PATTERNS OF ANTIBIOTIC USE IN ORTHOPAEDIC SURGERY AT THE KENYATTA NATIONAL HOSPITAL

A DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR THE AWARD OF THE DEGREE OF BACHELOR OF PHARMACY AT THE UNIVERSITY OF NAIROBI

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TABLE OF CONTENTS

DECLARATION

I, Josphat Miroyo Mugosa, hereby declare this as my original work and has not to the best of my knowledge been presented by any other person to this or any other university.

Signed.....

Date.....30/09/2010.....

This work has been submitted with approval from me as the supervisor.

Dr. james Ombega

Signed.....

Date.....30/9/2010.....

ACKNOWLEDGEMENT

First and foremost, I give gratitude to God for seeing me through this research alive and well. I recognize and appreciate the guidance and support rendered by my supervisor Dr. james Ombega.

I feel deeply indebted to my parents for giving me a chance to pursue education up to this level.

I wish to accord special recognition and thanks to Mrs. Radhika Lee, Nairobi Jaffrey academy and The Nairobi International School fraternity at large for the assistance they offered.

I sincerely thank everyone who participated in this study to make it a success.

Lastly, I would like to thank the Bachelor of Pharmacy level IV students for their support and company

DEDICATION

This research is dedicated to Mrs. Radhika Lee, my inspiration and role model, Founder and Director of The Nairobi International School and to the entire Nairobi Jaffrey Academ

LIST OF ABBREVIATIONS

CDC	Center for Disease Control and Prevention
cIAIs	complicated Intra-Abdominal Infections
cSSIs	complicated Skin and Skin structure Infections
DNA	Deoxyribonucleic Acid
GISA	Glycopeptide Intermediate *Staphylococcus aureus*
IV	Intravenous
KNH	Kenyatta National Hospital
MIC	Minimum Inhibitory Concentration
MRSA	Methicillin Resistant *Staphylococcus aureus*
MSSA	Methicillin Susceptible *Staphylococcus aureus*
Q-D	Quinupristin/Dalfopristin
RNA	Ribonucleic Acid
RTA	Road Traffic Accident
SSIs	Surgical Site Infections
VISA	Vancomycin Intermediate *Staphylococcus aureus*
VRE	Vancomycin Resistant *Enterococci*
VRSA	Vancomycin Resistant *Staphylococcus aureus*

ABSTRACT

Purpose

The purpose of this study was to assess the patterns of antibiotic use in treatment of surgical site infections at the Kenyatta National Hospital orthopaedic wards.

Methodology

This was a cross sectional study involving orthopaedic surgery patients who met the inclusion criteria.Data was collected using a questionnaire and an observation schedule.

In this study, only 40 patients met the inclusion criteria. The relevant information was extracted from these patients by a number of structured questiones. This information was then harmonized by consulting the patients' files and treatment sheets.

Results

It was found that the most common classes of antibiotics used in the treatment of surgical site infections in the orthopaedic wards were penicillins, cephalosporins and metronidazole. Intravenous administration was much more common than oral administration.Out of the 40 patients, 26 patients (65%) were on either double or triple antibiotic combination therapy while 35% were on monotherapy. Metronidazole appeared in more than 95% of the combination therapies. These were empiric therapies designed to cover both gram positive, gram negative and anaerobic bacteria.

Conclusion

Although vancomycin and cephazolin (a cephalosporin) are considered to be the gold standard antibiotics for the treatment of bone infection, KNH practice deviates from these guidelines. Instead the main antibiotics used are flucloxacillin, cefuroxime, ceftriaxone, metronidazole and gentamicin. The reason for this deviation was not conclusively established.

Treatment of surgical site infections is empiric and culture and sensitivity tests are rarely done.

CHAPTER 1

INTRODUCTON

Definition

Orthopaedic surgery is a branch of surgery that deals with the maintenance and restoration of the proper function of the musculoskeletal system. It involves the management of trauma such as fractures, joint and soft tissue injuries. Some of the common surgical procedures performed in orthopaedic surgery include hip replacement, arthroscopy, arthroplasty, repair of bone fractures and removal of support implants, insertion of prosthetic implants to repair fractures and debridement of skin, muscle and bone [1, 2].

Historic background

Orthopaedic surgery deals with deformity, diseases of bones and joints, and injuries to the musculoskeletal system. Because these are among the commonest things to affect mankind, there must always have been orthopedic surgeons of one kind or another, even in the most primitive communities. Wherever there was a witch doctor or a medicine man dealing with illness and diseases as General practitioners and Physicians do now, somewhere there would be a bone setter treating fractures and straightening limbs.

Despite these ancient origins, the word 'orthopedic' is a recent introduction derived from the title of a book published by a French Physician, **Nicolas Andry** in **1741** titled *orthopaedia:or the Art of Correcting and Preventing Deformities in Children: By such Means , as may easily be put in Practice by Parents themselves, and all such as are Employed in Educating Children.*

The word itself is derived from Greek, 'orthospais' which means only 'straight child', but orthopaedic surgery has expanded from correction of deformities in children to embrace every aspect of musculoskeletal surgery. Apart from coining the word Orthopaedics, Andry also designed a symbol which has now become the worldwide logo of Orthopaedic surgery.

orthopaedic surgery today

Modern orthopaedic surgery has changed radically since the time of **Andry** and now extends from the neonate to the elderly. The following are some of the more important segments of Orthopaedic surgery.

Neonates

The Orthopaedic surgeon takes care of the congenital deformity. Prompt treatment of some conditions in the first few days of life can produce an almost perfect result, but treating the same condition later may be more difficult.

Children

As in **Andry's** time, children 's deformities are the province of the Orthopaeedic surgeon, but children's Orthopaedics now presents too many unusual and difficult problems that it has become a specialty in its own right.

Trauma

Trauma has always filled much of the surgeon's time. Today, multiple injuries particularly road trauma keep many beds full and form a large part of Orthopaedic practice, sometimes to the exclusion of elective Orthopaedic surgery.

Sports medicine

In some countries, sports medicine is a separate specialty but in the UK, sports injuries a fall within the scope of Orthopaedics. Because the fitness of sportsmen attracts the interests of the public and the press, the orthopaedic surgeon can find this part of his work receiving special scrutiny.

Degenerative joint diseases

Like trauma, degenerative joint diseases occupy a great deal of Orthopaedic attention. Total joint replacement, particularly of hip and knee, is a huge successful operation which relieves pain and restores mobility to patients who would otherwise be condemned to persistent pain and restricted movement for rest of their lives[(3)].

The elderly

With increasing age, the bones become progressively more brittle until they fracture with negligible trauma. All too often, fracture of the neck of the femur in old patients living alone with little family support creates social problem that prove insuperable and mark the start of a downhill path that leads to death.

INVOLVEMENT WITH OTHER SPECIALTIES

Orthopaedic surgeons must have a working knowledge of many other disciplines in order to be able to carry out their work properly and efficiently. Some of the other specialties that work hand in hand Orthopaedics include:

(i) Rheumatologist

Rheumatologist and Orthopaedic surgeons deal with the same structures and must work closely together. A working knowledge of rheumatology is essential to the Orthopaedic surgeon, just as knowledge of Ortopaedics is essential to the rheumatologist. In some countries the Orthopaedic surgeon doubles as the rheumatologist.

(ii) Plastic surgeon

Management of trauma involves treating extensive skin loss and close liaison with the plastic surgeon is important to make the best use of available skin. If the initial management of a wound is bad, the work of the plastic surgeon is made difficult. This is true not only of extensive skin loss but also the suturing of seemingly simple wounds in the accident department.

(iii) Neurologist

Apparently simple orthopaedic problems, such as a recurrent sprain or weakness of an arm may be the first indication of a neurological disorder such as spinal tumor, muscular dystrophy or multiple sclerosis. To be able to detect the exceptional patient who has a neurological disorder and not a truly orthopaedic problem takes considerable experience.

(iv) General and Thoracic surgeon

In treatment of trauma, a good knowledge of management of thoracic and abdominal injuries is mandatory. Much major trauma is first seen by the orthopaedic surgeon because of the damage to the limbs and he /she must assess the damage to the chest or abdomen [3].

CHAPTER 2

JUSTIFICATION

Most of the orthopaedic surgery patients in Kenyatta National Hospital (KNH) undergo surgery to correct injury and trauma resulting from Road Traffic Accidents (RTAs). According to the Kenya Roads Board over 10 million people worldwide are crippled and injured each year due to RTAs. In 1998 the World Health Organization (WHO) ranked Kenya the fifth highest in terms of the number of RTAs per licensed vehicle out of 29 selected countries. A descriptive analysis of RTA and injury data in Kenya was done and non- fatal casualties rose by 506% between 1962 and 1992. RTAs exert a huge burden on the country's economy and health care services. There has been a four- fold increase in road casualties and fatalities over the last 30 years. Most of this casualties end up in KNH orthopaedic surgery to correct the injuries and trauma sustained in the accidents.

A study conducted by Saidi Et al on the outcome of hospitalized road trauma patients in KNH analyzed 233 patients. Information on case and treatment outcome was obtained for each patient through patient interviews, case notes and discharge summaries. Injury accounted for 48% of all emergency hospitalizations into the surgical units. Injury due to RTAs comprised 31%of trauma admissions. 54% of the admitted patients had injury to limbs. Operating room resources were utilized in 52% of the patients and major operations were performed in 12% of these patients. The overall complication rate was 12%. Although the overall mortality was 6%, 35.6% mortality rate was recorded among patients with major injury. This study recommends that additional studies need to explore factors contributing to high mortality and a system of care that can optimize patient outcome. It is in this regard that I intend to carry out this study to establish the type, class and dosages of the antibiotics used in the management of surgical site infections at the Kenyatta National Hospital.

CHAPTER 3

LITERATURE REVIEW

ORTHOPAEDIC ANATOMY

1. JOINTS

Types of joints

(a) Synovial joints

The shoulder, elbow, hip, knee and ankle are all synovial joints lined by synovium which secrets synovial fluid. The articular surfaces are covered by smooth hyaline articular cartilage and movement is determined by the shape of the bones, ligaments, surrounding tissue and the joint capsule which contain the proprioceptors which form the afferent segment of postural reflexes. Synovial joints can be classified according to the shape and movement that occurs between the bones as follows:

(i) Ball and Socket joint like hip and shoulder which allow movement in all planes.

(ii) Hinge joint like knee allows movement in one plane only.

(iii) Condyloid joints like radio carpal joint are elliptical and allow movement in two planes.

(iv) pivot/peg joints such as superior radio-ulnar and atlanto-axial joint which allow movement about one axis only.

(b) Cartilage joints

(i) Primary/Synchondroses

These are cartilage joints that link immature growing bones at the epiphyses in children and have no movement.

(ii) Secondary/Symphyses

Are only found in the midline of the body, have a mass of fibrocartilage linking the bones instead of a synovial cavity. Examples are pubic symphysis, intervertebral joints and manubriosternal joint.

(c) Fibrous joints/syndesmosis

The flat bones of the skull are linked at the suture lines by fibrous tissue which prevents any appreciable movement. These linkages are strictly speaking, joints, but their function is to limit movement rather than encourage it. Another example is the inferior tibiofibular joint which is the largest syndemosis in the body and is important for the sta

2. BONES

Types of bones

(a) Long bones

The epiphysis in a growing long bone is separated from the hollow shaft or diaphysis by the epiphyseal plate or physis. The part of the diaphysis next to the physis is the metaphysis. Any bone with such an arrangement is called a long bone even if it is quite short like the phalanges of the fingers, femur, tibia and humerus.

(b) Flat bones

Flat bones such as the skull, pelvis and ribs form in condensation of fibrous tissue and are often called membrane bones. Their function is to protect the soft viscera such as the brain and the lungs.

(c) Short bones

Short square bones like those of the tarsus and carpus form in blocks of cartilage and ossify from the centre. They do not have epiphyses.

(d) Accessory ossicles

In addition to the normal bones, accessory ossicles occur as variants of normal. These are entirely innocent structures but can be mistaken for fractures and treated as such. The os trigonum behind the talus and the accessory navicular are the most common.

3. EPIPHYSES

Growth of bones

Long bones grow from a physis (epiphyseal plate or growth plate) at each end. Although both ends grow, one will generally grow faster than the other and different epiphyses contribute different amounts to the length of a bone for instance the lower femoral and the upper tibial epiphyses contribute roughly 60% of limb length but the proximal humeral epiphyses is responsible for 80% of the length of the humerus.

4. APOPHYSES

A scale of growing bone or apophyses is present on some bones. Unlike epiphyseal plates, apophyses do not contribute to the length of the bone. The most important apophyses are at the acromion, olecranon, the tibial tubercle and the calcaneum. They look like fractures and can be mistaken as such and treated as such [3].

5. PERIOSTEUM

The outer half of the periosteum is fibrous but the inner half contains mesenchymal ccellswhich can differentiate into osteoblasts or osteoclasts. Periosteum like all living tissue must be treated gently at operation if its growth potential is to be preserved.

6. BLOOD SUPPLY

The nutrient artery supplies the bone marrow and some cortex in adult long bones but the periosteal vessels can take over if the nutrient artery is damaged by for example, a fracture or intramedullary nailing. The circulus vasculosus, the ring of vessels which surrounds most joints contributes to the supply of the large ends of long bones.

7. CARTILAGE

Types of cartilage

Hyaline/Articular cartilage

It is a highly organized tissue consisting of loops of type II collagen within a ground substance of proteoglycans produced by chondrocytes. The proteoglycans are hydrophilic and the tissue tension with the deep layers of hyaline cartilage is considerable.

Fibro cartilage

It varies from place to place according to its elasticity which depends on the relative amounts of elastin and collagen within it. The fibrocartilage of the ear and the nasal cartilage for example is different from that of the intervertebral discs.

8. COLLAGEN

Types of collagen

There are many types of collagen each of which is found in different part(s) of the body.

Type I collagen is found in bones.

Type II collagen is found in hyaline cartilage.

Type II collagen is found in fibrocartilage.

Type IV collagen is found in flexible structures such as ear and nose.

Other types of collagen are found elsewhere in the body.

GENERAL PRINCIPLES OF BONE AND JOINT INFECTION

ETIOLOGY

Bone and joint infection pose a very formidable challenge to the Orthopaedic surgeon. The high success rate obtained with antibiotic therapy in most bacterial diseases has not been obtained in bone and joint infections because of the physiological and anatomical characteristics of bone. The overall surgical site infection has been estimated by the United States Centre for Disease Control and Prevention (CDC) to be2.8% in USA. Although bacteremia is common-estimated to occur 25% of the time after a simple tooth brushing-other etiological factors must be present for an infection to occur. The mere presences of bacteria in bone whether from bacteremia or direct inoculation is insufficient to produce osteomyelitis [(4)].

Illness, malnutrition and inadequacy in immune system can also cause bone and joint infection. As in other parts, bone and joint produce inflammatory and immune responses to infections. Local skeletal factors also play a role in development of infection. The

relative absence of phagocytic cells in the metaphyses of bones in children may explain why acute hematogenous osteomyelitis is more common in this location.

The peculiarity of an abscess in bone is that it is contained within a firm structure with little chance of tissue expansion. As infection progresses, purulent material works its way through the haversian system and Volkmann canals and lifts the periosteum off the surface of bone. The combination of pus in the medullary cavity and in the subperiosteal space causes necrosis of the cortical bone. This necrotic cortical bone known as sequesrum, can continue to harbor bacteria despite antibiotic treatment. Antibiotic and inflammatory cells cannot adequately access this avascular area resulting in failure of medical treatment of osteomyelitis. Recognizing these unique characteristics of bone infection, the best course is prevention. The Orthopaedic surgeon should evaluate the risk of infection in each patient by considering patient-dependent and surgeon-dependent factors.

Patient-dependent factors

(i) Nutritional status

Patient's nutritional status and immunological responses are very important. If the patient is malnourished and immunocompromised and cannot mount a response to an infection, the effects of any treatment are diminished. Malnutrition adversely affects humoral and cell mediated immunity, impairs neutrophil chemotaxis, diminishes bacterial clearance and depresses neutrophil bactericidal function, delivery of inflammatory cells to the foci of infection and complement components. Basal energy requirements of a traumatized or infected patient increases from30% to55% of normal. Nutritional status can be determined preoperatively by:

- Anthropometric measurements (height, weight, triceps skin fold thickness and arm muscle circumference).
- Measurement of serum proteins or cell types (lymphocytes).
- Antibody reactions to certain antigens in skin testing.

Jensen Et al. found that 42% of patients undergoing orthopaedic surgery were clinically or sub-clinically malnourished. Malnutrition was identified by an albumin level of less than 3.4g/dl or total lymphocyte count of less than 1500cells/mm^3. Jensen Et al. recommended nutritional support before elective surgery for patients with recent losses of weight of more than 4.5Kg, serum albumin levels of less than 3.4g/dl or lymphocyte count of less

than 1500cells/mm^3. Patients who need nutritional support can also be screened using the nutritional index used by Rainey-McDonald Et al. by use of the albumin and transferring levels using the following formula[(1.2× serum albumin) + (0.013× serum transferring)]-6043. If the sum is 0 or a negative value the patient is nutritionally depleted and is at high risk of sepsis. Nutritional support should be instituted via enteral therapy or hyper alimentation if the gastrointestinal tract is non functional.

(ii) Immunological status

To fight infection the patient must mount inflammatory (white blood cell count) and an immune (antibodies) response that initially stop the spread of an infection and then ideally, destroy the infecting organism. The body's main defense mechanisms are:

- Neutrophil responses
- Humoral immunity
- Cell mediated immunity
- Reticuloendothelial cells

A deficiency in production or function of any of these predisposes host to infection by specific groups of opportunistic pathogens. The susceptibility to a micro organism depends on the specific defect in the immunity. Abnormal neutrophils or humoral and cell mediated immunity have been implicated in infections caused by encapsulated bacteria in infants and elderly patients, in the increased incidence of *Pseudomas* infection in heroin addicts and in salmonella and *pneumococcus* infection in patients with sickle cell anaemia.

If neutrophil count decreases to below 55cells/mm3, infections by *Staphylococcus aureus* gram negative *bacilli, Aspergillus* organisms *and Candida* organisms become a major threat. Patients with hypogammaglobulinemia or those who have had a splenectomy are at great risk of infection caused by encapsulated bacteria such as *Streptococcus pneumonia, Haemophilus influenza and Neisseria gonorrheae.*

Primary cell mediated deficiencies are rare but secondary cell mediated deficiencies are common and may be due to steroid therapy, malnutrition, lymphoma, systemic lupus erythematosus, immunodefiency in elderly and autoimmune deficiency syndrome. This predisposes the host to fungal and *mycobacteria*l infections, *herpesvirus* and *Pneumocystis carinii.*

Surgeon-dependent factors

(i) Skin preparation

Wound contamination exists anytime the skin barrier is broken, but proper skin preparation decreases skin contamination by bacteria present on the skin. Skin barriers may also reduce skin contamination during surgery.

The skin and hair can be sterilized using alcohol, iodine, hexachlorophene or chlorohexidine but it is almost impossible to sterilize the hair follicles and the sebaceous glands where the bacteria normally reside and reproduce because these agents do not penetrate the oily skin environment.

Hand washing is the most important procedure in prevention of nosocomial infections. Studies suggest that hand scrubbing for 2 minutes is as effective as traditional hand scrubbing for 5 minutes. The optimal duration of hand scrubbing has yet to be determined. Hand rubbing with an aqueous alcohol solution that is preceded by a 1 minute non antiseptic hand washing for the first case of the day was found by Parienti Et al. to be just as effective in prevention of surgical site infections as traditional hand scrubbing with antiseptic soap.

Hair removal at operative site is not recommended (unless done in the operating room) as it can cause local trauma that produces favorable environment for bacterial reproduction.

Glove perforation has been reported to occur in 48% of operations. Most frequently, the perforation occurs on the index finger or thumb of the non dominant hand. A meta-analysis by Tanner and Parkinson found that double gloving decreased skin contamination, and use Biogel indicator gloves (Regent Medical, Norcross, Ga) increased the awareness of glove perforation as long as the indicator glove was intact. Notably, at minimum surgical gloves should be changed every 2 hours [(5)].

(ii) Operating room

Airborne bacteria are another source of wound contamination in operating rooms. These are usually gram positive bacteria and originate almost exclusively from humans in the room. Between 5000 and 55000 particles are shed per minute by each individual in the room. Conventional operating room may contain 10 to 15 bacteria per cubic foot and 250000 particles per cubic foot.

The concentration of airborne bacteria in the operating room may be reduced by at least 80% with laminar flow air systems and even more with personnel-isolator systems. Uv light has also been shown to reduce incidence of wound infection by reducing the number of airborne bacteria. However ultraviolet light rooms are not recommended by the Hospital Infection Control Practice Advisory Committee.

(iii) Prophylactic antibiotic therapy

The first 6 hours after orthopaedic surgery is called 'golden period' during which the number of bacteria remain constant, with the bacteria that are multiplying and those that are being killed by the host defense being about equal. The administration of prophylactic antibiotics expands the golden period. The prophylactic antibiotic should be safe, bactericidal, and effective against most common organisms causing infections in orthopaedic surgery. Because the patient's skin remains the main source of orthopaedic infection, prophylactic antibiotics should be directed against the organisms commonly found on the skin which is *Staphylococcus aureus*, although the frequency of *Staphylococcus epidermidis* is increasing. Others to be covered include *Escherichia coli* and *proteus*.

Most commonly used antibiotics in prophylaxis are the 1st generation cephalosporins for the simple reasons that they are relatively non toxic, inexpensive and effective against most potential pathogens in orthopaedic surgery. Clindamycin can be given if a patient has a history of anaphylaxis to beta lactam antibiotics [(6)].

Antibiotic therapy should ideally begin before surgery (about 2 hours before incision). Maximum dose of antibiotics should be given and can be repeated after 4 hours intraoperatively or whenever blood loss exceeds 1000-1500ml.

Barie suggested that prophylactic antibiotics should not be extended beyond 24 hours even if drains and catheters are still in place to reduce the risk of side effects like super infections, allergic reactions, thrombophlebitits or drug fever. Evidence now shows that 24 hours of antibiotic administration is just as beneficial as 48 to 72 hours of the same [(7)].

Table 1-Antimicrobial Prophylaxis Recommendations for Orthopaedic Surgery [8, 9].

Procedure	Associated microorganism	Drug and dosage regimen	Comments
Joint replacement	*S. aureus* *S. epidermidis*	Cephazolin 1g preoperatively then every 8hours for 2 more doses	Vancomycin is reserved for penicillin allergic patients or where institutional prevalence of MRSA warrants use
Hip fracture repair	*S. aureus* *S. epidermidis*	Cephazolin 1g preoperatively then every 8hours for 48 hours	Compound fractures are treated as if infection is assumed
Open/compound fractures	*S. aureus, S. epidermidis,* gram negative bacilli, polymicrobial	Cephazolin 1g preoperatively then every 8hoiurs for a course of presumed infection. Gram negative coverage-gentamicin is indicated for severe open fractures	Gram negative coverage-gentamicin is indicated for severe open fractures.

The recommendations in the table are according to the American Society of Health System Pharmacists therapeutic guidelines in antimicrobial prophylaxis in surgery. They are strongly recommended and supported by well designed clinical, experimental and epidemiological studies. Other countries may cite cephalexin or cefuroxime for similar reasons [10].

CHAPTER 4

OBJECTIVES

Broad objectives

To carry out a study on the patterns of antibiotic use in treatment of surgical site infections in orthopaedic surgery at the Kenyatta National Hospital.

Specific objectives

1. To determine the classes of antibiotics used in treatment of surgical site infection in orthopaedic surgery.

2. To find out the doses and dosage forms administered in treatment of these infections.

3. To compare the findings of antibiotics used to the practice elsewhere globally.

CHAPTER 5

DESIGN AND METHODOLOGY

Area of study

The study was carried out at the Kenyatta National Hospital orthopaedic surgery wards where orthopaedic services are offered by specialists.

Study design

The study was a cross sectional study. It was a retrospective study.

Target population

The target population was adult patients admitted to the orthopaedic wards of Kenyatta National Hospital who had undergone surgery in the month of June and July 2010 and met the inclusion criteria.

Inclusion criteria

The inclusion criteria entailed adult patients between the ages of 18-65 years who had undergone surgery and were admitted to the orthopaedic wards in Kenyatta National Hospital during the study period.

Exclusion criteria

The paediatrics, geriatrics and the immunocompromised were not included in the study.

Data collection tools

Data collection tools included patient interviews and review of patient files and treatment sheets.

Ethical considerations

The permission to carry out the study was sort from The Ethics and Research Committee of Kenyatta National Hospital. The patient was also required to read and understand the consent form before signing it. For those who could not read, it was read and explained to them before they signed it.

CHAPTER 6

FINDINGS

Out of the targeted number of patients of 100, only 40 were realized representing 40% of the target. This is because most of the patients did not meet the inclusion criteria therefore were left out. Out of those included, 23 were male while 17 were female. The mean age of the patients was 32.5 (18-65).

Table 2-Age and gender distribution of the patients

Age (years)	Number of patients	Male	Female
18-25	6	3	3
26-35	18	11	7
36-45	10	4	6
46-55	4	3	1
56-65	2	2	0
TOTAL	**40**	**23**	**17**

Table 3-A list of the antibiotics used at the Kenyatta National Hospital in the treatment of surgical site infections.

Antibiotic	Number of patients on the antibiotic
Amoxicillin-clavulanic acid	1
Ceftriaxone	3
Cefuroxime	11
Clindamycin	1
Flucloxacillin	20
Gentamicin	6
Metronidazole	20
Nitrofurantoin	2
Norfloxacin	2
TOTAL	**40**

From the above table, it is evident that the major classes of antibiotics used at the Kenyatta National Hospital in the treatment of surgical site infections are penicillins majorly flucloxacillin, cephalosporins majorly ceftriaxone and cefuroxime, nitroimidazoles majorly metronidazole and aminoglycosides especially gentamicin. Other antibiotics used infrequently include clindamycin, nitrofurantoin and norfloxacin. Half of the patients are on flucloxacillin and half of them are also on metronidazole and slightly over a quarter of the patients are on cefuroxime. The three antibiotics are the single most antibiotics that are used most commonly.

Table 4a-Dose and dose frequency of oral antibiotics

Antibiotic	**Dosage**
Flucloxacillin	500mg four times daily
Metronidazole	400mg three times daily
Nitrofurantoin	100mg three times daily
Norfloxacin	400mg two times daily

Table 4b-Dose and dose frequency of intravenous antibiotics

Antibiotic	**Dosage**
Amoxicillin-clavulanic acid	1.2g once daily
Ceftriaxone	1g two times daily
Cefuroxime	750mg three times daily
Clindamycin	300mg three times daily
Flucloxacillin	500mg four times daily
Gentamicin	80mg three times daily
Metronidazole	500mg three times daily

It was found out that, out of the nine antibiotics in common use at the Kenyatta National Hospital; five of them were being administered through intravenous route exclusively, two others were being administered exclusively through the oral route while the other two could be given by either of the routes. Ceftriaxone, cefuroxime, clindamycin, amoxicillin-clavulanic acid and gentamicin were only being given intravenously. Nitrofurantoin and norfloxacin were being given orally while flucloxacillin and metronidazole could be given either intravenously or orally.

The dosages did not vary amongst patients; each patient received the same amount of a particular antibiotic and at the same frequency as the other who was also on the same antibiotic.

It was also found out that in most cases, the antibiotics were being used in combination. As many as three antibiotics could be used in combination for the same patient. Of all the available possible combination of the antibiotics, metronidazole seemed to be common in almost all the combinations. Out of the 40 patients, 26 of them, representing about 65% of the patients, were on antibiotic combination therapy. The following combinations were in use, some of which were used more commonly than others:

Table 5-Antibiotic combinations used at the KNH orthopaedic wards

Antibiotic 1	**Antibiotic 2**	**Antibiotic 3**
Flucloxacillin	Gentamicin	Metronidazole
Flucloxacillin	Cefuroxime	Metronidazole
Cefuroxime	Ceftriaxone	Metronidazole
Cefuroxime	Gentamicin	Metronidazole
Cefuroxime	Metronidazole	_
Flucloxacillin	Metronidazole	_
Flucloxacillin	Gentamicin	_
Norfloxacin	Metronidazole	_
Clindamycin	Metronidazole	_
Ceftriaxone	Metronidazole	_
Amoxicillin-clavulanic acid	Metronidazole	_

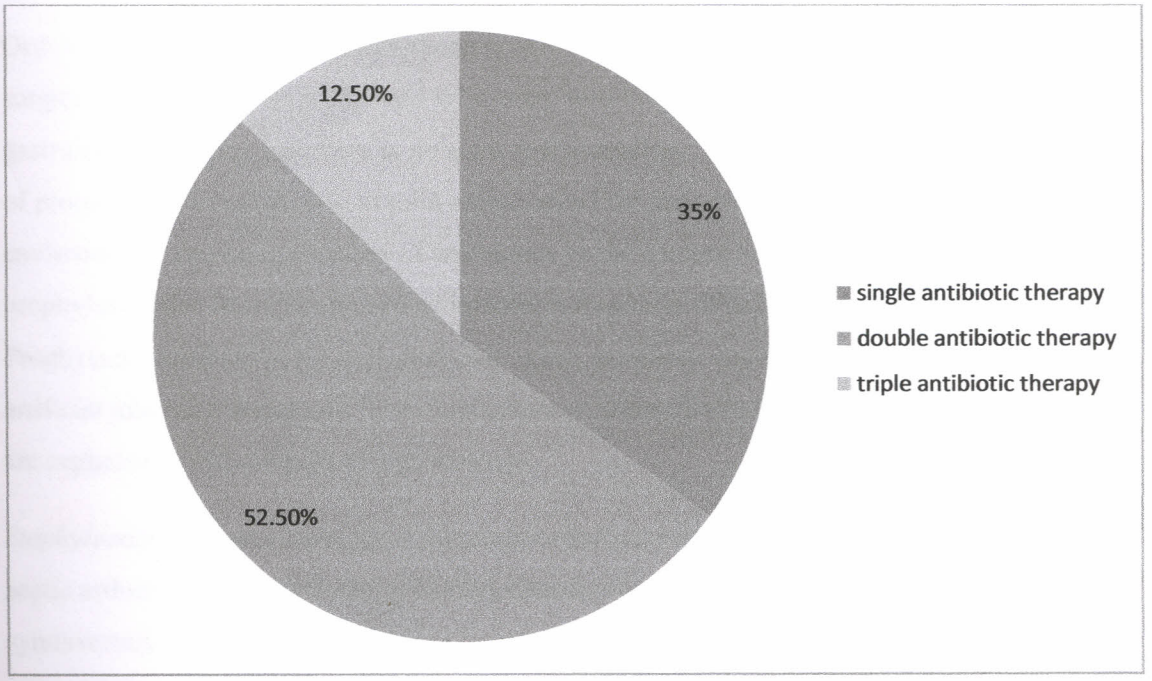
The doses of the antibiotics in the combinations were as indicated in table 4a and 4b. The most common combination was flucloxacilln + metronidzole which were used in 8 out of the 26 patients who were on antibiotic combination therapy. This represented about 31% of the patients who were on combination therapy. There were 11 possible combinations of which metronidazole appeared in 10 of them. This indicates that metronidazole is a very important antibiotic in treatment of surgical site infections at the Kenyatta National Hospital.

Since only 26 patients were on antibiotic combination therapy, the other 14 patients were on single antibiotic therapy. The antibiotics that were being given as single therapy were flucloxacillin, gentamicin, cefuroxime, norfloxacin and nitrofurantoin.

Table 6-A summary of the antibiotic combination regimens

Antibiotic regimen	Number of patients on	%
Single antibiotic therapy	14	35
Double antibiotic therapy	21	52.5
Triple antibiotic therapy	5	12.5
Total	**40**	**100.0**

Pie chart showing the number of patients on each antibiotic regimen



Generally, it was observed that most patients had been admitted mostly due to injuries from road traffic accidents. Most of them had incurred multiple injuries while others had fractured bones in their arms or legs. Only a few cases were due to other causes such as falling.

CHAPTER 7

DISCUSSION

Use of antibiotics in treatment of infections has played a very big role in reducing the morbidity and mortality rates due to infections for quite a long period of time. As already seen,there are several risk factors for patients developing surgical site infections and they include degree of bacterial contamination after surgery,virulence of the infecting organism and a range of host factors like immunusuppression, malnutrition, extremes of age and comorbid states. Moreover, there are also other possibilities of contamination from exogenous sources like the instruments and the operative team. There is therefore a great need for antimicrobial prophylaxis before surgery to reduce the chances of developing a surgical site infection after surgery. Several antimicrobial drugs are available and have been found effective in prophylaxis.

Orthopaedic surgery has generally been considered as a 'clean' surgery. This type of surgical procedure is not associated with entry into the genitourinary tract or gastrointerstinal tract and there is no acute inflammation. The infection rate for this kind of procedure is less than 5%. In joint replacement for instance, the use of clean theatre environment, high concentration of antibiotics in the cement and systemic antibiotic prophylaxis have been recognised as important measures of reducing infection. Prophylactic antibiotics are indicated only when prosthetic materials like pins, plates and artificial joints are implanted. The most common antimicrobial agents used in prophylaxis are cephazolin, vancomycin and gentamicin.

Staphylococcus aureus is the most common organism implicated in osteomyelitis and septic arthritis. Although the term MRSA denotes resistance to methicillin, it is synonymous with multidrug-resistant *S. aureus*, because many nosocomial MRSA strains are resistant to many other commonly used antibiotics. Approximately 20% of *S. aureus* isolates in Europe are reported as methicillin-resistant; the prevalence ranges from 33 to 55% in US hospitals. Since 1996, seven vancomycin-intermediate *S. aureus* (VISA) strains (i.e., vancomycin MIC = 8–16 mg/L) have been identified in Europe, Asia, and the United States, and VISA strains (vancomycin MIC $\geq$ 32 mg/L) were also reported in the United States between 2002 and 2005.

Vancomycin was the last available drug to which *S. aureus* had remained uniformly sensitive, until recent reports of low-level glycopeptide resistance and the transfer of high-

level vancomycin resistance from *Enterococcus* to *S. aureus*. A limited number of broad-spectrum antimicrobials are available to combat multidrug-resistant Gram-positive organisms.

Vancomycin

In 1997, the first clinical isolate of *S. aureus* having intermediate resistance to vancomycin was reported from Japan. Since then, many *S. aureus* isolates with reduced susceptibility to glycopeptides have been reported from various locales. The first report of vancomycin-resistant *S. aureus* in the United States occurred in 2002. The patient had been treated with multiple antibiotics, including vancomycin. MRSA bacteremia later developed, and the patient was treated with vancomycin and rifampin. The Centers for Disease Control and Prevention confirmed that the *S. aureus* isolated was resistant to oxacillin, vancomycin, and teicoplanin.

Vancomycin itself has poor bone penetration and in some animal studies has shown an inability to sterilize bone. When bone and joint pathogens are susceptible, vancomycin concentrations in serum must be monitored, and vancomycin-associated adverse events (e.g., marrow suppression, ototoxicity, nephrotoxicity, and rash) may discourage its use. Adverse effects, increasing MICs, and the increased prevalence of vancomycin-resistant enterococci (VRE), VISA, and vancomycin-resistant *S. aureus* (VRSA) are already limiting the use of vancomycin in the treatment of bone and joint infections. Vancomycin-susceptible clinical MRSA isolates demonstrate considerable heterogeneity in vitro with respect to vancomycin MIC and vancomycin killing, affecting the clinical efficacy of the drug. A significant risk for vancomycin treatment failure in MRSA bacteremia has been demonstrated, with increasing vancomycin MICs still well within the susceptible range. An increased risk of recurrence seen with vancomycin treatment of *S. aureus* osteomyelitis further diminishes the clinical utility of this agent for the treatment of bone and joint infections.

Quinupristin/dalfopristin

Quinupristin/dalfopristin (Q–D), the first parenteral streptogramin, achieves a response in approximately two-thirds of patients with MRSA infections. This combination product also has efficacy in patients with Gram-positive complicated skin and skin structure infections (cSSIs) and nosocomial pneumonia. Rifampin plus either Q–D or vancomycin

has been found significantly more effective than monotherapy in a preclinical trial of MRSA knee infection.

An evaluation of Q-D for the treatment of a variety of MRSA infections (44% bone and joint infections) in patients either intolerant of or failing prior therapy resulted in an overall success rate of 71.1% in the all-treated population ($n = 90$) and 66.7% in patients who were both clinically and bacteriologically evaluable ($n = 27$). The most common non-venous adverse events were arthralgias (10.8%), myalgias (8.6%), and nausea (8.6%). Q–D is not indicated for bone and joint infections, and little clinical data exist for the drug's use in that setting.

Linezolid

Linezolid is an oxazolidinone, a new class of antibacterial agents particularly effective against Gram-positive infections, including methicillin- and vancomycin-resistant strains. It is available in oral and intravenous (IV) formulations and has been approved by the Food and Drug Administration for the treatment of numerous infections, including cSSIs or uncomplicated SSIs, without concomitant osteomyelitis, caused by *S. aureus*. However, data on the effectiveness and tolerability of linezolid as prolonged therapy for bone and joint infections are lacking, and linezolid is not indicated for their treatment. No large, randomized trials have been published on the use of linezolid for orthopedic infections such as osteomyelitis and septic arthritis. Nevertheless, a recent retrospective study of linezolid for chronic osteomyelitis found that when used as monotherapy, or in combination with other antimicrobials and/or surgery, linezolid was associated with a cure rate of 85% at 12 weeks after the end of treatment and 78.8% at follow-up. Adverse events, including anemia and peripheral neuropathy, were reported in 51.5% of subjects, and 34.8% of subjects discontinued the study because of adverse events. Peripheral and optic neuropathy have been reported in patients treated with linezolid, primarily in patients treated for longer than the maximum recommended duration of 28 days. Early identification of linezolid-induced peripheral neuropathy is a particular concern, because this may be irreversible. Resistance to linezolid has been reported among strains of both MRSA and *Enterococcus faecium*.

Tigecycline

Tigecycline, the first glycylcycline approved in the United States, is indicated for cSSIs and complicated intra-abdominal infections (cIAIs), not for bone and joint infections. Tigecycline has activity against both methicillin-susceptible *S. aureus* (MSSA) and

MRSA. In four phase III trials in patients with cSSIs and cIAIs, tigecycline was noninferior to its comparators (vancomycin + aztreonam in two studies and imipenem/cilastatin in two studies), with clinical cure rates among clinically evaluable patients of >80% ($P < 0.001$ for noninferiority). Although there have been no human trials involving osteomyelitis, animal studies suggest tigecycline may have a role in treating bone infection. After 28 days of treatment of experimentally induced osteomyelitis, rabbits receiving tigecycline/oral rifampicin showed a 100% infection clearance. Frequently reported adverse events include nausea and vomiting, diarrhea, local IV-site reaction, infection, and fever. Resistance to tigecycline has been reported among both Gram-positive and Gram-negative strains.

Daptomycin

This novel cyclic lipopeptide is bactericidal against Gram-positive bacteria, including MRSA and VRE. Daptomycin kills Gram-positive bacteria by disruption of multiple bacterial plasma membrane functions, without penetrating the cytoplasm. Insertion of the lipophilic daptomycin tail into the bacterial cell membrane causes rapid membrane depolarization and a potassium ion efflux. Arrest of DNA, RNA, toxin production, and protein synthesis follows, resulting in bacterial cell death without lysis of the cell.

Resistance to Daptomycin

As with all antibiotics, orthopedic cases of resistance to daptomycin have been reported, including patients with vertebral or sternal osteomyelitis, diskitis, and septic arthritis, all positive for MRSA. Interestingly, patients in all four reports had received previous vancomycin treatment. A positive correlation between reduced daptomycin susceptibility and vancomycin resistance in VISA has been reported. Similar to the mechanism of vancomycin resistance, the physical barrier of a thickened cell wall may contribute to *S. aureus* resistance to daptomycin. However, a definitive mechanism of resistance to daptomycin has not yet been identified, and there are no known transferable elements conferring resistance to the drug. The isolation of glycopeptide-intermediate *S.aureus* (GISA) is rare (i.e., ≤0.3%), and cross-resistance of daptomycin with vancomycin is seen in only a fraction of GISA isolates. Of 15 GISA isolates, 86.7% were susceptible to daptomycin, as reported in the US SENTRY Antimicrobial Surveillance Program. Among almost 10,000 isolates tested, only four (0.04%) had a daptomycin MIC of 2 μg/mL (all were glycopeptide-susceptible *S.aureus*); only two (0.02%) GISA isolates were found (vancomycin MIC 4 μg/mL; daptomycin MIC 0.5–1.0 μg/mL).

To date, daptomycin has been largely used as salvage therapy following vancomycin failure. In the study by Fowler et al. most patients had received vancomycin therapy for a mean of 2 days before starting either daptomycin or standard therapy. A post hoc analysis of MRSA-infected patients from this study reported that previous vancomycin therapy did not affect the clinical outcome of daptomycin-treated patients. Nonetheless, the activity of daptomycin against MRSA may be best exploited in patients who are treated with daptomycin early; heavy exposure to vancomycin prior to treatment with daptomycin may increase the likelihood of a suboptimal response.

CONCLUSION AND RECOMMENDATIONS

Gram-positive organisms, particularly *S. aureus*, are responsible for the majority of bone and joint infections. The prevalence of increasingly resistant organisms is a major concern, both for achieving therapeutic success and because of broader cross-resistance implications. While vancomycin has long been the gold standard for the treatment of bone and joint infections, the emergence of glycopeptide tolerance and resistance to vancomycin, resulting in clinical failures, demonstrate the need for alternative treatments.

Daptomycin has exhibited activity in the treatment of Gram-positive bone and joint infections, including those caused by MRSA and VRE. It is rapidly bactericidal, with reported MIC_{90} concentrations against MRSA and coagulase-negative staphylococci at 0.5 μg/mL. Daptomycin appears effective against multidrug-resistant Gram-positive pathogens commonly found in osteomyelitis and joint infections, even when other first-line antibacterial treatments have failed. Daptomycin is well tolerated, with a low potential for adverse events, and the risk of spontaneous resistance appears low. The novel mode of action, rapid in vitro bactericidal activity against growing and stationary-phase bacteria, a once-daily dosing regimen, and no requirement for drug monitoring contribute to its potential therapeutic utility.

To reduce the rates of resistance, combination therapy is mostly preferred in many places around the globe. For instance, in the United States, Asia and many parts of Europe like Germany, Belgium, Norway and the United Kingdom use a combination of vancomycin and rifampicin or vancomycin and daptomycin. The classes of antibiotics used in a certain country can be determined by various factors among them being the resistance patterns of that region or the economic status of that region/country. In Kenya for example at the Kenyatta National Hospital, despite vancomycin being the gold standard for the treatment

of surgical site infections in orthopaedic surgery, it is not used as it quite expensive; instead other cheaper and effective antibiotics like flucloxacillin, cefuroxime, ceftriaxone and metronidazole are preferred.

From the study done at the Kenyatta National Hospital, it is evident that culture and sensitivity testing is not done, instead patients are put on empiric therapy containing a combination of antibiotics that ensure coverage of MRSA, gram positive bacteria and anaerobic bacteria. Even though *Staphylococcus aureus* is the main cause surgical site infections, it is not necessary to expose it to many other antibiotics repeatedly since this might lead to development of resistance to these antibiotics. Therefore, it is recommended that culture and sensitivity be done to establish the specific organism causing the infection and replace the empiric antibiotics with a specific antibiotic(s) therapy to which the organism is sensitive.

CHAPTER 8

WORK PLAN

Date	Activity
January 2010-February 2010	Literature review
March 2010-June 2010	Proposal writing
July 2010	Ethics Committee clearance
July 2010	Data collection
August 2010	Data analysis and report writing
October 2010	Presentation of findings

CHAPTER 9

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CHAPTER 10

APPENDIX I

INFORMED CONSENT FORM

Statement

My name is Josphat Miroyo Mugosa. I am a final year student at the University of Nairobi; admission number U29/2063/2006. I am carrying out a study titled "A review of the patterns of antibiotic use in orthopaedic surgery at the Kenyatta National Hospital" as a partial fulfillment for the award of a degree in Bachelor of Pharmacy.

The study aims at establishing the classes of antibiotics used in the treatment of surgical site infections in orthopaedic surgery. Your contribution therefore will go a long way in helping achieve the goals of the study. However, it is important that you understand the following general principles that apply to all respondents in the study:

Participation is voluntary. You may withdraw from the study or at any part of the study at any time. You are free to inquire any information that will allow you to understand fully the nature of this study.

Information relating to patients and respondents in this study will remain confidential. No names shall be used in any report resulting from this study.

Informed consent form

I..... (Patient's name) having full capacity of myself do hereby consent to my participation in the research study "Review of the patterns of antibiotic use in orthopaedic surgery at the Kenyatta National Hospital" done by Joshat Miroyo Mugosa.

Implications of my participation, nature, duration and purpose have been accepted by me. I understand that I may at any time during the course of the study revoke my consent and withdraw from the study.

Patient's signature ..... Date.....

Investigator's name.....

Investigator's signature..... Date.....

Investigator's phone number 0723013336 e-mail:miroyo07@yahoo.com

Supervisor's name.....

Supervisor's phone number 0712328999

Kenyatta National hospital/University of Nairobi-Ethics and Research Committee, tel:726300-9. Email: KNHplan@Ken.Healthnet.org

APPENDIX II

DATA COLLECTION SCHEDULE

1. Patient's profile.

(a) Name .....

(b) Age .....

(c) Sex .....

(d) Residence .....

(e) Marital status.....

(f) Occupation .....

2. Date of admission .....

3. Type of orthopaedic surgery undergone .....

4. Number and type of surgeries undergone before .....

.....

5. Any other disease suffered or suffering .....

.....

6. If yes in (5) above, was the disease treated or is it being treated?

.....

7. Any known drug allergies?

.....

8. Current treatment regimen for the surgical site infection:

Drug	Formulation	Dose	Duration
1.			
2.			
3.			
4.			
5.			

APPENDIX III

BUDGET

Item	Cost (Kshs.)
Printing and stationery costs	4,000
Computer work and software	1,000
Transport costs	1,000
Internet research	1,000
Binding of dissertation	2,500
TOTAL	**9,500**

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Ref: KNH-ERC/ UA/214

July 19, 2010

Josphat Miroyo Mugosa
U29/2063/2006
School of Pharmacy
University of Nairobi

Dear Mr. Miroyo

Research proposal: Clearance "Review of the patterns of Antibiotic use in Orthopaedic surgery at the KNH" (UP182/06/2010)

Your above revised proposal refers.

This is to inform you that permission has been granted by the KNH/UON-Ethics & Research Committee to carry out research on "Review of the patterns of Antibiotic use in Orthopaedic surgery at the KNH".

By a copy of this letter, I am requesting the relevant persons to accord you the professional support and other materials that may be useful to your research.

Yours faithfully,

PROF A N GUANTAI
SECRETARY, KNH/UON-ERC

c.c. Prof. K. M. Bhatt, Chairperson, KNH/UON-ERC
The Deputy Director CS, KNH
The Dean, School of Pharmacy, UON
The HOD, Records, KNH
Supervisor: Dr. J. Ombega, Dept. of Pharmaceutics & Pharmacy Practice, UON