

**DROP-OUT OF CHILDREN WITH END STAGE KIDNEY FAILURE FROM CHRONIC PERITONEAL DIALYSIS AND ASSOCIATED FACTORS; A TEN YEAR REVIEW AT RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL (RCWMCH), CAPE TOWN, SOUTH AFRICA.**

BY

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AJXJUD001

SUBMITTED TO THE UNIVERSITY OF CAPE TOWN

In partial fulfillment of the requirements for the degree

MPHIL PAEDIATRIC NEPHROLOGY

**Faculty of Health Sciences  
UNIVERSITY OF CAPE TOWN**

**Date of submission:** 2<sup>nd</sup> December 2021

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## **DEDICATION**

I dedicate this work to my lovely young family in Uganda, whose patience and support enabled me to take up this course and do this work. I also dedicate it to my supervisors.

## **ACKNOWLEDGEMENT**

This work has been made possible through the support of the ISN Salmasi family fellowship and the APFP for sponsoring my fellowship training.

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**Reference style: Vancouver**

## **List of acronyms**

AKI- Acute Kidney Injury

APD – Automated Peritoneal Dialysis

CAPD- Continuous Ambulatory Peritoneal Dialysis

CPD- Chronic Peritoneal Dialysis

CKD- Chronic Kidney Disease

ESKD- End Stage Kidney Disease

ESKF- End stage Kidney failure

GFR- Glomerular Filtration Rate

HD – Hemodialysis

Kt/V- Peritoneal clearance of urea

PD- Peritoneal Dialysis

PET- Peritoneal Equilibration Test

RRT- Renal Replacement Therapy

## **Operational definitions**

Acute PD- PD performed for AKI

AKI- Deterioration in renal function with presence of electrolyte disturbances and increase in urea and creatinine for not more than three months.

CKD- Functional or structural impairment in the kidneys for more than 3 months.

Chronic PD- PD performed for ESKD/ESKF.

Drop-out from PD- Termination of PD due to PD technique failure from any cause.

In this study defined as death on PD or permanent transfer to HD.

ESKD – CKD stage 5 (GFR <15), with requirement of Renal replacement therapy

PD adequacy- Achieved weekly Kt/v of 1.7, a measure of the adequacy of PD.

PD technique failure- permanent switch to HD, failure to perform PD, or death from PD related cause.

PD technique survival- a measure of number of patients still on PD over the years of follow up.

Patient survival- a measure of number of patients still alive while on PD over the years of follow up.

PD interruptions- Temporary switches to HD due to infectious and or mechanical (catheter related complications). Patient receives a temporary HD line and returns to PD when the complication is addressed.

Catheter manipulations- Unblocking a blocked catheter from theatre, such as following blockage by fibrin, omentum or adhesions.

RRT –Treatment instituted when a patient has kidney failure, it may be dialysis or kidney transplantation.

## **Abstract**

**Introduction:** Dialysis is a temporary renal replacement therapy (RRT) to keep the child healthy and alive when in end stage kidney failure (ESKF) while being worked up for kidney transplant, the preferred treatment.

Chronic peritoneal dialysis (PD) is the preferred first choice of dialysis modality in many centers because of its advantages over hemodialysis (HD). In recent years, there have been advances to improve the performance and survival of PD as a modality for renal replacement. Despite these improvements, complications still arise, sometimes warranting a switch to HD. We sought to investigate the extent to which children at Red Cross War Memorial Children's Hospital (RCWMCH) drop-out from chronic PD and describe some of the reasons for this drop-out.

**Objectives:** To describe the rate of drop-out of children with ESKD from chronic PD, the timing and factors associated with this drop-out at RCWMCH.

**Methods:** This was a retrospective descriptive study, carried out in the renal ward, E2, of RCWMCH in Cape Town. Eligible participants were identified from the renal transplant waiting lists over the study period. Patient folders were retrieved following ethical approval, for extraction of relevant data.

**Outcome measures:** Proportion dropping-out during the study period (permanent switch to HD or death from PD related complications), factors associated with drop-out and time from initiation of chronic PD to drop-out.

**Utility of the study:** Findings from this study will help in designing strategies to improve chronic PD patient outcomes, prolongation of PD technique survival and reducing the costs of chronic dialysis at RCWMCH.

**Results:** A total of 111 children were listed for transplantation between January 2009 and December 2018, 67 were treated with PD. Complete data was available for 52 of the 67 children who received PD. Overall, 17/52 (32.7%) dropped-out during the study period. Most (>50%) of them dropped-out within the first 1-2 years of being on PD. The only significant associated factor was one or more episodes of peritonitis.

**Recommendation:** There is a need to step up measures to prevent peritonitis in chronic PD patients so as to prolong stay on PD until a kidney transplant is

available, as well as improve kidney transplantation rates.

**Dissemination of results:** Results were presented at the Department of Pediatrics and Child Health Research Day 2019 and at the world congress of nephrology international conference 2021. Results will be submitted for publication in a peer reviewed journal.

## CHAPTER ONE

### 1.1 Purpose of the study.

This study was conducted to determine the drop-out from PD in children with ESKF at RCWMCH. The magnitude and timing of this drop-out was assessed to see how common it was and when it occurred. The study also sought to describe some of the associated factors for PD termination, so as to design strategies to prolong use of PD technique, as it has some advantages over HD, especially in paediatrics.

Primary objective: To describe the rate of drop-out of children with ESKF from chronic PD.

Secondary objectives: To describe the factors associated with drop-out from chronic PD, and the timing of this drop-out.

### 1.2 Introduction/background

Dialysis is a temporary renal replacement therapy (RRT) to keep children healthy and alive when in ESKF while workup for kidney transplant, the preferred treatment is being performed. Children with end stage kidney failure awaiting kidney transplantation may receive hemodialysis (HD) or peritoneal dialysis (PD). Kidney transplantation offers better quality of life and patient survival over dialysis, even better when performed preemptively(1).

Chronic PD is the preferred dialysis modality in children because of its advantages over hemodialysis. It can be automated with use of a cyclor machine (APD), or performed manually such as Continuous Ambulatory PD (CAPD). PD carries the convenience of dialysis being performed at home as opposed to repeated hospital visits required for HD, avoids problems associated with vascular access in HD, preserves residual renal function, enables ongoing routine activities like work and school and is associated with lower healthcare costs(2-4).

Despite improvements in the technique of PD, especially in the area of infection prevention and management such as use of the double bag system, Y connection, flush before fill approach, patient training programs and online monitoring systems for automated PD, PD still fails in some patients, who may switch to HD before transplantation for various reasons(5, 6). Ideally children should remain on PD until transplantation. Three and five year PD technique survival rates in children from

developed countries range from 63 to 86% and 75 to 85% respectively, little data exists in developing countries (1, 7). Survival of the PD technique is lower than that of HD from some chronic PD registries, but patient survival among those who switch to HD and those who remain on PD is not different (8, 9). PD technique failure rates in children requiring switch to HD range from 6 to 17% in developed countries (1, 10) and up to 28% in developing countries (11-16).

### **1.3 Literature review**

#### **1.3.1 Drop-out from chronic PD and associated factors**

Causes of PD technique failure leading to PD termination include membrane failure from glucose degradation products, peritonitis episodes and peritoneal adhesions, poor compliance to the PD prescription, prolonged duration of PD leading to burn out and catheter complications like infections, leaks, blockage and migration. Older age adults and younger age in children have also been described as predictive factors for PD failure, with peritonitis reported as the main cause of PD technique failure (3, 6, 9, 11, 12, 17, 18). Recurrent peritonitis can damage the peritoneal membrane leading to ultra-filtration failure (2, 19). There is a need to reduce the risk of PD failure due to peritonitis in order to prolong duration of PD treatment modality.

Richard E Neiberger, in a retrospective study among 172 children in the US found that 6% of children developed membrane failure, mostly due to peritonitis leading to sclerosis and required transfer to hemodialysis. He did not find longer duration of PD a significant cause of PD failure. Poor compliance to PD causing switch was at 2%(18). In a study involving adults in the US, Bernard G et al demonstrated that peritonitis and catheter related infections were the commonest cause of switching to HD, followed by fluid overload. In this prospective study, 25% of PD patients switched to HD (9).

In developing countries such as Turkey, Jordan and Brazil, studies on children on chronic PD have looked at peritonitis rates and outcomes. Frehat et al (15) in a retrospective 10 year study period 2009 to 2019 on forty children, reported that 6(15%) permanently switched to HD, 11 (27%) died and four (10%) were transplanted. Forty eight percent of them were still on PD at the end of the study period. Peritonitis was reported as the most common complication leading to PD failure. Other complications were exit site infections and catheter malfunction, which

was at 12.5%. Similarly, in a report from the BRAZPD 11 registry of 75 dialysis centers in Brazil by Danielle et al (20) from 2004 to 2011 involving children less than 18 years of age, PD technique failure rate was 12.1% out of 491 on PD, with peritonitis as the commonest cause. Specifically, Pseudomonas species and culture negative PD fluid cultures were predictive of technique failure. Both studies did not report the time from initiation of PD to failure.

In South Africa, studies looking at drop-out from PD have been done in adults, and on those using CAPD. Kapembwa et al in a study on PD technique survival at Tygerberg hospital among 170 adults from 2008 to 2014 found peritonitis as the commonest cause of technique failure, and older age of the patients(11). Another study by Ramon et al in Limpopo showed that 46.7% of the 152 patients died or developed technique failure requiring transfer to HD. This group had higher rates of peritonitis. It was the commonest cause of technique failure, requiring transfer to HD(12), especially more than one episode. Other factors that were found to be associated with poor outcome of PD were anemia, low Albumin and BMI. Factors like poor socioeconomic status, lack of electricity or running water at home were not found to be significant predictors of poor outcome(12).

Low serum Albumin has also been shown to be associated with an increased risk of chronic PD failure in children, from a study by Gulati et al in Canada(21).

Hypoalbuminaemia (<35mg/dl) at last date of follow up was present in 54/135 (40%) of children. Repeated (>2) episodes of peritonitis was still the commonest cause of technique failure requiring transfer to HD. He also showed that more than two episodes of peritonitis were predictive of low serum albumin. (21).

Catheter related complications cause drop-out from PD, but not at rates as high as those due to peritonitis(6, 22). Catheter complications include tunnel and exit site infections, and mechanical problems like blockage, displacement and tip migration.

Psychosocial factors in the patient or caretaker to a lesser extent contribute to PD drop-out, such as poor or inadequate pre PD education, and fatigue or burn out(2, 6, 9). For example, S.Mujais among US adults found that of the patients who transferred to HD, 15% of them had psychosocial problems(22). This can be prevented and improved by proper PD training, counseling and home visits(2, 6).

Young age, specifically less than 24 months of age at PD initiation, has been shown

to be a risk factor for poor outcome and mortality on PD in both HICs and LMICs (13, 23). Infants particularly have worse outcomes, with higher risk of mortality and low survival (8, 24, 25). However, a report on 628 infants initiating chronic PD from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS), which has been maintaining a pediatric renal registry since 1992, also showed that infants and neonates were surviving longer on PD in the second decade of their follow up, 2002- 2012, compared to 1992-1999, with more terminations of PD being for renal transplant, and fewer terminations due to death or transfer to hemodialysis (23, 24).

The outcomes of chronic PD in children at RCWMCH are not known. There is need to investigate the magnitude of drop-out of children from Chronic PD and the associated factors, in order to design strategies to improve PD technique survival, thereby prolonging stay on PD.

### **1.3.2 Timing of drop-out from chronic PD**

There is paucity of data on timing of drop-out from PD in children. Bernard G et al among US adults showed that more than 40% of patients switched to HD in the first year, and more than 70% in the second year. Most patients drop-out in the first one to two years because of infectious complications (6, 9). Nakysa et al (13) retrospectively studied 120 children aged zero to sixteen years of age at CAPD initiation, from the Iranian registry from 1993 to 2006. She reported about half of the patients (43.3%) died with 38.5% of this deaths occurring in the first three months of PD. Other outcomes were 8.3% renal transplants, 16.7% switch to HD and the rest were either still on PD, recovered or lost to follow up at the end of the study period. This indicates that most patients drop-out of PD early in the course of their treatment.

## **CHAPTER TWO**

### **2.1 Problem statement**

Chronic PD is still a cost effective approach for ESKF compared to HD and can be performed at home, allowing the child to live a relatively normal life. PD related infections especially peritonitis, continue to be a leading cause of PD failure among others, leading to permanent switch to HD, before kidney transplantation. Permanent switch to HD disrupts the normal home routine and environment of the child and family. RCWMCH renal unit also follows a PD first approach for ESKD children, but the rate/burden of drop-out from PD and potentially preventable contributing factors is not known. This is what the study sought to investigate.

### **2.2 Justification**

We need to perform this study to highlight the extent to which our children fail on PD leading to drop-out (switch to HD or death) before kidney transplantation, and to find out the common associated factors. Results from this study will help in designing strategies to improve chronic PD patient outcomes, thus prolonging stay on PD technique until kidney transplantation and reduce the costs of chronic dialysis at RCWMCH.

### **2.3 Research questions:**

1. What is the rate (burden) of drop-out of children with ESKD from chronic PD at RCWMCH?
2. What are the factors associated with drop-out from chronic PD?
3. When do the children drop-out of chronic PD.?

## CHAPTER THREE

### 3.0 Methods

#### 3.1 Study setting

The study was carried out at the renal unit of Red Cross War Memorial Children's hospital from 2018 to 2019. RCWMCH is a tertiary level referral hospital in Cape Town, South Africa and it receives children from birth to 18 years of age. It has general and super specialized pediatric renal services. It practices PD first policy and automated overnight chronic PD is offered to allow children to attend school during the day. The unit routinely starts PD with Dianeal (Baxter) 1.5% glucose solution for chronic PD and then use the 2.5% solution periodically if not ultra-filtering well enough. They avoid strong bags (4.25% glucose) in chronic patients as far as possible.

Senior fellows with training or experienced consultant surgeons with knowledge of inserting PD catheters insert these by laparoscopic technique, tunneled, with omentectomy and the catheter tip sutured to the bladder most often. Special protocols are also given to the surgeons on exit site direction and how to strap the catheter on the abdomen to minimize movement at the exit site. The unit mostly uses single cuff straight or pig tail PD catheters. Abdominal xrays are done to check catheter position in the pelvis, and the unit routinely waits 2 weeks prior to use of the catheter to ensure proper healing to avoid leakage.

PD patients are highly selected for those patients and families that are deemed to manage PD after comprehensive clinical and social worker assessment. Caretakers undergo thorough training on PD before discharge and have retraining after any PD related infection. The unit only offers chronic PD for children who are at least over one year of age, children below one year only receive PD for acute kidney injury (acute PD). Exit site care is done with topical Antibiotic cream, but no routine surveillance for nasal Staphylococcal carriage.

#### 3.2 Study design

This was a retrospective descriptive study, with a follow up component, involving review of records of patients who were on chronic PD over a 10 year study period. A

waiver of consent was obtained for data extraction.

### **3.3 Target population**

All children who were on, or started on chronic PD from January 2009 to December 2018. These were children with end stage kidney disease from any cause.

### **3.4 Study population**

All children who were on or started on chronic PD over the 10 year study period with available records. We expected about 50 to 80 children, at an average chronic PD initiation of 5 to 8 children per year.

The study sample involved all available folders of children on chronic PD during the study period. For data extraction, folders of children who were on chronic PD were identified from ward E2 renal transplant waiting lists, which are saved on the ward records. The waiting lists indicate which children are on dialysis and the dialysis modality. These names and folder numbers were copied down for the relevant 10 year study period. The folders were then retrieved with the help of the data clerk and records department. Some folders and or relevant volumes of folders could not be found.

### **3.5 Inclusion criteria**

All children with ESKD who were on chronic PD during the study period with available records were included.

### **3.6 Exclusion criteria**

Those with missing folders or missing volumes of folders with the relevant information.

### **3.7 Study procedure**

After obtaining ethical approval, the names and folder numbers of children on chronic PD during the study period were identified from ward E2 kidney transplant waiting lists. As mentioned earlier, the waiting lists also indicate which children are on dialysis and the dialysis modality.

Relevant information was extracted manually into a data collection sheet. The child record (folder) was followed until the point when one of the following five possible endpoints was reached; 1) kidney transplant; 2) transfer to adult services when deemed to be of appropriate age (18 years); 3) death while on PD; 4) permanent transfer/switch to HD (when a tunneled HD catheter was placed); 5) PD ongoing at

the end of the study period.

### **3.8 Study variables collected**

Sociodemographic characteristics: Date of birth, sex, location/address and distance from RCWMCH in kilometers, primary care taker, primary care taker's level of education and occupation.

Primary renal diagnosis or cause of end stage kidney disease (ESKD), history of AKI, previous PD for AKI, duration of ESKD diagnosis/follow up before PD initiation, GFR and Laboratory results (creatinine, phosphate, Albumin, Haemoglobin) at PD initiation, PET test results (Kt/V and membrane transporter type), Residual Renal Function (RRF) at PD initiation, date and technique of PD catheter insertion, date of PD initiation, age at initiation of PD, date of discontinuation of PD.

Weight, height, blood pressure and BMI at PD initiation and discontinuation, peritonitis episodes documented( by white cell count and PD fluid culture report), history of TB or fungal peritonitis, episodes of catheter malfunction documented and interventions( such as repositioning, change of transfer set or catheter replacement), symptoms at PD termination (oedema/fluid overload, hypertension, peritonitis), laboratory results at termination (Phosphate, Albumin, Haemoglobin), documentation of poor compliance with PD regimen, temporary switch to HD (referred to as PD interruptions in this study), permanent switch to HD or death while on PD, reasons for PD discontinuation/termination as stated in the folder and date of kidney transplant for those who received.

The drop-out cases were those who were permanently switched to HD, or those who died while on PD.

### **3.9 Data management**

The data was collected in a pre-coded pretested questionnaires. Only folder numbers and not patient names were used to identify the study records. The filled questionnaires were stored safely in a locked cupboard.

Data was entered into Microsoft Excel (version 12) and was crosschecked and cleaned before analysis. Data was then transferred to R-statistical software version 3.5.1 for analysis. The primary outcome was the proportion of children dropping-out, which was permanent switch to HD or death during the study period. Secondary

outcomes included time from initiation of PD to drop-out and associated factors.

Patient characteristics, duration of PD, and PD switch rate were analyzed using descriptive statistics with medians and interquartile ranges for continuous variables, frequencies and percentages for categorical variables. Factors associated with termination of PD were assessed using the chi-square test or Fischer's exact test where the numbers were small. A p value of < 0.05 with a 95% confidence interval was considered significant. Multivariate analysis was performed with a few variables due to few patient numbers, and few significant factors on bivariate analysis. Timing of drop-out was displayed using a Kaplan Meier curve.

### **3.10 Ethical considerations**

Approval was obtained from the Research committee of University of Cape Town (UCT) school of child and adolescent health on 5<sup>th</sup> December 2018, the UCT Faculty of Health sciences Human Research and Ethics Committee on 15<sup>th</sup> January 2019 (HREC Ref : 018/2019). Final approval to conduct the study was then obtained from the Red Cross Hospital manager on 31<sup>st</sup> January 2019 (RXH: RCC 170).

A waiver of consent to collect data from the patient folders was obtained.

### **3.11 Confidentiality**

Records were identified by numbers and not patient names. Paper based records were securely locked in a cupboard, only accessible to the research team. Computer based records were only accessible to the research team and the statistician.

### **Potential risks and discomforts**

No risks or adverse events were anticipated with this study, as it was a retrospective study with no physical contact with the patient. There was only a potential risk of loss of confidentiality.

### **3.12 Dissemination of results**

Results were presented at the Department of Pediatrics and Child Health Research Day 2019. Results were further presented at the world congress of nephrology 2021 international conference. A manuscript will be submitted for publication in a peer reviewed journal.

## CHAPTER FOUR

### 4.0 RESULTS

A total of 111 children were listed for transplantation between January 2009 and December 2018, 67 were treated with PD (of whom 18 had previously been treated with HD) and 11 were treated with HD alone. Thirty three (33) children were not yet on any dialysis modality and either received preemptive kidney transplantation or remained on the waiting list at the end of the study period. Complete data was available for 52 of the 67 children who received PD, who were then included in the study as shown in Figure 1. This represented 78% (52/67) available records.

The median age of all participants was 11 (interquartile range 6.0, 13.1) years. The minimum and maximum ages were 1.2 and 17.8 years respectively at PD initiation. The median duration of PD overall was 9 (range 1-60) months.

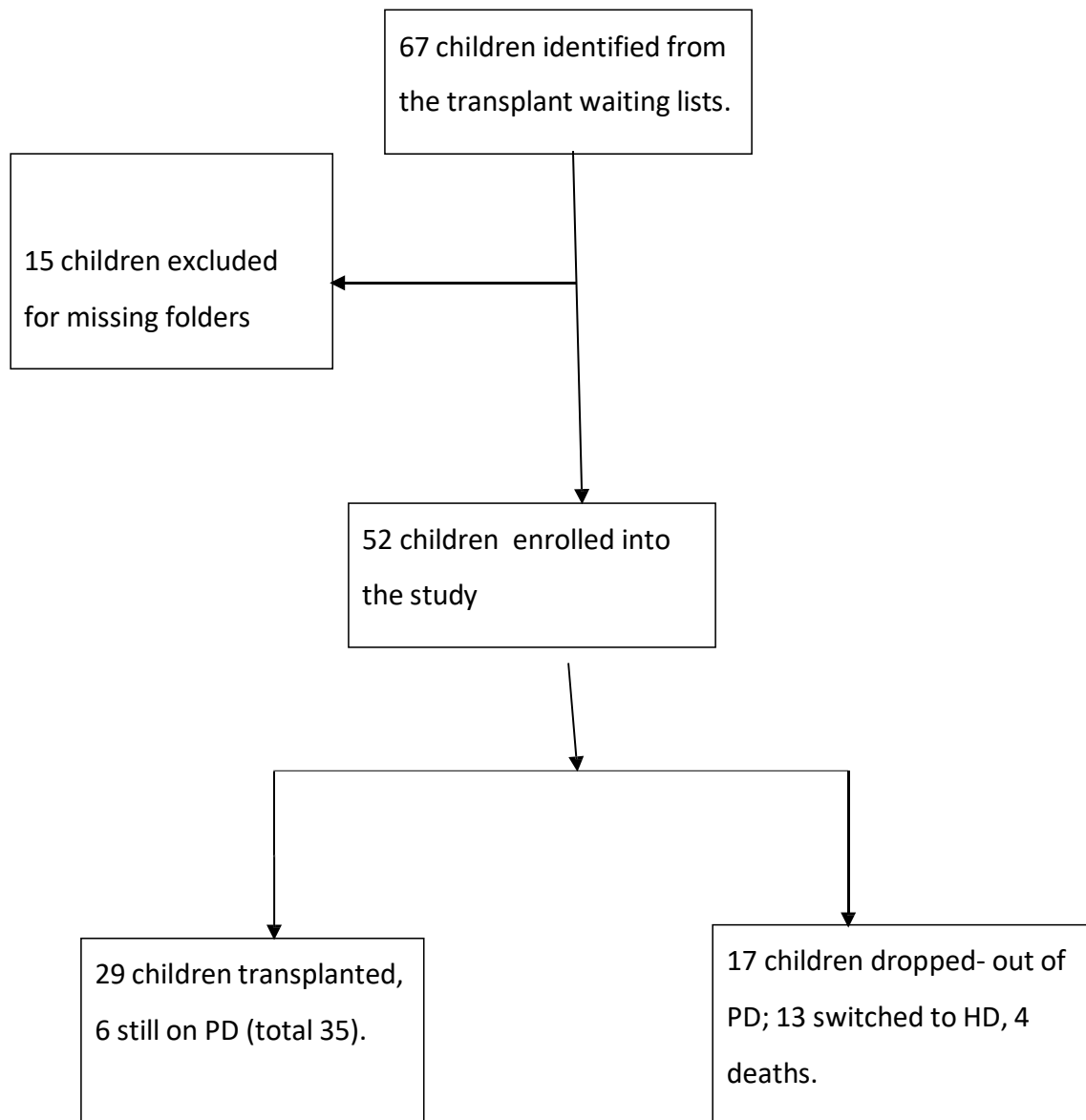
As shown in tables 1, there were 25 (48%) females and 27 (52%) males. More than half, 30 (58%) were above five years of age at PD initiation. Most children 47/52 (90%) were cared for by parents and lived <50km from the hospital. There was no significant difference between the drop-out and nondrop-out group in terms of age at PD initiation or primary care giver.

About 60% of the participants were on PD for less than one year. PD catheters were inserted laparoscopically in 80% of the children. Straight catheters were used in 91% of cases, coiled in 6% and unknown in 3%. Twenty seven (52%) of the 52 participants were low or low average transporters. More than half (74.5%) of the participants used only one catheter for the duration of their PD. This is shown in table 2.

The median duration of PD until transplantation among the non-drop-outs was 11 months (interquartile range 6, 24.5), compared with 4 months (interquartile range 2, 14) among those who dropped-out of PD ( $p=0.01$ ).

Seventeen children out of 52 (32.7%) dropped-out of PD while 35/52 (67.3%) either remained on PD until they got renal transplant or were still on PD.

**4.1 Study profile**  
**Figure 1: Study profile**



## 4.2 Baseline characteristics of study participants

**Table 1: Baseline characteristics of study participants**

	Still on PD/Kidney transplant N=35		PD drop-out N=17		Chi squared p-value
	n	%	n	%	
<b>Age at PD initiation</b>					
≤5yrs	6	17.1	6	35.3	0.14
>5yrs	29	82.9	11	64.7	
<b>Age at PD initiation</b>					
<2yrs	0	0	2	11.76	0.04
≥2yrs	35	100	15	88.24	
<b>Gender</b>					
Female	18	51.43	7	41.81	0.49
Male	17	48.57	10	58.82	
<b>Primary care-giver</b>					
Mum	17	48.57	7	41.18	0.86
Mum and Dad	15	42.86	8	47.06	
Other	3	8.57	2	11.72	
<b>Care giver occupation</b>					
known#	24	68.57	15	88.24	0.13
unknown	11	31.43	2	11.76	
<b>Distance from hospital</b>					
<50km	17	51.52	13	76.47	0.203
50-100km	2	6.06	1	5.88	
>100km	14	42.42	3	17.65	
<b>BMI Centiles</b>					
<5th	10	37.04	1	10	0.28
5-85th	15	55.56	8	80	
>85th	2	7.41	1	10	

Some missing information

**Table 2: PD baseline information of study participants**

	Still on PD/Kidney transplant		PD drop-out		Fischer's exact p-value
	N= 35		N=17		
	n	%	n	%	
<b>Duration on PD</b>					
<1yr	19	54.29	10	58.82	0.783
1-2yrs	7	20.00	2	11.76	
>2yrs	9	25.71	5	29.42	
<b>Number of catheters</b>					
1	24	68.57	14	87.50	0.15
>1	11	31.43	2	12.50	
<b>Technique of catheter insertion</b>					
Laparoscopic	31	91.18	11	64.71	0.01
Open Laparotomy	0	0	4	23.53	
Unknown	3	8.82	2	11.76	
<b>PD interruptions</b>					
Yes*	12	35.25	3	21.40	0.49
No	22	64.75	11	78.60	
<b>Catheter manipulation</b>					
yes^	10	28.60	2	12.50	0.59
No	25	71.40	14	87.50	
<b>Transporter type:</b>					
Low	9	28.12	1	10	0.193
Low average	12	37.50	5	50	
High average	10	31.25	2	20	
High	1	3.12	2	20	
<b>Residual urine output</b>					
<=100 mls	3	9.4	3	25	0.18
>100 mls	29	90.6	9	75	
<b>Total Kt/V^^</b>					
<1.7	1	3.57	2	28.57	0.04
≥1.7	27	96.43	5	71.43	

\* only 15/52 had PD

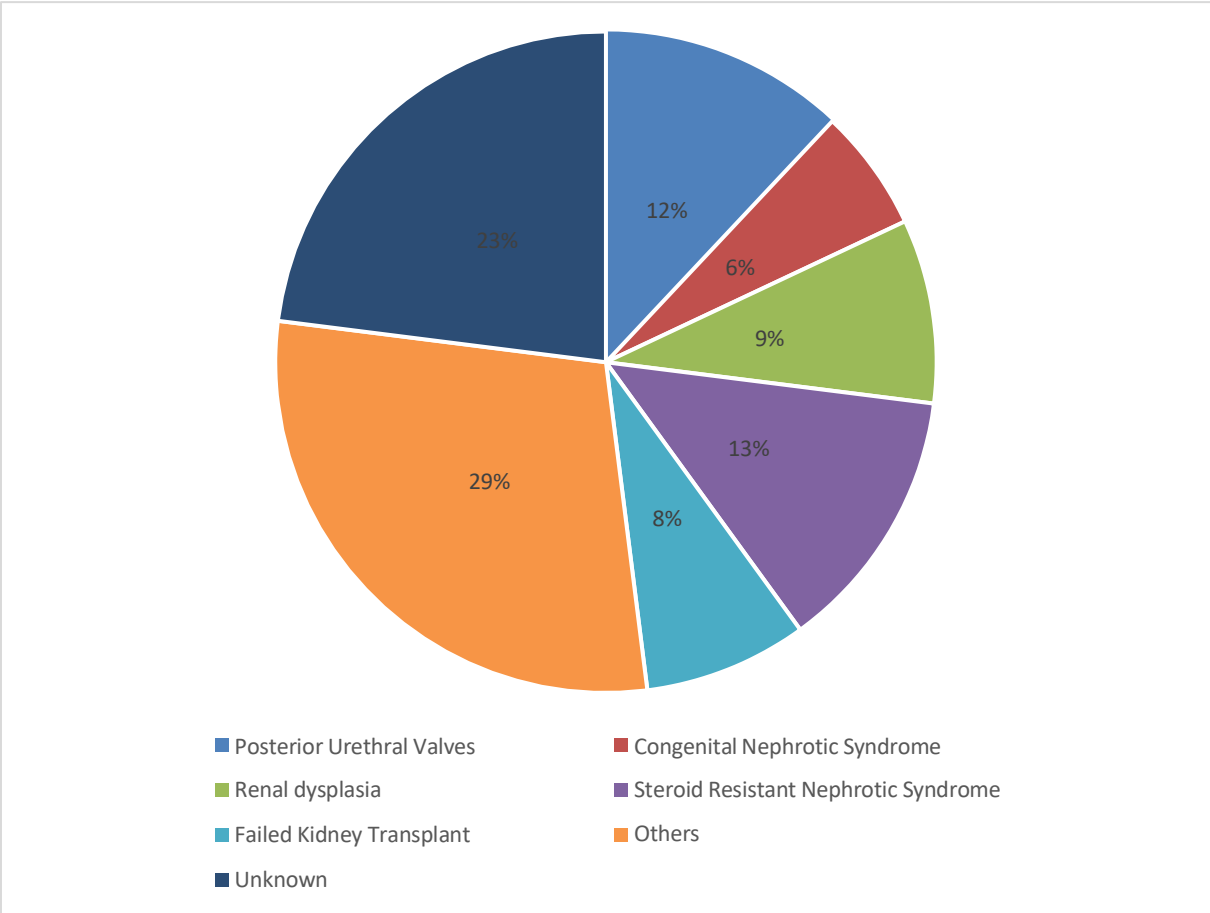
interruptions

^^ only 35/52 had results

About 28% of patients had PD interruptions in terms of temporary switches to HD due to some complications. Catheter manipulations which occurred in 25% of the patients were due to temporary blockages from fibrin, omentum or adhesions. Some patients had missing information on the variables.

### 4.3 Causes of End stage kidney disease (ESKD) among study participants

Figure 2: Causes of ESKD among participants

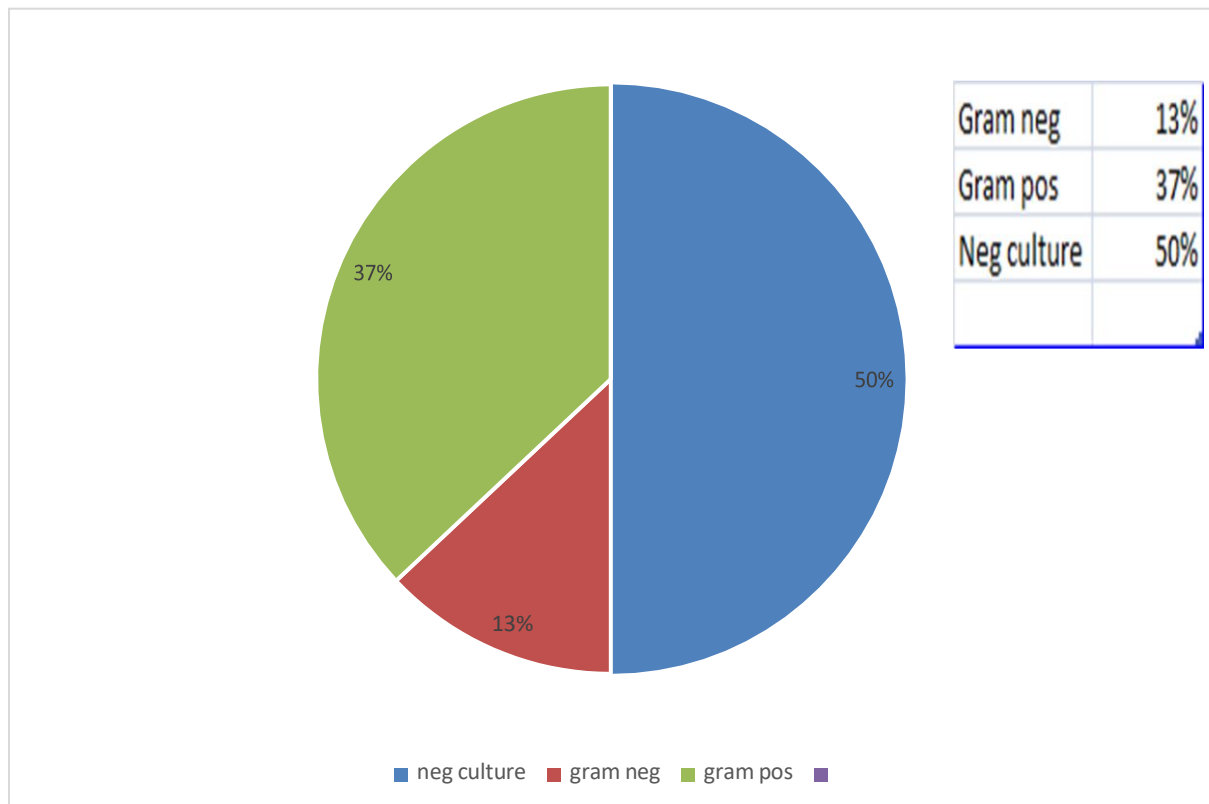


Thirteen percent of the participants had glomerular conditions that presented as steroid resistant nephrotic syndrome, followed by posterior urethral valves (PUVs) at 12%. Combining PUVs (12%) and renal dysplasia (9%), the commonest cause of ESKD was congenital anomalies of the kidneys and urinary tract at 21%. In about quota of the participants, the cause of ESKD was unknown.

Other causes of ESKD included conditions like cystic kidney diseases, nephronophthisis, hemolytic uremic syndrome (HUS), cystinosis, lupus nephritis, rapidly progressive glomerulonephritis and one renal TB.

#### 4.4 Peritoneal fluid culture results based on the first episode of peritonitis

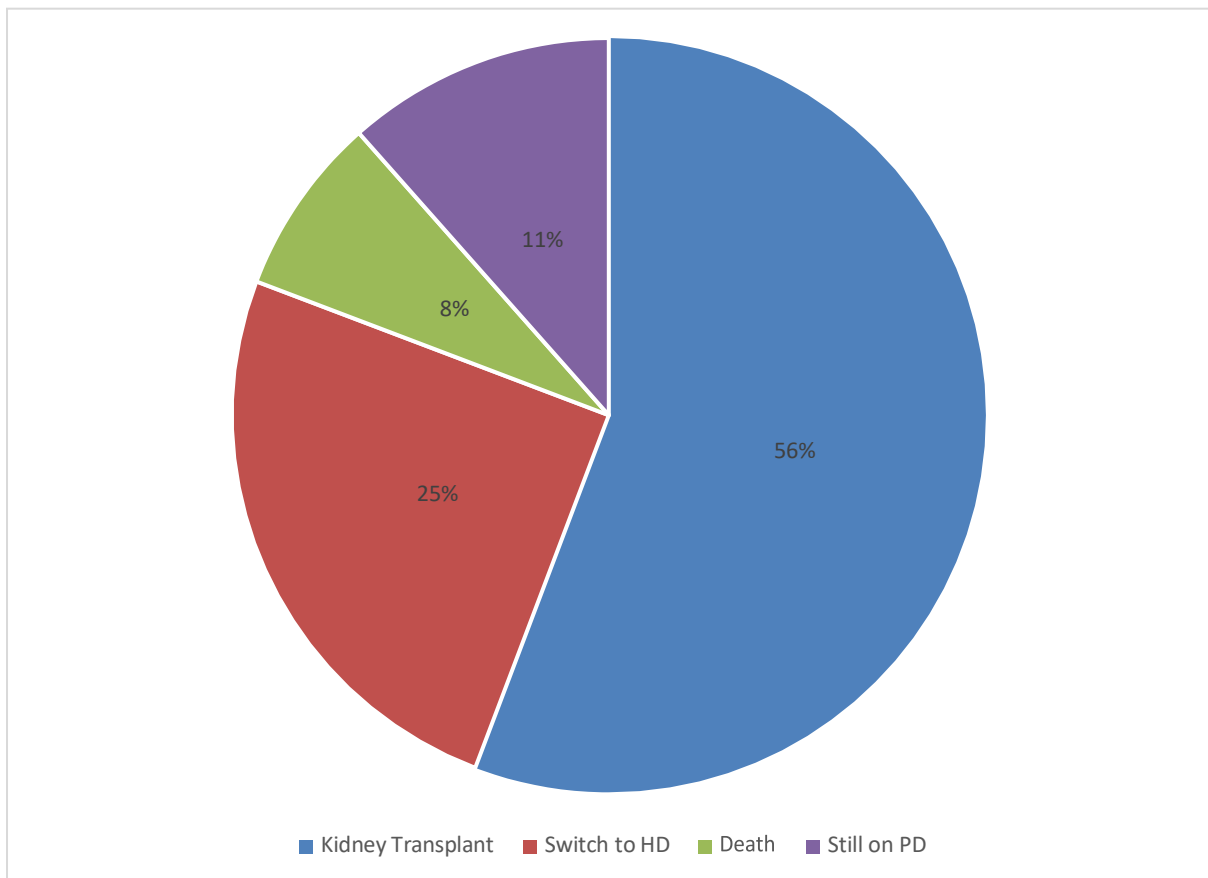
Figure 3: Organisms cultured on the first episode of peritonitis



Half of the participants had culture negative peritonitis, followed by gram positive organisms. Most of the gram positive organisms cultured were *Staphylococci aureus* and *epidermidis*; and the gram negatives were *Enterobacter*, *Klebsiella* and *Pseudomonas*.

#### 4.5 Peritoneal dialysis outcomes among the study participants

Figure 4: Peritoneal dialysis outcomes



The pie chart above shows the overall outcomes of children on PD. During the study period, 29(55.8%) of the children had a kidney transplant while 6 (11.5%) were still on PD at the end of the study period of which one was transitioned to adult services. Thirteen children (25%) permanently transferred to HD and four (7.7%) died while on PD, giving an overall drop-out rate of 32.7%.

#### 4.6 Description of the participants that dropped-out from PD

**Table 3: Description of the participants that dropped-out from PD**

Serial number	Age at PD initiation(months)	Duration of PD (Months)	Termination of PD	Reason for drop-out from PD
1	157	6	To HD	TB peritonitis plus low ultrafiltration
2	54	9	To HD	Tunnel infection
3	68	2	To HD	Fungal peritonitis
4	19	1	To HD	Gastro colic fistula from PEG
5	14	1	To HD	Peritonitis plus blocked catheter
6	141	1	To HD	Peritonitis
7	96	2	To HD	Peritonitis, blocked catheter and adhesions
8	101	4	To HD	TB peritonitis with peritoneal granulomas
9	144	2	To HD	Peritonitis plus leaking catheter
10	56	4	To HD	Peritonitis with obstructed necrotic bowel
11	110	26	To HD	Recurrent peritonitis plus low ultrafiltration
12	96	8	Death	Sepsis plus pleuroperitoneal shunt
13	12	12	Death	Peritonitis, poor compliance put on palliation
14	202	21	Death	Pancytopenia, multiple platelet transfusions
15	192	33	Death	Poor adherence, hypertension, palliation
16	40	48	To HD	Recurrent peritonitis
17	60	14	To HD	Peritonitis

HD=Hemodialysis, PD=Peritoneal dialysis

Table 3 shows and describes the reasons for drop-out from chronic PD as described in patient files. The duration of PD prior to drop-out ranged from 1 to 48 months. Three deaths were directly related to PD complications and one was a result of bone marrow suppression with recurrent bleeding requiring multiple transfusions. Switch to HD was mostly due to peritonitis complications, with one arising from a gastro-colic fistula from a gastrostomy feeding tube. Table 3 also shows that over half of the children dropped-out within the first 12 months of PD.

## 4.7 Factors for drop-out from chronic PD among the study participants

**Table 4: Factors associated with drop-out from PD**

Variables		Still on PD/Renal Transplant		PD drop-out		Fischer's exact p-value
		N=35	%	N=17	%	
<b>Sex</b>	F	18	51.4	7	41.2	0.48*
	M	17	48.6	10	58.8	
<b>Age at PD initiation</b>						
≤ 5 years		6	17.1	6	35.3	0.14
> 5 years		29	82.9	11	64.7	
<b>Bacterial peritonitis</b>						
None		19	54.3	3	17.6	<b>0.017</b>
≥ 1 episodes		16	45.7	14	82.4	
<b>Bacterial peritonitis</b>						
0-1 episode		22	62.9	8	47.1	0.28*
≥2 episodes		13	37.1	9	52.9	
<b>PD culture results</b>						
Negative (no growth)		10	62.5	5	35.7	0.27
Positive culture		6	37.5	9	64.3	
<b>PD catheter change</b>						
Yes		11	31.4	2	12.5	0.19
No		24	68.6	14	87.5	
<b>Acute dialysis before CPD</b>						
Yes		21	60	13	76.5	0.35
No		14	40	4	23.5	
<b>Transfer set change</b>						
Yes		16	45.7	4	25	0.22
No		19	54.3	12	75	
<b>Catheter manipulation</b>						
Yes		10	28.6	2	12.5	0.29
No		25	71.4	14	87.5	
<b>TB peritonitis</b>						
Yes		0	0	2	11.8	0.10
No		35	100	15	88.2	
<b>Fungal peritonitis</b>						
Yes		1	2.9	1	5.9	1
No		34	97.1	16	94.1	
<b>Tunnel infection</b>						
Yes		3	8.6	1	6.2	1
No		32	91.4	15	93.8	
<b>Exit site infection</b>						
Yes		3	8.6	1	6.2	1
No		32	91.4	15	93.8	
<b>Duration of PD</b>						
≤ 2years		26	74.3	12	70.6	1
>2 years		9	25.7	5	29.4	
<b>PD Interruptions</b>						
Yes		12	35.3	3	21.4	0.49
No		22	64.7	11	78.6	

CPD=Chronic PD, \*Chi-square p-value

Tables 4 outlines factors associated with drop-out from chronic PD. As shown, 22 (42.3%) participants did not have any peritonitis episode. One or more (>=1)

episodes of bacterial peritonitis was associated with drop-out from PD (14/30,  $p = 0.017$ ) however the numbers were small. The risk of drop-out was not different among those who had one episode versus two or more episodes of peritonitis. Age at PD initiation and gender were not significant factors for drop-out from PD in this study.

#### 4.8 Blood indices as risk factors for drop-out from PD

**Table 5: Serum Albumin and Haemoglobin as risk factors for drop-out from PD**

Variables	Still on PD/Renal Transplant N=35	PD drop-out N=17	OR	95% CI	p-value
<b>Albumin at baseline</b>					
≤ 25 g/dl	8	2	0.54	0.1, 2.95	0.70
>25g/dl	26	12			
<b>Albumin at month 6</b>					
≤25 g/dl	3	3	8.33	1.13, 61.5	0.05
>25 g/dl	25	3			
<b>Haemoglobin at baseline</b>					
≤10 g/dl	19	13	9.58	1.12-82.1	0.02
>10 g/dl	14	1			
<b>Haemoglobin at month 6</b>					
≤10 g/dl	8	2	1.12	0.17, 7.45	1
>10 g/dl	18	4			

For those with available data, Table 5 shows that children with low serum albumin ( $\leq 25$ g/dl) at 6 months tended to PD drop-out ( $p = 0.05$ ), although this was not statistically significant on multivariate analysis. There was a trend towards higher PD drop-out if baseline hemoglobin at initiation was  $\leq 10$ g/dl (13/32,  $p = 0.02$ ).

#### 4.9 Factors associated with drop-out from PD

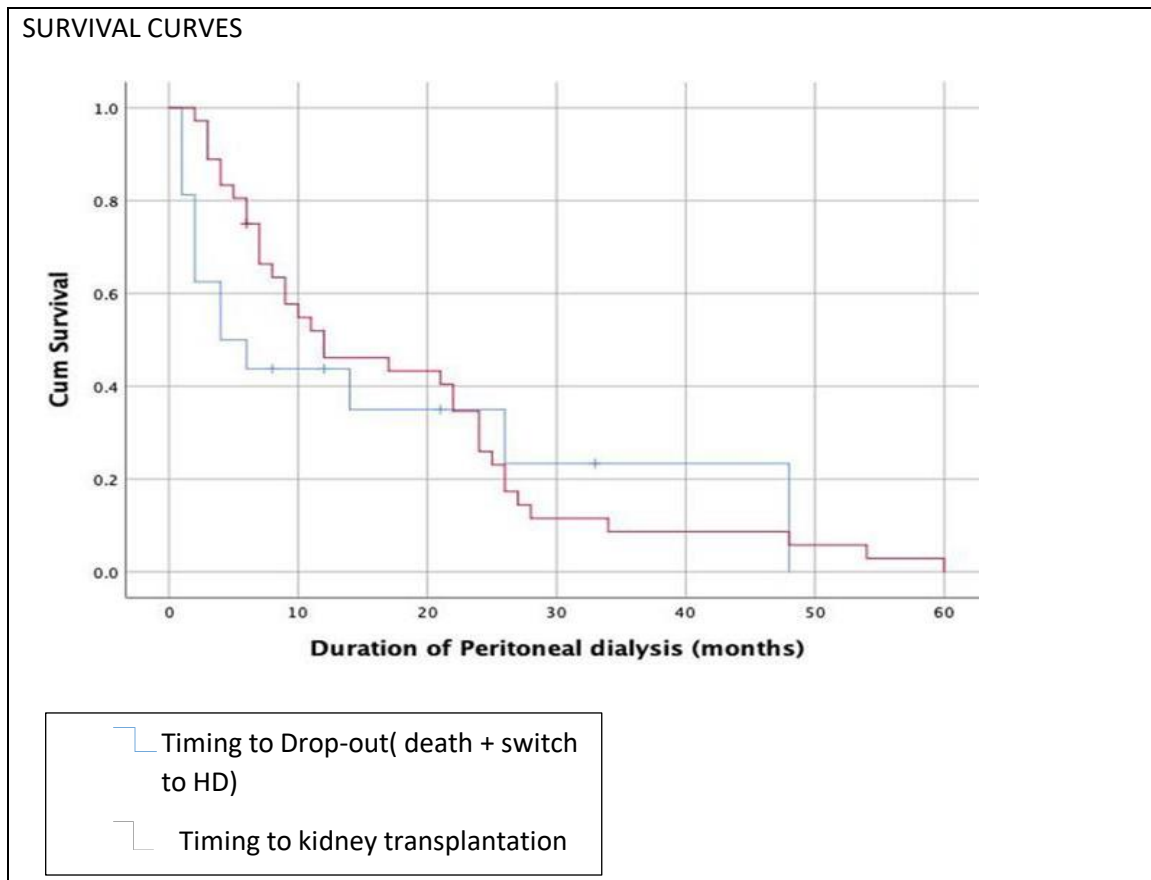
**Table 6: Factors associated with drop-out from PD**

	<b>Adjusted Odds Ratio</b>	<b>95% Confidence Interval</b>	<b>p-value</b>
<b>Age at PD initiation</b>			
≤5ys	1		
> 5 yrs	0.9863542	0.199-4.89	0.987
<b>Gender</b>			
Female	1		
Male	0.9152398	0.22-3.75	0.902
<b>Bacterial peritonitis episodes</b>			
None	1		
One or more	17.87847	2.08-153.69	0.009

On multivariate analysis, only one or more episodes of bacterial peritonitis was associated with drop out from PD, however the numbers were small hence the wide confidence interval, as shown in Table 6.

#### 4.10 Timing of drop-out from chronic PD

Figure 5: Timing of drop-out from chronic PD



Both curves depict the 52 children, with kidney transplantation as the outcome for the curve on time to kidney transplantation; and death or permanent switch to HD being the outcome for the curve of time to drop-out.

More than 50 % of the drop-outs occurred in the first 1-2 years, then the drop-out rate stabilizes. Looking at drop-outs, there was about 35% PD survival by 12 months and 25% by 24 months. Drop-out was either death on PD or permanent switch to HD. Children drop-out from PD in the first 1 to 2 years faster than the rate at which they receive kidney transplantation.

## CHAPTER FIVE

### 5.0 Discussion

In this study, we set out to investigate drop-out of children from chronic peritoneal dialysis (PD) before they receive a kidney transplant, assessing clinical factors associated with drop-out and the timing of drop-out. Over the ten year study period we identified 67 children on PD and enrolled 52 children with available records. Of the 52, 17 (32.7%) dropped-out which included 13(25%) permanently switching to HD and 4(7.6%) dying while on PD, while 35 (67.3%) either received a kidney transplant (29, 55.8%) or remained on PD (6, 11.5%) at the end of the study period.

The only factor significantly associated with drop-out from PD in this study was one or more episodes of peritonitis. Children with TB peritonitis, a lower level of hemoglobin at PD initiation, and a lower serum albumin at six months of PD also tended to drop-out more but the numbers were small.

### 5.1 Drop-out rates from PD

Drop-out from chronic PD with permanent switch to HD in South Africa has been investigated mostly in adults. Isla et al.(12) retrospectively studied 152 adults on CAPD in the northern province of South Africa between 2008 and 2012, of whom 71 (46.7%) terminated PD, with 32 (21.1%) deaths and 39 (25.7%) permanent transfers to HD over the 5 year study period. The number of PD terminations for transplantation was not mentioned. The commonest causes of transfer to HD were peritonitis (more than one episode), catheter malfunction and burnout. Other factors associated with the PD outcome of death or transfer to HD were low albumin, low hemoglobin and low BMI. Exclusive use of CAPD may have contributed to the higher drop-out rate observed among the adults in this study, compared with our cohort who were mainly on APD. Our findings are comparable with a study by Kapembwa et al (11) among 170 adults undergoing CAPD in the Western Cape from January 2008 to July 2014. PD technique failure (death from PD related complication, permanent switch to HD or withdrawal from PD) was reported in 53(31.2%) of patients, with peritonitis being the most frequent cause (72% of the cases), followed by adhesions. Overall, 20 patients died on PD, 45 transferred to HD, 2 withdrew due to inability perform PD, 39 were transplanted, and 55 remained on PD, while 9 either recovered

or transferred to other centers. This study was also done in Cape Town, where our hospital is also located.

Looking at other developing countries, our deaths and switch rates to HD were lower than those reported by Frehat et al (15) among children in Jordan, who reported deaths at 27.5%, switch to HD at 15% and a low transplant rate of 10%. The authors attributed these outcomes to longer stays on PD as they depend on only living related donors. Better outcomes in our study may reflect the use of both living related and cadaveric donors which reduced time to transplantation.

Nakysa et al(18) studied 120 Iranian children under 14 years on CAPD between 1993 and 2006. Overall there were 43.3% deaths, 16.7% switches to HD, 8.3% transplants and 23.3% remained on PD, with the rest being lost to follow up. Young age < 24 months was the most significant factor for poor outcome (death or switch to HD) of PD, which were more frequent compared to our findings. In contrast, age at initiation of PD was not significantly associated with outcome in our study, although we may have failed to detect an effect due to our smaller sample size, and few children initiating chronic PD before 24 months of age.

Among 55 Turkish children on both APD and CAPD who experienced peritonitis on PD by Osman et al (14) only 7 (12.7%) permanently transferred to HD in 7 years of follow up. This rate was low compared to our study despite the fact that their study included only patients with peritonitis. In contrast, among those with peritonitis in our study 46.6 % (14/30) dropped-out reflecting poorer outcomes. This could be because of their low overall peritonitis rate.

## **5.2 Factors associated with drop-out from chronic PD**

Factors associated with PD failure may be patient related, health facility related, or modality related. Interventions such as multidisciplinary team care, appropriate pre-dialysis training, ongoing training by dedicated PD nurses, home visits, psychosocial support, adequate nurse to patient ratio of 1:20, prevention of peritonitis and catheter related infections, and preservation of residual renal function, among others, have been shown to prolong use of PD (2, 6, 11, 26, 27). Osman et al (14) found that catheter type, mode of catheter insertion, and dialysis modality did not contribute to peritonitis risk. Frehat et al in Jordan found catheter related complication rate at 12.5%.

Similar to other studies (8, 11, 12, 16, 28) peritonitis was the commonest factor for drop-out in our study. Peritonitis episodes damage the peritoneal membrane and later lead to ultrafiltration failure. Additionally, over exposure of the peritoneal membrane to high concentration glucose solutions of 2.5% and 4.25% causes thickening and fibrosis of the peritoneum with eventual loss of ultrafiltration over time. This can be prevented by use of low glucose solutions and other biocompatible non glucose based solutions such as icodextrin (6, 26), although the use of such solutions is limited due their high cost and limited availability.

An earlier retrospective study among children on PD between 2000 and 2008 at our institution reported a peritonitis rate of 2.8 episodes per patient year (29). Low socioeconomic status and poor housing significantly contributed to peritonitis episodes. Temporary switch to hemodialysis was significantly higher in patients with a higher peritonitis rate. Both catheter related complications and peritonitis contributed to the need for a temporary switch to hemodialysis (29). From our study (table 5), of the 4 deaths, one was due to recurrent pancytopenia bleeds needing multiple platelet transfusions and one was due to poor adherence to PD leading to recurrent fluid overload and hypertension, thus put on palliation, so there was contribution to drop-out from other noninfectious or non-mechanical factors. One transfer to HD was due to a gastrocolic fistula from the PEG, 3 transfers to HD had peritonitis together with catheter related problems; 2 blocked and 1 leaking. So there was contribution of mechanical complications, but were not significant as stand-alone factors for drop-out.

In our study, we did not specifically assess for factors associated with peritonitis as the focus was on PD drop-out. The peritonitis rate in this study was 1.2 episodes per patient year, which shows an improvement over time from the 2.8. This rate is however still higher than the cutoff of 0.5 episodes per patient year that is recommended by the ISPD 2016 guidelines(27), and that found in developed countries like Australia and New Zealand at 0.71 (10), and other developing countries like Brazil at 0.43 (16) and Peru at 0.75(30).

Lee et al (31) found among 57 children in Korea significantly lower peritonitis episodes among children on APD, 0.06 episodes compared to 0.48 episodes per patient year on CAPD, but overall the rate was low at 0.43 episodes per patient year and low drop-out rate of 1.8%. Osman et al (14) among 55 children in contrast

did not find a significant difference in peritonitis rate between those on APD and CAPD over a seven year study period (14, 31). Despite our patients being managed on APD, our switch rates remained relatively high, therefore other factors must be explored to improve our peritonitis rates such as care taker education and adherence.

Children with anemia, low albumin and TB peritonitis tended to drop-out in our study. Gulati et al (21) reported that  $\geq$  two episodes of peritonitis was associated with a switch to HD, but was also predictive of low serum albumin, probably due to increased protein loss in the effluent, and systemic inflammation. These factors have also been reported by Isla Ramon et al (12, 32).

Children starting PD at a young age, especially infancy have been shown to have worse outcomes, with higher risk of mortality and low survival (23) as they tend to get more infectious and mechanical complications. This was not a significant factor for drop-out in our study when stratified at below or above five years of age at PD initiation. When stratified at two years, those below two years at initiation tended to drop out, although the numbers were very small (only two initiating PD below two years). In general, there has been improvement in PD outcomes in infants over the years due to better technology, experience, and increased transplantation rates (23).

### **5.3 Timing of drop-out from chronic PD**

Over 50% of our patients dropped-out from PD by 12 to 24 months, and 80% by 30 months. As in the Iranian cohort, almost half (38.5%) died in the first three months of PD(13). These findings are similar to those of Kolesnyk et al 2010(33) in Netherlands where the highest drop-out was in the first 3 months among adult patients, mostly due to catheter related complications, with transplants predominating with longer time of follow up. Also similar to the findings by Bernard G et al(9) where switch rates were highest in the first 1-2 years (40% in the first year and >70% in the first two years, although these are adult studies. Overall more patients were transplanted than switched to HD in our study.

### **5.4 Strengths and Limitations**

Our study has significant strengths and limitations. The retrospective nature of our study meant we had some missing records which reduced our sample size. How

those with missing data may have differed from those included in the study is not known. Similarly, the retrospective nature of the study did not allow one to identify the factors associated with peritonitis, which makes it difficult to predict which interventions will have meaningful impact in reducing peritonitis rates. Being a single center study, we had a small sample size. However the strength of the study is that it is the first pediatric study to look at drop-out from PD in Sub-Saharan Africa. In addition, RCWMCH is a tertiary center, the PD program is run by nephrologists and PD nurses, and the center uses overnight APD and therefore represents the best possible care under resource constrained circumstances. Guidelines are followed on PD catheter insertions, training of care takers and home visiting is done at initiation of PD, there is long term follow up and records are kept. This study provides important clinical information to help promote longer stay on PD at Red Cross Hospital.

## CHAPTER SIX

### 6.1 Conclusions

1. There was high drop-out rate from chronic PD of 32.7% among children with end stage kidney disease at Red Cross War Memorial Children's Hospital.
2. Drop-out from chronic PD was significantly associated with one or more episode of peritonitis.
3. Majority of the drop-outs (>50%) occurred within 12-24 months of initiation of PD, 35% PD technique survival at 12 months, 25% at 24 months.

### 6.2 Recommendations

4. We therefore recommend adherence to practices that prevent peritonitis as critical for PD success (especially in the first year) until a kidney transplant is available, and to increase kidney transplantation rates.
2. Ongoing education and training to the patients and their carers in the prevention of peritonitis.
3. More studies with bigger sample size and possibly prospective are needed to better understand the timing and factors associated with drop-out of children from chronic PD, including factors such as young age, low albumin levels, low haemoglobin level and TB peritonitis that tended to cause drop out.

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## Appendices

### Proposed Time Frame

Activity	JAN 2018	SEPT 2018	OCT 2018	NOV 2018	DEC 2018	JAN 2019	FEB 2019	MAR 2019	APR 2019	MAY 2019
Proposal Development	█	█								
Presentation to Dept/IRB		█								
Questionnaire Testing/Find Folders			█							
Data Collection				█						
Data Entry/Analysis					█					
Draft Thesis						█				
Presentation/Discussion of Results							█			
Writing Manuscript									█	
Letter of Intent/ Submission of thesis										█

## Data collection tool

### **DROPOUT RATE OF CHILDREN WITH ESKD FROM CHRONIC PD AND ASSOCIATED FACTORS; A TEN YEAR REVIEW AT RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL(RCWMCH), SOUTH AFRICA.**

Date of collection: d/m/yr

ID number:

1. DOB: d/m/yr
2. Sex: M/F
3. a)Address/Location: .....b) Distance from Red Cross hospital.....
4. Primary caretaker: mother/father/aunt/uncle/sibling/other
5. a) Occupation of primary caretaker.....b) Education of primary caretaker..... c) Caretaker occupation.....
6. a)Primary diagnosis/cause of ESRD..... b) Date of diagnosis.....c) biopsy diagnosis..... d)Cormobidities(other existing diagnoses).....
7. a) Date of PD catheter insertion: .....b) technique of catheter insertion (laparoscopic, open laparotomy). c) Type of catheter- straight/coiled? d) Omentectomy done Y/N e) Catheter sutured to pelvis? Y/N
8. Date of PD initiation: .....
9. Age at PD initiation (mths/yrs)
10. Duration of follow up before PD initiation (months).....
11. Running water in the house: YES/NO
12. Electricity in the house: YES/NO
13. At initiation: (xx.x) : a) WT b) HT c) BMI BP d) systolic... e)diastolic... f) GFR ... g) Dry weight ....h)BMI centile... i) HAZ(height for age z score) j) WAZ .....k) BP centile.....
14. a)PET test transporter type: ..... b) Intraperitoneal pressure (IPP) cm H2O....
15. PD cycles.....
16. a)Residual urine output (mls).....b)RRF: ..... c) Total KT/V.....
17. Labs at PD initiation: a)ALB .....b) Cr.....c) Hb d) PO4

18. Labs at 6 months of PD: a) ALB ..... b) PO4..... c) Hb
19. a) Fluid restriction..... b) Dietary prescriptions at initiation of PD/type of feed.....
20. a) Use of PEG for assisted feeding during follow up: YES/NO b) date of PEG insertion
21. Chronic medications taken by the child (list).....
22. Use of other RRT modality before PD: a) YES/NO b) If yes specify- -Renal Transplant? -HD, Acute PD?
23. a) PD catheter changed? Y/N: ..... b) number of catheters used for PD?.....
24. Specify dates of catheter removal-.....
25. Reasons for catheter removal:

catheter 1-.....

catheter 2-..... catheter 3.....

26. Transfer set changes? a) YES/NO b) If yes, number of times and the specific dates: .....

27. Reasons for transfer set changes:

.....  
 .....

28. a) Catheter manipulations ever done: YES/NO

- b) If yes, specify each date and its reasons: 1,

..... 2,

.....

3.....

29. Number of episodes of bacterial peritonitis and their dates of diagnosis: 0, 1, 2, 3, 4, 5...

30. Number of culture negative peritonitis episodes: .....

31. If positive, Organisms cultured for each episode

1 . ..... 2. ....3. ....4.

.....5. ....

32. a) History of TB peritonitis YES/NO    b) If yes, date of TB peritonitis diagnosis.....
- c) Fungal peritonitis Y/N    d) date.....
33. a) Episodes of tunnel infections: YES/NO ,    b) Total number.....
- c) If yes, specify dates for each infection diagnosis.....
34. a) Exit site infections: YES/NO    b) Total number.....
- c) If yes, specify dates for each diagnosis:
- .....
- .....
- .....
- 35 .Total number of hospitalizations while on PD.....? Reasons for hospitalization.....
36. a) Any PD interruptions? Y/N    b) reasons for interruptions .....c) Number of interruptions
37. a) PD outcome? .....Renal transplant/Drop out-transfer to HD, Drop out-death/Still on PD at time of study.
- b) Date of drop out.....
38. State reasons for Drop out eg .. Infections (bacterial, fungal or TB peritonitis), burn out, failure to perform PD, mechanical problems (blockage, leakage, hernia, fistula).....
39. Clinical features present at PD drop out or death
- a) Fluid overload    b) hypertension    c) Anemia HB <11.....
40. At PD drop out: (xx.x)    a) WT    b) HT    c) BMI    BP d) systolic..... e) diastolic.....f) Albumin    g) HB
41. Poor compliance queried during PD follow up period: YES/NO? To fluid restriction?
42. Date of renal transplant.....
- b) Type of donor:    1. Living Related Donor    2. Cadaveric Donor    3. Living non related

43. Total duration of PD.....

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44. a) Status at end of this study period: ALIVE/ DEAD

b) If dead, cause of death as stated in the folder.....