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DEPARTMENT OF CLINICAL AND SOCIAL PHARMACY

MANAGEMENT OF INFECTIONS IN SICKLE CELL PATIENTS UNDER 14 YEARS AT KOMFO ANOKYE TEACHING HOSPITAL

BY

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(PG 785981)

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DECLARATION

Candidate's Declaration

I hereby declare that this thesis is the result of my own research and that, to the best of my knowledge it contains no material previously presented for another degree in this University or elsewhere, except where due acknowledgement has been made in the text.

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DEDICATION

This work is dedicated to my parents Professor and Mrs. J.K. Kwakye for their encouragement and immense support as I pursued this programme.

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ABSTRACT

Background: Sickle cell disease affects millions of people across the globe. Microbial infections are common causes of sickle cell crises and mortality. Penicillin Prophylaxis has been used to prevent infections in sickle cell disease; however there have been reports of increased prevalence of resistant strains of streptococcus pneumonia against penicillins, which is one of the main causative organisms for infections in sickle disease patients. The aim of this study was to assess the pattern of microbial infections and antibiotic usage in sickle cell patients, and its impact on patient outcomes.

Methodology: This was a retrospective study undertaken at KATH in sickle cell disease patients under 14 years. Past records of the patients (N=253) who had been on admission for an infection between the periods of December 2011 to December 2014 were reviewed. Data was extracted on the diagnosis, drug history, laboratory results, drug administration and discharge summary which had been recorded in the patient folders. Data on therapy obtained was assessed for its appropriateness using recommendations in the Standard Treatment Guidelines (2010) and other international guidelines like the World Health Organization guidelines for the management of sickle cell disease. These guidelines been adapted by the clinicians at the Sickle Cell Unit, at KATH.

Results: More than 69% (n=157) of infection diagnosis in the sickle cell patients was informed by results of haematology investigations, 6.19% (n=14) were diagnosed based on microbiology data and 24.34% (n=55) were both haematology and microbiology. As a complication of sickle cell disease a quarter of the study population (n=62) were admitted with bronchopneumonia infection, 16.60% (n=42) had sepsis, 16.21 %(n=41) had acute chest syndrome and 12.25 %(n=31) had

osteomyelitis. Cefuroxime was the most prescribed antibiotic 71.15 %(n=180) followed by clindamycin 8.3% (n=20) and ciprofloxacin 6.3 %(n=16). Over 90% of the antibiotics were administered through the intravenous route (n=249). Also more than 80% of the patients were on Penicillin Prophylaxis (n=207). Few (n=2) were on other antibiotics for prophylaxis such as erythromycin. Based on the standard guidelines, All the patients (n=253) had the dosing frequency of antibiotic therapy correct; 94.07 %(n=238) were given the appropriate antibiotic, 90.91% (n=230) had the duration of therapy correct and 87.35% (n=221) had the dose also appropriate. Eighty nine percent of the patients had their symptoms resolved on antibiotic therapy before discharge, whilst 11% still had symptoms. Patient on Penicillin Prophylaxis presented with the same infectious diseases as those not on Penicillin Prophylaxis.

Conclusion: Bronchopneumonia, Sepsis, Acute Chest Syndrome and Osteomyelitis were the most common infections reported in the sickle cell disease patients. Cefuroxime, Clindamycin and Ciprofloxacin were the most frequently used antibiotics. Most of the investigations that guided infection diagnosis were haematological rather than microbiology (culture and sensitivity testing). It is recommended that as much as possible, antibiotics usage in sickle cell disease patients must be guided by culture and sensitivity testing for more definitive therapy. Such a practice may minimise the risk and the occurrence of antimicrobial resistance among pathogens responsible for infections in sickle cell disease patients.

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LIST OF ABBREVIATIONS

CD4	Cluster of Differentiation 4
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CHRPE	Committee on Human Research, Publication and Ethics
Hb	Hemoglobin
HbA	Hemoglobin A
HbC	Hemoglobin C
HbF	Fetal Hemoglobin
HbS	Hemoglobin S
IgM	Immunoglobulin M
IL-2	Interleukin 2
IQ	Intelligent Quotient
IQR	Inter quartile range
KATH	Komfo Anokye Teaching Hospital
MSH	Multicenter study of Hydoxyurea in patients with sickle cell disease
NHLB	National Heart, Lung and Blood Institute
NSAIDs	Non-Steroidal Anti-inflammatory drugs
Pen V	Phenoxymethyl Penicillin
PROPS	Penicillin Prophylaxis in sickle cell disease
SCA	Sickle cell anaemia
Th1	T-helper cells
WHO	World Health Organization

CHAPTER ONE

1.0 BACKGROUND

Sickle cell disease (SCD) affects millions of people around the world but there is no available cure for the disease (World Health organization (WHO), 2006). In Africa there are higher rates of childhood mortality, with 50% to 90% specific to homozygous SS (Serjeant, 2005). Scientists are constantly researching to improve on the treatment and care of sickle cell patients in order to prolong their lives (Odame et al, 2010).

SCD is one of the first diagnosed diseases linked to hemoglobin protein. In medical history, 1910, is regarded as the date for discovery for sickle cell disease. It is however known to have been present for at least more than five thousand years in Africa and has been known in different tribal languages as a devastating illness (Winter, 2010).

SCD is a collection of genetic conditions whose pathology comes from inheriting a sickle cell gene which is either homozygote or double heterozygote with another relating gene (Serjeant, 2013). In sickle cell disease there is a mutation of the beta globin gene of hemoglobin, which then causes a replacement of the glutamic amino acid for valine at position 6 of the beta chain, thus producing a defective haemoglobin, called haemoglobin S (Hb S), in place of the normal haemoglobin A (Hb A)(Marrota et al 1977; Rees et al,2010).

Again SCD is an inherited disease of the red blood cell. Red blood cell carry oxygen through a protein called hemoglobin. Red blood cells which contain normal hemoglobin are smooth, flexible and move easily through the small blood vessels but in sickle cell disease the red blood cell contains abnormal hemoglobin called sickle

cell hemoglobin. The shape of the red blood cells of these patients become stiff, sticky, curved shape like sickles. The sickle cell shape of the red blood cell gives sickle cell disease its name (Inati-Khoriaty, 2008).

This pathophysiological change leads to clinical manifestations of sickle cell disease that includes severe vaso-occlusive events. The severity of this condition varies from patient to patient. This severe obstruction can prevent organs and tissues from getting access to oxygen rich blood and this can eventually lead to organ damage mostly in the lungs, kidneys, spleen and brain and also recurrent painful episodes (Frewin et al, 1997).

Most of the patients have reduced life expectancy due to complications like pain, pulmonary hypertension, renal failure, acute chest syndrome and stroke, infections and unknown etiologies (Platt et al, 1994).Common reasons for death in children with SCD are infection, stroke and acute chest syndrome (Manci et al, 2003).

When early diagnosis and treatment is delayed most of these children die during the first few years of life, with mortality reaching up to 92% (Grosse et al, 2011).

Infections are common precipitants of pain and mortality among SCD patients. Children with sickle cell disease are at risk of bacteremia which can lead to sepsis and even death (William et al, 2009). Sickle cell patients with homozygous sickle cell are susceptible to increase risk of infection with Streptococcus pneumonia, Haemophilus influenza, Salmonella species, Escherichia coli and Klebsiella Species (Magnus et al, 1999; Powars et al, 2005; Ramakrishnan et al, 2010).

One contributing factor to infections is the early loss of splenic function which occurs in children under five years (Cober and Phelps, 2010; Pearson et al, 1979; Onwubalili 1982; Falletta et al, 1995). This hyposplenia increases patient susceptibility to

encapsulated microorganisms such as Streptococcus pneumonia (Bonshack et al,1986; Battersby et al, 2010), and this bacterial infection is a major cause of death in pediatric patient (Schnog, 2004; Pearson, 1977).

In children one of the routine management is prophylaxis against pneumococcal infections. Pneumococcal vaccination and penicillin prophylaxis are given to reduce the risk of infection in sickle cell patients (NHLB, 2002).

1.1 RATIONAL OF THE STUDY

Children with SCD are prone to infections such as *Streptococcus pneumonia*, which is especially common in children under five years due to the lacking or non-functional spleen and reduced immune response (Cober and Phelps, 2010). Penicillin prophylaxis has been used to prevent infections against the various serotypes of Streptococcus pneumonia, in sickle cell disease patients (Fixler and Styles, 2002). Studies have been done to prove the efficacy of Penicillin as prophylactic agent in the prevention of Streptococcus pneumonia (Gaston et al, 1986).

There is increased prevalence of resistant strains of *Streptococcus pneumonia* throughout the world (Kaplan et al, 1998). In Ghana antimicrobial therapies constitute a major form of treatment, with 41.4% of patients at the (out- patient) department receiving one or more antibiotics (Gyansa- Lutterodt, 2013). At Komfo Anokye Teaching Hospital a study done between January 1994 and June 1996, it was revealed that 30.6% of *Streptococcus pneumonia* isolates were resistant to Penicillin (Ohene Adjei, 1997). The purpose of the study is to assess antibiotic profile usage for sickle cell disease patients and its outcome.

1.2 AIM

To review antibiotics used for the management of infections in sickle cell disease patients under 14years at Komfo Anokye Teaching Hospital.

1.3 SPECIFIC OBJECTIVES

1. To identify common infections that complicates the health state of SCD patients.
2. To identify the types of antibiotics used in the management of infections in SCD patients.
3. To determine the proportion of SCD patients on antibiotic prophylaxis with Phenoxymethyl Penicillin and others.
4. To assess the appropriateness of antibiotic used for the management of SCD
5. To assess patient outcomes following therapy of the infections.

CHAPTER 2

2.0 LITERATURE REVIEW

2.1 PATHOLOGY OF SICKLE CELL DISEASE

A term, given to s haemoglobin which is structurally defective, leading to the formation of sickle shaped red blood cell, with a wide range of clinical manifestations is known as sickle cell disease (Booth et al, 2010).

In persons without sickle cell gene (HbA), two chains of alpha- globin and two of Beta- globin form a tetramer, within the RBC (Madigan et al, 2006), but in sickle cell disease (HbS) there is a mutation on the 6^{th} codon of the beta globin gene which is found on the short arm of Chromosome 11 (Ndefo et al, 2008), thus producing an abnormal beta globin chain. Under low oxygen concentration, it polymerizes into long fibers thus leading to an abnormally sickle shape red blood cells. This sickle shape red blood cells become sticky adhering to the endothelium (Hebbel, 2008; Hebbel, 1997). It then cluster together, blocking micro vessels and also damaging macro vessels, which eventually leads to occlusion of the blood vessels (Bunn, 1997). In sickle cell disease, the pathophysiological sequence that leads to complications comes as a result from a combination of vaso-occlusion and haemolysis (Neville, 2011). In Haemolysis there is a continuous hemoglobin depolymerization or polymerization as the sickle shaped red blood cells pick up and release oxygen into the blood circulation. Due to this process the red blood cells become abnormal and have a reduced life span (Neville, 2011; Solanki et al, 1988). In addition to haemolysis, there are episodes of vaso-occlusion causing tissue ischemia, which can result in chronic and acute multi organ damage (lane, 1996). Vaso- occlusion occurs due to the adhesive interaction of leukocytes and sickle cell RBCs to the endothelium (Frenette, 2002). This blockade leads to acute and chronic tissue ischemia and infarction, with a multisystem effect,

which normally occurs in the bone, brain, lung, kidney and spleen, resulting in acute painful episodes and long term complication (Booth et al, 2010). Bone is the usual site of vaso-occlusion pain. This painful event can last two or more hours (Behrens and Cymet, 2000). Cold weather, dehydration, hypoxia, emotional stress and infections are common precipitants of vaso-occlusive pain crises (Behrens and Cymet, 2000). These painful episodes are unpredictable and in about 80% of these episodes there are no known potential precipitating factors (Smith and Scherer, 2010).

The most generally considered severe form of sickle cell disease is Homozygous SS. In this condition heterozygotes (Hbs) is joined with a different mutation in the second B globin gene such as HbC , O, D or B –Thalassemia ,where β -globin synthesis is decreased which can also affect the phenotype in variable ways. The carrier state the HbAs does not cause significant disease, though in extreme conditions sickling may occur (Okpala, 2004).

2.2 CAUSES OF INFECTIONS IN SICKLE CELL DISEASE PATIENTS

Sickle cell patients have a higher than expected incidence of bacterial infections. It is one of the most common causes of hospitalization and early mortality (Landsmen et al, 1982).

This condition predisposes children to infections for varied reasons; this includes raised bone marrow turnover, reduced perfusion and functional asplenia which lead to reduced opsonisation of polysaccharide encapsulated organisms. Bacteria and viruses that normally cause severe infections in children with sickle cell disease are *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, *Salmonella spp*., *Escherichia coli, Staphylococcus aureus*, *Mycoplasma pneumoniae, Chlamydia pneumoniae, parvovirus B19* and *hepatitis A, B* and *C viruses*(Wong, 2011 ; Barrett-Connor,1971 ; Powars et al,1983 ; Wright et al,1997). Younger children are more

prone to infection caused by encapsulated organisms such as *Salmonella species*, *Haemophilus influenza* and *Streptococcus pneumonia*. The older children are mostly infected with gram negative organisms such as *Escherichia coli.* (Zarowsky, 1986)

The spleen plays a major role in the increased proneness to bacterial infections in sickle cell disease. The spleen functions by producing antibodies, discarding old and damaged cells, blood borne microorganisms and also act as a phagocytic filter (Booth et al, 2010).

Blood which comes from splenic artery first moves across the white pulp, which contains B and T lymphocytes in the periarteriolar lymphatic sheaths and the follicles. When these cells are activated by filtered antigenic materials, it helps in the initiation and increase of specific acquired immune response. When blood enters the splenic cords of the red pulp, cells flow over a fine reticular meshwork and then move through fenestrated epithelium which then enters the venous sinuses. This then causes a sluggish flow which helps splenic macrophage to discard damaged red blood cells and bacteria and present antigen to lymphocytes (Bonshack et al, 1986).

Macrophages recognize some bacteria but many have to first undergo opsonisation. Opsonised bacteria are discarded effectively by macrophages in the liver or spleen, but certain bacteria are poorly opsonised and these are cleared efficiently by the spleen. These pathogens include encapsulated bacteria such as *Steptococcus pneumonia* and *Haemophilus influenza (*Bohnshack et al, 1986).

Individuals with sickle cell disease normally suffer from hypo or asplenisim. In this condition the spleen does not function well, there is a slow circulation through the spleen, high rates of oxygen extraction and deoxygenation of Hbs caused by local acidosis. This promotes sickling leading to congestion and engorgement of the

sinusoids with sickled shape cells (William et al, 2007). Again macrophages which engulf abnormally shaped cells become blocked and thus will then impair their phagocytosis of other particles. The hyposplenic state is initially reversible but upon continuous occurrences of sickling and ischemic damage, it causes sclerosis of the arterioles which will lead to multiple infarcts of this spleen tissue, hence it will not be able to regenerate, rendering the spleen scarred and atrophied. The organ will shrink to a small remnant rendering the individual asplenic (Lucas, 2004). In sickle cell disease this sequence starts from 6months to 3years (William et al, 2007).

In individuals with impaired splenic function, there is lack of IgM memory B cells; hence it cannot fight against the encapsulated organisms. The main pathogen of concern is *S.* pneumonia, and without preventive measures, children with sickle cell disease are 30 -600 times at risk of developing pneumococcal disease including pneumonia, meningitis and septicaemia (Halasa et al, 2007).

Vaso-occlusion within the spleen is one of the most detrimental effects of SCA; this can result in functional asplenia in about 94% of sickle cell anaemia patients by the age of five years. This effect impairs the immune response of children with sickle cell disease (Pai and Nahat , 2000).

Deficiency in micronutrients such as zinc is a contributory factor in increasing susceptibility to infection in sickle cell patients. Zinc when deficient, is normally linked with lymphopenia, this is due to a possible activation of the hypo-pituitary adrenocortical axis, which causes chronic glucocorticoid production, this then stimulates apoptosis of the B and T cells in the bone marrow and the thymus. (Fraker et al, 2000). Again this causes a reduction in thymulin activity, natural killer cell lytic activity, interlukin (IL) - 2, CD4 and CD8 ratio and impairs Th1 function (Prasad et al, 1999).

In a study done by Prasad AS et al on zinc supplementation in 32 sickle cell patients, it was found out that additional zinc supplementation resulted in the raising of lymphocyte and granulocyte zinc, increased interlukin -2production, reduced the incidence of positive bacteriological infections, reduced number of hospitalizations and vaso-occlusive pain crises (Prasad et al, 1999).

Apart from impaired splenic functions and deficiency in micronutrient such as zinc, other factors which may predispose sickle cell disease patients to infections include: defective neutrophil kinetics, increased concentration of free serum iron with reduced serum transferrin levels, a deficiency of serum opsonin activity, overloading of reticulo-endothelial system and localized tissue hypoxia, as well as socio-economic factors related to the environment and nutrition (Davies and Brozovic, 1989).

2.3 MORBIDITY AND MORTALITY IN SICKLE CELL DISEASE

According to World Health Organization, about 5% of the world's population carries the genes with hemoglobin disorders and each year 30000 infants are born with this menace, this includes 200,000 cases of sickle cell anemia in Africa (WHO, 2006).

SCD is prevalent among people from the Sub Saharan Africa, South America, the Caribbean, Central America, Saudi Arabia, India, Turkey, Greece and Italy (National heart, lung and blood institute (NHLB), 2009). In Africa Countries such as Cameroon, Republic of Congo, Gabon and Nigeria the prevalence is between 20% and 30%, while in some parts of Uganda, the prevalence to sickle cell disease is as high as 45% (WHO, 2012). It has been found out that the geographic distribution of sickle cell trait is like that of malaria (Piel FB et al, 2010). Sickle cell trait has a partial protective effect against malaria. This partial protective effect comes about due to the enhanced immunity accelerated by the acquisition of antibodies to alter host antigens expressed on the parasite- infected red cell surface (Hebbel, 2003).

In Ghana, about 2% of newborns have sickle cell disease. In effect 16,000 annual births of children with SCD in Ghana, with about 20 -25% of the population at the southern part of the country has the sickle cell trait and about 10% having hemoglobin C (HbC) at the northern part of the country (Konotey, 1991). Early screening of newborn with SCD with constant follow up and support, prolong and improve the quality of life of the patient (Ohene-Frempong et al, 2008).

2.4 MANAGEMENT OF SICKLE CELL DISEASE PATIENTS

Generally SCD is managed both with preventive (avoiding crises) and symptomatic therapies (Shapiro et al, 1995).

Pharmacotherapies that are utilized in the management of sickle cell disease include: Disease modifying agent (Hydroxyurea), which has been shown to reduce the occurrence of painful crises, acute chest syndrome and overall, reduce mortality in adult patients (Steinberg et al, 2003). Supporting agents are analgesics (Paracetamol, ibuprofen, Codeine, morphine), antibiotics (Phenoxymethyl penicillin), pertinent vaccines (Pneumococcal vaccine) and systemic treatments (red blood transfusion, 5% dextrose, 0.45% sodium chloride) (WHO, 2011).

2.4.1 PREVENTION OF INFECTION IN SICKLE CELL DISEASE PATIENTS

2.4.1.1 ANTIBIOTIC PROPHYLAXIS

In the prevention of infections, simple general measures are vital in decreasing its risk. Much attention is given to hygiene, especially hand washing which is very important. To prevent infections such as salmonella, it is recommended that patients cook food thoroughly, keep items refrigerated and avoid contamination (Atkins et al, 1997). Again early identification of infections and initial start of treatment decrease complications (Dick, 2010).

Over the years infections have been the prominent cause of death in children with SCD. Strategies which have been implemented includes early immunization against *S. Pnuemonia* and daily prophylactic penicillin therapy (Amman et al, 1977).

Penicillin prophylaxis and vaccination has reduced the occurrence of infection-related morbidity and mortality considerably in children with Sickle cell anaemia (Wong, 2001). In the Prophylactic Penicillin study (PROPS study), which assessed the potency of penicillin prophylaxis in the prevention of severe bacterial infection in children with sickle cell anaemia, the conclusion drawn was that penicillin prophylaxis drastically reduce the risk of pneumococcal infection in children with sickle cell anemia(Gaston et al, 1986). In the PROPS study, patients who are younger than 5 years of age penicillin V potassium 125 mg twice daily was recommended, whilst patients above the age of 5 years 250mg of Penicillin V was recommended (Pickering et al, 2009). Children allergic to penicillin, 125mg twice daily erythromycin is recommended for children younger than 5 years and 250mg twice daily given to children 5 years and above (Knight and Serjent, 2001). Long term use of penicillin prophylaxis has its own problems. Prophylaxis or intermittent antibiotics use can lead to the development of resistance, so the recommendation for its continuation must represent a balance between the danger of resistant pose to the population and the risk to the individual with the pneumococcal infection (Hirst et al, 2002)

Compliance is very important when it comes to Penicillin prophylaxis in children with SCD (Berkovitch et al, 1998), since fast colonization rate and infection can occur after even one missed dose (Anglin et al, 1984)

2.4.1.2 VACCINATION

Another important medical strategy in the prevention of infection is vaccination. In SCD the risk of bacteraemia is higher with *Streptococcus pneumonia.* It is advised that children with SCD receive pneumococcal vaccine which contains 13-valent pneumococcal conjugate vaccine and pneumococcal polysaccharide. In developed countries the rate of infection from this organism has reduced significantly. (Halas et al, 2007). The use of 7-valent pneumococcal conjugate vaccine for the past years has been attributed to the significant reduction in mortality in children less than four years in developed countries like USA. Important studies suggest that this vaccine cover 77% of isolates with resistance to penicillin, which may help reduction in the frequency of resistant strains and avert prophylaxis failure (Adamkiewicz et al, 2003).

2.4.2 FOOD SUPPLEMENT

Malnutrition is a risk factor that contributes to infections in sickle cell disease patients. In Ghana the rate of malnutrition was 61.3% among SCD subjects and 28.6% among controls when a study was done. (Osei-Yeboah et al, 2010).

In developed countries foods are mostly fortified with folate and folate deficiency is rare. However in developing countries, where there are cases of malnutrition, folate is considered in sickle cell disease (Neville et al, 2011). In a study done at Komfo Anokye Teaching Hospital on the drug regimen mostly prescribed for SCD, at the end of the twelve month study folic acid was the most prescribed drug regimen (Nsiah et al, 2014).

2.4.3 THERAPIES FOR THE MANAGEMENT OF SICKLE CELL DISEASE

2.4.3.1 DISEASE MODIFIERS

Hydroxyurea is a minute molecule that prevents the synthesis of DNA by blocking ribonucleotide reductase, hence arresting cells in the S-phase (Davies et al, 2003). The

role of hydroxyurea in the clinical management of severely affected adults with genotype HbSS was established by a randomized controlled trial, The multi center study of hydroxyurea in sickle cell anaemia(MSH) in 1995 (Charache et al, 1995). In this study 299 adults of SS were enrolled from 21 centers in North America there was a history of three or more painful crises in the 12months prior to enrolment. At the end of the study it was suggested that there was enhancement in the quality of life of patients administered hydroxyurea over the placebo group (Charache et al, 1995). In a study reported by the Belgian study, children who were administered hydoxyurea had a mean hospital stay of 5.3 days as compared to the placebo who had 15.2 days (Ferster et al, 1996). Belgian Sickle cell disease Hydroxyurea treatment registry (Ferster et al, 2001) along with 12 other pediatric Phases I/II studies in the literature all backed the findings of the MSH studies (Montalembert et al, 1997). Two other studies have been done in younger children. In the first study, eight children aged 2-5 years were followed for 1-5 years and there was a decrease in hospitalization. . One of the children aged 3.5years had an infarctive stroke 56 weeks of therapy (Hoppe et al, 2000). In the second study, 28 infants with a median age of 15months were recruited. In this study although the hematologic responses to hydroxyurea was similar to the response observed in older patients, the hydroxyurea appeared to block the decline of HbF in the infants; they experienced a number of clinical adverse events including death. The adverse clinical effects that were experienced include three patients who had a total of seven occurrences of acute chest syndrome, two patients suffered priapism, and three suffered dactylitis, two patients developing splenic sequestration, one with transient ischemic attack and a second with cerebrovascular accident (Wang et al, 2001). Another issue of concern was the effect of Hydroxyurea on the developing brain in the first two years of life. A French study of 34 children treated

with hydroxyurea compared with 30 not given hydroxyurea found out that patients of hydroxyurea did well than those not treated with hydroxyurea on Full sacale IQ (Bernaudin et al, 1999). An adverse effect of hydroxyurea includes myelosuppression hence all patients should be monitored carefully (Vichinsky et al, 1994).

2.4.3.2 ANALGESICS

One of the most common problems faced by patients with SCD is vaso-occlussive pain (Tetrault et al, 1974 ; Brandow et al,2010).The pain which is often severe, intermittent and changeable can start as early as 6-9months of age, and lead on throughout adulthood(Serjeant,1985). The severity and pain frequency varies among and within individuals (Vichinsky et al, 1982). In mild painful crises patients are treated generally with NSAIDs such as ibuprofen or other non-opoid analgesics like paracetamol. However in SCD there is a compromise of renal blood flow and the possibility of acute renal failure, hence NSAIDs are employed based on the condition of the patient and should not be used in those with renal involvement (Neville et al, 2011). The general trend is to give opiods orally for mild pain and intravenously or subcutaneously for severe pain (Ballas, 2007).

2.4.3.3 SYSTEMIC AGENTS

Intravenous Fluids

Hydration in addition to analgesics may be used in the management of pain. Raised plasma osmolarity from a decreased plasma volume worsens vaso-occlusive crises leading to intracellular dehydration, haemoglobin polymerization and further sickling. Fluids (Glucose 5% in Sodium Chloride 0.9% in adults and Glucose 4.3% in Sodium Chloride in children) are given in sufficient quantity to correct existing deficits and also replace ongoing losses in order to maintain euvolumic state. Oral hydration is

normally indicated in patients with mild vaso-occlusive pains whilst parenteral hydration is used in patients with severe pain (Okpala, 1998; Yale et al, 2000).

Red Blood Cell Transfusion

B Blood transfusion is used for various indications in patients with SCD this includes acute chest syndrome, refractory pain, stroke etc. Red blood transfusion is utilized to suppress haemoglobin S. In the prevention of overt stroke, red blood cell transfusion is the basis for its prevention. The first three years after an overt stoke, the main aim of red blood cell transfusion is to reduce Haemoglobin S levels to 30% or less, After 3 years the main goal is to retain hemoglobin S level to 50% or less (Adams et al, 1998).

However chronic blood transfusion can cause iron overload resulting in premature death (Ballas, 2001; Shander, 2009; Harmatz et al, 2000 ; Raghupathy et al,2010; Oliveri, 2001) due to iron deposits in the heart and liver, and results in end organ damage and death from heart disease or liver cirrhosis (Brown et al, 2009). Over the years deferoxamine has been the mainstay drug for the treatment of iron overload. It normally requires a parenteral administration, and it is usually administered subcutaneously over several hours 5-7 days a week. In recent times an effective oral iron chelates such as deferasirox has been approved for use in European Medicine Agency and United States (Kwiatkowski, 2010).

CHAPTER THREE

3.0 METHODOLOGY

3.1 STUDY DESIGN

This research employed a retrospective approach for data. In medical terms, retrospective study is simply defined as a look back at patients past medical records (D. R. Hess, 2004). This study focused on five key areas. These are:

1. The common infections which complicate the health state of sickle cell disease patients
2. The antibiotics that are commonly used in the management of these patients.
3. The proportion of sickle cell disease patients on phenoxymethyl penicillin (Pen V) or any antibiotic.
4. The appropriateness of the antibiotics given.
5. The outcomes following antibiotic therapy.

3.2 STUDY SETTINGS

Komfo Anokye Teaching Hospital (KATH) was selected as the study site for the project. KATH is the second largest hospital in Ghana with about a 1000 bed capacity .It is situated in the second largest city in Ghana, Kumasi. Its strategic location provides easy access to major towns in Ashanti Regions and several other towns in regions nearby. KATH receives referral from the the Eastern, Volta, Brong Ahafo, Northern, Upper West and Upper East Regions. This study was carried out at the sickle cell unit which is under the Child Health Directorate.

The Child Health Directorate provides out-patient and in-patient services, emergency services and training of undergraduate and post –graduate medical and nursing students. Under the Child Health Directorate there are six main wards; this includes

Paediatric Intensive Care Unit (PICU), Pediatric Emergency Unit (PEU), Mother and Baby Unit(MBU) (MBU main and Septic), B4, B5 and C5. Patients are taking to the various wards depending on the condition they present. The PEU and PICU are the wards where patients are stabilized before Trans out to the other wards. Sickle cell patients after being stabilized are sent to ward B5 where they are further managed and after that enrolled at the Sickle cell clinic if not already going for review. The sickle cell clinic has their clinic day mainly on Monday but other days have recently been included in it. KATH was chosen for the study due to the fact that it has a well-established sickle cell clinic, where records of patients are well kept.

3.3 DATA COLLECTION

Data collection was guided by the objectives of this study. For the assessment of common infections that complicate the health state of sickle cell patients, data was extracted from the patients' folders of all those who were *diagnosed* of having an infection between December 2011 to December 2014 included in the study. Data was then entered into software (Epi-Info 7) and analysed. For the common antibiotics that were used in the management of sickle cell disease patients, data was extracted from the *drug administration chart*. For the proportion of sickle cell patients on Phenoxymethyl Penicillin (Pen V) or any other antibiotic for prophylaxis, data was also extracted from the *drug history* of the patient. Data obtained was entered into the statistical software and analysed. In assessing the appropriateness of antibiotic given for the management of infection, data was extracted from the *drug administration chart*. Data included the start and end date of the antibiotic therapy, the dose and the dosing frequency of each antibiotic being administered. Data obtained was stored in the Epi-Info software and analysed. The findings were then compared with the protocol used by the sickle cell unit, standard treatment guideline, 2010, and the

British National Formulary for children (July 2014 to July2015). For the assessment of patient outcome following therapy, the endpoint was the resolution of symptoms of the patient and general well being. This data was extracted from the clinicians discharge summary and that helped in the analysis and presentation of the study findings.

Target Population

The population that was targeted was sickle cell patients under the age of 14years, who had been admitted and treated for infection between the periods of December 2011 to December 2014 at Komfo Anokye Teaching Hospital. In all a total of Two hundred and fifty three (253) past patient records were used for this study.

Inclusion Criteria

Patients' records that were included in this study were:

- Children diagnosed as having sickle cell disease
- Children under the age of 14years
- Children on admission for one or more infections
- Children whose medical records were intact i.e. no gaps in the record keeping

Exclusion Criteria

Patients' records that were excluded in this study were:

- Children diagnosed as having SCD but were on admission for other disease condition apart from infection
- Children with SCD diagnosed of having infection but their medical records were not intact i.e. some parts of their records were not available.
- Sickle cell patients above the age of 14 years
- Sickle cell patients at the out-patient department

Sampling Procedure

According the World health organization (2012), the prevalence rate of SCD is 20% in Ghana. Using the World Health Calculation of sample size below, where *n* stands for the required sample size, *t* stands for the confidence level which is a standard value of 1.96, *p* stands for the prevalence of the disease, in this case it is 20%(0.2), and *m* stands for the margin of error which is a standard value of 5%(0.05).

Using the WHO calculation for sample size

$$n = \frac{t^2 \times p(1-p)}{m^2}$$

n= the required sample size

t= confidence level of 1.96 (Standard value)

p= prevalence

m= margin of error of 5% (Standard value)

$$n = \frac{1.96^2 \times 0.2(1-0.2)}{0.05^2}$$

n= 245.8624

n=246 persons

In all 246 persons was the estimated sample size for this study

Information was retrieved from existing data in patient folders using a data collection form. A total of 253 past records of patients were used in this study. Patients who fell within the inclusion criteria were used in this study. The collection of data was from 16th March, 2015 to 30th April 2015.

3.4 DATA ANALYSIS

The data collected were coded and then entered into the Epi- Info 7 data base for analysis. The demographics (Gender, Age, and weight) the common infections, the

common antibiotics, the proportion of sickle cell patients on Penicillin V or any other antibiotic patients were presented in a tabular form. The appropriate use of antibiotic was determined when the dose, dosing frequency, the duration of therapy and the choice were in line with Standard Treatment Guidelines of Ghana and other international standards adapted by the sickle cell unit. Each of the indicators of the appropriate use of antibiotic, the outcome, and the proportion of patients on penicillin prophylaxis was assigned a binary code of yes or no i.e. correct or wrong in relation to the patient. The results of the data analysis were presented in frequencies and percentages and in descriptive statistics.

3.5 ETHICAL CONSIDERATION

Ethical approval (CHRPE/AP/058/15) was given by the Committee on Human Research Publication and Ethics (CHRPE), KNUST. This was after the Head of the Sickle Cell Unit, KATH was contacted for consent to carry on the study after the rational of the study and the objectives have been explained to him. Anonymity and confidentiality of the patient data record was assured throughout the study and after.

CHAPTER FOUR

4.0 RESULTS

This chapter presents the results of the data collected from two hundred and fifty-three (253) sickle cell patients on the management of infection in SCD.

4.1 DEMOGRAPHIC CHARACTERISTICS AND LABORATORY INVESTIGATIONS OF SICKLE CELL PATIENTS

About 54% of the study participants (n=136) were males and 46% females. The median age had Interquartile range (IQR) of participants being 5(2-8) years and the weight of the patients were 16(11.5-21.2) Kg. Eighty-nine percent (n=226) of the laboratory investigation was done to support infectious disease diagnosis, with haematological investigations being the highest (69.47%; n=157). **Table 1**

Table 1: Demographics Characteristics and Laboratory Investigations of Patients

Factor, N=253	**Number n (%)**
Average Age(range)	*5(2-8)years*
Average Weight(range)	*16(11.5-21.2) Kg*
Gender	
Male	136(53.75)
Female	117(46.25)
Laboratory investigation for infection diagnosis, (N=253)	
Yes	226(89.33)
No	27(10.67)
Type of laboratory test,(N=226)	
Hematology	157(69.47)
Microbiology(Blood, Urine, CSF)	14(6.19)
Hematology/Microbiology	55(24.34)
Temperature before admission(^{o}C) (N=253)	
< 37.5	84(33.20)
≥ 37.5	169(66.80)
Temperature on discharge(^{o}C)	
< 37.5	244(96.44)
≥ 37.5	9(3.56)

4.2 COMMON INFECTIONS ASSOCIATED WITH SICKLE CELL DISEASE.

About 25% of the study participants (n=62) had Bronchopneumonia, 16.60% (n=42) had Sepsis, 16.21% (n=41) had Acute Chest Syndrome and 12.25% (n=31) had Osteomyelitis (**Fig. 1**).

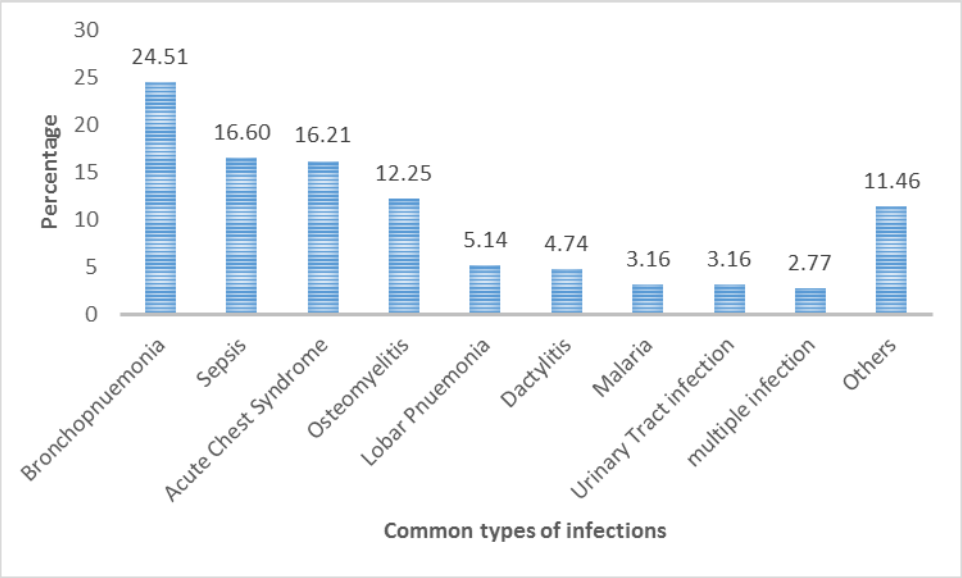

Figure 1: Common Infections of Sickle Cell Patients

Others included Cellulitis, Chronic Tonsillitis, Meningitis, Otitis Media, Scabies, and Septic Arthritis.

Multiple infections included Acute Chest Syndrome / Dactylitis, Bronchopneumonia / Dactylitis, Bronchopneumonia/Osteomyelitis, Urinary tract infection / Sepsis

4.3 ANTIBIOTICS USED IN THE MANAGEMENT OF INFECTIONS IN SICKLE CELL DISEASE PATIENTS

About 71% of patients (n=180) were administered Cefuroxime, 8.3% (n=20) Clindamycin and 6.3% (n= 16) Ciprofloxacin for the management of infections in sickle cell disease patients (**Fig 2**).

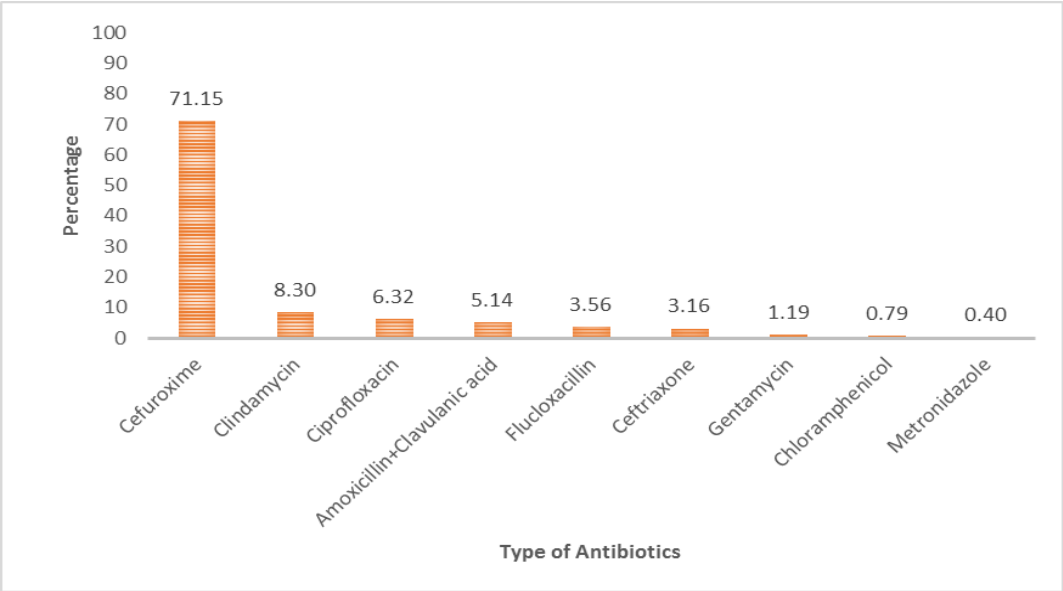

Figure 2: Types of antibiotics used for management of sickle cell

Table 2: Antibiotics used and Route of Administration

Type of Antibiotics	Route		Total
	Intravenous	Oral	
Amoxicillin+Clavulanic acid	13	0	13
Ceftriaxone	8	0	8
Cefuroxime	178	2	180
Chloramphenicol	2	0	2
Ciprofloxacin	16	0	16
Clindamycin	20	1	21
Flucloxacillin	8	1	9
Gentamycin	3	0	3
Metronidazole	1	0	1
Total	***249(98.42)***	***4(1.58)***	***253*(100.00)**

Most of the antibiotics (98.42%) were administered through intravenous route. (**Fig 3**)

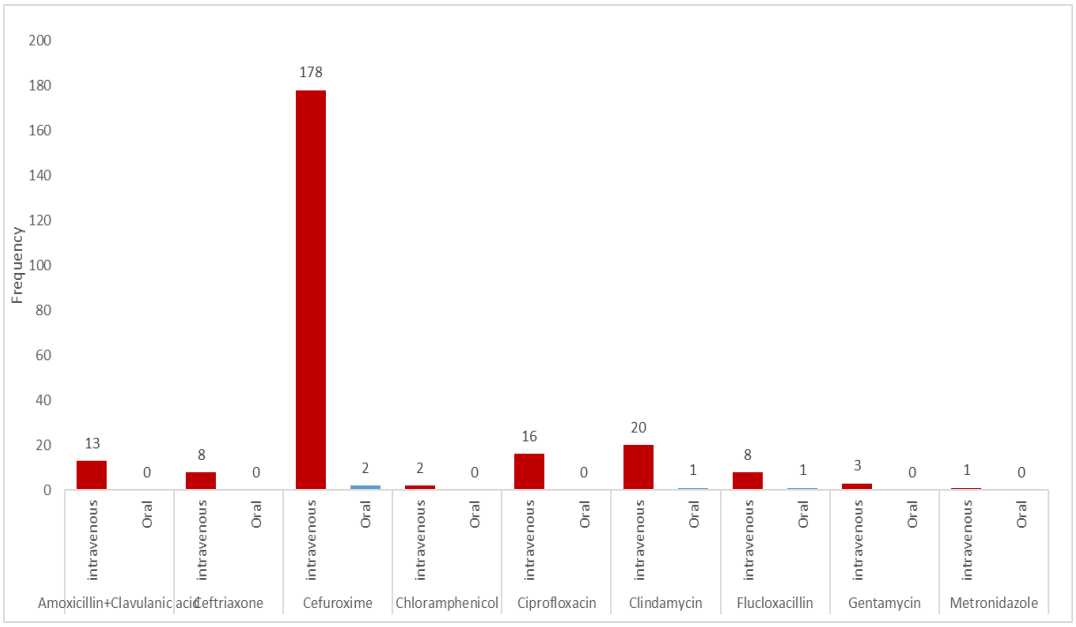

Figure 3: Types of Antibiotics and Route of Administration

4.4 ANTIBIOTIC PROPHYLAXIS WITH PHENOXYMETHYL PENICILLIN POTASSIUM AND OTHERS.

Over 80% of the participants (n=207) were on penicillin prophylaxis and less than 1 %(n=2) on other antibiotic for prophylaxis (e.g. Erythromycin). **(Fig 4)**

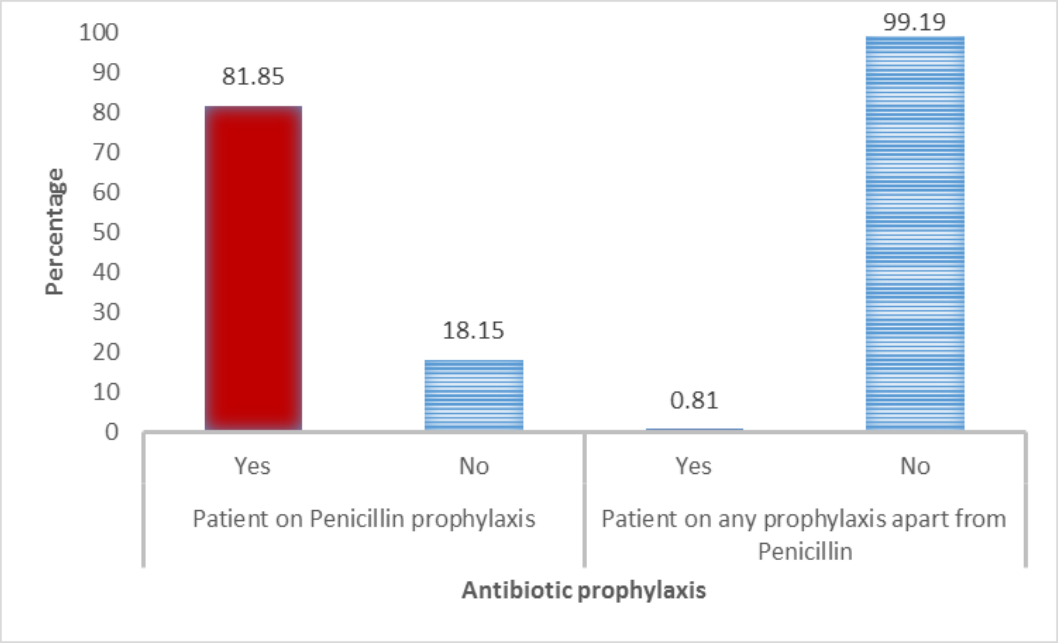

Figure 4: Antibiotic Prophylaxis with Phenoxymethyl Penicillin and others.

4.5 PATIENT ON PENICILLIN PROPHYLAXIS AND INFECTION

Common infections presented by patients on Pen V were Bronchopneumonia (n=49), Acute Chest Syndrome (n=37), Sepsis (n=33) and Osteomyelitis (n=23), see- **Table 3** below**.**

4.6 PATIENT NOT ON PENICILLIN PROPHYLAXIS AND INFECTION

Common infections presented by patients not on Pen V were Bronchopneumonia (n=13), Sepsis (n=9), Osteomyelitis (n=8) and Acute Chest Syndrome (n=4), see - **Table 3** below**.**

Table 3: Patient on Penicillin Prophylaxis and Type of Infections

	Patients on Pen V		
Type of Infections	**Yes**	**No**	**Total**
Acute Chest Syndrome	37	4	41
Bronchopnuemonia	49	13	62
Dactylitis	9	3	12
Lobar Pnuemonia	12	1	13
Malaria	7	1	8
Osteomyelitis	23	8	31
Sepsis	33	9	42
Urinary tract infection	8	0	8
multiple infections	4	3	7
others	25	4	29
Total	**207**	**46**	**253**

4.7 PATIENT ON PENCILLIN PROPHYLAXIS AND ANTIBIOTICS

Common antibiotics used for the management of infections in patients on penicillin V were Cefuroxime (n=149), Clindamycin (n=18), Ciprofloxacin (n=12) and Amoxicillin + Clavulanic acid (n=10), see-**Table 4** below**.**

4.8 PATIENTS NOT ON PENICILLIN PROPHYLAXIS AND ANTIBIOTICS

Common antibiotics used for the management of infections in patients not on Penicillin V were Cefuroxime (n=31), Ciprofloxacin (n=4), Amoxicillin +Clavulanic acid (n=3) and Clindamycin (n=3), see-**Table 4** below**.**

Table 4: Patient on Penicillin Prophylaxis and antibiotics used

	Patients on Pen V		
Types of Antibiotics	**Yes**	**No**	**Total**
Amoxicillin+Clavulanic acid	10	3	13
Ceftriaxone	6	2	8
Cefuroxime	149	31	180
Chloramphenicol	0	2	2
Ciprofloxacin	12	4	16
Clindamycin	18	3	21
Flucloxacillin	9	0	9
Gentamycin	3	0	3
Metronidazole	0	1	1
Total	**207**	**46**	**253**

4.9 APPROPRIATENESS OF ANTIBIOTIC USED FOR THE MANAGEMENT OF INFECTIONS IN SICKLE CELL DISEASE

Based on the Standard Treatment Guidelines, 100% (n=253) had their dosing frequency of antibiotic appropriate, 94.07% (n=238) had their choice of antibiotic given for infection appropriate, 90.91% (n=230) had the duration of therapy appropriate and 87.35% (n=221) had the dose of antibiotic given for infection appropriate (**Table 5**).

Table 5: Appropriateness of Antibiotic used for the Management of Infections in Sickle Cell Disease Patients

	Responses	
	Yes	**No**
Factor, N=253	**n (%)**	**n (%)**
Dose of antibiotic given for infection is appropriate	221(87.35)	32(12.65)
Dosing frequency of antibiotic appropriate	253(100.00)	0(0.00)
Duration of the therapy of the antibiotic given appropriate for the infection	230(90.91)	23(9.09)
The choice of antibiotic given for the infection appropriate	238(94.07)	15(5.93)

4.10 OUTCOMES FOR ANTIBIOTIC THERAPY FOR INFECTION IN SICKLE CELL DISEASE PATIENTS.

Eighty nine percent (n=224) of the patients had symptoms resolved after antibiotic therapy and 11% (n=29) still had symptoms **(Fig 5).**

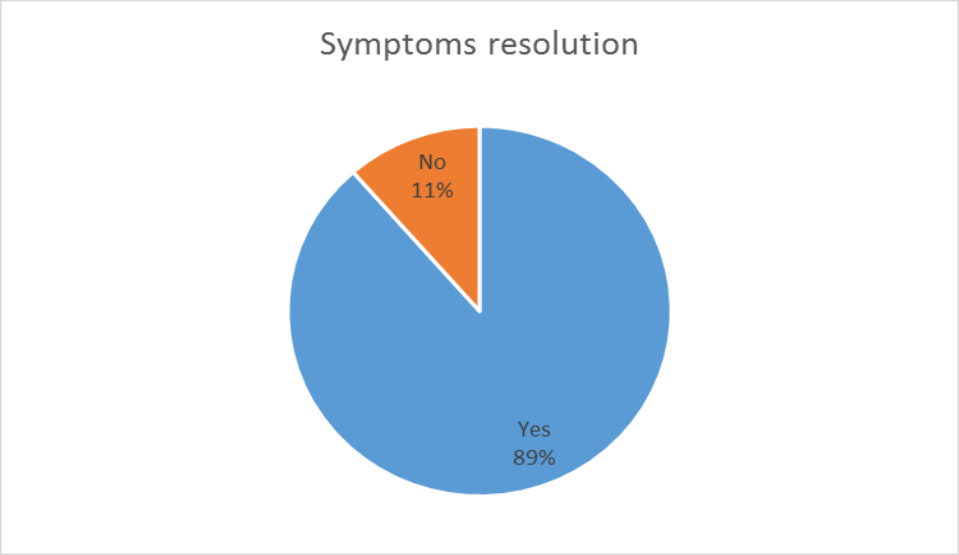

Figure 5: Outcome of antibiotic therapy for the infection in sickle cell disease patients.

4.11 LABORATORY INVESTIGATION AND OUTCOME OF THERAPY

About 89% of patients (n=200) who had some laboratory investigations to assess infection had their symptoms resolved; whilst those in which such labs were not done also had their symptoms resolved by the same proportion (**Table 6**).

Table 6: Laboratory investigation and Outcome of therapy

	Symptoms resolution			
Laboratory investigation to confirm infection	**Yes n(%)**	**No n(%)**	**Total n(%)**	**p value**
Yes	200(88.50%)	26(11.50%)	226(100.00%)	0.95
No	24(88.89%)	3(11.11%)	27(100.00%)	
Total	**224(88.54%)**	**29(11.46%)**	**253(100.00%)**	

4.12 TYPES OF ANTIBIOTICS AND OUTCOME OF THERAPY

Most of the antibiotics administered resulted in the relief of symptoms.

Table 7: Antibiotics used and Outcome of Therapy

	Symptoms resolution		
	Yes	**No**	**Total**
Type of Antibiotics	**n(%)**	**n(%)**	**n(%)**
Amoxicillin+Clavulanic acid	12	1	13
Ceftriaxone	6	2	8
Cefuroxime	160	20	180
Chloramphenicol	2	0	2
Ciprofloxacin	15	1	16
Clindamycin	17	4	21
Flucloxacillin	8	1	9
Gentamycin	3	0	3
Metronidazole	1	0	1
Total	**224(88.54)**	**29(11.46)**	**253(100.00)**

4.13 PATIENTS ON PENICILLIN PROPHYLAXIS AND OUTCOME

91% of patients not on Penicillin Prophylaxis had symptoms resolved compared to about 88% of those on Penicillin Prophylaxis that had their symptoms resolved after infection management, but there was no statistically significant difference, ($p = 0.52$) as shown in **Table 8** below.

Table 8: Patient on Penicillin Prophylaxis and Outcome to Therapy

	Symptoms resolution		**Total n(%)**	
	Yes	**No**		**p value**
Patient on Penicillin prophylaxis	**n(%)**	**n(%)**		
Yes	182(87.92)	25(12.07)	207(100.00)	0.52
No	42(91.3)	4(8.70)	46(100.00)	
Total	**224(88.53)**	**29(11.46)**	**253(100.00)**	

CHAPTER FIVE

5.0 DISCUSSION

Infections are one key leading cause of morbidity and mortality in sickle cell disease patients (Gupta et al, 2015). In a retrospective study done by Manci et al (2003) infections were found to be the most common cause of death in sickle cell disease patients.

From the results, the median age was 5 years meaning that younger children presented with more infections than the older ones. It has been found out that older children ≥ 5years have increased ability to produce immunologic response to encapsulated organisms e.g. S. pneumonia as compared to the younger population (Buchannan et al, 1982; Gaston et al, 1986).

From the demographics, laboratory investigations were done in about 90% of the study population. 89% of the patients (n=200) with Laboratory investigations done (N=226) had their symptoms resolved by the same proportion as those without any laboratory investigations (P=0.95). Most of the investigations done were hematology rather than culture and sensitivity testing which is definitive of the type microorganism; hence most of the infections were treated based on clinical judgment of the clinician rather than definitive therapy. This can result in antibiotic resistance as a result of patient's overexposure to antibiotics which may not be needed. In developing countries like Ghana, the lack of very good microbiology laboratories (in health institutions) that provide information on microbial type as well as sensitivity patterns, the high cost of laboratory investigations and the unavailability of drugs sometimes limit clinicians in their choice of antibiotics (Ansong et al, 2013).

Over 66% of the study participants presented with temperature higher than 37.5 ^{o}C. On discharge about 97% had their temperatures below 37.5 ^{o}C. This means that temperature is used as sign of wellness in sickle cell disease patients.

In this study it was found out that about a quarter of the study participants had Bronchopneumonia. Other causes of infections were Sepsis, Acute Chest Syndrome and Osteomyelitis respectively.

This evidence is similar to a retrospective study done by Magnus et al (1999) on the recurrence of infections in sickle cell patients in Jamaica. Out of 214 episodes of invasive bacterial infection among 176 patients, it was found out that *Streptococcus pnuemonia* was the main cause of infections (Magnus et al, 1999).

Antibiotics used in the management of infections included; Cefuroxime, Clindamycin, Ciprofloxacin, Amoxicillin + Clavulanic acid, Flucloxacillin, Ceftriaxone, Gentamycin, Chloramphenicol and metronidazole. At the end of the study it was found out that cefuroxime which is a cephalosporin was the highest administered antibiotic, followed by Clindamycin and ciprofloxacin. About 98.42% of the antibiotic administered was through the intravenous route because it has a faster onset of action. 75% (n=22) out of the total patients (N=29) whose symptoms were not resolved were administered cephalosporin for the management of infection. This means that there could be a possible resistance to cephalosporins. In a study done by Miller et al (2005) in children with sickle cell disease at Tennessee, about 21% of pneumococcal isolates were resistant to a cephalosporin (Cefotaxime).

207 patients representing 81.85% were on Penicillin V whilst 2 patients representing 0.81% were on other antibiotics for prophylaxis (Erythromycin). In a study done by Gaston et al (1986) on the use of oral penicillin in children with sickle cell disease,

there was about 84 % reduction in the occurence of infection, which was observed in the group treated with penicillin as compared with the group given placebo. In another study done by Hord et al (2002) it also supported routine penicillin prophylaxis. From this study, patients on penicillin prophylaxis presented with the same common infections as those not on penicillin prophylaxis. Hence the quality of the Penicillin V should be assessed and also the level of patient compliance too should be looked at, because a missed dose can cause rapid colonization of the causative organism (Anglin et al, 1984). Again it was noticed that 91.3% of patients not on penicillin prophylaxis had their symptoms resolved compared to 87.92% of those on penicillin prophylaxis. This is because the former have less exposure to antibiotic therapy, as such they responded well to therapy as compared to the later.

In this study there was a high level of appropriateness based on the standard guidelines. Dosing frequency was the most appropriate which achieved 100%. This was followed by the choice of antibiotic, the duration of therapy and the dose of the antibiotic. These achieved 94.07%, 90.91% and 87.35% respectively.

At the end of the study it was found out that about 224 patients representing 89% patients had their symptoms resolved meaning that Sickle cell patients who were on admission with an infectious disease were managed well at KATH amidst the challenges.

5.1 LIMITATIONS OF THE STUDY

- The scope of the study could have been expanded to cover other sickle cell units in the country. This was not possible due to resource and time constraints.

- Patients had different review dates and some also do not report to the facility after discharge. This makes it difficult to follow up on them. However it will be interesting to know the outcomes of such investigations.

CHAPTER 6

6.0 CONCLUSION

- Bronchopneumonia, Sepsis, Acute Chest Syndrome and Osteomyelitis were the most infections seen in the sickle cell disease patients.
- Cefuroxime, Ciprofloxacin and Clindamycin were the most common antibiotics used for management of the infections.
- Most of the study patients whose data were assessed were on Penicillin prophylaxis
- Based on the standard guidelines, majority of the study populace had all the parameters indicative of appropriate antibiotic therapy (i.e. correct choice of drug, correct duration of therapy, correct dose of drug and correct dosing frequency)
- More than 80% of the study population had their symptoms resolved on discharge but a little over 10% still had their symptoms persisting.
- There was no significance difference in the infection rates presented by patients on Penicillin V prophylaxis and those that were not on Penicillin V.

6.1 RECOMMENDATIONS

1. As much as possible, the use of antibiotics must be guided by culture and sensitivity testing for a definitive therapy and also prevent the possible emergence and spread of antimicrobial resistance in the hospital.
2. Further research should be conducted out on:
    a. The quality of the brand of Phenoxymethyl penicillin that are being used for prophylaxis of infectious disease in sickle cell patients
    b. The level of compliance to Phenoxymethyl penicillin for infection prevention in sickle cell disease patients

c. The level of cephalosporin or penicillin resistance in sickle cell disease patients on Penicillin Prophylaxis.

3. This research should be replicated in other sickle cell units across the country for national data.

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APPENDICES

APPENDIX 1: DATA EXTRACTION FORM

Form #: _____

Question	Response	
Section A: Demographics		
A1. Recruitment Date	_____/_____/_____	
A2: Folder Number	_____	
A3: Sex	1.Male 2.Female	_____
A4. Age(years)	_____	
A5: Weight(Kg)	_____	
A6: Date of Hospital attendance A7: Date Of Discharge	_____/_____/_____ …….	
A7. Temperature on admission	_____	
A8. Temperature on discharge	_____	
Section B: Infection		
B1. Type of infection diagnosed B2. Presenting Complaint	……..	
B2. Any Laboratory Investigation for infection diagnosis?	1.Yes 2. No	_____
B3. What type of Laboratory investigation(s) was done? ……		
B4. Results of laboratory investigation for infection diagnosis……		

Section C: Type of Antibiotic

C1: Type of Antibiotics	Strength	Route	Dosing frequency	Start Date	End Date	Duration o Therapy
1.						
2.						
3.						
4.						
5.						
6.						
7.						
8.						
9.						
10.						

Antibiotics grouped under penicillin and Cephalosporin

C2: Penicillin Antibiotics	Strength	Route	Dosing frequency	Start Date	End Date	Duration of Therapy
1.						
2.						
3.						
4.						
5.						

C3: CEPHALOSPORIN Antibiotics	Strength	Route	Dosing frequency	Start Date	End Date	Duration of Therapy
1.						
2.						
3.						
4.						
5.						

Section D: Antibiotic Prophylaxis

D1. Patient on Penicillin prophylaxis	1.Yes 2.No	_____
D2. Patient on any prophylaxis apart from Penicillin	1.Yes 2.No	_____

D3. Other antibiotic(s) for prophylaxis	Strength	Route	Dosing frequency	Start Date	End Date	Duration of Therapy
1.						
2.						
3.						
4.						

Section E: Appropriateness

E1. Dosing frequency for the antibiotic(s) given is appropriate	1.Yes 2.No	_____
E2. The strength of antibiotic(s) given is appropriate	1.Yes 2.No	_____
E3. The duration of therapy of antibiotic(s) given is appropriate	1.Yes 2.No	_____
E4.The choice of antibiotic(s) given is appropriate	1.Yes 2. No	_____

Section F: Patient Outcome

STATUS Symptoms Resolution	1.Yes 2.No	_____

APPENDIX 2: COPY OF ETHICAL APPROVAL LETTER

KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY
COLLEGE OF HEALTH SCIENCES
SCHOOL OF MEDICAL SCIENCES / KOMFO ANOKYE TEACHING HOSPITAL
COMMITTEE ON HUMAN RESEARCH, PUBLICATION AND ETHICS

Our Ref: CHRPE/AP/058/15 — 12th March, 2015.

Ms. Adwoa Oforiwaa Kwakye
Department of Clinical and Social Pharmacy
Faculty of Pharmacy and Pharmaceutical Sciences
College of Health Sciences
KNUST.

Dear Madam,

LETTER OF APPROVAL

Protocol Title: "Management of Infections and its Outcome in Sickle Cell Disease Patients at KATH."

Proposed Site: Komfo Anokye Teaching Hospital, Child Health Directorate.

Sponsor: *Principal Investigator.*

Your submission to the Committee on Human Research, Publications and Ethics on the above named protocol refers.

The Committee reviewed the following documents:

- A notification letter of 21st January, 2015 from Komfo Anokye Teaching Hospital (study site) indicating approval for the conduct of the study in the Hospital.
- A Completed CHRPE Application Form.
- Participant Information Leaflet and Consent Form.
- Research Protocol.
- Data Collection Form.

The Committee has considered the ethical merit of your submission and approved the protocol. The approval is for a fixed period of one year, renewable annually thereafter. The Committee may however, suspend or withdraw ethical approval at any time if your study is found to contravene the approved protocol.

Data gathered for the study should be used for the approved purposes only. Permission should be sought from the Committee if any amendment to the protocol or use, other than submitted, is made of your research data.

The Committee should be notified of the actual start date of the project and would expect a report on your study, annually or at close of the project, whichever one comes first. It should also be informed of any publication arising from the study.

Thank you Madam, for your application.

Yours faithfully,

Osomfuor Prof. Sir J. W. Acheampong MD, FWACP
Chairman

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