Bacteremia associated with central venous catheterization and their antibiogram among patients on hemodialysis therapy at Muhimbili National Hospital – Dar Es Salaam, Tanzania

Saning'o Sangeti, MD

MMed (Internal Medicine) Dissertation
Muhimbili University of Health and Allied Sciences
October, 2017

BACTEREMIA ASSOCIATED WITH CENTRAL VENOUS CATHETERIZATION AND THEIR ANTIBIOGRAM AMONG PATIENTS ON HEMODIALYSIS THERAPY AT MUHIMBILI NATIONAL HOSPITAL – DAR ES SALAAM, TANZANIA

By

Saning'o Sangeti

A dissertation Submitted in (Partial) Fulfillment of the Requirements for Degree of Master of Medicine (Internal Medicine) of the Muhimbili University of Health and Allied Sciences

Muhimbili University of Health and Allied Sciences
October, 2017

CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance by Muhimbili University of Health and Allied Sciences a dissertation entitled: "**Bacteremia associated with central venous catheterization and their antibiogram among patients on hemodialysis therapy at Muhimbili National Hospital, Dar es Salaam, Tanzania"** in (partial) fulfillment of the requirements for the degree of the of Master of Medicine (Internal Medicine) of Muhimbili University of Health and Allied Sciences.

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Dr. P. Ruggajo

(Supervisor)

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Date

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Dr. J. Manyahi

(Co-supervisor)

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Date

DECLARATION AND COPYRIGHT

I, **Saning'o Sangeti**, declare that this **dissertation** is my own original work and that it has not been presented and will not be presented to any other university for a similar or any other degree award.

Signature…….....…… Date…….

ACKNOWLEDGEMENT

I would like to express my sincere gratitude to my supervisors; Dr. P. Ruggajo and Dr. J. Manyahi for the fact that despite of being occupied by many academic and family commitments, still they could provide me with unmeasurable assistance and guidance from proposal development stage to final report writting. My grateful thanks also go to the former Head of Department Dr. P. Chillo and other members of the staff from department of Internal Medicine for their strong encouragement and support during my residency programme.

I am very thankful to the Principal (Prof. D. Mfinanga) and Deputy Principals (Prof. J. Buchwashaija and Prof. G. Mtui) of the Dar es salaam University College of Education for their permission to let me attend and finance my postgraduate studies.

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I would like to acknowledge the technicians of the Department of Microbiology at the Central Pathology Laboratory, Muhimbili National Hospital, especially James Balamashaga and Mary Martin for their technical assistance. My sincere thanks to all other members of the Nephrology Unit at MNH as well as secretaries at the office of Deputy Vice Chancellor (Academic, Research and Consultancy-MUHAS) for their co-operation during my study.

Last but not least, I wish to express my deep gratitude to my lovely wife and children, parents, brothers, sisters and sisters in law for their undestanding and their kind support.

DEDICATION

This dissertation is dedicated to my lovely wife Risper and to our son; Sangeti and two daughters; Sinyati and Neserian.

ABSTRACT

Background: For patients on maintenance hemodialysis therapy, vascular-associated infections contribute significantly to frequent morbidity and related mortality. To date, there is paucity of data in Tanzania on the magnitude of bacteremia associated with central venous catheterization, isolation of underlying bacterial etiologic agents and determining their respective antimicrobial susceptibility pattern.

Objective: To determine the prevalence of bacteremia associated with central venous catheterization, bacterial etiologic agents and antimicrobial susceptibility pattern among patients on hemodialysis at Muhimbili National Hospital – Dar es Salaam.

Methodology: A cross-sectional descriptive hospital based study was conducted for a period of 6 months involving patients receiving hemodialysis therapy via central venous catheters at Muhimbili National Hospital. A structured questionnaire was used to collect socio-demographic data, clinical characteristics and laboratory parameters of the participants. Two sets of blood samples (8mls each) for aerobic culture were collected aseptically from a central venous catheter and peripheral venopuncture (opposite to the central line), inoculated in the blood culture bottle broth and incubated in automated blood culture machine (BD- BACTEC FX 40). Time difference to positivity was noted and bacteria identification and susceptibility testing were performed according to standard guidelines.

Data was analyzed using SPSS version 23.0; continuous variables were summarized as means and standard deviation, categorical variables as frequencies and proportions. Multivariate analysis for teasing out independent risk factors was determined using logistic regression model.

Results: Out of 109 patients, 39 patients (35.7%) had significant positive blood cultures. *Staphylococcus albus* was the commonest isolate (35.9%), followed by *E.coli*(25.6%), *S.aureus*(15.4%), *P. aeruginosa*(12.8%) and *K. oxytoca*(10.3%). Proportion of resistant isolates for *Staphylococcus aureus* and *Staphylococcus albus* to various tested antibiotics wereas follows; penicillin (66.7% & 78.6%), trimethoprim-sulfamethoxazole (100% &

85.7 %), gentamicin (0% & 28.6%), ciprofloxacin (14.3% & 16.7%), clindamycin (0% & 7%) and cefoxitin (0% & 0%) respectively.

For *Escherichia coli* and *Klebsiella oxytoca,* respective resistant isolates patterns were to; amoxillin/clavulanic acid (100% & 100%), trimethoprim-sulfamethoxazole (100% & 100%), meropenem (0% & 0%), ceftriaxone (10% & 50%) and ceftazidime (20% & 25%) respectively. All pseudomonas isolates were resistant to aztreonam and amoxillin/clavulanic acid and 20% resistant to piperacillin and meropenem. No pseudomonas isolates were susceptible to piperacillin/tazobactam.

Independent predictors for bacteremia associated with central venous catheterization were; catheter duration of 30 days or more [OR 10.2, 95% CI (2.6-40.6), p=0.001], catheterization at femoral site [OR 6.7(3.2-10.8), p=0.042] and both fever within the last 48 hrs; [OR 6.1(1.7-21.6), p=0.005] and fever within the last 1 month; [OR 9.6 (2.6-34.9), p=0.001].

Conclusion and recommendations: Bacteremia associated with central venous catheterization is common among patients undergoing hemodialysis at MNH and both gram negative and gram positive bacteria are responsible etiological agents. The isolated underlying bacteriologic agents show rampant resistance to commonly prescribed antibiotics including drug combinations which have proven potency to other types of infections. Further, temporary catheters that are in use 30 days after insertion, femoral venous catheterization and fever are independent predictors for bacteremia among these patients.

We strongly recommend that due to multi-drug resistant isolates, blood cultures should be taken promptly from all patients suspected to have bacteremia associated with central venous catheterization. Further, we recommend that practitioners avoid femoral site catheterization, limit temporary catheter use for hemodialysis to less than 30 days since insertion and to aggressively investigate and treat fever in these patients

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LIST OF ABBREVIATIONS

CKD:	Chronic Renal Failure
CRB:	Catheter Related Bacteremia
GFR:	Glomerular Filtration Rate
HD:	Hemodialysis
HIV:	Human Immunodeficiency Virus
MNH:	Muhimbili National Hospital
MUHAS:	Muhimbili University College of Health Sciences
PaCO2:	Partial pressure of arterial Carbon dioxide
PTFE:	Polytetrafluoroethylene
SIRS:	Systemic Inflammatory Response Syndrome
SPSS:	Statistical Package for Social Sciences
URR:	Urea reduction ratio
VADs:	Vascular-access devices
WBC:	White Blood Cell

DEFINITION OF TERMS

1. Bacteremia is the presence of circulating bacteria in the blood.
2. Central venous Catheter: An intravascular catheter that terminates at or close to the heart or in one of the great vessels which is used for infusion, dialysis, withdrawal of blood, or hemodynamic monitoring.
3. Bacteremia associated with Central Venous Catheterization: Isolation of an identical micro-organism from cultures of peripheral blood and the catheter in the absence of an alternative source with or without systemic symptoms of infection. The growth differential time between peripheral and central venous blood of at least 2 hours. For Coagulase Negative Staphylococcus species both set of blood culture must grow the identical micro organism.
4. Possible bacteremia associated with Central Venous Catheterization: Presence of fever in the absence of an alternative source where microbiological criteria were insufficient to diagnose CRB.
5. Exit-site infection: Development of cellulitis or purulent exudate at the site of insertion.
6. Temporary central line: A non-tunneled, non- implanted catheter.
7. Permanent central line: Includes:-Tunneled catheters, including certain dialysis catheters; Implanted catheters (including ports).
8. Systemic Inflammatory Response Syndrome refers to presence of (≥2) of the following: Temperature >38^0c (100.4^0F) or <36^0c (96.8^0F), Heart rate >90bpm, Respiratory rate >20 or PaCO2 <32mmHg, WBC >12,000/$mm^{3,}$ <4,000/mm3 or >10% bands.
9. Sepsis refers to (Systemic Inflammatory Response Syndrome +source of infection).

CHAPTER ONE

1.1 BACKGROUND.

The Kidney Disease Outcome Quality Initiative (KDOQI) defines Chronic Kidney Disease (CKD) as either kidney damage or a decreased glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2 for 3 or more months(1). Whatever the underlying etiology, once the loss of nephrons and reduction of functional renal mass reaches a certain point; the remaining nephrons begin a process of irreversible sclerosis that leads to a progressive decline in the GFR (1) .

The different stages of CKD form a continuum pattern from the mild to a severe form. The KDOQI classification of the stages of CKD on the basis of serum creatinine levels is as follows (1)

- Stage 1: Kidney damage with normal or increased GFR (>90 mL/min/1.73 m^2)
- Stage 2: Mild reduction in GFR (60-89 mL/min/1.73 m^2)
- Stage 3: Moderate reduction in GFR (30-59 mL/min/1.73 m^2)
- Stage 4: Severe reduction in GFR (15-29 mL/min/1.73 m^2)
- Stage 5: End Stage Renal Disease (GFR < 15 mL/min/1.73 m^2 or dialysis)

Patients with stages 1-3 CKD are frequently asymptomatic. Clinical manifestations resulting from low kidney function typically appear in stages 4-5. The term end-stage renal disease (stage 5 kidney failure) represents a stage of CKD where the accumulation of toxins, fluid and electrolytes normally excreted by the kidneys results in the uremic syndrome. This syndrome leads to death unless the toxins are removed by renal replacement therapy (1).

The pathophysiology of CKD involves two broad sets of mechanisms of damage: initiating mechanisms specific to the underlying etiology (e.g., genetically determined abnormalities in kidney developmental integrity, immune complex deposition and inflammation in certain types of glomerulonephritis, or toxin exposure in certain diseases of the renal tubules and interstitium) and a set of progressive mechanisms, involving hyper filtration and hypertrophy of the remaining viable nephrons, that are a common consequence following long-term reduction of renal mass, irrespective of underlying etiology (2).

The responses to reduction in nephron number are mediated by vasoactive hormones, cytokines, and growth factors.

Eventually, these short-term adaptations of hypertrophy and hyper filtration become maladaptive as the increased pressure and flow within the nephron predisposes to distortion of glomerular architecture, abnormal podocyte function, and disruption of the filtration barrier leading to sclerosis and loss of the remaining nephrons (2). Increased intrarenal activity of the renin-angiotensin system (RAS) appears to contribute both to the initial adaptive hyper filtration and to the subsequent maladaptive hypertrophy and sclerosis (2).

The prevalence of end-stage renal disease (ESRD) patients requiring renal replacement therapy (RRT) has been increasing in the last decade and it is expected to keep on increasing over the next 10 years. Hemodialysis (HD), the main modality of RRT (3) depends on long-term and effective vascular access. Based on these characteristics, the vascular access of choice is the arteriovenous fistula (AVF), which should be used by at least 65% of the patients in a HD setting (3). Vascular grafts and central venous catheters (CVCs) are considered second and third options, due to the greater risk of infection, thrombosis, need of rescue procedures and the increase in mortality and hospitalization rates (3).

The two major sources of intravascular-device related infection includes the colonization of the device, and contamination of the fluid administered through the device (4). In order for micro-organisms to cause catheter-related infection they must first gain access to the extraluminal or intraluminal surface of the device where they can adhere and become incorporated into a biofilm that allows sustained infection and hematogenous dissemination (5). Micro-organisms gain access by one of three mechanisms: skin organisms invade the percutaneous tract, probably facilitated by capillary action (6), at the time of insertion or in the days following; micro-organisms contaminate the catheter hub (and lumen) when the catheter is inserted over a percutaneous guidewire or later manipulated (7); or organisms are carried hematogenously to the implanted device from remote sources of local infection, such as a pneumonia (8)

The diagnosis of catheter related blood stream infection (CRBSI) posses a great challenge. It requires a positive culture of blood from a peripheral vein and clear evidence that the catheter is the source. CRBSI means a patient with an intravascular catheter has at least one positive blood culture obtained from a peripheral vein, clinical manifestations of infections (i.e., fever, chills, and/or hypotension), and no apparent source for the blood stream infection, except the catheter.

In addition, one of the following is also present: A positive semi-quantitative (>15 CFU/catheter segment) (8) or quantitative (>10^3CFU/catheter segment) catheter tip culture also, the same organism (species and anti-biogram) is isolated from the catheter segment and peripheral blood culture. Simultaneous quantitative paired blood cultures with a >5:1 ratio Central Venous Catheter (CVC) versus peripheral, or differential time to positivity, whereby a non-quantitative blood culture drawn from the CVC that becomes positive at least 2 hr earlier than the peripheral blood culture, is a new method for the diagnosis of CRBSI without removing the catheter (9)

1.2 LITERATURE REVIEW

Chronic kidney disease (CKD), a non-communicable disease was ranked 18th among the global causes of death in 2008 by World Health Assembly where it was ranked 27th in 1990, and the number of deaths from CKD has risen by 82% during that time (10).

Chronic kidney disease (CKD) is recognized as a major health problem affecting approximately 13% of the US population (11); and the estimated prevalence of CKD stage 1–4 is 11·6% (about 26 million people) (12). These figures are similar to those reported in other high-income countries, such as Norway (10·2%), Japan (12·7%), Taiwan (11·8%), China (10·7%), and South Korea(13·7%)(13). Less information, however, is available from low-to-middle-income countries, where prevalence of mild-to-moderate CKD is variable but generally lower than 20% of the total adult population (13).

Data pertaining to CKD in Africa are largely scarce and unreliable. A systemic review and meta analysis carried by John Stanifer and colleagues found only 21 out of 90 articles to be of suitable quality for assessment. The overall prevalence of CKD in the region was 13·9%, with estimates ranging from 2% in Cote d'Ivoire to 30·2% in Zimbabwe, and approaching 20% in Ghana, Nigeria, Rwanda, and Democratic Republic of Congo (14). In a ten-year study of 368 patients with chronic renal failure in Nigeria, the etiology of renal failure was undetermined in 62%. Of the remaining patients whose etiology was ascertained, hypertension accounted for 61%, diabetes mellitus for 11% and chronic glomerulonephritis for 5.9% (15).

A community based survey study done in northern Tanzania demonstrated an overall prevalence of CKD to be 7.0% (16). Most participants with CKD were classified as Stage I (43.8%) or Stage II (31.6%) with fewer participants having Stage III (21.1%), or Stage IV/V (3.5%) (16).

Among those with CKD, 7.0% had diabetes alone, 19.3% had hypertension alone, 14.0% had diabetes and hypertension, 7.0% had HIV alone, and 3.5% had HIV and hypertension and half of the cases of CKD (49.2%) were not associated with any of the measured risk factors of hypertension, diabetes, or HIV (16).

Patients with ESRD need Renal Replacement Therapy (RRT) either through Dialysis or Renal transplantation in order to sustain life. Hemodialysis (HD) sustains life for more than 1 million patients throughout the world and without it, most would die within a few weeks (17). The availability of renal replacement therapy is limited in much of sub-Saharan Africa because of high costs; and though was accessed by approximately 1.8 million people worldwide in 2004; only 5% of the dialysis population was from sub Saharan Africa (18). A study by Lawrencia Mushi et al on the Cost of dialysis at MNH in Tanzania in 2014, established that the average unit cost per hemodialysis is 176 US$; which is enormous for a least developed country like Tanzania where resources and technology are rather limited (19).

Patients undergoing hemodialysis have their angio access either through a temporary vascular access which includes peripheral arteriovenous shunts and non-cuffed double lumen catheters or permanent vascular access that includes veno-venous access (tunneled cuffed catheter) and arteriovenous internal shunts, requiring vascular graft synthetic e.g. Polytetrafluoroethylene (PTFE) or biologic (saphenous vein) material or external shunt (20). The half-life for temporary access is less 90 days; 3 months to 3 years for midterm access (tunneled cuffed catheter) and more than 3 years for long term vascular access (native Arteriovenous Fistula (AVF), new generation PTFE) (21).

Central veins such as jugular, subclavian or femoral, can be used as insertion routes for dialysis catheters especially when there is an acute need but placement of AVFs is recommended to be initiated once the patient reaches CKD stage 4, or within 1 year of the anticipation for dialysis (22). Since the insertion of the first vascular-access devices (VADs) that made maintenance hemodialysis practical (i.e.hemodialysis VADs [HVADs]), VAD-associated infection has been a major issue (23). Impaired immunity due to renal failure, co-morbidities, malnourishment that increase the virulence and the adherence properties of hospital bacteria as well as the breakdown of the protective anatomical barriers due to repeated intravascular intervention required for hemodialysis, represent the main reasons for the high prevalence of bloodstream infection in those patients (24).

Catheter related bacteremia (CRB) is the most significant infectious complication of HD catheters, occurring in 16% of catheters and results in patient's morbidity or premature catheter removal (25).

A prospective analysis of infection rates in HD unit in T.N.Medical College and B.Y.L Nair Hospital, Mumbai, showed the incidence of primary bacteremia i.e. Catheter Related Blood Stream Infection (CRBSI), secondary bacteremia and colonization to be 15%, 5% and 8% respectively (26).

The United States Renal Data System (USRDS) showed that for the years 1991 and 1992, infection accounted for 12% of all deaths among HD patients in the United States (27).

The incidence of infection caused by the HD vascular access is highest when it is a central venous catheter and lowest when it is a native arteriovenous fistula (28) . In a large seven-year longitudinal study of 4005 incident ESRD patients in the case-mix study of the USRDS, Powe et al found temporary vascular access as an independent risk factor for septicemia (28).

The arteriovenous HD access includes the native arteriovenous fistula and the synthetic arteriovenous graft, and in 1995, a large U.S. national survey, conducted by the Centers of Disease Control (CDC) and involving 224,954 HD patients, showed that only 22% of patients were dialyzed through a native arteriovenous fistula (29). This was found to be unfortunate because the probability of dialysis access related infection is considerably less for patients with native arteriovenous fistula than for those with synthetic grafts (30). Though arteriovenous fistulas are crucial as part of strategy to reduce catheter related bacteremia burden; observation on patients on hemodialysis in our setting shows that none had arteriovenous fistula at the initiation of hemodialysis.

On the other hand additional risk factors for CRB that have been identified include poor patient hygiene, previous CRB, recent hospitalization, longer duration of catheter use, inadequate dialysis, hypoalbuminemia, *Staphylococcus. aureus* nasal carriage, diabetes mellitus, immunocompromised status, atherosclerosis, and hypertension (31) . In a study on the epidemiology of septicemia in HD patients in US, hospital admission rates for septicemia during the first year of HD rose by 51% over the 8-year period from 1991 to 1999 (32). Predisposing factors to bacteremia in patients undergoing hemodialysis through Central Venous Catheter in our setting have not been studied.

The average cost of standard treatment of an episode of blood stream infection (BSI) in US has been reported to be in the range of US $ 3,700 to US $ 29,000 per survivor besides the cost of an additional mean hospital stay of 6.5 days (21). Data from Duke’s medical centre, USA showed that over 60% of vascular access-related infections were Gram positive cocci

yet Gram negative bacilli made up significant proportion (24%), as well (33). Many of these infections are caused by gram-positive methicillin-resistant *Staphylococcus aureus* (MRSA) (34), and widespread vancomycin use (35) has contributed to the appearance in this population of vancomycin-resistant *Staphylococcus. aureus* (VRSA) (36) and vancomycin-resistant enterococci (VRE) (37). The magnitude of bacteremia, the etiological agent and the susceptibility pattern among hemodialysis population in our local setting is not known.

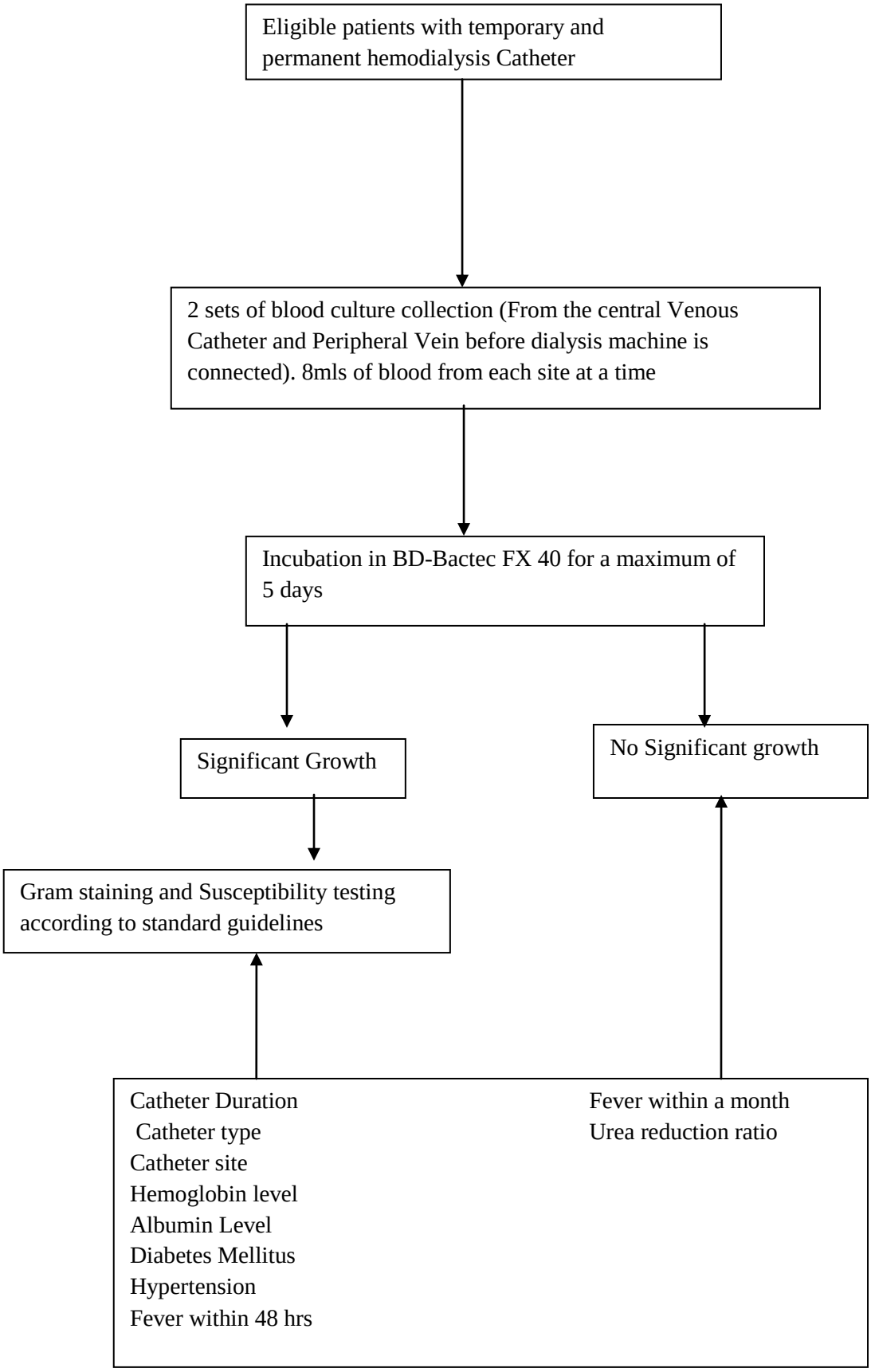
Another study reviewed medical records of 239 patients undergoing hemodialysis at the Department of Nephrology of the University Hospital of Heraklion, Crete, Greece over a 7-year period (1999 to 2005) and found a total number of pathogens isolated, including both uni- and polymicrobial episodes was 162; Forty out of 60 (67%) *Staphylococcus aureus* isolates and 19 out of 28 (68%) of *Staphyloccocus epidermidis which* exhibited resistance to methicillin and of the 48 gram-negative bacteria isolated 20 (42%) exhibited resistance to piperacillin-tazobactam, 18 (38%) to cefepime, 14 (29%) to ceftazidime, amikacin and ciprofloxacin and 12 (24%) to imipenem-cilastatin (38). Additionally, 3 out of 17 (18%) *Escherichia coli* isolates produced extended spectrum β-lactamase and 3 out of 8 isolated (37.5%) *Enterobacter* spp. strains, 4 out of 5 (80%) *Acinetobacter* spp. strains, and 2 out of 7 (29%) *Klebsiella* spp. strains were sensitive only to colistin (38).

In addition to bacteremia, catheter-related exit site infections are common complications of HD catheter use and it accounts for (8 to 21% of cases) and are important causes of catheter loss (39). With tunneled catheters, infections external to the cuff are classified as exit site infections, whereas infections that extend in the tunnel proximal to the cuff are labeled as tunnel infections (40).

A surveillance study on antimicrobial resistance carried at Muhimbili Medical Centre in 1998 (The specimens examined included urine, pus/secretions (swabs from skin, surgical and traumatic wounds, burns, umbilical cords, throat, nose, eye and ear discharge and genital swabs), blood, cerebrospinal fluid, other body fluids, stools and other specimens)demonstrated a high prevalence of gram negatives isolates 67.4% of which E. Coli, Klebsiella spp and Pseudomonas spp accounted for 25.4%, 23.3% and 7.9% respectively (41).

High proportion of isolated microorganism demonstrate resistance to commonly used antibiotics (Penicillins 80% E. Coli, 85% Klebsiella spp and 72% enterobacter spp compared to gentamicin(8%, 14%, 7%) and ceftazidime (5%, 6%,2%) where small proportions of bacteria demonstrated resistance (41). No studies have been done specifically to focus on antibiogram pattern among hemodialysis patients.

1.3 CONCEPTUAL FRAMEWORK



CHAPTER TWO

2.0 STATEMENT OF THE PROBLEM.

Hemodialysis through central venous catheter carries a high risk for acquisition of blood stream infections including bacterial and fungal; and these infections increases morbidity and mortality among patients with ESRD (42). Catheter related bacteremia (CRB) is the most significant infectious complication of HD catheters, occurring in 16% of catheters and results in patient's morbidity or premature catheter removal (25). A prospective analysis of infection rates in HD unit in T.N. Medical College and B.Y.L Nair Hospital, Mumbai, showed the incidence of primary bacteremia i.e. Catheter Related Blood Stream Infection (CRBSI), secondary bacteremia and colonization to be 15%, 5% and 8% respectively (26). Early diagnosis of these pathogens and identification of their susceptibility pattern to different antimicrobial is a crucial step towards reduction of morbidity, mortality and treatment cost. Several studies have been done on blood stream infections in Tanzania (43)(44), however, little is known on the magnitude of catheter related bacteremia, common bacterial isolates, their drug susceptibility pattern and predictors among patients undergoing hemodialysis.

2.1. RATIONALE

Chronic kidney disease is emerging fast as a major public health problem in the 21st century as a result of increased Diabetes (45) and hypertension (WHO 2009). Management of these patients with ESRD in Tanzania has recently received a new turn where hemodialysis access has increased dramatically. Catheters serves as the Achilles heels of hemodialysis and are used in approximately 80% of patients initiating hemodialysis and 25% of all prevalent patients as a bridge to a permanent vascular access or because the patient has exhausted all options for a permanent access (46). Unpublished admission data at Muhimbili National Hospital in the medical wards and dialysis unit indicates a steady rise in a number of febrile patients who are undergoing hemodialysis. The increase in the incidence of admission of these patients and empirical use of vancomycin for febrile patients during dialysis justifies the need to carry out a properly designed study to determine the magnitude of the problem, isolate causative pathogens, establish drug susceptibility patterns and determine the associated factors.

This study was therefore undertaken to determine the magnitude of bacterial pathogens, identify common bacterial isolates, describe their drug susceptibility pattern and associated factors among patients undergoing hemodialysis.

Information generated from this study will assists physicians on, selection of appropriate antibiotics, treat their patients promptly and hence reduce morbidity, mortality and treatment cost.

2.3. RESEARCH QUESTIONS

What is the magnitude of bacteremia among patients undergoing hemodialysis?

What are the common a etiological bacterial agents associated with bacteremia among patients undergoing hemodialysis?

What are the predictors of bacteremia among patients undergoing hemodialysis?

What is the antibiotic susceptibility pattern of bacterial isolates among patients undergoing hemodialysis?

2.3 STUDY OBJECTIVES

2.3.1. Broad Objectives

To determine the prevalence of bacteremia associated with central venous catheterization associated bacterial etiologic agent and their antibiogram and the predictors among patients undergoing hemodialysis at Muhimbili National Hospital – Dar es Salaam.

2.3.2. Specific Objectives

1. To determine the prevalence of bacteremia associated with central venous catheterization among patients undergoing hemodialysis at MNH
2. To determine common bacterial isolates from patients with bacteremia associated with central venous catheterization undergoing hemodialysis at MNH.
3. To describe predictors for bacteremia associated with central venous catheterization among patients undergoing hemodialysis at MNH.
4. To describe antimicrobial susceptibility pattern of bacteria isolated from patients with bacteremia associated with central venous catheterization undergoing hemodialysis at MNH.

CHAPTER THREE

3.0 METHODOLOGY

3.1 Study Design

This was a cross-sectional hospital based study.

3.2 Study Setting

This study was conducted at hemodialysis unit at Muhimbili National Hospital (MNH); a main referral hospital located at Eastern Zone of Tanzania in the capital city of Dar es Salaam. MNH receives referral patients from both public and private hospitals from all over the country. Patients with renal failure enroll themselves to nephrology unit through EMD or OPD.

The nephrology unit runs an out-patient clinic on every Wednesday for CKD patients and Mondays for transplant screening, with an approximately 50 patients who are at different renal disease stage being attended per day. The clinic receives as well prospective kidney donors for preliminary evaluation before donation. Staffing of the clinic and dialysis unit includes a team of five consultant physicians, two resident physicians/ nephrology fellows, three registrars, fifteen nurses and four nursing assistants. The clinic operates from 8 am to 4 pm.

The Unit has 15 hemodialysis machines and carries dialysis for both inpatient and outpatient with an average of 30 patients being attended per day. It operates for 6 days in a week (Monday to Saturday) from 8 am – 5pm, however emergency services can be provided during nights and public holidays. Each patient is allocated approximately three sessions per week and each session being run for four hours except for those who are in the initial hemodialysis session. Hemodialysis access sites for patient on hemodialysis at MNH include temporary and permanent central venous catheter and arteriovenous fistula.

3.3 Study Population

All patients undergoing hemodialysis through central venous catheter at MNH.

3.4 Study Duration

This study was conducted in a period of six months (September 2016 - February 2017).

3.5 Sample Size Calculation

Sample size for the required study was calculated by the following formula:

$N = Z^2 P (1-P)/ \varepsilon^2$

Where

N = Sample size

Z = Critical Value 1.96

P = Prevalence of catheter related bacteremia = 16%

(Lukas K. Kairaitis and Thomas Gottlieb: Outcome and complications of temporary haemodialysis catheters; Concord Repatriation General Hospital, Concord, NSW, Sydney, Australia 1997)

ε = Maximum Error 7%

The minimum sample size N was 105; therefore 109 patients were recruited into this study.

3.6 Sampling Technique

Consecutive enrollment of eligible patient was performed until the sample size was met.

3.7 Inclusion Criteria

1. All patients undergoing hemodialysis through central venous catheter
2. Central line catheter in situ for more than 2 days
3. Age of 18 or more years who consented to take part in the study.

3.8 Exclusion Criteria

1. Evidence of other source of possible bacteremia

3.9. Recruitment of Study Participants

Recruitment of the study participants was done on daily basis at hemodialysis unit. These patients were first seen by nurses where vital signs including pulse rate, blood pressure, temperature, weight and respiratory rate are recorded. After patients had passed through the nurse station, clinical assessment for exclusion of possible alternative explanation for bacteremia was performed and only eligible ones were consecutively recruited into the study after an informed consent has been sought.

During assessment for alternative explanation; patients were screened for cough, dysuria and, skin infection. Patients were given a written consent form to read. For illiterate patients; the consent form were read and interpreted to them by the investigator or his assistant. A signed consent was obtained from each patient upon agreeing to participate. The aim of the study and procedures involved were explained to the patients. Data were collected by the principal investigator and an assistant.

A structured questionnaire was used to collect socio demographic, clinical data and laboratory parameters of the patients.

3.10. Clinical Assessment.

3.10.1. Measurement of Body Temperature

Patients who reported to have had fever and or chills and those whose axillary temperature recording is $35.5^0C\leq$ or $\geq 37.5^0C$ were subjected to oral temperature check. The digital thermometer was used to obtain body temperature through oral cavity and after the exclusion of anything hot or cold in patient's mouth for 10 minutes before taking oral cavity temperature.

Thermometer was taken out of its holder; pointed end (probe) was cleaned with soap and rubbed with alcohol swab and then rinsed in cool water. Participants were asked to open the mouth; tip placed under the tongue and asked to close lips gently around the thermometer. The digital thermometer shall be kept under the tongue until it beeps. The thermometer was then removed and a number shown up in the "window" was recorded. Thermometer was placed back in its holder after cleaning and swabbing with alcohol.

Patients with oral temperature above $37.5\ ^0$ C were regarded as febrile patient and those with oral temperature below 36^0 C as hypothermic (47).

3.10.2. Anthropometric and other Vital signs Measurement

Patient's anthropometric measurement (weight and height) and other vital sign (Pulse rate, Blood pressure) were recorded from patient's records on the day of interview and blood sample collection.

3.10.3. Patient Preparation, Blood Collection and Transport

Two set of blood samples for culture were collected; one sample was drawn from the central line and a simultaneous sample from a peripheral vein. The time separation between samples collected was one to two hours and the blood volume collected was 16mls per session. The collected blood was transported to laboratory within one hour of collection. Hands were washed with soap and clean water or swabbed with 70% isopropyl alcohol and gloved with sterile gloves during blood collection. Culture bottles for aerobes (BACTEC^{TM} plus Aerobic/F) supplied by Benex limited, Shanon, County Clare -Ireland with antibiotic neutralization capacity (resins or charcoal mixture) were used after their tops have been disinfected with an alcohol pad prior to venopuncture for blood collection.

3.10.3.1 Collection Procedure-Peripheral Draw

Puncture site was selected and cleaned with alcohol pad followed by chlorhexidine (CHG) and allowed to dry for 30 seconds. A needle connected to 10cc syringe was inserted into the vein and 8 mls of blood was drawn from patient's vein opposite to the central venous line. The needle was then withdrawn from the patient vein; cap replaced with a sterile needle and then blood injected into aerobic culture bottle. The bottle was labeled by handwriting and laboratory request form was filled and patient's particulars included: patient's name and identification number, collection date and time, collector's initials and source or site. The venipuncture site was bandaged following standard protocol.

3.10.3.2 Collection Procedure-Line Draw

Blood was collected simultaneously from Central venous Catheter. Culture bottle was disinfected with an alcohol pad. Hep-lock cap was cleaned with alcohol pad and allowed to dry before proceeding (at least 30 seconds), clamp released, heparinized blood drawn and discarded and by using sterile 10-mL syringe, 8mls of blood was aspirated and injected though rubber top of a blood culture bottle.

3.10.4 Laboratory Procedure

3.10.4.1 Incubation, Subculture and Identification

Inoculated blood culture bottles broth were incubated for up to 5 days at 37°C aerobically (culture set) in an automated blood culture machine (BD- BACTEC FX 40). The machine detects growth of microbes by producing signal. Difference in detection time as defined by the signal between the catheter and peripheral growth signal was recorded. A gram stain was done from the broth with positive culture and sub-cultured into blood agar (BA), MacConkey (MCA), chocolate agar (CA) and Nutrient agar (NA) as previously described (48). Briefly, 1-2 drop of well mixed broth was drawn from sterilized culture bottle and inoculated in these media; and streak using standard method. While MCA and NA was incubated aerobically, inoculated BA and CA was incubated overnight at 35-37^{0}C in 5% atmosphere.

Bacterial identification was done using available phenotypically methods such as colonial morphology, gram staining, and biochemical test such as catalase, coagulase or API 20 etc and serological test. A quality control material or isolates was used for each test as per available laboratory Standard Operating Procedure (SoP).

3.10.4.2 Drug Susceptibility Testing

The antimicrobial susceptibility testing was done by Kirby Bauer Disk diffusion method with modification (49). Briefly, bacterial suspension was prepared from pure growth and compared to 0.5 McFarland turbidity standards. Using sterile cotton swab, this suspension was inoculated into Mueller-Hinton agar (MHA). A maximum of 6 antibiotic discs was arranged in inoculated plates within 15 minutes and incubated overnight at 35-37^{0}C aerobically. These procedures were repeated for quality control isolates. For example, standard *Staphylococcus aureus* for gram positive, *E.coli* for gram negative enterobactericeae and *Pseudomonas aeruginosa* if *P.aeruginosa* is isolated. The same antibiotics were tested for isolate and standard isolates. After incubation, the diameter of the zones of complete inhibition (including the diameter of the disk) of test and standard isolates were measured in millimeters by venire caliper. The two diameter of zone of inhibition for test and standard isolates was compared and interpreted as recommended by Clinical Laboratory Standards Institute guidelines and charts, to determine susceptibility of isolates to tested antibiotics the isolate were either susceptible (S), intermediate (I), or resistant (R) to tested antibiotic based on CLSI guideline and chart definition. For the susceptibility testing of gram positive isolates (Penicillin 10u, Cefoxitin 30 mcg, Gentamicin 10mcg, Ciprofloxacin 15mcg, Clindamycin 2mcg, Trimethoprim Sulfamethoxazole 12.5/23.75mcg) ; gram negative isolates (Amoxycillin + Clavulanic acid 20/10mcg, Gentamicin 10mcg, Ceftriaxone 30mcg, Ceftazidime 30mcg, Meropenem 10mcg , Trimethoprim Sulfamethoxazole 12.5/23.75mcg) and for pseudomonas isolates (Meropenem 10mcg, Piperacillin 100mcg, Piperacillin + Tazobactam 100/10mcg, Aztreonam 30mcg, Gentamicin 10mcg, Trimethoprime sulfamethoxazole 12.5/23.75mcg) were used.

3.11 Data Management

3.11.1 Data Collection

Demographic data were collected using a pre tested structured questionnaire. Each participant was assisted to complete a demographic and medical history survey which included a self-reported history of fever, type of dialysis access, site of dialysis access, duration of dialysis, duration of dialysis catheter in situ, number of attempts during dialysis catheter insertion and number of dialysis the patient has undergo per week. Supplementary information regarding the patient was gathered from the patient's medical record.

Pre and Post dialysis creatinine and urea levels, Random blood sugar, Full blood picture, and albumin level results on the date of blood sample for culture collection were recorded.
Blood culture reports were accessed through hospital information management system (Jeeva).

3.11.2. Quality Control and Quality Assurance

The Principal investigator in collaboration with other hospital staffs were involved directly in patients' assessment, recruitment and blood sample taking. In situation where the Principal Investigator was unable to attend; a trained assistant investigator assisted in data collection.

Filled questionnaires were assessed on daily basis for completeness and those patients with incomplete information were called through their mobile phone or seen on the next dialysis session. Double entry of the questionnaires was performed to ascertain wrong entry.

For blood culture reports; a hard copy from Central Pathology Laboratory was used to crosscheck retrieved data from Hospital Management Information System. In case of any discrepancy between the two reports; the Head of the Unit (Central Pathology Laboratory) was called to assist in sorting out the difference.

3.11.3. Data Analysis.

Data were entered into Epidata, cleaned and analyzed using SPSS version 23.0 Software. Patients' demographic characteristics, prevalence of bacterial infections, associated factors and their antimicrobial susceptibility pattern were summarized using frequency distribution tables.

Chi square was computed to determine the relationship between different patients' clinical parameters and bacteremia associated with central venous catheterization. Existence of association was determined by using regression analysis and the significance level was set at less than 0.05.

3.11.4. Ethical Consideration

The objectives of this study, its expected outcomes and utility of derived knowledge were explained to patients before enrollment and gave a written informed consent.

Participants who declined to consent continued to receive the same quality of care as those who consent to participate in the study.

All data collected during the study were treated confidential and were not open/accessible to an unauthorized person. The findings on the blood tests and any other results were clearly explained to the participant as well as any needed treatment to be offered.

Ethical clearance to carry out this study was obtained from the Research and Publications Committee of MUHAS and the director of clinical services of MNH**.**

3.11.5. Dissemination

This dissertation will be published in freely accessible Medical Journals and its soft copy will be available in the MUHAS Repository. Workshop for physicians especially in centers where hemodialysis is carried out will be organized.

CHAPTER FOUR

4.1. RESULTS

This study was conducted for a period of 6 months between September 2016 and February 2017. A total of 109 patients who were undergoing hemodialysis through Central Venous Catheter were enrolled in this study.

4.1.1. Sociodemograhic Characteristics.

Table1 summarizes the demographic characteristics of the study population. Out of 109 enrolled participants; (58.7%). of them were males The age range of the participants was between 18 and 82yrs; (50.5%) being over 55 years old. Most of them were married (76.2%); and had secondary school education and above (62.4%) and 62.4 % were employed (self employment or hired by an institution). About 23.9% and 48.6% reported previous history of smoking and alcohol use respectively. Most of them had hypertension (89%) and 37.6% had diabetes mellitus.

Table 1: Sociodemographic and Clinical Characteristics Among the Participants (N = 109)

Variables	Frequency, n	Percentage,%
Sex		
Male	64	58.7
Female	45	41.3
Age group		
18-34	22	20.2
35-54	32	29.3
55+	55	50.5
Marital status		
Single	14	12.8
Married	83	76.2
Widow/divorced	12	11.0
Education level		
No formal/Primary	41	37.6
Secondary	49	44.9
College/University	19	17.5
Occupation		
Un employed	41	37.6
Employed	29	26.6
Self employed	39	35.8
Smoking status		
Smoker	26	23.9
Non smoker	83	76.1
Alcohol use		
Yes	53	48.6
No	56	51.4
Hypertension		
Yes	97	89.0
No	12	11.0
Diabetes Mellitus		
Yes	41	37.6
No	68	62.4

4.1.2.Clinical and Laboratory Parameters of the Participants.

Table 2 summarizes the clinical and laboratory parameters of the study participarts. Most of the participants' 84.4 % had their hemodialysis catheter in situ for more than 30 days; where as 85.3% and 14.7% of the hemodialysis catheters were temporary and permanent respectively. Most of them had their catheter placed at the internal jugular vein (69.5%). Majority of the participants 91.7 % had hemoglobin level less than 11g/dl; and 76.2 % of participants had albumin level less than <35g/dl. About 30.3% of the participants reported the presence of fever within 48 hours of interview and 16.5% of all participants were actively on antibiotics at the time of interview. Within one month from the date of interview, 48.6% of the participants reported history of fever; and out of those who reported fever 18.3 % had their fever investigated and 13.8 % had the cause of fever found. Of those who reported fever within a month from the date of interview 47.7 % were treated using antibiotics.

Table 2:Laboratory and Clinical Parameters of the Participants (N = 109)

Variable	Frequency,n	Percentage %
Fever within 48 hrs		
Yes	33	30.3
No	76	69.7
Fever within one month		
Yes	53	48.6
No	56	51.4
Catheter type		
Temporary	93	85.3
Permanent	16	14.7
Catheter site		
Femoral	17	15.6
Internal Jugular	76	69.7
Subclavian	16	14.7
Catheter duration		
<1month	17	15.6
1-3 months	37	33.9
>3months	55	49.5
Albumin Level		
≥35gm/dl	26	23.8
<35gm/dl	83	76.2
Hemoglobin		
<11gm/dl	101	93.1
≥11gm/dl	8	7.9
Fever within 1month and antibiotics use		
Yes	25	47.7
No	28	52.7
Current antibiotics use status		
Yes	18	16.5
No	91	83.5

4.1.3. Magnitude of Bacterial Isolates Among Patients on Hemodialysis Through Central Venous Catheter

Figure 1 demonstrates the common bacterial isolates and their magnitude among patients who were undergoing hemodialysis through a central venous catheter. Among 109 patients whose samples were collected, 39 had a positive blood culture thus giving an overall prevalence of bacteremia of 35.7%. Out of 39 patients who had a positive blood culture; 51.3% had gram positive cocci isolates and 48.7% had gram negative rods. The common bacterial isolates among these patients and their magnitude included *Staphylococcus albus* 35.9%, *Escherichia. coli* 25.6%, *Staphylococcus aureus* 15.3%, *Pseudomonas aeruginosa 12.9%,* and *Klebsiella oxytoca* 10.2%. Further more there were no individual patient who was harbouring multiple isolates.

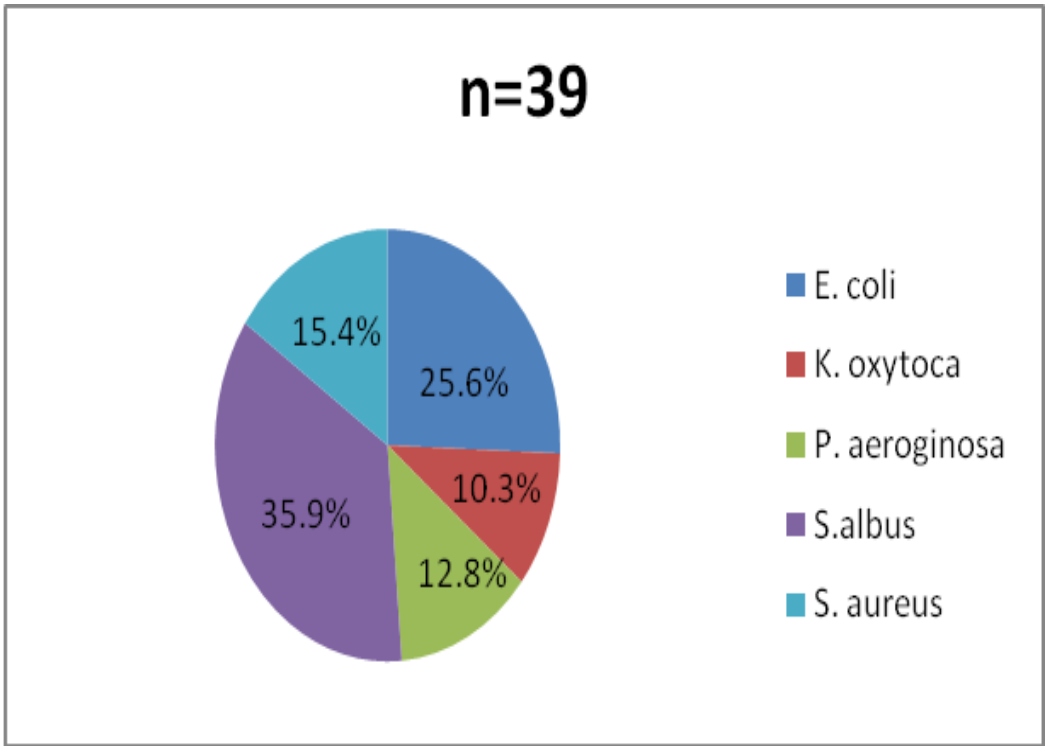


Figure 1. Percentages of common bacterial isolates among patients undergoing hemodialysis (n=39)

4.1.4. Clinical characteristics and Predictors of Catheter Related Bacteremia

Table 3 summarizes the clinical characteristics and predictors for bacterial growth among patients undergoing hemodialysis through the central venous catheter. The proportion of positive blood cultures (bacteria growth) among participants were significantly higher in those who reported presence of fever within 48hours of interview and sample collection (78.9%, visa vie 30.3% in those with no fever within 48 hours); those who reported fever within one month (60.4% visa vie 22.5% with no fever within a month); those having hemodialysis catheter for 30 or more days (73.7% visa vie 17.6 % less than 30 days) and for those having hemodialysis catheter at the femoral site (58.8% visa vie 18.8% at the subclavian) $p<0.049$.

Furthermore the proportion of bacteria growth among participants was high in those with a temporary catheters (38.7% visa vie 18.8% permenent catheters), hemoglobin level < 11gm/dl (55.4% visa vie 50% for hemoglobin ≥ 11gm/dl), albumin level < 35gm/dl (37.3/% visa vie 30.7% for albumin ≥35gm/dl), and to those reported being hypertensive (38.1% visa vie 16.7% in non hypertensive and diabetic 41.5% visa vie 32.4% in non diabetic) $p>0.05$.

Table 3.The Predictors of Bcteremia Associated with Central Venous Catheterization Among Patients undergoing Hemodialysis

Variables	Total N (%)	Yes n (%)	p-Value
Catheter type			
Permanent	16 (14.7)	3 (18.8)	0.124
Temporary	93 (85.3)	36 (38.7)	
Catheter site			
Femoral	17 (15.6)	10 (58.8)	
Internal Jugular	76 (69.7)	26 (34.2)	0.049
Subclavian	16 (14.7)	3 (18.8)	
Catheter duration			
< 1 month	17 (15.6)	3 (17.6)	
1-3 month	37 (33.9)	6 (19.3)	0.001
>3 month	55 (49.5)	30 (54.5)	
Albumin			
<35gm/dl	83 (76.2)	31 (37.3)	
≥35gm/dl	26 (23.8)	8 (30.7)	0.541
Hemoglobin			
<11gm/dl	101 (93.1)	36 (55.4)	
≥11gm/dl	8 (7.9)	4 (50)	0.395
Diabetes Mellitus			
Yes	41 (37.6)	17 (41.5)	
No	68 (62.4)	22 (32.4)	0.336
Hypertension			
Yes	97 (89)	37 (38.1)	
No	12 (11)	2 (16.7)	0.143
Fever within 48hrs			
Yes	33 (30.3)	23 (78.9)	0.001
No	76 (69.7)	16 (30.3)	
Fever within a months			
Yes	53 (48.6)	32 (60.4)	
No	56 (52.4)	7 (22.5)	0.001

4.1.5. Correlation between Bacteremia Associated with Central Venous Catheterization and Patients Clinical Parameters

Table 4 summarizes the relationship between various predictors and occurrence of bacteremia in patients undergoing hemodialysis. In a multivariate analysis,the duration of catheter of 30 or more days (OR 10.2,95% CI 2.56-40.6) p=0.001, fever within 48 hrs and within a month and bacteremia (OR 6.1, 95% CI 1.7-21.6) p=0.005 and (OR 9.5, 95% CI 2.6-34.9) p=0.001 and femoral catheter site (OR 6.7, 95% CI 3.2-10.8) p=0.042 were all independently associated with bacteremia associated with central venous catheterization.

Table 4: Predictors of Bacteremia Associated with Central Venous Catheterization Among Hemodialysis Patients identified in Logistic Regression Analysis.

Variable	OR (95% CI)	p-value	AOR (95% CI)	p-value
Catheter site				
Femoral	6.2(1.4-30.2)	0.024	6.7(3.2-10.8)	0.042
Internal Jugular	2.2(0.6-8.6)	0.24	0.469(0.11-2.0)	0.308
Subclavian	ref			
Catheter. Duration				
< 1 month	ref			
≥1 month	5.9(2.2-16.7)	0.001	10.2(2.56-40.6)	0.001
Fever 48hrs				
Yes	8.6(3.4-21.7)	0.001	6.109(1.726-21.6)	0.005
No	ref			
Fever within a months				
Yes	10.7(4.1-27.9)	0.001	9.56(2.6-34.9)	0.001
No	ref			

OR= odd ratio; AOR= adjusted odd ratio

4.1.6. Resistance Pattern of Bacterial Isolates to Selected Antibiotics.

Table 5 summarizes the resistance pattern expressed by different bacterial isolates among the participants. *Staphylococcus albus* was isolated from 14 patients and the proportion of the isolates which expressed resistance to penicillin, sulfamethoxazole trimethoprim and gentamicin were 78.5%, 50% and 28% respectively. Furthermore isolates resistant to clindamycin and ciprofloxacin were (7%) and (14.3%) and there were no isolate resistant to cefoxitin.

Out of 6 *Staphylococcus aureus* isolated, all isolates expressed resistance to sulfamethoxazole trimethoprim ; and 66.7% and 16.5% of them were resistant to penicillin and ciprofloxacin respectively.No any *Staphylococcus aureus* isolate resistant to clindamycin and gentamicin was isolated.

Out of 10 *Escherichia. coli* isolated, all isolates were resistant to amoxicillin + clavulanic acid and 80% of them were resistant to gentamicin. Only 10% and 20% of all isolates were resistant to ceftriaxone and ceftazidime respectively. None (0%) of the *E. coli* isolates were resistant to meropenem.

Out of 4 *Klebsiella oxytoca spp* isolated, all isolates were resistant to amoxicillin + clavulanic acid; 75% of them were resistant to gentamicin; 50% to ceftriaxone and trimethoprim sulfamethoxazole and 25% to ceftazidime. No *Klebsiella oxytoca* isolates were observed to be resistant to meropenem.

Among 5 *Pseudomonas aeruginosa* isolated, all isolates were resistant to aztreonam and trimethoprim and sulfamethoxazole while 40% of them were resistant to gentamicin. Only 20% were resistant to meropenem and piperacillin. None (0%) of the pseudomonas isolates were resistant to piperacillin + tazobactam

Table 5: Percentage of Resistant Bacterial Isolates to Selected Antibiotics.

Antibiotics	*S.albus* *n=14*	*E.coli* *n=10*	*S .aureus* *n=6*	*P. aeruginosa* *n=5*	*K.oxytoca* *n=4*
Penicillin	78.6		66.7	NA	NA
Cefoxitin	0		0	NA	NA
Gentamicin	28.6	80	0	40	50
Ciprofloxacin	14.3	NA	16.7	NA	NA
Clindamycin	7	NA	0	NA	NA
Trimethoprim + Sulfamethoxazole	85.7	60	100	100	75
Amoxycillin + Clavulanic acid,	NA	100	NA	NA	100
Ceftriaxone	NA	10	NA	NA	50
Ceftazidime	NA	20	NA	NA	25
meropenem	NA	0	NA	20	0
Piperazillin	NA	NA	NA	20	NA
Piperacillin + Tazobactam	NA	NA	NA	0	NA
Aztreonam	NA	NA	NA	100	NA

NA: Not tested for.

CHAPTER FIVE

5.1. DISCUSSION

Bacteremia associated with Central Venous Catheterization contributes to a high morbidity, mortality and treatment cost among patients undergoing hemodialysis. In this study, 109 patients who were actively undergoing hemodialysis through central venous catheter were enrolled and investigated to determine the magnitude of the bacteremia, common bacteria isolates, susceptibility pattern and the clinical predictors associated with bacteremia associated with central venous catheterization. The definitive diagnosis of Bacteremia associated with Central Venous Catheterization was made by a combination of the clinical condition of the patient and the result of blood cultures obtained from both peripheral vein and central venous catheter. Both gram positive and gram negative bacteria were isolated and most of them were resistant to commonly used antibiotics

Out of 109 patients enrolled 39 patients had a positive blood cultures and these accounted for the prevalence of 35.7% The prevalence of bacteremia associated with central venous catheterization found in this study is higher compared to previously reported prevalence of 16% in Concord Repatriation Hospital, Syndey Australia in 1997 and 3.3 % Al-Sayyed Hospital, Rawalpindi, Pakistan, a study conducted from June to December 2014 among patients with chronic kidney disease undergoing hemodialysis through the central venous catheter (25)(50). The possible explanation for this may include differences in the clinical characteristics of study population; the methodology and interpretation used for bacteremia associated with central venous catheterization. Furthermore the temporary vascular access overstay, poor general hygiene, unsterile environment and procedures observed during data collection may have contributed to higher rates of bacteria isolation in our study.

Our finding has demonstrated the slight predominance of gram positive bacteria which accounted for 51.3%. S*taphylococcus albus* being the commonest of all isolates followed by *Escherichia. coli, Staphylococcus. aureus, Pseudomonas aeruginosa and Klebsiella oxytoca.* The pattern of microbes associated with central venous catheterization in this study is almost similar to many previous studies carried in different setting where gram positive cocci predominated. A study on patient with bacteremia secondary to their

vascular access treated at a tertiary care hospital in South India over a period of 18 months from October 2011 to March 2013 demostrated predominance of gram positives microbes and

Staphylococcus. aureus alone accounted for 45.2% of all isolates and in a case–control study conducted between January 2010 and June 2013 at the hemodialysis satellite unit at the Kidney and Hypertension Hospital of Foundation Oswaldo Ramos in the city of São Paulo, Brazil demostrated predominance of gram positive cocci accounting for 72% (51)(52). The slight rise in the proportion (48.7%) of gram negative bacteria eg *Escherichia. coli* as one among the common catheter related bacteremia etiology particularly in this study population make our findings to slightly differ from some studies that consistently reported the predominance of gram positive microbes. Retrospective studies by Mark D. *et al* from 1996-2001, Loo L.W *et al* from Jan 2011 to June 2012 and Sandra *et al* from 2011-2013 in different settings consistently demostrated predominance of gram positive in over 60% of isolates (53)(54)(36). However; a similar findings demonstrating a rise in a gram negative microbe's frequency have been reported in one study conducted over 6 months in Universiti Kebangsaan Malaysia Medical Centre in 2012 and in that study 52.4% of all isolates were gram negative bacteria (55). This trend was consistent with the trend of catheter infection in nondialysis patient at the Hospital do Câncer, National Cancer Institute, Rio de Janeiro, Brazil s conducted from Jan 2000 to Febr 2002 where by 56% of isolates from patients had gram negative bacteria (56). The current practice in our setting where empirical use of antibiotics is common may have created an increased selection of antibiotic pressure against gram positive microorganisms and therefore a favor for the flourish of gram negative bacteria.

In this study hemodialysis catheter duration of 30 or more days and hemodialysis catheter at the femoral site remained to be independent predictors for occurence of bacteremia associated with central venous catheterization. (OR 10.2 ,95% CI 2.56-40.6 p=0.001) and (OR 6.7, 95% CI 3.2-10.8 p=0.042) respectively. The findings from this study is in concurrence with previous studies performed in other centers In St. Joseph's Hospital (Hamilton, Ontario, Canada), patients with central venous catheter were followed from December 1996 to December 1997 and the risk of bacteremia was found to vary significantly according to the duration of use and site of insertion . For the femoral site, the

bacteremia rate was 3.1% up to one week of placement, but increased to 10.7% by two weeks. The bacteremia rate at the internal jugular site was 5.4% up to three weeks of use, but increased to 10.3% by the fourth week and similar findings were also reported in a multicenter study involving Intensive Care Unit in 8 hospital in France in 1990 (52)(57). Hypertension, diabetes mellitus hemoglobin and hypoalbuminemia were not found to be predictors of bacteremia in our study population and this finding concur with a study conducted at Hasheminejad Hospital in Tehran, Iran in 2015 on patients with end stage renal disease on maintenance hemodialysis three times per week for 4 hours through a double-lumen catheter except for hypoalbuminemia in which it was found to be a significant predictor (38). This difference may be explained by differences in the study population characteristics, methodology used and small number of isolates collected in our study.

Furthermore patients reported fever within 48 hours.(OR 6.1, 95% CI 1.7-21.6) p=0.005; or fever within a month period (OR 9.5, 95% CI 2.6-34.9) p=0.001 from the date of interview also remained to be independent predictors of bacteremia associated with central venous catheterization.This finding is not in agreement with a study done in Hvidovre Hospital, Copenhagen, Denmark.1998 where 67 catheters in 43 patients were followed for 1 year and fever was not found to be a good predictor of septicemia (58). The study population in the study mentioned was mainly composed of elderly population and their low immune and inflammatory response to different types of infection and the study methodology may have contributed to the difference noted

Our study demonstrated bacterial isolates which expressed resistance against multiple commonly used antibiotics. These findings pose a great challenge to clinicians and patients in selection of appropriate antibiotics at an affordable cost.

Among the gram positives (*Staphyloccus albus* and *Staphyloccus aureus*) isolates; majority of the isolates were resistant to trimethoprim sulfamethoxazole (85.7% & 100%) and penicillin 78.6% & 66.7%); few *Staphyloccus albus* isolates produced resistance to gentamicin (28.6%) and clindamycin (7%), however no any *Staphyloccus aureus* isolate was resistant gentamicin. All gram positive isolates were susceptible to cefoxitin. The pattern of susceptibility from our study is similar to results from a 20 years review (1990-

2012) on antimicrobial resistance carried out in Tanzania, Zambia, Congo and Mozambique except for *Staphyloccus aureus* where 5% were resistant to gentamicin (36), and in a 2 years retrospective (June 2013 to May 2015) report of microbiological cultures of different samples at a tertiary hospital in Tanzania (Bugando Medical Centre) 34.6% were resistant to cefoxitin (51). Further more in a study carried at Muhimbili National Hospital in 2012 on the surgical site infection; *Staphylococcus aureus* isolates resistant to gentamicin was as high as 33% (60). The wide availability of penicillin and trimethoprim sulfamethoxazole; their low cost and being among common prescriptional drugs to patients with different medical conditions may have attributed to development of resistance by many isolates. Further more the differences clinical characteristics of the study subjects, frequent exposure to gentamicin in patients undergoing surgical intervention unlike in our study population where gentamicin use is restricted may all explain lack of staphylococcus isolates which were resistant to gentamicin. Interpretation of this finding however needs to be taken with caution because the number of isolates tested against gentamicin was very small.

In this study; gram negative bacteria (*E.coli* and *K. oxytoca*) exerted very high rates of resistance against the common prescribed antibiotics such as amoxillin/clavulanic acid (100% & 100%), gentamicin (80% & 50%) and trimethoprim sulfamethoxazole (60% & 75%) however, there were no isolates which expressed resistance against meropenem. These findings are consistent with a 20 years review (1990-2012) on antimicrobial resistance carried out in Tanzania, Zambia, Congo and Mozambique where resistance against these antibiotics was concistently been above a mean of 75% and 4% for meropenem (36) and other studies done in the western world (University Hospital of Federal University of Sao in 2012) demonstrated lethal multi-drug resistant gram negatives bacteria in hemodialysis patients (61). Furthermore, our study findings shows 20% strain of *E.coli* and *K. oxytoca* that were resistant to ceftazidime and ceftriaxone however the resistance rates were lower by 40% and 70% respectively from previously reported studies (5 yrs ago) in the same hospital on patients who developed surgical site infection (60). The huge difference noted may be explained by difference in the clinical characteristics of the study population and possibly the frequency of exposure of these antibiotics to the different study population. Furthermore the highest rates of gram negative isolates resistant to amoxicillin clavulanic acid and sulfamethoxazole trimethoprim; may have been attributed

by increased use of these antibiotics due to their easy availability, being commonly prescribed empirical antibiotic for various bacterial infection and being relatively affordable . The high cost of Meropenem and hence its limited use may have attributed to unobserved gram negatives strain resistant to it. Further more interpretation to these findings need to be taken with caution due to small number of isolated microoranism

All *Pseudomonas aeruginosa* spp isolated from this study were resistant to aztreonam (100%), sulfamethoxazole/trimethoprim (100%) and 20% of the isolates were resistant to meropenem, and piperacillin. Our susceptibility pattern findings are similar to other previous study performed at Muhimbili National Hospital in 2012 on patients who developed surgical site infections (60) and a 10 year single University Hospital in German between 2004 and 2014 except for piperacillin + tazobactam resistance which was observed in 25.6% unlike in our study where no resistance was observed to piperacillin + tazobactam.(62)(63). The difference observed may have been contributed by differences in the characteristics of in the study population The high resistance observed to sulfamethoxazole + trimethoprim may have been attributed by the fact that it is easily available and being commonly used in treatment of common conditions. For aztreonam which is commonly unavailable and not frequently used; no very clear explanation for all isolates to have been resistant, however extended monobactam expressed by many pseudomonas spp may explain this finding This findings however need to be interpreted with caution because the number of isolates tested for drug susceptibility was small.

These findings suggest therefore the need for bacteriological testing before embarking into empirical treatment of bacterial infections especially when gram negatives bacteria are suspected to be the cause

5.2. Strength of the study

The current wide spread use of hemodialysis in our country has provided opportunity for life prolongation among patients with endstage renal disease. While presumed bacterial infection is common; empirical use of antibiotics among patients undergoing hemodialysis is a common practice in our setting. This study is the first one to be done in our setting to determine the magnitude of bacterial infection, the common isolates and their antibiogram pattern among patients undergoing hemodialysis and therefore provided a plat form for more studies to be done.

5.3. Study Limitation

Molecular typing method for Coagulase-negative staphylococci was not performed to prove the identity of strains isolated from blood and catheter and therefore caution need to be taken into accounts on its interpretation.

Vancomycin is among a commonly empirical antibiotic used in our study population; its susceptibility pattern was not be established in this study due to technical difficulties.

Fever reported was obtained from history and this may have varied according to individual perception.

The number of microorganism isolated was small hence the susceptibility results should be taken with caution.

CHAPTER SIX

6.1 CONCLUSION

Bacteremia associated with central venous catheterization is common among patients undergoing hemodialysis at MNH and both gram negative and gram positive bacteria are responsible etiological agents. The isolated underlying bacteriologic agents show rampant resistance to commonly prescribed antibiotics including drug combinations which have proven potency to other types of infections. Further, temporary catheters that are in use 30 days after insertion, femoral venous catheterization and fever are independent predictors for bacteremia among these patients.

6.2 Recommendation

We strongly recommend that due to multi-drug resistant isolates, blood cultures should be taken promptly from all patients suspected to have bacteremia associated with central venous catheterization. Further, we recommend that practitioners avoid femoral site catheterization, limit temporary catheter use for hemodialysis to less than 30 days since insertion and to aggressively investigate and treat fever in these patients.

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APPENDICES

Appendix 1: English Version S/N.....

Date of interview _____ File Number_____ Tel Number _____

PART I: SOCIO-DEMOGRAPHIC CHARACTERISTICS

1. Sex_____[0=Female 1=Male,]
2. Year of birth_____
3. Level of education_____[0=No education, 1=Primary 2=Secondary, 3=Vocational, 4=University]
4. Marital status_____ [0=single, 1=Married, 2=Cohabiting, 3=Divorced, 4=Widowed]
5. Occupation_____[0=peasant,1=civil servant, 2=private, 3=others: specify……]

PART II: MEDICAL HISTORY

6. Do you smoke? _____ [0=No, 1=Yes, 2= Yes but stopped]
7. Do you drink alcohol? _____ [0=No, 1=Yes, 2 =Yes but stopped]
8. Do you have hypertension? _____[0=No, 1=Yes, 2=I don't know]
9. Do you to have diabetes mellitus? _____[0=No, 1=Yes, 2=I don't know]
10. Did you suffer fever/ chills in the last 48 hours? _____ [0=No, 1=Yes]
11. If yes, did you take any fever lowering medicine? _____ [0=No, 1=Yes]
12. Mention all your current medication _____

PART III: CLINICAL AND ANTHROPOMETRIC MEASUREMENTS

13. Pulse Rate _____beats/min [0= <60, 1= 60 – 100, 2 = ≥100]
14. BP _____mmHg [0= <140/90, 1= 140/90-159/100, 2 = ≥160/100]
15. Weight _____kg
16. Height _____cm
17. Oral temperature_____^{0}C[0= <36, 1= 36-37.5, 2 = ≥37.5]
18. Random blood glucose _____mmol/L[0= <7, 1= ≥7]
19. Albumin _____mg/dl[0=<35, 1= ≥35]
20. Pre dialysis creatinine _____ (mmo/l) Post dialysis creatinine_____(mmo/l)

21. Pre dialysisurea___(mmo/l)Post dialysis urea____(mmol/l)
    URR____%[0=<65 1,=≥65]
22. WBC_____ [0= <4,000, 1= 4,000 – 11,000 ,2 = ≥12,000]
23. Hemoglobin _____g/dl[0=<7 1,=7–11, 2=≥12]
24. For how long have been on hemodialysis?
    a. < 6months
    b. 6-12months
    c. >12 months
25. How often do you have hemodialysis per week?
    a. Once
    b. Twice
    c. Thrice
    d. >Thrice
26. Where is your vascular access for hemodialysis**?**
    a. Neck
    b. Subclavian
    c. Femoral
    d. Forearm
27. Which type of vascular device do you have**?**
    a. ArteriovenousFistula
    b. TemporaryCatheter
    c. Permanent Catheter
    d. Graft
28. For how long have you been having this device in your body (Temporary Catheter)?
    a. <30 days
    b. 30-90 days
    c. >90 days
29. For how long have you been having this device in your body (Other devices)?
    a. <3 years
    b. 3- 6 years
    c. >6 years

30. How many attempts were made before successful placement of the device?
    a. 1-2
    b. 3-5
    c. >5
31. Have you ever had your device removed because of suspected infection?
    a. Yes
    b. No
32. Did you suffer fever in the last month
    a. Yes
    b. No
33. How often do you suffer fever/chills?
    a. Nearlyeveryday
    b. Once per week
    c. Once per month
    d. Others (specify)…….
34. Was your fever investigated?
    a. Yes
    b. No
35. Was the cause of fever found?
    a. Yes
    b. No
36. How were you treated?
    a. Antibiotics
    b. Antimalaria
    c. Antipyretics
    d. Others (specify) …….
37. Bacteria growth
    a. Yes
    b. No
38. Bacterial isolated.....
39. Time difference in bacterial growth .....Minutes

40. Susceptibity testing

a. Penicillin 0 resistance 2 Susceptible
b. Cefotaxin 0 resistance 2 Susceptible
c. Gentamicin 0 resistance 2 Susceptible
d. Ciprofloxacin 0 resistance 2 Susceptible
e. Clindamycin 0 resistance 2 Susceptible
f. Cotrimoxazole 0 resistance 2 Susceptible
g. Amoxycillin+ Clavulinic acid 0 resistance 2 Susceptible
h. Piperacillin 0 resistance 2 Susceptible
i. Meropenem 0 resistance 2 Susceptible
j. Piperacillin + Tazobactam0 resistance 2 Susceptible
k. Aztreonam 0 resistance 2 Susceptible

Appendix II: Kiswahili Version

Dodoso – Kiswahili Na.....

Tarehe ya usaili _____ Namba ya faili _____ namba ya simu _____

SEHEMU I: TAARIFA YA KIJAMII

1. Mwaka wa kuzaliwa (miaka)_____
2. Jinsia_____[0=Ke,1=Me,]
3. Kiwango cha Elimu_____[0=sijasoma, 1=msingi 2=Sekondari, 3=ufundi, 4=chuo kikuu]
4. Hali ya ndoa_____ [0=sijaoa, 1=nimeoa/olewa, 2=naishi na mwanaume/mwanaume, 3=tumetalikiana, 4=mjane]
5. Kazi_____ [0=mkulima, 1=mtumishi wa umma, 2=mtumishi sekta binafsi, 3=nyingineyo: taja……..……]

SEHEMU II: HISTORIA YA KIAFYA

6. Je, umeshawahi kuvuta sigara? _____ [0=hapana, 1=ndio, lakini nimeacha, 2= ndio, bado naendelea]
7. Je, umeshawahi kunywa pombe? _____ [0=hapana, 1=ndio, lakini nimeacha, 2= ndio, bado naendelea]
8. Je, unakisukari? _____[0=hapana, 2=ndio, 3=sijui]
9. Je, una shinikizo la damu? _____[0=hapana, 2=ndio, 3=sijui]
10. Je, umepatwa na homa/ kutetemeka katika masaa 48 yaliyopita? _____ [0=hapana, 1=Ndio]
11. Kama ndio, je umemeza dawa za kushusha homa? _____ [0=Hapana, 1=Ndio]
12. Taja dawa zako zozote unazomeza kwasasa._____

SEHEMU YA III: UCHUNGUZI NA UPIMAJI WA MWILI

13. Kasi ya mapigo ya moyo _____mapigo/dakika [0=<60, 2=60-100, 3=≥100]
14. Shinikizo la damu _____mmHg [0=<140/90, 2=140/90-159/100, 3=≥160/100]
15. Uzito _____kg
16. Urefu _____sm
17. Joto la mwili (mdomoni)_____^{0}C [0= <36, 1= 36-37.5, 2 = ≥37.5]

18. Kiwango cha sukari kwenye damu _____(mmol/L) [0= <7, 1= ≥7]
19. Albumini_____mg/dl[0=<35, 1= ≥35]
20. Kreatini kabla _____ (mmo/l) Kreatini baada_____(mmo/l)
21. Urea kabla_____(mmo/l) Urea baada_____(mmol/l) URR _____%[0=<65 1,=≥65]
22. Chembenyeupe_____ [0= <4,000, 1= 4,000 – 11,000 ,2 = ≥12,000]
23. Hemoglobini _____g/dl[0=<7 1,=7–11, 2=≥12]
24. Je ,unasafishwa damu kwa muda gani sasa?
    a. <miezi 6
    b. miezi6-12
    c. >miezi 12
25. Unasafishwa damu mara ngapi kwa wiki?
    a. 1
    b. 2
    c. 3
    d. >3
26. Kifaa cha kuungnisha ushafishaji damu kipo wapi katika mwili wako ?
    a. shingoni
    b. kifuani chini ya mfupa wa bega
    c. pajani
    d. mkono wa mbele
27. Je ni aina gani ya kifaa umewekewa?
    a. fistula
    b. mrija wa muda
    c. mrija wa kudumu
    d. pandikizi
28. Kifaa hiki kipo mwilini mwako kwa muda gani (mrija wa muda)?
    a. < siku30 days
    b. Siku 30-90 days
    c. >siku 90 days

29. Kifaa hiki kipo mwilini mwako kwa muda gani (vifaa vinginevyo)?
    a. <miaka 3
    b. Miaka 3- 6
    c. >miaka 6
30. Kulifanyika majaribio mangapi kabla yakufanikiwa kuweka kifaa hicho?
    a. 1-2
    b. 3-5
    c. >5
31. Je, kifaa hicho kilishawahi kutolewa kwakudhaniwa kupata maambukizi?
    a. Ndio
    b. Hapana
32. Je ulishawahi kupata homa katika mwezi uliopita
    a. Ndio
    b. Hapana
33. Je, ni mara ngapi unapata homa/baridi?
    a. Karibia kila siku
    b. Mara moja kwa wiki
    c. Mara mojakwa mwezi
    d. mengineyo (taja)…….
34. Je, ulifanyiwa vipimo kwa ajili ya homa?
    a. Ndio
    b. Hapana
35. Je, kisababishi cha homa kilipatikana?
    a. Ndio
    b. Hapana
36. Je, ulitibiwaje?
    a. Antibiotiki
    b. Dawa za malaria
    c. Dawa za kushusha homa
    d. mengineyo (taja) …….

37. Uoto wa wadudu
    a. Ndio
    b. Hapana
38. Mdudu aliyepatikana.....
39. Tofauti ya masaa ya kuota.....Dakika
40. Kingamizi dhidi ya dawa zilizochaguliwa
    a. Penicillin 0 resistance 2 Susceptible
    b. Cefotaxin 0 resistance 2 Susceptible
    c. Gentamicin 0 resistance 2 Susceptible
    d. Ciprofloxacin 0 resistance 2 Susceptible
    e. Clindamycin 0 resistance 2 Susceptible
    f. Cotrimoxazole 0 resistance 2 Susceptible
    g. Amoxycillin+ Clavulinic acid 0 resistance 2 Susceptible
    h. Piperacillin 0 resistance 2 Susceptible
    i. Meropenem 0 resistance 2 Susceptible
    j. Piperacillin + Tazobactam 0 resistance 2 Susceptible
    k. Aztreonam 0 resistance 2 Susceptible

Appendix III: Information Sheet – English Version

Greetings Sir/Madam

My name is _____. I am collecting data for the study on Bacteremia associated with catheterization and their antibiogram among patients on hemodialysis therapy at MNH-Dar es Salaam Tanzania.

What is the aim of this research?

The aim of this study is to determine magnitude of CRB, Microbials isolates, Antimicrobial susceptibility and associated factors among patients on hemodialysis therapy.

What does Participation Involves?

It involves answering questions from a structured questionnaire and taking important measurement such as body weight, height, oral temperature, blood pressure and blood withdrawal from the catheter and/or peripheral vein. Your blood test results such as Full blood picture, Random blood sugar and Pre and Post dialysis creatinine and urea shall be recorded.

Confidentiality

All information obtained from you during the conduction of this research will remain confidential, and will only be shared to you and other personnel involved in your care. However, note that data collected will be analysed and shared scholarly among other people.

Are there risks and benefits if I participate in this study?

Generally there are no major risks involved in your participation in this research however little prick pain during venipuncture may be experienced. Your blood results shall be communicated to you promptly and to your primary physician for further management. There is no any direct individualized benefit if you participate in the study and equally there are is no harm if you decline to participate in the study.

Do I have a right to participate or withdraw from the study?

You are free to decide whether or not to participate in this study, and you may decide to withdraw at any time after you have consented.

Whom to Contact in case of any query?

If you have any questions about this study, Please contact, Dr Saning'o S. Liaulo, Department of Internal Medicine, Muhimbili University of Health and Allied Sciences (MUHAS), P.O.Box 65001, Dar-es-Salaam. Mobile: 0755 255 212.

If you have any questions about your rights as a participant in this study,

Please contact, The Chairman of the Research and Publications Committee, MUHAS, P.O.Box 65001, Dar-es-Salaam. Tel: 022 2152489.

7.2.2. Consent Form

I declare that I have read (or read for) and understood all the information above, and I hereby willingly and without coercion agree to participate in this study.

Signature _____Date _____

Appendix IV: Information Sheet – Swahili Version

FOMU YA MAELEZO

Salaam!

Jina langu ni _____.Ninashiriki kukusanya taarifa kwa ajili ya utafiti unaofanywa juu ya ukubwa wa tatizo la maambukizi ya bakteria kwenye mirija ya kuunganisha kusafishwa damu, aina ya bacteria na uwepo wa kinga dhidi ya antibiotiki kwa wagonjwa wanaosafishwa damu. Utafiti huu unafanyika hapa Muhimbili- Dar es Salaam, Tanzania.

Je, lengo la utafiti huu ni nini?

Lengo la utafiti huu ni kubaini ukubwa wa tatizo la maambukizi ya bakteria kwenye mirija ya kuunganisha kusafishwa damu, aina ya bacteria na uwepo wa pingamizi dhidi ya antibiotiki mbalimbali kwa wagonjwa wanaosafishwa damu

Je, ushiriki wangu unahusisha kitu gani?

Kushiriki kwako ni pamoja na kujibu maswali ya dodoso utakayoulizwa na pia kufanya upimaji wa uzito wa mwili, urefu, shinikizo la damu na uchukuaji wa damu kupitia mrija wa kusafisha damu na /au veni.Taarifa za damu kama vile picha ya damu, sukari, albumini na kiwango cha kreatini na urea kabla na baada ya kusafishwa damu zitanukuliwa pia.

Usiri

Taarifa zote tutakazokusanya zitakuwa siri na hazitatumiwa na mtu au taasisi nyingine yeyote zaidi ya mtafiti. Hata hivyo taarifa hizi zitatumika kwa minajili ya kitaaluma

Je zipo faida au hatari zozote nikiamua kushiriki kwenye huu utafiti?

Hakuna faida au hasara ya moja kwa moja ya wewe kuamua kushiriki katika utafiti huu isipokuwa unaweza kupata maumivu madogo hasa wakati wa kuchua damu kupitia veni. Majibu yako utapatiwa wewe pamoja na daktari wakobaada ya kutoka kwa ajili ya kupata matibabu kama yatahitajika.

Je, nina haki ya kushiriki au kujitoa kwenye utafiti muda wowote?

Una uhuru wa kuamua kukubali au kukataa kushiriki utafiti huu. Pia unaweza kujitoa wakati wowote.

Je, nikiwa na swali lolote juu ya utafiti huu niwasiliane na nani?

Ukiwa na maswali yeyote kuhusu utafiti huu tafadhali wasiliana na Dk. Saning'o S. Liaulo, Idara ya Tiba, Chuo Kikuu cha Tiba na Sayansi za Afya Muhimbili, S.L.P. 65001, Dar-es-Salaam, Simu ya mkononi: 0755 255212. Ukiwa na swali lolote kuhusu haki zako kama mshiriki wa utafiti huu tafadhali wasiliana na Mwenyekiti wa Kamati ya Utafiti na Uchapishaji, Chuo Kikuu cha Tiba na Sayansi za Afya Muhimbili, S.L.P. 65001, Dar-es-Salaam. Simu ya ofisini: 022 2152489.

Fomu ya Idhini

Nakiri kwamba nimesoma (kusomewa) maelezo yote yanayohusiana na utafiti huu na nimeelewa lengo lake na na kubali kushiriki kwenye utafti huu kwa hiari yangu mwenyewe bila kushurutishwa.

Sahihi _____Tarehe _____