FACTORS ASSOCIATED WITH POOR CLINICAL OUTCOMES IN CHILDREN ADMITTED WITH BLACKWATER FEVER IN EASTERN UGANDA: A RETROSPECTIVE STUDY

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DECLARATION

I, Paasi George hereby declare that this dissertation is my original work and to the best of my knowledge, it has not been presented to any institution of higher learning as a requirement for the award of a Master's degree in Public Health or any other similar qualification.

SIGNATURE: ---------- DATE: 05/08/2019

SUPERVISOR'S APPROVAL

I, certify that Paasi George a student pursuing a Master's Degree in Public Health at Busitema University's Faculty of Health Sciences worked under my direct supervision.

SIGNATURE: ---------- DATE: 05/08/2019

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(SUPERVISOR)

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LIST OF ABBREVIATIONS

ACT	Artemisinin-based Combination Therapy
AKI	Acute Kidney Injury
AQUAMAT	Artesunate versus Quinine in the Treatment of Severe falciparum Malaria i African children
BUN	Blood Urea Nitrogen
BWF	Blackwater Fever
DRC	Democratic Republic of Congo
DUS	Dark Urine Syndrome
EIR	Entomological Inoculation Rate
FEAST	Fluids Expansion as Supportive Therapy
G6PDd	Glucose Phosphate Dehydrogenase deficiency
GCP	Good Clinical Practice
HCC	Hillmen Colour Chart
HMIS	Health Management Information System
HIV/AIDS	Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome
ITNs	Insecticide Treated Nets
MOH	Ministry of Health
MRRH-REC	Mbale Regional Referral Hospital -Research Ethics Committee
PACU	Paediatric Acute Care Unit
PAR	Paediatric Admission Record
pRBC	parasitized Red Blood Cells
RDT	Rapid Diagnostic Test
SSA	Sub-Saharan Africa

UDHS	Uganda Demographic and Health Survey
UNCST	Uganda National Council for Science and Technology
WHO	World Health Organization
X^2	Chi square test

LIST OF OPERATIONAL DEFINITIONS

Blackwater fever A clinical syndrome characterized by an acute intravascular haemolysis presenting with a triad of passing tea-coloured/coca cola/dark urine (haemoglobinuria), jaundice/yellowing of eyes, anaemia and usually follows a febrile episode[1, 2]. The term Blackwater fever was used synonymously with dark urine syndrome and haemoglobinuria in this study.

Dark urine syndrome This condition of dark urine syndrome (DUS) was first described by O'Donnell and colleagues [2] and later by Olupot-Olupot [3], both of whom have showed that aetiology of dark urine was due to many causes and hence a syndrome. Two biologically different proteins have been isolated in coloured urine in severe malaria: haemoglobinuria and myoglobinuria, but with possible different pathophysiology. Haemoglobinuria, a marker of severe haemolysis is mainly associated with acute intravascular haemolysis, while myoglobinuria manifests mainly among children with cerebral malaria and hyperlactatemia; suggesting hypoxic muscle cell injury from sequestration of parasitized red blood cells[2] suggesting a multi-aetiological and pathophysiology process.

Dark urine Coca-Cola or tea coloured urine, which on (Hillmen Colour Chart) HCC scale was in the range of 5 -10.

Poor clinical outcomes Children who following admission with Blackwater fever/DUS develop prolonged hospitalization and in-patient death defined as:

- Prolonged hospitalization – prolonged length of stay was defined as patient admitted with a primary diagnosis of BWF whose length of hospitalization is above the 75^{th} percentile of length of hospitalization.

- In-patient death –death of a patient during the admission period following a primary diagnosis of BWF.

Anaemia	This is a decrease in the amount of red blood cells (RBCs) or haemoglobin (Hb) in the blood. It was categorised as moderate anaemia when Hb was 6 - 9g/ dL, severe anaemia when Hb was <5g/ dL or profound anaemia when Hb was <4g/dL.
Impaired consciousness	Measured using AVPU scale was defined when AVPU=<A
Prostration	Generalized weakness so that the patient is unable to walk or sit up without assistance [4].

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ABSTRACT

Background: Severe malaria remains an important public health problem in sub-Saharan Africa. Blackwater fever, a complication of malaria has in the past been considered a rare complication of malaria in children living in high transmission settings. More recently, however, a growing number of paediatrics case-series of Blackwater fever have been published from Africa. In Uganda, in particular eastern Uganda, clusters of Blackwater fever cases have been reported by local researcher, Olupot-Olupot, Engoru [34]. In this region BWF still remains an important cause of hospital admissions with a high burden of mortality and morbidity causing worse outcomes among children admitted to hospital.

Objective: This study seeks to determine the factors associated with poor clinical outcomes in children admitted with Blackwater fever in eastern Uganda.

Method:

A retrospective quantitative review of hospital-based records using patient case files was done. The admission registers in the two tertiary hospitals were used to identify all the children who presented to the Paediatric Acute Care Unit (PACU) of MRRH and SRRH within the period of study (2018) with a diagnosis of Blackwater fever/dark urine syndrome. Their case records were retrieved and the necessary information were obtained using a structured questionnaire. These included their demographic, clinical characteristic and outcome status. A diagnosis of BWF/dark urine syndrome was made at or during admission with the aid of the Hillmen Colour Chart (HCC). Bivariate and multivariate analysis using logistic regression was used to analyse the association between the predictors and poor clinical outcomes (prolonged hospitalisation and mortality) of admission with BWF.

Results:

Of the 9578, 1241 (13.0%) children were admitted with BWF/DUS to the Paediatric Acute Care Unit (PACU) of Mbale and Soroti regional referral hospital in the year 2018. The age of the study participants ranged from 4 months to 180 months with a median age of 60 months; interquartile range (IQR) 36 - 90) and a male preponderance (1.5:1 male to female ratio). 559 (45.04%) <5 years and 682 (54.96%) were ≥5 years. Besides all patients presenting with passing dark urine /tea-coloured urine, most of the patients also commonly presented with high fever 1109 (94.30%), vomiting 599 (53.01%) and abdominal pain 494 (45.11%). In addition, they presented with common clinical signs of pallor 742 (67.33%), clinical jaundice 369 (34.42%), prostration 231 (21.94%) and abdominal signs of abdominal tenderness 120 (9.67%) and splenomegaly122 (9.83%). Presumed sepsis and sickle cell disease were the

leading co-morbidity. 426/1241 (34.3%) of the patients received at least one blood transfusion. There were significant difference in the clinical characteristics observed between the <5 years and ≥5years and to a small extent between the males and females. 251 (27.3%) patients had prolonged hospitalization, which was defined as a baseline hospitalization stay longer than 5 days (>75 percentile of hospitalization duration) and 40 /1241patients (3.22%) had mortality during the study period. Multivariate logistic regression analysis indicated that the independent predictors for prolonged hospitalization were abdominal pain (aOR 1.91; 95% CI 1.04 -3.49; p=0.037), the presence of "*any pain*" (either of chest pain, hand pain or foot pain) (aOR 2.19; 95% CI 1.41 - 3.39; p<0.000) and delayed capillary refill time of >3 seconds (aOR 1.84; 95% CI 0.93 - 3.67; p=0.082).

Conclusion:

This study affirms that the independent predictors for prolonged hospitalization are abdominal pain, the presence of "*any pain*" (either of chest pain, hand pain or foot pain) and delayed capillary refill time of >3 seconds. Therefore, recognition of these predictors warrants more vigilance by clinicians to improve clinical examination during the triage of patients with BWF/dark urine syndrome to avert these unfavourable outcomes in children admitted with BWF/dark urine syndrome

Keywords: Blackwater fever, dark urine syndrome, severe malaria, predictors, prolonged hospitalization, Mortality**.**

CHAPTERS OUTLINE

This thesis was organized into six distinct chapters each beginning with a short synopsis.

Chapter 1: This chapter provided an introduction and background to my study describing the public health importance of severe malaria in particularly in Uganda. It highlighted the growing number of Blackwater fever cases in eastern Uganda and its consequences as a major cause of hospital admissions with worse outcomes. The primary objective of this study was to determine the factors associated with poor clinical outcomes in children admitted with Blackwater fever in eastern Uganda also included in this chapter is the study problem, justification study objectives and conceptual framework.

Chapter 2: In this chapter, I reviewed past and current literature on Blackwater fever, under the subtopics: what is known about Blackwater fever, evidence before this study, spectrum of severe malaria presentation in eastern Uganda, clinical features and outcomes of Blackwater fever and conclusion of literature review.

Chapter 3: In this chapter, the study area, study design and rationale, study population and sampling procedure, variables under study, methods of data collection, data management, statistical analysis, quality control, ethical considerations, results dissemination and limitations of the study were discussed.

Chapter 4: In this chapter, the results of this study were presented using tables and graphs. All statistical analyses are in this section.

Chapter 5: In this chapter interpretation of the study's findings and comparison to results from previous research were given. This chapter also covered the strength and limitations of the study.

Chapter 6: In this chapter a logical conclusion of the study's findings and recommendations for further research were given.

CHAPTER 1: INTRODUCTION

1.1 BACKGROUND

In many parts of the world, including several African countries, there has been a substantial reduction in malaria incidence, because of the scaling up of control measures [5-9]. Nevertheless some countries in Sub-Sahara Africa have either documented no decline [10], an increase in hospitalization with Plasmodium falciparum malaria during the same period [11, 12] or a resurgence of severe malaria following a period of sustained control[13]. Globally an estimated 216 million cases of malaria occurred with 90% in WHO African region in 2016, plasmodium falciparum malaria accounts for 99% of cases and causes 300-500 million clinical episodes. There were up to 445,000 direct deaths attributed to the disease in 2016 [14]. Malaria is a contributor to comorbidity with other disease leading to an estimated 3 million death annually [15], 90% of mortality is in African children <5 years. The annual average infection for children is 1.6-5.4 times. Every 1 minute, a child dies of malaria in Africa [10, 16]. Ten Sub-Sahara African (SSA) countries account for 87% of people exposed to highest malaria endemicities globally, with plasmodium falciparum rates in children 2-10 years >50% [14] .

Uganda is one of the ten countries in sub-Saharan Africa that account for approximately 70% of global malaria cases and deaths. Uganda is a malaria endemic country with active transmission in 99% of the country [14]. Uganda has a high, stable perennial transmission in 95% of the country and a low unstable transmission in 5% of the country (highlands), which are also epidemic prone areas. The stable transmission areas are divided in 3 epidemiological zones that is very high (eir >100) in 70% of areas (e.g.Apac, Tororo, Arua, Kamwenge), Apac has 1,564 infective mosquito bites per person per year, medium to high (EIR 10-100) in 20% of areas and low (EIR <10) in 10% of areas [17]. All four species of Plasmodia exist in Uganda with plasmodium falciparum accounting for 90-98% of cases and plasmodium malariea 1-3%. The common vectors are *Anopheles Gambiae* and *funestus.* Both are endophagic and endophilic and are efficient breeders in very small pools of water.

Whereas all people in Uganda are at risk of contracting malaria, children under-5 years of age and pregnant women are the most vulnerable. The 2016 Uganda demographic health survey (UDHS) estimated the prevalence of malaria by rapid diagnostic test in Uganda at 30% among children under the age of 5 years [18].

Malaria is Uganda's leading cause of morbidity and mortality with a total cases estimated at up to 60 million per year [19]. According to the Ministry of Health (MOH), malaria accounts

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