effectiveness of the proton pump is also supported by Alhazzani et al. who developed meta evaluating its effect compared to H2 receptor antagonist (RR 0.36, 0.19 to 0.68 95% CI, p=0.002) [7,8].

Table 1: Efficacy of prophylaxis gastrointestinal bleeding and risk of pneumonia development.

	Efficacy prophylaxis	Risk of pneumonia
Proton pump inhibitors	(OR) 0.38; 95% confidence interval (95% CI)	Comparison with sucralfate (OR 1.65, 95% CI 1.20, 2.27 Compared with antihistamines (OR 1.27, 95% CI 0.96, 1.68, moderate quality)
Sucralfate	OR 1.05; 95% CI: 0.69; 1.59; Moderate quality	Compared with antihistamine IC 0.95 (0.79, 1.16)
Antihistamines	OR 0.42; 95% CI: 0.28; 0.63, moderate quality	Comparison with sucralfate O of 1.30; 95% CI 1.08, 1.58; moderate quality

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Most critical children receive gastric acid suppressants in an attempt to reduce the risk of stress-induced ulcers. However, the quantity and quality of the evidence supporting the use of these in critical children are low, without firm evidence of benefit or

harm, and there is clinical balance. The cornerstone in the treatment of UGIB in the PICU is acid suppression. Acid suppression provides an environment for the recovery of gastric mucosa. It has not been studied whether acid suppression in intensive care patients with UGIB leads to faster recovery as such. Acid suppression therapy in critical patients can be questioned, since it is not obvious that critical patients produce acid in shock. In addition, Skillman demonstrated in 1970 that there was a 72% reduction in acid secretion in hemorrhagic shock. When acid production is limited, acid suppression will have no effect on the prevention or treatment of stress ulcer. Based on the pathophysiological concept as explained above, it is more logical to restore mucosal perfusion. Reversal of shock with fluids, inotropics and vasopressors can be useful in improving perfusion. However, trials on vasodilator therapy for the splanchnic region have not yet been conducted [4,9].

In conclusion, when comparing ranitidine vs. non-management in mechanically ventilated children showing significant difference for prevention with this medication, evidence has also been shown that Proton Pump Inhibitors (PPI) prevent gastrointestinal bleeding, but is related to increasing the risk of developing pneumonia compared to sucralfate. The fundamental treatment of this entity in intensive care patients is good clinical care: Restoring circulation, oxygenation and hemoglobin level. In addition, coagulation disorders should be treated to improve clot formation and hemostasis. Usually, these measures are enough to stop the bleeding. When bleeding occurs, the next step is to obtain an endoscopic examination with or without endoscopic treatment. There are several options available for local treatment, a discussion that is beyond the scope of this article. With this sequential and progressive approach, surgical treatment is rarely needed [9,10].

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