CYTOMEGALOVIRUS INFECTION AMONG KIDNEY TRANSPLANT RECIPIENTS ATTENDING KENYATTA NATIONAL HOSPITAL OUTPATIENT CLINIC: A RETROSPECTIVE OBSERVATIONAL STUDY

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Declaration

This dissertation is my original work and has not been presented for a degree at any other university

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The patients of Kenyatta National Hospital

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Abbreviations

AA: African- American

CAI: Chronic allograft injury

CGN: Chronic Glomerulonephritis

CMV: Cytomegalovirus

CMVD: Cytomegalovirus disease

CMVI: Cytomegalovirus infection

CMV DNA PCR: Cytomegalovirus deoxyribonucleic acid polymerase chain reaction

D: Donor

D+: Donor positive for cytomegalovirus IgG

D-: Donor negative for cytomegalovirus IgG

DM: Diabetes Mellitus

EBV: Ebstein Barr Virus

Egfr: Estimated Glomerular Filtration rate

ESRD: End Stage Renal Disease

FDA: Food and drug administration

HHV: Human Herpes Virus

HIV: Human immunodeficiency virus

KDIGO: Kidney Disease Improving Global Outcomes

KNH: Kenyatta National Hospital

KTR: Kidney Transplant Recipients

MDRD: Modification of Diet in Renal Disease

NBTS: National Blood Transfusion Unit

PI: Principal Investigator

PMN: Polymorphonuclear cells

Pp65 Antigen: Cytomegalovirus phosphoprotein 65

R: Recipient

R+: Recipient positive for cytomegalovirus IgG

R-: Recipient negative for cytomegalovirus IgG

RTI: Respiratory Tract Infections

SOT: Solid Organ Transplant

SOTR: Solid Organ Transplant Recipients

Abstract

Background: Cytomegalovirus (CMV) causes significant morbidity and mortality among Kidney Transplant recipients (KTR). Kidney transplant recipients are at risk of acquiring CMV infection and progressing to active disease. Recent studies have shown a marked reduction in all-cause mortality, CMV related mortality and morbidity following antiviral prophylaxis in solid organ transplant recipients (SOTRs). Hence the Kidney Disease Improving Global Outcomes (KDIGO) guidelines have come up with strategies to prevent cytomegalovirus infection (CMVI) and cytomegalovirus disease (CMVD) ultimately improving outcomes among KTR.

Study objectives: To determine the prevalence of CMV Infection among KTR

Methodology:

Study design: Retrospective observational cohort study

Setting: Kenyatta National Hospital Transplant Clinic Renal Unit.

Subjects: Kidney transplant recipients on follow up in Kenyatta National Hospital, Renal Unit.

Materials and methods: Kidney transplant recipients provided data sought for the study. The data was categorized as CMV serology (Donor/Recipient) pre-transplant and CMV clinical disease outcomes post-transplant.

Data collection and analysis: Continuous variables are expressed as means and standard deviations, prevalence expressed as percentages with 95% confidence interval. A *p* value of less than or equal to 0.05 was considered statistically significant.

Results: CMV sero-prevalence pre-transplant was very high with 191(97.5%) of recipients and 179 (91.8%) of donors being sero-positive for CMV IgG. None of the donors and recipients had active disease at the time of transplant. CMV serologic pairing at the time of transplant was 180 (92%) concordant positive (D+/R+), 4(2%) concordant negative (D-/R-) and 11(6%) discordant

pair of D-/R+. None of the R- received graft from a D+. The period prevalence of CMVD post-transplant was 8.2% among these 2.05% had confirmed CMVD and 6.15% had probable CMVD. The median post-transplant period to development of CMVD was 3 months. All patients with confirmed CMVD presented with CMV syndrome. Those with probable invasive CMVD presented with CMV colitis 7(58.3%), CMV hepatitis 2(16.67%) and CMV encephalitis 1(8.3%). Majority of patients with confirmed CMVD died 3(75%) and the remaining one (25%) developed graft rejection and is back on dialysis. Among those with probable disease 5(41.67%) have functioning grafts, 5(41.67%) developed chronic graft dysfunction, 1 (8.3%) developed graft rejection and is on dialysis and 1(8.3%) died of CMV related complications.

Conclusions: There is a very high CMV sero-prevalence among KTR in KNH (97.5%) however majority of KTR did not progress to CMVD (8.2%) in the background of no chemoprophylaxis possibly due to a pre-existing cell mediated immunity controlling viral replication. A majority of the patients with CMVD were D+/R+ (93.5%) probably through super infection with reactivation of different CMV genotypes. The impact of CMVD on patients' outcomes is considerable resulting in reduction in patient survival, graft survival and contributing to graft dysfunction. CMV prophylaxis for all KTR is as a result recommended. CMVD presented in the early pre-transplant period (median 3 months) with non-specific symptoms and hence a high index of suspicion in the early post-transplant period is also recommended.

Literature review

Introduction

Human Cytomegalovirus (CMV) is an important cause of morbidity and mortality among Kidney Transplant Recipients (KTR) [1]. CMV causes direct effects to tissues leading to hepatitis, retinitis, nephropathy, marrow suppression among others depending on the affected organ. Indirect effects to hosts infected with CMV include cardiovascular disease, cancer, acute graft rejection, graft dysfunction and failure, diabetes, chronic allograft nephropathy, bacterial and viral infections among others. [2, 3, 4, 5]. CMV causes 5-fold increase in all-cause mortality and 11-fold increase in CMV-related mortality in SOTR [6, 7]. Cytomegalovirus disease (CMVD) can be seen in 8 -32%, of KTR not on antiviral chemo-prophylaxis. [8, 9]

Consequently the Kidney Disease Improving Global Outcomes (KDIGO) guidelines have come up with strategies preventing cytomegalovirus infection (CMVI) and cytomegalovirus disease (CMVD) hence improving outcomes following kidney transplantation. Antiviral prophylaxis as a preventive strategy improves outcomes among solid organ transplant recipients (SOTR) causing marked reduction in all-cause mortality and CMV-related mortality [10-13]**.** D+/R- SOTR are at the highest risk of developing severe CMVD with a 60% incidence reduction upon administration of anti-viral chemo-prophylaxis [12]**.** Antiviral prophylaxis with gancyclovir and valgancyclovir for three months were found to be effective in preventing CMV active infection and ultimately CMVD.

Epidemiology

Cytomegalovirussero-prevalence

Cytomegalovirus (CMV) is ubiquitous with distribution worldwide and epidemiological variations depending on socio-demographic backgrounds and age. The highest CMV sero-prevalence being in Africa, Asia and South America, while the lowest incidence being The United states and Western Europe. [14]. A few changes on CMV sero-prevalence across age, sex and ethnic background have been observed over the past few decades upon analysis of various cross-sectional surveys. The prevalence was also noted to increase with age [15].

A meta-analysis of 25 published studies looking at CMV sero-prevalence around the Sub-Saharan region of Africa revealed a high prevalence among individuals from a low socio-economic background. The same meta-analysis reported the highest prevalence in Kenya (97% prevalence) while the lowest was in Nigeria (55% prevalence) among healthy adult blood donors [16]**.** In Kenya, this was a cross-sectional descriptive study recruiting 400 healthy adult blood donors at the National Blood Transfusion Unit in Kenyatta National Hospital. The prevalence in this population was found to be 97% (95% CI 96.45-97.53) and 3.6 %(95% CI (1.7%-5.2%) for IgG, IgM respectively. Leuco-reduction of blood products among sero-negative individuals undergoing transfusion was therefore recommended due to the high prevalence [17].

Cytomegalovirus disease (CMVD) among kidney transplant recipients

Cytomegalovirus disease (CMVD) prevalence ranges from 8-32% among kidney transplant recipients and this varies with socio-demographic characteristics, drug, dose and duration on immune-suppressants among others (Table 1).There is currently no study that has looked at CMV among Kidney Transplant Recipients in Kenyatta National Hospital renal unit or in Kenya according to the PubMed search.

Table 1 Prevalence of CMVD among Kidney Transplant Recipients

COUNTRY	Design	n	CMV sero-prevalence	CMVD	Clinical manifestations	Diagnosis	Risk	Outcomes	Ref
South Africa	Retrospective	73	80%	32%	Syndrome Nephropathy	PCR Pp65	D+/R+ D+/R-	Graft dysfunction Graft losses	[18]
Kingdom of Saudi Arabia	Retrospective	639	100%	3.6%	Syndrome Hepatitis Pneumonitis	PCR	D+/R+	↓patient survival ↓ graft survival Graft rejection	[40]
USA	Retrospective	94	58.3%	7%	Syndrome Hepatitis Colitis	PCR Pp65	D+/R-	↓patient survival ↓ graft survival	[19]
Greece	Prospective	392	12%	3.9%	Syndrome Hepatitis Colitis	PCR		↓patient survival	[20]
Mexico	Prospective	225	65.6%	17.8%	Syndrome Hepatitis Colitis	PCR		↓ graft survival Graft rejection	[21]

Risk factors

CMV D+/R- mismatch is a major risk factor due to lack of CMV specific cellular immunity. The severity of symptoms is also higher. Anti-viral chemo-prophylaxis has significantly reduced the incidence but a risk of developing Late Onset CMV disease has been observed [22].The net immune-suppressive state is also a significant risk factor. Immune-suppressive drugs like lymphocyte-depleting agents (muronomab CD3), anti-lymphocyte globulins, anti-thymocyte globulins, high dose corticosteroid, and mycophenolate mofetil increase the risks of CMV infection. Sirolimus, everolimus and tacrolimus have a lower risk of infection. The dose, duration and type of immunosuppressive therapy, age and underlying co-morbidity also affects CMV reactivation **[**23]. The peak viral load, acute allograft rejection has also been shown to affect CMV outcomes among SOTR [24]. Late subclinical CMV infections occur frequently and may lead to rapid graft loss. [25]. D+/R+ group has been associated with worse graft and patient

survival after three years possibly due to multiple viral strains and double CMV exposure with differing latent viral reactivation (donor & recipients) [25,26]

Pathogenesis and pathophysiology

Upon infection with CMV in immune-competent hosts the virus remains latent. The genomic material has been found in endothelial cells and leucocytes. Reactivation of the virus is an important step to the pathogenesis of active CMV infection and ultimately CMVD. The major determinant of CMVD is immune-suppression. Immunity controls viral persistence, cytotoxic T lymphocytes being the key defense. The severity of disease is dependent on the immunosuppressant, intensity of rejection and serology pre-transplant. Cell mediated immunity CD4+ and CD8+ T cell response is able to control viral replication. Upon activation of CMV by a depressed cellular immune function replication and dissemination ensues.

In SOTR, CMV can propagate into active infection among those with latent infection. Two patterns of active infection are observed; primary and secondary infection (reactivation and/ or super-infection). Primary infections mostly occur when a CMV negative recipients (R-) receives an organ carrying latent virus from a CMV positive donor (D+). It may also occur through the traditional methods of transmission that is direct contact with infected secretions like blood, saliva, urine, and stool among others. Reactivation latent CMV occurs post-transplant in R+ individual. Super-infection or re-infection occurs when CMV sero-positive host receives an organ from a donor who is CMV sero-positive with viral reactivation occurring from the donor's latent virus (strain). Specialized genetic studies are used to distinguish super-infection from reactivation.

Clinical manifestations

Cytomegalovirus disease (CMVD) commonly occurs in the first three months after solid organ transplant in patients not receiving anti-viral prophylaxis. Cytomegalovirus infection (CMVI) is categorized into asymptomatic (subclinical CMVI) and symptomatic disease (CMVD). CMVD is further classified as disease with tissue invasion (pneumonitis, myocarditis, hepatitis, nephritis, retinitis, gastro-intestinal) and without tissue invasion (CMV syndrome).

The diagnosis of end organ involvement is made on histology. CMVS (CMV syndrome) presents with fever, malaise, myalgia and arthralgia. Myelosupression as evidenced by leucopenia and thrombocytopenia is common. More than 60% of CMVD cases are due to CMVS. Less than 40% of CMVD cases are due to tissue invasive disease. It mainly presents with end-organ dysfunction. Any organ can be involved; multi-organ involvement is possible however the transplanted organ is at highest risk. Gastro-intestinal involvement is the most common form of tissue invasive disease manifesting with odynophagia, diarrhea, abdominal pains, nausea and vomiting.CMV pneumonia presents with dyspnea, cough and fever. It can be fatal. Typically manifests with an interstitial pattern of disease. Tubulointerstitial disease, renal artery stenosis, crescentric glomerulonephritis among others have been observed in KTR. [4]. CMV also has indirect effects in transplant patients due to its immune-modulatory properties including bacteremia invasive fungal infection, acute and chronic allograft rejection, New onset diabetes after transplant (NODAT) among others.

CMV diagnosis among kidney transplant recipients

Due to the significant morbidity and mortality caused by CMV in SOTR there's need to improve strategies on prevention, diagnosis and treatment. Significant breakthroughs have emerged in the last two decades in diagnosis facilitating prompt management of CMVD. Viral nucleic acid

detection and antigenemia are currently the main diagnostic techniques used in diagnosis of CMVI among SOTR due to their rapid turnaround times and high sensitivity. The most sensitive and highly recommended methods for diagnosis include pp65 antigenemia or PCR. [27, 28, 29].The correlation of CMV viral load and CMVI in immune-compromised individuals has been evaluated in various studies. Well defined criteria have become an important component in these definitions. Consistently, it has been observed that individuals symptomatic for CMVI have high viral loads. Viral copies of more than 500/ ml are highly predictive for CMVD among KTR. [30-32]

CMV PCR

Because of its ability to detect minute viral nucleic acids, PCR has become invaluable in the last decade. Recently quantitative results have been used to determine amounts through amplification reactions. CMV viral load burden correlates well with the development of CMVD [33]. Quantitative PCR can accurately and reproducibly determine the systemic and site-specific CMV load.

Management of CMVI among kidney transplant recipients

The proposed approaches to management of CMVI include prophylaxis and pre-emptive therapy. The current KDIGO guidelines recommend prophylaxis for all. Another option of management is pre-emptive therapy where patients with high viral loads receive anti-viral chemo-prophylaxis. Two meta-analyses have shown that prophylaxis significantly reduces the risk of CMVD compared to no prevention with reduction in the rate of graft rejection [34, 35]. CMVI, acute rejection, graft function, non-CMV infection, graft dysfunction and all-cause mortality incidence was lower in patients on prophylaxis than those with no treatment according to a prospective observational study of 387 CMV R+ participants. CMVD however occurred after cessation of

prophylaxis that is late onset CMVD [36]. Both prophylactic and pre-emptive therapy reduces the incidence of CMVD according to a nationwide prospective cohort of 1239 SOTR. However, patients on CMV prophylaxis were more likely to be free from graft failure [37]. Longer prophylaxis reduced the incidence of CMVD from 36.8% to 16.8%. It was therefore recommended that prophylaxis with valgancyclovir be extended to 200 days [38]. None of the D+/R- patients receiving anti-viral prophylaxis tested positive for CMV IgG or IgM. [39] Kenyatta National Hospital (KNH) patients do not receive prophylactic or pre-emptive therapy for CMV post-transplant. Vigilance for CMV active infection is however observed in the post-transplant period among symptomatic patients.

Problem statement and justification

At the Kenyatta National Hospital, there is a very high CMV sero-prevalence of virtually 100% among healthy adult blood transfusion donors; 97% (95%CI 96.45%-97.53%) IgG. [17]. KTR are at a higher risk of acquiring CMV infection (hospital and community acquisition) causing significant morbidity and mortality.

The study sought to generate data on CMV infection among KTR offering guidance regarding the best and most cost-effective option of prevention and management of CMV among KTR in a resource limited setting.

Sero-prevalence among transplant donors will also offer guidance regarding the likelihood of receiving allograft from a negative donor as well as the outcomes amongst KTR infected with CMV.

A number of studies have been carried out in the Western world looking at the prevalence of CMVI among KTR however no studies according to the PubMed search has been carried out in

our population. The only study that may be similar to the Kenyan population is a retrospective study in South Africa. In this setting however, due to higher risks of rejection there is use of potent immune-suppressants at the expense of opportunistic infections [18]. This is therefore not a true reflection of the KNH KTR population.

Research question

What is the burden of CMV Infection and CMVD among KTR attending KNH outpatient clinic?

Hypothesis

CMVD is not high among KTR in Kenyatta National Hospital

Objectives

Broad objectives

To determine the prevalence of CMV Infection among KTR attending KNH outpatient clinic

Specific objectives

- Determine CMV sero-prevalence pre-transplant among recipients
- Determine the Donor/Recipient match at the time of transplant using CMV antibody IgG/ IgM status
- Determine the prevalence of CMVD post-transplant and their outcome in form of:
    i. Dead
    ii. Alive
        a. Normal graft function
        b. Chronic graft dysfunction (CKD)
        c. Graft rejection (dialysis)
- Describe the clinical manifestations of CMVD as
    - CMV Syndrome

- Invasive CMVD: CMV Hepatitis, renal dysfunction, GIT disease, respiratory disease, neurologic manifestation or retinitis.

Secondary objectives

- Determine CMV sero-prevalence pre-transplant among donors

Methodology

Study design

A retrospective observational cohort study

Study site/ setting

Kenyatta National Hospital is a public hospital and National referral hospital in Nairobi, Kenya. It is the oldest hospital in Kenya. It was founded in 1901 and now has a bed capacity of 1,800. So far 140 patients have undergone renal transplantation in KNH since 2010. The patient survival is 97.5% and graft survival 92.5% in the first four years post-transplant.

Study population

The study population included records of KTR visiting Kenyatta National Hospital transplant clinic renal unit consenting to participation.

Patient selection

Case definition

Latent infection is defined as documented evidence of CMV IgG positivity pre-transplant without clinical manifestations or organ dysfunction.

CMV syndrome: documented body temperature of >38°C, CMV infection (CMV viremia >500 copies/ml) and no other apparent underlying cause recorded. The presence of one of the

following: leukocyte count <4,000 cells/mm3; atypical lymphocytes of ≥3%; platelet count<100,000 mm3 and symptoms suggestive of infection (arthralgia, myalgia, malaise, fever and/ or wasting syndrome).

***End-organ disease*:** CMV disease was defined as documented symptoms and signs of organ involvement associated with either immune-histochemical or virological detection of CMV in biopsy tissues or local secretions (independently of virus detection in blood), absence of other possible causes of organ disease with clinical and virological response to anti-CMV therapy.

***Probable end organ disease*:** is diagnosed in patients without documented histo-pathological evidence of CMV, with a compatible clinical presentation, recorded evidence of CMV viremia (viral loads >500 copies/ml),and clinical and/or virological response to specific anti-viral therapy. Compatible clinical manifestation defined as:

- *Renal involvement:* Documented rise in creatinine with eGFR calculated using MDRD, evidence of CMV viremia, clinical and/or virological response to specific antiviral treatment or no response to treatment for another underlying cause.
- *Liver:* Documented rise in liver transaminase twice the upper limit of normal with evidence of CMV viremia, clinical and/or virological response to specific antiviral treatment or no response to treatment for another underlying cause.
- *Gastrointestinal:* Documented esophagitis, gastritis, diarrhea with evidence of CMV viremia, clinical and/or virological response to specific antiviral treatment or no response to treatment for another underlying cause.
- *Respiratory:* Documented respiratory tract infection with evidence of CMV viremia, clinical and/or virological response to specific antiviral treatment or no response to treatment for another underlying cause.

- *Neurological complications:* Documented encephalitis, neurological deficit with evidence of CMV viremia, clinical and/or virological response to specific antiviral treatment or no response to treatment for another underlying cause.

$$\text{Prevalence of CMVI} = \frac{patientswithCMVinfectionpre-transplant}{\text{patients in the study population}}$$

$$\text{Period prevalence of CMVD} = \frac{patientswithCMVDatanytime \text{ during the post} - \text{transplant period}}{patientsinthestudypopulation}$$

Inclusion criteria

Records of KTR who were more than 18 years of age, consented to the same (for patients who were alive) and had sufficient records defined as KTR who were reviewed monthly or more often in the first 6 months and at least 3 months intervals thereafter with a minimum follow up of 6 months (for those who were alive) with information pre and post-transplant required for the study.

Exclusion criteria

We excluded insufficient records for the information required for the study.

Sample size was calculated using the formula below.

$$n_0 = \frac{Z^2 * p(1-p)}{e^2}$$ For defined populations (i.e. 10,000 and above), sample size for proportions is estimated as:

[Cochran (1963)]

Where

n_0 is the sample size for population >10,000,

Z^2 is the abscissa of the normal curve that cuts off an area α at the tails (1 - α equals the desired confidence level, e.g., 95%),

e is the desired level of precision,

p is the estimated proportion of an attribute that is present in the population which is obtained from previous similar study, (It is the prevalence of CMV infection kidney transplant recipients).

The study desired a 95% confidence level and ±5% precision. The study assumed p=0.5 since there is no similar study conducted in regions similar to our settings.

Substituting the above parameters, the sample size becomes:

$$n_0 = \frac{1.96^2 * 0.5(1-0.5)}{0.05^2} = 385$$

Since the target population is a defined population (cohort) less than 10,000 (i.e. target population =100 patients per year) then the sample size was adjusted downward.

The sample size (n_0) was adjusted using:

$$n_1 = \frac{n_o}{1 + \frac{(n_o - 1)}{N}}$$

[Cochran (1963)]

Where

n_1 is the adjusted sample size

N is the target population size.

Therefore the adjusted sample size becomes:

$$n_1 = \frac{385}{1 + \frac{(385 - 1)}{100}} = 80$$

Since the study allowed for 10% loss of information, the sample size was adjusted upward by 8 participants (i.e. 10% of 80).

The final sample size became

$$n = 80 + 8 = 88$$

We reviewed the files of all KTR on follow up in KNH renal unit as the KTR are a defined population with a small populace.

Sampling method

The sampling frame included records of patients attending transplant clinic at KNH renal unit who met the inclusion criteria (exhaustive sampling).

Study feasibility

According to the medical records a total number of 200 KTR are on follow up in KNH Renal unit Transplant clinic. Five files were reviewed five times in a week hence the desired sample size was achieved in eight weeks.

Screening and recruitment

All KTR were assessed for interest in study participation. An informed consent was taken (Appendix 1). Socio-demographic information and other study variables were obtained from the the file and filled in the study questionnaire and collecting data form shown in Appendix 2. CMV IgG of both Donor and Recipient was retrieved from their respective files and also filled in Appendix 2.

The principle investigator with the help of a research assistant retrieved and reviewed all files of KTR and their donors. Files which met the inclusion criteria were selected and analyzed.

Study variables

Dependent variables

Latent infection defined as evidence of CMV IgG positivity pre-transplant without CMV clinical manifestations or organ dysfunction at any time post-transplant categorized as present or absent.

CMV disease

- ***CMV syndrome*** categorized as present or absent
- ***End-organ disease*** categorized as present or absent
- ***Probable end organ disease*** categorized as present or absent

Independent variables

Socio-demographic variables:

- Age represented in years as stated in the records and categorized in 10 yrs bracket

- Gender categorized as male or female as stated in the records
- Location defined as the patient's residence over 6 months during the pre-transplant period as urban or rural as recorded in the file
- Employment status categorized as employed or not employed
- The level of education as recorded in the file categorized as none, primary, secondary or tertiary

Medical history

- Primary cause of ESRD as documented in file categorized as hypertension, diabetes, chronic glomerulonephritis, autoimmune disease or others.
- Length on dialysis before transplant categorized in years
- Duration post-transplant categorized in years as <1, 1-2, 2-3, 3-4, 4-5, >5yrs
- CMV IgG serology pre-transplant for both donor and recipient was paired and categorized as D+/R+, D-/R-, D+/R-, D-/R+
- HLA match classified from zero to six at matches of locus B, DR, DQ

Immunopharmacologic agents

- Drugs used categorized as a combination of either tacrolimus, mycofenolic acid and prednisone or cyclosporine levels, mycofenolic acid and prednisone or azathioprine, mycofenolic acid and prednisone
- Specific immunosuppressant used in each individual KTR classified as prednisone, tacrolimus, myfenolic acid, cyclosporine, azathioprine or thymoglobulin
- Records of induction with monoclonal antibodies categorized as present or absent
- Records of pulsing with methyl prednisone categorized as present or absent

Graft outcomes

- Graft dysfunction or rejection as stated in the file as present or absent

Ethical consideration

Ethical approval was obtained from the Kenyatta National Hospital-University of Nairobi Ethics and Research Committee before the study was undertaken. A written informed consent was obtained from the participants.

Risk to subjects

There was a potential risk of loss of confidentiality which was addressed (see Confidentiality of data below). The risk was explained clearly in the written consent.

Protection against risk

All participants were free to refuse to take part in the study. This did not compromise on their medical care. Study results were disseminated to the healthcare provider to aid in patients' management. The participants did not receive any compensation.

Confidentiality of data

Information regarding the study subjects was kept confidential. Patient's data was entered in a sheet of paper containing patient's name, record number and study number. A second sheet contained patients study number as well as variables for the study. These were stored confidentially in a locked filing cabinet with access being given only to the investigator. Contact information for the supervisors was made available. Participants were free to withdraw from the study at their own free will with no effect on their medical care.

Benefits to the subjects

The benefits outweighed the risk as the potential information gained sought to enlighten on an area scarcely investigated and possibly guide policy and improve outcome among transplant

patients. Participants benefited from education on post-transplant complications and CMV infection from the research team.

Benefits of the study

This research evaluated CMV sero-prevalence and disease burden among transplant patients hence allowing for deliberations on the benefits and costs of anti-viral chemoprophylaxis among post-transplant patients in Kenyatta National Hospital. The benefits therefore outweigh the risk to the participants and community.

Data management

Data collection entry and storage

After obtaining ethical approval and permission from the KNH-UON Ethics and Research committee, data was obtained from patient records at KNH renal unit. Data was abstracted from the patients file using a coded questionnaire by the research assistants. Patient's identifiers e.g. names and file number were left out for the sake of confidentiality. Data was extracted for the time period April 2016 to June 2016. Only the investigator and the research assistanthad access to the files for the purposes of this study. All the study proforma were reviewed by the principle investigator to ensure they were completed appropriately. Data collected was entered into an Excel spreadsheet in a password protected computer. Back-up copies were stored in an external hard drive and compact disc which was in sole custody of the principal investigator. The filled questionnaires were in the safe custody of the principal investigator who filed and stored them in a locked cabinet for verification during analysis. Further cleaning was carried out after entry using frequency distributions and cross-tabulations until no more errors were detected. The final step in the preparation for analysis was coding of the data and the creation of any composite variables from the cleaned data set.

Data analysis

In order to achieve the objectives of the study, data analysis which was done using Statistical Package for Social Sciences Programme (SPSS) version 17.0, was carried out using the univariate analysis which involved descriptive statistics (means, medians, standard deviations) for continuous variables. Categorical variables (e.g. causes of CMVD) were presented using bar charts and frequency distribution tables. Statistical significance will be set at p less or equal to 0.05.

Study administration

The PI retrieved all the data from the records department. All recorded data was verified by the PI who also ensured that all relevant forms were completed. The supervisors offered guidance to the PI. The statistician offered guidance during proposal development, data entry, data analysis, and presentation of the final statistical analysis.

Timeline

Data collection took place during the month of April through June 2016.

Results

Patient's characteristics at renal transplant

All renal transplants on follow up in Kenyatta National Hospital (KNH) Renal unit were included for retrospective analysis. 200 files were retrieved, 195 had sufficient records.

Figure 1 Flow chart illustrating patient recruitment and data collection process

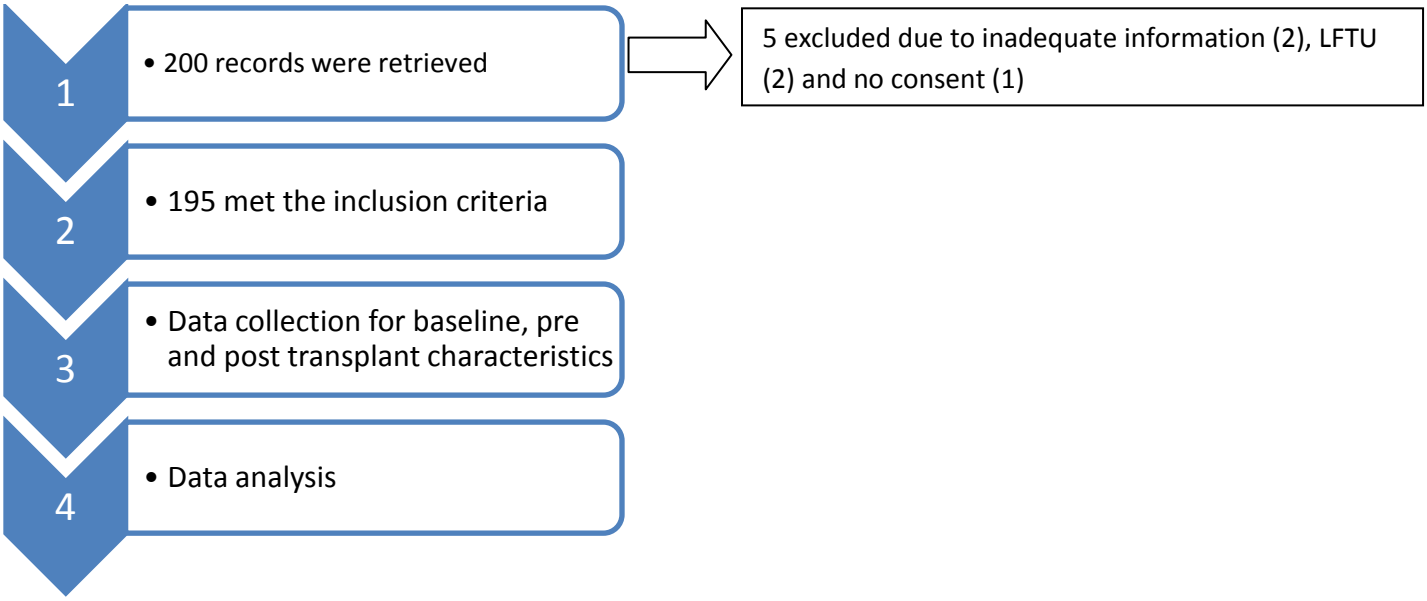

Figure 1 is a flow chart demonstrating the recruitment, data collection and analysis process. 200 records were retrieved and 195 met the inclusion criteria. Data was then collected and analyzed among the 195 KTR that met the inclusion criteria.

Table 2 Baseline characteristics of KTR before and after transplant

Baseline characteristics of KTR	n(%)
Age	
<20	9 (4.62%)
20-29	7(3.59%)
30-39	38(19.49%)
40-49	49(25.13%)
50-59	39(20%)
>60	53(27.18%)
Sex	
M:F	3:1
Males	145(74.38%)
Females	50(25.64%)
Residence	
Urban	118(60.59%)
Rural	77(39.5%)
Employment status	
Employed	131(64%)
Unemployed	64(32.82%)
Level of education	
Primary	25(12.82%)
Secondary	84(43.08%)
Tertiary	86(44.10%)
Location of kidney transplant	
KNH	140(71.8%)
Outside KNH	55(28.2%)

Table 2 represents the baseline characteristics of KTR on follow up in KNH renal unit. KTR were likely literate males 145(74.39%) of more than 40 years of age (72%) residing in an urban setting 118 (60.59%) with secondary and tertiary level of education 170(87%). 140 of KTR (71.8%) underwent transplant in KNH and 55 KTR (28.2%) underwent transplant outside KNH.

Table 3 Duration on dialysis before transplant

Duration on dialysis in years	n(%)
Median = 2yrs	
1	95(48.7%)
2	66(33.85%)
3	14(7.18%)
4	8(4.1%)
=>5	12(6.15%)

Table 3 represents the duration on dialysis before transplant period in years. The median period on dialysis was 1.8 years, mean 2 years.

Table 4 Post-transplant follow up period

Post-transplant follow up period in years	
<1	10(5.13%)
1-2	16(8.21%)
2-3	32(16.41%)
3-4	22(11.28%)
4-5	18(9.23%)
>5	61(31.28%)
N/A (Died)	33(15.9%)
Missing	2(2.56%)

Table 4 illustrates the post-transplant follow up time period. The post-transplant follow up period was likely to be less than 5 years in this cohort (60.5%). The median post-transplant period was 3 years (mean 3.2, SD 1.95, IQR 2-5).

Figure 2 Causes of ESRD among Kidney Transplant Recipients in KNH

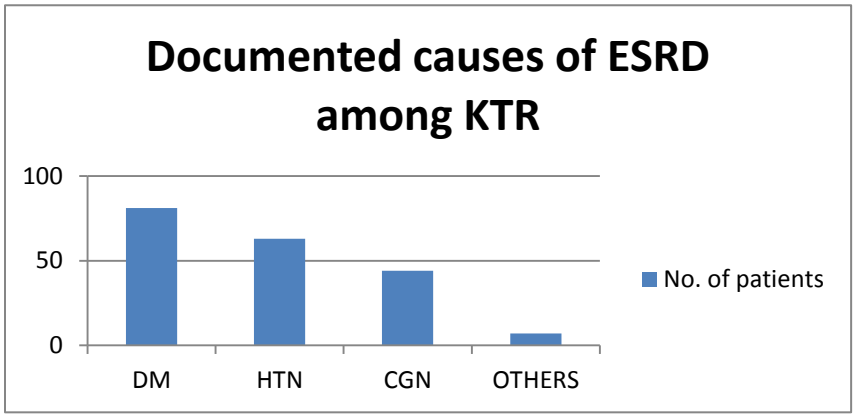

Figure 2 depicts the documented causes of ESRD among KTR. The common causes of ESRD were DM 81(42%), HTN 63(32%) and CGN 44(23%). However an overlap of results is expected among the CGN and HTN group of patients since patients with CGN commonly present in ESRD when renal biopsies are not done to confirm diagnosis and may be falsely categorized as having primary hypertension.

Immunosuppressive regimen

Table 5 Different combinations of immunosuppressive regimens used among KTR in KNH renal unit

Combination of immunosuppressive regimens	n(%)
Prednisone + Mycophenolate + Cyclosporine	114(61.03%)
Prednosine + Mycophenolate + Thymoglobulin	59(30.25%)
Prednosine + Azathioprine + Cyclosporine	11(5.61%)
Prednosine + Azathioprine + Mycophenolate	2(1.02%)
Thymoglobulin+Azathioprine+ Mycophenolate	1(0.5%)
Prednosine+Azathioprine + Mycophenolate+ Thymoglobulin	1(0.5%)
Prednosine + Azathioprine + Thymoglobulin	2(1.05%)
Thymoglobulin+Mycophenolate+Cyclosporine	2(1.05%)
Prednosine +Mycophenolate+Cyclosporine+Thymoglobulin	3(1.54%)

Table 5 represents different immunosuppressive regimens used among KTR in KNH. Patients were likely to be on prednisone, mycophenolate mofetil and cyclosporine combination 114(61.03%).

T lymphocyte reactivity and HLA typing was documented in 153(78.5%). For HLA B, DR, and DQ the number of patients with more than 3 out of 6 matches were 136(86%). 17(12%) had <3 matches.

Majority of KTR of two-haplotype matched living related donor kidneys received triple immunosuppressive therapy 191 (97.9%). A small proportion 4 (2.1%) received quadruple immunosuppressive regimen with inter-operative induction of polyclonal anti-thymocyte globulin, lymphocyte depleting agent or anti-lymphocyte globulins.

Table 6 Different immunosuppressants and the number of KTR on each immunosuppressant

Immunosuppressants	n(%)
Prednisone	193
Mycophenolatemofetil	176
Cyclosporine	126
Tacrolimus	61
Azathioprine	17
Thymoglobulin	4

Table 6 represents the different immunosuppressants and the number of KTR on each of them. Prednisone was used in 193 KTR with stable graft function. This was gradually titrated downwards for 6 months. Mycophenolate mofetil was used in a majority of KTR 176(90%). Substitutions and deletions were made to special group of patients with contraindications and adjustments based on clinical status, presence of infections or rejections.

The median graft survival was 3 years (mean 3.1, SD 1.989, IQR 1.2-5 yrs). Acute graft rejection was treated with intravenous corticosteroids this occurred in 47(24%). There were two re-transplants secondary to graft rejection 1(0.5) and recurrence of the primary disease (FSGS) 1(0.5%).

CMVI, CMVD and its outcomes

Table 7 CMV sero-prevalence pre-transplant among donors and recipients

CMV serology pre-transplant	
Latent infection (CMV IgG positive) Donor Recipient	 179(91.8%) 191(97.9%)
Active infection (CMV IgM positive) Donor Recipient	 0 0

Table 7 depicts the CMV serology pre-transplant of both donors and recipients. Majority of donors 179 (91.8%) and recipients 191(97.5%) were sero-positive for CMV IgG. None of the donors and recipients had active disease at the time of transplant.

Table 8 CMV Donor (D)/ Recipient (R) serologic matching pre-transplant

CMV D/R match	n(%)
D+/R+	180(92%)
D-/R+	11(6%)
D-/R-	4(2%)
D+/R-	0

Table 8 shows the various Donor (D)/ Recipient (R) serologic pair pre-transplant. KTR on follow up in KNH predominantly had a sero-concordant positive match D+/R+; 180 (92%). None of the CMV negative recipients received grafts from a CMV sero-positive donor.

Table 9 Prevalence of CMVD among KTR visiting the KNH transplant clinic renal unit

CMVD post-transplant	n(%)
Confirmed CMVD	4(2.05%)
Probable CMVD	12(6.15%)
Confirmed and probable CMVD	16(8.2%)

Table 9 indicates the number of patients with confirmed and probable CMVD. The period prevalence of CMVD (confirmed and probable) was 8.20%. That of probable disease being 6.15% while of confirmed disease 2.051%. The median post-transplant period of CMVD presentation was 3 months. The overall incidence of CMVD was not associated with HLA-matching. All had a HLA match of >3/6.

Table 10 Clinical manifestation of CMVD among KTR

Clinical manifestations	Confirmed CMVD	Probable CMVD	Confirmed+ probable
CMV syndrome	4	2	6
CMV colitis	0	7	7
CMV hepatitis	0	2	2
CMV encephalitis	0	1	1

Table 10 depicts the clinical manifestations of CMVD among patients with confirmed and probable disease. All patients with confirmed disease were diagnosed with CMV syndrome. Those with probable disease had CMV colitis 7 (58.3%) followed by CMV syndrome in 6 (50%). Two (16.7%) had CMV hepatitis and one (8.3%) CMV encephalitis.

Table 11 Outcomes among KTR diagnosed with CMVD

Outcomes	Confirmed CMVD	Probable CMVD	Confirmed + probable
Death	3	1	4
Graft rejection	1	1	2
Chronic graft dysfunction	0	5	5
Functioning graft	0	5	5

Table 11 looks at CMVD outcomes among KTR visiting the KNH transplant clinic renal unit. Majority of patients with confirmed CMVD died 3 and the remaining one developed graft rejection and is back on dialysis. Among patients with probable CMVD; 5(41.67%) have

functioning grafts, 5 (41.67%) developed chronic graft dysfunction, one (8.3%) developed graft rejection and is on dialysis and one (8.3%) died of CMV complications. Adverse outcomes were therefore observed in 100% of patients with confirmed CMVD and 58.3% with probable CMVD

Table 12 CMVD prevalence among the different CMV serologic D/R pairs

	Frequency (%)
CMV D/R	
D-/R-	1 (6.2)
D+/R+	15 (93.8)
D-/R+	0
D+/R-	0

Table 12 shows CMVD prevalence among the various CMV serologic Donor (D)/ Recipient (R) pairs. Among patients with CMVD, the CMV serology of D/R was predominantly a concordant pair. Majority of patients were concordant positive i.e. D+/R+ 15 (87.5%) and a minority were concordant negative i.e. D-/R- 1(12.5%). None of the KTR with CMVD was a discordant pair.

Discussion

The demographic distribution depicts a young (mean 45yrs) literate African population predominantly males living in an urban setting with good socio-economic background. Kidney Transplant Recipients (KTR) in Kenyatta National Hospital (KNH) undergo a selection criterion in which most patients over 60 years of age are generally excluded. Hence this population is significantly younger than in the developed world (>60 yrs) where the incidence of disease appears to be higher with older age being a risk factor. In this cohort, diabetics are particularly represented 81(42%) since this is a considerable primary cause of End stage renal disease (ESRD). CMVD has been observed to be higher in diabetics; conversely CMVD can cause New Onset Diabetes After Transplant (NODAT). Other risk factors of CMVD include immune-suppressive drugs like lymphocyte depleting agents, anti-lymphocyte globulins, antithymocyte globulins, high dose corticosteroids and mycophenolate mofetil. Majority of KTR were exposed to high dose corticosteroids and mycophenolate mofetil. Tacrolimus on the other hand, has been reported to have a lower risk of infection; its use in this cohort was only 61(31%).

Despite the very high CMV sero-prevalence among the transplant population (donor 91.8% and recipients 97.5%) reflecting the very high positive concordance amid the D/R pairs majority of KTR did not progress to CMVD post-transplant (8.2%) probably due to a pre-existing cell mediated immunity among R+ controlling viral replication. Majority of the patients confirmed to have CMVD presented with CMV syndrome hence a high index of suspicion among KTR ought to be anticipated in patients with fever, myelosuppression and features to suggest infection in the early post-transplant period. Despite the low incidence of CMVD, patients diagnosed with the

same suffered significant adverse events; 100% of those confirmed to have CMVD and 58.3% of those with probable disease died, lost their graft or developed chronic graft dysfunction.

Table 1 is a summary of various studies looking at CMVI and CMVD among KTR. CMV sero-prevalence with CMVD outcomes among KTR has been studied mostly in the developed world. Although the KNH cohort was a selected population that cannot be generalized to all KTR in KNH renal clinic we observed that CMVsero-prevalence among KTR in the developed world is relatively lower (13-70%) than among KTR attending KNH renal unit (94%). CMVD progression in developed world ranged from 3.9%-17.8% [9, 19, and 21]. The clinical manifestations of CMVD among KTR were relatively like the KNH cohort, CMV PCR being the predominant diagnostic tool in all these settings. CMVD caused significant reduction in graft and patient survival as well as causing considerable graft dysfunction.

A retrospective study carried out in the Kingdom of Saudi Arabia among 639 KTR having a relatively similar CMV sero-prevalence to that among KTR attending KNH renal unit revealed a lower prevalence of CMVD (3.6%) compared to KTR in KNH renal unit (8.2%). In this population however all concordant positives (D+/R+) receive anti-viral chemoprophylaxis for CMV [41]. The prevalence of CMVD among KTR attending KNH renal unit was observed to be significantly lower (8.2%) than that in a retrospective study in South Africa (32%) despite the relatively similar CMV sero-prevalence in both populations. In this setting however, due to higher risks of rejection with the use of cadaveric and nonrelated donors, potent immunosuppressants are used at the expense of opportunistic infections [18]. The lowest incidence of CMVD among KTR was observed in Greece a prospective study recruiting 392 KTR. This can be explained by the very low CMV sero-prevalence (12.8%) in the population [20].

Patients who developed CMVD were predominantly a sero-concordant pair i.e. D+/R+ this was similar to the South Africa and Saudi Arabia studies which both had a high CMV sero-prevalence [18, 40].This is postulated by some to be through co-infection and super infection by different CMV genotypes. D+/R+ groups have been associated with worse patient survival, graft survival and significant graft dysfunction; this is evident in the KNH KTR cohort where adverse outcomes were seen in the D+/R+ pair. This has been hypothesized to be due to the multiple viral strains and double CMV exposure with differing reactivation [25, 26]. Other studies have revealed D+/R- as the highest risk for CMVD however none of the R- patients received graft from a CMV sero-positive donor in the KNH KTR cohort. In settings with high CMV sero-prevalence, majority of the population consists of a sero-concordant pair (D+/R+; 92%) and hence an underrepresentation of other D/R pairs.

The clinical manifestations of CMVD observed in KNH renal unit included disease with tissue invasion (GIT, CNS and hepatic disease) and without tissue invasion (CMV syndrome). Due to its high sensitivity, CMV PCR has been used across the board for diagnosis of CMVD among KTR and SOTR [31, 32, 33]. CMV syndrome was the commonest presentation in this cohort. Similar patterns were observed in other studies where >60% of SOTR and KTR presented with the same and most recommending a high index of suspicion for CMV syndrome in patients presenting with fever, myalgia, arthralgia, and myelosuppression in the early post-transplant period [4, 18, 9, 19, 20, 21, 40]. Invasive disease occurs in <40%. Any organ can be involved, the transplanted organ is mostly at risk and GIT is the commonest system involved among all SOTR [4]. Similarly in this cohort CMV colitis was the commonest invasive CMVD. CMVD causes graft dysfunction conversely graft dysfunction can cause reactivation of CMVD. Most studies like the KNH KTR cohort have highlighted challenges in diagnosing invasive CMVD

due to lack of tissues for histology. With no histologic diagnosis it is difficult to know if CMVD or graft dysfunction preceded the other. Reliance on CMV PCR which is less costly and invasive equally carries a high sensitivity for invasive disease has been used in most studies [18, 19, 41]. CMVD caused significant mortality and morbidity. CMVD contributed to patient survival, graft survival and graft dysfunction. Similar results were seen in the South African study, Kingdom of Saudi Arabia among others. [9, 18, 19, 40]

While many experts previously felt universal prophylaxis and preemptive therapy were both acceptable in preventing CMVD among SOTR, newer data is providing more evidence in favor of universal prophylaxis [11, 12, 13]. CMV prophylaxis significantly reduces all-cause mortality, CMVD related mortality and CMVD. Preemptive therapy on the other hand has shown a significant reduction in CMVD but not CMV related mortality. Other limitations of pre-emptive therapy include high costs, failure of SOTR to comply with pre-emptive virologic monitoring and the safety of chemoprophylaxis. Its potential benefit however is the limited exposure to anti-viral therapy. The current KDIGO guidelines recommend prophylaxis for all KTR. CMVD in D+/R+ bears the majority group of KTR in KNH Renal Unit. CMVD caused adverse outcomes in the KNH cohort with significant reduction in patient survival, graft survival and caused graft dysfunction. Preventive therapy is therefore recommended. In a resource limited setting like KNH transplant clinic renal unit where costs benefit analysis is paramount and preemptive therapy entails virologic monitoring with frequent visits and very high costs for the regular investigations, the safety and benefits of chemoprophylaxis, this study supports CMV prophylaxis for all KTR.

Conclusion

There is a very high CMV sero-prevalence among KTR in KNH (97.5%) however majority of KTR did not progress to CMVD (8.2%) possibly due to a pre-existing cell mediated immunity controlling viral replication. A majority of the patients with CMVD were D+/R+ (93.5%) probably through co-infection and super infection by different CMV genotypes. CMVD caused significant adverse events among KTR. CMVD affected patient and graft survival and contributed to graft related complications. The impact of CMVD on patient's outcome is considerable. CMV prophylaxis for all KTR is as a result recommended. CMVD presented at a median time period of 3 months post-transplant with non-specific symptoms like fever, hepatitis, colitis, myelosuppression among others. A high index of suspicion at the early pre-transplant period is therefore required to make CMVD diagnosis. The results however cannot be generalized to all KTR attending KNH renal unit since this was a selected population.

Study limitations

Due to its retrospective nature, the study faced challenges that included over reliance on past record users for adequate record keeping, diagnosis of CMVD and confounding factors were also anticipated limitations. Our experience highlighted challenges of making definite diagnosis of end organ CMVD among clinicians for frequent lack of biological tissues and due to its retrospective design CMVD was not actively sought for.

Recommendations

KTR are at risk of CMVD, its complications and adverse outcomes. They should therefore be considered for interventional measures such as prophylaxis. Local adaptation and implementation of KDIGO guidelines on CMV prophylaxis is therefore recommended.

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Appendix

Consent (English)

CONSENT TO BE PART OF A RESEARCH STUDY ON CYTOMEGALOVIRUS POST-TRANSPLANT

IMPORTANT INFORMATION

This is a research study on cytomegalovirus in post-transplant patients carried out by me, Dr Deborah Barasa in part fulfillment of the requirements for the award of Masters of Medicine in Internal Medicine of the University of Nairobi.

As a prospective participant, this form is proposed to give you adequate information regarding the research study. It will explain the reasons, risks and benefits of this research. Read through the information and feel free to ask and discuss with your researcher and others.

If you opt to take part in the study, you will be requested to sign the form upon understanding the purpose, risks and benefits.

STUDY TITLE: Prevalence of cytomegalovirus in post-transplant patients visiting the Kenyatta National Hospital.

RESEARCHER:

Dr. Deborah Barasa, SHO, University of Nairobi

SUPERVIRORS

DR. A.J.O. Were

Department of Clinical Medicine and therapeutics, Consultant Nephrologist, Nairobi University

Prof. Kayima

Department of Clinical Medicine and Therapeutics, Consultant Nephrologist Nairobi University

Dr. M. Maritim

Department of clinical Medicine and Therapeutics, Consultant Infectious disease, Nairobi University

Prof. Joshi

Department of Clinical Medicine and Therapeutics Consultant Cardiologist and Epidemiologist, Nairobi University

What do you intend to study?

Cytomegalovirus (CMV) is a virus with a worldwide distribution. There is a high occurrence of CMV in the developing countries like Kenya. CMV is mainly transmitted by direct contact with infected secretions such as saliva, urine, stool, blood, breast milk and semen. It is a self-limiting condition in most people; however, in post-transplant patients there are risks of developing mild to severe forms of disease. We hope to determine the occurrence of CMV infection among post-renal transplant patients in Kenyatta National Hospital. We wish to achieve this by recruiting a large proportion of kidney transplant patients who agree to take part in the study with the hope of finding the level of occurrence and to later provide guidance in approach to this condition.

We request that you may take part in the study after which we will review your records looking at your health before and after transplantation. This will help enlighten us on the condition in the transplant patients.

Any vital information obtained from the study regarding your health will be discussed with you and consultation with the senior nephrologists will be made and prompt management will follow thereafter.

We hope that this study will lead to a better understanding of CMV among kidney transplant patients.

Who will participate in the study?

Taking part in the study is voluntary that is you may opt in or opt out at your own will. This will not affect your management and follow up in the transplant clinic.

Kidney transplant patients who are eligible for the study are the participants in mind.

We hope to recruit 80 participants to the study.

What goes on during the study?

Once eligible and upon voluntarily choosing to take part, we will review your medical records including any medical conditions and their outcomes before and after transplant. This will be inform of a proforma targeting your overall health, your CMV results before transplant and your current medications.

How long will I take part?

Only one visit is sufficient, taking approximately 15 minutes to obtain consent from you.

What risks do I face and how am I protected?

You may face a risk to breach of confidentiality. Your privacy is vital and we will use all measures to guard and keep everything confidential. The measures that have been set to avoid this include accessibility of your documents by the principal investigator only, files kept under locked cabinet and a password protected worksheet and samples labeled with a study number.

How will I benefit from the study?

There are no personal benefits or compensations.However detection, diagnosis and management under consultation with the senior nephrologist and SHOs will be made promptly if any

abnormality is detected in your records. The study will also add a lot of information regarding CMV in our transplant clinic.

Will I be charged?

You will not be charged.

Who can I contact for any questions or concerns?

For any questions and concerns contact the Principal Investigator Call 0723855 875

KNH-UoN ERC committee P. O. Box 19676 Code 00202Nairobi

Tel. (254-020) 2726300-9 Ext 44355 E-mail: uonknh_erc@uonbi.ac.ke

Will I be provided with any documents about the study?

Yes, you will receive copies of all documents upon consenting or on request.

SIGNATURES

I have read the information (the information has been read to me). Questions and concerns have been addressed or explained to my satisfaction by.....

I therefore consent to participate in this study. I have received a copy of the information. Contacts have been given for any concerns I may have.

Research…… Date …… Signature……

Witness……. Date …… Signature……

Principle investigator…….. Date…… Signature…….

Consent (Kiswahili)

IDHINI YA KUHUSIMISHWA KATIKA UTAFITI WA CYTOMEGALOVIRUS KWA WALIOPANDIKIZWA FIGO

RIPORTI MUHIMU

Utafitihuuambaounaangaliavirusivya Cytomegalovirus katikawagonjwawaliopandikizwafigoutaendelezwanampelelezimkuu Dr Deborah Barasakwakuhitimishamatarajioyakutuzwashahadaya Masters of Medicine in Internal Medicine ya Chuo Kikuu cha Nairobi.

Mshirikimtarajiwa, karatasihiiimetayarishwa kukupa habarizakutoshakuhusuutafiti, nia, hatari, madharanafaidazautafitihuukwamshiriki. Tunakushauriusomekinagaubaga, jiskiehurukuulizamaswaliyeyotenakuzungumuzanawataalamuamawenzako.

Utakapoamuakushiriki, utaulizwakupigasahihi.Kablayakupigasahihi, hakikishaumesomanakuelewakikamilifu.

STUDY TITLE: Kiwango cha uambukiziwavirusivya cytomegalovirus kwawaliopandikizwafigokatikahospitalikuuya Kenyatta.

MPLELELEZI MKUU:

Dr. Deborah Barasa, Chuo Kikuu cha Nairobi.

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Sababuyahiiutafitininini?

Virusivya cytomegalovirus (CMV) vimetapakaadunianzima.Virusihivivinapatikanasananchizakiafrikakama Kenya. Mtuhuambukizwanavirusihivikupitiamkojo, kinyezi, jasho,damunamaziwaya mama aliyeambukizwanavirusihivi.

Kingayamwilihuwezakupambananavirusilakinikwawagonjwawaliopandikizwaviuongokamafigo virusihivivinawezakusababishaugonjwaambaowakatimwingineunawezakuwahatarishanakuwadhurumaisha.

Tunatarajiakuamuakiwango cha uambukizikatikawagonjwawaliopandikizwafigo.Tutafanyautafitihuukwakiwangokikubwa cha wagonjwawanaofuatiliwakatikaklinikiyakupandikizwafigoambaowatakubalikushirikikatikamradi huuwautafitikwaniayakupatasuluhudhidiyaugonjwahuuwa CMV.

Tunakuulizakushiriki, iwapoutakubali, tutaangaliarecordizakozaklinikitukithibitishaafyayakokablanabaadayakupandikizwafigo,ustawiwakonamadawaambayounatumia.

Hakunafaidayakibinafsilakiniiwapokunakasoroyoyoteitapatikanakatikautafiti, tutamuarifudaktariwakonawataalamuwakuuwafigowatakaochukuahatuayakusuluhishatatizohili. Majibuhayopiayatasaidiakatikautafitihuunakwawagonjwakatikaklinikiyakupandikizwafigo. Utafitihuuutatufanyatuelewevizurikuhusuvirusivya CMV namadharayakekwawagonjwawaliopandikizwafigo.

Ni naniatakayeshirikikwautafitihuu?

Mshirikimwenyeweatajitoleakwautafitihuu. Haulazimishwikushiriki. Kutoshirikihakuletiadhabuyoyote, kukatizahudumayoyote au faidanyingineunayopata. Wagonjwawaliopandikizwafigondiowatakaoshirikikatikautafitihuu. Tunatarajiakuhusishawatuthemaniniwaliopandikizwafigokwajumla.

Ninihutokeakatikautafitihuu?

Kama utakubalikuhusishwakwahiariyako, mtafitiataangaliakwarecordizakohistoriayamatibabu, afyayakokablanabaadayakupandikizwafigo,ustawiwakonamadawaambayounatumia.

Utafitihuuutanichukuamdagani?

Ziaramojatuitatosha, hiiitachukuatakribanrobosaa.

Ni hatariganizinazotarajiwanikihusikanahatuaganizimechukuliwakunilinda?

Sirizakonimuhimukwetunatutatumianamnazotetuwezayokuhakikishayabakihivyo. Formuzakozitawekwakwakabatiiliyofungwananenosirikwaformuzakompyuta. Upatikanajiwaripotihiiukiwakwamtafitimkuupekeyake.

Nitafaidikajekwakujumuishwakwautafitihuu?

Hakunafaidayakibinafsilakiniiwapokunakasoroyoyoteitapatikanakatikautafiti, tutamuarifudaktariwakonawataalamuwakuuwafigowatakaochukuahatua.

Naniatanufaikakwautafitihuu?

Majibuyakoyatasaidiakatikautafitihuunakwawagonjwakatikakliniki cha kupandikizwafigo. Utafitihuuutatufanyatuelewevizurikuhusuvirusivya CMV namadharayakekwawagonjwawaliopandikizwafigo.

Je,nitalipishwanikiwamshirikiwautafiti? La, hautalipishwa.

Iwaponinamaswalininawezakuwasilianananani?

Kwamaswali au shakakuhusuutafiti, wasilianamplelelezimkuukatikanambari 0723855875

Au

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Je, nitapewahatiyoyote?

Ndio, sahihiyakoinamaanaumepatanakalaamaiwapoutaulizautapewa.

THIBITISHO

Nimesomamaelezonahabarikuhusuutafitihuu (au nimesomewa). Maswalinashakakuyahusuyameelezewanamtafitinanimeridhika.....

Nakirikwahiariyangukushirikikwautafitihuu.

Nimepewaformuyareportiyautafitinanambarizasimuiwaponatakakuwasilianawatafitikuhusuma swali au shakalolote.

MshirikiUtafiti……. Tarehe …… Sahihi……..

Aliyeshuhudia ……. Tarehe ……. Sahihi……...

Mplelezimkuu……. Tarehe……. Sahihi……

Study proforma

SOCIO-DEMOGRAPHICS						
AGE	<20	20-29	30-39	40-49	50-59	>60
SEX	MALE	FEMALE				
RESIDENCE	URBAN	RURAL				
EMPLOYMENT STATUS	EMPLOYED	NOT EMPLOYED				
LEVELOF EDUCATION	1^{o}	2^{o}	3^{o}			
MEDICAL HISTORY						
1^{o} CAUSE ESRD	HTN	DM	CGN	AUTOIMMUNE	OTHERS	
COMORBIDS	HTN	DM	CGN	AUTOIMMUNE	OTHERS	
DURN POST-TP	0-3	3-6	6-12	12-24	24-60	
CMV IgG	D+/R+	D+/R-	D-/R+	D-/R-		
HLA MISMATCH	**0**	**1**	**2**	**3**	**4**	**5**	**6**
IMMUNO-PHARMACOLOGICAL AGENTS						
REGIMEN	TAC/MF/PRED	AZA/MF/PRED	CYA/MF/PRED			
DOSE	TAC↑	TAC↓↔	MF↑	MF↓↔	PRED↑	PRED↓↔	AZA↑	AZA↓↔	CYA↑	CYA↓ ↔
DURN ISS	0-3	3-6	6-12	12-24	24-60	>60				
DURN	0-3	3-6	6-12	12-24	24-60	>60				
GRAFT OUTCOME						
EGFR	1T	2T	3T	4T	5T					
HEMOGRAM						
WBC	LOW	NORMAL	HIGH			
HB	LOW	NORMAL	HIGH			
PLTS	LOW	NORMAL	HIGH			
VIROLOGY						
CMV PCR VL	LOW	HIGH				
PP65	LOW	HIGH				
CMV IgM	LOW	HIGH				

Infections	YES	NO
1. Diagnosed with infection		
2. Treated for other infection with improvement		
3. Treated for other infection without improvement		
4. Treated for infection without improvement and CMV investigated		

5. Diagnosed with CMVI							
6. Medication for CMVI given							
7. CMVI outcome is patient alive?							
Time onset	0-3	3-6	3-12	12-24	24-60	>60	
Location	Sepsis	RTI	GUT	CNS	GIT	CVS	AFI

Elevated creatinines	YES	NO
1. Diagnosed with elevated creatinines		
2. Treated for other cause with improvement		
3. Treated for other cause without improvement		
4. Treated for other cause without improvement then CMV investigated		
5. Diagnosed with CMVI		

6. Medication for CMVI						
7. CMVI outcome is patient alive?						
Time onset	0-3	3-6	3-12	12-24	24-60	>60

Surgical complication	YES	NO
1. Diagnosed with surgical complication		
2. Treated for other cause with improvement		
3. Treated for other cause without improvement		
4. Treated for other cause without improvement then CMV investigated		
5. Diagnosed with CMVI		
6. Medications for CMVI given		

7. CMVI outcome is patient alive?						
Time onset	0-3	3-6	3-12	12-24	24-60	>60

Cardiovascular complication				YES	NO	
1. Diagnosed with cardiovascular complication						
2. Treated for other cause without improvement						
3. Treated for other cause without improvement then CMV investigated						
4. Diagnosed with CMVI						
5. Medications for CMVI given						
6. CMVI outcome is patient alive?						
Time onset	0-3	3-6	3-12	12-24	24-60	>60

Neurological complication				YES	NO	
1. Diagnosed with neurological complication (encephalitis, neurological deficit or behavioral abnormality)						
2. Treated for other cause with improvement						
3. Treated for other cause without improvement						
4. Treated for other cause without improvement then CMV investigated						
5. Diagnosed with CMVI						
6. Medications for CMVI given?						
7. CMVI outcome is patient alive?						
Time onset	0-3	3-6	3-12	12-24	24-60	>60

Endocrine metabolic complication				YES	NO	
1. Diagnosed with endocrine metabolic complication						
2. Treated for other cause with improvement						
3. Treated for other cause without improvement						
4. Treated for other cause without improvement then CMV investigated						
5. Diagnosed with CMVI						
6. Medications for CMVI						
7. CMVI outcome is patient alive?						
Time onset	0-3	3-6	3-12	12-24	24-60	>60

Gastrointestinal complication				YES	NO	
1. Diagnosed with GIT complication(esophagitis, gastritis or diarrhea)						
2. Treated for other cause with improvement						
3. Treated for other cause without improvement						
4. Treated for other cause without improvement then CMV investigated						
5. Diagnosed with CMVI						
6. Medications for CMVI given						
7. CMVI outcome is patient alive?						
Time onset	0-3	3-6	3-12	12-24	24-60	>60

Liver complication				YES	NO	
1. Diagnosed with transaminitis						
2. Treated for other cause with improvement						
3. Treated for other cause without improvement						
4. Treated for other cause without improvement then CMV investigated						
5. Diagnosed with CMVI						
6. Medications for CMVI given						
7. CMVI outcome is patient alive?						
Time onset	0-3	3-6	3-12	12-24	24-60	>60
Respiratory complication				YES	NO	
1. Diagnosed with respiratory complication						

2. Treated for other cause with improvement						
3. Treated for other cause without improvement						
4. Treated for other cause without improvement then CMV investigated						
5. Diagnosed with CMVI						
6. Medications for CMVI given						
7. CMVI outcome is patient alive?						
Time onset	0-3	3-6	3-12	12-24	24-60	>60

Visual complication				YES	NO	
1. Diagnosed with visual disturbance						
2. Treated for other cause with improvement						
3. Treated for other cause without improvement						
4. Treated for other cause without improvement then CMV investigated						
5. Diagnosed with CMVI						
6. Medications for CMVI given						
7. CMVI outcome is patient alive?						
Time onset	0-3	3-6	3-12	12-24	24-60	>60

Hematologic abnormality	YES	NO
1. Diagnosed with hematologic complication		
2. Treated for other cause with improvement		
3. Treated for other cause without improvement		
4. Treated for other cause without improvement then CMV investigated		
5. Diagnosed with CMVI		
6. Medications for CMVI given		
7. CMVI outcome is patient alive?		

↑wbc		↓wbc	↑hb	↓hb	↑plts	↓plts
Time D x	0-3	3-6	3-12	12-24	24-60	>60

										YES		NO
Lab test for CMV done												
Are lab results positive?												
If yes were prednisone dosage high at the time (>1mg/kg/day)												
If yes were trough levels for AZA or Tacrolimus high at the time												
Frequency of test done >1												
Outcome after diagnosis is patient alive												
Antiviral given standard medications (valgancyclovir)												
Duration of antivirals <3 months												
Lab tests	Serology	Qualitative PCR	Quantitative PCR	Histology	Virologic isolation	Clinical symptoms						
Time Dx	0-3	3-6	3-12	12-24	24-60	>60						

Mortality	YES	NO
1. Did the patient die		
2. Cause for mortality was CMV		
3. Rx for other cause without improvement then CMV investigated		
4. Diagnosed with CMVI		
5. Medications for CMVI were given		

0-3	3-6	3-12	12-24	24-60	>60