Peritonitis in Patients on Continuous Ambulatory Peritoneal Dialysis at Universitas Academic Hospital Nephrology Unit

by

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of the requirements for the degree of
Masters in Medicine

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Declaration

I, Qwako Jacob Mosia hereby declare that this mini-dissertation is my own work. It is submitted for the Master's degree in Medicine in the Department of Internal Medicine, and the whole work has never been submitted for another degree at this or any other university.

I hereby cede copyright of this publication in favour of the University of the Free State.

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Dr QJ Mosia

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PERITONITIS IN PATIENTS ON CONTINUOUS AMBULATORY PERITONEAL DIALYSIS AT UNIVERSITAS ACADEMIC HOSPITAL NEPHROLOGY UNIT

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List of abbreviations in this study

CAPD	*Chronic ambulatory peritoneal dialysis*
CKD	*Chronic Kidney Disease*
ESRD	*End-stage renal disease*
PD	*Peritoneal dialysis*
RRT	*Renal replacement therapy*
RT	*Renal transplant*
WHO	*World Health Organization*

Abstract

Background

Continuous ambulatory peritoneal dialysis (CAPD) is an important option for treatment of end-stage renal disease (ESRD) in developing countries. Peritonitis remains the major cause of CAPD failure, leading to patients discontinuing peritoneal dialysis (PD) and switching to haemodialysis (HD). As access to haemodialysis is limited, it is important to focus the attention on preventing peritoneal dialysis failure.

Objectives

To ascertain the microbiology profile in patients on CAPD presenting with peritonitis at the Nephrology Unit at the Universitas Academic Hospital, to identify the antibiotic sensitivity patterns of the causative organisms, and to determine the treatment outcome of this complication.

Method

A descriptive retrospective study on 66 patients hospitalised between January 2005 and December 2014 was carried out in Bloemfontein, South Africa.

Results

One hundred and twenty-three episodes of peritonitis were identified. 22.0% (n=27) of these episodes were culture negative and 35.0% (n=43) were due to coagulase negative *staphylococcus*. The coagulase negative *staphylococcus* episodes were sensitive to cloxacillin in 53.5% and to vancomycin in 46.5%. The peritoneal dialysis catheter was removed in 28.5% of the episodes; and the most frequent co-morbidity was hypertension – in 48.5% (n=32) of the 66 patients.

Conclusion

The current empiric antibiotics remain appropriate for PD peritonitis. Coagulase negative *staphylococcus* is confirmed as the most common cause of PD peritonitis at the unit. CAPD units should be encouraged to adapt and optimise the general guidelines with regard to local infections.

1. Introduction

1.1 Background

Chronic kidney disease (CKD) is defined as kidney damage for ≥3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased glomerular filtration rate (GFR) of <60mL/min/1.73m2.[1] CKD is categorised into five stages of increasing severity as indicated in the table below.

Stages of Chronic Kidney Disease of all Types		
Stage	**Qualitative Description**	**Renal Function (mL/min/1.73 m²)**
1	Kidney damage-normal GFR	≥90
2	Kidney damage-mild ↓ GFR	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	End-stage renal disease	<15 (or dialysis)

Table 1. Stages of CKD[2]

Chronic kidney disease has a poor prognosis.[3] Firstly, it may progress to end-stage renal disease (ESRD), i.e. the disease stage where the body functions cannot continue without renal replacement therapy (RRT); secondly, it amplifies the risk for cardiovascular complications which often lead to premature death.

Chronic kidney disease is a major public health challenge worldwide as indicated by the rising number of patients requiring treatment for end-stage renal disease (ESRD).[4,5] The number of patients with ESRD is five times the world population growth (1.3%) and continues to escalate beyond expectations, showing no sign of reaching a plateau within the next two decades.[6] The impact is even more severe in sub-Saharan Africa (SSA), which includes approximately 70% of the developing countries in the world.[7] Specifically in South Africa, treatment of ESRD is an important public health issue due to limited resources.[8]

In 2004, renal replacement therapy (RRT) was accessed by approximately 1.8 million patients worldwide.[9] Seventy-seven percent of patients received RRT, and the remainder

underwent renal transplantation. On a global scale less than 5% of patients on dialysis are from SSA.[10] In developing countries only a minority of patients with ESRD have access to RRT, culminating in many patients dying of untreated CKD and its complications.[11]

In developing countries some form of rationing has always been practised as a result of limited access to dialysis. In South Africa, the National Department of Health drew up guidelines in 1997 to formalise the selection process and assist nephrologists in the difficult task of patient selection.[11] The majority of renal units in South Africa have incorporated the "peritoneal dialysis (PD) first" rule into their guidelines because of the scarcity of haemodialysis (HD) slots. This means that all patients who are found eligible for the public sector RRT programme are started on PD, and only considered for HD once the PD had failed. Because it is the only option available, this rule applies even to patients who have suboptimal socioeconomic circumstances that may predispose them to PD failure.

Continuous ambulatory peritoneal dialysis (CAPD) is an important option for the treatment of ESRD in developing countries, mainly because patients are taught to perform dialysis independently at home. Several complex and interdependent factors make PD a challenging treatment option in SSA. PD-related peritonitis remains the Achilles' heel of PD worldwide, as indicated by a study from Groote Schuur Hospital, Cape Town, which reported peritonitis as a major factor leading to PD failure.[12]

The success of treating PD-related peritonitis depends on prompt diagnosis and effective treatment. Empiric antibiotic treatment is started immediately whenever PD peritonitis is suspected. This is done after PD effluent is sent for cell count with differential count, Gram stain, and culture. The International Society of Peritoneal Dialysis (ISPD) Committee recommends centre-specific selection of empiric therapy, dependent on the local history of sensitivities of organisms causing peritonitis. The ISPD also recommends that renal units should monitor causative organisms cultured on PD effluents of patients presenting with PD-related peritonitis. During this process, infection rates could be monitored, modifiable risk factors identified, and especially antibiotic response patterns established to decide on appropriate empiric antibiotics regimens.[13]

The primary objective of this study was to describe the causative organisms cultured from PD effluents of patients presenting with PD-related peritonitis at the Universitas Academic

Hospital Nephrology Unit, Bloemfontein. Secondary objectives were to describe antibiotic sensitivity patterns and treatment outcomes.

1.2 Literature review

1.2.1 Burden of non-communicable diseases (NCDs)

NCDs as an entity have emerged as important causes of morbidity and are currently listed as the leading cause of death in the world.[4,14] In 2005, NCDs were estimated to cause more than 60% (35 million) of all deaths globally; however, this increased to 68% (38 million) of 56 million incidences of death by 2012.[4] More than 40% (16 million) of these deaths were premature, meaning they occurred in patients who were are under the age of 70 years. Almost three-quarters of all NCD deaths (28 million) occur in low- and middle-income countries, and the majority is premature (82%).[15]

1.2.2 Impact of CKD on NCDs and worldwide prevalence

CKD is an important contributor to the NCD burden and is regarded as a public health threat worldwide.[4] An important observation in 2010 described CKD to be the second leading cause of premature deaths caused by non-communicable diseases, and the 18th highest cause of death worldwide.[7,16] In the United States, the overall prevalence of CKD increased from 8.2% in men and 12.1% in women during1988-1994 to 11.1% in men and 15.0% in women during 1999-2004.[4] The authors of the National Chronic Kidney Disease fact sheet (2014) estimated that more than 10% of adults in the United States (more than 20 million people) may suffer from CKD of varying levels of seriousness.[17]

1.2.3 The impact of CKD on NCDs in SA

Since the election of the first democratic government in 1994, South Africa has experienced a rise in statistics for non-communicable diseases. At the end of 2004, about 1.8 million people worldwide were undergoing treatment for ESRD; 1.3 million (77%) were on dialysis treatment and 412 000 (23%) were living with a functioning renal transplant.[9] In South Africa, the prevalence of ESRD patients on treatment increased from 2843 in 1994 to 8559 in 2012; these estimates are from public and private sectors.[18] The prevalence of

patients with ESRD is unknown, because the South African registry does not include ESRD patients from the public sector who did not meet the selection criteria for RRT.

In 2004, the WHO estimated 28% of the total disease burden in South Africa to be caused by non-communicable diseases.[19]

1.2.4 Global, SSA and SA renal registries

Over the years, an increasing number of national and international renal registries have provided valuable demographic and epidemiologic information on renal diseases. The first report of the European Renal Association-European Dialysis and Transplant Registry (ERA-EDTA) was published in 1965.[6] The first new report of the South African Renal Registry summarises the provision of RRT across South Africa from 31 December 2012. Subsequent to the last reported data from 1994 there was a lack of reliable data on RRT in South Africa for the past two decades.[18]

The South African Dialysis and Transplant Registry (SADTR) reflects the patients who were selected for RRT where public sector (state) facilities will offer RRT only to patients who are eligible for renal transplantation.[20] The SADTR does not accurately reflect the aetiology of CKD for the South African population at large, because it only contains statistics of patients who are on RRT. In 1994, glomerulonephritis was recorded by the SADTR as the cause of ESRD in 1771 (52.1%) and hypertension in 1549 (45.6%) of patients.

1.2.5 Monetary cost of CKD and RRT

The global economic impact of CKD is tremendous.[4] Total therapy cost per patient per year in the United States amounts to approximately $66,000.[6] It is estimated that by 2030, more than 70% of patients with ESRD will be living in low-income countries, such as those in SSA, where the annual gross domestic product per person is on average less than US$1500.[15] This estimate is alarming in view of the fact that the global prevalence of dialysis has doubled since 1990, and that RRT was accessed by 1.8 million people worldwide in 2004 – with less than 5% of that population coming from SSA.[20]

There is a global need to raise awareness of CKD and to incorporate prevention of CKD progression programmes into the public health agenda. It is paramount to implement programmes for early screening and detection of CKD, especially in high-risk populations to allow early detection and early implementation of therapeutic measures to retard the progression of CKD.[4] It is anticipated that this may reduce the CKD burden globally over time and, most importantly, improve the health outcomes of patients with CKD.

South Africa was classified as an upper-middle income country by the World Bank in 2013. Its population increased from 40.4 million in 1994 to 52.3 million in 2012.[18] The majority of South Africans do not have medical aid and 83.4% of the population rely on the public health sector for services.

The majority of the population in the SSA countries cannot afford RRT, therefore they become a burden to the public sector facilities. Abu-Aisha and Elamin 2010, reported the total annual cost per patient for HD and PD respectively were about R82 500 and R141 400 in South Africa.[21] This does not take into account the costs of human resources, vascular access creation or PD catheter insertion and dialysis fluid.[22]

1.2.6 CKD in Africa: major risk factors

Kidney Disease Improving Global Outcomes (KDIGO) is the global organisation developing and implementing evidence-based clinical practice guidelines in kidney disease. It is an independent volunteer-led self-managed charity incorporated in Belgium accountable to the public and the patients it serves.

KDIGO recommend that all countries should have a targeted screening programme for CKD. Target groups should include patients with hypertension, diabetes and cardiovascular disease. Other groups may include families of patients with CKD, individuals with hyperlipidaemia, obesity, metabolic syndrome, smokers, patients treated with potentially nephrotoxic drugs, a number of chronic infectious diseases, patients with certain cancers, and patients aged > 60 years.[23]

Hypertension

Hypertension is a leading cause of CKD in SSA especially in black patients. In South Africa hypertension affects about 25% of the adult population and 45.6% of CKD cases are

attributed to undiagnosed or poorly controlled hypertension.[5] Hypertension is the underlying cause of ESRD in 21% of patients requiring RRT.

The cause of the increased risk of hypertensive nephropathy in individuals of African ancestry has remained elusive over the years.[24] The following risk factors have been implicated: low socio-economic status, lack of access to adequate healthcare, and a higher blood pressure. Dramatic changes occurred in the past few years in our understanding of the disease process that had historically been labeled hypertensive nephrosclerosis. Modern molecular genetic techniques have shown that variation in the apolipoprotein L1 gene (APOL1) on chromosome 22q adds to the excess risk of nondiabetic ESRD in African Americans.

Data from the Free State province in South Africa indicate that most patients who are referred with CKD for RRT assessment present late in the course of their disease.[25] Hypertensive nephropathy was the most likely aetiological factor in 52% of these patients but could only be proven histologically in about 3% of the patients who were eligible for kidney biopsy.

Glomerulonephritis

Glomerular disease is a major cause of ESRD in reports from SSA.[26] In Okphechi's series the most common indication for kidney biopsy was a nephrotic range of proteinuria, and the main secondary cause was lupus nephritis (17.2%) respectively followed by HIV-associated nephropathy (12.2%) and membranous glomerulonephritis (11.6%).[27] Some registries report asymptomatic urinary abnormalities as the next common indication for kidney biopsy. Van Rensburg *et al*.'s review of adults admitted to a nephrology unit in the Free State province of South Africa concurred that patients without a medical background history were referred late for evaluation.[25]

Okpechi *et al*. also reported that, overall, mesangiocapillary glomerulonephritis (and not IgA nephropathy) was the dominant form of glomerular disease especially in blacks and coloured patients while mesangial proliferative glomerulonephritides was more frequently seen in whites.[27] Focal segmental glomerulosclerosis was found to be more common in blacks.

Mesangiocapillary glomerulonephritis frequently present as type I or III, and is commonly associated with cryoglobulinaemia and HCV infection in adults. Secondary mesangiocapillary glomerulonephritis is typically associated with autoimmune diseases and chronic infections like HCV, malaria, schistosomiasis and HIV.[27]

HIV chronic kidney disease

Data on the actual prevalence of HIV-related glomerular disease in Africa are scarce.[26] Levey *et al*. showed that the prevalence of CKD in HIV-infected patients in SSA not receiving antiretroviral treatment (ART) ranged from 6-45% with HIV-associated nephropathy (HIVAN) diagnosed by biopsy in 5-83%. In most clinical settings where HIV positive patients present with nephrotic syndrome and with a bland urine sediment and no clinical evidence to suggest another cause for nephrotic syndrome, kidney biopsies are not routinely done. In such cases HIVAN is the presumed diagnosis and ART consequently commenced. HIVAN in individuals of African descent has been attributed to the presence of APOL1 genetic variants.[28]

Antiretroviral therapy and other medical therapies for HIV-associated infections have been associated with both short- and long-term toxicities including nephrotoxicity.[29] The nucleotide analogue tenofovir disoproxil furamate (TDF) is actively taken up into the proximal tubules and secreted into the lumen via multi-drug resistance-associated protein 4. TDF-induced nephrotoxicity is more likely to occur in HIV patients with pre-existing renal insufficiency or poorly controlled HIV disease with associated longer overall antiviral treatment duration. Complications of TDF or TDF plus other antivirals include acute kidney injury (AKI), nephrogenic diabetes insipidus, Fanconi syndrome, and severe hypokalemia. Most of these adverse effects may be reversed by discontinuation of the drug, although some patients will develop CKD. Patients who are taking TDF in combination with protease inhibitors such as ritonavir appear to be more susceptible to renal toxicity.

1.2.7 RRT

When CKD patients reach ESRD the remaining management option is RRT. Different RRT therapies that are currently available are hemodialysis (HD), peritoneal dialysis (PD) and

renal transplant (RT).[30] Survival, morbidity and quality of life are the main factors to guide the selection of the most suitable RRT modality for a particular patient. The outcome comparisons suggest that renal transplant is a better overall treatment for ESRD patients. However, these RRT modalities should not be seen as competing therapeutic options; but rather as complementary methods of dealing with uremia.

Kidney transplantation is the preferred form of RRT for ESRD. However, its broad applicability has been limited by immunologic rejection, adverse effects of immunosuppressant agents, and a shortage of organs.[31]

Hemodialysis has evolved as first-line treatment for ESRD since 1972 with the implementation of Medicare funding for RRT in the US.[31] The UK Renal Association recommends that for long-term dialysis, renal units should actively discourage the use of central venous catheters (CVCs) and encourage permanent access with preemptive ateriovenous fistula creation.[32] The reason is to avoid the risk of catheter-related infections and to reduce the risk of central vascular thrombosis and stenosis. Patients are usually dialysed three times a week in a dialysis unit, and each session lasts about four hours. There is also an option of home HD where patients who have poor access to the dialysis unit obtain their own machine, and are trained to independently dialyse themselves at home. In this setting the limitation is often high water and electricity bills to the patient.

Continuous ambulatory peritoneal dialysis (CAPD) has gained worldwide acceptance as a form of RRT since its introduction in the 1980s.[33] It is favoured because of ease of performance and less frequent patient visits to hospital.[34] PD is performed by dwelling dialysate in the patient's abdomen and the peritoneum acting as a semi-permeable membrane.[32] This is via a permanent tunneled catheter known as a Tenckhoff or swan-neck. The dialysate contains glucose, which provides an osmotic gradient to remove solutes and toxins such as urea, electrolytes and excess fluid from the patient's circulation. The fluid is left to dwell for four to six hours during which time the patient is free to continue with daily activities. After this time, the solution is drained from the peritoneum and exchanged for fresh solution. CAPD exchanges are performed four times a day and take 30 to 40 minutes per exchange.

Renal replacement therapy (RRT) is not freely available in South Africa because of limited availability of HD machines, expertise and human resources. Patient selection for dialysis is based on the state criteria for acceptance to the transplant programme. However,

patients in the private sector who can afford it or who have medical insurance may be able to utilise these expensive therapies.[35]

Although patients with ESRD may have fulfilled state criteria for acceptance into the RRT programme, some patients are denied RRT due to unavailability of funds, staff and equipment at the point of care.[35] The optimal form of RRT is renal transplant. Therefore dialysis is seen as a bridge to transplant and the state 'criteria' are underpinned by the 'transplantability' of the patient. In 2006, the initial cost of a renal transplant was between R100 000 and R130 000 in South Africa.[36]

1.2.8 Conservative management

Non-dialysis management of CKD, also known as conservative management, entails careful attention to fluid balance, treatment of anaemia, and correction of acidosis and hyperkalemia.[37] Blood pressure, calcium and phosphorus metabolism must also be monitored. Despite the importance of conservative management as an option for patients with ESRD, many clinicians are unfamiliar with this approach and lack the information to counsel patients and families. In general, patients who refuse dialysis have a median life expectancy of 6.3 to 23.4 months.

1.2.9 Peritoneal dialysis-related peritonitis

Peritonitis and exit-site or tunnel infections remain the principal cause for CAPD technique failure, and is responsible for 68% of all catheters lost.[33] This is followed by catheter malfunction and inadequate dialysis (including ultrafiltration failure). Psychosocial factors such as burnout and difficulty in learning to perform PD-related tasks may play a role as well.[38]

Typically, patients with peritonitis present with abdominal pain and cloudy effluent. A small portion of patients may present with clear PD effluent and with nonspecific abdominal symptoms such as abdominal pain, nausea, vomiting or diarrhoea.[13]

When PD peritonitis is suspected, an effluent sample should be collected and sent for cell count including differential count, gram stain, and culture. An effluent white blood cell count exceeding 100/μL (after a dwell time of at least 2 hours), with at least 50%

polymorphs, indicates the presence of inflammation, with peritonitis being the most likely cause.[13]

1.2.10 International Society of Peritoneal Dialysis (ISPD) guidelines[13]

All peritoneal dialysis centres should monitor patients for exit-site infections, tunnel infections and PD peritonitis. Every centre should not have more than 1 episode of peritonitis every 18 months, and peritonitis rate not more than 0.5 episodes per year at risk.

The majority of exit-site and tunnel infections are caused by *staphylococcus aureus* and *pseudomonas aeruginosa*; therefore empiric treatment should always cover these organisms.

Exit-site and tunnel infections due to *staphylococcus aureus* should be treated with a broad spectrum penicillin or first-generation cephalosporin. If the exit-site infection is resolving slowly, rifampicin may be added. Vancomycin will only be required for methicillin-resistant *staphylococcus aureus* infections. Exit-site infections due to *pseudomonas aeruginosa* often require a longer duration of antibiotics. The first choice of antibiotics is the fluoroquinolones.

Exit-site and tunnel infections are usually treated for a minimum of 2 weeks, and infections due to *pseudomonas aeruginosa* treatment for 3 weeks if necessary. Infections that fail to resolve with appropriate antibiotics for a duration longer than 3 weeks require PD catheter removal. Infections that progress into peritonitis also require PD catheter removal, except when peritonitis is due to coagulase negative *staphylococcus*.

The decision on empiric antibiotics for PD-related peritonitis must be stratified for residual renal function. Drug levels must be closely monitored during treatment with aminoglycosides to prevent nephrotoxicity. Amikacin and other aminoglycosides must not be used in patients who are not anuric.

When *enterococcus* is cultured, antibiotics should be switched to a combination of ampicillin and aminoglycoside; and if ampicillin-resistant, vancomycin or clindamycin should be administered. When *staphylococcus aureus* is cultured, administer a

combination of cephalosporin and rifampicin; and if MRSA is cultured, administer vancomycin or clindamycin. Coagulase negative *staphylococcus* should be treated with cephalosporin only.

Gram-negative organisms are treated with either aminoglycosides (<100ml/day) or ceftazidime (>100ml/day) depending on the urine output or respectively. When *pseudomonas* or *stenotrophomonas* is cultured, treatment is a combination of ceftazidime and either aminoglycoside (urine output <100ml/day) or ciprofloxacin (urine output >100ml/day), depending on output.

In case of PD peritonitis due to fungal infection the PD catheter must be removed immediately as soon as the culture is available, to reduce the risk of death.

Peritoneal dialysis centres must strive for culture-negative PD effluent of less than 20% of episodes of peritonitis. The centres should implement the standard culture technique of inoculating blood culture bottles with PD effluent.

2. The aims of this study were to:

1. Describe the microbiological profile in patients on CAPD presenting with peritonitis at the Universitas Academic Hospital Nephrology Unit;
2. Identify the antibiotic sensitivity patterns of the causative organisms, and
3. Determine the treatment outcomes of this complication, i.e. resolution of peritonitis or PD catheter removal.

3. Methodology and sampling

3.1 Methods

This was a retrospective audit of data for all patients on CAPD at Universitas Academic Hospital Nephrology Unit diagnosed with peritonitis between 1 January 2005 and 31 December 2014. The researcher compiled a list of names of patients who were diagnosed with peritonitis during this period from records kept at the Nephrology Unit. The diagnosis of peritonitis was first confirmed by reviewing the PD effluent results from National Health Laboratory Services (NHLS) systems before accessing the patients' medical records.

Patients' peritoneal fluid culture results were accessed from the DISA and LabTrack systems. The medical records of patients who fulfilled the diagnostic criteria were retrieved from the MediTech system.

An episode of peritonitis was defined as a PD effluent white cell count of more than 100 polymorphs/mm³. Organisms cultured were classified as gram-negative bacteria, gram-positive bacteria, polymicrobial, and culture-negative. The culture method at the unit was initially collection of PD effluent with a dwelling time of at least 6 hours. Since 2013, two blood culture bottles were inoculated with 5 milliliters of PD effluent with a dwelling time of at least 6 hours. The treatment outcomes were classified as intraperitoneal and oral antibiotics, intraperitoneal antibiotics, and PD catheter removal.

A primary cure was defined as an initial response to antibiotic therapy (clinical improvement) plus no need to remove the PD catheter. Refractory peritonitis was defined as failure of effluent to clear within 5 days of appropriate antibiotics. Recurrent peritonitis was defined as an episode of peritonitis occurring within 4 weeks of completion of antibiotics with a different organism. Death within 4 weeks of the onset of peritonitis was classified as a patient death related to peritonitis, even if the episode had responded to treatment.

The antibiotic protocol at the unit is empirical intraperitoneal vancomycin 1g and amikacin 500mg stat, and thereafter drug levels in the blood are used as a guide for further doses.

3.2 Pilot study

A pilot study was conducted on ten patients, and these cases were included in the main study.

3.3 Analysis

Data collected from the patients' records were entered into an Excel spreadsheet. The data were analysed by Prof G Joubert from the Department of Biostatistics, University of the Free State. Descriptive statistics were used, with means ± standard deviations (normally distributed data), medians and interquartile range (data not normally distributed), and frequencies with percentages.

3.4 Ethical aspects

The protocol was approved by the Research Ethics Committee of the University of the Free State (ECUFS 221/2015). The Free State Department of Health gave permission that patients' information may be used for data collection. Patient confidentiality was maintained by allocating a unique 3-digit reference code to each patient.

4. Results

Among the 255 patients who received CAPD in the unit between January 2005 to December 2014, 150 patients were suspected of having PD-related peritonitis. After excluding peritonitis episodes which did not fulfill the diagnostic criteria, the study population consisted of 66 patients who had experienced a total of 123 peritonitis episodes. Table 2 reflects the demographic characteristics of these patients.

Table 2. Patient characteristics

Category	Characteristic	Number
Gender	Male	41 (62.1%)
	Female	25 (37.9%)
Age (years)	Median age	39
	Lower quartile (25%)	31
	Upper quartile (75%)	50
CKD diagnosis	Hypertension	24 (36.4%)
	Glomerulonephritis	10 (15.2%)
	Diabetes Mellitus	5 (7.6%)
	Others	4 (6.1%)
	Unknown	23 (34.8%)
Catheter type	Swan-neck	62 (94.0%)
	Standard Tenckhoff	1 (1.5%)
	Unknown	4 (6.1%)

Hypertension was the leading cause of ESRD seen in 24 patients (36.4%), followed by glomerulonephritis in 10 patients (15.2%), and unknown in 23 patients (34.8%).

The types of organisms implicated in the 123 episodes of peritonitis are shown in Figure 1.

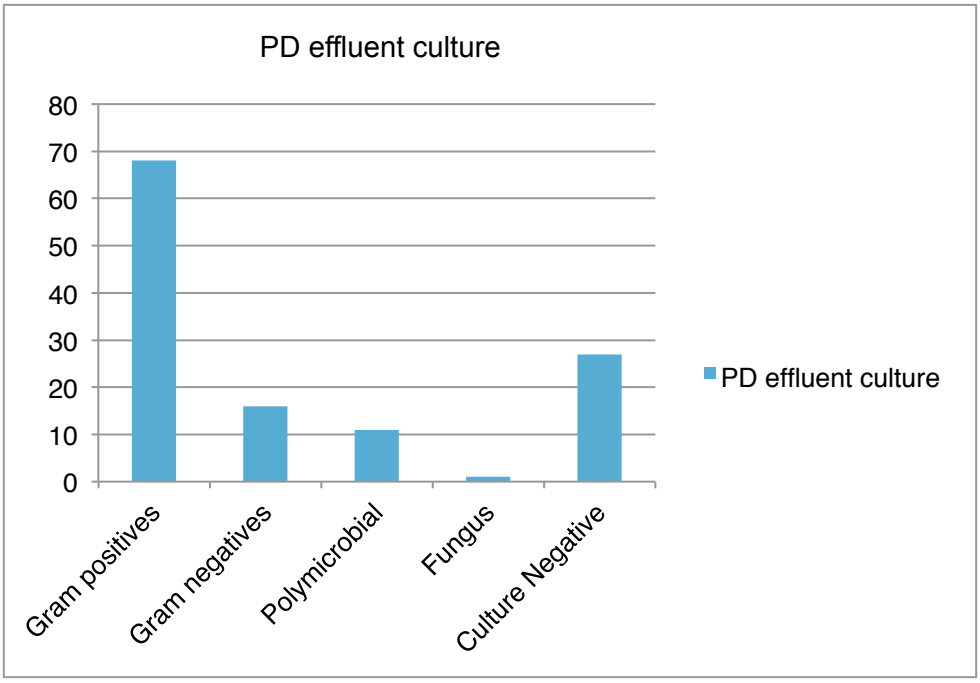
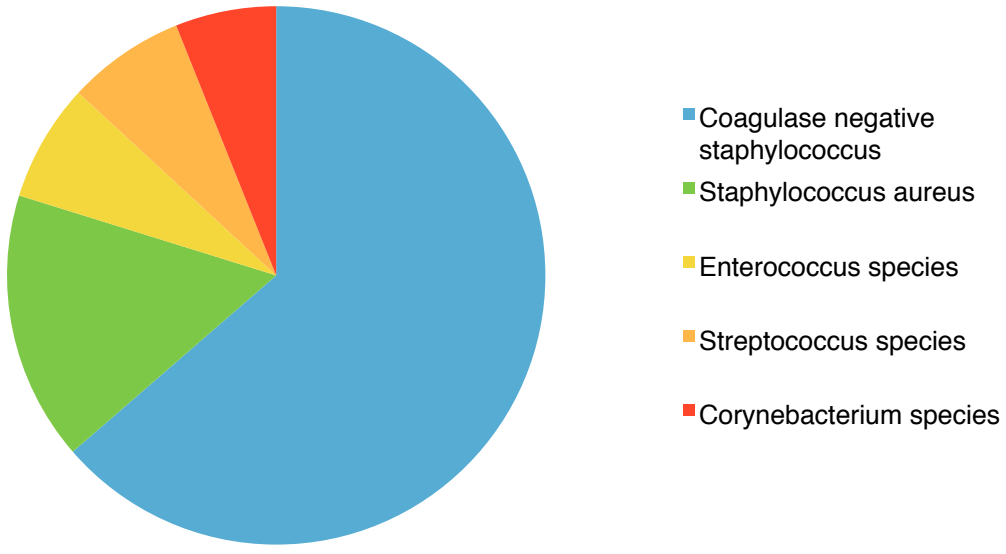


Figure 1. The type of organism causing peritonitis in the study population

A total of 66 episodes of peritonitis were due to gram-positive organisms.

The specific gram-positive organisms are outlined in Figure 2.

Figure 2. Causative organism for the gram-positives



The specific gram-negative organisms are outlined in Figure 3.

Figure 3. Causative organism for gram-negatives

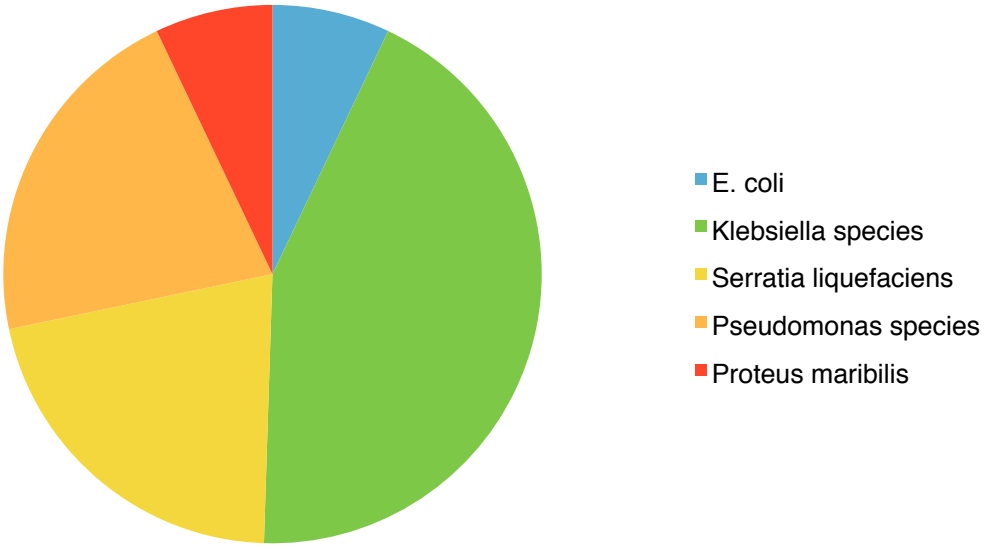


Figure 4 shows the frequency of the organisms isolated as part of the polymicrobial PD effluent.

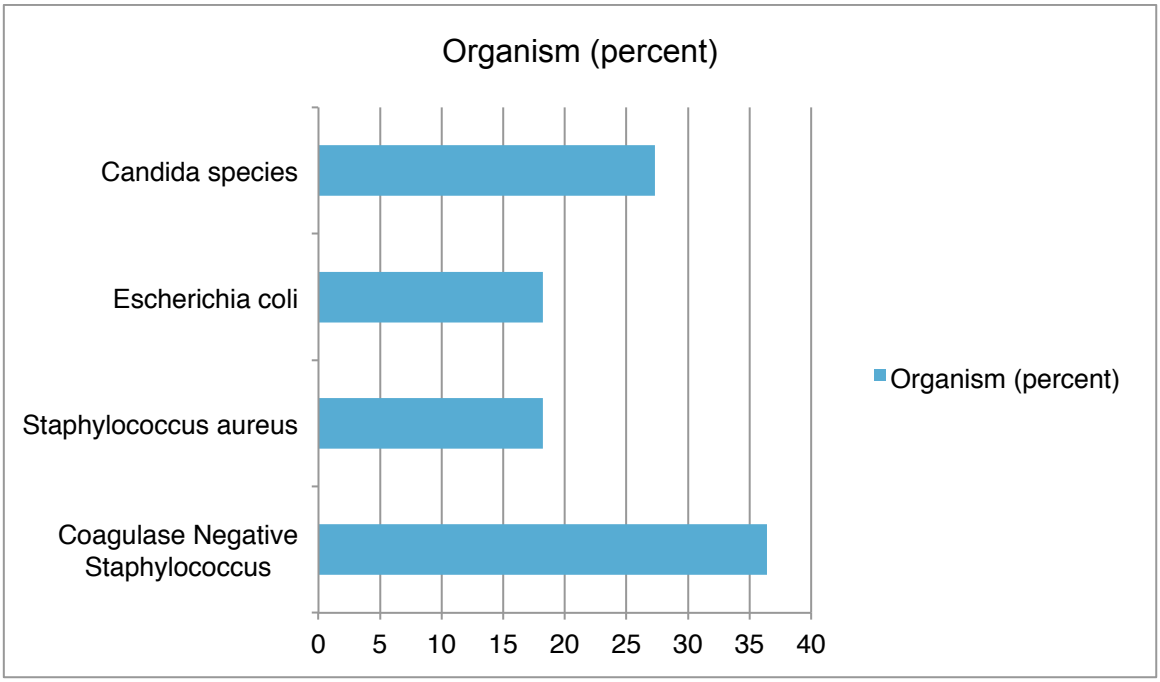


Figure 4. Organisms isolated as part of polymicrobia

The coagulase negative *staphylococcus* (CNS) isolated was sensitive to cloxacillin and vancomycin in 23 episodes (53.5%), and sensitive to vancomycin only in 20 episodes (46.5%).

The gram negatives were sensitive to cefepime in 27.8%, cefuroxime in 22.2%, and cefotaxime in 5.6%. However, all gram negatives were sensitive to amikacin.

Treatment outcome is outlined in Table 3 while Table 4 shows the duration of antibiotic treatment, which was predominantly for 2 weeks. Duration of treatment was not identified in 11 of the 123 episodes.

Table 3. Treatment outcome	**Episodes %**
Resolved peritonitis	71.5
Removal of PD catheter	28.5

Table 4. Duration of antibiotics	**%**
2 weeks	64.3
3 weeks	34.8
>3 weeks	0.9
Unknown	8.9

5. Discussion

In this study, PD-related peritonitis was mainly caused by gram-positives which accounted for 68 (55.3%) of a total of 123 episodes. PD-related peritonitis caused by gram-negatives followed with 16 episodes (13.0%). 11 episodes (8.9%) were of a polymicrobial nature. Culture-negative peritonitis accounted for 27 episodes (22.0%) of all peritonitis episodes. The most common gram-positive causative organism was CNS (63.0%) followed by *S. aureus* (16.0%). However, CNS was isolated in 36.6% episodes of all PD-related peritonitis.

Ghali *et al.* reported gram-positives in 53.4% of all cases of PD-related peritonitis in their series followed by gram-negatives in 23.4% of cases and culture-negatives in 14.6%.[39] In

the US and Canada, the gram-positive rates were higher; accounting for 62.0% and 61.0% of peritonitis episodes respectively.[40] Culture-negatives accounted for 15.9% and 18.5% of episodes in the US and Canada respectively.

The most common gram-negative causative organism in this series was *Escherichia coli* (43.0%), followed by *Klebsiella* species (21.0%) and *Seratia liquefaciens* (21.0%), then *Pseudomonas* species (7.0%) and *Proteas maribilis* (7.0%). *Escherichia coli* accounts for 7.0%, *Klebsiella* species for 3.4%, and *Pseudomonas* species for 1.1% of all peritonitis episodes respectively. Fungal peritonitis as a single organism isolated was observed only in 1.0% of all peritonitis episodes.

Mashiloane *et al*.'s study at Groote Schuur Hospital, Cape Town reported most of the episodes in their series to be culture-negative (65%), followed by *Klebsiella pneumoniae* in 16% of cases, gram-positive *cocci* in 10%, other gram-negative organisms in 6%, and *Candida albicans* in 3%.[41]

Szeto *et al*. indicated the lowest rates of CNS peritonitis, cultured in 11.4% of all peritonitis episodes; but with culture-negatives responsible for 17.9% of all peritonitis episodes.[42] Fahim *et al*. reported CNS in 26.0% of all peritonitis episodes.[21]

Ghali *et al*. reported almost similar findings to this study. The most common gram-negative organism in their series was *E. coli* (6.3%), followed by *Pseudomonas* (4.1%), and *Klebsiella* species (4.0%).[39]

Coagulase negative *staphylococcus* isolated were all sensitive to vancomycin. The treatment outcome was intraperitoneal antibiotics only in 52 episodes (42.3%), while the PD catheter had to be removed in 35 episodes (28.5%). The duration of antibiotics treatment was 2 weeks in 64.3% of the peritonitis episodes.

In Ghali's series the most commonly used empiric antibiotic combination was vancomycin and an aminoglycoside (36.6% of all episodes).[39] Cephalosporins were used as follows: 90% were first-generation agents, 8.5% were third-generation, 0.8% were second-generation, and 0.7% were fourth-generation. In Ghali's series treatment was changed to

single-agent therapy in 77.2% of episodes after a median of 4 days. Vancomycin use as the primary antibiotic regimen increased from 47% (in 2003 – 2004) to 52% (in 2008).

Literature shows elderly age (>65 years) as a risk factor for PD peritonitis. Our results showed a median age of 39 years. There are fewer patients above the age of 65 years because of rationing, and patients above the age of 60 years are excluded from the chronic dialysis program. An interesting finding in this study was that males were more affected than females. It is difficult to explain these findings because we do not know the total number of males and females during the study period.

6. Limitations of this study

The diagnostic criteria excluded patients who had culture-positive PD effluent with a leukocyte count <100 cells/ml, whereas in literature these cases often form part of the diagnosis. This was a retrospective study; therefore it was difficult to confirm cure rates, or episodes of repeated or recurrent peritonitis. It was difficult in some cases to determine the duration of antibiotics.

A prospective study will assist to assess our unit and to examine to what extent if our performance is based on the ISPD recommendations for PD dialysis units.

7. Conclusion and recommendations

The use of the current antibiotic regimen empirically is still deemed appropriate, and generally results in a satisfactory initial response to treatment. As is the case elsewhere, prevention remains the cornerstone of treatment in our setting.

Future research in our unit should also focus on the cure rate of PD-related peritonitis, recurrent and refractory peritonitis.

Improved record keeping might change the microbiological profile and therefore necessitate alterations in the initial empiric management of PD peritonitis.

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9. Appendices

9.1 Ethics protocol approval letter

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

IRB nr 00006240
REC Reference nr 230408-011
IORG0005187
FWA00012784

27 January 2016

DR QJ MOSIA
C/O DR JA COETSER
DEPARTMENT OF INTERNAL MEDICINE
FACULTY OF HEALTH SCIENCES
UFS

Dear Dr Mosia

ECUFS NR 221/2015
DR QJ MOSIA (DR JA COETSER)
DEPARTMENT OF INTERNAL MEDICINE
PROJECT TITLE: PERITONITIS IN PATIENTS ON CONTINUOUS AMBULATORY PERITONEAL DIALYSIS AT UNIVERSITAS ACADEMIC HOSPITAL NEPHROLOGY UNIT

1. You are hereby kindly informed that, at the meeting held on 26 January 2016, the Health Sciences Research Ethics Committee (HSREC) approved the following project after all conditions have been met when the signed permission letters from the Free State Department of Health was submitted.

2. The Committee must be informed of any serious adverse event and/or termination of the study.

3. Any amendment, extension or other modifications to the protocol must be submitted to the HSREC for approval.

4. A progress report should be submitted within one year of approval of long term studies and a final report at completion of both short term and long term studies.

5. Kindly use the ECUFS NR as reference in correspondence to the HSREC Secretariat.

6. The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

Yours faithfully

.....
PROF WJ STEINBERG
FOR CHAIR: HEALTH SCIENCES RESEARCH ETHICS COMMITTEE
Cc Dr JA Coetser

Health Sciences Research Ethics Committee
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Block D, Dean's Division, Room D104 | P.O. Box/Posbus 339 (Internal Post Box G40) | Bloemfontein 9300 | South Africa
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9.2 Ethics protocol amendments approval letter

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

IRB nr 00006240
REC Reference nr 230408-011
IORG0005187
FWA00012784

19 May 2016

DR QJ MOSIA
C/O DR BF MISIWE
DEPARTMENT OF INTERNAL MEDICINE
FACULTY OF HEALTH SCIENCES
UFS

Dear Dr Mosia

ECUFS NR 221/2015
PROJECT TITLE: PERITONITIS IN PATIENTS ON CONTINUOUS AMBULATORY PERITONEAL DIALYSIS AT UNIVERSITAS ACADEMIC HOSPITAL NEPHROLOGY UNIT

1. You are hereby kindly informed that the Health Sciences Research Ethics Committee (HSREC) approved the following. This decision will be ratified at the next meeting to be held on 24 May 2016:

   1.1 Administrative amendment to the protocol:
   1.2 Change of supervisor: Dr JA Coetser changed to Dr BF Bisiwe
   1.3 To include antibiotic sensitivity patterns of the causative organisms into the research question

2. Kindly use the **ECUFS NR** as reference in correspondence to the Ethics Committee Secretariat.

3. The Ethics Committee functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the Ethics Committee of the Faculty of Health Sciences.

Yours faithfully

.....
DR SM LE GRANGE
CHAIR: HEALTH SCIENCES RESEARCH ETHICS COMMITTEE

Cc Dr BF Bisiwe

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