MICROBES ASSOCIATED WITH PERITONITIS AND THE CLINICAL OUTCOMES OF PERITONITIS ON PERITONEAL DIALYSIS AT CHRIS HANI BARAGWANATH HOSPITAL; RETROSPECTIVE STUDY FROM 1ST JANUARY 2011 TO 31ST DECEMBER 2018.

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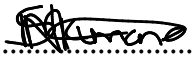
Declaration

I, Siphelele Nkumane declare that the research report is my own work and any publication used have been appropriately referenced. This research report is submitted for the Degree of Master of Medicine in Internal Medicine at the University of the Witwatersrand. It has not been submitted for any other degree or to any another university.

Signed:  Date: 11/11/2024

Author contributions

Dr Siphelele Nkumane chose the research topic about the review of peritonitis in patients on peritoneal dialysis at Chris Hani Baragwanath Academic hospital (CHBAH). Dr U Nqebelele and Dr M Mashabane were the supervisors of this research from the inception to completion. Dr Nkumane wrote the final research report which was reviewed and corrected by the supervisors for submission.

Dedication

I dedicate this research to my late parents, Sikhumbuzo Samuel and Thandi Grenaha Nkumane. You shall forever be in my heart.

Acknowledgements

I would to thank my supervisors Dr Unati Nqebelele and Dr Mduduzi Mashabane for their support, guidance and encouragement during this research project. I am very grateful for their valuable time taken to assist with this research.

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1.1 Lists

List of abbreviations

APD- Automated Peritoneal Dialysis
CAPD- Continuous Ambulatory Peritoneal Dialysis
CHBAH- Chris Hani Baragwanath Academic Hospital
ESRD- End Stage Renal Disease
Gene Xpert MTB/RIF- TB test that detects Mycobacterium Tuberculosis complex and resistance for rifampicin
HIV- Human Immunodeficiency Virus
HD- Haemodialysis
IP- Intra Peritoneal
IPD- Intermittent Peritoneal Dialysis
ISPD- International Society for Peritoneal Dialysis
IV- Intravenous
NHLS- National Health Laboratory Services
PCR- Polymerase chain reaction
PD- Peritoneal dialysis
RRT- Renal Replacement Therapy
TB- Tuberculosis

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ABSTRACT: MICROBES ASSOCIATED WITH PERITONITIS AND THE CLINICAL OUTCOMES OF PERITONITIS ON PERITONEAL DIALYSIS AT CHRIS HANI BARAGWANATH HOSPITAL; RETROSPECTIVE STUDY FROM 1ST JANUARY 2011 TO 31ST DECEMBER 2018

Background: Peritonitis is one of the common complications of chronic peritoneal dialysis (PD). The associated microbes and their antibiotics susceptibility varies amongst institutions. African literature on the impact of clinical and demographic factors on the outcomes of peritonitis in patients on PD is insufficient.

Objectives: To determine the peritonitis rate, analyse the microbes cultured from the peritoneal fluids of patients with peritonitis and their antimicrobial sensitivity. To assess factors that may contribute to the overall outcome of peritonitis and to assess if these factors could be used to predict further peritonitis related complications.

Methods: A retrospective study of 177 patients on PD who developed peritonitis at Chris Hani Baragwanath academic hospital between 01 January 2011 to 31 December 2018. The relevant clinical and demographic factors were obtained from medical records and laboratory results of the specimens culture and sensitivity were obtained from the laboratory services.

Results: A total of 177 incidence of peritonitis in this review. The median age was 42 years (IOR 32years – 48years, with 89.3% being black African. The unemployment rate among the patients was 61%, however the majority reported not living in overcrowded environment (93.2%). Overall peritonitis rate was 0.23 episodes/patient-year. The rate of peritonitis (in percentages) has fluctuated over the study period with the lowest rate of 18% in 2011 and the highest rate of 28.4% in 2018. There was a predominance of gram-positive microbes, followed by gram-negative at 48% and 23.2% respectively. Poor peritonitis outcome increased with increase in age [OR 1.14 (95% CI 1.02 – 1.29) p=0.02] and nearly 19-fold increase in mortality in HIV positive patients [OR 18.93 (95% CI 2.04 – 175.45) p=0.01].

Conclusion: Gram-positive microbes are the commonest isolates in culture positive peritonitis and the appropriate antibiotics of choice is vancomycin and ampicillin. There was strong association between HIV infection and peritonitis-associated mortality.

Keywords: Peritonitis rate, peritoneal dialysis, microbes, gram-positive (Word count: 299)

1.2 BACKGROUND

Chronic kidney disease is a significant health burden and those with end stage renal disease require a limited and expensive treatment (1). According to the World Health Organisation (WHO), there was an estimate of about 220 million people globally with chronic kidney disease (CKD) in 2012 (2). This high burden of CKD is likely to worsen as a result of increasing prevalence of hypertension and obesity, especially in low-to-middle income countries (LMIC) (2). Lack of access to primary health care and delayed consultation, combined with different methods used to detect kidney damage which influences the diagnosis and staging of CKD affects the reported prevalence of this burden in our settings (3).

Liyanage et al, estimated that there is between 4.9 and 9.7 million persons with end stage renal disease (ESRD) who need renal replacement therapy in LMIC (4). Similarly, it has been estimated that about 3.2 million people die each year as a result of failure to access treatment (4). The South African Renal Registry annual report of 2015 found that 1440 patients were on peritoneal dialysis while 7529 patients were on haemodialysis (2). Chronic dialysis modalities in the form of peritoneal dialysis (PD) and haemodialysis (HD) remain the most readily available forms of renal replacement therapy for patients with end stage renal disease in developing countries (2). Although renal transplantation is the ideal option in patients with ESRD due to better quality of life and prolonged survival, it is underutilized due to poor infrastructure in developing countries and the taboo that surrounds organ donation as a result of cultural beliefs (5).

Peritoneal dialysis gained popularity because of patients' independence from frequent hospital visits and its ease of performance. However, in developed countries like the United States and western Europe, its utilization is on a downward trend because they tend to have an older population, often suffering from obesity with an increased abdominal circumference, making HD a better dialysis option for them (6). Haemodialysis requires frequent visits to the dialysis unit; it might be thought that PD would be the most utilized form of dialysis in many African countries because of poor access to health care facilities in these countries, however it seem not to be the case. The lack of facilities for the manufacturing of PD fluids and relying on imports increases the cost of PD (7). Challenges exist with the utilization of peritoneal dialysis in Africa; most have to do with socioeconomic factors like poor housing, overcrowding in households, poor education, no water, and electricity, which all contribute to the increased risk of peritonitis (5). In South Africa, PD is gaining popularity, especially because HD is limited in the public sector and PD is cheaper than HD as the PD fluid is locally manufactured (6).

Unfortunately, the increased number of complications of PD threatens the effectiveness of this modality (8). Complications of PD range from non-infectious to infectious causes. Non-infectious complications are usually mechanical, ranging from catheter blockage, dialysate leak, haemoperitoneum, inflow pain, and umbilical hernias (9). Infectious complications include i) exit-site infections, which are diagnosed by inflammation with a purulent discharge around the exit of the catheter, ii) tunnel infection, which presents with pain and tenderness along the tunnel of the catheter, and iii) peritonitis. The diagnostic criteria of peritonitis as per International Society for Peritoneal Dialysis (ISPD) guidelines is as follows: 1) clinical features consistent with peritonitis: abdominal pain and/or cloudy dialysis effluent, 2) dialysis effluent white cell count

>100/microlitre with >50% polymorphonuclear leukocytes 3) positive dialysis effluent culture (10).

The most common complication of PD is peritonitis at 61.4% which is the commonest cause of modality switch, followed by ultrafiltration failure at 24.5% and mechanical problems at 15% (11). Therefore efforts to reduce peritonitis rate can improve the PD modality survival (12). In their review, Sunnyraj et al found that gram-negative pathogens were associated with high rate of PD discontinuation (12). Most importantly this was found to be a major challenge especially in settings where there are limitations regarding the access to HD or renal transplant. Majority of renal dialysis centres have found that simple measures like training in sterile technique can significantly reduce the risk and improve the PD modality survival (12).

1.3 PERITONITIS

1.3.1 Epidemiology

Globally, continuous ambulatory peritoneal dialysis (CAPD) related peritonitis rates are estimated to be 0.24-1.66 episodes per patient-year, with gram-positive organisms being the most cultured organisms (8). There is a predominance of gram-positive organisms as a cause of peritonitis at a rate of 50%, with coagulase-negative *Staphylococcal* species like *Staphylococcus epidermidis* and *Staphylococcus aureus* being the most common pathogens (8). Gram-negative organisms are the second commonest and account for 25%, with the highest rates reported in Asia and Australia, of which *Escherichia coli* is the commonest, accounting for 30-50% of cases; followed by *Klebsiella, Enterobacter*, and *Pseudomonas* species usually accounting for less than 5% of cases (8).

Fungal peritonitis contributes to 5-15% of the isolates, with *Candida* species accounting for more than 90% of cases (4). Poly-microbial cases account for 10% of cases, with *Mycobacterial* peritonitis showing an increasing incidence in regions where *Mycobacterial* infection is prevalent (Asia and Africa) (13). A large metanalysis of African studies was done in which the prevalence of peritonitis in Africa was found to be between 0.55-2.8 episodes per patient-year (8). Gram-positive organisms were the commonest cause of peritonitis, and amongst the gram-negatives, *Pseudomonas aeruginosa* was predominant. *Mycobacterial tuberculosis* caused peritonitis in only 0.8-3% of cases (8).

Local South African data from a centre in Cape Town in 2010, showed their peritonitis rate was 1.7 episodes per patient-year. Gram-positive organisms were the most cultured at a rate of 50%, followed by gram-negative organisms at 30.8% and culture-negative and fungal peritonitis at 15.4% and 3.8%, respectively (6).

A study done in Limpopo province in rural South Africa showed the overall peritonitis rate to be 0.82 per year, and the majority of episodes were culture-negative at a rate of 62.3%, and only 37.7% yielded organisms on culture (7). Gram-positive organisms were still the predominantly cultured organisms at 50.6% of the culture positives, and gram-negative accounted for 38% with tuberculosis and fungal peritonitis accounting for 7.6% and 3.8%, respectively.

A rate of more than 15% culture-negative peritonitis requires intervention (10). The specimen sampling techniques and culture methods are to be reviewed and improved as per ISPD guidelines (10). The high rate of culture-negative peritonitis could be due to antibiotic use before reaching the hospital or as a result of poor sample collection in this region (7). Another reason that could

explain the increased rate of culture-negative peritonitis was demonstrated by a study done in Kwa-Zulu Natal, South Africa, which is burdened by the high prevalence of HIV. The study showed an increased rate of 28.7% culture-negative cases in HIV-positive patients compared to 18.5% in HIV-negative patients (14). The ISPD classifies culture-negative peritonitis into two groups: 1) firstly, infectious peritonitis with recent antibiotics exposure, suboptimal sample collection, misclassification from slowly growing atypical organisms 2) secondly, non-infectious peritonitis caused by chemical reaction or eosinophilic peritonitis (10). There has been reports of high rates of more than 20% culture negative peritonitis especially in developing countries where sample collection technique is thought to be suboptimal (13).

Peritonitis has multiple risk factors, of which human immunodeficiency virus (HIV) infection and diabetes mellitus have been identified as common causes of immunosuppression in our settings (12). The access to antiretroviral treatment has significantly improved over the past decades. Some renal dialysis centres do not require documented viral suppression and high CD4 count before initiating dialysis therapy provided that other criteria for the initiation of dialysis are met (12). It is worth highlighting that a recent local South African review found that HIV seropositivity was not significantly associated with an increased risk of developing peritonitis (12). Patients who are on PD for a longer period are susceptible to low albumin levels and malnutrition which results in immunosuppression and subsequent reduced host response to infections (15).

Socioeconomic status of the patients who require PD plays a major role in the overall outcome once the treatment is started. Sunnyraj et al, 2023 highlighted that nurse practitioners trained in peritoneal dialysis must assess the social circumstances before the patient is enrolled in chronic

PD treatment (12). The three areas of interests were: access to running water required for sterilisation, adequate space that can be prepared for the actual dialysis and clean area to safely store the dialysate (12). The home circumstances might change with time as some of the patients with chronic kidney may not be economically active for various reasons especially in a setting where there is already lack of employment opportunities.

1.3.2 Clinical presentation

The majority of renal units follow the ISPD guidelines in which the diagnosis of peritoneal dialysis-related peritonitis is made if at least two of the criteria are met (10). The challenge in the diagnosis of peritonitis is that peritoneal dialysis fluid does not always yield an organism in patients suspected of having peritonitis, and the ISPD guidelines recommend that there should be less than 15% of culture-negative cases (10). If an episode of peritonitis occurs within four weeks of completion of therapy of a previous episode, but with a different organism, then it is said to be recurrent. An episode that occurs within four weeks of completion of therapy of a previous episode with the same organism, it is said to be relapsing. Lastly if the effluent fails to clear after five days of appropriate antibiotics, then it is refractory peritonitis (16). Polymicrobial peritonitis is the isolation of more than one organism in a single peritonitis episode (13).

For patients with suspected peritonitis, PD fluid should be collected in bacterial culture bottles before antibiotics are given. Upon collection of culture samples, if after three days no organism is isolated, then one should suspect other pathogens that are difficult to culture or growth is known to be slow (17). It is recommended that the fluid should then be sent for repeat cell count, fungal

cultures, and investigation for *Mycobacterial* TB peritonitis (13). *Mycobacterial* peritonitis poses a diagnostic challenge for clinicians as presentation is not different from other bacterial peritonitis, except that the presentation is often sub-acute (18). In regions where TB is endemic, mycobacterial species should always be considered in a patient not responding to conventional peritonitis treatment or remains culture-negative or with refractory peritonitis. The PD effluent needs to be sent off for acid-fast bacilli (AFB), TB culture, and sensitivity (17). Acid fast bacilli are rarely positive and have a low diagnostic yield with a sensitivity of less than 20%.

Tuberculosis culture remains the gold standard test for confirmation of tuberculosis disease. AFB cultures are performed using the Bactec system which has a documented sensitivity of about 70% (7). In this test a specimen is processed to remove potential contaminants, after which it is inoculated into a culture media for incubation (13). The mycobacterium tuberculosis strain that is isolated from the culture allows for drug susceptibility testing to be performed. Polymerase chain reaction (PCR) has a low sensitivity of 28.7%, hence it has poor diagnostic accuracy for abdominal TB (19). The PCR method for diagnosing TB is GeneXpert MTB/RIF test for *Mycobacterium Tuberculosis* and rifampicin sensitivity testing. It primarily tests for rifampicin sensitivity thus providing guidance on the appropriate treatment option.

In an attempt to make the correct diagnosis in a suspected *Mycobacterium Tuberculosis* cases, peritoneal biopsy is an option. which shows the presence of granulomatous inflammation in positive cases(13). The main disadvantage of performing a peritoneal biopsy is that it is a very invasive procedure. Making diagnosis of TB peritonitis remains challenging, as currently available tests have limitations: measurement of adenosine deaminase (ADA) in the dialysate is a screening

test but has a very low specificity, similarly the polymerase chain reaction (PCR) analysis to detect the mycobacterium has low sensitivity as previously highlighted (10).

The ISPD guidelines recommend < 15% culture-negative peritonitis rate; however, higher rates are often as a result of non-adherence to ISPD guidelines regarding specimen collection for culture and processing methods and the use of antibiotics before collection of PD fluid; this phenomenon being common in resource restraint countries. This results in broader spectrum antibiotics being used unnecessarily for long periods of time and increased risk of resistant strains (20).

1.3.3 Treatment of peritonitis

It is recommended that therapy should be started after microbiological specimens have been taken, and antibiotic regimens should be centre-based (16). The empiric antibiotic cover should be broad, covering both gram-positive and gram-negative organisms (vancomycin or first-generation cephalosporin for the gram-positives and an aminoglycoside or a third-generation cephalosporin for the gram-negatives) (16). The duration of treatment is usually 14-21 days depending on the identity of the cultured organism.

The Intraperitoneal (IP) route of administration of the drug is preferred to the intravenous method because of better bioavailability (18). If organisms producing extended-spectrum beta-lactamases are cultured, the treatment of choice is usually the carbapenems (10). *Candida albicans*, the commonest cause of fungal peritonitis, is treated with fluconazole. Certain species of candida are resistant to fluconazole (*Krusei* and *Globrata species)* in which Amphotericin B or flucytosine are used.

It has been suggested that failure to respond to known effective anti-microbial agents should prompt the clinician to consider the possibility of TB peritonitis especially in our setting were TB is endemic (18). Tuberculosis peritonitis is treated as per South African Department of Health national tuberculosis guidelines 2023 (25). The guideline recommends four drugs: rifampicin, isoniazide, pyrazinamide and ethambutol for the first two months of intensive phase followed by two drugs; rifampicin and isoniazide for the remainder of continuation phase. The dosages adjustment for renal dysfunction is recommended to reduce the risk of side effects of mainly ethambutol and isoniazide (25).

1.3.4 Clinical outcome

The association between peritoneal dialysis related peritonitis and mortality outcome has been investigated with some literature showing inconclusive results (15). In their review it was found that the significant association between peritonitis and mortality was stronger in patients dialysed longer than two years. It is important to highlight that death related to peritonitis was defined as death of a patient with active peritonitis or admitted with peritonitis within two weeks of peritonitic episode (15). However, there is a difficulty in conclusively evaluating the impact of peritonitis on mortality for the following reasons: lack of standard definition of peritonitis related mortality and the indirect long term effects of peritonitis on mortality (15).

The mortality rate for an episode of peritonitis is 5%, and so the prevention of peritonitis requires early diagnosis and appropriate therapy for the long term success of PD (13). The outcome of peritonitis is usually dependant on the type of organism that is cultured as different organisms have different virulent factors. As a general rule; patients with gram-positive peritonitis tends to have a better outcome than gram-negative peritonitis, except for *Staphylococcal aureus*, which has a 40% relapse rate, with 23% of cases being associated with catheter removal, 18% modality switch (PD to HD) and a 2% mortality rate (13). Gram-negative organisms tend to have higher treatment failure rates despite adequate therapy, and this phenomenon is often seen with *Pseudomonas* species, which often causes a "frozen" abdomen and permanent transfer to HD (13).

Fungi are associated with prolonged infections, worse clinical outcomes, and PD failures secondary to the biofilms that these organisms form, which ultimately results in membrane failure, catheter removal, and conversion from PD to HD (20). Although being HIV positive increases the risk of peritonitis, it is not associated with technique failure because most episodes of peritonitis in this population group are associated with gram-positive organisms, and technique failure is linked to gram-negative organisms (14).

Other predictors of mortality from an episode of peritonitis apart from the type of organism cultured include older age (> sixty years), underlying cardiovascular disease, diabetes mellitus (12). Conditions associated with severe inflammatory states which include higher C- reactive protein at baseline, low haemoglobin (<8.5g/dl), low corrected calcium (<2mmol/l) are independently associated with an increase in all-cause mortality from a single peritonitis episode (5).

Mycobacterial peritonitis is associated with a high mortality rate; a study done in Limpopo (South Africa) found a 58% mortality rate, and 83% of patients had to be transferred to HD despite optimal diagnosis and treatment (18). In this review it was established that duration between admission and initiation of anti-TB treatment was about 6 weeks. This delay is explained by various reasons; current available test for TB takes long for culture to be positive and secondly clinician would have started the patient on antibiotics as bacterial peritonitis is more common. It is possible that the delay in the initiation of correct treatment contributes to poor outcome associated with tuberculosis peritonitis (18).

AIM

The aim of the study is to evaluate the peritonitis rate; the various microbes associated with peritonitis and the clinical outcomes of peritonitis for patients on peritoneal dialysis at Chris Hani Baragwanath Hospital.

1.4 Objectives

The primary objectives of the study are: 1) to determine the peritonitis rate, 2) to analyse the microbes cultured in the peritoneal fluid of patients with peritonitis and 3) to identify the antibiotic sensitivity of the isolated organisms.

The secondary objectives of the study include assessing the factors that may contribute to the overall outcomes of peritonitis (socio-demographics, comorbidities, microbes cultured, and

baseline laboratory data), and to determine if there are significant associations between clinical and sociodemographic factors and the risk of peritonitis.

1.5 Subjects and methods

This was a retrospective review study of 177 patients with peritonitis on peritoneal dialysis at Chris Hani Baragwanath academic hospital (CHBAH) between January 2011 to December 2018. The demographic data included: age, employment, socioeconomic factors and ethnicity. The clinical data included comorbidities and diagnosis of peritonitis. Laboratory data included: microbes cultured, antimicrobial details, dialysis modality, inflammatory markers biochemistry, HIV status which were captured from medical records used in the dialysis unit over the study period (Appendix D).

1.6 Ethics

The review was approved by the Human Research Ethics Committee of the University of the Witwatersrand (Certificate number M210501). The patient's confidentiality was maintained throughout by ensuring that each data is de-identified.

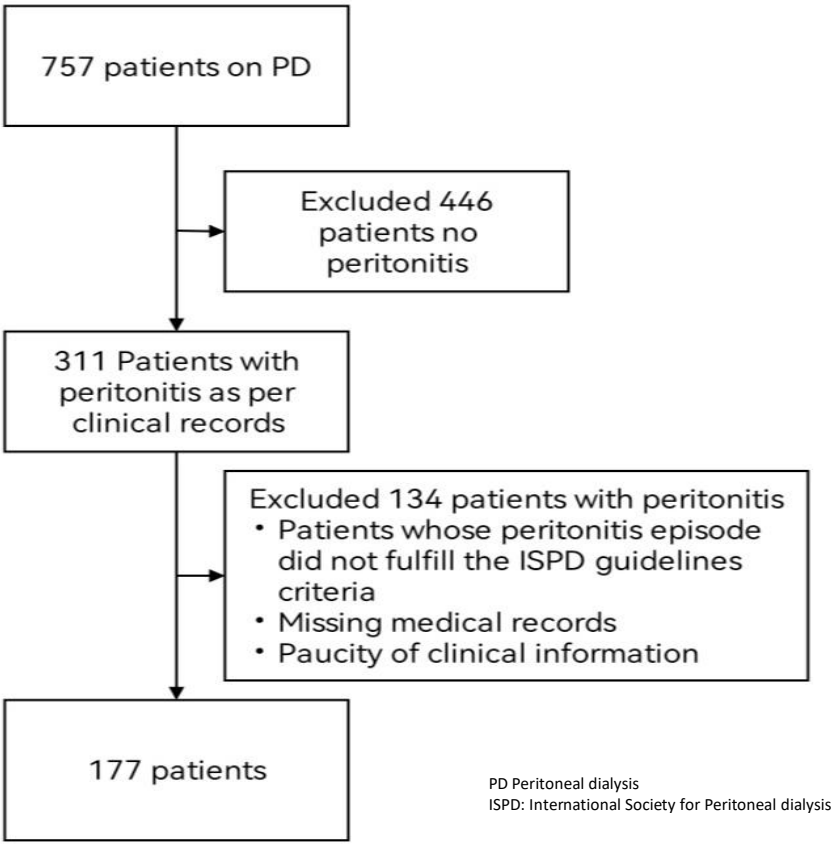
1.7 Statistical analysis

Stata version 15 (Stata Corp Ltd, College Station, TX) software was used for data analysis. Shapiro-Wilk test to test if age was normally distributed. Categorical variables were described as frequencies and percentages. Continuous variables were summarised as medians and interquartile ranges owing to skewed distribution of the data. Univariate and multivariate logistic regression models were fitted to explore associations between variables and outcome of peritonitis A *p*-value of less than 5% was considered to be statistically significant.

1.8 Results

There was a total of 757 patients with chronic kidney disease who were on peritoneal dialysis over the study period. Further analysis of the clinical records as per review inclusion/exclusion criteria, 134 patients were subsequently excluded (i.e. patients whose peritonitis episode did not fulfil the ISPD guidelines criteria and incomplete medical records). There was a total of 177 cases of peritonitis in this review, with demographic characteristics shown in Table 1. The median age was 42 years (IQR 32 – 48 years), range of age was between 16-64 years and 89.3% were blacks. Patients with peritonitis aged between 46 – 55 years accounted for 28.8%(n = 51). Unemployment rate among the patients was very high at 61%; however, the majority reported not living in overcrowded (i.e. more than three people per habitable room, WHO, 2018) environments (93.2%). The commonest co-morbidity was hypertension (n=78, 44.07%) while systemic lupus erythematosus and HIV infection were both the second commonest comorbidity at (n=26 and 14.69%). CAPD was the most common peritoneal dialysis modality (n =159, 89.83%).

Figure 1: The study population of all the patients who were attending the nephrology unit for dialysis at Chris Hani Baragwanath Academic Hospital between January a2011and December 2018



The overall rate of peritonitis (defined as a total case treated as peritonitis/population of patients who were on peritoneal dialysis over the 8-year period) was as 23.3% (177/757) over the period study; however the trend with fluctuations over time (see figure 1), with the lowest rate of 18% in 2011 and the highest rate of 28.4% in 2018.

Figure 2: Prevalence of peritonitis from year 2011 to 2018

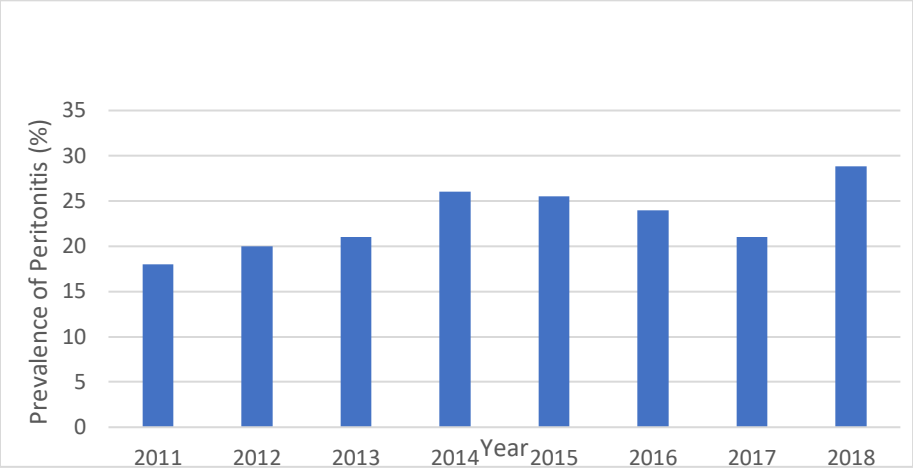


Table 1: Demographic characteristics of the study participants (To simplify your table, present your results as n (%), then you only have one column, I'll do the first 4 as an example. Also convert to one decimal point to make it clearer and to decrease your word count

Variables		**N(%)**
Age (years) median	42 yrs. (IQR 32 - 48)	
Ethnicity		
Black	158 (89.3)	
Caucasian	7 (4)	
Coloured	6 (3.4)	
Indian	6 (3.4)	
Co-morbidities		
HIV	26 ——	14.69
Diabetes Mellitus	22	12.43
Hypertension	78	44.07
Lupus nephritis	26	14.69
Reflux nephropathy	8	4.52
Other	17	9.58
Peritoneal dialysis modality		
APD	10	5.65
CAPD	159	89.83
IPD	8	4.52
Employment		
No	108	61.02
Yes	69	38.98
Overcrowding (177)		
No	165	93.18
Yes	12	6.82

HIV: Human immunodeficiency virus, **FSGS**: Focal segmental glomerulosclerosis, **APD:** Automated peritoneal dialysis, **CAPD**: Continuous ambulatory peritoneal dialysis, **IPD**: Intermittent peritoneal dialysis

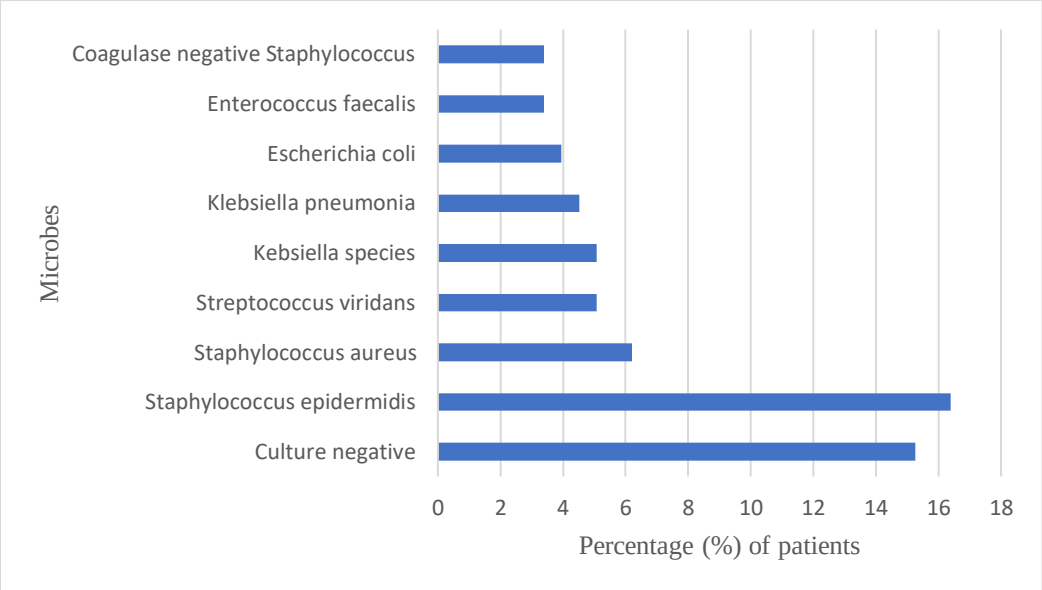
Microbes culture results

The most common microbes were gram positive organisms at 48%, followed by and gram-negative microbes(23.2%). *Staphylococcus epidermidis* and *Staphylococcus aureus* were the commonest gram-positive isolates cultured from the peritoneal fluids (Table 3). The culture negative peritonitis in our study was 15.3 %. Polymicrobial isolates represented 9.6%, while the mycobacterial and fungal microbes represented less than 5% of the positive cultures.

Table 2: Prevalence of microbes cultured from the peritoneal fluid of patients with peritonitis (N=177)

Microbes		N (%)
Gram negative	41 (23.2)	
Gram positive	85	48.0
Polymicrobial	17	9.6
Mycobacterial	4	2.3
Fungal	3	1.7
No growth	27	15.2

Figure 3: The percentage of specific microbes cultured



Majority of microbes were sensitive to vancomycin (23.1%), ampicillin (13%), cloxacillin (9.0%) and gentamicin (5.6%). The most common isolated microbe (*S Epidermidis* at 16.3%), and a majority of gram-positive microbes were sensitive to ampicillin, cloxacillin and vancomycin. The majority of *Staphylococcus aureus* isolates were methicillin sensitive (sensitive to cloxacillin and ampicillin at 81.8%) and only 18.2% were methicillin resistant *Staphylococcus aureus (MRSA) species* (only sensitive to vancomycin).

The most common gram- negative organism was the *Klebsiella species* at 5%, which was sensitive to gentamicin, second and third generation cephalosporins. Two species of fungal infection were isolated; *Candida Parapsilosis* and *Candida Glabrata*, both sensitive to Voriconazole bringing the fungal infection rate at 1.7%. During the study period there were four patients who cultured *Mycobacterial Tuberculosis* in their peritoneal fluid, all of these cases occurred in people with HIV infection and were sensitive to rifampicin. Poor peritonitis outcome (catheter change, modality switch or even death) increased with increase in age [OR 1.14 (95% CI 1.02–1.29) p=0.02], with a nearly 19-fold increase in HIV positive patients [OR 18.93 (95% CI 2.04 – 175.45) p=0.01]. We fitted multivariable logistic regression models to further explore associations between peritonitis outcomes and demographics, comorbidities, microbes cultured and baseline laboratory data. There was a significant association between peritonitis outcome and positive HIV status (p=0.02*)*. After controlling for HIV status, serum calcium and overcrowding, age was no longer associated with peritonitis outcome.

1.8 Discussion

The rate of peritonitis in patients on CAPD varies amongst countries, and in some countries different institutions have reported varying rate. According to ISPD the recommended overall peritonitis rate per year should be below 0.40 episode per patient-year. In developed countries with more resources, the rate of peritonitis is low, with the United States of America (USA) reporting 0.26 episodes/patient year and 0.40 episodes/patient year in Thailand (21). Locally, a study done in Johannesburg reported a peritonitis rate of 0.51 episode/patient year (14). Advancement in the equipment used for peritoneal dialysis and other evidence-based interventions has resulted in overall decreasing trend of peritonitis (12).. The peritonitis rate in our study was found to be 0.23 episodes/patient-year which is low than the peritonitis rates reported from other dialysis unit centers in South Africa and also lower than the ISPD recommended peritonitis rate. In Cape Town, the rate was 0.87 episodes/patient year while Bloemfontein reported 1.45 episodes/patient year (27)(28). Isla et al in their study done in Limpopo province, South Africa found a high rate of 0.82 episode per patient-year (5). Poor nutrition was highlighted as a possible explanation for high peritonitis rate (5).

Davidson et al highlighted the steady decline of peritonitis over the past years, however the reason for the high rate in their study was not clear (26). Bloemfontein study suggested that the reason for high rate of 1.45 episode/patient year is rather multifactorial, and highlighted risk factors like prior

HD, use of PD-first rule and poor socio-economic factors in their study population (27). Sunnyraj et al found a low peritonitis rate which they attributed to centre-specific practices that have been found to assist reduce peritonitis (12).

HIV infection was the second commonest co-morbidity (14,6%). Ndlovu et al found that the rate of peritonitis was 1.86 episodes/patient-years in HIV seropositive patients compared to 0.76 episodes/patient-years in HIV negative patients (14). In their cohort, Sunnyraj et al found that peritonitis rate was higher in HIV-positive patients than HIV-negative (0.69 vs. 0.45 per patient-year). However HIV seropositivity was not found to be independently associated with an increased risk of developing peritonitis (12). It is important to highlight that the peritonitis rate in their cohort was found to be 0.51 episodes per patient-year which is lower than the reported rate from other local units in Limpopo and Kwa-Zulu natal provinces (7), (8), (14).

There is a suggestion that there is dominance of gram-positive microbes in majority of culture positive cases of peritonitis globally as previously highlighted (22) (23). This is followed by gram-negative microbes which can cause severe illness, which can untimely lead to death. In our study, the most common microbes were *Staphylococcus epidermidis* and *Staphylococcus aureus*.

Gram positive microbes like Staphylococcus epidermidis and other skin commensals are the common causes of CAPD associated peritonitis mainly as a results of contamination when sterility is breached (27). Gram negative microbes are mainly as a results of translocation of micro-organisms from the gut and usually patients present with severe episode associated with hypotension, sepsis and high lactate in some instances (27). It has been suggested that positive culture with multiple organisms, especially combination of gram-positive and gram-negative is

highly suggestive of enteric peritonitis and patients might have worse outcome (21). In contrast polymicrobial peritonitis caused by gram-positive microbes is reported to be associated with good clinical outcome and patients can be managed with a course of antibiotics without removing the catheter (21). Occasionally, it might be difficult to differentiate between pathological isolates versus a contaminant. Culture samples from exit site without exudate are highly likely to grow isolates that are not infectious but are colonizes of the PD catheter. Indiscriminate use of antimicrobials in these cases will expose patients to unnecessary antibiotics, predisposing to an increase in multidrug resistant microbes in the future (13).

This is in contrast with culture samples collected from exit site with purulent discharge which are generally accurate reflection of infectious isolates (13).

Fungal infection are rare in healthy immunocompetent adults. In settings where HIV is common, uncontrolled diabetes mellitus and other associated chronic conditions which suppress the immune system, there is high prevalence of fungal infection (14). Peritonitis caused by *Mycobacterium tuberculosis* is still a serious problem in developing countries across Africa and Asia (17), especially in countries like South Africa with a high prevalence of *Mycobacterium tuberculosis*, which is estimated to be 468 per 100 000 of the population in 2022 (29). In our study, there were 2.3 % cases of TB peritonitis. Study done by Isla et al found a similar low percentage in their study sample (5).

Empiric courses of antibiotics with good Gram-positive and Gram-negative coverage is recommended as soon as clinical suspicion of peritonitis is made (13). In our setting the most

commonly prescribed drug that the microbes were sensitive to were vancomycin, ampicillin, cloxacillin and gentamicin. The ISPD guidelines recommend vancomycin or first generation cephalosporin for gram-positive infection therefore good sensitivity for vancomycin is a positive findings for our peritonitis patients (22). As there is emergence of multidrug resistance infections like MRSA, vancomycin is reserved for such identified cases. Ampicillin which was found to show good results is routinely used in our settings. An Aminoglycoside or 3rd generation cephalosporin is a recommended choice for Gram-negative microbes (22). Gentamycin is an affordable and easily accessible antibiotic even in developing countries. The optimal choice of antibiotics should be strongly guided by local unit spectrum of antibiotics resistance patterns and monitored regularly (21)(27).

Fifteen percent of the patients with peritonitis had no growth on the specimen culture. This is a positive findings because it is lower than the ISPD recommended rate of acceptable culture negative peritonitis of 15% (10). Several factors have been found to contribute to negative cultures: poor sample collection technique and use of antibiotics before reaching the hospital (10). Ndlovu et al highlighted that peritonitis caused by infection with fastidious organisms and mycobacterium could potential be explanation for high culture negative peritonitis in HIV-positive patients (14). However, collecting the culture specimen and reviewing the results and selecting the appropriate choice of antibiotics remains an essential part of management of peritonitis in patient on peritoneal dialysis. A Sudanese study showed how the improvement on clinical practice and following the ISPD recommendations has markedly reduced their culture negative rate, specifically implementing high hygiene practice (24).

In our study there were two factors which were found to have statistically significant impact on the outcome of peritonitis. Firstly, increasing in age ~~was~~ negatively associated with death [OR 1.14

(95% CI 1.02 – 1.29) p=0.02]. Comorbidities like diabetes mellitus which is more common and likely to develop complications with advanced age could potentially contribute towards the outcome for patients with ESRD on peritoneal dialysis.

Secondly, HIV infection was associated with a nearly 19-fold increase in death [OR 18.93 (95% CI 2.04 – 175.45) p=0.01]. Immunosuppression is common in patients on PD due to protein loss through the dialysis. This potentially serious complication when combined with HIV infection can predispose patients to increase rates of peritonitis and/or relapses (12). Peritonitis with gram-negative, mycobacterium and fungi are more common in HIV-infected patients and these infections are generally associated with worse outcome. Recurrent peritonitis can result in dialysis modality change due to loss of peritoneal ultrafiltration capacity caused by peritoneal membrane fibrosis.

In developing countries like South Africa, high unemployment rate and poverty remain some of the major social challenges. There is limited access to facilities that offers dialysis with trained nephrologists. It is positive findings of our study that the socioeconomic factors, did not have any significant impact on the overall outcome of peritonitis. A study conducted in Limpopo, one of South Africa's poor rural provinces did not find significant impact of socioeconomic factors on the outcome of patients on CAPD who developed peritonitis (7). In view of the cost effectiveness of PD compared to HD it would then be recommended that more patients are provided with renal replacement therapy regardless of the level of poverty in their communities (2)

Peritonitis is generally a clinical diagnosis with clear signs and symptoms. In this study ,there were no significant associations between clinical presentation, duration of therapy and route of antibiotics administration. It is important to emphasise that the renal unit at CHBAH follows the

latest available ISPD guidelines and local microbes resistance patterns when managing patient with PD associated peritonitis.

1.10 Study limitations and conclusions

There were limitations due to the retrospective nature of this review. Clinical and sociodemographic information of the participants was pre-recorded and it was impossible to verify incomplete data. Extra efforts were taken to ensure that there is no duplication of peritonitis episode.

In conclusion, the rate of peritonitis is low for patients on peritoneal dialysis at CHABH mention the study period , was 0.23 episodes per patient year. Gram positive microbes are the commonest isolates in culture positive peritonitis and the appropriate antibiotics of choice is Vancomycin and Ampicillin. There was strong association between HIV infection and peritonitis associated-mortality.

1.11 References

1. Fiseha T, Osborne NJ. Burden of end-stage renal disease of undetermined etiology in Africa. Ren Replace Ther. 2023 Sep 5;9(1):44.

2. Makhele L, Matlala M, Sibanda M, Martin AP, Godman B. A Cost Analysis of Haemodialysis and Peritoneal Dialysis for the Management of End-Stage Renal Failure At an Academic Hospital in Pretoria, South Africa. PharmacoEconomics - Open. 2019 Dec;3(4):631–41.

3. George C, Stoker S, Okpechi I, Woodward M, Kengne A. The Chronic Kidney Disease in Africa (CKD-Africa) collaboration: lessons from a new pan-African network. BMJ Glob Health. 2021 Aug;6(8):e006454.

4. Liyanage T, Ninomiya T, Jha V, Neal B, Patrice HM, Okpechi I, et al. Worldwide access to treatment for end-stage kidney disease: a systematic review. The Lancet. 2015 May;385(9981):1975–82.

5. Tamayo Isla RA, Ameh OI, Mapiye D, Swanepoel CR, Bello AK, Ratsela AR, et al. Baseline Predictors of Mortality among Predominantly Rural-Dwelling End-Stage Renal Disease Patients on Chronic Dialysis Therapies in Limpopo, South Africa. Jha V, editor. PLOS ONE. 2016 Jun 14;11(6):e0156642.

6. Okpechi IG, Rayner BL, Swanepoel CR. Peritoneal Dialysis in Cape Town, South Africa. Perit Dial Int J Int Soc Perit Dial. 2012 May;32(3):254–60.

7. Isla RAT, Mapiye D, Swanepoel CR, Rozumyk N, Hubahib JE, Okpechi IG. Continuous Ambulatory Peritoneal Dialysis in Limpopo Province, South Africa: Predictors of Patient and Technique Survival. Perit Dial Int J Int Soc Perit Dial. 2014 Jul;34(5):518–25.

8. Moloi MW, Kajawo S, Noubiap JJ, Mbah IO, Ekrikpo U, Kengne AP, et al. Prevalence of peritonitis and mortality in patients treated with continuous ambulatory peritoneal dialysis (CAPD) in Africa: a protocol for a systematic review and meta-analysis. BMJ Open. 2018 May;8(5):e020464.

9. Mekki M, Fedail H, Ali E, Abdelraheem M, Al-Sanousi H, Elamin S, et al. Non-infectious Complications of Peritoneal Dialysis among Sudanese Patients: Five Years Experience. Arab J Nephrol Transplant [Internet]. 2011 Jan 11 [cited 2023 Nov 9];4(1). Available from: http://www.ajol.info/index.php/ajnt/article/view/63152

10. Li PKT, Chow KM, Cho Y, Fan S, Figueiredo AE, Harris T, et al. ISPD peritonitis guideline recommendations: 2022 update on prevention and treatment. Perit Dial Int J Int Soc Perit Dial. 2022 Mar;42(2):110–53.

11. Lasfar L, Guedri Y, Zellama D, El Meknassi I, Azzebi A, Mrabet S, et al. Long-term clinical outcomes of peritoneal dialysis patients: 10-year experience of a single unit from Tunisia. Saudi J Kidney Dis Transplant. 2019;30(2):451.

12. Sunnyraj MM, Davies M, Cassimjee Z. Peritoneal dialysis outcomes in a tertiary-level state hospital in Johannesburg, South Africa: Ethnicity and HIV co-infection do not increase risk of peritonitis or discontinuation. S Afr Med J. 2023 Feb 1;98–103.

13. Salzer WL. Peritoneal dialysis-related peritonitis: challenges and solutions. Int J Nephrol Renov Dis. 2018 Jun;Volume 11:173–86.

14. Ndlovu KCZ, Sibanda W, Assounga A. Peritonitis outcomes in patients with HIV and end-stage renal failure on peritoneal dialysis: a prospective cohort study. BMC Nephrol. 2017 Dec;18(1):48.

15. Ye H, Zhou Q, Fan L, Guo Q, Mao H, Huang F, et al. The impact of peritoneal dialysis-related peritonitis on mortality in peritoneal dialysis patients. BMC Nephrol. 2017 Dec;18(1):186.

16. Wilkie M. The 2016 ISPD Update on Prevention and Treatment of Peritonitis—Grading the Evidence. Perit Dial Int J Int Soc Perit Dial. 2016 Sep;36(5):469–70.

17. Wang HH, Huang CH, Kuo MC, Lin SY, Hsu CH, Lee CY, et al. Microbiology of peritoneal dialysis-related infection and factors of refractory peritoneal dialysis related peritonitis: A ten-year single-center study in Taiwan. J Microbiol Immunol Infect. 2019 Oct;52(5):752–9.

18. Tamayo-Isla RA, De La Cruz MC, Okpechi IG. Mycobacterial Peritonitis in CAPD Patients in Limpopo: A 6-Year Cumulative Report from a Single Center in South Africa. Perit Dial Int J Int Soc Perit Dial. 2016 Mar;36(2):218–22.

19. Ahmad R, Changeez M, Khan JS, Qureshi U, Tariq M, Malik S, et al. Diagnostic Accuracy of Peritoneal Fluid GeneXpert in the Diagnosis of Intestinal Tuberculosis, Keeping Histopathology as the Gold Standard. Cureus [Internet]. 2018 Oct 15 [cited 2023 Nov 9]; Available from: https://www.cureus.com/articles/15286-diagnostic-accuracy-of-peritoneal-fluid-genexpert-in-the-diagnosis-of-intestinal-tuberculosis-keeping-histopathology-as-the-gold-standard

20. Andy Tang SO, Carolisna YI, Sakura D, Yeo ST, Koh KH. Demographic characteristics and outcomes of continuous ambulatory peritoneal dialysis related peritonitis in Miri General Hospital, Malaysia. Med J Malaysia. 2019 Aug;74(4):270–4.

21. Li PKT, Szeto CC, Piraino B, De Arteaga J, Fan S, Figueiredo AE, et al. ISPD Peritonitis Recommendations: 2016 Update on Prevention and Treatment. Perit Dial Int J Int Soc Perit Dial. 2016 Sep;36(5):481–508.

22. Szeto CC, Li PKT. Peritoneal Dialysis–Associated Peritonitis. Clin J Am Soc Nephrol. 2019 Jul;14(7):1100–5.

23. Perl J, Fuller DS, Bieber BA, Boudville N, Kanjanabuch T, Ito Y, et al. Peritoneal Dialysis–Related Infection Rates and Outcomes: Results From the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS). Am J Kidney Dis. 2020 Jul;76(1):42–53.

24. Kheir SM, Kafi SK, Ryden P, Elbir H, Soliman MA, Ali S, et al. Results of application of the ISPD guidelines to the management of peritoneal dialysis in a single center in Sudan. J Infect Public Health. 2017 May;10(3):348–52.

25. National Guidelines on Treatment of Tuberculosis Infection, National Department of Health 2023. Guidelines accessed on the 19th October 2023 from: https://knowledgehub.health.gov.za/elibrary/national-guidelines-treatment-tuberculosis-infection

26. Davidson B, Crombie K, Manning K, Rayner B, Wearne N. Outcomes and challenges of a PD-first program, a South African perspective. Perit Dial Int 2018; 38 (3): 179 - 186

27. Musoke J, Bisiwe F, Natverlal A, et al. The prevalence and bacterial distribution of peritonitis amomngst adults undergoing continous ambulatory peritoneal dialysis at Universitas Hospital. S Afr J Infect Dis 2020 Mar 16;35(1):104

28. Global tuberculosis report 2023. Accessed on 26 March 2024 at https://www.who.int/publications/i/ item/9789240083851 (2023).

UNIVERSITY OF THE
WITWATERSRAND
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R49 Dr SM Nkumane

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M210501

NAME: **(Principal Investigator)**	Dr SM Nkumane
DEPARTMENT:	School of Clinical Medicine Department of Medicine Division of Internal Medicine Medical School University
PROJECT TITLE:	*Microbes associated with peritonitis and the clinical outcomes of peritonitis on peritoneal dialysis at Chris Hani Baragwanath Academic Hospital*
DATE CONSIDERED:	2021/05/28
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Drs M Mashabane and U Nqebelele
APPROVED BY:	CB Penny Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2021/08/30

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **May** and therefore reports and re-certification will be due in the month of **May** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator _____ Date _____

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

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DATE:	2021/08/30
REF:	R14/49
PROTOCOL NO:	**M210501** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)
PROJECT TITLE:	*Microbes associated with peritonitis and the clinical outcomes of peritonitis on peritoneal dialysis at Chris Hani Baragwanath Academic Hospital*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

APPROVED RESEARCH PROTOCOL

Master of Medicine (MMed) in the Department of Internal Medicine.

TITLE

Microbes associated with peritonitis and the clinical outcomes of peritonitis on peritoneal dialysis at Chris Hani Baragwanath Academic Hospital.

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

APD-	Automated Peritoneal Dialysis
CAPD-	Continuous Ambulatory Peritoneal Dialysis
CHBAH-	Chris Hani Baragwanath Academic Hospital
ESRD-	End Stage Renal Disease
HIV-	Human Immunodeficiency Virus
IP-	Intra Peritoneal
IPD-	Intermittent Peritoneal Dialysis
ISPD-	International Society of Peritoneal Dialysis
IV-	Intravenous
NHLS-	National Health Laboratory Services
PD-	Peritoneal dialysis
TB-	Tuberculosis

1. REVIEW OF LITERATURE

1.1 BACKGROUND

Chronic dialysis modalities in the form of peritoneal dialysis (PD) and haemodialysis (HD) remain the most readily available forms of renal replacement therapy for patients with endstage renal disease (ESRD) in developing countries. Although renal transplantation is the ideal option for ESRD due to better quality of life and prolonged survival, it is underutilized due to poor infrastructure in developing countries and the taboo that surrounds organ donation as a result of cultural beliefs. (1)

Peritoneal dialysis gained notoriety because of patients' independence from frequent hospital visits and its ease of performance. However, in developed countries like the United States and western Europe, its utilization is on a downward trend because they tend to have an older population often suffering from obesity with an increased abdominal circumference, making HD a better dialysis option for them. (2) Haemodialysis requires frequent visits to the dialysis unit; it might be thought that PD would be the most utilized form of dialysis in many African countries because of poor access to health care facilities in these countries, but it is not. The lack of facilities for the manufacturing of PD fluids and relying on imports increase the burden of the cost of PD.(3) Challenges exist with the utilization of peritoneal dialysis in Africa. Most have to do with socioeconomic factors (poor housing, overcrowding in households, poor education, no water, and electricity), which all contribute to the increased risk of peritonitis. (1) In South Africa, however, PD is gaining popularity, especially because HD is limited in the public sector, and PD is cheaper than HD because PD fluid is locally manufactured. (2)

1.2 INTRODUCTION

Peritoneal dialysis (PD) remains the most cost-effective modality of dialysis for patients with ESRD in South Africa. However, the increased number of complications of PD threatens the effectiveness of this modality. (4) Complications of PD range from non-infectious to infectious. Non-infectious complications are usually mechanical. They can range from catheter blockage,

dialysate leak, haemoperitoneum, inflow pain, and umbilical hernias. (5) Infectious complications are related to exit-site infections, which are diagnosed by inflammation with a purulent discharge around the exit of the catheter, tunnel infection, which presents with pain and tenderness along the tunnel of the catheter, and peritonitis. The most common complication of PD is peritonitis at 61.4% and the common cause of modality switch, followed by ultrafiltration failure at 24.5% and mechanical problems at 15%.(6)

1.3 PERITONITIS

Epidemiology

Globally continuous ambulatory peritoneal dialysis (CAPD) related peritonitis rates are estimated to be 0.24-1.66 episodes per patient-year with gram-positive organisms being the most cultured organisms. (4) There is a predominance of gram-positive organisms as culprits of peritonitis at a rate of 50%, with coagulase-negative *Staphylococcal* species like *Staphylococcus epidermidis* and S. *aureus* being the most common pathogens. Gram-negative organisms are the second commonest and account for 25%, with the highest rates reported in Asia and Australia, of which *Escherichia coli* is the commonest, accounting for 30-50% of cases; followed by *Klebsiella* and *Enterobacter* species, and *Pseudomonas* species usually accounts for less than 5% of cases. Fungal peritonitis contributes to 5-15% of the isolates, with *Candida* species accounting for more than 90% of cases. Poly-microbial cases account for 10% with *Mycobacterial* peritonitis showing an increasing incidence in regions were *Mycobacterial* infection is prevalent (Asia and Africa). (7) A large metanalysis African study was done in which the prevalence of peritonitis in Africa was found to be between 0.55-2.8 episodes per patient-year. Gram-positive organisms were the commonest cause of peritonitis, and amongst the gram-negatives, *Pseudomonas aeruginosa* was predominant. *Mycobacterial tuberculosis* caused peritonitis in only 0.8-3% of cases. Culture-negative peritonitis cases should be less than 20%, but higher rates of more than 20% have been reported in developing countries where sample collection techniques are sub-optimal. (7)

Local data does exist; in 2010, a centre in Cape Town, South Africa, showed their peritonitis rate was 1.7 episodes per patient-year. Gram-positive organisms were the most cultured at a rate of

50%, followed by gram-negative organisms at 30.8% and culture-negative and fungal peritonitis at 15.4% and 3.8%, respectively. These high peritonitis rates are thought to result from a lack of home visits and the absence of a permanent nursing coordinator. (2)

A study done in Limpopo province in rural South Africa showed the overall peritonitis rate to be 0.82 per year, and the majority of episodes were culture-negative at a rate of 62.3%, and only 37.7% yielded organisms on culture. Gram-positive organisms were still the predominantly cultured organisms at 50.6% of the culture positives, and gram-negative accounted for 38% with tuberculosis (TB) and fungal peritonitis, accounting for 7.6% and 3.8%, respectively. The high rate of culture-negative peritonitis could be due to antibiotic use before reaching the hospital or as a result of poor sample collection in this region. (3) Another reason that could explain the increased rate of culture-negative peritonitis was demonstrated by a study done in Kwa Zulu Natal, South Africa, which is burdened by the high prevalence of HIV, which showed an increased rate of culture-negative cases in this population. (8)

Clinical presentation

Diagnosis of peritonitis is made if at least two of the following are met; clinical features consistent with peritonitis, (abdominal pain, and/or cloudy dialysis effluent, cloudy fluid with a white cell count of more than 100/micro-litre (with > 50% being neutrophils), positive gram stain or positive culture of the peritoneal effluent. (9) The challenge in the diagnosis is that peritoneal dialysis fluid does not always yield an organism in patients suspected of having peritonitis, and the ISPD guidelines recommend that there should be less than 20% of culturenegative cases. (7) If an episode of peritonitis occurs within four weeks of completion of therapy of a previous episode, but with a different organism, then it is said to be recurrent. If an episode occurs within four weeks of completion of therapy of a previous episode with the same organism, it is relapsing. If the effluent fails to clear after five days of appropriate antibiotics, then it is refractory peritonitis. (9) Polymicrobial peritonitis is the isolation of more than one organism in a single peritonitis episode. (7)

Investigation for the causative organism

For suspected patients, PD fluid should be collected in bacterial culture bottles before antibiotics are given. If, after three days and no organism is isolated, then one should suspect fastidious bacteria, fungal or mycobacterial infections. The fluid should then be sent for repeat cell count, fungal cultures, and investigate for *Mycobacterial* TB peritonitis. (7) *Mycobacterial* peritonitis poses a diagnostic challenge for clinicians as presentation is not different from other bacterial peritonitis, except that the presentation is often sub-acute. In regions where TB is endemic, mycobacterial should always be considered in a patient not responding to conventional peritonitis treatment or remains culture-negative and with refractory peritonitis. The PD effluent needs to be sent off for acid-fast bacilli (AFB), TB culture, and sensitivity. (13) AFB's are rarely positive and have a low diagnostic yield with a sensitivity of less than 20%, AFB cultures using the Bactec system has a sensitivity of about 70% but takes about 4- 6 weeks to obtain the results. A peritoneal biopsy is usually positive showing the presence of granulomatous inflammation, but it is invasive. (7) Polymerase chain reaction (PCR), the Gene Xpert MTB/RIF has a low sensitivity of 28.7% and hence has poor diagnostic accuracy for abdominal TB.(10)

Culture-negative peritonitis

The International Society for Peritoneal Dialysis (ISPD) guidelines recommend a < 20% culture-negative peritonitis rate; however, higher rates are often as a result of non-adherence to ISPD guidelines regarding specimen collection for culture and processing methods and the use of antibiotics before collection of PD fluid; this phenomenon being common in resource restraint countries. This results in broader spectrum antibiotics being used unnecessarily for long periods of time and increased risk of resistant strains. (13)

Treatment

As per ISPD guidelines, it is recommended that therapy should be started after microbiological specimens have been taken, and antibiotic regimens should be centre-based. (9) The empiric antibiotic cover should be broad, covering gram-positive and gram-negative organisms (vancomycin or first-generation cephalosporin for the gram-positives and an aminoglycoside or a third-generation cephalosporin for the gram-negatives.). (9) The duration of treatment is usually 14-21 days depending on the cultured organism. The Intraperitoneal (IP) route of administration of the drug is preferred to the intravenous method because of better bioavailability. (3) If organisms producing extended-spectrum beta-lactamases are cultured, the treatment of choice is usually the

carbapenems (ertapenem or imipenem). *Candida albicans*, the commonest cause of fungal peritonitis, is treated with fluconazole. Certain species of candida are resistant to fluconazole (*Krusei* and *Globrata)* in which Amphotericin B or flucytosine are used. TB peritonitis is treated as per national guidelines. (7)

Clinical outcome

The mortality for an episode of peritonitis is 5%, and so the prevention of peritonitis requires early diagnosis and appropriate therapy for the long term success of PD. The outcome of peritonitis is usually dependant on the type of organism that is cultured as different organisms have different virulent factors. As a general rule; patients with gram-positive peritonitis tends to have a better outcome than gram-negative peritonitis, except for *Staphylococcal aureus*, which has a 40% relapse rate, 23% of cases are associated with catheter removal, 18% modality switch (PD to HD) and a 2% mortality rate. Gram-negative organisms tend to have higher treatment failure rates despite adequate therapy, and this phenomenon is often seen with *Pseudomonas* species, which often causes a "frozen" abdomen and permanent transfer to HD. (7) Fungi are associated with prolonged infections, worse clinical outcomes, and PD failures secondary to the biofilms that these organisms form; this then ultimately results in membrane failure, catheter removal, and conversion from PD to HD. (13) Although being HIV positive increases the risk of peritonitis, it is not associated with technique failure because most episodes of peritonitis in this population group are associated with grampositive organisms, and technique failure is linked to gram-negative organisms. (8) *Mycobacterial* peritonitis is associated with a high mortality rate; a study done in Limpopo (South Africa) found a 58% mortality rate, and 83% of patients had to be transferred to HD despite optimal diagnosis and treatment. (14)

Other predictors of mortality from an episode of peritonitis apart from the type of organism cultured include older age (> sixty years), underlying cardiovascular disease, diabetes mellitus, conditions associated with severe inflammatory states which include; higher C- reactive protein at baseline, low haemoglobin (<8.5g/dl), low corrected calcium (<2mmol/l are independently associated with an increase in all-cause mortality from a single peritonitis episode. (1)

2. JUSTIFICATION FOR THE STUDY

There is a paucity of data in South Africa regarding the microbes found on the peritoneal fluid of patients with peritonitis. The guidelines that are followed are international, but local data is not available. Knowledge of these microbes would help to create local protocols as microbes differ with geographical variations, and they evolve over time due to the exposure of certain antimicrobials, and so guidelines need to be reviewed regularly.

3. AIM

Microorganisms vary from centre to centre; the aim of the study is to evaluate the peritonitis rates, various microbes associated with peritonitis and the clinical outcomes of patients diagnosed with PD peritonitis at Chris Hani Baragwanath Hospital (CHBAH).

4. OBJECTIVES

4.1 **Primary objective :**

To determine the peritonitis rate.

To analyse the microbes cultured in the peritoneal fluid of patients with peritonitis.

To identify the antibiotic sensitivity of the isolated organisms.

4.2 **Secondary objectives :**

To assess the factors that may contribute to the overall outcome of peritonitis (demographics, comorbidities, microbes cultured, and baseline laboratory data).

To assess if the above factors have any statistical significance on the outcome of peritonitis and if it would be plausible to predict which patients are likely to develop complications.

To assess the clinical course and outcomes from appropriate therapy (cured, modality switch or death)

5. MATERIALS AND METHODS

5.1 Study site

The study will be conducted at the renal unit of CHBAH where the peritoneal dialysis unit is run and clinical files with patients' records are kept.

5.2 Study period

1st January 2011 to 31st December 2018

5.3 Study design

Single-centre, retrospective analysis of peritoneal fluid of peritonitis suspects. Information will be obtained from the monthly statistics done on patients on PD and tracing back their results on the NHLS lab track system, which is electronically captured. Additional data pertaining to the patients' demographics and the medical background will be retrieved from the renal outpatient department and also on monthly statistical reports done by the peritoneal dialysis unit.

5.4 Study population

5.4.1Inclusion criteria

In order to be able to calculate the peritonitis incidence rate; data will be collected on all patients on PD during the study time period (irrespective of the aetiology of the renal disease). For the analysis on complications and microbes associated with peritonitis, only those patients who fulfilled the diagnostic criteria for peritonitis as per ISPD 2016 guidelines will be included.

5.4.2 Sample size calculation

We computed the required sample size for a multiple logistic regression model exploring the association between adverse outcomes (mortality, catheter removal or modality switch) with demographic (such as age, ethnicity, social circumstances) and clinical factors (microbes, drugs, PD modality, laboratory features etc.) using the "A- priori Sample Size Calculator for Multiple Regression" (http://www.danielsoper.com/statcalc/calculator.aspx?id=1). Assuming a minimum effect size of 0.15, power of 90% and a maximum number of predictors of 12, a minimum of 157 patients is required to explore associations between patient characteristics and adverse outcomes of PD.

5.4.3 Exclusion criteria

Individuals whose data is unavailable or clinical information cannot be retrieved due to inadequate data capturing in the PD clinic files or NHLS results system.

5.5 Limitations and potential bias

Data collection may be limited by the adequacy of doctor's notes in the clinic files

Data may be limited due to poor adherence to following up on scheduled appointments.

6. STATISTICAL ANALYSIS

Epi Data software (https://www.epidata.dk/) will be used to create an electronic data entry form to capture the information listed in the Data Collection Sheet (Appendix A). The electronic data entry form will have check codes, drop down menus, minimum and maximum plausible ranges for specific variables (such as age, laboratory tests) to minimize data entry errors. Data analysis will be done using Stata Statistical Software Release 15 (College Station, TX: StataCorp LLC). Statistical significance will be set at $p<0.05$.

Frequencies and percentage will be used to describe categorical variables, mean and standard deviation will be used to describe normally distributed continuous variables, while median and interquartile range will be used to describe non-normal continuous data. Student's T-test will be used to compare means and Wilcoxon rank-sum tests to compare medians. Univariate and multivariate logistic regression models will be used to explore associations between patient factors and outcomes (death, modality switch and catheter change). Details of analysis by objective are given in the table below.

Objectives	**Variables**	**Analysis**
Primary objectives		
I. To determine	Diagnosis of peritonitis	The prevalence of peritonitis

peritonitis rate		will be described using frequencies and percentages. Binomial 95% confidence intervals will be reported.
II. To analyse the microbes cultured in the peritoneal fluid of patients with peritonitis.	Microbes (gram+/-, fungal, mycobacterial or polymicrobial	The spectrum of microbes cultured will be described using frequencies and percentages. Bar graphs will also be used.
III. To identify the antibiotic sensitivity of the isolated organisms	Drugs (sensitivity, resistance, drugs used, dosage, route, frequency, duration)	Antibiotic sensitivity of the isolated organisms will be described using frequencies and percentages. We will compare proportions of resistance by drug and route using Chi squared tests. We will use Student's T-tests to compare mean and Wilcoxon rant-sum test to compare median dose, frequency and duration for those with resistance and those without.
Secondary objectives		

I. To assess the factors that may contribute to the overall outcome of peritonitis (demographics, microbes cultured, and baseline laboratory data).	**Predictors**: *Demographics* -Age, ethnicity, social circumstances *Clinical Features* -Comorbidities -Diagnosis of peritonitis -Microbes -Drugs -PD modality	Continuous variables (age, inflammatory markers, viral load CD4 count etc.) will be assessed for normality using quantile-quantile plots. Normally distributed variables will be described using mean and standard deviation, while non-normal data will be described using
	-Episode -Inflammatory markers -Biochemistry -HIV status, CD4 count -Viral load and duration on ART -Other laboratory indices **Outcomes:** Cure, death, modality switch, catheter removal	median and interquartile range.
II. To assess if the above factors have any statistical significance on the outcome of peritonitis and if it would be plausible to predict which patients are likely to develop complications.	As above	Univariate and multiple logistic regression models will be used to explore associations between patient factors and outcomes (death, modality switch and catheter removal)

III.	To assess the clinical outcomes from appropriate therapy (cured, modality switch or death)	**Predictors:** -Drugs (sensitivity, resistance, drugs used, dosage, route of administration) -PD modality **Outcomes:** Cured, catheter change, modality switch or death	As above

7. ETHICS

Patients will not be recorded by name but rather identified by a sample number. Data will be collected from patient files and statistical reports by the researcher and will be kept confidential. The protocol will be submitted to the postgraduate committee of the University of the Witwatersrand as well as the Human Research Ethics Committee of the Witwatersrand University for permission to conduct the study. Consent will be obtained from the head of the department of the division of nephrology as well as the chief executive officer at Chris Hani Baragwanath Academic Hospital.

8. TIMING

	July 2020	August 2020	Sept 2020	Oct 2020	Nov 2020	Dec 2020	Jan 2020	Feb 2020	March 2020	April 2021	May 2021	June 2021	July 2021	August 2021
Literature review	■	■												
Preparing protocol		■												
Protocol review by supervisors			■											
Postgraduate submission				■										
Ethics application					■	■	■							
Data collection								■	■	■				

Data analysis													
Write up													

9. FUNDING

Costs for stationary and transport will be funded by the researcher and are projected to be R2500.00.

10. REFERENCES

1. Tamayo Isla RA, Ameh OI, Mapiye D, Swanepoel CR, Bello AK, Ratsela AR, et al. Baseline Predictors of Mortality among Predominantly Rural-Dwelling End-Stage Renal Disease Patients on Chronic Dialysis Therapies in Limpopo, South Africa. PloS one. 2016;11(6):e0156642.
2. Okpechi IG, Rayner BL, Swanepoel CR. Peritoneal dialysis in Cape Town, South Africa. Peritoneal dialysis international: journal of the International Society for Peritoneal Dialysis. 2012;32(3):254-60.
3. Isla RA, Mapiye D, Swanepoel CR, Rozumyk N, Hubahib JE, Okpechi IG. Continuous ambulatory peritoneal dialysis in Limpopo province, South Africa: predictors of patient and technique survival. Peritoneal dialysis international: journal of the International Society for Peritoneal Dialysis. 2014;34(5):518-25.
4. Moloi MW, Kajawo S, Noubiap JJ, Mbah IO, Ekrikpo U, Kengne AP, et al. prevalence of peritonitis and mortality in patients treated with continuous ambulatory peritoneal dialysis (CAPD) in Africa: a protocol for a systematic review and meta-analysis. BMJ Open. 2018;8(5):e020464.
5. Mekki MO, Fedail HM, Ali EM, Abdelraheem MB, Al-Sanousi H, Elamin S, et al. Non-infectious complications of peritoneal dialysis among Sudanese patients: five years experience. Arab journal of nephrology and transplantation. 2011;4(1):27-30.
6. Lasfar LB, Guedri Y, Zellama D, El Meknassi I, Azzebi A, Mrabet S, et al. Long-term clinical outcomes of peritoneal dialysis patients: 10-year experience of a single unit from Tunisia. Saudi journal of kidney diseases and transplantation: an official publication of the Saudi Center for Organ Transplantation, Saudi Arabia. 2019;30(2):451-61.
7. Salzer WL. Peritoneal dialysis-related peritonitis: challenges and solutions. International journal of nephrology and renovascular disease. 2018;11:173-86.
8. Ndlovu KC, Sibanda W, Assounga A. Peritonitis outcomes in patients with HIV and end-stage renal failure on peritoneal dialysis: a prospective cohort study. BMC nephrology. 2017;18(1):48.
9. Wilkie M. The 2016 ISPD Update on Prevention and Treatment of Peritonitis-Grading the Evidence. Peritoneal dialysis international: journal of the International Society for Peritoneal Dialysis. 2016;36(5):469-70.
10. Ahmad R, Changeez M, Khan JS, Qureshi U, Tariq M, Malik S, et al. Diagnostic Accuracy of Peritoneal Fluid GeneXpert in the Diagnosis of Intestinal Tuberculosis, Keeping Histopathology as the Gold Standard. Cureus. 2018;10(10):e3451.

11. Andy Tang SO, Carolisna YI, Sakura D, Yeo ST, Koh KH. Demographic characteristics and outcomes of continuous ambulatory peritoneal dialysis-related peritonitis in Miri General Hospital, Malaysia. The Medical journal of Malaysia. 2019;74(4):270-4.
12. Perl J, Fuller DS, Bieber BA, Boudville N, Kanjanabuch T, Ito Y, et al. Peritoneal DialysisRelated Infection Rates and Outcomes: Results From the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS). American journal of kidney diseases: the official journal of the National Kidney Foundation. 2020.
13. Wang HH, Huang CH, Kuo MC, Lin SY, Hsu CH, Lee CY, et al. Microbiology of peritoneal dialysis-related infection and factors of refractory peritoneal dialysis-related peritonitis: A ten-year single-center study in Taiwan. Journal of microbiology, immunology, and infection = Wei mian yu gan ran za zhi. 2019;52(5):752-9.
14. Tamayo-Isla RA, de la Cruz MC, Okpechi IG. Mycobacterial Peritonitis in CAPD Patients in Limpopo: A 6-Year Cumulative Report from a Single Center in South Africa. Peritoneal dialysis international: journal of the International Society for Peritoneal Dialysis. 2016;36(2):218-22.

11. DATA COLLECTION SHEET PERITONITIS STUDY- CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

Sample number: _____

Ethnicity: African ☐ Caucasian ☐ coloured ☐

Asian Indian ☐ ☐

Age: _____

Comorbidities:

Diabetes mellitus ☐ hypertension ☐ HIV ☐

Connective tissue disease ☐ others ☐

Diagnosis of peritonitis:

Abdominal pain ☐ cloudy effluent ☐

Dialysis white cell count:

_____

Neutrophil count

_____

Lymphocyte count

Microbes:

Gram + ☐ gram - ☐ fungal ☐

Mycobacterial ☐ polymicrobial ☐

Identification of microbe _____

☐ ☐

Drugs:

Drug/s used to treat:

gentamycin ☐ ceftazidime ☐

Sensitivity

Resistance

fluconazole ☐ cefazolin ☐

Others: ☐

Dosage: _____

Route of administration:

Intravenous ☐ intraperitoneal ☐ orally ☐

Frequency: _____

Duration: _____

Peritoneal dialysis modality:

☐

CAPD ☐ IPD ☐ APD

Episode of peritonitis:

Index ☐ recurrent ☐ relapsing ☐

Refractory ☐

Inflammatory marker:

C- reactive protein: ……

Biochemistry:

Haemoglobin: ……..

Albumin:…….

Serum calcium:……

HIV status: Neg / Pos

Duration of treatment: ……

CD4 cell count:……

Viral load:…..

Other laboratory indices:

HbA1c percentage: ……..

<u>Hepatitis studies:</u>

Hepatitis B surface antigen: positive ☐ negative ☐

Hepatitis C antibody: positive ☐ negative ☐

Outcome:

Cured ☐ catheter removal ☐

Modality switch ☐ death ☐

Social circumstances:

Employment:	yes	☐	No	☐
Overcrowding	yes	☐	No	☐

12. CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL RENAL UNIT EMPERIC PERITONITS TREATMENT PROTOCOL

Loading dose

6 Vancomycin 2g IP (Intraperitoneal) as a bolus 7

Gentamycin 1.5mg/kg IP as a bolus. **Maintenance dose**

Intermittent dosing currently being used

- Vancomycin 15-30mg/kg IP every 5 days.
- Gentamycin 0.6mg/kg IP daily.

The duration of the protocol is 14-21 days depending on the organism cultured.

Antimicrobial specificity is then based on the specific microorganism cultured.

Certain organisms require special mentioning:

If Staphylococcus aureus is cultured:

- Stop gentamicin
- Continue with vancomycin
- Add rifampicin 600mg orally per day for 5-7 days to prevent relapse.

Fungal peritonitis:

- Start fluconazole 200mg orally as a loading dose and then 100mg orally daily and until two weeks after catheter removal.

Pseudomonas aeruginosa peritonitis:

- Catheter to be removed immediately
- Until the catheter has been removed, treat with 2 IP agents (gentamicin and ceftazidime).

Tuberculous peritonitis

Treatment is with four drugs: rifampicin, isoniazid, pyrazinamide, and ethambutol as per South African National TB guidelines.

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I _____ (Student number: _____) am a student registered for the degree of _____ in the academic year _____.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.

- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: _____ Date: _____

Academic Affairs and Research
Modderfontein Road, Sandringham, 2031
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Fax: +27 (0)11 386 6296
Email: babatyi.kgokong@nhls.ac.za
Web: www.nhls.ac.za

05 October 2021

Applicant: Siphelele Nkumane
Institution: University of the Witwatersrand
Department: Internal Medicine
Email: siphelele.nkumane@gmail.com
Tel: 011 938 2095 **Cell:** 082 310 7592

Re: Approval to access National Health Laboratory Service (NHLS) Data

Your application to undertake a research project **"Microbes associated with peritonitis and the clinical outcomes of peritonitis on peritoneal dialysis at Chris Hani Baragwanath Academic Hospital, Ref No: PR2118919"** using data from the NHLS database has been reviewed. This letter serves to advise that the application has been approved and the required data will be made available to you ***without patient names*** to conduct the proposed study as outlined in the submitted application. Submissions should be made annually on the AARMS system – https://aarms.nhls.ac.za.

Please note that approval is granted on your compliance with the NHLS conditions of service and that the study can only be undertaken provided that the following conditions have been met.

- Processes are discussed with the relevant NHLS departments (i.e. Information Management Unit and Operations Office) and are agreed upon.
- Confidentiality is maintained at participant and institutional level and there is no disclosure of personal information or confidential information as described by the NHLS policy.
- NHLS Data cannot be used to track patients as no pre-approval/consent is obtained from Patients.
- All data requested should be in accordance with the research protocol submitted and approved by the relevant Ethics Committee.
- Request for the inclusion of the NHLS as a source of data in the original protocol to be approved by Ethics as NHLS does not have a Human Research Ethics Committee.
- A final report of the research study and any published paper resulting from this study are submitted and addressed to the NHLS Academic Affairs and Research office and the NHLS has been acknowledged appropriately.

Please note that this letter constitutes approval by the NHLS Academic Affairs and Research Office. Any data related queries may be directed to NHLS Corporate Data Warehouse, contact number: 011 386 6074 email: zarina.sabat@nhls.ac.za

07/10/2021
Dr Babatyi Malope-Kgokong
National Manager: Academic Affairs and Research

Author Guidelines

Author Guidelines

The *SAMJ* has launched a new submission and tracking system. Authors will be required to register a profile on the in order to submit a manuscript.

Author Guidelines

Please watch the Author Tutorial for guidance on how to submit online.

Please take the time to familiarise yourself with the policies and processes below. If you still have any questions, please do not hesitate to ask our editorial staff (tel.: +27 (0)21 532 1281, email: publishing@samedical.org).

SAMJ policies

- Types of articles considered by the SAMJ
- Article Processing Charges
- Authorship
- Conflict of interest
- Research ethics committee approval
- Clinical trials
- Protection of patient's rights to privacy
- Copyright notice
- Privacy statement
- Ethnic classification
- CPD

Manuscript preparation

- Preparing an article for anonymous review
- General article format/layout
- Preparation notes by article type
- Illustrations
- Tables
- References

From submission to acceptance

- Submission and peer-review
- Production process
- Changing contact details or authorship

Publication

- Online versus print
- Errata and retractions
- Indexing

SAMJ Policies

Type of articles considered by the SAMJ

The *SAMJ* will no longer limit the articles accepted to those that have 'general medical content', but is intending to capture the spectrum of medical and health sciences, grouped by relevance to the country's burdens of disease. This content will include research in the social sciences and economics that is relevant to the medical issues around our burden of disease. Please see 'A new vision for the *SAMJ* – and a call for papers' for a full discussion of the new directions for the *SAMJ*.

We accept the following types of articles:

- Research
- Reviews
- Clinical trials
- Editorials
- In Practice (Previously Forum incl. Case Reports)
- Correspondence
- Obituaries
- Book reviews
- Ad hoc supplements e.g. guidelines, conference/congress abstracts, Festschrifts*

The following articles are by invitation only:

- Guest editorial
- Continuing Medical Education (CME)

*Contact claudian@hmpg.co.za for information on submitting ad hoc/commissioned supplements, including guidelines, conference/congress abstracts, Festschrifts, etc.

Publication Fees

All articles published in the *South African Medical Journa*l are open access and freely available online upon publication. This is made possible by applying a business model to offset the costs of peer review management, copyediting, design and production, by charging a publication fee of R7 440 (VAT incl.) for each research and In Practice article published. The publication fee is standard and does not vary based on length, colour, figures, or other elements.

The publication fee is payable when your manuscript is editorially accepted and before production commences for publication. The submitting author will be notified that payment is due and given details on the available methods of payment. Prompt payment is advised; the article will not enter into production until payment is received.

Authorship

Named authors must consent to publication. Authorship should be based on: (*i*) substantial contribution to conceptualisation, design, analysis and interpretation of data; (*ii*) drafting or critical revision of important scientific content; or (*iii*) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org)

If authors' names are added or deleted after submission of an article, or the order of the names is changed, all authors must agree to this in writing.

Please note that co-authors will be requested to verify their contribution upon submission. Non-verification may lead to delays in the processing of submissions.

Author contributions should be listed/described in the manuscript.

Conflicts of interest

Conflicts of interest can derive from any kind of relationship or association that may influence authors' or reviewers' opinions about the subject matter of a paper. The existence of a conflict – whether actual, perceived or potential – does not preclude publication of an article. However, we aim to ensure that, in such cases, readers have all the information they need to enable them to make an informed assessment about a publication's message and conclusions. We require that both authors and reviewers declare all sources of support for their research, any personal or financial relationships (including honoraria, speaking fees, gifts received, etc) with relevant individuals or organisations connected to the topic of the paper, and any

association with a product or subject that may constitute a real, perceived or potential conflict of interest. If you are unsure whether a specific relationship constitutes a conflict, please contact the editorial team for advice. If a conflict remains undisclosed and is later brought to the attention of the editorial team, it will be considered a serious issue prompting an investigation with the possibility of retraction.

Research ethics committee approval

Authors must provide evidence of Research Ethics Committee approval of the research where relevant. Ensure the correct, full ethics committee name and reference number is included in the manuscript.

If the study was carried out using data from provincial healthcare facilities, or required active data collection through facility visits or staff interviews, approval should be sought from the relevant provincial authorities. For South African authors, please refer to the guidelines for submission to the National Health Research Database. Research involving human subjects must be conducted according to the principles outlined in the Declaration of Helsinki. Please refer to the National Department of Health's guideline on Ethics in Health research: principles, processes and structures to ensure that the appropriate requirements for conducting research have been met, and that the HPCSA's General Ethical Guidelines for Health Researchers have been adhered to.

Clinical trials

As per the recommendations published by the International Committee of Medical Journal Editors (ICMJE), clinical trial research is any research that assigns individuals to an intervention, with or without a concurrent comparison/control group to study the cause-and-effect relationship between the intervention and health outcomes. All clinical trials should be registered with the appropriate national clinical trial registry (or any international primary register, if relevant), and the trial registration number should be cited at the end of the abstract. All clinical trial reports must also contain a data sharing statement as per the recommendations of the ICMJE. Statements are to indicate:

- whether individual deidentified participant data will be shared;
- what data in particular will be shared; whether additional, related documents will be available;
- when the data will become available and for how long; by what access criteria data will be shared.

Please see the ICJME announcement for further details and illustrative examples of data sharing statements: ICMJE Data Sharing Statements for Clinical Trials

Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register. The SAMJ therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrollment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Please refer to the general guidelines for all papers at the top of this article for additional requirements with respect to ethics approval, funding, author contributions, etc. The format of original research articles should be followed for reporting of clinical trial results.

Patient Consent

Information that would enable identification of individual patients should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) has given informed written consent for publication and distribution. We further recommend that the published article is disseminated not only to the involved researchers but also to the patients/participants from whom the data was drawn. Refer to Protection of Research Participants. The signed consent form should be submitted with the manuscript to enable verification by the editorial team.

Other individuals

Any individual who is identifiable in an image must provide written agreement that the image may be used in that context in the *SAMJ*.

Copyright notice

Material submitted for publication in the *SAMJ* is accepted provided it has not been published or submitted for publication elsewhere. Please inform the editorial team if the main findings of your paper have been presented at a conference and published in abstract form, to avoid copyright infringement. All research already published as 'Conference proceedings' needs to be substantially re-written, with a new title, a new abstract and new and important results to back up any study before it will be considered for a new publication. The *SAMJ* does not hold itself responsible for statements made by the authors.

Previously published images

If an image/figure has been previously published, permission to reproduce or alter it must be obtained by the authors from the original publisher and the figure legend must give full credit to the original source. This credit should be accompanied by a letter indicating that permission to reproduce the image has been granted to the author/s. This letter should be uploaded as a supplementary file during submission.

Privacy statement

The *SAMJ* is committed to protecting the privacy of its website and submission system users. The names, personal particulars and email addresses entered in the website or submission system will not be made available to third parties without the user's permission or due process. By registering to use the website or submission system, users consent to receive communication from the *SAMJ* or its publisher SAMA on matters relating to the journal or associated publications. Queries with regard to privacy may be directed to publishing@hmpg.co.za.

Ethnic/race classification

Use of racial or ethnicity classifications in research is fraught with problems. If you choose to use a research design that involves classification of participants based on race or ethnicity, or discuss issues with reference to such classifications, please ensure that you include a detailed rationale for doing so, ensure that the categories you describe are carefully defined, and that socioeconomic, cultural and lifestyle variables that may underlie perceived racial disparities are appropriately controlled for. Please also clearly specify whether race or ethnicity is classified as reported by the patient (self-identifying) or as perceived by the investigators. Please note that is not appropriate to use self-reported or investigator-assigned racial or ethnic categories for genetic studies.

Continuing Professional Development (CPD)

SAMJ is an HPCSA-accredited service provider of CPD materials. Principal authors can earn up to 15 CPD continuing education units (CEUs) for publishing an article; co-authors are eligible to earn up to 5 CEUs; and reviewers of articles can earn 3 CEUs. Each month, *SAMJ* also publishes a CPD-accredited questionnaire relating to the academic content of the journal. Successful completion of the questionnaire with a pass rate of 70% will earn the reader 3 CEUs. Administration of our CPD programme is managed by Medical Practice Consulting. To complete questionnaires and obtain certificates, please visit MRP Consulting

Manuscript preparation

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this are Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

- An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.
- Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
- Mask self-citations by referring to your own work in third person.

General article format/layout

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state ‘none’.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAMJ is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.

- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

**NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. ‘188del11’ can be glossed as ‘an 11 bp deletion at nucleotide 188.’

- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

- Research
- Editorials
- CME
- In Practice and Case reports
- Reviews
- Clinical trials
- Correspondence
- Obituaries
- Book reviews
- Guidelines

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text.

Structured abstract

This should be 250-400 words, with the following recommended headings:

o **Background:** why the study is being done and how it relates to other published work.

o **Objectives:** what the study intends to find out

o **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.

o **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.

o **Conclusion:** must be supported by the data, include recommendations for further study/actions.

- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Here is an example of a good abstract.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Editorials

Guideline word limit: 1 000 words

These opinion or comment articles are usually commissioned but we are happy to consider and peer review unsolicited editorials. Editorials should be accessible and interesting to readers without specialist knowledge of the subject under

discussion and should have an element of topicality (why is a comment on this issue relevant now?) There should be a clear message to the piece, supported by evidence.

Please make clear the type of evidence that supports each key statement, e.g.:

- expert opinion
- personal clinical experience
- observational studies
- trials
- systematic reviews.

CME (by invite only)

CME is intended to provide readers with practical, up-to-date information on medical and related matters. It is aimed at those who are not specialists in the field.

From January 2016, all CME articles will be printed in full in the *SAMJ*. Please try to adhere strictly to the guidelines on word count as we have a page limit for the print issue of the *SAMJ*. We reserve the right to place some tables and reference lists online if this is necessary for space.

In practice, this means that each CME topic usually covers two issues of the print issue of the *SAMJ*.

The guest editor, in consultation with the editor, is responsible for convening a team of authors, deciding on the subjects to be covered and for reviewing the manuscripts submitted. The suggestion is for 4 - 5 articles, although there is some room for flexibility contingent on discussions with the editor.

For queries about these guidelines please feel free to contact the CME editor, Dr Bridget Farham, by email (ugqirha@iafrica.com) or telephone (+27 (0)82 452 2860)

Review process

The guest editor reviews the articles and returns them to the CME editor for review and final approval.

Guest editorials

Guideline word limit: 1 000 words

- Include the guest editor's personal details (qualifications, positions, affiliation, e-mail address, and a short personal profile (50words)).
- If possible, include a photograph of the author(s) at high enough resolution for print. It is preferable to provide two guest editorials, one for each issue, so that the content of the articles in each issue is covered.

Articles

Guideline word limit: 2 000 - 3 000 words

- Each article requires an abstract of ±200 words.
- The editor reserves the right to shorten articles but will send a substantially shortened article back for author approval.

Personal details

Please supply: Your qualifications, position and affiliations and MP number (used for CPD points); Address, telephone number and fax number, and your e-mail address; and a short personal profile (50words)and a few words about your current fields of interest.

In Practice

Guideline word limit: 2 000 - 3 000words

This section includes articles that would previously have been accepted into the Forum section, and case reports.

In practice articles are those that draw attention to specific issues of clinical, economic or political interest regarding medicine and healthcare in southern Africa. They are assigned to a topic:

- Case report
- Clinical practice
- Clinical alert
- Issues in medicine
- Issues in public health
- Healthcare delivery
- Medicine and the environment
- Medicine and the law
- Cochrane corner

An In Practice article should follow the following format – sub-headings are not necessary, but may be used for clarity:

- Author affiliations and qualifications: to be the same as for Research. Provide all authors' names and initials, qualifications and full affiliations, and corresponding author.
- Short abstract: does not need to be structured, but should capture the essential features of the article
- Introduction: the reason for the article and the issue being addressed
- Recent research, discussion, local policy around the issue – include your own research where appropriate
- All statements should be referenced and, if opinion only, this should be stated
- Discussion: how this article adds to the discussion around a particular topic
- If a clinical practice or policy point is at issue, this needs to be emphasised, using a box with highlights if appropriate.

Essentially In practice is an opportunity for a more discursive approach to topics of clinical, economic or political importance in southern African health systems. It is not an opportunity to put forward unsubstantiated opinions!

Case reports

The *SAMJ* has recently started to accept case reports. The cases must come from Africa, preferably southern Africa unless the condition is common to all African countries, and must be either a completely new description of a clinical condition or result (use Google!) or a case that highlights important practice or management issues.

Please use the following format for case reports:

- Title of case: do not include the words 'a case report' in the title
- Summary/abstract: up to 150 words summarising the case presentation and outcome
- Background: why is this case important and why did you write it up?
- Case presentation: presenting features, medical, social, family history as appropriate
- Case management: should be according to best practice, and if not, please explain why
- Investigations, if relevant: save space by simply saying 'normal' if, for example, renal function was completely normal, rather than listing normal results, highlight the abnormal – or indeed the normal if this is clinically significant
- Differential diagnosis, if relevant
- Treatment, if relevant
- Outcome and follow-up
- Discussion – a VERY BRIEF review of similar published cases

- Teaching points: 3 - 5 bullet points
- References: as per the *SAMJ* house style
- Tables and figures: keep to a minimum. Use clinical images where relevant – we need hi-res versions for print, and identifiable persons must have a consent form
- Patient consent: please include a statement about patient consent to a written case report. This should be uploaded as a supplementary file.

Clinical trials

Guideline word limit: 4000 words

As per the recommendations published by the International Committee of Medical Journal Editors (ICMJE), clinical trial research is any research that assigns individuals to an intervention, with or without a concurrent comparison/control group to study the cause-and-effect relationship between the intervention and health outcomes. All clinical trials should be registered with the appropriate national clinical trial registry (or any international primary register, if relevant), and the trial registration number should be cited at the end of the abstract. Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register. The *SAMJ* therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrolment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Please refer to the general guidelines for all papers at the top of this article for additional requirements with respect to ethics approval, funding, author contributions, etc. The format of original research articles should be followed for reporting of clinical trial results.

Review articles

Guideline word limit: 4 000 words

These are welcome, but should be either commissioned or discussed with the Editor before submission. A review article should provide a clear, up-to-date account of the topic and be aimed at non-specialist hospital doctors and general practitioners.

Please ensure that your article includes:

- Abstract: unstructured, of about 100-150 words, explaining the review and why it is important
- Methods: Outline the sources and selection methods, including search strategy and keywords used for identifying references from online bibliographic databases. Discuss the quality of evidence.
- When writing: clarify the evidence you used for key statements and the strength of the evidence. Do not present statements or opinions without such evidence, or if you have to, say that there is little or no evidence and that this is opinion. Avoid specialist jargon and abbreviations, and provide advice specific to southern Africa.
- Personal details: Please supply your qualifications, position and affiliations and MP number (used for CPD points); address, telephone number and fax number, and your e-mail address; and a short personal profile (50 words) and a few words about your current fields of interest.

Correspondence (Letters to the Editor)

Guideline word limit: 500 words

Letters to the editor should relate either to a paper or article published by the SAMJ or to a topical issue of particular relevance to the journal's readership

- May include only one illustration or table
- Must include a correspondence address.

Book reviews

Guideline word limit: 400 words

Should be about 400 words and must be accompanied by the publication details of the book. Provide a hi-res image of the cover if possible (with permission from the copyright holder).

Obituaries

Guideline word limit: 400 words

Should be offered within the first year of the practitioner's death, and may be accompanied by a photograph.

Guidelines

Guidelines should always be discussed with the Editor prior to submission.

Because of the intensive review process required to ensure Guidelines are independent, evidence-based and free from commercial bias, they are usually published as a supplement to the *SAMJ*, the costs of which must be covered by sponsorship, advertising or payment by the guideline authors/association. We will provide a quote based on the expected length of the guideline and whether it is to appear online only, or in print, which must be accepted by the body putting the guidelines together before submitting the work to the SAMJ.

The Editor reserves the right to determine the scheduling of supplements. Understandably, a delay in publication must be anticipated dependent upon editorial workflow.

All guidelines should include a clear, transparent statement about all sources of funding and an explicit, clear statement of conflicts of interest of any of the participants in the guidelines about industry funding for lectures, research, conference participation etc.

All guidelines should be structured according to Agree II.

Please access this website before putting the guidelines together, download the Agree 11 instrument and use this to put the guidelines together.

All submitted guidelines will be sent to the local Agree II appraisal committee for review and must be endorsed by an appropriate body prior to consideration and all conflicts of interest expressed.

A structured abstract not exceeding 400 words (recommended sub-headings: *Background, Recommendations, Conclusion*) is required. Sections and sub-sections must be numbered consecutively (e.g. 1. Introduction; 1.1 Definitions; 2.etc.) and summarised in a Table of Contents.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF or jpeg form.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) and refer to consecutively in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ ‖ then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make 'new rows':

Rather:

Each row of data must have its own proper row:

Do not: use separate columns for *n* and %:

Rather:

Combine into one column, *n* (%):

Do not: have overlapping categories, e.g.:

Rather:

Use <> symbols or numbers that don't overlap:

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and not with the use of reference manager software. Endnotes must* ***not*** *be used.*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:

- On the Crossref homepage, paste the article title into the 'Metadata search' box.
- Look for the correct, matching article in the list of results.
- Click Actions > Cite
- Alongside 'url =' copy the URL between { }.
- Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx.doi.org/10.1000/hgjr.182
- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references

• Government Gazettes:

National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.

In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

• Provincial Gazettes:

Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

• Acts:

South Africa. National Health Act No. 61 of 2003.

• Regulations to an Act:

South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

• Bills:

South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

• Green/white papers:

South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

• Case law:

Rex v Jopp and Another 1949 (4) SA 11 (N)

Rex v Jopp and Another: Name of the parties concerned

1949: Date of decision (or when the case was heard)

(4): Volume number

SA: SA Law Reports

11: Page or section number

(N): In this case Natal - where the case was heard. Similarly, (C) woud indicate Cape, (G) Gauteng, and so on.

NOTE: no . after the v

- *Other references (e.g. reports) should follow the same format:* Author(s). Title. Publisher place: Publisher name, year; pages.

- Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.
- Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

From submission to acceptance

Submission and peer-review

To submit an article:

- Please ensure that you have prepared your manuscript in line with the SAMJ requirements.
- The following are required for your submission to be complete:

o Anonymous manuscript (unless otherwise stated)

o Manuscript

o Any supplementary files: figures, datasets, patient consent form, permissions for published images, etc.

- Once the submission has been successfully processed, it will undergo a technical check by the Editorial Office before it will be assigned to an editor who will handle the review process. If the author guidelines have not been appropriately followed, the manuscript may be sent back to the author for correcting.

Peer-review process

Production process

Please note that there is a 6-month waiting time for publication, once an article has been sent to the production team.

The following process will follow:

1. An accepted manuscript is passed to a Managing Editor to assign to a copyeditor (CE).
2. The CE copyedits in Word, working on house style, format, spelling/grammar/punctuation, sense and consistency, and preparation for typesetting.
3. If the CE has an author queries, he/she will contact the corresponding author and send them the copyedited Word doc, asking them to solve the queries by means of track changes or comment boxes.
4. The authors are typically asked to respond within 1-3 days. Any comments/changes must be clearly indicated e.g. by means of track changes. Do not work in the original manuscript - work in the copyedited file sent to you and make your changes clear.
5. The CE will finalise the article and then it will be typeset.
6. Once typeset, the CE will send a PDF of the file to the authors to complete their final check, while simultaneously sending to the 2nd-eye proofreader.
7. The authors are typically asked to complete their final check and sign-off within 1-2 days. No major additional changes can be accommodated at this point.
8. The CE implements the authors' and proofreader's mark-ups, finalises the file, and prepares it for the upcoming issue.

Changing contact details or authorship

Please notify the Editorial Department of any contact detail changes, including email, to facilitate communication.

Publication

Online v. print

The *SAMJ* is an online journal. The online version of the journal is the one that has the widest circulation, is indexed by bibliographic databases including PubMed and SciELO, and is accessible in academic libraries. A printed edition , containing material selected by the Editor is also published each month and distributed to the membership of the South African Medical Association.

Online

- The full text of all accepted articles is published in full online, open access.
- Citation information of each article is based on its online publication.
- You may want to make use of the advantages of online publication e.g. specify web links to other sources, images, data or even a short video.

Print

- Not all articles will be selected for print.
- An article may be selected for print in a different month from that in which it was published online.
- Research articles will appear *in abstract form only*, if selected for a print edition.

Errata and retractions

Errata

Should you become aware of an error or inaccuracy in yours or someone else's contribution after it has been published, please inform us as soon as possible via an email to publishing@samedical.org, including the following details:

- Journal, volume and issue in which published
- Article title and authors
- Description of error and details of where it appears in the published article
- Full detail of proposed correction and rationale

We will investigate the issue and provide feedback. If appropriate, we will correct the web version immediately, and will publish an erratum in the next issue. The correction will be indexed, as PubMed has a function for linking errata back to the original article. All investigations will be conducted in accordance with guidelines provided by the Committee on Publication Ethics (COPE).

Retractions

Retraction of an article is the prerogative of either the original authors or the editorial team of SAMA. Should you wish to withdraw your article before publication, we need a signed statement from all the authors.

Should you wish to retract your published article, all authors have to agree in writing before publication of the retraction. Send an email to publishing@hmpg.co.za, including the following details:

- Journal, volume and issue to which article was submitted/in which article was published
- Article title and authors
- Description of reason for withdrawal/retraction.

We will make a decision on a case-by-case basis upon review by the editorial committee in line with international best practices. Comprehensive feedback will be communicated with the authors with regard to the process. In case where there is any suspected fraud or professional misconduct, we will follow due process as recommended by the Committee on Publication Ethics (COPE), and in liaison with any relevant institutions.

When a retraction is published, it will be linked to the original article.

Indexing

The *SAMJ* has an impact factor of 1.5.

Published articles are covered by the following major indexing services. As such articles published in the *SAMJ* are immediately available to all users of these databases, guaranteed a global and African audience:

- Index Medicus (Medline/PubMed)
- ExcerptaMedica (EMBASE)
- Biological Abstracts (BIOSIS)
- Science Citation Index (SciSearch)
- Current Contents/Clinical Medicine
- Scopus
- AIM
- AJOL
- Crossref
- Sabinet
- Scielo

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Contact claudian@samedical.org for information on submitting ad hoc/commissioned supplements, including guidelines, conference/congress abstracts, Festschrifts, etc.

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