UNIVERSITY OF NAIROBI

SCHOOL OF PHARMACY

THE USE AND IMPACT OF ANTIMICROBIAL PROPHYLAXIS IN NEUROSURGERY AT KENYATTA NATIONAL HOSPITAL, AND THE ECONOMIC IMPACT OF TREATMENT OF NEUROSURGICAL SITE INFECTIONS.

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U80/95607/2014

A thesis submitted in partial fulfilment of the requirements for the Degree of Doctor of Philosophy in Clinical Pharmacy of the University of Nairobi.

NOVEMBER, 2016

Declaration

This thesis is my original work and has not been submitted to any other university for a degree award.

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Dedication

To the Almighty God who enabled me to start, perfect and complete this good work (Philippians 1:6).

To my father, The Late Walter Raleigh Opanga, for being the best dad, believing in me and always encouraging me to achieve the highest degree of excellence while he was alive.

Acknowledgements

I would like to thank The Almighty God who has been with me every step of the way, guiding me and equipping me with the wisdom I needed to start and complete this thesis. I acknowledge my supervisors for guiding me from the start of the thesis to the end. I acknowledge the Gandhi Smarak Nidhi Fund for providing me a partial scholarship that enabled me to carry out the research. Finally, I would like to thank my best friend Gabriella Ligami for constantly encouraging me and praying with me when I was discouraged and things were not moving forward.

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List of Acronyms

AIC	**Antimicrobial impregnated shunt catheters**
AIC	Akaike information criterion
AIIMS	All India Institute of Medical Sciences
ASA	American Society of Anaesthesiologists
ASHP	American Society for Health System Pharmacists
ATC	Anatomic Therapeutic Chemical
BGA	Blood gas analysis
CDC	Centres for disease control
CDSR	Cochrane database of systematic reviews
CENTRAL	Central register for controlled trials
CI	Confidence interval
CNS	Central nervous system
COI	Cost of illness
CSF	Cerebrospinal fluid
CT	Computed tomography
DALY	Disability adjusted life years
DDD	Defined daily dose
EMBASE	Excerpta medica database

FBC	Full blood count
GCP	Good clinical practice
GCS	Glasgow coma score
GDT	Guideline development tool
GRADE	Grading of recommendations, assessment, development and evaluation
GXM	Group cross-matching
HIV/AIDS	Human immunodeficiency virus/ acquired immunodeficiency syndrome
ICU	Intensive care unit
IQR	Interquartile range
KES	Kenya Shilling
KNH	Kenyatta National Hospital
MEDLINE	Medical Literature Analysis and Retrieval System
MeSH	Medical subject headings
M-H	Mantel- Haenszel
MRI	Magnetic resonance imaging
MRSA	Methicillin Resistant *Staphylococcus aureus*
NHIF	National Hospital Insurance fund
NHSN	National healthcare safety network
NICU	Neuro-intensive care unit

NNIS	National nosocomial infections surveillance
ODK	Open Data Kenya
OIS	Optimal information size
OR	Odds ratio
PI	Principal investigator
PICO	Population, Intervention, Comparator, Outcome
PNS	Peripheral nervous system
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta- Analyses
QALY	Quality adjusted life years
RMB	Renminbi (Chinese currency)
RCT	Randomised controlled trial
RevMan	Review manager
RTA	Road traffic accident
RR	Risk ratio
Sd	Standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
SSI	Surgical site infection
STATA	Statistics and data analysis software
TEO	Tetracycline eye ointment

UEC	Urea, electrolyte, creatinine
USA	United States of America
USD	United States of America dollar
WHO	World Health Organisation

Definition of Terms

Craniectomy is a neurosurgical procedure that involves removal of part of the skull without replacement of the bone.

Craniotomy is the surgical removal of a section of bone from the skull, with subsequent replacement of the bone.

Direct non- medical costs refer to costs incurred for non-health-care related activities such as transport to the hospital and household expenditure incurred during the illness period.

Discectomy refers to surgical removal of herniated disc material that presses on a nerve root.

Indirect costs refer to productivity losses due to the illness and its associated morbidity and mortality.

Intangible costs refer to pain, debilitation and suffering associated with disease.

Transsphenoidal surgery is surgery performed by entry through the sphenoid bone.

Ventriculitis is the inflammation of the ventricles in the brain.

Ventriculoartrial shunting refers to the drainage of cerebrospinal fluid from the ventricular system into the right atrium

Ventriculoperitoneal shunting is the drainage of cerebrospinal fluid from the ventricular system into the peritoneal cavity.

Abstract

Background

Neurosurgical site infections are associated with high morbidity and mortality and increased hospitalisation costs. There is paucity of data on the incidence, impact and cost of neurosurgical site infections among trauma patients with contaminated to dirty wounds in East Africa. There are no systematic reviews and meta-analyses evaluating antimicrobial prophylaxis in neurosurgery in the region.

Objectives

The objectives of the study were to generate and appraise quality of evidence for antimicrobial prophylaxis, measure the prevalence and incidence of surgical site infections among trauma patients and identify independent patient and surgical risk factors for development of surgical site infection. The study also set out to evaluate the effectiveness of antimicrobial prophylaxis, identify the patterns of antimicrobial use and medication errors and evaluated the cost of treating neurosurgical site infections.

Methods

The study was conducted between September 2013 and January 2016 at the Kenyatta National Hospital Neurosurgical unit. Adult neuro-trauma patients with contaminated to dirty wounds were recruited. A systematic review and meta-analysis were carried out to evaluate the quality of evidence for antimicrobial prophylaxis. A cross sectional study was conducted to identify patient and procedure related risk factors for infection. A cohort study was conducted to determine the incidence of surgical site infections, efficacy of antimicrobial prophylaxis and patterns of

antibiotic use. A cost of illness study was carried out to determine the impact of surgical site infections on patient expenditure. Descriptive and inferential data analysis was done using STATA version 13 software. Approval to carry out the study was obtained from the Kenyatta National Hospital- University of Nairobi Research and Ethics Committee.

Results

Moderate quality evidence supported the use of systemic antimicrobial prophylaxis. For the cross sectional study, the prevalence of surgical site infections was high, at 21%. The commonest causes of trauma were assault (40%) and road traffic accidents (34%). There was a statistically significant association between the cause of trauma and development of infection (p=0.004). The independent risk factor for development of surgical site infections was trauma due to assault (OR 0.27; 95% CI 0.07, 1.02) and this was statistically significant (p=0.054).

From the cohort study, craniotomy was the most common surgical procedure performed (56.5%, n=39). Only 26.1% (n=18) patients received antibiotics for prophylaxis, with ceftriaxone being the most commonly used (78%, n=14). The incidence of surgical site infection was 37.7% (n=26). Presence of an epidural haematoma was an independent risk factor for development of infection (OR 7.368, 95% CI 1.396, 38.894). Craniotomy and evacuation of haematoma procedures, when done on the same patient, were protective for patients with epidural haematomas. Following effect measure modification, antimicrobial prophylaxis was only effective in patients who had undergone both craniotomy and evacuation of haematomas (OR 0.50, 95% CI 0.18, 1.38). Unexpectedly, the effectiveness of prophylaxis also increased with an

increase in the number of surgical procedures and the duration of surgical procedures for those who underwent craniotomy.

Several medication errors were noted: overdoses, unspecified dose, route and frequency of administration for all antibiotics, prolonged duration of antibiotic use, inappropriate choice and combinations of antibiotics, inappropriate doses, and an unclear distinction between prophylaxis and treatment of infection. The total expenditure on all health commodities was higher in patients with infection than those without infection. The key cost drivers were expenditures on meropenem, phenytoin, urea, electrolyte and creatinine tests and CT scans.

Conclusion

Systemic antimicrobial prophylaxis is effective in preventing neurosurgical site infections. Use of antimicrobial impregnated shunts is too expensive. The incidence of infection among trauma patients with contaminated to dirty wounds is high. Antimicrobial prophylaxis effectiveness increases when craniotomy and evacuation of haematomas are done on the same patient. Irrational antibiotic use has no impact on the rates of surgical site infection. Neurosurgical site infections increase treatment costs of neurosurgical trauma patients.

CHAPTER 1: INTRODUCTION

1.1 Neurosurgery

Neurosurgery is a branch of surgery that is involved in the surgical management of diseases and neurological conditions of the central nervous system (CNS) and peripheral nervous system (PNS). It involves the management of conditions that affect the brain, spinal cord, peripheral nerves and their surrounding tissues as well as vascular conditions of the head and neck. Some of the common surgical procedures performed in neurosurgery include management of congenital malformations, epilepsy surgery, functional neurosurgery, surgical management of vascular conditions of the brain and spinal cord and surgery of the peripheral nervous system (Chang et al., 2011).

1.2 Infections in Neurosurgery

Neurosurgical procedures should ideally have a low rate of surgical site infections because they are not associated with entry into potentially contaminated fields like gastrointestinal and genitourinary tract procedures. However, infections that may occur after surgery may lead to high morbidity that may necessitate readmission and re-operation, which is associated with high mortality (Walcott et al., 2012). These infections include superficial wound infections, meningitis, subdural empyemas, bone flap infections, brain and epidural abscesses, ventriculitis and infected shunts and drains (Chang et al., 2012).

Infections in neurosurgery may occur due to several factors such as contamination from the surgical team and environment, previously infected patients or patients with known risk factors for infection. Infection rates for clean cranial neurosurgical site infections have been estimated to

range from 0.5-6.6% (Abu et al., 2015), but these vary depending on the setting. Slightly higher infection rates have been reported in low and middle income settings. An infection rate of about 7.7% was reported in a study carried out in Malaysia (Buang and Haspani., 2012). Similarly, a study carried out at Kenyatta National Hospital reported infection rates of 7.5% for patients undergoing clean elective craniotomy (Njiru et al., 2015). The independent risk factors that influenced the development of infections were surgery performed by medical officer and senior medical officer and surgery done for infective causes. The American Society of Anaesthesiologists (ASA) score of 2 and clean contaminated wounds were predictive risk factors for surgical site infections.

1.3 Surgical Site Infections

The Centres for Disease Control define surgical site infections (SSIs) as infections that occur at or beyond the site of a surgical incision after surgery (Mangram et al., 1999). According to Mangram et al., (1999) and Hendrick et al., (2006), SSIs are the most common complications of surgery and the primary cause of nosocomial infections in surgical patients. They lead to increased hospital stay by an average of 7 days as well as increased hospitalisation costs amounting to 5-10 billion US dollars per year in the United States of America (USA).

SSIs occur within 30 days of surgery but if a prosthetic or an implant is inserted, a deep incisional or organ space SSI can occur up to one year from the date of surgery. There are several risk factors for patients developing SSIs, which include the degree of bacterial contamination after surgery, virulence of infecting organism, host factors like obesity, malnutrition, immunosuppression, extremes of age, co-morbid states, smoking and

immunosuppressive therapy. Bacterial contamination from exogenous sources like the operating team, instruments, poor infection control procedures also play a key role. Infection can also arise from endogenous sources such as the patient's microflora in the skin (Chang et al., 2012).

Late occurring infectious complications in patients with implants or prostheses can result in substantial morbidity hence prosthesis failure and subsequent removal or re-do procedures. By preventing surgical site infections, prophylactic antibiotics have the potential to decrease patient morbidity and mortality together with hospitalization costs for many surgical procedures that pose significant risk of SSIs (Chang et al., 2012).

The rates of neurosurgical site infections vary depending on the setting. In 2008, the National Healthcare Safety Network (NHSN) surveillance system of the Centres for Disease Control reported rates of 2.15% (for patients with NHSN risk index score of 0 or 1) to 4.66% (Edwards et al., 2009). The rates of infection at Kenyatta National Hospital have been reported to be higher, at 7.5% (Njiru et al., 2015).

1.4. Study Problem

Neurosurgical site infections remain low in incidence, but are associated with significant morbidity and mortality when they occur. A study by Njiru et al., (2015) on patients undergoing clean craniotomy established the risk factors for development of infections as : age, smoking, long pre-operative hospital stay, wound type, obesity, operations lasting more than 4 hours and those done in the afternoon. There is no published data on risk factors for infection for patients undergoing emergency surgery due to trauma and have potentially contaminated to dirty wounds. This study is therefore a follow up to the study by Njiru et al., (2015) which aims at establishing

the infection rates and associated risk factors for infection in trauma patients with potentially contaminated wounds.

Cost implications of neurosurgical site infections are unknown, because of paucity of data on the same in the East African region. This study sets out to enumerate the costs incurred by patients in the treatment of surgical site infections.

1.5 Research Questions

This study sought to answer the following questions:

1. What is the quality of available evidence on antimicrobial prophylaxis in neurosurgery?
2. What is the prevalence and associated risk factors of development of surgical site infections in neurosurgical trauma patients at KNH?
3. What is the pattern of antibiotic use in neurosurgery at KNH?
4. What medication errors are associated with antibiotic use at the neurosurgical unit of KNH?
5. What infection control procedures are used in neurosurgery at KNH?
6. What are the determinants of the effectiveness of antimicrobial prophylaxis at the neurosurgical unit of KNH?
7. What is the cost incurred in the treatment of neurosurgical site infections at KNH?

1.6 Study Objectives

Main objective

To gather clinical and economic data on antimicrobial use and prophylaxis, as well as evidence from a systematic review on the effectiveness of antimicrobial prophylaxis in preventing neurosurgical site infections.

Specific Objectives

The specific objectives of this study were to:

1. Synthesise and appraise the quality of evidence on the efficacy of existing antibiotics in preventing neurosurgical site infections by conducting a systematic review and meta-analysis.
2. Determine the prevalence and risk factors for postoperative infections of trauma patients with potentially contaminated neurosurgical wounds at Kenyatta National Hospital by conducting a cross sectional study .
3. Identify the determinants of the effectiveness of antimicrobial prophylaxis in neurosurgical trauma patients at Kenyatta National Hospital by conducting a prospective cohort study.
4. Identify the patterns of antibiotic use and medication errors with antibiotic use at the neurosurgical unit of Kenyatta National Hospital by conducting a prospective cohort study.
5. Determine the economic impact of neurosurgical site infections at Kenyatta National Hospital through a cost of illness study.

1.7 Conceptual Framework for the Study:

The study was carried out to address several factors that lead to development of surgical site infections among trauma patients with potentially contaminated wounds, and those that impact the prevention and management of SSIs. These factors will later be modified to develop a KNH-specific infection control protocol.

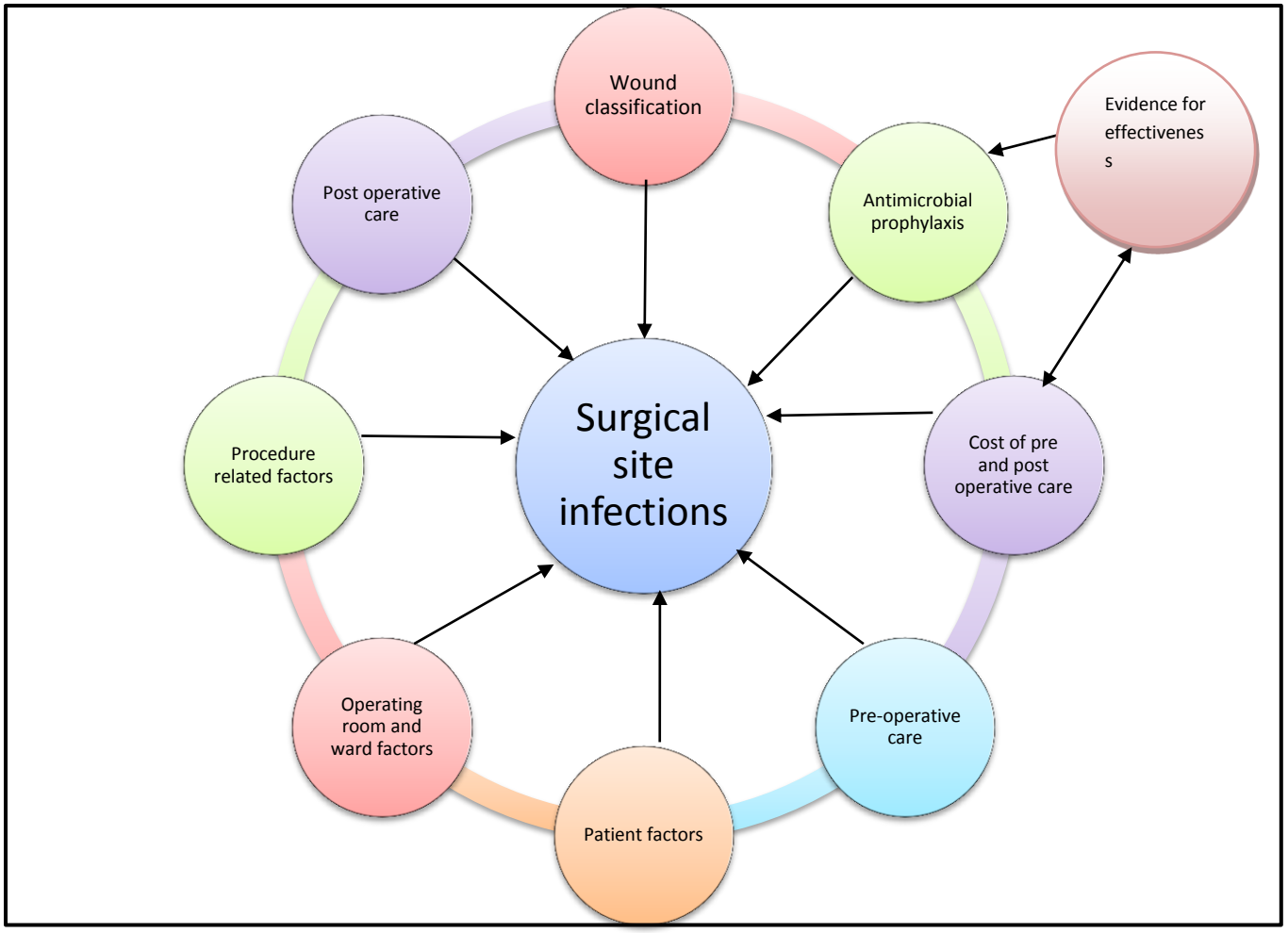

Figure 1.1: Conceptual Framework for the study.

1.8 Justification of the Study

This study is being carried out against the background that most of the patients admitted at the neurosurgical unit at KNH suffer trauma from road traffic accidents. Such patients have a high rate of morbidity and mortality (Mwang'ombe and Shitsama 2013; Saidi et al., 2005).Factors that are associated with poor outcome among these patients include Glasgow coma scale of less than 5, diffuse axonal injury and intracerebral mass lesions, blood sugar greater than 10mmol/l, age of greater than 60 years and cerebrospinal fluid rhinorrhoea (Opondo and Mwang'ombe, 2007). The impact of infections in relation of outcome has not been explored.

To generate quality evidence that informs practice, systematic reviews that evaluate the quality of evidence across studies are good sources of evidence. There is a paucity of local systematic reviews evaluating antimicrobial prophylaxis in neurosurgery among Kenyan patients in literature. The systematic review was carried out to generate evidence that will be used to inform policy and practice, regarding antimicrobial prophylaxis.

There is no infection control protocol in use at the KNH neurosurgical unit. This is likely to be associated with high infection rates. Use of protocols or infection prevention guidelines has been shown to reduce infection rates and the associated morbidity and mortality associated with SSIs (Gouvea et al., 2015). Dissemination of findings from this study will offer education and evidence based information on infection control, which will improve the practice of the health care workers in the unit.

Kenyatta National Hospital as an institution will benefit from this study in several ways. Currently, in a bid to reduce antimicrobial resistance, morbidity and mortality associated with

infections, KNH, through the Antimicrobial Stewardship Committee, is currently conducting research that will aid in developing antibiotic use protocols in all of its departments. The findings from this study will be used to develop a protocol for neurosurgery, which will be adopted for use. The economic evaluation will inform the policy makers of KNH on cost drivers in the prevention and management of SSIs. This will influence the procurement of effective antibiotics and ensure cost effectiveness in prevention and treatment of surgical site infections. Since the protocol developed from the findings of this study will be the first of its kind in Kenya and KNH, the neurosurgical unit could benefit by being accredited as a centre of excellence in neurosurgical infection control. The protocol may also be adapted by other similar institutions in the country and in the region. This study will generate new knowledge on the determinants of antimicrobial prophylaxis in neurosurgery and since it will be the first of its kind in Kenya and worldwide, it will set a trend in which studies that evaluate antimicrobial prophylaxis will factor in effect measure modification in the analysis.

This study will exclusively look at neurosurgical site infections among neurosurgical patients with potentially infected wounds. Most studies in neurosurgery have focused on patients with clean surgical wounds. The incidence of infection in this group of patients will be established and this will guide future infection prevention and antibiotic use strategies among this group of patients.

1.9. Summary of the Methodological Approach in The study

Figure 1.2: Summary of the methodological approaches of the study.

CHAPTER 2: LITERATURE REVIEW

2.1. NEUROSURGICAL PROCEDURES AND RISK OF CONTAMINATION

2.1.1. Classifications of Surgical Wounds in Neurosurgery

Neurosurgery has for a long time been associated with a low risk of surgical site infections. According to the Centres for Disease Control (CDC) classification, it is a clean procedure which is assumed to be carried out in a "sterile" environment. However, this is not the case as there is no sterile surgical environment. There are millions of microbes in the environment, including the operating room (Walcott et al., 2012). Surgical wounds in neurosurgery can be classified in four groups according to the duration of surgical procedure and level of contamination, for the purposes of the institution of antimicrobial prophylaxis or presumptive therapy of SSIs as presented in Table 2.1.

Contaminated and dirty wounds are more likely to be infected than clean wounds (Korinek, 1997; Kaye et al., 2005 and Shinoura et al., 2004). However, some studies have shown no association between development of SSIs and wound classification. (Korinek et al., 2005; Sanchez- Arenas, 2010).

Table 2.1: Classification of Wounds in Neurosurgery

Class of wound	Duration and Type of Surgery
Clean	< 4hours
Clean contaminated	4-6 hours or breach in sterility
Contaminated	>6 hours
	All emergency cases
	Trans-sphenoidal surgery
	Frontal or mastoid air cells opened
	Implants
	Diabetic patients
	Re-do procedures
	Osteomyelitis
Dirty	Abscesses, suspected meningitis
	Penetrating head injuries

Adapted from Mangram et al.,1999.

2.2. PATHOLOGY AND CLINICAL FEATURES OF SURGICAL SITE INFECTIONS

2.2.1. Clinical Examination of Surgical Site Infections

SSIs can also be defined or classified according to the physical findings obtained on examination of the wound or site of incision. Organisms are isolated from the organ/space by aseptic culturing technique. The second feature is the identification of an abscess in the organ/space by direct examination, during reoperation, or by histopathologic or radiologic examination. The third feature is the diagnosis of organ/space SSI is made by the surgeon or attending physician.

2.2.2. Classification of Surgical Site Infections

Surgical site infections are classified as Incisional and Organ Space infections (CDC National Nosocomial Infections Surveillance system). Incisional SSIs are further subdivided into Superficial and Deep Incisional SSIs. Superficial SSI involves the skin and subcutaneous tissues. Deep incisional SSIs, on the other hand involve the muscle and the fascia as well as both superficial and deep incision sites. Organ/space SSI involves any part of the body deeper than the fascial and muscle layers. It produces purulent drainage from a drain that is placed into the organ/ space (Mangram et al., 1999; Olsen et al., 2003).

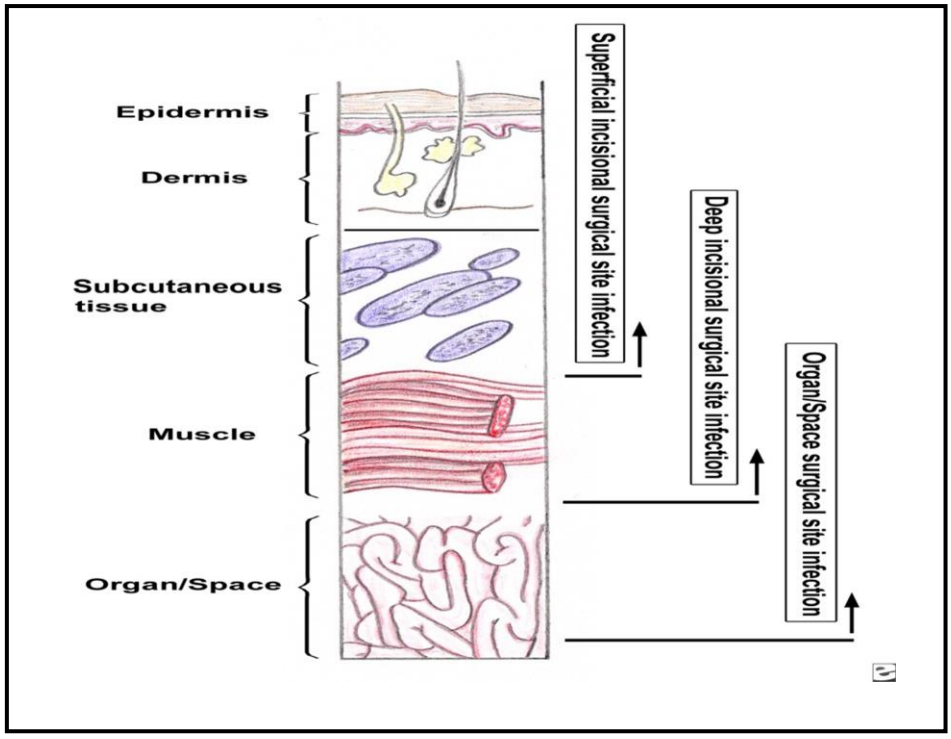

Figure 2.1: Classification of Surgical Site Infections (*Adapted from Owens and Stoessel, 2008)*

Superficial incisional infections are more common than deep incisional and organ/space SSIs. They account for more than half of all SSIs for all categories of surgery. In neurosurgery, examples include scalp infections and cellulitis. The postoperative hospital stay is longer for patients with these SSIs, when adjusted for other factors influencing length of stay (Mangram et al., 1999; Owens and Stoessel, 2008).

According to a report by the National Nosocomial Infections Surveillance (NNIS) program, a wound is not considered a superficial incisional SSI if a stitch abscess is present; if the infection is at an episiotomy, a circumcision site, or a burn wound; or if the SSI extends into fascia or muscle. A superficial SSI involves only the skin or subcutaneous tissue. In addition, at least one of the following features should be present.

i) Presence of purulent drainage, of which documentation of culture is not required.

ii) Organisms are isolated from fluid or tissue of the superficial incision.

iii) Presence of at least one sign of inflammation like pain or tenderness, induration, erythema and local warmth of the wound. If the wound is deliberately opened by the surgeon, (or attending physician) who declares the wound infected then it also qualifies as a superficial SSI (Mangram et al., 1999; Owens and Stoessel, 2008).

Sub-galeal infections in neurosurgery are the most common type of deep incisional infections. They occur within 30 days of the operation or within one year if an implant is present. They involve deep soft tissues (like fascia and/or muscle) and at least one of the following features:

i. Presence of purulent drainage from the deep incision but without organ/space involvement, fascial dehiscence or deliberate separation of fascia by the surgeon because of signs of inflammation.

ii. Identification of a deep abscess by direct examination or during reoperation, by histopathology, or by radiologic examination.

iii. If the surgeon or physician declares that a deep incisional infection is present (Culver et al., 1991, Mangram et al., 1999; Owens and Stoessel, 2008).

The organ space SSIs involve any anatomical area other than the incisional site which was opened or manipulated during operation. They may involve a large space, an organ or body cavity. These infections include osteomyelitis, meningitis, subdural empyema, cranial, epidural and cerebral abscesses. An organ space SSI occurs within 30 days of the operation or within 1 year if an implant is present. It involves anatomical structures not opened or manipulated during the operation and at least one of the following:

i. Presence of purulent drainage from a drain placed by a stab wound into the organ/space (Culver et al., 1991; Mangram et al., 1999; Owens and Stoessel, 2008), with isolation of organisms from the organ/space by aseptic culturing technique.

ii. Identification of an abscess in the organ/space by direct examination, during reoperation, or by histopathologic or radiologic examination.

iii. Diagnosis of organ/space SSI is made by the surgeon or attending physician.

The common organisms responsible for these neurosurgical infections are *Staphylococcus aureus, Streptococcus epidermidis* and *Candida albicans* (Barker, 1994).

2.3. RISK FACTORS FOR SURGICAL SITE INFECTIONS

Several risk factors predispose patients to surgical site infections. They can be classified into patient factors and procedure or surgery related factors. Physiological factors such as trauma, shock, anaemia and need for blood transfusion, hypothermia and hypoxia are also associated with the development of SSIs. This section will focus on the patient and procedure related risk factors for development of SSIs.

2.3.1. Patient Risk Factors for Development of SSIs

Several patient factors increase their susceptibility to surgical site infections. The factors that will be considered include: obesity, diabetes mellitus, malnutrition, corticosteroid use and immunosuppression, the patients' ASA scores, age and cigarette smoking.

Obesity has significant effects on the immune surveillance system. Immune system cells and adipocytes show similarities in their structure and function. They secrete adipokines like leptin which mediate inflammatory and immune responses (Hultunen and Syrjanen, 2013). They also interfere with differentiation of macrophages. In addition, complex interactions between immune cells further depress their immune function (Hultunen and Syrjanen, 2013). The well balanced system of adipocytes and immune cells is altered in obesity, such that there are more adipocytes. This results in a poorly regulated immune response as well as impaired chemotaxis and macrophage differentiation (Hultunen and Syrjanen, 2013).

Apnoea and the narrowing of pulmonary vessels associated with obesity leads to reduced tissue perfusion, decreased wound oxygen tension, tissue hypoxia and eventually reduced wound healing. Adipose tissue is impenetrable by prophylactic antibiotics so this reduces their

effectiveness. The associated metabolic syndrome leads to interference with platelet aggregation, which is an important step in the initialisation of wound healing. Furthermore, surgical manipulations in obese patients are often difficult and lead to prolonged procedures, which further increase the risk of developing infections (Friedman et al., 2007; Yuan and Chen, 2013).

Several studies have shown that obesity is a major risk factor for infection in neurosurgical procedures in adults (Bellusse et al., 2015; Njiru et al., 2015) and paediatric patients (Linam et al., 2009), regardless of the type of procedure being performed (Arabshashi and Beyhaghi, 2005; Brown and Velmahos, 2006). This applies to clean and clean contaminated wounds (Bellusse et al., 2015; Njiru et al., 2015). As the percentage of body fat increases, the risk of SSIs increases (Waisbren et al., 2010).

Diabetes or high intraoperative blood glucose levels are associated with a high risk of infection (Maragakis and Crosgrove, 2009; Veeragu et al., 2009; Harrop et al., 2012), even with antimicrobial prophylaxis (Erman et al., 2005; Mollahoseini et al., 2009). This is seen in different types of neurosurgical procedures such as spinal surgery (Chen and Anderson, 2009; Demura and Kawahara 2009; Gunne et al., 2009,). Similarly, this has been observed in craniotomy and craniectomy procedures (Sanchez-Arenas et al., 2010).

Malnutrition increases the risk of developing surgical site infections among different cohorts of patients (Kaye et al., 2005; Neumayer et al., 2007; Culebras 2013). It is a risk factor in different types of surgical procedures (Arabshashi and Beyhaghi, 2005; Schuster et al., 2010). Markers of malnutrition used are pre-operative protein deficiency and low serum albumin (McPhee et al., 1998; Gibbs et al., 1999).

Glucorcorticosteroids inhibit several immune functions via down-regulation of cytokine gene expression. They also interfere with adhesion and migration of inflammatory cells. They inhibit lymphocyte adhesion to the endothelium through down modulation of lymphocyte adhesion molecules (McPhee et al., 1998). Preoperative corticosteroid administration was associated with a high risk of development of SSIs in patients who underwent neurosurgery (Merkler et al., 2014).

Increase in age is consistent with increased risk of development of SSIs (Kaye et al., 2005; Neumayer et al., 2007; Schuster et al., 2010). Advanced age is associated with reduced organ function, immune function and tissue perfusion. Above 70 years, there is increased mortality, hospital stay and cost of hospitalisation from staphylococcal SSIs (McGarry et al., 2004). This is seen in neurosurgical procedures (Shinoura et al., 2004; Schuster et al., 2010). However, Kaye et al., 2005 showed that there was a reduced risk of SSIs in the young and very old patients. The study showed that increasing age up to 65 years was associated with increase in SSI risk, while age above 65 years was an independent predictor of a decrease in SSIs. Talbot et al., 2005 re-examined this study and showed the contrary.

Cigarette smoking is associated with reduced oxygen carrying capacity of blood. It also causes vasoconstriction that further reduces tissue perfusion. Smoking is a significant risk factor for development of organ/ space surgical site infections (Durand et al., 2013). Smokers are more likely to develop postoperative healing complications compared to non-smokers. Perioperative smoking cessation reduces surgical site infections, but not other wound healing complications (Sorensen, 2012).

2.3.2 Procedure Related Risk Factors for SSIs

Factors related to the surgical procedure have been shown to predispose patients to surgical site infections even in the absence of patient related risk factors. They are classified according to those that increase risk of infection and those that reduce risk of infection. Factors that increase SSI risk include: wound classification, CSF leak, length of surgical procedure, re-do procedures and presence of shunts and drains. Use of antimicrobial prophylaxis, hair removal, surgical scrubbing, gloving, hand decontamination and use of drapes and gowns reduce the risk of SSIs (Chiang et al., 2012; Abu et al., 2014; Njiru et al., 2015).

The presence of foreign bodies is an independent risk factor for development of neurosurgical SSIs (McClelland et al., 2008). Cerebrospinal fluid drains like ventricular and lumbar drains introduce micro-organisms into the CNS through drain catheters. External drains used to monitor intracranial pressure divert CSF from an obstructed ventricular system can introduce micro-organisms from other adjacent organs as well as the environment. There is an increased risk of development of meningitis with the use of external ventricular drains (Sneh-Arbib et al., 2013; Njiru et al., 2015).

Internal drains like ventriculoperitoneal shunts used to treat hydrocephalous can also be a source of infection in the CNS especially after craniotomy and craniectomy procedures. There is an increased risk of bacterial meningitis caused by the use of ventricular and lumbar CSF catheters (Alexander and Susla, 2013). The duration of ventriculostomy with external drainage is an independent risk factor for the development of meningitis. This includes extended duration of catheterisation (Sneh-Arbib et al., 2013). Infections can develop even with the use of

antimicrobial prophylaxis (Alleyne et al., 2000). However, antimicrobial prophylaxis generally reduces the risk of infection though the benefit remains uncertain after the first 24 hours, according to Ratilal et al., 2008. Procedures involving ventriculoperitoneal shunts have been associated with an increasing risk of infection (Chang et al., 2011; Alexander and Susla, 2013).

Cerebrospinal fluid leakage is associated with basilar skull fractures sustained in trauma. It is also likely to occur in cranial surgery that involves dural opening (Hutter et al., 2014). Patients with CSF leak are more likely to develop surgical site infections (Chiang et al., 2012; Cassir et al., 2015; Njiru et al., 2015).

The duration of neurosurgical procedure contributes to the development of surgical site infections. Craniotomy procedures longer than 4 hours are associated with an increase in the incidence of SSIs (Abu et al., 2014; Njiru et al., 2015). As neurosurgical procedure progresses in length, the cumulative time possible for bacteria to mount an invasion increases (Edwards et al., 2009). Preoperative antimicrobial prophylaxis loses its effectiveness depending on the pharmacokinetic profile of the antibiotic given for prophylaxis as well as the patient factors. In very long procedures, intraoperative re-dosing may be necessary (Walcott et al., 2012).

Redo procedures are associated with an increased risk of SSIs (Gaberel et al., 2011; Njiru et al., 2015). This is because of several factors such as introduction of new micro-organisms to a potentially infected area, tissue and endothelial injury that enhance penetration of infecting bacteria and chances of development of resistance from previously administered prophylactic antibiotics. Blood loss from previous surgery and physiological changes that occur during

surgery, such as release of corticosteroids may further suppress the patient's immunity and predispose them to infection.

2.4. RISK CATEGORIZATION OF PATIENTS UNDERGOING SURGICAL PROCEDURES

The American Society of Anaesthesiologists (ASA) score is used to classify patients based on their physical status and severity of disease. It is an accurate predictor of post -surgical outcomes of patients. The scoring system is presented in Table 2.2.

Table 2.2: American Society of Anaesthesiologists (ASA) Classification of Physical Status ***(Adapted from American Society of Anaesthesiologists, 2014)***

ASA Score	Definition	Mortality (%)
1	Normal healthy individual	0.05
2	Mild systemic disease that does not limit activity	0.4
3	Severe systemic disease that limits activity but is not incapacitating	4.5
4	Incapacitating systemic disease which is constantly life-threatening	25
5	Moribund, not expected to survive 24 hours with or without surgery	50
6	Brain dead patient awaiting organ donation	100%

Several studies have also identified high patients' ASA scores as risk factors for development of SSIs (Neumayer et al., 2007; Maragakis and Crosgrove, 2009 and Schuster et al., 2010). Most studies have reported that ASA scores >2 and severe systematic disease are associated with significant postoperative infections, morbidity and mortality.

The National Nosocomial Infections Surveillance System (NNIS) is a basic risk index that incorporates the ASA classification in the stratification of patients (Gaynes et al., 2001). It is a more accurate predictor of the risk of infection than wound classification.

The risk category of a patient in the NNIS risk index is obtained by the total sum of the risk factors present at the time of surgery. A point is allocated for each risk factor and the risk index ranges from 0 - 3.This risk index considers three main determinants of infection which include: the bacteria present, the local environment and the patient health status. Using this risk index, patients at high risk of getting an infection fall under the following three categories. The first category includes patients assessed by an anaesthesiologist and found to have an ASA score of > 3. In the second category Patients with dirty or contaminated wounds are included. The third category includes patients undergoing operations lasting > t hours, where t is the 75^{th} percentile of the specific operation being performed. For neurosurgery, t has been calculated at 126 minutes (NNIS, 2003) as shown in Table 2.3.

Table 2.3: Predictive Percentage of SSI Occurrence by Wound Type and Risk Index

Risk Index	Predictive risk of developing SSI (%)
0	1.5
1	2.9
2	6.8
3	13.0

2.5. PREVENTION OF SURGICAL SITE INFECTIONS

The major approaches for prevention of surgical site infections are: antimicrobial prophylaxis, scrubbing, and aseptic techniques that are commonly practised in all wards and theatres.

2.5.1 Antimicrobial Prophylaxis

Guidelines for recommendation of antimicrobial prophylaxis for neurosurgical procedures were for a long time non-existent (Hosein et al., 1999). However, when infection occurs it leads to high morbidity and mortality. Administration of prophylactic antimicrobials reduces the rate of post craniotomy meningitis by one half (Barker et al., 2007). The absence of antimicrobial prophylaxis is an independent risk factor for development of meningitis (Walcott et al., 2012).

The major goal of antimicrobial prophylaxis is to reduce bacterial counts below critical levels necessary to cause infection at and around the surgical site (Thirion et al., 2007). This targets normal flora that is suspected to inhabit the incision site.

Procedures involving placement of shunts and ventricular drainage are associated with higher rates of infections due to placement of a foreign body. Choice of antimicrobial agents should consider the spectrum of activity and penetration into the CSF.

Factors that affect the choice of antimicrobials include drug allergies, safety profile and efficacy (Rahman and Anson., 2004). Antimicrobial agents should be given one hour before the initial incision and stopped 24 hours later (Owens et al., 2008; Walcott et al., 2012). Intraoperative re-dosing during long procedures reduces the infection rate (Zanetti et al., 2001; Thirion et al., 2007).

First or second generation cephalosporins are appropriate for prophylaxis in clean procedures (Ratilal et al., 2006 and Thirion et al., 2007). Vancomycin can be given in the case of beta-lactam hypersensitivity and Methicillin Resistant *Staphylococcus aureus* (MRSA) prevalence. Topical vancomycin has been shown to be effective in reduction of neurosurgical site infections after craniotomy (Abdullah et al., 2015). Single doses of cefotaxime and trimethoprim-sulfamethoxazole are equally effective in preventing surgical site infections in patients undergoing shunt surgery (Whitby et al., 2000). Table 2.4 presents recommendations for antimicrobial prophylaxis in neurosurgery according to recent evidence.

Table 2.4: Choice of Antimicrobials for Prophylaxis in Neurosurgery

Procedure	Likely Organisms	Recommended prophylaxis	Comment	Grade of evidence
Cerebrospinal fluid shunt procedures	*S.aureus, S. epidermidis*	Cefazolin 1g q 8hrs x 3 dosesor Ceftriaxone 1g x 1	No agents have been shown to be better than cefazolin in randomised comparative trials	1A
Craniotomy	*S.aureus, S. epidermidis*	Cefazolin 1g x1 or Cefotaxime 1g x1	Trimethoprim/Sulfamethoxazole 160/800 mg iv x1can be substituted for patients with penicillin allergy.	1A
Spinal Surgery	*S.aureus, S. epidermidis*	Cefazolin 1g x 1	Limited number of trials comparing different treatment regimens	1B
*Head and neck cancer resection	*S. aureus, streptococci oral anaerobes*	Cefazolin 2g or Clindamycin 600mg at induction then q 8hrs for 2 more doses	Add Gentamicin for clean contaminated procedures	1A

(Adapted from Salmaan and Devlin, 2008)

Grade 1A: strongly recommended and supported by well-designed experimental, clinical or epidemiological studies.
Grade 1B: strongly recommended and supported by some experimental, clinical or epidemiological studies and strong theoretical rationale.

2.5.1.1 Adverse Effects of Antimicrobials:

Although antimicrobial prophylaxis is important in preventing neurosurgical site infections, antibiotic use is associated with several adverse effects, which range from mild to fatal. The risk factors for the development of adverse effects of antibiotic include the class of drug, patient characteristics and co-morbidities, co-administered medication and route of administration of drugs (Goodman and Gillman, 2013). Paediatrics, geriatrics, critically ill and immunosuppressed patients are more likely to develop adverse effects of drugs. The changes in the pharmacokinetic profile of drugs in pregnancy predispose patients to adverse effects. Patients with renal and

hepatic dysfunction are more likely to suffer from drug related toxicity due to reduction in metabolism and elimination of the drugs (Goodman and Gillman, 2013). Antibiotics have class specific adverse effects which could contribute to significant morbidity and mortality of patients. They are summarized in Table 2.5.

Table 2.5: Class Specific Adverse Effects of Antimicrobials used for Prophylaxis

Antibiotic class	**Adverse effects**
Sulfonamides	Crystalluria, acute haemolytic anaemia, agranulocytosis, aplastic anaemia, hypersensitivity skin reactions like urticaria, pemphigoid, purpura; life threatening hypersensitivity reactions like Stevens Johnson syndrome, erythrema multiforme, exfoliative dermatitis, photosensitivity. Focal or diffuse liver necrosis is rare
Trimethoprim-sulfamethoxazole	Exfoliative dermatitis, Stevens Johnson syndrome, toxic epidermal necrolysis, gastrointestinal disrurbances, allergic cholestatic hepatitis, headache, depression, hallucinations, anaemias, coagulation disorders, granulocytopenia, agranulocytosis and renal impairment in patients with renal disease
Quinolones	Gastrointestinal upsets, abdominal discomfort,diarrhea,headaches, dizziness, hallucinations, delirium, seizures, Achilles tendon rupture, tendonitis. Rare-leukopenia, eosinophilia, mild increase in serum transaminase levels
Penicillins	Life threatening anaphylactic reactions in susceptible patients. Others-depression, granulocytopenia, hepatitis and injection site reactions
Cephalosporins	Hypersensitivity reactions like penicillins, nephrotoxicity, diarrhoea, bleeding due to thrombocytopenia or platelet dysfunction
Aminoglycosides	Ototoxicity, nephrotoxicity, neuromuscular blockade, scotomas, peripheral neuritis, paraesthesias, rare hypersensitivity reactions like angioedema and anaphylactic shock
Tetracyclines	GI irritation, photosensitivity, renal toxicity, Fanconi syndrome, thrombophlebitis, hypersensitivity reactions like anaphylaxis and angioedema
Macrolides	Allergic reactions, cholestatic hepatitis, epigastric distress, cardiac arrhythmias, transient auditory impairment
Clindamycin	Potentially fatal *Clostridium difficile* pseudomembranous colitis,skin rash, Stevens Johnson syndrome, erythrema multiforme, elevation of transaminases, thrombocytopenia, inhibition of neuromuscular transmission
Vancomycin	Skin rash, anaphylaxis, erythrematous reactions on the upper body, urticarial, flushing, hypotension on rapid administration; ototoxicity, nephrotoxicity

Adapted from Goodman and Gillman, 2016

2.5.2 Surgical Procedures that Prevent SSIs

Several procedure- related factors can be implemented to prevent the development of SSIs. These include hair removal, double gloving and scrubbing. Reduction of the bacteria in the operating room has also been shown to be beneficial in reduction of SSIs. Local tissue oxygenation and maintenance of normothermia are also vital in preventing SSIs.

Hair removal is necessary to enable easy access to the surgical site and to minimise the risk of contamination of the surgical site. Shaving using razors increases micro abrasions on the skin which may cause contamination of the site by flora and encourage development of SSIs (Tanner et al., 2006). Shaving a few hours prior to surgery increases risk of SSIs. Hair clipping and depilation are associated with lower risk of SSIs compared to shaving (Tanner et al., 2006; Celik and Kara, 2007).

Disinfection of the operating room is vital. Although it is not possible to remove all bacteria from the air, measures should be taken to reduce the innoculum in the wounds. Such measures include cleaning surgical loupes, head lamps and operating microscopes as well as surgical gowns and microscope drapes (Walcott et al., 2012). Use of laminar air flow reduces the number of aerosolised bacteria (Walcott et al., 2012).

Scrubbing reduces the microbial load on the surgeon's skin and reduces the chances of contamination. Though in ideal cases the surgeon's skin does not come into direct contact with the surgical wound, defects or breaks in surgical gloves and gowns can lead to direct contact and subsequent contamination (Walcott et al., 2012). Alcohol rubs or aqueous scrubs are usually used

and studies have not shown one being superior over the other. However, alcohol rubs are better tolerated and scrubbing takes a shorter time (Tanner et al., 2008).

Perforations can occur in gloves during surgery especially in procedures where there is implantation of hardware, for example in instrumental spinal fusions (Walcott et al., 2012). Changing of gloves has been advocated for, though there is a risk of contamination of wounds in case of small perforations in the gloves that cannot be easily detected (Tanner and Parkinson, 2006). Double gloving has therefore been recommended as it reduces the chances of perforation of the inner gloves, hence reducing the chances of surgical wound contamination (Tanner and Parkinson, 2006).

During neurosurgical procedures, deliberate alteration of perfusion and oxygenation of tissues is commonly done to provide neural protection (Leslie- Mazwi et al., 2011). However, these procedures may put patients at high risk of developing SSIs because hypothermia causes peripheral vasoconstriction that may reduce oxygen tension in subcutaneous tissues (Lopez et al., 1994). Phagocytes and neutrophils also require high oxygen content for antimicrobial activity (Maragakis and Crosgrove, 2009). Intraoperative and postoperative administration of high concentration of oxygen is associated with decreased incidence of SSIs (Maragakis and Crosgrove , 2009). Maintenance of normothermia has also been associated with reduced SSIs (Kurz et al., 1996).

2.6: IMPLEMENTATION OF INFECTION CONTROL PROTOCOLS

Several infection control protocols have been developed following studies on risk factors for SSIs. These include Boyce and Pittet (2002) who developed protocols on hand hygiene, Martin (1994) who developed protocols on antimicrobial prophylaxis and Sturm (2009) who developed infection control strategies based on risk factors identified for SSIs as well as antimicrobial prophylaxis.

Historically, Malis is credited for developing and using a vancomycin-gentamicin- topical streptomycin based protocol in the 1970s which was so effective that it was able to eliminate all primary post- operative infections for over 20 years. There was an ethical dilemma regarding this protocol, due to exposure of patients to the toxicity of vancomycin (flushing, cardiotoxicity, fever and hypotension). The combination of gentamicin and vancomycin exposed patients to nephrotoxicity and ototoxicity. Another setback was development of vancomycin resistant bacterial strains. Although Malis was able to demonstrate that the benefits of this regimen outweigh the risks, this regimen is not routinely used due to the underlying ethical dilemma (Savitzet al., 2002).

The All India Institute of Medical Sciences (AIIMS) has developed several protocols for antimicrobial prophylaxis in neurosurgery since 1994. The protocol that used a ciprofloxacin-amikacin based regimen was in use between 1994 and 2000. This was revised to a cefotaxime-netilmicin based regimen, which was a comprehensive written protocol. This was used until 2004 when a chloramphenicol-netilmicin based regimen was used. It was further revised to a more comprehensive regimen that uses different antibiotics for prophylaxis at different doses,

durations and frequencies depending on the wound classification (clean, clean contaminated, contaminated and dirty). This protocol incorporates the need for culture and sensitivity testing to treat contaminated and dirty wounds.

The American Society of Health System Pharmacists together with the Infectious Disease Society of America, Surgical Infection Society and the Society for healthcare Epidemiology of America has also come up with clinical practice guidelines for antimicrobial prophylaxis in surgery based on findings from systematic reviews and other forms of recent evidence (Bratzler et al., 2013). In the United Kingdom, the Scottish Intercollegiate Guidelines Network (SIGN) developed comprehensive national clinical guidelines on antibiotic use protocols in surgery based on recent evidence, antimicrobial susceptibility patterns and cost (SIGN guideline 104) in 2008. These were revised in 2014. The South Australian government has developed an infection control protocol which uses a cephazolin based regimen for antimicrobial prophylaxis in clean neurosurgical procedures and vancomycin where there is high risk of MRSA. The protocol includes risk factors for infection that should be checked out for as well as wound care procedures.

Literature Gap: There are no such protocols in sub Saharan African countries.

2.7 THE GRADE SYSTEM FOR EVALUATING QUALITY OF EVIDENCE

Systematic reviews are important in generating evidence that informs policy. The quality of evidence can be appraised using several systems, including the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. GRADE is a system that is used to rate the quality of evidence obtained from systematic reviews, health technology assessments and guidelines. It is also used to grade recommendations in healthcare, which in turn, are used to develop clinical practice guidelines and inform policy (Schunemann et al., 2013).

This system is designed to rate the quality of evidence especially for systematic reviews and guidelines that evaluate alternative interventions. It evaluates bodies of evidence that deal with diagnosis, treatment, screening and prevention of diseases. Using this system, one is able to specify healthcare questions, choose outcomes of interest, rate the importance of outcomes of interest according to their importance, evaluate quality of evidence, make recommendations using the evidence while incorporating the values of patients, society and health care practitioners, guide clinicians on how to use the recommendations in clinical practice and inform policy (Schunemann et al., 2013).

According to Schunemann et al., 2013, GRADE has several advantages over other systems that evaluate the quality of evidence. It clearly separates the judgement in the confidence estimates and strength of recommendations. It is able to explicitly rate outcomes of interest according to their importance. Using GRADE, one is able to use a clear, predefined criterion to upgrade and downgrade the quality of evidence. One is able to move from evidence to recommendations for clinical practice in a structured way. This system also incorporates societal, patient and clinician

values and preferences when making recommendations for practice. The recommendations made can be classified into strong or weak, according to the applicability to clinicians, patients and policy makers.

There are several steps involved in this process. The first step involves framing the healthcare question using the PICO framework. This framework formulates a research question that incorporates the patient/population of interest (P), the intervention (I), Control or comparator (C), and the Outcome (O). The next step involves selection and rating of the outcomes according to their importance in terms of decision making. The outcomes are rated as critical, important but not critical and of limited importance. Critical and important outcomes are usually considered when making recommendations and informing policy and practice. Once this is done, a systematic review is carried out to generate evidence, after which the evidence is graded. Grading of evidence is done using five criteria: risk of bias, indirectness, inconsistency, imprecision and publication bias. Using this, the quality of evidence is graded as high, moderate, low or very low. This quality of evidence can be downgraded when there are limitations in the study design or where there is inconsistency of results, indirectness of evidence, imprecision or publication bias. The evidence can be upgraded when there is a large magnitude of effect, dose response gradient or where "all plausible confounding would reduce the demonstrated effect or increase the effect if no effect was observed" (Schunemann et al., 2013). These are usually summarised in GRADE Evidence Profiles and Summary of Findings tables. Evidence Summary Tables are used to summarise the recommendations. These are generated using the GRADEpro Guideline Development Tool software (GRADEPro GDT, 2015).

GRADE has been used to generate evidence and inform policy in several countries. In Kenya, several systematic reviews have used this system to create recommendations for clinical practice and clinical guidelines especially among the paediatric population. In The "Child Health Evidence Week", evidence from a systematic review was used to develop national clinical guidelines for several paediatric conditions (Irimu et al., 2008; Opiyo et al., 2012). GRADE has also been used to evaluate evidence of the use of hydroxyurea in the management of the complications of sickle cell disease in children in low income countries (Mulaku et al., 2013). Another systematic review evaluated evidence on the effectiveness of topical umbilical cord care for preventing infections in neonates (Karumbi et al., 2013). A review that included adult patients was carried out to evaluate evidence on the efficacy of calcium channel blockers for patients with chronic kidney disease requiring dialysis (Mugendi et al., 2015).

Literature Gap: There is a paucity of local systematic reviews evaluating antimicrobial prophylaxis in neurosurgery among Kenyan patients in literature.

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CHAPTER 3: SYSTEMATIC REVIEW, META-ANALYSIS AND GRADING OF EVIDENCE ON THE EFFECTIVENESS OF ANTIMICROBIAL PROPHYLAXIS FOR NEUROSURGICAL SITE INFECTIONS

3.1. Introduction

Systematic reviews and meta-analyses are an important component of evidence based health care. According to Cochrane (2013), evidence based health care refers to "the conscientious use of current best evidence in making decisions about the care of individual patients or the delivery of health services." He further defines current best evidence as "up- to-date information from relevant, valid research about the effects of different forms of healthcare, the potential for harm from exposure to particular agents, the accuracy of diagnostic tests, and the predictive power of prognostic factors." Evidence based clinical practice on the other hand, is a decision making process in which the clinician uses the best available evidence, while incorporating patient values and preferences to decide on the best therapeutic plan for the patient (Sackett, 1997). He defined evidence based medicine as "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients."

A systematic review is the study in which the best evidence regarding a particular research question is obtained. It is "a high level overview of primary research on a particular research question." It aims to identify, select synthesise and appraise all the available high quality evidence regarding a particular research question. While collating all the evidence that fits pre-specified eligibility criteria in order to address specific research questions, systematic reviews also seek to minimise bias using explicit well defined methods (Cochrane, 2013).

A meta-analysis on the other hand, assesses the effectiveness of healthcare interventions by pooling data from two or more randomised controlled trials and analysing it using statistical approaches (Petiti, 2000). Analysis includes testing of heterogeneity across studies. Many systematic reviews contain meta-analyses. This is because they provide more precise estimates of the effects of health care interventions than individual studies contained in a systematic review (Cochrane, 2013).

While selecting studies to be included in a systematic review or a meta-analysis, the quality of evidence is important. The hierarchy of evidence is consistent with its quality. In evidence based practice, studies are ranked based on the rigour of their research methods. Rigour in this case refers to the strength and precision of the methods. Well conducted systematic reviews, evidence syntheses and randomised controlled trials are regarded as the highest quality evidence, while expert opinion and anecdotal reports are regarded as the lowest quality evidence (Hoffman et al.,; 2013).

The quality of evidence from systematic reviews and meta-analyses can be evaluated using the GRADE approach, which uses the predefined criteria of risk of bias, directness, consistency, precision and publication bias to rate the quality of a body of evidence across outcomes (Schunemann, 2013). This study used these concepts to generate and evaluate the quality of evidence that would inform antimicrobial prophylaxis in neurosurgery at Kenyatta National Hospital.

3.2. Objective

The main objective of this systematic review was to synthesise and appraise the quality of evidence on the effectiveness of existing antibiotics in preventing neurosurgical site infections.

3.3. METHODS:

3.3.1. Selection of Studies: PICO and Search Strategy:

To generate evidence that would inform antimicrobial prophylaxis, a systematic review was conducted between October 2014 and December 2015. Two investigators formulated the research question and search strategies together. The research question, which incorporates the Population, Intervention, Comparison and Outcome (PICO) aspects was formulated to guide the systematic review. The population (P) of interest in this case was “adult neurosurgical patients”, while the intervention (I) for our study was antimicrobial prophylaxis. The study comparator /control (C) was “no antimicrobial prophylaxis or placebo” while the outcomes of interest (O) were: all-cause mortality, development of neurosurgical site and non-surgical site infections, shunt revision and adverse effects of antibiotics. The search was done between October 2014 and December 2014.

Antimicrobial prophylaxis was defined as the use of systemic antibiotics or antibiotic impregnated shunt catheters for the prevention of neurosurgical site infections. All-cause mortality was defined as death from any cause during the course of treatment. Surgical site infections were defined as infections occurring at and around the surgical site according to the CDC classification (Mangram et al., 1999). Non-surgical site infections were defined as any other infections at distant sites, not directly related to the surgery. Shunt revision was defined as

the removal or replacement of a shunt through a subsequent surgical procedure, due to development of surgical site infection (Zabramski, 2003). Adverse effects of antibiotics were defined as any untoward effects on the patient arising from use of antimicrobials (Goodman and Gillman, 2016).

The PICO research question formulated was: **"For adult neurosurgical patients, does antimicrobial prophylaxis compared to no antimicrobial prophylaxis, reduce the risk of development of surgical site infections?"**

After formulation of the PICO question, a search strategy was formulated using Medical Subject Headings (MeSH) terms that were then entered into the databases for searching. Boolean operators "AND" and "OR" were used in the search to include all aspects of neurosurgical patients and infection control. Brackets were used to narrow the search so that any information on infection control was not excluded, while limiting the search results to the studies that complied with PICO. Three search strategies were formulated as follows:

Search Strategy 1: (Effectiveness OR Efficacy) AND (antibiotics OR antimicrobials OR anti-infectives) AND (Prophylaxis OR Prevention) AND infection control.

Search Strategy 2: (Effectiveness OR Efficacy) AND (antibiotics OR antimicrobials OR anti-infectives) AND (Prophylaxis OR Prevention) AND (infection control) AND (neurosurgical OR neurosurgery OR neurosurgical site infections).

Search Strategy 3: (Effectiveness OR Efficacy) AND (antibiotics OR antimicrobials OR anti-infectives) AND (Prophylaxis OR Prevention) AND (infection control) AND

(neurosurgical trauma patients OR neurosurgery trauma) AND (neurosurgical site infections)

After pre-testing the search strategies, Search strategy 2 was used in the search as it yielded relevant studies. Search strategy 1and 3 yielded results that were not relevant to the search.

3.3.2. Inclusion and Exclusion Criteria for the Studies:

We sought to include systematic reviews and randomised controlled trials which addressed the population, interventions, comparators and outcomes of interest. Specifically, we sought to include studies that evaluated our patient population of interest (patients over 18 years old, undergoing neurosurgical procedures, including spinal instrumentation surgery), interventions of interest (administration of systemic antibiotics for antimicrobial prophylaxis versus no antibiotics or placebo, or the use of antibiotic impregnated shunts, catheters and drains versus standard shunts), and our outcomes of interest (all-cause mortality, development of surgical site and non-surgical site infections as well as adverse effects of antibiotics).

Studies that involved paediatric patients, those that compared two different antibiotics and studies involving local irrigation of wounds using antiseptics were excluded. Studies which were not in English and could not be translated were also excluded from the review. We also excluded studies that were not either systematic reviews or randomised controlled trials. No restrictions on the publication date of the studies were set. Studies with small sample size that was too small to meet the normal distribution, that is, studies with less than 30 participants were excluded. Studies that compared the use of antibiotic impregnated shunts versus systemic antibiotics were also excluded.

3.3.3. Search for Systematic Reviews and Randomised Controlled Trials:

Two investigators carried out the search and study selection independently. The differences were sorted by discussion and consensus building by the two investigators. Separate searches were done for systematic reviews and for randomized controlled trials (RCTs).

For the Systematic Reviews, search strategy 2 was entered into MEDLINE and the Cochrane Database of Systematic Reviews (CDSR). The search was filtered as "Reviews". This yielded 16 systematic reviews. The same was repeated for the randomised controlled trials, with the search being filtered for "randomised controlled trials" into the MEDLINE database and the Cochrane Central Register for Controlled Trials (CENTRAL). This yielded 31 results.

3.3.4. Title Screening:

The 16 systematic reviews were reviewed by their titles for compliance with the PICO and 12 were selected. 4 reviews did not comply with the PICO (by title) and were rejected. The Cochrane Database of Systematic Reviews search yielded only one review (Ratilal et al., 2011, n=208 patients). On reviewing the title, the study was rejected because it did not comply with the PICO.

The titles of the 31 selected randomised controlled trials were scrutinized for compliance with the PICO. 4 studies were excluded for non-compliance and the remaining 27 included for abstract screening.

3.3.5. Abstract Screening:

Twelve systematic reviews were selected for abstract screening. The abstracts were scrutinised for the population, interventions, control and outcomes of interest. From these studies, only one

systematic review abstract (Ratilal et al., 2008, n=2134) fully complied with the PICO and was included for further full text analysis. Six abstracts were excluded on the basis of non-compliance of content with the PICO (Parker et al., 2011; Ratilal and Sampaio 2011; Gutierrez-Gonzalez et al., 2010; Dellamonica et al., 1993; Guglielmo et al., 1983; Everett and Strausbaugh 1980). Three studies were excluded because they were not systematic reviews (Ratilal et al., 2006; Fujiwara et al., 2000; Haines, 1989). One study, (Ratilal et al., 2006, n=2,134) complied with the PICO but was excluded because it was a duplicate of a follow up systematic review (Ratilal et al., 2008), which was more comprehensive. The last study, (Djindjian 1994), was excluded because it was in French and the investigators could not get someone to translate and interpret it in English. Twenty seven RCTs were included for abstract screening. From these, 12 studies were chosen for full text analysis as they complied with our PICO. Twelve studies were rejected on the basis of noncompliance with PICO, while 2 were not RCTs. In addition to non-compliance with PICO, one study, Mewe et al., 1991 was excluded as it was written in German and the authors could not find an English version. The details of the excluded studies are found in the Appendices 8 and 9.

3.3.6. Full Text Analysis of Selected Studies:

The selected systematic review (Ratilal et al., 2008) was subjected to a full text analysis for compliance with PICO. This process involved scrutinizing the patients, interventions, comparators and outcomes to establish if they met our selection criteria. There were 17 RCTs included in this systematic review by Ratilal et al (2008), and these 17 RCTs were also retrieved and scrutinized for compliance with PICO. Eight of these studies (Bayston, 1975, n=132; Blum

1989, n=169; Haines 1982, n= 76; Odio 1984, n=37; Reider 1987, n= 63; Walters 1992, n=294; Wang 1984, n= 127 and Yogev 1985, n=190) were excluded as they included only children. The remaining nine studies (Blomstedt 1985, n= 174; Bullock 1988, n=417; Djindjian 1986, n=60; Govender 2003, n=153; Rocca 1992, n=78; Schmidt 1985,n=152; Young 1987,n=133; Zabramski 2003,n=306; and Zentner 1995,n=129) complied to PICO and were included in our systematic review.

Similarly, the previously selected 12 RCTs were also subjected to a full text analysis for compliance with PICO. The Methods for all the RCTs were scrutinised to find out if clear randomisation procedures were carried out as had been stated in the abstracts. A total of 11 RCTs proceeded for data abstraction. The details of the excluded studies are presented in Appendices 8 and 9. The systematic review (Ratilal et al 2008) was excluded from the final analysis because individual studies which complied with PICO were retrieved and analysed. Figure 3.1 illustrates this.

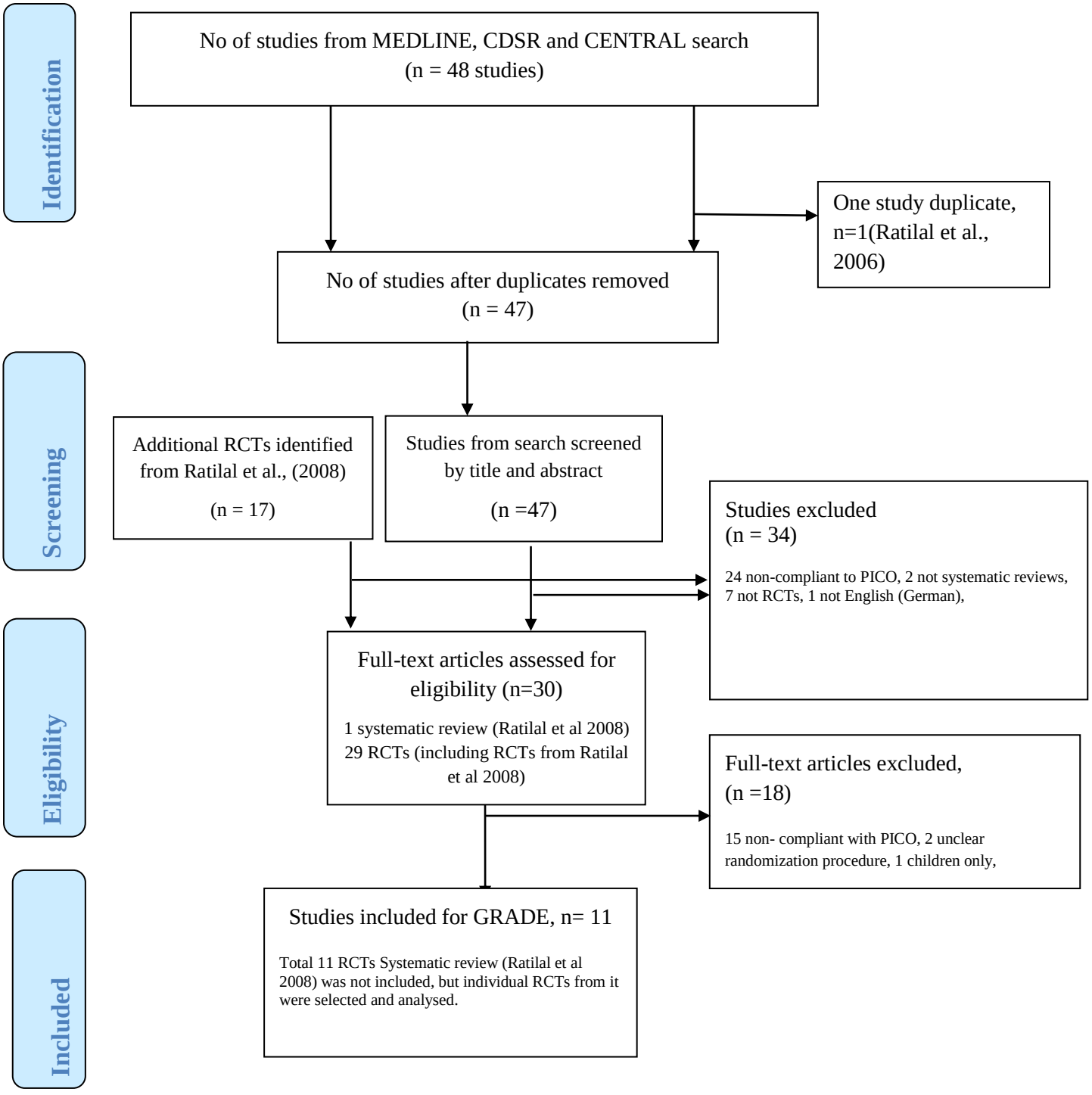

Figure 3.1: PRISMA Flow Diagram for the Included Studies

3.3.7. Data Abstraction:

Comprehensive data abstraction from the selected studies was done. One investigator abstracted the data, which was verified by the second investigator. The abstraction is summarised in Table 3.1. Data abstracted from the additional RCTs selected from the Ratilal et al., 2008 study, is summarized in Table 3.2.

Table 3.1: Studies Included in the Systematic Review

Author/year	Study design &Sample size, n	Population	Intervention	Comparator	Outcome
Ratilal et al., 2008	Systematic review of 17 randomised studies, n= 2,134	Patients of any age undergoing intracranial ventricular CSF shunt surgical procedures.	Perioperative Systemic antibiotics at any dosage AIC shunt systems	Placebo Standard catheters	Evidence of infection in: • Shunt equipment, • Overlying wound, • CSF • Site related to distal drainage route • Organism identified from tissue cultures • Material in and around the shunt • Cultures from fluid or CSF drawn from the shunt system Death from CNS infection Shunt revision Adverse events caused by antibiotics
Djindjian et al.,; 1990	Randomized double blind study n=356 No details on blinding Randomization procedures unclear No allocation concealment Duration 27 months Study site : France	Patients undergoing clean neurosurgery of ≥ 2hrs Age not specified Study site= France Patients characteristics clearly described	Oxacillin 200mg/kg/24 hrs in 4 divided doses n=171	Placebo n= 185	Surgical site infection as defined by the Malis criteria or by clinical judgement of the attending surgeon Follow up 1week to 10 weeks
Petignat et al.,; 2008	Double blind placebo controlled trial n=1,237 study duration 59 months computer generated randomization double blinding done- surgeon, patient, investigator allocation concealment done Study site: Switzerland	Patients 18-86 yrs undergoing surgery for herniated disc Hospital based study Study site= Switzerland Patients characteristics clearly described	Cefuroxime 1.5g single dose n= 613	Placebo n= 624	Primary • Surgical site infection as defined by CDC criteria Secondary • Non SSIs • Drug toxicity • Adverse drug events (allergic reaction or anaphylactic shock) • Follow up 6 weeks to 6 months

Table 3.2: Characteristics of Studies Selected from Ratilal 2008

Author/year	Study design & Sample size, n	Population	Intervention	Comparator	Outcome
Blomstedt, 1985	Randomised, placebo controlled, double blinded n= 174 unclear allocation concealment Site: Finland	Patients > 12 years Patients characteristics clearly described	Trimethoprim 90mg-sulfamethoxazole 400mg N=87	Placebo N=87	Wound infection Shunt infection Follow up minimum 6 months
Bullock 1988	Randomized, placebo controlled, double blinded, n=417 Allocation concealment done Site: South Africa	Any age Patients characteristics clearly described	Piperacillin 2g iv N= 48 Results for others not reported	Placebo N=56	Sepsis defined as: • Discharge from wound • Meningitis • Positive culture from exudate Follow up 90 days
Djindjian 1986	Randomised, controlled, not blinded, n= 60 Unclear allocation concealment France	Any age	Oxacillin 200mg/kg/day or Oxacillin 6x2g for adults + standard shunt N= 30	Standard shunt, no antibiotic N=30	CSF infection: • Meningitis • Abscess of wall with meningeal reaction • CSF cell count Follow up minimum 6 months
Govender 2003	Randomized, controlled, single blinded n=153 unclear allocation concealment Site: South Africa and UK	Any age	AIC impregnated with clindamycin and rifampicin + Cephalosporin iv pre and postoperatively N= 50	Standard shunt + Cephalosporin Iv Preoperatively and postoperatively N= 60	Shunt infection • Evidence of infection on shunt equipment, overlying wound, CSF, distal drainage route, site related to ventriculoperitoneal shunt Shunt revision due to infection/ no infection Mortality Follow up median 9 months (1-20 months)
Rocca 1992	Randomised, controlled trial, n=78 Unclear allocation concealment France	Any age	Cefamandole 1.5g iv preoperatively and postoperatively N= 13	No antibiotic N=14	Local and remote infections defined by: • Discharge from wound • Fever • Leucoytosis • Positive culture Follow up 15 days Duration 2yrs
Schmidt, 1985	Randomised, controlled, not blinded, n=152 Duration 18 months Allocation concealment done Denmark	Any age Patients characteristics clearly described	Methicillin 200mg/kg in 6 doses within 24hrs N= 79	No antibiotic N= 73	Shunt infection defined by: • Clinical signs of infection • Septicaemia • Peritonitis • Meningitis • Bacterial cultures Mortality Follow up min 6 months
Young, 1987	Randomised, controlled, single blinded, n=846 Duration – 56 months Allocation concealment done USA	Any age Patients characteristics clearly described	Cefazolin 1g and gentamicin 80mg in adults or 1mg/kg and 25mg/kg in children n= 64	No antibiotic n= 69 Unreported results for the rest of the patients	Post - operative infection on positive culture of: Wound infection Meningitis, Ventriculitis Follow up 1 year

Zabramski 2003	Randomised controlled trial, n= 306 Duration 27 months Allocation concealment done USA	≥ 18 years Patients characteristics clearly described	Catheter impregnated with minocycline and rifampicin + second generation cephalosporin n= 149	Standard non-impregnated silicone catheter + second generation cephalosporin n= 139	CSF infection defined as positive CSF culture Mortality Follow up 1 week
Zentner, 1995	Randomised controlled trial, n=129 Duration 1 year Allocation concealment done Germany	Any age Patients characteristics clearly described	Cefotiam iv 2g for adults n= 67	No antibiotics n= 62	Shunt infection defined by: Clinical symptoms Elevated cell counts Bacterial contamination of CSF requiring shunt removal and antibiotic therapy Adverse events of antibiotics Follow up 6 months

Adapted from Ratilal et al., 2008

3.3.8. Meta- Analysis:

A meta- analysis of the included studies was carried out to determine the overall estimate of effect and aid in evaluating the quality of evidence using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system. A meta-analysis is defined as "The statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating the findings" (Gordis, 2014).) RevMan (Review Manager) software version 5 was used in the meta- analysis.

Two meta-analyses were performed, based on the interventions. The first intervention considered was antibiotics versus placebo; the second intervention focused on antibiotic impregnated shunt catheters versus standard shunts. One study could not be included in the meta-analysis (Djindjian 1986) because it compared use of systemic antibiotics or no antibiotics in patients with standard shunts. For this study, a narrative synthesis was done. The following data was abstracted from the studies per outcome, which was in turn used in the meta-analyses, as summarised in Table 3.3.

Table 3.3: Data Abstracted for Meta-analysis

Study	Estimate of effect	No in Treatment group	No in comparator
Outcome 1: All-Cause Mortality			
Govender 2003	OR 2.11 (0.48, 9.31)	5/50	3/60
Zabramski 2003	OR 1.38 (0.74, 2.58)	28/149	20/139
Outcome 2: Surgical site Infections			
Blomstedt 1985	OR 0.23 (0.07,0.73)	4/62	14/60
Bullock 1988	OR 0.38 (0.04, 3.74)	1/48	3/56
Djindjian 1986	OR 0.14 (0.02,1.23)	1/30	6/30
Rocca 1992	OR 3.48 (0.13, 93.30)	1/13	0/14
Schmidt 1985	OR 1.68 (0.47.5.98)	7/79	4/73
Young 1987	OR 0.53 (0.05, 6.01)	1/64	2/69
Zentner 1995	OR 0.54 (0.17, 1.76)	5/67	8/62
Petignat et al., 2008	OR 0.45 (0.29, 1.03)	8/613	18/624
Djindjian 1990	OR 0.12 (0.01, 0.92)	1/171	9/185
Govender 2003	OR 0.32 (0.08, 1.23)	3/50	10/60
Zabramski 2003	OR 0.13 (0.03, 0.60)	2/149	13/139
Outcome 3: Non –Surgical Site Infections:			
Djindjian 1990	OR 1.09 (0.44, 2.68)	10/171	10/185
Petignat et al., 2008	OR 1.02 (0.50, 2.06)	16/613	16/624
Outcome 4: Shunt Revision:			
Govender 2003	OR 0.66 (0.26, 1.67)	9/50	15/60
Outcome 5: Adverse Effects of Antibiotics:			
Petignat et al., 2008	OR 0 (0.0, 0.0)	0/613	0/624
Zentner 1995	OR 0 (0.0, 0.0)	0/67	0/62

3.4. RESULTS:

The results of the meta-analyses performed and grading of evidence for quality are outlined in this section.

3.4.1. Antibiotics versus Placebo/ No Antibiotics:

Eight studies evaluated the effectiveness of systemic antibiotics versus placebo or no antibiotics, and were included in this meta-analysis. Several forest plots were generated based on each outcome of interest.

3.4.1.1. Outcome 1: All-Cause Mortality:

All -cause mortality is a critical outcome in neurosurgical patients. Antimicrobial prophylaxis has been shown to reduce mortality that is associated with surgical site infections (Bratzler et al., 2013).In this meta- analysis which compared the use of antibiotics versus placebo or no antibiotics, there were no such events as none of the included studies evaluated this outcome. It is therefore not possible to establish the effect that the use of antimicrobial prophylaxis versus no antimicrobial prophylaxis has on all-cause mortality.

3.4.1.2. Outcome 2: Development of Surgical Site Infections:

All 8 studies included in our systematic review evaluated the development of surgical site infections as a primary outcome. Several clinical and laboratory criteria were used to define surgical site infections and/or shunt infection and these include: discharge from wounds, CSF cell count and bacterial contamination, clinical signs and symptoms of infection, Clinical criteria like the CDC and Malis criteria for diagnosis of surgical site infections, positive cultures from exudates, evidence of infection from shunt equipment, evidence of infection on overlying

wounds and leucocytosis. Ventriculitis and meningitis were common infections, and peritonitis occurred in studies where patients had ventriculoperitoneal shunts. The results of the meta-analysis are summarised in Figure 3.2.

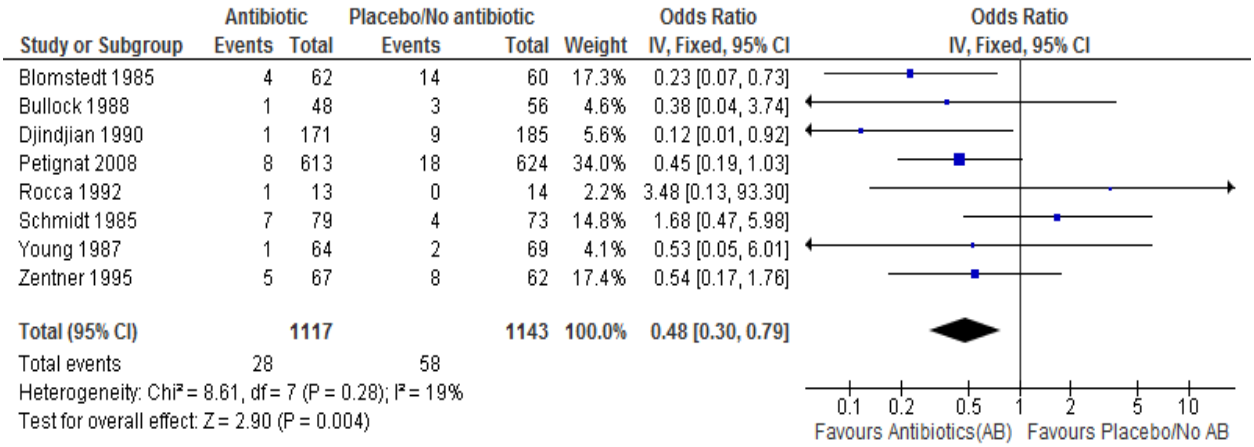

Fig 3.2: Forest Plot for Outcome 2, Surgical Site Infections

From this meta-analysis, use of systemic antibiotics demonstrated an overall protective effect of 52% from development of surgical site infections [OR 0.48 (95% CI 0.30, 0.79)]. 48 out of 100 patients are more likely to develop surgical site infections if they are not on antimicrobial prophylaxis. In six studies, use of antimicrobial prophylaxis demonstrated a protective effect (Blomstedt 1985, n=174; Bullock 1988, n=417; Djindjian 1990, n=356; Petignat 2008, n=1,237; Young 1987,n=846; and Zentner 1995,n=129). There was low observed heterogeneity across the studies as the I^2 statistic was 19%. Generally, an I^2 statistic of above 40% indicates significant heterogeneity across studies (Schunemann, 2013).

3.4.1.3. Outcome 3: Non-Surgical Site Infections:

Two studies, (Djindjian 1990 and Petignat 2008), which used systemic antibiotics versus no antibiotics, evaluated patients for development of non-surgical site infections. A total of 784

patients were on antibiotics while 809 patients were on no antibiotic or placebo. The average effect size of the studies for this outcome was about 1 [OR 1.04 (95% CI 0.60, 1.82)]. However, there's a slight leaning of the studies towards placebo, or no antibiotics, but this is not significant. Overall, there was no difference in development of NSSIs between patients who were on antibiotics or those who were on placebo. This means that development of non-surgical site infections is not prevented by antimicrobial prophylaxis. The I^2 statistic is zero, which suggests no heterogeneity between the effect sizes of the two studies.

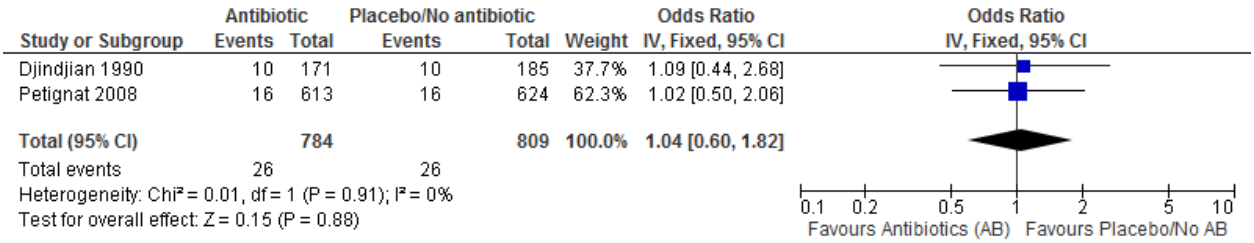

Fig 3.3: Forest Plot for Outcome 3, Non-Surgical Site Infections

3.4.1.4. Outcomes 4: Shunt Revision

There were no events reported for outcome 4 (Shunt Revision) because the studies included in this meta-analysis considered only systemic antimicrobial prophylaxis as opposed to antibiotic impregnated shunts.

3.4.1.5. Outcome 5: Adverse Effects of Antibiotics:

There were no reported events for Outcome 5 (Development of adverse effects of antibiotics).

3.4.1.6 Grading of Evidence for Systemic Antibiotics versus No Antibiotics/Placebo

GRADE Pro GDT version 2015 software was used to evaluate the quality of evidence of the 8 RCTs that were included. The RCTs were assessed for study design, risk of bias, inconsistency, indirectness and imprecision. The outcome measures were rated as critical or important depending on the impact to patients.

GRADE evaluates the quality of evidence per outcome from pooled studies. Data from included studies was used to generate an estimate of each outcome as well as measures of uncertainty associated with the outcomes, in this case, confidence intervals. Overall, the evidence for antimicrobial prophylaxis was of moderate quality. Moderate quality evidence means that "we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there's a possibility that it is substantially different" (Schunemann et al.,; 2013). The overall quality of evidence of a body of evidence is determined by the quality rating of the critical outcome and not an average of the quality ratings (Schunemann et al.,; 2013). The results of the quality of evidence from GRADE are summarised in Table 3.4.

Table 3.4: GRADE Summary of Findings for Antimicrobial Prophylaxis versus Placebo

Antimicrobial prophylaxis compared to placebo or no antimicrobial prophylaxis for prevention of neurosurgical site infections

Patient or population: adult neurosurgical patients

Setting: low and middle income countries

Intervention: antimicrobial prophylaxis

Comparison: placebo or no antimicrobial prophylaxis

Outcomes	Anticipated absolute effects*(95% CI)		Relative effect (95% CI)	№ of patients (studies)	Quality of the evidence (GRADE)	Importance
	Risk with placebo or no antimicrobial prophylaxis	Risk with antimicrobial prophylaxis				
Development of surgical site infections (SSIs) assessed with: wound infection, positive cultures, CDC classification, Malis Criteria, fever, leukocytosis, clinical signs follow up: range 1 weeks to 1 years	**Study population**		**OR 0.48** (0.30 to 0.79)	2260 (8 RCTs)	⊕⊕⊕◯ MODERATE [1]	CRITICAL
	51 per 1000	**25 per 1000** (16 to 41)				
Development of non-surgical site infections (NSSIs) assessed with: pneumonia, UTIs follow up: range 1 weeks to 6 months	**Study population**		**OR 1.04** (0.60 to 1.82)	1593 (2 RCTs)	⊕⊕⊕◯ MODERATE [1]	CRITICAL
	32 per 1000	**33 per 1000** (20 to 57)				
Development of adverse effects of antibiotics (A/Es) assessed with: Clinical signs follow up: mean 6 months	**Study population**		not estimable	1366 (2 RCTs)	⊕⊕⊕◯ MODERATE [1]	IMPORTANT
	0 per 1000	**0 per 1000** (0 to 0)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. unclear allocation concealment, random sequence allocation, blinding, incomplete outcome data, selective reporting for all studies

The first outcome of all-cause mortality could not be graded because the studies included did not evaluate this outcome.

3.4.1.6. Outcome 2: Development of Surgical Site Infections:

A total of 2,260 patients were included in all the 8 studies which evaluated this outcome. Patients who were on antimicrobial prophylaxis were less likely to develop surgical site infections compared to those who were on placebo or no antibiotic. 28 out of 1117 patients on antimicrobial prophylaxis developed infection while 58 out of 1143 of those without prophylaxis developed infection [OR 0.48 (95% CI 0.30. 0.79)]. The overall quality of evidence for this critical outcome was moderate, based on the five GRADE criteria: Risk of bias, indirectness, inconsistency, imprecision and publication bias.

3.4.1.7. Risk of Bias:

There was a high risk of selection bias in seven studies (Blomstedt, 1985; Djindjian et al., 1990; Petignat, 2008; Rocca 1992; Schmidt, 1985; Young, 1987; Zentner 1995) due to unclear allocation concealment procedures. Bullock 1988 had clear allocation concealment procedures, hence a low risk of selection bias. The details of allocation concealment are found in Appendix 15. Four studies (Bullock, 1988; Petignat, 2008; Schmidt, 1985; Young, 1987; Zentner, 1995) described in detail how they came up with the randomisation sequence. These studies had a low risk of selection bias due to randomisation. There was a high risk of selection bias in three studies (Blomstedt, 1985; Djindjian, 1990; Rocca, 1992) because random sequence generation methods were either not mentioned or were unclear.Lack of blinding occurs when patients, those administering the interventions and those recording outcomes are aware of the interventions

allocated to the patients in a trial. Double blinding was done in two studies (Blomstedt, 1985; Bullock, 1988) using interventions that looked identical. One study, (Young, 1987) was single blinded. In one trial (Schmidt 1985), patients were not blinded while in four other trials, (Djindjian et al.,1990; Petignat et al., 2008; Rocca, 1992 ; Zentner, 1995) it was unclear whether blinding was done though Djindjian et al., 1990 reported that the intervention and placebo were identical. Because of this, there was an overall high risk of performance bias. The risk of detection bias was overall, very high. This is because blinding to outcome assessment was done only in one study (Bullock 1988). The blinding procedure was unclear in six studies (Blomstedt, 1985; Djindjian, 1990; Petignat, 2008; Rocca 1992; Young, 1987; Zentner 1995). Blinding was not done in one study (Schmidt, 1985). The details of the blinding procedures are found in Appendix 15.

There was incomplete outcome data in two studies (Bullock, 1988; Rocca, 1992). All the outcome data was accounted for in three studies (Blomstedt, 1985; Djindjian, 1990; Petignat , 2008) while for three other studies (Schmidt, 1985; Young, 1987; Zentner, 1995), it was unclear whether all the outcome data was accounted for. Therefore, attrition bias was evident across the studies. There was an overall high risk of reporting bias. This is because selective reporting was observed in two studies (Bullock, 1988; Rocca, 1992). There was no selective reporting in three studies (Blomstedt, 1985; Young, 1987; Zentner, 1995) while it was unclear whether there was selective reporting in three studies (Djindjian, 1990; Petignat, 2008; Schmidt, 1985). It was unclear whether there were any other forms of bias in all studies except for Petignat 2008 which had no evidence of any other bias. Figure 3.4 illustrates this.

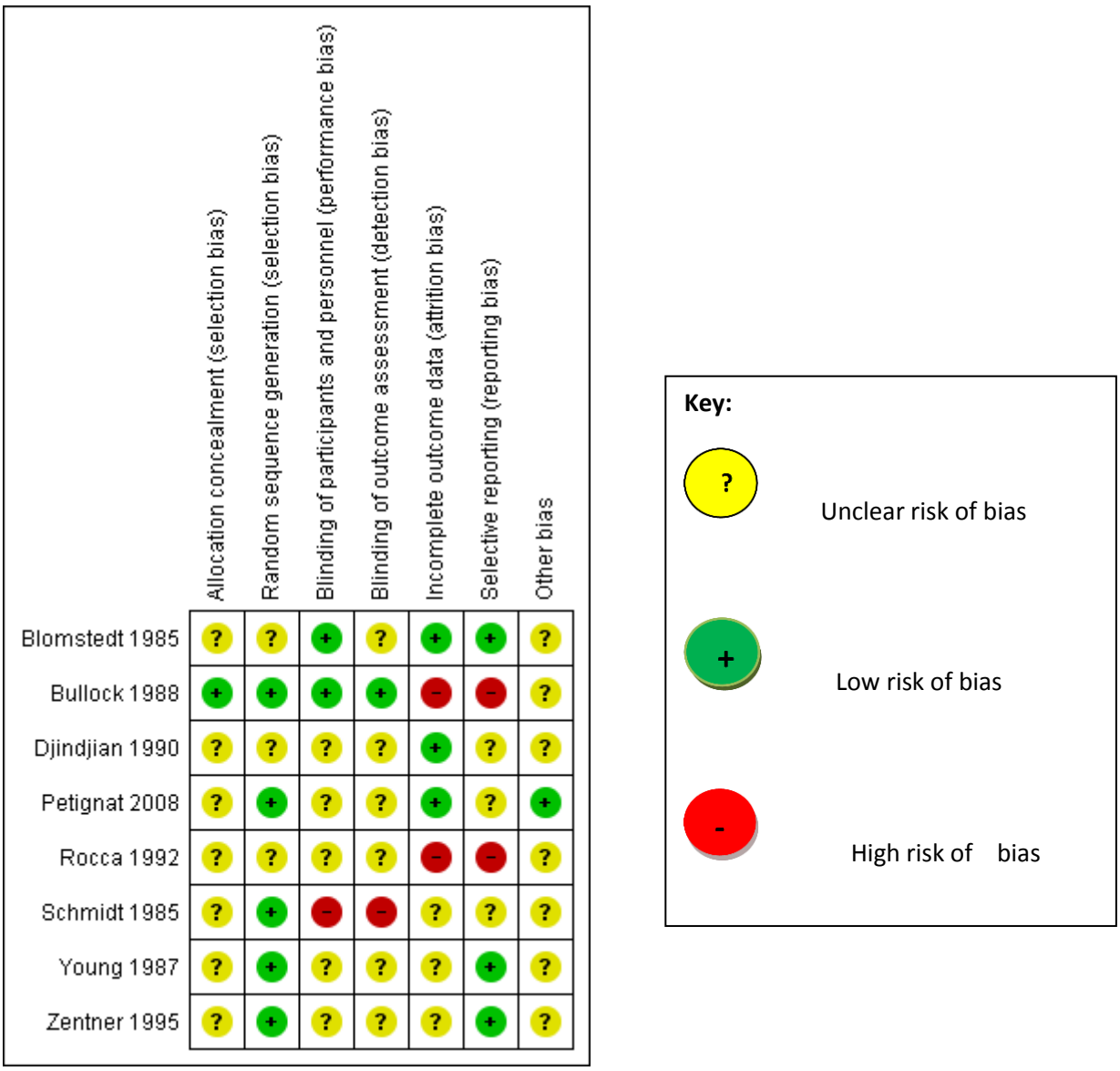

Figure 3.4: Risk of Bias Summary: Review Authors' Judgments about Each Risk of Bias Item for Each Included Study.

3.4.2.8. Indirectness:

Indirect evidence refers to research that "does not compare to the interventions we are interested in, delivered to the population we are not interested in and measures outcomes that are not important to our study population" (Schunemann et al., 2003). There are several sources of indirectness according to the GRADE criteria: differences in population, differences in interventions and their applicability and differences in outcome measures (Schunemann et al., 2003).

Indirectness with regard to Population: We examined all the studies for this outcome and there was no indirectness with regard to population. All the studies that were included had patients with characteristics that match our patient population. All patients were adults undergoing neurosurgical procedures. It should however be noted that ten of the studies were carried out in high income countries with Caucasian populations (USA, France, Denmark, the United Kingdom, Germany, Italy, Switzerland and Finland). One study was carried out in an Asian country (Hong Kong) while two were carried out in South Africa (Bullock 1988 and Govender, 2003), which are similar to our patient population in terms of socio-economic status and disease burden. Most of the patients were from Caucasian populations. Race and ethnicity could influence the pharmacokinetic and pharmacodynamic profiles of the antibiotics given, hence their effectiveness. Overall, it should be concluded that indirectness with regard to population does not arise.

Indirectness due to Intervention: Adult patients undergoing neurosurgical procedures were given antibiotics for prophylaxis systemically. Eight studies administered systemic antibiotics

versus placebo or no antibiotics. The antibiotics administered include: Oxacillin 200mg/kg/ 24 hours in divided doses (Djindjian, 1990); Cefuroxime 1.5g single dose (Petignat et al., 2008); Trimethoprim 90mg- Sulfamethoxazole 400mg (Blomstedt, 1985); Piperacillin 2g iv (Bullock, 1988); Cefamandole 1.5g iv (Rocca 1992); Methicillin 200mg/kg (Schmidt 1985); Cefazolin 1g and Gentamicin 80 mg (Young, 1987) and Cefotiam 2g iv (Zentner, 1995). The antibiotics administered are commonly available in our settings except Oxacillin and Methicillin, which are not available in the Kenyatta National Hospital formulary. These drugs are administered orally or intravenously, just like in our setting. Indirectness due to intervention does not therefore arise. The choice of these antibiotics for every setting is guided by local guidelines, antimicrobial resistance patterns, Methicillin Resistant *Staphylococcus aureus* (MRSA) prevalence, formularies and cost of drugs as well as patient characteristics, which all vary across settings. Indirectness due to interventions does not arise.

Indirectness due to Outcome Measures: It does not arise because this outcome of interest is critical to our study setting. The criteria used to evaluate this outcome measure in the systematic review are similar to the methods used in evaluating such outcomes in our study setting.

3.4.1.9. Imprecision:

Precision refers to the confidence in estimates of effect. Imprecision results when there are very few patients, few events and resultant wide confidence intervals. This can result in uncertainty about the results and lead to rating down of evidence. We applied the optimal information size (OIS) rule (Schunemann et al., 2013) to test for imprecision across this outcome. The OIS rule states that “if the total number of patients included in a systematic review is less than the number

of patients generated by a conventional sample size calculation for a single adequately powered trial, consider rating down for imprecision." Considering this rule, there was no imprecision for this outcome, because a total of 2,260 patients were enrolled in these studies, which is more than the number of patients generated by a conventional sample size calculation. Additionally, the confidence interval for the estimate of effect is narrow and does not include 1. The events on the control arm are twice as many as the events in the treatment arm. This further rules out imprecision.

3.4.1.10 Inconsistency:

Inconsistency refers to unexplained heterogeneity of results (Schunemann et al., 2013). Three tests were used to check for inconsistency. Using the eye ball test, the confidence intervals were assessed and they were found to be overlapping. There was minimal heterogeneity. The Chi squared test yielded a p value of 0.28, which is greater than 0.05. This indicates that there was no evidence from the p value to show heterogeneity across studies. The I^2 statistic was 19%, less than 40%, which indicates minimal heterogeneity across included studies (Schunemann et al., 2013).

3.4.1.11. Publication Bias:

Publication bias is the "systematic underestimation or overestimation of the underlying beneficial or harmful effect due to the selective publication of studies" (Schunemann et al., 2013). A comprehensive search was carried out in the accessed databases for these studies to minimise publication bias. The studies obtained from this comprehensive search were too few to generate a funnel plot, so publication bias could not be detected.

3.4.1.12. Outcome 3: Development of Non-Surgical Site Infections:

Two trials, (Djindjian, 1990; and Petignat et al., 2008) considered this as a secondary outcome. Non- surgical site infections were defined as a diagnosis of pneumonia, urinary tract infections and sepsis. A meta- analysis gave the estimate of effect for this outcome as shown in Figure 3.3. The five GRADE criteria were used to evaluate the quality of evidence for this outcome.

3.4.1.13. Risk of Bias:

When the risk of bias for each of the included studies was determined, Petignat 2008 had allocation concealment while Djindjian 1990 had unclear allocation concealment. The latter study therefore had a high risk of selection bias. Petignat et al., 2008 used computer generated randomisation, while Djindjian 1990 had no clear randomisation procedure, hence a high risk of selection bias in the latter study. There was a high risk of performance bias because the blinding procedure for Djindjian, 1990 was unclear. Petignat et al., 2008 blinded surgeons and patients to the intervention. For this study, the risk of performance bias was low. For Djindjian, 1990, it was not clear whether there was selective outcome reporting. There was no evidence of any other bias in Petignat, 2008. Both studies used per protocol analysis. Overall, the risk of bias for this outcome was serious and led to rating down the quality of evidence from high to moderate. The risk of bias for these two studies is summarized in figure 3.5.

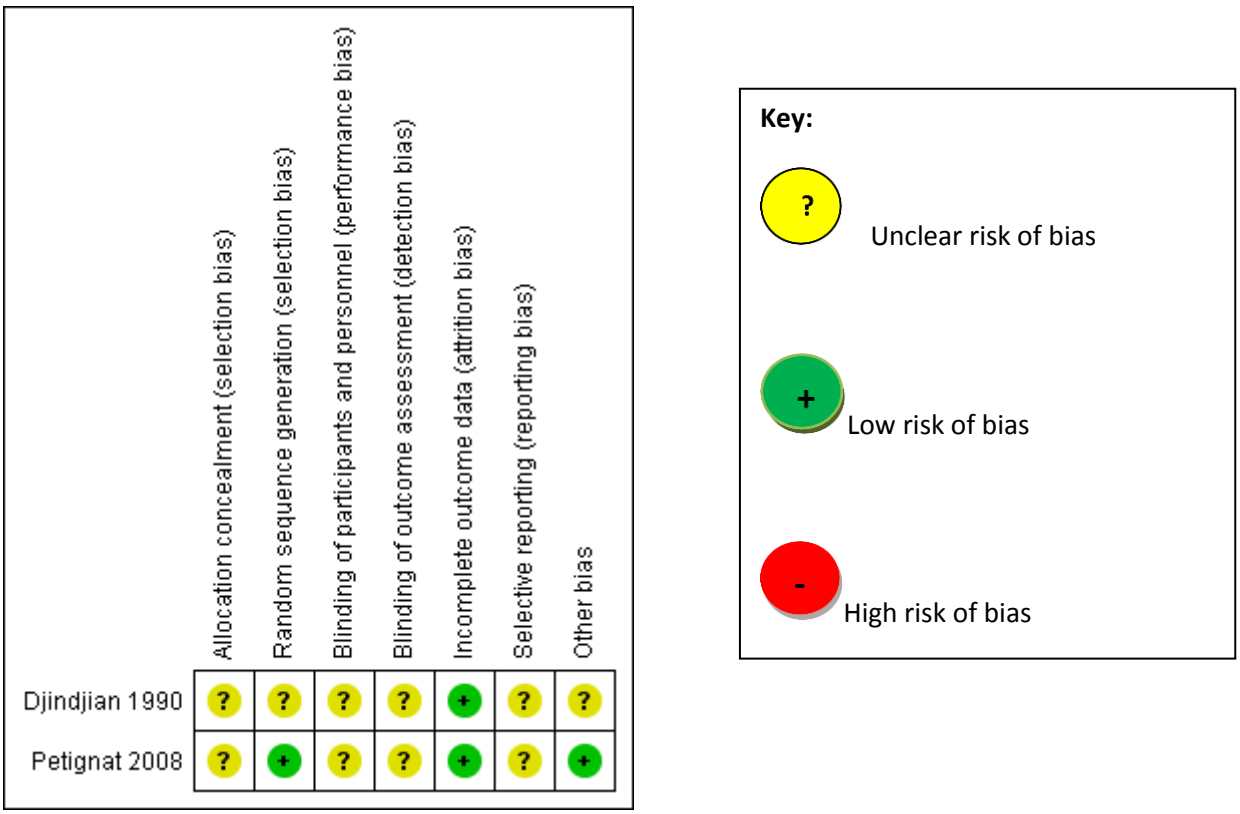

Figure 3.5: Risk of Bias Summary: Review Authors' Judgments about Each Risk of Bias Item for Each Included Study.

3.4.1. 14. Indirectness:

There was no significant indirectness with regard to population, interventions, their applicability and outcome measures to warrant downgrading the evidence for this outcome to moderate quality. In the Djindjian 1990 study, patients were randomised to oxacillin or placebo. Oxacillin is not commonly used in our hospital setting due to unavailability in the market, as well as increased resistance patterns. This is an old study, which could have been carried out before newer penicillinase- resistant penicillins were available in the market. This indirectness is

minimal and did not warrant downgrading the quality of evidence. Petignat et al., 2008 randomised patients to cefuroxime, a second generation cephalosporin which is available and widely used in our setting for antimicrobial prophylaxis. Therefore, indirectness with regard to population, interventions, applicability and outcome measures was minimal.

3.4.1.15. Inconsistency:

The eyeball test shows overlapping confidence intervals. The p value from the Chi square test is 0.91, which indicates no heterogeneity in the included studies. The I^2 statistic for all studies form the meta-analysis was 0% less than 40%, which showed that the studies were perfectly homogeneous as shown in Figure 3. There was therefore no inconsistency.

3.4.1.16. Imprecision:

There was a wide confidence interval which included 1. The total number of events in the included studies was few. On applying the OIS rule, imprecision was detected.

3.4.1.17. Publication bias:

A comprehensive search from the available databases was done to minimise publication bias.

The studies that were included were too few to generate a funnel plot, so publication bias could not be detected.

3.4.1.18. Outcome 4: Development of Adverse Effects of Antibiotics:

From the meta-analysis, there were no events reported, although 2 studies (Petignat et al., 2008 and Zentner, 1995) assessed the outcome. The estimate of effect for this outcome could therefore not be obtained. The five GRADE criteria for evaluation of the quality of evidence were used for these studies. Petignat et al., 2008 and Zentner, 1995 showed a serious risk of bias. In the

Zentner 1995 study, it was unclear whether there was selection bias, performance bias, detection bias and attrition bias as illustrated in Figure 4. Petignat et al., 2008 also demonstrated similar risk of bias. This warranted the downgrading of the quality of evidence to moderate. Since there were no events and confidence intervals, it was not possible to assess imprecision. Inconsistency of results was not detected, neither was publication bias.

3.4.2. Meta-Analysis 2: Antimicrobial Impregnated Shunt Catheters versus Standard Shunts:

A second meta- analysis was performed, which evaluated the use of antibiotic impregnated shunt catheters (AICs) versus use of standard shunts. Two studies (Govender 2003 and Zabramski 2003), were included in the meta-analysis and they studied two outcomes: all -cause mortality and surgical site infections. The results are illustrated in Figure 3.6.

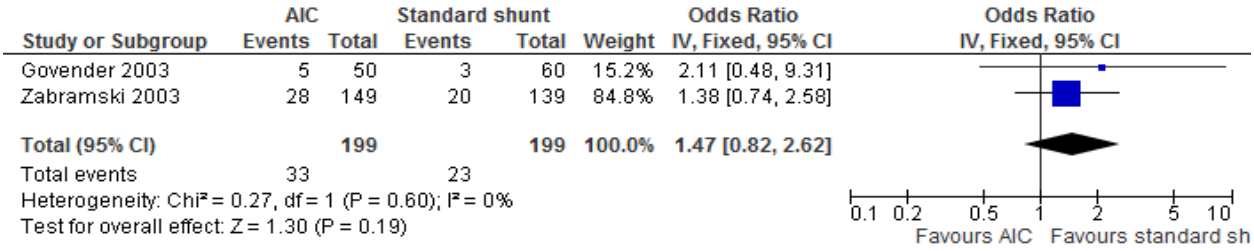

Figure 3.6: Outcome 1, All-cause Mortality

Two studies evaluated all- cause mortality as a critical outcome. The use of antibiotic impregnated shunt catheters was associated with a higher risk of mortality compared to the use of the standard shunt [(OR 1.47(95% CI 0.82, 2.62)]. This is corroborated in the individual studies; Govender, 2003 [(OR 2.11 (95% CI 0.48, 9.31)], where patients with AICs were twice as likely to die compared to those with standard shunts and Zabramski, 2003 [(OR 1.38 (95% CI 0.74, 2.58)], where patients with AICs were 1.4 times more likely to die than those with standard shunts.

3.4.2.1. Risk of Bias:

Govender, 2003 and Zabramski, 2003 had a high risk of bias. The study conducted by Govender, 2003 had unclear allocation concealment, unclear generation of randomization sequence, unclear attrition, selection bias and publication bias. Zabramski, 2003 did not make it clear how allocation concealment was done, although they had a clear randomization sequence using random numbers. It was not clear if blinding was done to patients, personnel and to the outcome. It was also not clear if there was reporting and publication bias. These setbacks warranted downgrading of the evidence to moderate quality. This is illustrated in Figure 3.7.

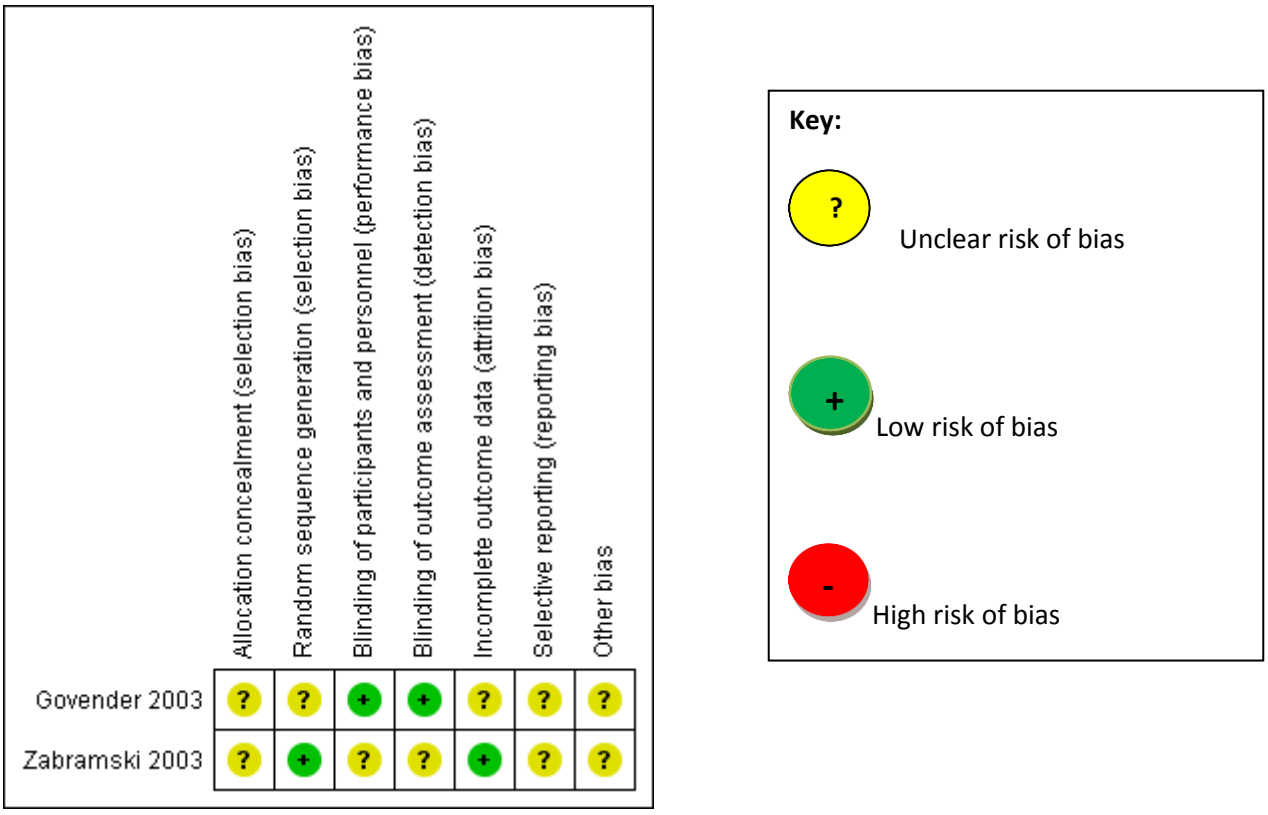

Figure 3.7: Risk of Bias for studies included in all-cause mortality outcome

3.4.2.2. Indirectness:

There was indirectness with respect to intervention. Antimicrobial impregnated shunts are not commonly used in our setting because they are too expensive. One AIC costs approximately KES. 40,000 (US Dollars 400), which is beyond the reach of the patients who are treated at Kenyatta National Hospital. In addition, there is limited expertise in their use because most of those who operate on these patients are surgeons undergoing training and might not have the skill to insert AICs. This warranted the downgrading the level of evidence from moderate to low quality.

3.4.2.3. Inconsistency:

The eyeball test on the forest plot revealed overlapping confidence intervals. The p value from the Chi square test was 0.39, which indicated homogeneity. There was no heterogeneity in the estimate of effect between studies as demonstrated by the I^2 statistic of zero, hence no inconsistency for this outcome. The quality of evidence therefore remained low.

3.4.2.4. Imprecision:

There was Imprecision because the included studies did not comply with the OIS rule. There were also wide confidence intervals. This led to the downgrading of evidence from low quality to very low quality evidence.

3.4.2.5. Publication bias:

A comprehensive search was done across the relevant databases to minimise publication bias. The studies obtained were too few to generate funnel plots, so we were not able to detect publication bias.

The results of the meta-analysis are summarised in Figure 3.8.

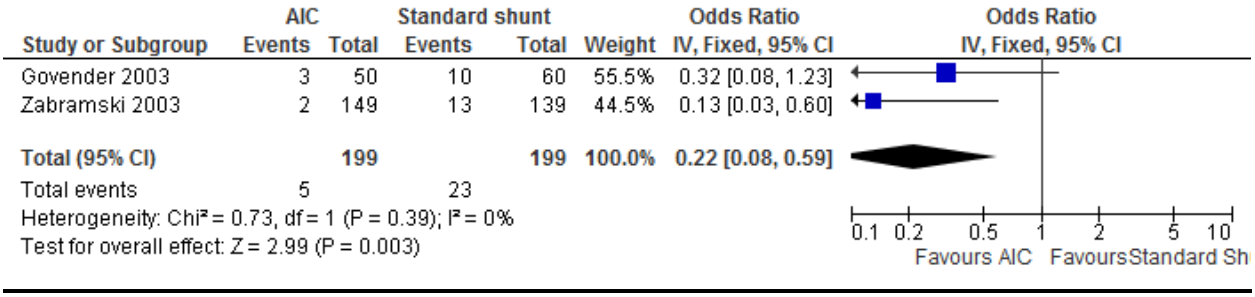

Figure 3.8: Outcome 2, Surgical Site Infections

The forest plot shows that use of AICs has a strong protective effect against development of surgical site infections [OR 0.22 (95% CI 0.08, 0.59)]. The protective effect of AIC is about five times greater than that of standard shunts.

3.4.2.5. Risk of bias:

Govender, 2003 and Zabramski, 2003 were associated with a high risk of bias. The former study had unclear allocation concealment, unclear generation of randomization sequence, unclear attrition, selection bias, selective reporting and publication bias. Zabramski, 2003 did not make it clear how allocation concealment was done, although they had a clear randomization sequence using random numbers. It was not clear if the patients and personnel were blinded to the outcome. Additionally, it was not clear if there was reporting and publication bias. These setbacks warranted downgrading of the evidence from high to moderate quality. Figure 3.9 illustrates the risk of bias of the two studies.

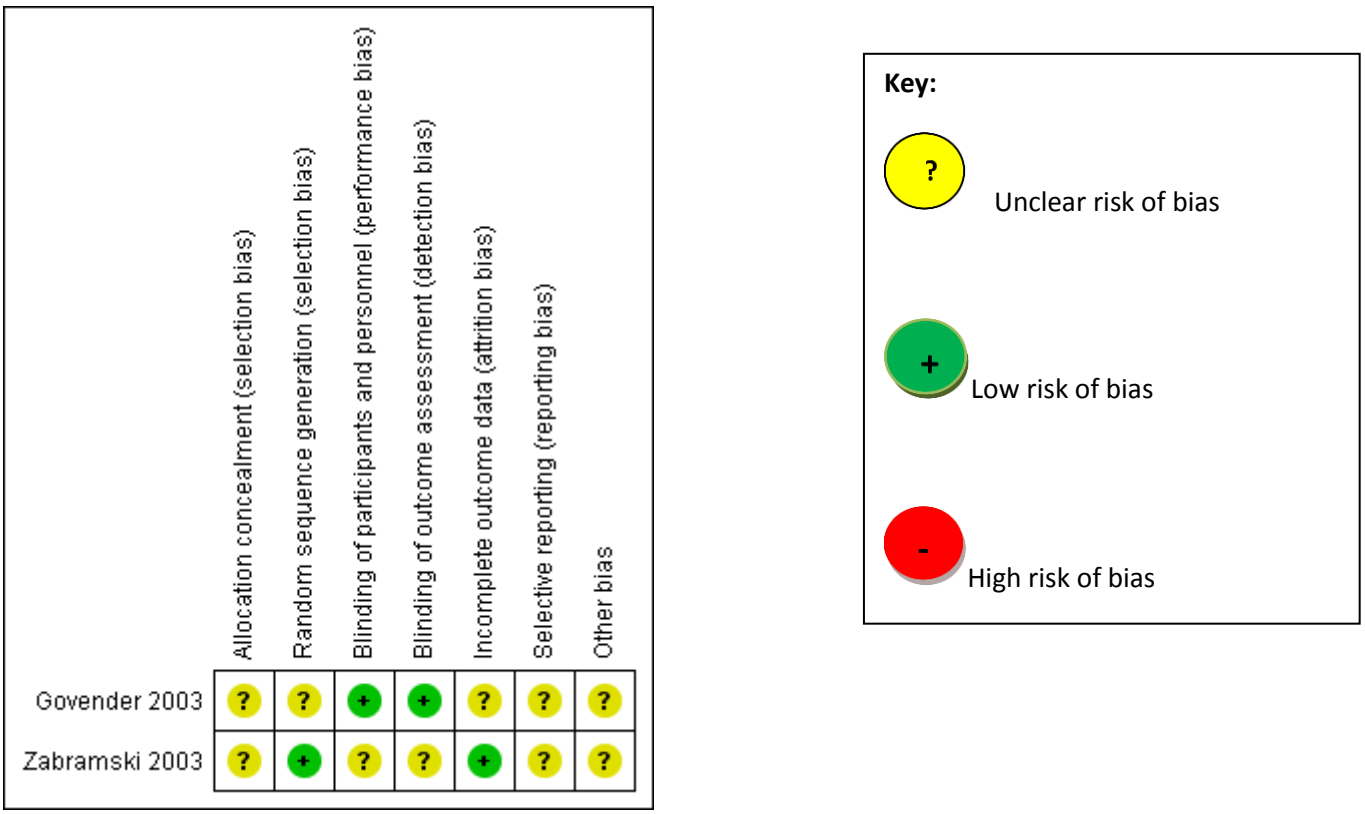

Figure 3.9: Risk of bias of included studies

3.4.2.6. Indirectness:

There was indirectness with respect to intervention. Antimicrobial impregnated shunts are not commonly used in our setting because they are too expensive. One AIC costs approximately KES 40,000 (US Dollars 400), which is beyond the reach of the patients who are treated at Kenyatta National Hospital. In addition, there's low expertise in their use because most of the surgeons who operate on these patients are surgeons in training who might not have the skill to administer AICs. Because of this, evidence was downgraded from moderate to low quality evidence.

3.4.2.7. Inconsistency:

The eyeball test on the forest plot revealed overlapping confidence intervals. The p value from the Chi square test was 0.39, which indicated homogeneity. There was no heterogeneity in the estimate of effect between studies as demonstrated by the I^2 statistic of zero, hence no inconsistency for this outcome.

3.4.2.8. Imprecision:

There was Imprecision because the included studies did not comply with the OIS rule. Although the studies were few with a narrow confidence interval in the estimate of effect, the number of events was very few. The level of evidence was downgraded from low to very low because of this.

3.4.2.9. Publication bias:

Publication bias was minimised following a comprehensive search across all the relevant databases. The studies in this meta-analysis were too few to generate a funnel plot, so the investigators were not able to detect publication bias.

3.4.2.10. Outcome 3: Non-Surgical Site Infections

There were no events for this outcome because the studies did not evaluate this outcome.

3.4.2.11. Outcome 4: Shunt Revision:

One study, Govender, 2003 evaluated this outcome. Patients were less likely to undergo shunt revision with AICs, compared to standard shunts [(OR 0.66 (95% CI 0.26, 1.67)].

There was a high risk of bias in this study. Therefore, the quality of evidence was downgraded from high to moderate quality. Since it was a single study, inconsistency could not be determined

for this outcome. Imprecision was noted because of the wide confidence intervals and few events. This warranted downgrading of the level of evidence from moderate to low. There was indirectness with respect to intervention. Antimicrobial impregnated shunts are not commonly used in our setting because they are too expensive. One AIC costs approximately KES 40,000 (US Dollars 400), which is beyond the reach of the patients who are treated at Kenyatta National Hospital. In addition, there's low expertise in their use because most of the surgeons who operate on these patients are surgeons in training who might not have the skill to administer AICs. Publication bias could not be detected for this single study. Because of this, the level of evidence was downgraded from low to very low.

3.4.2.12. Outcome 5: Adverse Effects of Antibiotics:

The two studies did not assess the adverse effects of antibiotics as an outcome, so there were no events. However, it is important to evaluate the effects of the combinations of antibiotics impregnated within the catheters as well as those concurrently administered systemically. These combinations could be a contributing factor to the all- cause mortality. Govender, 2003 used shunts impregnated with clindamycin and rifampicin. Additionally, cephalosporins were administered systemically, pre and post operatively. Zabramski, 2003 used shunts impregnated with minocycline and rifampicin, together with systemic second generation cephalosporins in the perioperative period.

3.4.2.13. Overall Quality of Evidence for AICS versus Standard Shunts:

GRADE Pro GDT Software version 2015 was used to evaluate the quality of evidence for this intervention. The quality of evidence supporting the use of AICs in our setting was very low, due

to serious indirectness, risk of bias and imprecision for all the critical outcomes. This means that "we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect." The quality of evidence is summarised in Table 3.5.

Table 3.5: GRADE Summary of Findings for AICs versus Standard Shunts:

Antimicrobial impregnated shunts compared to standard shunts for prevention of neurosurgical site infections

Patient or population: adult neurosurgical patients
Setting: low and middle income countries
Intervention: antimicrobial impregnated shunts
Comparison: standard shunts

Outcomes	Anticipated absolute effects*(95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with standard shunts	Risk with antimicrobial impregnated shunts				
Development of surgical site infections (SSIs) assessed with: wound infection, positive cultures, CDC classification, Malis Criteria, fever, leukocytosis, shunt infection clinical signs follow up: range 1 weeks to 20 months	Study population 116 per 1000	28 per 1000 (10 to 72)	OR 0.22 (0.08 to 0.59)	398 (2 RCTs)	⊕◯◯◯ VERY LOW [1,2,3]	CRITICAL
All- cause mortality (Death) assessed with: death follow up: range 1 weeks to 20 months	Study population 116 per 1000	161 per 1000 (97 to 255)	OR 1.47 (0.82 to 2.62)	398 (2 RCTs)	⊕◯◯◯ VERY LOW [1,2,3]	CRITICAL
Shunt Revision (Shunt. Rev) assessed with: Redo surgery follow up: range 1 weeks to 20 months	Study population 167 per 1000	117 per 1000 (49 to 250)	OR 0.66 (0.26 to 1.67)	110 (2 RCTs)	⊕◯◯◯ VERY LOW [1,2,3]	CRITICAL

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio;

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

unclear allocation concealment, random sequence allocation, blinding, incomplete outcome data, selective reporting for all studies
did not comply to IOS rule for imprecision
Indirectness. AICs are too expensive for our study setting

3.4.3. Studies Excluded from Meta-Analysis and Grade Evaluation:

3.4.3.1. Djindjian 1986:

This study included all patients with standard shunts and randomized the adults to systemic oxacillin 2g six times a day for adults or no antibiotic. The only outcome of interest in this study was the development of surgical site (shunt) infection. Use of oxacillin had an 86% protective effect from development of shunt infections [OR 0.14 (95% CI 0.02, 1.23)]. The other outcomes were not considered in this study.

3.5. DISCUSSION:

There are different causes of mortality in patients undergoing neurosurgical procedures. Haemorrhage, anaesthetic accidents, venous air embolism, stroke and infections are the leading causes. Factors that predispose patients to mortality include poor pre and post- operative clinical condition, old age, pulmonary embolism, venous air embolism and intracranial haematomas requiring evacuation (Hammers et al., 2010). Mortality can also result from adverse effects and anaphylactic reactions from drugs administered in the perioperative period (Bratzler et al., 2013). Antimicrobial prophylaxis has been shown to reduce infection related mortality in neurosurgical patients (Bratzler et al., 2013). Although this is a critical outcome, none of the studies evaluating systemic antibiotics versus placebo or no antibiotics evaluated this outcome. It is therefore difficult to establish the effect that the use of antimicrobial prophylaxis versus placebo/no antibiotic prophylaxis has on all-cause mortality.

In the second meta-analysis, whose intervention was antibiotic impregnated shunt catheters versus standard shunts, the use of antibiotic impregnated shunt catheters was associated with a

higher risk of mortality than standard shunts. In the Govender, 2003 study, five patients on AICs died, but the deaths were not attributed to the AICs but to the underlying pathological process, HIV positivity and brain tumours. Similarly, three patients on standard shunts died due to shunt unrelated causes. The Zabramski, 2003 study also recorded more deaths in the AIC group compared to the standard shunt group. There is paucity of data on the relationship between the use of intracranial ventricular shunts and all-cause mortality (Ratilal et al., 2006), although AICs have been shown to be effective in preventing surgical site infections, which in turn, reduces infection related morbidity and mortality (Parker et al., 2011).

Surgical site infections in neurosurgery contribute to significant morbidity, mortality, prolonged hospital stay and increased hospitalisation costs for neurosurgical patients, according to the CDC 2015. These infections can be superficial, deep seated or organ space (Kourbeti et al., 2012).Wound infections are the most common, followed by meningitis and ventriculitis. Less common surgical site infections include shunt infections, bone flap osteitis, osteomyelitis, Palacos infections, abscesses and epidural empyemas (Kourbeti et al., 2012).

The two meta-analyses demonstrated the effectiveness of systemic antibiotics as well as antibiotic impregnated shunts in preventing surgical site infections. These findings are consistent with other studies in literature which have demonstrated the same effect (Sciubba et al., 2005; Ratilal et al., 2009; Farber et al., 2011; Bratzler et al., 2013).

Non- surgical site infections contribute to significant morbidity and mortality in the neurosurgical patient population. They are also a risk factor for the development of surgical site infections in the neurosurgical patients (Kourbeti et al., 2012). This outcome was considered as a

critical outcome in our systematic review based on this. Two studies, Djindjian, 1990 and Petignat et al., 2008, evaluated this outcome in our study. The infections that were documented were pneumonia, urinary tract infections and sepsis. The meta-analysis that was evaluating the use of shunt catheters did not evaluate this outcome.

Although there is scanty literature on the development of non-surgical site infections in neurosurgical patients, several studies have documented ventilator associated pneumonia and catheter related urinary tract infections as the most common nosocomial infections (Celik 2004; Kourbeti et al., 2012; Kupronis et al., 2004). Other non- surgical site infections that are likely to occur in this population are ventriculitis, meningitis, blood stream infections, intravascular catheter related infections, lower respiratory tract infections and gastrointestinal infections (Celik 2004; Kourbeti et al., 2012; Kupronis et al., 2004). Patients with traumatic brain injury sustained from motor vehicle accidents, falls, assault and blunt trauma are more likely to develop non-surgical site infections compared to other neurosurgical patients (Kourbeti et al., 2012). Other risk factors for development of non-surgical site infections include low Glasgow Coma Score, (GCS) and low Glasgow Outcome Scale. These patients are more likely to be intubated and catheterised (Kourbeti et al., 2012). Other risk factors include CSF leak, prolonged ICU stay, insertion of lumbar and ventricular drains and patient co-morbidities (Kourbeti et al., 2012).

Adverse effects of antibiotics occur commonly, but the life threatening ones are rare. For this reason, our study classified this outcome as important but not critical. In the antibiotics versus placebo meta-analysis, two studies (Zentner 1995; Petignat et al., 2008) evaluated this outcome but there were no events reported. In the second meta-analysis involving use of AICs and

standard shunts, the adverse effects of antibiotics were not evaluated. Zentner, 1995 compared the use of Cefotiam with no antibiotics, while Petignat et al., 2008 compared the use of cefuroxime and placebo. These cephalosporins are associated with hypersensitivity reactions, nephrotoxicity, diarrhoea and bleeding due to thrombocytopenia or platelet dysfunction (Goodman and Gilman, 2013). None of these were recorded in the patients included in these studies.

The second meta-analysis used combinations of cephalosporins and shunts impregnated with clindamycin and rifampicin (Govender, 2003) and minocycline and rifampicin (Zabramski, 2003). Even though this outcome was not evaluated, it is important to note the possible adverse effects of these drugs. Rifampicin is associated with several adverse effects like flu like symptoms, cutaneous reactions like rashes, gastrointestinal symptoms, haemolytic anaemia, shock and acute renal failure when given systemically (Goodman and Gilman 2013). Clindamycin can cause potentially fatal *Clostridium difficile* pseudomembranous colitis as well as skin rash, Stevens Johnson syndrome, erythrema multiforme, elevation of transaminases, thrombocytopenia and inhibition of neuromuscular transmission of impulses. Minocycline is associated with adverse effects like gastrointestinal irritation, photosensitivity, renal toxicity, fanconi syndrome, thrombophlebitis and hypersensitivity reactions like anaphylaxis and angioedema. There are no published studies that have evaluated the adverse effects of these antibiotics when administered through AICs.

The only study that evaluated shunt revision (Govender, 2003) demonstrated that use of AICs protected patients against shunt related infections. Shunt revision was done for non-infective and

not infective causes. There was no evidence of infection during the procedure. This is in agreement with similar studies (Cui et al., 2015).

Use of systemic antibiotics versus placebo or no antibiotics yielded moderate quality evidence. Moderate quality evidence means that "we are moderately confident in the estimate of effect. The true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different" (Schunemann et al., 2013). The second meta-analysis on the use of antimicrobial impregnated shunts yielded very low quality evidence. This means that "we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect" (Schunemann et al., 2013).

Overall, our systematic review is in agreement with Ratilal et al., 2008, as it shows the benefit of systemic antimicrobial prophylaxis in preventing neurosurgical site infections. In both systematic reviews, the efficacy of antimicrobial impregnated shunts could not be determined.

Our study had several limitations. The studies obtained were generated from three databases only- The CDSR, CENTRAL and MEDLINE. Other databases like EMBASE could not be accessed. Access to other studies could have influenced study selection and the overall quality of evidence. There was a paucity of studies from low and middle income countries and this affected the quality of evidence, with regard to directness of evidence. Some outcomes of interest like all-cause mortality and adverse effects of antibiotics were not evaluated by most of the studies included. The adverse effects of antibiotics in the antimicrobial impregnated shunts were not documented. Our study did not include studies that compared the use of different antibiotics in

preventing surgical site infections. Our study excluded any RCTs and systematic reviews that were not in the English language, because we could not get an interpreter.

3.6. CONCLUSION AND RECOMMENDATIONS

Antimicrobial prophylaxis using systemic antibiotics or antibiotic impregnated shunt catheters is effective in preventing neurosurgical site infections. Antibiotic impregnated shunts are expensive to acquire but are associated with overall reduction in treatment and hospitalisation costs.

The evidence from this systematic review can be used in generating guidelines and an infection control protocol in antimicrobial prophylaxis if other aspects are incorporated in the decision making process. These aspects are: balance between beneficial and adverse outcomes of use of antibiotics, values and preferences of the patient and the clinicians, and the cost of the antibiotics. A follow up systematic review comparing the efficacy of different antibiotics in preventing neurosurgical site infections should be carried out. Finally, more randomised controlled trials should be carried out to evaluate the adverse effects of antibiotics used for prophylaxis in neurosurgery, since there was paucity of such data in our study.

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CHAPTER 4: A SURVEY OF THE PREVALENCE AND PATIENT RISK FACTORS FOR THE DEVELOPMENT OF SURGICAL SITE INFECTION AND INFECTION CONTROL PROCEDURES IN THE NEUROSURGICAL WARD OF KENYATTA NATIONAL HOSPITAL

4.1 Introduction

Apart from antimicrobial prophylaxis, a number of strategies are used in neurosurgical theatres and wards to minimise the risk of surgical site infections. These strategies are used in the perioperative period. Some of the methods used to prevent SSIs include hair removal, draping, gloving, tissue oxygenation and maintenance of normothermia. In the post- operative period, wound management is a critical component of infection prevention. In addition, surgeons require knowledge of patient related risk factors for developing infection. These risk factors include amongst others diabetes, obesity, ASA score >3 and smoking.

Hair removal has been routinely done to reduce chances of postoperative infections. It has also been done to facilitate planning, attachment of drapes and wound closure (Broekman et al., 2011). There is conflicting evidence regarding the benefits of hair removal. Several studies indicate that preoperative hair shaving does not reduce infection rates, but rather, increases the rate of infection (Broekman et al., 2011; Sebastian, 2012). Although use of depilatory creams has been touted as a better method of hair removal compared to shaving (Adisa et al., 2011), there are no significant differences between shaving, clipping and use of depilatory creams in the prevention of surgical site infections (Tanner et al., 2011).

Hypothermia is defined as a core body temperature of 34-36˚C. Perioperative hypothermia is a risk factor for development of surgical site infections and maintenance of normothermia is important in preventing surgical site infections (William, 2006). Hypothermia reduces subcutaneous tissue perfusion due to vasoconstriction. It also reduces oxygen supply to tissues, thus reducing the amount of oxygen required for oxidative killing of infecting micro-organisms by neutrophils (William, 2006). Hypothermic patients are three times more likely to develop surgical site infections (Melling et al., 2001). Anaemia has been associated with an increase in rate of infection. Blood replacement or transfusion reduces rates of infections as well as tissue oxygenation. Intraoperative and postoperative administration of high concentration of oxygen is associated with decreased incidence of SSIs (Maragakis and Crosgrove , 2009).

During surgical procedures, perforations can occur in gloves, especially in procedures where there is implantation of hardware (Walcott et al., 2012). Changing of gloves has been advocated for, though there is a risk of contamination of wounds in case of small perforations in the gloves that cannot be easily detected (Tanner and Parkinson, 2006). Double gloving has therefore been recommended as it reduces the chances of perforation of the inner gloves, hence reducing the chances of surgical wound contamination (Tanner and Parkinson, 2006).

Scrubbing reduces the microbial load on the surgeon's skin that could contaminate the surgical site in case of breakage of gloves (Walcott et al., 2012). Alcohol rubs or aqueous scrubs are usually used and studies have not shown one being superior over the other. However, alcohol rubs are better tolerated and scrubbing takes a shorter time (Tanner et al., 2008).

The presence of foreign bodies is an independent risk factor for development of neurosurgical SSIs (McClelland et al., 2008). Cerebrospinal fluid drains like ventricular and lumbar drains introduce micro-organisms into the CNS through drain catheters. External drains used to monitor intracranial pressure divert CSF from an obstructed ventricular system, can introduce micro-organisms from other adjacent organs as well as the environment. There is an increased risk of development of meningitis with the use of external ventricular drains (Korinek et al., 1997; Erman et al., 2005; Kourbeti et al., 2007 and Leitard et al., 2008). Internal drains like ventriculoperitoneal shunts used to treat hydrocephalous can also be a source of infection in the CNS especially after craniotomy and craniectomy procedures. There is an increased risk of bacterial meningitis caused by the use of ventricular and lumbar CSF catheters (Reichert et al., 2002; Schade et al., 2005; Kourbeti et al., 2007).

Re-do procedures are associated with an increase in the risk of development of infection due to introduction of micro-organisms from potentially infected areas, as well as development of bacterial resistance to previously administered antibiotics (Leitard 2008; Gaberel et al., 2011). Increased release of corticosteroids from previous surgery may lower the immune system.

4.1.1 Study Problem

Infection prevention and management in a surgical ward requires a holistic approach that integrates multiple interventions. Knowledge and gaps of existing practice is a critical element in the redesign of an infection control protocol. Patients with contaminated to dirty wounds are particularly at risk. To date only one survey has been conducted at the Kenyatta National Hospital Neurosurgical unit to identify infection control strategies in surgical wards. This study

however focused only on a subset of patients who underwent craniotomies and had clean wounds (Njiru et al., 2015). To date therefore there is no data on infection prevention in neurosurgical patients with contaminated to dirty wounds. Knowledge of patient and surgery related risk factors for SSIs are also missing in this population. This study therefore sought to fill this gap so as to guide future interventions for infection prevention.

4.1.2 Research Questions

1. What is the prevalence of known patient related risk factors for SSIs in the neurosurgical ward of KNH?
2. What infection prevention strategies are practised in the perioperative period in trauma patients with potentially contaminated to dirty wounds?
3. What is the prevalence of SSIs among trauma patients with potentially infected wounds in KNH?

4.1.3 Objectives

The main objective of the study was to measure the prevalence of patient related risk factors and to identify the perioperative procedures for infection prevention in patients with contaminated to dirty traumatic wounds in the neurosurgical unit of KNH.

Specific objectives

1. To determine the patient related risk factors for surgical site infection among trauma patients at the neurosurgical unit of KNH
2. To describe the infection prevention procedures carried out for trauma patients at the neurosurgical unit of KNH

3. To determine the prevalence of surgical site infections among the trauma patients admitted at the neurosurgical unit of KNH.

4.2. METHODS

4.2.1 Study Design and Population

This was a cross sectional study that was conducted on trauma surgical patients admitted in the Neurosurgical wards between September 2014 and February 2015. This cross sectional study was done before the inception of a cohort study. The patient population comprised of patients undergoing emergency surgery following trauma and patients with potentially contaminated and dirty wounds.

4.2.2 Inclusion and Exclusion Criteria

Patients who met the following criteria were included in the study: adult patients over 18years old, those who sustained traumatic injury through road traffic accidents, assault, falls or any other cause, those who were admitted at the KNH neuro-intensive care unit and ward 4C for elective and emergency neurosurgery between September 2014 and March 2015.

Patients who were scheduled to undergo neurosurgery for reasons other than trauma, for example patients with degenerative diseases, congenital diseases, spine and brain tumours and metastases were excluded. Patients who were brought in by good Samaritans and whose next of kin did not arrive within 24 hours of admission were excluded from the study. Conscious patients, or the next of kin of unconscious or confused patients who did not provide informed consent, were excluded from the study.

4.2.3 Sample Size Calculation

The sample size was estimated using the Fischer's formula as follows:

$$n = \frac{Z^2 p (1-p)}{\sigma^2}$$

Where n= estimated sample size

p= prevalence

σ = error margin set at 5%.

Z= standardised normal variable value corresponding to 95% confidence interval in a normal frequency distribution and which is 1.96

A study carried out by Saidi et al., 2014 reported that infectious complications were noted in 12% of the patients who had surgery. Using this information a prevalence of 12% was used to calculate the sample size of 162 patients.

$$n = \frac{1.96 \times 1.96 \times 0.12 \times 0.88}{0.05^2} = 162$$

4.2.4. Sampling and Study Participant Recruitment

Convenient sampling was used such that all patients who met the inclusion criteria were included in the study. The investigator perused patient files in the neurosurgical ward to identify patients who had been admitted due to trauma. Patients who met the inclusion criteria were identified in the ward in the afternoons to minimise interruptions in the normal workflow. The patients were invited to participate in the study with the aid of an informed consent form (Appendix 1). All patients who consented were included in the study. No inducements were provided.

4.2.5 Data Collection

Patient files were perused and information abstracted with the guide of a pretested data collection form. The form (Appendix 1) was designed to collect information on the patient socio demographic characteristics, cause of injury, presenting signs and symptoms, diagnosis, wound classification, patient risk factors for infection and the presence of SSIs. This information was used to classify patients as to whether they had clean contaminated, contaminated or dirty wounds. Additional information was obtained on the wound prevention and management procedures from the surgical summaries and patient files. The first part of the data collection tool was administered to the next of kin to obtain more information on the circumstances surrounding the trauma, in case patients were unable to answer the questions due to severity of injury.

For patients who were comatose, incoherent or with a low Glasgow coma score, information on risk factors for infection was obtained from their relatives through care giver interviews after obtained informed consent by proxy.

4.2.6 Case Definition

Patient wounds were classified as clean, clean contaminated, contaminated or dirty according to the CDC classification 2016. Clean wounds refer to wounds those which undergo elective and not emergency surgery, those which are primarily closed, and have no acute inflammation and no break in aseptic technique.

Clean contaminated wounds are those which are urgent or emergency cases that are otherwise clean and have a minor break in technique. Contaminated wounds refer to those with non-purulent inflammation, major break in technique, penetrating trauma < 4hrs old; chronic open

wounds to be grafted or covered. Dirty wounds refer to those with purulent inflammation like abscess and those with penetrating trauma > 4hrs old.

Patients were classified according to the American Society of Anaesthesiologist (ASA) scores, (American Society of Anaesthesiologists, 2014) which are used to classify patients based on their physical status and severity of disease. It is an accurate predictor of post -surgical outcomes of patients. Patients with ASA score 1 were defined as those with no systemic illness while patients with ASA score II were those with mild systemic disease but it did not limit them. Patients with ASA score III had severe systemic disease that limited activity but was not incapacitating. Those with ASA score IV were defined as those with incapacitating severe systemic disease while those with ASA score V were moribund and unlikely to survive. A newer score, ASA score VI which includes brain dead patients whose organs are being removed for donor purposes, was not considered. This is because this is not routine practice in Kenya.

For the purposes of this study, a surgical site infection was defined as a record in the patient file in which a surgeon made a diagnosis of infection.

4.2.7 Variables

The main outcome of interest was the development of a surgical site infection. The covariates of that were considered were patient, wound, /trauma, surgical and procedure related characteristics.

Patient related covariates included patient demographics (age, sex, weight, education level and place of residence) and patient co-morbidities such as diabetes, anaemia, HIV status and immunosuppression, obesity, malnutrition and ASA score. The smoking status of the patient

was also recorded. The trauma/wound related characteristics included: cause of injury (road traffic accident, assault, accidental falls), if an open wound resulted after injury, initial wound management before surgery, time elapsed before admission and degree of contamination of the any wounds at the time of admission.

The surgery related covariates included: type of antimicrobial prophylaxis administered, duration of the procedure, type of procedure, anatomical site operated, gloving, preoperative hair removal (either through clipping or shaving using razors and blades), oxygenation and maintenance of normothermia, preoperative scrubbing, surgeon who carried out the procedure, time and day of the week the procedure was done. The time and frequency of administration of prophylaxis was noted. Post- surgical wound management procedures such as wound cleaning, materials used to clean wounds, occlusive dressing, frequency of wound cleaning, debridement, post-surgical antimicrobial prophylaxis and other indications for antimicrobials after surgery were considered as covariates. Results obtained on culture and sensitivity testing were also considered.

4.2.8 Data Analysis

All variables were subjected to descriptive data analysis. Continuous variables were expressed as the mean and standard deviation of the mean or as the median and interquartile range. Categorical variables were summarized at the frequency and proportion. The characteristics of those who developed a surgical site infection were compared to those who did not by bivariable comparison using inferential tests such as Chi square test, unpaired t-test and Kruskal Wallis tests for categorical and continuous variables respectively. Logistic regression was used to

identify the key risk factors for SSI using a manual forward model stepwise building approach. The level of significance was set at 0.05.

4.2.9 Data Management

Data was collected manually. Every day, data was entered into the Open Data Kenya (ODK) data management tool. It was regularly checked for inaccuracies in data entry. Accuracy of data entry was evaluated by looking for missing values and irrational values. Inconsistencies were reconciled by examination of the source documents. This was done on alternate days. To prevent unauthorised access and manipulations to data, the data was protected by a password which was only accessible to the principal investigator, the data analyst and the supervisor.

Patient identification (file) numbers were on the questionnaire, which were kept under lock and key. For purposes of privacy in data analysis, the patient hospital numbers were replaced by codes to ensure confidentiality and minimise access to data by unauthorised people. To avoid any loss of data, the data was backed up in a separate computer. Back up of data was done every 3 days.

All patient identifier information was only available in the informed consent form. These forms were stored under lock and key by the principal investigator and nobody else accessed them. The questionnaires only had the assigned study number. Patient identifier forms were later destroyed.

All primary data according to Kenyan law all documents should be stored for five years from date of commencement of study. All study material has been archived according to principles of Good Clinical Practice (GCP) by International Conference for Harmonisation (2010 version). At

the conclusion of the study, all the raw data will be destroyed according to principles of Good Clinical Practice.

4.2.10 Quality Assurance

The data analyst and research assistants were trained on all procedures involved in the collection and management of data. The data analyst had a minimum of a Bachelor's degree while the research assistants had a Bachelor's degree in Nursing. The data collection tools were pretested in a pilot study of five patients and adjustments made to the data collection tools.

4.2.11 Ethical Considerations

Approval to carry out the study was sought from the University of Nairobi/ Kenyatta National Hospital Research and Ethics Committee (Appendices 2 and 3). Informed consent was sought from the patients and health care worker met the inclusion criteria of the study or their relatives. The informed consent forms are appended (Appendix1). The principal investigator took the relevant patient histories and explained all the consent procedures. Proxy consent was obtained from the next of kin for patients who were comatose or were too ill to respond. Proxy consent was not sought from patients who had been brought it by good Samaritans and other unknown people.

All the information obtained was treated with confidentiality and serial numbers used instead of the patient names to protect their identity. Informed consent was sought from the patients who met the inclusion criteria of the study. All the information obtained from patients was confidential and access restricted to the researcher and the supervisor. During data analysis only the study number was used so the patient's identity was concealed.

There were no risks involved in this study as the patients included in the study were recruited into the study while undergoing the usual surgical and pharmacologic therapy in the wards during the Perioperative period. There were no additional or novel invasive procedures on the patients included in this study and no new drugs apart from the routinely recommended and used drugs.

4.3. RESULTS

4.3.1. Baseline Characteristics and Demographics of Patients

This study recruited 121 trauma patients who underwent neurosurgical procedures and were admitted to the neurosurgical unit between October 2014 and March 2015. Of these, 92% were male, while 8% were female. The median age was 35 years, with the median weight being 65kg. Most of the patients (43%) had achieved secondary level of education. Most of the patients were drawn from Nairobi and its environs as illustrated in Table 4.1.

Table 4.1: Demographics of Study Participants

Characteristic	Category	n (%)
Sex	Male	111 (91.7%)
	Female	10 (8.3%)
Place of residence	Nairobi	57 (47.1%)
	Central	28 (23.1%)
	Eastern	19 (15.7%)
	Rift-Valley	8 (6.6%)
	Western	1 (0.8%)
	Unknown	8 (6.6%)
Education	None	9 (9.1%)
	Primary	36 (36.4%)
	Secondary	43 (43.4%)
	Tertiary	11 (11.1%)
Age, Median [IQR]		35, [15.52]
Weight, Median [IQR]		65, [11.11]

4.3.2. Medical and Surgical History of the Patients

Table 4.2 summarises the medical and surgical histories as well as documented wound classification at admission.

Table 4.2: Medical and Surgical History of Study Participants

Variable	Description	n	%
Presenting complaints	Headaches	27	22.3
	Bleeding	20	16.5
	Unconsciousness	16	13.2
	Other complaints	14	11.6
	Scalp wound	12	9.9
	Seizures	6	5.0
	Vomiting	6	5.0
	Skull fracture	4	3.3
	CSF Leakage	0	0.0
Details of trauma	Assault	48	40.3
	Road accident	40	33.6
	Fall	29	23.4
	Blunt trauma of unknown cause	2	1.7
Wound classification	Unclassified	55	45.5
	Clean contaminated	29	24.0
	Contaminated	19	15.7
	Clean	16	13.2
	Dirty	2	1.7

Most of the patients presented with headaches (22%) followed by bleeding (16.5%). Thirteen percent of the patients were brought to the hospital unconscious while 5% of the patients presented with vomiting and seizures respectively. Three percent of the patients had skull fractures. None of the patients admitted in this period had CSF leakage. Fourty percent of the patients sustained injury due to assault, followed by 34% who sustained injury from road traffic accidents. Twenty four percent of the patient sustained injury through falls while 2% sustained unspecified blunt trauma to the head.

Most of the wounds were not classified at admission (46%). Of those that were classified, 24% were clean contaminated, 16% contaminated, 13% clean and 2% dirty.

4.3.3. Prevalence of Patient Related Risk Factors

Blood loss was the most common patient related risk factor for development of surgical site infections with a prevalence of 29%. This was followed by smoking (26%) and malnutrition with a prevalence of 10%. Obesity and diabetes mellitus accounted for prevalence rates of 9% and 6% respectively. Only one patient had an ASA score of >3. This could be due to the fact that the ASA scores of patients were not calculated during the study period (Table 4.3).

Table 4.3: Prevalence of Known Patient Related Risk Factors for SSIs

Patient related risk factors	Frequency, % (n)
Hypovolemia	28.9% (33)
Smoking	26.3% (30)
Malnutrition	9.6% (11)
Obesity	8.8% (10)
Diabetes mellitus	6.1% (7)
Concomitant Systemic Infection	5.3% (6)
Immunosuppression	2.6% (3)
ASA score > 3	0.9% (1)

The presence of these known risk factors was established from history taking and information obtained from patient records**.**

4.3.4. Perioperative Infection Control Procedures:

Several infection control measures were undertaken to prevent surgical site infections as illustrated in Table 4.4.

Table 4.4: Perioperative Infection Control Procedures:

Procedure	n	%
Wound management after surgery	65	58.0%
Hair shaving	84	75.0%
Hair Clipping	8	7.1%
Maintenance of normothermia	81	72.3%
Blood replacement/transfusion	50	44.6%
Tissue oxygenation	64	57.1%
Antimicrobial prophylaxis	80	72.1%
[a]Single gloving	5	4.5%
[b]Double gloving	5	4.5%
Scrubbing	82	73.9%

[a]Even though all the surgeons did single gloving, only five documented having done it

[b]Five surgeons who double gloved documented it

4.3.5. Surgical Procedures and Duration of Surgery

Presence of foreign material in the operative field and re-do procedures are associated with an increase in the rate of surgical site infections. In our study, 28.8% of our patients (n=30) underwent surgery that involved implantation of prostheses. 14.7% (n=15) had surgical drains and catheters inserted while 5.9% (n=6) underwent repeat surgery.

Different operating theatres were used. Most of the patients (43%) were operated in the trauma theatre. It was not documented where almost half of the surgeries were done (47.1%). The rest of the patients (9.9%, n=12) were operated in the main theatre. The mean duration of surgical procedures was 3.48 hours.

4.3.6 Prevalence and Types of Surgical Site Infections

The prevalence of surgical site infections was 21%. Of the patients who developed infections, the most common infections were superficial scalp wound infections (28%), intracranial abscesses (24%), catheter and drain related infections (24%) and subdural empyemas (16%).The patient who developed bone flap osteomyelitis had undergone surgery one year before (Table 4.5).

The wounds were classified in 16 patients; and of these, most of the wounds were either contaminated or dirty. Classification of wounds is important as it determines the choice of antibiotic to use in the management of infections. Our study shows that classification of wounds was not considered for many patients who developed infections as shown in Table 4.5.

Table 4.5: Prevalence and types of Surgical Site Infections:

Infection	Type	n	%
Infection	No infection	96	79.3%
	Infection	25	20.7%
Diagnosis	Intracranial abscess	6	4.9%
	Superficial wound infection	7	5.8%
	Epidural abscess	1	0.8%
	Catheter related infections	6	4.9%
	Osteomyelitis of craniotomy flap	1	0.8%
	Subdural empyema	4	3.3%
Classification	Clean contaminated	2	1.7%
	Contaminated	7	5.8%
	Dirty	7	5.8%

4.3.7. Bi-variable Analysis- Comparison Traits of Those Who Developed Infections and Those Who Did Not.

4.3.7.1. Study Participant Demographics and Development of Surgical Site Infections

There was no statistically significant association between patient demographic traits and development of surgical site infections as shown in Table 4.6.

Table 4.6: Study Participant Demographics and Development of Surgical Site Infections:

Trait		No infection		Infection		P value
		n	%	n	%	
Place of residence	Central	20	71.4%	8	28.6%	0.400
	Eastern	15	78.9%	4	21.1%	
	Nairobi	47	82.5%	10	17.5%	
	Rift-Valley	5	62.5%	3	37.5%	
	Western	1	100.0%	0	0.0%	
	Unknown	8	100.0%	0	0.0%	
Sex	Male	90	93.8%	21	84.0%	0.115
	Female	6	6.2%	4	16.0%	
Education	None	7	8.9%	2	10.0%	0.541
	Primary	30	38.0%	6	30.0%	
	Secondary	35	43.3%	8	40.0%	
	Tertiary	7	8.9%	4	20.0%	
Age (Mean, sd)		92	(36.6,43.2)	25	(30.3,41.9)	0.287
Weight (Mean, sd)		32	(58.3,66.6)	6	(64.9,75.1)	0.128

The mean age for those who developed infection was 36.1 years, with a standard deviation of 14.026, while that for those who did not develop infection was 39.9 years, with a standard deviation of 15.877. The mean weight for those who developed infection was 70.0 kg, with a standard deviation of 4.858. For those who did not develop infection, the mean weight was 62.4 kg, with a standard deviation of 11.581.

4.3.7.2 Patient Presenting Complaints on Admission and Development of SSIs

There was no statistically significant difference between the various presenting complaints and the development of surgical site infections as illustrated in Table 4.7. None of the patients presented with CSF leakage.

Table 4.7: Presenting Complaints at Admission and Development of Surgical Site Infections

Trait		Infection				P value
		No infection		Infection		
		n	%	n	%	
Coma	No	84	87.5%	21	84.0%	0.645
	Yes	12	12.5%	4	16.0%	
Seizures	No	92	95.8%	23	92.0%	0.432
	Yes	4	3.2%	2	8.0%	
Headaches	No	74	77.1%	20	80.0%	0.755
	Yes	22	22.9%	5	20.0%	
Hypovolemia	No	78	81.2%	23	92.0%	0.197
	Yes	18	18.8%	2	8.0%	
Skull fracture	No	92	95.8%	25	100.0%	0.299
	Yes	4	3.2%	0	0.0%	
Scalp wound	No	85	88.5%	24	96.0%	0.266
	Yes	11	11.5%	1	4.0%	
Vomiting	No	92	95.8%	23	92.0%	0.432
	Yes	4	3.2%	2	8.0%	
[a]Other complaints	No	84	87.5%	23	92.0%	0.635
	Yes	12	12.5%	2	8.0%	

[a]Other complaints refers to injuries to other parts of the body than head injury

4.3.7.3. Impact of Causes of Trauma and Wound Classification at Admission on Development of Surgical Site Infections

Patients who sustained injury through road accidents had the highest prevalence of infection compared to patients who sustained injury through other forms of trauma and this was statistically significant (p=0.004). The two patients who were admitted due to unspecified blunt trauma all developed surgical site infections. There was no statistically significant association between wound classification and development of infection (p=0.599), as illustrated in Table 4.8.

Table 4.8: Cause of Trauma, Wound Classification at Admission and Development of SSIs.

Description		No infection		Infection		
		n	**%**	**n**	**%**	**P value**
Cause of trauma	Road accident	28	70.0%	12	30.0%	
	Assault	43	89.6%	5	10.4%	**0.004**
	Fall	24	82.8%	5	17.2%	
	Blunt trauma	0	0.0%	2	100.0%	
Classification of wound on admission	Clean contaminated	23	85.2%	4	14.8%	0.599
	Contaminated	17	89.5%	8	10.5%	
	Dirty	2	50.0%	2	50.0%	
	Unclassified	44	80.0%	11	20.0%	

4.3.7.4. Influence of known Risk Factors on Prevalence of Surgical Site Infections

There was no statistically significant difference between known patient risk factors and development of surgical site infections as illustrated in Table 4.9. However, patients with blood loss were twice more likely to develop infection than those who did not lose blood.

Table 4.9: Association between Patient Risk Factors and Development of Surgical Site Infection:

Known Risk Factor		No infection		Infection		P value
		n	%	n	%	
Diabetes mellitus	No	85	79.4	22	20.6	0.615
	Yes	5	71.4	2	28.6	
Hypovolemia	No	61	75.3	20	24.7	0.135
	Yes	29	87.9	4	12.1	
Obesity	No	81	77.9	23	22.1	0.369
	Yes	9	90.0	1	10.0	
Immunosuppression	No	87	78.4	24	21.6	0.365
	Yes	3	100.0	0	0.0	
Smoking	No	66	78.6	18	21.4	0.869
	Yes	24	80.0	6	20.0	
Malnutrition	No	80	77.7	23	22.3	0.306
	Yes	10	90.9	1	9.1	
Concomitant System Infection	No	83	77.6	24	22.4	0.191
	Yes	6	100.0	0	0.0	
ASA score > 3	No	88	78.6	24	21.4	0.602
	Yes	1	100.0	0	.0	

4.3.7.5 The Impact of Perioperative Infection Control Procedures and Surgical Factors on Prevalence of Surgical Site Infections

Patients who underwent clipping were more likely to develop infection than those who did not. Those who were clipped had equal chances of developing surgical site infection as those who were not clipped. The association was statistically significant (p=0.041).

Implantation of prostheses was associated with lower infection rates. This association was statistically significant (p=0.023). This is because patients with prostheses are more likely to receive more intense antimicrobial prophylaxis. Some prostheses are impregnated with antibiotics. There was no statistically significant association between maintenance of

normothermia, blood replacement, tissue oxygenation, gloving, scrubbing and theatre cleanliness and development of surgical site infections.

The operating theatre used had a contribution to development of surgical site infections, but this was not statistically significant (p=0.477). Of note, the Trauma Theatre contributed the highest number of patients who developed infection. This is because the trauma theatre handles most of the patients admitted for surgery. There could have been cross contamination and cross infection between patients. Because of the large volume of patients it handles and the number of surgeries performed, strict infection control procedures are not likely to be carried out. This is illustrated in Table 4.10.

Table 4.10: Infection Control Procedures and Development of Surgical Site Infections

Procedure		**No infection**		**Infection**		
		n	**%**	**n**	**%**	**P value**
Hair shaving	No	22	78.6%	6	21.4%	0.999
	Yes	66	78.6%	18	21.4%	
Hair Clipping	No	84	80.8%	20	19.2%	**0.041**
	Yes	4	50.0%	4	50.0%	
Maintenance of normothermia	No	24	77.4%	7	22.6%	0.854
	Yes	64	79.0%	17	21.0%	
Blood replacement/transfusion	No	48	77.4%	14	22.6%	0.741
	Yes	40	80.0%	10	20.0%	
Tissue oxygenation	No	39	81.3%	9	18.7%	0.550
	Yes	49	76.6%	15	23.4%	
Single gloving	No	84	79.2%	22	20.8%	0.307
	Yes	3	60.0%	2	40.0%	
Double gloving	No	84	96.6%	22	91.7%	0.307
	Yes	3	3.4%	2	8.3%	
Scrubbing	No	23	26.4%	6	25.0%	0.887
	Yes	64	73.6%	18	75.0%	
Theatre cleanliness and limited traffic flow	No	26	29.9%	6	25.0%	0.640
	Yes	61	70.1%	18	75.0%	
[a]Implantation of prostheses (Duragraft)	No	62	76.5%	11	47.8%	**0.023**
	Yes	19	23.5%	12	52.2%	
Surgical drains and shunts	No	69	83.1%	18	90.0%	0.507
	Yes	13	15.9%	2	10.0%	

[a] This variable was determined from an observation of the theatre check list for each patient. It was assumed to be done if it was ticked or recorded on the checklist.

4.3.7.6. Risk Factors for Development of Surgical Site Infections: Logistic Regression Analysis

Logistic regression using a model stepwise building approach was used to identify the risk factors for development of SSIs in our patient cohort. The level of significance was set at 0.05. Crude and adjusted odds ratios were obtained. Trauma due to assault was the one independent risk factor for development of surgical site infection.

Table 4.11: Independent Risk factors for development of SSIs

Variable	Infection (n, %)	Crude OR	Adjusted OR	P value
Hair clipping	4 (50.0%)	3.2 (0.970, 18.250)	3.89 (0.68, 22.11)	0.126
Implantation of prostheses	11 (47.8%)	2.99 (1.14, 2.89)	2.26 (0.76, 6.78)	0.144
Trauma due to				
[a]RTA	12 (30%)	Ref	Ref	-
Assault	5 (10.4%)	0.27 (0.09, 0.85)	0.27 (0.07, 1.02)	0.054
Fall	5 (17.2%)	0.49 (0.15, 1.58)	0.43 (0.11, 1.65)	0.219
Unknown blunt trauma	2 (100%)	>1000	>1000	0.999

[a]While carrying out logistic regression analysis, trauma due to road traffic accidents was used as a reference cause of trauma.

4.4. DISCUSSION

The prevalence of infection was high, at 20.7%, compared to rates of 3-7% that have been reported in many studies (Buang and Haspani, 2012). This can be attributed to the fact that the study exclusively selected trauma patients, who are likely to have had clean contaminated, contaminated and dirty wounds on admission. Contamination could have occurred at the time of injury or during transportation to the hospital. This high prevalence of infection is of concern. An infection control protocol for the unit should be developed and adhered to, to reduce the prevalence of surgical site infections.

A study in Brazil reported a high infection rate of 9.4%, which is still lower than the prevalence of infection in our study (Belluse et al., 2015). Our findings contrast with a study done by Njiru et al., 2015, at the same unit, which reported an incidence of 7.5%. In the latter, the study patients were patients who underwent elective, clean craniotomy procedures. This illustrates that the rates of infection are affected by the classification of the wounds, since both studies were done in the same ward. In our study however, wound classification was not done routinely. This finding has an implication on practice, such that it should be routine to classify patient wounds at admission so that they are managed according to the level of wound contamination. This would greatly reduce the infection rates.

The rate of surgical site infections across populations would not vary based on the case definition of a surgical site infection, because the CDC definition where a diagnosis is made by a surgeon constitutes one of the diagnostic criteria for SSIs, is used widely across different surgical settings.

Trauma sustained from assault was an independent risk factor for development of surgical site infections ($p= 0.054$). Violence and assault is common in areas with high levels of poverty, dense population, high unemployment levels and crime rates. This could very well mirror the socio-demographic characteristics of our study population (Wekesa et al., 2013). The infections in assaulted patients could be because of several factors such as use of crude weapons like machetes which could be dirty or rusty at the time of assault.

Patients who underwent hair clipping were at high risk of developing infection than those who were not clipped. This could be attributed to the fact that in our study, very few patients

underwent clipping (n=8) and half of them developed surgical site infection. Clipping is not common practice, as preoperative shaving is more commonly done. Clipping of hair is does not introduce micro-abrasions in the skin like shaving, and this reduces the areas that could be potentially colonised by normal flora to cause infection.

Our findings are inconsistent with other studies (Sebastian 2012; Adisa et al., 2011; Broekman et al., 2011) which suggest that clipping is beneficial in reducing the incidence of surgical site infections. Some studies have reported that there is no benefit of hair removal by whichever method, in reducing surgical site infections (Tanner et al., 2007). Our findings are consistent with this because, even among those who were clipped, the number of patients who developed surgical site infection was the same as those who did not develop SSI. Surgeons and infection control nurses at Kenyatta National Hospital should be sensitised and trained on incorporating hair clipping into practice as opposed to preoperative shaving to reduce the prevalence of infection.

Patients in whom implantation of prostheses was done had low infection rates, a finding that is not consistent with many other studies (Chiang et al., 2014; Buang and Haspani, 2012). Prostheses can act as culture medium for bacteria. The process of implanting the prostheses can lead to contamination of the wounds and increase the risk of SSIS (Bellusse et al., 2015; Chiang et al., 2014). In procedures where prostheses are required, it is important that infection control procedures are carried out to minimise infection. Antimicrobial prophylaxis is important to further reduce the rate of infection (Chiang et al., 2014). The low infection rates among these

patients can be attributed to antimicrobial prophylaxis that is effectively done at Kenyatta National Hospital in all patients who have prostheses implanted.

Although the impact of the type of theatre on development of surgical site infection was not statistically significant, the theatre contributed the largest number of patients who developed surgical site infections. This theatre handles most of the trauma patients (Njiruet al., 2015) and is likely to have a high patient turnover. Infection rates could be attributed to cross contamination between patients and inadequate theatre cleanliness. Theatre cleanliness as a way of controlling infections should be emphasised.

Gloving is important in preventing surgical site infections. There was no statistically significant association between single and double gloving and development of infection. These findings conflict with studies that have demonstrated a better protective effect with double gloving compared to single gloving (Walcott et al., 2012). Although all surgeons practised single gloving, this procedure was recorded for very few patients. This could be attributed to poor documentation by the surgeons. A surgical checklist should be developed and adhered to by every surgeon so that all procedures done are documented.

Our study showed a male predilection to development of injuries and subsequent surgical site infection. This is because there were more men in the study than women. Men are more prone to high risk behaviour than women such as careless and drunk driving and assault. Our findings are consistent with those in another study which show high prevalence of head injury in men (Saidi et al., 2014). Patients who developed infection were heavier than those who did not develop infection, although there were no obese patients in our study.

There were several limitations to our study. Information on patient and surgery risk factors was obtained from patient files and surgery records. There was a risk of information bias as some of the information could have been missing in the patient records due to poor documentation practices. The impact of antimicrobial prophylaxis was not accounted for in this study. The strength of this study is that it focused only on neurotrauma patients with potentially contaminated to dirty neurosurgical wounds, which could have raised the infection rates of otherwise known clean procedures with low infection rates.

4.5. CONCLUSION

The prevalence of surgical site infection was high, at 20.7%. The independent risk factors for development of infection in our trauma patient cohort were: hair clipping, implantation of prostheses and sustaining trauma from assault. Some infection control procedures were not carried out as should be or if they were carried out, they were not documented. The trauma theatre recorded the highest rate of infection.

4.6. RECOMMENDATIONS

An infection control protocol detailing the procedures that should be carried out for trauma patients should be developed and adhered to, to reduce the prevalence of surgical site infection among this cohort. Documentation of all infection control procedures should be done. Wound classification should be promoted to aid in treatment of surgical site infections. A large, multi-centre randomised controlled trial should be carried out to identify risk factors for infection and test for the effectiveness of an infection control protocol among this patient cohort.

4.7. References

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CHAPTER 5: IMPACT OF ANTIMICROBIAL PROPHYLAXIS ON INCIDENCE OF SURGICAL SITE INFECTIONS

5.1. INTRODUCTION

Antimicrobial prophylaxis is important in preventing surgical site infections. In neurosurgery, which is deemed to be a clean procedure, prophylaxis is indicated for procedures which involve shunting of cerebrospinal fluid using catheters and shunts, implantation of prostheses and implants or for those which are potentially contaminated (Chiang et al., 2014)

The choice of antibiotics for prophylaxis depends on the knowledge of infecting bacteria, local antimicrobial susceptibility patterns, safety and cost of the antibiotic. Recent evidence proposes the use of first and second generation cephalosporins for prophylaxis in neurosurgery, with metronidazole for anaerobic cover (ASHP guidelines, 2016). For effective prophylaxis, several principles should be adhered to. Firstly, antibiotics should be given 30 minutes to one hour before the initial incision to allow for the drug tissue concentration to rise above the minimum inhibitory concentration (Hawn et al., 2013). Additional doses of prophylactic antibiotics may be required for prolonged procedures (ASHP guidelines, 2016). Prophylaxis should be stopped within 24 hours for clean procedures but for patients with contaminated and dirty wounds, antibiotics should be given for the treatment period. Studies have shown that only one antibiotic is effective for prophylaxis and the use of multiple antibiotics increases risk of infection and treatment costs for surgical patients (Testa et al., 2015).

Antimicrobial prophylaxis alone may not prevent surgical site infections. Other infection control procedures such as hair removal, scrubbing, skin disinfection, gloving and maintenance of

normothermia are important. Optimal tissue oxygenation, maintenance of euglycaemia and ASA risk categorization of patients are important in lowering the incidence of surgical site infections. Identification and modification of patient risk factors such as obesity, smoking is crucial. Maintaining an optimal and potentially sterile operating room is important in reducing surgical site infection risk (Anderson et al., 2014).

5.1.1 Study Problem

Neurosurgical site infections are not common because these procedures are classified as clean. Therefore, antimicrobial prophylaxis may not be routinely practiced, and if practiced, it may be sub-optimal. There is debate about the effectiveness of antimicrobial prophylaxis. Some studies suggest that it is beneficial (Walcott et al., 2012) while others have reported that it is not (Hoseini et el., 1999). The effectiveness of antimicrobial prophylaxis may be influenced by many factors such as the type of surgical procedure, but this has not been explored in any study in literature.

However for trauma patients, the rates of infections tend to be high because of possible wound contamination on injury. A lot of studies have elucidated infection rates for clean neurosurgical procedures but there is paucity of data for potentially contaminated to dirty procedures. Antimicrobial prophylaxis for patients with contaminated to dirty wounds remains controversial. This study seeks to evaluate the impact of antimicrobial prophylaxis among these patients.

5.1.2 Research Questions

We sought to answer the following questions with our study:

1. What are the patterns of antimicrobial prophylaxis among trauma patients admitted to the neurosurgical unit of KNH?
2. What is the incidence of SSIs in trauma patients who have undergone surgery?
3. What are the risk factors for development of surgical site infections among this cohort?
4. What are the determinants of the effectiveness of antimicrobial prophylaxis?

5.1.3. Objectives

The main objective was to determine the incidence of surgical site infections and identify determinants of the effectiveness of antimicrobial prophylaxis among trauma patients with potentially contaminated and dirty wounds in the neurosurgical ward of Kenyatta National Hospital.

The specific objectives were to:

1. identify the patterns of antimicrobial prophylaxis among neurosurgical trauma patients
2. measure the incidence of infection among those who received antimicrobial prophylaxis and those who did not
3. identify the risk factors for development of surgical site infections among this patient cohort
4. identify the determinants of the effectiveness of antimicrobial prophylaxis

5.1.4. Hypotheses

Null Hypothesis: The risk of surgical site infections in patients who have received prophylaxis is the same as for those who have not received prophylaxis.

Alternative hypothesis: The risk of surgical site infections in patients who have received prophylaxis is not equal to that of patients who have not received prophylaxis.

5.2. METHODS

5.2.1. Study Design and Population

It was a prospective cohort which followed up trauma surgical patients admitted in the Neurosurgical unit of KNH between April 2015 and July 2015 for development of surgical site infections. All the patients admitted at the neurosurgical unit, who met the inclusion criteria, were recruited in the study.

5.2.2. Inclusion and Exclusion Criteria

Patients who met the following criteria were included in the study: adult patients over 18years old, those who sustained traumatic injury through road traffic accidents, assault, falls or any other cause, those who had contaminated to dirty wounds and were admitted at the KNH neuro-intensive care unit and ward 4C for elective and emergency neurosurgery in the study period. Paediatric patients, those with clean wounds and those who underwent neurosurgery for reasons other than trauma were excluded.

5.2.3. Sampling and Participant Recruitment Strategies

The sample size was calculated using the following formula for prospective incidence studies (Daniel 2010):

$$n = \frac{N Z^2 \times p (1-p)}{d^2 (N-1) + Z^2 p(1-p)}$$

Where n= estimated sample size

N= population size

p= prevalence of neurosurgical site infections at KNH

d= level of significance 5% (0.05)

Z= standardised normal variable value corresponding to 95% confidence interval in a normal frequency distribution and which is 1.96.

A study carried out by Njiru et al., (2015) found an incidence of SSIs of 7.5% in patients who were undergoing elective craniotomy procedures at the neurosurgical unit of Kenyatta National Hospital. Using this incidence and the population of Kenyatta National Hospital to be 1800 patients according to the records department, a sample size of 100 patients was estimated.

5.2.4 Sampling

The investigator perused through patient files in the neurosurgical ward to identify patients who had been admitted due to trauma. Universal sampling was used such that all patients who met the inclusion criteria were included in the study. Consent was sought from patients and/or caregivers before recruitment into the study. Patients were recruited daily in the afternoons, when the workload in the ward was reduced. The patient consent form in Appendix 1 was used.

5.2. 5. Data Collection

The data collection tools that were used in the cross sectional study (Chapter 4) were used in this study. The recruited patients were classified as those having clean, clean implant, contaminated and dirty wounds. For each group of patients, the incidence of SSIs and associated risk factors was documented on a developed and pretested data collection form (Appendix 4).

Patients were followed up in the ward for development of SSIs. The time taken to develop infection in days was recorded, as well as the treatment given and its outcome. For patients who

were comatose, incoherent or with a low Glasgow coma score, information on risk factors for infection was obtained from their relatives through care giver interviews after obtaining informed consent by proxy. All the patients were followed up daily for the admission period. Patterns of antimicrobial prophylaxis were identified in this period.

5.2.6. Case Definition

For this study, antimicrobial prophylaxis was defined as administration of antibiotics for a period of 24 hours before surgery and up to 3 days after surgery. Any antimicrobials given after this period were considered as presumptive treatment for infection. Stat doses given before surgery were also considered to be antimicrobial prophylaxis.

5.2.7 Variables

The main outcome of interest was the development of a surgical site infection. The presence of a superficial surgical site infection was determined by the surgeon on clinical observation of the wounds during the ward rounds. The diagnosis of deep and organ space infections was determined through the analysis of CT scans by the surgeons. The main predictor of interest was antimicrobial prophylaxis. Patient related covariates included patient demographics (age, sex, weight, education level and place of residence). Antibiotics and other medications used by patients were considered. The trauma/wound related characteristics included: cause of injury (road traffic accident, assault, accidental falls and any other type of trauma). The number, type and duration of surgery were also included as potential co-variates.

5.2.8 Data Analysis

All variables were subjected to descriptive analysis to obtain measures of central tendency and dispersion. Continuous variables were tested for normality using the Shapiro-Wilk test. For normally distributed variables, the mean and standard deviation were reported. For those which were not normally distributed, the median and interquartile ranges were reported. Categorical variables were summarized as counts and proportions. The socio-demographic characteristics, diagnosis and causes of trauma of patients who developed surgical site infections and those who did not were compared. The Wilcoxon Rank Sum test was used to compare continuous variables. The Fischer exact Chi Square test was used to compare the distribution of categorical variables. The odds and risk ratios were computed. To identify risk factors for SSIs, binary logistic regression was conducted. The co-variates /potential predictors were socio-demographic characteristics, surgical procedures performed and their duration, and patient related factors.

Variables for which there was a statistically significant difference on bivariable analysis with a p value of < 0.10 were considered for inclusion in logistic regression analysis. Bivariable analysis was initially conducted to obtain the crude measure of association between predictor variables and the main outcome, which was development of SSIs.

To adjust for confounding, multivariable analysis was conducted by using two or more predictor variables. Model building was done using a manual forward stepwise model building approach. Akaike Information Criterion (AIC) was used to compare models.

The last step of model building entailed testing for statistical interaction between key variables. All possible combinations of two way to four way interactions between predictor variables were

evaluated. The interaction variable was generated as a product of predictive variable. P values of the interaction variable were considered significant if they had a value of 0.05 or less.

To further evaluate the presence of interaction or effect measure modification, stratified data analysis was conducted. The Mantel- Haenszel (M-H) test for homogeneity of stratum specific measures of association was used as an indicator of the presence of effect measure modification /interaction. The pooled test was used to test for homogeneity of risk differences of internally standardized risk differences across strata. To explain the findings of the logistic model, marginal analysis was conducted and this generated the predictive probabilities of infection. Data analysis was done using STATA version 13 software. The level of significance was set at 0.05.

5.2.9 Data Management and Ethical Considerations

Data management was conducted as previously described for the baseline cross sectional study (Chapter 4). Approval to carry out the study was sought from the University of Nairobi/ Kenyatta National Hospital Research and Ethics Committee (Appendix 3). Other ethical considerations were applied as described in Chapter 4.

5.3. RESULTS

5.3. 1. Patient Recruitment

Of the 84 patients who were recruited in this study, 83.3 % (n=70) of the patients underwent surgery. Eleven patients did not undergo surgery for several reasons as outline in Figure 5.1. It was unclear whether three patients had undergone surgery or not. The total number of patients who underwent surgery and whose data was analysed was 69.

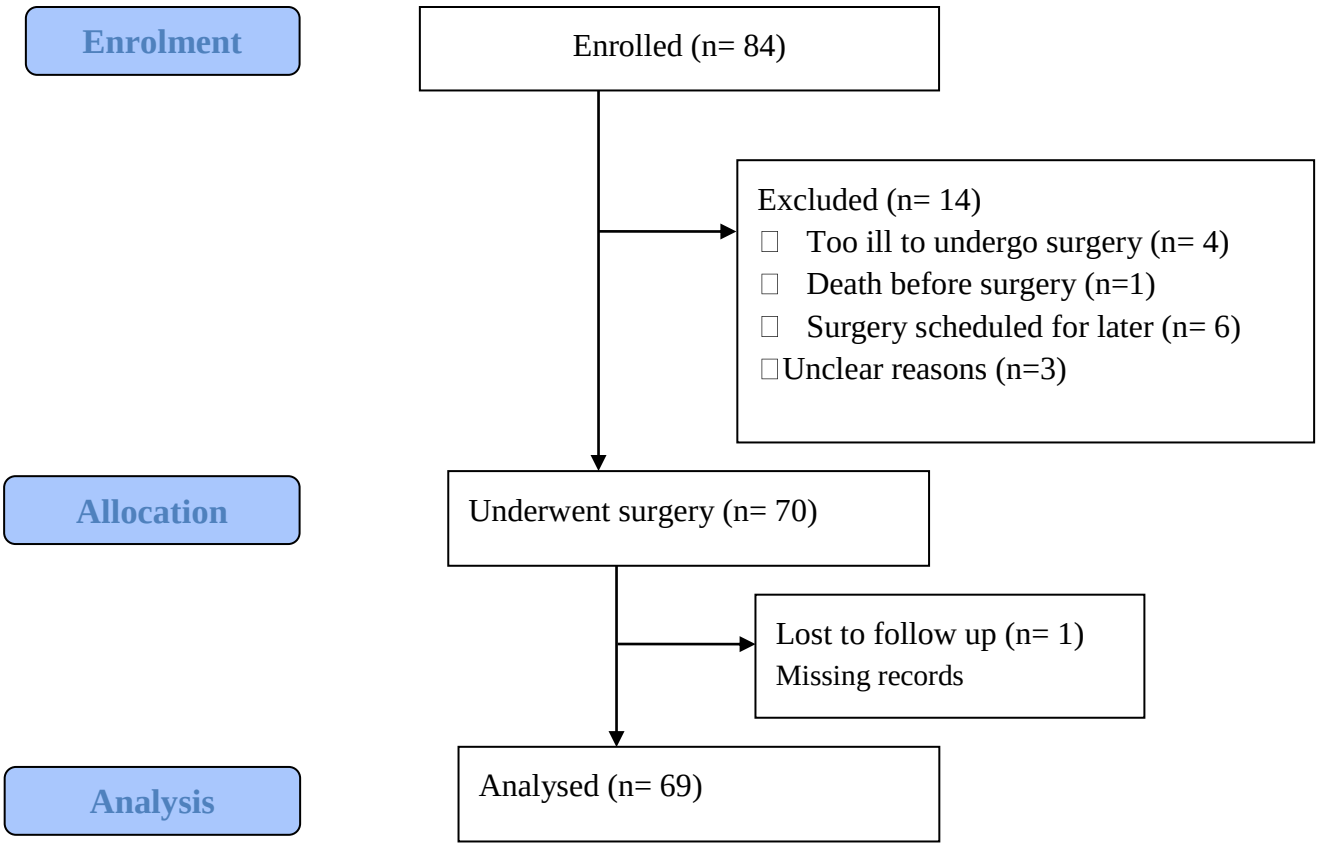


Figure 5.1: Participant recruitment for the cohort study

5.3.2. Socio-Demographic Traits of Neurosurgical Patients

The socio-demographic characteristics of the patients are summarized in Table 5.1.

Table 5.1: Comparison of demographic traits of patients who underwent surgery and those who did not

Trait	No Surgery	Surgery	Risk Ratio (95% Confidence interval)	P value
Sex				
Male	10 (13.2%)	66(86.8%)	0.73 (0.26,2.07)	0.665
Female	1 (20.0%)	4 (80.0%)		
Age: Median [Interq. Range]	40 [29,48], n=11	35 [27,50], n=69		0.543
Age group				0.552
Age <35yrs	5 (45.4%)	38 (55.1%)	0.94 (0.79, 1.13)	
Age >35 yrs	6 (54.5%)	31(44.9%)		
Cause of trauma versus other trauma				
Other trauma	10 (20.8%)	38 (79.2%)	1.23 (1.04, 1.43)	**0.017**
Assault	1(2.9%)	34 (97.1%)		
Other trauma	3(5.3%)	54 (94.7%)	0.73 (0.56, 0.95)	**0.001**
RTA	8 (30.8%)	18 (69.2%)		
Other trauma	10 (14.5%)	59 (85.5%)	1.09 (0.91, 1.29)	0.460
Fall	1(7.1%)	13 (92.9%)		
Other trauma	10 (12.7%)	69 (87.3%)	0.85 (0.48, 1.52)	0.478
Blunt trauma	1(25.0%)	3 (75.0%)		
Hospital stay (days) Median [Interq. Range]	4 [3,8], n=11	10 [7,15], n=70		**0.006**
Education level				
Unknown	0 (0.0%)	10 (100.0%)	1.00 (1.00, 1.00)	-
No education	0 (0.0%)	3 (100.0%)		
Primary	4 (13.3%)	24 (85.7%)		
Secondary	6 (20.0%)	24 (80.0%)		
Tertiary	1(10.0%)	9 (90.0%)		
Cardiovascular disease				
Patients with no [a]CVS	8 (11.0%)	65 (89.0%)		**0.003**
Hypertension	0 (0.0%)	3 (100.0%)		
Congestive heart failure	1(100.0%)	0 (0.0%)		
Diabetes mellitus	1(100.0%)	0 (0.0%)		
Admission in intensive care				
Patients not in [b]NICU	9 (12.0%)	66 (88.0%)		0.278
Patients in NICU	1(33.3%)	2 (66.7%)		

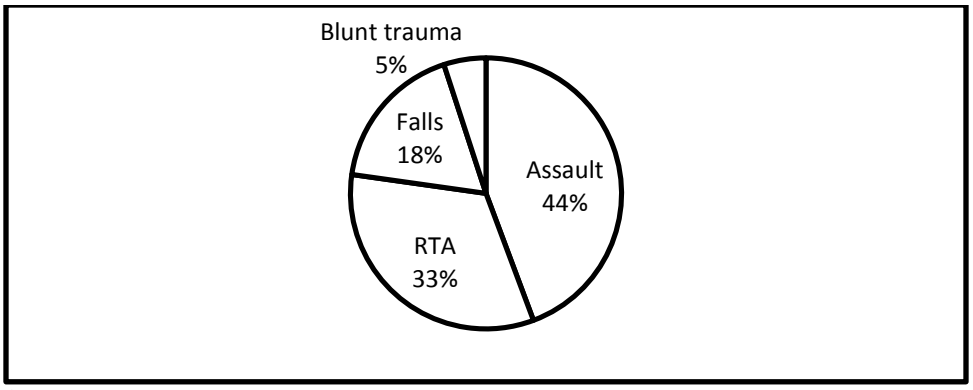
[a]Cardiovascular disease,[b]neuro-intensive care unit

Of the patients who underwent surgery, 94.3% (n=66) were men while 5.7% (n=4) were women. Seventy three percent of the men were more likely to undergo surgery than women (RR 0.73, 95% CI 0.26, 2.07) but this was not statistically significant (p=0.665).

The median age for those who underwent surgery was 35 years with an interquartile range of 27 to 50 years. Nearly half (53.7%, n=43) patients were aged less than 35 years while 46.2% (n=37) were more than 35 years old. Patients aged less than 35 years were slightly less likely to undergo surgery than those above 35 years of age (unadjusted RR 0.94, 95% CI 0.79, 1.13). Five patients had cardiovascular co-morbidities which were hypertension (n=3), congestive cardiac failure (n=1) and diabetes mellitus (n=1). All the hypertensive patients underwent surgery.

5.3.3. Causes of trauma among the study participants

Figure 5.2 presents the different causes of trauma for the patients who underwent surgery. Nearly all patients who sustained trauma from assault (97.1%) underwent surgery. For those who were involved in road traffic accidents, 69.2% underwent surgery, as opposed to 92.9% who sustained injury from falls. Most (75%) of those who sustained injury from blunt trauma underwent surgery. Two patients underwent surgery after sustaining injury from unknown causes. The association between the causes of trauma and surgery was statistically significant (p=0.024).



[a] **RTA refers to road traffic accidents**

Figure 5.2: Causes of Trauma for Patients who Underwent Surgery

Patients who sustained injury through assault were 1.23 times more likely to undergo surgery than patients who sustained all other forms of trauma combined (RR 1.23, 95% CI 1.04, 1.43). Of those who sustained head injury through road traffic accidents, 73% were more likely to undergo surgery (RR 0.73, 95% CI 0.56, 0.95). Patients who sustained injury through falls were almost equally likely to undergo surgery as the other patients (RR 1.09, 95% CI 0.91, 1.29) but this association was not statistically significant. Nearly all (85%) of those who had blunt trauma were likely to undergo surgery (RR 0.85, 95% CI 0.48, 1.52) but this was not statistically significant (p=0.478).

5.3.4. Patterns of Injury and Diagnostic findings

Most patients sustained only one injury. The most common diagnostic finding was heamatoma. Most haematomas were subdural and only 8 were located epidurally. Most haematomas were described as acute and 6 were sub-acute. Ten patients had skull fractures while one had haemorrhage. Nine patients had a diagnosis of head injury and of these**,** four were described as mild. For three patients, the severity of injury was not indicated. Patients had other diagnoses

such as brain contusion, mandibular fractures, and complications of previous surgery, abscesses and cerebral oedema but these were present only in one patient each.

Three patients were admitted into the neuro-intensive care unit due to severe head injury and two of them underwent surgery (Table 5.1). The median hospital stay for patients who underwent surgery was 10 days as opposed to 4 days for those who did not undergo surgery. The anatomical site of injury was described in detail for only 10 patients.

5.3.5. Incidence of Surgical Site Infections

Out of a cohort of 69 patients who underwent surgery, 37.7% (n=26) developed surgical site infections. Most of the patients who developed infections were male (92.3%, n=24), while the females comprised 7.7% (n=2). Of those who did not undergo surgery, only one developed infection at the site of injury. Two patients were excluded from this analysis because they had infection on admission. One of the patients had post craniotomy infection and was admitted for management through re-do surgery and the other had an infection at the site of injury.

The infection rate among patients who underwent craniotomy procedures was 43.6% (n=17), as opposed to 33.3% (n=7) who underwent evacuation of hematomas. Of the patients who underwent burr hole procedures, 42.9% developed infection. Infection resulted in a longer duration of hospital stay. The median duration of hospital stay for the patients who developed infection was 10days, with an interquartile range of 7 to 30days, as opposed to 8 days, with an interquartile range of 5 to 14 days for those who did not develop infection.

Tables 5.2 and 5.3 present the comparison between those who developed surgical site infections and those who did not. There were not statistically significant differences between these two

groups. Of the patients who were in theatre once, the incidence infection was 73.0% (OR 0.73, 95% CI 0.42, 1.27). Patients with epidural haematoma had a higher risk of developing infections (75%) compared to those with subdural haematoma (37.5%).

5.3.6 Comparison of the Demographic Traits of Patients who developed infection and those who did not

On comparing the socio-demographic traits of patients who developed SSI and those who did not, there were no statistically significant differences across categorical variables. All the patients admitted to the neuro-intensive care unit developed infection. All those with cardiovascular co-morbidities did not develop infection. Older patients were less likely to develop infection (RR 0.67; 95% CI 0.34, 1.30). This is illustrated in Table 5.2.

Table 5.2: Demographic traits of patients who developed infection and those who did not

Trait	No Infection, n	Infection, n	Risk Ratio (95% Confidence interval)	P value
Sex				
Male	41(63.1%)	24 (36.9%)	0.73 (0.26.2.07)	0.600
Female	2 (50.0%)	2 (50.0%)		
Age group				0.226
Age <35yrs	21(56.8%)	16 (43.2%)	0.67 (0.34, 1.30)	
Age >35 yrs	22(71.0%)	9(29.0%)		
Education level				
Unknown	4 (40.0%)	6(60.0%)	1.743(0.944, 3.218)	0.123
No education	2(66.7%)	1(33.3%)	0.872(0.171,4.443)	0.864
Primary	18(78.3%)	5(21.7%)	0.474 (0.206, 1.092)	0.005
Secondary	15(62.5%)	9(37.5%)	0.979 (0.521,1.841)	0.948
Tertiary	4(43.4%)	5(55.6%)	1.566 (0.798,3.072)	0.246
Patient co-morbidities				
Cardiovascular disease	2(100.0%)	0(0.0%)	-	0.214
Hypertension	2(100.0%)	0(0.0%)		
Neurointensive care unit admission				
NICU*	0(0.0%)	2(100.0%)	-	0.103

* neurointensive care unit

5.3.7 Patterns of Injury and Development of Surgical Site Infections

All the patients with blunt trauma did not develop infections. Most patients with epidural haematomas (75%) developed surgical site infections. There was no statistically significant association between causes and patterns of injury and development of surgical site infections as presented in Table 5.3.

Table 5.3: Surgical procedures, patterns of injury in patients with and without infection

Trauma	No infection, n (%)	Infection, n (%)	Risk of Infection, RR (95%CI)	P value
Cause of trauma				
Assault vs other causes	20 (58.8%)	14 (41.2%)	1.17 (0.64, 2.12)	0.600
RTA vs other causes	12 (66.7%)	6 (33.3%)	0.84 (0.40, 1.75)	0.635
Fall vs other causes	8 (66.7%)	4 (33.3%)	0.85 (0.36, 2.02)	0.713
Blunt trauma vs other causes	3 (100.0%)	0(0.0%)	0.00 (0.00,0.00)	0.166
Total no of injuries				
1	34 (65.4%)	18 (34.6%)	-	0.526
2	9(56.3%)	7 (43.8%)		
3	1 (50.0%)	1(50.0%)		
Type of hematoma			-	
Subdural	15 (62.5%)	9 (37.5%)		**0.031**
Epidural	2 (25.0%)	6 (75.0%)		
Intracerebral	1(100.0%)	0 (0.0%)		
Position of hematoma not indicated	1(100.0%)	0(0.0%)		
Unknown	0(0.0%)	1(100.0%)		
Head injury				
Mild	3 (75.0%)	1 (25.0%)	0.48 (0.13, 1.68)	0.274
Moderate	1 (100.0%)	0 (0.0%)		
Severe	0 (0.0%)	1(100.0%)		
Severity not indicated	3 (100.0%)	0 (0.0%)		
Skull fracture				0.194
No skull fracture	38 (65.5%)	20 (34.5%)	1.562 (0.844, 2.890)	
Skull fracture	6 (46.2%)	7 (53.8%)		
Haemorrhage	1(100.0%)	0 (0.0%)	0.00 (0.00,0.00)	0.385
Surgical Procedures				
No of surgical procedures per patient				
1				
2	16 (51.6%)	15 (48.4%)	1.064 (0.580, 1.951)	0.840
3	14 (70.0%)	6 (30.0%)	0.729(0.379, 1.425)	0.338
4	1 (50.0%)	1 (50.0%)		-
Unspecified	0 (0.0%)	1 (100.0%)		-
Procedure Type	12 (100.0%)	0 (0.0%)		
Craniotomy				
Evacuation	22	17	1.369 (0.678,2.764)	0.362
Burr hole	14	7	0.645(0.337,1.233)	0.169
	4	3	0.861 (0.325,2.284)	0.756

5.3.7.1 Types and duration of Surgical Procedures performed on the patients

The number of surgical procedures the patients underwent varied from 1 to 4 depending on the injuries sustained by the patients. Craniotomy was the most common surgical procedure (56.5%, n=39), followed by evacuation of hematomas (30.4%, n=21) and burr hole procedures (10.1%, n=7). The median duration of surgical procedures was 3hrs. There was no statistically significant difference between the type of surgical procedure, duration of surgery amongst patients with and without surgical site infection. However, evacuation of haematomas seemed to have a protective effect as less than a third of the patients who underwent this procedure developed infection. This is presented in Table 5.3.

5.3.8 Patterns of Antimicrobial Prophylaxis

In this study it was assumed that antibiotics given for a period of ≤ 3days were given for prophylaxis. Eighteen patients (26.1%) received antibiotics for prophylaxis. The most commonly used drug for prophylaxis was ceftriaxone and this was used by 78% (n=14) of patients on prophylaxis. Only two patients were put on prophylaxis with Amoxicillin clavulanate and one patient each were put on cefuroxime and meropenem.

The duration of prophylaxis from the onset of surgery ranged from 1 to 3 days. Ten patients (55.6%) received prophylaxis for one day only. Three patients (16.6%) were on prophylaxis for two days and five were on prophylaxis for three days. For the purposes of this study, administration of antibiotics for more than five days was not considered as prophylaxis.

5.3.9. Effect of Antimicrobial Prophylaxis on Risk of Surgical Site Infections

Patients on prophylaxis were slightly less likely to be infected than those who did not receive prophylaxis (RR 0.87, CI 0.40-1.893). This was equivalent to a risk reduction of 4.0% (CI 26.12 to -18.0%, p=0.790). The bivariable analysis however showed that the effect of antimicrobial prophylaxis was not statistically significant. Patients on Amoxicillin clavulanate and cefuroxime prophylaxis did not develop surgical site infections.

Given that antimicrobial prophylaxis did not seem to have a beneficial effect, it was necessary to conduct logistic regression and data analysis to gain a better understanding of the determinants of the effectiveness of antimicrobial prophylaxis.

Table 5.4: The Effect of Type of Antimicrobial Prophylaxis on Risk of Surgical Site Infections

Drug	Infection	No Infection	Total	Risk ratio (95% CI)	P value
Total on Prophylaxis	5 (35.0%)	13(65.0%)	18	0.87 (0.40, 1.893)	0.790
Amoxicillin clavulanate	0(0.0%)	2(100.0%)	2	0.00 (0.00, 0.00)	0.152
Cefuroxime	0(0.0%)	1(100.0%)	1	0.00 (0.00, 0.00)	0.417
Meropenem	1(100.0%)	0(0.0%)	1	2.61 (1.89, 3.60)	0.211
Ceftriaxone	4 (33.3%)	8 (66.7%)	12	1.12 (0.43, 2.27)	0.759

5.3.10. Risk Factors for Surgical Site Infections- Logistic Regression Analysis

The covariates that are known to influence the risk of surgical site infection are presence of cardiovascular comorbidities, age, duration of surgery and duration of antimicrobial prophylaxis. Unexpectedly, all patients with cardiovascular comorbidities did not develop surgical site

infection. Additionally, all patients who were treated with dexamethasone (n=5) for raised intracranial pressure developed infection. Logistic regression analysis was done to identify the key risk factors for development of surgical site infections. Bivariable analysis was done and yielded the crude measures of association in Table 5.5. Multivariable analysis was done to identify any confounding factors. On bivariable analysis, the only variable that was significantly associated with risk of surgical site of infection was the presence of an epidural haematoma (OR 7.368, 95% CI 1.396, 38.894).

Table 5.5: The Association between Selected Variables and Surgical Site Infection

Variable	Crude OR (95% CI)	P value
Sex	0.63(0.08, 4.79)	0.657
Age	0.99 (0.96, 1.03)	0.635
Age group	0.56 (0.20, 1.57)	0.271
Cause of trauma	0.64(0.36,1.14)	0.132
Assault	1.08 (0.41, 2.86)	0.882
Road traffic accidents	0.86 (0.27, 2.72)	0.794
Falls	0.82 (0.21, 3.13)	0.771
Education level	0.94 (0.62, 1.41)	0.756
Ceftriaxone use	1.37 (0.49, 3.86)	0.547
No. of injuries	1.43 (0.55, 3.68)	0.462
Epidural haematoma*	7.368 (1.396,38.894)	**0.019**
Duration of hematoma	1.00 (0.99, 1.01)	0.375
Site of injury	0.99 (0.77, 1.29)	0.965
Head injury unspecified	0.96 (0.84, 1.09)	0.491
Skull fracture	1.28 (0.74, 2.21)	0.384
Other diagnosis	1.09 (0.92, 1.29)	0.317
No. of radiologic tests	1.46 (0.66, 3.20)	0.349
Burr hole	0.68 (0.19, 4.01)	0.864
Evacuation of hematoma	0.50 (0.18, 1.38)	0.180
Craniotomy	1.54 (0.52, 4.52)	0.434
Combinations of surgical procedures*	0.967 (0.553, 1.692)	0.906
Other procedures	1.09 (0.86, 1.37)	0.488
Procedure duration	1.23 (0.74, 2.06)	0.429
No of times in theatre	1.97 (0.29, 13.62)	0.491
Number of procedures	1.14 (0.54, 2.39)	0.734

* evacuation of haematomas and craniotomy performed

5.3.11. Risk of Infection in Patients with Epidural Haematoma

Out of 8 patients with a diagnosis of epidural haematoma, 7 (87.5%) developed surgical site infection. On the other hand, 59 patients did not have a diagnosis of epidural haematoma and of these, only 19 (32.2%) developed surgical site infection. In these patients, the risk of infection was dependent on the type of procedure performed (Table 5.6).

Table 5.6: Incidence of Surgical site Infections in patients with and without epidural haematoma stratified by type of surgical procedure

Types of surgical procedures done	Incidence of SSI with epidural hematoma	Incidence of SSI without epidural hematoma	Standardised Risk difference (95% Confidence Interval)
No craniotomy and no evacuation	1 (100.0%), n=1	2 (40.0%), n=5	0.600 (0.171, 1.030)
Evacuation only	2 (100.0%), n=2	2 (15.4%), n=13	0.846 (0.650, 1.042)
Craniotomy only	4 (100.0%), n=4	10 (35.7%), n=28	0.643 (0.465, 0.820)
Craniotomy and evacuation	0 (0.0%), n=2	5 (38.4%), n=13	-0. 385 (-0.649, - 0.120)

All patients who had an epidural haematoma and had only one surgical procedure performed (either or no craniotomy or evacuation), developed a surgical site infection. Those on whom both procedures were performed were totally protected from SSIs. The difference in the incidence of SSIs in patients with epidural haematoma and those without was computed, and a standardized risk difference was obtained for each of the strata (Table 5.6). In the arm in which craniotomy and evacuation were both performed, the risk difference was negative, indicating that these procedures were protective and reduced the risk of SSIs by 38.5%. There was a statistically significant difference in the risk differences across the four strata ($p<0.010$).

Table 5.7: Risk of Surgical site infection in patients with epidural haematoma stratified by antimicrobial prophylaxis

Nature of surgical procedure	Incidence of SSI with epidural hematoma	Incidence of SSI without epidural hematoma	Standardised Risk difference (95% Confidence Interval)
No antimicrobial prophylaxis	5 (100.0%), n=5	14 (32.7%), n=43	0.674 (0.534,0.814)
Antimicrobial prophylaxis	2 (50.0%), n=4	5 (31.3%), n=16	0.188(0.352, 0.728)

All five patients with an epidural haematoma who did not receive prophylaxis developed SSIs. Antimicrobial prophylaxis seemed to reduce the risk of infection in patients with epidural haematomas because only 50% of the patients who received prophylaxis developed SSIs. In both strata, patients without an epidural haematoma had a lower incidence of SSIs. In patients who received antimicrobial prophylaxis, the difference in the incidence of infections in patients with epidural haematoma and those without was almost the similar because the standardized risk difference was very small with a value of 0.188 infections.

5.3.12. Determinants of the Effectiveness of Antimicrobial Prophylaxis – Effect Measure Modification

Additional regression analysis was performed to determine which variables apart from the presence of an epidural haematoma determined the risk of infection. As previously stated (Table 5.5), all variables apart from the presence of an epidural haematoma were not significantly associated with infections on bivariable analysis. Even after adjusting for confounding on multivariable analysis, no significant associations were noted. In the last step of model building, the presence of statistical interaction was evaluated. Interaction is also loosely referred to as effect measure modification. This refers to a phenomenon whereby a predictor variable on its

own may lack an association with the outcome of interest but in combination with other variables it produces a significant effect on the outcome of interest. We screened for over twenty combinations of three variables. The most parsimonious model showed there was a three way interaction between type and combinations of surgical procedures, prophylaxis and age of the patient. The most parsimonious model is presented in Table 5.8.

Table 5.8: Five way interaction between key variables

Variable	**Crude OR (95% CI)**	**P value**	**Adjusted OR 95% CI**	**P value**
Age	0.99 (0.96, 1.03)	0.635	1.00 (0.963, 1.047)	0.821
Epidural haematoma*	7.368 (1.396,38.894)	**0.019**	11.22 (1.369, 92.052)	0.024
Evacuation of hematoma	0.50 (0.18, 1.38)	0.180	-	-
Antimicrobial prophylaxis	0.822 (0.277, 2.434)	0.723	3.198 (0.539, 32.697)	0.171
Craniotomy	1.54 (0.52, 4.52)	0.434	-	-
Combinations of surgical procedures*	0.967 (0.553, 1.692)	0.906	1.553 (0.681, 3.543)	0.295
Procedure duration	1.23 (0.74, 2.06)	0.429	1.358 (0.691, 2.669)	0.375
Interaction term	-	-	0.991 (0.983, 0.999)	**0.028**

In the parsimonious model, the interaction term is a variable that is a product of the variables that work in synergy to bring about the outcome of interest. In this case the parsimonious model was a product of the variables: evacuation, craniotomy, duration of the procedure, age and antimicrobial prophylaxis. Individually, each of these variables had no effect on risk of infection. The p value for the interaction variable was statistically significant, which was indicative of the presence of interaction of variables. Given that it is difficult to understand the output of a logistic

regression model, we performed stratified data analysis and marginal analysis to help in the interpretation of the findings.

Marginal analysis is a statistical procedure that uses the results obtained on logistic regression analysis to compute the probabilities of developing the outcome of interest. These probabilities are used to generate graphs that illustrate the effects of a variable on the outcome of interest. As previously stated the only variable that independently was predictive of the risk of infection was diagnosis of epidural haematoma. The subsequent analysis describes the effects of each of the interacting variables.

5.3.13. Effect of Type of Surgical Procedures on Effectiveness of Antimicrobial Prophylaxis

Evacuation, antimicrobial prophylaxis and craniotomy each on their own were not associated with risk of infection as seen in the measures of association in Table 5.5. However, evacuation of hematoma on its own had a protective effect on the development of infection (OR 0.50, 95% CI 0.18, 1.38) and reduced risk of infection by almost 50%, but this was not significant. The ability of antimicrobial prophylaxis to reduce the risk of SSIs depended on whether a patient had undergone evacuation and/or craniotomy. Patients were stratified on these two variables. Antimicrobial prophylaxis was only effective in reducing the risk of infection in patients who had undergone both craniotomy and evacuation. It reduced the risk of infection in this stratum by 62.5% (CI, 29.0% , 96.0%). In patients who had undergone only one of these surgical procedures, antimicrobial prophylaxis seemed to be totally ineffective. The standardized risk difference across arms was different and this was statistically significant ($p < 0.001$) as seen in Table 5.9.

Table 5.9: Risk differences in Incidence of SSIs with and without prophylaxis

Types of surgical procedures done	Incidence of SSI with prophylaxis	Incidence of SSI with no prophylaxis	Standardised Risk difference (95% Confidence Interval)
No craniotomy and no evacuation	3(60.0%), n=5	0 (0.0%), n=1	0.750 (0.326, 1.174)
Evacuation only	3 (50.0%), n=6	1 (11.1%), n=9	0.269 (-0.461, 0.999)
Craniotomy only	9 (50.0%), n=18	5 (35.7%) n=14	-0.011 (-0.426, 0.404)
Craniotomy and evacuation	2 (18.2%), n=11	3 (75.0%), n=4	-0.625 (-0.960, -0.290)

5.3.14. The effect of number of surgical procedures on effectiveness of antimicrobial prophylaxis

Most (n=41, 57.8%) patients underwent only one surgical procedure while 26 (36.6%) underwent 2 surgical procedures. Three patients underwent 3 procedures while only 1 underwent 4 different surgical procedures.

The effectiveness of antimicrobial prophylaxis was measured by the percentage risk reduction. To see how the risk reduction varied with increase in total number of surgical procedures a patient underwent, the risk reduction associated with antimicrobial prophylaxis was plotted against the number of surgical procedures.

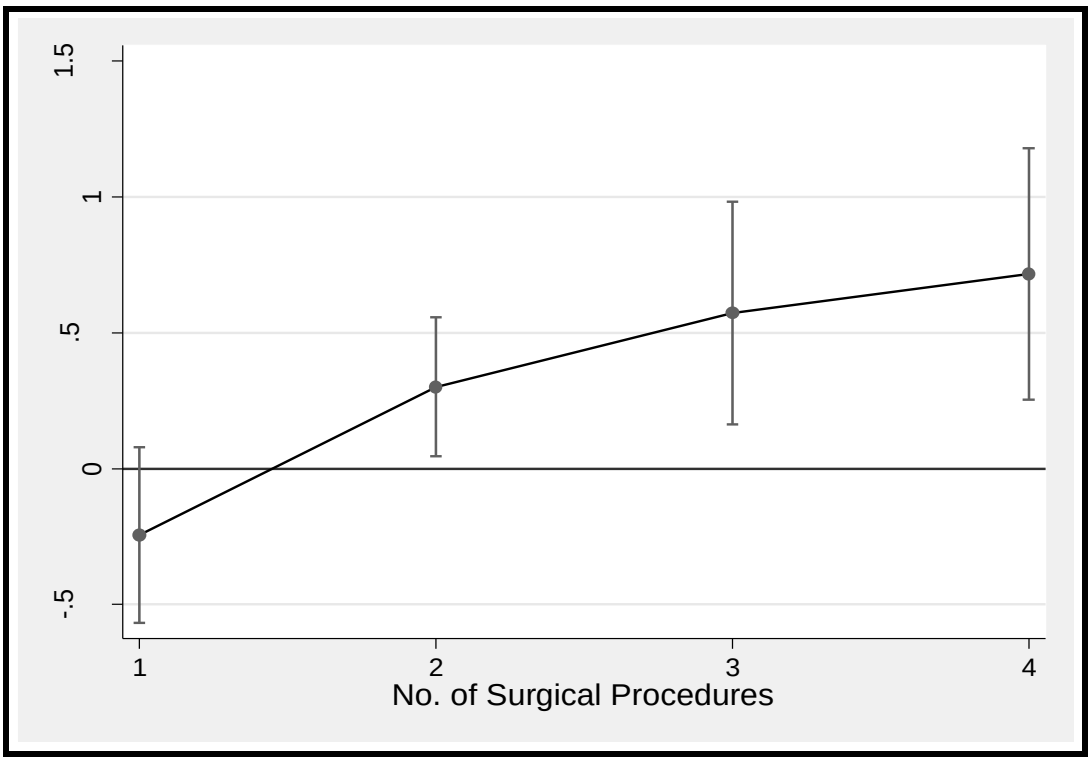


Figure 5.3: The dependence of effectiveness of antimicrobial prophylaxis on the number of surgical procedures

From the graph, as the number of surgical procedures performed on the patient increased, the effectiveness of antimicrobial prophylaxis increased. This observation was statistically significant because the confidence intervals for risk reduction did not cross zero (Figure 5.3).

In patients who underwent only one procedure, antimicrobial prophylaxis has no protective effect. In patients who underwent two procedures, the predictive risk reduction brought about by antimicrobial prophylaxis is 30.1% (4.6%, 55.6%). This was statistically significant (p=0.021). This explains why patients who underwent both evacuation and craniotomy had a lower risk of infection. The effect of prophylaxis plateaus off as the number of procedures increases. For those

who underwent three procedures, the protective effect was 57.2% risk reduction (CI 16.3%, 98.2%) and this was statistically significant (p=0.006). For those who underwent four surgical procedures, antimicrobial prophylaxis had an even higher protective effect of 71.7% risk reduction (25.4, 118.0) and it was statistically significant (p=0.002).

5.3.15. Interaction between antimicrobial prophylaxis, number of surgical procedures and Craniotomy on surgical site Infections

To illustrate that the effects of antimicrobial prophylaxis are simultaneously dependent on the number of surgical procedures and whether the patient had undergo surgery, we plotted risk reduction for infection against the number of surgical procedures a participant had undergone. A separate graph was generated for patients who had undergone craniotomy and other who had undergone other surgical procedures (Figure 5.4).

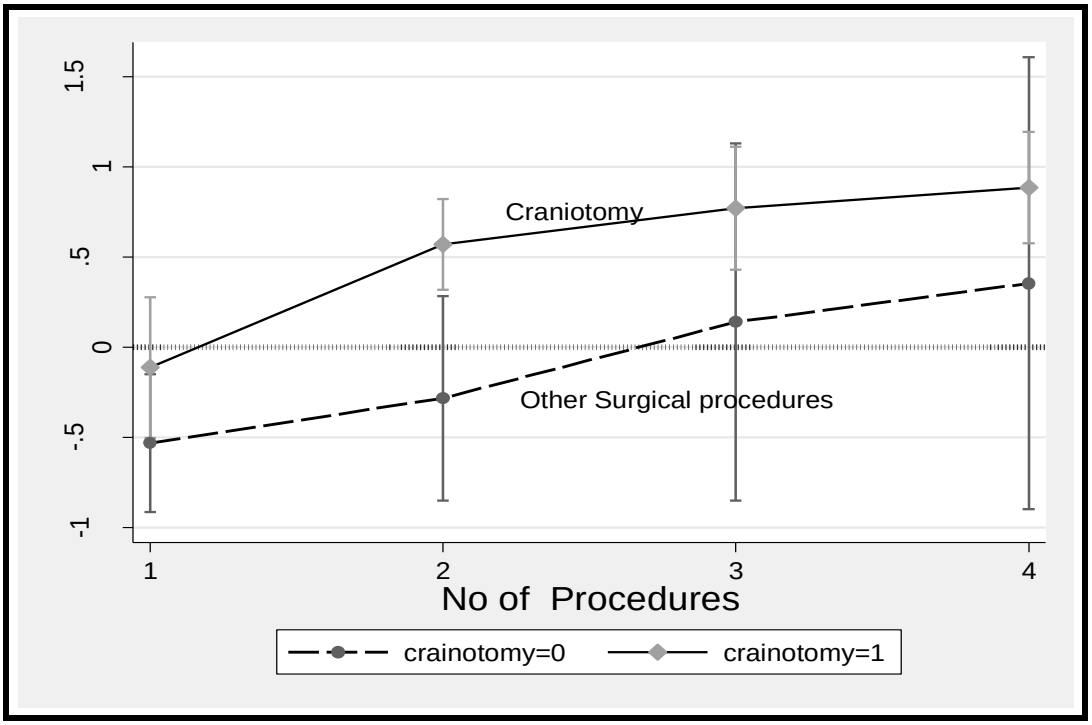


Figure 5.4: Comparison of the effectiveness of antimicrobial prophylaxis in craniotomy and non-craniotomy patients

From Figure 5.4, patients who had undergone craniotomy consistently had lower risks of infection. In patients who had only undergone one procedure, antimicrobial prophylaxis was less effective. Antimicrobial prophylaxis was more effective in patients who underwent craniotomy. The overlap in confidence intervals for craniotomy and non-craniotomy patients indicates that though prophylaxis seemed to be more effective in the craniotomy group, the difference was not statistically significant.

In both the patients who had undergone craniotomy and those who did not, as the number of procedures performed increased, the effectiveness of antimicrobial prophylaxis as measured by age and % risk reduction, seemed to increase. These results have implications for practice, such that additional methods for reducing infection, other than antimicrobial prophylaxis especially in patients undergoing craniotomy need to be explored.

5.3.16 Effect of the Duration of the Surgical Procedure on the effectiveness of antimicrobial prophylaxis

The difference in the effectiveness of antimicrobial prophylaxis could have been attributed to the differences in duration of surgical procedures. In general, the duration of the surgery for patients who underwent craniotomy was longer when compared to patients who underwent other surgical procedures. The median duration of surgery of patients who underwent craniotomy was 3 hours, with a range of 2 to 6 hours (n=49). On the other hand the median duration of surgery of patients who underwent other surgical procedures was 2 hours with a range of 2 to 7.5 hours (n=33). The

difference in the duration of surgery was statistically significant ($p<0.001$). The duration of surgery was also dependent on the total number of procedures a patient underwent while in theatre ($p=0.001$). The duration of surgery was expected to be a mediator in the association between the number of procedure and risk of infection. If mediation was complete, controlling for the effects of duration of surgery was expected to abolish any effect of number of procedures on the risk of infection.

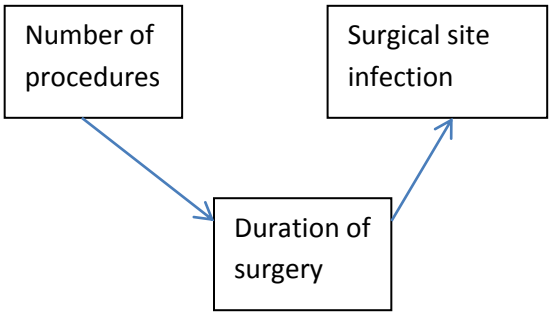


Figure: 5. 5: Path diagram that shows that the duration of surgery mediates the effects of number of procedures.

When duration of surgery was added to the parsimonious model, the interaction term became insignificant and the effect of number of procedures on risk of infection reduced. A mediator variable can substitute an antecedent variable. When this was done, the interaction effect remained significant.

In the next step of the analysis, we sought therefore to determine whether the duration of surgery and number of procedures were either confounding variables or effect measure modifiers.

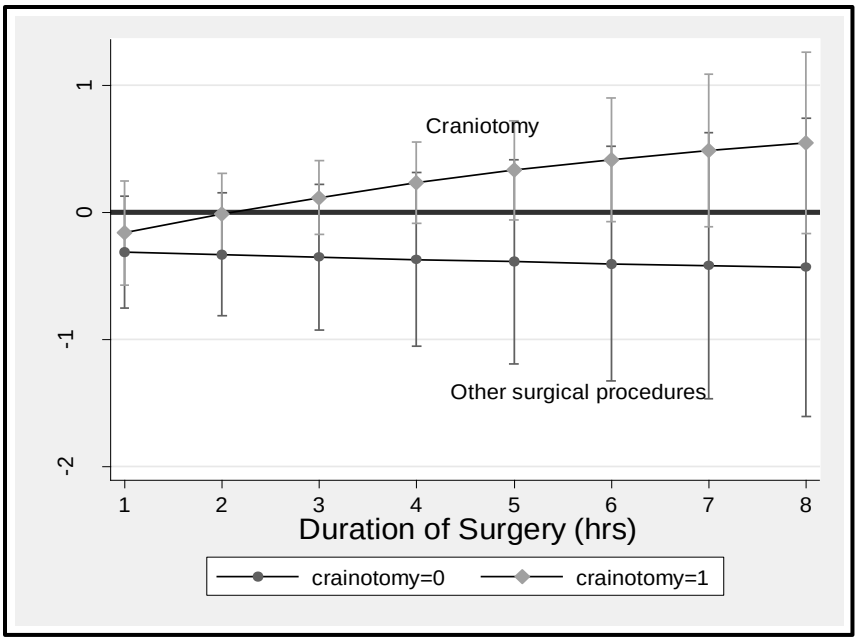


Figure 5.6: Effect of duration of surgery on effectiveness of antimicrobial prophylaxis

From the graph, as the duration of surgery increased, the effectiveness of prophylaxis increased in patients who had undergone craniotomy. In this stratum, prophylaxis had a beneficial effect (with a risk reduction <0) if the duration was less than 2 hours. For patients undergoing the other procedures, increasing the duration of the procedure did not increase the effectiveness of antimicrobial prophylaxis. However the confidence interval increased in duration of the procedure.

5.3.17 Effect of age on the effectiveness of antimicrobial prophylaxis

In patients undergoing other procedures, the effect of prophylaxis is expected to remain constant regardless of increase in age. In patients who underwent craniotomy, the effectiveness of prophylaxis increased with age, but it was not statistically significant (Figure 5.7).

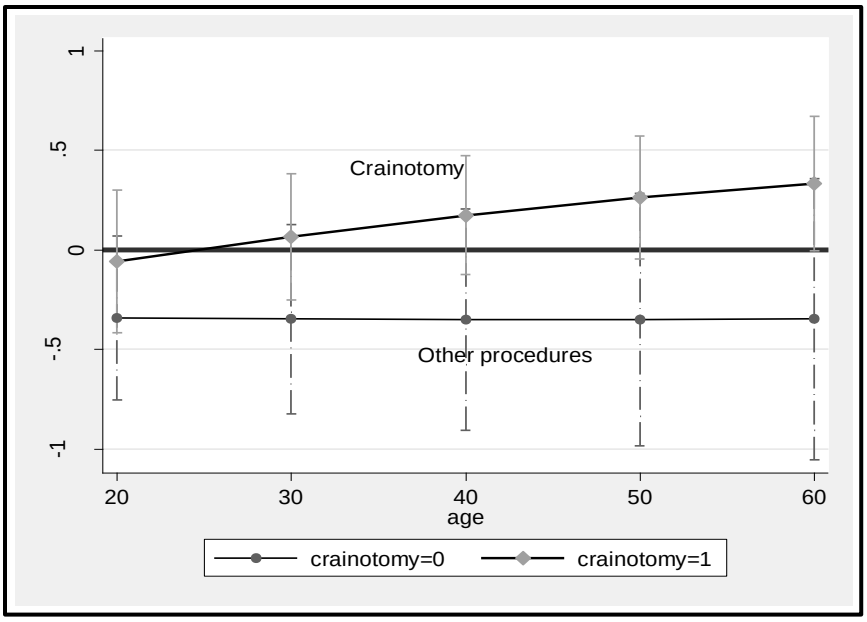


Figure 5.7: Effect of age and type of procedure on antimicrobial prophylaxis

5.4. DISCUSSION

This study recruited patients with a median age of 35 years with an interquartile range of 27 to 51 years. The demographics are similar to other local studies which reported similar age groups (Njiru et al., 2015; Saidi et al., 2014; Kiboi et al., 2011). Some studies however have reported recruited older trauma patients (Belluse et al., 2015; Saidi et al., 2013). Most of the patients in this study were male (94.0%) with the females at 6.0%. This is consistent with other local studies which have shown a male predilection (Saidi et al., 2014); although Njiru et al., (2015) reported an almost equal number of males and females. These results could suggest that men are more likely to be involved in assault and other risky behaviour like careless and drunk driving as well as falls sustained after a drunken stupor, which could lead to head and brain injury.

Most of the patients in our study had a low level of education and subsequent low socioeconomic status. Most of them were employed as casual labourers. These findings are consistent with another local study (Wekesa et al., 2013) which stated that most patients who developed traumatic brain injury had a low level of education and were employed in low paying jobs.

In our study, assault was the most common cause of trauma, followed by road traffic accidents and falls. These results are consistent with another local study which reported that assault was the most common cause of injury followed by road traffic accidents (Wekesa et al., 2013).Violence and assault is common in areas with high levels of poverty, dense population, high unemployment levels and crime rates. This could very well mirror the socio-demographic characteristics of our study population (Wekesa et al., 2013). Other local studies have however listed road traffic accidents as the main cause of traumatic injury (Saidi et al., 2014; Mwang'ombe and Shitsama 2013) in neurosurgical patients. Road traffic accidents and falls are the most common causes of injury among the geriatric patients in Kenya (Saidi and Mutiso., 2013).

The study patients sustained several injuries such as skull fractures and head injury. Others had multiple injuries and fractures on other parts of the body such as the mandibles. Most of the patients had only one injury, while others sustained multiple injuries. Diagnoses of cerebral oedema, brain contusion and intracranial haemorrhages were also made. These findings are consistent with another local study which reports similar injuries (Kiplagat and Steyl, 2016). These patterns of injury from literature are from patients who have sustained injury mostly from

road traffic accidents. There's paucity of data on the patterns of injuries sustained from assault, falls and other blunt trauma.

In our study, the most common type of hematoma was subdural hematoma, followed by epidural and intra-cerebral haematoma. These results are consistent with those of another local study (Wekesa et al., 2013) which reported the most common types of hematoma to be subdural and intra-cerebral (with an equal proportion) followed by epidural haematomas. In the latter study, subarachnoid haemorrhage was the least prevalent type of haematoma. On the chronicity of haematomas, most of the bleeds were acute, followed by sub-acute and chronic hematomas in that order.

Similarly, Wekesa et al., (2013) reported the most common hematoma to be acute, followed by chronic and sub-acute haematomas. Most of the haematomas in our study were located in the subarachnoid region, followed by the tempero-parietal, left occipital, front occipital and left fronto-parietal regions. In a related study, (Wekesa et al., 2013) the anatomic location of hematomas differed, with the most common being located in the left hemispheric region, followed by the right parietal region, with the least affected region being the left temporal region. This shows that the anatomical site of injury varies with the different populations as well as the cause of injury.

In our study, the incidence of infection was very high, at 37.7%. This is unlike a study that was done by Njiru et al., (2015) at the same unit, that reported a much lower infection rate of 7.5%. Several other studies done in middle income countries have recorded similar infection rates (Buang and Hispani 2012; Bellusse et al., 2015). These studies mainly recruited patients

undergoing clean neurosurgical procedures while our study recruited patients who had sustained injury through trauma and were therefore more likely to be infected. The high infection rates in our study can be attributed to the class of wounds that the patients were admitted with. Patients are most likely to have been admitted with contaminated and dirty wounds. Open wounds sustained during traumatic injury such as from road traffic accidents could be contaminated with foreign objects such as glass and plastic, soil and other material as well as be colonised by normal flora, causing infection. Patients could as well have already infected dirty wounds on admission to the neurosurgical unit (Zinn and Swofford., 2014)).

According to Kenyatta National Hospital standard operating procedures, all head trauma patients admitted after 24 hours of injury are admitted in the neurosurgical ward .Those with critical head injury with a Glasgow Coma Scale of less than 8 are managed from the main Intensive Care Unit and later transferred to the neurosurgery ward on clinical improvement (Wekesa et al., 2013). This shows that most patients admitted to the neurosurgical unit following trauma already have either contaminated (Class III) wounds (open, fresh traumatic wounds that are less than 12 hours old or lacerations that are more than 8 hours old) or dirty (Class IV) wounds which are defined as old traumatic wounds over 24 hours old, purulent, those with foreign bodies or contamination by external material (Zinn and Swofford., 2014). Contaminated wounds more than 5 hours old have been shown to grow more than 10^5bacteria per gram of tissue (Notley et. al., 2015). Patients with severe head injury who are first treated at the main ICU before being transferred to the neurosurgical unit could already be infected at the ICU and could be sources of infection at the

neurosurgical unit. Revision of these operating procedures could reduce the infection rates of such trauma patients.

Another likely explanation of the high incidence of infection rate is the pattern of injury sustained by patients who undergo head injury. Penetrating wounds of the brain are likely to occur during trauma and foreign bodies like skin, hair and bone fragments from skull fractures are likely to be favourable culture medium for bacteria. Other foreign objects like soil, glass, metal particles and shrapnel from damaged vehicles could easily lodge into the brain can be potential contaminants and causes of infection (Notley et al., 2015). Multiple injuries to the head can increase the surface area of colonisation by normal flora and contaminating bacteria. Infection rates as high as 58.8% have been recorded among such patients, without the use of antibiotics (Kazim et al., 2011).

All the patients on dexamethasone treatment for raised intracranial pressure developed infection. This finding is consistent with the findings of another study which reported the use of corticosteroids as a risk factor for development of surgical site infection. Dexamethasone and other steroids have not shown any benefit in management of intracranial hypertension caused by traumatic brain injury, and have been associated with an increase in the risk of death (Rangel-Castillo et al., 2008). In addition, corticosteroids are known immunosuppressive agents, which act by interfering with the function of, and the differentiation of all immune cell lines (Coutinho and Chapman., 2011). These immunosuppressive effects may explain why all the patients who were on dexamethasone developed infection. It appears from the study that the patients who were put on dexamethasone were refractory to treatment with mannitol. For such patients, the

use of hypertonic saline, induction of barbiturate coma, hypothermia or decompressive craniectomy have been advocated for (Rangel- Castillo et al., 2008).

Despite the fact that diabetes mellitus and other cardiovascular co-morbidities have been shown to increase the risk of development of surgical site infections, all patients with cardiovascular co-morbidities in our study did not develop infection. Studies have demonstrated an association between pre and postoperative hyperglycaemia and development of surgical site infections, and a diagnosis of diabetes mellitus has been shown to be a stronger risk (Zhang et al., 2015; McCall B, 2015; Cheng et al., 2015; Chiang et al., 2014). Tight glycaemic control has been shown to reduce the incidence of surgical site infection (Boreland et al., 2015). This could have been the case with the one participant in our study who had diabetes. Two patients had hypertension and two others congestive cardiac failure. These conditions have also been associated with the development of surgical site infections, but the association has not been as strong as that of diabetes mellitus (Pugely et al., 2015; Madeira and Trabasso 2014; Korol et al.,2013).

The impact of systemic disease on the development of surgical site infection depends on the patient's America Society of Anaesthesiologists (ASA) score. It could be that our study patients with cardiovascular co-morbidities were in the ASA score range of I to II, and therefore were less susceptible to infection.

Admission to the neurosurgical intensive care units is associated with an increased risk of development of surgical site and non- surgical site infection. Because of the severity of injury and brain damage in these patients, they have altered consciousness and sensorium, weakened immune systems and protective reflexes, which make them susceptible to infections. Invasive

diagnostic and therapeutic procedures as well as increased duration of hospital stay further increase their chances of developing infections (Mehndiratta et al., 2014; Djordevic et al., 2012). In our study, all the patients admitted in the neuro-intensive unit of the ward developed infection, and this can be attributed to the aforementioned factors.

Patients who had epidural haematomas were the most likely to develop infection. Epidural haematomas develop in the setting of trauma that results in skull fractures and stripping off the dural membrane from bone. Additionally, epidural haematomas tend to accumulate very fast. The skull fractures and rapidly expanding haematomas could contribute to colonization of the injured areas by normal flora, causing infection (Price et al., 2014). This may explain why patients with epidural haematomas were more likely to develop infection.

The most common surgical procedure was craniotomy, followed by evacuation of hematomas and burr hole procedures. The highest infection rates were recorded among patients who underwent craniotomy alone, followed by those who underwent burr hole drainage procedures. Those who underwent evacuation of hematomas were less likely to develop infection. In fact, evacuation of haematomas reduced the risk of surgical site infections. Studies have shown that infections that develop after craniotomy are a major problem in neurosurgery, and are associated with high morbidity and mortality rates (Buang and Haspani., 2012).

Craniotomy procedures involve temporary removal of a bone flap or section of the skull to allow for access to the brain. The bone flap is replaced at the end of surgery. Intraoperative contamination from the surgical team can occur and lead to infection (Chiang et al., 2014). Craniotomies are the most common emergency procedures carried out on trauma patients. These

patients are likely to have contaminated wounds and this increases the likelihood of development of infection (Buang and Haspani., 2012). Multiple craniotomies further increase the risk of infection (Sturm, 2009).

The risk of development of infection in our study was dependent on a combination of three different variables: duration of procedure, craniotomy procedures and strict prophylaxis. Prolonged duration of surgical procedure is a major risk factor for development of neurosurgical site infections (Bellusse et al., 2015; Abu et al., 2014). In our study, the median duration of surgical procedure was 3 hours. Studies have recorded durations of 3 to 5 hours or longer (Chiang et al., 2014; Buang et al., 2012). Procedures that last more than two to four hours have been associated with an increase in the incidence of surgical site infections, because of an increase in the time of wound contamination as well as reduced efficacy of antibiotics administered for prophylaxis (ASHP Therapeutic Guidelines, 2016). In our study, the increase in effectiveness of prophylaxis with increase in duration of the procedure can be explained by the fact that additional intra-operative doses are routinely administered for neurosurgical procedures longer than two hours at Kenyatta National Hospital.

The duration of surgical procedure depends on the type of procedure being performed. From the results of our study, the duration of procedure was longer for the patients who underwent craniotomy than those who underwent other procedures. Prolonged surgery increases the chances of contamination of the surgical wound and the surgical field by normal flora and bacteria from the environment (Chiang et al., 2014). In addition, the minimum inhibitory concentration of antibiotics reduces with time and this affects the efficacy of antibiotics given for prophylaxis.

Our study showed that antimicrobial prophylaxis was effective for procedures which were less than two hours long. This finding espouses the need for intraoperative re-dosing of prophylactic antibiotics for prolonged procedures (ASHP Therapeutic Guidelines, 2016).

Antimicrobial prophylaxis alone is not protective of infection since a proportion of trauma patients or patients with contaminated wounds still develop infection even with prophylaxis (Notley et al.,. 2015, Siritongtaworn et al., 2014, Erman et al., 2005). In our study, initially antimicrobial prophylaxis seemed to have no benefit. This finding agreed with previous studies that found that prophylaxis is of no benefit (Notley et al., 2015). However, after accounting for confounding and effect measure modification, antimicrobial prophylaxis was particularly beneficial in patients undergoing both craniotomy and evacuation of haematomas. This means that on its own, prophylaxis may not be effective but its effectiveness is highly dependent on the types of surgical procedures. This suggests that data from previous published studies on effectiveness of antimicrobial prophylaxis may need to be re-analysed, keeping in mind the interaction between surgical procedures and antimicrobial prophylaxis.

Proper antimicrobial prophylaxis requires that antibiotics be given one hour to thirty minutes before the initial incision and for antibiotics with a short duration of action, a repeat intraoperative dose is given. The choice of antibiotic should be such that it targets the resident flora of the incision site. Antibiotics should not be given beyond 24 hours of the incision (Bratzler et al., 2013).

Antimicrobial prophylaxis has been shown to drastically reduce the incidence of surgical site infection. However in our study, patients on antibiotics had a higher chance of developing

infections than those who were not on antibiotics. Studies have shown that despite prophylaxis, infections still occur with contaminated traumatic wounds, but at a lower rate (Notley et al., 2015; Siirijatuphat et al., 2014; Ghafouri et al., 2012).

Antimicrobial prophylaxis alone did not seem to be effective in preventing surgical site infections. However, craniotomy procedures, evacuation of haematomas, prolonged craniotomy procedures and increasing age for patients undergoing craniotomies seemed to potentiate the effect of antimicrobial prophylaxis. There are no studies in literature which explain these findings, so we postulate that infection control procedures during craniotomy and evacuation of haematoma procedures such as disinfection of the site and other intraoperative sterile procedures contribute to reduction of infection in this patient cohort.

Our study had several limitations. Some of the patient data was missing from patient files, and it caused us to make assumptions during data analysis. For example, since there was no clear distinction between antimicrobial prophylaxis and presumptive treatment for infection, we assumed prophylaxis to be antibiotic use for up to a period of three days. The sample size for this study was small. The number of patients included in the sub-group analyses, particularly those with epidural haematomas was not enough to represent a normal distribution. There is need for larger studies to be conducted to establish the effect of the epidural haematoma on development of surgical site infections as well as effectiveness of antimicrobial prophylaxis.

The study had several strengths which show cased its originality. This is the first study to factor in effect measure modification in the effectiveness of antimicrobial prophylaxis. Subsequent studies should consider this. The effectiveness of antimicrobial prophylaxis is dependent on the

number and type of surgical procedures. This is also the first study which shows that patients with epidural haematomas have a high risk of surgical site infections compared to other types of injury. Seven out of nine of these patients developed surgical site infections.

5.5 CONCLUSION AND RECOMMENDATIONS

The presence of epidural haematoma was an independent risk factor in the development of infection for our patient cohort. Antimicrobial prophylaxis with amoxicillin clavulanate, cefuroxime and meropenem was effective as no patients on these antibiotics prophylactically developed infection. Antimicrobial prophylaxis alone was not effective in preventing surgical site infections, but craniotomy procedures, prolonged craniotomy procedures and evacuation of haematomas increased the effectiveness of prophylaxis. More studies should be carried out to establish why craniotomy and evacuation procedures, when done together, increase the effectiveness of antimicrobial prophylaxis.

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CHAPTER 6: PATTERNS OF ANTIMICROBIAL USE AT THE NEUROSURGICAL WARD OF KENYATTA NATIONAL HOSPITAL

6.1 INTRODUCTION

Antibiotic use among neurosurgical patients serves two purposes; prophylaxis and treatment of already established infections. Antimicrobial prophylaxis should be of a shorter duration, not more than 24 hours. The prophylactic antibiotics should not be given more than one hour or less than 30 minutes before the initial incision. Prolonged procedures require additional intraoperative dosing. The choice of antibiotic for prophylaxis should be based on the knowledge of causative organisms at the incision site, antimicrobial susceptibility and resistance patterns at the unit, safety and cost effectiveness of the antibiotic (ASHP Therapeutic Guidelines, 2016).

Guidelines exist on the presumptive treatment of intracranial infections. For brain abscesses, treatment with intravenous antibiotics is indicated for a period of 4 to 8 weeks, depending on the response of the patient. Abscess drainage accompanies antibiotic treatment. The long duration of treatment is required because of the long time required for the brain tissue to repair and close the abscess space. The recommended antibiotics should adequately cross the blood brain barrier and achieve adequate concentrations in the brain. Empiric therapy with penicillin G or third generation cephalosporins like ceftriaxone or cefotaxime should be done if streptococcal infection is suspected. In case of staphylococcal infection, especially MRSA, vancomyin should be used. Alternatives to vancomyicn include linezolid, daptomycin and trimethoprim-sulfamethoxazole. Metronidazole is indicated on suspicion of anaerobic infection. In case of

suspicion of *Pseudomonas aeruginosa* infection, cefepime or ceftazidime should be used empirically (Brook, 2015).

Specific treatment based on culture and sensitivity tests should include drugs which penetrate well into the abscess cavities like penicillin, chloramphenicol, third generation cephalosporins and aminoglycosides. Other drugs like carbapenems can also be used for treatment (Brook, 2015).

Several medication errors can occur with the use of antibiotics in the neurosurgical setting. A medication error is defined as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in control of the healthcare professional, patient or consumer." They may be related to professional practice, health care products, procedures and systems. They can occur at any stage during the drug use process such as prescribing, dispensing, administration, order communication, product labelling, compounding, education, monitoring and use (European Medicines Agency, 2015).

6.1.1 Study Problem

Common practice in neurosurgery across studies shows that antibiotics are used to cover for infection pre and postoperatively (Jiang et al., 2016; Ha et al., 2012). This has led to prolonged prophylaxis, which in turn increases the risk of surgical site infections (Bozkurt et al., 2013; Ha et al., 2012). This is not uncommon in our set up, where antibiotics are generally used indiscriminately among surgical patients and there is a thin line between antimicrobial prophylaxis and treatment of already established intracranial infections, in terms of choice of drug, dosage, frequency of administration and duration of use. Lack of antimicrobial stewardship

and guidelines for antibiotic use have further compounded the problem. Our study sets out to establish the extent of this problem at the neurosurgical unit of Kenyatta National Hospital since such a study has not been carried out.

6.1.2 Objectives

The main objective was to identify antibiotic use patterns and their association with development of surgical site infections as well as identify medication errors in antibiotic use.

The specific objectives were to:

1. Compare patterns of antibiotic use among patients who underwent surgery and those who did not, as well as those who developed SSIs and those who did not.
2. Determine the number and types of medication errors in antibiotic use and their association with development of surgical site infections

6.2 METHODS

The Methods described for the cohort study (Chapter 5) apply.

6.3. RESULTS

6.3.1. Prevalence and Types of Antibiotics Used in Surgical and Non-surgical Patients

The total number of patients who were put on antibiotics was 68 (87.2%). Of those who underwent surgery, 89.5% (n=51) used antibiotics. The number of antibiotics used by each patient ranged from one to four. Patients who underwent surgery were less likely to use antibiotics than those who did not undergo surgery. Patients who underwent surgery were more likely to use multiple antibiotics compared to those who did not undergo surgery, as presented in Figure 6.1.

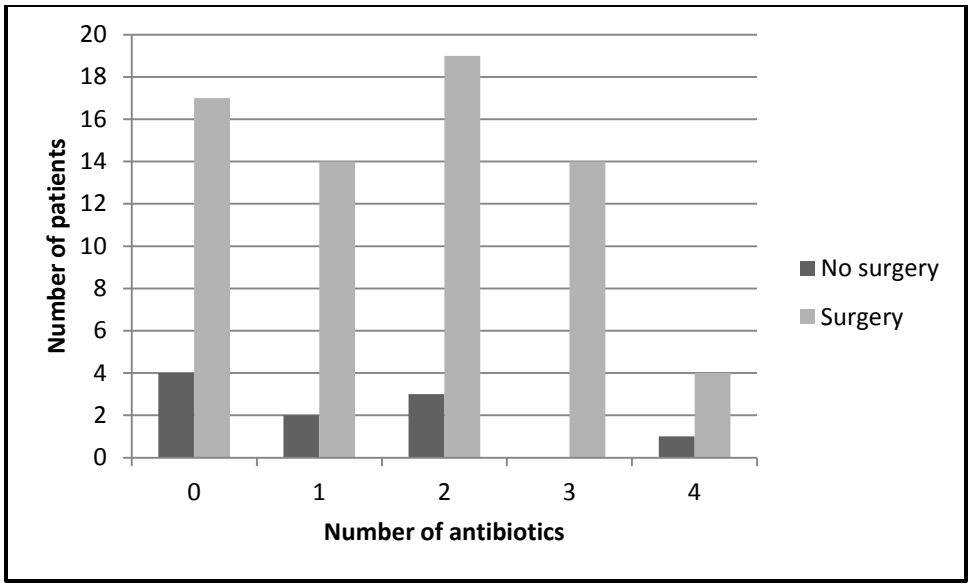

Figure 6.1: Number of antibiotics used with and without surgery

6.3.2. Types of antibiotics used in the neurosurgical ward of KNH

Ceftriaxone was the most commonly prescribed antibiotic (78.9%, n=45), followed by metronidazole, Amoxicillin clavulanate, cefuroxime and meropenem. Seven patients were put on l other antibiotics depending on any additional diagnosis. All these patients underwent surgery, but the association was not statistically significant (p=0.987). This is summarized in Figure 6.2.

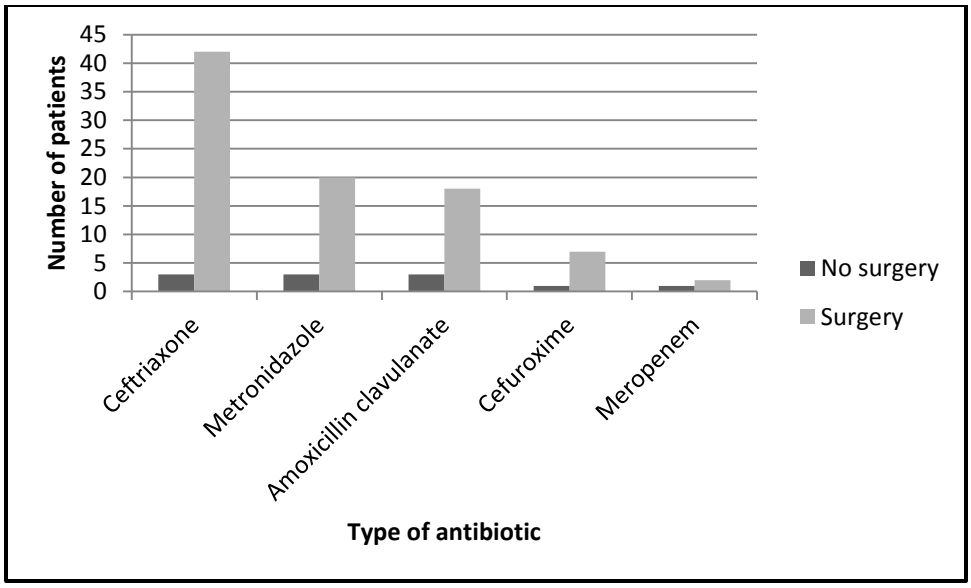

Figure 6.2: Types of antibiotics used with or without surgery

Other antibiotics that were used by one patient each were: gentamicin, clindamycin, ampiclox, flucloxacillin and tetracycline eye ointment. Two patients used amikacin. Their dosing regimens are found in Appendix 16.

6.3.3. Patterns of Antibiotic Use for Patients who developed Surgical Site Infection and those who did not

6.3.3.1 Number and types of antibiotics used

The patients who were on antibiotics and underwent surgery during this study period were 51 (89.5%).Patients on antibiotics were 1.9 times more likely to develop surgical site infections compared to those not on antibiotics (RR 1.87, 95% CI 0.75- 4.65) but this association was not statistically significant (p=0.135).

The number of antibiotics prescribed per patient varied between one and four. Those who were put on one antibiotic were 20.3%, (n=14) while 26.1% (n=18) received two antibiotics. Fourteen

patients (20.3%) received three antibiotics while 5.8% (n=4) were on four antibiotics during the time of hospitalization. Of those who received one antibiotic, 28.6% (n=4) developed surgical site infection, as opposed to 38.9% (n=7) of those who were on two antibiotics. The incidence of SSIs for those who were on three antibiotics was 57.1% (n=8) as opposed to 75% for those who were on four antibiotics. As the number of antibiotics used increased, the likelihood of development of infection increased, and this was statistically significant (p=0.015). It is likely that patients deemed to have severe infection were put on multiple antibiotics. This is illustrated in Figure 6.3.

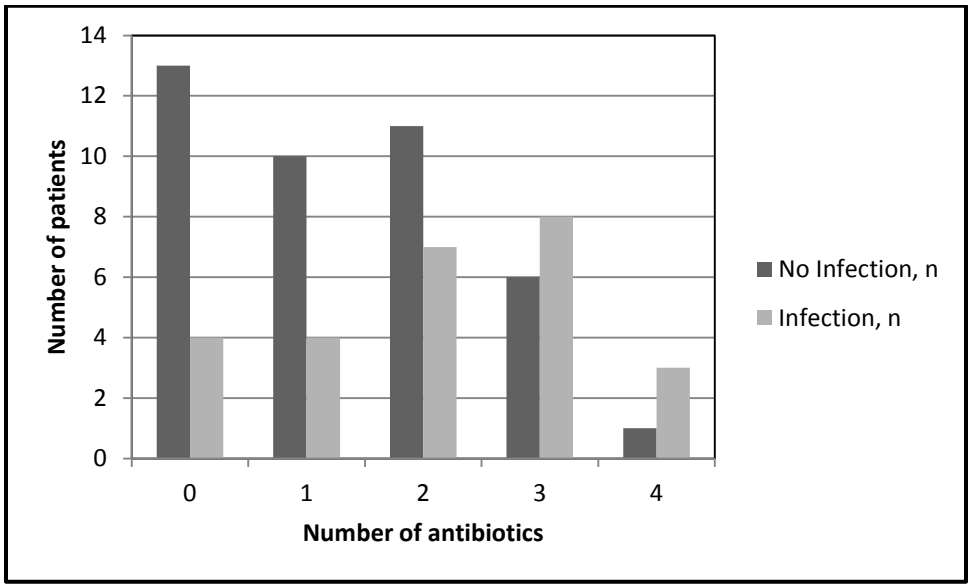

Figure 6.3: Number of antibiotics per patient, with and without surgical site infection

Ceftriaxone was the most commonly prescribed antibiotic, at 63.7% (n=44), followed by metronidazole at 27.5% (n=19), amoxicillin clavulanate at 26.1% (n=18), cefuroxime at 10.1% (n=7) and meropenem at 2.9% (n=2).

6.3.4 Use of Ceftriaxone in the Neurosurgical Ward

Ceftriaxone was more commonly used in patients who underwent surgery than those who did not undergo surgery but this difference was not statistically significant (p=0.066). This drug was prescribed at varying frequencies. The patients who underwent surgery were more likely to receive a once daily dose than those who did not undergo surgery. These patients were also more likely to receive ceftriaxone at an unspecified frequency of administration .This was not statistically significant (p=0.337).

Thirty one patients had one ceftriaxone prescription. Out of these, one patient's dose was not indicated (3.2%), although two doses were administered: 1g (58.1%, n=18) and 2g (38.7%, n=12). This applies to the patients whose dose was indicated. The frequency of administration ranged from one to three times a day. Ten patients (32.3%) received once daily injections while 19 patients (61.3%) received a twice daily dose. Two patients received ceftriaxone three times daily.

The daily defined dose for Ceftriaxone is 2g according to the WHO ATC DDD Classification, 2016. Slightly over half of the patients (54.8%) received the daily recommended dose of Ceftriaxone as illustrated in Figure 6.4.

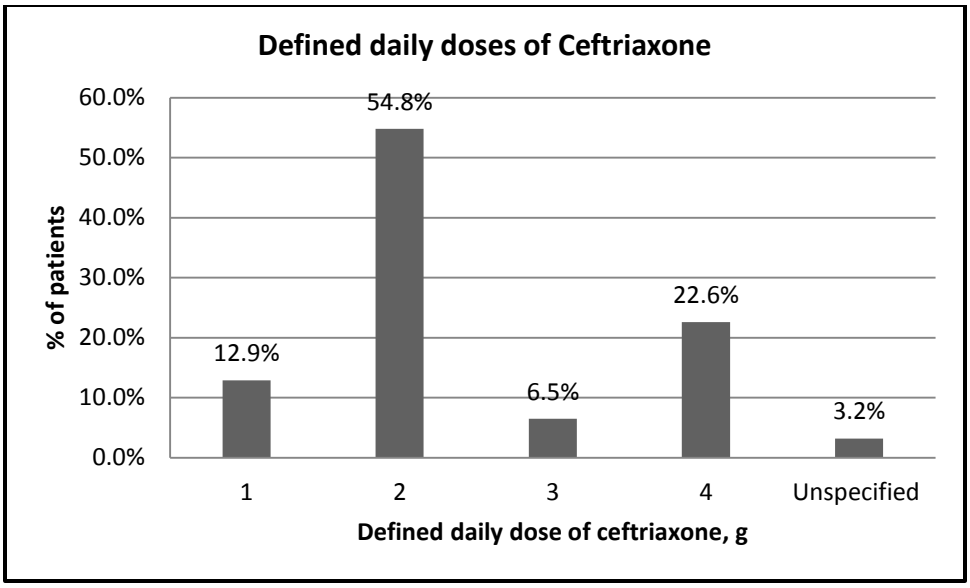

Figure 6.4: Defined daily doses of Ceftriaxone

Twelve patients had a second prescription of ceftriaxone (17.4%). For eleven patients (24.4%), the duration of use was not indicated. Use for less than 3 days was assumed to be for prophylaxis (Figure 6.5).

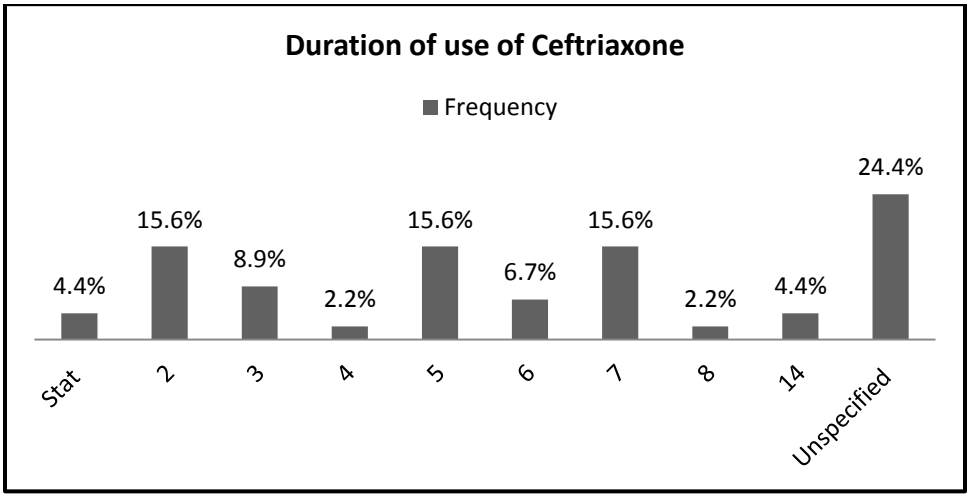

Figure 6.5: Duration of use of Ceftriaxone in days

The dosing pattern of ceftriaxone varied among patients. Out of 21 patients who had an initial dose of 1g of ceftriaxone, 3 received a second dose which was increased to 2g, while 18 did not receive a second dose. Twenty one patients received an initial dose of ceftriaxone of 2g. Out of these, 9 received a second dose. For one patient, the initial dose was not specified and this patient did not receive a second prescription. This amounted to irrational prescribing. Figure 6.6 presents the dosing patterns of the twelve patients who received a second prescription of ceftriaxone.

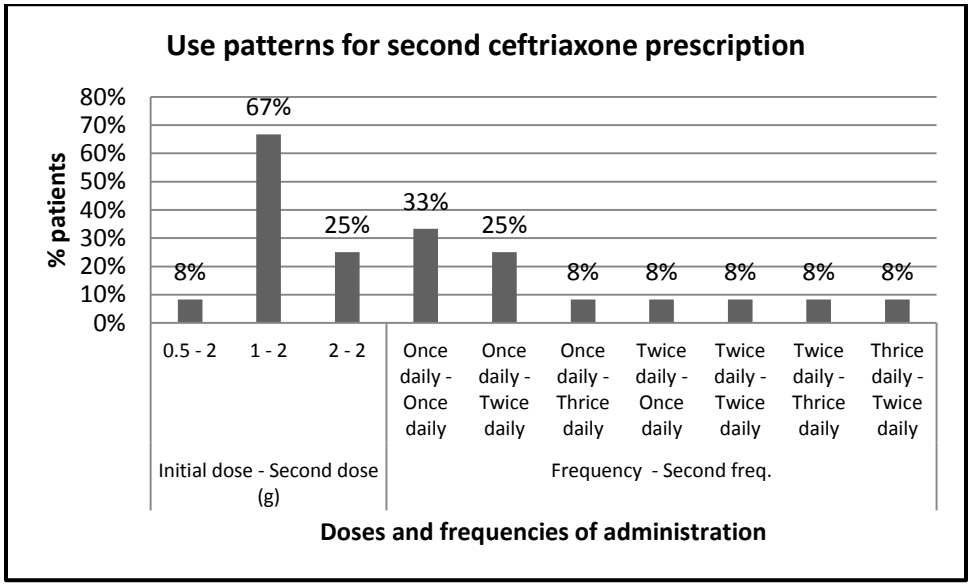

Figure 6.6: Dosing and frequency of use patterns for patients who received second prescription of ceftriaxone

Of the patients on only one prescription of ceftriaxone, 38.6% (n=17) developed surgical site infection, but the association between being on one ceftriaxone prescription and development of surgical site infections was not statistically significant (p=0.478). The details on the associations are presented in Appendix 16. For those who received a second prescription of ceftriaxone,

15.9% (n=11) developed surgical site infection. The association between the second ceftriaxone dose and development of infection was not statistically significant (p=0.720). There was no statistically significant association between the dose, route, frequency and duration of administration of ceftriaxone and development of surgical site infections as illustrated in Figures 6.7 and 6.8 (Appendix 16).

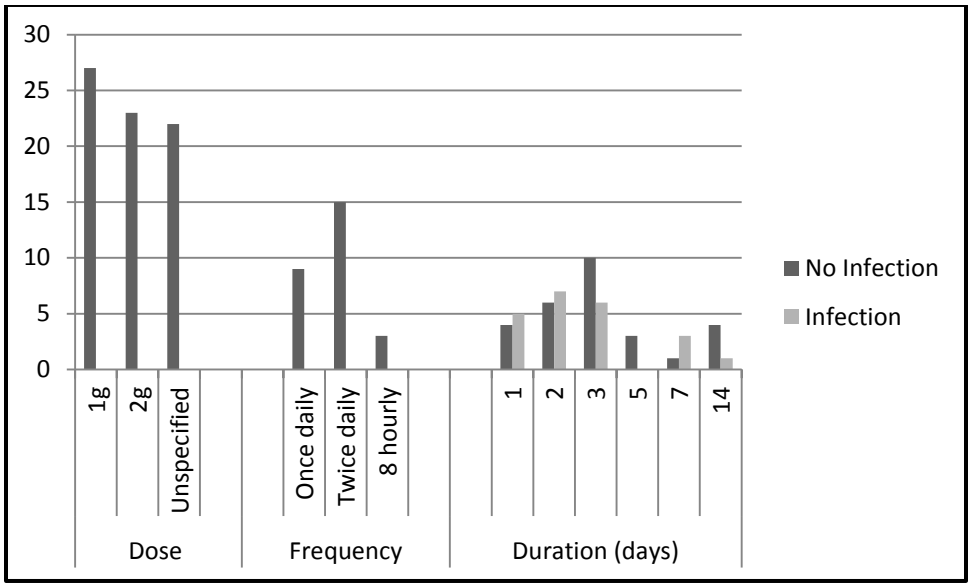

Figure 6.7: Use of ceftriaxone for patients on the first prescription of ceftriaxone who developed infection and those who did not

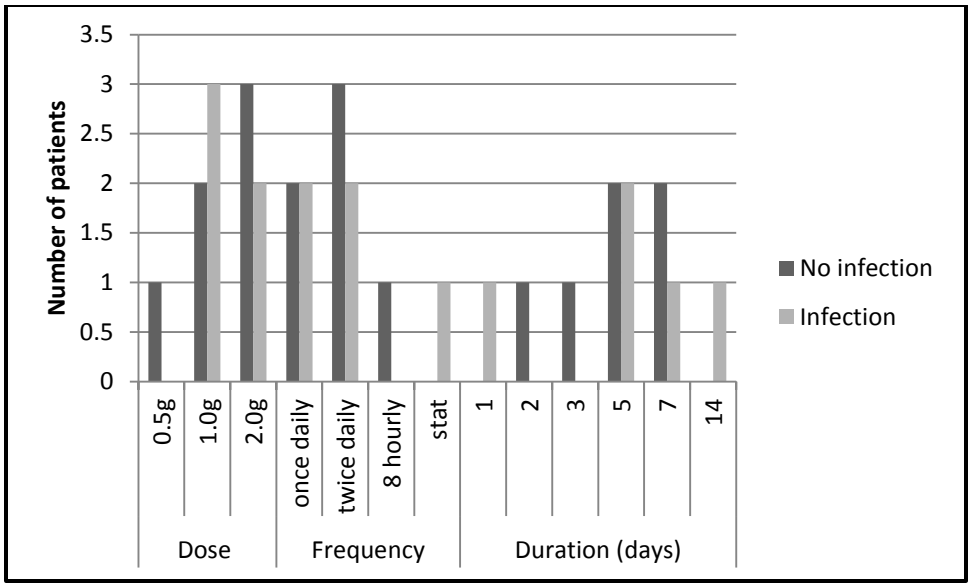

Figure 6.8: Use of ceftriaxone for patients on the second prescription of ceftriaxone who developed infection and those who did not

There was no significant association between the daily dose of ceftriaxone prescribed and infection rates (p=0.677) for the patients who received one prescription of ceftriaxone. For the patients on two prescriptions of ceftriaxone, the additional prescription was driven by infection because nearly 50% of the patients who had a second prescription developed infection, compared to 40% (n=12) of those who only had one prescription. This association was not statistically significant (p=0.513).

6.3.5. Metronidazole use patterns at the Neurosurgical ward

Metronidazole was used by 40.4% (n=23) of the patients who were on antibiotics. 87.0% (n=20) of the patients who were on metronidazole underwent surgery. Almost all patients who were on metronidazole underwent surgery. There was no statistically significant association between the

prescription patterns of metronidazole and surgical procedure (p=0.121) as presented in Figure 6.9 (Appendix 16).

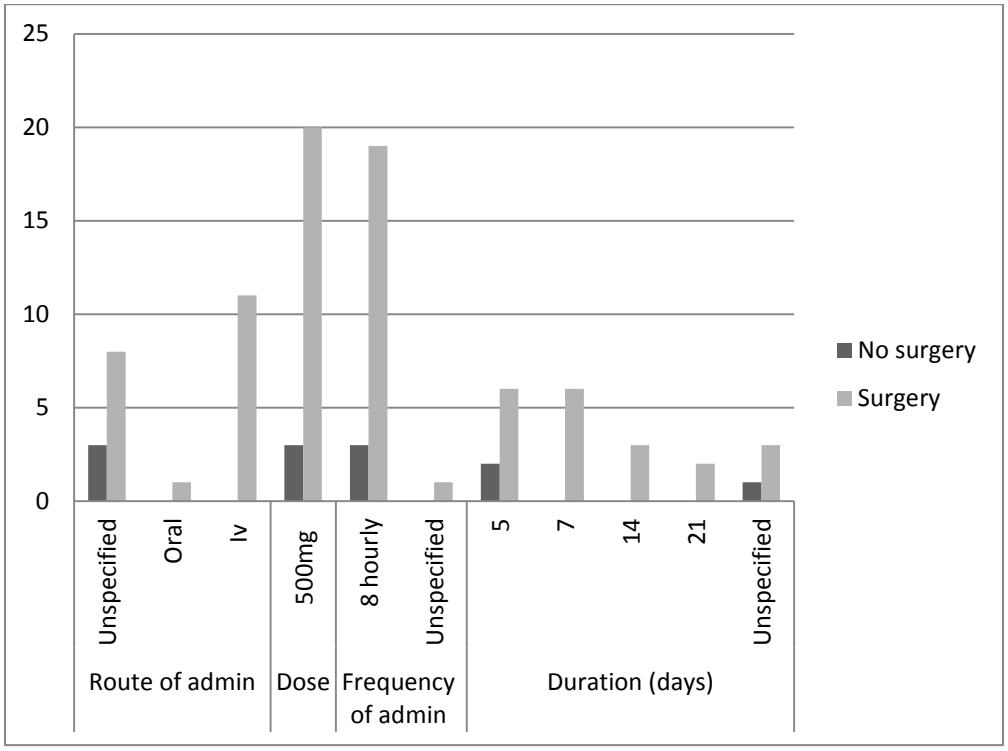

Figure 6.9: Metronidazole use patterns with and without surgery

All the patients received 500 mg of metronidazole three times a day. This translates to a daily dose of 1.5g, which is the recommended daily dose for metronidazole according to the WHO ATC DDD classification. Of the patients on metronidazole who underwent surgery, 57.9% developed infection (n=11), but this was not statistically significant (p=0.121).There was no statistically significant association between the dose, frequency, duration of use of metronidazole and development of surgical site infections as shown in Figure 6.10.

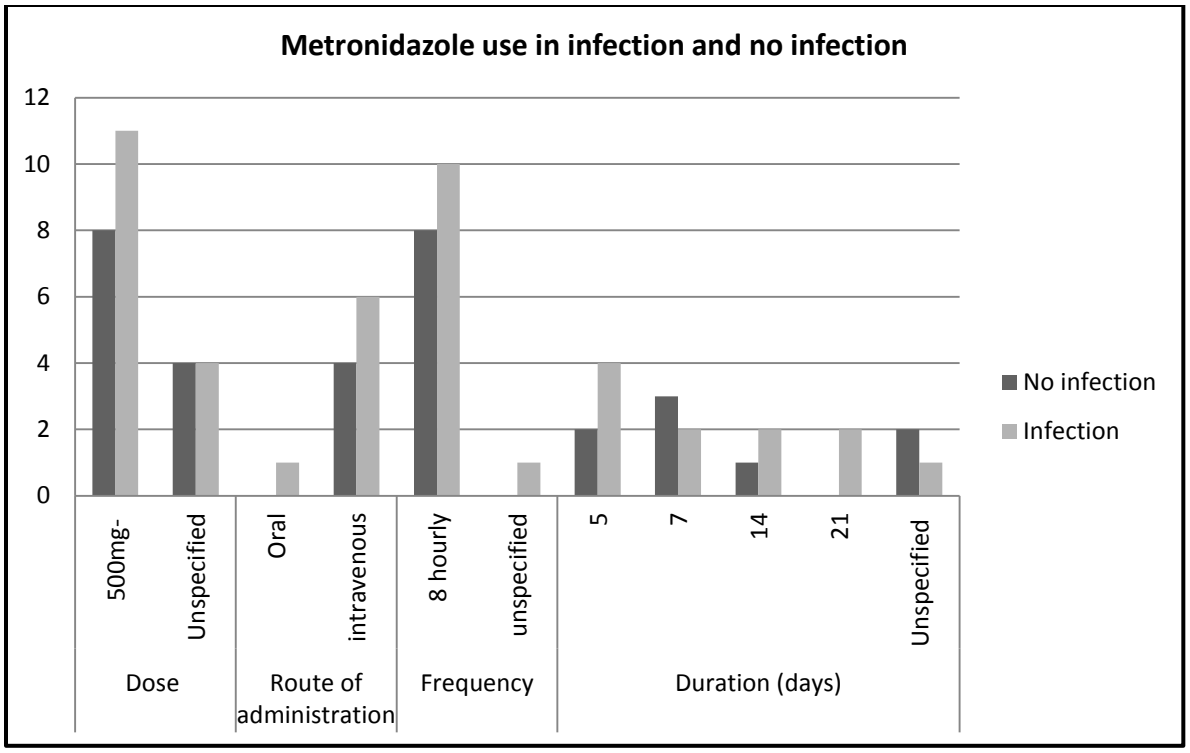

Figure 6.10: Metronidazole use patterns in patients who developed infection and those who did not

6.3.6 Patterns of use of Amoxicillin Clavulanate

Amoxicillin clavulanate was prescribed for 23 patients. Of these, 78.3% (n=18) underwent surgery. The route of administration of most patients who received amoxicillin clavulanate (72.2%, n=13) was not specified. Of these patients, 76.9% underwent surgery (n=10). There was no statistically significant association between the dose (p=0.695) , frequency (p=0.801) and duration of amoxicillin clavulanate use (p=0.770) and surgical procedure as illustrated in Figure 6.11.

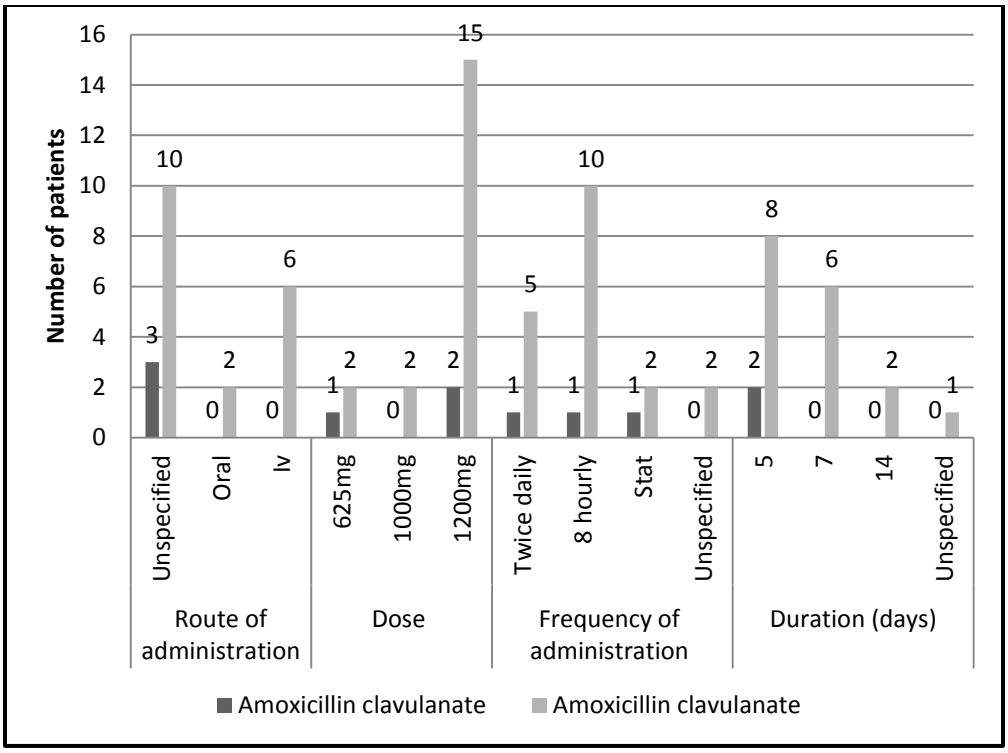

Figure 6.11: Use of Amoxicillin clavulanate for those who underwent surgery and those who did not

The daily defined dose (DDD) was computed for patients on Amoxicillin Clavulanate. According to the WHO ATC DDD Classification, the daily recommended dose for this drug is 1000mg of the amoxicillin component for the oral drug and 3g for the intravenous form. Only two patients were on the oral formulation while 19 were on the intravenous form. Assuming the two were on 1000mg of amoxicillin, (the assumption is made because the products available in the market and procured by the hospital contain 1000mg of amoxicillin) it shows that they likely exceeded the recommended dose two fold.

Ten patients who were on amoxicillin clavulanate developed surgical site infection. There was no statistically significant association between the route, dose, frequency and duration of use of the drug and development of surgical site infection as illustrated in Figure 6.12.

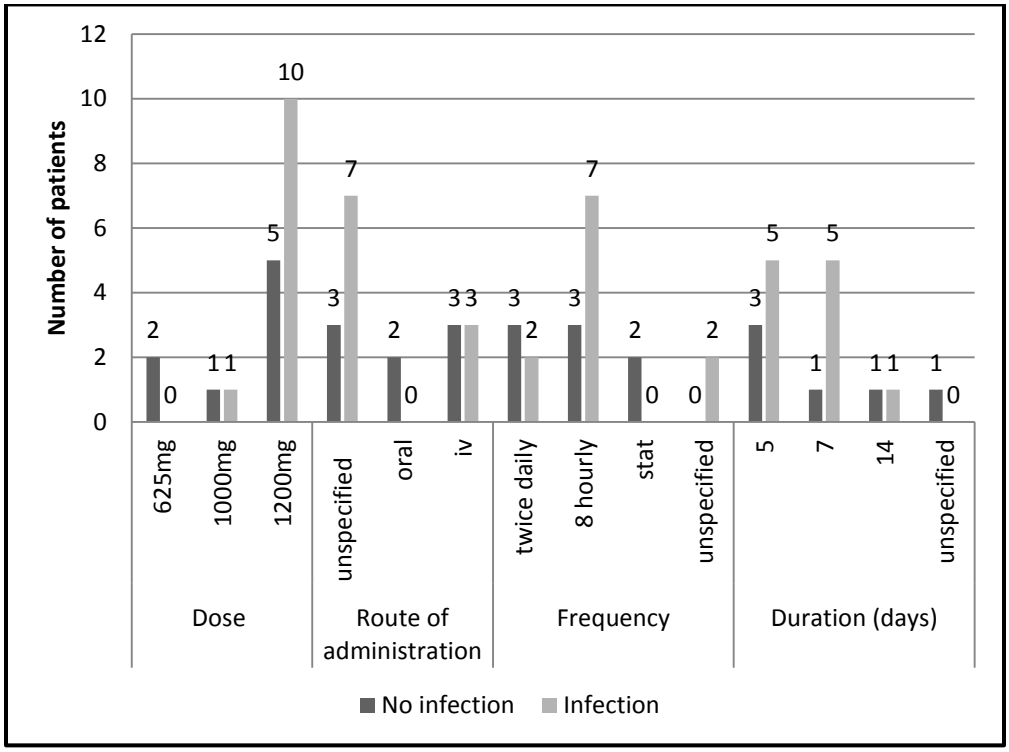

Figure 6.12: Use of Amoxicillin Clavulanate in patients with and without Infection

6.3.7 Cefuroxime Use Patterns at the Neurosurgical ward

Eight patients received cefuroxime during the study period. 87.5% (n=7) of them underwent surgery. The route of administration for most of the patients (75%, n=6) was unspecified. Half of the patients received doses of 500 mg , with the other half receiving 750 mg. All the patients on 500mg underwent surgery as opposed to 3 who received 750 mg of cefuroxime. Most of the patients (n=5) received a twice daily dose of cefuroxime. The duration of treatment varied from 3

days to 14 days, although some patients were treated for an unspecified duration. There was no statistically significant association between the cefuroxime use patterns and surgical procedure as presented in Figure 6.13 (Appendix 16).

The daily recommended dose for oral cefuroxime is 0.5g while that of the parenteral version is 3g. Only two patients were on oral cefuroxime while the rest were on an unspecified route of administration. Assuming two of those on oral cefuroxime were on 500mg (because it is the available oral formulation at the hospital), both given twice daily, it shows that they could have exceeded the dose by twice the recommended dose.

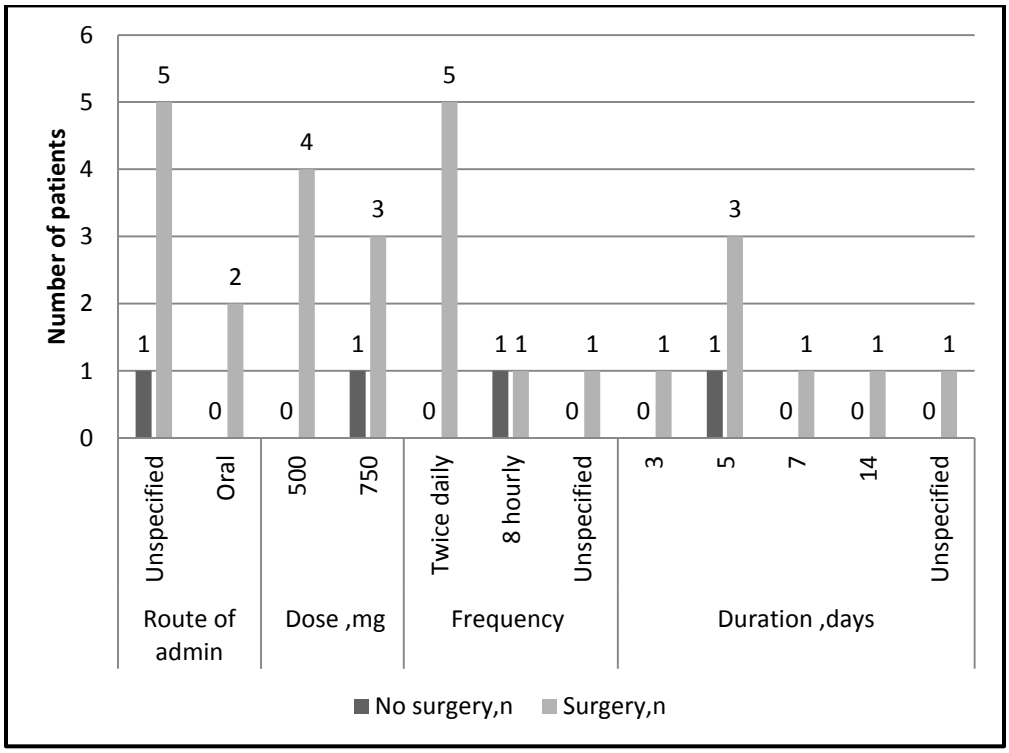

Figure 6.13: Use of Cefuroxime in patients who underwent surgery and those who did not

Four out of the patients who received cefuroxime (57.1%) developed surgical site infection. This was not statistically significant (p=0.450). There was no statistically significant association between the dose (p=0.683), route (p=0.730), frequency (p=0.447) and duration of administration of cefuroxime (p=0.438) and development of surgical site infection as shown in Figure 6.14.

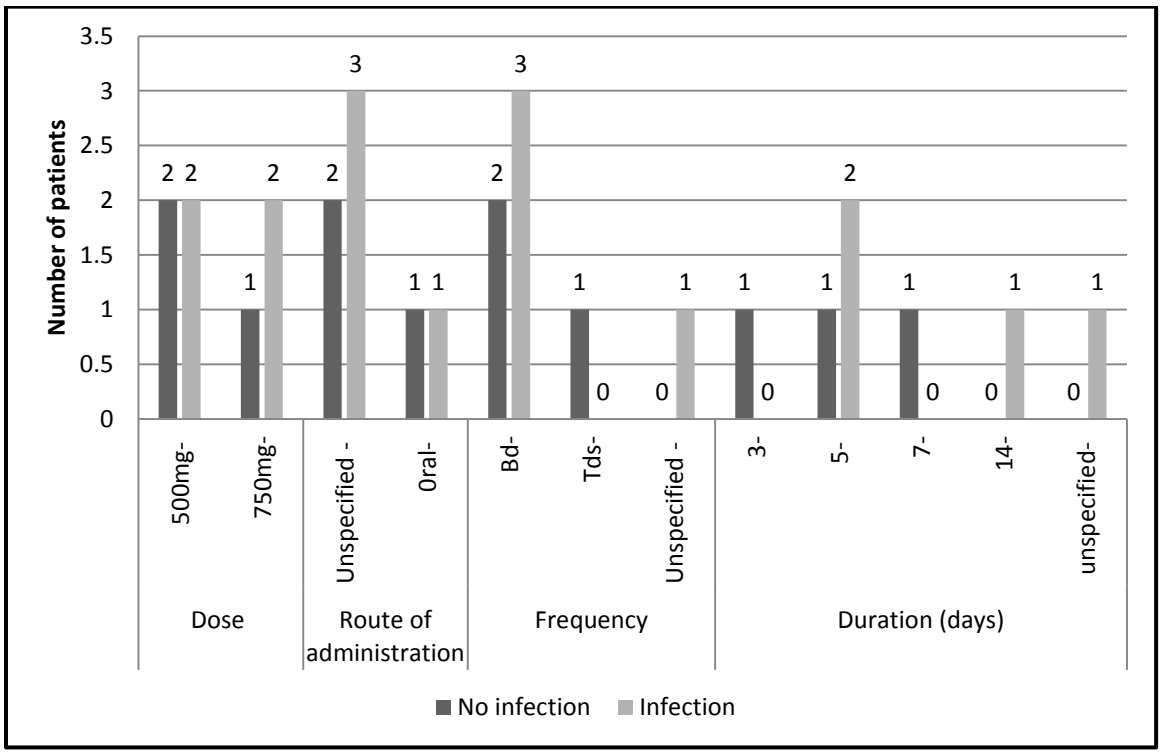

Figure 6.14: Use of Cefuroxime in patients who developed infection and those who did not

There was no statistically significant association between infection rates and the daily recommended dose of cefuroxime (p=0.714).

6.3.8 Meropenem use Patterns at the Neurosurgical ward

Three patients were on meropenem and two of them underwent surgery. There was no statistically significant association between the dose and route of administration of meropenem, and surgical procedure. There was a statistically significant association between the frequency of administration of meropenem and surgical procedure (p=0.028). There was also a statistically significant association between the duration of use of meropenem and undergoing surgery (p=0.068), as shown in Figure 6.15.

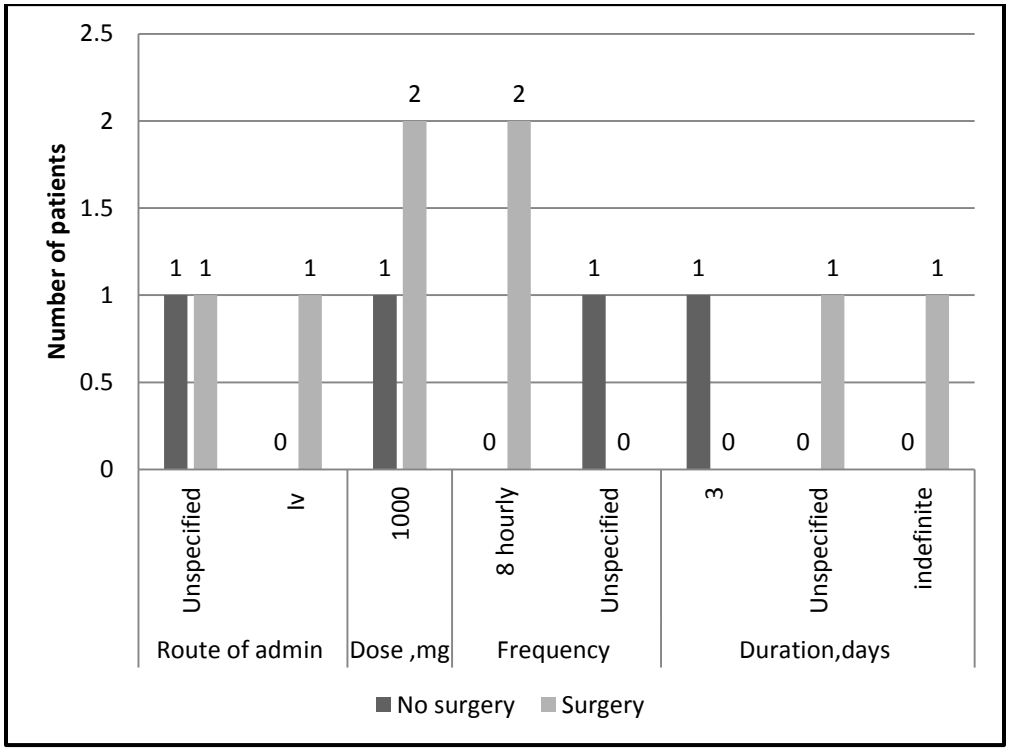

Figure 6.15: Use of meropenem among patients who underwent surgery and those who did not

Meropenem was the least commonly prescribed antibiotic at 2.9% (n=2).The association between the dose, frequency, route and duration of administration of meropenem and development of infection was not statistically significant (p=0.103). This is presented in Figure 6.16.

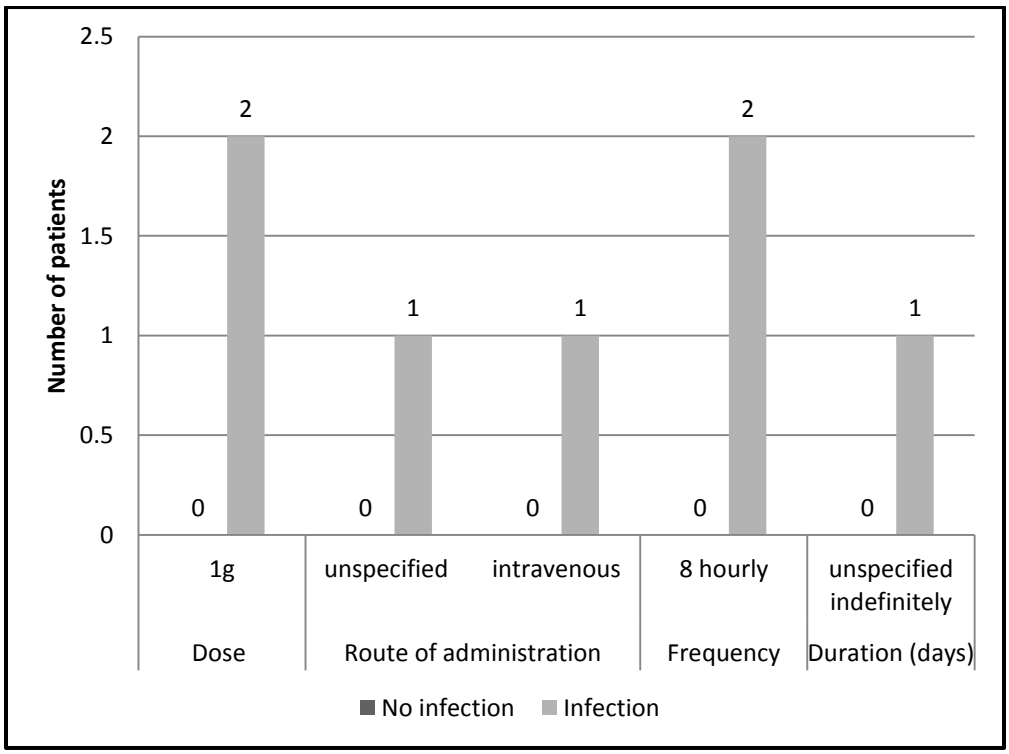

Figure 6.16: Meropenem use in patients who developed surgical site infection

6.3.9. Medication Errors in Antibiotic Use at the Neurosurgical ward

The most common medication errors in antibiotic use among these patients were prescribing errors. According to the National co-ordinating council for medication error reporting and prevention (NCC-MERP, 2001), classification, prescribing errors can occur in form of: dose omission, improper dosage (underdose or overdose), wrong strength, wrong drug, wrong dosage

form, wrong route of administration, wrong duration, inappropriate drug selection, lack of a clear purpose of a drug on a prescription and medication prescribed to the wrong patients. Several prescribing errors were recorded in this study.

6.3.9.1 Prescribing in trade names

Among the cohort of patients who underwent surgery and those who did not, Metronidazole (64.0%,n=23), Amoxicillin clavulanate (42.0%, n=21) and cefuroxime (16.0%, n=8) were prescribed in trade names. Metronidazole was the most likely drug to be prescribed using trade names. The trade names used were Flagyl for Metronidazole, Augmentin for Amoxicillin Clavulanate and PowerCef for cefuroxime. It could not be established whether there was a significant association between the prescribing in trade names and development of surgical site infections.

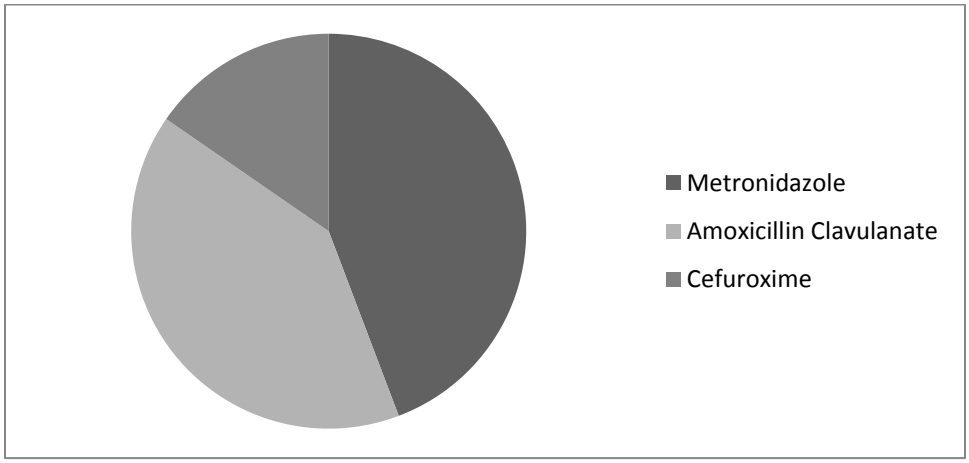

Figure 6.17: Drugs that were prescribed using trade names

6.3.9.2 Unspecified dose, route and frequency of administration and duration of antibiotics used

For many prescriptions, the dose, frequency and duration of administration was not specified. This could have led to errors in administration of the antibiotics. This is illustrated in Table 6.1. Patients who underwent surgery were more likely to have medication errors than those who did not undergo surgery.

Table 6.1: Unspecified dose, route and frequency of administration of antibiotics

Drug	**No Surgery (%)**	**Surgery, n (%)**
Gentamicin qidx7days	0 (0.0%)	1(100.0%)
Drug	**No Surgery (%)**	**Surgery, n (%)**
Metronidazole	3 (27.3%)	8(72.7%)
Amoxicillin clavulanate	3(23.1%)	10 (76.9%)
Cefuroxime	1 (16.7%)	5 (83.3%)
Meropenem	1 (50.0%)	1 (50.0%)
Gentamicin	0 (0.0%)	1(100.0%)
Flucloxacillin	0(0.0%)	1(100.0%)
Amikacin	0(0.0%)	1(100.0%)
Drug	**No Surgery (%)**	**Surgery, n (%)**
Ceftriaxone		
Metronidazole	0(0.0%)	1(100.0%)
Amoxicillin clavulanate	0(0.0%)	2(100.0%)
Cefuroxime	0(0.0%)	1 (100.0%)
Meropenem	1 (100.0%)	0(0.0%)
Drug	**No Surgery, n (%)**	**Surgery, n (%)**
Metronidazole	1(25.0%)	3 (75.0%)
Amoxicillin clavulanate	0 (0.0%)	1 (100.0%)
Cefuroxime	0 (0.0%)	1(100.0%)
Meropenem	0 (0.0%)	1(100.0%)
Flucloxacillin	1(100.0%)	0 (0.0%)
Wrong dose		
Amikacin 50mg	0 (0.0%)	1(100.0%)
Abbreviations		
TEO	1(100.0%)	0 (0.0%)

6.3.9.3 Prolonged duration of administration of antibiotics

Several patients were given antibiotics for prolonged periods as shown in Table 6.2. All the patients who received antibiotics for prolonged periods developed surgical site infections. It could also be that those who were being treated for prolonged periods had already established infections. Twelve patients were treated with repeat regimens of ceftriaxone following an initial five to seven day course of ceftriaxone. One patient on this additional course of ceftriaxone was treated with the drug for a prolonged period of 14 days.

Table 6.2: Prolonged duration of antibiotic use in patients who underwent surgery and those who did not

	Ceftriaxone	Metronidazole	Coamoxiclav	Cefuroxime	Clindamycin	Amikacin	Meropenem
14 days	12	3	2	1	1	-	-
21 days	1	2	-	-	-	-	-
Indefinite	-	-	-	-	-	1	1

6.3.9.4 Inappropriate combinations of antibiotics

Nineteen patients received inappropriate antibiotic combinations. Inappropriate antibiotic combinations refer to a combination of two or more antibiotics from the same or related class, with the same antimicrobial spectrum. The caveat to this observation is that the antibiotics could have been switched following poor clinical response or using culture and sensitivity reports.

Table 6.3: Inappropriate combinations of antibiotics

Antibiotic combination	Frequency, n
Ceftriaxone, cefuroxime	2
Amoxicillin clavulanate, Ceftriaxone	3
Ceftriaxone, Ampiclox	1
Ceftriaxone, metronidazole, cefuroxime	1
Amoxicillin clavulanate, ceftriaxone, metronidazole, clindamycin	1
Amoxicillin clavulanate, ceftriaxone, metronidazole	5
Amoxicillin clavulanate, ceftriaxone, metronidazole, cefuroxime	2
Amoxicillin clavulanate, ceftriaxone	1
Amoxicillin clavulanate, cefuroxime	1
Amoxicillin clavulanate, ceftriaxone, metronidazole	1
Amoxicillin clavulanate, cefuroxime, metronidazole	1
Total	**19**

6.3.9.5 Inappropriate Selection of Antimicrobials

Prescription of antibiotics for prophylaxis or presumptive treatment was not based on any guidelines, recent evidence or antimicrobial susceptibility patterns for patients who underwent surgery as well as those who developed infection. A study done by Njiru et al., 2015 on antimicrobial resistance patterns in this neurosurgical unit reported that the most common infecting gram positive organism was *Staphylococcus aureus*, and it was resistant to Penicillin, Ampicillin and Amoxicillin clavulanate, yet in this study, Amoxicillin clavulanate was among the most commonly prescribed antibiotic (36.0%, n=18). The most common infecting gram negative organisms were *Pseudomonas, E.Coli, Klebsiella and Proteus*, and they were resistant to amikacin, doxycycline, gentamicin, ceftazidime, cefuroxime, piperacillin tazobactam and meropenem. In our study, Amikacin, gentamicin, cefuroxime and meropenem were prescribed. To illustrate this, we used resistance data from the study by Njiru et al 2015, and using

Staphylococcus aureus and Klebsiella as our reference organisms (since they are the most common causes of gram positive and gram negative neurosurgical site infection), we found out that all patients on Amoxicillin clavulanate, cefuroxime and meropenem were unlikely to benefit from the antibiotics as illustrated in Table 6.4. The findings of the study by Njiru et al (2015) have been disseminated in several neurosurgical and infectious disease conferences and seminars over the past year, some of which I have attended. Despite this, these findings have not impacted on practice at the neurosurgical ward.

Table 6.4: Antimicrobial resistance patterns and antimicrobial use ***(Adapted from Njiru et al., 2015)***

	Staph. aureus	*Klebsiella*	Prevalence of use	Predicted no. of cases of resistance
Amoxicillin clavulanate	100%	-	23	23
Cefuroxime	-	100%	8	8
Meropenem	-	100%	3	3

6.3.9.6 Unclear Indication of Antimicrobial Prescription

In the study, for all antibiotics, there was no clear indication for administering antibiotics, whether for prophylaxis or not in both the infection versus no infection groups and the surgery versus no surgery groups. For purposes of discussion, we made an assumption that any antibiotic given for three days or less was given for prophylaxis and presumptive treatment was for those antibiotics that were given for more than three days.

6.3.9.7 Inappropriate doses

Using the WHO ATC DDD recommended daily doses of the major antibiotics, it was noted that some patients received more than the daily recommended doses of different antibiotics as shown in Table 6.5. Ceftriaxone was the most commonly used drug, and also the most overdosed.

Table 6.5: Inappropriate doses of antibiotics

Drug	Daily recommended dose (DDD),mg	No of patients on inappropriate dose	Comments
Ceftriaxone	2000	9 (20.0%)	Overdose iv
Amoxicillin Clavulanate	1000 oral, 3000 iv	2 (8.7%)	Overdose on oral drug
Cefuroxime	500 oral, 3000 iv	2 (25.0%)	Overdose on oral drug

6.4 DISCUSSION:

In our study, instances of irrational antimicrobial use were identified and several medication errors, specifically prescribing errors were noted. The irrational use stemmed from improper drug selection, unclear indication for antibiotic, inappropriate doses and wrong frequency and duration of administration of antimicrobials. This could be due to lack of antimicrobial use protocols and guidelines at Kenyatta National hospital to guide antimicrobial use. Prophylactic use of antibiotics may have been prolonged.

Our findings are similar to other studies in which antibiotic overuse and misuse was noted (Apostolopoulou et al., 2016; Testa et al., 2015; Sharma et al., 2012). As seen in our study, less effective antibiotics to which the infecting microbes were resistant were still given despite the information on antimicrobial resistance patterns being available. The same trend was seen in another study in which 94% of the patients received less effective antibiotics. Just like in our

study, there was antibiotic overuse in another study where, although antibiotics were indicated for only half of the patients, all the patients received prophylaxis (Apostolopoulou et al., 2016). Another study reports contrary results where there was underuse of antibiotics and missed doses (Lundine et al., 2010). The few patients who received prophylaxis did not receive it as should be given, just like in our study.

According to the American Society of Health System Pharmacists (ASHP) guidelines on antimicrobial prophylaxis in surgery, safety of antibiotics should be considered before being given to patients. This includes checking for information on drug allergies. Choice of antibiotic considered allergy to drugs like penicillin in some studies (Lundine et al., 2010). This consideration was not observed in our study. Comprehensive drug histories should be taken for patients who take antibiotics to ensure safety.

It was difficult to distinguish between antimicrobial prophylaxis and treatment regimens in our study. The same was also seen in other studies (Testa et al., 2015; Sharma 2012). Antibiotics were also not administered when required but this was not seen in our study. The choice of antibiotics varied across studies.

The most common antibiotics used in our study were ceftriaxone, metronidazole, cefuroxime, Amoxicillin clavulanate and meropenem. Other studies also used glycopeptides, first second, third and fourth generation cephalosporins, quinolones, daptomycin, lincosamides and linezolid (Apostolopoulou et al., 2016., Hammad et al., 2013; Sharma et al., 2012; Lundine et al., 2010). Other studies used combinations of antibiotics, something that was also seen in our study (Hawnet al., 2013; Lundine et al., 2010). The use of some antibiotic combinations increased the

risk of development of infections while some combinations reduced the risk (Hawn et al., 2013). Some of the choices of drugs in these studies were deemed inappropriate just like in ours study (Testa et al., 2015).

Some studies in which prophylactic antibiotics were given for three doses from the time of operation and stopped after 24 hours complied with international guidelines on timing and frequency of administration of antibiotics. This was not so in our study and other studies in which antibiotics were given for longer than this period. There was prolonged antibiotic use beyond the treatment or prophylaxis duration in several studies just like in our study (Testa et al., 2015; Lorensia et al., 2012). Prolonged antibiotic use does not prevent the development of surgical site infections (Sharma et al., 2012). The duration of prophylactic use of antibiotics should be shorter than treatment duration. An antibiotic use protocol detailing this should be developed and adhered to at our study site.

Several studies reported that antimicrobial prophylaxis did not conform to guidelines or protocols, and there were variations in compliance regarding the choice of antibiotic, indication for prophylaxis, timing and discontinuation of prophylaxis (Gouveau et al., 2015; Testa et al., 2015). This is unlike in our study where there were no local protocols against which appropriate use of antibiotics could be compared. This calls for development of an antibiotic use protocol in the neurosurgical unit of Kenyatta National Hospital as the use of protocols is effective in reducing neurosurgical site infections (Jiang et al., 2016). The quality of antimicrobial prophylaxis can be improved through continuous training, compliance with available guidelines

and supervision of the use of antibiotics (Bozkurt et al., 2013). There is need to develop antibiotic use guidelines to ensure the effective use of antibiotics at the study site.

Irrational prescribing of prophylactic antibiotics has been shown to increase health care costs and hospital stay (Ulu- Kilic et al., 2015; Bozkurt et al., 2013; Collins, 2013; Sharma et al., 2012). It also leads to increased nursing workload (Apostolopoulou et al., 2016). The interventions of clinical pharmacists in antimicrobial prophylaxis have been shown to result in low incidence of surgical site infections, reduce medication errors, lower overall treatment costs, drug charges and laboratory charges, and fewer hospitalization days (Hammad et al., 2013; Bond et al., 2007). Pharmacists should be involved in antibiotic use at the neurosurgical unit of Kenyatta National Hospital to assist in rational use of antibiotics.

6.5 CONCLUSION AND RECOMMENDATIONS

Various forms of irrational antimicrobial use were recorded. There was no clear distinction between antimicrobial prophylaxis and treatment of intracranial infections. Some antibiotics were used despite the fact that there was data on resistance to those antibiotics. Guidelines on antimicrobial use should be developed and adhered to, so as to reduce surgical site infections and improve outcomes of prophylaxis and treatment of neurosurgical site infections. Studies should be conducted to monitor the clinical effectiveness of antimicrobials alongside resistance patterns. Studies should be conducted to evaluate the overuse of antibiotics at the KNH neurosurgical unit. Studies that demonstrate that administration of antibiotics for shorter durations result in good outcomes should be conducted.

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CHAPTER 7: THE IMPACT OF SURGICAL SITE INFECTIONS ON PATIENT EXPENDITURE

7.1 INTRODUCTION

Cost of illness studies (COI) are used to quantify the financial burden of disease on an individual, society, country or region. They itemise the economic burden of disease in terms of direct, indirect and intangible costs accrued due to illness. These studies are useful in formulating health care policies with an aim of prioritising the already scarce resources (Changik, 2014).

The underlying assumption in COIs is that the economic cost of illness represents the potential benefits of an intervention that eradicates the illness. Cost of illness studies can be used to provide data for cost effectiveness and cost benefit analyses (Segel, 2006). Together with utility data, data from COIs can be used to measure the burden of disease in terms of Quality Adjusted Life Years (QALYs) and Disability Adjusted Life Years (DALYs) (Changik, 2014). These studies are not considered full economic evaluations as they do not assess the solutions to health problems, but just quantify the costs (Drummond, 2005). Another disadvantage of COIs is that they do not provide enough information to identify inefficiency or waste in the healthcare system (Byford et al., 2000).

Direct costs on healthcare, which include costs of medicines, diagnostic tests, consultation fees, and cost of nursing and other services as well as hospitalization costs, are computed. Direct non-medical costs include costs of hiring care-givers, transport and costs on supplies not provided for at the hospital. Productivity losses such as costs of absence from work and employing other people to replace the ill person at work are also included.

Several studies have computed direct medical costs associated with surgical site infections. In America, the cost of surgical site infections per year have been estimated to range from 1 to 10 billion US dollars in direct costs and productivity losses (Perencevich et al., 2003). The average cost of treatment of a single surgical site infection in America has been estimated to be 2,734 US dollars (Shepard et al., 2013).

Using the hospital administrator perspective, a multi-centre study computed the costs of treatment of surgical site infections for patients undergoing several types of surgery, including craniotomies to be 7,924 US dollars for those who developed SSIs as opposed to 7,493 US dollars for those who did not develop infections (Shepard et al., 2013). The same trend has been observed in China, where the median cost of treatment of patients with surgical site infections was 75967 RMB [51006, 188330] with an additional median cost of antibiotics being 4073 RMB [1440, 9896] (Wang et al.,2015).

A study in Germany estimated the costs incurred by insurance companies in the treatment of surgical site infections to be € 22407.350 for hip replacement and € 13,760.280 for knee replacement. This did not include medical and pharmaceutical costs (Hanstein and Gaiser., 2011). In India, the costs of medicine and surgical procedures for patients who were undergoing several surgical procedures including neurosurgery and developed infections was 29,000 rupees as opposed to 16,000 for those who did not develop infections. The costs increased by 3.8% for those with mild SSIs, 14.7% for those with moderate SSIs and 29.4% for those with severe SSIs (Tan et al., 2016).

The cost of treatment of surgical site infection varies depending on the site of the infection. It is cheaper to treat a superficial surgical site infection than it is to treat deep incisional and organ/ space SSIs. The estimated cost of treating a superficial SSI is 400 US dollars per case, while that of treating an organ/space infection has been estimated to be 30,000 US dollars per case (Urban, 2006).

7.1.1 Study problem

Neurosurgical site infections do not occur at a high rate in most clinical settings. Their economic impact has been assumed to be minimal, and most studies have not exclusively studied their economic impact. Those which do, study them alongside other surgical site infections (Shepard et al., 2013). Hospitals accrue profits from treatment of surgical site infections, and this money can be used to fund infection control programs. However, this has not been the case in many hospitals or countries (Shepard et al., 2013) as this money is used in other interventions. There is paucity of data on the cost of treatment of neurosurgical site infections in both high and low income countries. The economic impact of surgical site infections at Kenyatta National hospital is not known as no study has been carried out to assess this. This study seeks to fill this gap for the neurosurgical patients.

7.1.2 Research Questions and Hypotheses

1. What is the expenditure on direct medical and non-medical resources incurred by neurosurgical patients?
2. What are the productivity losses incurred due to hospitalization and treatment?

3. What is the difference in expenditure between patients with surgical site infections and those without?
4. What are the key drivers of cost among these patients?

Null hypothesis: Patients with SSIs incur high direct and productivity costs compared to patients without SSIs in the neurosurgical ward.

Alternative hypothesis: Patients with SSIs do not incur higher direct and productivity costs than patients without SSIs in the neurosurgical ward.

7.1.3 Objectives

General Objective

To assess the economic burden of treatment of head injury and surgical site infections among patients admitted at the neurosurgical unit of Kenyatta National Hospital.

Specific Objectives

1. To compute the expenditure on antibiotics, other medications, diagnostic tests and productivity losses incurred due to hospitalization
2. To compare the expenditure in patients with surgical site infections and those without
3. To identify the key cost drivers among this patient cohort.

7.2 METHODS

A prospective cost of illness study of patients admitted at the neurosurgical unit between April and June 2015 was conducted. The cost analysis was part of a prospective cohort study that has been described in Chapter Five.

The patient perspective was adopted and this included all costs incurred by the patients during treatment. Time horizon refers to the time in which the risks and benefits of the intervention are considered. For our study, we considered the time horizon to be the time between admission and discharge. No discounting of costs was done because the study was done in less than one year and all the costs were incurred within the year.

7.2.1 Costing

A micro costing approach was used to compute direct costs. This approach involves quantifying all the components of resource use and estimating their unit costs. Most of the quantities and prices of resources consumed were obtained from the participant files. In our study, we computed the direct costs which included the following categories of expenditure: surgery, bed occupancy, nursing care, medicines, laboratory and diagnostic tests. For the direct non-medical costs, we computed costs incurred on food and transport for patients and their caregivers during the hospitalization period.

To compute the expenditure on medicines, the 2014 acquisition price list of Kenyatta National Hospital (Table 7.1) was used to obtain unit prices of the medicines. The final price was computed as a product of the price of unit dose, number of unit doses, frequency of administration and duration of administration. Where there was missing data on the dose, duration, frequency and route of administration, imputation was done by replacing the missing data with the median dose, frequency, route and duration of use. To calculate the costs incurred by the patients, we used a mark -up of 30%. To obtain prices of items not available in the

patient records, we inquired from patients how much they paid. These cost items included laboratory and radiological tests, expenditure on transport and food.

Productivity losses incurred during the time of illness were calculated using the human capital approach. These were computed as a product of daily income and the hospitalization days, with 30 days allowed for recuperation. The estimated daily income was obtained by participant interview. Overhead costs such as administrative charges, utilities such as water and electricity were ignored.

7.3 RESULTS

7.3.1 Expenditure on Antibiotics

To calculate the costs of antibiotics, the provider (The Kenyatta National Hospital) acquisition price list for the year 2014 (Table 7.1) was used. Meropenem was the most expensive antibiotic to acquire, followed by Clindamycin injection. The least costly antibiotic was metronidazole tablets.

Table 7.1: Kenyatta National Hospital Acquisition Prices, 2014

Antibiotic	Unit	Price, KES
Ceftriaxone 1g	Vial	33.24
Ceftriaxone 500mg Injection	Vial	88.34
Amoxicillin + Clavulanic Acid -Tablet, 500mg+125mg	Tablet	9.50
Amoxicillin+Clavulanic Acid Inj 1.2 g inj	Vial	97.0
Amoxicillin + Clavulanic Acid -Powder for Injection 600mg	Vial	173.87
Meropenem 1gm	Powder for Injection	636.11
Meropenem 500mg	Powder for injection	350.00
Metronidazole -Tablet, 200mg	Tablet	0.67
Metronidazole -Injection, 500mg Bottle/collapsible bags	100ml Vial	82.61
Cefuroxime - 750mg(sodium salt)	Powder for Injection	57.93
Cefuroxime -Tablet 250 mg(axetil)	Tablet	10.74
Amikacin -Injection 500mg	Amp/Vial	46.85
Clindamycin -Injection, 150mg / ml (as phosphate)	Vial	346.27
Gentamicin -Injection 40mg/ml, (as sulfate)	2ml Amp/Vial	8.97
Flucloxacillin -Injection 500mg	Vial	60.00
Tetracycline eye ointment	Tube	20

The median expenditure on antibiotics over the three month study period is summarized in Table 7.2. Meropenem was the most expensive antibiotic, though it was the least used, for only three patients. This is because it had the highest unit cost. Meropenem is reserved for use in patients with severe infections and this explains its use among few patients. Ceftriaxone was the most commonly prescribed antibiotic but it was not very expensive.

Table 7.2: Median expenditure on commonly used antibiotics

Antibiotic	**Provider cost(KES) Median,[IQ]**	**[a]Patient costs (KES), Median [IQ]**
Meropenem	38,166.60[25,762.46, 191, 549.70]	49,616,58 [33,491.20, 249,014.61]
Metronidazole	1734.81 [1239.15, 1858.73]	2255.25 [1610.90, 2416.35]
Cefuroxime	579.30 [257.76, 735.195]	753.09 [335.09, 955.75]
Ceftriaxone	479.36 [342.40, 47, 456.64]	623.17 [445.12, 61,693.63]
Co-amoxiclav	291.0 [266.0, 2037]	378.3 [345.80, 2648.10]
Total expenditure	**1438.50 [1183.16, 3,696.24]**	**1870.05 [1539.41, 4805.11]**

[a]Patient cost was computed as product of provider cost and the hospital mark up with is 30%

7.3.2 Expenditure on other medications

The KNH acquisition prices of medications were used. Prices for the years 2013 to 2015 were obtained. For some medicines, the prices for all these years were not available. The cost of each drug was computed as previously described for antibiotics. The 2014 prices were used for consistency. The prices of most drugs remained fairly constant over the years. However for some medicines such as domperidone and esomeprazole 20mg, the prices increased substantially over the years. The prices of some medicines such as ranitidine hydrochloride reduced to more than half the initial price. Some medicine prices fluctuated over the years as in the case of ondansetron injection. Table 7.3 presents the price lists of the different classes of drugs. The prices were used in computing the median expenditure on each of the classes of drugs.

Table 7.3: Kenyatta National Hospital Acquisition prices for non-antibiotic medicines

Class of Drugs Used	Unit	2013	2014	2015
Antiemetics				
Domperidone -Tablet 10mg (Maleate)	Tablet	1.57	2.50	4.95
Metoclopramide -Injection, 5mg(hydrochloride)/ml	2ml Amp	8.50	8.44	8.00
Ondansetron -Injection, 2mg/ml (hydrochloride)	2ml Amp	171.00	147.21	171.00
Ondasetron -Tablet 4mg, as hydrochloride	Tablet	10.00	15.87	10.00
Metoclopropamide HCL -20mg tablets	Blister pack,Tablet	0.65	0.65	0.65
Antiulcer drugs				
Omeprazole 20mg capsule	Caps	0.83	1.28	0.83
Omeprazole injection 40mg/5ml	Amp	103.0	111.59	120.0
Ranitidine injection 25mg/ml	2ml amp	7.95	10.99	
Ranitidine HCl 150mg	Tablet	1.80	1.59	0.17
Esomeprazole 20mg	Tablet	4.00	1.75	10.00
Esomeprazole sachet	10 mg sachet	73.47	73.47	73.47
Vitamin Preparations				
[a]Iron sucrose -Injection 20mg/ml*	5ml Amps	-	150.0	-
[b]Ferrous +folic salts with Zinc and vit B complex *	Tablet/caps	-	2.30	-
[c]Multivitamin -Vitamin A, D, E,C Folic, B complex *	Tablet/caps	-	6.00	-
[d]Multivitamin -Vitamin A, D,E C, B complex *	100ml bottle	-	37.00	-
[e]Vitamin B complex*	Tablet	-	6.50	-
[f]Ranferon bottle*	Bottle	-	80.00	-
[g]Ferrous Sulphate , Vitamin C, Vitamin B complex*	Tablets	-	7.00	-
[h]Soluble Vitamin B + Vitamin C –Injection*	Amp	-	418.50	-
Cardiovascular drugs				
Metformin controlled release, 500mg	Tablet	4.9	4.9	-
Hydrochlorothiazide 25mg scored	Tablet	0.7	2.0	-
Nifedipine 20mg retard	Tablet	1.2	1.26	1.2
Losartan potassium 50 mg	Tablet	2.18	2.23	2.18
Enalapril 10mg	Tablet	0.96	0.97	0.96
Digoxin 250 micrograms scored	Tablet	6.0	6.0	6.0
Amlodipine 5mg	Tablet	0.785	0.98	0.79
Enalapril 5mg	Tablet	0.65	1.12	2.0

[a,b,c,d,e,f,g,h]the details of the vitamin combinations are in Appendix 16

Table 7.4 summarises the median expenditure on of each of the drug classes. The most costly therapeutic medication was phenytoin because it was prescribed to the most patients (n=39) and for a long duration. Vitamins and minerals were the second most expensive medications because they are all available as branded products. The median expenditure on medications to lower

intracranial pressure were the third most expensive due to the high unit cost of mannitol. Expenditure on drugs such as antidiabetics and antihypertensives was the least costly. The expected expenditure on these drugs during admission was KES. 182.52 [163.80, 253.28]. The expected total expenditure on non-antibiotics for a patient admitted in the neurosurgical unit would therefore be KES. 3,303.09 [1177.98, 8,956.39]. This was low, and could be attributed to the widespread use of generic formulations.

Table 7.4: Median Costs of Non Antibiotic medicines

Drug Class	**Median acquisition cost, KES. [IQ]**	**Median patient expenditure, KES [IQ]**
Anti-seizure drugs Phenytoin	375.6 [87.64, 7,356.60], n=39	464.88 [113.93, 9563.58]
Vitamins, minerals and haematinics	320 [80, 720], n= 12	416.00 [163.80, 936.00]
[b]**Drugs for raised intracranial pressure (**Dexamethasone and Mannitol)	249 [63, 348.60], n=9	323.7 [81.90, 453.18]
Anti-ulcer drugs Total cost of anti-ulcer drugs	190.8 [49, 461.58], n= 19	248. 04[63.70, 600.05]
Analgesics Paracetamol Tramadol Total cost of analgesics	84 [60, 3,825] , n=25 178.50 [84.96, 423.20], n=28 178.50 [84 to 3,936] n=53	109.2[78, 4972.50] 232.05[110.45, 551.46] 232.05[109.20, 5116.80]
[c]**Antiemetics** Metoclopramide,ondansteron, domperidone	177.24 [75.96 , 177.24], n= 27	230.41[98.75, 230.41]
Cardiovascular drugs	140.4 [126, 195.60], n=5	182.52 [163.80, 253.28]
Total Cost	**2540.84** **[906.14 to KES. 6889.53]**	**3,303.09** **[1177.98, 8956.39]**

7.3.3. Expenditure on Laboratory and Radiological Tests

Out of the 84 patients enrolled in the study, 81 underwent several laboratory and radiological tests. The costs for each test were computed as a product of the number of tests done and the price of the test. The most costly tests were blood gas analysis and group cross matching for blood (GXM). The least costly was random blood sugar testing. The patients spent between KES 1,700 to 5,700 on laboratory tests with a median of KES 2000. On the other hand, radiological tests were considerably more expensive than laboratory tests with expenditure ranging from KES 5,500 to 13,000.Table 7.5 summarises the median costs of each of the laboratory tests.

Table 7.5: Median Expenditure on Laboratory and Radiological tests

Test	**Median cost [IQ], KES.**
Urea electrolyte and creatinine (UECs)	700 [700,700]
Liver function tests (LFTs)	700 [0,700]
Blood gas analysis (BGA)	1000[1000, 3000]
Full blood count (FBC)	300[200,300]
Random blood sugar (RBS)	100 [100,100]
[a]Group cross matching (GXM)	1000 [1000, 2000]
Total expenditure on lab tests	**2000[1700, 5700]**
Total expenditure on radiological tests	**5,500 [5,500, 13,000].**

[a]group cross matching for blood transfusion

Expenditure on some laboratory tests, particularly the FBCs and UECs varied based on the laboratory where the patients undertook the tests. The tests which were done at the Kenyatta National Hospital laboratories were cheaper than those done outside the facility. Table 7.6 shows the laboratory tests for which the prices varied. The expenditure on other laboratory tests, namely blood gas analysis, liver function tests and random blood sugar were constant. Although the price

of blood gas analysis (BGA) was constant at KES 1000, most of the patients (69.2%, n=9) underwent one test.

Table 7.6 Variations in the Number and Prices of Laboratory Tests

Expenditure on FBCs, KES.	**Frequency (%)**
200	13 (19.4%)
300	52 (77.6%)
500	1(1.5%)
900	1 (1.5%)
Expenditure on UECs, KES.	
700	70 (95.9%)
1400	1 (1.4%)
2100	2 (2.7%)
Number of times patients underwent BGA	
1	9 (69.2%)
3	2 (15.4%)
4	1(7.7%)
5	1(7.7%)
Unknown	1(7.7%)

All patients (n=80) had at least one radiological test done. Two thirds had one test done (n=54) while nearly 30% (29.6%, n=24) had two radiological tests done. Only three patients underwent three or more radiological tests (3.7%).

The expenditure on various radiological procedures varied depending on site of the body. For instance chest X rays were cheaper than X rays of the skull (KES 700 as opposed to KES. 900). Some radiological procedures were done outside the hospital and these included the X rays, Computed Tomography (CT) scans and Magnetic Resonance Imaging (MRIs). As expected, the prices outside the facility were higher than those done within the facility. The cost of MRI for the patients who underwent this test (n=2) ranged from KES 9000 to 13000.All the patients (100.0%) took the CT scan test and the prices of this test are presented in Table 7.7.

Table 7.7: Prices of Computerised Tomography (CT) scans

Price of CT scan	Frequency, %
0	1 (1.2 %)
4000	1 (1.2%)
5500	57 (70.4%)
6000	4 (4.9%)
6500	1 (1.2%)
6700	1 (1.2%)
7000	13 (16.1%)
7700	3 (3.7%)
Total	81(100.0%)

7.3.5 Costs of hospital stay, surgery and nursing care

These costs for the study period were computed using the 2014/2015 Kenyatta National Hospital Revenue Projections for the Surgical Division. The price for each procedure is presented in Table 7.8

Table 7.8: Charges for hospital stay, surgery and nursing care

Item/ Procedure	Daily charges , KES.	Total Cost for 10 days
Surgical procedure*	-	20000
Ward stay (bed occupancy)	800	8000
Consultation fees	300	3000
Nursing procedures		
Wound dressing	250	2500
Drug administration	60	600
Bed bath	100	1000
Vital sign monitoring	50	500
Iv fluid administration	100	1000
NG tube and assisted oral feeding	100	1000
Catheterization	300	3000
Shaving	50	500
Catheter removal	-	300
Injections	50	500
Removal of stitches	-	300
Total (if no surgery performed)		**22,200**
Total (if surgery performed)		**42,200**

*****charges for the of procedure are constant, regardless of the type

The median cost for all these procedures for the hospitalization period is KES. 22,200 for those who did not undergo surgery and KES.42,200 for those who underwent surgery.

7.3.6 Direct Non-medical Costs and Productivity Losses

These costs were computed as a product of daily expenditure and number of days in hospital. Patients and their households incurred additional expenses on food and transport to the hospital by relatives and caregivers. The median daily expenditure on food was KES. 100[0,200] for the patients who spent on food (n=79). The median daily expenditure on transport for relatives was KES 200[0, 300] for patients who were visited by relatives (n=80). The cost for care-giving services was computed by multiplying the duration with the minimal legal daily wage for labour which was KES 1000. The estimated total cost of care giving services was KES. 81,900.

The median daily income for these patients was KES 300[0, 500]. The median total expenditure on direct non-medical costs was KES. 2,450 [220, 24,000].

Productivity losses were computed as a product of proxy income and the hospitalisation days, with 30 days allowed for recuperation. The median loss of productivity was KES 12,250, with an interquatile range of KES. 0 and KES. 70,000.

The total expenditure incurred during the study period is summarized in Table 7.9.

Table 7.9: Summary of all costs incurred

Type of costs	Median costs [IQ], KES.
Antibiotics	3303.09 [1177.98, 8956.39]
Non antibiotics	1870.05 [1539.41, 4805.11]
Surgery and nursing care	42,200
Laboratory tests	2000 [1700, 5700]
Radiologic tests	5500 [5500, 13000]
Caregiver costs	81,900
Productivity losses	12,250 [0, 70,000]

7.3.7 Comparison of expenditure in patients with and without surgical site infection

The comparative analysis of patient expenditure based on whether they developed infections or not is presented in Table 7.10. There was a statistically significant association between the expenditure on full blood count and development of surgical site infection.

Table 7.10: Association between Expenditure on Laboratory, Radiologic tests and Surgical Site Infection

Expenditure on Tests				
Expenditure on UECs, KES.	**No Infection**	**Infection**	**Total**	**P value**
700	44 (62.9%)	26 (37.1%)	70 (100.0%)	
1400	1 (100.0%)	0(0.0%)	1 (100.0%)	0.417
2100	**2 (100.0%)**	**0 (0.0%)**	**2 (100.0%)**	
Expenditure on FBC, KES	**No Infection, n**	**Infection, n**	**Total**	
200	6 (46.2%)	7 (53.8%)	13 (100.0%)	**0.010**
300	40 (76.9%)	12 (23.1%)	52 (100.0%)	
500	0 (0.0%)	1(100.0%)	1(100.0%)	
900	1(100.0%)	0 (0.0%)	1(100.0%)	
Total	49 (65.3%)	26 (34.7%)	75(100.0%)	
Expenditure on RBS KES.	**No infection**	**Infection**	**Total**	
100	24 (48.9%)	15 (57.7%)	39 (52.0%)	0.472
Total	49 (100.0%)	26 (100.0%)	75 (100.0%)	
Expenditure on BGA, KES.				
1000	10 (76.9 %)	3(23.1%)	13 (100.0%)	0.229
Median costs with infection or no infection				
Test	**Median cost, No infection**	**Median cost Infection**		**P value**
UECs	700[700,700], n= 49	700 [700,700], n=26		0.417
LFT	700[700,700], n= 49	700[700,700], n= 23		0.182
BGA	1000[1000,1000], n= 10	1000[1000,1000], n= 3		0.229
FBC	300[300,300], n= 49	250[200,300], n= 26		**0.010**
RBS	100[100,100], n= 24	100[100,100], n= 15		0.472
Radiologic tests	5500 [5500,7000], n=49	5500[5500,8000], n=26		0.574

There was a statistically significant association between the cost of FBCs and the development of infection (p=0.010). This is because in practice, patients who are suspected to have infection routinely undergo full blood count to establish the white blood cell count, which is a marker of

infection. There was no significant association between the cost of the other laboratory tests (random blood sugar testing, blood gas analysis, and UECs) and the development of surgical site infection. Similarly, there was no statistically significant association between radiologic tests and development of infection (p=0.574). Table 7.11 presents the comparison between the median costs of laboratory and radiologic tests and development of surgical site infection.

A comparison was made between the total costs of all the procedures and development of infection. Of note, the median total costs, for each type, were higher in the group which developed infection, as shown in Table 8.12. As expected, there was a statistically significant association between the total expenditure (p=0.028), total direct medical cost (p= 0.004), the total cost of medicine (p=0.026) and development of surgical site infection. There was no statistically significant difference between the total costs of radiological tests, laboratory tests non-medical costs, and development of surgical site infections. This is expected because radiologic and laboratory tests can be ordered for any other reason apart from diagnosis of infection. Direct non-medical costs have no impact on development of surgical site infections. This is illustrated in Table 7.11.

Table 7.11: Comparison of the total costs between those who developed surgical site infection and those who did not

Type of total cost	Median [IQR] Expenditure , No infection (KES)	Median [IQR] Expenditure, Infection (KES.)	P value
Total cost	14119.84 [11495.46,21280.0], n=49	20394.61[14022.42, 28500, n=24	**0.028**
Total direct medical cost	9800 [8166.9, 13362.6], n=51	12483.52[9333.64, 26127.67], n=27	**0.004**
Total medicines cost	906.14 [0, 3150.76], n=53	2483.185[502.58, 8616.65], n=28	**0.026**
Total radiologic tests	5500[5500,7000], n=53	5500[5500,8000], n=27	0.574
Total lab tests	1800[1600, 2800], n=53	2250 [1650, 2850], n=28	0.683
Total non-medical costs	2400[0,7600], n=51	4200 [1750, 5940], n=25	0.158

7.3.8 Key Cost Drivers for Medicines and Laboratory tests

We identified the key cost drivers among antibiotics, non-antibiotics, laboratory and radiologic tests. For antibiotics, meropenem was the key cost driver, accounting for 92.5 % of the total cost of antibiotics. Similarly, phenytoin accounted for 15% of the expenditure on non-antibiotics as the key cost driver. Urea, electrolyte and creatinine (UECs) tests accounted for a large proportion of expenditure on laboratory tests, because about 36.8% of all the patients underwent this test, with a maximum of about 41.1% (median 36.8%, IQ 25.0% to 41.1%). This was followed by liver function tests (median 25.9%, IQ 14.6% to 41.2%) and full blood count (median 12.0%, IQ 7.7% to 16.7%. All patients (100.0%) underwent at least one CT scan, making it a key cost driver for radiologic tests.

7.4 DISCUSSION

Our study computed the costs of treatment of neurosurgical patients only. This is unlike other studies which computed the costs of treatment of patients undergoing different types of surgeries (Ulu- Kilic et al., 2015; Wang et al., 2015; Borzkut et al., 2013; Collins, 2013; Shepard et al., 2013, Sharma et al., 2012; Hanstein et al., 2011). There were no studies that computed the costs of treatment of neurosurgical patients alone. Most of these studies also computed costs across different hospitals, unlike our study which was a single centre study (Shepard et al., 2013, Wang et al., 2015; Ulu- Kilic et al., 2015; Collins, 2013; Sharma et al., 2012; Hanstein et al., 2011).

In our study, we computed direct medical costs associated with treatment of patients who had undergone surgery, some of who developed infection. These were the median costs incurred on medication and diagnostic tests over the median 10 day hospitalisation period. We used the 2014 exchange rate of KES. 100 for 1 US dollar, since the pricing was done using the KNH 2014 acquisition price list. The total median direct medical costs were KES 13,673.14 [10,417.39, 35,211.50]. These included costs of medication, laboratory tests, cost of surgical procedures and nursing services as well as bed occupancy. This is equivalent to 137 US dollars. The median direct non-medical costs incurred on food, transport by relatives to the hospital and other morbidity related costs incurred by the family was KES. 2,450 (USD 24.50).

The costs in our study appear much lower than expenditure quoted in similar studies, most of which have quoted prices amounting to thousands of US dollars (Ulu- Kilic et al., 2015; Collins, 2013; Sharma et al., 2012; Borzkut et al., 2013). This can be attributed to the short duration of hospital stay for our patients, which we used to calculate the costs, compared to other studies

which computed costs of hospitalisation for months or years. The subsidised cost of antibiotics could also explain the relatively low costs of treatment. Kenyatta National Hospital mainly procures generic antibiotics for the patients in the general wards, which are much cheaper than their original versions. Our study also had a small sample size and estimated the costs in a small unit of a major hospital, compared to the other studies which estimated either costs of large populations of surgical patients in multiple hospitals (Wang et al., 2015; Borzkurt et al., 2013; Shepard et al., 2013; Sharma et al., 2012; Hanstein et al., 2011).

Although there is very scanty data on the costing of laboratory and radiologic tests for surgical patients, a very old study reported that in the recent years, the cost of radiologic tests has risen and forms a huge part of patient health expenditure. This is particularly so, considering the routine use of more sophisticated tests such as CT scans and MRI scans (Hofman et al., 2000). This can be mirrored in our study in which CT scans were mostly used for diagnosis. Radiologic tests were the fourth most costly intervention after surgical and nursing procedures and bed occupancy.

Another old study computed the costs of several radiologic examinations (Saini et al., 2000). The costs were a computation of labour and non-labour costs. The average cost radiography, CT scan and MRI was USD 41, 112 and 267 respectively. These charges are much higher than the costs of these tests in our study. This can be explained by the fact that after introduction of these tests, the costs have significantly gone down over the years. A newer study has advocated for the reduction in the number of radiological examinations done as they increase health care costs and expose patients to unnecessary radiation (Kendall and Quill, 2014). This however should not

overlook the importance of radiological tests in informing diagnosis and guiding treatment (Hofman et al., 2000). Variations in the cost of radiologic and laboratory examinations were seen in our study, depending on the site where the patients underwent the test. This is also seen in studies which showed such variations (Spence et al., 2014; Chatterjee et al., 2013).

The median cost of antibiotics was KES. 1,870.05 (18.70 US dollars). In the study period, 50 patients were on antibiotics, and 22 of them developed infection. The total median cost therefore, of treating all the infected patients with antibiotics (n=22) was KES 41,13.10, as opposed to KES. 52,361.40 for those who did not develop infections (n=28). These findings are contrary to several studies which show that the cost of antibiotics increases with those who have developed infection (Bozkurt et al., 2013; Sharma et al., 2012;Ulu- Kilic et al., 2015). Looking at our antibiotic consumption data, it is clear that antibiotics were given equally to patients, regardless of whether they developed infection or not, suggesting indiscriminate antibiotic use. More patients without infections received multiple antibiotics, compared to those who developed infections, because those who developed infections were fewer than those who did not.

Although the cost on antibiotics was higher in the patients who did not develop infections, the overall cost of treating infected patients was higher than that of treating uninfected patients. This included the direct medical costs, productivity losses and direct non-medical costs. These findings agree with other studies (Shepard et al., 2013; Sharma et al., 2012).

Apart from direct medical costs, patients spent a median of KES. 100 and KES 200 on food and transport respectively, for the relatives who visited them in hospital. This is against a median daily income of KES. 300. This shows that these costs literally took up all the income for the

day. Even though Kenyatta National hospital provides meals for all its patients, the relatives opted to supplement that with food bought from outside the hospital. This increased the household income spent on taking care of the ill.

The patients were employed in low paying jobs, with a median average income of KES 300. The productivity costs were very high, almost a third of the direct medical costs. This finding is contrary to that in other studies that have stated that productivity losses can be higher than direct medical costs (Changik, 2014). This is because such studies have been carried out in high income areas where patients are on high salaries and the cost of replacing them during the illness and recuperation period is high. Our patients worked menial jobs with no fixed salaries, so they could easily be replaced by other casual labourers at the time of illness.

In this study, the costs of medicines, diagnostic tests, surgery and nursing care, direct non-medical costs and productivity losses were computed. Care giver costs were the highest, followed by costs of surgical and nursing procedures and productivity losses. The cost on medicines was the lowest. They key cost drivers for laboratory, radiologic procedures and medicines were CT scans, UECs and meropenem respectively. The total expenditures were higher in patients who developed infection than patients who did not. Patients who underwent full blood count tests were likely to be infected. Productivity losses and cost of hiring caregivers was higher than the patients' income.

From our study, it is evident that the costs of treating a neurosurgical trauma patient were much higher than the patients' household incomes, assuming that the daily income is a reflection of household income. This is against the fact that the Kenyan healthcare system heavily relies on

out of pocket payments for healthcare (Chuma and Okungu, 2011). The Ministry of health is underfunded and cannot take care of the costs of all patients. The National Health Insurance Fund (NHIF) pays for some inpatient costs of patients, but only caters for inpatient hospital stay. Some hospitals, Kenyatta National Hospital included, have adopted a waiver system to take care of the costs of extremely poor patients, but this still has challenges as they are not able to cover the costs of all patients (Kamanda et al., 2015). This calls for a revision in healthcare financing policies in Kenya, to meet the WHO standards for equity in healthcare (Chuma and Okungu, 2011).

Our study had several strengths. It is the first such study to be carried out in a neurosurgical unit in East Africa. It will definitely be a model cost of illness study for surgical patients in the region. Other studies worldwide computed costs of surgical site infections using a combination of different surgical patients, but our study focused only on neurosurgical patients, making it unique. This study quantified the costs of different components of direct medical and direct non-medical costs, as opposed to most studies which have quantified only direct medical costs. In this study, we identified key drivers to costing, which has not been the case in other studies.

The limitation in this study was that we were unable to compute intangible costs. These refer to the pain and suffering associated with disease. This is because we were unable to take history for most of the patients with head trauma because of low Glasgow coma scales, confusional states and general disorientation which was associated with head injury.

7.5 CONCLUSION AND RECOMMENDATIONS

Neurotrauma and associated surgical site infections affect the youth of productive age in our setting. The direct costs of treatment, and household expenses incurred are a heavy burden to the patients and their families, most of whom cannot afford the out of pocket expenses. The productivity losses are also high, although the patients in this cohort were not employed in jobs with a steady income. Costs due to antibiotic use are higher in the patients who do not develop infections than those who develop infections. This points to irrational antibiotic use and associated unnecessary costs. The costs of diagnostic tests do not vary with infection rates, but vary with the site at which the tests are done. The acquisition costs of some medicines varied with the year. The null hypothesis that stated that "Patients with SSIs incur higher direct and productivity costs compared to patients without SSIs" was accepted.

Kenyatta National Hospital and the Kenya government at large should come up with a comprehensive insurance scheme to cater for the healthcare costs of this group of patients. As discussed earlier, irrational antibiotic use contributed to an increase in medication costs. The neurosurgical unit should develop antibiotic use guidelines for its patients to ensure rational and economic use of medicines. Kenyatta National Hospital tender committee should evaluate yearly acquisition prices of all the medication so to prevent the wide variations in prices seen in some medications. Finally, a study should be carried out to compute the intangible costs incurred by neurosurgical trauma patients at Kenyatta National Hospital.

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CHAPTER 8: GENERAL DISCUSSION OF KEY FINDINGS FROM ALL SECTIONS OF THE STUDY, CONCLUSION AND RECOMMENDATIONS.

8.1 General Discussion and Conclusion

This study incorporated a systematic review, a cross sectional study, a cohort study and a cost of illness study. Findings from this study will be used in development of an infection control protocol at the neurosurgical unit of Kenyatta National Hospital.

The systematic review and meta-analysis highlighted that systemic antimicrobial prophylaxis is effective in preventing neurosurgical site infections, though the cohort study indicated that this was dependent on the type and duration of surgical procedure. Use of antimicrobial impregnated shunts is effective but expensive for patients in low and middle income countries. From the cross sectional and cohort studies, the prevalence and incidence of surgical site infections in patients with potentially contaminated wounds is very high (20.7% and 37.7% respectively). The known risk factors for development of surgical site infections did not apply, but the independent risk factors were presence of epidural haematoma and trauma from road traffic accidents and assault. This is the first study to report that epidural haematoma is a risk factor for development of surgical site infection.

Antimicrobial prophylaxis was useful in preventing surgical site infections, but its effectiveness was dependent on the type of surgical procedure. In this case, patients who underwent both craniotomy and evacuation of haematomas were more likely to benefit from antimicrobial prophylaxis than those who did not. The use of antimicrobials was irrational in this study, but this had no impact on the development of surgical site infections. Of note, there was no distinction between the use of antimicrobials for prophylaxis and for presumptive treatment of

infections. The total costs incurred by patients were higher in those who developed surgical site infections than those who did not.

8.2. Strengths, Originalities and Limitations of the Study

This study had several strengths and originalities. We conducted the first systematic review that assesses the use of antimicrobial prophylaxis in the neurosurgical setting in East Africa. We also conducted the first cost of illness study in a neurosurgical unit in East Africa. This study is the first to illustrate that the presence of epidural haematomas is a risk factor for development of surgical site infections. It is also the first study to incorporate marginal analysis and effect measure modification in the assessment of the effectiveness of antimicrobial prophylaxis. It is the first study to show that the effectiveness of antimicrobial prophylaxis in neurosurgery depends on the type of surgical procedure, namely craniotomy and evacuation of epidural haematomas.

There were several limitations to this study. First of all the study had a small sample size. Documentation of infection control procedures and patient data was incomplete. Classification of surgical wounds and the use of antimicrobial susceptibility and resistance data was not routinely done to guide the selection of antimicrobial drugs. In the cost of illness study, we were unable to compute intangible costs.

8.3. Recommendations for Research and Practice

From the findings of this study, several recommendations can be made for practice and future research at Kenyatta National Hospital. Documentation should be improved. Rational antimicrobial use should be improved by developing an antimicrobial use protocol and

incorporating clinical pharmacists in the neurosurgical team as they are experts in drug therapy. Interventional studies that evaluate the effectiveness of infection control protocols at this unit should be carried out. Larger, multi-centre randomised controlled trials should be carried out to compare the effectiveness of individual antimicrobials in preventing neurosurgical site infections. A systematic review and meta-analysis evaluating the use of commonly used antimicrobials should be carried out.

APPENDICES

APPENDIX 1: PATIENT VOLUNTEER INFORMATION AND CONSENT FORM

No 001. Version 1, 0721296448

To be read in a language that the respondent understands.

Title of the Study

Evidence in Support of Antimicrobial Prophylaxis, Incidence And Risk Factors of Surgical Site Infection, Patterns of Antimicrobial Use and the Economic Impact of Neurosurgical Site Infections at Kenyatta National Hospital.

Principal Investigator

Dr Sylvia Atisa Opanga U80/95607/2014

Department of Pharmaceutics and Pharmacy Practice

Supervisors

Prof Kimani A.M Kuria

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Prof NimrodJuniahs Mwang'ombe

Division of Neurosurgery,Department of Surgery, School of Medicine

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INSTITUTIONS

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2. Division of Neurosurgery, Department of Surgery, School of Medicine, University of Nairobi, P.O.BOX 30197 00100, Nairobi.
3. Department of Pharmacology and Pharmacognosy, School of Pharmacy, University of Nairobi, P.O.BOX 30197 00100, Nairobi.

Ethical Approval

Kenyatta National Hospital/ University of Nairobi Ethical and Research Committee, P.O.BOX 20723-00100, Nairobi.Tel 2726300/ 2726450 Ext 44102.

PREAMBLE

Permission is requested from you to enrol in this medical research study. We are requesting you to volunteer freely in this study. Before you decide to join, we would like to provide you with information about the study. This document is a consent form; it has information about the study and will be discussed with you by the investigators. Please, study it carefully and feel free to seek any clarification especially concerning terminologies or procedures that may not be clear to you. If you agree to join this study, you will be asked to sign this consent form and a copy will be given to you for safekeeping.

PURPOSE OF THE STUDY

The purpose of this study is to find out what factors lead to development of infections and which antibiotics are the most effective and safe in preventing these infections.

Introduction: In this study, I am assessing the risk factors that may lead to infections in patients who have undergone neurosurgery and the use of antibiotics to prevent these infections.

Procedures to be followed

With your permission I will obtain information on your personal data and the antibiotics that have been prescribed from your file. I will ask you a few questions regarding your treatment and any other illnesses you may have. All information obtained will be handled with confidentiality. I will follow you up as you undergo treatment to ascertain whether you develop infection or not. In case you develop infection, a sample of your blood or cerebrospinal fluid will be collected to identify the organisms causing infection in order to design the best treatment for you. Even after discharge, I will follow you up in the clinic to determine whether you develop any infections and if you need to use antibiotics, I will also ask you questions regarding your overall health and if you are able to carry out normal activities that you did before undergoing this operation. In case you need further treatment, it shall be availed to you during the follow up. I will follow you up in the clinic for a period of up to three months from the date of your operation to ensure that you are responding well to treatment and that you fully recover.

I will be conducting an economic evaluation to how your condition and treatment have cost you, financially, so that we may be able to provide you with cost effective treatment in future. I will

ask you questions on how much the treatment and admission has cost you, as well as any income you may have lost as a result of missing work due to admission.

Risks: There will be no risks involved in this study to you.

Benefits: There will be some direct benefits to you in the study. If we find any factors that increase your chances of getting infection, we will reduce them. If we also find any infection we will treat you with the most safe and effective antibiotic.

Assurance on confidentiality

All information obtained from your file will be kept confidential and used for the purpose of this study only. Your name will not be used during data handling or in any resulting publications. Codes will be generated and used instead.

Voluntary participation/withdrawal from study

The decision to take part in this research study is your choice. You may choose not to take part or to stop participating at any time.

Questions

You are free to ask any questions at any time about the study and regarding your right as a research volunteer. You will not be giving up any of your legal rights by signing this consent form.

Further Information and Contacts

For further information or complaints about this study you may contact:

1. Dr Sylvia Opanga, The School of Pharmacy, University Nairobi. P O Box 19676-00202 Nairobi Tel: 0721296448.
2. Department of Pharmaceutics and Pharmacy Practice, School of Pharmacy, University of Nairobi. Tel: +254 02 2725099, 0727499537.

For questions related to your rights as a volunteer in this research study, you may contact:

Prof Chindia, Secretary of the Kenyatta National Hospital Ethics and Research Committee (KNH – ERC), School of Pharmacy, P. O. Box 19676, Nairobi. Tel: +254 020 2726300 Ext 44102.

STATEMENT OF CONSENT

I have read, or have had this consent form read to me. I have had the chance of discussing this research study with the investigators. I have had my questions answered in a language I understand. The risks and benefits have been explained to me. I understand that my participation in this study is voluntary and that I may choose to withdraw at any time. I freely agree to participate in this research study.

By signing this consent form, I have not given up any of the legal rights that I have as a participant in a research study.

I _____ give consent to the investigator to use my medical records in her study. The nature of the study has been explained to me by Dr Sylvia Opanga.

Signature_____ Date_____

I confirm that I have explained the nature and effect of the study.

Signature_____ Date_____

CODE NUMBER_____ DATE_____

APPENDICES 2 AND 3 ETHICAL APPROVAL AND RENEWAL LETTERS

APPENDIX4- DATA COLLECTION FORM FROM PATIENT FILES

No 004 Version 1, 0721296448

a) ELIGIBILITY CHECKLIST:

	YES	NO
Admitted in the Neurosurgery Unit	☐	☐
Signed the informed consent form	☐	☐

b) PATIENT BIODATA

IP No

Sex

Date of Admission

Place of Residence

Age

Education level

Weight

c) MEDICAL AND SURGICAL HISTORY

Chief Complaint: (Tick where appropriate)

Unconsciousness

Seizures

Headaches

Bleeding

CSF leakage

Other (Specify)

Details of Trauma: (Tick where applicable)

Road accident ☐

Assault ☐

Fall ☐

Other blunt trauma ☐

Classification of wound on admission (Tick where applicable)

Clean ☐

Clean contaminated ☐

Contaminated ☐

Dirty ☐

Patient related risk factors (Tick where applicable)

Diabetes mellitus/ hyperglycaemia ☐

Anaemia ☐

Blood loss ☐

Obesity ☐

Immunosuppression ☐

Smoking ☐

Malnutrition ☐

☐

CSF leak

Concomitant systemic infection ☐

ASA score >3 ☐

Medication History

Past Medication History

Tick where appropriate the medications the patient has taken before

Corticosteroids ☐

NSAIDs ☐

Immunosuppressant drugs ☐

Cytotoxic drugs ☐

Antidiabetic drugs ☐

Current Medication

Drug	**Dose**	**Frequency**	**Duration**	**Indication**

Procedures Carried Out:

Pre-surgical Procedures (Tick where applicable)

Initial wound management before surgery	☐
Hair shaving	☐
Hair Clipping	☐
Maintenance of normothermia	☐
Blood replacement/transfusion	☐
Tissue oxygenation	☐
Antimicrobial prophylaxis	☐
Single gloving	☐
Double gloving	☐
Scrubbing	☐
Theatre cleanliness and limited traffic flow	☐

Surgical Procedures:

Implantation of prostheses	☐
Surgical drains and shunts	☐
Re-do procedures	☐

Duration of Procedure (hours):

Theatre used for procedure:

Age and qualification of operating surgeon:

Postoperative management of patient:

Postoperative wound cleaning:

Antimicrobial prophylaxis:

Other procedures:

Development of SSIs after Procedure:

Diagnosis of Infection:

Classification of infected wound:

Clean	☐
Clean contaminated	☐
Contaminated	☐
Dirty	☐

Duration after surgery when infection is diagnosed (days):

Intervention:

APPENDIX 5: CHOICE OF ANTIBIOTICS FOR PROPHYLAXIS AND CONCURRENT PERIOPERATIVE MEDICATION

First line Antibiotics:

Drug	Dose	Frequency	Duration	n
Amikacin	500mg	BD	5	1
Ceftriaxone			6	1
	1g	BD		4
			2	2
			3	1
			7	4
	2g	BD		1
			14	5
			7	4
		OD	1	1
			2	1
			5	1
		QID	7	1
Cefuroxime	500mg	BD	14	1
			7	1
Co-amoxiclav	1.2g	BD	5	1
		TDS	5	2
	625mg	BD	5	2
Flucloxacillin	500mg	TDS	3	1
Metronidazole	500mg	OD		1
		TDS	14	2
			5	2

2nd line - Antibiotics

Drug	Dose	Frequency	Duration	n
Ampiclox	500mg	OD	5	1
Ceftriaxone	1g	BD	3	1
			5	2
			7	2
	2g	OD	7	1
Cefuroxime	150mg	TDS	5	1
	500mg	TDS	5	1
Co-amoxiclav	1.2g	TDS		1
			7	2
Metronidazole	500mg	TDS		2
			14	3
			5	1
			7	5

3rd line Antibiotics

Drug 3	Dose 3	Frequency 3	Duration 3	n
Ceftriaxone	1g	BD	5	1
Metronidazole	500mg	TDS	1	1

4th line – Antibiotics

Drug	Dose	Frequency	Duration	n
Ceftriaxone	1g	BD	5	1
		OD		1
Cefuroxime	750mg	TDS		1
Metronidazole	500mg		7	1
		TDS	7	1
Vancomycin	500mg	BD		1

Perioperative medication	n	%
NSAIDS	51	45.1%
Antidiabetic Drugs	7	6.6%
Corticosteroids	2	1.8%
Immunosuppressant drugs	1	0.9%
Cytotoxic Drugs	0	0.0%

APPENDIX 6: ECONOMIC EVALUATION DATA COLLECTION FORM

No 005 Version 1, 0721296448

Part A: Costing Data:

a) Costs of Antibiotics Used in Prophylaxis

Antibiotic	**Unit cost,KES.**	**Total cost per dose used, KES.**

b) Costs of Radiologic Tests

Test	**Cost, KES**
X-ray	
CT scan	
MRI scan	
Other	

c) Costs of Laboratory Tests:

Lab Test	**Cost, KES**

d) Administrative Costs

Designation of administrator:

Please fill the following table on the costs below:

Utilities	**Average cost per month, KES**	**Estimated cost per operation, KES**
Electricity		
Water		
Operating room equipment		
Hiring surgeons		
Hiring nurses		
Hiring anaesthetists		
Hiring radiologists		
Hiring pharmacists		
Building maintenance costs		

Part B: Questionnaire for Patients

Patient Biodata:

IP number:

Age:

Sex:

Diagnosis:

Questions:

1. On average, how much money in KES.has been spent, out of pocket on the following items since your admission?

a) Medicines

b) Medical and surgical supplies

c) Food

d) Transport by relatives to the hospital

e) Hiring any caregiver(s)

1. What is your daily source of income?

2. Do you work every day?

3. How much time has been lost from work as a result of admission and treatment?

4. How much money on average, in terms of your income has been lost during the duration of treatment?

5. How much time has been lost from your leisure activities?

Appendix 7: GRADE Evidence Summary Table

Factor	Comment
Quality of evidence	
Benefits/desired effects	
Risks/ undesired effects	
Values/acceptability	
Cost/ feasibility	

Appendix 8: Characteristics of Excluded Systematic Reviews

Study	**Reasons for Exclusion**
Abla et al., 2011	Not a systematic review
Bayston et al., 2007	Not a systematic review
Dellamonica et al., 1993	Non-compliance with PICO. Included procedures other than neurosurgery
Djindjian et al., 1994	Article in French
Fujiwara et al., 2000	Not a systematic review
Guglielmo et al., 1983	Non-compliance with PICO. Study population not neurosurgical patients
Gutierrez- Gonzalez et al., 2010	Non-compliance with PICO, looked at nosocomial infections and not SSIs
Haines, 1989	Not a systematic review
Nesvick et al.,2014	Not a systematic review, but a review of case control studies
Parker et al., 2011	Non-compliance with PICO. The study included paediatric patients
Ratilal and Sampaio, 2011	Non-compliance with PICO. The study included use of anticonvulsants which were not interventions of interest in our study
Ratilal et al., 2006	Duplicate, not a systematic review
Savitz et al., 2002	Not a systematic review
Shapiro, 1991	Not a systematic review. Mixed otolaryngologic surgery and neurosurgery
Venkatesan et al., 2010	Not a systematic review

Appendix 9: Characteristics of Excluded RCTs:

Study	Reason for Exclusion
Alleyne et al., 2000	Not RCT, non-compliance with PICO as it included patients undergoing other forms of surgery
Bayston et al., 1990	Included children
Bayston, 1975	Non-compliance with PICO. Included only children
Blum, 1989	Non-compliance with PICO. Included only children
Everett and Strausbaugh, 1980	Non-compliance with PICO. Deals with treatment of infection, not antimicrobial prophylaxis.
Eymann et al., 2008	Not RCT. A case control study focusing on economic evaluation
Haines, 1982	Non-compliance with PICO. Included only children
Holloway et al., 1996	Not RCT. Prospective study
Mewe et al., 1991	In German
Nejat et al., 2008	Non-compliance with PICO, included children
Odio, 1984	Non-compliance with PICO, included children
Pattavillakom et al., 2007	Not RCT
Reider, 1987	Non-compliance with PICO. Included only children
Saini et al., 2012	Not RCT. Very small sample size, n=15 not adequate for normal distribution
Tacconelli et al., 2008	Non-compliance with PICO. Evaluated two antibiotics, Vancomycin versus Cefazolin
Van Ek et al., 1991	Not RCT, a prospective study that's a follow up to an RCT
Wang, 1984	Non-compliance with PICO. Included only children
Walters, 1992	Non-compliance with PICO. Included only children
Yamamoto et al., 1996	Non-compliance with PICO, used local irrigation with antibiotics and saline
Yogev 1984	Non-compliance with PICO. Included only children
Zhu et al., 2001	Non-compliance with PICO. Evaluated two antibiotics, Ampicillin Sulbactam versus Ceftriaxone

Appendix 10: GRADE Evidence Profile for Quality of Evidence of Systemic Antimicrobial Prophylaxis versus Placebo/ No Systemic Antibiotics

Author(s): Sylvia A. Opanga. Mercy N. Mulaku, Faith A. Okalebo, Nimrod J. Mwang'ombe, Kimani A.M. Kuria

Date: 7/12/2015

Question: Antimicrobial prophylaxis compared to placebo or no antimicrobial prophylaxis for prevention of neurosurgical site infections

Setting: Low and middle income countries

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	antimicrobial prophylaxis	placebo or no antimicrobial prophylaxis	Relative (95% CI)	Absolute (95% CI)		
Development of neurosurgical site infections (follow up: range 2 weeks to 1 years; assessed with: wound infections, CDC classification, positive cultures, clinical signs, leukocytosis, wound discharge, fever, Malis criteria)												
8	randomised trials	serious [1]	not serious	not serious	not serious	none	28/1117 (2.5%)	58/1143 (5.1%)	**OR 0.48** (0.30 to 0.79)	**26 fewer per 1000** (from 10 fewer to 35 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Development of non-surgical site infections (follow up: range 1 weeks to 6 months; assessed with: pneumonia, meningitis, UTIs)												
2	randomised trials	serious [1]	not serious	not serious	not serious	none	26/784 (3.3%)	26/809 (3.2%)	**OR 1.04** (0.60 to 1.82)	**1 more per 1000** (from 13 fewer to 25 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Adverse effects of antibiotics (follow up: mean 6 months; assessed with: clinical assessment)												
2	randomised trials	serious [1]	not serious	not serious	not serious	none	0/680 (0.0%)	0/686 (0.0%)	not estimable		⊕⊕⊕◯ MODERATE	IMPORTANT

MD – mean difference, RR – relative risk

1. all included studies had unclear allocation concealment, random sequence generation, blinding procedures, incomplete outcome data and selective reporting

Appendix 11: Grade Evidence Profile for AICs versus Standard Shunts

Author(s): Sylvia A. Opanga. Mercy N. Mulaku, Faith A. Okalebo, Nimrod J. Mwang'ombe, Kimani A.M. Kuria

Date: 7/12/2015

Question: Antimicrobial impregnated shunts compared to standard shunts for prevention of neurosurgical site infections

Setting: Low and middle income countries

Bibliography:

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**antimicrobial impregnated shunts**	**standard shunts**	**Relative (95% CI)**	**Absolute (95% CI)**		
Development of neurosurgical site infections (follow up: range 1 weeks to 20 months; assessed with: shunt infection, wound infections, CDC classification, positive cultures, clinical signs, leukocytosis, wound discharge, fever, Malis criteria)												
2	randomised trials	serious [1]	not serious	serious [2]	serious [3]	none	5/199 (2.5%)	23/199 (11.6%)	**OR 0.22** (0.08 to 0.59)	**88 fewer per 1000** (from 44 fewer to 105 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
All cause mortality (follow up: range 1 weeks to 20 months; assessed with: death)												
2	randomised trials	serious [1]	not serious	serious [2]	serious [3]	none	33/199 (16.6%)	23/199 (11.6%)	**OR 1.47** (0.82 to 2.62)	**46 more per 1000** (from 19 fewer to 139 more)	⊕◯◯◯ VERY LOW	CRITICAL
Shunt Revision (follow up: range 1 weeks to 20 months; assessed with: redo procedure)												
2	randomised trials	serious [1]	not serious	serious [2]	serious [3]	none	3/50 (6.0%)	10/60 (16.7%)	**OR 0.66** (0.26 to 1.67)	**50 fewer per 1000** (from 84 more to 117 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

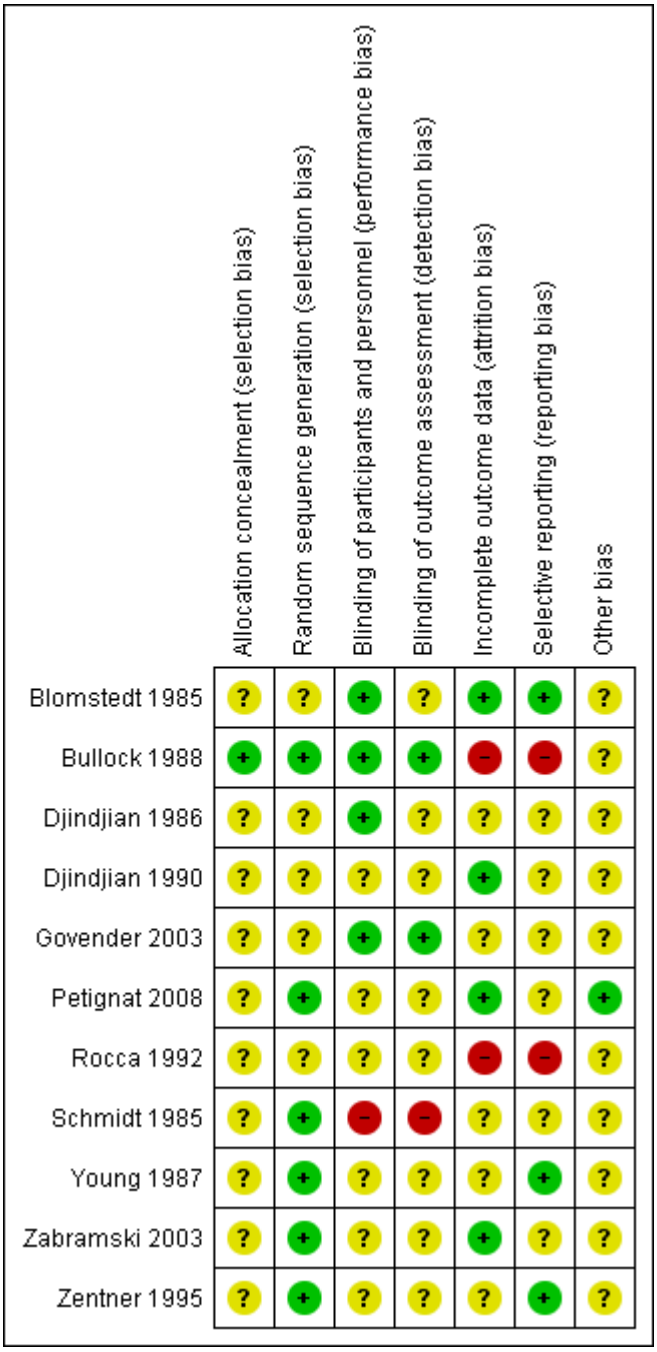
MD – mean difference, RR – relative risk

1. all included studies had unclear allocation concealment, random sequence generation, blinding procedures, incomplete outcome data and selective reporting
2. AICs too expensive for our study setting
3. does not comply to IOS rule

Appendix 12: Data Abstraction for Risk of Bias for Included Studies

Study	Randomisation Procedure	Allocation Concealment	Blinding	Analysis
Blomstedt 1985	Unclear	Unclear	Double blinding using identical appearance interventions	Per protocol
Bullock 1988	Clear	Clear /done	Double blinding using identical appearance interventions	Per protocol
Djindjian 1986	Unclear	Unclear	No blinding	Per protocol
Rocca 1992	Unclear	Unclear	Unclear	Per protocol
Schmidt 1985	Clear –use of random numbers	Done /clear	No blinding	Per protocol
Young 1987	Clear- table of random nos	Done/clear	Single blinded	Per protocol
Zentner 1995	Clear- use of computerized lists	Done/clear	Unclear , used no antibiotics as control	Per protocol
Zhu et al., 2001	Clear- computer generated randomisation	Done, clear	Done – double blinded	Per protocol
Petignat et al., 2008	Clear- computer generated randomisation	Done, clear	Double blinding	Per protocol
Tacconelli et al., 2008	Clear. Quasi-randomised according to letter of last name using 1:1 ratio	Not done	No blinding	Intention to treat analysis and per protocol analysis
Djindjian 1990	Unclear	Not done	Unclear	Per protocol
Govender 2003	Unclear	Unclear	Single blinded	Per protocol
Zabramski 2003	Clear-use of central automated system	Unclear	Unclear	Per protocol

Appendix 13: OVERALL RISK OF BIAS SUMMARY FOR ALL INCLUDED STUDIES



Appendix 14: Risk of Bias Tables for Included Studies

Blomstedt 1985

Risk of bias table

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)		There was no mention of allocation concealment in the study
Random sequence generation (selection bias)		They stated , they had randomized the patients but the method for random sequence generation was not stated
Blinding of patients and personnel (performance bias)		They used identical appearance of both the antibiotic and placebo, both patients and health care providers could not tell which was intervention and which was placebo
Blinding of outcome assessment (detection bias)		It is not stated clearly though we assume it could be low risk given the intervention and placebo had identical appearance
Incomplete outcome data (attrition bias)		All patients recruited were accounted for in the analysis
Selective reporting (reporting bias)		The results don't seem to lean on one side,per protocol analysis
Other bias		Unclear

Bullock 1988

Risk of bias table

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)		Clear allocation concealment.Used sealed envelopes
Random sequence generation (selection bias)		Clear Randomization procedure.Use of random number list

Blinding of patients and personnel (performance bias)		Double blinding using identical appearance of antibiotic and placebo
Blinding of outcome assessment (detection bias)		Blinding was for surgeons and patients
Incomplete outcome data (attrition bias)		Had incomplete outcome data, they had 417 participants but reported for 104 patients, per protocol analysis
Selective reporting (reporting bias)		Did not account for all the patients
Other bias		Unclear

Djindjian 1986

Risk of bias table

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)		It was not clear whether they had allocation concealment.They did not report about allocation concealment.
Random sequence generation (selection bias)		The method of randomization was not stated, but the study was randomised
Blinding of patients and personnel (performance bias)		There was no blinding, however patients are unlikely to alter response to treatment
Blinding of outcome assessment (detection bias)		No blinding
Incomplete outcome data (attrition bias)		Per protocol analysis
Selective reporting (reporting bias)		Per protocol analysis
Other bias		Not applicable

Djindjian 1990

Risk of bias table

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)		Not done. No allocation concealment
Random sequence generation (selection bias)		Unclear
Blinding of patients and personnel (performance bias)		Unclear.no blinding details yet they stated it is double blinded
Blinding of outcome assessment (detection bias)		Unclear
Incomplete outcome data (attrition bias)		Per protocol analysis
Selective reporting (reporting bias)		Unclear
Other bias		unclear

Govender 2003

Risk of bias table

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)		Unclear
Random sequence generation (selection bias)		Unclear
Blinding of patients and personnel (performance bias)		single blinded.Blinded only the surgeons.as much that they were not blinded, it was not easy for the patients to detect any changes to the shunts with regard to infection.
Blinding of outcome assessment (detection bias)		done(surgeons were blinded)
Incomplete outcome data (attrition bias)		per protocol
Selective reporting (reporting bias)		unclear
Other bias		unclear

Petignat 2008

Risk of bias table

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)		done, using sealed envelopes
Random sequence generation (selection bias)		cumputer generated sequence
Blinding of patients and personnel (performance bias)		Double blinding
Blinding of outcome assessment (detection bias)		Unclear
Incomplete outcome data (attrition bias)		All patients accounted for
Selective reporting (reporting bias)		per protocol
Other bias		Unclear

Rocca 1992

Risk of bias table

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)		unclear. Did not report allocation concealment
Random sequence generation (selection bias)		unclear randomisation procedures
Blinding of patients and personnel (performance bias)		unclear blinding procedures
Blinding of outcome assessment (detection bias)		Unclear
Incomplete outcome data (attrition bias)		reported for 27 patients out of 78 patients.
Selective reporting (reporting bias)		reported results for 27 patients undergoing shunting procedures
Other bias		Unclear

Schmidt 1985

Risk of bias table

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)		Clear(confirm which method)
Random sequence generation (selection bias)		Use of random numbers, not sure if it is from tables or computer generated
Blinding of patients and personnel (performance bias)		No blinding
Blinding of outcome assessment (detection bias)		No blinding
Incomplete outcome data (attrition bias)		Per protocol analysis
Selective reporting (reporting bias)		Unclear, as there was no blinding
Other bias		Unclear

Young 1987

Risk of bias table

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)		Done
Random sequence generation (selection bias)		Used table of random numbers
Blinding of patients and personnel (performance bias)		Single blinded
Blinding of outcome assessment (detection bias)		Unclear.It is not clear who were doing the outcome assessment ,however the personnel giving the intervention were blinded
Incomplete outcome data (attrition bias)		Per protocol analysis
Selective reporting (reporting bias)		All patients accounted for
Other bias		Unclear

Zabramski 2003

Risk of bias table

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)		allocation concealment done using sealed envelopes
Random sequence generation (selection bias)		Use of central automated system
Blinding of patients and personnel (performance bias)		Unclear blinding procedures
Blinding of outcome assessment (detection bias)		unclear
Incomplete outcome data (attrition bias)		All data accounted for
Selective reporting (reporting bias)		Per protocol
Other bias		Unclear

Zentner 1995

Risk of bias table

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)		Done using sealed envelopes
Random sequence generation (selection bias)		Use of computerized list
Blinding of patients and personnel (performance bias)		Unclear
Blinding of outcome assessment (detection bias)		Unc lear. Blnding procedures not reported
Incomplete outcome data (attrition bias)		Per protocol
Selective reporting (reporting bias)		All patients accounted for
Other bias		Unclear

Appendix 15: Costs of antibiotics, no-antibiotics, diagnostic tests and direct non-medical costs

Cost of Antibiotics per prescription

Total cost of Co-amoxiclav per prescription

Cost, KES	Frequency,n	Percentage
0	65	77.4
19	2	2.4
194	2	2.4
266	1	1.2
291	6	7.1
970	1	1.2
2037	6	7.1
4074	1	1.2

Metronidazole		
Cost, KES	**Frequency ,n**	**Percent**
0	60	71.4
56.28	1	1.2
247.83	1	1.2
1239.15	9	10.7
1734.81	7	8.3
1982.64	1	1.2
3469.62	3	3.6
5203.43	2	2.4

Cefuroxime		
Cost, KES	**Frequency, n**	**Percentage**
0	76	90.5
193.32	1	1.2
214.8	1	1.2
300.72	1	1.2
579.3	2	2.4
601.44	1	1.2
868.95	1	1.2
28675.35	1	1.2

Cost of Other Drugs by Prescription Patterns
The consumption and cost of dexamethasone.

Cost of dexamethasone , KES	**Frequency, n**	**Percentage**
0	79	95.0
56	1	1.2
63	1	1.2
249	1	1.2
348.6	1	1.2
672.3	1	1.2
Total	**84**	**100.0**

Cost of Metoclopramide per prescription pattern

Cost., KES	Frequency, n	Percentage
0	61	72.6
25.32	1	1.2
50.64	3	3.6
75.96	2	2.4
101.28	1	1.2
126.6	2	2.4
177.24	14	16.7
	84	100.0

Cost of antiemetics by prescription

Cost ,KES	Frequency	Percentage
0	58	69.0
15	1	1.2
25.32	1	1.2
50.64	3	3.6
70	1	1.2
75.96	2	2.4
101.28	1	1.2
126.6	2	2.4
177.24	13	15.5
510.51	1	1.2
3091.41	1	1.2
Total	**84**	**100.0**

Costs of vitamins and supplementsper prescription.

Cost, KES	**Frequency,n**	**Percentage**
0	71	84.5
80	4	4.8
195	1	1.2
252	1	1.2
320	1	1.2
480	1	1.2
540	1	1.2
720	1	1.2
1600	1	1.2
2092.5	1	1.2
2929.5	1	1.2
Total	**84**	**100.0**

Summary of cost of anti-ulcer drugs per prescription

Cost, KES	Frequency,n	Percentage
0	65	77.4
13.31	2	2.4
24.5	1	1.2
49	1	1.2
53.76	1	1.2
65.94	1	1.2
76.8	1	1.2

Cost of Multivitamin preparations

Vitamin Preparation	Unit	Cost
Iron sucrose -Injection 20mg/ml	5ml Amps	150.00
Ferrous +folic salts with Zinc and vit B complex -Equivalent to elemental iron 50 - 100mg tab/cap and not more than 0.5mg-1.5mg/Tablet Folic ,ascorbic Acid, pyridoxine, cyanocabalamine or equivalent.	Tablet/caps	2.30
Multivitamin -Vitamin A 2500IU,Vit. D 400IU, Vit.E 15iu,Vit.C mg,Folic acid 0.3mg,Vit.B11.05mg,Vit.B21.2mg,Nicotinamide13.5mg,Vit.B61.05 mg,Vit.b12 4.5mcg or equivalent.	Blisters,Tablet/caps	6.00
Multivitamin -Vitamin A 7500IU,Vit. D 2000IU, Vit.E 20.5iu,Vit.C1225 mg,Vit.B12.5mg,Vit.B21.2mg,Nicotinamide40mg,Vit.B6 2mg,Vit.b12 12.5mcg/5ml or equivalent	100ml Bottle	37.00
Vitamin B1+B6+B12 -Tablet (High Potency) B1 200mg, B6 50mg, B12 1000mcg.	Tablet	6.50
Ranferon bottle		80
Ferrous Sulphate -equivalent to elemental iron 50-60mg	Tablets	7
Soluble Vitamin B + Vitamin C -Injection, ascorbic acid 500 mg + nicotinamide 160 mg + pyridoxime hydrochoride 50 mg + riboflavin 4 mg + thiamine hydrochoride 250 mg/ml	Amp	418.50

Costs of CT scans

Price of CT scan	Frequency	Percentage
0	1	1.2
4000	1	1.2
5500	57	70.4
6000	4	4.9
6500	1	1.2
6700	1	1.2
7000	13	16.1
7700	3	3.7
Total	81	100.0

Cost of other laboratory Tests

Cost of Other lab cost, KES	Frequency, n	Percentage
0	70	88.6
100	1	1.3
200	2	2.5
300	1	1.3
700	2	2.5
1000	1	1.3
1200	1	1.3
2000	1	1.3
Total	**1**	**100.0**

Number of radiologic Tests per patient

No of tests	Frequency
1	54 (66.7%)
2	24 (29.6%)
3	2 (2.5%)
4	1 (1.2%)
Total	81

Cost of other laboratory Tests

Cost of Other lab cost, KES	Frequency, n	Percentage
0	70	88.6
100	1	1.3
200	2	2.5
300	1	1.3
700	2	2.5
1000	1	1.3
1200	1	1.3
2000	1	1.3
Total	**1**	**100.0**

APPENDIX 16: PATTERNS OF ANTIBIOTIC USE AT KENYATTA NATIONAL HOSPITAL NEUROSURGICAL UNIT

Antibiotic use combinations for patients who developed infection and those who did not

Drug	Frequency ,% (n)	No Infection, n	Infection, n	P value
Patients on antibiotics	72.5 (n=50)	28 (56.0%)	22 (44.0%)	0.135
No of antibiotics per patient	0	13 (26.0%)	4 (8.0%)	**0.015**
	1	10 (20.0%)	4 (8.0%)	
	2	11 (22.0%)	7 (14.0%)	
	3	6 (12.0%)	8 (16.0%)	
	4	1(2.0%)	3 (6.0%)	

Defined Daily doses of ceftriaxone for patients who received one ceftriaxone prescription

Ceftriaxone daily dose (g)	Frequency
1	4 (12.9%)
2	17 (54.8%)
3	2 (6.5%)
4	7 (22.6%)
Unspecified	1 (3.2%)

Duration of use of Ceftriaxone

No of days	Frequency
1	2 (3.4%)
2	7 (15.6%)
3	4 (8.9%)
4	1 (2.2%)
5	7(15.6%)
6	3 (6.7%)
7	7(15.6%)
8	1 (2.2%)
14	2 (3.4%)
Unspecified	11 (23.4%)

Dose combinations of those who received two prescriptions of ceftriaxone

Initial dose ,g	Second dose, g	N (%)
0.5	2.0	1(8.3%)
1.0	2.0	8 (66.7%)
2.0	2.0	3 (25.0%)
Frequency	**Second freq.**	
Once daily	Once daily	4 (33.3%)
Once daily	Twice daily	3 (25.0%)
Once daily	Thrice daily	1(8.3%)
Twice daily	Once daily	1(8.3%)
Twice daily	Twice daily	1(8.3%)
Twice daily	Thrice daily	1(8.3%)
Thrice daily	Twice daily	1(8.3%)

Other antibiotics prescribed for those who underwent surgery

Other antibiotics prescribed	Surgery	P value
Ampiclox 500mg qidx5/7	1(13.3%)	0.987
Flucloxacilin 500mg qid	1(13.3%)	
Gentamicin qid 7days	1(13.3%)	
Amikacin 500mg bd x5/7	1(13.3%)	
Amikacin 50mg iv 8 hourly indefinitely	1(13.3%)	
Clindamycin 200mg iv 8 hourly x2/52	1(13.3%)	
TEO apply qid x7/7	1(13.3%)	

Patterns of use of Metronidazole with or without surgery

Drug	Description	No surgery, n (%)	Surgery, n (%)	P value
Metronidazole				
No of patients on drug		3 (13.0%)	20 (87.0%)	0.970
Route of administratio				
	Unspecified	3 (13.0%)	8 (34.8%)	0.281
	Oral	0 (0.0%)	1(3.3%)	
	Iv	0(0.0%)	11 (47.8%)	
Dose	500mg	3 (13.0%)	20 (87.0%)	0.970
Frequency of admin	8 hourly	3(13.0%)	19 (82.6%)	
	Unspecified	0 (0.0%)	1 (3.3%)	0.923
Duration (days)	5	2 (8.7%)	6 (26.0%)	
	7	0(0.0%)	6(26.0%)	0.668

	14 21 Unspecified	0(0.0%) 0(0.0%) 1(3.3%)	3(13.0%) 2(8.7%) 3(13.0%)	

Figure 6.10:Metronidazole use patterns in patientswho developed Surgical Site Infection and those who did not.

Metronidazole (Flagyl)	Description	No infection	Infection	P value
Patients on drug		8 (42.1%)	11 (57.9%)	0.121 0.121
Dose	500mg- Unspecified	8(42.1%) 4 (21.1%)	11(57.9%) 4(21.1%)	0.342
Route of administration	Oral intravenous	0 (0.0%) 4(21.1%)	1 (5.3%) 6 (31.6%)	0.206
Frequency	8 hourly unspecified	8(42.1%) 0 (0.0%)	10 (52.6%) 1(5.3%)	
Duration (days)	5 7 14 21 Unspecified	2 (10.5%) 3 (15.8%) 1(5.3%) 0(0.0%) 2(10.5%)	4(21.1%) 2(10.5%) 2(10.5%) 2(10.5%) 1(5.3%)	0.357

Use of Amoxicillin Clavulanate with and without surgery

Drug	Description	No surgery, n (%)	Surgery, n (%)	P value
Amoxicillin clavulanate No of patients on drug		3 (13.3%)	18 (85.7%)	0.814
Route of administration	Unspecified Oral Iv	3 (13.3%) 0 (0.0%) 0 (0.0%)	10 (47.6%) 2 (9.5%) 6 (28.6%)	0.491
Dose	625mg 1000mg 1200mg	1 (4.76%) 0(0.0%) 2(9.5%)	2(9.5%) 2(9.5%) 15(71.4%)	0.695
Frequency of administration	Twice daily 8 hourly Stat Unspecified	1(4.76%) 1(4.76%) 1(4.76%) 0(0.0%)	5 (23.8%) 10(47.6%) 2(9.5%) 2(9.5%)	0.801
Duration (days)	5 7	2(9.5%) 0 (0.0%)	8 (38.1%) 6(28.6%)	0.770

	14 Unspecified	0(0.0%) 0(0.0%)	2(9.5%) 1(4.76%)	

Use of Amoxicillin Clavulanate in Patients who developed infection and those who did not

Drug	**Description**	**No infection**	**Infection**	**P value**
% of patients on Amoxicillin clavulanate		8 (43.4%)	10(55.6%)	0.217
Dose				
	625mg	2 (11.1%)	0 (0.0%)	
	1000mg	1 (5.6%)	1(5.6%)	0.130
	1200mg	5 (27.8%)	10 (55.6%)	
Route of administration				
	unspecified	3 (16.7%)	7 (38.9%)	
	oral	2(11.1%)	0(0.0%)	
Frequency	iv	3(16.7%)	3(16.7%)	0.175
	twice daily	3(16.7%)	2(11.1%)	
	8 hourly	3(16.7%)	7(38.9%)	
	stat	2(11.1%)	0(0.0%)	
Duration (days)	unspecified	0(0.0%)	2(11.1%)	0.099
	5	3(16.7%)	5(27.8%)	0.125
	7	1(5.6%)	5(27.8%)	
	14	1(5.6%)	1(5.6%)	
	unspecified	1(5.6%)	0(0.0%)	

Use of Cefuroxime in patients who underwent surgery and those who did not

Drug	**Description**	**No surgery, n (%)**	**Surgery, n (%)**	**P value**
Cefuroxime No of patients on drug		1 (12.5%)	7 (87.5%)	0.977
Route of admin	Unspecified	1 (12.5%)	5(62.5%)	
	Oral	0 (0.0%)	2 (25.0%)	0.830
Dose ,mg	500	0 (0.0%)	4 (50.0%)	0.571
	750	1(12.5%)	3 (37.5%)	
Frequency	Twice daily	0 (0.0%)	5 (62.5%)	
	8 hourly	1(12.5%)	1(12.5%)	0.340
	Unspecified	0 (0.0%)	1(12.5%)	

Duration ,days	3 5 7 14 Unspecified	0(0.0%) 1(12.5%) 0(0.0%) 0(0.0%) 0(0.0%)	1(12.5%) 3(37.5%) 1(12.5%) 1(12.5%) 1(12.5%)	0.952

Figure 6.14: Use of Cefuroxime in patients who developed infection and those who did not

Description		**No infection**	**Infection**	**P value**
Patients on Cefuroxime		3 (42.9%)	4 (57.1%)	0.450
Dose	500mg- 750mg-	2 (28.6%) 1 (13.3%)	2(28.6%) 2(28.6%)	0.683
	Unspecified -	2(28.6%)	3(42.9%)	
Route of administration	0ral-	1(13.3%)	1(13.3%)	0.730
Frequency	Bd- Tds- Unspecified -	2(28.6%) 1(13.3%) 0 (0.0%)	3(42.9%) 0(0.0%) 1(13.3%)	0.447
Duration (days)	3- 5- 7- 14- unspecified-	1(13.3%) 1(13.3%) 1(13.3%) 0(0.0%) 0(0.0%)	0(0.0%) 2(28.6%) 0(0.0%) 1(13.3%) 1(13.3%)	0.438

Meropenem		**No surgery**	**Surgery**	**P value**
Patients on drug		1(33.3%)	2(66.7%)	0.278
Route of admin	Unspecified Iv	1(33.3%) 0 (0.0%)	1(33.3%) 1(33.3%)	0.264
Dose ,mg	1000	1(33.3%)	2(66.7%)	0.278
Frequency	8 hourly Unspecified	0(0.0%) 1(33.3%)	2(66.7%) 0(0.0%)	**0.028**
Duration,days	3 Unspecified indefinite	1(33.3%) 0(0.0%) 0(0.0%)	0(0.0%) 1(33.3%) 1(33.3%)	0.068

Meropenem	Description	No infection	Infection	P value
Patients on drug		n=0 (0.0%)	n=2(100.0%)	0.103
Dose	1g	n=0(0.0%)	n=2(100.0%)	0.103
Route of administration	unspecified intravenous	n=0(0.0%) n=0(0.0%)	n=1 (50.0%) n=1(50.0%)	0.266
Frequency	8 hourly	n=0(0.0%)	n=2(100.0%)	0.103
Duration (days)	unspecified indefinitely	n=0(0.0%) n=0(0.0%)	n=1(50.0%) n=1(50.0%)	0.266

Types of antibiotics used with and without Surgery

	No surgery	Surgery	P value
Ceftriaxone	3 (6.7 %)	42 (93.3%)	0.066
Metronidazole	3 (13.0%)	20 (87.0%)	0.970
Amoxicillin clavulanate	3 (13.3%)	18 (85.7%)	0.814
Cefuroxime	1 (12.5%)	7 (87.5%)	0.977
Meropenem	1 (33.3%)	2 (66.7%)	0.278

Number of antibiotics with and without surgery

Drug	Description	No surgery, n	Surgery done, n	P value
No antibiotics Antibiotics used		4 (19.1%) 6 (10.5%)	17 (80.9%) 51(89.5%)	0.318
Total no of antibiotics used	0 1 2 3 4	4 (19.1%) 2 (12.5%) 3 (0.0%) 0 (0.0%) 1 (20.0%)	17 (80.9%) 14 (87.5%) 19 (100.0%) 14 (100.0%) 4 (80.0%)	0.552

Ceftriaxone use patterns in patients who developed infection and those who did not

Drug	Frequency ,% (n)	No Infection, n	Infection,n	P value
Ceftriaxone				
patients on drug			17 (38.6%)	0.478
Dose	1g	27 (61.4%)		
	2g	23 (50.0%)		
		22 (47.8%)		
Frequency	Unspecified	1 (2.2%)		
	Once daily			
	Twice daily			
	8 hourly			
	Stat			
Duration (days)				
	1	4 (9.1%)	5 (11.4%)	0.284
	2	6 (13.6%)	7 (15.9%)	
	3	10 (22.7%)	6(13.6%)	
	5	3 (6.8%)	0 (0.0%)	
	7	1 (2.3%)	3(6.8%)	
	14	4(9.1%)	1(2.3%)	
Second prescription				
patients on drug		11		
Dose	0.5g	1(9.1%)	0(0.0%)	
	1.0g	2 (18.1%)	3(27.2%)	0.720
	2.0g	3 (27.2%)	2(18.1%)	
Frequency	once daily	2(18.1%)	2(18.1%)	0.708
	twice daily	3(27.2%)	2(18.1%)	
	8 hourly	1(9.1%)	0(0.0%)	
	stat	0 (0.0%)	1(9.1%)	
Duration (days)				
	1	0(0.0%)	1(9.1%)	0.634
	2	1(9.1%)	0 (0.0%)	
	3	1(9.1%)	0(0.0%)	
	5	2(18.1%)	2(18.1%)	
	7	2(18.1%)	1(9.1%)	
	14	0(0.0%)	1(9.1%)	