

**ACUTE CHEST SYNDROME IN SICKLE CELL DISEASE: CLINICAL  
PRESENTATION AND PHARMACOLOGICAL MANAGEMENT**

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## DECLARATION

The data collection and work described in this thesis was carried out at the Child Health Department at Komfo Anokye Teaching Hospital (KATH), and I hereby declare that this thesis is my own work and to the best of my knowledge, all references consulted have been duly cited. This work has not been submitted for a degree in any other institution of academic organization.

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## DEDICATION

I dedicate this work to my family for their company, morale, concern and inspiration in varied ways.

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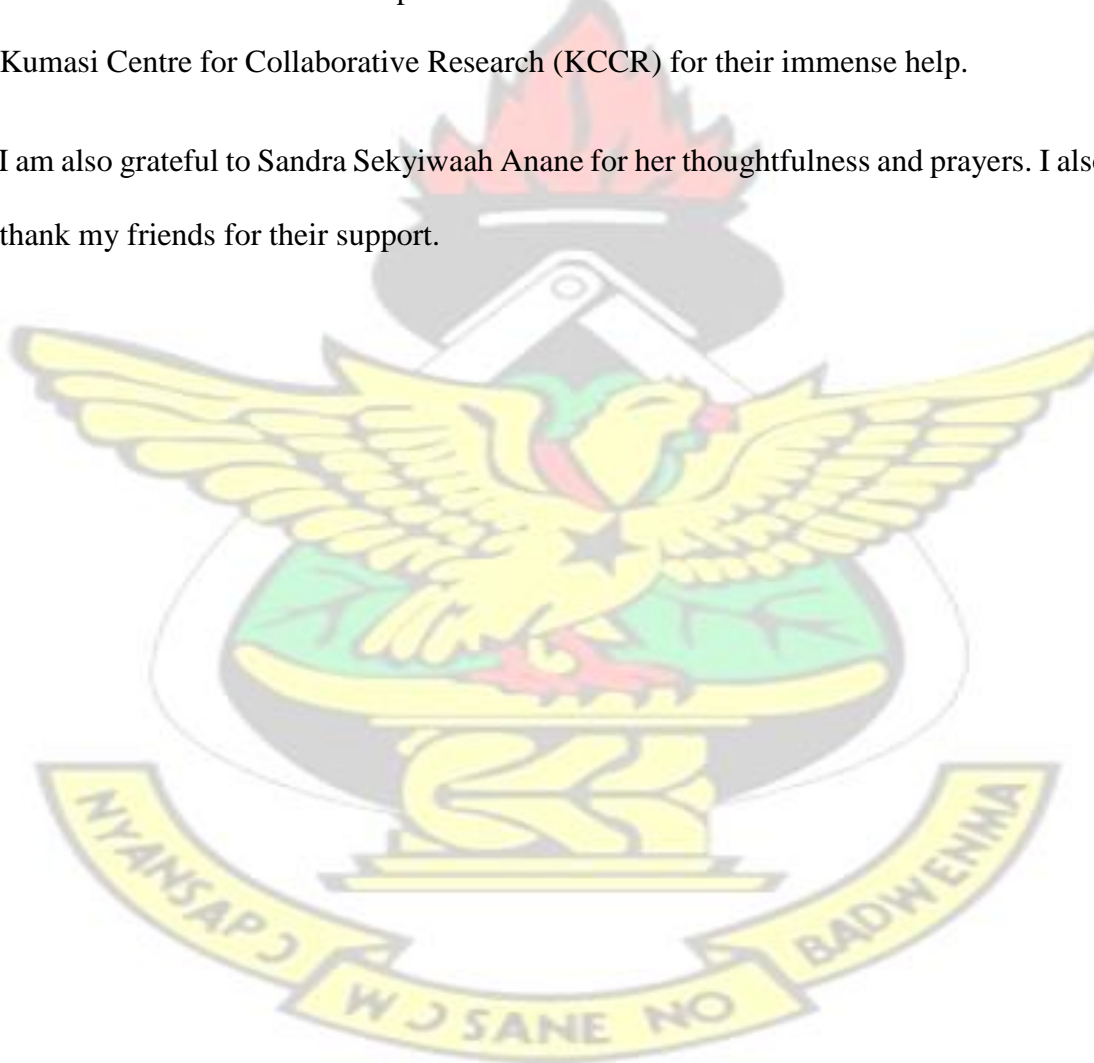


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## ABSTRACT

**Background:** Acute chest syndrome (ACS) is a common cause of hospitalization and mortality in sickle cell patients across the globe. There appears to be paucity of data concerning ACS and its pharmacological management in Ghana and Africa as a whole. This study was aimed at assessing the prevalence and clinical presentation of ACS, and its pharmacotherapy in children with Sickle Cell Disease (SCD) at Komfo Anokye Teaching Hospital (KATH) in Kumasi, Ghana.

**Method:** The design of the study was retrospective, in which medical records of the children 14 years and below with SCD and at least an episode of ACS were retrieved and assessed at the Sickle Cell Clinic of KATH. One hundred and seven cases among 1336 children with sickle cell disease met the criteria for inclusion in the study.

**Results:** The ages of the patients ranged from 8 months to 14 years with a mean of  $5.7 \pm 3.5$  years. The prevalence of ACS was 8%, with a 2.2 episodes/ month rate of occurrence. Forty percent of the patients were between the ages of 5 to 9 years. Seventy five percent (n=80) presented with fever and 65% (n=70) presented with cough. Other symptoms like rhinorrhoea and irritability were common in younger patients (< 5 years),  $p = 0.012$  and  $0.001$  respectively. Abdominal pain and chest pain occurred mostly in the older patients ( $\geq 5$  years),  $p = 0.024$  and  $< 0.001$  respectively.

Bacteria isolates were found in 12 of 79 cases (15.2%) that had blood culture information. Eighty four patients (80.7%) received cefuroxime and gentamicin dual therapy for empiric treatment of infection in ACS. The dose range of gentamicin used in the hospital was 3 to 9 mg/kg body weight as opposed to the recommended 5 to 7 mg/kg, as a single daily dose. The empiric antibiotic therapy for infections in ACS patients did not cover for atypical bacteria as recommended in standard guidelines.

Forty seven patients received paracetamol alone for pain management and 47 received paracetamol and ibuprofen. Morphine was the preferred opioid prescribed, which is in line with recommendation by WHO guidelines for pain management in SCD patients.

**Conclusion:** The prevalence of ACS was 8%. The majority of patients were between the ages 2 to 9 years. Fever and cough were among the common clinical symptoms presented. Other clinical features like rhinorrhoea, irritability, chest pain and abdominal pain varied with age. Treatment regimen for ACS in the hospital included pharmacotherapy for infections, pain management, hydration with IV fluids and blood transfusion in patients with severe anaemia. All of these were in conformity with standard guidelines and literature.



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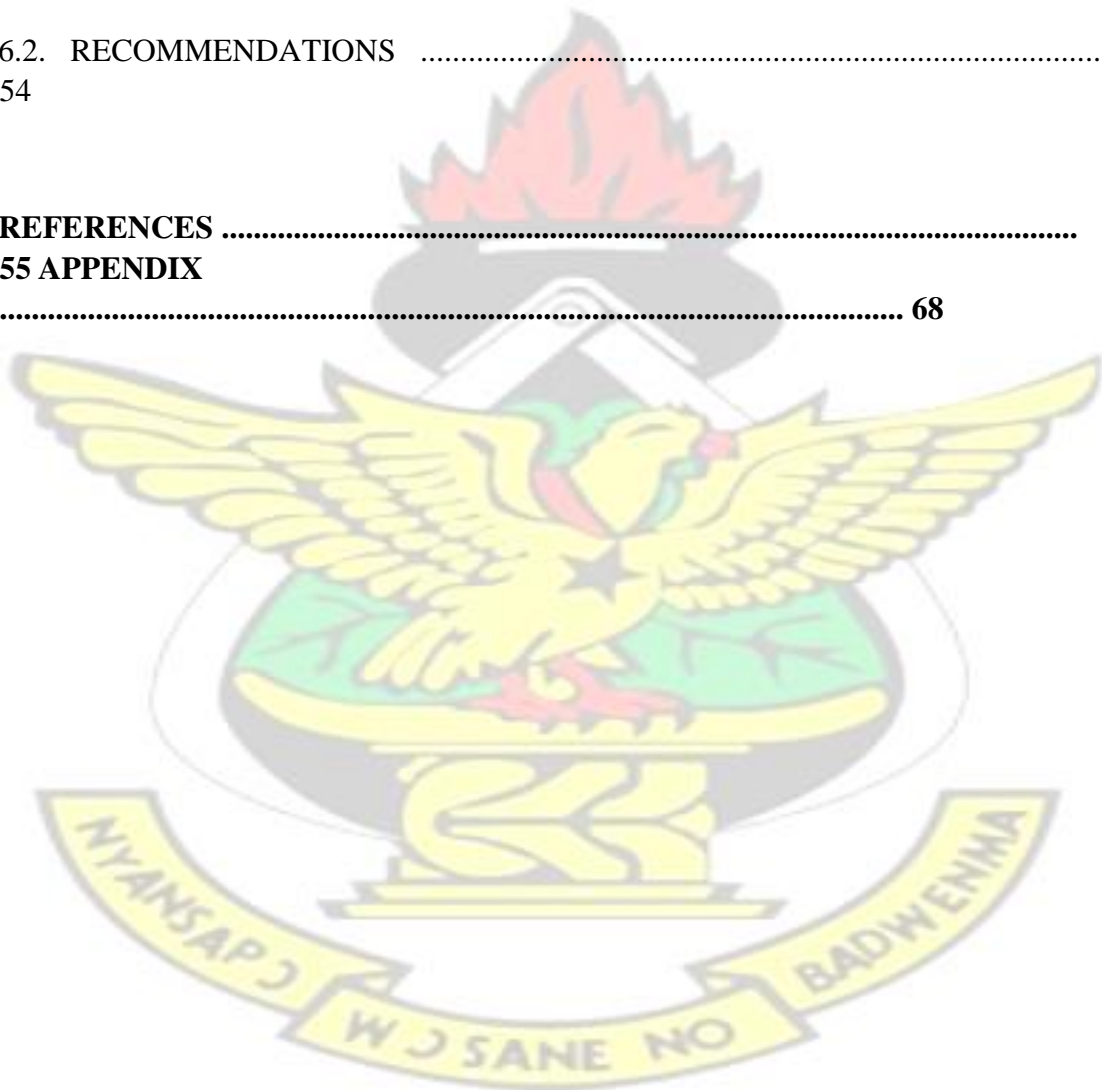
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## ABBREVIATION



ACS	–	Acute Chest Syndrome
BNF	–	British National Formulary
CHRPE	–	Committee on Human Research, Publications and Ethics
ET-1	–	Endothelin – 1
Hb	–	Haemoglobin
HbF	–	Foetal Haemoglobin
ICAM – 1	–	Intercellular Adhesion Molecule
IL – 1	–	Interleukin - 1
KATH	–	Komfo Anokye Teaching Hospital
NSAID	–	Non-steroidal Anti-inflammatory Drugs
RDU	–	Research and Development Unit
SCD	–	Sickle Cell Disease
sPLA2	–	Secretory Phospholipase A2
TNF – $\alpha$	–	Tumour Necrosis Factor - $\alpha$
VCAM – 1	–	Vascular Adhesion Molecule
VOC	–	Vaso-occlusive crisis
WHO	–	World Health Organization

## CHAPTER ONE

### 1.0. INTRODUCTION

#### 1.1. GENERAL INTRODUCTION

Sickle Cell Disease (SCD) is a common monogenetic disorder which is of great concern in Sub-Saharan Africa. It is a disorder of great public health concern as over 200,000 children are born with the disorder yearly in Africa (Diallo and Tchernia, 2002; Weatherall and Clegg, 2001; Angastiniotis and Modell, 1998). SCD involves deformed red cells which results in haemolytic anaemia. Haemolytic anaemia combined with vaso-occlusion leads to numerous complications in SCD. One of such complications is Acute Chest Syndrome (ACS). ACS as a pulmonary complication of SCD is a common cause of hospitalization and mortality in sickle cell patients (Birken *et al.*, 2013; Vchinsky *et al.* 2000; Martin and Buonomo, 1997; Haskell, 1994; Platt *et al.*, 1994).

ACS describes a new pulmonary infiltrate on chest radiograph in individuals with sickle cell disease (SCD) (Miller, 2011, Platt, 2000). It is a pneumonia-like illness or a severe pulmonary illness in sickle cell patients (Al-Dabbous, 2002; Castro *et al.*, 1994). It is regularly characterized by cough, dyspnoea, hypoxemia, tachypnoea, fever, chest pain, wheezing, effusion or an infiltrate on chest radiograph (Crabtree *et al.* 2011; Dipiro *et al.*, 2008; Atz and Wessel 1997).

Its aetiology has been shown to be multifactorial. This makes ACS very difficult to diagnose and manage (Miller, 2011; Boyd *et al.*, 2006). The pharmacological management of ACS in sickle cell patients is complicated and may be underlined with various challenges. Studies regarding the prevalence, clinical presentation and pharmacological management of ACS in Ghana and Africa are scarce. Moreover, there

is no previous study on the pharmacological management of acute chest syndrome at the Komfo Anokye Teaching Hospital (KATH) and in Ghana.

The study was thus aimed at assessing the prevalence, clinical presentation and pharmacological management of ACS at KATH, Kumasi. This will help provide information for development of hospital and national guidelines to enhance the management of ACS in SCD patients.

The study retrospectively reviewed medical records of 107 ACS episodes in 1336 children (aged 14 years and below) with SCD. The pharmacological management of ACS in the hospital was described and evaluated against other guidelines. The strengths of the current management of ACS have been stated and the weaknesses identified have been stated to help enhance the management of ACS in patients with SCD.

## **1.2. PROBLEM STATEMENT**

There is paucity of data on the prevalence, clinical presentation and pharmacological management of specific SCD-related complications like ACS in Africa. Patients' response to pharmacological management options and how they affect progression of the complication are scarce. The case prevalence of ACS at KATH is unknown. There are conflicting reports on the clinical presentation of ACS making diagnosis and management very challenging.

The aetiology of ACS is unclear (Miller, 2011). In a study by Boyd *et al.*, in 2006, no cause was identified in about half of the ACS cases. This makes the management of ACS very complicated which leads to the use of multidrug therapies in managing ACS. The management of ACS may be associated with treatment failures and development of several other complications.

Pain management in children with ACS may also present with several difficulties. Self-reporting which may be the best method of assessing the impact of pain may be difficult in children. The point of the pain in children may also be difficult to recognize. This may make the identification of pain and its management challenging in SCD patients who develop ACS. Opioid use has also been reported to be associated with prolonged hospital stay in patients with ACS (Kopecky *et al.*, 2004).

Antibiotic therapy used in the management of ACS may come with variations in efficacy and safety depending on the type of organism present and demographic properties of the individual. Resistance to the use of antibiotics may also develop in individuals. Transfusion and hydration may also lead to fluid overload which may worsen the condition.

This study therefore sought to elucidate among study patients the prevalence of ACS, give a clear description and understanding of the pharmacological management of ACS at KATH.

### **1.3. RESEARCH QUESTIONS**

- What is the prevalence of ACS at the Komfo Anokye Teaching Hospital?
- What are the clinical presentations of patients with sickle cell disease who develop ACS and how does that affect therapy and outcomes?
- What pharmacological options are used in the management of ACS and therapeutic response to therapy?
- What problems are associated with drug therapy management of acute chest syndrome at the hospital?
- How does the pharmacological management of ACS at KATH conform to national and other hospital guidelines?

#### 1.4. OBJECTIVES

- To assess the prevalence and clinical presentations of ACS among study patients.
- To determine medications used in the management of ACS in the study patients.
- To assess the pattern of medications and how it compares to recommended standard guidelines.

#### 1.5. JUSTIFICATION

Assessing the magnitude of ACS may help throw more light on the burden of the complication in sickle cell patients at KATH. This will help create awareness to the effect and seriousness of the condition. This will subsequently help physicians and other health workers become more vigilant in diagnosing and managing the complication to improve patients' outcomes.

The documentation and assessment of the clinical presentation of ACS will help in the accurate identification and diagnosis of the condition. This will help incite a more intensive treatment of the condition in sickle cell patients.

The assessment of medications, the dosing variations and effect on clinical outcomes will help improve therapeutic safety and provide improved dosing strategies for the management of ACS. This will also help stress the need or otherwise for newer interventions or pharmacological options.

The study will also help generate data to support and improve existing knowledge on the prevalence, clinical presentation and pharmacological management of ACS. It will also provide an initial baseline data for further studies regarding ACS in Ghana.

## CHAPTER TWO

### 2.0. LITERATURE REVIEW

#### 2.1. GENERAL INTRODUCTION

Charache *et al.*, in 1979 studied sickle cell anaemia in 28 adults and suggested the term acute chest syndrome (ACS) for episodes of fever, chest pain, leukocytosis and pulmonary infiltrate. It is one of the main causes of hospitalization and death in patients with sickle cell disease (Birken *et al.*, 2013; Vchinsky *et al.* 2000; Sprinkle *et al.*, 1986; Ashcroft and Serjeant, 1981). It may also be defined as a chest radiograph showing a pulmonary infiltrate with chest pain, cough, wheezing, tachypnoea and fever (Crabtree *et al.* 2011; Dipiro *et al.*, 2008; Atz and Wessel, 1997; Platt *et al.*, in 1994). It has also been compared to a severe pulmonary illness or pneumonia (Aldabbous, 2002; Castro *et al.*, 1994).

#### 2.2. EPIDEMIOLOGY OF ACS

The incidence of ACS has been reported to be 12.8% in a study by Castro *et al.*, in 1994 in the Cooperative study of SCD conducted in the United States of America. It is estimated that about half of sickle cell patients worldwide would have at least an episode of ACS in their lifetime (Martin and Buonomo, 1997; Vichinsky 1994). In a study in Cameroon, ACS was found to be associated with 6.2% of SCD hospitalizations, with a rate of 2.1 episodes every month (Nansseu *et al.*, 2015). Higher prevalence of 10-20% was reported in a review by Miller and Gladwin in 2012. The hospital admissions in Brussels, French Guiana, Brazzaville and Antananarivo however, suggests lower admissions rate of 1.9 (Bertholdt *et al.*, 2012), 0.2 (Elenga *et al.*, 2014), 1.4 (Babela *et al.*, 2005) and 0.3 (Hunald *et al.*, 2010), SCD patients per month respectively.

Among age groups, the incidence of ACS has been shown to be lower in younger children under 2 years but increases in children between 2 and 4 years (25.3/100 ptyears) (Castro O *et al.*, 1994). The incidence is however lower in adults (8.8/100 ptyears), and older children (Castro O *et al.*, 1994).

Children mainly present with ACS on admission (Habibi *et al.*, 2004). A steady state haemoglobin and increased foetal haemoglobin (HbF) are suggested to decrease ACS rate (Castro *et al.*, 1994).

### **2.3. DISEASE AETIOLOGY**

The aetiology of ACS has been reported to be infection, infarction, and fat embolism (Miller and Gladwin, 2012; Gladwin and Vchinsky, 2008; Bernard *et al.*, 2007; Vchinsky *et al.* 2000). Reports on infection as a cause of ACS has been a matter of debate in several studies. Some studies suggest less or no infection. However, antibiotics remain an important treatment option in ACS. This is due to the possibility of pneumococcus infection from encapsulated bacteria, as most SCD patients are predisposed (Fawibe, 2007; Bernard *et al.*, 2007; Vchinsky *et al.* 2000).

A high leukocyte count in patients with ACS may also be suggestive that infection may precipitate ACS development. However, blood cultures do not usually show bacteria growth (Nansseu *et al.*, 2015; Castro O *et al.*, 1994). It is thus suggested that, without invasive techniques or procedures for bacterial or viral detection, infectious cause in ACS should not be ruled out (Howard *et al.*, 2015; Bernard *et al.*, 2007). Infections have been reported to be likely associated with ACS in children than in adults (Martin and Buonomo, 1997).

Vaso- occlusion (VOC) has also been reported to be involved with ACS development.

Triggers of vaso-occlusion include dehydration, hypoxia, trauma, and infections.

These triggers may lead to increase adherence of red cells and leukocytes to the endothelium and finally, occlusion (Yusuf *et al.*, 2014; Lal and Vchinsky, 2005).

Presence of red cell aggregates in circulation has been indicated to increase the risk of ACS (Lamarre *et al.*, 2012). In a study at Maidugri and Kano teaching hospitals, 2.11% cases of ACS were reported in patients with vaso-occlusive crises (Ahmed *et al.*, 2012).

There is evidence from publications suggesting a relationship between VOC and the development of ACS (Neocleous *et al.*, 2013; Miller and Gladwin, 2012; Bernard *et al.*, 2007; Castro O *et al.*, 1994).

Considering the risk factors for development of ACS, age, HbF level, anaemia and white blood cell count have been reported to be significant predictors of ACS development in HbSS patients. HbF has been shown to lower the risk or incidence of ACS in sickle cell patients (Elenga *et al.*, 2014; Lamarre *et al.*, 2012; Castro *et al.*, 1994).

#### **2.4. PATHOGENESIS**

Regional hypoxia has been suggested to be an underlying cause of ACS. Hypoxia prevents oxygenation of red cells in the pulmonary circulation thus maintaining their sickled shape. This leads to increased expression of adhesion molecules, inflammatory mediators and free radicals including reactive oxygen species. One important free radical source is red cells in sickle cell disease (Osarogiagbon *et al.*, 2000). Sickled red cells are known to produce large amounts of  $O_2^-$ ,  $H_2O_2$ , and  $OH^-$  (Hebbel *et al.*, 1982). This has been studied in transgenic sickle cell mice, where higher levels of markers of oxidative stress were observed in hypoxic situations (Osarogiagbon *et al.*, 2000).

Reactive oxygen species are directly toxic to vascular endothelium. Through lipid peroxidation, they increase the expression of endothelin – 1 (ET-1), vascular adhesion molecule (VCAM-1) and intercellular adhesion molecule (ICAM-1). These molecules

increase adhesion of the sickle red cell and white cells to vascular endothelium enhancing vaso- occlusion (Klings and Farber, 2001). Up regulation of vasoconstrictor ET-1 participates in the early stages or phase of development of ACS (Hammerman *et al.* 1997).

Elevated secretory phospholipase A2 (sPLA2) has also been reported in acute respiratory distress (Rae *et al.*, 1994; Baur *et al.*, 1989; Vadas 1984). In a study by Styles *et al.*, in 1996, sPLA2 was found to be elevated in SCD patients with ACS but not those with VOC and non- SCD patients with pneumonia. Secretory PLA2 levels increased with the onset of ACS but the levels declined as ACS improved (Styles *et al.*, 1996). Secretory PLA2 has been suggested as a useful marker for ACS diagnosis (Styles *et al.*, 1996).

Secretory PLA2 is an important inflammatory mediator which can hydrolyze eicosanoids (Fink, 1993). This leads to the production of free fatty acids and several mediators like prostaglandins and leukotrienes which can directly cause lung injury (Henderson, 1991; Lewis *et al.*, 1990; Henderson 1987). Its expression is up regulated in response to pro-inflammatory cytokines such as tumour necrosis factor -  $\alpha$  (TNF-  $\alpha$ ) and interleukin – 1 (IL-1) (Przanski and Vadas 1991; Pfeilschifte, 1989; Clark 1988).

Fat embolism associated with ACS development may also suggest a relation between ACS and free fatty acids. Increases in oleic acid and palmitic acid levels as well as total free fatty acids in ACS have been reported by Phelan *et al.*, in 1995.

## **2.5. CLINICAL PRESENTATION AND DIAGNOSIS**

The main symptoms of ACS have been identified to be fever, cough and chest pain.

With wheezing and shortness of breath reported as less frequently occurring ones

(Nansseu *et al.*, 2014; Taylor *et al.*, 2003; Vchinsky *et al.*, 2000; Vchinsky *et al.*,

1997). Symptoms have been suggested in studies to be age dependent (Bernard *et al.*, 2007; Taylor *et al.*, 2003; Vchinsky *et al.*, 2000). Fever and cough have been suggested to be more common in children while shortness of breath and chest pain occur mostly in older children or adults (Bernard *et al.*, 2007; Taylor *et al.*, 2003; Vchinsky *et al.*, 2000).

About half of patients who develop ACS are initially admitted for other reasons (Bernard *et al.*, 2007; Vchinsky *et al.*, 2000). Children also present with higher temperatures, respiratory rate and pulse rate than adults (Vchinsky *et al.*, 1997). Taylor *et al.*, in 2003, observed higher respiratory rate (>30/ min) in children below 9 years. Patients had a mean temperature of 38.9 degree celsius, with mean haemoglobin of 7.7g/dl and mean white blood cell count of 23000 cells/ ml (Taylor *et al.*, 2003). There is a suggested white cell increase in ACS episodes (Vchinsky *et al.*, 1997).

In a study by Vchinsky *et al.* 1997, the most common physical signs were dullness, percussion and rales. Normal physical sign was the second most common physical finding (Vchinsky *et al.* 1997). This was contrary to a study by Taylor *et al.* in 2003, which reported normal signs to be the most common physical finding. Multilobar involvement was mainly associated with adult cases. Pleural effusion was also more common in adults (Vchinsky *et al.* 1997).

Chest radiograph is the main test for diagnosis. Positive radiograph reveals an infiltrate involving a lower lobe. There may be associated effusion with multilobar involvement (Bernard *et al.*, 2007; Vchinsky *et al.*, 2000; Vchinsky *et al.*, 1997; Sprinkle *et al.*, 1986). Radiographs may not be appropriate tests for appreciating the clinical severity or the degree of hypoxia in ACS (Bhalla *et al.*, 1993) Infiltrates may also develop in latter stages of the condition. Therefore a single chest x-ray with a negative result should

not be used as the sole basis to exclude the condition (Neocleous *et al.*, 2013; Rucknagel *et al.*, 2001; Vchinsky *et al.*, 2000).

Other important tests that are important in ACS diagnosis and prognosis include serial haematological tests on blood cultures (Bernard *et al.*, 2007). Decreased Hb level on the average 0.7g/dl below baseline has been observed in ACS patients (Vchinsky *et al.*, 1997). Progressive anaemia, increased white blood cell count and a platelet count below  $199 \times 10^3/\mu\text{l}$  are associated with ACS and also a prolonged hospital stay (Vchinsky *et al.* 2000). Lactate dehydrogenase and bilirubin tests can be performed to detect associated haemolysis (Bernard *et al.*, 2007).

## 2.6. MANAGEMENT OF ACS

Guidelines for the management of ACS used in the study include;

- The management of Sickle Cell Disease by the National Institute of Health (SCD-NIH) (USA)
- Guidelines on the management of ACS in SCD (Howard *et al.*, 2015)
- Treatment guidelines, Child Health directorate, KATH, 2010

The management of ACS is mainly supportive involving antibiotics to treat infection, adequate pain control, careful hydration and blood transfusion (Ansong *et al.* 2013; Fawibe 2008). Management aims at preventing acute respiratory failure and ultimately death. The key to a successful prognosis is early recognition or diagnosis and starting treatment without delay. This will reduce associated sequelae and lung damage (Howard *et al.*, 2015). The management of ACS is complicated and poorly understood because the aetiology is multifactorial (Boyd *et al.*, 2008).

In a review by Ansong *et al.* 2013, management options for ACS should include antibiotics mainly broad spectrum antibiotics and macrolides targeted against

Mycoplasma and Chlamydia. This was also reiterated by Fawibe, in 2007, who also states the need for IV antibiotics. Macrolides or quinolones were recommended to cover atypical pathogens (Ansong *et al.* 2013; Awogbade *et al.*, 2012).

Optimal hydration is required although excessive hydration can worsen pulmonary status of patients (Howard *et al.*, 2015; Haynes and Allison, 1986). Trials to assess the efficacy of the type or quantity of administered intravenous (IV) fluid and route is lacking (Okomo and Meremikwu, 2007). However, intravenous fluids are still important in the management of ACS since patients hardly maintain oral hydration.

Transfusion is also necessary, as it has been shown to provide the needed oxygen carrying capacity (Swerdlow, 2006; Lawson *et al.*, 1999). Non-ionic surfactants (Ballas *et al.*, 2004) and anticoagulants (Ahmed *et al.*, 2004) have been also suggested to have beneficial effects.

Hydroxyurea has also been stated to be beneficial in reducing recurrent episodes of acute chest syndrome (Ferster *et al.*, 2001). Oxygen therapy may be instituted to keep oxygen saturation above 96 % (Awogbade *et al.*, 2012). In the review by Fawibe in 2007, narcotic analgesics preferably morphine should be used in pain management associated with ACS.

### **2.6.1. Antibiotic use in ACS**

Acute chest syndrome presents as a medical emergency (Howard *et al.*, 2015). The presence of infection should be assessed in all patients with ACS. Most published data on the underlying bacteria cause suggests the dominance of atypical bacteria involving *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* (Harris *et al.*, 2011; Lin *et al.*, 2009; Vichinsky *et al.*, 2000). Full course of antibiotic therapy is recommended regardless of the result from culture tests. Inherent limitations associated with blood

cultures make it difficult to exclude bacteria involvement (Bernard *et al.*, 2007). It is also difficult to exclude pneumonia or infection of lung infarction (Fawibe, 2007; National Heart, Blood and Lung Institute, 2002). All patients should be treated empirically for severe community acquired pneumonia unless data suggests otherwise (Bernard *et al.*, 2007). This should take into consideration the sensitivity pattern of the locality and the disease severity (Fawibe, 2007).

In the study by Vchinsky *et al.*, 2000, erythromycin and cephalosporin were the mostly used antibiotics. A study in Cameroon by Nansseu *et al.* 2015 also indicated the use of 2 or 3 antibiotics which included beta lactams (either ampicillin or ceftriaxone) and macrolides (oral azithromycin) with the addition of an aminoglycoside when needed. Vancomycin was also administered to patients who presented with fever for several days after initial antibiotic therapy. Antibiotic use however did not impact on the duration of hospitalization.

Prophylactic penicillin has been shown to reduce the development of pneumococcal disease and thus reduces incidence by *Streptococcus pneumoniae* which may be involved in ACS (Gaston *et al.*, 1986). In a study by Vchinsky *et al.*, in 1997 bacterial infection was indicated in 3.5% of the ACS episodes. The most common were *Streptococcus pneumoniae* and *Haemophilus influenzae*. Others isolated were *Salmonella typhi*, *Staphylococcus aureus*, Enterobacter and Clostridia.

Antibiotics used include penicillins, aminoglycosides, quinolones, cephalosporins and macrolides. In selecting the antibacterial agent factors such as history of allergy, renal and hepatic function, severity of illness etc., should be considered.

### **2.6.1.1. Aminoglycosides**

Aminoglycosides act by interfering with protein synthesis by irreversibly binding to 30S bacteria protein. When used together with penicillin they have an enhanced activity against Enterococci and Streptococci species. Since they are polycationic, they show binding affinity for nucleic acids. They are all bactericidal and active against some gram positive and many gram negative organisms (Vakulenko and Mobasberry, 2003). Aminoglycosides include gentamicin, amikacin, streptomycin and kanamycin.

The aminoglycosides have broadly similar toxicological features (Garrod *et al.*, 1983). Ototoxicity has been a major limitation in their use. Other adverse effects include nephrotoxicity and neuromuscular blockade. Ototoxicity and nephrotoxicity have been suggested to increase in patients who are dehydrated and with impaired renal function (BNF for children, 2012).

They have a concentration dependent bacteria activity, post antibiotic effect and synergism with other antibiotics. Concentration dependent activity and post antibiotic effect in combination with attenuation risk of nephrotoxicity and ototoxicity are the major reasons for once daily dosing with aminoglycosides in patients with normal renal function. Prolonged use is still associated with toxicity. Inadequate plasma concentrations will also lead to treatment failure thus therapeutic monitoring of serum gentamicin concentration remains very important (Croes *et al.*, 2012).

Guidelines suggest the use of 5-7mg/kg body weight gentamicin in a once daily administration (Buabeng *et al.*, 1999; BNF for children, 2012).

### **2.6.1.2. Penicillins**

Penicillins are bactericidal beta-lactam antibiotics that inhibit bacterial cell wall synthesis. Their use in ACS is mainly to manage and prevent infections by

*Streptococcus pneumoniae* and *Staphylococcus pneumoniae*. They are also active against *Streptococcus pyrogenes*, Enterococci, *Neisseria meningitidis* etc. Penicillins include benzylpenicillin, phenoxymethylpenicillin, Amoxicillin, among others. The use of penicillins with clavulanic acid (Amoxicillin and clavulanic acid) has the added advantage of inhibiting beta lactamases making them active against beta-lactamase producing bacteria. Their major side effect is hypersensitivity (BNF for children 2012; Martindale, 2007).

### **2.6.1.3. Quinolones**

Quinolones are known to inhibit the action of type II topoisomerase, DNA gyrase and topoisomerase IV. Ciprofloxacin is one of the potent fluoroquinolones. It is mainly active against Gram-negative bacteria like Salmonella, shigella, Neisseria and pseudomonas. It also has some activity against Gram-positive bacteria (Emerson and Jones, 2003). Ciprofloxacin is generally well tolerated. Adverse effects most often involve the gastrointestinal tract, CNS or skin. Quinolones have been shown to cause arthropathy and are generally not recommended for use in children (BNF for children, 2012).

### **2.6.1.4. Macrolides**

Sensitivity of various atypical bacteria involved with ACS development has been studied. Most have been shown to be susceptible to macrolides. The antibacterial spectrum of erythromycin is similar to that of penicillin. Azithromycin has an enhanced activity against Gram-negative organisms such as *Haemophilus influenzae* (BNF for children, 2012).

Studies show low mortality rate in patients placed on macrolides in bacterial pneumonia. There is also the achievement of a broader spectrum when used in

combination with B- lactams (Metersky *et al.*, 2007). Infectious aetiology has been shown to present with cytotoxic effects. Mycoplasmas mainly involved in ACS have been shown to produce a wide range of immunoregulatory effects. The ability of some of these bacteria to stimulate the production of cytokines involved in mediating inflammation has been well documented (Metersky *et al.*, 2007).

Macrolides are well known to have immunomodulatory effects and can suppress inflammation through lymphocyte activity and neutrophil proliferation. They have also been documented to have tremendous activity against atypical bacteria (Metersky *et al.*, 2007).

Macrolides inhibit drug metabolism by microsomal cytochromes mainly CYP1A2 and CYP3A4 by competitive inhibition. Common side effects include abdominal cramps, nausea and vomiting (BNF for children, 2012; Garold *et al.*, 1983).

#### **2.6.1.5. Cephalosporins**

Cephalosporins are semi-synthetic antibiotics produced from *Cephalosporium acremonium*. Their pharmacology is similar to that of penicillins by inhibiting cell wall synthesis. They are broad spectrum antibiotics. They are beneficial in treating septicaemia and pneumonia. The main side effects are hypersensitivity and antibiotic associated colitis. Higher generations of cephalosporins generally have increased activity against gram negative bacteria with less activity against Gram positive bacteria. The higher generations are also relatively stable to beta- lactamases. Ceftriaxone has a longer half-life and can be administered in a once daily dose regimen (Martindale, 2007; BNF for children, 2012).

### 2.6.2. Pain Management

Pain in children with ACS may be described as uncomfortable, throbbing and strenuous. Pain may be deep somatic or visceral pain. Adequate analgesia allows patients to take deep breaths (Needlene *et al.*, 2002). Rees *et al* in 2003 suggested pain management in ACS should be done by the WHO analgesic ladder developed in 1986. Over the years the three step ladder has been abandoned for children in favour of a 2-step approach in the WHO guidelines on the pharmacological treatment of persisting pain in children with medical illness in 2012. The two steps also depend on a child's level of severity. There are limited numbers of analgesics that can safely be used in children. The WHO analgesic ladder suggests the management of pain based on certain underlined principles.

It suggests the use of appropriate route of analgesic administration whenever necessary. For persistent pain, medications are required to be given at regular intervals and not when required unless the pain episodes are actually intermittent and irregular. There should be rescue doses for breakthrough pain. It also suggests adapting and tailoring pain treatment to meet individual needs.

The 2-step approach involves

- For the first step, the management of pain should be started with non-opioids like paracetamol and ibuprofen with the dose increased to maximum, if necessary for mild to moderate pain. For patients, below 3 months paracetamol is the only option. Aside ibuprofen, no other NSAIDs has been studied in paediatrics in terms of efficacy and safety. There is evidence of superior analgesic property of ibuprofen than paracetamol in acute pain. Both of them have potential toxicity. Renal and gastrointestinal irritation and bleeding may

be associated with ibuprofen and other NSAIDs. Risk of hepatotoxicity may be associated with acute paracetamol overdose.

Ibuprofen and paracetamol are cheap, readily available and safer compared to other analgesics. They are also available in child appropriate dosage forms such as oral liquid forms. It is important that factors that can affect their metabolism like poor nutritional state, other medications and malnutrition are considered.

- The second step, for moderate and severe pain is to use a strong opioid. Morphine is the opioid of choice for this step. Bypassing the first step should be based on clinical judgment of the attending physician or medical team. For intolerable side effects of morphine, other opioids can be considered. There is a need for titration of opioid analgesics to the individual basis. The doses should be adapted in steps until the correct dose is attained based on the patients reaction to the medication. The goal of titration is to prevent child from experiencing pain between doses using the lowest effective dose. There is the need for frequent assessment of the child's pain relief response and adjusting the doses as necessary.

Differences in anti-inflammatory action of NSAIDs are small but there is considerable variation in individual responses and tolerance. Thus, it is important that the choice of NSAID for patients is individualized. NSAIDs reduce prostaglandins by inhibiting cyclooxygenase. Ibuprofen has an anti-inflammatory, analgesic and antipyretic effect. It has been shown to have the lowest side effect profile among the NSAIDs. Paracetamol is an analgesic and an antipyretic with negligible anti-inflammatory effect. It does not cause the respiratory depression by opioids and cause less irritation to the stomach as compared to NSAIDs (BNF for children, 2012).

Opioids are mainly for moderate to severe pain particularly of visceral origin. They are to be used with caution in patients with impaired respiratory function. They are to be avoided in acute respiratory distress and conditions which raise intracranial pressure. In addition to the respiratory distress, opioids may cause constipation, nausea, vomiting and hypotension. Strong opioids include morphine and tramadol and weak opioids include codeine and dihydrocodeine. Tramadol has two mechanisms of analgesia. It has an opioid effect and also can enhance serotonergic and adrenergic pathways. It produces less opioid side effects like constipation and respiratory depression (BNF for children, 2012).

### **2.6.3. Use of Bronchodilators**

Randomized control trials to assess the benefits and risks of inhaled bronchodilator therapy for ACS in SCD patients are lacking (Fawibe, 2008). A review by Bernard *et al.*, 2007 recommended that treatment with bronchodilators should be routine regardless of the presence or absence of audible wheezing. ACS patients with wheezing may respond to bronchodilators (Mak and Davies, 2003). In a study on the outcomes of ACS by Vchinsky *et al.*, in 2000, 61% of patients were reported to have been treated with bronchodilators, with a quarter of them improving clinically. ACS may also be involved with a reactive airway component with a high prevalence of asthma in sickle cell patients.

### **2.6.4. Blood Transfusion**

Transfusion has been shown to be a significant part of ACS management. It has been shown to significantly improve oxygen saturation and the partial pressure of oxygen (Vchinsky *et al.*, 2000; Emre *et al.*, 1995).

Transfusion as stated by Miller in 2011 can be associated with hyperhydrosis or haemolytic crises. These could be delayed in patients. Delayed haemolytic transfusion and hyperhydrosis syndrome presents as fever, haemoglobinuria and pain. This may occur even in completely matched cells (Talano *et al.*, 2003). Simple transfusion is clinically effective for most children (Miller, 2011). Transfusion may not impact on the duration of hospitalization, though it significantly increases haemoglobin levels (Nansseu *et al.*, 2015) and improves oxygenation (Vchinsky *et al.*, 2000).

Exchange transfusion has been found to be an important option for rapid or fast resolution of ACS. This suggests the involvement of vaso-occlusion or ischemia and infarction in ACS aetiology. Packed red blood cells are also preferred in certain cases to whole blood transfusion because it can reduce the risk of infections and immunogenic responses (Nansseu *et al.*, 2015). Although, packed cell increment may negatively affect viscosity as shown in in vitro studies (Miller 2011; Alexy *et al.*, 2006; Swedlow 2006; Lawson *et al.*, 1999)

A review by Alashimi *et al.*, 2010 suggests that there is no reliable evidence from randomized control trials to support or refute the use of blood transfusions. Decreased sickled red cells can improve clinical outcomes of patients (Mallouh and Asa, 1999). Transfusion delay should be avoided. Transfusions of red blood cells depend on degree of hypoxia, respiratory distress and anaemia. Prompt recovery for patients transfused within 24 hours of admission have been reported in a retrospective review by Miller in 2011.

#### **2.6.5. Intravenous Fluids**

Optimal hydration is necessary to maintain the volume and electrolyte balance of patients (Fawibe, 2007). Hydration needs care as over hydration can worsen patients' condition through pulmonary oedema (Ansong *et al.*, 2013; Haynes and Allison, 1986).

Pulmonary oedema can be prevented by loop diuretics. Furosemide is used extensively in children. It is important that electrolytes are monitored in patients on furosemide. Ototoxicity, gastrointestinal disturbances, postural hypotension and pancreatitis are side effects that may be associated with furosemide use.

Patients admitted for pain may also develop hyponatremia, which may likely happen in ACS patients due to sodium-losing nephropathy (Miller 2011; Radel *et al.*, 1976; Itano *et al.*, 1956). Reduction of the incidence and extent of hyponatremia and maintenance of sodium levels can be beneficial to patients (Miller 2011).

#### **2.6.6. Other Therapies**

Inhaled nitric oxide has also been shown as an attractive therapy in ACS. It is known to improve oxygenation in ACS conditions although it may not improve mortality in these cases. By increasing oxygenation it may reduce polymerization associated with hypoxic sickled cells (Laurie, 2010). Other supportive therapies include folic acid supplementation, prophylactic penicillin, and mechanical ventilation. A daily folic acid supplementation which has been a standard care is known to prevent megaloblastic anaemia.

#### **2.7. DURATION OF HOSPITALIZATION AND ACS COMPLICATIONS**

In the study by Nansseu *et al.*, 2015, hospital duration ranged from 3 to 12 days with a mean duration of 6.8 days. There was an associated mortality rate of 4.8% and this is comparable to 4% reported by Bertholdt *et al.* Averagely the length of duration for ACS has been reported to be about 5.4 days in children and 10.5 days in adults (Vchinsky *et al.*, 2000; Vichinsky *et al.*, 1997).

A history of cardiac disease, lower platelet counts and multilobar involvements have been indicated to predict the need for mechanical ventilation. Neurological

complications have also been shown to be common in hospitalized patients. Patients present with altered mental status, brain injury etc. Neurological complications may impact on the duration of hospitalization, respiratory failure and death. Cause of death in ACS patients has mainly been attributed to respiratory failure. Other causes include hypovolemia, sepsis, seizure and intracranial haemorrhage (Vchinsky *et al.*, 2000).

## **CHAPTER THREE**

### **3.0. METHODS**

#### **3.1. STUDY DESIGN/DATA COLLECTION**

The design of the study was retrospective. Medical records of all children (14 years and below) with SCD admitted to the sickle cell clinic of the Child Health Department, KATH in Kumasi from January, 2011 to December 2014 were carefully perused. Records of patients with at least an episode of ACS were then selected and reviewed by a single reviewer and included in the study. The total number of folders carefully perused was 1336. ACS cases identified within the study period were 107. Eight episodes of ACS with less detailed information (less than 20% of the required information) were not included in the analysis. ACS was defined according to the physician's diagnosis.

The requisite data on the clinical, laboratory and pharmacotherapy of each ACS episode were collected and analyzed. This included the demography, symptoms at diagnosis of the condition, laboratory findings (involving the complete blood counts, urinalysis, and kidney function tests), physical examinations, medical history and drug therapy.

The collected data was transferred on to a spreadsheet before data analysis was done using IBM SPSS statistics version 20.

### **3.2. PRETESTING OF DATA COLLECTION TOOL**

A structured data collection tool was employed in collecting the data. The pretesting was done to assess the data collection instrument's accuracy and feasibility in gathering relevant information for the study. The medical folders of 142 patients were carefully perused. The pretesting was done using 19 SCD patients with at least an episode of ACS. The actual collection of the data was done after a month of careful evaluation of the pilot study. The necessary changes to the data collection instrument to reflect results from the pretesting were done.

### **3.3. STUDY SITE**

The study was carried out at the sickle cell clinic of the Child Health Department at KATH. The hospital is one of the major teaching hospitals in Ghana. It is the second largest hospital in Ghana and the only tertiary hospital in the Ashanti region. The clinic is the only Sickle Cell Clinic in the Ashanti Region of Ghana and serves sickle cell patients in the northern sector of Ghana. The clinic has devoted and experienced specialists and physicians. This makes the SCD clinic of the hospital most suitable for this study.

### **3.4. SAMPLING OF PATIENTS**

Sample size calculation was done using the Cochran formula developed in 1977. The proportion of ACS episodes for the sample size calculation was estimated using 19 ACS episodes in 142 SCD cases obtained from the pilot study. Assuming a margin of error of 0.05 and a z value of 1.96 for a confidence interval of 95%, a minimum of 79 patients

was required for the study. The minimum sample size for the study was estimated using the formulas:

- Sample Size = (Distribution of 50%) / ((Margin of Error% / Confidence Level Score)<sup>2</sup>) and
- True Sample = (Sample Size X Population) / (Sample Size + Population - 1)

$$\begin{aligned} \text{The proportion of ACS episodes from the pilot study} &= \text{ACS episodes/SCD cases} \\ &= 19/142 = 0.134 \end{aligned}$$

$$\text{Proportion without ACS episodes} = 1 - 0.134 = 0.866$$

With a confidence interval of 95% and a margin of error of 5%, the minimum sample size required =  $(0.134 \times 0.866) / (0.05/1.96)^2 = 178$

$$\begin{aligned} \text{The true sample size required will thus be} &= (178 \times 142) / (178 + 142 - 1) \\ &= 79+ \end{aligned}$$

The minimum sample size needed for the study was 79 patients.

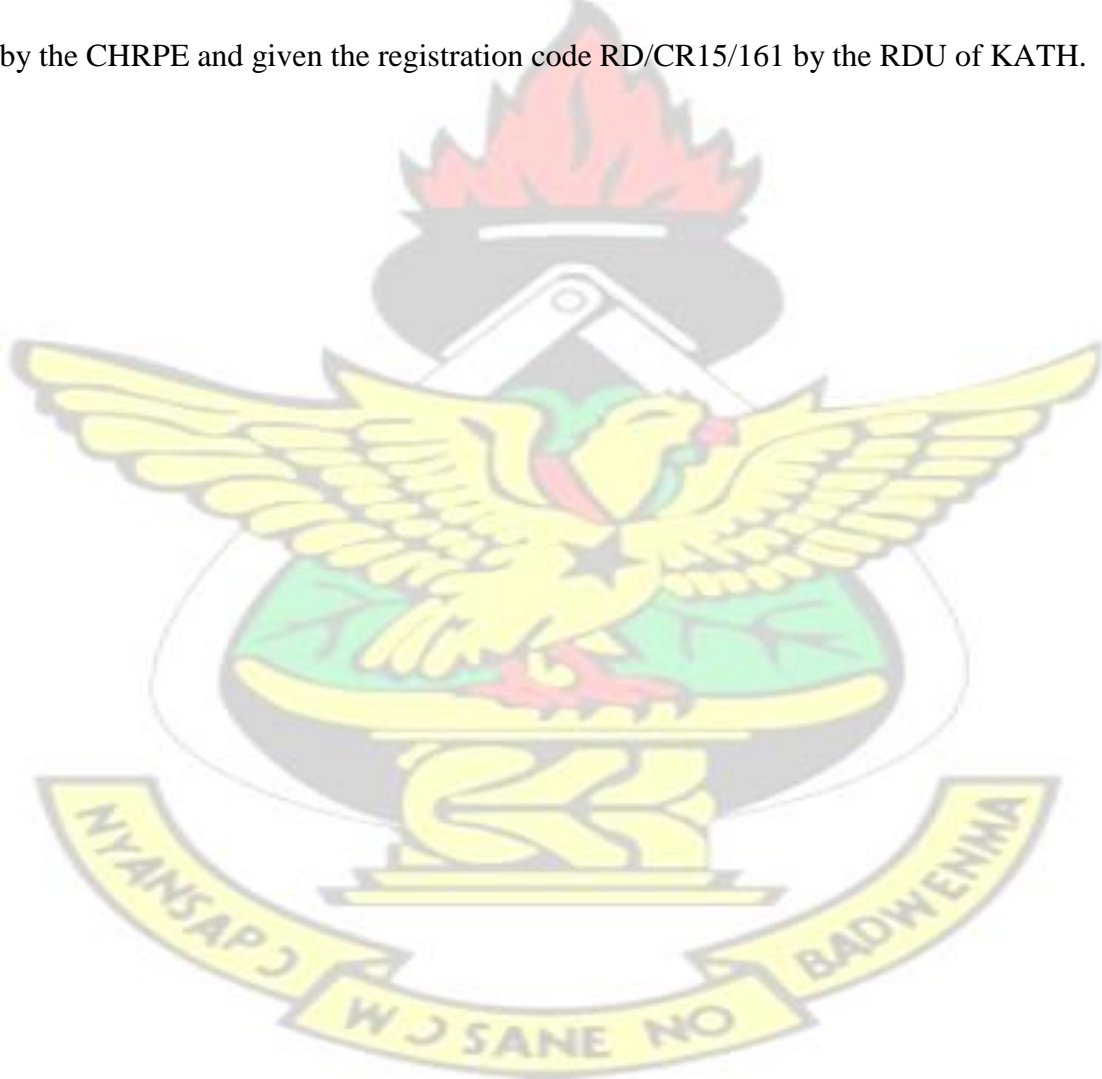
### 3.5. STATISCAL ANALYSIS

Statistical software used was SPSS, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Graphs were drawn using Microsoft Excel, 2010. Results are expressed as mean (Standard Deviation) or count (proportion) as appropriate. The chi-square ( $\chi^2$ ) with Fisher's exact test was used to analyze categorical variables such as the presence or absence of a symptom. The Student t test or the one way analyses of variance were used to analyze the difference in means between comparable groups or values. When assumptions for parametric test were not met, the Kruskal-Wallis test was used. Odds ratios with 95 % confidence intervals were used to appreciate the impact of different

variables on the duration of hospital stay, and were calculated by logistic regression analyses. All confidence intervals were two-sided, and a P value of  $< 0.05$  was considered to indicate statistical significance.

### **3.6. ETHICAL APPROVAL**

A proposal of the study was sent to the Committee on Human Research, Publications and Ethics (CHRPE) of the School of Medical Sciences, KNUST and the Research and Development Unit (RDU) at the KATH for approval. The study protocol was approved by the CHRPE and given the registration code RD/CR15/161 by the RDU of KATH.



## CHAPTER FOUR

### 4.0. RESULTS

#### 4.1. DEMOGRAPHIC CHARACTERISTICS AND CLINICAL PRESENTATION

##### 4.1.1. Population characteristics

###### 4.1.1.1. Prevalence

The hospital case prevalence of ACS was 8%, with a rate of 2.2 ACS episodes per month. Of the 107 patients, 58.4 % (n = 55) were admitted with ACS. The remaining (48.6%, n=52) were admitted with vaso-occlusive crises (VOC) (n=33) and bronchopneumonia (n=19) but they later developed ACS during the hospital stay.

###### 4.1.1.2. Age and Sex of patients

The patients' ages ranged from 8 months to 14 years. The mean age was  $5.7 \pm 3.5$  years. The mean age for the males was  $5.3 \pm 3.5$  years and that of females was  $6.3 \pm 3.6$  years. There was no difference in the proportion of males and females with ACS, according to age,  $p = 0.061$  (Table 4.1).

Fifty five percent (n = 51) were males and 45 % (n = 42) were females. About Forty percent (n = 43) of the study subjects were within the age group 5 to 9 years, followed by 31.8 % (n = 34) in the age group 2 to 4 years, 17.8% (n = 19) in 10 to 14 years and 10.3% (n = 11) who were less than 2 years (Table 4.1). The average weight and height of the patients were  $17.2 \pm 6.4$  kg and  $108.3 \pm 23$  cm respectively.

**Table 4.1. Characteristics of the Study Population Stratified by Age**

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**Sex** All <2 years 2-4 5-9 10-14 P value† patients years years years

	n (%)	n (%)	n (%)	n (%)	n (%)	
Male	59 (55)	10(91)	18(53)	23(53)	8(42)	0.061
Female	48(45)	1(9)	16(47)	20(47)	11(58)	
Total	107 (100)	11(10.3)	34(31.8)	43(40.2)	19 (17.8)	

‡ P value was calculated by chi-square analyses, p value ≤ 0.05 was considered statistically significant

About 76% (n=81) had their haemoglobinopathies documented. Of these, 71.6 % (n = 58) had sickle cell anaemia (HbSS), 24.7 % (n = 20) had HbSC, and 3.7 % (n = 3) had other forms of SCD (sickle cell β-thalassemia (HbS β+-thal and HbS β0-thal)

#### 4.1.2. Past Medical History of Patients

Of the 107 cases, 48.6% (n = 52) were on prophylactic antibiotic therapy with phenoxymethyl penicillin. Forty three percent (n = 46) had been previously admitted and 30% (n = 31) had previously received transfusion. Previous development of vasoocclusive crises (VOC) was found in 4.7% (n = 5) of the cases (Table 4.2).

**Table 4.2. Past Medical and Drug History of the Patients**

Variable	n (%)
Prophylactic antibiotic therapy	52(48.6)
Previous admission	46(43.0)
Blood Transfusion	31(30.0)
VOC*	5 (4.7)
Surgery	2(1.9)
Asthma	2(1.9)
Sepsis	2(1.9)
Mesenteric crises	2(1.9)
Osteomyelitis	2(1.9)
Cardiac disease	1(0.9)
Hepatomegaly	1(0.9)
Haemolytic crises	1(0.9)
Pneumonia	1(0.9)

**\*VOC – Vaso-occlusive crises**

### **4.1.3. Presenting symptoms and signs of ACS**

The common presenting symptoms of ACS were fever and cough, which occurred in 74.8% (n = 80) and 65.4% (n = 70) of the patients, respectively. Other presenting symptoms included chest pain (37.4%, n = 40), shortness of breath (29.9%, n = 32), pallor (24.3%, n = 26), tachypnoea (13.1%, n = 14), lethargy (10.3%, n = 11) and pains in the arm and leg (7.5%, n = 8).

Rhinorrhoea and Irritability were more common in younger patients (< 5 years), p = 0.012 and p = 0.001 respectively. The occurrence of abdominal and chest pain were more common in older patients (≥ 5 years), p = 0.024 and <0.001 respectively (**Table 4.3**).

**Table 4.3. Presenting Symptoms of Patients with ACS Stratified by Age**

Symptoms	<2 years (n = 11)	2 - 4 years (n = 34)	5 - 9 years (n =43)	10 - 14 years (n = 19)	P value‡
Fever (%)	72.7	79.4	74.4	68.4	0.084
Cough (%)	72.7	76.5	58.1	57.9	0.138
Abdominal pain (%)	0	17.6	34.9	31.6	0.024
Chest pain (%)	9.1	11.8	58.1	52.6	<0.001
Irritability (%)	27.3	11.8	0	0	0.001
Rhinorrhoea (%)	27.3	32.4	11.6	5.3	0.012

**‡ P value was calculated by chi-square analyses, p value ≤ 0.05 was considered statistically significant**

Vital signs were taken at the presentation ACS. Eighty five percent (n = 91) of the patients had a respiratory rate greater than 30 beats per minute. About 58 % (n = 62) of the patients showed abnormal physical signs on examination. This was manifested as

flaring alae nasi, intercoastal recession and lower chest in-drawing. Forty two percent (n = 45) of the patients showed no abnormal physical signs on examination.

The mean temperature and heart rate were  $38 \pm 0.9^{\circ}\text{C}$  and  $45 \pm 12.0$  beats per minute respectively (**Table 4.4**)

**Table 4.4. Vital findings on examination of the ACS patients**

Variable	Mean	$\pm$ Standard deviation
Respiratory rate (per min)	45	12.0
Temperature ( $^{\circ}\text{C}$ )	38	0.9
Heart rate (beats/ min)	127	21.0

#### 4.1.4. Laboratory Investigations

Full blood count was performed in 94 out of the 107 cases. The haemoglobin concentration at the time of diagnosis was below 12.0 g/dl in most patients with a mean of 7.38 g/dl. Red cell count and mean cell haemoglobin concentration were also low with averages of  $2.9 \times 10^{12}$  cells/L and 33.6% respectively (**Table 4.5**).

Blood counts showed very high levels of leukocytes and neutrophil count with mean values of  $27.5 \times 10^9$  cells /L and  $14.7 \times 10^9$  cells/ L respectively (**Table 4.5**).

**Table 4.5. Summary of laboratory findings**

Lab investigations	Minimum	Maximum	Mean	$\pm$ SD	Standard ranges
Haematocrit (%)	9.3	37	22	4.1	35 – 49
Haemoglobin (g/dL)	2.4	12.5	7.38	1.5	12.0 – 17.5
Leukocytes( $10^9$ /L)	4.2	104.3	27.5	17	4.5 – 11.0
Erythrocytes( $10^{12}$ /L)	1.5	4.5	2.9	0.65	3.8 – 5.7
Platelet( $10^9$ /L)	63	839	374.8	164.8	150-450
Monocytes( $10^9$ /L)	0.4	7.61	2.3	1.5	0.2 – 1.0

Neutrophil( $10^9/L$ )	0.75	47	14.7	10.9	2.0 – 7.0
Urea(mmol/L)	0.78	8.4	2.4	1.3	1.1 – 2.2
Mean Cell Haemoglobin concentration(g/dL)	21.6	38.4	33.6	2.5	33 – 37
Mean cell haemoglobin(pg)	2.5	31	25.0	3.7	26 – 34

When stratified by age, the mean lymphocyte count was significantly different among the age groups,  $p = 0.03$  (Table 4.6).

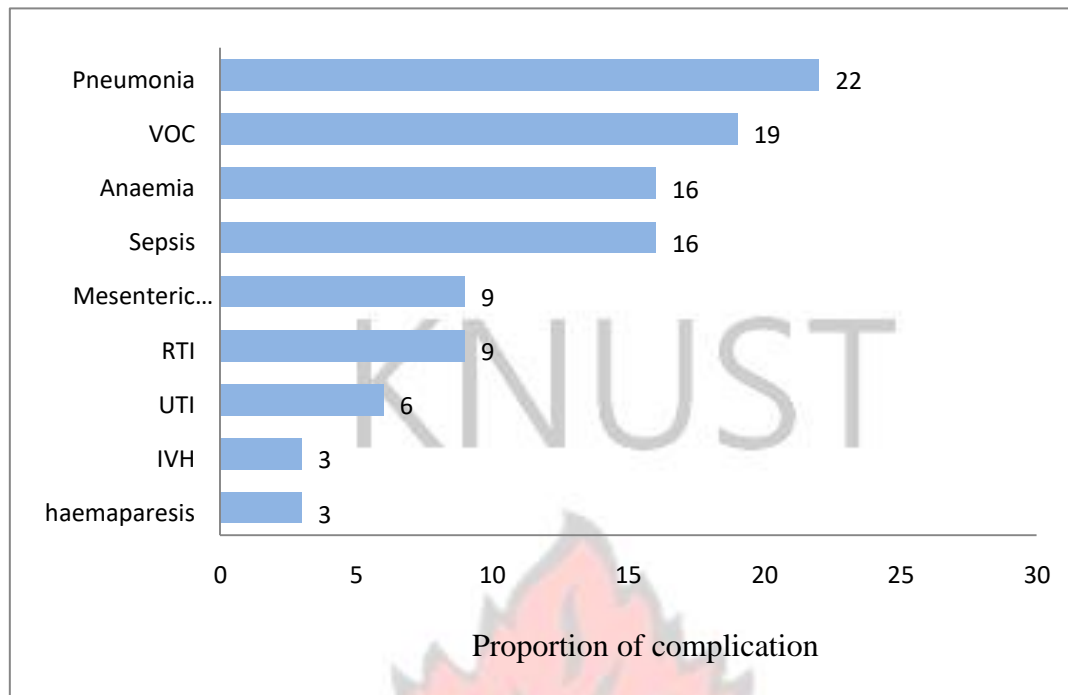
**Table 4.6. Mean Lymphocyte count stratified by age**

Variable	All patients	<2 years	2-4 years	5-9 years	10-14 years	P value
Lymphocytes ( $10^9/L$ )	6.1(4.7)	13(7.8)	7.5(6.0)	4.9(1.9)	3.7(2.1)	0.03 <sup>‡</sup>

<sup>‡</sup> P value was calculated by ANOVA,  $p$  value  $\leq 0.05$  was considered statistically significant

#### 4.1.5. Other complications encountered by patients after ACS diagnosis

Thirty two cases of complications were reported in the ward. Twenty two percent ( $n = 7$ ) were bronchopneumonia, 19% ( $n = 6$ ) were VOC, 15 % ( $n = 5$ ) were anaemia and another 15% ( $n = 5$ ) were sepsis. Less common complications observed were haemaparesis (3%,  $n = 1$ ) and intraventricular haemorrhage (3%,  $n = 1$ ) (Figure 4.1).



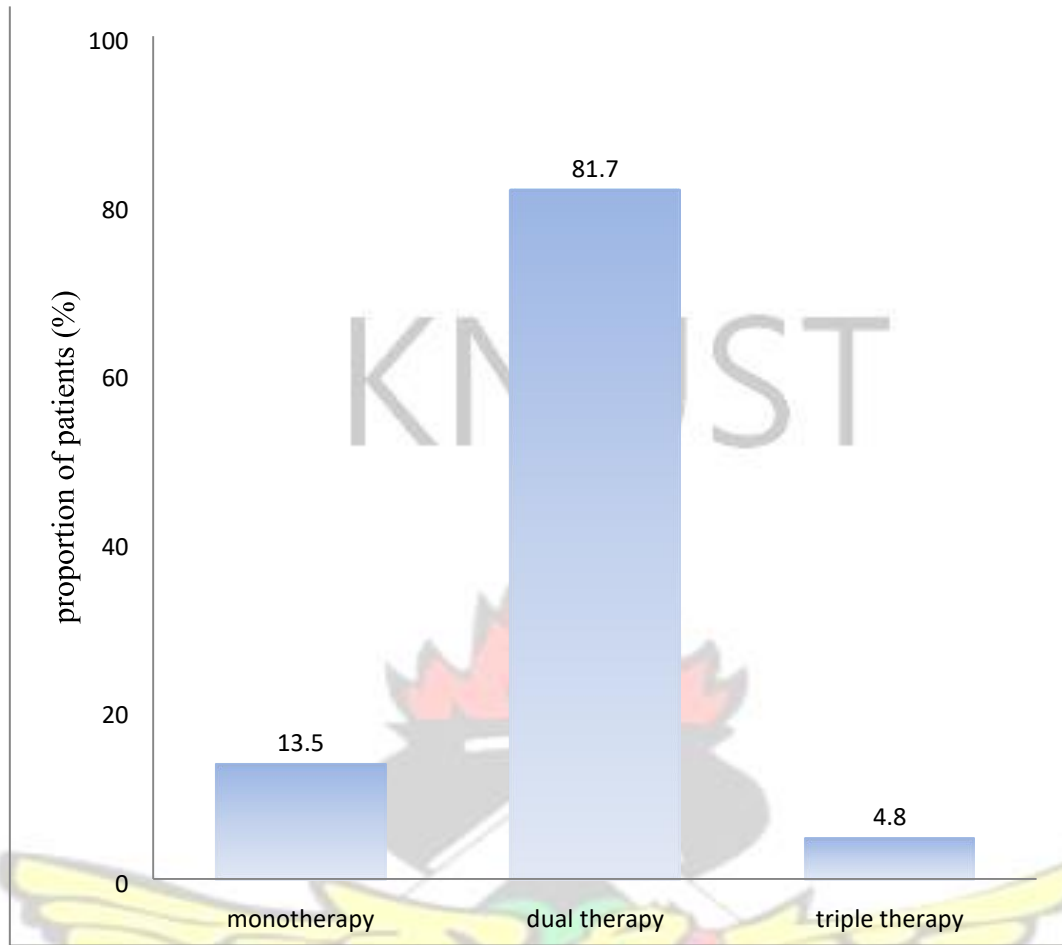
**Figure 4.1. Proportion of Developed Complications**

\*VOC – Vaso-occlusion crisis, RTI – Respiratory tract infection, UTI – Urinary tract infection, IVH - Intraventricular haemorrhage

## 4.2. MANAGEMENT OF ACS

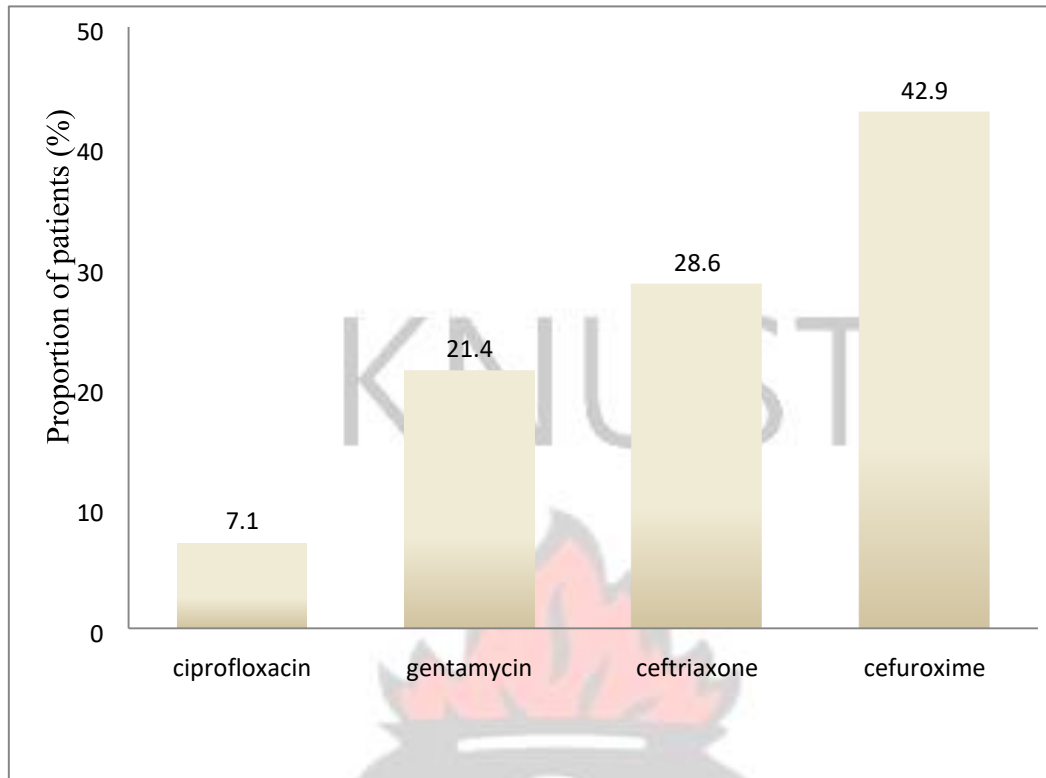
### 4.2.1. Antibiotic use in ACS patients

Of the 107 patients, 97.2% (n = 104) were given antibiotics. Of these, 13.4% (n = 14) were given one antibiotic, 81.7% (n = 85) were given two antibiotics and 4.8% (n = 5) were given three antibiotics (**Figure 4.2**).



**Figure 4.2. Pattern of antibiotic administration**

Of the patients who received one antibiotic ( $n = 14$ ), 42.9% ( $n = 6$ ) were given IV cefuroxime, 28.6% ( $n = 4$ ) were given IV ceftriaxone, 21.4% ( $n = 3$ ) were given IV gentamicin, and one patient was given IV ciprofloxacin (**Figure 4.3**).



**Figure 4.3. Pattern of antibiotic administration as a monotherapy**

For the patients who were given two antibiotics (n = 85), 98.8% (n = 84) received two antibiotics (cefuroxime and gentamicin) after initial diagnosis of ACS, with the replacement of cefuroxime with ceftriaxone in patients with persistent fever (n = 10, 11.9%). Gentamicin therapy was discontinued a day before discontinuation of cefuroxime therapy in patients that received both antibiotics. Gentamicin was administered in one daily dosage regimen with cefuroxime and ceftriaxone being administered in an 8 hourly and 24 hourly respectively. Dose range for gentamicin was 3 - 9mg/kg after calculations of administered doses with respect to the weight of patients. Twenty five percent (n = 21) of patients on the gentamicin and cefuroxime therapy received <5mg/kg body weight dose for gentamicin.

One patient had both Gentamicin and Ciprofloxacin (**Table 4.7**). For those who received three antibiotics (n = 5), four had Cefuroxime with Gentamicin and Ciprofloxacin. One patient had Cefuroxime with Gentamicin and Crystalline penicillin (**Table 4.7**).

**Table 4.7. Pattern of Antibiotic Administration as a Dual and Triple Therapy**

Antibiotic Therapy	n (%)
<b>Dual therapy</b>	
Cefuroxime + Gentamicin	84 (98.8)
Gentamicin + Ciprofloxacin	1 (1.2)
<b>Total</b>	<b>85 (100)</b>
<b>Triple therapy</b>	
Cefuroxime + Gentamicin + Ciprofloxacin	4 (80)
Cefuroxime + Gentamicin + Penicillin	1 (20)
<b>Total</b>	<b>5 (100)</b>

#### 4.2.3. Bacteria isolates from culture

Blood culture information was available for 79 of the 107 patients (80 %). Of these bacteria growth were found in 12 (15.2%) of the cases. The bacteria isolated are as shown in **Table 4.8**. In one culture the isolated bacteria was not stated although the presence of a bacteria growth was stated.

**Table 4.8. Bacteria Isolated in the ACS Cases**

Bacteria present	Number of cases
Bacillus spp.	3
Coliforms	2
Klebsiella spp.	2
Coagulase negative staphylococcus	2
Staphylococcus spp.	1

#### 4.2.4. Antibiotic Treatment for the Infection Complications

Seventeen cases of infectious complications were reported. Of these, 7 were bronchopneumonia, 5 were sepsis, 3 were respiratory tract infections and 2 were urinary tract infection cases.

Of the seven bronchopneumonia cases, 3 were managed with ciprofloxacin, 2 were managed with ciprofloxacin and clindamycin and 2 were managed with Amoxicillin/clavulanic acid (Amoksiklav) (Table 4.9).

Of the five sepsis cases, 3 were managed with ciprofloxacin and 2 were managed with both amoksiclav and ciprofloxacin (Table 4.9).

Urinary tract infections in the patients were managed with erythromycin and the respiratory tract infections were managed with Amoxicillin/clavulanic acid (Table 4.9).

Fifteen of the cases were seen in patients on dual therapy with Gentamicin and Cefuroxime. Of the 15 patients, 3 received <5mg/kg body weight of gentamicin.

**Table 4.9. Antibiotic Treatment of Infectious Complications**

Antibiotic treatment	n (%)
<b>Bronchopneumonia</b>	
Ciprofloxacin	3 (42.9)
Ciprofloxacin + Clindamycin	2 (28.6)
Amoxicillin/clavulanic acid	2 (28.6)
<b>Total</b>	<b>7 (100)</b>
<b>Sepsis</b>	
Amoxicillin/ clavulanic acid	3 (60)
Ciprofloxacin	2 (40)
<b>Total</b>	<b>5 ( 100)</b>
<b>Respiratory tract infection</b>	
Amoxicillin/clavulanic acid	3 (100)

## Urinary tract infection

Erythromycin

2 (100)

### 4.2.5. Penicillin prophylaxis, Folate and vitamin supplementation

As part of the management of ACS, patients were given prophylaxis against infection, folic acid therapies as well as vitamin supplements. Thirty eight percent (n = 41) of the study participants received phenoxymethyl penicillin (penicillin V) as prophylaxis against infection. Sixty seven percent (n = 72) of the patients had folic acid and 29.9% (n = 32) of the patients had zincovit.

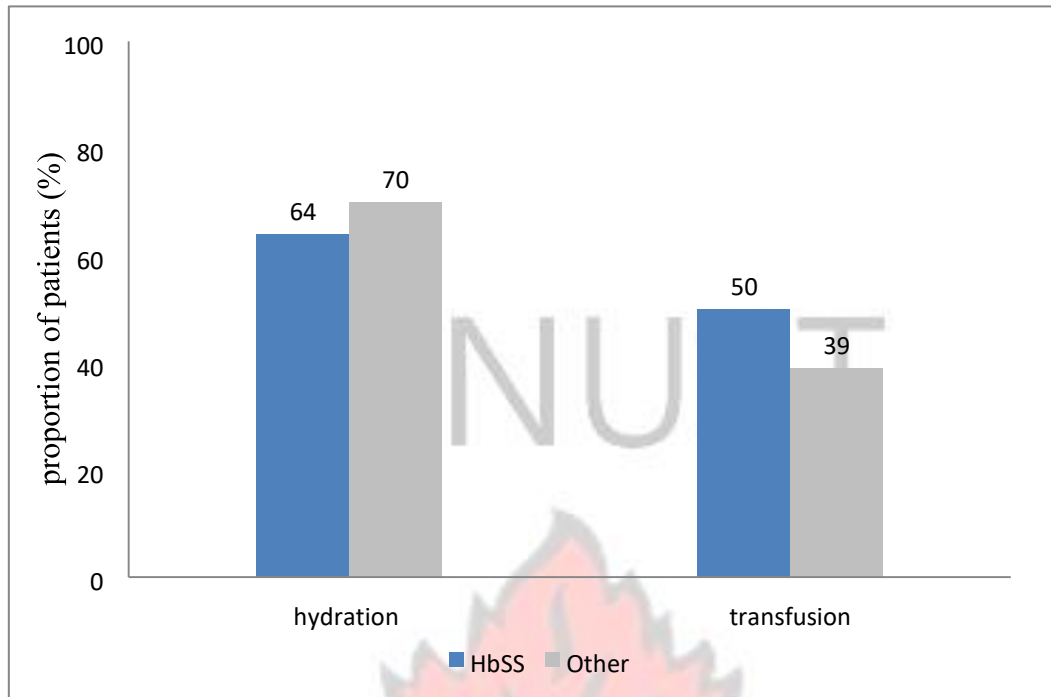
### 4.2.6. Hydration and Blood transfusion

Adjuvant therapy including IV fluids and blood transfusion was administered to 81% (n = 87) of the patients. Those who received IV fluids alone were 39 (44.8%). Those who received blood transfusion alone were 15 (17.2%) and those who received both were 33 (37.9%) (Table 4.10). Of the patients who received blood transfusion (n = 48), 66.7% (n = 32) were given packed red cells while 33.3% (n = 16) received whole blood.

**Table 4.10. Fluids Administered to Patients**

Therapeutic options	n(%)
IV fluids alone	39 (44.8)
IV fluids + transfusion	33 (37.9)
Transfusion alone	15 (17.2)
<b>Total</b>	<b>87 (100)</b>

Patients who received transfusion and IV fluids in the study population as stratified by haemoglobinopathy are shown in figure 4.4. Fifty percent of the sickle cell anaemic patients received transfusion compared to the 39% of patients with other haemoglobinopathies (Figure 4.4).



**Figure 4.4. Hydration and Transfusion Stratified by Haemoglobinopathy**

The mean volume of hydration and transfused blood was significantly different among the different age groups,  $p = 0.03$  and  $p < 0.001$  respectively (**Table 4.11**). **Table 4.11. Mean Volumes of Hydration and Transfusion Stratified by Age**

Fluid administered	<2years	2-4years	5-9years	10-14years	P value†
IV fluids volume(ml)	189	255	398	602	0.03
Transfusion volume(ml)	1117	1609	1844	2500	<0.0001

†P value was calculated by Kruskal-Wallis test,  $p \text{ value} \leq 0.05$  was considered statistically significant

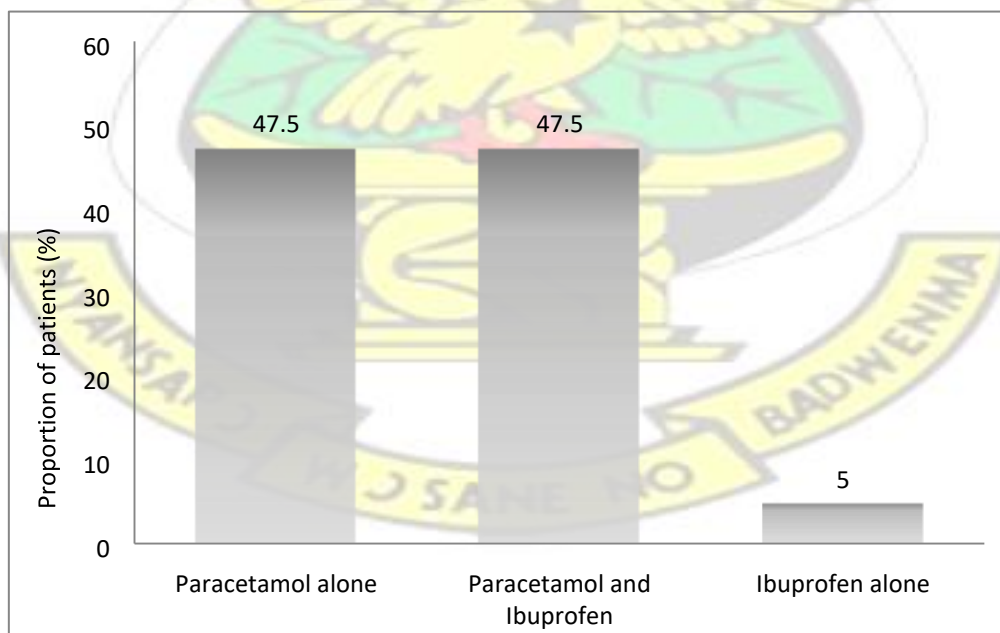
Of the 107 patients, 39% ( $n = 37$ ) received furosemide. Of these, 62.1% ( $n = 23$ ) were given blood transfusion and IV fluids, 24.3% ( $n = 9$ ) were given only transfusion and 13.5% ( $n = 5$ ) were given only IV fluids (**Table 4.12**).

**Table 4.12. ACS Patients who received Furosemide for the Prevention or Management of Fluid Overload**

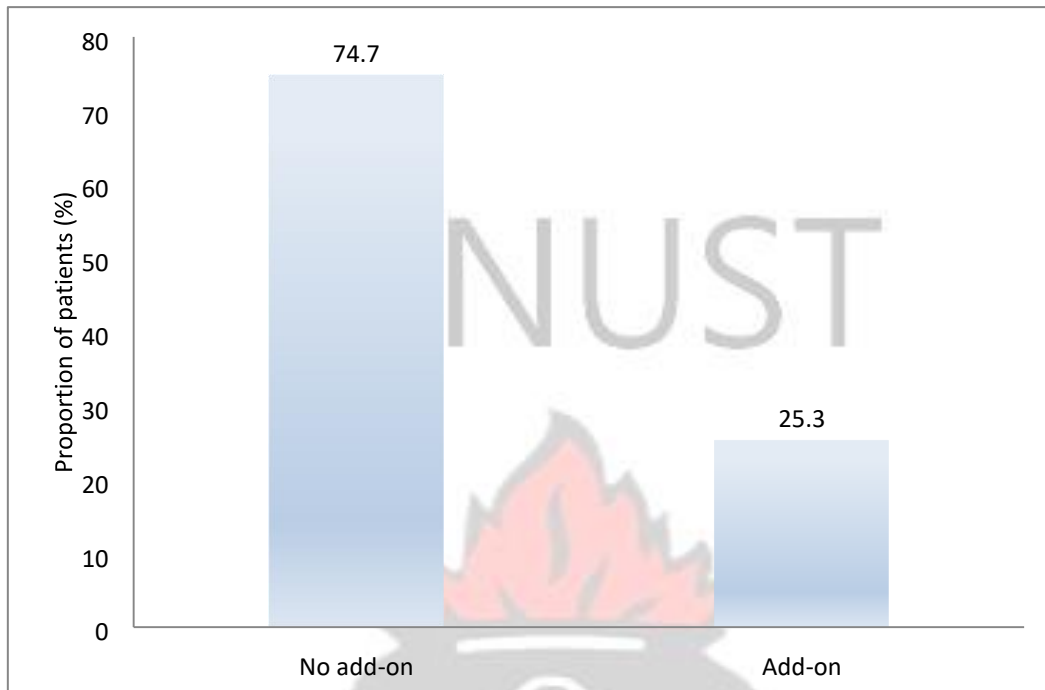
Fluid administered	Proportion who received furosemide
IV fluids + transfusion (n=33)	23 (62.1)
IV fluids only (n = 39)	9 (24.3)
Transfusion only (n = 15)	5 (13.5)
<b>Total</b>	<b>37 (100)</b>

#### 4.2.7. Management of Pain and Pyrexia

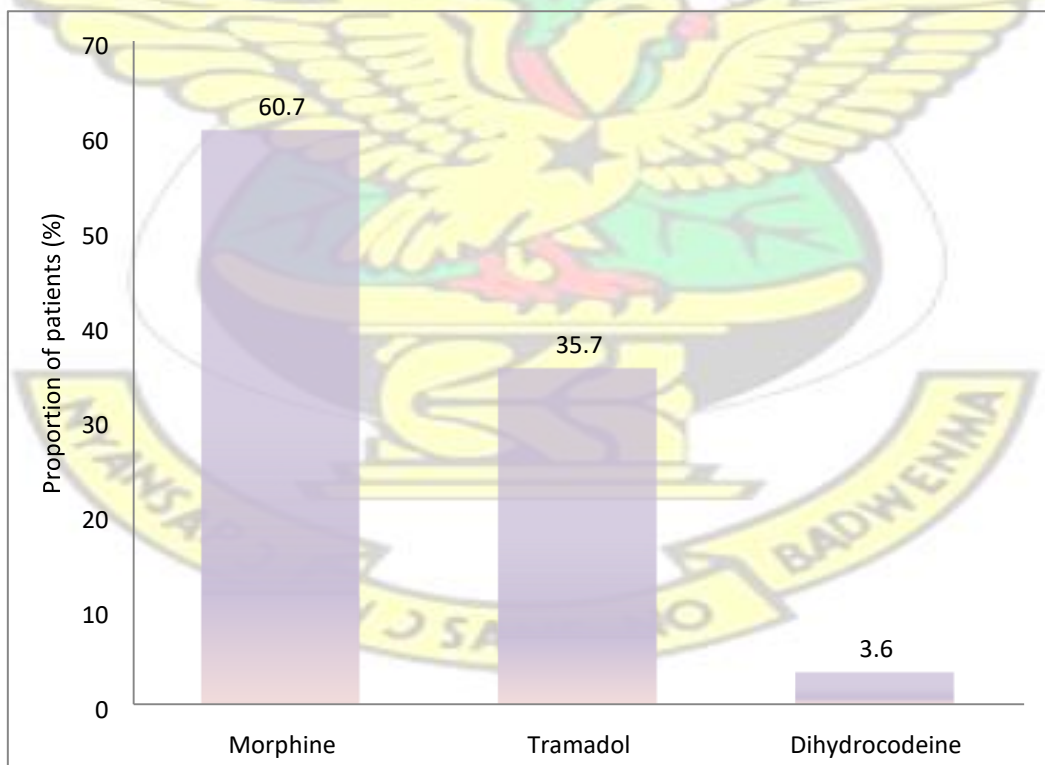
Of the 107 patients, 94 received paracetamol for pain and fever initially, and 5 had ibuprofen (**figure 4.5**) and 8 received no analgesic. Of the 94 who received paracetamol, 47 received ibuprofen in addition to the paracetamol for initial pain management (**figure 4.5**). About 75% (n = 74) of the patients, who received analgesics for initial pain management, had their pain managed with no added on opioid analgesic (**figure 4.6**). The opioid analgesics that were often prescribed were morphine and tramadol as shown in **figure 4.7**.



**Figure 4.5. Proportion of Initial Analgesic Administered to Patients**



**Figure 4.6. Analgesic Prescription Modifications in Patients**



### Figure 4.7. Opioid Analgesic Administration

Of the 47 patients who were given paracetamol in addition with ibuprofen to for pain management, 12.8% (n = 6) had IM diclofenac as a stat dose in addition, 4% (n = 2) had tramadol added to the ibuprofen and paracetamol (**Table 4.13**). Eleven percent (n = 5) had morphine in addition to paracetamol and ibuprofen, and 8.5% (n = 4) had tramadol and morphine added on to their therapy for pain (**Table 4.13**). One patient also had tramadol dihydrocodeine and morphine added on to the initial ibuprofen and paracetamol therapy (**Table 4.13**).

**Table 4.13. Add-on Analgesics to Patients on Initial paracetamol and Ibuprofen**

Drug	n(%)
No add-ons	35 (74.5)
Tramadol + morphine	4 (8.5)
Morphine	5 (11)
Tramadol	2 (4.3)
Tramadol with dihydrocodeine + morphine	1 (2.1)
<b>Total</b>	<b>47 (100)</b>

Of the other 47 patients who had paracetamol but no ibuprofen, 10.6% (n = 5) had received an initial dose of IM diclofenac. Seven patients (14.9%) had morphine added on to their baseline therapy. Two patients (4.3%) had tramadol added to paracetamol at baseline for pain (**Table 4.14**). One patient (2.1%) had tablet diclofenac added to the paracetamol for pain therapy (**Table 4.14**). The remaining 37 patients were maintained on paracetamol without addition of any other analgesic.

**Table 4.14. Add-on Analgesics to Patients on Initial Paracetamol Therapy**

Drug	n(%)
No add-ons	37 (78.7)

Morphine	7 (14.9)
Tramadol	2 (4.3)
Diclofenac	1 (2.1)
<b>Total</b>	<b>47 (100)</b>

Of the 5 patients given ibuprofen only at baseline for pain, 2 had a stat dose of IM diclofenac in addition, and another 2 were given tramadol as add on to the ibuprofen. One patient however, had morphine added to the baseline pain management with ibuprofen (Table 4.15).

**Table 4.15. Add-on Analgesics to Patients on Initial Ibuprofen Therapy**

Drug	n(%)
Tramadol	2 (40)
No add-ons	2 (40)
Ibuprofen	1 (20)
<b>Total</b>	<b>5 (100)</b>

#### 4.2.8. Other Supportive Treatment

These included inhaled nitric oxide to 19.6% (n = 21) patients. Bronchodilators were given to 3 patients representing 2.8% of the study population. Of these, 2 had salbutamol nebulizer and one patient had Budesonide inhaler (pulmicort), for the breathlessness associated with ACS in the sickling patients.

#### 4.2.9. Anti-malaria Treatment

Of the 107 patients, 43.9% (n = 47) received anti-malaria treatment, and among those, 57.4% (n = 27) were confirmed clinically as having malaria.

With regards to the anti-malaria treatment, 23.4 % (n = 11) received artesunate injection stat, after which they were put on artemether/lumefantrine for 3 days. The remaining

68% (n = 32) were given artemether/lumefantrine, Three patients (6.4%) received only artesunate injection and one patient received quinine for 3 days. All the patients were successfully treated for malaria.

#### 4.2.10. Duration of Hospitalization

The duration of hospitalization ranged from 2 to 18 days. Patients spent an average of  $6.6 \pm 3.4$  days in the hospital. Forty two percent (n = 45) of the patients spent more than 6 days in the hospital. Patients placed on ceftriaxone after initial antibiotic treatment failure spent an average of  $8.9 \pm 4.6$  days in the hospital. Patients who received transfusion were 2.29 times more likely to spend more than 6 days in the hospital (p = 0.04). Age, sex, haemoglobinopathy, hydration, morphine use and number of antibiotics did not impact the length of hospital stay (**Table 4.16**).

**Table 4.16. Factors affecting duration of Hospitalization (above 6 days)**

Variable	Odds ratio	P value
<b>Age</b>		
< 2 years	1	
2 - 4 years	1.429	0.621
5 - 9 years	0.680	0.585
10 - 14 years	0.286	0.140
<b>Gender</b>		
Male	1	
Female	0.643	0.270
<b>Haemoglobinopathy</b>		
HbSS	1	
Other	0.742	0.554
<b>Antibiotics used</b>		
Mono	1	
Dual	0.766	0.645
Triple	1.500	0.702
<b>Transfusion</b>		
No	1	
Yes	2.29	<b>0.040</b>
<b>Hydration</b>		
No	1	
Yes	0.948	0.901

<b>Morphine</b>	No	1	
	Yes	1.509	0.402

## CHAPTER FIVE

### 5.0. DISCUSSION

#### 5.1. PREVALENCE OF ACS AND ITS CLINICAL PRESENTATION

The rate of occurrence of ACS was 2.2 episodes per month, with a case prevalence of 8%. The rate of ACS per month was higher than rates in studies from Brazzaville, Antananarivo and French Guiana, which showed prevalence rates of 1.4, 0.3 and 0.2 episodes per month respectively. The prevalence in this study is comparable to that reported in Cameroon and Brussels (i.e. 2.1 and 1.9 episodes per month respectively). The prevalence is lower than the 12.8% and 50% reported by Castro *et al.* and Golden *et al.* respectively (Nansseu *et al.*, 2015; Golden *et al.*, 1998; Castro *et al.*, 1994). The prevalence could be higher as patients perform a single chest x-ray for the diagnosis of ACS. However, chest x-ray used in the diagnosis may not always show positive development at early stages of the condition which might lead to several cases being overlooked (Neocleous *et al.*, 2013; Rucknagel *et al.*, 2001; Vchinsky *et al.*, 2000).

Majority of the patients were sickle cell anaemia (HbSS) patients and patients from the ages 2 to 9 years. However, fewer numbers of cases were reported in patients less than 2 years old. This may be attributed to a higher percentage of foetal haemoglobin (HbF) in patients in this age group. A high proportion of HbF has been shown to lower the risk of ACS by reducing intermolecular binding and polymer formation involved in sickling process (Lamar *et al.*, 2012; Dipiro *et al.*, 2008).

Patients most commonly presented with ACS on admission. Children have been reported in studies elsewhere to present with ACS on admission compared to adults who mainly develop ACS after admission for VOC (Habibi *et al.*, 2014).

Nevertheless, 31% of the patients presented with VOC on admission and later developed ACS. This may support reports that suggest a relationship between VOC and ACS (Neocleous *et al.*, 2013; Miller and Gladwin, 2012; Bernard *et al.*, 2007; Martin and Buonomo, 1997).

The signs and symptoms observed in the patients involved in the study was consistent with those reported in previous studies (Nansseu *et al.*, 2014; Taylor *et al.*, 2003; Vchinsky *et al.*, 2000; Vchinsky *et al.*, 1997). The common symptoms reported in this study were fever and cough. There was an observed age dependency of presenting symptoms. Rhinorrhoea and irritability occurred mostly in younger patients (< 5 years). Abdominal pain and chest pain occurred mainly in older patients ( $\geq 5$  years) as self-reporting may be difficult in children (Bernard *et al.*, 2007; Taylor *et al.*, 2003; Vchinsky *et al.*, 2000). The occurrence of fever and cough was however not age dependent which is similar to findings by Vchinsky *et al.*, in 1997.

More than half of the patients in the study presented with abnormal physical signs. This is consistent with observations reported by Agtmael *et al.* in 1994, which suggests that majority of ACS patients, may present with abnormal physical signs. Nevertheless, a considerable number of patients presented with normal physical signs as reported in other studies (Taylor *et al.*, 2004; Vchinsky *et al.* 1997). This may make diagnosis and management in such patients delusive and difficult.

The mean values of haemoglobin concentration hematocrit and red cell count were lower in patients. Anaemia is seen as a significant predictor of ACS in SCD patients

(Dipiro *et al.*, 2008). High leucocyte counts were also recorded in the patients. This may suggest the involvement of infection in the aetiology of ACS in the patients although blood culture revealed the presence of bacteria in only 15.2% of patients.

The estimated mean duration of hospitalization of  $6.6 \pm 3.4$  days seen in this study was similar to the 5.4 days and 6.8 days reported by Vchinsky *et al.* in 1997 and Nansseu *et al.* in 2015 respectively. The mean duration is lower than the 10 days of hospitalization reported in another study by Vchinsky *et al.* (Vchinsky *et al.*, 1997; Vchinsky *et al.*, 2000). The duration of hospitalizations for both male and female were similar.

## **5.2. BACTERIA ISOLATES AND ANTIBIOTIC MANAGEMENT**

Microorganisms identified in the 12 out of 79 ACS cases included *Bacillus* spp., Coliforms, *Klebsiella* spp. and *Staphylococcus* spp. This was different from those reported in other studies which suggest involvement of *Mycoplasma* spp., and *Chlamydia* spp. (Harris *et al.*, 2011; Lin *et al.*, 2009; Vichinsky *et al.*, 2000). However, in a study by Nansseu *et al.* in 2015 from Cameroun, no bacteria were identified in bacteria culture.

Without invasive techniques involving bronchoscopy, it is recommended that infection should not be ruled out in ACS. Penicillin prophylaxis which has been instituted in the hospital for SCD patients might have helped reduce etiological involvements by *Streptococcus* and *Staphylococcus* species. This might have resulted in an increased role of atypical bacteria in the ACS development as reported in several studies (Harris *et al.*, 2011; Lin *et al.*, 2009; Vichinsky *et al.*, 2000). Atypical organisms and viruses may require advanced methods like immunofluorescent staining and immunofluorescent antibody techniques for detection, which may be lacking in available facilities (Waites *et al.*, 2004; Neumayr *et al.*, 2003; Robison,

1995)

Regardless of blood culture, most studies and standard guidelines suggest that full antibiotic therapy should be given to patients (Howard *et al.*, 2015; Miller, 2011; Ansong *et al.* 2013; Awogbade *et al.*, 2012; Fawibe, 2007; National Heart, Blood and Lung Institute, 2002). From the study, 97.2% of patients received antibiotic therapy. The preferred therapy involved combination of more than one antibiotic. Patients were mainly given a combination of cefuroxime and gentamicin, with the replacement of cefuroxime with ceftriaxone in patients with persistent fever. Ciprofloxacin was the preferred antibiotic for the management of bronchopneumonia. With amoxicillin + clavulanic acid and erythromycin being preferred in managing respiratory tract infection and urinary tract infections respectively.

Gentamicin was administered in a one daily dose regimen which has been shown to reduce the risk of nephrotoxicity and ototoxicity involved with the use of aminoglycosides (Croes *et al.*, 2012; Buabeng *et al.*, 1999; Gilbert, 1997). However, the dose range of gentamicin was 3 - 9mg/kg as opposed to the recommended dose range of 5 - 7mg/kg body weight of gentamicin in a once daily dosage regimen (BNF for children, 2012; Buabeng *et al.*, 1999). Sub-optimal doses of gentamicin may be associated with treatment failure. Higher doses of gentamicin may increase the risk of developing the side effects of gentamicin (Croes *et al.*, 2012; Buabeng *et al.*, 1999; Gilbert, 1997). Nonetheless, further studies should be done to assess the safety and efficacy of gentamicin use in ACS patients at the hospital.

Local sensitivity pattern is very important in managing infections in ACS patients.

Sensitivity tests were not often available during the patients stay in the hospital. Various guidelines on the management of ACS suggest the addition of a macrolide or quinolone to the antibiotics in the empirical therapy for infections, to help cover atypical

microorganisms like Mycoplasma due to their predominance in ACS cases (Howard *et al.*, 2015, Ansong *et al.* 2013; Awogbade *et al.*, 2012; Treatment guidelines, KATH, 2010).

Macrolides are reported to have immunomodulatory effects and can suppress inflammation associated with ACS through lymphocyte activity and neutrophil proliferation. They have also been documented to have tremendous activity against atypical bacteria (Metersky *et al.*, 2007). However, from the study, macrolides or quinolones were not normally included in the management of ACS at KATH.

### **5.3. BLOOD TRANSFUSION AND HYDRATION IN ACS PATIENTS**

Blood transfusion in ACS patients depends on the degree of hypoxia, respiratory distress and anaemia (Howard *et al.*, 2015; National Heart, Blood and Lung Institute, 2002; Treatment guidelines, KATH, 2010). The administration of blood transfusion was mainly to patients with a haemoglobin level 7g/dl or below. Blood transfusion requires monitoring of the mean PaO<sub>2</sub>, serial HbS percentage and iron overload (National Heart, Blood and Lung Institute, 2002). Data on these were not available making it difficult to assess the outcome of the transfusion therapy. However, patients given transfusion were more likely to spend a longer time (2 more days) in the hospital than patients who were not.

Most patients who were given transfusion frequently received packed red cells instead of whole blood transfusion to reduce the risk of infections and immunogenic responses (Nansseu *et al.*, 2013). Patients who received blood transfusion received it within the first 48 hours of admission. Early transfusion within the first 24 hours of admission is encouraged in most studies and guidelines. Repetitive transfusion is also encouraged to prevent hyperhaemolysis syndrome and readmissions (Miller, 2011).

Patients with ACS are generally not able to maintain oral hydrations (Howard *et al.*, 2015). Post hydration status and fluid monitoring on the fluid balance chart were not available thus assessment of hydration status of patients was not done in the study although, all patients were successfully hydrated. The mean volumes of IV fluids and blood transfused were higher in older patients. The percentage of patients who received IV fluids and blood transfusion did not significantly vary between age groups.

#### **5.4. PAIN MANAGEMENT IN ACS PATIENTS**

Patients experienced abdominal pain, chest pain, and pain in the arm and leg. Pain management in children with ACS should be subjective and assessment should involve self-reports by patients, validated tools and should be repeated severally. Major barriers to pain management in ACS patients may include limited knowledge on ACS, inadequate pain assessment and bias in opioid use or prescription.

The preferred medication for initial pain management in ACS patients in the hospital was paracetamol alone or in combination with ibuprofen. This is in accordance with WHO guidelines on the pharmacological treatment of persisting pain in children with medical illness in 2012. There is a considerable evidence of the safety and efficacy of paracetamol and ibuprofen in children. They are readily available in child appropriate dosage forms like oral liquids. Pain in ACS is considered as acute. In these settings ibuprofen has been shown to have superior analgesic property than paracetamol. Pain control in most of the patents was achieved by the initial therapy with paracetamol and ibuprofen.

Thirteen patients received IM diclofenac as a stat dose for initial pain relief.

Intramuscular administration of medications for pain is advised to be avoided if possible as absorption is erratic. Intramuscular administration may also be frightening to

children and painful (WHO guidelines, 2012; National Heart, Blood and Lung Institute, 2002).

In the study, morphine was the preferred choice for opioid analgesic use in ACS patients at the hospital followed by tramadol. The WHO recommends a strong opioid in pain management for children as this has been shown to be more beneficial than intermediate opioid use. Although, morphine is the recommended first choice opioid, caution is required to avoid hypoventilation. Morphine use in patients did not impact on the duration of hospital stay.

It is also recommended that, opioid analgesic dose should be titrated on an individual basis until the correct dose is found. This will help achieve the best possible pain relief with acceptable side effects. However, patients were mainly given fixed doses of morphine.

#### **5.5. ANTI-MALARIAL THERAPY IN ACS**

Although, malaria parasite was not observed in laboratory findings, about 44% of patients received anti-malaria therapy. This included more than half of patients who received transfusion. The preferred choice for anti-malaria treatment was artemether lumefantrine, which is a first line for malaria therapy in Ghana (Anti-malaria drug policy for Ghana, 2014). Malaria therapy in patients who received transfusion can also help to prevent transfusion-related malaria transmission. Ensuring that blood supply is free from malaria may be problematic. Nansseu *et al.* in 2013, suggests that artemisinin based combination therapy (ACT) should be given as anti-malaria therapy for every transfusion in sickle cell patients.

## 5.6. LIMITATIONS OF THE STUDY

Data was collected in only one Teaching Hospital in Ghana; hence the results may not be generalized. However, the results obtained could be a reflection of ACS and its management in other hospitals in Ghana.

The study design was retrospective and as such most vital information like side effects of medication and deaths from ACS were often missing from the folders.



## CHAPTER SIX

### 6.0. CONCLUSION AND RECOMMENDATIONS

#### 6.1. CONCLUSION

The prevalence of ACS was 8%. The patients with ACS were mainly between the ages 2 to 9 years. Fever and cough were among the common clinical symptoms documented. Clinical features like rhinorrhoea, irritability, chest pain and abdominal pain varied with age. The mean duration of hospitalizations was  $6.6 \pm 3.4$  years.

Therapeutic package for ACS in the hospital involved the management of infections, pain management, use of IV fluids and blood transfusion as recommended in standard guidelines like National Institute of Health, USA, Guidelines on the management of ACS in SCD (Howard *et al.*, 2015) and Treatment guidelines of the Child Health directorate, KATH.

Antibiotic therapy for the infections was done empirically with a combination of cefuroxime and gentamicin. Cefuroxime was replaced with ceftriaxone in cases where fever persisted after therapy. The antibiotic therapy did not cover for atypical bacteria commonly known to be involved in ACS. Dosage ranges of gentamicin were 3 to 9 mg/kg for a once daily dose regimen, in contrast to 5 to 7 mg/kg body weight recommended in the standard treatment guidelines.

Mild pain was managed with paracetamol and ibuprofen, whereas morphine and tramadol were the preferred opioid for severe pain management.

## 6.2. RECOMMENDATIONS

The introduction of antibiotics to cover for atypical organisms in the empiric management of infections in ACS patients at the hospital should be considered as suggested by various guidelines.

Diagnostic techniques for the detection of bacteria involving bronchoscopy should be introduced in the hospital to help provide better microbiology samples for bacteria culture.

Pain management should include the titration of opioid analgesic doses on an individual basis and the avoidance of intramuscular administration of analgesics to help achieve the best possible pain relief.

Education of guardians of patients is required to aid in early recognition of signs and symptoms and early diagnosis.

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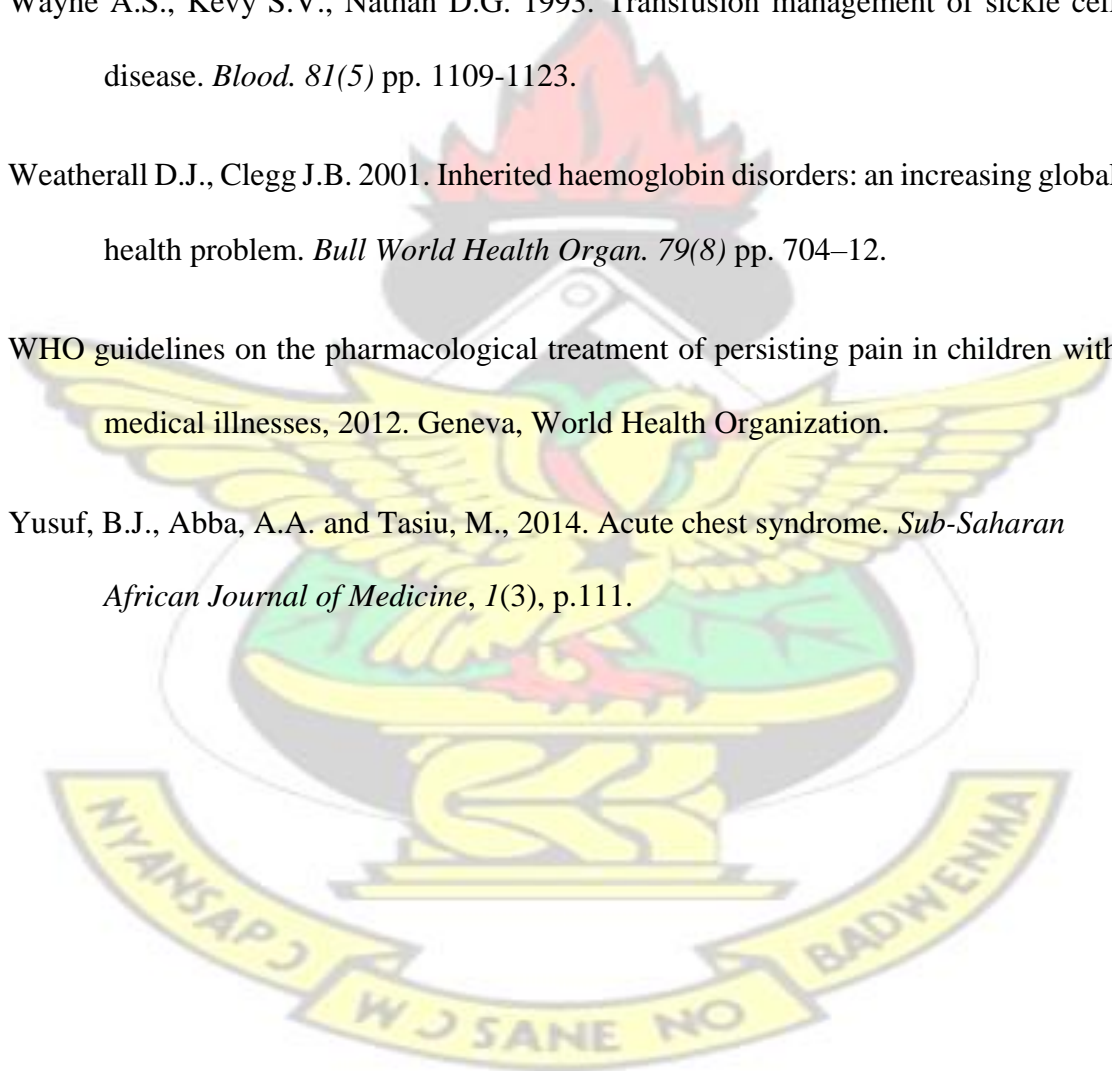
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**APPENDIX**

**DATA COLLECTION TOOL**

**CODE**: .....

**DATE**: .....

**PART I**

**1.0. PATIENT INFORMATION**

**SEX:**     MALE                       FEMALE

**ADMISSION DATE**..... **DISCHARGE DATE**:..... **WEIGHT**:.....  
**HEIGHT**:.....

**AGE AT EPISODE OF ACUTE CHEST SYNDROME**:.....

**SCD GENOTYPE:**  HbSS     HS b Thalasaemia     Hb SC     Hb+ SC

Others, specify.....

**BLOOD GROUP TYPING**.....

**PART II**

**2.0. SIGNS AND SYMPTOMS, VARIOUS TESTS AND PHYSICAL EXAMS**

**2.1. SYMPTOMS AT DIAGNOSIS OF ACS**

- |  |       |         |   |
|--|-------|---------|---|
| <input type="checkbox"/> Fever                       |       | Chest   | <input type="checkbox"/> pain             |
| <input type="checkbox"/>                             | Cough |         | <input type="checkbox"/> Tachypnea        |
| <input type="checkbox"/> Shortness of breath         |       | Pain    | <input type="checkbox"/> in arms and legs |
| <input type="checkbox"/> Abdominal pain              |       | Ribs    | <input type="checkbox"/> or sternal pain  |
| <input type="checkbox"/> Reactive airway dysfunction |       | disease | <input type="checkbox"/> Neurological     |
| <input type="checkbox"/> Cyanosis                    |       |         | <input type="checkbox"/> Heart failure    |

Others symptoms, .....

## **2.2. FINDINGS ON EXAMINATION**

Respiratory rate at diagnosis..... Peak respiratory rate.....

Peak Temperature..... Temperature at diagnosis.....

Heart rate..... Random blood sugar.....

Flaring Alae Nasi  Intercoastal Recession  Lower Chest Indrawing

Effusion..... Lobes involved.....

## **2.3. URINALYSIS**

Urobilinogen  Bilirubin  Blood  Nitrite  Protein

Glucose  ketone  Leucocyte **pH**  acidic basic

neutral

**Specific Gravity**  high  Low  normal

## **2.4. HAEMATOLOGY (CBC AND DIFFERENTIAL)**

Haemoglobin(g/dl).....Haematocrit(%).....Red cell count (\*10<sup>6</sup>/ul) .....

Reticulocyte(%)..... Mean Cell Volume(um<sup>3</sup>) ..... Mean Corpuscular

Haemoglobin(pg).....Mean Haemoglobin Concentration(g/dl).....Red Cell

Distribution width -SD(CV)..... Platelet Count ..... White Blood Cell

Count.....Lymphocyte.....Monocyte..... Neutrophils.....

Platelet distribution width.....Mean platelet volume.....Platelet larger

cell ratio.....Basophil.....Eosinophil.....PCT.....

## **2.5. KIDNEY FUNCTION TEST**

Creatinine.....Urea.....BUN/creatinine ratio.....

**ELECTROLYTES:** Na+.....K+.....Cl-.....

**2.6. OTHER BASELINE LABORATORY VALUES**

Partial pressure of arterial pressure on diagnosis.....

Oxygen saturation.....

**2.7. MICROBIOLOGY**

CASE	SITE/SOURCE	ORGANISM ISOLATED	DATE

**2.8. SENSITIVITY TEST**

ORGANISM ISOLATED	AGENT (ANTIBIOTIC)

**PART III**

**3.0. ACS EPISODES, HOSPITALIZATION AND READMISSIONS**

**3.1. HOSPITALIZATION**

CURRENT ADMISSION	ADMISSION DATE	RESOLUTION DATE	DURATION

**3.2. ACS EPISODES**

ONSET	HOSPITALIZATION(Y/N)	DURATION	SEVERITY

**3.3. READMISSIONS (within 14 days after Hospitalization)**

READMISSION	ADMISSION DATE	DISCHARGE DATE	DURATION

**KNUST**  
**PART IV**

**4.0. ACS COMPLICATIONS, CO-MORBIDITIES AND OTHER SCD**

**COMPLICATIONS**

**4.1. PAST MEDICAL HISTORY**

- Vaso-occlusive crises  Prophylactic antibiotic therapy  Major surgery  
 Acute Chest syndrome  Asthma  Urinary Tract Infection  Renal disease  
 Pneumonia  Transfusion  Cardiac disease  Pulmonary oedema

Others, .....

**4.2. COMPLICATIONS**

COMPLICATION TYPE	ONSET	DURATION

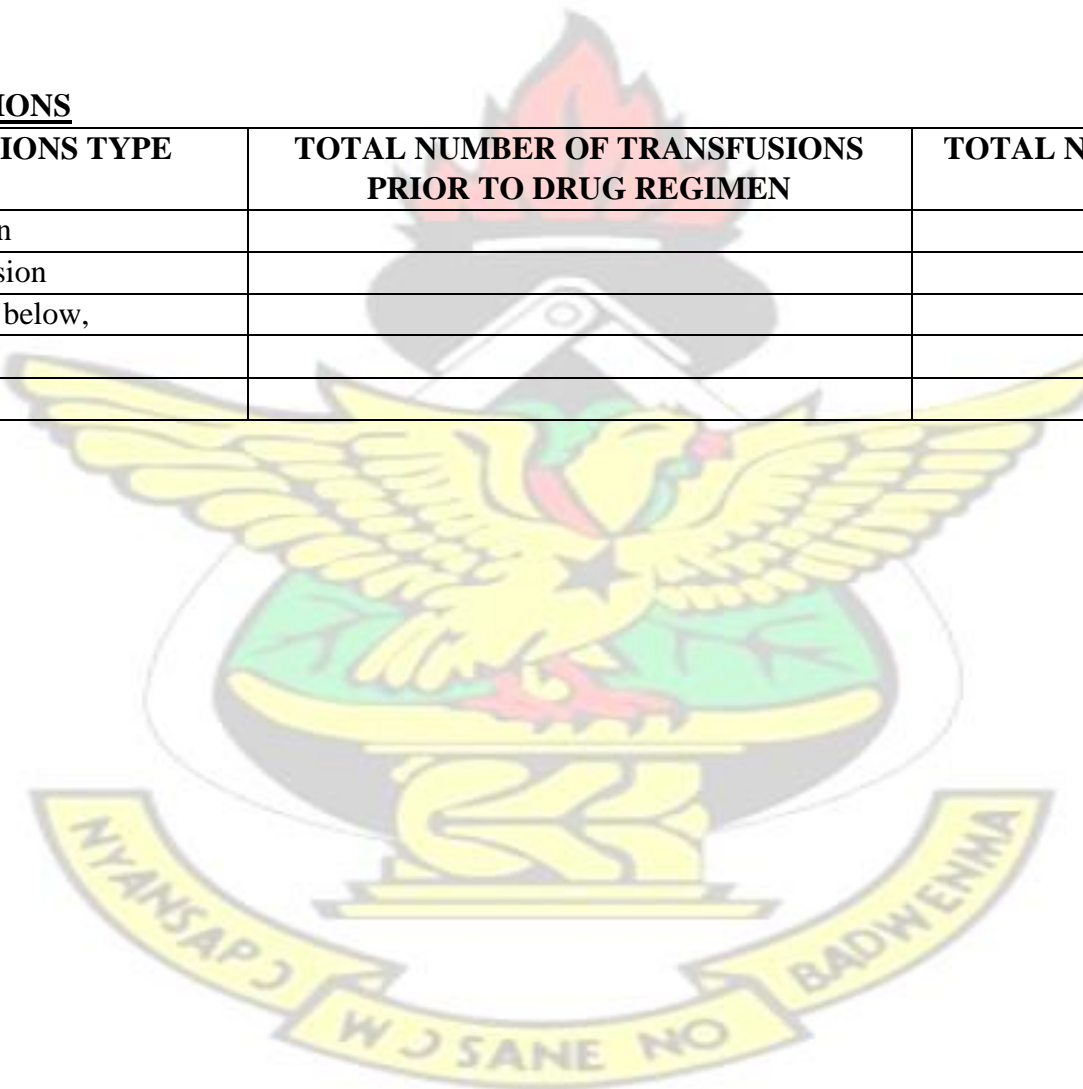


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## 5.2. TRANSFUSIONS

<b>TRANSFUSIONS TYPE</b>	<b>TOTAL NUMBER OF TRANSFUSIONS PRIOR TO DRUG REGIMEN</b>	<b>TOTAL NUMBER SINCE FIRST EPISODE</b>
Simple transfusion		
Exchange transfusion		
OTHERS specify below,		

## NOTES



# KNUST

