INTRODUCTION

Gastrointestinal mucosal damage as a result of physiologic stress in the intensive care unit (ICU) continues to be a problem for acutely ill patients despite many available prophylactic modalities. At least three-quarters of ICU patients will develop stress related mucosal disease (SRMD) within the first ٢٤hrs of their ICU stay *(Brett, ٢٠٠٥)*.

These mucosal lesions occur as a direct consequence of stressors on other organ systems. SRMD can manifest as superficial injuries or deep mucosal lesions that have a high probability of bleeding *(Sprit, ٢٠٠٣)*.

SRMD increases patients' morbidity and mortality through complications such as ulcer development which can cause significant gastrointestinal hemorrhage, increased length of stay in the ICU, cost of care, as well as increased risk for adverse reactions related to blood transfusions *(Brett, ٢٠٠٥)*.

A guideline on stress ulcer prophylaxis recommended pharmacologic intervention in adults

admitted to the ICU who have coagulopathy, require mechanical ventilation for ٤٨-hrs, have a history of gastrointestinal ulceration or bleeding within ١year before admission, or have at least two of the following risk factors: sepsis, ICU stay of ١wk, occult bleeding lasting ٦ days, and use of ٢٥٠mg of hydrocortisone or the equivalent *(Sprit et al., ٢٠٠٦)*.

Pathophysiology of SRMD appears to be multifactorial and have not been fully elucidated. Ischemia and reperfusion are thought to cause the mucosal defenses to break down, resulting in mucosal injury and ulceration *(Sprit, ٢٠٠٣).*

The major factors of SRMD recognized to date include reduced blood flow, mucosal ischemia, hypo perfusion, and reperfusion injury. Lesions develop when the mucosal barrier is unable to block the harmful effects of hydrogen ions and oxygen radicals *(Fennerty, ٢٠٠٢).*

Several agents such as antacids, sucralfate, and histamine-٢ receptor antagonists (H٢RAs) have been used for stress related UGI bleeding prophylaxis among patients admitted to ICU. Guidelines by American Society of Health System Pharmacists and Surviving Sepsis Campaign suggested that patients at

higher risk should receive stress ulcer prophylaxis, and the medication mostly suggested was H٢RA, even though the definitive recommendation about choice among H٢RAs and all other agents cannot be made based on available evidence *(Dellinger et al., ٢٠٠٨)*.

Because hypoperfusion appears to be an important factor in the development of SRMD, high risk patients should be aggressively monitored and treated. In order to maintain hemodynamic optimization, frequent assessments should include determination of physiological, clinical (i.e., blood pressure, skin color and appearance, skin warmth, and mental status), and laboratory (i.e., hemoglobin and hematocrit levels and white blood cell counts) measures and serum electrolyte levels. If possible, early enteral nutrition should be considered in certain patients. The gastroprotective effect of enteral feedings is an area of continued debate. Enteral feedings initiated within ١٢hrs of trauma were as effective as histamine receptor antagonists (H٢RAs) and/or antacids for reducing the risk of clinically significant hemorrhage in the upper gastrointestinal tract (i.e., hemoglobin reduction >٣g/dL, shock, or the need for blood transfusion or surgical intervention) *(MacLaren et al., ٢٠٠١)*.

AIM OF THE WORK

The aim of the work is to discuss how to treat and prevent stress related mucosal bleeding in ICU.

EPIDEMIOLOGY AND RISK FACTORS OF STRESS RELATED MUCOSAL BLEEDING (SRMB) IN ICU

Epidemiology of SRMB:

According to several studies,٦٪ Of patients who are critically ill have overt bleeding, while fewer than ٢-٣٪ have clinically significant hemorrhage. Endoscopy has revealed evidence of intraepithelial hemorrhage in ٥٢-١٠٠٪ of patients in the ICU within ٢٤hrs of the onset of the stressor *(Feldman et al., ٢٠٠٢).*

Clinically significant bleeding, defined as gastroduodenal bleeding associated with clinically important complications (e.g., a spontaneous drop in blood pressure >٢٠/mmHg within ٢٤/hrs; an increase in pulse >٢٠ beats/min and a ١٠/mmHg drop in systolic blood pressure within ٢٤/hrs; or a decrease in hemoglobin >٢g/dL within ٢٤/hrs, requiring transfusion, and the hemoglobin does not increase by the number of units transfused minus ٢g/Dl). Occurs in approximately ٢٪ to ٦٪ of ICU patients *(Cook et al., ١٩٩٦).*

The criteria used to define bleeding in clinical studies vary widely (e.g., nasogastric aspirate, overt hematemesis, or the need for a blood transfusion) *(Sprit, ٢٠٠٣)*.

Severe SRMD is associated with significant mortality. Mortality ranges from ٥٠٪ to ٧٧٪ in critically ill patients who develop bleeding during hospitalization. Patients with clinically significant bleeding often do not die due to the bleeding itself, but most commonly die as a result of multiorgan failure *(Faisy et al., ٢٠٠٣).*

Mortality/morbidity figures are high in older patients because of several factors, including atherosclerosis that leads to reduced blood supply and impaired host defenses. The severity of the injury leads to a further reduction in blood flow to the gastrointestinal (GI) tract, thereby resulting in further compromise of the mucosal barrier and an increased risk of gastritis. The presence of *Helicobacter pylori* may also contribute to the mucosal barrier breakdown and lead to stress gastritis *(Constatin et al., ٢٠٠٩).*

There is no differences among the races with respect to the bleeding rates associated with stress

gastritis. Also no differences have been noted between the sexes with respect to stress gastritis. With increasing age, atherosclerosis may play a role in the decreased blood supply to the gastric mucosa. This, in the setting of a stressor, will lead to decreased mucous production and, hence, greater susceptibility to erosions and ulcerations *(Reveiz et al., ٢٠٠٩).*

Clinically important stress-related mucosal bleeding can lead to increased mortality also it can lead to prolonged length of hospital stay, thereby having an impact on hospital costs. In general, the mean length of hospital stay is reportedly increased in ICU patients who bleed compared with patients who do not have this complication (٣٠ days vs. ١١ days, respectively). More specifically, the excess length of ICU stay attributed to stress ulcer bleeding is estimated at ٤ days-٨ days *(Cook et al., ٢٠٠١).*

However improvements in ICU care, such as oxygenation, fluid resuscitation, nutrition, antibiotics, and cardiac care have led to improved microcirculation and tissue oxygenation in critically ill patients. This may in turn have led to the declining incidence of clinically significant gastrointestinal bleeding *(Faisy et al., ٢٠٠٣).*

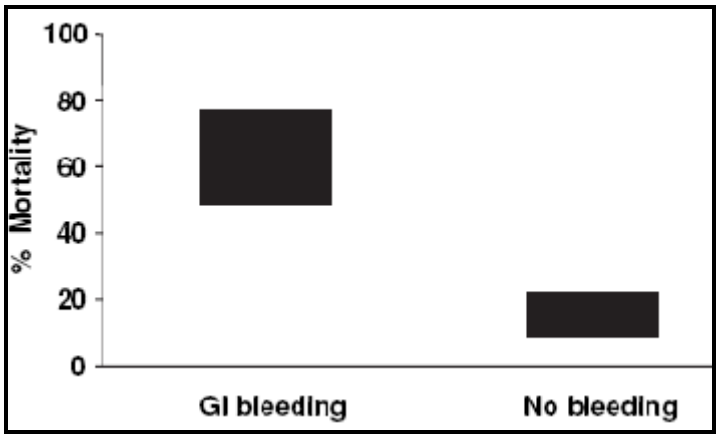

Fig. (١): Mortality rates associated with upper gastrointestinal (GI) bleeding in stress-related mucosal disease *(Cook et al., ١٩٩٤)*.

Risk factors:

A- Patients in ICU with coagulopathy [International normalized ratio (INR) >١,٥ or platelet count <٥٠/١٠^{٩}/L] or requiring mechanical ventilation for >٤٨hrs are statistically more likely to develop stress related mucosal bleeding.

B- Shock, hypotension, sepsis and major burns (>٣٥٪ body surface area) are common causes also.

C- Patients with acute intracranial head trauma and coma (curling's and cushing's ulcers, respectively) are also at increased risk.

D- The incidence of GI bleeding increases with each risk factor up to two, additional risk factors do not further increase the incidence.

E- Patients with minor burns, chronic brain disease, malignancy, chronic obstructive pulmonary disease, transient respiratory illness, dialyzed chronic renal failure, myocardial infarction, arrhythmias, and congestive heart failure are presumed not to be at high risk.

(Irwin and Rippe, ٢٠١٠)

Risk Factors Associated with stress related mucosal diseases (SRMD):

- Respiratory failure requiring mechanical ventilation*.
- Coagulopathy*.
- Renal failure
- Hepatic failure
- Sepsis
- Hypotension
- Trauma and neurotrauma
- History of gastrointestinal bleeding
- Burns
- Prolonged surgery
- Glucocorticoid administration
- Myocardial infarction
- Neurosurgery

- Multiple organ failure
- Ileus
- Organ transplantation
- Anticoagulant therapy

*= Risk factors proven to be associated with clinically significant gastrointestinal bleeding in ICU patients *(Martindale, ٢٠٠٥)*

Mechanical ventilation and SRMB

Mechanical ventilation (MV) can be life saving by maintaining gas exchange until the underlying disorders are corrected, but it is associated with numerous organ system complications, which can significantly affect the outcome of critically ill patients *(Mutlu et al., ٢٠٠١).*

SRMD is the most common cause of GI bleeding in patients receiving MV. Within a few hours of critical illness, macroscopic damage becomes evident as sub epithelial petechiae progress to lesions ranging from superficial erosions to true gastric ulcers. Overt bleeding because of SRMD occurs in up to ٢٥٪ of critically ill patients who do not receive prophylactic therapy *(Peura andJohnson., ١٩٨٥)*.

Coagulopathies and SRMB

Coagulopathies defined as platelet count ٥٠،٠٠٠/mL, INR ١,٥, partial thromboplastin time more than twice the control value, are at the highest risk

and should receive prophylactic therapy *(Schuster et al., ١٩٨٤)*.

Prolongation of the PT suggests that the single most common cause was vitamin K deficiency ,quoted risk factors for the development of vitamin K deficiency include increasing age, the use of broad spectrum antibiotics, total parental nutrition (TPN),gastro intestinal disorders, and major surgery *(Alperin, ١٩٨٧)*.

Risk factors of Stress ulcer in trauma patients

A number of risk factors have been associated with stress ulceration in trauma patients including sex, lung injury or pneumonia, renal or hepatic failure, sepsis, and severity of injury, two factors that appear to be independently predictive of bleeding are severe injury as defined by an Injury Severity Score greater than ١٦ and single system injuries (e.g. head and spinal cord injuries) of the central nervous system *(Cochard et al., ١٩٩٧)*.

Gastrointestinal bleeding in high risk survivors of myocardial infarction

GI bleeding is an important cause of morbidity and mortality in the general population as well as in patients with heart disease *(Chen et al., ٢٠٠٧)*.

GI bleeding was independently associated with an increased length of hospitalization and higher

mortality. Because the management of acute coronary syndromes (ACS) often necessitates the combined use of potent anti-platelet and anti-thrombotic medications, the potential risk of GI bleeding may be substantially increased in the ACS and post MI populations *(Cryer, ٢٠٠٥)*.

Dual antiplatelet therapy with aspirin and a thienopyridine derivative reduces ischaemic events in patients with ACS and after PCI. The current American College of Cardiology-American Heart Association guidelines advocate extended (up to ١yr) treatment with dual antiplatelet therapy for ACS patients treated medically with or without bare metal stenting, and for at least ١yr when a drug eluting stent is used. Bleeding complications, in particular those originating from the GI tract, can limit the use of antiplatelet drugs in these patients *(Androson et al., ٢٠٠٧)*.

Increasing age is a predictor of GI bleeding in a cardiovascular population. Also the presence of advanced heart failure symptoms, which are markers of haemodynamic instability, to be associated with increased risk of GI bleeding. Reduced cardiac output can cause mucosal ischaemia, increasing the likelihood of developing ulcerations and subsequent bleeding. Renal dysfunction, which has been related to impairment of platelet aggregation and alteration of

their interaction with the vessel wall, was also a risk factor *(Kaplan et al., ٢٠٠٢)*.

Male gender may increased risk of GI bleeding in the general population. While hormonal factors may play a role in ulcer development and healing, smoking and other risk factors such as high alcohol intake may be relevant as well. Gastrointestinal bleeding has also been associated with diabetes and may be related, in part, to micro vascular ischaemia increasing the vulnerability to drug induced injury and concomitant impaired healing of mucosal damage *(Roberts et al., ٢٠٠٧).*

Also the simultaneous presentation of acute myocardial infarction (MI) and GI hemorrhage is very serious and unfortunately common. An acute MI occurring simultaneously with or after GI bleeding is usually precipitated by massive bleeding causing hypovolemia, hemodynamic compromise, and hypoperfusion. Conversely, the anticoagulant, antiplatelet, or thrombolytic drugs given to treat MI can precipitate GI bleeding. This distinction is important because the two scenarios have different clinical courses and prognoses. GI bleeding that precipitates an acute MI tends to be massive, whereas GI bleeding after treatment of acute MI tends to be

self-limited and often resolves with reversal of underlying coagulopathy *(Cappell and Schein., ٢٠٠٠)*.

Endoscopy carries a higher than average risk in patients with recent acute MI, with all cause mortality rates as high as ١٪. (The usual rate is ٠,٠٠٠٤٪). Nevertheless, endoscopy can be safely performed early on in patients with acute MI if it is done under strict monitoring in a coronary care unit *(Lin et al., ٢٠٠٦)*.

Helicobacter pylori (H.pylori) infection is not associated with an increased hemorrhagic risk in patients in the ICU:

The potential role of *H.pylori* in acute stress ulcer in patients in the intensive care unit (ICU) is more controversial. Indeed, the pathogenesis of stress ulcers has multiple causes, such as mucosal ischemia and/or ischemia reperfusion, acid back-diffusion, and bile reflux. Some of these factors have been linked to *H. pylori* infection *(Asaka et al., ٢٠٠٤)*.

H.pylori infection is difficult to detect in ICU patients. Direct isolation by ulcer biopsy is rarely possible because of the bleeding risk. Serologic testing is simple but cannot discriminate current from past infection, and the antibody titer can be affected by hemodilution *(Halm et al., ٢٠٠٠)*.

H.pylori infection can also be detected by the [١٣C] urea breath test, but this technique cannot be used routinely, especially in ICU patients. *H.pylori* antigen detection in stool samples was recently validated; the method is noninvasive and a positive result is indicative of active infection. A rectal swab may appear to be an easy way to collect stool samples in ICU patients, because it is routinely done in ICU to detect colonization with multi resistant bacteria. ***(Dore et al., ٢٠٠٤)***.

H.pylori infection in antiplatelet drug users

Before starting any long term antiplatelet therapy, patients with a history of ulcers should be tested and treated for *H.pylori*. Confirmation of eradication is required after *H pylori* treatment in patients with upper GI bleeding. Some suggest that for patients with a history of bleeding ulcer who need aspirin, eradication of *H.pylori* substantially reduces the risk of recurrent ulcer bleeding ***(Chan, ٢٠٠٥).***

Entral versus parenteral nutrition in ICU patient

Enteral nutrition offers many benefits to critically ill patients. It may provide protection from postoperative sepsis by supporting mucosal immunity and modulate progression from gut ischemia to the systemic inflammatory response syndrome ***(Fukatsu et al., ٢٠٠١).***