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REVIEW ARTICLE

Gastrointestinal Prophylaxis in Neurocritical Care

Clemens M. Schirmer · Joshua Kornbluth · Carl B. Heilman · Anish Bhardwaj

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Abstract The aim of this study is to review and summarize the relevant literature regarding pharmacologic and non-pharmacologic methods of prophylaxis against gastrointestinal (GI) stress ulceration, and upper gastrointestinal bleeding in critically ill patients. Stress ulcers are a known complication of a variety of critical illnesses. The literature regarding epidemiology and management of stress ulcers and complications thereof, is vast and mostly encompasses patients in medical and surgical intensive care units. This article aims to extrapolate meaningful data for use with a population of critically ill neurologic and neurosurgical patients in the neurological intensive care unit setting. Studies were identified from the cochrane central register of controlled trials and NLM PUBMED for english articles dealing with an adult population. We also scanned bibliographies of relevant studies. The results show that H_2A, sucralfate, and PPI all reduce the incidence of UGIB in neurocritically ill patients, but H_2A blockers may cause encephalopathy and interact with anticonvulsant drugs, and have been associated with higher rates of nosocomial pneumonias, but causation remains unproven and controversial. For these reasons, we advocate against routine use of H_2A for GI prophylaxis in neurocritical patients. There is a paucity of high-level evidence studies that apply to the neurocritical care population. From this study, it is concluded that stress ulcer prophylaxis among critically ill neurologic and neurosurgical patients is important in preventing ulcer-related GI hemorrhage that contributes to both morbidity and mortality. Further, prospective trials are needed to elucidate which methods of prophylaxis are most appropriate and efficacious for specific illnesses in this population.

Keywords Gastrointestinal · Neurocritical · Ulcer · Prophylaxis · GI bleed

C. M. Schirmer · C. B. Heilman · A. Bhardwaj
Department of Neurological Surgery, Tufts University School of Medicine, Boston, MA 02111, USA

J. Kornbluth · A. Bhardwaj
Department of Neurology, Tufts University School of Medicine, Boston, MA 02111, USA

C. M. Schirmer (✉)
Baystate Neurosurgery, 2 Medical Center Drive, MOB Suite 503, Springfield, MA 01107, USA
e-mail: clemens.schirmer@baystatehealth.org

Introduction

It is well established that there is an increased risk of developing stress-related gastrointestinal (GI) ulcers, and hemorrhage in critically ill patients. There is an abundance of the literature on the prevention and treatment of GI mucosal disease in critically ill medical and surgical patients; however, there is a paucity of such data in critically ill neurological and neurosurgical patients. Neurological injury combined with severe physiologic stress, critical illness, has been shown to increase the risk for GI ulcer disease and subsequent hemorrhage [1–6]. The risk is potentiated by coagulopathy, renal failure, and mechanical ventilation [7]. The precise pathophysiological mechanisms of this stress-related GI mucosal disease are not fully delineated at present, but may be associated with impairment of mucosal protective mechanisms resulting from compromised mucosal microcirculation [8]. GI bleeding due to ulcer hemorrhage may cause acute anemia, hemodynamic instability, and may induce nausea and vomiting, all of which

may contribute to morbidity and mortality among critically ill neurological and neurosurgical patients.

As it pertains to patients with neurological injury, a Cushing ulcer signifies a gastric ulcer resulting from elevated intracranial pressure (ICP) [9]. A neurogenic basis for stress ulcerations was first proposed by Carl Rokitansky in 1841, who observed pre-mortem ulcerations of the GI tract in patients with intracranial tumors, other central nervous system (CNS) disease, and cachectic states [10]. In addition to the stomach, it may also develop in the proximal part of the duodenum and distal esophagus. In his classic work in 1932, Harvey Cushing [9] reported on a series of 11 patients with similar findings after neurosurgical procedures. He hypothesized the role of parasympathetic centers of the hypothalamus with their connections to vagal nuclei in the medulla. Today's postulated pathophysiological mechanism is that the vagus nerve stimulates acetylcholine, which stimulates the M3 receptor on the parietal cell, and activates the second messenger to stimulate IP3/Ca^{2+} to stimulate the hydrogen/potassium ATPase pump, which increases gastric acid production and, consequently leads to gastric erosions. After Cushing's report the syndrome became known as Rokitansky-Cushing syndrome.

The literature regarding gastric ulcer prophylaxis in patients with neurological conditions is vast and conflicting. This review focuses on the pathophysiology of stress-related mucosal lesions, defines risk factors for GI hemorrhage, and summarizes previous studies pertaining to stress ulceration in neurosurgical patients. It also reviews the pharmacology and evaluates the efficacy of prophylactic therapy in critically ill neurological and neurosurgical patients as well as addresses related issues such as enteral nutrition, corticosteroid therapy, and nosocomial pneumonia.

Pathophysiology and Risk Factors

The genesis of GI stress ulcers is multi-factorial and represents an imbalance between protective and destructive factors acting on the gastric mucosa. Destructive factors include gastric acid, pepsin, bile, and splanchnic hypoperfusion. Another important factor involved in the development of stress-related mucosal disease is the reperfusion injury. As local blood flow is restored after long periods of hypoperfusion, elevated levels of nitric oxide synthetase lead to hyperemia, cell death, and an enhanced inflammatory response [11]. Gastric acid is a prerequisite component in the pathobiology of gastric ulcers, and has been shown to be overproduced along with pepsin in patients with intracranial diseases. This effect peaks 3–5 days after the insult [12]. Proteolytic enzymes within gastric fluid may add to the destruction of GI mucosa already damaged by excess acid. A common finding among critically ill patients is the reflux of bile salts, and this is thought to disrupt the gastric mucosal barrier and accentuate mucosal injury. Protective factors from stress ulcers include a thin layer of bicarbonate-containing mucus, which depends on normal gastric acid secretion, and a glycoprotein matrix that serves as a physical barrier to the influx of pepsin and hydrogen ions [11].

The risks for development of stress ulcers and subsequent hemorrhage are many (see Table 1). Critically ill patients are predisposed to the development of gastric ulcers and GI bleeding regardless of the presence of premorbid peptic ulcer disease. These patients are put at risk both by their underlying disease and by therapeutic interventions. Quenot et al. [13] identified 14 independent risk factors (Table 1) for stress ulcer-related bleeding among patients who are critically ill. Specific risks prevalent among neurological and neurosurgical critically ill patients are: respiratory failure requiring more than 48 h of mechanical ventilation, severe head or spinal cord injury (SCI), ischemic or hemorrhagic stroke, anticoagulation, major surgery (lasting more than 4 h), and administration of high-dose corticosteroids ($>$250 mg/day of equivalent hydrocortisone). Certain medications predispose the patients to peptic ulcer disease with considerable odds, see also Table 2 [14]. The presence of intracranial hypertension can be universal to any mechanism of cerebral injury, and will not be analyzed separately. Presence of more than one of these risk factors seems to increase the risk of symptomatic gastric ulcers. In patients with traumatic brain injury (TBI), the risk correlates with the severity of the

Table 1 Risk factors for stress ulcer-related bleeding, adapted from [13].

Respiratory failure requiring mechanical ventilation for more than 48 h
Coagulopathy (international normalized ratio more than 1.5 or platelet count less than 50,000 platelet/μl)
Acute renal insufficiency
Acute hepatic failure
Sepsis syndrome
Hypotension
Severe head or spinal cord injury
Anticoagulation
History of gastrointestinal bleeding
Low intragastric pH
Thermal injury involving more than 35% of the body surface area
Major surgery (lasting more than 4 h)
Administration of high-dose corticosteroids (250 mg/day of steroids or equivalent hydrocortisone)
Acute lung injury

Table 2 Relative risks for peptic ulcer hemorrhage (adapted from [14]).

Factor	RR factor (95% CI)	Analyzed cases	Reference
NSAIDs[a]	3.7 (3.1–4.3)	1,561	[86]
Coxibs[a]	2.6 (1.9–3.6)		
NSAIDs	5.3 (4.5–6.2)	2,777	[87]
Rofecoxib	2.1 (1.1–4.0)		
Clopidogrel/ticlopidine	2.8 (1.9–4.2)		
ASA (100 mg/day)	2.7 (2.0–3.6)		
Anticoagulants	2.8 (2.1–3.7)		
Preexisting peptic ulcer	4.3 ($P = 0.043$)	822	[88]
Smoking	3.1 ($P = 0.023$)		
Use of antiplatelet agents	6.5 ($P = 0.046$)		
NSAIDs/Coxibs	4.9 ($P = 0.060$)		

NSAIDS non-steriodal anti-inflammatory drugs

[a] Dose-dependant effects

injury, irrespective of the presence or absence of other risk factors [15].

Gastric Ulcer Development in Special Patient Populations

Critically Ill Patients in General

Critically ill patients regardless of etiology seem to be predisposed to gastric ulceration and bleeding [8], see Table 3. The clinical significance of this has been debated with some studies citing incidences as low as 1.5% among all ICU patents for clinically significant GI ulceration and hemorrhage, and others showing significantly increased morbidity and mortality among critically ill patients [16].

Table 3 Gastric ulcer prophylaxis is recommended for the following medical conditions [89].

Condition
Mechanical ventilation longer than 48 h
Coagulopathy
Glasgow coma scale $\leq$10
Multi-system trauma or spinal cord injury
Burn injuries to $\geq$35% of body surface area
Liver failure or status post partial hepatectomy
Patients with organ transplants
At least two of the following
Intensive care unit stay $>$7 days
Sepsis
High-dose steroid use ($>$250 mg/day hydrocortisone equivalent)
Evidence of occult bleeding $>$6 days

The discordance among these studies and subsequent meta-analyses have been attributed to the incomplete identification of relevant studies, differential inclusion of non-english language and nonrandomized trials, different definitions of bleeding, provision of additional information through direct correspondence with authors, and different statistical methods [17].

Regardless of its incidence, morbidity from stress-related gastric ulceration and subsequent bleeding can increase the length of stay in the ICU from 4 to 8 days [18]. Mortality rate can range from 50 to 77% in critically ill patients who develop stress-related mucosal bleeding during hospitalization, which can be as much as four times higher than it is in ICU patients without this complication [19].

Brain and Spinal Cord Injury

Autopsy studies in neurosurgical patients have shown the probable existence of Cushing's ulcers. One review revealed an incidence of hemorrhagic ulcers of 12.5%, almost double to that in patients succumbing to non-neurological diseases [20]. Neurosurgical patients exhibit hypersecretion of pepsin and gastric acid [1, 21–24]. Severe TBI and Glasgow Coma Scale scores (GCS) of $<$9 have been associated with gastric acid hypersecretion and GI hemorrhage exceeding 17% [12, 15, and 25–32]. In two series, bleeding occurred during the first 2 weeks of hospitalization [21, 33]. Other risk factors associated with GI mucosal disease and brain injury are the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), CNS infection, respiratory failure, hypotension, and gastric pH $<$ 4 [1, 21, 22, and 28]. Age being $>$60 years is an independent risk factor, and all the mentioned risk factors appear to be cumulative [1, 30]. A recent study from Li et al. [34] has shown that acute head injury was associated with elevations in plasma cortisol which, along with advanced age, were independent predictors of stress ulcer formation after acute TBI. Significant morbidity and mortality rates can arise from GI complications; one series reports a 2.1% directly attributable mortality rate [1].

Incidence of gastric ulcer disease (GUD) is commonly accentuated after SCI, ranging between 2 and 20% [35–39]. Further studies have postulated a multi-factorial causation [2, 38, and 40]. Uninhibited and persistent vagal activity coupled with reduced or absent sympathetic outflow after SCI have been proposed as the basis for this association [2, 37–39, 41, and 42], and patients with SCI at cervical levels are especially prone to stress-related mucosal disease compared with injuries involving lower spinal cord segments [2, 37, 39, and 42]. Symptomatic upper GI hemorrhage incidence peaks at 4–10 days and can occur within the first 4 weeks after SCI [2, 36, and 39].

Corticosteroids Use

Use of high-dose corticosteroids (>250 mg/day of hydrocortisone equivalent) in critically ill neurological and neurosurgical patients are usually limited to patients with brain tumors and SCI. Corticosteroids may also be employed in the management of myasthenia gravis exacerbation, severe exacerbation of multiple sclerosis, meningoencephalitits, and comorbid COPD. Glucocorticoids may in fact have a dual mechanism on gastric mucosa, both providing physiologic protection as well as being pathologically pro-ulcerogenic by the inhibition of gastric mucus secretion, epithelial proliferation, and prostaglandin biosynthesis as well as synchronous dysregulation of glucose homeostasis [43]. Studies in animal models of dexamethasone support this premise. Filaretova et al. [43] data suggest that short-course (<12 h) dexamethasone maybe protective due to its part through membrane stabilization.

Mechanical Ventilation

Mechanical ventilation for a longer duration than 48 h has been independently associated with stress-induced mucosal disease [16]. A "mechanical ventilation care bundle" has been implemented in many ICU's, and includes routine gastric ulcer prophylaxis regardless of comorbid conditions, antithrombotic or anticoagulant use, or etiology of ventilator failure [44].

Acute Ischemic Stroke

The pathophysiology underlying the mechanisms by which acute ischemic stroke leads to an increased risk of stress-related ulceration and hemorrhage are poorly understood. One proposed mechanism is vagal hyperactivity resulting in increased gastric acid secretion [6].

Theoretically, patients with ischemic stroke are at additional risk for GI hemorrhage since they are often treated with antithrombotic or anticoagulant drugs; however, initial published data does not support this notion, and describes a low incidence of significant upper GI bleeding without contribution to excess morbidity or mortality [45, 46]. This has recently been reevaluated and one study described GI bleeding after major vascular events as "grossly underestimated" [5]; an incidence of 1.5% of GI hemorrhages after ischemic stroke. It is unclear if the risk for GI hemorrhage is independent of antithrombotic use. Another study including 115 patients with acute ischemic stroke identified GI bleeding in 5.2% of patients [47]. For unclear reasons, independent predictors of GI bleeding were age (OR 1.25; 95% CI 1.07–1.50), and middle cerebral artery territory infarcts (OR 9.47; 95% CI 1.62–55.5). Furthermore, the presence of GI bleeding increased mortality in this population (OR 24.97; 95% CI 1.97–316.91).

Intracerebral Hemorrhage

There is limited data on the incidence and clinical significance of stress-related mucosal disease and GI hemorrhage following acute intracerebral hemorrhage. One study by Misra et al. [3] evaluated predictive factors for GI hemorrhage in patients with primary ICH. Of the 51 patients included in the study, 30% had evidence of GI hemorrhage, as determined by "coffee ground", hemorrhagic emesis or gastric aspirates, hematochezia or melena. Multivariate analysis suggested that the best set of predictors of GI hemorrhage included size of hematoma, presence of septicemia, and lower GCS score. A follow-up study in the form of a randomized placebo- controlled trial by the same team to evaluate ranitidine versus sucralfate in patients with spontaneous intracerebral hemorrhage for prevention of gastric hemorrhage, showed that neither drug seemed to significantly prevent GH or reduce 1-month mortality [4].

Subarachnoid Hemorrhage

There is little data in humans specifically addressing the incidence of stress-related mucosal disease following subarachnoid hemorrhage (SAH). Davenport et al.'s [45] evaluation of 613 patients specifically excluded patients with SAH in their study. Another retrospective analysis of 16,672 stroke patients identified only 17 patients with clinically significant GI hemorrhage, none of whom had a SAH [46]. Experimental models of SAH show stress-related mucosal disease, but direct correlation with human data is lacking [48, 49].

Methods for Stress Ulcer Prophylaxis

The primary goal in stress-induced gastric mucosal injury is to prevent clinically relevant hemorrhage. Several methodologies that are both pharmacologic and non-pharmacologic have been utilized for this purpose.

Histamine Receptor Antagonists

Histamine receptor inverse agonists (H_2A; Table 4) reversibly inhibit acid secretion mediated through the type-2 histamine receptor (H_2) of the parietal cell in a dose-dependent fashion. H_2A inhibit the cytochrome P_{450} enzyme system, interfere with antibiotic activity, and can cause hypotension and thrombocytopenia. Important drugs that are affected include theophylline, phenytoin, and

Table 4 Characteristics of drugs commonly used for GUD prophylaxis.

Class	Generic name (trade name)	Common adult dosage range	Comments
Antacids	Magnesium hydroxide (milk of magnesia)		All may interact with concomitant medication absorption
	Aluminum (Gaviscon)		
	Aluminum–magnesium mixtures (maalox liquid)		
Histamine receptor type-2 antagonists	Cimetidine (Tagamet)	50 mg/h continuous 300 mg every 6 h	Adjust dosage for renal insufficiency
	Ranitidine (Zantac)	6.25 mg/h continuous 50 mg every 12 h IV 150 mg every 12 h PO/PNG	
	Famotidine (Pepcid)	1.7 mg/h continuous 20 mg every 12 h	
Proton pump inhibitors	Esomeprazole (Nexium)	40 mg daily	May increase risk of bone fracture [90] May reduce clopidogrel efficacy [61]
	Lansoprazole (Prevacid)	15–30 mg daily	
	Omeprazole (Prilosec)	20–40 mg daily	
	Pantoprazole (Protonix)	40 mg daily	
Prostaglandin analog	Misoprostol (Cytotec)	200 μg every 6 h PO/PNG	Caution in women [74]
Other	Sucralfate (Carafate)	1 g every 6 h	No parenteral form available. Should not be administered distal to stomach

warfarin; thus appropriate monitoring of their levels is recommended. Rapid bolus administration may cause hypotension, which can be avoided with slower infusion rates [50, 51]. Concurrent use of cimetidine and phenytoin has been associated with thrombocytopenia [52]. A meta-analysis by Messori et al. [53] concluded that ranitidine is ineffective in the prevention of GI hemorrhage in patients in ICUs and may increase the risk of pneumonia. Studies on sucralfate have been inconclusive [53].

Both cimetidine and ranitidine cross the blood–brain barrier and dose-related toxicity has been reported in $<3\%$ of patients [54]. Serum levels >2 μg/ml can produce muscular twitching, seizures, unresponsiveness, and apnea in addition to more common side effects such as restlessness, confusion, disorientation, agitation, and visual hallucinations [54]. Intermittent bolus administration shows a demonstrable effect within 30 min that last about 3–4 h, but is prone to large variations between peaks and troughs of the gastric pH, into the alkaline pH range [51]. Continuous dosing regimes allow a more precise control.

While the ability of H_2A to decrease upper gastrointestinal bleeding (UGIB) in critically ill patients, compared with placebo or untreated groups has been demonstrated, [55] the efficacy for the stress ulcer prophylaxis remains controversial. H_2A efficacy is comparable with the preventive action of antacids [55]. In studies that enrolled patients with increased severity of illness and risk factors, and employed intermittent dosing regimes, antacids fared slightly better [56], but when continuous infusion protocols were used, H_2A were superior to control treatment, antacids, or intermittent H_2A administration [57]. A limited number of studies in neurosurgical patients revealed poor control of the gastric pH after CNS injury despite continuous administration of H_2A [58, 59].

Proton Pump Inhibitors

Proton pump inhibitors (PPI's, Table 4) produce a pronounced and long-lasting effect on gastric acid production. The PPI's were developed after the H_2A's and because they are generally safe and effective, they have essentially replaced H2A for most chronic indications because of these perceived advantages [14]. PPI's act on the secretory canaliculus of actively secreting parietal cells in the stomach and irreversibly block the H^+/K^+ ATPase (the gastric proton pump). The parietal cells are responsible for secreting H^+ ions into gastric fluid and thereby, increasing its acidity. The effects of PPI's are dose-related, and can effectively suppress both basal and stimulated secretion of acid; PPI's inactivate about 75% of the proton pumps of each parietal cell. The PPI's are metabolized by the CYP450 system and excreted primarily in the urine [14]. PPI's are available in oral and intravenous formulations making them an attractive option for in-hospital use.

Systemic effects of PPI's on the CNS have not been found. Recent meta-analysis has revealed that the PPI's carry a 2- to 3-fold increased risk of nosocomial or community-associated *Clostridium difficile*-associated disease [60]. There is also evidence for unfavorable interaction between some of the PPI's and clopidogrel, a medication frequently encountered in patients with vascular disease in the neurological ICU. There is emerging data suggesting that PPI's, including omeprazole and rabeprazole may decrease the antiplatelet effect of clopidogrel especially

when given in combination with aspirin [61, 62]. Whether this holds true for patients with cerebrovascular disease and ischemic stroke remains to be seen.

A recent meta-analysis by Lin et al. [63] compared the efficacy of H_2A's versus PPI's for stress ulcer prophylaxis among critically ill patients among seven randomized, placebo-controlled trials with a total of 936 patients. They found no significant difference between the H_2A's and PPI's for reduction of stress ulcer- related hemorrhage prophylaxis, pneumonias, or total mortality among patients admitted to intensive care units.

Leontiadis et al. [64] addressed the clinical efficacy and cost-effectiveness of PPI in the prevention and treatment of acute UGIB, as well as to compare this with H_2A, *Helicobacter pylori* eradication (in infected patients) or no therapy, for the prevention of first and/or subsequent bleeds among patients who continue to use the non-steroidal anti-inflammatory drugs. PPI treatment compared with placebo or H_2A reduces mortality following peptic ulcer bleeding among patients with high-risk endoscopic findings, and reduces re-bleeding rates, and surgical intervention.

Antacids/Buffers

Gastric acid is a key player in the pathogenesis of stress-related GUD. Raising the pH (normal value of 1–3 to 3.5) decreases incidence of GI bleeding [22]. Antacids (Table 4) elevate pH quickly for prolonged periods of time. However, larger doses and increased frequency of administration maybe needed in critically ill patients raising the likelihood of unwanted side effects including diarrhea, constipation, metabolic alkalosis, and electrolyte abnormalities, especially hypophosphatemia secondary to their phosphate binding properties [65].

Magnesium hydroxide may be more efficacious than aluminum or aluminum–magnesium mixtures [65]. Meta-analyses of several clinical studies have also borne out the efficacy of antacid therapy in reducing UGIB [55, 66].

Sucralfate

Sucralfate is a sucrose–sulfate–aluminum complex that exerts its protective effects through a multimodal action making it an attractive choice of the pharmacological prophylaxis of stress-related mucosal disease. Sucralfate increases the viscosity, mucin content, and hydrophobicity of the gastric mucus [67]. Other beneficial properties include increased mucosal blood flow, inhibition of gastric digestion, stimulation of prostaglandins, protection of the mucosal proliferative zone, facilitation of mucosal regeneration and healing, bactericidal, and phosphate-binding properties [68, 69]. Interaction with a number of drugs including quinolone and tetracycline antibiotics, theophylline compounds, phenytoin, antacids, digoxin, and amitriptyline results in decreased bioavailability, but can be avoided by separating administration in time by at least 2 h [70]. In a prospective cohort study, the frequency of gastric lesions was 13.5% at admission, increasing to 18% in patients receiving sucralfate, and 36% in patients receiving ranitidine after 4 days of therapy [71]. Two meta-analyses concluded that sucralfate was equally effective as antacids, but significantly more efficacious than H_2A, in the prevention of upper GI hemorrhage [56, 72].

Prostaglandins

Prostaglandin analogs have not been extensively studied for use in stress ulcer prophylaxis. The available prostaglandin E1 analog, misoprostol used for this indication exhibits anti-secretory as well as gastric mucosal protective properties [73]. It should be used with caution in women of childbearing age because of its labor-inducing and abortifacient properties [74]. Common side effects of misoprostol include diarrhea and abdominal pain, which can be exacerbated by concomitant use of magnesium-containing antacids. Diarrhea can be dose-related, and may result in discontinuation of therapy [73]. Prostaglandin analogs are currently indicated for prevention of non-steroidal anti-inflammatory drug induced-gastric ulcers, but not for stress ulcer prophylaxis [73].

Helicobacter pylori Eradication

The role of *H. pylori* in the pathogenesis of stress-related mucosal damage is uncertain. In one prospective observational study by Maury et al. [75], all patients admitted consecutively to seven ICUs during a 1-year period were monitored for signs of clinically relevant upper GI bleeding. *H. pylori* infection was more frequent in patients who bled than in matched controls (36 vs. 16%; $P = 0.04$). Antibiotic treatment of *H. pylori* infection in the ICU setting carries the potential for unwanted consequences such as selection for resistant organisms, acquisition of methicillin-resistant *Staphylococcus aureus* (MRSA), promotion of ventilator-associated pneumonia, and induction of *C. difficile* colitis [76]. In a general critical care population, the use of antibiotics for eradication of *H. pylori* in the acute setting cannot be recommended until further evidence proves that the benefit of early treatment outweighs the risks. No particular recommendation can be made for the neurocritical care population.

Nutrition

Enteral nutrition has been linked with protection from GUD. A positive nitrogen balance develops after feeding,

resulting in a dilutional alkalinization from a gastric feeding tube and the reparative effects on the gastric mucosa that are possible explanations for this. Kuric et al. [38] retrospectively demonstrated significantly lower incidence of GUD in patients with SCI when enteral nutrition was used. The combination of enteral nutrition and stress ulcer prophylaxis with ranitidine conferred significantly lower GI bleeding rates in blinded studies [77]. This treatment conferred no significant differences in the rates of ventilator-associated pneumonia, the duration of the stay in the ICU, or morality [77].

Monitoring of Prophylaxis

Typical regimens for prophylaxis against stress-related mucosal disease are based on FDA approved regiments of various medications or an individual ICU's protocols. It is not customary to routinely monitor for gastric pH for prophylactic efficacy. A few studies have used gastric acid pH as a therapeutic endpoint in randomized trials, but the utility of monitoring during routine ICU care has not been established in a general patient population [78] or in neurosurgical patients [79].

Discontinuation of Prophylaxis

Patients deemed appropriate for stress ulcer prophylaxis regardless of the method should be assessed daily, and the need for continued prophylaxis reevaluated. Many clinicians choose to modify or discontinue stress ulcer prophylaxis when enteral feeding is resumed, or when patients from a general critical care population are transferred out of the ICU [80]. In a 2002 survey of 188 level 1 trauma centers, 39% of institutions reported that approximately 50% of patients who received stressulcer prophylaxis in the ICU were continuing treatment, mostly intravenous agents, after being discharged to non-ICU settings [81]; however, there seems to be little evidence to support this practice.

Prophylaxis in Specific Conditions and Recommendations

The basis for the use of prophylactic measures in neurosurgical patients with brain injury is based on the published literature and is well accepted. There are conflicting data on the efficacy of various preventative medications, leading to weak recommendations from an evidence-based on medicinal perspective [1, 21, 24, 27, 30, 33].

The most appropriate prophylactic agent in the setting of SCI is unknown. Lin et al. [63] performed a meta-analysis of seven randomized trials but failed to find strong evidence that proton pump inhibitors were different from HA in terms of stress-related upper GI bleeding prophylaxis, pneumonia, and mortality among patients admitted to intensive care units.

Yang et al. [8] reported that the available evidence supports the use of stress ulcer prophylaxis in patients with risk factors for bleeding and hypothesize that more potent acid suppression by PPI may offer additional benefit in the prevention of stress ulcer bleeding.

Conrad et al. [78] showed that in a randomized trial, omeprazole suspension in a general critical care population is effective in preventing upper gastrointestinal bleeding, and more effective than intravenous cimetidine in maintaining gastric pH of >4 in critically ill patients. Conversely, Pimentel et al. [82] showed that UGIB in a population where prophylaxis is used, has a low incidence. Their data suggested that especially medications that increase gastric pH could increase the risk for nosocomial pneumonia, and concluded that routine prophylaxis for stress-related bleeding even in high-risk patients seems not justified [83, 84]. These concerns were confirmed by a meta-analysis [53]. A recent meta-analysis by Lin et al. [56] found no significant difference between H_2A's and PPI's for pneumonias among patients admitted to intensive care units. Antibiotic treatment of *H. pylori and* infection in the ICU setting carries the potential for unwanted consequences such as selection for resistant organisms, and consequentially the promotion of ventilator-associated pneumonia [76]. Enteral feeding promoting gastric flora may colonize the trachea, and cause nosocomial pneumonia [85], but the combination of enteral nutrition and stress ulcer prophylaxis with ranitidine conferred no significant differences in the rates of ventilator-associated pneumonia [77].

The discordant evidence regarding prophylaxis for GUD was addressed more than a decade ago by Cook et al. [17], who found strong evidence of reduced, clinically important UGIB with H_2A. Sucralfate maybe effective in reducing bleeding as a gastric pH-altering drugs, and is associated with lower rates of pneumonia and mortality. However, the net effect of sucralfate compared with no prophylaxis was impossible to delineate based on the available data [17]. The risk of pneumonia is thus not clearly related to the choice of GI prophylaxis and a relatively weak data evidence suggests a link with H_2A.

Conclusions

The incidence of stress-related mucosal disease varies widely among studies, and furthermore, the incidence of subsequent clinically significant bleeding has been reported as low as 1.5%. Enteral feeding alone is possibly effective as a non-pharmacologic method of ulcer prophylaxis, and

in combination with ranitidine, significant reduction in GI bleeding rates have been achieved. H_2A, sucralfate, and PPI all reduce the incidence of UGIB in neurocritically ill patients but H_2A blockers may cause encephalopathy, and interact with anticonvulsant drugs and have been associated with higher rates of nosocomial pneumonias, but causation remains unproven and controversial. For these reasons, we advocate against routine use of H_2A for GI prophylaxis in neurocritical patients.

Currently, recommendations for prophylaxis against stress-related mucosal disease in a neurocritically ill population are similar to those previously published for general critical care with the exception of the above mentioned pharmaceutical considerations (Table 4).

Given the unique requirement for concomitant medications in patients with neurological diseases (e.g. clopidogrel), careful studies will be useful to elucidate the optimal GI prophylaxis regimen for patients at different ends of the spectrum of neurological injury and may lead to a degree of difference in the recommendations e.g., for patients with TBI compared to patients with ischemic stroke.

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