ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCES

SCHOOL OF ALLIED HEALTH SCIENCES

DEPARTMENT OF MEDICAL LABORATORY SCIENCES

BACTERIURIA, CANDIDURIA AND ANTIMICROBIAL RESISTANCE PATTERNS AMONG HEMODIALYSIS PATIENTS AT SELECTED DIALYSIS CENTERS, ADDIS ABABA, ETHIOPIA.

BY: TESFAYE SEBOKA

A THESIS SUBMITTED TO THE SCHOOL OF GRADUATE STUDIES, ADDIS ABABA UNIVERSITY IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTERS IN CLINICAL LABORATORY SCIENCES (DIAGNOSTIC AND PUBLIC HEALTH MICROBIOLOGY SPECIALTY)

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This is to testify that the thesis prepared by Tesfaye Seboka which is entitled with "*BACTERIURIA, CANDIDURIA AND ANTIMICROBIAL RESISTANCE PATTERNS AMONG HEMODIALYSIS PATIENTS AT SELECTED DIALYSIS CENTERS, ADDIS ABABA, ETHIOPIA*" And submitted in partial fulfillment of the requirements for the degree of Master of Clinical Laboratory Sciences (Diagnostic and Public Health Microbiology Specialty) complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

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List of abbreviations

AST-------------------------------------Antimicrobial Susceptibility Test

CDC------------------------------------Center for Disease control and prevention

CRD------------------------------------Chronic Renal Disease

CLSI------------------------------------Clinical and Laboratory Standards Institute

MDR----------------------------------Multidrug resistance

QC-------------------------------------Quality control

SOPs -----------------------------------Standard Operating Procedures

SPSS -----------------------------------Statistical Package for the Social Sciences

UTIs-------------------------------------Urinary tract infections

WHO -----------------------------------World Health Organization

Operational definitions

i. Hemodialysis patient------a patient who were dialyzed at least once

ii. Multidrug Resistance (MDR) **----** is a bacterium that is simultaneously resistant for two or more antibiotics belonging to different chemical classes.

Abstract

Background: Hemodialysis patients are uniquely vulnerable for urinary tract infections at rates of 3 to 4 times than the general population. It is mostly associated with increased rate of complications due to often subclinical presentations and it is an important cause of morbidity and mortality among this group of patients.

Objective: To determine the prevalence of bacteriuria, candiduria and antimicrobial resistance pattern among hemodialysis patients at selected dialysis centers, Addis Ababa, Ethiopia.

Method: A cross sectional study was conducted from January to May 2017 at selected dialysis centers, Addis Ababa, Ethiopia. A total of 222 hemodialysis patients were included. Urine samples were collected and cultured on Blood agar and MacConkey agar for bacterial and on Sabroud dextrose agar for *Candida ssp.* isolation. All culture positive samples were characterized by colony morphology, gram stain and biochemical tests using the standard procedure. *Candida* spp. was identified by germ tube technique. Antimicrobial susceptibility testing was performed for bacterial isolates using Kirby-Bauer method. Data was analyzed using SPSS version 20.

Result: The overall prevalence bacteria was 27.5% (n=61/222) and the predominant bacteria isolated were *E coli 37.7% (n=23/61)* and *K. oxytoca 23% (n=14/61). S. aureus 4.9%* (n=3/61) was the only gram positive isolate. The prevalence of candiduria was 2.7% (n=6/222) in which *Candida albicans* accounted 66.7% (n=4/6) while non- *albicans* were 33.3% (n=2/6). Multidrug resistance level was recorded 100% (n=61/61) for both Gram positive and Gram negative bacteria. Gram negative isolates were highly resistant to Ampicillin (88.5%), amoxicillin-clavulanic (82%) and chloramphenicol (82%). All isolated *S. aureus* were methicillin resistant.

Conclusion: Assessing hemodialysis patients for bacterial UTIs at regular period is necessary for minimizing the possible occurrence of morbidity and/or mortality due to the infections. Isolations of *Candida species* from hemodialysis patients were significant in number. The possible choices of antibiotic options for treatment of urinary tract infections are few due to wide scale resistance to commonly used antibiotics. To prevent further emergence and spread of MDR bacteria rational use of antibiotics and regular monitoring of antimicrobial resistance patterns is essential.

Key terms: Bacteria, Candida, antimicrobial resistance, hemodialysis, Addis Ababa, Ethiopia

1. Introduction

1.1. Background

Urinary tract infection (UTI) is an infection that affects part of the urinary tract causing cystitis (a bladder infection) and pyelonephritis (a kidney infection). It is the second most common infectious diseases in human which can be symptomatic or asymptomatic that usually requires urgent treatment(1). Symptomatic UTI infection is associated with a wide spectrum of morbidity from mild irritative voiding symptoms to bacteremia, sepsis and occasionally death while asymptomatic UTI is isolation of bacteria from urine in quantitative counts consistent with infection, but without localizing genitourinary signs and or symptoms (2). UTI is considered to be uncomplicated when it occurs in patients with urinary tracts that are normal from both a structural and functional perspective (2). Recurrent UTIs are common and can lead to irreversible damage of kidneys, resulting in renal hypertension and renal failure in severe cases (1, 2).

Though symptoms and signs of UTI vary depending on sex, age, immune status and site of infection, some unique symptoms develop depending on the infecting agent. It is accompanied by variety of clinical signs including dysuria, pyuria, strong urge to urinate frequently, painful burning sensation, discomfortable pressure and bloody urine. Females have a higher risk for UTIs than males probably because of their anatomy. Other risk factors for UTIs include any condition that may impede urine flow like enlarged prostate, congenital urinary tract abnormalities and inflammation (2, 3).

Hemodialysis patients are uniquely vulnerable to the development of infections because of multiple factors including exposure to invasive devices, immunosuppression, the lack of physical barriers between patients in the outpatient hemodialysis environment, and frequent contact with healthcare workers during procedures and care (5). UTIs are common in hemodialysis patients, an important cause of morbidity and mortality in these patients((4) which occur at rates 3 to 4 times the general population(5).It is also associated with increased rate of complications, and may be difficult to diagnose due to often subclinical presentation (6).

The clinical presentation of urinary tract infection in a dialysis patient is similar to that of an individual without renal failure. By comparison, anuric patients may present with only bladder discomfort and/or fever. The presence of pyuria, including white blood cell casts, without bacterial infection is common in dialysis patients. Some investigators have suggested that pyuria is a marker for urinary tract infection, even in asymptomatic dialysis-dependent patients(6) When undiagnosed and untreated, significant complications may occur, leading to the need for drainage procedures, nephrectomy or death (4).

The higher UTI susceptibility in the Chronic kidney disease (CKD) group may be explained, in part, by a greater incidence of urinary obstructions, which in turn leads to infections, commonly seen in those with benign prostatic hypertrophy, kidney stones and urinary tract cancers. Chronic kidney disease (CKD) is common, and its prevalence is increasing. Infection is a major cause of mortality in end-stage renal disease (ESRD) and hospitalization at all stages of CKD(7).

Bacterial UTI starts when bacteria entered to the opening of urethra from the digestive tract and begin to multiply and major uropathogens are *Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Staphylococcus aureus*(2, 3). The gold standard of diagnosing bacterial uropathogen is urine culture. Greater than or equal to 10^5 colony- forming units per milliliter (CFU/ml) on urine culture is significant for diagnosis. Antimicrobial treatment of UTIs is necessary both to alleviate symptoms and to reduce the risk of renal complications associated nephropathy, pyelonephritis, and acute and chronic kidney diseases (8).

1.2. Statement of the problem

Chronic kidney disease (CKD) is fast emerging as a major public health problem in the 21st century. According to the National Kidney Foundation, 4.5% of the United States population (more than 14 million people) suffers from CKD. The CKD population is predisposed to adverse infectious events because of overwhelming uremia, which is associated with alterations in primary host defense mechanisms and increases the risk of bacterial infections(5).End stage renal disease patients have a higher risk of contracting bacterial infections and that the 3 most commonly seen infectious complications are urinary tract infections (UTI), pneumonia, and sepsis. The major known risk factors for CKD, particularly in higher income countries, include diabetes, hypertension, cardiovascular disease and obesity. However, in lower income countries common causes of CKD are often associated with chronic glomerulonephritis and interstitial nephritis, which are generally ascribed to infectious and parasitic agents (9, 10).

Hemodialysis patients, during the normal course of treatment, are exposed to several infectious risks and the majority of patients require at least 1 hospitalization every year for treatment of infections(5).They are more susceptible to urinary tract infections with a significant impact on morbidity and mortality (11) due to defects in cellular immunity and severe clinical conditions (12). *E. coli, Pseudomonas, Klebsiella, Enterobacter, Citrobacter, Staphylococcus aureus*, *Proteus spp. Acinetobacter spp. and also Candida spp.* are common uropathogens of hemodialysis patients (13).

Complicating UTI happens in patients with underlying risk factors that include urinary tract instrumentation (e.g., catheterization, cystoscopy), anatomic abnormalities, urine out flow obstruction or poor bladder emptying, immunocompromised population such as post renal transplant, diabetic and chemotherapy recipients (14). Recurrent infections are common and can lead to irreversible damage of kidneys, resulting in renal hypertension and renal failure in severe cases (14).

In addition to symptomatic UTIs, asymptomatic bacteriuria is a common condition and its prevalence differs significantly between certain patient populations. The prevalence of both symptomatic and asymptomatic UTIs depends on age, sex, sexual activity, pregnancy, the presence of genitourinary abnormalities, indwelling urinary catheters, and co-morbidities including diabetes mellitus and immunosuppressive conditions. It more often affects women than men (15). *Enterococcus* species and gram-negative bacilli are common in men (16).

In the community, women are more prone to develop UTI than males. Pregnancy also makes them more susceptible to infections (14).Chronic kidney disease it is a common problem among males compared to females due to stress, alcoholism, hypertension and diabetes mellitus. In addition incidence of urinary tract infection is higher among males who are on hemodialysis than males who are not hemodialysis (1).

Antimicrobial treatment in hemodialysis patients who develope UTIs is necessary both to alleviate symptoms and to reduce the risk of renal complications and associated mortality and morbidity (8).However, resistance to commonly prescribed antibiotics for UTI is an expanding global problem both in developed and developing countries. Since bacterial pathogens of UTIs are variable regionally hence infection control and treatment depends on knowledge of common causative organisms and their antibiotic resistance level in local scenario (8).

The urinary tract is often overlooked as a source of infection in dialysis patients, especially because UTI symptoms are mostly related to voiding, which is reduced or absent in these patients (4). In Ethiopia, so far, many studies have been conducted on identifying uropathogens among different groups like HIV patients, pregnant women and diabetes patients. (17-21). However no studies have been conducted yet to address bacterial and *Candida* spp. profiles as well as their antibiotic resistance patterns among hemodialysis patients which are big problems that need to be addressed. Hence, the aim of this study was to determine the prevalence of bacteriuria, Candiduria and antimicrobial resistance patterns among hemodialysis patients at selected dialysis centers, of Addis Ababa, Ethiopia.

1.3. Rationale of the study

As clearly indicated in the statement of the problem, hemodialysis patients are more vulnerable to common uropathogens. Therefore, this study

- Provided new information on the frequency and distributions of bacteriuria among hemodialysis patients in local scenario.
- Has also assessed candiduria from hemodialysis patients.
- Add information on drug resistance level of isolated bacteria for clinicians which guides the safe & effectiveness of empirical therapies and for rational prescription programs revision or development.
- The information obtained on drug resistance level can also help concerned bodies for controlling and intervention on further spread of multidrug resistance bacteria in the community.
- Provide information for policy makers for controlling urinary tract infections among hemodialysis patients and also monitoring use of antibiotics and their level of resistance in hemodialysis patients as well as in the community.
- Can also be used as a baseline source for further studies

2. Literatures review

A study conducted by Hsiao *et al.*,Turk 2014 recorded that a total of 276 bacteriuria patients on chronic kidney disease were admitted to wards with symptoms of upper UTIs and possible lower UTIs. Among these patients, (26.4%, 73/276) were confirmed to have upper UTIs and (73.6%, 203/276) have lower UTIs. Bacterial species causing Upper UTI (n = 73) were *Escherichia coli* 43 (58.9%), *Proteus* 6(8.2%), *Klebsiella* 3(4.1%), *Enterococcus* 0 (0%), *Pseudomonas* 2 (2.7%), *Staphylococcus* 0 (0%) and Lower UTI (n = 203) *Escherichia coli* 104 (51.2%), *Proteus* 6 (3.0%), *Klebsiella* 16 (7.9%), *Enterococcus* 12 (5.9%) ,*Pseudomonas14* (6.9%), *Staphylococcus* 1 (0.5%) (22).

According to a study conducted in Nepal by Richa C *et al.,* in 2016; from 150 urine cultures of chronic renal failure patients undergoing for hemodialysis, 39 (26%) showed culture positive results whereas 111(74%) showed culture negative results. Of those hemodialyzed patients, 76.9% (30/39) were male and 23.1% (9/39) were female. Female population, higher rate of culture positivity was observed in 61-70 years age group 33.3%. *Gram-negative bacteria* were isolated in 33(84.6%) of 39 cases with *Escherichia coli* 13(33.3%), *Proteus vulgaris* 7(17.9%), *Klebsiella oxytoca* and *Pseudomonas aeruginosa* 3(7.7%), *Proteus mirabilis* and *Enterobacter aerogenes* 2(5.1%) and *Klebsiella pneumoniae, Providencia alcalifacience* and *Morganella morganii* 1(2.6%). Among 39 isolates 23 isolates were MDR isolates and were showed resistant towards more than two groups of antibiotics. MDR was observed in both groups of isolates that were Gram negative 19 as well as Gram positive 4(2).

Another study conducted in Nepal by Jaiswal *et al* 2013 on a group of 50 male patients undergoing dialysis due to chronic kidney disease showed that 60.0% cases showed no growth upon culture, 30.0% were found to have significant bacterial growth, 4.0% were found to have multiple growth and 6.0% cases were found to have insignificant growth causing UTI. a bacteria isolated were E. coli 5 (33.33%), *S. aureus* 4 (26.66%), *CONS* 2 (13.33%), *S. pyogenes* 2 (13.33%) and *Klebsiella* spp. 2 (13.33%) (1).

A study conducted by Payandeh *et al* in Iran 2015, of 103 patients with renal failure on hemodialysis, 31 patients had leukocytosis that 12 of them were located in pyuria (>10 WBC/HPF) group and 19 of them in pyuria (<10 WBC/HPF). And from 12 patients who showed pyuria (>10 WBC/HPF) 10 (83.3%) had positive urine culture result. Bacteria isolated in this study were *Escherichia coli, Staphylococci, Enterococcus spps. and Klebsiella pneumoniae (*12*)*.

From a study conducted in Baghdad by Manhal *et al*., 2012;in Hemodialysis patients with renal failure on demographic and clinical presentation on patients, the number of male patients was higher than that of females, 27 (67.5%) versus 13 (32.5%). The study revealed that 14 (35%) of patients were at the age range of 41-50 years. It was shown that 37 (92.5%) of the patients were with *hypertension* and 3 (7.5) with *diabetes mellitus*. Only 3 (7.5%) of study patients were detected with *nephrotic syndrome,* the remainder were with *chronic renal failure* 37 (92.5). in addition that the isolation frequency of pathogenic *bacteria* was 15 (37.5%); 6(15%) patients had been infected with *E. coli*, 5(12.5%) patients with *Klebsiella spp*., and one (2.5%) with *Acinetobacter, α-hemolytic Streptococci, Coagulase negative Staphylococci*, and *Proteus spp*. All *E. coli* and *Klebsiella* isolates were sensitive to *Amikacin* and resistant to *Ampicillin (6)*.

Another study conducted in Indian by John. MS *et al*., in 2015 showed that from a total of 200 urine samples collected in the study period, 143 (91.6%) were from females and 57 (40.3%) samples were from males. Of these collected specimens, 131 samples were positive among females and 23 samples were positive among males. Highest number of samples was collected from females. Bacteria isolated were*; E. coli* 66 (42.8%)*; Klebsiella* 26 (16.8%); *Acinetobacter* 20 (12.9%)*; Citrobacter* 10 (6.4%)*, CONS* 6 (3.8%); *Staphylococcus* 5(3.2%*); Pseudomonas* 3 (1.9%) *and Proteus* 1 (0.6%) (23).

A study conducted in Yemen by Mawhoob N. Alkadasi *et al*; 2014 a total of 70 midstream urine specimens were collected for patient renal stones disease (41.4%) (29/70), were males, and 58.57% (41/70) were females. Out of 70 patients (55/70) examined for renal stones disease. Out of 55 patients with renal stone disease patients; (41/55) of the total positive growth were Gram negative bacteria predominant organisms with a ratio (55%) and the gram positive bacteria isolates were (14/55) with a ratio (55%), The commonest bacteria isolated according to culture report were *E. Coli* (71%), *Klebsiella* (12%), *Proteus* (7%). However Ampicillin was more resistant for *E. coli* (18/41) with a ratio 43.9% , *Klebsiella* (8/9) with a ratio 88.9% and *Proteus* (6/8) with a ratio 75%; Amoxicillin for *E. coli* (15/41) with a ratio 36.6%; *Klebsiella* (8/9) with a ratio 88.9% and Proteus (6/8) with a ratio 75% ,and ciprofloxacin for *E. coli* (11/41) with a ratio 26.8%; *Klebsiella (7/9)* with a ratio 77.8% and Proteus (5/8) with a ratio 62.5% (24).

Another study conducted in Yemen by Gondos *et al* in 2015 of 150 patients, who undergoing for Kidney transplant, bacterial UTI was found in 50 patients (33.3%): *E coli* 22 (44%); S. *saprophyticus* 17 (34%); *Enterobacter* pp 6 (12%); *Klebsiella spp.* 3 (6%); *Pseudomonas aeruginosa* 2 (4%). The prevalence among females 40.3% was higher than males 29%. The UTI was higher in the age group between 41–50 years with a percentage of 28% and this result was statistically significant (showed a significant association with bacterial UTI). The younger group had a much lower risk of UTI only 2%. *Escherichia coli*: the most effective antibiotic was Amikacin 82% effectiveness, followed by Gentamycin 73%. Ampicillin was the least effective antibiotic, with a percentage of 9% (25).

A study conducted in Nigeria by Ezejiofor TIN in 2016 showed that out of 40 urine sample results, 28 samples had significant *bacteriuria* (i.e 70% *bacteriuria*). Bacteria isolated were *Escherichia coli* (29%), *Klebsiella spp.* (22%), *Proteus mirabilis* (14%), *Pseudomonas aeruginosa* (7%), *Streptococcus faecalis* (7%), *Staphylococcus aureus* (7%) and *Staphylococcus epidermidis*(14%) as the dominant bacterial organisms responsible for urinary tract infections. and Sex distribution of the isolated organisms are shown in and revealed that while *Staphylococcus aureus* (33%) was isolated only from the males, *E. coli*, *Proteus mirabilis*, *Streptococcus faecalis* and *Pseudomonas aeruginosa* were isolated only from the females; *Klebsiella spp.* was isolated from the males (33%) and females (67%) respectively, while *Staph epidermidis* was isolated equally (50%) from both sexes (10).

3. Objectives

3.1 General objective

- To determine the prevalence of bacteriuria and Candiduria with antimicrobial resistance patterns among hemodialysis patients at selected dialysis centers, Addis Ababa, Ethiopia

3.2 Specific objectives

- To determine the prevalence of bacteria from urine cultures of hemodialysis patients
- To assess profile of *Candida spp*. from urine cultures of hemodialysis patients.
- To determine antimicrobial resistance pattern of bacterial isolates to the commonly prescribed antibiotics.

4. Hypothesis

Bacterial and *Candiduria* isolates and antimicrobial resistance patterns in urine cultures of hemodialysis patients were not different with other patient groups.

5. Materials and methods

5.1. Study area

The study were conducted at selected dialysis centers [Tikur Anbessa Specialized hospital, St. Paulo's hospital, Zewditu memorial hospital, Santé medical center, Tom Nephrology specialty Clinic, Tsegereda dialysis specialty clinic, Hayat hospital and Ayenalem hospital] in Addis Ababa, Ethiopia. The homodialysis patients flow averagely from each dialysis centers within a week were 5 patients at Tikur Anbessa Specialized Hospital, 8 patients at Paulo's Specialized Hospital, 3 patients at Zewditu Memorial Hospital and 7 patients at Sante medical Clinic,9 patients at Tom Nepherology speciality clinic, 3 patients at Tsegereda dialysis speciality clinic,4 patients at Hayat hospital and 2 patients at Ayenalem hospital.

Tikur Anbessa Specialized Hospital is diagnosing and treating for approximately 370,000-400,000 patients yearly with 800 beds, 130 specialists and 50 non-teaching doctors. The emergency department sees around 80,000 patients per year and 40 are hemodialysis patients. Similarly, St. Paulos specialized hospital is one of the largest referral and teaching hospital for medical faculty that provides services mainly in general service and treatment for patients throughout the country. The hospital is diagnosing and treating for approximately 800,000-970,000 patients yearly, of these 92 were dialysis patients both acute and chronic kidney disease. In addition, Zewditu memorial hospital is is diagnosiing and treating for approximately 230,200 and 410,000 for both out patients and in patients respectively in a year. Of those patients 32 were dialysis patients.

Sante medical center is one of the private clinic that located at Kirkos sub city, established in 1994 e.c. the clinic provides general medical service and dialysis for both acute and chronic renal failure approximately 11,000 patients seen yearly. Of these 60 were dialysis patients.Tom nepherology speciality clinic is the otherprivate clinic that provides services mainly in general medical service and dialysis for renal failure. The Clinic is located at the yeka Sub city, Addis Ababa, Ethiopia which was established in 2002 E.C and approximately 7,700 patients visiting per year. Out of these around 70 were dialysis patients (chronic kidney disease).Tsegereda dialysis speciality clinic is also the private clinic that located at Addis ketema sub city near to Addisu Michael, established in 2003 E.C. the clinic provides general medical service and dialysis for both acute and chronic renal failure. approximately 3,400 patients visiting per year. Of these 36 were dialysis patients.

Hayat hospital is t located at Bole sub city, established in 1988 E.C. the hospital provides mainly in general medical service and dialysis for both acute and chronic renal failure forapproximately 10,000 patients visiting per year. Of these 46 were dialysis patients. Ayenalem hospital is alsoa private hospital that located a*t Kolfe keranio* sub city, established in 2004 E.C. the hospital provides mainly in general medical service and dialysis for chronic renal failure. Approximately 9200 patients visits the hospital per year and of these 30 patients were dialysis patients.

5.2. Study Design and Period

- ❖ A cross-sectional study was conducted from January to May 7/2017.

5.3. Source Population

- ❖ All patients who had hemodialysis in Addis Ababa during the study period were the source population.

5.4. Study Population

- ❖ All patients who went or admitted for hemodialysis in the selected dialysis centers during the study period.

5.5. Inclusion and Exclusion criteria

5.5.1. Inclusion Criteria

- All age and sex group who undergo hemodialysis at least once.
- All patients with symptomatic and asymptomatic UTIs.
- Patients who gave written informed consent to participate in this study.

5.5.2. Exclusion Criteria

- ❖ Patients on antibiotics within the last 2 weeks
- ❖ Patients who failed urination
- ❖ Recent history of instrumentation.

5.6. Sample Size

The sample size was calculated based on single population proportion sample size estimation as shown below by taking a value of P as 11.3% from previous study(26).

$$n = \frac{Z^2 P(1-P)}{d^2}$$

Where n = sample size, Z = Z statistic for a level of confidence, P = expected prevalence or proportion (P = 0.5), and d = precision (d = 0.05), Z = Z statistic: For the level of confidence of 95%, which is conventional, Z value is 1.96.

$$\frac{(1.96)^2 \times 0.113(1-0.113)}{(0.05)^2} = 154.1$$

With the 10 % non-response rate which was 15.4 the sample size became 169.5. Keeping the calculated sample size, 222 hemodialysis patients were recruited in this study.

5.7. Sampling Method and procedure

- A total of 222study participants were recruited using convenient sampling technique and study sites were selected using purposive sampling technique.

5.8. Study Variable

5.8.1.Dependent Variable

- Prevalence of bacterial isolates
- Profile of *Candida spp*.
- Antimicrobial resistance pattern.

5.8.2.Independent Variable

- Age, sex, educational status, residence(address), kidney disease, occupation, history of diabetes mellitus, history of hypertension …etc

5.9. Data Collection

5.9.1. Socio-demographic data and associated risk factors

After obtaining informed consent, socio-demographic data were collected from study participants using a data collection sheet. The data collectors were the principal investigator, trained nurses and medical laboratory technologist who were employee of the selected study sites.

5.9.2. Urine sample collection, storage and transportation

Five (5) ml of midstream urine samples were collected from every study participants after orientations towards how to collect midstream urine. All samples were kept at 2-8^{o}C till transported to Tikur Anbessa Specialized hospital microbiology laboratory. Samples collected from each dialysis centers were transported using ice-box within 12hrs of collection for bacteriological and *Candida* investigation.

5.9.3. Bacteriological and *Candida species* investigation

5.9.3.1. Culture

Using a sterile calibrated wire loop (0.001 ml), all urine samples were inoculated onto blood agar, MacConkey agar (Oxoid, England) and Sabroud dextrose agar and then incubated at 37^{o}C for 24 hours. For each bacterial growth, significant bacteriuria was determined. Identification of bacteria was done using colony characteristics, gram stain and biochemical tests following standard procedure. Gram positive bacteria were identified at species level using catalase, coagulase, latex agglutination test and Pastorex TM staph-plus (for *Staphylococcus aureus* identification). Biochemical tests used for identification of Gram negatives to species level were triple sugar iron, indole, citrate, urea, Lysine decarboxylase (LDC), malonat and motility. Germ-tube test was performed for identification of *Candida albicans* from other *Candida species*. For all bacterial isolates antimicrobial susceptibility testing was carried out on Muller-Hinton agar.

5.9.3.2. Bacterial drug susceptibility testing

The disk diffusion method was performed on Muller-Hinton agar and after 16-18hours of incubation at 37^{o}C zone of inhibition was measured and interpreted as recommended by the Clinical and Laboratory Standards Institute (CLSI)(27). Using a sterile wire loop, 3-5 pure colonies were picked from blood agar for Gram positive and MacConkey agar for Gram negative and emulsified in nutrient broth. Standard inoculums adjusted to 0.5 McFarland were swabbed onto Muller-Hinton agar (dispensed on 100mm plate). Drug susceptibility testing of bacterial isolates was performed using disk diffusion method incubating at 37^{o}C for 24 hours. Each gram negative isolates were tested against amikacin (10µg, Oxoid), amoxicillin (30µg, BD), Amoxicillin-Clavulanic acid (30µg, BD), Chloramphenicol (30µg, BD), ciprofloxacin (5µg, BD), Gentamycin (10µg, BD), TMP-SXT (1.25µg, BD), Cefepime (30µg, BD), Ceftriaxone(30µg, BD), Ceftazidime (30µg, BD), Nitrofurantoin (300µg, BD), Piperacillin-tazobactam (gµ100/10µg, oxoid), imipenem (10µg, Oxoid) and Meropenem(10µg, Oxoid). *Staphylococcus aureus* were tested against Penicillin G (10units, BBL), clindamycin (2µg, BD), oxacillin (5µg, BD) and erythromycin (15µg, BD). Oxacillin susceptibility of *Staphylococcus aureus* was interpreted using 30 µg cefoxitin as a surrogate test. The zone of inhibition was measured to the nearest millimeter and isolates were classified as sensitive and resistant according to the standardized table supplied by CLSI.

5.9.3.3 Germ tube test

Germ tubes are short outgrowth, non-septate germinating hyphae. They are ½ the width and 3– 4 times the length of the cell from which they arise. When cells of Candida are incubated in human serum at 370C for 2-4 hours Candida albicans produce short, slender, tube like structures called germ tubes. Formation of germ tubes is associated with increased synthesis of protein and ribonucleic acid. Various media like fetal bovine serum may be used as a substitute to human pooled serum.

5.10. Quality Control

Standard Operating Procedures (SOPs) were strictly followed verifying that media meet expiration date and quality control parameters per CLSI. Visual inspections of cracks in media or plastic petridishes, unequal fill, hemolysis, evidence of freezing, bubbles, and contamination was performed. Quality control was performed to check the quality of medium. Each new lot was quality controlled before use by testing the *E. coli ATCC 25922* and/or *Staphylococcus aurous ATCC25923* standard strains. Socio-demographic data was collected using data collection sheet which was checked for its completeness, readability and clearness using pretest that was delivered for 5% of participants.

5.11. Statistical analysis and interpretation

The data was entered and analyzed using SPSS version 20 for analysis and double checked before analysis. The descriptive statistics (mean, percentages or frequency) was calculated. The bi-variant logistic regression analysis was used to assess the relation between dependent variable and independent variables and the association was checked using multiple logistic regressions. Finally, the results were presented in words, charts, graphs and tables.

5.12. Data quality Assurance

Socio-demographic characteristics of the patient were collected appropriately using data collection sheet after getting informed consent form which was prepared carefully. Samples were collected in accordance with SOPs and stored within 2-8^{o}C in refrigerator till transportation. All urine samples were taken to microbiology laboratory for analysis using ice box within 12 hours of collection. Culture results were recorded carefully before entry to statistical tool and before analysis the data was double checked.

5.13. Ethical considerations

The study was approved by "Department Research and Ethical Review Committee(DRERC)" of the Department of Medical Laboratory Science, School of Allied Health Sciences, College of Health Sciences, Addis Ababa University. Permission letter was also obtained from the study sites. The purpose and procedures of the study was explained to the study participants within the study period. Those patients who gave informed consent were selected and enrolled as the participants of the study. A patient result was communicated to the attending physicians. Information obtained at each course of the study was kept confidential. Those identified positives for bacteria and *Candida* were referred to attending physicians for appropriate treatment.

6. Results

6.1. Socio-demographic characteristics

A total of 222 patients who had renal failure and went for hemodialysis were recruited from 8 hemodialysis centers (figure 1). All patients were investigated for bacteria and *Candida* causing urinary tract infections. Of these patients, 70.3% (n=156/222) of them were males and 29.7% (n=66/222) were females with males to females ratio of 2.36:1. The majority of patients 40.1% (n=89/222) were >50 years of age and the mean (std. deviation) ages of patients were 44.4(16.3) with age range of 5-75 years. Among these patients, the majority of them 77.9% (n=173/222) had chronic renal disorder. Socio-demographic characteristics of patients have shown in table 1.

Table 1. Socio-demographic characteristics of hemodialysis patients with bacterial culture result at different hemodialysis centers from January to May 2017

Variables		**Culture results (n=222)**		
		Positive n (%)	**Negative n (%)**	**Total n (%)**
Gender	**Male**	34(21.8)	122(78.1)	156(100)
	Female	27(40.9)	39(59.1)	66(100)
Age in Year	<10	0(00)	2(100)	2(100)
	11-20	10(58.8)	7(41.2)	17(100)
	21-30	12(33.3)	24(66.7)	36(100)
	31-40	12(30)	28(70)	40(100)
	41-50	9(23.7)	29(76.3)	38(100)
	>50	18(20.2)	71(79.8)	89(100)
Educational level	**Illiterate**	5(31.3)	11(68.8)	16(100)
	Elementary	11(27.5)	29(72.5)	40(100)
	High school	31(30.7)	70(69.3)	101(100)
	University	14(21.5)	51(78.5)	65(100)
Diabetic status	**Diabetic**	32(32.7)	66(67.3)	
	Non-diabetic	29(23.4)	95(76.6)	
Kidney disease	**Acute**	33(67.5)	16(26.5)	49(100)
	Chronic	28(16.2)	145(83.8)	173(100)
	Total	**61(27.5)**	**161(72.5)**	**222(100)**

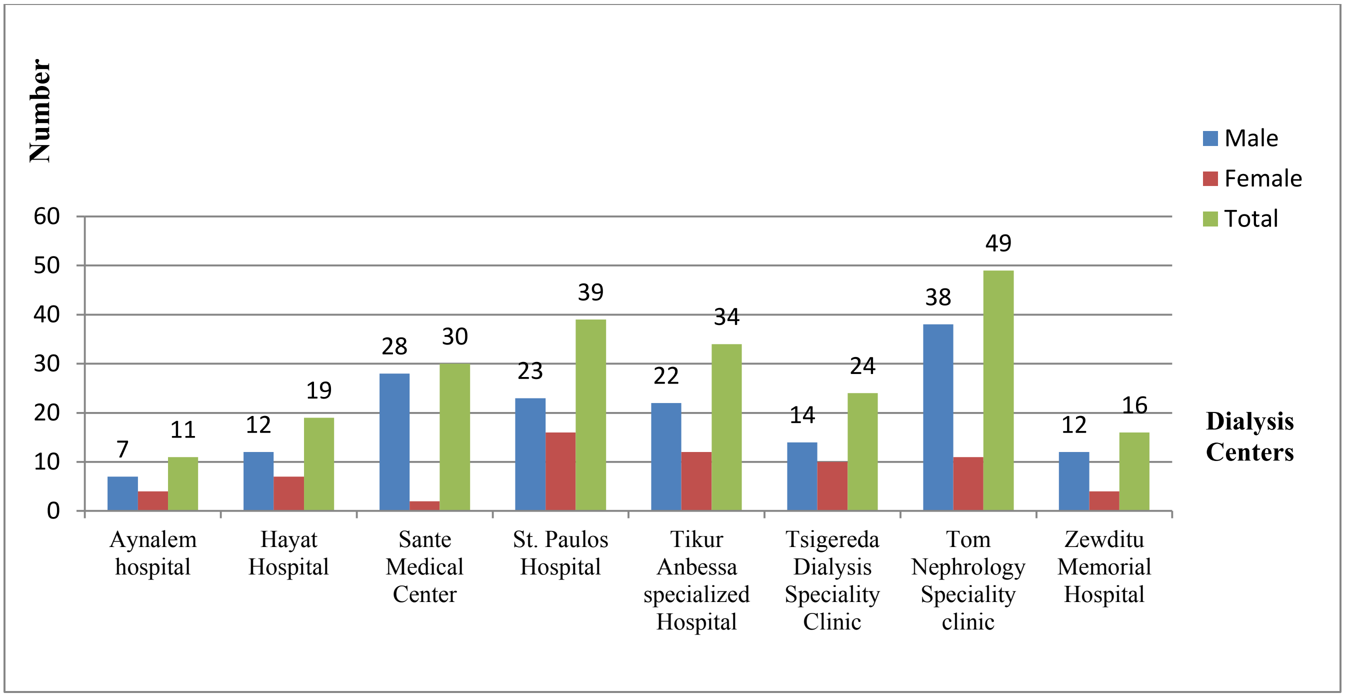

Figure 1. Frequency of hemodialysis patients by sex with culture result at different hemodialysis centers in Addis Ababa from January to May 2017

6.2 Prevalence of bacteria from urine cultures of hemodialysis patients

The overall prevalence of bacteria isolates from urine cultures of hemodialysis patients was 27.5% (n=61/222). Of all bacterial isolates, 21.8% (34/156) were from males and 40.9% (n=27/66) were from females. Gram positive and Gram negative isolates constitutes 4.9% (n=3/61) and 95.1% (n=58/61) respectively with Gram positives to Gram negatives ratio of 0.052:1. The frequent bacterial isolates were *Escherichia coli 37.7% (n=23/61* and *Klebsiella oxytoca 23% (n=14/61)*. Other bacterial isolates were *Acinetobacter spp.11.5% (n=7/61), Pseudomonas spp.4.9% (n=3/61), Staphylococcus aureus 4.9%* (n=3/61), *Klebsiella pneumoniae* 4.9%(n=3/61), *Providencia rettgeri* 4.9%(n=3/61), *Enterobacter spp.* 1.64%(n=1/61), *Citrobacter diversus 1*.64%(n=1/61), *Klebsiella ozaenae* 1.64%(n=1/61), *Proteus vulgaris* 1.64%(n=1/61) *and Proteus mirabilis* 1.64%(n=1/61). In our study, no gram positive bacteria were isolated other than *S. aureus* 4.9% (n=3/61).

The spectrum of bacterial UTI among hemodialysis patients varied with age of patients (table 1) and the majority of patients 40.1% (n=89/222) were greater than 50 years old. However, there was no statistical significant association between age of patients and culture results (P=0.093, OR=0.317, 95%CL=0.083-1.214 (table 2). In our study, highest proportion of bacteria were isolated from females 40.9% (n=27/66) than males 21.8 (n=34/156). However, no statistical significant association seen between sex and culture results (P=0.088, OR=1.967, 95%CL=0.904-4.283). In this study, 67.5% (n=33/49) of culture positive result was found among patients who had acute kidney disease; there was significant association between acute or chronic kidney disease with culture results (P=0.030, OR=0.248, 95%CL=0.071-0.872). In addition, the highest proportion of bacteria were isolated from patients who had diabetes mellitus 36.7% (n=36/98) than non-diabetes though no statistical significant association shown between status of diabetes mellitus with culture results

Table 2. Association of variables with bacterial urine culture results of hemodialysis patient from January to May 2017 at selected dialysis centers, Addis Ababa, Ethiopia.

Variables		**Bacterial Culture results (n=222)**		**P-value**	**COR**	**95%CL**	**P-value**	**AOR**	**95%CI**
		Positive n. (%)	**Negative n (%)**						
Gender	Male	34(21.8)	12(78.2)	0.004	2.484	[1.335-4.621]	0.088	1.967	[0.904-4.283]
	Female	27(40.9)	39(59.1)	1					
Age in Year	<10	0(0.00)	2(100.0)	0.999	4097007.9	[0.000]			
	11-20	10(58.8)	7(41.2)	0.002	0.177	[0.059-0.531]	0.093	0.317	[0.083-1.214]
	21-30	12(33.3)	24(66.7)	0.124	0.507	[0.214-1.204]			
	31-40	12(30	28(70)	0.227	0.592	[0.252-1.386]			
	41-50	9(23.7)	29(76.3)	0.663	0.817	[0.329-2.028]			
	>50	18(20.2)	71(79.8)	1					
Kidney disease	Acute	33(67.3)	16(32.7)	0.000	0.094	[0.046-0.193]	0.030	0.248	[0.071-0.872]
	Chronic	28(16.2)	145(83.8)	1					
Residence	Urban	51(27.1)	137(72.9)	0.784	1.119	[0.501-2.503]			
	Rural	10(29.4)	24(70.6)	1					
Educational level	Illiterate	5(31.3)	11(68.7)	0.414	0.604	[0.180-2.028]			
	Elementary	11(27.5)	29(72.5)	0.487	0.724	[0.291-1.801]			
	High school	31(30.7)	70(69.3)	0.197	0.620	[0.300-1.282]			
	University	14(21.5)	51(78.5)	1					
Occupation	Government	11(33.3)	22(66.7)	0.344	2.005	[0.476-8.403]			
	Private	26(24.3)	81(75.7)	0.091	3.115	[0.836-11.615]			
	Merchant	15(27.8)	39(72.2)	0.173	2.600	[0.657-10.285]			
	At home	3(17.6)	14(82.4)	0.086	4.667	[0.804-27.007]			
	Farmer	1(100)	0(0.0)	1.000	0.000	0.000			
	Student	5(50)	5(50)	1					
History of hypertension	Yes	40(24.8)	121(75.2)	0.155	1.588	[0.839-3.005]			
	No	21(34.4)	40(65.6)	1					
Diabetes Mellitus	Yes	32(32.7)	66(67.3)	0.126	0.603	[0.347-1.139]			
	No	29(23.4)	95(76.6)	1					
Previous recurrent UTI	Yes	28(38.9)	44(61.9)	0.009	0.443	[0.241-0.817]			
	No	33(22.0)	117(78.0)	1					
Smoking	Yes	6(23.1)	20(76.9)	0.594	1.300	[0.496-3.410]			
	No	55(28.1)	141(71.9)	1					
Other chronic diseases	HIV	0(0.0)	1(100)	1.000	5809983.2	0.000			
	Congestive heart failure	4(66.7)	2(33.3)	0.052	0.182-	0.032-1.018			
	MTB	0(0.0)	1(100)	1.000	5809983.2	0.000			
	No	57(26.6)	157(73.4)						
Frequency of hemodialysis	One time	25(71.8)	7(21.2)	0.000	0.053	[0.021-0.138]	0.015	0.160	[0.037-0.700]
	Two times	4(20.0)	16(80.0)	0.650	0.760	[0.233-2.482]			
	Three times	5(27.8)	13(72.2)	0.29	0.494	[0.161-1.520]			
	Four times	4(50.0)	4(50.0)	0.025	0.190	[0.044-0.815]	0.584	0.595	[0.093.821]
	More than four times	23(16.0)	121(84.0)	1					
	Total	**61(27.5)**	**161(72.5)**						

COR—Crud odds ratio, CI--confidence interval, AOR--adjusted odds ratio

6.3 Prevalence of Candiduria from Hemodialysis patients

The prevalence of candiduria from hemodialysis patients was 2.7% (n=6/222) with a 1.8% (n=4/222) and 0.9% (n=2/222) prevalence of *Candida albicans* and non *albicans* respectively. *Candida albicans* accounted 66.7% (n=4/6) while non-*Candida albicans* were 33.3% (n=2/6). Of those isolated *Candida albicans*, 3 of them were identified from females while all non-*Candida albicans* were isolated from males. Of the 4 *Candida albicans, 2* of them were isolated from patients above 50 years old. From patients below 20 years old, no *Candida albicans* were isolated however 1 of the non-albicans *Candida spp*. was isolated from patients below 10 years old. Almost all *Candida spp.* 83.3% (n=5/6) were isolated from diabetic patients. The 3 *Candida albicans* were isolated from patients who had history of hypertension and from patients who hadn't previous history of recurrent UTI. All *Candida spp.* were isolated from patients who didn't have a history of smoking and patients whose residence was urban. Related to frequency of dialysis, 2 of the *Candida albicans* were isolated from patients who had more than 4 times hemodialysis.

6.4 Antibiotic resistance patterns of bacterial isolates

The overall multidrug resistance level (MDR ≥2 different classes of drugs) of isolated bacteria was 100% (n=61/61) (Table 5). All gram negative isolates were resistance for at least two different classes of antibiotics. The antimicrobial resistance level of Gram negative organisms causing UTIs in hemodialysis patients were ranging from 0 - 100% and they showed 100% (n=58/58) MDR level. Among the antibiotics tested ampicillin (88.5%), amoxicillin-clavulanic (82%) and chloramphenicol (82%) were least effective against gram negative isolates. Almost all gram negative isolates were sensitive for Piperacillin-tazobactam (resistance level=8.2%) followed by meropenem (resistance level=13.1%). The most frequent bacterial isolates, *Escherichia coli* 37.7% (n=23/61) showed 100% of MDR level. It demonstrated highest resistance level to amoxicillin (87%) and amoxicillin-clavulanate (78.3%) and least resistance for nitrofurantoin and Piperacillin- tazobactam (4.3% each). The second frequent bacterial isolate, *Klebsiella oxytoca* also showed 100% MDR level and almost all isolates were resistant for drugs belonging four different classes. Among the Gram positive bacteria, the only isolate *Staphylococcus aureus* showed 100% (n=3/3) MDR level. All isolated *Staphylococcus aureus* were methicillin (oxacillin) resistant.

Table 3. Antimicrobial resistance pattern of bacteria isolated from urine cultures of hemodialysis patients.

Gram negative bacteria	Resistance Pattern	AMP	AMC	GN	C	SXT	CIP	CRO	CAZ	CEF	FN	IMI	MER	PIT	AN
E. coli(23)	R	20(87)	18(78.3)	15(65.2)	14(60.9)	14(60.9)	13(56.1)	13(56.1)	8(34.8)	11(47.8)	1(4.3)	2(8.7)	2(8.7)	1(4.3)	9(39.1)
K. oxytoca (14)	R	13(92.9)	13(92.9)	7(50)	12(85.7	12(85.7)	11(78.6)	12(85.7)	10(71.4)	10(71.4)	4(28.6)	4(28.6)	4(28.6)	0(00)	4(28.6)
Acinetobacter spp.(7)	R	7(100)	6(85.7)	6(85.7)	7(100)	7(100)	6(85.7)	4(57.1)	4(57.1)	4(57.1)	7(100)	2(28.6)	2(28.6)	0(00)	5(71.4)
Pseudomonas spp.(3)	R	3(100)	3(100)	1(33.3)	3(100)	2(66.7)	1(33.3)	2(66.7)	2(66.7)	1(33.3)	1(33.3)	0(00)	0(0)	0(00)	1(33.3)
K. pneumoniae (3)	R	3(100)	3(100)	2(66.7)	3(100)	1(33.3)	2(66.7)	2(66.7)	2(66.7)	2(66.7)	2(66.7)	0(00)	0(0)	1(33.3)	2(66.7)
P. rettgeri (3)	R	3(100)	2(66.7)	1(33.3)	3(100)	1(100)	0(0)	0(0)	0(0)	1(100)	0(0)	3(100)	0(0)	3(100)	0(0)
K. ozaenae(1)	R	1(100)	1(100)	1(100)	0(00)	1(100)	0(00)	1(00)	1(100)	1(100)	1(100)	0(00)	0(0)	0(00)	0(0)
Enterobacter spp.(1)	R	1(100)	1(100)	1(100)	1(100)	1(100)	0(0)	1(100)	1(100)	1(100)	1(100)	0(00)	0(00)	0(00)	0(00)
C. diversus(1)	R	1(100)	1(100)	1(100)	1(100)	1(100)	1(100)	1(100)	1(100)	1(100)	0(00)	0(00)	0(00)	0(00)	0(00)
P. vulgaris(1)	R	1(100)	1(100)	1(100)	1(100)	1(100)	1(100)	1(100)	1(100)	1(100)	0(0)	0(0)	0(0)	0(0)	0(00)
P. mirabilis(1)	R	1(100)	1(100)	1(100)	1(100)	1(100)	0(00)	1(100)	1(100)	1(100)	0(0)	0(0)	0(0)	0(0)	0(0)
Total (61)	**R**	**54(88.5)**	**50(82)**	**37(60.7)**	**50(82)**	**42(68.9)**	**35(57.4)**	**38(62.3)**	**31(50.8)**	**34(55.7)**	**17(27.9)**	**11(18.0)**	**8(13.1)**	**5(8.2)**	**21(34.4)**

Gram Positive bacteria

Isolated bacteria	R	P-G	AMP	OX	CLD	ERY
***S. aureus* (3)**	**R**	3(100)	2(66.7)	3(100)	2(66.7)	3(100)

NA--Not applicable: AMP—Ampicillin, AMC--Amoxicillin-Clavulanic acid, GN—Gentamycin, C—Chloramphenicol, SXT—Sulphamethoxazole-trimethoprim, CIP—ciprofloxacin, CRO-ceftriaxone, CAZ-Ceftazidime, CEF---Cefepime, FN----Nitrofurantoin, IMI----Imipenem, MER----Meropenem, PIT----Piperacillin-tazobactam, AN—Amikacin, P-G—Penicillin G, OX--Oxacillin, ERY--Erythromycin, CLD—Clindamycin

Table 4. Multidrug resistance patterns of bacterial isolates from urine of hemodialysis patients.

Isolated bacteria	R1 n (%)	R2 n(%)	R3 n(%)	R4 n(%)	R5 n(%)	R6 n(%)	R7 n(%)	R8 n(%)	Total MDR n (%)
E. coli(23)	0(0)	1(4.3)	4(17.4)	5(21.7)	4(17.4)	7(30.4)	2(8.7)	0(0)	**23(100)**
K. oxytoca (14)	0(0)	0(0)	0(0)	1(7.1)	2(14.3)	4(28.8)	4(28.8)	3(21.3)	**14(100)**
Acinetobacter spp.(7)	0(0)	1(14.3)	4(57.1)	0(0)	2(28.6)	0(0)	0(0)	0(0)	**7(100)**
Pseudomonas spp.(3)	0(0)	0(0)	1(33.3)	2(66.7)	0(0)	0(0)	0(0)	0(0)	**3(100)**
K. pneumoniae (3)	0(0)	0(0)	0(0)	0(0)	1(33.3)	0(0)	2(66.7)	0(0)	**3(100)**
***P. rettgeri* (3)**	0(0)	0(0)	1(33.3)	0(0))	1(33.3)	0(0)	1(100)	0(0)	**3(100)**
***K. ozaenae* (1)**	0(0)	0(0)	0(0)	0(0)	1(100)	0(0)	0(0)	0(0)	**1(100)**
Enterobacter spp.(1)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1(100)	0(0)	**1(100)**
C. diversus(1)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1(100)	0(0)	**1(100)**
P. vulgaris(1)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1(100)	0(0)	**1(100)**
P. mirabilis(1)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1(100)	0(0)	**1(100)**
***S. aureus* (3)**	0(0)	1(33.3)	2(66.7)	NA	NA	NA	NA	NA	**3(100)**

NA---not applicable, R1=resistance to one antibiotic class, R2= resistance to two antibiotic classes, R3= resistance to three antibiotic classes, R4= resistance to four antibiotic classes, R5= resistance to five antibiotic classes, R6= resistance to six antibiotic classes, R7= resistance to seven antibiotic classes, R8= resistance to eight antibiotic classes

7 Discussion

7.1 Prevalence of bacteriuria among hemodialysis patients

The overall prevalence of bacteriuria among hemodialysis patients was 27.5% (n=61/222). This finding was almost a similar result with a study done in Nepal that showed a 26% of bacterial prevalence (2). However, our finding was relatively lower than the finding of a study done in Baghdad which recorded a 37.5% bacterial prevalence (6). Many reasons can be mentioned for this difference however current immune status and early medical checkup of patient plays the major role for the variability of these different studies (7). Additionally, it could be due to varying distribution of bacterial etiology with geography, time and infection prevention practice and also differences in identification methods.

Of all hemodialysis patients, many of them were males 70.3% (n=156/222) however bacterial prevalence of urinary tract infections was more common in females 40.9% (n=27/66) than in males 21.8% (34/156). This was in agreement with studies done in other country (6).There was no significant association between sex of patient and culture results (OR=0.65, 95%CI=0.340-1.262, P = 0.205). The high number of male hemodialysis patients might be explained by more exposure of males to external environment than females which expose them for renal failure (10). In our study, 14.8% (n=23/156) of males were smokers hence smoking could be also a contributing factor for renal failure in males than females.

The spectrum of bacterial UTI among hemodialysis patients varied with age of patients and the majority of patients 40.1% (n=89/222) were greater than 50 years old. However, there was no statistical significant association between age of patients and culture results [P=0.093, OR=0.317, 95%CL=0.083-1.214]. In our study, highest proportion of bacteria were isolated from females 40.9% (n=27/66) than males 21.8 (n=34/156). However, no statistical significant association seen between sex and culture results (P=0.088, OR=1.967, 95%CL=0.904-4.283). The higher occurrence of bacteriuria among females than males could be explained by the anatomical difference where urethra is short in females compared to males which makes female more exposed to urinary tract infections.

In this study, 67.5% (n=33/49) of culture positive result was found among patients who had acute kidney disease; there was significant association between acute or chronic kidney disease with culture results (P=0.030, OR=0.248, 95%CL=0.071-0.872). In addition, the highest proportion of bacteria were isolated from patients who had diabetes mellitus 36.7% (n=36/98) than non-diabetes though no statistical significant association shown between status of diabetes mellitus with culture results. Similarly, patients with hypertension revealed higher bacteriuria than patients with no history of hypertension. A Similar findings has been recorded in other study (6). Both diabetes and hypertension are taken as underlining disease for higher rate of urinary tract infection occurrences.

In our study, Gram positive and Gram negative isolates constitutes 4.9% (n=3/61) and 95.1% (n=58/61) respectively which had similarity with a study done in Nepal (2). *Escherichia coli* 37.7% (n=23/61) were the most frequent isolates which was a similar finding with studies done in Nepal (2, 23). The higher isolation rate of *Escherichia coli* from urinary tract infection was a similar finding with studies done previously in Ethiopia (28-32). The second most frequently isolated bacteria were *Klebsiella oxytoca 23% (n=14/61)*. This was a contrary with most previous studies done throughout the world (33-35). The high occurrence of this bacterium than the commonest bacteria was an indicator of the possible shift of bacterial uropathogens. *Klebsiella pneumoniae* 4.9%(n=3/61), *Providencia rettgeri* 4.9%(n=3/61), *Enterobacter spp*. 1.64%(n=1/61), *Citrobacter diversus 1*.64%(n=1/61), *Klebsiella ozaenae* 1.64%(n=1/61), *Proteus vulgaris* 1.64%(n=1/61) *and Proteus mirabilis* 1.64%(n=1/61). The only gram positive bacteria isolated in this study were *Staphylococci aureus 4.9%* (n=3/61). It showed similarity with a study done in Nepal (2).

7.2 Prevalence of Candiduria from Hemodialysis patients

The prevalence of candiduria from hemodialysis patients was 2.7% (n=6/222) with a 1.8% (n=4/222) and 0.9% (n=2/222) prevalence of *Candida albicans* and non *albicans* respectively. *Candida albicans* accounted 66.7% (n=4/6) while non-*Candida albicans* were 33.3% (n=2/6). It is known that *Candida albicans* is the most common cause of fungal urinary tract infections; however, isolation of non-albicans *Candida species* showed the expected distribution of *Candida* species is changing (36).

Of those isolated *Candida albicans*, 3 of them were identified from females while all non-*Candida albicans* were isolated from males. Almost all 83.3% (n=5/6) *Candida spp.* were isolated from patient who were diabetic patients. The occurrence of *Candida spp*. from diabetic patients was supported by other study done in Ethiopia (37). Of the 4 *Candida albicans, 2* of them were isolated from patients above 50 years old. The 3 *Candida albicans* were isolated from patients who had history of hypertension and from patients who hadn't previous history of recurrent UTI. All *Candida spp.* were isolated from patients who didn't have a history of smoking and patients whose residence was urban. Related to frequency of dialysis, 2 of the *Candida albicans* were isolated from patients who had more than 4 times hemodialysis.

7.3 Antimicrobial resistance patterns of bacterial isolates

The overall multidrug resistance level (MDR ≥2 different classes of drugs) of isolated bacteria was 100% (n=61/61). This finding was a similar result with a previous study in Ethiopia; Dessie (32). This study result was also comparable with other study finding done in Ethiopia (21). However, a relatively lower finding has been recorded in Ethiopia which was 78.4% (26). In our study, both Gram positive and Gram negative bacteria showed 100% multiple drug resistance and all bacterial isolates were resistance for at least two different classes of antibiotics. The high frequency of multiple antibiotics resistance might be a reflection of inappropriate use of antimicrobials, lack of laboratory diagnostic tests, unavailability of guideline for the selection of antibiotics, unskilled practitioners, expired antibiotics, self-medication and inadequate hospital control measures as well promote the development of resistance in clinical isolates.

The antimicrobial resistance level of Gram negative organisms causing UTIs in hemodialysis patients were ranging from 0 - 100%. The frequent bacterial isolates, *Escherichia coli* 37.7% (n=23/61) showed 100% (n=23/23) MDR level (18). It demonstrated highest resistance level to amoxicillin (87%) and amoxicillin-clavulanate (78.3%) and least resistance for nitrofurantoin and Piperacillin- tazobactam (4.3% each). A Similar finding has been reported from previous study conducted in Ethiopia (18, 26, 28, 38). However, a lower multidrug resistance level has been reported from previous studies in other parts of Ethiopia (31). The difference could be due to the difference in prescribing this antibiotic for the treatment of the bacteria from hospital to hospital. The second frequent bacterial isolate, *Klebsiella oxytoca* also showed 100% MDR level and almost all isolates 92.9% (n=13/14) were resistant to at least four drugs belonging in different classes. Among the Gram positive bacteria, the only isolate *Staphylococcus aureus* showed 100% (n=3/3) MDR level and All isolated *Staphylococcus aureus* were methicillin (oxacillin) resistant.

Of tested antibiotics, ampicillin (88.5%), amoxicillin-clavulanic (82%) and chloramphenicol (82%) were least effective against gram negative isolates. this finding comparable with other study findings in Ethiopia (26, 28). However, a lowered resistance level of this drug has been reported in other parts of Ethiopia (31). Almost all gram negative isolates were sensitive for Piperacillin-tazobactam (resistance level=8.2%) followed by meropenem (resistance level=13.1%).

8 Strengths and limitations

8.1 Strength

- The study has assessed bacterial and *Candida* prevalence among hemodialysis patients who are at risk for urinary tract infections but not addressed before this study.
- Many study sites were selected and included to maximize the sample size

8.2 Limitations

- Hemodialysis patients who didn't attended those selected study sites were not captured and included in the study.
- Shortage of literatures made result comparison and interpretation difficult.

9 Conclusion

The overall 27.6% (n=61/222) prevalence of bacterial isolates from urinary tract infections of hemodialysis patients was high. The most frequent isolated bacteria were *Escherichia coli 3*7.7% (n=23/61*)* followed by *Klebsiella oxytoca 23.0%* (n=14/61). Assessing hemodialysis patients for bacterial urinary tract infections at regular period is necessary for minimizing the possible occurrence of morbidity and/or mortality due to the infections. Isolations of *Candida species* from hemodialysis patients were significant in number. The choice of drugs for the treatment of bacterial isolates from urinary tract infections especially for bacterial strains resistant to most classes of antibiotics is quite narrow due to their wide scale resistance for most common drugs which have been used previously. To prevent further emergence and spread of MDR bacterial pathogens, rational use of antibiotics and regular monitoring of antimicrobial resistance patterns are essential and mandatory.

10 Recommendation

- Routine bacterial and *Candida* assessment of hemodialysis patients for urinary tract infections and selection of antibiotics based on culture result is recommended so that patient management will be improved.
- A regular monitoring of antimicrobial resistance patterns is essential and mandatory to prevent further emergence and spread of antimicrobial resistance among bacterial pathogens especially in the case of multidrug resistance bacteria.
- Effective antibiotic policy like antibiotic restriction, combination therapy and antibiotic cycling, and infection control programs combined with good medical practices can help to prevent the occurrence and spread of multidrug resistant bacterial strains.

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Annexes

Annex I: Laboratory procedures for sample collection, biochemical reactions, drug susceptibility testing (CLSI guidelines).

1. **Sample collection**
    1. Using a sterile wide mouthed container, collect 5ml of midstream urine sample after genital washing.
    2. Label the specimen and as soon as possible deliver it with a completed form to the laboratory
2. **Culture and identification**

i. Bacteria growth from the blood and MacConkey agar

Positive/present □ Negative/absent □

ii. Identification steps for suspected colonies

a) Gram stain result ___________________________
b) Oxidase test positive □ /negative □
c) Colony morphology
d) Lactose fermentation from MacConkey agar
    - Lactose Fermenter
    - Late Lactose fermenter
    - Non lactose fermenter

iii. Biochemical reactions

Identification of bacterial isolates involves the use of biochemical screening Medias. Indole, Urease, Mannitol, Triple sμgar iron (TSI), Citrate, Motility, Lysine Decarboxylase, Mannolet and Oxidase tests.

Biochemical reactions		Indole	Urea	Man	TSI	Cit	Mot	LDC	OX
Result	Positive								
	Negative								
Gram negative rods									

Key: LDC = Lysine decarboxylase, Man = Mannitol (mannite), Triple sμgar iron (TSI), Ox = Oxidase test, Cit = Citrate test, Mot = Motility, Ind = Indole test, Urea = Urease, H2S = Hydrogen sulphide (blackening), R = Red-pink (alkaline reaction), Y = Yellow (acid reaction), d = different strains give different results.

A. **Indole test**: Few colonies of the culture will be inoculated into peptone water and incubated at 37oC for 24 hours. Few drops of indicator (Kovac's reagent) will be added and gently shake to mix well. Colour change will be then observed. If the layer of indicator reagent turns to red within 1 minute, it is Indole positive (positive result). If the layer of indicator reagent remains yellow within 1 minute, it is indole negative (negative result).

B. **Urease test (Christensen's (modified) urea broth)**: Urea agars will be inoculated heavily over the entire surfaces of the slants in bijou bottles. The cap will be loosened and then incubated at 37oC for 3-12 hours. A urease-positive culture produces an alkaline reaction in the medium, evidenced by pinkish red color of the Medium. Urease-negative organisms do not change the color of the medium, which is pale yellow-pink.

C. Triple Sugar Iron (TSI) Agar Slant: Using a sterile inoculating needle, stab the butt of the LIA slant twice then streak back and forth along the surface of the agar with the organism. Incubate at 37◦C for 18 to 24 h. If acid slant–acid butt (yellow–yellow): glucose and sucrose and/or lactose fermented. If alkaline slant–acid butt (red–yellow): glucose fermented only. If alkaline slant–alkaline butt (red–red): glucose not fermented. The presence of black precipitate (butt) indicates hydrogen sulfide production, and presence of splits or cracks with air bubbles indicates gas production.

D. **Citrate utilization test using Simmon's citrate agar**: Simmon's citrate slopes will be prepared in bijou bottles as recommended by the manufacturer (stored at 2-8oC). And the slopes will be then stabbed and incubated at 37oC aerobically for 48 hours. Blue colour indicates a positive reaction and if Simmon's citrate agar slopes remained as green in colour indicate negative reaction.

E. **Motility Test (using motility agars)**: Motility agar will be prepared and inoculated with a straight inoculating needle making a single stab about 1-2cm down into the medium. The motility will be examined after 35-37oC for 24 hour. Motility will be indicated by the presence of diffuse growth (appearing as coloring of the medium) away from the line of inoculation.

F. Lysine decarboxylase: Decarboxylation of lysine can be detected by culturing bacteria in a medium containing the desired amino acid, glucose, and a pH indicator bromcresol purple. The acids produced by the bacteria from the fermentation of glucose will initially lower the pH of the medium and cause the pH indicator to change from purple to yellow. The acid pH activates the enzyme that causes decarboxylation of lysine to amines and the subsequent neutralization of the medium. This results in another color change from yellow back to purple. Bacteria that decarboxylate lysine turn the medium purple. In addition bacteria that produce H2S appear as black colonies.

G. **Oxidase test:** A piece of filter paper is soaked with a few drops of oxidase reagent. A colony of the test organism is then smeared on the filter paper. Alternatively an oxidase reagent strip can be used. When the organism is oxidase-producing, the phenylenediamine in the reagent will be oxidized to a deep purple colour.

3. Antibiotics susceptibility result for Bacteria isolates

Isolated bacteria	Antibiotics		AM	AM	SXT	FOX	C	CTX	GE	TE	NO	FN	OX	IMI	ME
	Drug Susceptibility	S													
		I													
		R													

***NOTE**: AML--Amoxycillin, AmC--Amoxycillin-Clavulanic acid, SXT----Sulphamethoxazol-trimethoperem, FOX----Cefoxitin, C---Chloramphenicol, CTX----Cefotaxime, GM--Gentamycin, TE--- Tetracycline, NOR---Norfloxacin, OX--- Oxacillin, IMI--- Imipenem, MEM--- Meropenem*

Procedure for Performing the Disk Diffusion Test

Inoculum Preparation

- At least three to five well-isolated pure colonies of the same morphological type will be selected from Blood or MacConkey agar plate. The top of each colony is touched with a loop, and the growth is transferred into a tube containing 4 to 5 ml of tryptone soy broth.
- The turbidity of the broth culture will be adjusted with that of the 0.5 McFarland standards.

Inoculation of Test Plates

- Optimally, within 15 minutes after adjusting the turbidity of the inoculum suspension, a sterile cotton swab is dipped into the adjusted suspension. The swab should be rotated several times and pressed firmly on the inside wall of the tube above the fluid level.
- The dried surface of a Mueller-Hinton agar plate is inoculated by streaking the swab over the entire sterile agar surface.
- The lid may be left ajar for 3 to 5 minutes, but no more than 15 minutes, to allow for any excess surface moisture to be absorbed before applying the drug impregnated disks.

NOTE: Extremes in inoculum density must be avoided. Never use undiluted overnight broth cultures or other unstandardized inocula for streaking plates.

Application of Disks to Inoculated Agar Plates

- The predetermined battery of antimicrobial disks is dispensed onto the surface of the inoculated agar plate. Each disk must be pressed down to ensure complete contact with the agar surface.
- The plates are inverted and placed in an incubator set to 37°C within 15 minutes after the disks are applied.

Reading Plates and Interpreting Results

After 16 to 18 hours of incubation, each plate will examine. The diameters of the zones of complete inhibition (as judged by the unaided eye) are measured, including the diameter of the disk. Zones are measured to the nearest whole millimeter, using sliding calipers which is hold on the back of the inverted plate.

Annex II: English version of participant information sheet and consent form

1.1 Participant information sheet

Department of Medical Laboratory Science, School of Allied Health Sciences, Collage of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia

Title: To determine the bacteriuria, Candiduria and their antimicrobial susceptibility pattern among hemodialysis patients at selected dialysis centers, Addis Ababa, Ethiopia from January to May 2017.

First of all we would like to thank you in advance for your cooperation and consent in participation in this study. Please read or listen when it is read for you about the general information of the study. If you have any question regarding the study please ask freely.

Background information

Hemodialysis patients are uniquely vulnerable to the development of urinary tract infection because of multiple factors which is an important cause of morbidity and mortality. Urinary tract infections occur in these groups at rates 3 to 4 times the general population and it is also associated with increased rate of complications, and may be difficult to diagnose due to often subclinical presentation. Common etiologic agents of hemodialysis patients are *Staphylococcus aureus, Staphylococci saprophyticus, P. aeruginosa, E. coli, Klebsiella spp. and Enterobacter* take the leading. Drug resistance is the challenge for controlling such bacteria now days due to wide scale resistance to commonly used antibiotics.

In addition to their high prevalence the development of drug resistance is the challenge for controlling now days. As the frequency and antibiotic sensitivity pattern to common pathogen has been changing day by day, choice of appropriate antibiotics depends on the knowledge of common organisms and their antimicrobial susceptibility pattern.Hence the aim of this study is to determine the prevalence of bacteriuria and their antimicrobial susceptibility pattern among hemodialysis patients at selected dialysis centers, Addis Ababa, Ethiopia from January 2017 to May 2017.

Aim of the study

The purpose of the study is to determine the prevalence of bacteriuria, candiduria and their antimicrobial susceptibility pattern among hemodialysis patients at selected dialysis centers, Addis Ababa, Ethiopia from January 2017 to May 2017.

Benefits for participants

Study participants will not have any financial incentives or other inducements from participating on this study. However, results will be given to their physician for treatment or to get counseling. Most importantly, this study will contribute to provide information or data for future and further nationwide study and to develop health programs for health policy makers.

Risks and complication

There is no considerable risk(s) in participating in this study.

Confidentiality

In order to maintain the confidentiality of participants' information, the name will not be given and the samples will be coded. Participants will not be prohibited to stop or withdraw at any time from the study. No personal information will be disclosed to third party or will not appear in any report from this study.

Assurance of Principal Investigator

I put my signature below to confirm you that I take over the responsibility for the scientific ethical and technical conduct of the research project and for provision of progress reports for all stakeholders of the research project.

Tesfaye Seboka(PI): Signature: __________________ Date: __________________

Note: If you have any questions about this study, feel free to ask now or anytime throughout the study by contacting:

PI Address: Tesfaye Seboka: Department of Medical Laboratory Sciences, School of Allied Health Sciences, Collage of health sciences, Addis Ababa University, Addis Ababa, Ethiopia

E-mail: Tesfayeseboka1@gmail.com; Tel.: +251911146561

1.2 Informed consent

I will inform about the study which plans To determine the bacteriuria, Candiduria and their antimicrobial susceptibility pattern among hemodialysis patients at selected dialysis centers, Addis Ababa, Ethiopia from January to May 2017. The objective and the application of the study will briefly explain to me. Moreover, I will well inform of my right to refuse information, decline to cooperate and drop out of the study if I want and none of my actions will have any bearing at all on my overall health care.

It is therefore with full understanding of the situation that I agree to give the inform consent voluntarily to the researcher to give for the mentioned study. I will have the opportunity to ask questions about the project and receive clarification to my satisfaction in a language I understand. I will also inform that results will be given to the Doctor who follow me and that I may ask the information if I want.

I ___________________________________ hereby give my consent for giving of the requested information and specimen for this study.

Participant code:__________________ Signature: _____________ Date: ________________

Annex III: Amharic Version of the participant information sheet and Consent form (የተሳታፊዎችመረጃቅጽ ና የፈቃደኝነትማረጋጫ)

1.1 የተሳታፊውችመረጃቅጽ

አዲስአበባዩኒቨርሲቲጤናሳይንስኮላጅየህክምናላቦራቶሪሳይንስዲፓርትመንት

አርስት፡ በአዲስአባባከተማ፣ በ

በተለያዩዲያሊሲስክሊኒኮችየዲያሊሲስህክምናበሚጣቸውታካሚዎችለባክቴሪያዎችኢንፌክሽንስርጭቱንእናለመድሀኒትያለወንግትርነትማወቅ

አጠቃላይመረጃ

በጥናቱበማተፍዎከልብእያጣነንከመወሰንዎበፊት፡ - ይህንንቅጽበትክክልያንብቡወይምኒ በብልዎበትክክልያደምጡ፤ እንዲህምግልፅያልሆነ ልዎትንነገርበማሱብነፃነትይጠይቁ::

መግቢያ

የዲያሊሲስህክምናየሚጣቸውታካሚዎችበተለያዩተህዋስያንየሚመጣለሽንትመሻኛአካልኢንፌክሽንችግርበተጨማሪየተጋለጡሰሆኑበዓለምላይየሚደርሱትየሞትእናየኢኮኖሚቀውስከፍተኛውንደረጃይይዛል፡ ፡

በተለይምበታዳጊህግሮችወስጥችግሩሰፊነው፡ ፡

ለዚህምዋነኛመንስኤውብዙአይነትባክቴሪያዎችሲሆንበሚያጣጠትበሽታዎካንያትየሚሞቱትሰዎችከፍተኛውንቁጥርይይዛሉ፤ በተጨማሪምእነዚህባክቴሪያዎችለመድሐኒቶችበከፍተኛደረጃየግትርነትባህሪ (drug resistance) እያሳዩመሆኑችግሩንወስብስብአድረጎታል፡ ፡

ሥለሆነምይህንበሽታከፍተኛጉዳትከሚከተሉብፊትበመካላከልየሕብረተሰቡንሞትለመቀነስያለወንስርጭትእንዲህምለመድሃኒቶችምያለወንየግትርነትማዎቅበጣምአስፈላጊነው፡ ፡

የጥናቱአላማ

በአዲስአባባከተማ፣

የዲያሊሲስህክምናበሚጣቸውታካሚዎችበባክቴሪያዎችለሽንትመሻኛኢንፌክሽንለተጋላጠታካሚዎችስርጭቱንእናለመድሀኒትያለወንግትርነትማወቅ፡ ፡

ለጥናቱተሳታፊዎችያለወልዩጥቅም

በጥናቱለሚተፉፍቃደኛተሳታፊዎችምንምአይነትየገንዘብክፍያየለውም:

ነገርግንወጤታቸውለሚከታተላቸውሀኪምእንዲደርሰወይደረጋል፡ ፡

በጥናቱተሳታፊዎችላይያለወጉዳትእናተዛማጅችግር

በዚህጥናትላይበማተፍዎሊደርስብዎየሚችልአንደምጉዳትአይኖርም፡ ፡

የመረጃሚስጥራዊአጠበበቅ

የሚጠቅሚ ጃበጥና ቱወቅትምሆን ከዛበኃላባሉትጊዜያትማሉብማሉሚ ጥራዊነ ቱየ ሚጠብቅናሚ ጃወዎየ ሚየዘወበስማ ይሆ ንበማ ያቁጥር ይሆናል፡ ፡ በጥና ቱላ ይእ ያሉብፈለጉትጊዜየ ማቆምወይምየ ማቋረጥመብትአለዎት፡ ፡ ይህሚ ጃበጥን ቃቄየ ሚየ ዝናሚ ጃወን በፈለጉጊዜሊያገ ኙየ ሚቹሉይሆና ል፡ ፡
በሚጨሻምየ ጥናቱወጤትለሚሞ ከተወአካልለጥና ቱአላማበቻየ ሚ ለፅ ይሆናል፡ ፡
ያስታውሱ፤ ስለዚህጥና ትማንኛወምጥያቄካልዎትበማንኛወምጊዜከዚህበታችበተጠቀሱትአድራሻዎችማጠየ ቅይችላሉ፡ ፡
የ ዋናተመራማሪ ወአድራሻ፤

- **ተስፋየ ሰቦቃ፡** የ ሕክምና ላቦራቶሪ ቴክኖሎጂዲፓርትመን ት፣ የ ጤና ሳይንስኮሌጅ፣ አዲስአበባዩኒቨርሲቲ- አዲስአበባ፣ ኢትዮጵያ
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1.2 የ ፈቃደኝነ ትሚ ጋገ ጫቅፅ

በአዲስአባባከተማ፣
የ ዲያሊሲስህክምና በሚጣቸወታካሚዎችለባክቴሪያዎችኢንፌክሽንስርጭቱንእናለመድሀኒትያለወን ግትርነ ትማወቅበሚካር ዕስለይለማጥና ትበተማ ከተበሚደረገ ወጥና ትላ ይለማ ተፍማሆኑ፤ የ ጥና ቱዓላማ ጥቅምተገ ልጾልኛል፡ ፡ የ ናሙና ወወጤቱበሚ ጥርእንደሚየ ዝተነ ግሮኛል፡ ፡
በተጨማሪ ምጥና ቱወስጥአለማ ተፍመብቴእደሆነ ናበማንኛወምጊዜከጥና ቱበራሴወሳኔ መዉጣትእንደምችልናበዚህምክን ያት ምን ምአይነ ትመጉላላትእንደሚደርስብኝበሚ ባተረድቻለሁ፡ ፡ ስለሆነ ምሁኔ ታወን በሚ ባበሚጠን በፈቃደኝነ ትበምርምሩ ላ ይለማ ተፍለተማራሚ ወፈቃደኝነ ቴንሰጥቻለሁ፡ ፡
ማንኛወን ምዖልገ ባኝንነ ገ ርየ ማጠየ ቅዕድልተሰጥቶኝበሚ ባኝቋን ቋሚልስአግኝቻለሁ፡ ፡
በተጨማሪ ምየ ሁሉምየ ላብራቶሪ ምርሚራወጤቶችለተቋሞችእንደሚ ጥና ወጤቱን ማወቅከፈለኩማግኘትእንደምችልተነ ግሮኛል፡ ፡

እኔ ____
የ ተባልኩግለሰብይህን ሁሉብሚ ናዘብምርምሩላ ይስለኔ ሚ ጃእናየ ደምወይምየ ሽንትናሙና ለማ ጠትተስሚሞቻለሁ፡ ፡

ፊርማ____________ ቀን ______________

ሚ ጃወን ያስረዳወአካል _______________________ ፊርማ______