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The use of proton pump inhibitors in selected public hospital intensive care units in Johannesburg

Biyase, Ntombiyethu

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THE USE OF PROTON PUMP INHIBITORS IN SELECTED PUBLIC HOSPITAL INTENSIVE CARE UNITS IN JOHANNESBURG

Ntombiyethu Biyase

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Masters of Medicine in Anaesthesia
Johannesburg 2015

DECLARATION

I, Ntombiyethu Biyase, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in Anaesthesia in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

..... (Signature)

..... day of ....., 20.....

ABSTRACT

Stress ulcer prophylaxis (SUP) is an important part of management of critically ill patients in Intensive Care Unit (ICU). However inappropriate use of these drugs has important clinical implications such as ventilator-associated pneumonia (VAP) and gastrointestinal tract (GIT) infections to name a few. Strict adherence to guidelines is the corner stone to gaining maximal desired clinical effect with minimal adverse events. The overuse of proton pump inhibitors (PPIs) as SUP is a rapidly growing problem internationally. In Chris Hani Baragwanath Academic Hospital (CHBAH), Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Helen Joseph Hospital (HJH) there are no studies that have been conducted to investigate this.

The aim of this study was to describe the use of PPIs in ICU patients at CHBAH, CMJAH and HJH over a three-month period.

A retrospective, descriptive, contextual study design was used. Data were collected from ICU charts of adult patients admitted to CHBAH, CMJAH and HJH ICUs that fulfilled the inclusion criteria. Data were collected over a three-month period.

A total of 174 patients were included in the study. Of these patients 156 were on SUP, 95 (60.9%) were appropriately started on SUP and 61 (39.1%) were inappropriately on SUP. This shows overuse of SUP. The number of patients that actually qualified for SUP according to the ASHP guidelines was 113. In that group of patients only 32 (28.3%) were on PPIs and the remainder of the patients 81 (71.7%) were either on other agents or were not on any SUP, reflecting an underuse of PPIs.

Our study found inappropriate overuse of SUP according to the ASHP guidelines, however there were patients who qualified for SUP but were not on SUP. In the group of patients that were appropriately on SUP, a large number of them were on other agents and not PPIs even though it is the drug of choice.

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LIST OF ABBREVIATIONS

SUP	stress ulcer prophylaxis
CSB	clinically significant bleeding
PPI	proton pump inhibitor
H_2RA	histamine 2 receptor antagonist
PEEP	positive end expiratory pressure
SRMD	stress related mucosal disease
ICU	intensive care unit
VAP	ventilator associated pneumonia
GIT	gastrointestinal tract
SIRS	systemic inflammatory response syndrome
CHBAH	Chris Hani Baragwanath Academic Hospital
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
HJH	Helen Joseph Hospital

CHAPTER ONE
OVERVIEW OF THE STUDY

1.1 Introduction

In this chapter the background, problem statement, aim and objectives, research assumptions and definitions, ethical considerations, demarcation of study field, research methodology, significance of the study as well as validity and reliability are discussed.

1.2 Background

Since the 1800s, ICU patients have been shown to develop gastric ulceration secondary to physiological stress. The aetiology of stress ulcer is multifactorial. A prominent factor in the development of stress ulcers is the development of splanchnic hypoperfusion. This occurs as a result of the body's stress response to critical illness. The stress response involves the activation of the sympathetic nervous system, an increase in circulating catecholamines, vasoconstriction, hypovolaemia, a decrease in cardiac output and an increase in pro-inflammatory cytokines (1) are some of the factors that contribute to the development of stress ulcers in critically ill patients (2). The overall effect of these substances is a decrease in the blood flow to the gastrointestinal system, which results in a decrease in oxygen and bicarbonate delivery, which promotes damage to gastric mucosa (1). Gastrointestinal hypoperfusion leads to a decrease in peristalsis which delays removal of acid, increasing exposure of the damaged mucosa to acid and amplifying the risk of developing stress ulcers (3-5). Bleeding from stress ulcers increases morbidity thus prolonging ICU stay of patients by four to eight days. It also has an impact on mortality rate with a relative risk of 1-4 (6). Each episode of CSB results in additional haematological tests and a mean of eleven blood products transfusion leading to increased medical cost overall (6, 7).

There are certain factors that put the critically ill patients in ICU at increased risk for developing a stress ulcer. Major factors independently predispose patients to stress ulcers such as mechanical ventilation for more than 48 hours and coagulopathy (4, 8, 9).

Minor risk factors have an additive effect of increasing the risk of developing stress ulcers and they are: sepsis, burns, renal failure, hepatic failure, the use of high dose glucocorticoids, heparin or warfarin and spinal cord injury (1, 8). According to the guidelines prophylaxis is indicated in ICU patients with the following: mechanical ventilation for more than 48 hours, coagulopathy and patients with more than one minor risk factors (2, 8).

Proton pump inhibitors (PPIs) have proved to be the most superior in efficacy for stress ulcer prophylaxis (SUP) and have gained widespread use (10). The low intra gastric pH plays a pivotal role in the pathophysiology of stress ulcers (3). PPIs can produce sustained suppression of acid secretion that is dose dependent and their efficacy grows exponentially with continuous use without tachyphylaxis (11). The other agents used as SUP do not produce these results (12).

International literature shows that there is a tendency to overuse PPIs in ICU (13-15). In a retrospective study by Farrel et al (4) 68% of patients without any risk factors were placed on prophylaxis on ICU admission, This raises concerns of drug-drug interactions, adverse effects such as hospital acquired pneumonia (16) and costs (17). No literature detailing the extent of the use of PPIs in South African ICUs could be identified.

1.3 Problem statement

It is well documented that patients in ICU are at an increased risk of developing stress ulcers (4). PPIs are regarded as the drug of choice for prophylaxis (10), and overuse of these drugs has serious medical implications as mentioned in the introduction.

There are guidelines in terms of risk stratification as to which patient should be put on prophylaxis for stress ulcers (8). Despite good intentions, there is often a gap between evidenced based guidelines and actual clinical practice (18) . The use of PPIs is one area where such a gap exists. It has been shown internationally that prophylaxis for stress ulcers is still overused in ICU (4). Nardino et al (14) showed that up to 65% of patients receive stress ulcer prophylaxis without any risk factors in the general medical unit. It is not known whether PPIs are overused in the ICUs of South African hospitals, specifically Chris Hani Baragwanath Academic Hospital (CHBAH), Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Helen Joseph Hospital (HJH).

1.4 Aim and objectives of the study

1.4.1 Aim

The aim of this study was to describe the use of PPIs in ICU patients at CHBAH, CMJAH and HJH over a three-month period.

1.4.2 Objectives

The objectives of this study were to:

- describe the use of SUP in these ICUs
- describe the risk factors that necessitate the initiation of SUP
- describe the SUP received by patients with no risk factors
- describe the risk factors in those patients inappropriately not on SUP
- describe the appropriate use of PPIs in ICU versus the inappropriate use according to the risk factors of the patient as per ASHP guidelines.

1.5 Research assumptions and definitions

The following definitions will be used in this study.

Stress ulcer: damage to the gastric mucosa caused by physiological stress (8).

Risk factors associated with stress ulcer development: ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis (8) categorise the risk factors into major and minor risk factors.

Major risk factors are: mechanical ventilation for more than 48 hours and coagulopathy.

Minor risk factors are: sepsis, burns, renal failure, hepatic failure, use of high dose glucocorticoids, heparin, warfarin, major surgery and spinal cord injury.

Stress ulcer prophylaxis: administration of two or more doses of H_2RA, antacids, sucralfate, prostaglandin analogues or PPIs (9).

Appropriate use of PPIs: the presence of one or more major risk factor or the presence of more than one minor risk factor or presence of both major and minor risk factors.

Inappropriate use of PPIs: presence of only one minor risk factor or the absence of risk factors. For the purpose of this study omission of treatment in patients who qualified for SUP was classified as inappropriate.

Mechanical ventilation: use of ventilator or respirator to improve the exchange of air between the lungs and the atmosphere.

Coagulopathy: platelet count of less than 50,000 mm^3, an International Normalised Ratio of more than1.5, or a partial thromboplastin time of more than 2 times the control value control (8).

SIRS: two or more of the following, temperature of more 38°C or less than 36°C, heart rate of more 90 beat per minute, respiratory rate of more than 20 breaths per minute, white cell count of more than12 000 mm^{-3} or less than 4000 mm^{-3} (19).

Sepsis: SIRS plus source of infection (19).

Burns: injury involving more than 35% of body surface area (8).

Renal failure: a creatinine clearance less than 40 ml/min or serum creatinine more than 2.8 mg/dl (141,1 mmol/l) (4).

Hepatic failure: aspartate aminotransferase of more than 500 U/L or total bilirubin of more than 8.8 mg/dl (150.5 umol/l) (4).

Major surgery: surgery lasting more than 4 hours (4).

High dose corticosteroids: an equivalent of more than 250 mg of hydrocortisone per day (8).

Spinal cord injury: trauma or disease that affects the conduction of sensory and motor signal across the site(s) of lesion(s) (20).

Adult patients: participants who are 18 years and older.

1.6 Ethical considerations

Ethical approval to conduct this study was obtained from the relevant authorities (appendix 1). Consent to perform the study was obtained from the relevant authorities (Appendix 2,3,4& 5).

The researcher observed the principles of the Declaration of Helsinki (21) and the South African Good Clinical Practice Guidelines (22).

1.7 Demarcation of the study field

The study was conducted at CHBAH, CMJAH and HJH in Johannesburg, Gauteng. CHBAH and CMJAH are central hospitals and HJH a tertiary hospital. All three hospitals are affiliated to the University of the Witwatersrand. These are multidisciplinary ICUs in these hospitals.

1.8 Research methodology

1.8.1 Research design

A retrospective, descriptive, contextual study design was used.

1.8.2 Study population

The ICU charts of adult patients admitted to CHBAH, CMJAH and HJH ICUs that fulfilled the inclusion criteria formed the population group studied, data was collected over a three-month period.

1.8.3 Study sample

Sample size

The number of patients admitted into the ICUs over a three-month period will determine sample size.

Sampling method

Convenience, consecutive sampling of ICU charts was used.

1.8.4 Inclusion and exclusion criteria

Inclusion criteria

All complete and legible ICU charts of adult patients admitted to these selected ICU's during the study period.

Exclusion criteria

The ICU charts of patients with the following will be excluded:

- existing upper gastrointestinal bleeding
- previous total gastrectomy
- died or discharged within 24 hours of admission
- on PPIs prior to admission.

1.8.5 Data collection

A data collection sheet (Appendix 8) was used to collect data from ICU charts of patients admitted into ICU during the study period.

The researcher collected the data personally and the data were entered into a Microsoft Excel® spreadsheet. Data were collected from ICU charts dated from 1st August up to and including 31st October 2013. However since this was a retrospective study the actual physical collection of data were from November 2013.

1.8.6 Data analysis

Data were analysed in consultation with a biostatistician using STATA 12.5.

1.9 Significance of the study

SUP in patients at high risk for developing stress ulcer not only improves morbidity and mortality (9) but it is also cost effective in that it reduces financial burden to health (23).

However the drugs used for SUP have side effects with significant consequences therefore it is imperative that guidelines for SUP are adhered to and the risk: benefit ratio for each patient is assessed (24).

This study may give insight into the PPI prescribing practices. If they are inappropriately prescribed according to the guidelines, feedback measures such as educational strategies and awareness can be put in place.

1.10 Validity and reliability

Measures were taken to ensure the validity and reliability of this study.

1.11 Study outline

The outline of this study is as follows:

- Chapter 1: Overview of the study
- Chapter 2: Literature review
- Chapter 3: Research methodology
- Chapter 4: Results and discussion
- Chapter 5: Summary, limitations, recommendations and conclusion.

1.12 Summary

In this chapter an overview of the background, problem statement, aim and objectives, research assumptions, demarcation of study field, ethical considerations, research methodology, significance, validity and reliability, and study outline was presented. The following chapter will discuss literature review of this study.

CHAPTER TWO
LITERATURE REVIEW

2.1 Introduction

In this chapter the literature on stress ulcer prophylaxis is reviewed. This includes the physiology of gastric acid secretion, pathophysiology, risk factors, and stress ulcer prophylaxis. Pharmacology of PPIs as well as the use, benefits, adverse effects and overuse of PPIs and the ASHP guidelines are also discussed.

2.2 Physiology of gastric acid secretion

Stomach acid is secreted by parietal cells. The parietal cells are enriched with mitochondria, which are essential for generation of energy required for hydrogen ion secretion by tubulovesicular and canaliculi structures. These structures contain hydrogen ion pumps, which are H/K ATPase pumps that exchange hydrogen ions for potassium ions across the apical membrane. At rest the parietal cell cytoplasm is filled with tubulovesicular structures. When stimulated the tubulovesicles coalesce into canaliculi and become filled with microvilli. This results in the membrane area of the canaliculi draining to the apical surface of the parietal cells in preparation for high rates of acid secretion. Upon withdrawal of stimulation the canaliculi collapse and microvilli recede (25, 26). Figure 2.1 illustrates the different phases of a parietal cell.

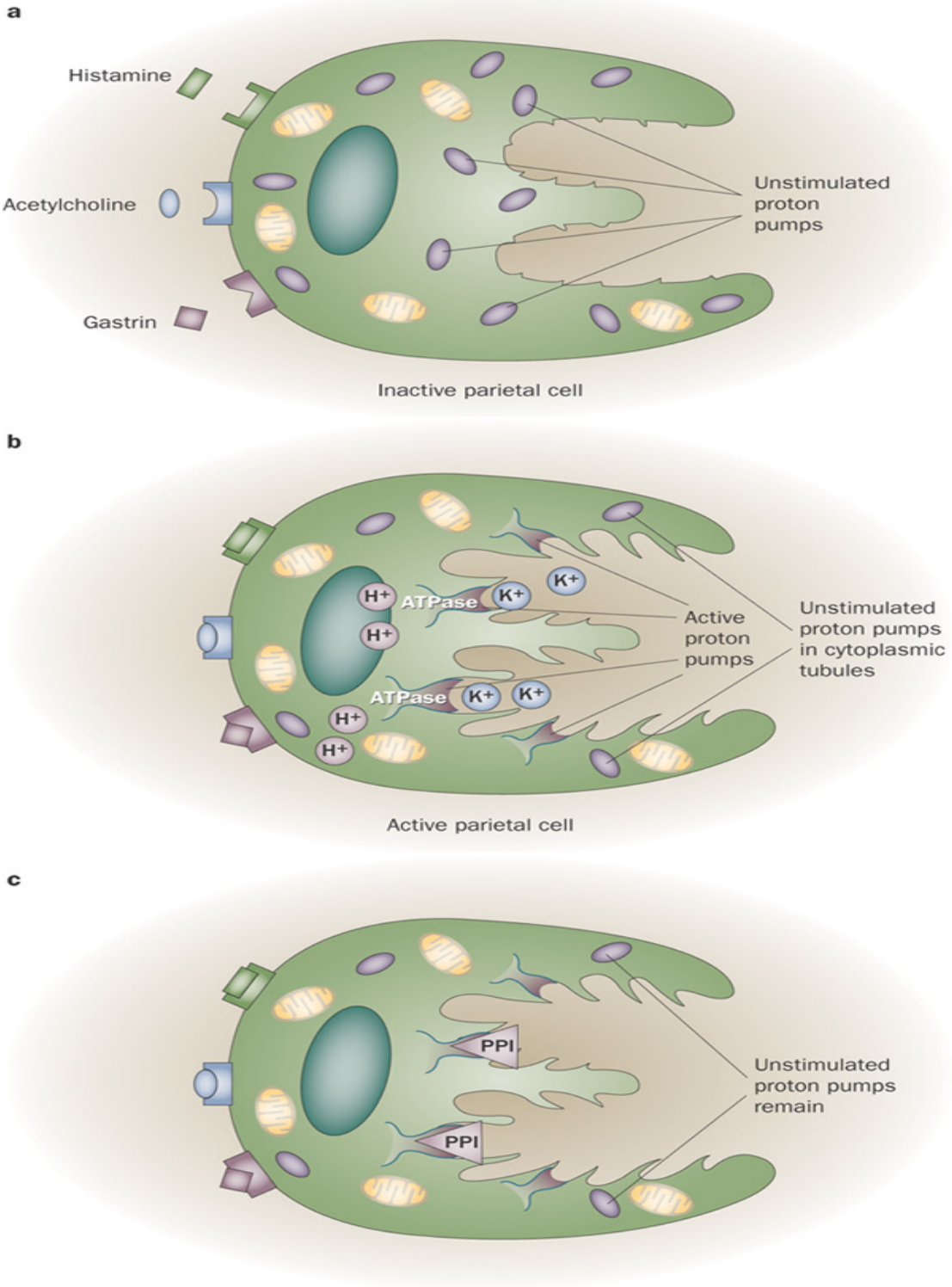


Figure 2.1 Parietal cells in the various phases (27)

The different pathways that are involved in acid secretion are as follows:

- Parasympathetic nervous system via the vagus nerve: stimulation of the cholinergic activity promotes the stimulatory mechanisms that lead to the activation of parietal cells and gastrin release from G-cells
- Paracrine pathway: the enterochromaffin-like cells (ECL) secrete histamine that activates H_2 receptors.
- Endocrine pathway: gastrin that is produced by G-cells around the antrum stimulates parietal cells in the antral mucosa through histamine release and also has tropic activity towards ECL that increases the release of stored histamine.
- Somatostatin: inhibit histamine release and gastrin release from ECL and G cells (28).

Binding of histamine to H_2 receptors of the parietal cells stimulates cell function by increasing cyclic AMP-dependent protein kinases. Acetylcholine and gastrin appear to stimulate the parietal cells by stimulating the release of additional cytosolic calcium in the parietal cells (26, 29).

The sight, smell and/or taste of food results in an increase in vagal efferent activity and the release of acetylcholine. Acetylcholine directly increases acid production by stimulating the parietal cells. The presence of food in the stomach increases acid production in various ways. Food stimulates the G cells to secrete gastrin. Gastrin has a tropic action on the parietal cells causing them to enlarge, it also stimulates the ECL cells to produce histamine that increases acid production from the parietal cells. Secondly gastric distension caused by food excites a long vagal reflex to release more acetylcholine (25).

A pH below 2,5 in the antrum inhibits the release of gastrin and once the pH is below 1,2 gastrin secretion is completely blocked. This is a negative feedback pathway (14). Figure 2.2 demonstrates the various pathways involved in gastric acid secretion.

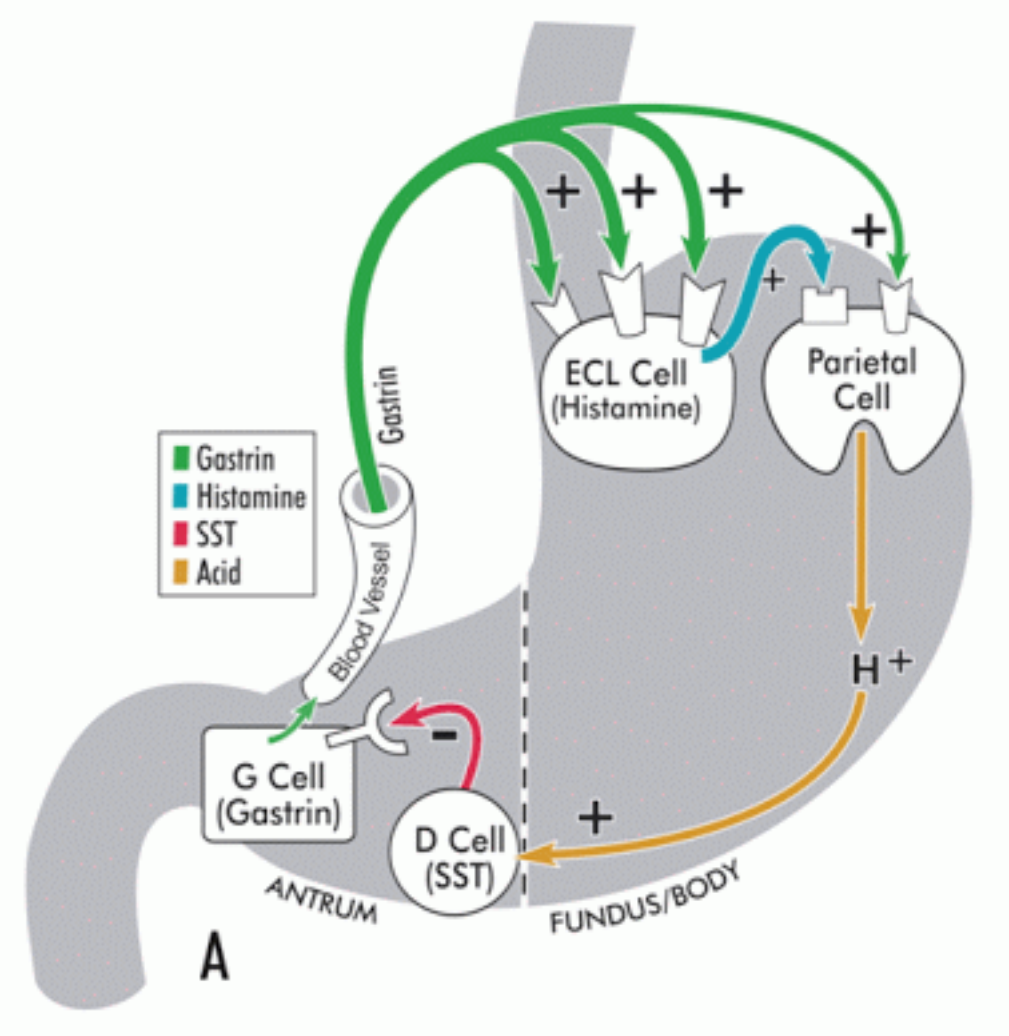


Figure 2.2 Pathways involved in gastric acid secretion

Adapted from BMJ Publishing Group Ltd

2.3 Pathophysiology of stress related mucosal disease

The pathophysiology of stress related mucosal disease (SRMD) is multifactorial. The interaction of these multiple factors causes a breakdown of mucosal defenses leading to damage of the mucosa by the aggressive physiological factors (1).

A prominent factor in the development of stress ulcer is the development of splanchnic hypoperfusion. This occurs as a result of the body's stress response to critical illness. The stress responses include activation of the sympathetic nervous system, increase in circulating catecholamine, vasoconstriction, hypovolaemia, decrease in cardiac output and increase in proinflammatory cytokines (1).

The overall effect of these substances is to redistribute blood flow from the gastrointestinal system and skin to more essential organs such as the brain, heart and kidneys. This response is beneficial initially, but as the response continues, the decrease in splanchnic blood flow results in a decrease in oxygen delivery and bicarbonate, which promote damage to gastric mucosa. The permeability of the mucosa is compromised and the backflow of hydrogen ions and pepsin further damages the mucosa. Gastrointestinal hypoperfusion leads to a decrease in peristalsis which delays removal of acid, increasing exposure of the damaged mucosa to acid and amplifying the risk of developing stress ulcer (1-3, 30).

A further contributing factor is reperfusion injury. After a prolonged period of hypoperfusion, when blood flow is restored, the increase in nitric oxide synthetase leads to hyperaemia, cell death and an increased inflammatory response, which leads to further mucosal damage (2, 3).

Mechanical ventilation has adverse effects on splanchnic haemodynamics, when PEEP is used. PEEP decreases mesenteric blood flow by decreasing cardiac output (2, 3, 5).

2.4 Risk factors for developing a stress ulcer

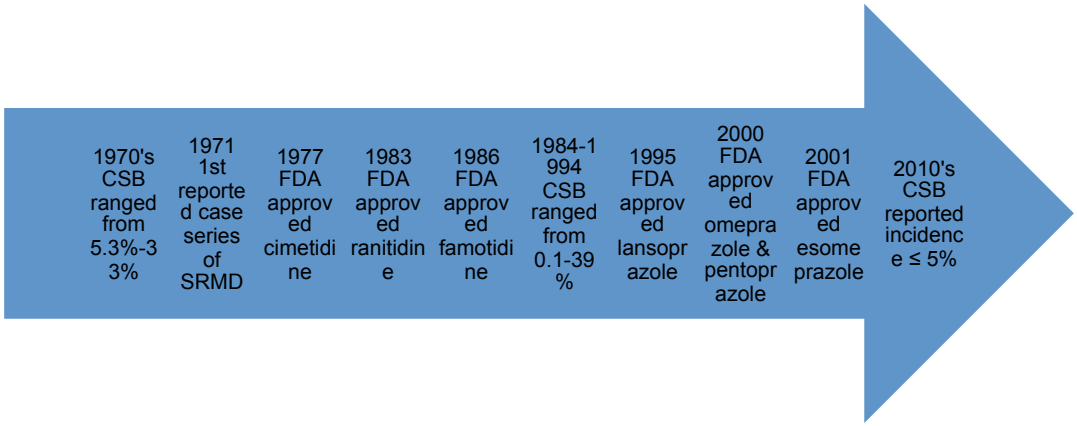
The University of Arizona under contract of ASHP prepared the ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis in November 1998. A literature search on Medline from the period 1966 -1997 was done and International Pharmaceutical Abstracts (IPA) from 1970-1997 were used. The authors then compiled risk factors from the data collected. These guidelines are the only existing guidelines for SUP since 1999. They have never been updated since their publication and therefore some recommendations are outdated. They are discussed further in section 2.7 of this document (8).

The two major risk factors are those that can individually predispose patients to stress related mucosal disease (SRMD) such as mechanical ventilation for more than 48 hours and coagulopathy, defined as a platelet count of <50,000 mm^3, an International Normalised Ratio of >1.5, or a partial thromboplastin time of >2 times the control value (1, 8, 9). When these risk factors are present the frequency of bleeding is 3.7%, compared to those patients without which is 0.1% (9).

Minor risk factors are those that, while individually they do not increase the risk of ulcer formation, when added together they increase the risk of developing stress ulcers. These minor risk factors include sepsis, burns, renal failure, hepatic failure, the use of glucocorticoids (>250mg per day of hydrocortisone or the equivalent), heparin, warfarin, and spinal cord injury (1, 8). Patients with minor risk factors only, have an extremely low risk of developing clinically important bleeding 0.1-0.5% (9).

2.5 Stress ulcer prophylaxis

Prophylaxis for stress ulcer is the administration of two or more doses of H_2RA, antacids, sucralfate, prostaglandin analogues or PPIs (9). Figure 2.3 shows the progressive drop in the incidence of clinically significant bleeding (CSB) secondary to SUP. The administration of SUP to patients with high risk reduces the relative risk of clinically significant bleeding by approximately 50% (9).



CSB: clinically significant bleeding

FDA: Food and Drug Administration

Figure 2.3 Stress ulcer prophylaxis timeline (31)

The PPIs have proven to be superior in efficacy to other forms of SUP and have gained widespread use (10, 32). The low intra gastric pH plays a pivotal role in the pathophysiology of stress ulcers (3) and PPIs can produce sustained suppression of acid secretion that is dose dependent and their efficacy grows exponentially with continuous use (11). The other agents used as SUP do not produce these results. H_2RA are known to develop tachyphylaxis within 72hours of initiation (1, 33) and do not consistently maintain gastric pH above 3.5 (12) which is the pH required to prevent stress ulcer related bleeding (8) . Another important consideration when dealing with critically ill patients is the pharmacokinetic/ pharmacodynamics of a drug in the face of organ dysfunction. PPIs have a drug within their class that does not need dose adjustment in the presence of renal and liver dysfunction. Both H_2RA and sucralfate need dose adjustment in patients with renal dysfunction (12). The surviving sepsis guidelines of 2012 recommend the use of PPIs as the sole agent for SUP (19), unlike previous editions, which recommended the use of either PPIs or H_2RA. This highlights the change in trend in the literature supporting PPIs as the drug of choice. Table 2.1 shows a summary of studies comparing the efficacy of PPIs versus H_2RA and sucralfate. It shows a consistent trend of PPIs having a lower incidence of stress ulcer related CSB compared to the other agents.

Table 2.1 Summary of studies looking at the efficacy of PPIs

Author Year	Population	Intervention	UGI Bleeding
Powel et al. 1993 (34)	Post-CABG surgical ICU	Omeprazole i.v. 80mg ×1,then i.v. 40mg/day Omeprazole i.v. 80mg×1, then i.v. 40mg/8h Ranitidine i.v. 50mg/8h	0(0%) 0(0%) 0(0%)
Levy et al.(35) 1997	Medical and surgical ICU	Omeprazole NG 40mg/day ranitidine i.v. 50mgbolus,then i.v. 50mg/day	1(3%) 11(35%)
Kantorova et al 2004 (36)	Surgical ICU	Omeprazole i.v. 40mg/day Famotidine i.v. 40mg/12h Sucralfate NG 1mg/6h Placebo	1(1%) 2(3%) 3(4%) 1(1%)
Conrad et al 2005 (37)	General ICU	Omeprazole NG 40mg×2, then NG 40 mg/day Cimetidine i.v. 300mg bolus, then c.i.v. 1200mg/24/h	7(4%) 10(6%)
Hata et al. 2005 (38)	General ICU	Rabeprazole PO 10mg/day Ranitidine PO 300 mg/day Teprenone NG 150 mg/day	0(0%) 4(6%) 4(6%)

Somberg et al 2008 (39)	Mixed ICU	Pantoprazole i.v. 40mg/day Pantoprazole i.v. 40mg/12h Pantoprazole i.v. 80mg/day Pantoprazole i.v. 80mg/12h Pantoprazole i.v. 80mg/8h Cimetidine i.v. 300mg bolus, then c.i.v. 1200mg/12h	0(0%) 0(0%) 0(0%) 0(0%) 0(0%) 0(0%)
Solouki and Kouchak 2009 (40)	General ICU	Omeprazole NG 20mg/12h Ranitidine i.v. 50mg/12h	4(7%) 18(26%)
Brophy et al. 2010(41)	ICU Neurosurgery Patients	Lansoprazole suspension NG 30mg/day Famotidine i.v. 20mg/12h	0(0%) 1(2%)

CABG: coronary artery bypass graft; c.i.v: continuous intravenous infusion; i.v: intravenous; NG: nasogastric; PO: per oral; UGI: upper gastrointestinal.

Alhazzani et al (7) in 2013 did a meta-analysis looking at PPIs versus H_2RA for SUP in critically ill patients, they concluded that PPIs are more effective than H_2RA in preventing CSB. The superiority of PPIs as stress ulcer prophylaxis is due to their more profound acid suppression. The pH dependent clot stabilisation prevents ulcer rebleeding (42) .

2.6 Proton Pump Inhibitors

2.6.1 Pharmacology of proton pump inhibitors

PPIs are weak bases which selectively and irreversible inhibit the gastric H/K ATPase, the pKa of these drugs is between 3,8 and 4,9. This enables PPIs to accumulate selectively in the acidic space of the secretory canaliculi of the stimulated parietal cells, where the pH is about 1.0. This results in a concentration at the luminal surface of the pump that is much greater than blood concentration. PPIs are administered as prodrugs, which are converted to their active form by an acid dependent process. The active form of the drug then forms disulphide bonds with the H/K ATPase enzyme. It is the covalent binding with the ATPase that inhibits their activity (29, 42, 43).

The main pharmacokinetic parameters of the commonly used PPIs are compared in the Table 2.2 (42).

Table 2.2 Pharmacokinetics of PPIs

Parameter	Omeprazole	Esomeprazole	Lansoprazole	Pantoprazole	Rabeprazole
t_{max} (h)	1-6	1-3.5	1.2-2.1	2-4	3-5
F (%)	25-40 increase upon multiple dosing	50 (acute dosing) 70-80 (chronic dosing)	80-90	77	52
V (l/kg)	0.13-0.35	0.22-0.26	0.4	0.15	_
CL (ml/min)	400-620	330 acute 160-250 chronic	400-650	90-225	-
Effect of age	CL⇔ $T_{1/2}$↑ F↑	CL⇔ $T_{1/2}$ ⇔	CL↓ $T_{1/2}$ ↑	CL⇔ $T_{1/2}$ ⇔	CL↓ $T_{1/2}$ ↑
Renal insufficiency	CL⇔ $T_{1/2}$ ⇔ F⇔	-	CL⇔ $T_{1/2}$ ↑	CL⇔ $T_{1/2}$ ⇔	CL↑ $T_{1/2}$ ⇔
Hepatic dysfunction	CL↓ $T_{1/2}$ ↑ F↑	CL↓ $T_{1/2}$ ↑	CL↓ $T_{1/2}$ ↑	CL↓ $T_{1/2}$ ↑ F⇔	CL↓ $T_{1/2}$ ↑

T_{max} time to maximal plasma concentration, F oral bioavailability, V apparent volume of distribution, $T_{1/2}$ elimination half-life, ↑ increase, ↓ decrease ⇔ no significant change.

Overall pharmacodynamics and clinical data indicated that rabeprazole could provide the greatest degree of acid suppression among the available PPIs. It also may provide a faster onset toward a maximal antisecretory effect than other drugs of this class. This can be of therapeutic relevance, as clinical outcome depends on extent and duration of secretory inhibition (42). Critically ill patients often have organ dysfunction, which impairs drug metabolism. They are commonly on multiple drugs, which make drug interaction an important consideration. Pantoprazole does not require dose adjustment in patients with renal failure and has low potential for drug interaction making it an ideal SUP for critically ill patients (12).

2.6.2 Uses of proton pump inhibitors

PPIs are used to treat conditions such:

- peptic ulcer disease
- gastroesophageal reflux disease
- non-steroidal anti-inflammatory drug induced gastric lesions
- Zollinger-Ellison syndrome
- dyspepsia.

PPIs are also used as part of eradication therapy for *Helicobacter pylori* with two antibiotics

Also used as first line agent for SUP (10, 42, 44).

2.6.3 Administration of proton pump inhibitors

PPIs can be administered intravenously (IV) or orally (PO). These drugs are very costly and there is a concern over their contribution to total health cost in ICU patients (24). A question has arisen of whether giving PPIs orally is inferior to intravenous administration, and whether this will improve health cost (45).

Javid et al (46) conducted a study in the Sher-i-Kashmir Institute of Medical Science from May 2004-January 2007 comparing the two routes of administration, intravenous versus oral. The aim was to establish if one route was more efficacious than the other in increasing gastric pH. The authors came to the conclusion that high doses of different groups of PPIs given via different routes (intravenous or oral) after successful endoscopic therapy showed an insignificant difference among various PPIs on 72h intragastric pH, thus routes of administration does not influence efficacy.

2.6.4 The benefits of proton pump inhibitors

Stress ulcer related bleeding increases morbidity and mortality, and lengthen the number of days in ICU by four to eight days (6). Endoscopic evidence of mucosal damage is seen in most patients within hours of admission to the ICU.

The prevalence of endoscopic evident mucosal damage is 74-100%, for occult bleeding is 15-50% and for clinically overt bleeding is 5-25% (2, 3, 9). Each episode of CSB results in additional haematological tests, a mean of eleven blood products transfusion resulting in overall increased medical cost (6).

Levy et al (35) conducted a landmark study comparing omeprazole with ranitidine in patients with risk factors for stress ulcer related bleeding. They found significantly more clinically important bleeding in the ranitidine group than in the omeprazole group (31% versus 6%, $p< 0.05$) and concluded that a single oral daily dose of omeprazole was superior in efficacy and safety compared to continuous intravenous infusion of ranitidine.

Acid suppressive therapy prevents rebleeding from stress ulcers by increasing gastric pH and preventing clot instability caused by gastric acid. Over the last two decades the incidence of stress related mucosal bleeding has decreased dramatically, however SUP still remains as one of the corner stones to improving clinical outcome of critically ill patients (1).

2.6.5 Adverse effects of proton pump inhibitors

One of the prominent adverse effects in patients in ICU receiving PPIs is hospital-acquired pneumonia. PPIs reduce gastric acidity, leading to colonisation of the upper gastrointestinal tract. Retrograde contamination and micro aspiration to the lower airways lead to infection of the lungs (47, 48).

In a study by Herzig et al (16) conducted in Boston in 2009. They evaluated the association between acid suppressive therapy and hospital-acquired pneumonia. The authors found that hospital-acquired pneumonia was higher in the group exposed to acid suppressive therapy (4.9%) than in the unexposed group (2%) with a 95% confidence interval of 2.3 - 2.8. They concluded that acid suppressive therapy was associated with a 30% increase in the risk of hospital-acquired pneumonia.

The gastrointestinal tract has many defence mechanisms, such as gastric acidity and an intact gastric mucosa. Decrease in gastric acidity leads to changes in the microbial flora with bacterial overgrowth causing diarrhea (24). Diarrhoea is the most frequent adverse event in the long-term use of PPIs with a reported incidence ranging between 3.7 and 4.1% (49).

Salmonella, Campylobacter and Clostridium difficile are some of the organisms that cause GIT infection associated with the use of PPIs. The risk of infection is increased by 1.46 for Campylobacter and 1.2 for Salmonella in patients on PPIs. The use of PPIs for longer than a month confers a ten-fold risk of developing Campylobacter related infection (28, 49, 50).

Links have been made between PPI use and Clostridium difficile. PPIs increase the incidence of Clostridium difficile associated diarrhoea by two fold (30). The proposed mechanism for the increased risk is that gastric acid suppression allows ingested spore survival in the upper gastrointestinal tract and eventual proliferation in the colon (44, 50). The risk increases with high dose of PPIs and long duration of treatment.

Acid suppression from the PPIs leads to a rise in pH in the small intestine. This impairs calcium absorption, which is greatly enhanced by the presence of hydrochloric acid in normal physiology. This may lead to increased parathyroid hormone levels resulting in accelerated bone resorption and an increased risk of bone fractures (30, 51). Yang et al (52) conducted a nested case control study using the General Practice Research database in the United Kingdom. Authors evaluated an association between PPIs and H_2RA use and the development of hip fractures. The risk of hip fracture was significantly higher in patients on long-term high dose PPIs (>1yr), and it increased with increasing duration of treatment.

Gastric acid is required for the release of cobalamin from dietary proteins, suppression of gastric acid secretion impairs this process thus impairing the absorption of vitamin B12 (49).

There is concern that patients who are on PPIs may develop rebound hypersecretion of gastric acid and hypergastreamia once they discontinue PPI treatment (30).

PPIs are metabolised in the liver via the cytochrome P450 enzyme system. The potential for individual PPIs to influence P450 enzyme activity raised a concern about possible drug-drug interaction. Certain PPIs may slow the hepatic metabolism of certain drugs that are metabolised by the P450 enzyme system. This becomes a concern when the drugs involved have a narrow therapeutic index and marginal increases in plasma concentration may result in serious clinical adverse events (44).

Clopidogrel is a prodrug that is activated in the liver by the same isoenzyme that is responsible for the metabolism of PPIs. There are studies that suggest that the concomitant use of PPIs and clopidogrel may lead to suboptimal therapeutic levels of clopidogrel and therefore suboptimal clinical efficacy (44, 53).

Ho et al (54) conducted a retrospective cohort study across Veterans Affair Hospitals in USA between October 2003-January 2006 on patients taking clopidogrel after discharge post-acute coronary syndrome (ACS). The reported risk of hospitalisation for recurrent ACS was higher (14.6%) in the group taking PPIs plus clopidogrel compared to the group who were taking clopidogrel alone (6.9%).

The COGENT trial (55) was an international study conducted between January 2008-December 2008 that looked at giving clopidogrel with or without omeprazole in coronary artery disease. The primary cardiovascular end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction and revascularisation. The two groups did not differ significantly in the rate of serious adverse events. The trial was terminated prematurely due to lack of funds.

It is of paramount importance for the clinician to appropriately assess the risk of patient to develop stress ulcer in order to avoid the unwanted side effects that compromise quality of life for the patient (2, 24).

2.6.6 Overuse of proton pump inhibitors

In a retrospective study by Farrel et al (4) conducted in Pennsylvania between December 2006-March 2007, they studied all ICU admissions for four months looking at risk factors for stress ulcer bleeding. Results showed that of all the ICU admissions, 87% received stress ulcer prophylaxis and 68% of patients without any risk factors were placed on prophylaxis on ICU admission.

In another study that was done by Nardino et al (14) in Yale Connecticut they looked at patients admitted to a general medicine unit over a period of three months. They evaluated the indications for SUP. In the group that received SUP, 65% had no indications and concluded that there was overuse of SUP.

In the Netherlands, Van Vliet et al (15) conducted a study from October 2004-April 2005 with the aim of determining the indications for PPIs use in two pulmonary medicine wards and to assess whether the use was appropriate. The study found that in 40% of the patients using PPIs on admission, there was no indication for their use, which demonstrated overuse.

Heidelbaugh et al (17) conducted a study in a multi-specialty teaching hospital in Michigan. They looked at all outpatients who had received a prescription for a PPI between February 2006 and January 2007. The authors found that 36% had no indication for PPI therapy. The total cost of inappropriate PPI use was $ 233,994 based on over the counter PPI cost and $ 1,566,252 based on average wholesale price costs in that time period. They concluded that PPIs were overused with a consequence of a substantial burden of cost to health care.

In an observational study conducted by Slattery et al (45) in Dublin, Ireland over a three month period, the authors found that intravenous PPI use in hospital was inappropriate. The cost of standard IV PPI doses is approximately £5 (2007) excluding pharmacy, nursing and infusion costs, compared to oral formulation that ranges from 50p to £1 (2007). This highlights the health cost implications of inappropriately used intravenous PPIs.

2.7 ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis

The University of Arizona under contract of ASHP prepared the ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis. The authors did a detailed literature search on Medline from the period 1966 -1997 and International Pharmaceutical Abstracts (IPA) from 1970-1997. The guidelines that were formulated were categorised according to the strength of the evidence (8).

Aim of the guidelines

These guidelines are for stress ulcer prophylaxis in the acute setting immediately after the onset of the “stressor”, where the stress response is still active. They are not applicable in chronic disease states.

Summary of the recommendations

Indication for prophylaxis:

Adults: prophylaxis is recommended in patients with coagulopathy or patients on mechanical ventilation for more than 48h. Also recommended in patients with more than one of the following sepsis, burns, renal failure, hepatic failure, high dose steroids, anticoagulation therapy, major surgery, spinal cord injury.

Agent of choice

Adults and paediatrics: this should be according to the institution.

Adverse effects

Adults and paediatrics: drugs used for SUP to be avoided in patients with a positive history of severe adverse effects.

Monitoring

Adults and paediatrics: patients on SUP to be monitored for gastrointestinal bleeding and adverse effects.

Prevention of rebleeding

Adults and paediatrics: currently no concrete evidence however increasing the dosage of the prophylactic agent should be considered.

Non-ICU patients

Adults and paediatrics: SUP not recommended in non-ICU patients

Institution-specific guidelines

Adults and paediatric: it is recommended that institutions develop guidelines that are more suited to their resources.

Criticism of the guidelines: they were published in 1999 and certain aspects are outdated. The recommendation of agent of choice being according to institution is outdated. Current literature has demonstrated PPIs as being the superior agent and currently recommended as agent of choice for SUP (Table 2.1). The length of stay in ICU is currently infrequently used in the literature as a minor risk factor and anticoagulants are recognised as a minor risk factor (1, 9).

2.8 Summary

This chapter discussed the physiology of gastric acid secretion, pathophysiology, risk factor, prophylaxis of stress ulcers. The pharmacology of PPIs was also discussed as well as problems surrounding the appropriate and inappropriate use of PPIs. The next chapter will discuss the research methodology of this study.

CHAPTER THREE
RESEARCH METHODOLOGY

3.1 Introduction

In this chapter the problem statement, aim and objectives, ethical considerations, research methodology and the validity and reliability of this study are discussed.

3.2 Problem statement

It is well documented that patients in ICU are at an increased risk of developing stress ulcers (4). PPIs are regarded as the drug of choice for prophylaxis (10), and overuse of these drugs has serious medical implications such as drug-drug interactions (42), adverse effects like hospital acquired pneumonia (16) and has financial implications (17).

There are guidelines in terms of risk stratification as to which patient should be put on prophylaxis for stress ulcers (8). Despite good intentions, there is often a gap between evidenced based guidelines and actual clinical practice (18). The use of PPIs is one area where such a gap exists. It has been shown internationally that prophylaxis for stress ulcers is still overused in ICU (4). Nardino et al (14) showed that up to 65% of patients receive stress ulcer prophylaxis without any risk factors in the general medical unit. It is not known whether PPIs are overused in the ICUs of South African hospitals, specifically Chris Hani Baragwanath Academic Hospital (CHBAH), Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Helen Joseph Hospital (HJH).

3.3 Aim and objectives of the study

3.3.1 Aim

The aim of this study was to describe the use of PPIs in ICU patients at CHBAH, CMJAH and HJH over a three-month period.

3.3.2 Objectives

The objectives of this study were to:

- describe the use of SUP in the ICUs
- describe the risk factors that necessitate the initiation of SUP
- describe the SUP received by patients with no risk factors
- describe the risk factors in those patients inappropriately not on SUP
- describe the appropriate use of PPIs in ICU versus the inappropriate use according to the risk factors of the patient as per ASHP guidelines.

3.4. Ethical considerations

Ethical approval was obtained from the Human Research Ethics Committee (Medical) and the Post-Graduate Committee of the University of the Witwatersrand (Wits) (Appendix 1&2).

Once these requirements were fulfilled, consent to perform the study was attained from the Chief Executive Officer of CHBAH, CMJAH, HJH (Appendix 3,4&5) and consent was obtained from the respective ICU directors (Appendix 6&7).

The data collection sheet (Appendix 8) did not reflect patients' name or hospital numbers. The researcher kept a separate list of patients' names in order to link them to participant number should it be necessary. Only the researcher was privy to the names of the patients, this ensured confidentiality, privacy and anonymity of patients' information. Data will be stored securely for a period of six years following completion of the study.

Due to the retrospective nature of the study the researcher was not able to intervene where there was inappropriate treatment according to the ASHP guidelines. The researcher abided by the principles of the Declaration of Helsinki (21) and the South African Good Clinical Practice Guidelines (22).

3.5. Research methodology

3.5.1 Research design

A retrospective, descriptive, contextual study design was used.

A retrospective study uses existing data that has been recorded for purposes other than research (56). This study was retrospective in nature as it involved the analysis of recorded data from patients' ICU charts.

A descriptive study aims to describe a situation or identify problems through observation, description or classification, without manipulating variables (57). This study is descriptive in nature as it described the use of PPIs in ICU as appropriate or inappropriate according to ASHP guidelines on stress ulcer prophylaxis.

A contextual study is one that takes place in a specific location (58). This study is contextual, as it was conducted in the ICU's of specific hospitals.

3.5.2 Study population

The ICU charts of all adult patients admitted to CHBAH, CMJAH and HJH ICUs during the study period formed the population group studied.

3.5.3 Study sample

Sample size

The number of patients admitted into the ICUs over a three-month period determined the sample size.

Sampling method

Convenience, consecutive sampling of ICU charts was used. Convenience sampling involves the choice of readily available subjects or objects for the study (58). Consecutive sampling entails utilising every available individual or event within an accessible population (59).

3.5.4 Inclusion and exclusion criteria

Inclusion criteria

All complete and legible ICU charts of adult patients admitted to ICU in CHBAH, CMJAH and HJH during the study period.

Exclusion criteria

The ICU charts of patients with the following were excluded:

- existing upper gastrointestinal bleeding
- previous total gastrectomy
- died or discharged 24 hours after admission
- on PPIs prior to admission.

3.5.5 Data collection

A data collection sheet (Appendix 8) was used to collect data from ICU charts of patients admitted into ICU during the study period.
The data collection sheet was used to capture the following data:

- Age
- Gender
- Admission diagnosis
- Major risk factors:
- Mechanical ventilation longer than 48h
- Coagulopathy
- Minor risk factors:
- Sepsis
- Burns
- Renal failure
- Hepatic failure
- High dose glucocorticoids
- Heparin
- Warfarin
- Major surgery
- Spinal cord injury.

Stress ulcer prophylaxis received in ICU:

- Drug name
- Dose
- Route of administration
- Duration of prophylaxis
- Method of administration (infusion or bolus)
- Introduction of feeds (after how many days of starvation).

The researcher collected the data personally and the data were entered into a Microsoft Excel® spreadsheet. Data were collected from ICU charts dated from 1st August up to and including 31st October 2013.

3.5.6 Data analysis

Patients were categorised into the following groups:

- one or more major risk factors present
- two or more minor risk factors present
- no major or minor risk factors present
- patients not on PPIs but meet the criteria for SUP
- patients who received PPIs for SUP
- patients who received other drugs for SUP
- appropriate versus inappropriate use of PPIs
- overuse of SUP.

Patient demographics were described using descriptive statistics: mean and standard deviation where the distribution was normal, median and interquartile range, where the distribution was not normal.

3.6 Validity and reliability of the study

Validity is the extent to which the instrument actually reflects or measures what it is supposed to measure (57). Reliability is concerned with how consistently the measurement technique measures a variable or concept (57).

Validity and reliability were maintained by the following:

- the data were collected from patients' records by a single researcher
- standardised data collection sheet was used
- the risk factors that were used in the study were clearly defined
- appropriate study design was used
- data analysis was done in consultation with a biostatistician.

3.7 Summary

In this chapter the problem statement, aim and objectives, ethical considerations, research methodology and the validity and reliability of this study were discussed. Discussion of the research methodology included the research design, study population, study sample, data collection and data analysis. In the next chapter, results of the study as per objectives are presented and discussed.

CHAPTER FOUR
RESULTS AND DISCUSSION

4.1 Introduction

This chapter presents the results of the study and the discussion thereof according to the objectives.
The objectives of this study were to:

- describe the use of SUP in the ICUs
- describe the risk factors that necessitate the initiation of SUP
- describe the SUP received by patients with no risk factors
- describe the risk factors in those patients inappropriately not on SUP
- describe the appropriate use of PPIs in ICU versus the inappropriate use according to the risk factors of the patient as per ASHP guidelines.

4.2 Sample realisation

A total of 174 patients were included in the study. Of the 174 patients in this study, 156 were on SUP and 18 patients who should have been on SUP according to the guidelines were not.

4.3 Results

The numbers in percentages were rounded off to one decimal place so they may not add up to 100%. The data was collected from ICU charts dated from 1 August up to and including 31 October 2013 across three ICUs.

4.3.1 Demographic data

Of the 174 patients, 49% (85) were male and 51% (89) were female. The minimum age was 18 years and maximum 88 years and the average age was 44 years (SD17.6). The patients came from nine disciplines as shown in Table 4.1.

Table 4.1 Disciplines patients were referred from

Discipline	Number	Percentage
General surgery	46	26.4
Trauma	29	16.7
O&G	15	8.6
Orthopaedic	7	4.0
Vascular surgery	6	3.4
Internal medicine	60	34.5
Urology	2	1.1
Neuro surgery	3	1.7
ENT	6	3.4
Total	**174**	**99.8**

The minimum duration on SUP was one day and maximum was 23 days. The minimum starvation period was one day and the maximum was five days. The starvation period of the patients on SUP is presented in Table 4.2.

Table 4.2 Starvation periods of the patients on SUP

Period of starvation	Number	Percentage
0 day	36	23.1
1 day	78	50
2 days	21	13.5
3 days	16	10.3
4 days	3	1.9
5 days	2	1.3
Total	**156**	**100**

4.3.2 Objective: describe the use of SUP in the ICU

Of the 174 patients included in the study 156 were on SUP and 18 who should have received SUP according to the ASHP guidelines and were not on SUP. Table 4.3 shows SUP practice in the ICUs.

Table 4.3 SUP practice in the ICUs

Type of SUP	Number	Percentage
PPIs	49	31.4
H_2RA	80	51.3
Sucralfate	27	17.3
Total	**156**	**100**

Of the 156 patients that were on SUP, 59.6% (93) received SUP intravenously and 40.4% (63) orally. This data is represented in Table 4.4

Table 4.4 Route of administration of SUP

Route	Number	Percentage
Oral	63	40.4
Intravenous	93	59.6
Total	**156**	**100**

Of the 93 patients that received their SUP intravenously, 81,8% (76) received intravenous bolus doses and 18.2% (17) received an infusion.

4.3.3 Objective: describe the risk factors that necessitate the initiation of SUP

Of the 156 patients on SUP, 60.9% (95) were appropriately prescribed SUP and 39.1% (61) were receiving SUP inappropriately according to the ASHP guidelines. Of these 95 patients, 41 had either 1 or both major risk factors only (i.e. no minor risk factors) that initiated the prescribing of SUPs. This is shown in Table 4.5

Table 4.5 Major risk factors only as an indication for SUP

Major risk factor	Number	Percentage
Mechanical ventilation	39	95.1
Coagulopathy	1	2.4
Both	1	2.4
Total	**41**	**100**

Forty three (45.3%) of the 95 patients appropriately prescribed SUP according to the ASHP guidelines had 1 major risk factor and ≥ 1 minor risk factors. This is shown in Table 4.6

Table 4.6 Major and minor risk factors as an indication for SUP

Major and minor risk factors	Number	Percentage
Mechanical ventilation and 1 minor risk factor	31	72.1
Mechanical ventilation and 2 minor risk factors	6	14.0
Mechanical ventilation and 3 minor risk factors	5	11.6
Coagulopathy and 1 minor risk factor	1	2.3
Total	**43**	**100**

Ten (10.5%) of the 95 patients appropriately prescribed SUP according to the ASHP guidelines had both major risk factors and ≥ 1 minor risk factors. This is shown in Table 4.7

Table 4.7 Both major and minor risk factors as an indication for SUP

Major and minor risk factors	Number	Percentage
Both major and 1 minor risk factor	6	60
Both major and 2 minor risk factors	2	20
Both major and 3 minor risk factors	2	20
Total	**10**	**100**

One (1.1%) patient of the 95 on SUP had 3 minor risk factors that necessitated initiation of SUP and no major risk factors.

The SUP received by the 95 patients that were appropriately on SUP is presented in Table 4.8.

Table 4.8 SUP received by patients with risk factors

Type of SUP	Number	Percentage
PPIs	32	33.7
H_2RA	42	44.2
Sucralfate	21	22.1
Total	**95**	**100**

4.3.4 Objective: describe the SUP received by patients with no risk factors

Of the 156 patients on SUP, 39.1% (61) had no risk factors that required the initiation of SUP. The SUP received by these patients is shown in Table 4.9

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Table 4.9 SUP received by patients with no risk factors

Type of SUP	Number	Percentage
PPIs	17	27.9
H_2RA	38	62,3
Sucralfate	6	9.8
Total	**61**	**100**

4.3.5 Objective: describe the risk factors in those patients inappropriately not on SUP

Eighteen patients with risk factors that qualified them for SUP according to the ASHP guidelines were not receiving any prophylaxis. The risk factors of these 18 patients are shown in Table 4.10

Table 4.10 Risk factors of patients inappropriately not receiving SUP

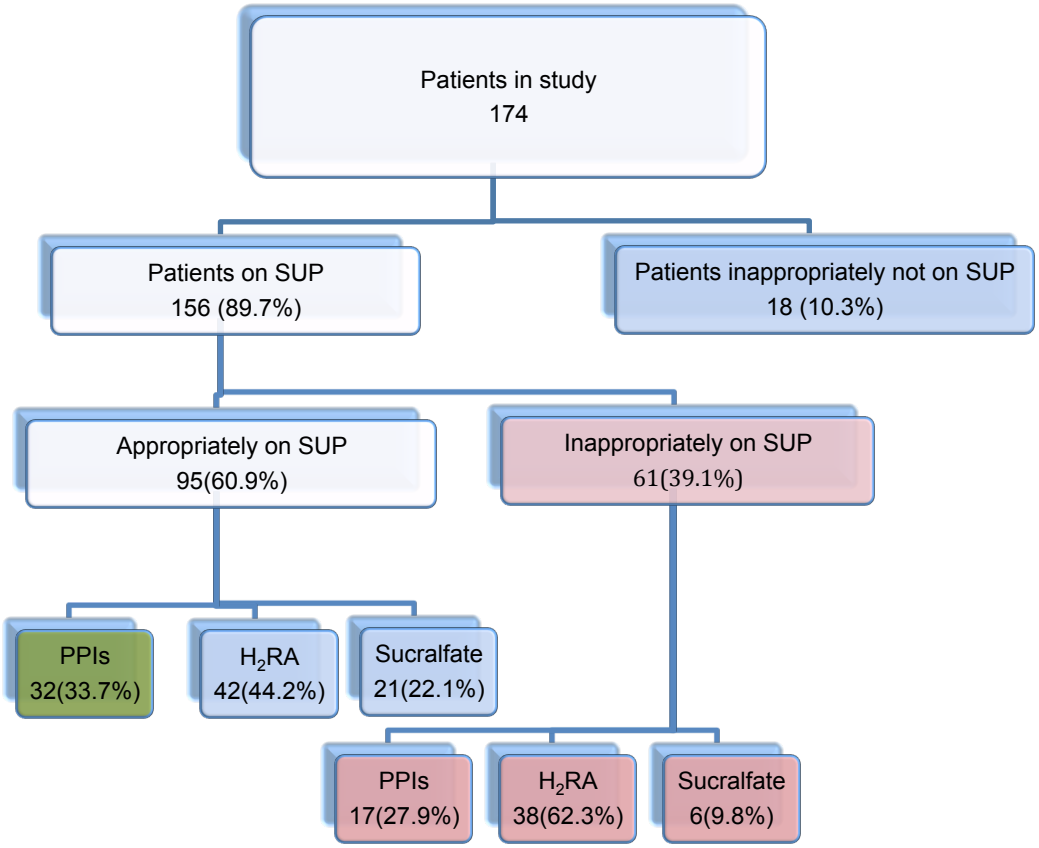
Risk factor(s)	Number	Percentage
Both major plus minor risk factors	2	11.1
0ne major plus minor risk factors	7	38.9
Major risk factors only	7	38.9
Minor risk factors only	2	11.1
Total	**18**	**100**

4.3.6 Objective: describe the appropriate use of PPIs in ICU versus the inappropriate use according to the risk factors of the patient

Of the 156 patients on SUP, 60.9% (95) with a 95% CI of 53.1-68.2% were appropriately on SUP and 39.1% (61), 95%CI of 31.8-46.9% were inappropriately on SUP. Of the 95 patients that were appropriately on SUP, 33.7% (32) were appropriately on PPIs and 66.3% (63) who should have been on PPIs were on other SUP agents. Of those patients who were inappropriately on SUP, 27,9% was on PPIs and 72.1% were on other agents as first line for SUP.

There were 18 patients who according to the ASHP guidelines had risk factors that qualified them for SUP but were inappropriately not on SUP. This SUP should have been PPIs.

Of the 174 patients included in the study, 64.9% (113) qualified for SUP according to the ASHP guidelines (i.e. the 95 who were appropriately on SUP and the 18 who should have been on SUP) and should have been on PPIs. Only 28.3%(32), 95% CI of 20.8-37.3% were on PPIs, leaving 71.7% (81), 95%CI of 64.3-78.1% inappropriately not on PPIs. This is illustrated in Figure 4.1



Key

Inappropriately not on PPIs

Appropriately on PPIs

Inappropriately on SUP

Figure 4.1 The appropriate versus the inappropriate use of proton pump inhibitor

Figure 4.1 shows an underuse of PPIs of 71.7% (81of 113), 95% CI of 64.3-78.1% and only 28.3% (32), 95% CI of 20.8-37.3% appropriate use.

4.4 Discussion

Stress ulcers in critically ill patients increase morbidity and mortality (9). The adoption of SUP as part of patient care in the ICU has led to the significant decline in the incidence of CSB over the years from 5.3 to 33% in the 1970's to < 5% in the 2010's (1) . The literature shows that PPIs have a superior efficacy in preventing CSB compared to the other agents (7, 32). Levy et al (35) compared omeprazole and ranitidine and the results of his study showed significantly more CSB in the ranitidine group. A meta-analysis by Alhazzani et al (7) also concluded that there is less CSB when PPIs are used as compared to H_2RAs. This body of evidence led to the use of PPIs as first line agents for SUP, which later on brought about the concern of inappropriate overuse of PPIs (33).

In our study a total of 39.1% of patients on SUP had no indication for SUP according to the ASHP guidelines reflecting overuse of SUP. The significance of this lies in the cost incurred (2, 13) and the unnecessary exposure of critically ill patients to side effects of the drugs used for SUP (16, 50). This is in keeping with a study conducted by Van Vliet et al (15) where they found an overuse of SUP of 40%. Other studies had significantly higher incidence of overuse, Farrell et al (4) had 68% overuse, Zeitoun et al (60) found 67% overuse and Mohebbi et al (33) found 66% overuse.

Analysis of prescription practice in the patients that were on SUP yielded the following: H_2RA were the most commonly used at 51.3%, followed by PPIs at 31,4% and sucralfate at 17.3%. Nardino et al (14) had 62% H_2RA, 33% PPI and 5% sucralfate. Zeitoun et al (60) found 61.6% PPIs, 38.4% H_2RA and non on sucralfate. Compared to other studies we had a higher use of sucralfate. There are several factors that influence the choice of drug used for SUP, such as cost, efficacy, side effect profile, availability and hospital practice. A meta-analysis done by Barkun et al (32) showed that PPIs are the superior agent for SUP. In our study only the use of PPIs as SUP was deemed as appropriate practice, and the use of any other drug was deemed as inappropriate (11, 12, 23, 35).

Of the 113 patients that qualified for SUP only 28.3% were on PPIs showing underuse of 71.7% (81). PPIs when used appropriately in patients at high risk of developing SRMD are cost effective compared to H_2RA as shown by Barkun (23). In their study where they were assessing the cost-effectiveness of SUP using either PPIs or H_2RA, they found PPIs to be more cost effective taking into consideration the risk of VAP and number of days in ICU. Schupp et al (61) came to the same conclusion in their study. However Mac Laren and

Campbell (62) have different conclusion to the ones above, their cost effectiveness analysis suggest that H_2RA reduce cost with comparable clinical outcomes to PPIs and recommend prospective study to validate their finding.

Most patients received medication intravenously (59.6%) compared to the oral route (40.4%). Alsultan et al (63) showed 19% inappropriate intravenous PPI use in ICU and 90.4% inappropriate intravenous PPI use in non-ICU patients. Zeitoun et al (60) found 71.6% of the patients on intravenous treatment could have tolerated oral medication. Literature shows that intravenous administration of PPIs has the same clinical outcome as the oral route (45, 46). The oral route must be utilised whenever possible as it has the added advantage of decreasing cost (45) and achieving the same clinical outcome.

The maximal number of days that a patient was on SUP was 23. The risk of developing SUP associated GIT infection and hospital acquired pneumonia is proportional to the duration of SUP (16, 64). SUP must therefore be discontinued upon resolution of risk factors (24, 30). Fohl and Regal (48) site the dose as well as duration of treatment as risk factors for developing pneumonia specifically when PPIs were used as SUP. In our study the duration of treatment was assessed while the patients were in ICU and not assessed upon discharge. In the literature generally authors commented on the number of patients discharged to the general ward on SUP inappropriately but not the number of days on SUP while in ICU. The common trend was that a high number of patients were discharged to the ward inappropriately on SUP ((4, 60, 63).
In our study the most common practice was early feeding. The longest starvation period was five days. Feeding has the advantage of maintaining gut integrity and confers mucosal protection (1, 24, 30). At the same time feeding mechanically ventilated patients is associated with the risk of VAP (65, 66). These are some of the factors that have to be considered when choosing a SUP agent. Giving protection against SRMD without increasing the risk of VAP in these patients is one of the corner stones of SUP management (67). Although the risk of VAP when using PPIs is equal to that of H_2RA, PPIs give more protection against CSB and are the agent of choice (7, 33).

In 39.1% SUP was used inappropriately and only a small number (27.9%) of those patients were on PPIs. Other agents were inappropriately used as first line agents for SUP. Of the 95 patients on SUP only 33.7% were on PPIs and 66.3% were on other agents.

There was a small group of patients (10.3%) who had risk factors that qualified them for SUP but did not receive any SUP. This group of patients had a high risk of developing CSB, which can be reduced by 50% with the use of SUP (9). Van Vliet (15) in his study had 6% of patients not on SUP even though they should have been. This was far less compared to our results. Most studies did not comment on underuse of SUP.

4.5 Summary

In this chapter the results of the study as defined by the objectives were presented followed by a discussion of the results. In the following chapter, the summary, limitations, recommendations and conclusion of this study will be presented.

CHAPTER FIVE
SUMMARY, LIMITATIONS, RECOMMENDATIONS AND CONCLUSION

5.1 Introduction

In this chapter the summary of the study, main findings and research methodology of this study will be presented. The limitations will be explored, recommendations will be made and a conclusion presented.

5.2 Summary of the study

5.2.1 Aim

The aim of this study was to describe the use of PPIs in ICU patients at CHBAH, CMJAH and HJH over a three-month period.

5.2.2 Objectives

The objectives of this study were to:

- describe the use of SUP in the ICUs
- describe the risk factors that necessitate the initiation of SUP
- describe the SUP received by patients with no risk factors
- describe the risk factors in those patients inappropriately not on SUP
- describe the appropriate use of PPIs in ICU versus the inappropriate use according to the risk factors of the patient as per ASHP guidelines.

5.2.3 Methodology

A retrospective, descriptive, contextual study design was used. The ICU charts of adult patients admitted to CHBAH, CMJAH and HJH ICUs that fulfilled the inclusion and exclusion criteria from August to October 2013 were included in the study.

A data collection sheet (Appendix 8) was used to collect data from ICU charts of patients admitted into ICU during the study period. Data were entered into a Microsoft excel spreadsheet and analysed in consultation with a biostatistician using STATA 12.5.

5.2.4 Main findings

A total of 174 patients were included in the study. Of these patients 156 were on SUP, 60.9% of them were appropriately started on SUP and 39.1% were inappropriately on SUP indicating overuse. Of the 156 patients on SUP, 51.3% were on H_2RA, 31.4% were on PPIs and 17.3% were on sucralfate. The number of patients that actually qualified for SUP was 113. In that group of patients only 28.7% were on PPIs and the remainder of the patients 71.7% were either on other agents as first line or were not on any SUP, reflecting an underuse of PPIs.

5.3 Limitations

This was a retrospective study looking at patient's charts, which meant that the data obtained depended on the accuracy of the medical record keeping.

The route of administration of SUP was delineated to oral or intravenous but the intravenous route was not further analysed to determine if it was appropriate or the patient could have tolerated oral SUP. It was not part of the scope of our study. This is important as it has impact on cost.

The univariate/multivariate analysis would have been useful to determine which risk factors prompted clinicians to start SUP, but the study was not powered for this.

The practice of discontinuation of SUP was not assessed in this study, follow up on continued SUP use in the general ward was beyond the scope of this study.
This study was contextually done in the CHDAH, CMJAH and HJH therefore the results may not be generilisable to other ICUs.

5.4 Recommendations

5.4.1 Clinical practice

- Conducting a survey in the form of a questionnaire to determine the level of knowledge and then addressing the deficiency of knowledge where applicable
- Having a set of printed guidelines distributed among new members of the ICU might add to their knowledge.

5.4.2 Further research

- A study looking into how medical personnel choose the drugs used as SUP, what informs their decision and the role played by cost and availability of PPIs as contributing factor to the underuse
- A study analysing the various practices in these ICUs can add value by identifying substandard practice and improving practice where it is applicable.

5.5 Conclusion

Our study found inappropriate overuse of SUP according to the ASHP guidelines, however there were patients who qualified for SUP but were not on SUP. In the group of patients that were appropriately on SUP, a large number of them were on other agents and not PPIs even though it is the drug of choice.

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APPENDIX 1

M130104

R14/49 Dr Ntombiyethu Biyase

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M130104

NAME: (Principal Investigator)	Dr Ntombiyethu Biyase
DEPARTMENT:	Department of Anaethesiology CM Johannesburg Academic Hospital
PROJECT TITLE:	The Use of Proton Pump Inhibitors in Selected Public Hospital Intensive Care Units in Johannesburg
DATE CONSIDERED:	25/01/2013
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Mrs Helen Perrie
APPROVED BY:	Professor PE Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 05/06/2013

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX 2

Faculty of Health Sciences
Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172040

Reference: Ms Thokozile Nhlapo
E-mail: thokozile.nhlapo@wits.ac.za

07 January 2014
Person No: 700950
PAG

Dr NG Biyase
Postnet Suite 125
Private Bag X121
Halfway Gardens
1685
South Africa

Dear Dr Biyase

Master of Medicine: Approval of Title

We have pleasure in advising that your proposal entitled *The use of proton pump inhibitors in selected public hospital intensive care units in Johannesburg* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

APPENDIX 3

health and social development
Department: Health and Social Development
GAUTENG PROVINCE

PERMISION FOR RESEARCH

DATE: 17/01/2014

NAME OF RESEARCH WORKER: DR. N.G. BIYASE

CONTACT DETAILS OF RESEARCH (INCLUDE ALTERNATE RESEARCHER):

Email Nana.biyase@yahoo.com.

Contact NO 082 304 7627.

TITLE OF RESEARCH PROJECT THE USE OF PROTON PUMP INHIBITORS IN SELECTED PUBLIC HOSPITAL INTENSIVE CARE UNIT

OBJECTIVES OF STUDY (Briefly or include a protocol):

Protocol included.

METHODOLOGY (Briefly or include a protocol):

protocol included.

THE APPROVAL BY THE SUPERINTENDENT IS STRICTLY ON THE BASIS OF THE FOLLOWING:

(i) CONFIDENTIALITY OF PATIENTS MAINTAINED: Yes

(ii) NO COSTS TO THE HOSPITAL: Yes

(iii) APPROVAL OF HEAD OF DEPARTMENT: Yes

(iv) APPROVAL BY ETHICS COMMITTEE OF UNIVERSITY: Yes.

SUPERINTENDENT PERMISION

Signature: [signature] Date: 24/01/2014

SUBJECT TO ANY RESTRICTIONS: NO COST TO HELEN JOSEPH HOSPITAL

Helen Joseph Hospital
Perth Road
Tel: 011 489 1011

Private Bag X47
Auckland Park
2006

APPENDIX 4

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries: Mrs. L. Mapaisa
Office of the Director: Clinical Services
Tel: (011)488-3365
Fax: (011)488-3753
24 November 2014

Dr. Ntombi Biyase
Anaesthesia Registrar
Department of Anaesthesiology
University of the Witwatersrand

Dear Dr. Biyase

RE: The use of proton pump inhibitors in selected public hospital intensive care units in Johannesburg

Permission is granted for you to conduct the above recruitment activities as described in your request provided:

1. Charlotte Maxeke Johannesburg Academic hospital will not in anyway incur or inherit costs as a result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall be observed at all times.
4. Informed consent shall be solicited from patients participating in your study.

Please liaise with the Head of Department and Unit Manager or Sister in Charge to agree on the dates and time that would suit all parties.

Kindly forward this office with the results of your study on completion of the research.

Supported / ~~not supported~~

Dr. M.I. Mofokeng
Director: Clinical Services
DATE: 27/11/2014

Approved / not approved

Ms. G. Bogoshi
Chief Executive Officer
DATE: 28/11/2014

APPENDIX 5

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE
CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 02 April 2014

TITLE OF PROJECT: The use of proton pump inhibitors in selected public hospital intensive care units in Johannesburg

UNIVERSITY: Witwatersrand

Principal Investigator: N Biyase

Department: Anaesthetics

Supervisor (If relevant): H Perrie

Permission Head Department (where research conducted): Yes

Date of start of proposed study: April 2014
Date of completion of data collection: December 2015

he Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Hospital. The CEO /management of Chris Hani Baragwanath Hospital is accordingly informed and the study is subject to:-

- Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.
- the Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- the MAC will be informed of any serious adverse events as soon as they occur
- permission is granted for the duration of the Ethics Committee approval.

.....
Recommended
(On behalf of the MAC)
Date: 02 April 2014

.....
Approved/Not Approved
Hospital Management
Date: 08/04/14

DEPARTMENT OF HEALTH

APPENDIX 6

CHARLOTTE MAXEKE
JOHANNESBURG ACADEMIC
HOSPITAL

12/11/2014

Re: MMed data collection- Dr Ntombi Biyase

Permission is hereby granted to Dr Ntombi Biyase an anaesthesia registrar to collect data from ICU files to complete her MMed.

I have received a copy of her ethics approval and protocol.

Yours sincerely,



GA Richards

MBBCh PhD FCP (SA) FRCP FCCP

Academic Head Division of Critical Care University of the Witwatersrand

Director Critical Care Charlotte Maxeke Johannesburg Academic Hospital and

Associate Professor and Chief Physician Departments Medicine and Pulmonology

University of the Witwatersrand.

APPENDIX 7



health and
social development
Department: Health and Social Development
GAUTENG PROVINCE



CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL
Intensive Care unit

Dr JM Brown
Jacqui.Brown@wits.ac.za
Tel: 0119381596
Fax:0119381595

Re: MMED data collection – Dr Ntombi Biyase

Permission is hereby granted to Dr Ntombi Biyase an anaesthesia registrar to collect data from ICU files to complete her MMED.
The files may not leave the ICU offices, but she can us the conference room to go through the records.
A copy of her ethics approval and protocol has been received by us.

Regards

Dr J.M.Brown
Deputy Director
Intensive Care Unit
Chris Hani Baragwanath Hospital

APPENDIX 8

Demographics		
Age		
Gender		
Admission diagnosis		
Risk factors		
Major		
Mechanical ventilation more than 48 hours		
Coagulopathy		
Minor		
Sepsis		
Burns		
Renal failure		
Hepatic failure		
Use of high dose steroid more than 250 mg/day		
Heparin		
Warfarin		
Major surgery		
Spinal chord injury		
Stress ulcer prophylaxis		
Drug		
Dose		
Route of administration		
Mode of administration (infusion/bolus)		
Introduction of feeds (days of starvation)		