

**A study of Epidemiology and Microbiology of
Peritonitis in Continuous Ambulatory Peritoneal
Dialysis Patients at Inkosi Albert Luthuli Central
Hospital, Durban, South Africa.**

October 2015

By

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Dedication

I dedicate this dissertation to a number of individuals who have made a difference in my life and career:

Firstly, to Prof **Thumbi Ndung'u**, who introduced me in June 2008 to **Prof Adriaan Willem Sturm**, the man who decided to enrol me in the speciality training program regardless of my background and social support in the University of KwaZulu-Natal.

Secondly, I dedicate this dissertation to my best friend and mentor Professor **Wolfgang Kraemer and his wife Birgit Kraemer** who met me while I was 15 and we remained close up to date. He contributed to my moral and finances support while I was in South Africa. I still remember my last journey to his home town in Ingolstadt, Bavaria, Germany when he shed tears.

Thirdly, this dissertation is dedicated to my friend Dr **Huub Cornelius Gelderblom** who was very supportive in guiding and encouraging me in my life.

To all my friends **Dr Francois Siemefo Kamgang, Dr Baloyi Kaizer, Dr Irene Abibi Amegiede, Dr Puati Darsi Prince, Dr Tsilomba Jean Pierre, Dr Mubiyayi Bertin, Dr Osee Behuhuma, Dr Albert Kalombo, Dr Adebayo Okesola, Dr Michel Amani Lukabu, Dr Akeem Ngomu, Jean Luc Lukuitshi, Dr Coco Sadiki** and others.

I will not forget my family **Aberua, Ikabu in DRC** and my **uncle DR Joseph Banutelo, Dr Sammy LUNDA, Dr Caleb Banakyamonu, and Cousin DR Aleke and family.**

Finally, I dedicate this work to the almighty God.

Samuel.

Acknowledgement

I would like to thank the University of KwaZulu-Natal for the support directed towards this project. I am grateful to my supervisor, who has had a marked impact on this work and my life, Prof Alain **Guy Honoré Assounga**. I will never forget my co-supervisor Prof **Yacoob Mohamed Coovadia** who never got tired of improving my knowledge in this subject.

Lastly, I offer my regards and blessings to **Prof Benjamin Longo-Mbenza and Dr Teke Apalata** for their outstanding support in broadening my ideas in the analysis of data. Without forgetting **Prof Koleka Mlisana** and the whole microbiology department who did play massive contribution in my training in the department of Microbiology.

List of Acronyms and Abbreviations

CAPD	Continuous Ambulatory Peritoneal Dialysis.
ESRD	End Stage Renal Disease.
PD	Peritoneal Dialysis.
HD	Haemodialysis.
IALCH	Inkosi Albert Luthuli Central Hospital.
CCPD	Continuous Cycler Peritoneal Dialysis.
NIDDKD	National Institute of diabetics and Digestive and Kidney Diseases.
NIH	National Institute of Health.
IPPR	International Paediatric Peritonitis Registry (IPPR).
MRSA	Methicillin resistant <i>Staphylococcus aureus</i>
M.tb	<i>Mycobacterium tuberculosis</i> .
WBC	White Blood Cells.
PMN	Polymorphonuclear neutrophil.
VRE	Vancomycin Resistant Enterococci.
APD	Automated Peritoneal Dialysis.
IP	Intraperitoneal.
IV	Intravenous.
LD	Loading Dose.
MD	Maintenance Dose.
GP/GN	Gram Positive/Gram Negative.
DM	Diabetes Mellitus.
BMI	Body Mass Index.
ESR	Erythrocyte Sedimentation Rate.
CRP	C-reactive protein
PDF	Peritoneal Dialysis Fluid.
PDInt	Peritoneal Dialysis International.

BREC	Biomedical Research Ethic Committee.
AST	Antimicrobial Susceptibility Test.
NHLS	National Health Laboratory Services.
SOP	Standard Operating Procedures.
CoNS	Coagulase negative <i>Staphylococcus</i>
HPT	Hypertension
GN	Glomerulonephritis.

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CHAPTER 0: ABSTRACT

End Stage Renal Disease is a serious burden for both patients and health care professional mainly in the public service in South Africa.

Haemodialysis is currently overstretched.

All patients accepted in the state renal programme have to start with Continuous Ambulatory Peritoneal Dialysis (CAPD). Our study focused on patients treated by CAPD. One of the most common complications of CAPD is peritonitis.

The files of 115 patients who attended the Renal Unit were reviewed and 91 met our inclusion criteria. This is a case control study where the cases were patients with peritonitis.

Forty five patients developed peritonitis. The racial composition was: twenty four Indians (53.3%), followed by the eighteen Africans (40%), the coloured and white group had two and one respectively, a total of three participants (6.7%). The study revealed that females were significantly more affected by peritonitis than males $p=0.00466$

There was no significant difference between Africans and Indians ($p=0.2048$). The study showed that among the co morbidities, only obesity and Diabetes Mellitus (DM) were significantly associated with the development of peritonitis.

While bacterial peritonitis was the most prevalent at any stage, fungal peritonitis occurred only after one year.

In conclusion this study highlights the spectrum of microbiology of peritonitis in CAPD patients. Furthermore the study showed there is a need to broaden the laboratory routine method screening for emerging microorganisms like *Rhodotorula* sp, a fungus-isolated during our study, to reduce the percentage of culture negative peritonitis.

CHAPTER 1: INTRODUCTION

1.1 Introduction

Globally, peritonitis presents acute complications of peritoneal dialysis that leads to increase in hospitalization, morbidity and mortality amongst continuous ambulatory peritoneal dialysis patients (Okpechi *et al.* 2010; Canusa.1996). According to Vikrant *et al.* (2013) peritonitis is a leading cause of catheter loss and technical failure of the equipment used to manage peritonitis. Peritonitis which is the inflammation of the peritoneum may not be caused by infection and arguably rendering it the leading cause of catheter and technical failures in the management of this condition (Kerschbaum *et al.* 2012; Vikrant *et al.* 2013). Literature demonstrates that there are different micro-organisms responsible for peritonitis depending on a number of variables such as geographical space, socio-demographic factors and the status of the immune system (Troidle *et al.*1998; Prasad *et al.* 2007). Hence, this study sought to understand the peritonitis incidences and dynamics over two years using the Continuous Ambulatory Peritoneal Dialysis (CAPD) cases (patients), at Inkosi Albert Luthuli Central Hospital (IALCH), Durban in South Africa.

Literature demonstrates that the concept of peritonitis has evolved more through experience and gradual dynamics in the epidemiology (Chow *et al.* 2005). Research on CAPD peritonitis shows signs of decreasing trends in the Gram-negative pathogens (Vikrant *et al.* 2013). Different patterns of the microbiological organisms associated with peritonitis show variations between the developed and developing countries. Developing countries are the worst affected because of different risk factors such as poverty, environmental degradation, education levels and climate change (Dunkle *et al.* 2013; Goldstein *et al.* 2013; National institute of health.2006). Research conducted in Australia and Europe when compared to studies done in Asian and Latin America, shows discrepancies in causative micro-organisms involved in CAPD peritonitis in the different regions (Troidle *et al.*1998; Dunkle *et al.* 2013; Piraino *et al.* 2003). However, African countries seldom have official registers or reports of the number of dialysis patients and organisms that result in complications (National institute of health.2006). However there is evidence of African countries using simple and cheap tests for diagnosis and treatment to delay complications of kidney failure. Levey *et al.* (2007) argues that translating these advances to simple and applicable technologies to be adopted in public health facilities is still a challenge that requires a multi-institutional involvement.

Continuous Ambulatory Peritoneal Dialysis modality of treatment of CRF is one of the easier methods of treating CRF due to its practicability. CAPD is a relatively easy treatment method since it doesn't require needles or complicated equipment, on the down side; patients can develop peritonitis (Canusa.1996; Kerschbaum *et al.* 2013). This infection is caused by microorganisms (gram positive bacteria, gram negative bacteria, fungi, and to some extent viruses). These are isolated in the peritoneal fluid during infection and play an important role in the outcomes of the different types of dialysis modalities, this complication remaining a burden among CAPD patients (Vikrant *et al.* 2013; Prasad *et al.* 2007). In Africa, some patients contract peritonitis within the hospital. The microorganisms associated with peritonitis are nosocomial and they usually develop resistance towards the first line antimicrobial agents which are more affordable than the second line that are costly for most of African countries.

The dearth of research on the incidence and cost burden of peritonitis leads to neglect of the condition by stakeholders such as policy makers and multinational organisations that deal with health issues. Chertow *et al.* (2005) conducted studies from which the results showed that Chronic Renal failure (CRF) is not only a significant public health burden but also a major cost driver of medical expenses worldwide. Levey *et al.* (2007) noted that the prevalence of CRF amongst non-institutionalised adults in America and Europe was as high as 9.6% of the population. A study in Boston, conducted by Chertow *et al.* (2005) noted that CRF was associated with 6.5 fold increases in odds of death, a 3.5 increase in length of stay (LOS) in medical institutions and about \$7500 in excess hospital costs. Thus research from developed countries show the burden of CRF, but the situation is vaguely understood in the African context. CRF that occurs at the End Stage Renal Diseases, are a serious burden for both the patients caregivers and health care professionals, especially in the public service (Okpechi *et al.* 2010). There is evidence to suggest that peritonitis possess as a problem in the public health sector in South Africa, hence need to understand its prevalence and dynamics in order to develop effective management guidelines.

A study conducted by Abu-Aisha *et al.* (2010) found the prevalence of patients on CAPD in South Africa was 3660 in 2007. The highest prevalence of patients on CAPD was found in the province of KwaZulu-Natal. However, Abu-Aisha's study focused on country level records and this study sought to investigate the incidences of peritonitis at the micro-level. In order to

achieve a micro-understanding of CAPD and peritonitis the study took a case study Inkosi Albert Luthuli Central Hospital in KwaZulu-Natal. The hospital is the highest ranked public hospital according to the South African government rankings. On clinical impression, our experience at Inkosi Albert Luthuli Central Hospital (IALCH) Durban, the microbiological spectrum of peritonitis during CAPD is changing among poor patients in South Africa, a country with a high prevalence of HIV¹ (Mujais *et al.* 2006). IALCH is the one of well-equipped tertiary hospital without valid information about the burden of infections for managing patients on CAPD using evidence based knowledge. Therefore, the objective of this study is to estimate the incidence of peritonitis and to describe the types of microorganisms related with peritonitis amongst CAPD patients according to gender, age, ethnicity, months, microbiological culture, severity of renal failure, treatment.

Having an overview of the commonest microorganisms involved in peritonitis might be a helpful tool to suggest syndromic treatment guidelines while awaiting the susceptibility results from laboratories for adequate management. This may prevent and avoid emerging resistant strains of microorganisms due to inappropriate use of antimicrobial drugs. There are many cases of emerging resistances among CAPD patients; however there is dearth of knowledge on this condition in KZN.

1.2 The Problem statement

Bacteria and fungi are the leading cause of peritonitis in adults and children undergoing CAPD (Vas *et al.* 2001). Peritonitis has been associated with patients undergoing CAPD resulting in complications of their conditions. Furthermore, there is growing evidence that demonstrate the microbiological spectrum of patients are different depending on region and are showing signs of changing (Dunkle *et al.* 2013). Management of CAPD peritonitis has been dependent on laboratory tests and simple technologies which are expensive for developing countries like South Africa to adopt throughout all public hospitals. The poor understanding of microorganism responsible for peritonitis amongst CAPD patients might result in complication or even possibly death. In order to reduce complications amongst patients, clinical indicators

¹ According to Human Sciences research Council's 2012 report, the national HIV prevalence was 12.3% ,and KwaZulu-Natal had the highest (27.6%) HIV prevalence of all the provinces.

could help earlier response by clinicians while awaiting laboratory results. The complexity of the diagnosis and management of CAPD peritonitis falls is experienced in the background of resource poor facilities and the large burden of CAPD patients in the KwaZulu-Natal province. Hence the study sought to explore the prevalence and socio-demographic characteristics that predisposes CAPD patients to microbiological organisms associated with peritonitis at Inkosi Albert Luthuli Central Hospital.

1.3 Research Questions

1. What were the prevalence and microbiological features of peritonitis in CAPD patients at IALCH.
2. What were the demographic factors and clinical factors associated with the development of peritonitis in CAPD patients in our settings?

1.4 General and Specific Objectives

The study sought to establish the nature and extent of peritonitis amongst CAPD patients at IALCH in Durban

Therefore, the specific objectives of this study were:

1. To establish the prevalence of CAPD peritonitis.
2. To establish the socio-demographic predictors and clinical predictions of CAPD peritonitis
3. To describe the types of peritonitis microorganisms in CAPD patients
4. To make recommendations to clinicians and other health stakeholders

1.5 Layout of research report

This research is presented in five Chapters, which present the thesis of the study.

Chapter zero will present the Abstract.

Chapter one will present the introduction to the dissertation in the following sections; the background of the study, statement of the study, research questions, objectives and the structure of the dissertation.

Chapter two will present the literature review chapter. The literature review of this dissertation reviews literature on the following issues: peritonitis dialysis; microbiology of peritonitis; cultural and laboratory diagnosis; empiric treatment and drug dosing and stability.

Chapter three will describe the study area, sampling techniques, data collection and analysis techniques used.

Chapter four will present results of the research. Data presented will be on: the incidence of peritonitis; microbiological organisms associated with CAPD peritonitis and socio-demographic data of the patients.

Chapter five will present the discussion of the results reflecting on the literature, methodology and introduction chapters.

Chapter 2: REVIEW OF THE LITERATURE

2.1 Introduction

This chapter reviews the literature relevant to this study, and addressed how Peritoneal Dialysis works; diagnosis and management of peritonitis. The literature reviewed in this chapter mainly draws from case studies from the developed world and little from African countries due to literature gap in Africa.

2.2 Peritoneal Dialysis

Kidney failure can lead to uraemia and insufficient excretion of other substances that are normally excreted in the urine. This results in a blood pressure increase, oedema, anaemia, osteoporosis due to kidney failure. The most common treatment options for kidney failure are peritoneal dialysis (PD) and specify haemodialysis, with the latter using an extracorporeal blood circuit to free the blood of waste.

CAPD removes toxins by entering the abdomen, with a catheter being permanently placed in the peritoneal cavity and connected to a bag that contains the dialysis solution (National institute of health.2006).The peritoneum membrane plays the role of removing waste from the blood into the dialysis solution, which will be drained and exchanged, according to the schedule time.

There two types of PD:

- CAPD is the main type used at IALCH, is less complicated than dialysis as it does not require a machine, and the patient can manage their treatment easier.
- Continuous Cycler Peritoneal Dialysis (CCPD) or automated peritoneal dialysis requires a cycler to fill and drain the abdomen with dialysis fluid (National institute of health.2006).

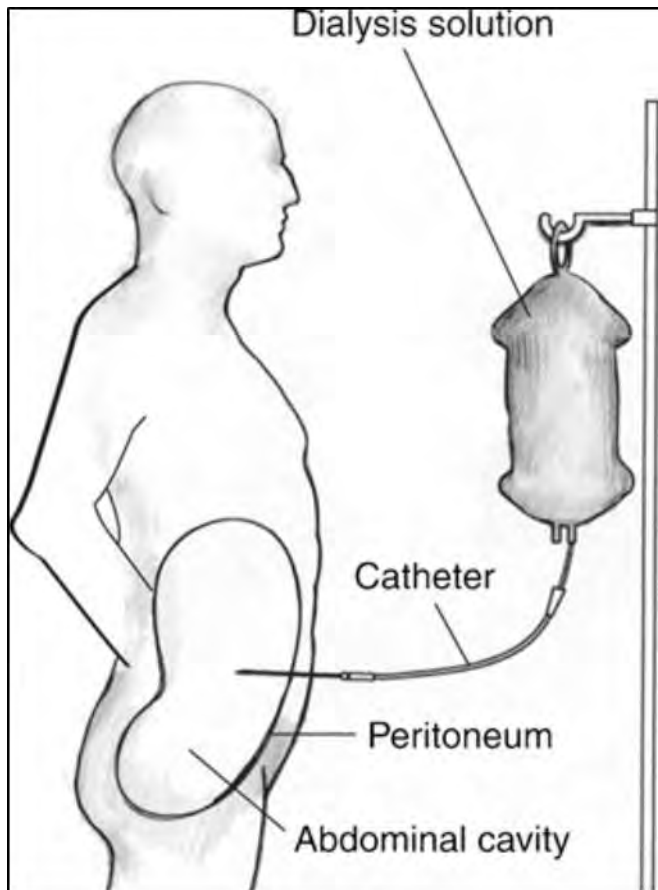


Figure 2.1: The normal CAPD set up

Copied image from National Institute of Diabetics and Digestive and Kidney Disease (National institute of health. 2006).

2.3 Microbiology of Peritonitis

The improvement in connecting catheters, exit site cleansing, and the topical management of *Staphylococcus aureus* have contributed to the decline of peritonitis (Zelenitsky *et al.* 2000; Piraino *et al.* 2003). Literature shows that the microbial distribution in peritoneal dialysis population is consistent amongst many dialysis centres, even though minor disparities may exist (Schaefer *et al.* 2007). The International Paediatric Peritonitis Registry (IPPR) data shows homogeneity in the microbiological organisms associated with peritonitis in adults and children. (Schaefer *et al.* 2007).

Data from IPPR on 501 episodes of peritonitis from the period of October 2001-December 2004 has shown 392 occurrences of peritonitis in children in whom 10% were caused by fungi, 44% by gram positive bacteria, and 24% by gram negative bacteria and culture negatives in 31% of cases (Fig. 2.2). Even though these findings support the decrease of gram positives ; their species differ from the study conducted by Mujais *et al.* (2006), in a survey of more than 4000 episodes peritonitis in adults patients from the USA and Canada.

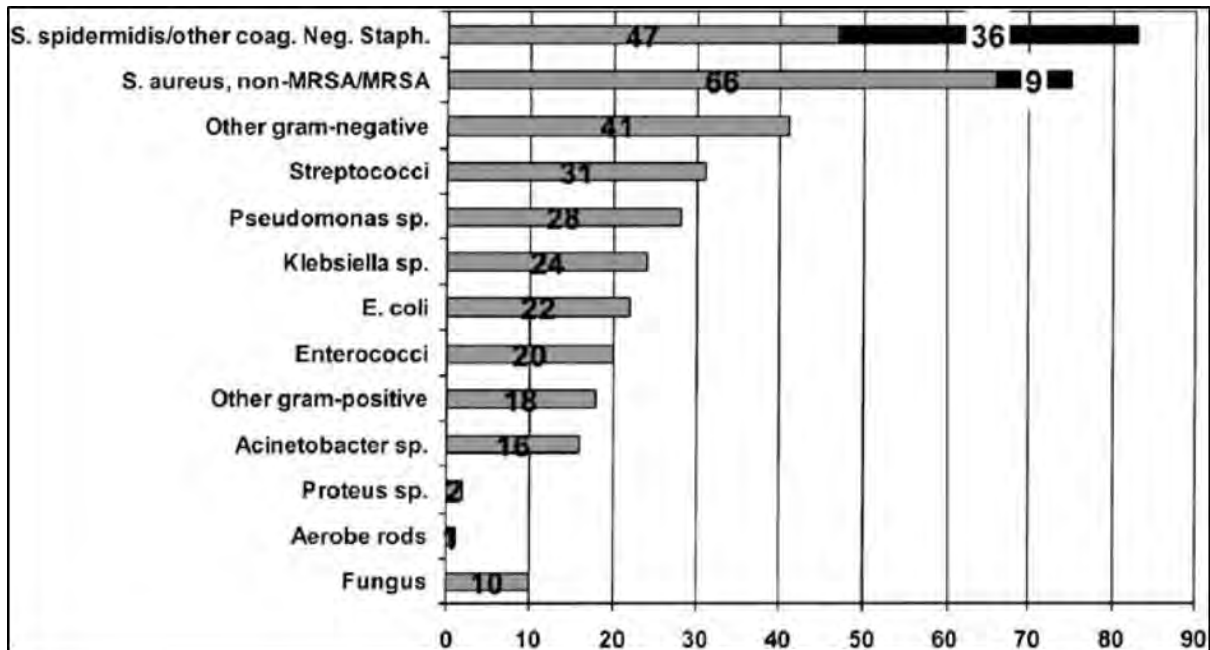


Figure 2.2: Distribution of causatives organisms among 501 episodes of peritonitis reported by the IPPR copied from Warady *et al.* (2007).

Furthermore, there is variation in the distribution of organisms among the different regions of the world (fig 2.3). The bacteriological profile differs from region to region according to IPPR data. Hence, making it difficult to predict the causative organisms involved in peritonitis, since they vary depending on geography and environmental variability across the World (Szeto *et al.* 2003). European countries were dominated by the occurrences of gram positives: Eastern region with coagulase negative *Staphylococcus* and *Staphylococcus aureus* in the western region (Mujais *et al.* 2006). In Turkey and Mexico, culture negatives were found in 42% and 67% respectively in comparison to other regions surveyed in Europe (Mujais *et al.* 2006).

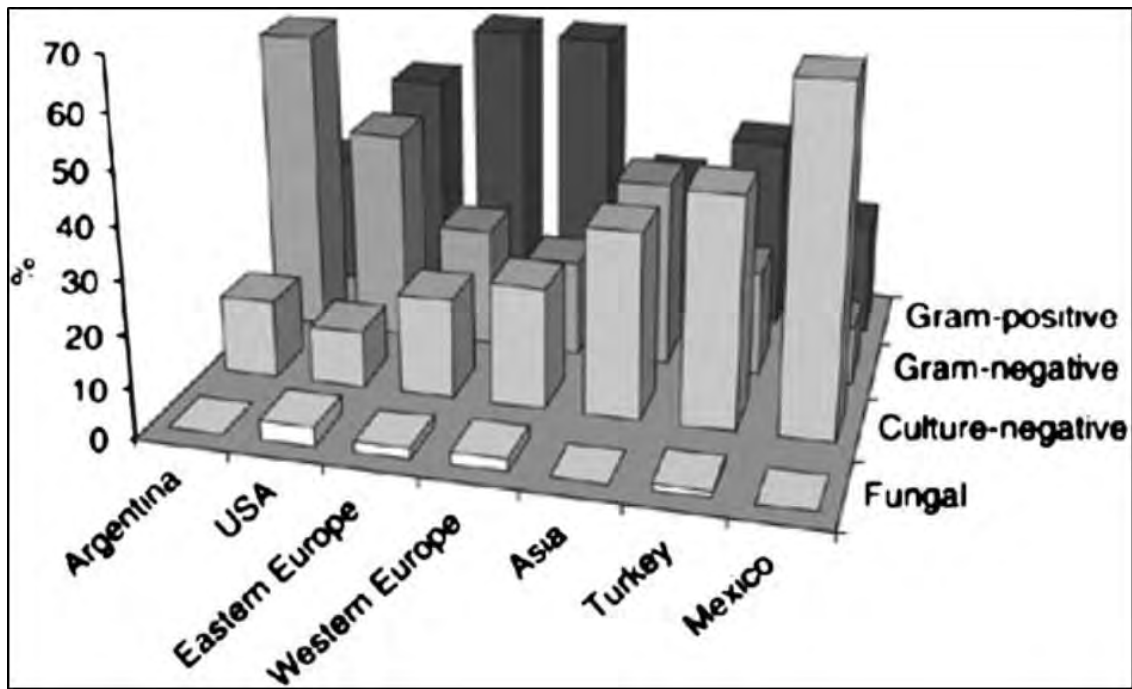


Figure 2.3: Distribution of causative organisms according to the regions among 501 episodes of peritonitis reported by the IPPRU: Copied from Schaefer *et al.* (2007).

Yeasts, mainly *Candida* species are the most common fungal organism associated with peritonitis, *Diphtheroids* species are associated with skin contamination, and viruses are not among the peritonitis causatives organism.

Tuberculosis is one of the conditions that are identified in the literature as being responsible for complication of patients on CAPD. *M. tuberculosis* an intracellular microorganism that affects the cellular immune system among the CAPD patients who are already immune-compromised (Warady *et al.* 2007; Goldie *et al.* 1996; Chadha *et al.* 2010).

Some technical drawbacks such as insufficient effluent volumes, transplantation in rural areas, transportation, temperature variation, manipulation of icodextrin solution for PD may impact the culture results (Martis *et al.* 2005). Yet as the culture of the PD is important for the rest of management since it will help to appropriately use antimicrobial agents.

2.4 Pathogenesis

Literature demonstrates the peritonitis routes include: touch contamination, tunnel infection, enteric haematogenous, and ascending via vagina (Chadha *et al.*2010). Scholars attribute Coagulase negative *Staphylococcus* (CoNS) as resulting from touch contamination of the peritoneum in all the cases (Vas *et al.* 2001; Piraino *et al.* 2000). Its incubation period is between 24 -48 hours, and the same organisms is associated with the recurrent peritonitis due to biofilm, the impression that the decrease in gram positive organisms is mainly due to the management of this organism (Chadha *et al.* 2010). In the literature it is well known that CoNS are among the most encountered Gram positives microorganisms that are isolated in CAPD patients.

There are a number of routes that have been documented as responsible for peritonitis in CAPD patients. Scholars describe *Staphylococcus aureus* route as emanating tunnel /exit site contamination, and research ranks *Enterococci* species and *Streptococcus* species are among the very fewer causes of CAPD peritonitis (Vas *et al.* 2001; Piraino *et al.* 2000). Peritonitis caused by *Enterococcus* sp, a gut normal flora suggesting trans mural infecting route, and are also accompanied by the emergence of Vancomycin resistant strains ,making them very dangerous bug that maybe accompanied by a high rate of morbidity (Troidle *et al.* 1996; Von Baum *et al.*1999).

There are many Gram negative bacilli, that are involved in CAPD peritonitis and their acquisition varies according to the contamination. The enteric bacteria detection and multiple gram negative detection are strongly suggestive of faecal intra-abdominal contamination respectively whereas *Pseudomonas* and *Stenotrophomonas* species (spp) are among the Multidrug resistant bugs suggestive of Catheter and /or tunnel contamination (Warady *et al.* 2012; Zurowska *et al.* 2008). The biofilm is formed by the organism on the catheter preventing antibiotic effect; therefore the removal of the catheter is the first step towards effective infection management (Zurowska *et al.* 2008; Warady *et al.*1999). *Acinetobacter* species are non-fermented micro-organisms are mostly in relation with environment, soil and water contamination (Alflaiw *et al.*1999).

2.5 Empiric diagnosis of peritonitis

The International Society for Peritoneal Dialysis (ISPD) has drawn up a quick diagnosis for peritonitis in both children and adults. According to ISPD an empiric diagnosis can be made to determine peritonitis by using clinically presented signs and symptoms (America FMCCN. 2010). These signs and symptoms include: The cloudiness of effluent and abdominal pain (which can range from mild to severe according to the causative organism). The severity of pain can be related to specific organisms (mild pain with Coagulase Negative *Staphylococcus* (CoNS), and severe pain with gram-negative rods, *Streptococcus* sp, and *Staphylococcus aureus*). The effluent cell count with differential should be obtained, and if after 2 hours of dwell time, the white blood cell count (WBC) $\geq 100/\mu\text{L}$ with the minimum of half being polymorphonuclear neutrophil cells (PMN) is suggestive of inflammation. The Gram stain is important in defining the presence of yeasts, differential diagnosis initiative is important to exclude other surgical diseases beside peritonitis (America FMCCN. 2010).

2.6 Culture and Laboratory Diagnosis

Getting the proper microbiological culture is mandatory to identify the causative organism, to perform antimicrobial sensitivity testing, and subsequently to commence the appropriate treatment in South Africa. Most of the peritonitis causative organisms can be grown in the traditional cultures media using the standard culture technique. The outcomes of culture are expected within three days to initiate the appropriate treatment. Failing to establish the diagnosis through culture results within three days, may lead to the subculture of miscellaneous and slow growing organisms.

2.7 Treatment

The specimens are collected prior to initiation of any antibiotic; the preferred route of administration of drugs is intra-peritoneal. The treatment option for gram positive bacteria options are, vancomycin, or cephalosporin. Gram- negative bacteria are Aminoglycosides or third generation cephalosporin, for yeasts, fluconazole is the first choice. Once the culture results are known, it is recommended to shift from the empiric treatment to a narrow spectrum antibiotic to cover the specific organism.

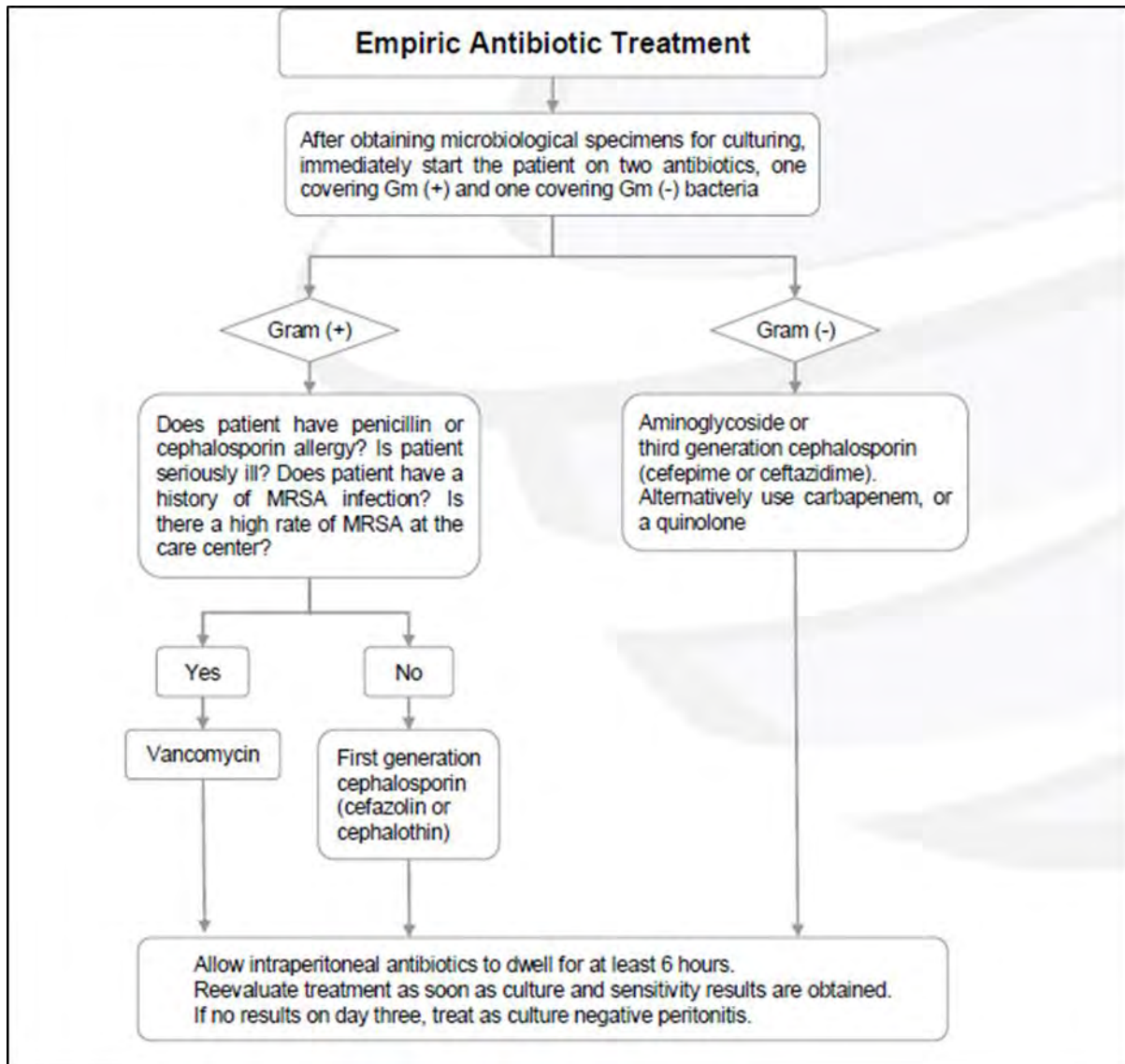


Figure 2.4: Empiric treatment adapted from LI *et al.*2010).

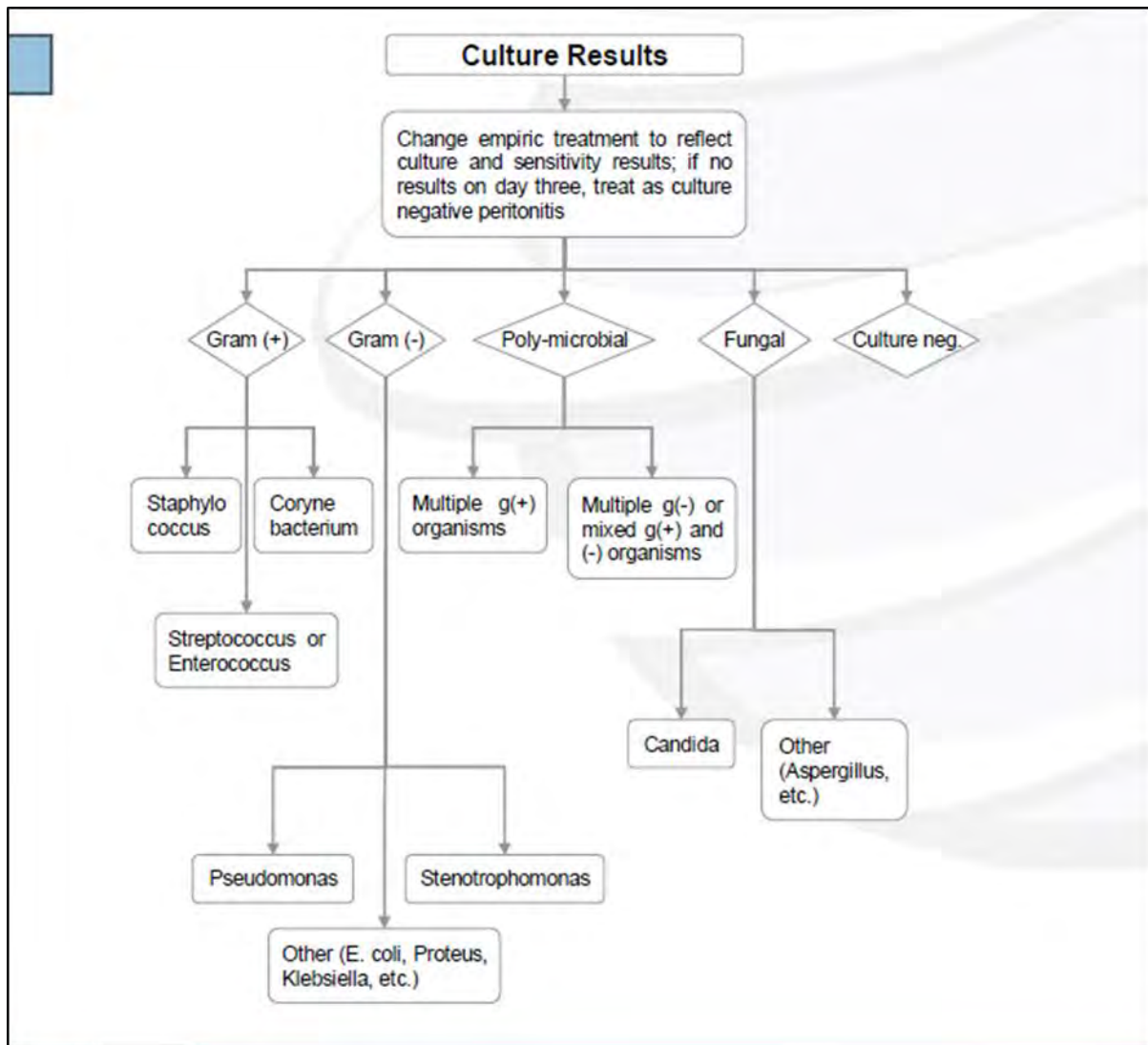


Figure 2.5 Culture results. Copied from Li *et al.* (2010).

2.7.1 Gram Positive

In general, penicillin derived agents are used as the first line to treat gram positive bacteria. Among the leading causes of contamination Coagulase negative *Staphylococcus*, *Staphylococcus epidermidis* is another gram positive that is involved in CAPD peritonitis, with vancomycin, rifampicin and teicoplanin being the drugs of choice. Peritonitis caused by *Streptococcus* and is treated by ampicillin; risk factors are associated with peritonitis caused by vancomycin-resistant *enterococcus* (VRE). Ampicillin may be used for VRE if it is susceptible, and linezolid, quinupristin/dalfopristin, and daptomycin are alternative choices. *Corynebacterium* is a normal skin flora and may be difficult to be considered as a pathogen. These bacteria are seen as the cause of relapsing peritonitis, repeating peritonitis.

2.7.2 Gram negative

Pseudomonas aeruginosa is one of the causes of severe peritonitis, and associated with a catheter infection. The eradication of *Pseudomonas aeruginosa* is very important to avoid the shift to haemodialysis. *Klebsiella* species, *E.coli*, *Proteus* species are other causative organisms and are also implicated to the biofilm formation (fig 2.6). *Stenotrophomonas* is another causative agent which can be treated by administering thrimethoprin /sulfamethoxazole.

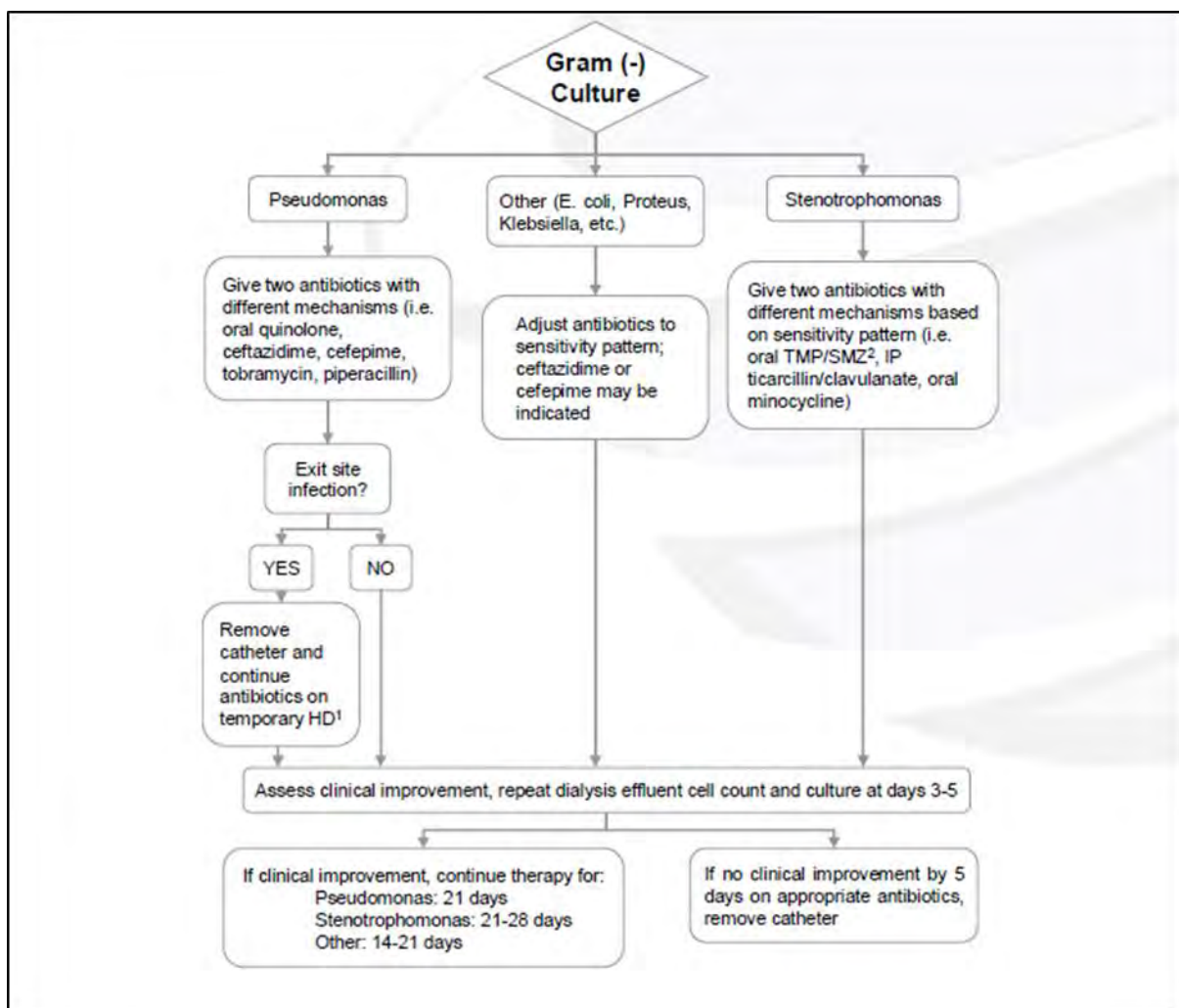


Figure 2.6 Gram negative culture. Copied from Li *et al.* (2010).

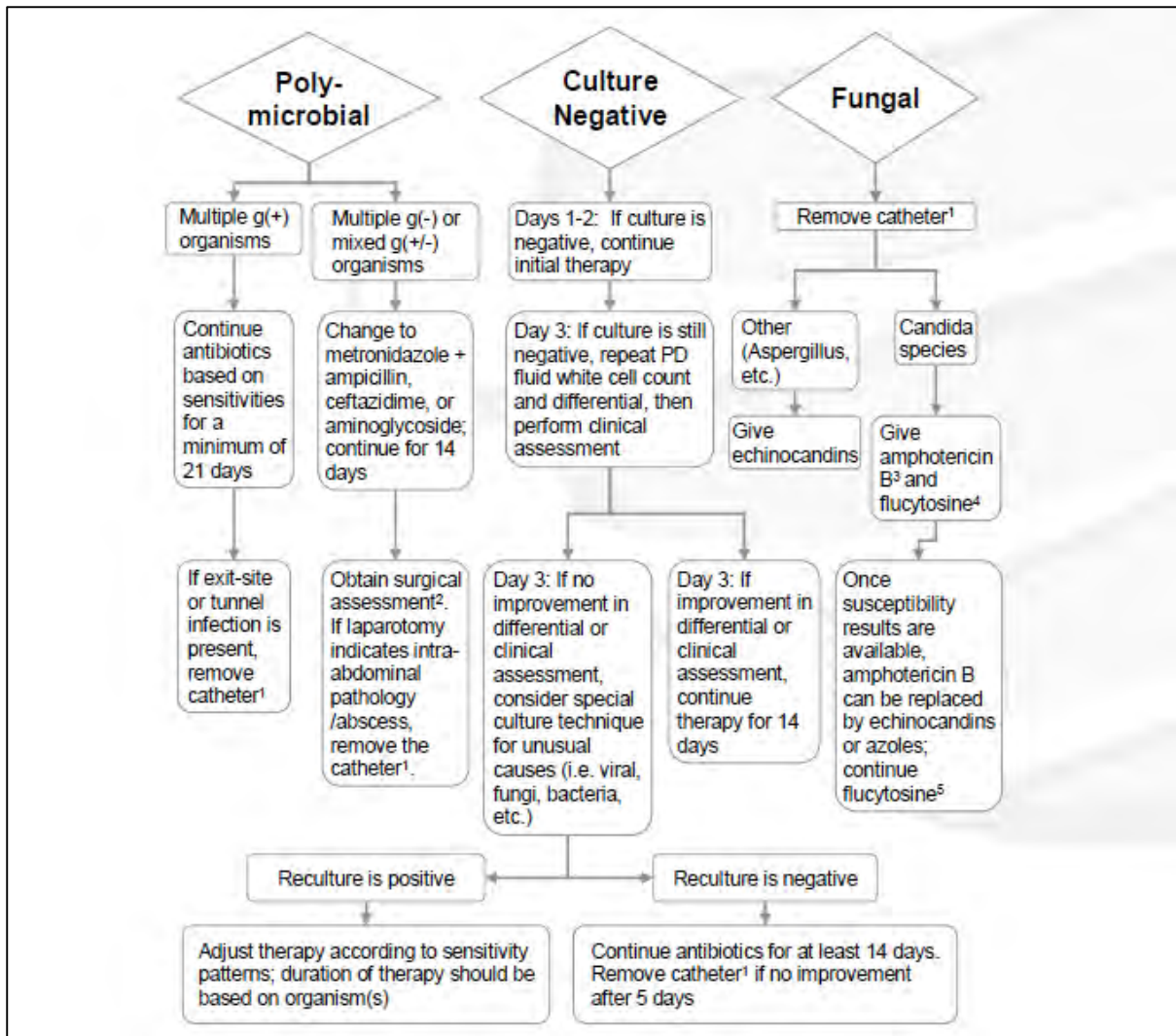
Antibiotics must be continued for two weeks while the patient is on HD, however, the duration of antibiotic therapy following catheter removal and timing or resumption of peritoneal dialysis may be modified depending on clinical course, Trimethoprim and Sulfamethoxazole.

2.8 Polymicrobial, fungal and culture negative peritonitis

Anaerobes are the cause of this type of peritonitis, and mainly come from contamination through the infections of the catheter. Removal of the catheter is part of the resolution for this infection. These mixed microorganisms have a superior prognosis in comparison to the multiple enteric organisms with the latter evolving intra-abdominal source like diverticulitis, ischemia bowel, cholecystitis or appendicitis. The combination of metronidazole, with ampicillin, and aminoglycosides have shown efficacy against anaerobes.

As the consequence of multiple antibiotic treatments, the fungal peritonitis results in a high incidence of death. The treatment ranges from fluconazole, flucytosine for the empiric treatment of *Candida* species, to amphotericin B, caspofungin, anidulafungin and micafungin are recommended for *Aspergillus*. Different combinations are recommended like casposfungin and Amphotericin B, Echinocandin, fluconazole, voriconazole or posaconazole may replace Amphotericin after culture and sensitivity results. The use of azole is recommended only after culture and sensitivity results, due to the high rate of resistance emerging. Antibiotic use must be monitored to avoid the fungal peritonitis as a complication of antibiotic mismanagement.

Culture –negative peritonitis rates is the source of reviewing cultures methods and also introduction of new methods to optimize the diagnosis of a typical peritonitis like *Mycobacterium tuberculosis*, yeasts, *Legionella* sp, *Campylobacter*, slow-growing bacteria, enteric viruses, *Mycoplasma*, *Ureoplasma*. Certain clinical conditions, such as hypotension, sepsis, lactic acidosis, and elevation of peritoneal amylase may be considered threatening and may lead to surgical peritonitis. IP amphotericin B is one of the causes of chemical peritonitis, flucytosine requires serum concentrations and monitoring since it is the source of bone marrow toxi



city.

Figure 2.7 Polymicrobial, fungi or culture negative. Copied from Li *et al.* (2010).

2.9 Drug dosing and Stability

Aminoglycosides, vancomycin and cephalosporin are among the drugs that can be added to one dialysis solution bag by observing strict infection control measures, each being applied with a different syringe. The chemical incompatibility is seen between penicillin and the aminoglycosides. There are some studies suggesting the modification of dialysate composition by reducing certain molecules that might be the factors of developing infections.

The possibility for those antibiotics being stable for a long period of time has not been proven, and more research is therefore needed to identify the optimal stability conditions for dialysis solutions. Substances such as Icodextrin, once introduced in dialysis solutions, are compatible with drugs such as vancomycin, ampicillin, cloxacillin, ceftazidime, gentamycin and amphotericin B, with opposition to heparin that impact in stability.

Table. 2.1: Antibiotic stability in dextrose-containing dialysis solutions. Copied from Li *et al.* (2010).

Antibiotic	Concentration	Stability (days)	Storage temperature
Vancomycin	25mg/l	28	RT
Gentamycin	8mg/l	14	
Cefazolin	500mg/l	8	RT
Ceftazidime	200mg/l	10	Refrigerated
Cefepime	100 μ /l	14	Refrigerated

Intermittent or Continuous Dosing of Antibiotics: Special considerations for APD: Intraperitoneal (IP) is better than intravenous (IV) dosing. IP can be performed by the patient at home after proper training, to avoid the venepuncture needed for IV access and the dwelling of antibiotics lasts at least 6 hours allowing adequate absorption. For both APD and CAPD there are few antibiotic dosing recommendations (Table 2.2).

Dosing of drugs in patients with residual renal function (defined as >100mL/day urine output), should be empirically increased by 25%. Vancomycin should be re-dosed if serum trough levels fall below 15 µg given in conjunction with 500 mg quinupristin/dalfopristin intravenous twice daily. CAPD loading dose (LD). Maintenance dose (MD).

Table 2.2 Peritoneal dialysis and recommendations regarding related infections.

Copied from Li *et al.* (2010).

Medication	CAPD IP Dosing ¹		Automated PD IP Dosing Intermittent (per exchange, once daily)
	Intermittent (per exchange, once daily)	Continuous (mg/L, all exchanges)	
Aminoglycosides			
Amikacin	2 mg/kg	LD 25, MD 12	
Tobramycin	0.6 mg/kg	LD 8, MD 4	LD 1.5 mg/kg IP in long dwell, then 0.5 mg/kg IP daily in long dwell
Gentamicin, netilmicin	0.6 mg/kg	LD 8, MD 4	
Cephalosporins			
Cephalothin, cephradine	15 mg/kg	LD 500, MD 125	
Cefazolin	15 mg/kg	LD 500, MD 125	20 mg/kg IP in long day dwell
Cefepime	1000mg	LD 500, MD 125	1 g IP in 1 exchange daily
Ceftazidime	1000-1500 mg	LD 500, MD 125	
Ceftizoxime	1000mg	LD 250, MD 125	
Penicillins			
Amoxicillin	No data	LD 250-500, MD 50	
Ampicillin, oxacillin, nafcillin	No data	MD 125	
Azlocillin	No data	LD 500, MD 250	
Ampicillin/sulbactam	2 g every 12 hrs	LD 1000, MD 100	
Penicillin G	No data	LD 50000 units MD 25000 units	
Quinolones			
Ciprofloxacin	No data	LD 50, MD 25	
Others			
Aztreonam	No data	LD 1000, MD 250	
Daptomycin	No data	LD 100, MD 20	
Linezolid	Oral 200-300 mg daily		
Teicoplanin	15 mg/kg	LD 400, MD 20	
Vancomycin (Dose depends on serum trough levels)	15-30 mg/kg every 5-7 days ²	LD 1000, MD 25	LD 30 mg/kg IP in long dwell; repeat dosing 15 mg/kg IP in long dwell every 3-5 days
Imipenem/cilastin	1g twice daily	LD 250, MD 50	
TMP/SMZ	Oral 960 mg BID		
Quinupristin/dalfopristin	25 mg/L in alternate bags ³		
Antifungals			
Amphotericin B	Not applicable	1.5	
Fluconazole	200 mg IP every 24-48 hrs		200 mg IP in 1 exchange per day every 24-48 hours

2.10 Refractory, Relapsing, Recurrent, and Repeat Peritonitis

According to the 2010 ISPD Guidelines, the following definitions are acceptable and applied in CAPD practice:

- a. Refractory peritonitis: occurs when after five days of appropriate anti-biotherapy there is a failure of the effluent to clear.
- b. Relapsing peritonitis: any episode occurring within four weeks of completion of therapy of a prior episode with the same organism or one sterile episode.
- c. Recurrent peritonitis: any episode with a different causative organism occurring within 4 weeks of completion of therapy of a prior episode
- d. Repeat peritonitis: any episode that occurs within a period of more than four weeks after completion of therapy of a prior episode with the same organism.

Recurrent, relapsing and repeat peritonitis are associated with worse outcomes, and as a palliative method of treatment, catheter removal should be performed in an optimal period of time.

2.11 Patient Education

It is essential for any patient to undergo the PD education by suitable trained personnel such as a nurse. It should cover the following: any symptoms of abdominal pain, cloudiness of effluent, or fever, the dialysate fluid must be drained and sent for analysis to the laboratory. In addition, the patient should be prepared to understand that the treatment lasts a minimum of 3 weeks, if no clearance of the fluid the patient should report.

Several studies have shown discrepancies among the causative gram negative (GN) and gram positive (GP) organisms in CAPD peritonitis patients across the world making this complication a very serious public health problem contributing to occasional disability amongst many patients who are part of the active population group and therefore affecting the Economy severely affected countries. This trend varies in different countries but the economics studies to ascertain level of impacts are very limited.

In 2012, Lioussfi *et al.* conducted a study from which data were collected between 2006 -2009 and found that among adult patients who are aged between 19 and 78 years (mainly male) their onset period from dialysis commencement was 7.9 ± 8 (1-29) months. Their findings were in contrast with documented trends of causative microorganisms in CAPD patients. They found that gram negative were found in 55% vs 45% of gram positive microorganisms. In another study conducted by Nessim *et al.* (2011) that used data from the Canadian multicentre Baxter Poet (peritonitis, organisms Exit Sites, Tunnel infections) it showed that between 1996 and 2005, the large proportion of patients with 2 or more were caused by the same organisms. Their findings suggested that out of 558 patients, 181(32%) had at least 2 episodes with the same organisms, and in addition to their findings ,the organism commonly associated with the occurrence of repeat infection was Coagulase negative *Staphylococcus*, accounting for 65.7% of cases vs. peritonitis caused by other organisms (Lioussfi *et al.* 2012).

A first Coagulase negative *Staphylococcus* peritonitis was associated with an increased risk of subsequent Coagulase negative *Staphylococcus* peritonitis within 1 year (odd ratio: 2:1.955) confidence interval: 1.5 to 2.8, $p < 0.0001$). Among patients with repeat Coagulase negative *Staphylococcus* peritonitis, 48% of repeat episodes occurred within 6 months of the earlier episode. Their findings are in contrary to those of Lioussfi *et al.* (2012).

Nessim *et al.* (2011) demonstrated also that males were more vulnerable than females, and also among the predictor causes for CAPD peritonitis, diabetes mellitus was a leading comorbidity followed by Hypertension and Glomerulonephritis. Other studies have focused on how socio-demographic characteristics influence one's susceptibility to peritonitis. Mehrotra *et al.* (2011) analysed the relationship of selected patient's socio-demographic profile by focusing on geographical location specifically comparing incidences of peritonitis in rural and urban areas. In the United States of America it was observed that there are significant regional differences in the outcomes of PD amongst patients from 'country sides' (rural) and those from urban areas. Understanding the differences in clinical practices that underlie these regional differences might help to further improve PD outcomes. In another case, a multicentre observational study conducted by Martin *et al.* (2011) from 2004 through 2007, concluded that clinical dialysis-related with demographic, and socioeconomic variables. Patients were followed up until the first peritonitis. The Cox proportional model was used to determine independent factors associated with first peritonitis. The results of 2032 patients were that 474(23.3%) presented a

first peritonitis episode. Their findings demonstrate that lower levels of education, on-white race, region where patients live affect their risk.

Lo *et al.* (2012) reported 9 cases of exit –site infection in China and CAPD peritonitis associated with *atypical mycobacteria*. All patients have been using topical gentamycin cream as prophylaxis for exit-site infection before the onset of these infections. Gentamycin cream is postulated to be potential risk factor for a typical mycobacterial infection because of selective pressure on their microorganisms. The microbiology of atypical mycobacterial infections is discussed. Yap *et al.* (2012) in a retrospective study from 1995-2010 found that, the overall rate of peritonitis was low after contamination. Wet contamination was associated with a much higher risk of peritonitis prophylactic antibiotics after wet contamination were effective in preventing the occurrence of peritonitis, this contrasting with a study conducted by Lo *et al.* (2012). A cohort study by Dong *et al.* (2013) demonstrates that gram positive coagulase negative *staphylococcus* organisms are a leading cause of CAPD peritonitis. This is an issue of concern among the health professional due to its unpredictability with regard of causatives organisms. These results are in a contradiction to those of Lioussfi *et al.* (2012). Increasingly scholarship is studying the relationship between peritonitis and climatic factors (Cho *et al.* 2013; Chan *et al.* 1983). In one of the early studies on the link between peritonitis and climate Chan *et al.* (1983) examined the relationship of all the episodes of peritonitis in CAPD patients to climatic factors, such as temperature and relative humidity. Such early studies are important for prioritising the role of climate factors to understanding the features and dynamics in peritonitis. In a more recent study in Australia, Cho *et al.* (2013) demonstrated that the impact of climatic variations on peritoneal dialysis PD-related peritonitis has not been studied in detail. In their retrospective study they considered influence of climate, and climatic regions were defined according to the Koppen Classification. The overall peritonitis rate was 0.59 episodes per patients –years. Most of the patients lived in temperate regions (65%), with others residing in the following regions: subtropical (26%); tropical (6%); and other climatic regions (desert 1%, Grassland 2%). Compared with patients in temperate regions ,those in tropical regions demonstrated significantly higher overall peritonitis rates and a shorter time to a first peritonitis episode [adjusted hazard ratio: 1.15;95% confidence interval: 1.01 to 1.31]. Culture negative peritonitis was significantly less likely in tropical regions [adjusted Odd Ratio: 0.42; 95%CI: 0.25 to 0.73], but its occurrence in subtropical and other regions was comparable to that in temperate regions.

Fungal peritonitis was independently associated with tropical regions (OR:2.18;95%CI1.22 to 3.90) and others regions (OR:3.46;95%CI:1.73 to 6.91) rates of antifungal prophylaxis were lower. Outcomes after first peritonitis episodes were comparable in all groups. Their conclusions were that tropical regions were associated with higher overall peritonitis rates (Including fungal peritonitis) and a shorter time to a first peritonitis episode. Increasing peritonitis prophylactic measures such as antifungal therapy and exit-site care should be considered in PD patients residing in tropical climates. In Sweden, Pihl *et al.* (2013) have demonstrated the extend in which bacteria are presents on catheters from PD patients without clinical signs of infection. The bacteria were detected on 12 of the 15 catheters from patients without signs of infection. Single-species and mixed microbial communities containing up to 5 species were present on both the inside and the outside along the whole length of colonized catheter. Stinghen *et al.* (2007) demonstrated that the peritonitis rate and patterns show a consistent variation that mirrors geographic location in relation to the health centre influences the progression of peritonitis. For instance, the distance from a PD centre and weather characteristics represent geographic risks factors that are linked to peritonitis characteristics and particularly to clinical outcomes. Their study revealed that co morbidities and others factors influencing the selection of dialysis modality showed that patients living more than 30 miles (48 kms) from the nearest dialysis centre had significant higher odds of being prescribed.

According to the study conducted by Mizumasa *et al.* (2013) ,their findings revealed that submesothelial connective tissue thickness was significantly greater in the Diabetes Mellitus group than in the non-DM group ($p<0.0001$). Based on the multivariate linear regression analysis, diabetes was identified as a significant independent variable of both submesothelial connective tissue thickness and number of capillaries. ($p<0.001$).

2.12 Summary

In the introduction it was discussed that socio-demographic, environmental, contamination and features of microbiological organisms shape the incidence and complexity of peritonitis. The literature review in this chapter demonstrates that these factors have been alluded to as being linked to peritonitis. Literature reviewed in this chapter shows that incidence rates are known in the developed countries like USA and Europe. By contrast very little is known about the incidences of peritonitis in Africa except in a few countries where case specific studies have been carried out. Furthermore literature reviewed demonstrates how micro-organisms associated with peritonitis are influenced by climatic conditions resulting in different species being responsible for the condition in different regions. Hence the need to understand features of micro-organisms associated with peritonitis in South Africa.

CHAPTER 3: MATERIALS AND METHODS

3.1 Introduction

In order to address the objective presented in chapter one the study adopted a quantitative methodology that is informed by positivism. The study adopted a retrospective case-control approach that involved drawing data from medical records of patients (cases) who underwent CAPD treatment and developed peritonitis and those who did not were recruited. This chapter will present the study location and its attributes first. Then the chapter will present the sampling techniques used including the criteria for population selection. Thirdly, the chapter will present the data collection method and its justification. Finally, the chapter will present the data analysis techniques.

3.2 The Study Area

The study was conducted at Inkosi Albert Luthuli Central hospital, Durban, situated in the KwaZulu-Natal province, South Africa. KwaZulu-Natal is located on the eastern part of South Africa, stretching along the eastern coast of the Indian Ocean. The province has a population of 10.3 million people according to the 2011 census (Beck. 2013). The province is a multiracial community comprising mainly of: blacks, whites, Indians and other minor ethnic groups. Durban is the biggest city in the province.

Amongst all the public hospitals in the province Inkosi Albert Luthuli is the biggest and the only one endowed with all available specialised services in the province. As a public health facility, the patients admitted to the dialysis unit are referred from hospitals across the province. These patients are unable to afford private health care and rely on public health services to meet their health needs. Patients admitted to unit are those in end stage of renal failure, who have not been able to secure a kidney transplant, but whose chances of survival with dialysis are good. This includes those who are HIV positive which were not selected and qualified for CAPD during the study period, irrespective of their CD4 count.

3.3 Sampling Framework and the Definition of study population

Inkosi Albert Luthuli Central Hospital was purposively sampled since the special services including PD are conducted at the institute. Furthermore the researcher was working at the institution and resided in Durban.-As it was a retrospective review, it was not possible to decide on an optimal study size, but rather all participants who met the inclusion criteria would become the study sample. The following inclusion and exclusion criteria applied for the case and control groups:

a. Cases:

Inclusion criteria:

- All the patients with End Stage Renal Disease (ESRD), attending IALCH,
- Those who underwent CAPD treatment and developed peritonitis between 2009 January 01- 2010 December 31.

Exclusion criteria:

- All the CAPD patients who developed other type of infection than peritonitis.

b. Controls:

Inclusion criteria:

- A selection of 2 first CAPD patients with no history of peritonitis that attended each clinic during the study period.

Exclusion criteria:

- The following exclusion criterion was used:
- Patients who regularly attended the clinic but were lost to follow up.

3.4 Data collection tools

A data collection sheet was developed as a data collection tool. The tool was developed to collect the following data from the patient's records:

Demographic details:

- age,
- gender,
- race ,
- residence (urban/rural)
- medical history:

- time of onset,
- obesity,
- hypertension,
- diabetes mellitus,
- other underlying factors
- serum creatinine
- erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), initial treatment modality
- Microbiological culture types of pathogens, treatment duration: the time between the starting date and cessation date.

The abnormalities were defined by, $ESR \geq 100$, $PDF \geq 1140$, and $Creatinine \geq 750$. Seasonality included variations of months and winter in Durban (June to August), summer (between September and April), winter is between autumn (mid-February to April) and springs (August-mid October).

The laboratory staff has a standardised method of collection of samples and processing. The data captured on the patient charts followed the Department of Clinical Microbiology/ National Health Laboratory Service standard operating procedures. The diagnosis of peritonitis was determined by using the following criteria: Abdominal pain, peritoneal fluid containing more than 100 white cells/ ml with at least 50% polynuclear cells, and the pathogens in the peritoneal dialysis fluid (Warady *et al.* 2007). The standard microbiological test (culture) consisted of the pathogens being isolated from peritoneal dialysis fluid (PDF) and cultured on standard media agar plates for three days, and for fungi on Sabouraud agar, anaerobes rods are not cultured in IALCH laboratory.

We conventionally use mixed anaerobes organisms to express the multiplicity of infection and culture of anaerobes is expensive we don't routinely culture anaerobes in our laboratory and we use partial identification based on microscopic morphology appearance. In this study other organisms' refer to those who are not usually isolated in our laboratory.

3.5 Data Analysis

The researcher with the help of a research assistant extracted the data from the hospital patient register computer frame. The data was manually entered on to the data collection sheets. The

data on the sheets was coded and entered into a computer package called the Statistical Package for the Social Sciences (SPSS version 21, IBM incorporated Chicago, IL, USA). The demographic data was analysed using descriptive statistics: sum, mean, average and presented in tables and graphs. As presented above the study collected socio-demographic data and it was split into categories for easier analysis. Data on the age (in years) of patients was categorised into three age groups namely less than 35 years was the first, 36-50 years was the second and then finally above 51years.. Data on race was disaggregated into four categories namely: blacks, Indians, Coloureds and Whites. Data was also disaggregated by gender and if is referred to as female or/and male. Data was also disaggregated using the area of residency of the patient and this data was analysed as either rural or/and urban.

Cox proportional hazards was performed to estimate hazards ratios (HR) with corresponding 95%CI for the occurrence of new onset of CAPD peritonitis associated with the variables of interest. In risk stratification analysis, we divided participants into exposed (presence) and non-exposed (absence) arms

Differences between exposed and non-exposed arms were assessed, and Kaplan-Meier survival curves generated for each arms. The differences between arms were analysed by log rank, chi-square or t test as appropriate.

Data were expressed as means \pm standard deviation (SD) for continuous variables and proportions (%) for categorical variables. Percentages across group were compared using chi-square test. Means values between two groups' ≥ 3 groups were compared using *t student test* and analysis of variables (ANOVA), respectively. The *P* Value of <0.005 was considered significant different in statistical parameters. Univariate and multivariate logistic regression analysis were performed using statistical package software for social sciences (SPSS) version 21.0 for windows (IBM*Incorporated) Chicago, IL, USA.

3.6 Ethical consideration

The study observed ethical codes of conducting medical research. The study was ethically cleared by the University of KwaZulu-Natal REF: BF190/010 (UKZN) ethics office and the Biomedical Research Ethics committee. Data were manipulated using the IALCH Speed miner Software to access the medical records of our sample patients. All names or any other

information that could lead to linking the data and the patient was removed before data analysis. Thereafter, the manager of the data was contacted and an appointment made for the researcher to have access to the patient charts. The researcher printed out the data collection sheets and sat at the computer in the records department to access the relevant files.

All the data collection sheets were kept in a locked cupboard in the researcher's office, and the digital data was only accessed on a password protected computer. Only the researchers, the statistician and the supervisor had access to the raw data. The data will only be disseminated as aggregated information at various forms, as well as made available in publications.

3.7 Summary

Chapter four has presented the research methodology, sampling framework, data collection tools, data analysis and ethical considerations. The study is dominantly quantitative and utilises data collected from the patient's charts. Only patients on CAPD were included in the study since the study aims to address issues around peritonitis. CAPD peritonitis patients formed the experiment population while the rest formed the control group. The two groups were not statistically drawn since it depended on the condition of the CAPD patients who presented themselves to IALCH, Durban. Both descriptive and analytical data analysis techniques were used to varying degrees depending on the research question to be answered. Finally, high levels of ethical conduct were observed throughout the research process including the entry, data collection process and the exit.

CHAPTER 4: RESULTS

4.1 Introduction

This chapter presents the study results that address the study objectives. The objectives set out in chapter one stipulates that the study address the following issues: explore socio-demographic characteristics of CAPD patients; establish the prevalence of peritonitis; and to describe the microbiological organisms associated with peritonitis. The chapter will establish the patient's socio-demographic data first, then, clinical prediction. Finally, the incidence and features of micro-organisms associated with peritonitis are presented last.

4.2 Results

Between January 2009 and December 2010, 115 patients underwent CAPD of which 91 patients met the inclusion criteria. Amongst the 91 patients recruited in the study, 45 (49%) presented with peritonitis (cases) and 46 (51%) did not have peritonitis (control) (Table 4.1). The results presented in Table 4.1 indicate that out of 45 CAPD patients with peritonitis, 24 (53.3%) were Indians, followed by 18 (40%) blacks, 2 (4.4%) coloureds and 1 (2.2%) white. Of the 45 participants diagnosed with peritonitis, 29 (64.4%) and 16 (35.6%) were females and males respectively. The Total case and rate of peritonitis in year 2009 were presented and analysed as followed: The number of patients' months= numbers of patient's day/30.42.

The overall 100 patients $\times 365$ days/30.42=1.19986/30 episodes =39.99=40 months of peritonitis free.

Since in 2009 we had 30 episodes, and only 15 episodes in 2010 which reflect the $\frac{1}{2}$ of the episodes observed in 2009.

Among patients with peritonitis, 93.3% (42/45) were living in urban areas while 6.7% (3/45) were residents in rural areas. The age of the study population ranged between ≤ 35 - ≥ 50 years. There was significantly more females than males among the cases group ($p=0.00466$), but no significant difference was observed between the two groups (control and cases). There was no significant difference observed between blacks and Indians ($p= 0.2048$). However, a statistically significant difference was observed between both black and Indians when compared to either whites or coloured ($p < 0.01$). Obesity, hypertension, diabetes mellitus were

significantly associated with the development of peritonitis ($p=0.03$, 0.00652 , 0.00782 , respectively).

Table 4.1 Summary of demographics and Clinical characteristics of CAPD patients with and without peritonitis.

Demographics & Clinical Characteristics	Cases Group		Controls Group		P. value
	No. 45	%	No. 46	%	
AGE					
≤35 years	17	37.8%	13	28.3%	0.33204
35-50 years	20	44.4%	26	56.5%	0.2654
≥50 years	8	17.8%	7	15.2%	0.1936
GENDER					
Female	29	64.40%	23	50%	0.16452
Male	16	35.50%	23	50%	0.16452
RESIDENCE					
Urban	42	93.30%	39	84.80%	0.1936
Rural	3	6.70%	7	15.20%	0.1936
ETHNICITY					
Blacks	18	40%	14	30.40%	0.33706
Indians	24	53.33%	28	60.90%	0.4654
White	1	2.22%	0	0%	-
Coloured	2	4.44%	4	8.70%	0.41222
OBESITY					
Obese	18	41%	34	73.9%	0.003
Not obese	26	59%	12	26.1%	0.17702
HYPERTENSION					
HPT	36	80%	45	98%	0.00652
Non HPT	9	20%	1	2%	0.00652
DIABETES					
DM	5	11%	20	43.5%	0.00782
Non DM	40	89%	26	56.5%	0.00782
GLOMERULONEPHRITIS					

GN	16	35.60%	30	65.20%	0.02034
Others	29	64.40%	16	34.80%	0.02034

During univariate analysis (Table 4.2), there was no association between gender, age, residence and ethnicity with the development of peritonitis. However, obesity, diabetes mellitus, and hypertension were significantly associated with peritonitis among CAPD patients (Table 4.2).

Table 4.2. Univariate associations between selected demographics and clinical variables and peritonitis in CAPD patients

Variables	Pvalue	OD ratio	95% CI	Significance
Age	0.666	1.308	[0.387-4.41]	NS
Gender	0.193	1.750	0.753-4.067	NS
Residence	0.204	2.571	[0.607-10.405]	NS
Ethnicity	0.205	2.714	[0.434-16.961]	NS
Obesity	0.044	3.763	1.038-13.646	S
Diabetes	0.013	6.0	1-467-24.547	S
Hypertension	0.026	11	1.33-90.95	S
Creatinine	0.037	2.875	1.068-7.742	S
CRP				

(* variables with insufficient data were not included in the analysis)

During the multivariate analysis using logistic regression models, diabetes mellitus, CRP levels ≥ 100 and black ethnicity were independently associated with peritonitis among CAPD patients (Table 4.3).

Table 4.3 Independent predictors of the incidences of peritonitis among CAPD participants

Independent Predictors		B	SE	HR95%CI	P
<i>Diabetes mellitus</i>	Yes	0.763	0.359	2.2 (1.1-43)	0.034
	No		References	1	
<i>CRP</i>	≥ 100	1.05	0.379	2.9 (1.4-6)	0.006
	<100		References	1	

<i>Ethnicity</i>	Blacks	1.85	0.929	6.4 (1.03-39.3)	0.046
	Others	0.492	0.359		

Table 4.4 confirms the presence of a significant relative risk of peritonitis for diabetic patients when corrected for hypertension. (OR = 5.314, $p = 0.023$). However, the RR of peritonitis associated with hypertension was not confirmed after correcting, therefore making HPT a confounder.

Table 4.4: Correction between hypertension and diabetes associated with development of peritonitis in CAPD peritonitis.

Variables	P.value	OD Ratio	95%CI	Significance
Diabetes corrected for Hypertension	0.023	5.314	[1.256-22.489]	S
Hypertension corrected for Diabetes	0.532	2.032	[0.220-18.765]	NS

The aetiological agents of peritonitis among the cases are displayed in Table 4.5 below. Of 45 cases, microbiological confirmation was done in 29 patients. The predominant causative agent was *Staphylococcus aureus* (8 cases) followed by *Candida albicans* (7 cases), mixed anaerobes (6 cases) and *Pseudomonas aeruginosa* (3 cases).

Table 4.5. Proportions of isolated micro-organisms from CAPD patients with peritonitis

Type of microorganisms	n (%)
Gram negative microorganisms	5 (17.2)
<i>Escherichia coli</i>	1
<i>Pseudomonas aeruginosa</i>	3
<i>Klebsiella pneumoniae</i>	1
Gram positive microorganisms	9 (31)
<i>Staphylococcus aureus</i>	8
<i>Staphylococcus epidermidis</i>	1
Fungi	9 (31)
<i>Candida albicans</i>	7
<i>Rhodotorula species</i>	2
Anaerobic microorganisms	6 (20.7)

Table 4.6 displays the susceptibility patterns of the causative agents of peritonitis isolated from the study population.

Table 4. 6: Summary of causatives micro-organisms and antimicrobial sensitivity profile in CAPD peritonitis patients.

Microorganisms	Sensibility	Resistance	Antibiotic prescribed
<i>Staph aureus</i>	Cloxacillin		Protocol
<i>Staph aureus</i>	Cloxacillin		Protocol
<i>Staph aureus</i>	Cloxacillin		Amikacin and ciprofloxacin
<i>Staph aureus</i>	Cloxacillin		Protocol
<i>Staph aureus</i>	Cloxacillin		Protocol
<i>Staph aureus</i>	Cloxacillin		Vanco+cipro
<i>Staph aureus</i>	Cloxacillin		Protocol
<i>Staph aureus</i>	Cloxacillin		Protocol
<i>Staph epidermidis</i>	Vancomycin		Protocol
<i>Candida albicans</i>	Fluconazole		Fluconazole
<i>Candida albicans</i>	Amphotericin B	Fluconazole	Amphotericin B
<i>Candida albicans</i>	Fluconazole		Fluconazole
<i>Candida albicans</i>	Fluconazole		Fluconazole
<i>Candida albicans</i>	Fluconazole		Fluconazole
<i>Candida albicans</i>	Amphotericin B	Fluconazole	Amphotericin B
<i>Candida albicans</i>	Fluconazole		Fluconazole
<i>Rhodotorula spp</i>	Amphotercin B		Amphotericin B
<i>Rhodotorula spp</i>	Amphotercin B		Amphotericin B
<i>Pseudomonas aeruginosa</i>	Piperacillin and Gentamycin		Protocol
<i>Paseudo aeruginosa</i>	Meropenem	Ciprofloxacin and amikacin	Meropenem and ciprofloxacin
<i>Pseudo aeruginosa</i>		Piperacillin and Gentamycin	Amikacin and ciprofloxacin
<i>E.coli</i>	Gentamycin and amoxicillin and clavulanic acid		Protocol
<i>Klebsiella pneumonia</i>	Piperacillin and tazobactam and cefuroxim	Ciprofloxacin	Others

All 8 isolates of *S. aureus* were susceptible to cloxacillin, a first-line drug of choice used in the management of staphylococcal infections in our facility. The only isolate of *S. epidermidis* was however resistant to cloxacillin but susceptible to the second-line vancomycin. Whilst the 2 isolates of *Rhodotorula* spp were resistant to fluconazole, 5/7 isolates of *C. albicans* were susceptible to fluconazole, the first-line antifungal drug used in our facility. All fungi that displayed resistance to fluconazole were all shown to be susceptible to amphotericin B. Susceptibility profile of *P.aeruginosa* and other isolated Gram negative bacteria varied and can be seen in Table 4.6.

The associations between types of microorganisms and mean levels of serum creatinine, age and onset of peritonitis among CAPD patients are depicted in Table 4.7.

Table 4.7: The mean level of age, serum creatinine, and month of onset across different types of microorganisms.

Microorganisms Types	Ages Means±SD	Serum creatinine Mean±SD	Month of onset Mean±SD
<i>S.aureus</i>	31.6±10.6	1691.5±184.7	8±3
<i>E.coli</i>	43±14.1	821.5±10.6	4±2
<i>S.epidermidis</i>	61	970	1
<i>P.aeruginosa</i>	25±0.01	1379.3±103.3	4±1
<i>C.albicans</i>	46.9±8	1443.4±417.5	10±3
Other pathogens	41	1096	2
Mixed(anaerobes)	33.5±9.2	1510±413.9	6±2
Negative culture	38.5±12.3	1077.1±407.8	6±3
ANOVA,P	0.021	0.012	0.040

The mean age of CAPD patients with peritonitis was 37.64 (±10.86) years (Figure 4.1). Among patients aged below 40 years, *P. aeruginosa*, *S.aureus* and mixed anaerobes were shown to be the predominant pathogens (Table 4.7 and Figure 4.2). However, for older patients (> 40 years), *C. albicans*, *E. coli* and *S. epidermidis* were predominant (Table 4.7 and Figure 4.2).

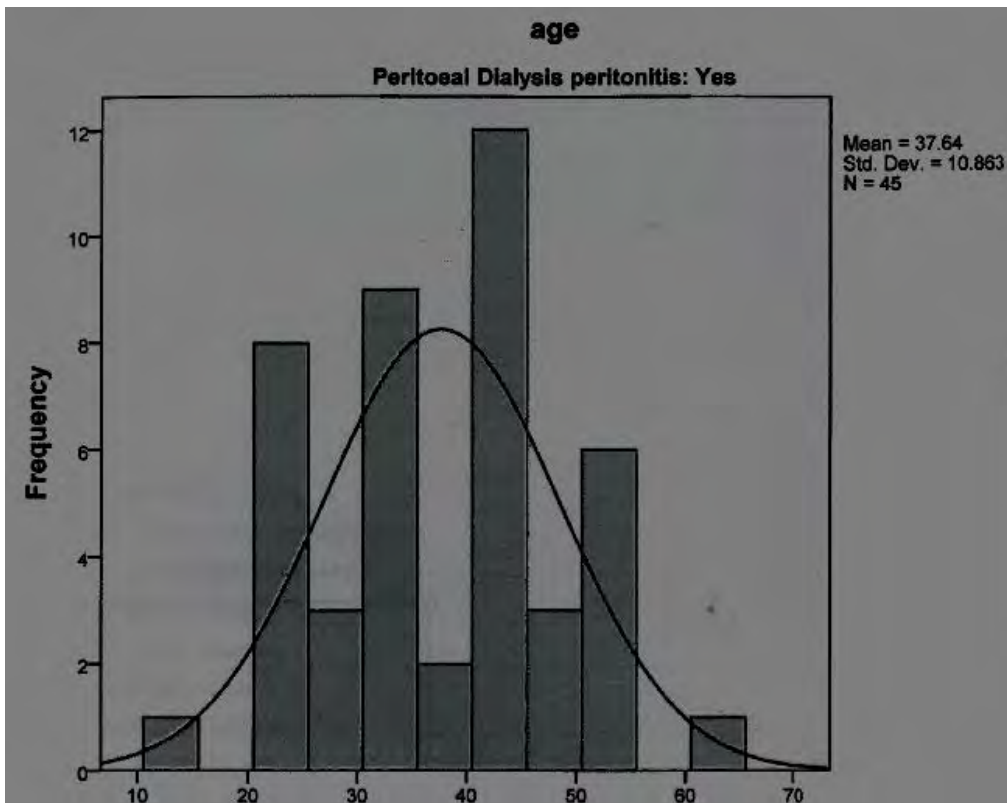


Figure 4.1 The age distribution of CAPD associated with peritonitis.

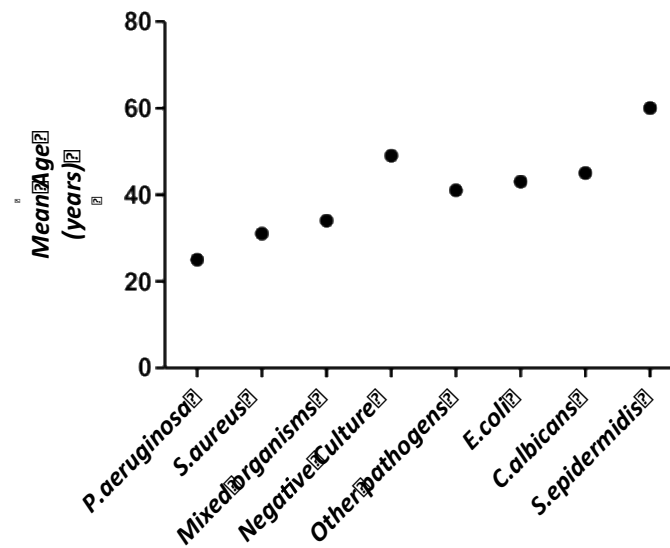


Figure 4.2 variation of level of age according to the causatives organisms.

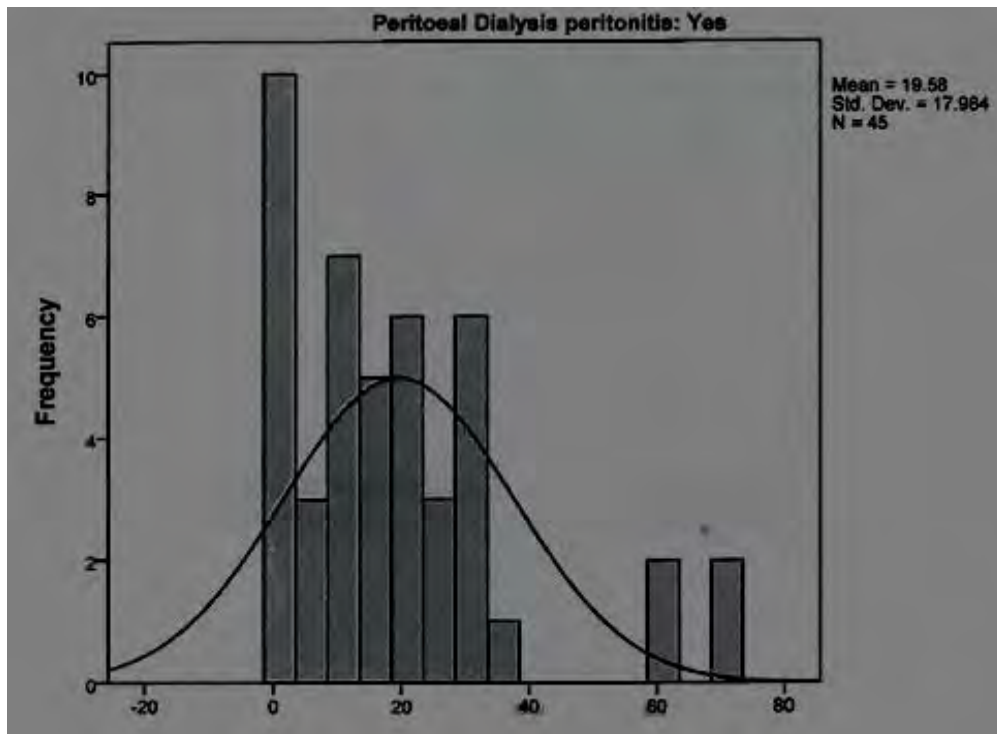


Figure 4.3 Peritonitis mean of onset (in months)

The onset of peritonitis among the study population appeared after 19.58 (± 17.98) months of undergoing CAPD (Figure 4.3). *Staphylococcus epidermidis* and *Rhodotorula species* (represented as “others”) were shown to cause early onset of peritonitis among CAPD patients whilst *S. aureus* and *C. albicans* were associated with the late onset of peritonitis (Table 4.7 and Figure 4.4).

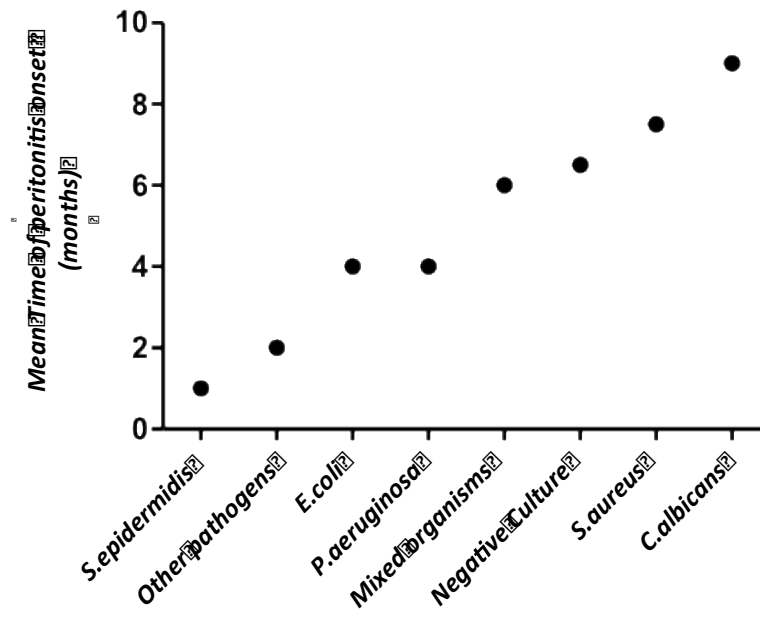


Figure 4.4 Onset of peritonitis (in months).

Figure 4.5 below shows that the highest level of serum creatinine (>1000) was associated with the presence of *Staphylococcus aureus*, *mixed organisms (anaerobes)*, *Candida albicans*, *Pseudomonas aeruginosa*, and others pathogens (*Rhodotorula* spp) as the causative agents for peritonitis in CAPD patients. Culture negative samples obtained from patients diagnosed clinically with peritonitis were also shown to be associated with high levels of serum creatinine (Table 4.7 and Figure 4.5).

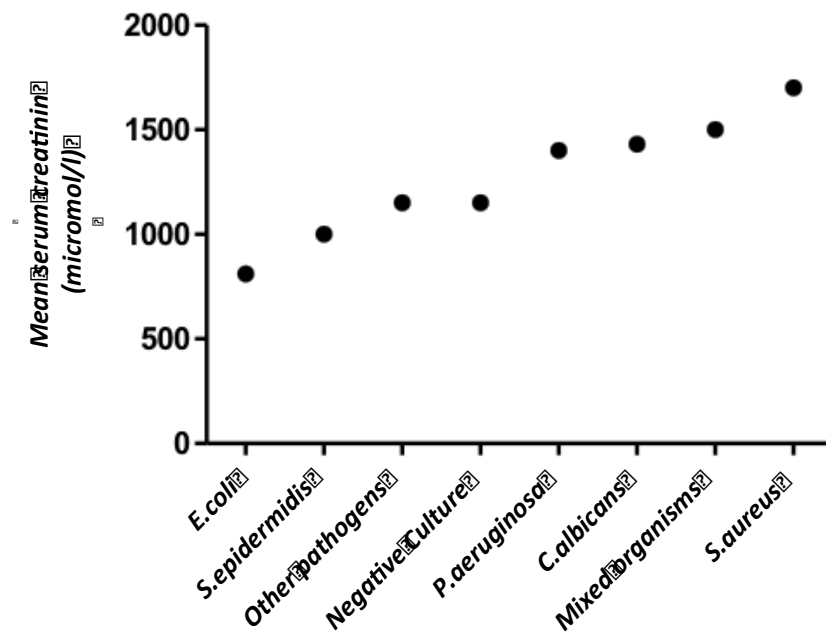


Figure 4.5 serum creatinine variations by types of micro-organisms ($p < 0.0001$).

Figures 4.6-10 below describe Kaplan Meir curves and show significant associations between age ≥ 40 years, obesity, *CRP*, *PDF*, *DM* with the occurrence of peritonitis in CAPD patients after adjusting for years of admission, residence, type of causative pathogens, seasons using Cox

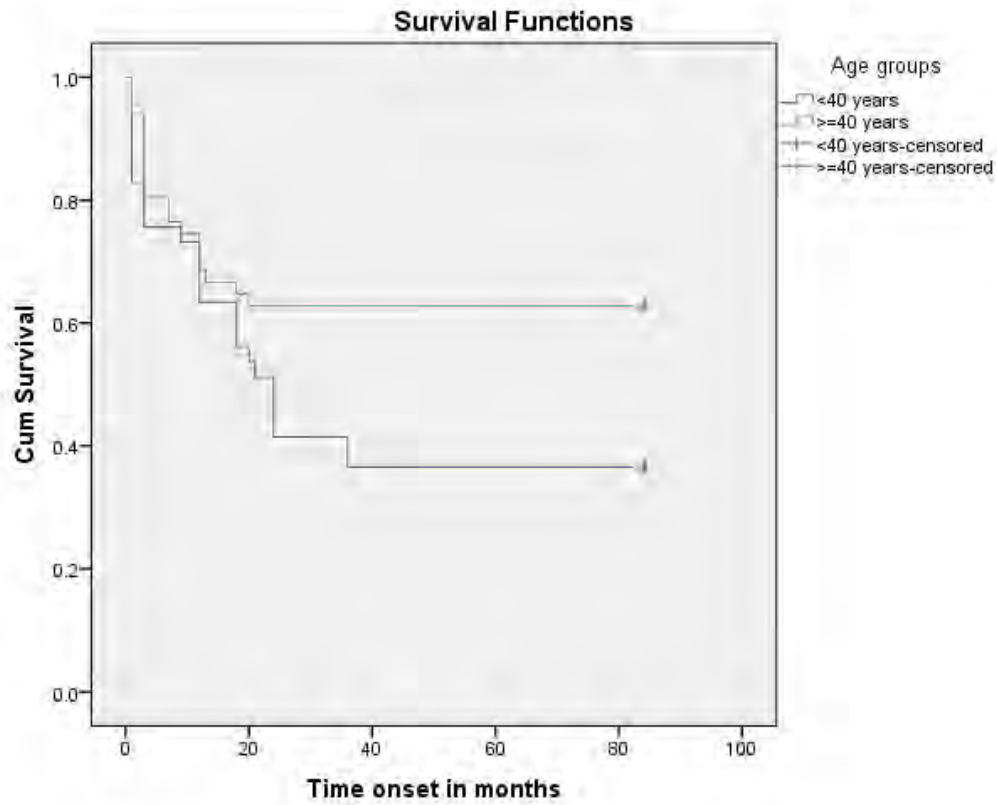


Figure 4.6 Kaplan Meier Curve for relationship between survival functions and age stratification by peritonitis incidence.

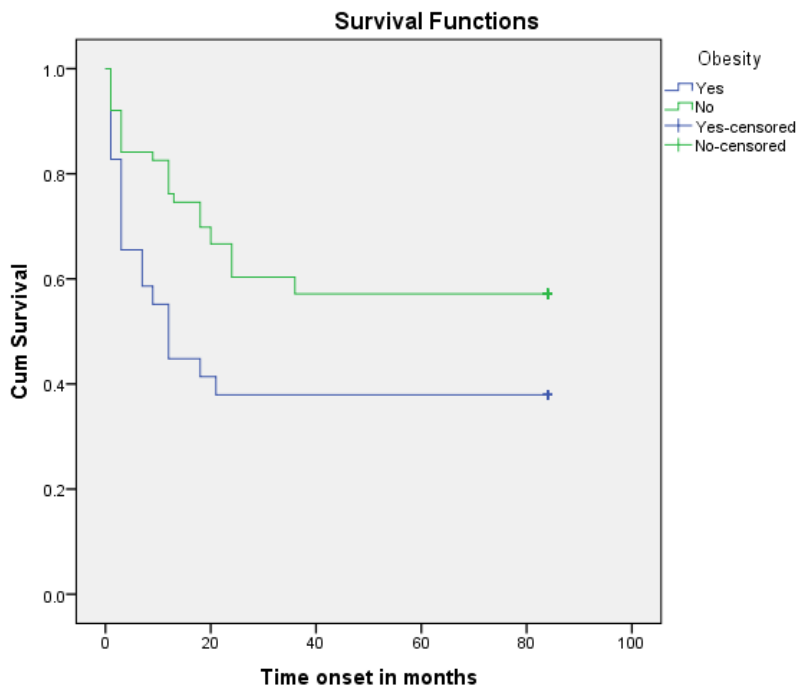


Figure 4.7 Relationship between survival and nutritional status by incidence of peritonitis

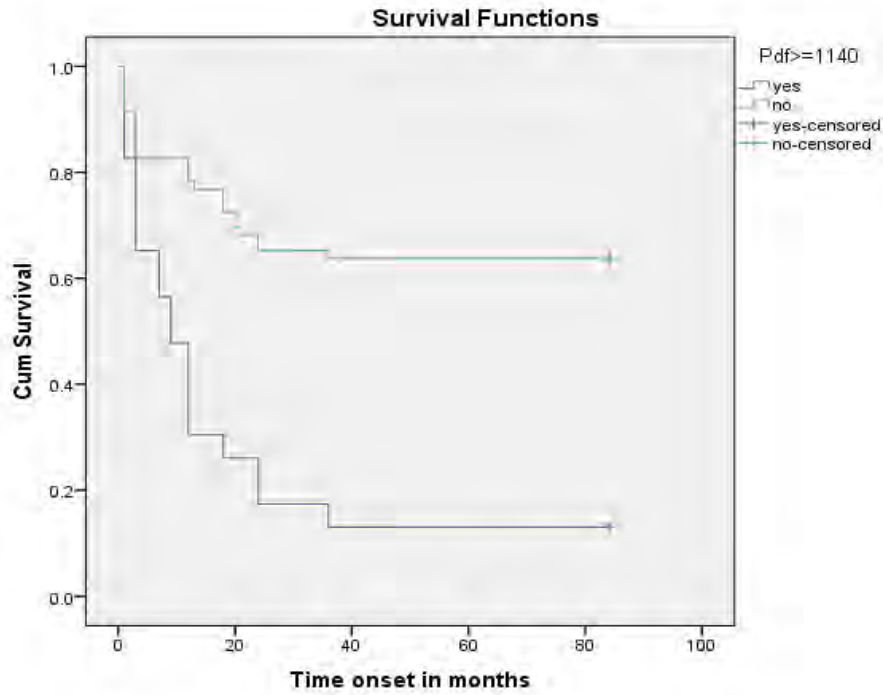


Figure 4.8 Association between survival function and the level of peritoneal dialysis fluid count (PDF) by peritonitis incidence.

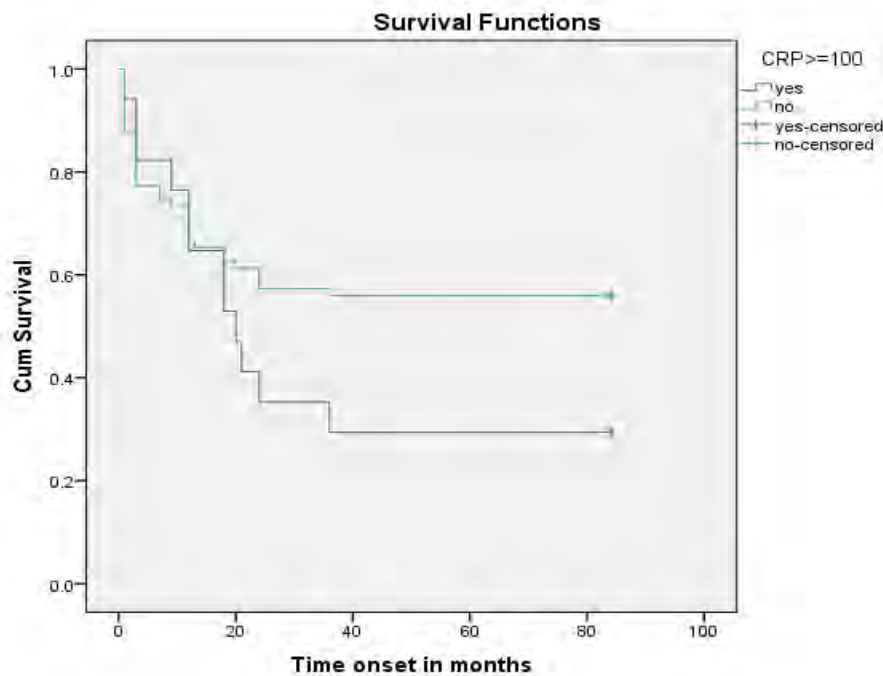


Figure 4.9 Relationship between survival function and levels of CRP by peritonitis incidence

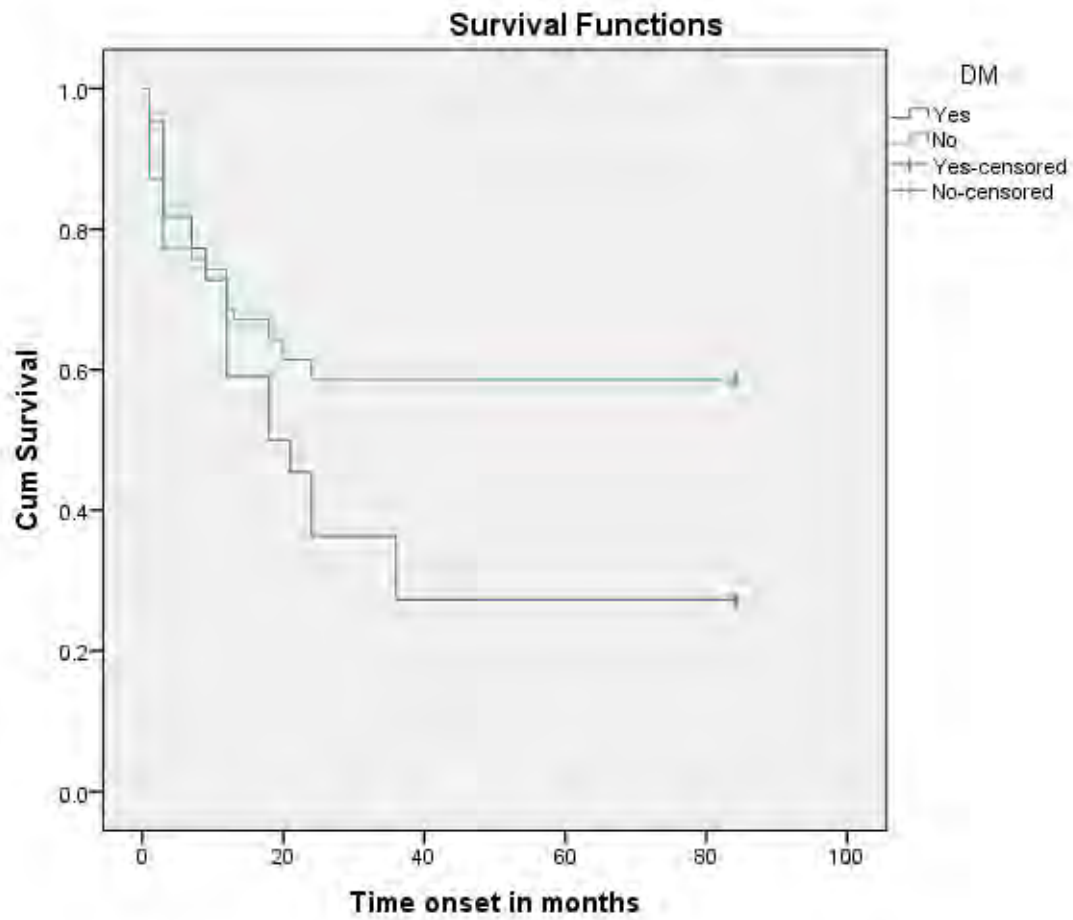


Figure 4. 10: Association between survival function and diabetes mellitus (DM) status by peritonitis incidence.

CHAPTER 5:DISCUSSION

5.1 Introduction

This chapter discusses the study results presented in Chapter 4 and relates them to the literature reviewed in focus with the study objectives. The discussion brings together the following three components namely: socio-demographic data, medical history, risk factors and incidence of peritonitis as well as the associated microbiological organisms.

5.2.Socio-demographic and risk factors associated with peritonitis among CAPD patients

Findings from this study suggest that diabetes mellitus and black ethnicity were independently associated with the development of peritonitis. These results concur with findings from Vikrant *et al.* (2014) during a study done in India, from a government tertiary care hospital where a high proportion of their patients (47%) were diabetics and the mortality was higher for diabetic patients than non-diabetic patients. Another Indian study conducted in 2011 by Bunnag *et al.* found that one of the significant risk factors associated with peritonitis was DM (62.5%) in patients with peritonitis within the first years of CAPD as compared to 18.2% of patients without peritonitis or had or developed peritonitis after the first year of CAPD ($p=0.047$).

A retrospective study conducted by Figueiredo *et al.* (2013) in Brazil, also found that most of their patients were females and DM was a risk factor associated with the development of peritonitis. Similar findings were observed in Senegal by Niang *et al.* (2014).

The study done by Remon-Rodriguez *et al.* (2014), suggested that the main comorbidities associated with peritonitis among their CAPD patients were diabetes mellitus and cardiovascular diseases, particularly hypertension.

The present study however found that hypertension was significantly associated with peritonitis only during univariate analysis. We found that there was a significant relative risk (RR) of peritonitis for diabetic patients after statistically correcting for hypertension. In contrary, the RR of peritonitis among patients with hypertension was not confirmed to be significant after correcting for DM, making hypertension to be a confounder in our study population. The fact that many patients have DM and hypertension at the same time might explain these findings.

In addition to DM, another independent variable associated with peritonitis in this study was the black ethnicity. Our multivariate analysis showed that Black Africans had 6-fold higher risk of developing peritonitis than other ethnic groups. The following contributory factors of high probability for peritonitis among black South Africans might be: living in less developed environment, lower level of education, lower number of qualified professionals, poor housing, lack of electricity and water supplies, and the high cost of peritoneal dialysis fluid (Vikrant *et al.* 2013; Troidle *et al.* 1998; Chow *et al.* 2005; Goldie *et al.* 1996).

Among the socio-demographic factors studied, the present study did not show a significant association between age, gender and area of residence and the occurrence of peritonitis among CAPD patients. In contrary, a study from Chili reported high incidence of peritonitis among patients older than 65 years as compared to younger patients under automated peritoneal dialysis (Wang *et al.* 2001). In addition, during a Brazilian survey on CAPD, peritonitis free-time-findings were observed similar in patients of all ages, the majority of patients with lower socioeconomic status experienced peritonitis while on CAPD modality of treatment (Warady *et al.* 2007). In 2014, another Brazilian study conducted by De Moraes *et al.* reported during a study of 474 patients, that an older age was associated with the death during peritonitis, and the multivariable regression analysis, non-resolution of peritonitis was independently associated with older age, odds ratio (OR) 1.02: $p < 0.05$) The collagenosis amongst the elderly patients impacts negatively on treatment and the development of infection like peritonitis in CAPD patients.

The literature also confirms significant associations between dependency on social security assistance, lower education level, low income and high risk of peritonitis (Warady *et al.* 2007; Chadha *et al.* 2010; Piraino *et al.* 2000).

In regards to the total number of months of peritonitis free, previous studies in Hong-Kong find similar result as ours (Li *et al.* 2002). However another study in Brazil by Lobo *et al.* (2010) found 28 months of peritonitis free, while the International Peritoneal Dialysis Society recommends 18 months, suggesting that we are on a good track as an African country with limited resources.

In our study, the following factors were shown to be significantly associated with high incidence and early onset of peritonitis after using the Cox regression analysis: age > 40 ,

obesity and DM, while cell count ≥ 1140 in peritoneal dialysis fluid and CRP ≥ 100 , and serum creatinine >1000 .

The onset of peritonitis among our study population appeared after 19.58 months. Early onset of peritonitis was defined as any episode of peritonitis that occurred before 19.58 months of starting CAPD. A recent study by Kim *et al.* (2004) showed that peritonitis occurred within seven months following the beginning of CAPD. The difference between our study and the study by Kim *et al.* might due to the fact that our study population was composed of adult patients while the study by Kim *et al.* involved children.

The present study showed however that adults aged > 40 years had early onset of peritonitis. Higher peritonitis rate in older patients has been reported by several researchers (Holta *et al.* 1998; Cho *et al.* 2012; Nishima *et al.* 2014). In contrary, some studies in developed and emerging countries reported earlier onset of peritonitis among patients aged ≥ 65 years (Barretti *et al.* 2007; Cho *et al.* 2012; Lee *et al.* 2013). It can be hypothesised that this difference might be the result of genetic anticipation (Young *et al.* (2007).

The average age of peritonitis patients from our study at IALCH is comparable to a study from Senegal that reported the mean age of peritoneal patient to be 49 ± 5 years (Cisse *et al.* 2012). Furthermore, the majority of patients are black and are from bantu ethnic (Wolof from Senegal, and Zulu in South Africa, Xhosa in south Africa, Bakongo from the Democratic Republic of Congo) (Longo Mbenza unpublished data), others factors such as poverty, uncontrolled hypertension(91,1%) was more severe among blacks in Africa and Diaspora (Cisse *et al.* 2012; Cisse *et al.* 2011).

Obesity, an underlying condition associated with DM and hypertension, is also among the leading and valid risk factors associated with peritonitis in CAPD patients in many studies across the world. (Courivaud *et al.* 2015; Cho *et al.* 2014).The results of this study showed a positive correlation between patients' progression to peritonitis and obesity only during univariate analysis. In 2013, Nessim *et al.* enrolled 938 CAPD cases among Canadians patients who experienced 1338 peritonitis episodes and 1194 exit –site infections. Their findings revealed an increased risk of peritonitis in patients who had the highest BMI quartile (median: 33.5, interquartile range: 31.9-36.4).

The present study has shown that cases of early onset of peritonitis were associated with a strong inflammatory response (while cell count ≥ 1140 in peritoneal dialysis fluid and CRP ≥ 100). In agreement with our findings, Chow *et al.* (2014) confirmed that inflammatory response at both systemic and local intraperitoneal levels commonly affects PD patients. They found that the type of peritoneal dialysis solution might be involved in high inflammatory response. However, Hsieh *et al.* (2013) in Taiwan found early peritonitis patients were older, with DM and had lower serum creatinine than the late peritonitis patients which is in agreement with our findings where high mean level serum creatinine suggested the End Stage Kidney Renal Disease in patients with peritonitis.

Although this study did not use a data set for weather conditions over prolonged periods of time to assess the impact of climate variability on the occurrence of peritonitis, it echoes however on the importance of weather and climatic conditions by showing a high variability of incidence of peritonitis according to the different seasons over a year. Other studies published elsewhere have related weather conditions with the high incidence of peritonitis (Okpechi *et al.* 2010; Vikrant *et al.* 2013; Piraino *et al.* 2003; Schaefer *et al.* 2007).

In developed and Latin American countries, studies have shown a strong decrease in the incidence of peritonitis among patients with CAPD. (Mujais *et al.* 2006) due to introduction and dissemination of novel technology. South Africa like in many developing countries however, the delay in the incorporation of novel technologies for patients at the End Stage Kidney Renal Disease compounded with high rates of HIV may explain the high incidence of peritonitis.

5.3. Microbial agents (and their susceptibility patterns) associated with peritonitis in CAPD patients

The predominant causative agent was *Staphylococcus aureus* followed by *Candida albicans*, mixed anaerobes and *Pseudomonas aeruginosa*. The presence of *S. aureus* and *P. aeruginosa* are strongly suggestive of exit site and tunnel infection respectively. In a Danish nationwide, population-based cohort in patients with ESRD conducted by Nielsen *et al.* (2015), it was concluded that patients with ESRD and haemodialysis had increased risk of developing *Staphylococcus aureus* bacteraemia as compared to the control groups control groups. In Senegal, a study by Niang *et al.* (2014) found out that *S.aureus* was the leading cause of

peritonitis. Similarly, findings from Okpechi *et al.* (2012) at Cape Town in South Africa had shown that *S.aureus* was the most Gram-positive microorganism isolated among CAPD patients.

Although *S. epidermidis*, a coagulase negative Staphylococcus, was not shown to be predominantly associated with peritonitis among our study population, it was however an important causative agent in patients with an inserted device. Coagulase negative Staphylococci are not generally the cause of infections except for patients with devices such as catheters that enable them to form bio-films in order to cause infections. In addition, the formed bio-films negatively interfere with the antimicrobial therapy since microorganisms that adhered into bio-films down-regulated their metabolic pathways. Another reason why coagulase negative Staphylococci can cause infections is immune suppression. For example, diabetic patients are generally immune-compromised patients and therefore are vulnerable to Coagulase negative staphylococcus infection (Ananthakrishnan *et al.* 2014).

Fungal peritonitis, often caused by *Candida. albicans*, mainly occurs in the context of inappropriate use of antibacterial broad spectrum therapy. In 2014, Kumar *et al* reported that when fluconazole is used as a prophylactic agent in the setting of bacterial peritonitis might significantly reduce the incidence of subsequent fungal peritonitis in CAPD patients.

Mixed anaerobic bacteria were also found to be among the predominant causative agents of peritonitis among CAPD patients. Although the significance of anaerobes is increasingly recognised from the literature (Ghali *et al.* 2011; Chao *et al.* 2013), the diagnosis of anaerobes in our study was only based on microscopic presumptive findings. Confirmation from appropriate cultures was not performed.

Among patients aged below 40 years, *P. aeruginosa*, *S.aureus* and mixed anaerobes were shown to be the predominant pathogens whilst for older patients (> 40 years), *C. albicans*, *E. coli* and *S. epidermidis* were predominant. The difference can be explained at least partially by a decreased immune system in older individuals. Moreover, *P. aeruginosa* and *S.aureus* have necessary virulent factors able to cause infection in young patients. The pathophysiology underpinning these findings might also be related to host and/or organisms related factors (Szeto *et al.* 2003; Cho *et al.* 2012).

The onset of peritonitis among the study population appeared after 19.58 (\pm 17.98) months of undergoing CAPD. *Staphylococcus epidermidis* and *Rhodotorula species* (represented as

“others”) were shown to cause early onset of peritonitis among CAPD patients whilst *S. aureus* and *C. albicans* were associated with the late onset of peritonitis. The presence of fungi like *Rhodotorula* spp can be explained by the poor compliance of infection prevention and control measures while inserting peritoneal catheter. *Rhodotorula* spp are common airborne contaminant fungi but are most importantly considered as normal inhabitants of the skin, lungs, urine, and faeces in humans, hence can become important infectious agents among immunocompromised patients. In 2013, a study conducted by Seifi *et al.* in Iran showed *Rhodotorula* spp as the most contaminant isolated from samples obtained from phones and mobiles cellular phones, floor, and windows.

It can be hypothesised that *Rhodotorula* spp and *S. epidermidis* could have been introduced during peritoneal catheter insertion due to poor infection prevention and control measures. Due to the fact that many CAPD patients become immunocompromised, these microorganisms are rapidly able to cause early onset of peritonitis.

The present study also showed a high rate (35.5%) of peritonitis with negative culture. The proportion of culture-negative peritonitis maybe explained by the lack of some laboratory services or other pathogens of peritonitis not isolated during routine diagnostic laboratory workup. Other reasons might include inadequate sample collection and transport. This rate of peritonitis with culture negative was higher than the rate of 24.7% of peritonitis without isolated organism among Korean patients (Kwon *et al.* 2014). In addition, according to a study conducted by Lee *et al.* (2014), it was found that the incidence of cultures negative among 30 patients was 24%. Furthermore in another study conducted by Ghali *et al.* (2011) in Australia between October 2003 and December 2008, cases of culture negative peritonitis represented 13% of the 6639 patients enrolled. Moreover, Kent *et al.* (2000) and Holley *et al.* (1989) claimed that despite many improvements in culture techniques, negatives cultures account for 5-33% of catheter related infections, but in 2014 the results from a study conducted by Ram *et al.* showed 33.16% of cultures negatives peritonitis, contrasting with a another one conducted by Lan *et al.* (2014) who concluded that culture negatives were associated with the type of peritoneal dialysis. According to these authors, APD was associated with lower rate of culture negative peritonitis compared to CAPD.

Among the positive cultures, more than 50 % of the isolated micro-organisms were Gram positive bacteria. The higher rate of Gram positive reported in this study was similar with that from Senegal, West Africa (Cisse *et al.* 2012). Among the Gram positive organisms, *Staphylococcus epidermidis* and *Staphylococcus aureus* were the most frequent organisms observed in a study in Latin America. (Barretti *et al.* 2007).

There was no significant association between gender and pathogens such as *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, *Candida albicans*, and others micro-organisms. However, *Escherichia coli* isolates were common in females than males; there was males' predominance among patients infected with *Staphylococcus aureus*. Ethnicity did not impact on the incidence of *Staphylococcus aureus*, *Escherichia coli*, *Staphylococcus epidermidis*. However, *Pseudomonas aeruginosa* was predominant among whites but *Candida albicans* was predominant among coloured patients with peritonitis.

All isolates of *S. aureus* were susceptible to cloxacillin, a first-line drug of choice used in the management of staphylococcal infections in our facility. The isolate of *S. epidermidis* was however resistant to cloxacillin but susceptible to the second-line vancomycin. Some isolates of *Rhodotorula* spp were resistant to fluconazole while many isolates of *C. albicans* were susceptible to fluconazole, the first-line antifungal drug used in our facility. All fungi that displayed resistance to fluconazole were all shown to be susceptible to amphotericin B. Most Gram negative isolates were susceptible to ciprofloxacin, amikacin and meropenem.

Limitations

This study had several limitations. Firstly, we analysed only data from a single centre and also we had only few cases of peritonitis; our study design was a retrospective cohort study. Secondly, the study population in the present study did not reflect the demographic profile of the population in Durban.

Conclusions

1. Among the causative agents, *Staphylococcus aureus*, *Candida albicans*, mixed anaerobes and *Pseudomonas aeruginosa* were the commonest causes of peritonitis among the CAPD patients.
2. Age > 40, obesity and DM, while cell count ≥ 1140 in peritoneal dialysis fluid and CRP ≥ 100 , and serum creatinine >1000 were shown to be significantly associated with high prevalence and early onset of peritonitis.
3. *Staphylococcus epidermidis* and *Rhodotorula* species were shown to cause early onset of peritonitis among CAPD patients whilst *S. aureus* and *C. albicans* were associated with the late onset of peritonitis. The presence of fungi like *Rhodotorula* spp can be explained by the poor compliance of infection prevention and control measures while inserting peritoneal catheter. Fungus like *C. albicans* isolates maybe due to prior and inadequate use of antimicrobial agents, calling both clinicians and facility managers to reinforce the infection control measures and antibiotic stewardship policies.

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