Acute Kidney Injury and electrolyte abnormalities among patients admitted with Cholera in Kenyatta National Hospital in Nairobi, Kenya, in the year 2017

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Declaration

I declare that this is my original work and that it has never been presented for any award or degree in any university.

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Acknowledgement

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Abstract

Title: Acute Kidney Injury and electrolyte abnormalities among patients admitted with Cholera in Kenyatta National Hospital (KNH) in Nairobi, Kenya in the year 2017

Background: Cholera is an acute secretory diarrheal illness caused by toxin-producing strains of the gram-negative bacterium *Vibrio cholera*. Cholera primarily affects resource-limited settings where there is inadequate access to clean water sources and is endemic in many countries mostly in Africa and Asia. In Kenya, cholera still remains a cause of severe diarrhea in areas with poor sanitation conditions, with trends indicating translation of cholera to an endemic disease. Severe cholera is characterized by profound fluid and electrolyte losses in the stool and vomitus, volume depletion and the rapid development of hypovolemic shock. Complications such as acute renal failure, metabolic acidosis, circulatory failure, arrhythmias and death occur if timely treatment is not initiated. Epidemiologic data on the current cholera epidemic in Kenya is largely available but no study has evaluated these complications. The aim of this study is to evaluate acute kidney injury and electrolyte abnormalities among patients admitted with cholera in KNH during the year 2017.

Broad objective: To describe the frequency of acute Kidney Injury (AKI) and electrolyte abnormalities among patients admitted with cholera in KNH during the months of July to December 2017

Specific objectives:

1. To determine the proportion of patients who developed AKI among patients admitted to the cholera isolation ward in KNH in the year 2017
2. To describe abnormalities in the Blood Urea Nitrogen (BUN): creatinine ratio and electrolytes among patients admitted in cholera isolation ward in KNH in the year 2017

3. To describe the association between patients' clinical and demographic characteristics and acute kidney injury

4. To describe the association between patients' clinical and demographic characteristics and death

Study design: Cross sectional study: A retrospective review of records of patients admitted in KNH with cholera in the year 2017.

Study population: Patients admitted to the cholera isolation ward in KNH during the year 2017

Methodology:

Data collection: Records of patients admitted to the cholera isolation ward in KNH during the study period were retrieved and evaluated for eligibility. Social demographic data, clinical and laboratory parameters were reviewed and recorded in a data collection tool.

Inclusion criteria: Patients that were admitted to the cholera isolation ward in KNH with a diagnosis of either suspected or confirmed cholera during the study period, whose records of at least one urea, creatinine, sodium and potassium measurements was available.

Exclusion criteria:

1. Patients who from hospital records, are known to have chronic kidney disease

2. Patients who from hospital records, are known to have a condition that is recognized as a risk factor for renal impairment: Diabetes mellitus, Hypertension, acute glomerulonephritis, infection with Human Immunodeficiency Virus (HIV)

3. Incomplete records

4. Negative Cholera diagnosis test

Statistical Analysis: Descriptive statistics were carried out: Frequency tables, percentages and proportions were generated for categorical variables while Mean, Standard deviation, median and interquartile ranges were generated for continuous variables. Association analysis (chi square, student t-test) was carried out to determine the association between patients' characteristics and AKI or death.

Results: Of the 127 patients enrolled into the study, 67% were males and the mean age was 36years (±12.6). The mean duration of symptoms prior to admission was 2.1± 1.2 days. AKI was present in 60.6% and majority of these patients had AKI at the time of admission (97%), 17.6% of these patients received renal replacement therapy. Among those with AKI that did not receive renal replacement therapy, 56.2% had normal creatinine levels at the time of discharge. Among those with elevated serum creatinine levels, the mean BUN: Creatinine ratio (mg/dl) was 8.9(±3.7). On association analysis, there as a significant association (p value<0.001) between AKI and duration of hospital stay, total WBC counts, serum hemoglobin levels, cholera diagnosis and serum sodium levels at admission (p value=0.032).The most frequent electrolyte abnormality was hyponatremia at 40.2 %. Other electrolyte abnormalities seen were hypokalemia (26.8%), hyperkalemia (15.0%) and Hypernatremia (10.2%). Serum bicarbonate, chloride and PH were not assessed in majority of these patients (>90%). The in-hospital case fatality rate was 5.5 %. On bivariate analysis, there was a statistically significant association (p value<0.05) between death and age, duration of symptoms prior to admission, blood pressures at admission, total WBC counts and serum urea levels at admission.

Conclusions and recommendations

The prevalence of AKI among patients admitted in the cholera isolation ward during the cholera outbreak in Kenya in the year 2017 was high and was present at the time of admission in the

majority of patients. The frequency of electrolyte abnormalities was high and the in-hospital case fatality rate was also high. We recommend inclusion of a nephrologist to guide management and follow up of patients who develop AKI and electrolyte abnormalities. We also recommend close monitoring of serum electrolytes to include serum bicarbonate, PH, chloride and other electrolytes. It is worthwhile to enhance public awareness on the importance of seeking healthcare early during cholera epidemics for volume repletion to prevent progression to AKI.

List of abbreviations and Acronyms

AKI: Acute Kidney Injury

ARF: Acute renal failure

BUN: Blood Urea Nitrogen

CBC: Complete Blood Count

CKD: Chronic kidney disease

eGFR: estimated glomerular filtration rate

Hb: Hemoglobin level

HHD: Hemodialysis

IVF: Intravenous fluids

KDIGO: Kidney Disease, Improving Global Outcomes

Kg: Kilogram

KNH: Kenyatta National Hospital

MEq: Mill equivalent

Ml: Milliliter

Mmol: Millimole

PD: Peritoneal dialysis

RRT: Renal replacement therapy

UON: University of Nairobi

WBC: White blood cells

Operational definitions:

For the purpose of this study, the following definitions will be used (4, 15):

Cholera diagnosis:

1. Confirmed cholera: Which was defined as isolation of *V.Cholera*e from stool from a person with classical signs and symptoms of cholera (acute onset of watery diarrhea with more than 4 episodes in 12hours, effortless, or 'rice water', with or without vomiting and abdominal pains)

2. Suspected cholera: Cases where no *V.cholerae* microbiologic test was done

Suspected cholera was defined as a person with classical signs and symptoms of cholera (acute onset of watery diarrhea with more than 4 episodes in 12hours, effortless, or 'rice water', with or without vomiting and abdominal pains), that can be epidemiologically linked to a confirmed case or geographical area during a cholera outbreak

Acute kidney injury:

KDIGO definition and grading of severity was used to define AKI:

Where baseline was not known, the upper limit of normal was used as the baseline value

AKI:

Increase in serum creatinine by =/>0.3 mg/dl (=/>26.5 micromole/l) within 48 hours;

Or increase in Serum creatinine to =/>1.5 times baseline, which is known or presumed to have occurred within the prior 7 days

Or Urine volume < 0.5 ml/kg/h for 6 hours.

KDIGO grading of severity of AKI into 3stages will be applied as follows:

Stage1:

Increase in creatinine of 1.5–1.9 times baseline

Or creatinine increase of =/>0.3 mg/dl (or =/>26.5 mmol/l)

Or urine output of < 0.5 ml/kg/h for 6–12 hours

Stage 2:

Increase in creatinine of 2.0–2.9 times from baseline

Or urine output < 0.5 ml/kg/h for =/>12 hours

Stage 3:

Creatinine Increase of =/>3.0 times baseline

Or urine output <0.3 ml/kg/h for =/>24 hours or anuria for =/>12hours

Or increase in serum creatinine to =/>4.0 mg/dl (=/>353.6 mmol/l)

Or initiation of renal replacement therapy

Or, in patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m2, or urine output<0.3 ml/kg/h for =/>24 hours or anuria for =/>12 hours

Normal laboratory values:

The following values were used as reference for normal laboratory parameters, as reported by the KNH laboratory**.**

Values above the normal range were described as ‘high’, while values below the normal range were described as ‘low’:

Parameter	Normal Range
Sodium (mmol/l)	135-145
Potassium (mmol/l)	3.5-5.0
Chloride (mmol/l):	95.0-106.0
Bicarbonate (mmols/l):	22-24
White blood cells (10^9/ml):	4.00-11.00
Neutrophils (%)	37.0 -70.0
Lymphocytes (%):	20.0-50.0
Hemoglobin (g/dl):	10.0-15.5
Platelets: (10^9/ml)	150-450
Urea (mmol/l):	2.3-8.2
Creatinine (umol/l):	60-130
PH	7.35-7.45

Calculation of the BUN: Creatinine Ratio: Since the KNH laboratory reports urea in mmols/l, this was converted to BUN in mg/dl by using the following conversion factor: Urea (mmol/L) divided by 0.357 = BUN (mg/dL). Similarly, creatinine reported in micromols/l was converted to mg/dl using the following conversion factor: Creatinine in micromols/l divided by 88.4= creatinine in mg/dl. The BUN: Creatinine Ratio is expected to be >20:1 in prerenal AKI. The ratios were categorized into 3: <10:1, 10.1-20:1, and >20:1

1.0: Chapter one: Background

1.1: Introduction

Cholera is an illness caused by toxin producing strains of the bacterium *Vibrio cholera* which clinically presents with acute, profuse diarrhea with or without vomiting and abdominal cramps. The organism is classified serologically with more than 200 serogroups reported, but only serogroups O1 and O139 have been reported as the causative agent in cholera epidemics (1, 2). Cholera most commonly occurs in resource-limited settings with inadequate access to clean water sources and is endemic in approximately 50 countries mostly in Africa and Asia (Cholera endemic areas are defined as having reported cholera cases in at least three of the five past years) (3). Cholera still remains a cause of severe diarrhea in Kenya, especially in areas with poor sanitation conditions. According to the Ministry of Health in Kenya, cases of cholera have been reported every year since 2007, a trend indicating translation of cholera to an endemic disease in the country (4).

Since the beginning of the year 2017, Cholera cases have been reported in various counties including Tana River County, Nairobi, Murang'a, Vihiga, Mombasa, Turkana, Kericho, Nakuru, Kiambu, Narok and in the refugee camps. As of 17 July 2017, a total of 1216 suspected cases including 14 deaths (case fatality rate: 1.2%) had been reported. Among the samples tested at the National Public Health Laboratory in the capital city Nairobi, 124 cases tested positive for *Vibrio cholera*, with 18 samples testing positive for *Vibrio cholerae Ogawa* by culture. The following were reported as the main Causative factors of the outbreak: the high population density that is conducive to the propagation and spread of the disease, mass gatherings (for instance, a wedding party held in one of the suburbs in the capitol city Nairobi and in a hotel during an international

conference), low access to safe water and proper sanitation and the massive population movements in the country and with neighboring countries (5).

Cholera is usually acquired by ingesting contaminated food or water or through person to person contact. The typical incubation period is one to two days but can range from several hours to as long as three to five days, depending on other factors such as host susceptibility and inoculum size. Once the organisms reach the small intestines, they produce cholera toxin (CT). The cholera toxin causes the profuse secretory diarrhea that is the hallmark of cholera, but it can also result in asymptomatic intestinal colonization (6).

In its severe form, cholera is characterized by marked fluid and electrolyte losses in the diarrheal stools and vomitus, resulting to intravascular volume depletion. Hypovolemic shock can rapidly develop, often within 24 hours from the onset of diarrhea and vomiting. Other complications that arise from this volume depletion and electrolyte loss include: acute renal failure, muscle cramps and metabolic acidosis. If timely treatment is not initiated, circulatory failure, arrhythmias and death may occur. Of these complications, acute kidney injury, metabolic acidosis and uncorrected electrolyte are the major causes of death.

In untreated cholera patients, the mortality may reach up to 50 to 70% but replenishing intravascular volume through administration of appropriate rehydration therapy can reduce this mortality to less than 0.5 %. Early and aggressive volume expansion is necessary to prevent these complications and WHO recommends urgent administration of intravenous fluids, with Lactated Ringer's (LR) solution (preferred over normal saline) because it also replenishes bicarbonate and potassium (7).

While epidemiologic reports of the most recent cholera epidemic in Kenya in the year 2017 are available, no study has evaluated the complications associated with this disease such as acute

kidney injury and electrolyte abnormalities. This study aims to describe the frequency and outcomes of these complications among patients admitted to the cholera isolation ward in KNH, a National referral hospital in Nairobi, the capital city of Kenya.

1.2: Problem statement:

The aim of this study was to evaluate the frequency and outcomes of acute kidney injury and electrolytes abnormalities among patients admitted with a diagnosis of Cholera in Kenyatta National Hospital (KNH) in the year 2017.

The most common cause of death from cholera is the hypovolemic shock, AKI, electrolytes and acid-base disorders. Epidemiologic reports of the most recent cholera epidemic in Kenya are available, but none has evaluated the above complications associated with this disease. It is therefore important to quantify the burden and outcomes of this complication. Results of this study can be applied to further advice the prevention and clinical care of cholera patients who develop these complications.

1.3: Research Questions

1. What was the frequency of AKI among patients admitted with cholera in KNH in the year 2017?

2. What electrolyte abnormalities were observed in patients admitted with cholera in KNH in the year 2017?

3. Was there any relationship between patients' clinical or demographic characteristics and acute kidney injury or death, in patients with cholera?

1.4: Study Objectives

Broad objective:

To describe the prevalence of acute Kidney In jury and electrolyte abnormalities among patients admitted with cholera in KNH during the months of July to December 2017

Specific objectives:

1. To determine the proportion of patients who developed AKI at admission or during the hospital stay, and the outcomes at time of discharge (renal replacement therapy, recovery of AKI, death) among patients admitted to the cholera isolation ward in KNH in the year 2017
2. To describe abnormalities in the Blood Urea Nitrogen (BUN)/creatinine ratio and electrolytes among patients admitted in cholera isolation ward in KNH in the year 2017

Secondary objectives**:**

1. To describe the association between patients' characteristics and acute kidney injury among patients admitted to the cholera isolation ward in KNH in the year 2017
2. To describe the association between patient's characteristics and death among patients admitted to the cholera isolation ward in KNH in the year 2017

2.0 Chapter 2: Review of literature

Cholera: Etiologic agent:

V. cholera is a gram negative bacteria, a broad species with many variants. Some strains *of V. cholera* species are pathogenic while others are non-pathogenic. Only the pathogenic toxin-producing strains (toxigenic strains) have been shown to cause cholera. The bacterium is classified serologically to more than 200 serogroups but only serogroups O1 and O139 have been reported as the causative agent in epidemics of cholera. The rest of the serogroups are classified together as *V. cholerae* "non-O1, non-O139." This category of *V. cholerae* strains has been shown to cause diarrhea, gastroenteritis and sepsis either as isolated cases or in small outbreaks (2).

V. cholerae *"*O1" serogroup has two major serotypes: Inaba and Ogawa. The difference between these two serotypes is the presence of a single methyl group on the Ogawa polysaccharide antigen. The "01" serogroup is also divided into two biotypes: El Tor and classical. The differences between these biotypes are in their biochemical characteristics and their specific susceptibility to certain bacteriophages. *V. cholerae* "O1" is the main etiologic agent in the current global pandemic of cholera (8, 9). The "O139" serogroup was responsible for the cholera epidemics for approximately a decade since its emergence in 1992, but is no longer a major cause of cholera epidemics. Structurally, the genome of "O139" strain has the *rfb* region, which contains the genes required for synthesis of the O139 antigen (10). The organism is otherwise similar to the *V. cholerae* "O1" serogroup.

Cholera: Epidemiology

V. cholerae infection is mainly acquired through fecal-oral transmission by ingestion of contaminated food or water. The other mode of transmission is direct person-to-person contact.

One liter of stool contains up to 10^{10} to 10^{12} organisms in persons with severe cholera. Ingestion of approximately 1-million *V. Cholerae* are needed to cause disease. It has also been shown that organisms in stools of infected persons tend to be more infectious than organisms from water bodies. It has been reported that human colonization with *V. cholerae* creates a hyper infectious bacteria through high expression of genes required for nutrition and motility of the bacterium (11). It appears that the rapid transmission that is seen during cholera epidemics is driven by contact with the hyper-infectious *V. cholerae* bacterium recently shed through stools of infected persons, either directly or through ingestion of contaminated food or water (12).

Cholera epidemics often occur in resource-limited settings with poor sanitary conditions, where access to clean water is a challenge. The disease is endemic in more than fifty countries worldwide. However, most epidemics reported occurred in Africa and Asia, with a few epidemics reported from South and Central America, the Caribbean and the Middle East. The few Cholera Cases reported in high income countries are often imported from travel to regions where the disease is endemic or during epidemics. In Kenya, the disease trend indicates a translation to an endemic disease, as cases of cholera have been reported every year since 2007 (4). During the 2007-2010 epidemic, among the samples that were tested at the national reference laboratory, *Vibrio cholerae* serogroup "O1", serotypes Inaba and Ogawa were isolated and majority of the samples tested for the Inaba serotype. In 2009, the Division of Disease Surveillance and Response (DDSR) in the Ministry of Public Health and Sanitation reported a case fatality rate of 2.3% among those infected with cholera (8).

Cholera: Pathogenesis and clinical features

Cholera is usually acquired through the fecal-oral route, either by direct contact with infected stools or by ingestion of contaminated water or food. The incubation period is approximately two

days but can range from several hours to five days, depending on other factors such as host susceptibility and inoculum size (6).

Once ingested, *V. cholerae* must survive the acidic environment of the stomach, be transported to the intestines where it then forms colonies on the surface of the small intestine. The bacteria then attaches to the intestinal wall and multiply. Toxigenic strains produce the cholera toxin (CT), which is a potent stimulator of adenylate cyclase, resulting to high cyclic AMP levels. It is this elevation in cyclic AMP that causes the large amounts of fluid rich in sodium, chloride, bicarbonate, and potassium secretion into the intestinal lumen. The volumes secreted are often large and may exceed the absorptive capacity of the epithelial cells lining the intestines, leading to the rapid development of intravascular volume depletion and derangement in the respective electrolytes (1).

Most *V. cholerae* infections are asymptomatic or result to mild diarrhea, similar to that from other infectious agents that cause diarrhea. Other *V.Cholerae* infections result in severe disease, referred to as 'Cholera gravis', characterized by a sudden onset of profuse diarrhea that is painless and watery, with flecks of mucus in the stool , often referred to as the "rice water" stools. Bloody stools are not characteristic of cholera and warrant evaluation of another causative agent. The other symptom that is observed in these patients is vomiting, usually also watery and occurs early at the onset of the illness. Other symptoms such as abdominal cramps have been reported. Patients may have fever, although this occurs more commonly in children than adults. The diarrhea is often most severe during the first one to two days and usually reduces and clears after four to six days of appropriate treatment. Volume losses during the course of the illness may be as high as 100% of the patient's body weight (16, 17). Dehydration therefore occurs rapidly, characterized clinically by sunken eyes, dry mouth, cold clammy skin, decreased skin

turgor and wrinkled hands and feet, often referred to as "washer woman's hands". Patients with severe dehydration also tend to appear lethargic and apathetic. Hypovolemic shock with marked electrolyte abnormalities ensues, sometimes within just a few hours after onset of the symptoms. These findings were illustrated by reports from the cholera epidemic in Haiti which indicated that, the median time between onset of symptoms and death without treatment was 12 hours (18). Due to the massive bicarbonate losses in stool, metabolic Acidosis develops often compounded by lactic acidosis from reduced tissue perfusion. This is clinically manifested by deep labored breathing due to compensatory hyperventilation, often referred to as Kussmaul breathing. As circulatory failure ensues, peripheral pulses become rapid and weak, and may not be palpable as systemic blood pressures falls. Loss of calcium and potassium in stool and vomitus may lead to muscle cramps and even muscle weakness. Hypoglycemia may occur as result of impaired gluconeogenesis and depletion of glycogen stores. Another complication that is rarely occurs in patients with severe cholera is "Cholera sicca", where fluid accumulates in the intestinal lumen. In such cases, severe volume depletion and the complications that arise from intravascular volume contraction including death can occur in the absence of the profuse diarrhea typical of severe cholera (19).

Fluid losses and AKI in Cholera

Compared to other causes of acute diarrhea, cholera leads to more marked, rapid fluid and electrolyte losses. Patients with severe cholera present with more severe dehydration, often more than >5%. It has been shown that fluid losses in cholera stools are high, up to 1000mls/hour. Assessment of the degree of dehydration and appropriate replacement of both fluid and electrolytes in patients with cholera cannot be overemphasized. Ongoing volume losses in stool can be estimated to be between 10 to 20 mL/kg (kilogram body weight) for each stool or episode

of vomiting. Difficulties with assessment of ongoing volume losses in stool can be addressed by use of Cholera cots (20, 21, and 22).

Pre renal acute kidney injury in these patients usually results from severe intravascular volume depletion, decreased effective circulating volume, and impaired blood flow to the kidneys. If the volume depletion is not rapidly corrected, acute tubular necrosis may develop. Acute tubular necrosis is potentially reversible but indicates more severe structural renal injury (intra renal AKI). AKI in these patients often resolves with volume repletion but a few patients progress to renal failure requiring renal replacement therapy. A study in Tehran evaluated 121 patients with acute diarrhea of which 48.8% was caused by cholera. The study reported that 23.9% of the participants had acute kidney injury, with serum Creatinine level higher than 133.2micromoles/l at the point of admission and of these patients with AKI, 23.8% required renal replacement therapy during their hospital stay (23).

There are several parameters that can be used to distinguish Pre-renal AKI from Intra- renal AKI such as the Blood Urea Nitrogen (BUN) to creatinine ratio, Fractional Excretion of Urea and Fractional excretion of Sodium (FENA) (24). In prerenal AKI, volume depletion results in increased absorption of urea from the tubular luminal epithelium, so the urea clearance falls more than the creatinine clearance, leading to a disproportionate rise in BUN. The release of anti-diuretic hormone in response to the fall in intravascular volume is also thought to contribute by promoting urea reabsorption. As such, a BUN to creatinine ratio of more than 20:1 usually indicates prerenal AKI. The AKI in cholera is presumed to be prerenal, driven by the volume depletion. The BUN creatinine ratio in these patients is therefore expected to be high (>20:1). However, some studies have described unusually low BUN/Creatinine ratios in patients with cholera. Various explanations for this low BUN /creatinine ratio have been theorized: in other

states of volume depletion, the increase in BUN usually takes time. It has therefore been proposed that perhaps cholera patients are so acutely dehydrated that there is not enough time for the serum urea concentration to rise. It is also possible that creatinine loss through the gastrointestinal tract is much lower than urea loss in cholera, perhaps through a mechanism mediated by the cholera toxin. It has also been proposed that perhaps the rapid fluid loss in cholera leads to early onset of acute tubular necrosis (ATN), interfering with urea tubular reabsorption (25). These theories however need to be explored further.

Caution should be exercised during volume replacement in cholera patients with already established AKI. Administration of large volumes of fluids at this stage can lead to fluid overload with pulmonary edema, often requiring renal replacement therapy.

Electrolyte and acid base abnormalities in cholera

The secretory diarrhea in cholera is associated with loss of electrolytes in stool and vomitus. It is estimated that a liter of Cholera stools in an adult contains approximately 130 milimoles of sodium, 20 milimoles of potassium, 100 milimoles of chloride and 45 milimoles of bicarbonate (20, 22). Common electrolyte abnormalities in cholera patients include hypokalemia, hyponatremia and metabolic acidosis.

Abnormalities in Serum Potassium: Gastrointestinal potassium losses have been reported to be approximately 15-20mmols/l of stool in cholera. With these high potassium losses, serum potassium levels would be expected to be low and hypokalemia is a common finding in patients with severe cholera. In a study of 121 patients with acute diarrhea of which 48.8% the causative agent was cholera, 33.8% had hypokalemia and only 2.4% had hyperkalemia. Of those with hypokalemia, 78% had persistent hypokalemia that was not corrected during the hospital stay (23). However, it has been observed in previous reports that cholera patients with severe volume

contraction may present with normal serum potassium levels. In a study of 142 cholera patients in Peru, <1% presented with serum potassium of <3mmols/l and 8% presented with serum potassium of >5mmols/l. The rest had normal serum potassium (7). This unexpected normalkalemia in the setting of massive potassium loss in stool in cholera was thought to be a result of substantial transcellular shifting of potassium from the intracellular space to the extracellular space, mediated by alpha-adrenergic inhibition of insulin in extracellular volume contraction state. Hyperkalemia has also been documented during volume re-expansion using potassium containing formulations in these patients. On the other hand, hypokalemia has been reported during volume replacement with normal saline without oral/ intravenous potassium replacement. Potassium monitoring is therefore essential both at presentation and during volume repletion in these patients, and Potassium replacement should continue as long as gastrointestinal losses are ongoing (26).

Abnormalities in serum sodium: It is estimated that there is 130 Milimoles of sodium per litre of stool in cholera. Although cholera is most often associated with normal serum levels, hyponatremia or hypernatremia may occur.

In a study of 121 patients with acute diarrhea in Tehran, hyponatremia was the most common abnormality in serum sodium at 67.8% (plasma sodium < 137 mEq/L), while only seven patients (5.7%) developed hypernatremia (plasma Na >143 mEq/l (23). Monitoring and correction of serum sodium levels is therefore a critical consideration during volume replacement in these patients.

Metabolic acidosis: Metabolic acidosis is a common complication of severe diarrheal illnesses including cholera. In a study of 121 patients with acute diahrrea in Tehran, 56.75% had acidosis (pH <7.34) (23). Although diarrhea with bicarbonate loss is usually associated with

hyperchloremia and a normal anion gap, a high anion gap is characteristic of cholera. This high anion gap in cholera is thought to be multifactorial: the very large chloride and water content of stool in choleric diarrhea causes a rapid and significant sodium chloride and bicarbonate loss, making these anions less available for tubular reabsorption. This results in a significant hemoconcentration and hyperproteneimia. Tissue hypoperfusion further increases lactic acid production and translocation of phosphate from the intracellular space to the extracellular compartment. Lactic acidosis has been found to contribute approximately 4.05mmols/l to the anion gap in patients with cholera. Overall, hyperproteinemia, lactic academia, and hyperphosphatemia account for upto 50%-70% of the anion gap. In addition, production of other organic acids in the gastrointestinal tract and systemically is also a possible mechanism for the increased anion gap (27). It is therefore critical to monitor and replace serum bicarbonate levels in these patients.

Cholera Diagnosis

The gold standard for the definitive diagnosis of cholera is based on isolation of the organism from cholera stools using selective media such as thiosulfate citrate bile sucrose (TCBS) agar or taurocholate tellurite gelatin agar (TTGA). The antibiotic susceptibility profile of the organism is also carried out. The serogroup and serotype is then assigned by testing with specific antibodies. There are commercially available Rapid test kits for *V.Cholerae* which detect the presence of the O1 or O139 antigen in stool samples. This may be performed to make a presumptive diagnosis, in settings with limited laboratory testing and during cholera epidemics. However, the limitation of the rapid tests is that antimicrobial susceptibility and serotype subtyping cannot be carried out. It is therefore recommended that stool specimens that test positive for *V. cholerae* O1 and/or O139 by the rapid tests be confirmed using a culture-based method. The other test that can be

carried out is Dark field microscopy of fresh stools (at 400x magnification), to identify the highly motile Vibrios (13, 14).

However, in epidemic settings and in regions where cholera is endemic, most cases of cholera are diagnosed from the clinical features. *V. Cholerae* should be considered a potential causative agent in any case of acute severe watery diarrhea, especially in those individuals that develop rapid severe dehydration from the diarrheal illness, especially in adults with such a presentation. Management of cholera should therefore be initiated on the basis of clinical suspicion. This recommendation is based on the fact that the morbidity of severe cholera is high, diagnostic testing may not be readily available in low resource settings, and the general applicability of fluid resuscitation to other causes of severe watery diarrhea. World Health Organization (WHO) recommendations indicate that cholera should be suspected when any person five years or older develops severe dehydration from acute watery diarrhea, even in an area where cholera is not known to be endemic (15).

In Kenya, the ministry of health guidelines for Cholera diagnosis indicate that cholera can be either "Confirmed cholera", Which is defined as isolation of *V.Cholerae* from stool from a person with classical signs and symptoms of cholera (acute onset of watery diarrhea which is effortless, or 'rice water', with or without vomiting and abdominal pains) . The other category is "suspected cholera" which is defined as a person with classical signs and symptoms of cholera, that can be epidemiologically linked to a confirmed case". In addition, during epidemics, once the presence of cholera in an area has been confirmed, it is not a requirement to confirm all subsequent cases in that region (4).

Cholera Treatment

The mortality in untreated patients with cholera is high, reaching up to 50%. The major causes of death in these patients is hypovolemic shock, acute kidney injury and metabolic acidosis. However, with timely, aggressive fluid replacement and correction of electrolyte abnormalities, this mortality can be reduced to less than 0.2% (25).

Like in any other patient with dehydration, the first step in the management these patients is to assess the degree of volume depletion. Patients are then classified according to the degree of dehydration: having no dehydration, some dehydration or severe dehydration. Fluid therapy is guided by the severity of volume depletion and an assessment of ongoing losses. Oral rehydration solution (ORS) are used to correct the volume depletion in those with mild volume depletion. They have been shown to be as effective as intravenous fluids and more practical in this setting (15). Intravenous fluids should be urgently administered in patients with more severe volume depletion or hypovolemic shock to rapidly restore the effective circulating volume in order to mitigate the development of complications arising from reduced tissue perfusion such as acute kidney injury and metabolic acidosis. Patients with severe volume depletion will often require an average of 200 mL/kg (kilogram body weight) of replacement fluids in the first 24 hours of therapy. Some patients may require more than 350 mL/kg. One approach to fluid therapy in these patients is to administer an initial fluid volume of 30 mL/kg given over the first half-hour, and 70mL/kg over the following two and a half hours, with a goal of administering a total of 100Ml/kg in the first three hours. Once the initial volume loss has been replaced, the patient should be monitored for ongoing losses which should be factored and replaced until the diarrhea stops (15).

The other aspect of fluid therapy in these patients is the choice of replacement fluid. Cholera diarrhea is a secretive diarrhea characterized by massive luminal secretion of electrolytes, including potassium and bicarbonate. Lactated Ringer's (LR) solution is therefore preferred over normal saline as a replacement intravenous fluid because it contains potassium and bicarbonate. In cholera endemic regions and during epidemics, fluids can be prepared locally. An example is the "Dhaka solution", prepared by addition various electrolytes and dextrose.

The other aspect of management of cholera is antibiotic treatment. Administration of antibiotic is recommended and has been shown to decreases stool volume and duration of diarrhea by up to 50%. Oral antibiotics maybe given in patients who are not vomiting. The choice of antibiotic is guided by the susceptibility results. In endemic regions and during cholera epidemics, tetracyclines are the antibiotic class for which there has been the most clinical experience and single dose doxycycline is recommended as has been shown to be as effective as multiple doses of tetracycline. Fluoroquinolones and macrolides are reasonable alternatives in regions known to have tetracycline resistance (29)

In Kenya, guidelines for fluid management in cholera patients, similar to the WHO guidelines have been provided by the disease outbreak management unit of the division of communicable and vector borne diseases, Ministry of health (Appendix 3) (60). During the 2017 cholera outbreak in Kenya, these guidelines were applied in managing patients admitted to KNH with suspected or confirmed cholera. Patients received various combinations of ringer's lactate, normal saline, and oral rehydration solutions (ORS). All patients received single dose oral doxycycline 300mg, others received oral ciprofloxacin or a macrolide.

3.0 Chapter Three: Materials and Methods

3.1: Study design: This was a Cross sectional study, a retrospective review of records of patients admitted to the cholera isolation ward in KNH between July and December 2017

3.2: Study population/Site: Patients admitted to the cholera isolation ward in KNH from July to December 2017.

KNH is national referral hospital, located in the capital city of Kenya, Nairobi. During the cholera epidemic in 2017, KNH received patients both directly or as referrals from the various parts of the county of Nairobi, and from other counties. Patients confirmed or suspected to have cholera were admitted through the accident emergency department to the Cholera isolation ward. A total of approximately 530 patients had been admitted to the cholera isolation at the time the ward was closed in January 2018. Approximately 160 patients were admitted during the study period (July to December 2017).

3.3: Inclusion/exclusion criteria:

Inclusion criteria: Patients that were admitted to the cholera isolation ward in KNH with a diagnosis of either suspected or confirmed cholera during the study period, whose records of at least one urea, creatinine, sodium and potassium measurements will be available

Exclusion criteria:

1. Patients who from hospital records, are known to have chronic kidney disease
2. Patients who from hospital records, are known to have a condition that is recognized as a risk factor for renal impairment: Diabetes mellitus, Hypertension, acute glomerulonephritis, infection with Human Immunodeficiency Virus (HIV)

3. Incomplete records (cases where records of urea, creatinine or electrolytes measurements are not available)

4. A negative cholera diagnosis test

3.4: Data collection

The files of all the patients admitted to the cholera isolation ward during the study period were retrieved and evaluated for eligibility according to the inclusion/exclusion criteria above. Data for those meeting the inclusion criteria was recorded in a data collection sheet and the following data was recorded:

- Social demographic characteristics (age, gender, area of residence)
- Clinical characteristics at presentation: Presenting symptoms, duration of symptoms Blood pressure, Temperature, hydration status, urine output (where available)
- Duration of symptoms prior to admission and duration of hospital stay
- Urea and creatinine measurements at admission, during the hospital stay and at discharge
- Diagnosis and treatment of AKI
- Electrolytes (sodium, potassium, chloride, bicarbonate) measurements at admission, during hospital stay and at discharge
- Complete blood count, Cholera microbiologic tests
- Treatment: Antibiotic use, volume repletion fluids administered
- Outcomes at time of discharge:

    Resolution of AKI (creatinine at discharge)

    Requirement for renal replacement therapy at time of discharge

    Normalization of electrolyte abnormalities

3.5: Data management and Statistical analysis

At the end of data collection, data collection forms were reviewed for completeness and coded by the investigator. Data was then entered into an excel database and exported to SPSS (Statistical package for social sciences) for analysis.

Descriptive statistics were carried out: Frequency tables, percentages and proportions were generated for categorical variables while Mean, Standard deviation, median and interquartile ranges were generated for continuous variables. Association analysis was carried out to determine the association between patients' characteristics and AKI or death. The chi- square test was used to check for association between categorical variables and AKI, and similarly to check for association between patients' characteristics and death. In cases where the cell counts were small, the Fisher's exact test was used to assess associations. The independent sample t-test was used to compare mean differences for continuous variables after tests of normality were carried out and found to be varied. A P-value <0.05 (at 5% level of significance) was considered significant at all analysis. The data was analyzed as follows:

1. Social demographic data:
    - Age: Mean/SD
    - Gender: proportions (%)
    - Duration of symptoms: mead/sd
    - Duration of hospital stay: Mean/sd
    - Symptoms: frequency/proportions (%)
2. Clinical parameters:
    - Blood pressure: proportions (%) with low, high, normal
    - Dehydration: proportions of: dehydrated, not dehydrated

3. Laboratory test data:

a) Cholera diagnosis:

- Suspected cholera: Proportion

- Confirmed cholera: proportion

For confirmed cholera: Rectal swab with cultures or Cholera Rapid test: proportions

b) Urea: mean /SD, proportions of normal and high

c) Creatinine: Mean (SD), proportions of normal and high

d) BUN/ Creatinine ratio: Mean, Proportions with high (>20:1), normal (<20:1)

e) Sodium, potassium, chloride, Bicarbonate at admission: Means/sd, proportions with low, normal, high

f) White blood cells (WBC): Mean/sd, Proportions with low, normal, high, very high

g) HB (Hemoglobin) and platelets: Mean/sd, Proportions with low, normal, high

5. Acute kidney injury data:

a) Total Proportion with and without AKI, proportions of stages of AKI

- Proportion with AKI at admission, Proportion who developed AKI in hospital

b) Those with AKI:

- Proportion that received renal replacement therapy (RRT) and those that did not receive RRT

- AKI receiving RRT: proportion discharged to continue with RRT as outpatient

- AKI (not requiring RRT) resolution at time of discharge: Proportion with normal creatinine and those with elevated creatinine at discharge, Mean creatinine at time of discharge for both categories

6. Electrolytes at discharge: (sodium, potassium, chloride): Means/sd, proportions of low, normal, high

3.6: Ethical considerations

Authority and Approval to carry out the study was obtained from the respective institutions' ethics committee (KNH-UON research ethics committee). Authority to use the medical records at the Kenyatta National Hospital was obtained from the Head of Department, Health Management Information Systems (appendix 4) (62). Upon ethical approval and before commencement, the study was registered and a certificate obtained as required by the Kenyatta National Hospital Research department.

This was a review of records and there was no direct contact with the participants. Participant Confidentiality was maintained by use of coded identification numbers and participant names were not indicated in the data collection forms. Data collection forms were stored under lock and key and only accessible to study personnel. Electronic data was password protected and only accessible to study personnel.

3.7: Study limitations

This was a retrospective review of records. As such, missing data was an expected challenge. To overcome this challenge, the minimum requirement for inclusion in the study was the availability of a clinical or microbiologic diagnosis of cholera (as described in the definition of terms above) and at least one measurement of urea, creatinine, sodium and potassium. The other limitation of this study was that it was a period prevalence study and may not have been adequately powered for the association analysis that was carried out.

4.0 Chapter four: Results

4.1: Social demographic and clinical characteristics (Tables 1 and 2 below)

A total of 127 participants were enrolled into the study. Out of these, 66.9% were males, 33.1% were females. The mean age was 36±12.6 years. The common presenting symptoms were watery diarrhea, rice water diarrhea, vomiting and abdominal pains. The mean duration of symptoms prior to admission was 2.1± 1.2 days and the mean duration of hospital stay was 4.7± 3.7 days. Majority of the patients had normal blood pressures at first encounter at the accident emergency department (70.8%).The in hospital case fatality in this cohort was 5.5%.

Participants were defined as having either confirmed cholera or suspected cholera (refer to operational definitions). Confirmed cholera was found in 48.8% of the study participants. The rest met the definition of suspected cholera. Among those with confirmed cholera, majority were diagnosed by a rectal swab culture at 77.4%.

Most of the participants had higher than normal total white blood cell counts (WBCs) with some having WBC counts higher than $20x10^9$/mL (27.4%), and the mean total WBC count was $14.4x10^9$/ml (± 7.9). Majority of the patients had a higher than normal serum hemoglobin level (69.2%), with a mean hemoglobin level of 16.6g/dl (±3.3). Most of the patients had normal serum platelet counts (81.2%).

Table 1: Table showing the Social, demographic and clinical characteristics of the study participants

Characteristic	**Overall: n= 127**	**Males: n=85**	**Females: n=42**	**P value**
Age(years): Mean(SD)	36.0 (12.6)	35.3 (11.4)	37.8 (15.2)	0.357
Duration of symptoms (days): mean(SD)	2.1 (1.2)	2.1 (1.2)	2.2 (1.3)	0.488
Duration of hospital stay(days) Mean(SD)	4.7 (3.7)	4.9 (3.8)	4.4 (3.4)	0.525
Outcome: n (%)				
Discharged from hospital	120 (94.5)	80 (93.9)	40 (95.0)	1.000
Deaths	7 (5.5)	5 (6.1)	2 (5.0)	
Frequency of symptoms: n (%)				
Watery diarrhea	64 (50.4)	45 (54.9)	19 (47.5)	0.444
Vomiting	105 (82.7)	69 (84.1)	36 (85.0)	0.903
Rice water Diarrhea	68 (53.5)	43 (51.2)	25 (57.5)	0.514
Abdominal pains	38 (29.9)	22 (26.8)	16(35.0)	0.353
Others: muscle pains	24(18.9)	17(70.8)	7(29.1)	
Blood pressure: n=106 n (%)				0.840
Low	29 (27.4)	19 (25.7)	10 (27.3)	
Normal	75 (70.8)	51 (72.9)	23 (69.7)	
High	2 (1.9)	1 (1.4)	1 (3.0)	

Urea, creatinine and BUN: Creatinine ratios (Table 3 below)

The mean serum urea level was 5.4mmols/l (±3.0), with 48% of the participant having a serum urea level above the upper limit of normal. The mean serum creatinine level was 137.5Umol/l (±80), with 64% of the participants having a serum creatinine level above the upper limit of normal. Among those with elevated serum creatinine levels, the mean BUN: Creatinine ratio (mg/dl) was 8.9(±3.7), with majority of the participants having a low BUN: Creatinine ratios of <10:1(75%).

Table 2: Table showing a summary of the laboratory investigations of the study participants

Characteristic	overall	male	female	p-value
Cholera diagnosis; n (%)				
Confirmed	62 (48.8)	40 (48.8)	19 (47.5)	0.894
suspected	65 (51.2)	42 (51.2)	21 (52.5)	
For confirmed cholera, Cholera tests done: n (%)				0.167
Rectal swab Positive	48 (77.4)	30 (71.4)	18 (90.0)	
Cholera Rapid antigen test Positive	14 (22.6)	12 (28.6)	2 (10.0)	
WBC: Mean(SD) n=110	14.4 (7.9)	14.6 (8.1)	16.6 (7.8)	0.560
Low: n (%)	6 (5.1%)	4 (5.4%)	2 (5.3%)	
Normal	45 (38.5%)	25 (33.8%)	19 (50.0%)	0.136
High	34 (29.1%)	27(36.5%)	6 (15.8%)	
Very high	32 (27.4%)	18 (24.3%)	11 (28.9%)	
Hemoglobin: Mean(SD)n=110	16.6 (3.3)	17.4 (2.9)	14.5 (3.1)	<0.001
Low: n (%)	3 (2.6%)	1 (1.4%)	2 (5.3%)	
Normal	33 (28.2%)	11 (14.9%)	21 (55.3%)	<0.001
High	81 (69.2%)	62 (83.8%)	15 (39.5%)	
Platelets: Mean(SD)n=110	297 (115.0)	287.9 (107.4)	315 (130.2)	0.228
Low	11 (9.4%)	7 (9.5%)	4 (10.5%)	
Normal	95 (81.2%)	61 (82.4%)	30 (78.9%)	0.891
High	11 (9.4%)	6 (8.1%)	4 (10.4%)	

Table 3: Table showing a summary of the Urea, creatinine and BUN: Creatinine ratio at admission

Laboratory test	Overall	Male	Female	P value
Urea: Mean(SD)	5.4 (3.0)	5.3 (2.7)	5.5 (3.8)	0.882
Low	6 (3.2%)	4(4.7.0%)	2 (4.7%)	
Normal	61 (48.8%)	28(32.9%)	33 (78.5%)	0.596
High	60 (48.0%)	53(62.3%)	7 (16.7%)	
Creatinine: Mean(SD)	137.5 (80.0)	297.3 (277.6)	192 (142.2)	0.007
Low	6 (3.2%)	3 (3.5%)	3 (7.1%)	
Normal	41 (32.8%)	28(32.9%)	13 (30.9%)	
High	80 (64.0%)	54 (63.5%)	26 (61.9%)	0.832
BUN: Creatinine ratio(for those with high creatinine only): n=80				
Mean(SD)	8.9 (3.7)	8.9 (3.7)	9.1 (4.3)	0.910
≤10.00	60 (75.0%)	38 (71.6%)	22 (81.4%)	
10.01-19.99	19 (23.8%)	14 (26.4%)	5 (18.50%)	
≥20.0	1 (1.3%)	1 (1.8%)	0 (0.0%)	0.834

4.2: AKI diagnosis and outcome at time of discharge (Table 4 below)

A diagnosis of AKI was made in 60.6% of the study participants and there was no difference in the frequency of AKI between males and females (p=0.248). Among those participants who met the KDIGO definition of AKI, 36.4% were classified as KDIGO stage 1 while 24.7% were in stage 2 and majority were classified as stage 3 (39.0%). AKI was present at the time of

admission in 96.1% and only 3.9% of patients developed AKI during their hospital stay (they had a normal creatinine at admission).

Among those with AKI, 17.6% received renal replacement therapy and all received hemodialysis. Hemodialysis had been stopped at the time of discharge in 23.0% of these patients. The rest of those receiving RRT (69.2%) were discharged home while still on hemodialysis to continue RRT as outpatients. One patient receiving RRT died.

Among patients with AKI who did not receive RRT, 56.2% had complete recovery of AKI with serum creatinine measurements within the normal range at the time of discharge. There were patients who still had elevated creatinine levels at the time of discharge (25.0%), and in the remaining 18.8% of patients with AKI who did not receive RRT, serum creatinine measurements were not available at the time of discharge (i.e. there was only one creatinine measurement in their records). AKI was present in all the patients who died and the mortality among patients with AKI was 9.1%.

4.3: Electrolyte abnormalities (Table 5 below)

At the time of admission, 26.8% patients had a serum potassium measurement that was below the lower limit of normal while 15.0% had hyperkalemia. At the time of discharge, 11.0% still had serum potassium levels below the lower limit of normal (hypokalemia) and 1.6% had hyperkalemia.

At the time of admission, 40.2% had serum sodium levels below the lower limit of normal while 10.2% of the patients had hypernatremia. At the time of discharge, 10.2% of the patients still had hyponatremia. Only 2.4% of patients had hypernatremia at the time of discharge.

Among those participants where an arterial blood gas had been performed, all had low serum bicarbonate levels and a low PH indicating presence of severe metabolic acidosis.

Table 4: Table showing AKI Diagnosis and outcome at the time of discharge

AKI diagnosis	Overall	Male	Female	P value
Total AKI n (%)N= all participants				0.248
Yes:	77 (60.6)	55 (64.7)	22 (52.3%)	
No	50 (39.4)	30 (35.2)	20 (47.6%)	
AKI KDIGO Stage: n (%)				
1	28 (36.4)	19 (34.5)	9 (40.9 %)	0.087
2	19 (24.7)	13 (23.6)	6 (27.2 %)	
3	30 (39.0)	23 (41.8)	7 (31.8%)	
AKI at admission (N= Total AKI): n (%)				
Yes	74 (96.1)	51 (98.1)	23 (92.0%)	0.139
No	3 (3.9)	1 (1.9)	2 (8.0%)	
AKI RRT(N=Total AKI)				
Yes	13 (17.6)	10(20.4)	3 (12.0)	0.268
No	64 (83.1%)	45(80.7)	19 (88.0)	
AKI RRT, Modality of RRT				
Hemodialysis: n (%)				-
Peritoneal Dialysis: n (%)	13 (100.0)	10 (100.0)	3 (100.0)	
	-	-	-	
AKI RRT, receiving RRT at discharge				1.000
Yes	9 (69.2)	6 (60.0)	3 (100.0)	
No	4 (30.7)	4(40.0)	0 (0.0)	
AKI RRT, not receiving RRT at discharge, with Normal creatinine at discharge(AKI Recovery after RRT)			-	-
Yes	2 (50.0)	2 (50.0)		
No	1(25.0)	1 (25.0)		
Death	1(25.0)	1 (25.0)		
AKI no RRT				
Normal creatinine at discharge: n (%)	36 (56.2)	22 (48.8)	14 (73.6)	0.503
High creatinine at discharge: n (%)	16 (25.0)	12 (26.6)	4(21.1)	
Not known	12 (18.8)	11 (24.3)	1 (5.3)	
AKI Death (N=Total AKI): n (%)				1.000
Yes	7 (9.1)	5 (9.1)	2 (9.1)	
No	70(90.9)	50 (90.1)	20 (90.1)	

Table 5: Table showing a summary of serum electrolytes of the study participants

Electrolyte	At admission	At discharge
Potassium: Mean(SD)	4.02 (1.2)	3.9 (0.8)
Low	34 (26.8%)	14 (11.0%)
Normal	71 (55.9%)	44 (34.6%)
High	19 (15.0%)	2 (1.6)
Not available	3 (2.4%)	67 (52.8)
Sodium: Mean(SD)	133.1 (15.1)	138.2 (5.6)
Low: n (%)	51 (40.2%)	13 (10.2%)
Normal	39 (30.7%)	44 (34.6%)
High	13 (10.2%)	3 (2.4%)
Not available	24 (18.9%)	67 (52.8)
Bicarbonate: Mean(SD)	9.9 (2.7)	-
Low: n (%)	7 (5.5%)	
Normal	-	
High	-	
Not available	120 (94.5%)	
Chloride: Mean(SD)	83.2 (16.4)	97.7 (4.5)
Low: n (%)	4 (3.1%)	1 (0.8%)
Normal	4 (3.1%)	2 (1.6%)
High	1 (0.8)	-
Not available	118 (92.9)	124 (97.6%)
PH : Mean(SD)	7.1 (0.1)	-
Low: n (%)	7 (5.5%)	
Normal	-	
High	-	
Not available	120 (94.5%)	
Creatinine (at discharge): mean/sd	[redacted]	137.5 (80.0)
Low		2 (1.6%)
Normal: (%)		37 (29.1%)
High		21 (16.5%)
Not available		67 (52.8)
Urea(at discharge): mean/sd		5.5 (3.0)
Low		10 (7.9%)
Normal		43 (33.9%)
High		7 (5.5%)
Not available		67 (47.2%)

4.4: Association between patients' characteristics and AKI or Death (Table 6, table 7 below)

On bivariate analysis, there was a statistically significant association (p value<0.001) between AKI and duration of hospital stay, total WBC counts, serum hemoglobin levels, serum sodium levels at admission (p value=0.032) and cholera diagnosis. There was a tendency for patients with AKI to have significantly higher total WBC counts and serum hemoglobin levels compared to those without AKI. Patients with AKI had longer mean duration of hospital stay compared to those without AKI. Majority of patients with AKI had low sodium levels at admission (p value=0.032)

There was a statistically significant association (p value<0.05) between death and age, duration of symptoms prior to admission, blood pressures at admission, total WBC counts and serum urea levels at admission.

Table 6: Table showing the Association between Patients' characteristics and AKI

Characteristic	Overall	AKI	No AKI	P-value
Age: Mean(SD)	36.0 (12.6)	36.9 (12.7)	50 (12.3)	0.344
Gender Male Female	 85 (67.2) 42 (32.8)	 55 (71.2%) 22 (28.8%)	 40 (61.2%) 20 (38.8%)	 0.248
Duration of symptoms prior to admission: Mean(SD)	2.1 (1.2)	2.1 (1.1)	2.1 (1.4)	0.904
Duration of hospital stay: mean(SD)	4.7 (3.7)	5.6 (3.9)	3.3 (2.8)	<0.001
WBC Low Normal High Very High	 6 (5.1) 45 (38.5) 34 (29.1) 32 (27.4)	 1 (1.4%) 15 (20.8%) 29 (40.3%) 27 (37.5%)	 5 (11.1%) 30 (66.7%) 5 (11.1%) 5 (11.1%)	 <0.001
Hemoglobin: n (%) Low Normal High	 3 (2.6) 33 (28.2) 81 (69.2)	 1 (1.4%) 10 (13.9%) 61 (84.7%)	 2 (4.4%) 23 (51.1%) 20 (44.4%)	 <0.001
Cholera diagnosis: n (%) confirmed suspected	62 (48.8) 65 (51.2)	48 (62.3) 29 (37.7)	14 (28.0) 36 (72.0)	<0.001
Blood pressures at admission: n (%) low Normal High	 29 (27.4 75 (70.8) 2 (1.9)	 24 (36.4) 42 (63.6) 0 (0.0)	 5 (12.5) 33 (82.5) 2 (5.0)	 0.008
Potassium at admission Low Normal High	34 (27.4) 71 (57.3) 19 (15.3)	23 (30.7%) 38 (50.7%) 14 (18.7%)	11 (22.4%) 33 (67.3%) 5 (10.2%)	0.169
Sodium at admission Low Normal High	 51 (49.5) 39 (37.5) 13 (12.6)	 33 (53.2%) 18 (29.0%) 11 (17.7%)	 18 (43.9%) 21 (51.2%) 2 (4.9%)	 0.032
PH at admission Low	 7 (100.0)	 6 (100.0%)	 1 (100.0%)	 -
Bicarbonate at admission Low	 7 (100.0)	 6 (100.0%)	 1 (100.0%)	 -

Table 7: Table showing the association between Patient Characteristics and death

Characteristic	Overall	Discharged home	Death	P-value
Age: Mean(SD)	36.0 (12.6)	35.5 (12.1)	45.6 (17.6)	0.038
Gender: n (%)				
Male	82 (67.2)	77 (67.0)	5 (71.4)	1.000
Female	40 (32.8)	38 (33.0)	2 (28.6)	
Duration of symptoms prior to admission: Mean(SD)	2.1 (1.2)	1.9 (1.1)	4 (1.6)	<0.001
Duration of hospital stay: mean(SD)	4.7 (3.7)	4.8 (3.5)	4.0 (6.2)	0.593
WBC				
Low	6 (5.1)	4 (3.6)	2 (28.6)	0.003
Normal	45 (38.5)	45 (40.9)	0 (0.0)	
High	34 (29.1)	33 (30.0)	1 (14.3)	
Very High	32 (27.4)	28 (25.5)	4 (57.1)	
Hemoglobin: n (%)				
Low	3 (2.6)	3 (2.7)	0 (0.0)	0.633
Normal	33 (28.2)	30 (27.3)	3 (42.9)	
High	81 (69.2)	77 (70.0)	4 (57.1)	
Cholera diagnosis: n (%)				
confirmed	62 (48.8)	57 (47.5)	5 (71.4)	0.266
suspected	65 (51.2)	63 (52.5)	2 (28.6)	
Blood pressures at admission: n (%)				
low	29 (27.4	25 (24.8)	4 (80.0)	0.026
Normal	75 (70.8)	74 (73.3)	1 (20.0)	
High	2 (1.9)	2 (2.0)	0 (0.0)	
Admission creatinine:				
Low	4 (3.2)	4 (3.4)	0 (0.0)	0.459
Normal	41 (32.8)	40 (33.9)	1 (14.3)	
high	80 (64.0)	74 (62.7)	6 (85.7)	
Admission urea: n (%)				
Low				0.018
Normal	4 (3.2)	4 (3.4)	0 (0.0)	
High	61 (48.8)	61 (51.7)	0 (0.0)	
	60 (48.0)	53 (44.9)	7 (100.0)	
AKI: n (%)				
Yes	77 (60.6)	71 (59.2)	6 (85.7)	0.244
No	50 (39.4)	49 (40.8)	1 (14.3)	
AKI received RRT: n (%)			2 (33.3)	0.238
Yes	13 (17.6)	11 (16.2)	4 (66.7)	
No	61 (82.4)	57 (83.8)		
Potassium at admission:				
Low	34 (27.4)	30 (25.6)	4 (57.1)	0.177
Normal	71 (57.3)	69 (59.0)	2 (28.6)	
High	19 (15.3)	18 (15.4)	1 (14.3)	
Sodium at admission				
Low	51 (49.5)	45 (46.9)	6 (85.7)	0.089
Normal	39 (37.5)	39 (40.6)	0 (0.0)	
High	13 (12.6)	12 (12.5)	1 (14.3)	

5.0 Chapter 5: Discussion

Cholera still remains a cause of severe diarrhea in third world countries with poor sanitation conditions. The most common cause of death from diarrhea is the shock caused by dehydration, AKI, electrolytes and acid-base disorders. In this cohort of 127 patients with acute diarrhea of which 48.8% were confirmed cholera, majority were males (67%) and the mean age was 36years (±12.6). This is consistent with results of a study done in Tehran where of 121 patients, 53% were male (23). A study done in Karachi however reported a mean age of 42.3(±618.34) years and majority of the patients were females at 57% (25). The duration of symptoms prior to admission was 2.1 days which is consistent with results of other studies (25).

Majority of the study patients had elevated total WBC counts, with a mean total WBC count of 14.4±7.9 with 27.4% having WBC counts higher than 20,000/ml. The white blood cell count is generally high in patients with severe cholera. This maybe a result of a systemic inflammatory response to the infection with *V.cholerae*. Majority of the patients had hemoglobin levels higher than the upper limit of normal for gender (69.2%), with a high mean hemoglobin of 16.6g/dl. This is an expected finding in patients with cholera and is a result of haemoconcentration secondary to volume depletion.

The in hospital case fatality rate in our study was 5.5%, which is higher than the national average reported for the 2017 cholera epidemic by the ministry of health in July 2017 (case fatality of 1.2%) (5), and that reported in other epidemics. The 2010 cholera epidemic in Haiti reported a hospital case fatality rate of 2.3% (18). In our study, all the mortalities occurred in patients who had AKI (Table 4). This is concerning as mortality in cholera patients can be reduced to < 0.5% with adequate volume repletion and correction of electrolyte abnormalities. An attempt was made to identify the risk factors of this high mortality among these patients through association

analysis: There was a significant association between death and age, duration of symptoms prior to admission, total WBC counts, Blood pressures at admission and serum urea levels at admission. There was a tendency for patients who died to be older (mean age 45yrs, p value 0.038). Patients who died also reported a longer duration of symptoms prior to admission (4 ±1.6days, p value<0.001).This is likely a reflection of more marked volume depletion as a result of longer duration of diarrhea and vomiting. Majority of the patients who died also had high total WBC counts (71.4%, p value= 0.003), elevated urea at admission (100%, p value= 0.018) and lower BP at admission (80%, p value= 0.026). The association between elevated WBC count and death is likely a reflection of patients with more severe infection and sepsis. The association between low BPs and death could also be a reflection of more severe volume depletion at the time of admission. Other factors such as inadequate volume repletion or uncorrected electrolyte abnormalities may have contributed but this was a retrospective study that did not evaluate fluid management and treatment of electrolyte abnormalities. We recommend a larger prospective study be conducted to address this aspect of management of patients with cholera.

WHO recommends antibiotics use in patients with cholera as they have been shown to reduce the stool volume and duration of diarrhea. All the patients in this study received treatment with antibiotics. The antibiotics administered this study included: one dose of oral doxycycline 300mg either alone or in combination with courses of intravenous ceftriaxone, oral ciprofloxacin or a macrolide.

Acute renal failure is the most severe complication of cholera. The frequency of AKI in this cohort of patients admitted to the cholera isolation ward in KNH was 60.6%, much higher than that reported in other studies. Majority of the patients who developed AKI recovered with conservative management, with only 17% requiring RRT. In a study done in Tehran that reported

a prevalence of AKI among patients with Cholera of 23.9 % (23), 23.8% required dialysis during hospitalization while a study in Karachi reported a prevalence of 31.4% (25). The high frequency of AKI in our study could be explained by late presentation to a healthcare facility. The mean duration of symptoms prior to admission was 2.1 days. Massive fluid losses can occur within a relatively short period of diarrhea in cholera as fluid loss in cholera can go up to 1000mls per stool. It is therefore likely that the patients had marked volume loss prior to admission. This is a public health issue and we recommend enhancing awareness on the importance of seeking health care earlier during cholera epidemics. In our study, more than half of the patients with AKI met the criteria for KDIGO stage 2 and above (stage 3 at 39%, stage 2 at 24.7%). It is therefore possible that the requirement for supportive RRT may have been underestimated. However, this could not be evaluated in this retrospective study.

Follow up creatinine levels indicated that more than half of the patients with AKI who did not receive RRT recovered to normal creatinine values at the time of discharge (56.2%), and 25% of patients with AKI still had elevated creatinine at the time of discharge. There was a proportion of patients with AKI in whom the creatinine level was not known at the time of discharge i.e. no follow up serum creatinine was done after the admission serum creatinine level. Among those patients that received RRT, there was a proportion that was still receiving RRT at the time of discharge from the hospital (69%). In all the patients who had either elevated creatinine or were still receiving RRT at the time of discharge, there was evidence in the Hospital discharge record indicating referral to the renal clinic. We recommend a prospective study to establish outcome of these patients after discharge from hospital.

In an attempt to identity the risk factors of this high prevalence of AKI in these patients, association analysis was carried out to determine association between patients' characteristics

and AKI. In this analysis, there was a statistically significant association between duration of hospital stay (p value=<0.001), total WBC count (p value<0.001), Hemoglobin levels (p value <0.001), serum sodium levels at admission (p value =0.032) and cholera diagnosis (p value<0.001). There was a tendency for patients with AKI to have higher total WBC counts than those without AKI. This is most likely a reflection of a higher degree of a systemic inflammatory response in those with sepsis secondary to infection with *V. cholera* infection. A larger proportion of Patients with AKI had high hemoglobin concentration compared to those without AKI. This reflects more hemoconcentration in patients with more volume depletion. It can therefore be theorized that the association of AKI and elevated WBC and high hemoglobin levels was a result of severe volume depletion and sepsis, both increasing the risk of developing AKI. The association between confirmed cholera diagnosis and AKI is possibly because patients who were more clinically ill were more likely to have a longer hospital stay and thus get a microbiologic cholera test.

AKI in cholera is presumed to be prerenal, secondary to volume depletion. It is therefore expected that AKI in these patients would be associated with high BUN: Creatinine ratios of >20:1. The mean BUN: Creatinine ratio in our study was 8.9:1, which is lower than would be expected in prerenal AKI. Majority of the patients with elevated serum creatinine levels had BUN: Creatinine ratios of < 20:1, with 75% having BUN: Creatinine ratios of <10:1, and 23.8% having BUN: Creatinine ratios of 10.01-19.9: 1. Only 1 patient had BUN: Creatinine ratios of > 20:1. This is consistent with findings of a study done in Karachi which reported similarly low BUN: Creatinine ratios, with a mean of 11.63:1±5 in patients with cholera (25). Several theories have been proposed to explain this disproportionately low BUN: Creatinine ratios: the increase in BUN with dehydration takes a while, perhaps patients with cholera are so acutely dehydrated

that they have not had enough time for the urea to reach equilibrium. This could be the reason that the BUN: creatinine ratio in cholera is low. It is also possible that the rapid volume depletion with reduced renal perfusion leads to acute tubular necrosis resulting to a reduction in tubular urea absorption. A Fractional Excretion of Sodium (FeNa) would have made this clearer. It is also possible that urea is lost from the gut more rapidly than creatinine in cholera (25). However, Serum urea or BUN levels are largely determined by protein intake. The low serum urea levels probably reflect a low protein intake in this cohort. Further larger prospective studies are needed to study urea metabolism in pre-renal failure in cholera and the effects of cholera toxin on intestinal urea transport.

Biochemical and acid-base laboratory abnormalities in cholera include metabolic acidosis with a high anion gap, low serum potassium levels, low sodium and chloride levels. The calcium and magnesium content in plasma is often high as a result of hemoconcentration. Other laboratory abnormalities that are seen in severe cholera include increases in packed cell volume, serum specific gravity, and total protein and reflect the isotonic dehydration that is characteristic of cholera. Hyperglycemia caused by high concentrations of epinephrine, glucagon, and cortisol stimulated by hypovolemia is more commonly seen than hypoglycemia (23). In our study, the most frequent electrolyte abnormality was hyponatremia with a mean serum sodium concentration of 133.1mmols/l, and 40.2% of the patients having levels lower than the lower limit of normal. Hyponatremia had been corrected in majority of the patients at the time of discharge, with only 10.2% having hyponatremia. The second most frequent electrolyte abnormality was hypokalemia at 26.8%. Hyperkalemia was reported in 15% of the patients at admission. Hyperkalemia is an unexpected finding in cholera patients who lose potassium in stool and vomitus. It likely reflects potassium retention in patients with AKI. A high anion gap

metabolic acidosis is a common presentation in Cholera due to the bicarbonate and chloride loss in stool and vomitus. In a study done in Tehran, 67.8% of the patients had hyponatremia on admission (serum sodium of <137meq/l), 5.8% had hypernatremia, 33.8% had hypokalemia, 2.4% had hyperkalemia and 56.75% had metabolic acidosis. It is therefore concerning that arterial blood gases, serum bicarbonate, PH and chloride measurements were not routinely done in this cohort of patients at KNH, with only 5.5% having these measurements in their records. We therefore recommend that electrolyte assessment in patients with cholera include an extended electrolyte panel with Bicarbonate, chloride, magnesium and calcium.

5.1: Conclusions

1. Prevalence of AKI among patients admitted to the isolation ward in KNH was high at 60.6%.
2. The mean duration of symptoms prior to hospital admission was 2.1 days and more than half of the patients already had severe volume depletion with AKI at the time of admission.
3. Utilization of RRT among patients with cholera and AKI in KNH was relatively low at 17%.
4. Electrolyte abnormalities among patients admitted to the cholera isolation ward in KNH included hyponatremia, hypokalemia and hyperkalemia, with hyponatremia being the most common abnormality at 40.2%.
5. Acid base abnormalities such as metabolic acidosis are common in cholera due to the electrolyte losses in stool and vomitus. However, assessment and monitoring of electrolytes such as bicarbonate and chloride, and serum PH was not routinely done in patients with cholera at KNH, with only 5.5% having these measurements in their records.
5. Despite a report of having followed the WHO cholera management guidelines, there was a higher hospital case fatality among patients admitted to the cholera isolation ward in KNH at 5.5%.

6. BUN: Creatinine ratios among patients with cholera and AKI at KNH were unusually low for AKI that is presumed to be prerenal secondary to intravascular volume depletion.

5.2: Recommendations, Policy and Research Implications

1. It might be worthwhile to include a nephrologist in the cholera management team at KNH to guide the management of patients who develop AKI and plan the post discharge follow up of those with persistent derangement in kidney function and electrolytes

2. It might be worthwhile for the public health department to enhance community awareness on the importance of seeking healthcare early during cholera epidemics to prevent severe volume depletion and development AKI and electrolyte abnormalities.

3. We recommend close monitoring of electrolytes and laboratory evaluation of patients with cholera to include assessment of serum bicarbonate, PH and chloride.

4. We recommend a larger prospective study to assess fluid and electrolyte management among patients with Cholera to further advise the management of these patients

5. The low BUN: Creatinine ratios seen among patients with Cholera and AKI could not be adequately explained and require further evaluation.

6.0 Chapter six: Appendices

6.1 Appendix 1: References

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6.2: Appendix 2: Fluid management in cholera

Kenya cholera Control Guidelines

Ministry of health, division of communicable and vector borne diseases, disease outbreak management unit

Section 1.2: Management of a patient with Cholera

Step 1: Assess for dehydration

Step 2. Rehydrate the patient and monitor frequently. Then reassess hydration status.

Step 3. Maintain hydration: replace ongoing fluid losses until diarrhoea stops.

Step 4. Give an oral antibiotic to patients with severe dehydration.

Step 5. Feed the patient

STEP 1. Assess for dehydration

Determine whether the patient has:

• Severe dehydration

• Some dehydration

• No signs of dehydration

STEP 2. Rehydrate the patient, and monitor frequently; reassess hydration status

For Severe Dehydration:

• Give IV fluid immediately to replace fluid deficit. Use Ringer's lactate solution or, if not available, normal saline.

Start IV fluid immediately. If the patient can drink, begin giving oral rehydration salts (ORS) solution my mouth while the drip is being set up.

For patients aged 1 year and older, give 100ml/kg IV in 3 hours, as follows: -

- 30ml/kg as rapidly as possible (within 30 minutes); then

- 70ml/kg in the next 2½hours.

• Monitor the patient very frequently. After the initial 30ml/kg have been given, the radial pulse should be strong (and blood pressure should be normal.) If the pulse is not yet strong, continue to give IV fluid rapidly.

• Give ORS solution (about 5 ml/kg) as soon as the patient can drink, in addition to IV fluid.

• Reassess the patient after 3 hours (infants after 6 hours), using Table 1:

- If there are still signs of severe dehydration, repeat the IV therapy already given.

- If there are signs of some dehydration, continue as indicated below for some dehydration.

- If there are no signs of dehydration, go on to Step 3 to maintain hydration by replacing ongoing fluid losses.

For Some Dehydration:

Give ORS solution*:*

6.3 Appendix 3: Letter of Authorization to use medical records

Beatrice Wangari Ndege

H114/10265/2018,

East African Kidney Institute, College of Health Sciences,

University of Nairobi,

24th July 2018.

TO,

Head of Department, Health Management Information Systems,

Kenyatta National Hospital.

REF: Request for authorization to use health records in the conduction of a study

I am a physician currently undertaking a Fellowship in Nephrology under the East African Kidney Institute, University of Nairobi.

I kindly request for authorization to use medical records for purposes of conducting a study titled: Acute kidney injury and electrolyte abnormalities among patients admitted with Cholera in Kenyatta National Hospital, Nairobi, Kenya, in the year 2017.

Sincerely,

Dr Beatrice Wangari Ndege