

T.R.N.C

**NEAR EAST UNIVERSITY
INSTITUTE OF HEALTH SCIENCES**

**Rational Drug Use in Stress Ulcer prophylaxis at Near East University
Tertiary Hospital in Northern Cyprus**

**A THESIS SUBMITTED TO THE GRADUATE INSTITUTE OF
HEALTH SCIENCES NEAR EAST UNIVERSITY**

BY:

SYED SIKANDAR SHAH

**In Partial Fulfillment of the Requirements for the Degree of
Master of Science in Clinical Pharmacy**

NICOSIA 2015

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Advisor:

Assoc.Prof. Bilgen Basgut

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DEDICATION

Dedicated to my parents, sisters, brothers

And all of my friends

Especially Mr. Abdul Majid khan (MPhil scholar) and

Sidra Tariq (MPhil scholar)

At Near east University North Cyprus

Who encourage me to higher ideas of life,

Took pains and sacrificed their comforts for my brilliant

future

And because of their prayers and love I got a reasonable

position in the society.

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ABSTRACT

The project titled as "Rational Drug Use in Stress Ulcer Prophylaxis at NEU Tertiary Hospital in Northern Cyprus" was conducted in different inpatients wards at Near East University Hospital.

Clinical pharmacists are a primary source of scientifically valid information and advice regarding the safe, appropriate, and cost-effective use of medications having wide scope in drug therapy management and optimization using evidence based tools and recommendation. Regarding stress ulcer one of the main cause of morbidity and mortality despite the presence of effective strategies for prevention of stress ulcer, a considerable proportion of patients at risk for stress do not receive prophylaxis during hospitalization while others receive it irrationally though not candidates according evidence based recommendations.

Appropriate utilization of stress ulcer prophylaxis should be limited to high-risk, intensive care unit (ICU) patients. However, the inappropriate use of stress ulcer prophylaxis among all hospitalized patients remains a concern. The purpose of this study was to evaluate the trends of prescribing stress ulcer prophylaxis in ICU and general ward patients.

The study was carried as an observational prospective 70 days at a tertiary university hospital, 69 Patients suffering from different diseases from multiple clinics were enrolled to investigate risk for stress ulcer and observe rational use of stress ulcer prophylaxis for inpatients in healthcare settings using the American society of health system pharmacists (AHSP) guidelines for stress ulcer prophylaxis. The relevant information's were recorded with respect to patient's demographic data, disease incidence, drug costs and lack of patient education.

All patients enrolled in our study were found to be given at least one AST during hospitalization. Omeprazole was the most frequently used AST, followed by pantoprazole. Parental route was commonly used which cost 3 times more than oral AST.

In conclusion the rational use of stress ulcer prophylaxis will be associated with a decrease in inappropriate acid suppression rates during hospitalization and upon discharge as well as significant costs-savings.

Key words: Stress Ulcer Prophylaxis, Proton Pump Inhibitor, Histamine 2 Receptor Blocker, Clinical Pharmacy, ASHP, and Acid Suppression Therapy.

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LIST OF ABBREVIATIONS

| S. # | ABBREVIATIONS | EXPLANATION |
|------|---------------|--|
| 1 | ASHP | American Society of Health System Pharmacist |
| 2 | ACTH | Adrenocorticotrophic Hormone |
| 3 | CIB | Clinical implications of bleeding |
| 4 | COX | Cyclooxygenase |
| 5 | CLD | Chronic liver disease |
| 6 | FDA | Federal Drug Authority |
| 7 | GI | Gastro intestinal |
| 8 | HCL | Hydro chloric corrosive |
| 9 | H2RAs | Histamine 2 Receptor Antagonists |
| 10 | HP | H pylori |
| 11 | ICU | Intensive Care Unit |
| 12 | IRB | Institutional Review Board |
| 13 | INR | International Normalized Ratio |
| 14 | LIS | Laboratory information system |
| 15 | LT,s | leukotriene's |
| 16 | NSAIDs | Non-Steroidal Anti-Inflammatory Drugs |
| 17 | PPT | Partial thromboplastin time |
| 18 | PPIs | Proton Pump Inhibitors |
| 19 | PGs | Prostaglandins |
| 20 | PUD | Peptic Ulcer Disease |
| 21 | ROS | Responsive Oxygen Species |
| 22 | SRMD | Stress Related Mucosal Disease |
| 23 | SPSS | Statistical Package for the Social Science |
| 24 | SUP | Stress Ulcer Prophylaxis |
| 25 | SURB | Stress Ulcer Related Bleeding |
| 26 | UGIB | Upper Gastro Intestinal bleeding |

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Introduction

1. Overview of Stress ulcer

Stress ulcers are single or various gastro duodenal mucosal deformities that cause a wide scope of clinical indications from shallow mucosal disintegrations or mellow extreme ulceration to life-undermining dying. At the point when patients are hospitalized the danger of stress ulcers increments. This is especially valid for patients admitted to concentrated consideration settings taking after the physiologic stress of genuine disease, for example, surgery or injury. (Anderberg B et al 1985). Inside 24 hours of admission to the emergency unit), (endoscopic confirmation of stress related mucosal disease (SRMD) was archived in 75% to 100% of basically sick patients. Although mucosal disintegrations may be of minimal clinical essentialness due to quick mending, they can't be disregarded. Stress ulcers exhibit a danger of clinically imperative dying, which is connected with hemodynamic unsteadiness, for example, hypotension, tachycardia or respiratory disappointment, or results in sickliness or the requirement for transfusion. Clinically noteworthy draining happens in more or less 1% to 4% of basically sick patients with a death rate that methodologies 50%. The pathophysiology of SRMD is hazy yet most likely is identified with a decrease in mucosal blood stream or a breakdown in others typical mucosal resistance instruments in conjunction with the damaging impacts of corrosive and pepsin on the gastro duodenal mucosa. Since corrosive does give off an impression of being included in the pathogenesis of these sores, corrosive suppressive regimens can possibly avoid SRMD. (Abeer Zeitoun et al, 2011).

The treatment of stress ulcer ordinarily begins with preventive estimation. The main confirmation based and created rule for stress ulcer prophylaxis (SUP) was distributed by American Society of Health-System Pharmacists (ASHP). The rule expressed that SUP ought to be recommended just for high hazard patients, essentially patients in the Intensive Care Unit (ICU) settings. For non-ICU patients, SUP may be endorsed if the patient presents with two or more hazard components. The most well-known SUP specialists utilized as a part of late clinical practice are proton pump inhibitors (PPI) and histamine-2 receptor foes (H2RA).

As indicated by the rule, omeprazole can be given orally with a stacking dosage of 40 mg, trailed by 20 to 40 mg every day for the following day. Different PPIs, for example, pantoprazole may be offered because of their comparative viability at equivalent measurements. Ranitidine can be given orally with measurement of 150 mg twice day by day or intravenously with the dose of 50 mg three to four times day by day. (M.S. Mohamad et al, 2014).

Wrong endorsing of SUP may add to antagonistic occasions, for example, pneumonia, Clostridium difficile colitis, and intense interstitial nephritis. More seasoned patients are more prone to experience the ill effects of unfriendly occasions and medication collaborations from wrong recommending due to change in the physiologic, pharmacokinetic and pharmacodynamics frameworks with expanding age. (D.B. Nash et al, 2000).

Here the clinical drug specialist is the man who can assume a vital part on the grounds that he is the main individual who is legitimately qualified and master on medication. Clinical drug specialists give pharmaceutical consideration and Medication Therapy Management administrations which have been demonstrated to help diminish prescription mistakes, unfriendly medication occasions, and expenses. Such administrations are no more viewed as discretionary and ought to be incorporated in every human services framework. The clinical drug specialist significant part is currently seen as (a procedure in which a drug specialist participates with a patient and other wellbeing experts in planning, executing, and observing a helpful arrangement that will deliver particular restorative results for the patient. Drug specialists' trade off to get the greatest advantage from the pharmacological medicines of the patients , and since the idea began at USA before around 26 years prior it got to be currently a standout amongst the most discriminating parts a great many drug specialists do all around the globe , and a significant part of the advantages of this practice is as of late very much recorded and evaluated by clinicians in contrast with conceivable expenses for this practice on health awareness organizations, particularly for normal pathologies, for example, diabetes, hypertension, asthma, hyperlipidemia, incessant torment, rheumatic illnesses or psychiatric issue, and additionally in poly medicated patients.(Abdi karim Muhammad abdi,2014).

Dorland's Medical Dictionary defines clinical medicine as "the study of disease by direct examination of the living patient." That is, clinical pharmacists are involved in direct interaction with, and observation of, the patient. In addition, it is noted that clinical pharmacists practice both independently and in consultation or collaboration with other health care professionals, making it clear that they are members of an autonomous profession within their scope of practice yet also function as members of a cooperative health care team. Finally, attention is drawn to the scientific impact of clinical pharmacist researchers by stating that they generate, disseminate, and apply new knowledge that contributes to improved health and quality of life. (Dorland medical dictionary, 31st ed).

As the pervasiveness of unseemly SUP in different nations seemed high, there is a need to inspect the present practice of SUP among patients in our nearby setting as the extent of patients is expanding in our neighborhood healing facilities. Fitting usage of anxiety ulcer prophylaxis ought to be restricted to high-hazard, emergency unit patients. On the other hand, improper stress ulcer prophylaxis use among every single hospitalized patient remains a worry. The motivation behind this study is to assess the patterns of endorsing anxiety ulcer prophylaxis in ICU and general ward patients. The Rational utilization of stress ulcer prophylaxis will be connected with a lessening in unseemly corrosive concealment rates amid hospitalization and upon release and in addition noteworthy expenses investment funds. The Research is done in near east university hospital North Cyprus and information is gathered from patients in diverse wards utilizing a legitimate questionnaire structure in view of danger component of stress ulcer prophylaxis.

2. Anatomy of stomach

Stomach is a J-molded or tubular sac like chamber lying between the throat and the small digestive tract. (Lauralee Sherwood, 2013)

The stomach is situated in the left depressed person and epigastric districts of the belly in light of the fact that it is suspended by mesenteries and is a versatile and effectively uprooted organ with no settled position. The stomach is just about tubular aside from the lump of fundus and may be totally under the rib cage. As it is exceptionally distensible and can suit

more than 2L, the stomach might pendulate to the extent the pelvis. The stomach is made out of two sides, two bends and two holes. The more noteworthy arch, which speak to the primitive dorsal surface and get ligamentous support from the primitive dorsal mesentery, and The lesser ebb and flow which speak to the primitive ventral surface and get ligamentous support from the subsidiaries of the primitive ventral mesentery. The cardiovascular and pyloric sphincters which characterize the oral and aboral ends. (Ernest et al, 1990).

The stomach is divided into four regions; Cardia is a district situated in the prompt region of the esophagus.it is recognized just by the heart organs in its mucosa. There is no outer line of outline between the cardiovascular part and the fundus or body. The fundus is the piece of the stomach over the level of the passageway of the esophagus.it generally contains gulped air (on the normal around 50 ml) and is thusly unmistakable in customary radiograms of this area. The mucosa of fundus is comparative in structure to that of body. Both contain legitimate gastric organs. The group of stomach is the part between the fundus and the pyloric part. There is no outside line of boundary between the body and fundus above, or between the body and the pyloric part underneath. The line of division between the body and pyloric part can be precisely found just by uncommon strategies which recognize their mucosae. The line of division is approximately correct when drawn from the intersection of the proximal three-fifths and distal two-fifths of the lesser ebb and flow, diagonally descending to the more noteworthy bend. The Pyloric piece of stomach is lined by mucosa containing pyloric glands.it is subdivided into pyloric antrum and pyloric canal. The pylorus which is the pyloric opening between the first piece of duodenum and the stomach is encompassed by the pyloric sphincter. This sphincter however is not differentiated from whatever remains of round layer of muscle, nor is there any detectable physiological difference. (Gardner et al, 1967).

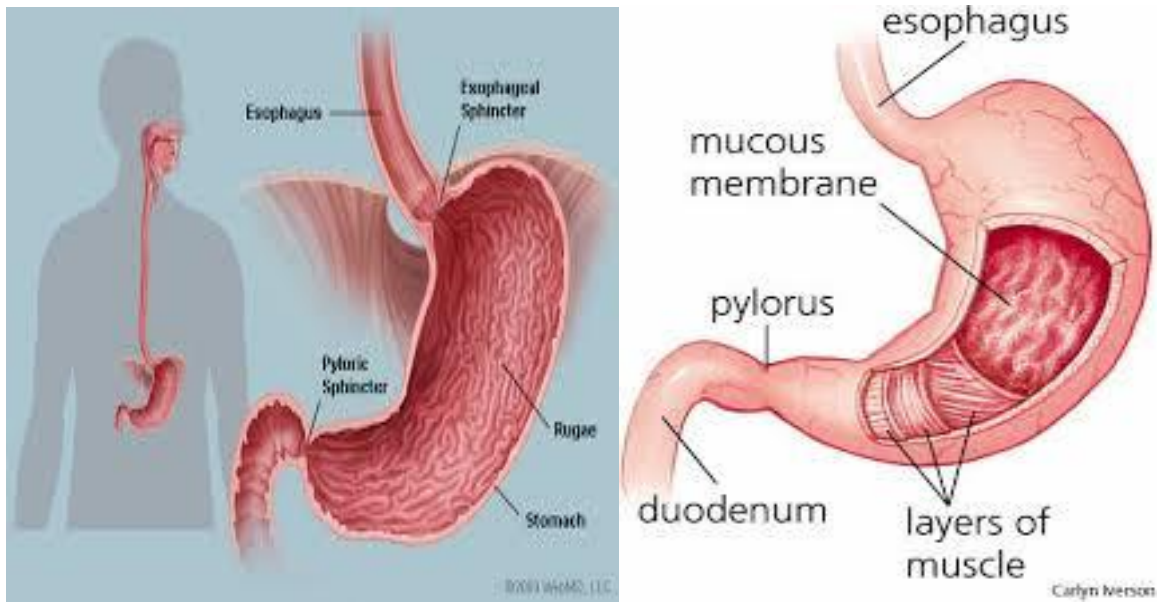


Fig1. Structural representation of stomach (Lauralee Sherwood, 8th edition)

3. Physiology of stomach:-

The stomach comprises of three fundamental anatomically and practically unmistakable locales. The body, which makes up roughly 80% to 90% of the stomach, contains the parietal cells (otherwise called oxyntic cells), which discharge corrosive and characteristic element which is needed for the ingestion of vit B12. the body additionally contains boss cells which emit pepsinogen. The antrum constitute approximately 10% to 20% of the stomach and contain the G-cells which emit the hormone gastrin, in this way each of three noteworthy exocrine emissions of the stomach –mucus, corrosive and pepsinogen is discharged by three unique sorts of cell. Likewise enterochromaffin –like cells, which discharge the paracrine specialist histamine, and cells that emit the peptide flag-bearer somatostatin, are scattered all through the tubular glands. (Widmaier et al, 2006).

3.1 Elements of Stomach:-

The stomach performs three noteworthy capacities. The most imperative capacity is to store ingested nourishment until it can be exhausted into the small digestive tract at a rate proper

for ideal absorption and absorption.it takes hours to process and retain a dinner that was expended in just a matter of minutes. Since the small digestive tract is the essential site for the processing and retention, it is vital that the stomach store the nourishment and forward it into the duodenum at a rate that does not surpass the small digestive system's abilities. The stomach secretes hydrochloric corrosive (HCL) and catalysts that start protein absorption. Through the stomach's blending developments, the ingested sustenance is pummeled and blended with gastric discharges to deliver a thick fluid mixture known as chyme. The stomach substance must be changed over to chyme before they can be purged into the duodenum. (Lauralee Sherwood, 2013).

System for mucosal security; - Several instruments shield the gastro duodenal mucosa from the digestive impacts of pepsin and corrosive. Prostaglandin E and somatostatin, situated on the basolateral film of oxyntic cell, hinder gastric corrosive discharge, keep up mucosal blood stream, and invigorate creation of bodily fluid and bicarbonate .The emission of bodily fluid by shallow epithelial cells and mucous cells all through the stomach ensures against the erosive impact of corrosive. gastric bodily fluid is a thick gel that serves as a mucosal oil ,a trap for small scale living beings ,and an obstruction to the back dissemination of hydrogen particle from the mucosa, bicarbonate likewise is emitted all through the stomach and makes a PH angle that kill the hydrogen particles.

A system of vascular vessels underneath the surface epithelium gives yet another level of resistance against gastric corrosive damage. Mucosal blood stream, through arterioles and vessels, transports oxygen and substrates to the mucosa and evacuates acids that are destructive to the epithelium of stomach or duodenum. The quick and nonstop recharging of gastro duodenal epithelial cells likewise improves imperviousness to damage from discharged acids. In the dominant part of cases, disturbance of surface epithelium can be relieved incompletely by the arrangement of a fibrin top over the harmed territory (a methodology known as restitution).these activities of prostaglandin E, somatostatin, bicarbonate, gastric bodily fluid, mucosal blood stream, epithelial cell recovery, and compensation all join to shield the gastric epithelium against harm from discharged acid. (Mary anee et al, 2005).

4. Ulcer:-

"A sore of the skin or of a mucous layer, for example, the one coating the stomach (gastric ulcer) or duodenum (duodenal ulcer), that is joined by the development of discharge and putrefaction of encompassing tissue, normally coming about because of aggravation or ischemia"

Ulcers range from little, excruciating bruises in the mouth to bedsores and genuine sores of the stomach or digestive tract.

4.1 Types of Ulcer

- Dermatological Ulcer, a brokenness of the skin or a break in the skin.
- Pressure ulcers, otherwise called bedsores
- Genital ulcer, a ulcer situated on the genital region
- Ulcerative dermatitis, a skin issue connected with bacterial development frequently started without anyone else injury
- Corneal ulcer, a provocative or infective state of the cornea
- Mouth ulcer , an open sore inside the mouth
- Aphthous ulcer, a particular kind of oral ulcer otherwise called a blister
- Peptic ulcer, an intermittence of the gastrointestinal mucosa (stomach ulcer)
- Venous ulcer, an injury thought to happen because of shameful working of valves in the veins
- Stress ulcer, found anyplace inside the stomach and proximal duodenum
- Trophic ulcer, one because of flawed nourishment of the piece of body.
- Ulcerative colitis, a manifestation of inflammatory bowel disease (IBD).
- Ulcerative disposition, an issue or inconvenience that causes extreme stomach trouble, regularly connected with chronic gastritis. (Anderson Price et al, 1982).



Fig 2. Bed sores (pressure ulcer)



Fig 3. Mouth ulcer

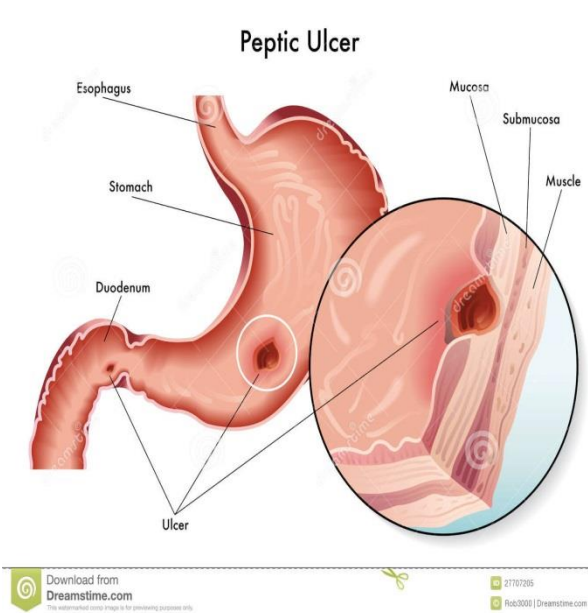


Fig 4. peptic ulcer



Fig 5. Leg ulcer

Source.Fig2.<http://isabelmelville.hubpages.com/hub/How-to-Prevent-Bed-Sores-Pressure-Sores>

Source.Fig3. <http://www.100homeremedies.com/category/natural-cure/home-remedies>

Source.Fig4.<http://www.dreamstime.com/royalty-free-stock-photo-peptic-ulcer-image27707205>

Source.Fig5. <http://www.scienceofwoundhealing.org/types.php>

4.2 Pathophysiology of Ulcer

A peptic ulcer is a sore on the coating of stomach or duodenum. The two most normal sorts of ulcer are "gastric ulcer" and "duodenal ulcer". Peptic ulcer created at the level of throat is called esophageal ulcer. Peptic ulcer are discovered to be because of awkwardness between forceful variables, for example, HCL (Hydro chloric corrosive), pepsin, refluxed bile, leukotriene's (LTs), responsive oxygen species (ROS), and protective components, which incorporate the capacity of bodily fluid bicarbonate obstruction, prostaglandins (PGs), mucosal blood stream, cell recharging and movement, non-enzymatic and enzymatic cancer prevention agents and some development elements. Ulcer has a tendency to influence the whole gastrointestinal tract, beginning from the covering of the mouth and completion with the rectal district. At the point when gastric corrosive is created in overabundance, the mucosal layer that shields the stomach and inward organs from threat is harmed, empowering the microorganisms *Helicobacter pylori* to infiltrate the boundary and reason inner diseases. In this manner, on account of peptic ulcer, both gastric corrosive and microscopic organisms are in charge of the advancement of the issue. (Dr Shah Nawaz, 2011). Despite far reaching research, the etiology of peptic ulcer illness stays indistinct. Given the numerous courses of action that control acid and pepsin discharge and protection and repair of the gastro duodenal mucosa, it is likely that the reason for ulceration varies between people. Acid and pepsin seem, by all accounts, to be important yet not adequate fixings in the ulcerative procedure. It

is important that the dominant part of gastric ulcers and a considerable number of duodenal ulcers don't have expanded gastric acid secretion. (Price, Wilson, 1982).

Truly, our comprehension of the pathophysiology of peptic ulcer infection concentrated on anomalies in the emission of gastric corrosive and pepsin, and on the concealment of corrosive as a treatment technique. Today, gastric hyper emission connected with gastrinoma in Zollinger–Ellison disorder, antral G-cell hyperplasia, an increment in parietal-cell mass, and a physiological irregularity between the hostile gastric hormones gastrin and somatostatin—is still a vital issue in peptic ulcer infection. Besides, it is realized that cholinergic touchiness and parasympathetic strength are identified with the incitement of hydrochloric corrosive as well as pepsin, which is frequently ignored as a cofactor in the advancement of erosive damage to the gastric mucosa. Mental anxiety, cigarette smoking, liquor utilization, utilization of non-steroidal anti-inflammatory drugs (NSAIDs) including ibuprofen, oral bisphosphonates, potassium chloride, immunosuppressive drugs, and an age related decrease in prostaglandin levels have all been demonstrated to add to peptic ulcer malady.(Yuan et al, 2005).

4.2.1 Impacts of NSAIDs on gastric mucosa

NSAIDs are profitable therapeutics that demonstrations as an incendiary, as well as an analgesics and antipyretics. They are utilized as a part of a wide mixed bag of clinical conditions, including joint pain and musculoskeletal issue. Shockingly their utilization has been constrained by their gastric ulcer-inciting impact. Almost 25% of perpetual clients of these medications create gastric ulcer infection. (Kaur amandeep et al, 2012).

The two noteworthy etiologic elements for PUD are: (1) utilization of no steroidal calming medications (NSAIDs) or COX-2's (COX-2's give just a little lessening in GI entanglements contrasted with NSAIDs, and just in the short term) and (2) HP contamination. Patients taking NSAIDs or COX-2's who experience manifestations of an uncomplicated peptic ulcer ought to promptly quit taking the NSAIDs or COX-2's and start taking hostile to secretory drug. In the event that the NSAIDs are the reason for the indications, the manifestations

ought to determine a couple inside days, by and large fewer than 14. (A. Mark Fendrick et al, 2005).

The pathophysiology of gastric damage connected with NSAID organization depends halfway on cyclooxygenase hindrance and somewhat on cyclooxygenase-free instruments, which come about principally from neighborhood direct activities. (Matteo Fornai et al, 1994). COX-1 restraint by the NSAIDs prompts a critical arrival of endothelin-1(ET-1) which is a strong vasoconstriction which has been demonstrated to incite mucosal harm. NSAIDs by repressing prostaglandin combination prostaglandins cause the initiation of neutrophils and the neighborhood arrival of receptive oxygen species (ROS) and subsequently start gastric harm (Whittle BJ et al, 2002). Cyclooxygenase barricade has been demonstrated to build the weakness of gastric mucosa to NSAID-instigated damage by concealment of various prostaglandin-intervened defensive capacities. Case in point, prostaglandins diminish the actuation of neutrophils and the neighborhood arrival of receptive oxygen species (ROS). The generation of prostacyclin by the endothelium of mucosal microcirculation is likewise exceedingly applicable in guaranteeing a tonic hindrance of neutrophil attachment. Along these lines, NSAIDs can move the mucosal equalization toward the enrollment and endothelial attachment of circling neutrophils through the restraint of prostaglandin biosynthesis. Once followed, neutrophils obstruct the microvasculature creating a neighborhood diminish in mucosal blood stream and a checked arrival of tissue harming elements, including proteolytic chemicals and leukotrienes, which improve the vascular tone, fuel tissue ischemia, fortify the generation of ROS, and advance the decimation of intestinal grid, prompting a serious level of central tissue corruption, especially in the vicinity of a low luminal ph. (Matteo fonai et al, 1994).

Moreover, NSAIDs additionally causes checked lessening in mucosal blood stream, bodily fluid bicarbonate discharges, hindered platelets conglomerations, lessened epithelial cells reestablishment and expanded leukocyte adherence that are in charge of pathogenesis of ulceration. (Allen an et al, 1993). Gastric corrosive decline the NSAIDs impacts by extending shallow sores, meddling with platelets collection and weakening the ulcer mending procedure. (Valkhoff VE et al, 2012).

4.2.2 H. pylori-related ulcer

H. pylori is a gram-negative, motile, microaerophilic, banded bacillus that is found in the bodily fluid layer overlying the gastric epithelium. (Lee DH et al, 1996). Amid the 1980s, H. pylori disease was found in more than 90% of patients with duodenal ulcers, and by most accounts 70% of patients with gastric ulcers. The declining rate and commonness of peptic ulcer in created nations has paralleled the falling predominance of H. pylori contamination, particularly in populaces with high disease rates.(Yuan et al, 2006) Only H. pylori annihilation is a powerful treatment for both duodenal and gastric ulcers. Antisecretory medications function admirably for controlling manifestations and permitting ulcers to recuperate, and without a doubt the advantage of killing H. pylori disease is little regarding recuperating alone. In a Cochrane meta-investigation the annihilation of H. pylori disease consolidated with the utilization of a ulcer-mending medication essentially expanded duodenal recuperating to 83% (intentto-treat investigation), with the relative danger of the ulcer enduring being 0.66 (95% CI 0.58–0.76) contrasted and the ulcer-recuperating medications alone; however annihilation was not fundamentally better than ulcer-mending medications for gastric-ulcer mending (relative hazard 1.32; 95% CI 0.92–1.90). (Ford An et al, 2004).

In 1981, Marshall and Warren led a planned investigation of 100 back to back patients experiencing endoscopy to correspond gastric mucosal biopsy discoveries with clinical and endoscopy information. In this examination, they separated microaerophilic, catalase-positive bacterium. (Cello JP, 1995). H. pylori contamination has been perceived as the essential driver of unending gastritis and peptic ulcer ailment. In 1994, United States (U.S.) National Institutes of Health Consensus Development Panel inferred that contamination seems to assume an essential contributory part in the pathogenesis of peptic ulcers, The part of H. pylori disease is very much clarified in peptic ulcer disease by O'Connor.(Rakesh Pahwa et al, 2010).

Endless gastritis connected with H. pylori disease is regularly seen in youngsters with essential duodenal ulcer. Colonization of the gastric mucosa by H. pylori is as of now

unprecedented among kids who live in industrialized nations, contrasted with the individuals who live in creating nations, with pervasiveness up to the tenth year of life of 5 % - 10 % and up to 80 %, individually (Kawakami et al, 2004). Presently, 70 % of every gastric ulcer happening in the U.S. can be credited to H. Pylori disease. Notwithstanding an increment in corrosive discharge, bacterial disease likewise inclines patients to ulcer malady by disturbing mucosal honesty. In created nations, then again, contamination with H. pylori is exceptional before age 10 and increments to 10 % in 18 – 30 years of age, contrasted and 50 % in those more established than 60. In creating countries, 60 % - 70 % of kids are contaminated with the microscopic organisms by age 10, likely in light of congestion and poor sanitation. (Rakesh Pahwa et al, 2010).

4.2.3 Cigarette smoking

Various instruments have been proposed to clarify the impact of smoking on peptic ulcer. (Eastwood GL, 1988). These incorporate the incitement of corrosive discharge, modification of blood stream or motility, affectation of bile reflux, and lessening in the era of prostaglandins. (Muller-Lissner SA, 1986). Gastric and duodenal ulcers happen more oftentimes in smokers than in non-smokers. Peptic ulcers recuperate less well in smoker when contrasted with non-smokers. Neither the dynamic tobacco segment nor the instrument by which it works is known, in any case, due to its all-around perceived pharmacological properties, nicotine has been broadly examined as causative specialists. (K desai et al, 1996).

4.2.4 Psychological stress;-

Stress ulceration of the stomach is connected with clinical conditions like injury, head harm, smolders, stun, sepsis and neurological issue, and is currently viewed as a multifactorial marvel. It is accounted for to result from connections between mucosal, vascular and neuro-humoral variables, and the autonomic sensory system assumes an urgent part (Fig. 3). Incitement of gastric mucosa, because of anxiety is transmitted by cerebral minimal framework and hypothalamus to the medulla oblongata and spinal line. Medulla oblongata fortifies the vagus which builds the gastric discharges and increases gastric motility. The spinal rope causes the incitement of the splanchnic nerve to deliver an unsettling influence

available for use because of utilitarian narrowing of the gastric vessels; which prompts a reduction of gastric blood stream. The capacity of foremost pituitary additionally gets aggravated because of stress discharging adrenocorticotrophic hormone (ACTH) which eventually prompts expanded gastric discharges and diminished gastric mucosal resistance. Circulatory unsettling influences and the nourishing inadequacy are therefore prompted in the nearby tissue, which are then trailed by a quick appearance of a profound ulcer. (Tobe T et al, 1996).

Different reasons for ulcer incorporate viral ailments and certain uncommon tumors. Smoking, hereditary qualities, and liquor utilization may be contributing variables. Mental stretch and eating regimen (fiery nourishments, and so on.), which were once thought to be causative, are no more thought to be huge. (Peura, D. A, 2007).

5. Complications of peptic ulcer illness;-

Muddling of peptic ulcer illness incorporate

1. Interior dying;-when gastric acid or a peptic ulcer breaks a vein
2. Deterrent;-when peptic ulcer hinders the way of sustenance attempting to leave the stomach
3. Puncturing;-when a peptic ulcer becomes more profound and breaks totally through the stomach or duodenal divider
4. Peritonitis;-when contamination or aggravation grows in the peritoneum, or coating of the stomach hole. (Momtaz H et al, 2012).

6. Stress Ulcer

The portrayal of stress ulcerations has a long history. The primary reports of ulcerations in the upper gastrointestinal tract in patients with over the top smolders were by Swan in 1823. (Swan J. 1823) and by Curling in 1842 (twisting T.B). In 1853, Virchow related mucosal ulceration to hypoxaemia and hypoperfusion. The vicinity of ulcers in a postoperative patient

was accounted for by Billroth in 1867. Moreover, in 1932 Cushing depicted mucosal ulcerations in head injury patients (Cushing H, 1932). Since that time the term 'stress ulcer' was utilized. The presentation of anti-infection agents and change in surgical procedures diminished the mortality of extremely sick patients. The drawn out survival of seriously sick patients brought about confusions that were occasionally confronted anytime recently. Stress ulceration was accounted for much of the time subsequent to the 1950's.(Selye H, 1948).

In spite of the generally utilized term 'stress ulceration', there is no all-around acknowledged definition. Typically push ulcerations are characterized as numerous shallow mucosal disintegrations of the stomach in basically sick patients. More profound ulcers may create from these shallow disintegrations and may prompt stress ulcer related bleeding (SURB). (Crawford F.A. et al, 1971). The genuine commonness of anxiety ulcerations stays obscure on the grounds that in many studies endoscopy is not routinely performed. The frequency of upper gastrointestinal draining as a surrogate for SURB has been examined all the more broadly (Cook D et al, 1998). Upper gastrointestinal draining is normally characterized as clinically critical when clear draining is joined by (an) a diminishing in circulatory strain of 20 mm Hg inside 24 hours of onset of draining or (b) a decline in pulse of 10 mm Hg and an increment in heart rate of 20 pulsates every moment on orthostatic change or (c) a reduction in hemoglobin level of 1.2 mmol/L and transfusion of 2 units of blood inside 24 hours or when gastric surgery is needed. Then again, different definitions are utilized also and this variability in definition ought to be considered when studies are thought about. (Cook D.J et al, 1996).

Stress ulceration is a condition where aggravation happens at the gastric mucosa and if left untreated can prompt gastric dying. It is the primary concern in hospitalized patients who present with basic ailments which brings about physiological anxiety prompting gastric ulceration. The created danger components connected with anxiety ulceration may be seen in patients with genuine wounds who are discriminatingly sick.(ASHP, 1998). This is the motivation behind why the greater part of anxiety ulceration cases happen in ICU contrasted with general restorative patients who are considered at generally safe of anxiety ulceration. (M.E. Anderson, 2013) . Studies have demonstrated that the frequency of anxiety ulceration

is low particularly in non-ICU settings. One multicenter planned associate study demonstrated that patients at okay of gastrointestinal (GI) draining represented 0.1% of clinically critical dying. (D.J. Cook, 1994).

Regardless of the low rate of GI draining in non-ICU settings, SUP has been accounted for to be overprescribed without legitimate evidence. A study by Jain et al. (2013) demonstrated that out of the aggregate of 74.1% of non-basically sick patients endorsed with SUP, just 15% were fitting. (G Jain et al, 2013). An imminent study did in a showing clinic in the U.S. uncovered that up to 70% of okay broad prescription patients got wrong SUP and more than a large portion of them were released with the medicine. (R.J. Nardino et a, 2000). Moreover, another study in United Kingdom demonstrated that among the study populace, just around 15% of patients (mean age 68 years) recommended SUP had suitable signs. (D.G. Craig et al, 2010).

Stress ulcers, ulcerations of the upper piece of the gastrointestinal (GI) mucosa in the setting of intense ailment generally include the fundus and assemblage of the stomach. The stomach is lined with a glycoprotein mucous layer rich in bicarbonates, shaping a physiologic boundary to shield the gastric divider from corrosive affront by killing hydrogen particles. Disturbance of this defensive layer can happen in discriminatingly sick patients (e.g. those with stun or sepsis) through overproduction of uremic poisons, expanded reflux of bile salts, traded off blood stream, and expanded stomach sharpness through gastrin incitement of parietal cells. More than 75% of patients with real smolders or cranial injury create endoscopic mucosal anomalies inside 72 hours of damage. In discriminatingly sick patients, the danger of ulcer-related obvious draining is evaluated to be 5% to 25%. Furthermore, 1% to 5% of anxiety ulcers can be sufficiently profound to dissolve into the sub mucosa, creating clinically huge GI dying, opposed as draining convoluted by hemodynamic bargain or a drop in hemoglobin that obliges a blood transfusion. Interestingly, in inpatients, which are not basically sick, the danger of obvious draining from anxiety ulcers is under 1%. (Naseem Eisa et al, 2014).

6.1 Types of stress ulcer

There are two sorts of ulcer. Ischemic ulcer grows inside hours of an occasion, for example, discharge, multisystem injury, extreme copies, heart disappointment, or sepsis that causes ischemia of stomach and duodenal mucosa. Stress ulcer that grows as a consequence of smolder harm are habitually called twisting ulcer. The stun, anoxia, and thoughtful reactions delivered by the encouraging occasion diminish mucosal blood stream, prompting ischemia. As the digestion system of the mucosal cell decays as a consequence of absence of blood vessel blood, the mucosal coating ruffians. Acid diffuses again into mucosa, bringing about aggravation, ulceration, discharge, and putrefaction. The ulcerative methodology is quickened if bile or pancreatic chemicals are spewed from the duodenum. Cushing ulcer is an anxiety ulcer connected with serious head injury. This ulcer results from hyper discharge of corrosive brought on by overstimulation of the vagal cores. (Kathryn L.McCANCE et al, 1990).

6.2 Prevalence of stress ulceration, upper gastrointestinal bleeding and stress ulcer related bleeding

Routine endoscopy in chose patient gatherings uncovers mucosal injuries in the lion's share of basically sick patients. Cocoa depicted mucosal sores in 91 % of the patients after head trauma. (Brown TH et al, 1988). In surgical patients a pervasiveness of 82% was found. (Bank S et al, 1989). A range of sores can be found from hemorrhagic gastritis to disintegrations and ulcerations. Lucas and colleagues indicated movement from petechiae to disintegrations and dying. (Lucas C.E et al, 1971). These discoveries were affirmed by Eddleston who discovered mucosal injuries and haemorrhagic gastritis which formed into disintegrations and ulcerations in 88.9% of placebo and 37.5% of treated patients. (Eddleston J.M et al, 1994). Just a minority of the sores will bring about plain or critical dying. The frequency of upper gastrointestinal draining in discriminatingly sick patients shifts from 0.6 to 8.9% and has demonstrated a critical decrease in commonness from 12 to 5% in the course of the most recent years brought about by a change all in all serious consideration treatment and conceivably by anxiety ulcer prophylaxis.(Navab F et al, 1995). Upper

gastrointestinal draining may be because of different reasons than anxiety ulceration. Draining from esophagitis, tumors and varices may be mistaken for SURB when upper gastrointestinal endoscopy is not performed. Hence, the definite recurrence of SURB stays obscure in many studies, however is most likely lower than the rate of UGIB.

6.3 Pathogenesis

The gastric mucosa is presented to a low intraluminal pH under ordinary physiologic conditions, the uprightness of this tissue relies on upon a harmony between forceful variables (i.e. gastric corrosive discharge, protein emission, and disease) and countervailing mucosal resistance components. (Beejay U et al, 2000). Studies in creature models have demonstrated that mucosal resistance is personally identified with satisfactory microcirculation through tissues of the upper GI tract (This flow gives supplements and uproots waste items, especially oxygen free radicals. In a rodent model, Itoh and Guth found that oxygen determined free radicals, especially O₂⁻, seem to assume an imperative part in the arrangement of gastric sores created by ischemia in addition to hydrochloric corrosive. In another study in rats (Itoh M et al, 1985), Yasue and Guth found that even without intragastric hydrochloric corrosive, systemic ischemia took after by retransfusion of shed blood brought about histologic mucosal harm in the corpus and antrum. They likewise found that a restricted time of ischemia alone (systemic hypotension for 20 minutes without retransfusion) brought about no more histologic sores than happened in controls not subjected to discharge. These specialists reported that a more drawn out time of ischemia created more injuries and that reperfusion (retransfusion) was a discriminating calculate injury improvement. (Yasue N et al, 1988). In a canine model, Chung et al found that neighborhood ischemia and blockage went before the improvement of gross mucosal ulcerations. These studies point to a multifactorial etiology for stress ulcers in which the breakdown of mucosal guards as a rule by ischemia and reperfusion, permits forceful physiologic methods, especially gastric corrosive emission, to create damage and ulceration (Chung SC et al, 1991).

The pathogenesis of stress ulceration in discriminatingly sick patients is unpredictable and multifactorial. (Stoutenbeek Ch.P et al, 1993). Ischemia prompts intramucosal acidosis

which, at present, must be measured by tonometry. Fiddian-Green exhibited that 30% of post-heart surgery patients have mucosal acidosis utilizing gastric tonometry. It was likewise demonstrated that gastric intramucosal acidosis was a danger element for upper gastrointestinal dying.(Fiddian-Green R.G et al, 1983). Intramucosal acidosis controlled by gastric tonometry is identified with disabled gastric mucosal blood stream. (Brinkmann An et al, 1998). Mucosal cell ischemia and hypoxia lead to cell brokenness and at last mucosal sores. (Menguy R et al, 1974). Amid hypovolaemic stun vasoconstriction of the splanchnic dissemination prompts submucosal shunting and ischaemia of the intestinal mucosa. These impacts will proceed for quite a long time, even after adequate volume substitution. (Edouard A.R et al, 1994). Dynamic vasodilation restores blood stream to the splanchnic territory which may be helpful for the ischemic mucosa. On the other hand, reperfusion incites free oxygen radical generation which may further expand mucosal harm. (Flynn R et al, 1993). Degranulation of pole cells assumes a vital part in reperfusion harm and goes before tissue damage (Kubes P, 1996). Since the 1960's the vicinity of sepsis at the season of onset of draining was accounted for 30%. (Fogelman M.J et al, 1966). The diminishment in gastric mucosal blood stream in septic stun is more noticeable than in hypovolaemic stun. Richardson and Sales depicted a decline in mucosal. blood stream of 62% amid septic stun where the heart yield diminished by 12%. They and others found that endotoxins and vasoactive atoms delivered amid septic stun like histamine, serotonin and (nor) adrenaline, impeded splanchnic blood stream more broadly than the vasoconstriction without endotoxins in different types of stun. (Nicoloff D.Met, 1964). Also, endotoxins apply a direct dangerous impact on the mitochondria of mucosal cells. Accordingly, oxygen extraction and usage hinders prompting mucosal damage. (Haglund U et al, 1989). Also, actuated leukocytes in sepsis will stick to the vascular endothelium by the selectine group of bond particles which further debilitates microcirculation by stopping and luminal obstruction. (Bevilacqua MP et, 1993). It was demonstrated that aversion of fine luminal deterrent by hostile to platelet aggregators restrains the improvement of anxiety ulcers in rats. (Kumashiro R et al, 1985). To sepsis related coagulopathy may build the danger of draining from the mucosal sores that have grown by ischaemia. Gastric corrosive encourages stress ulcer development in the vicinity of ischaemia. The ischaemic mucosa will permit back dispersion of corrosive which makes further mucosal damage. (Skillman J.J et al, 1965). Subsequently corrosive decrease

by H2RA and acid neutralizers is utilized for aversion and treatment of anxiety ulceration. However 20-50% of basically sick patients treated with H2RA achieves a gastric acid pH over 4. (Harrison A.M et al, 1998). Also, this treatment may not be vital in all patients as in roughly 45% of discriminatingly sick patients hypo secretion of gastric corrosive is available. These outcomes show that gastric corrosive cannot be the main element prompting anxiety ulceration and related dying. (Stannard V.A et al, 1988).

6.4 What are the danger elements for bleeding?

A huge planned companion study including discriminating consideration patients demonstrated that respiratory disappointment (requirement for mechanical ventilation for no less than 48 hours) and coagulopathy (platelet check <50,000/cubic millimeter, universal standardized proportion >1.5, or actuated fractional thromboplastin time >2 times the furthest reaches of ordinary) were the main components connected with expanded danger of CIB. Of 847 patients who had one or both danger variables, 3.7% created CIB, while just 0.1% of 1405 patients without both of those danger elements created CIB.

In an ensuing planned multicenter accomplice investigation of 874 patients in the ICU, 79 patients (9%) created clear GI bleeding (the rate of CIB was not reported in this study). (Cook DJ et al, 1994) In that second study, a few components were discovered to be connected with expanded danger of unmistakable draining in multivariate examination: intense hepatic disappointment, nasogastric tube situation for more than 5 days, history of liquor misuse, interminable renal disappointment, and a positive *Helicobacter pylori* serology. In mechanically ventilated patients, intense renal disappointment was connected with expanded danger of draining in a multivariate examination performed amid yet another study. Different elements that have been connected with expanded danger of draining include: extreme head or spinal string harm, warm damage including more than 35% of the body surface.

6.5 Risk Factors

Several factors contribute to stress ulcer formation, including acid hyper secretion; alteration of normal protective mechanisms such as mucus and bicarbonate secretions; release of mediators such as arachidonic acid metabolites, cytokines, and oxygen free radicals; and ischemia to the GI system. These erosions may occur quickly (within 24 hours of admission) or take longer to develop (>10-14 days).² Stress ulcers and related bleeding cause significant morbidity and mortality in critically ill patients. One study reported a mortality rate of 46% in critically ill patients with GI bleeding compared with 21% in those without bleeding ($P < .001$).³ Other studies have confirmed this high mortality rate. (Zuckerman et al, 1987).

Large studies have indicated that the strongest risk factors for stress-related GI bleeding are prolonged mechanical ventilation and coagulopathy. (Cook et al, 1994). The risk increases with increasing number of days of mechanical ventilation and length of ICU stay. (Harris et al, 1977). Other risk factors include recent major surgery, major trauma, severe burns, head trauma, hepatic or renal disease at admission, sepsis, and hypotension.¹ **TABLE 1** provides a complete list of risk factors. (Lindsay E. Kaun, 2011).

| Table 1. Risk Factors for Stress-Related Bleeding |
|---|
| Very High Risk |
| Prolonged mechanical ventilation (>48 h) Coagulopathy (INR >1.5 or platelet count <50,000 mm ³) |
| High Risk |
| Sepsis Renal failure Hepatic failure Hypotension Trauma Major surgery (lasting >4 h) Severe burns (>35% of body surface area) Anticoagulation Severe head or spinal cord injury Myocardial infarction Neurologic surgery Multiple organ failure Ileus High-dose corticosteroids History of gastrointestinal bleeding Low intragastric pH |
| <i>INR: international normalized ratio. Source: References 1, 7.</i> |

6.6 Stress ulcer prophylaxis;-

Upper gastrointestinal tract bleeding (UGIB) is a typical spin-off of discriminating sickness. Although just 1.5 to 6.0% of patients admitted to the emergency unit will have plain UGIB, the vast majority of them will display clinical danger variables, particularly mechanical ventilation for more than 48 hours and the vicinity of a coagulopathy. (Ben-Menachem T et al, 1994). Up to 50% of patients will kick the bucket as a consequence of stress ulcer bleeding, generally from multi-organ disappointment and weakening of the fundamental condition. It is generally acknowledged that stress ulcer prophylaxis (SUP) is demonstrated for ICU patients at high hazard for dying. (Spirt MJ et al, 2006).

Stress ulcer prophylaxis has truly been an ailment process with a high level of commonness in the setting of smolders and injury. Numerous conventions exist for prophylaxis of stress ulcer; however there are no generally acknowledged regimens. This has prompted across the nation confusion in current practice an stress ulcer prophylaxis. There likewise remains no all-inclusive determination of requirement for stress ulcer prophylaxis in the injury populace. The advancement of clinically critical gastrointestinal discharge has been connected with noteworthy increment of grimness and mortality. Expansion of mortality may be expanded as high as 50%. (Oscar D. Guillamondegui et al, 2008).

The high chaperon mortality and horribleness connected with the advancement of draining from stress ulceration has brought about a mixed bag of procedures intended to keep its event. Disregarding eight all around planned meta-examinations straightforwardly tending to this question, the perfect prophylactic regimen remains a matter of debate. The regimens vary in their system of activity, adequacy, side effects, ease of administration and expense. (Cook D.J et al, 1995).

6.7 Current Guidelines & Evidence

Key guideline points

6.7.1 The major four (start SUP if patient has one of these four factors):

- 1 – Coagulopathy, Platelet count of $<50,000\text{mm}^3$, INR >1.5 , PTT of >2 times the control
- 2 - Mechanical Ventilation Longer than 24 hours
- 3 - Recent GI ulcers/bleeding Within 12 months of admission
- 4-Traumatic brain injury, traumatic spinal cord injury, or thermal injury (>35 percent of the body surface area)

6.7.2 The minor: 2 or more of the following:

1-sepsis, 2-shock, 3- ICU >1 week, 4- Occult Bleeding within 6 days, 5-High dose corticosteroids (250mg Hydrocortisone ,50mg Methyl prednisone), 6- hepatic failure, renal failure, 7- organ transplantation, 8-administration of no steroidal anti-inflammatory agent, 9- ISS >15 .(Injury severity score).(Gerald L et al, 1995) as shown in Table no 2.

Pharmacological anticipation of stress ulcer has been performed by Antacids, pirenzepine, H2RA, sucralfate and proton pump inhibitors (PPI). The point of acid suppressive medications is to decrease back dispersion of corrosive in ischaemic mucosa and accordingly counteractive action of further harm. (Skillman J.J et al, 1970).

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Table 2

| Absolute Indication | Relative indication 2 or more of the following |
|---|---|
| <p>Intensive care unit (ICU) patient plus one of the following.</p> <p>, Coagulopathy (i.e, platelet count of <50,000 mm³, international normalized ratio (INR) >1.5, or an activated partial thromboplastin time (aPTT) > 2 times control)</p> <p align="center">OR</p> <p>Mechanical ventilation for >48 hours</p> | Respiratory Failure |
| | Renal Failure |
| | Heart Failure |
| | Hepatic Dysfunction |
| | Jaundice |
| | Sepsis |
| | Stroke |
| | Hypertension |
| | Previous Gastrointestinal Disease |
| | High-Dose Corticosteroids (>250 Mg/Day Of Hydrocortisone) |
| | Thermal Injury To>35% |
| | Heparin Or Warfarin |
| | Kidney Or Liver Transplant |
| | Head Injury |
| Spinal Cord Injury | |

6.7.2.1 Antacids;

The soonest prophylactic regimens comprised of acid neutralizers managed through nasogastric tube and titrated to keep up an intragastric pH > 3.5. Stomachs settling agents or antacids are generally given as a 20–40 ml bolus with extra boluses as needed to accomplish a pH > 3.5. Although moderately cheap, the necessity for rehashed evaluation of gastric pH and the recurrence of administration make this an extremely asset serious regimen. The huge volumes of directed stomach settling agents or antacids expanded the danger of aspiration, especially in the vicinity of a nasogastric tube. At last, the vast measure of aluminum or magnesium may bring about loose bowels, hypophosphatemia, hypomagnesaemia or metabolic alkalosis. (Avery B Nathens et al, 2001).Antacids kill gastric acids in extensive measurements, yet low dosages can likewise be viable. The advantage may be identified with the release of endogenous prostaglandins. By instigating creation of prostaglandins antacids expand bodily fluid and bicarbonate emissions, which is the under stress. Finding here are for the most part from exploratory studies, though in human studies the viability of acid neutralizers has not been so unmistakably illustrated. The onset of activity of these medications is not sufficiently quick for utilization as monotherapy. (cannon et al, 1987). Since these medications must be directed enterally and this is frequently troublesome not long after conception, their utilization is uncommon in neonatology. In grown-ups studies they have been utilized as a prophylactic treatment with great results. (Tryba, 1991).

6.7.2.2 Pirenzepine

Pirenzepine, a M1-cholinoceptor antagonist, has been demonstrated to reduce gastric causticity during discriminating sickness. Correlation of pirenzepine, 10 mg, with ranitidine exhibit that both build the pH of gastric suction adequately, in spite of the fact that ranitidine is marginally more powerful. (Takakura K et al, 1994). One potential issue with its utilization in basically sick patients is its generally low receptor specificity. Accordingly, quick infusion prompts a critical tachycardia because of blockage of M2-cholinoceptors. Further, its viability in decreasing the rate of clinically significant gastrointestinal draining

has not been evaluated to any incredible degree. Thus, it has discovered just constrained utility in stress ulceration prophylaxis. (Tryba M et al, 1985).

6.7.2.3 Proton Pump Inhibitors (PPIs) vs H2RAs

Phillips et al. performed an imminent, open-label trial assessing the adequacy of omeprazole suspension for stress ulcer prophylaxis in 75 basically sick patients. Patients were considered for the study in the event that they were admitted to the surgical or smolder ICU with an intact stomach, a nasogastric tube, and an expected ICU length of stay > 48 hours. They likewise needed to have a gastric pH < 4, be on mechanical ventilation, and have an extra hazard element for stress ulceration. Patients were prohibited in the event that they were getting enteral feedings through the nasogastric tube. Omeprazole suspension was regulated as 40 mg, trailed by a second 40 mg measurement 6 to 8 hours later, then 20 mg every day until there was no more a requirement for stress ulcer prophylaxis. Ten patients got H2RAs before omeprazole suspension. Of the 65 patients who got omeprazole suspension as their starting prophylaxis, none created plain or clinically critical upper gastrointestinal bleeding. Omeprazole fundamentally expanded the mean gastric pH inside of 4 hours of begin of treatment (3.5 to 7.1). (Phillips JO et al, 1996). PPIs and H2RAs present diverse pharmacological efficacies in forestalling anxiety ulcer draining in the ICU. One study found that the probabilities of stress ulcer draining and ventilator-helped pneumonia were 1.3% and 10.3%, individually, for PPIs versus 6.6% and 10.3%, separately, for H2RAs. (Barkun AN et al, 2013). In one methodical audit and meta-examination of 1720 patients admitted to ICUs, PPIs were more compelling than H2RAs at lessening unmistakable UGIB (relative hazard, 0.35; 95% certainty interim, 0.21 -0.59; $p < 0.0001$; I Z 15%). However, there were no contrasts in between PPIs and H2RAs as to the danger of nosocomial pneumonia, ICU mortality, or ICU length of stay (Alhazzani W et al, 2013). In another overview of 100 physician (39 attending physician, 61 occupants) with respect to SUP, all inhabitants favored a PPI for SUP compared with 85% of attending physicians ($p < 0.05$). However, more attending physicians than occupants concurred that utilizing PPIs expanded the danger of group procured pneumonia ($p < 0.05$) (Koczka CP et al, 2013). A meta-examination pooled an aggregate of 936 patients from seven randomized, controlled trials to think about the

viability and safety of H2RAs to PPIs for stress ulcer prophylaxis. There was not a factually huge distinction found in the occurrence of upper gastrointestinal draining in between PPIs and H2RAs. Also, no critical distinction was found in the safety results of pneumonia and ICU mortality. (Lin PC et al, 2010).

Levy et al. analyzed the viability of omeprazole versus ranitidine for prophylaxis against clinically vital gastrointestinal drain in 67 patients admitted to an ICU who had no less than one danger component for stress ulceration. Patients were randomized to get ranitidine (50 mg bolus took after by 150 mg day by day by continuous infusion or irregular administration) or omeprazole (40 mg every day orally or through nasogastric tube). Clinically critical draining happened in fundamentally more ranitidine patients contrasted with omeprazole patients (31% versus 6%; $p=0.013$). It ought to be noticed that the ranitidine patients had altogether more hazard variables for stress ulceration than the omeprazole patients did. The utilization of enteral sustenance was not addressed. (Levy MJ et al, 1997).

Clearly, the most ideal approach to avert mucosal harm is to anticipate ischemia and vasoconstriction of the splanchnic circulation. Inotropes don't fundamentally enhance splanchnic perfusion (Silva E et al, 1998). Conversely, it is estimated that discriminatingly sick patients may benefit by the standard utilization of vasodilators (Zandstra D.F et al, 1994). In animals studies vasodilators enhance splanchnic perfusion by lessening vasoconstriction, thereby anticipating stress ulcers. (Cullen J.J et al, 1994). Disease, endotoxaemia and sepsis all lead to vasoconstriction and mucosal harm. Prevention of disease ought to in this manner get the most astounding conceivable consideration in the emergency unit. Selective decontamination of the digestive tract (SDD) is a successful approach to avert essential and auxiliary endogenous contamination (D'Amico R.D et al, 1998). Notwithstanding SDD an exclusive expectation of cleanliness ought to avert exogenous diseases. It was indicated in animal studies that gut sterilization diminished the rate of stress ulceration. (Goldman H et al, 1964). In this proposal the theory is made that *H. pylori* assumes a part in stress ulcer development and concealment of this smaller scale creature by SDD might hence add to the counteractive action of stress ulceration. To decrease the systemic inflammatory reaction in basically sick patients, corticosteroids may be

utilized. The utilization of corticosteroids is not a danger variable for stress ulceration and may even lessen stress ulcer formation. (Cook DJ et al, 1994). Dexamethasone lessens inducible nitric oxide synthetase (iNOS) generation, which applies lethal impacts on mucosal cells. Enteral encouraging enhances mucosal blood stream viably. Furthermore, gastric pH increments during persistent enteral encouraging which may decrease ulcer development. Sander and colleagues demonstrated that orally sustained rats were less susceptible to stress ulcer formation than parenterally encouraged rats. In addition, a well working stomach specially prevent against back diffusion of H⁺ particles, pepsin and bile acids into the gastric mucosa. (van der Voort, 1999).

Patients receiving SUP should be assessed daily and when their risk factors resolve and clinical condition improves, discontinuation of SUP should be considered. Enteral nutrition may have prophylactic benefit in patients who are critically ill by optimizing splanchnic blood flow, enhancing secretion of cytoprotective prostaglandins, buffering acid, or other mechanisms .Thus, many clinicians discontinue stress-related ulcer prophylaxis when patients begin enteral feeding; however, the efficacy of enteral nutrition in this regard is controversial and further studies are warranted. Discontinuation of SUP should also be considered when patients are transferred from the ICU. Outside of the ICU, the only indications for initiation of PPI in the inpatient setting are GI diagnoses that warrant treatment, therefore there is an FDA approved indications for PPIs use (Marik et al. 2010) as mentioned in Table 3.

FDA approved indication for PPIs use

Table 3

| FDA approved indication for PPIs use. |
|--|
| • Healing of erosive esophagitis |
| • Maintenance of healing of erosive esophagitis |
| • Symptomatic gastro esophageal reflux disease |
| • Helicobacter pylori eradication in combination with antibiotics |
| • Short-term treatment of active gastric ulcer |
| • Short-term treatment of active duodenal ulcer |
| • Maintenance of healed duodenal ulcer |
| • Healing of NSAIDs associated gastric ulcer |
| • Risk reduction of NSAIDs associated gastric Ulcer |
| • Risk reduction of upper gastrointestinal bleeding in critically ill patients |
| • Pathological hypersecretory conditions including Zollinger-Ellison syndrome |

6.8 Treatment:-

The standards of administration are the same with respect to the chronic ulcer. (Bailey & love 23rd Edition). The objective of administration is prophylaxis. This has been demonstrated to decrease the frequency by 50% when begun on admission. Screen the pH of the gastric substance. The objective pH quality ought to be more noteworthy than 4.0. Anything less ought to incite the clinician to twofold the dose of the drug used if the patient was previously on prophylaxis. (Rohan C Clarke et al, 2014).

Treatment of stress ulceration usually not starts with counteractive action, but start with prevention. Watchful regard for respiratory status, acid base equalization, and treatment of different sicknesses aides keep the conditions under which stress ulcers happen. Patients who create stress ulcers normally don't discharge expansive amounts of gastric acid; then again, corrosive or acids does seem, by all accounts, to be included in the pathogenesis of the sores. In this way it is sensible either to kill acids or to repress its discharge in patients at high hazard. (L.Eastwood, 1994).

Sucralfate is the essential operators for prophylaxis of stress gastritis. It has long been utilized as a method for diminishing the occurrence of gastritis. This medication is promptly accessible, simple to manage, and economical. Sucralfate (complex salt of sucrose aluminum hydroxide and sulfate) has a positive charge and ties to the negative charge of the ulcer base to shape a gel, which acts to viably plug the ulcer base and to counteract declining of the gastritis. For patients on mechanical ventilation, this activity has been indicated to lessening the danger of nosocomial pneumonias by aspiration. (Huang et al, 2010).

Histamine 2 (H₂) receptor blockers (e.g., ranitidine, famotidine) have additionally been utilized for prophylaxis. Their activity specifically blocks H₂ receptors on the parietal cells, consequently lessening the creation of hydrogen particles. The H₂ blockers are promptly moderate and can be managed intravenously. For active drain, a persistent implantation of H₂ blockers more than a 24-hour period can be utilized on the grounds that this conveys a consistent focus to the gastric mucosa, thus improving healing. The major unfavorable impact of this class of medications is the danger of nosocomial pneumonia, which is thought to result from the concealment of gastric corrosive and which prompts colonization by secondary organisms and consequent desire pneumonia. The part of proton pump inhibitors (PPIs) in prophylaxis has not been completely assessed. The value has been exhibited in a couple of little studies; however no substantial randomized, clinical studies have been done to date. PPIs are prodrugs and ordinarily require an acidic medium to be activated. Consequently, in the fasting stressed patient, this may not be the situation. PPIs obstruct the last normal pathway of acid discharge by obstructing the H-K-ATPase enzyme. PPIs are accessible in different structures (e.g., tablets, microspheres, fluid [IV]). In patients who are

basically sick and intubated for nasogastric tube or percutaneous endoscopic gastrostomy (PEG) nourishing, the administration of microspheres or intravenous arrangements can be helpful if the patients are thought to be draining from stress gastritis, particularly if they have not reacted to any of the already talked about measures.(Rohan C Clarke et al, 2014).

Little studies have demonstrated the viability of PPIs in mechanically ventilated patients to diminish stress gastritis furthermore to be safe and practical. A correlation of PPIs and placebo was performed and exhibited the predominance of PPIs over placebo in instances of draining peptic ulcer. PPIs were likewise demonstrated to be more compelling for rebleed prophylaxis versus H2 blockers. (Alhazzani W et al, 2013).

Angiography may be helpful in recognizing the site of draining when endoscopy has fizzled as a consequence of retained clump or poor perception. if the source of draining is distinguished then intra-arterial vasopressin infused by means of the celiac pivot or the left gastric corridor, this will bring about a lessening of mucosal blood stream and constriction or suspension of hemorrhage. Local infusion of 0.2–0.4 units/min forestalls the antagonistic impacts of bigger systemic doses. A nonstop implantation for 48–72 hrs may be compelling in more than 70–80% of cases. (Gomes A S et al, 1984).

If the exact draining site can be recognized then angiographic embolization utilizing autologous clump, gelfoam or curls may be considered. Ischemic ulceration with persistent drain, full thickness necrosis or puncturing are potential complications, subsequently this methodology ought to be considered when different techniques have fizzled and experienced interventional radiologists are accessible.(Eckstein M yet al, 1984).

Endoscopic means of treating stress ulceration may be ineffective and operation required. (Bailey & love 23rd Edition). It is believed that shunting of blood away from the mucosa makes the mucous membrane ischaemic and more susceptible to injury. (Hai et al, 2003).

In case of severe hemorrhagic or erosive gastritis and stress ulcers, a combination of antacids and H2-blockers may stop active bleeding and prevent re bleeding. In selected patients, either endoscopic therapy or selective infusion of vasopressin into the left gastric artery may help control the hemorrhage. (Robert J et al, 1994).

6.9 Role of clinical pharmacist;-

The clinical pharmacist is an expert in the therapeutic use of medications. The clinical pharmacist is recognized as providing a unique set of knowledge and skills to the health care system and is therefore qualified to assume the role of drug therapy expert. In addition, this expertise is used proactively to ensure and advance rational drug therapy, thereby averting many of the medication therapy misadventures that ensue following inappropriate therapeutic decisions made at the point of prescribing. Stating that the clinical pharmacist is a primary source of scientifically valid information and advice on the best use of medications emphasizes that the clinical pharmacist serves as an objective, evidence-based source of therapeutic information and recommendations. This expertise extends beyond traditional medications to include nontraditional therapies as well. Finally, indicating that clinical pharmacists routinely provide therapeutic evaluations and recommendations underscores the fact that their daily practice involves regular consultation with patients and health care professionals regarding medication therapy evaluations and recommendations.

The drug specialist can make a noteworthy commitment to the prevention and treatment of UGIB. The redesigned global consensus rules ought to be deliberately inspected with the goal that drug specialist can give proper medication treatment proposals. Patients at danger of UGIB ought to be recognized in all practice settings, and the ideal treatment arrangement ought to be concocted for individual patients. Patients at danger of UGIB in light of *H. pylori* infection ought to be screened, and *H. pylori* sign treatment ought to be offered who test positive. Drug specialist can assume a vital part in patient guiding for adherence and good remedial results. Patient obliging long term NSAIDs treatment ought to be referred to their PCP (primary care physician) for suitable gastroprotective drugs to anticipate GI lethality. For people obliging aspirin for cardioprotective impacts, the danger of GI inconvenience ought to be evaluated and direction gave on the need to GI-protective agents. Patients ought to likewise be directed on modifiable danger variables for UGIB (e.g. smoking). Drug specialist ought to recognize discriminatingly sick patients at danger of SRMD and prescribe proper prophylaxis. Furthermore, antagonistic impacts, especially with PPIs (e.g. pneumonia, *C.difficile* infection), can be minimized by drug specialist who are cautious about the proper sign for prophylactic agents. At the point when patients no more oblige PPIs for the

anticipation of UGIB, the agents ought to be suggested for stopping, and discharge counseling should be advocated to prevent the long term use of PPIs without substantial sign.

Efforts by clinicians to check the utilization of ASDs in non-ICU patients can prevent significant patient morbidity and diminish both doctor's facility expenses and expenses to the general human services framework. It is vital to precisely measure the risks and advantages of ASDs before utilizing these medications as a part of the inpatient setting. special considerations must be given to patients as of now at danger for pneumonia, for example, the elderly, those with endless lung sickness, and those taking immunosuppressant. Each exertion ought to be made to critically assess AST treatment in inpatients and to suspend treatment at whatever point possible. At the point when SUP is indicated, the patient ought to get the most reduced measurements possible.

Drug specialists can help stem the utilization of ASDs by distinguishing patients who are improperly prescribed these medicaments, and they can be instrumental in instructing doctors about which patients ought to get SUP. Drug specialists included in preparing release medicines can help guarantee that patients are not sent home on acid suppressive treatment without an appropriate sign. Shockingly, the measures taken to counteract stress ulcers in hospitalized patients have made another issue, and by cooperating the human services group can help prevent further unnecessary morbidity by enforcing guideline proposals at their institution.

7. Background Aims & Rationale

Clinical pharmacists are a primary source of scientifically valid information and advice regarding the safe, appropriate, and cost-effective use of medications having wide scope in drug therapy management and optimization using evidence based tools and recommendation. Regarding stress ulcer one of the main cause of morbidity and mortality despite the presence of effective strategies for prevention of stress ulcer, a considerable proportion of patients at risk for stress do not receive prophylaxis during hospitalization while others receive it irrationally though not candidates according evidence based recommendations.

Stress ulcers are acute mucosal ulceration of the gastric or duodenal mucosa that occurs after physiologically stressful events such as shock, burn, severe sepsis and multiple organ traumas and if it is not treated properly it leads to upper gastro intestinal bleeding and hemodynamic instability. Up to 50% of patients will die as a result of stress-ulcer bleeding, mostly from multi-organ failure and deterioration of the underlying condition. Stress ulcer is common in ventilator-dependent patients after trauma or surgery. Endoscopy within 24 hours after injury reveals shallow erosions of the stomach wall by 72 hours, multiple gastric erosions are observed. When the patient recovers the lesions are reversed. It is widely accepted that stress ulcer prophylaxis (SUP) is indicated for ICU patients at high risk for bleeding.

Appropriate utilization of stress ulcer prophylaxis (SUP) should be limited to high-risk, intensive care unit (ICU) patients. However, the improper utilization of stress ulcer prophylaxis among all hospitalized patients remains a concern.

The primary purpose of this study was to evaluate the trends of prescribing stress ulcer prophylaxis in ICU and general ward patients in North Cyprus hospitals and inspect rational use of AST (Acid Suppressive Therapy) in preventing stress ulcer in hospitalized patients.

Several studies from the globe, have reported that AST is prescribed improperly in most of hospitalized critically and non-critically ill patients. In medical wards most prescriptions of acid suppressive therapy are prophylaxis of stress ulcer or they are prescribed without any licensed indication. Improperly prescribed AST has potential for drug-drug interaction and drugs specific adverse events. Beside this, AST can increase the risk of hospital acquired pneumonia and clostridium difficile infection. Furthermore, The cost of using medicaments like proton pump inhibitors (PPIs), Histamine 2 receptor blocker (H2R blocker) for an individual person, particularly for long-term is of utmost concern. In north Cyprus, where data on the suitability of AST in general wards was available scarcely. Therefore, we carried this study to see the appropriateness of acid suppression therapy and to avoid such kind of complication in the patients admitted to general wards of NEU hospital.

Yet to our knowledge this is the first study done to inspect trends of stress ulcer prophylaxis prescribing in turkey and north Cyprus, where many of the hospitals don't have a clearly defined protocol on use of AST for prophylaxis purposes.

8. Materials and methods

This 70 days study was carried out in the general wards from 14 July 2015, to 25 September, 2015 at Near East University Hospital, which is one of the tertiary teaching care Hospital in private sector, and also the largest and one of the leading medical facilities in Nicosia, North Cyprus. It offers extensive medical services with its highly experienced specialist staff to patients from all over the world. The Hospital of Near East University has a 56,000 square-meter closed area comprising 209 private, single patient rooms, 8 operating theatres, 30-bed Intensive Care Unit, 17-bed Neonatal Intensive Care Unit and more than 30 different clinics and departments. The study is carried out in the general wards including patients from cardiology, internal medicine, neurology, orthopedics and traumatology and geriatric clinics. All inpatients admitted to general wards were included except some patients of physicians not intending to participate with their patients and those who refused to give personal information were also excluded from the study. Cases from all medicine wards were collected on their respective admission day. All the Patients who were prescribed AST after admission in the medical ward were included in the study. 8 physicians' four consultants and four senior residents were in charge of the patients. Details were taken regarding age, sex, height, weight, primary diagnosis, chief complaints, other morbidity, drug used for AST and on a specifically designed Proforma. All the patients were categorized into 3 groups A, B, and C respectively. Group A included those patients who were prescribed AST for stress ulcer prophylaxis. Group B included those who were started with AST for a FDA approved indications. Group C included those patients who were given AST without any licensed indication. Patients receiving SUP were defined as patients prescribed AST indicated for stress ulcer prophylaxis only and not for other indications such as treatment of peptic ulceration and other GI problems. We followed ASHP Guidelines to judge the fittingness of AST for SUP. prescription of AST for SUP was viewed correct if the patient had 1 supreme sign i.e. Coagulopathy (characterized as platelet count $<50\ 000\ \text{mm}^3$ or an international

normalization ratio of > 1.5 , or a partial thromboplastin time > 2 times the control esteem, or requiring mechanical ventilation for > 48 h), or 2 or more relative signs (Respiratory Failure ,Renal Failure, Heart Failure ,Hepatic brokenness ,Jaundice ,Sepsis, Stroke ,Hypotension ,Previous Gastrointestinal Disease, High-Dose Corticosteroids (>250 Mg/Day Of Hydrocortisone),Thermal Injury To $>35\%$, Heparin Or Warfarin, kidney or liver transplant, head harm). Treatment for Non-SUP was viewed as proper if patient had any of the FDA endorsed signs for AST that includes,(Healing of erosive esophagitis, Maintenance of healing of erosive esophagitis, Symptomatic gastro esophageal reflux sickness, Helicobacter pylori destruction in blend with anti-infection agents, Short-term treatment of active gastric ulcer ,Short-term treatment of active duodenal ulcer, Maintenance of healed duodenal ulcer, Healing of NSAID-Associated gastric ulcer, Risk diminishment of NSAIDs related gastric Ulcer, Pathological hypersecretory conditions including Zollinger-Ellison disorder) . AST was viewed as inappropriate in every one of those patients who had no FDA endorsed signs for AST and in addition had no sign said in ASHP rules for SUP. Suitability was assessed by evaluating the sign, right decision of AST specialists, route of administration, term of treatment and the dosage given in light of the ASHP rules. Patients who were given SUP with less than two major risks components were likewise viewed as inappropriate.

8.1 Study design;

The Study is an observational review study conveyed at a tertiary near east university hospital for inpatients and archived over a time of 70 days. Those patients who were recently endorsed SUP were enlisted in the study. Patients were enrolled from the general wards with various pathologies and enlisted to determine hazard for stress ulcer and to investigate rational utilization of stress ulcer prophylaxis for inpatients in this health services setting utilizing the FDA sanction signs for PPIs use, and AHSP (American society of health system pharmacist) rules for stress ulcer prophylaxis in adult hospitalized patients.

8.2 Data collection;

69 Patients were enrolled in this study. Data was collected from the patients' therapeutic records and pharmaceutical outline, laboratory information system (LIS) and pharmacy information system (PIS). Patient information in regards to vicinity of stress ulcer danger components were gathered reported and enlisted in a work sheet alongside the included

patient data and current clinical status. Uniquely composed forms were filled for every patient, gathering demographic data of patient age, sex, height, weight, date of conception, ward admission information including date of admission, date of discharge and length of doctor's facility in hospital. Clinical information gathered included finding upon admission and prior comorbidities. Prescription information gathered were the drug history, surgical history, past medicinal history, sensitivities, start of SUP including type, dosage and recurrence of AST. The level of rank of the prescribing doctor was additionally extracted from the therapeutic record. Labs taken and pharmaceuticals given during their clinic stay and on discharge were gathered. The information was gathered by utilizing the table (Appendix).

8.3 Data analysis and validation:

Distinct investigation was utilized to analyze the study's consequences. An information collection form was utilized to facilitate the information extraction process. All gathered information was examined statistically by utilizing Statistical Package for the Social Science (SPSS) programming version 22.0 and Graph pad prism version 6.07. The values are given as a percentage of total case number. Chi square test or fisher's exact test was used as an appropriate for categorizing the data. $P < 0.05$ was accepted as statistically significant. Continuous data was expressed as mean (\pm standard deviation) or median (range), while absolute information was communicated as frequency and percentage (%).

8.4 Ethical Considerations:

Confidentiality was guaranteed during the study and furthermore patient's persistent privacy, a Letter of moral clearance was submitted to the Institutional Review Board (IRB) of Near East University Hospital that assigned this research as being just observational study and hence viewed as not requiring moral regard. Just Initials were utilized during the study without recording patient's location or other related not clinical essential individual data.

RESULTS

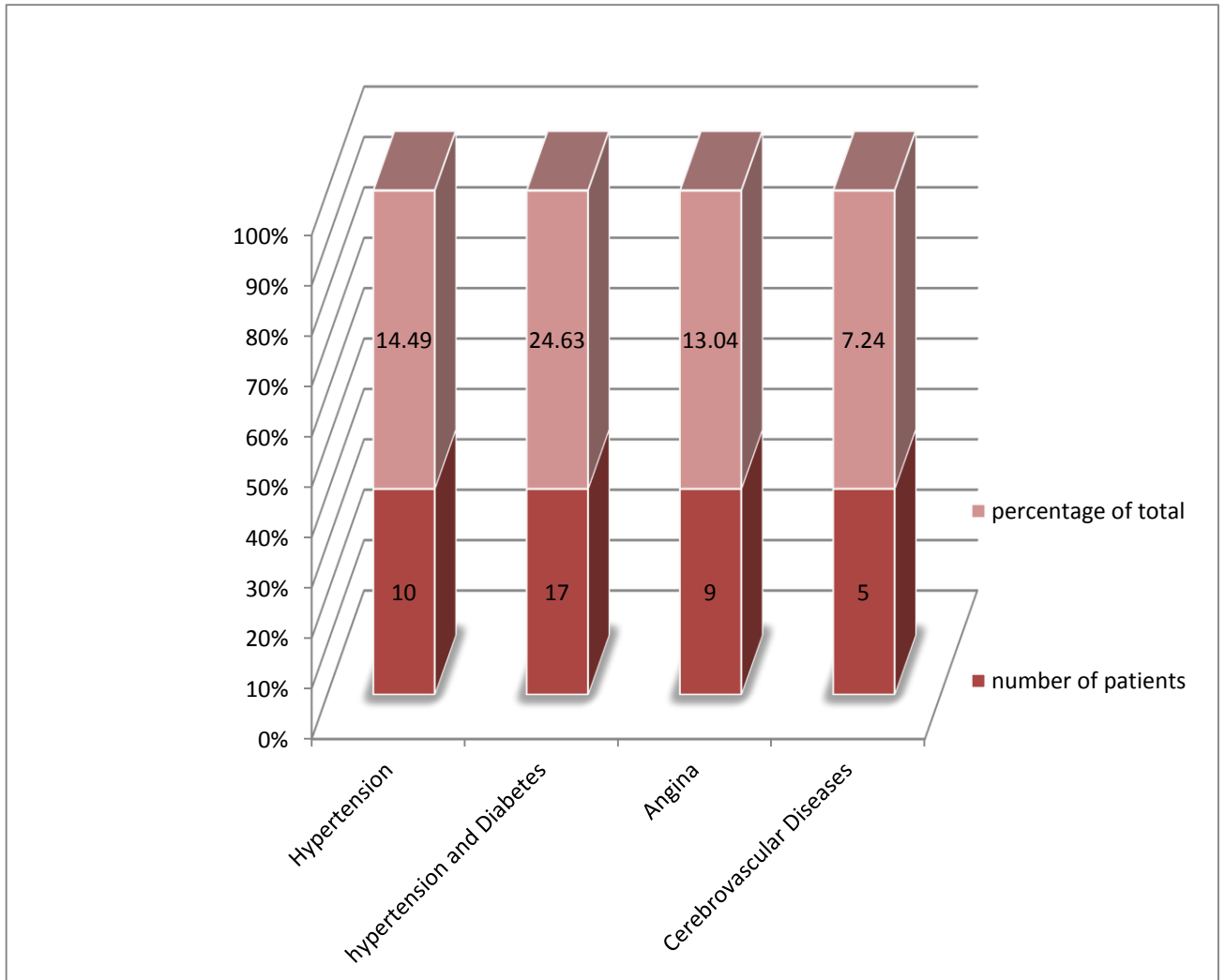
We included 69 patients in our study. Patients were enrolled from patients of five physicians from five clinics that accepted to carry the study. All patients in our study were given AST at the time of admission to Internal Medicine ward, cardiology, geriatrics, allergy and chest diseases and orthopedics & traumatology. The average number of medications is almost 9 medications for each patient. 38 (55.07%) patient's received less than & equal to 8 medications while 31 (44.92%) patients received more than 8 medications for each prescription. Nearly 45 (65.21%) patients were male and 24 (34.78%) patients were female. Their mean age was $67.50 \text{ kg} \pm 13.41$ (mean in $\text{kg} \pm \text{SD}$). Their mean weight and height was (70.72 kg) and (168.65 cm) respectively. 51 (73.91%) cases were considered rational and 18 (26.08%) cases were considered irrational. In rational cases 9 (13.04%) patients received AST therapy that had an FDA approved indication while 42 (60.86%) patients received AST therapy for SUP (stress ulcer prophylaxis). Out of 42 cases 13 (18.84%) patients had an absolute indication for SUP, 29 (42.02%) patients had 2 or more relative indications for SUP. 18 (26.08%) patients received AST without any appropriate indication. The main cause of hospitalization was heart diseases 26 (37.68%), followed by geriatrics 19 (27.53%), followed by allergy and chest diseases 11 (15.94%) as shown in Table 4. The major concurrent disease was diabetes mellitus and hypertension 17 (24.63%), followed by hypertension 10 (14.49%) as shown in fig no 6. The most common risk factor was hypertension and heart failure 13 (18.84%) patients. Omeprazole was the most frequently used AST 25 (36.23%), followed by pantoprazole 18 (26.08%), followed by lansoprazole 11 (15.94%). Table No 5 shows the main demographic and clinical characteristics of study patients while Fig no 7 show the rationality of cases according to FDA (Federal drug authority) and ASHP (American society of health system pharmacist guidelines) for SUP (stress ulcer prophylaxis in percentage).

Table No.4 Main Cause of Hospitalization

| Main cause of Hospitalization | Number of Patients | Percentage of total |
|------------------------------------|--------------------|---------------------|
| Heart Diseases **** | 26 | 37.68 |
| Geriatrics | 19 | 27.53 |
| Allergy and chest diseases | 11 | 15.94 |
| Diabetes Mellitus and Hypertension | 03 | 4.34 |
| Cerebrovascular diseases | 05 | 7.24 |
| Hypertension | 01 | 1.44 |
| Liver and heart failure | 01 | 1.44 |
| Allergy and chest disease | 01 | 1.44 |
| Orthopedics | 01 | 1.44 |
| Pneumonia | 01 | 1.44 |

Heart diseases were significantly higher as the main reason for hospitalization compared to other groups ($p < 0.0001$).

Fig No.6 Concurrent Disease

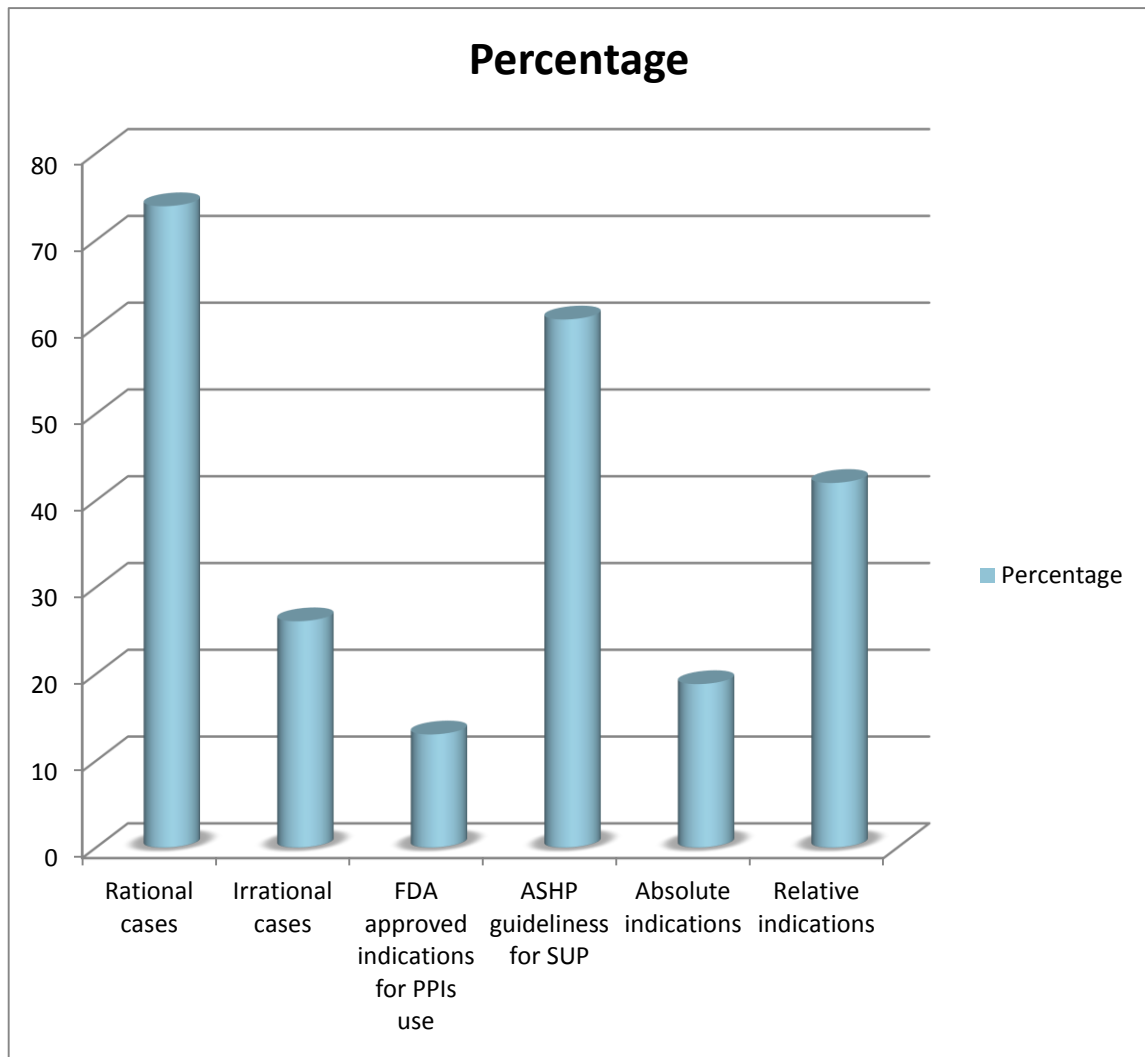


Similarly hypertension & diabetes mellitus were significantly higher as concurrent diseases within sampled patients. ($P < 0.05$)

Table No 5. Demographic and rationality according to FDA and ASHP guidelines

| Table 5. Demographic and rationality according to FDA and ASHP guidelines | | | | | |
|---|------------|-------------------------|---|-------------------|-------------|
| Clinics | Cardiology | Allergy & chest disease | Geriatrics | Internal medicine | Orthopedics |
| Number | n(26) | n(11) | n(19) | n(6) | n(7) |
| Average age | | | 67.50 years | | |
| Average number of drugs | | | 8.82 | | |
| Total number of patients | | | n(69) | | |
| Rational managed cases**** | | | n (51) (73.91%) | | |
| Irrational cases | | | n (18) (26.08%) | | |
| Average weight | | | 70.72 kg | | |
| Average height | | | 168.65 cm | | |
| Males | | | n (45) (65.21%) | | |
| Females | | | n (24) (34.78%) | | |
| FDA approved indications | | | n (9) (13.04%) | | |
| ASHP Guidelines for SUP**** | | | n (42) (60.86%) | | |
| Absolute indications n(13) (18.84%) | | | Relative indications*** n (29) (42.02%) | | |

Fig no.7 Rationality according to FDA and ASHP guidelines in percentage



Though irrationally managed patients for stress ulcer prophylaxis were significantly less than rational managed cases within sampled groups ($p < 0.0001$), yet 26% of the sampled patients received irrational AST during their hospitalization.

Out of 51 rational cases in which AST was used 17.64% were using AST for an FDA approved indication while the significantly higher portion, 82.35% ($p < 0.0001$) were using

AST for stress ulcer prophylaxis, of these 31% were due to an absolute ASHP indication while 69% were due to relative indication.

Table no.6 Irrationally Managed Cases

| Characteristics | Number of Patients | Percentage of total |
|-----------------|--------------------|---------------------|
| All Patients | 18 | 100 |
| Cardiology**** | 10 | 55.55 |
| Geriatrics | 5 | 27.77 |
| Other clinics | 3 | 16.66 |

Out of 18 irrational cases (55.55%) from cardiology were considered statically significant having ($p < 0.0001$) when compared to other clinics, i.e., (27.77%) were from geriatrics, while (16.66%) were from other clinics, 56% were using > 8 drugs per patients. 38.88% patients had HTN + DM as a concurrent disease while (27.77%) were hospitalized due to cerebrovascular diseases.

Omeprazole was most commonly used AST in parenteral dosage form which was 3 times costly when it was compared to oral dosage form.

Stress ulcer prophylaxis was provided rationally to only about 73.91% of patients who received adequate prophylaxis, alone or associated with compression elastic stockings during the hospitalization period according to ASHP guidelines; while 13.04% of patients received treatment according to FDA approved indications for PPIs. 13 (18.84%) of patients received stress ulcer prophylaxis although there were only one major risk factor instead of two or more which was considered irrational and 5 (7.24%) of patients received prophylaxis of stress ulcer although there were no indications and risks factors for its use.

Discussion

Stress ulcers are single or various gastro duodenal mucosal imperfections that cause an expansive scope of clinical appearances from shallow mucosal disintegrations or gentle serious ulceration to life-threatening bleeding dying. At the point when patient are hospitalized, the hazard of stress ulcers increments. This is especially valid for patients admitted to ICU following after the physiologic stress of genuine ailment, for example, surgery or injury. (Anderberg B et al, 1985). Inside of 24 h of admission to the emergency unit), (endoscopic confirmation of stress related mucosal disease (SRMD) was archived in 75% to 100% of critically sick patients. Although mucosal disintegrations may be of minimal clinical significance due to fast healing, they can't be disregarded. Stress ulcers introduce a risk of clinically critical bleeding, which is connected with hemodynamic instability, for example, hypotension, tachycardia or respiratory distress, or results in iron deficiency (anemia) or the requirement for transfusion. (Fennerty MB, 2002). Clinically significant bleeding happens in around 1% to 4% of fundamentally sick patients with a death rate that approaches 50%. (Ben-Menachem et al, 1996).

Right now, A little data is accessible on the medicine of anti-suppressive therapy (AST) in North Cyprus. In our study we aimed to evaluate the appropriateness of prescription of AST & Rational Drugs Use in Treatment and Prophylaxis of Stress Ulcer Therapy at NEU Hospital patients admitted to different wards of Internal Medicine, cardiology, Geriatrics and Orthopedics & traumatology in Northern Cyprus.

Our study recommends that AST is normally prescribed improperly in Internal Medicine ward, geriatrics, cardiology, neurology, and Orthopedics and traumatology. We incorporated an aggregate number of 69 patients in our study. All patients in our study were given AST at the time of admission to Internal Medicine ward, cardiology, geriatrics, neurology and orthopedics and traumatology. 45 (65.21%) patients were male and 24 (34.78%) patients were female .Their mean age was 67.50 kg \pm 13.41 (mean in kg \pm SD). 9 (13.04%) patients had a FDA approved indication (Table 3). 42 (60.86%) patients got AST treatment for SUP (stress ulcer prophylaxis). Out of that 13 (18.84%) patients had an absolute sign for SUP, 29

(42.02%) patients had 2 or more relative signs for SUP (Table 2). 18 (26.08%) patients got AST with no proper sign. Omeprazole was the most frequently utilized AST 25 (36.23%), followed by pantoprazole 18 (26.08%), followed by lansoprazole 11 (15.94%).

The present study showed that 65.21% of patients admitted to NEU Hospital got stress ulcer prophylaxis (SUP). Our study concur with the past studies did on the same subject with slight variations inside of the outcomes. A study led in USA in a huge group clinic reported that 54% of the hospitalized patients got AST of which 65% were inappropriate. (Nardino et al, 2000). Inappropriate utilization of SUP was accounted for in a study led in Iran with a rate of 54% improper SUP medicine. (M. Mousavi et al, 2013). In addition, Hwang et al likewise directed the comparable study in non-critically hospitalized patients in a teaching hospital reported that 54.9% got AST of which 58.5% were improper. Moreover, In Italy gullotta et al completed a single day review of hospitalized patients at 20 focuses and found that 27% got AST of which 51% was improper. In another study by Abeer Zeitoun et al, A sum of 1004 patients was incorporated. 67% of the patients who got prophylaxis did not have a sign for SUP. In contrast, in one study, 96.4% of patients endorsed SUP had inappropriate prescriptions with absence of danger elements. (M.S. mohamad et al, 2014). Comparative discoveries were accounted for in a study in Switzerland and US, where inappropriate utilization of SUP was accounted for to be 97% and 85%, separately. (G. Jain et al, 2013) and (C. Bez et al, 2013). Treatment with AST in a large portion of the patients who got AST unnecessarily was ascribed to SUP. In spite of the fact that rules of ASHP (Table 2) are accessible to choose the patient to manage AST for SUP and accessible medical literature likewise support sign of SUP just in ICU patients Nevertheless, routine of beginning AST for SUP in non-fundamentally sick patient admitted to therapeutic ward has been expanding day by day with no experimental writing to support this practice. This is a critical discovering in light of the fact that wrong prescriptions may prompt antagonistic medication responses, potential medication collaborations and unnecessary polypharmacy, particularly in older patients who are more defenseless against these issues. (M.A. Koda-Kimble et al, 2012).

The ASHP rules published, in 1989, do exclude PPIs for SUP yet in our study Omeprazole was the most widely recognized AST utilized for this reason (36.23%). Other restorative sources likewise reported that PPIs are all the more ordinarily endorsed drugs for SUP

regardless of limited information is accessible to support this practice (ASHP, 1999). Our concentrate additionally demonstrate that proton pump inhibitors (PPIs) was the most frequently recommended SUP agent (36.23%), with omeprazole being the most endorsed. This was affirmed by another study by Qaisar et al. (2013) revealed that the most regular medication utilized was omeprazole (55%), followed by ranitidine (45%). In contrast, a study by Parente et al. (2003), which revealed that most regular medication utilized was ranitidine (44.4%), trailed by pantoprazole (31.8%) and omeprazole (23.0%). In other study it was inferred that ranitidine (60.3%) was the most ordinarily endorsed drug for stress ulcer prophylaxis. (M.S mohamad et al, 2014). Proton pump inhibitors were the ruling corrosive suppressive medications in our study. Just 8% of the selected patients got H-2-receptor antagonists. Different studies led in the US and England on the use of AST, have exhibited that H-2-receptor drug entities were more utilized than PPIs. Diverse results were noted between the studies that may be due to differences in local drug strategies or inclinations between nations. This is presumably might likewise be clarified by varying prescriptions traditions in diverse nations. Why PPI have been the ruling acid suppressive medications in Sweden may be because of the way that the first PPI (omeprazole) was produced in Sweden. Powerful promoting may additionally be an imperative component. An impressive monetary advantage is liable to be picked up by the health care system by recommending H-2-receptor antagonists rather than PPI. Despite the fact that it would have been interesting to perceive what number of our patients who had been treated with a H-2-receptor antagonists preceding PPI treatment, this data was not accessible in our study.

It was also investigated in our study that the number of omeprazole injections 19 (27.53%) used was 3 time more as compared to omeprazole capsule 6 (8.57%) out of 69 patients (100%). The cost of omeprazole injection is more than 5 dollars while that of omeprazole capsule is 1.23 dollars. Again our study agrees with the previous studies carried out on the same topic with slight variations within the results. A study by Abeer Zeitoun et al investigated 1004 patients accepting AST, Out of 1004 patients 771 (76.8%) patients were administered the medication parentally, of which 551 (71.6%) patients had the capacity to tolerate oral course. The route of administration was lacking in most of the patients so our study proposes that the insufficiency in directing the medications is because of the misguided

judgment that parenteral meds are more successful than oral ones. Then again, studies failed to demonstrate any safety or efficacy of interest of one dosage form over the other. Accordingly, to minimize the potential antagonistic impacts and extra expenses of parenteral route, the parenteral course ought to be held for patients who can't endure oral medicines.

This study fortifies the consequences of past studies embraced in the Middle East. Recently an observational study by Mayet (n = 661) was done at King Khalid University Hospital, a tertiary showing healing center in Saudi Arabia. Its goal was to assess the inappropriate utilization of pantoprazole and ranitidine. Additionally Khudair et al, in a MUE study directed at Hamad General Hospital in Qatar (389 patients) evaluating the recommending pattern of acid suppressive therapy in restorative inpatients, found that the use of SUP was unjustified in 66% of patients. The outcomes demonstrated that inappropriate utilization of these medicines was seen in 43% of the patients, underscoring the need to implement guidelines keeping in mind the end goal to lessen the abuse of AST.

Strength and Limitations

This study, assessing the practical example of stress ulcer prophylaxis in NEU hospital which is the first study of its kind in North Cyprus. The quality of our examination lies in that beside of being the first of its kind in North Cyprus, the ASHP rules for stress ulcer prophylaxis utilized is a world generally all around accepted and validated. Besides, the study assessed the suitability of stress ulcer prophylaxis and was not restricted to critically ill patients. One important thing which was noted in the study was that, to majority of patients (AST) was prescribed in parental form as compared to oral form which is 3 times costly as compared to oral form. Clinical drug specialists in guiding and managing treatment have the benefit of being medication specialists had some expertise in defending medication use and in this way can to a great extent characteristic in directing stress ulcer treatment which is not yet assessed in North Cyprus. Patients were selected in this study from different centers served by more than 15 doctors, while the study discoveries were practically identical to others conveyed somewhere else in US, Canada, Sweden, Europe and Pakistan. This study had a few limitations. Because of time requirement, the study was done for a period of ten

weeks, which brought about a little number of looked into patients. Missing information was a noteworthy limitation, particularly data about the continuation of SUP after discharge, which was inadequate in majority of the sample. Also, the relationship between proper SUP practice and clinical results, as far as safety and efficacy of AST, were not evaluated in our study. Another limitation also deserves attention. Firstly and most importantly, patients were not followed up for complications post hospital discharge , the numbers sampled also were few compared to the numbers enrolled in other comparable studies ,this could be overcome in the future by recruiting patients also from other centers in Turkey and North Cyprus so to achieve more precision and validity for our findings. Despite that, every single qualified patient was effectively surveyed and the patients included represented typical older adults admitted to different medical wards (cardiology, neurology, geriatrics, orthopedics and traumatology) in our setting. It is additionally beneficial to note that the study depends on a single hospital and may not represent the same SUP routine of different doctor's facilities from distinctive cities of North Cyprus.

Conclusion

Taking everything into account, this study evaluated the propriety of SUP practice in relationship with the main accessible guidelines, the ASHP guidelines. Our outcomes propose that the ASHP rule is a commonsense and powerful instrument to survey the risk of SUP among hospitalized patients in North Cyprus. The outcomes of this study highlight the requirement for the usage of amendment measures and practice rules in ICU and additionally non-ICU settings. So for this clinical drug specialist at hospital, will be an essential source of logically substantial data and guidance with respect to the protected, suitable, and cost effective utilization of meds .More mindfulness and training ought to be considered in NEU hospital, and different hospital in non-teaching areas where the act of evidenced based medication may be insignificant. Without firm suggestions, the non-critically sick population requires extra consideration. This can be accomplished by: (1) obviously characterizing the risk components for clinically huge bleeding in this populace; and (2) occasionally observing the practice example of SUP to further minimize its abuse in non-critically sick patients.

PPIs have revolutionized the treatment of various upper GI tract issues. However, PPI treatment is not without danger of antagonistic impacts. The general advantages of treatment and change in personal satisfaction essentially exceed potential dangers in many patients, in spite of the fact that patients with no clinical sign for use are just presented to the dangers of PPI remedy. Risk stratification of more established, fragile, malnourished, and chronically hospitalized patients ought to direct clinicians to quantify advantages of treatment against adverse effects. It is foremost for clinicians to reassess their individual persistent requirements for continuation of PPI treatment long term, considering cost recommending practices. Large randomized, planned trials are expected to all the more firmly established direct cause and end results connections in between PPIs and antagonistic events. The present study observed that one fifth of elderly patients who were admitted to general therapeutic wards in our study were recommended with SUP and most of the SUP endorsed was improper. Consequences of this study recommend the need to actualize guidelines for stress ulcer prophylaxis for non-critically ill patients in our neighborhood setting. Instruction on confirm based practice and rules for stress ulcer prophylaxis in our nearby medicinal services settings are required with a specific end goal to lessen improper prescriptions in future. In conclusion, if the physician follows the ASHP guidelines for SUP, the number of irrationally managed patients will be significantly decreased which will lead to a decrease in inappropriate acid suppression rates during hospitalization and upon discharge as well as significant cost-savings

Recommendations:

The act of recommending AST unnecessarily can increase expenses, drug interactions, and adverse effects. It is of key significance in North Cyprus where generally patients are non-bearing. Usage of institutional conventions, confirmation based medicine practice during residency training, and incessant audit of treatment by consulting advisor during ward rounds may be useful to advance proper utilization of AST in medication ward and also clinical drug specialist will assume a fundamental part to record the sign for continuous treatment both major and minor and to stop treatment if not demonstrated, so Reduce the danger to patients, Reduce costs and to discuss the signs with the patient/supplier..

Future studies ought to be conveyed in multi settings including surgery, patients could be selected from multi centers, a drug specialist intervention arm ought to be compared with normal consideration, patients must be taken after post hospitalization for three months to follow up complications of Stress ulcer or bleeding, additionally SUP could be analyzed and affirmed utilizing symptomatic methodology (diagnosing) for recognizing SUP beside clinical signs and manifestations to guarantee more surrogate endpoints.

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