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Infectious diseases consultations at a South African academic hospital: a six-month review of inpatient consultations

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INFECTIOUS DISEASES CONSULTATIONS AT A SOUTH AFRICAN ACADEMIC HOSPITAL: A SIX-MONTH REVIEW OF INPATIENT CONSULTATIONS

Lauren Richards

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfillment for the requirements of the degree of Master of Medicine in Internal medicine

Johannesburg 2019

DECLARATION

I, Lauren Richards declare that this Research Report is my own, unaided work. It is being submitted for the degree of Master of Medicine in the department of internal medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other university.

Signature: ……

Date: ……

Place: ……

ACKNOWLEDGEMENTS

I would like to thank the following people without whom I could not have completed this report:

To my supervisors: Dr D Spencer and Prof P Ive. You have guided me through this experience and gave me the encouragement to push myself further. Thank you for always being available and reassuring me during my uncertain times.

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ABSTRACT

Background

The infectious diseases (ID) department is becoming increasingly valuable in an era of evolving antimicrobial resistance and an enlarging immunocompromised population. To date, there has been little evaluation of the infectious diseases consultation services in South African hospitals.

Methods

A review of ID inpatient consultations was performed over a period of six months at Helen Joseph Hospital, a South African tertiary hospital. Data from each consultation was recorded on a computerised database and analysed.

Results

A total of 749 ID consultations were reviewed representing an average of 4.8% of hospital admissions. The most common reasons for consultation were for initiation of antiretroviral therapy (ART) (27.8%), lipoarabinomannan antigen (LAM) testing (24.8%) and change of ART (21.6%). Of all patients reviewed, 93.3% were human immunodeficiency virus (HIV) positive and the median CD4 count was 52 cell/mm^3.

The infectious diagnoses (excluding HIV) that were most frequently encountered were pulmonary and abdominal tuberculosis (TB) and acute gastroenteritis. When all subcategories of TB infection were combined, 42.9% of patients reviewed were found to be infected with TB. The most common non-infectious co-morbidities were acute kidney injury, hypertension and diabetes mellitus.

Conclusion

The ID department sees a high volume of cases. HIV, TB and their management dominate the workload and the patient disease profile. Non-infectious comorbidities

were infrequent in this population, possibly due to the relatively young median age. Due to the large numbers of HIV- and TB-related cases, only a small proportion of the inpatient ID service was devoted to antibiotic stewardship, infection prevention and control, and the spectrum of cases seen more frequently by ID departments in the developed world.

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LIST OF ABBREVIATIONS

AIDS	Acquired immune deficiency syndrome
ART	Antiretroviral therapy
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CVA	Cerebrovascular accident
DILI	Drug induced liver injury
DM	Diabetes Mellitus
ELISA	Enzyme-linked immunosorbent assay
HAND	HIV associated neurocognitive disorder
HIV	Human immunodeficiency virus
HJH	Helen Joseph Hospital
ICU	Intensive care unit
ID	Infectious diseases
IQR	interquartile range
LAM	Lipoarabinomannan antigen

MAC	Mycobacterium avium complex
NHLS	National Health Laboratory Services
NOS	Not otherwise specified
OR	Odds ratio
PCP	Pneumocystis jirovecii pneumonia
PCR	Polymerase chain reaction
SA	South Africa
TB	Tuberculosis

CHAPTER ONE: PROTOCOL WITH EXTENDED LITERATURE REVIEW

1.1 INTRODUCTION

Infectious Diseases (ID) is a subspecialty of internal medicine that is relatively new in South African medicine. ID specialists have been present in South Africa since 2004 [1].The value of a physician specially trained in infectious diseases and management thereof is becoming increasingly apparent in an era of greater antimicrobial resistance and enlarging immunocompromised populations. ID specialist consultation has been shown to decrease mortality, improve patient outcomes and reduce expenditure on care [2-5]. Paulsen et al. reviewed 22 studies looking at the impact of an ID specialist consultation in patients with *Staphylococcus aureus* bacteraemia. Most studies reviewed showed a benefit on all-cause mortality and there was improved quality of management when patients were seen by an ID specialist [6]. A study by Lobati et al. showed that there was increased bone salvage in patients with osteomyelitis when seen by an ID specialist [7]. Takakura et al. examined two groups of patients with *Candida* blood stream infections: The group that had treatment intervention by an ID specialist had an improved 30-day survival rate; an increased likelihood of receiving appropriate antifungal therapy and had their central lines removed timeously [8].

Antimicrobial resistance threatens the management of common infectious diseases. The steady increase in antimicrobial resistance has not been matched with the development of new antimicrobial agents. This underpins the urgent need for antibiotic stewardship. ID specialist intervention improves the appropriateness of antibiotics prescribed and these specialists can be instrumental in antibiotic

stewardship programs [3, 9]. In a review by Rieg et al. on the impact of an ID consultation on patient outcome and care they found that the “quality of antibiotic therapy” (based on the Kunin-criteria) was improved in 18-32% of cases when comparing patients seen by an ID specialist with those who were not [5]. This review reported that the frequency of the ‘correct’ (as defined by internal, national or international guidelines) empiric antimicrobials used was increased with an ID consultation and de-escalating antibiotics based on microbiological results was often done first by an ID physician. Pulcini et al. reviewed 31 studies from around the world evaluating the effect that ID specialists have on antimicrobial prescription in hospitals [4]. Appropriate antibiotic prescription was improved in almost all of the studies reviewed. This was across a range of diseases, clinical settings and types of antimicrobials used.

Aside from increased resistance to antibiotics, ID specialists are becoming more relevant as the population develops an expanding number of immunocompromised patients. This is of particular importance in South Africa. According to Stats SA, in 2015 11,2% of the South African population was human immunodeficiency virus (HIV) positive and the average life expectancy of South Africans had risen to 62 years. This rise in life expectancy is in part due to a decrease in the number of acquired immune deficiency syndrome (AIDS) related deaths and to the increasing use of antiretroviral therapy (ART) [10,11]. The HIV positive population is therefore living longer and this brings new challenges to their medical management in addition to frequent opportunistic infections [12]. Therefore, there is an increased need for specialists in this field.

In many South African hospitals, ID specialist input is mainly in the form of bedside consultations, as typically there is no specific ID ward. This makes evaluation of the role of ID specialists more difficult. To date there has been little information on the spectrum of patients and problems that South African ID departments encounter. This review may assist in displaying the type of patient typically referred to infectious diseases, areas that may need further attention or improvement and areas where further education would benefit all parties involved.

In order to understand the burden on the infectious diseases services in South Africa, it is pertinent to compare the role of ID specialists in South Africa to each other and to their counterparts further afield. Several studies of this nature have been published, predominantly from high-income countries. Selected findings are summarized here.

1.2 LITERATURE REVIEW

Bursle et al. retrospectively reviewed formal inpatient ID consultations for a period of thirteen and a half years (July 1999- December 2012) in an Australian tertiary hospital [13]. All ID consultations were recorded by the ID registrar providing the consultation onto a computerized database. The specific information recorded included: team requesting the ID consultation, patient demographics, syndrome initiating the consultation, final diagnosis and microbiological results. Telephonic consultations, informal consultations and ID admissions were excluded.

From the 11511 consultations reviewed they found that 1.3% of hospital admissions required an ID consult. It was reported that ID consults increased over the years from 2000 to 2012. This may be due to several reasons but the authors hypothesized that it was as a result of a rise in complex infections due to the increase in the number of vulnerable patients, for example the elderly and the immunocompromised (related to HIV, chemotherapy, transplantation and the use of immunosuppressant therapies), and the rise of resistant organisms. The authors did note that this rise was not accounted for by hospital occupancy. Another hypothesis was that there was recognition for improved prescription of antibiotics. Consults were most frequently requested by orthopaedic surgeons, followed by general medicine. The most common syndromes initiating an ID consultation were bacteraemia (13.9%), complicated soft tissue infection (7.8%), osteomyelitis (7.2%), cellulitis (5.2%) and surgical site infection (5.2%). Final diagnoses made were ‘other diagnosis’ (10%), which were non-infective or malignant in nature, followed by osteomyelitis, soft tissue and surgical site infections.

The limitations of this study include the fact that it represents only one hospital and therefore it is difficult to extrapolate the data to other hospitals. The duration over which the data was collected (1999-2012) resulted in substantial variability in the data entries by different registrars during the study period. Evaluation of diagnoses was especially vulnerable to user variability and therefore the most common diagnosis was “other” due to inadequate standardization of these. The fact that only one diagnosis was permitted per consultation may have skewed the spectrum of diseases seen. This study did not include informal, phone or repeat consultations, which usually represent a large component of the ID specialist’s function. An additional limitation includes the generalizability of the data to non-Australian

contexts and specifically southern Africa where HIV/AIDS is a defining context of health care.

A 14-year review of formal ID consultations in a tertiary paediatric hospital, in Melbourne, Australia, by Gwee et al. was similar to the study previously discussed [14]. Formal ID consultations were prospectively recorded on a database by an ID fellow. Informal and telephonic consultations were not included. Variables recorded were referral details, patient demographics, clinical and microbiological details. For 500 of the most recent consultations reason for referral; advice given and how management changed after the consultation were documented and reviewed. Overall, ID consultations were requested for 2.2% of admissions to the hospital. There was also an increase in consultations over their study period. The rise in consultations over the study period was attributed to increased recognition of the value of the service, the rise in multidrug resistant organisms and the increased number of immunocompromised patients. The authors found that general medicine requested consults most frequently and oncology the least. In terms of reasons for consulting the ID department, diagnostic and management advice were the most common. More specifically, in the most recent 500 consultations, the most frequent reason for consult was for assistance in choice of antimicrobial agent in the context of a positive culture result (47.8%). Assistance in making a diagnosis, advice on the duration of treatment and empiric antibiotic regimens followed this. Of the patients with a documented immune status, 24.5% were immunocompromised. The most common site of infection was the bloodstream. The limitations to this study are similar to the review by Bursle et al. in that the duration of the study resulted in significant variability in entry of data [13]. Telephonic and informal consults were also

not included and this study included only children, the results of which cannot easily be applied to an adult population.

A study by Vehreschild et al. conducted in a German tertiary hospital, over a five-month period, aimed to evaluate the impact of ID specialist consultations [15]. An electronic system was set up for the requesting of an ID consultation. The doctor requesting the services of the ID department was obliged to fill in a standardized form. A total of 251 consultations were reviewed. All consultations were reviewed including telephonic consults, which were only allowed for minor issues. Evaluation found that the haematology/oncology department requested consults most often. Consultations were made on average 12.8 days after the patient's admission. Most consultation requests (52%) were to assist in "optimizing an initiated anti-infective treatment", advice on diagnostic procedures and duration of treatment followed. Renal dysfunction (21%), solid tumours (20%) and "haematological diseases" (20%) were, in order of appearance, the most frequent co-morbidities found in patients; 8% of patients were HIV positive. The final diagnosis of the patient was infectious in 81% of the consultations, 17% were non-infectious and 2% were questionable. The authors reported that after an ID consult, there was improvement in patient care, clinical outcomes and antibiotic prescription. Diagnostic investigations recommended by ID specialists confirmed provisional diagnoses (which were provided by the ID specialist in more than 25% of cases) in 80% of those consults where diagnostic assistance was requested. In terms of patient outcome, 49% of the patients had a positive response after the ID consult, 37% were stabilized and in 9% the condition worsened. Overall the recommendations provided by the ID specialists on antimicrobial agents resulted in cost savings rather than increased expenditure. Limitations of this study are the relatively short study period of 5 months and

therefore a small sample size. As with previous studies this review was conducted in a First World country and results cannot easily be applied to developing countries.

An article by Schlessinger et al. documented 4184 ID consultations over an 18-month period in a general hospital based in Jerusalem [16]. Data was entered onto a computerized database program by 2 full-time ID consultants. Consults were requested by the primary physician 80% of the time, the other 20% were due to a laboratory result or to prescribe a restricted antimicrobial. The type of consultation was formal in 50% of cases, 25% were curbside and 25% were telephonic consultations. During the study period 6.9% of all hospital admissions required ID consultations. The comparatively high rate of ID consultations reported in this study may be accounted for by the inclusion of non-bedside consults. The departments requesting the most consultations were the medical department and the emergency department. The purpose of consultations was mostly for advice on diagnosis and treatment, followed by advice on treatment alone. The most common specific diagnoses made by the ID department was “miscellaneous” followed by bacteraemia/sepsis and respiratory infections. Limitations of this study are the fact that it is based in one hospital in a developed country. The most frequent diagnosis made was “miscellaneous” which is not very informative. Only one ‘diagnosis’ and one ‘purpose of consult’ was allowed per consultation. This may have under-estimated these parameters as patients may have had more than one diagnosis or purpose of consult.

A follow up study to the previous review discussed by Yinnon was performed in 2001 [17]. There were 14005 ID consultations analysed over a 5-year period in the same

Jerusalem based hospital. This review analysed data entered by a single infectious diseases consultant which differs from most other studies discussed. The same variables as the 1998 review were documented [16]. Of the 14005 consults, 64% were new and 35% were follow up consultations. With this data they were able to assess how many follow-up visits would be most beneficial to patients as well as the most cost-effective. The conclusion that they came to was that 1-2 follow up visits was adequate for most patients, patients who were admitted to an intensive care unit (ICU), haematology-oncology or transplant units may have needed additional visits. The author reported that the rate of ID consultations was 6% of admissions. Again, this high rate may be accounted for by the inclusion of telephonic and outpatient consultations. Excluding non-bedside consults; the rate of ID consultation was 2.6% of admissions. The most frequent reason for the consultation was assistance with treatment, thereafter assistance with diagnosis *and* treatment and thirdly diagnosis alone. The most common diagnoses were 'sepsis' with new ID consultations and respiratory tract infections when looking at follow up consultations. Departments most commonly requesting an ID consult in this review were ICU and the haematology-oncology unit, reflecting that immunocompromised and vulnerable patients often have more complex infections. The monthly expenditure on antimicrobials per admission decreased significantly during the analysis period demonstrating the favourable economic benefit of having an active ID department. Limitations to this review are that these consultations were performed by one consultant which may skew the data as he may have had a bias when diagnosing certain conditions clinically.

The only available data on a South African ID unit was from an article that reviewed the role of the ID unit at Groote Schuur Hospital in Cape Town [18]. This is a tertiary

institution where the ID unit was established in 2007. A total of 2142 patients were reviewed over a 4-year period (2008-2011) with an average of 535 patients per year. The review was very similar to previous articles mentioned in that they were an inpatient consultation based department and each consult was recorded on a computerised database. The data recorded included the patient's sex; the referring team; HIV status (CD4 count if the patient was positive and whether the patient was on ART); presenting clinical features, discharge diagnosis, co-morbidities and if the patient died. Approximately 80% of the patients seen were HIV positive with a median CD4 count of 128. Tuberculosis (TB) was the most common discharge diagnosis in both HIV positive and negative patients. Pulmonary TB was the most common form of the disease with disseminated and meningeal TB following this. Drug hypersensitivity syndromes were the most frequently encountered diagnoses after TB. These findings show that most of the patients seen by this ID unit were HIV-infected. The authors speculate that this could be due to the fact that HIV is a relatively new disease and therefore some physicians may lack the confidence in treating these patients alone. The other reason could be attributed to the fact that it was hospital policy that only the ID department could initiate ART in hospitalised patients. The in-hospital mortality was 5.8% with "overwhelming sepsis" as the predominant cause. Sepsis in these cases was mostly due to hospital-acquired infections, particularly in the HIV positive patients. Co-morbidities in addition to the primary diagnoses (infectious and non-infectious) were present in 54% of HIV positive patients and 50% of HIV seronegative patients. This highlights the complexity of patients seen by this department. Limitations of this review include a potential for incomplete or inaccurate data collection; patient outcome was restricted to the patients' admission, outcome post discharge was not documented and this

data didn't include all aspects of the ID units work load – they provided support via telephonic consults and outreach programs at secondary institutions.

Meintjes et al. further demonstrates the burden of HIV in South Africa (SA) with a review of medical admissions at a public sector district level hospital in Cape Town between June 2012 and October 2013 [19]. Of the 1018 admissions 60% of patients were HIV positive. Of these HIV positive patients 84.4% knew their status prior to admission but only 45% were on ART (35.7% were ART naïve and 19.3% had interrupted their treatment). The most frequent diagnoses made in these patients were TB, "other bacterial infection" and AIDS defining illnesses (other than TB). At the 90-day post discharge follow up 29.9% had required re-admission and 13.3% had died. In a world-wide systematic review and meta-analysis by Ford et al., AIDS-related illnesses and bacterial infections were the most common reasons for hospital admission amongst adults living with HIV [20].

In a time where ART is easily available, people with HIV are still presenting to health facilities at an advanced stage of their disease. Ford et al. in an editorial commentary states that, according to the European consensus definition of a late presenter, "the vast majority of patients starting ART in sub-Saharan Africa are late presenters" [21]. This could account for the fact that "AIDS-defining illnesses" is one of the leading reasons for admission in HIV positive individuals in the reviews by Meintjes et al. and Ford et al.

In reviewing the above articles, it is evident that the degree of activity in each ID department varies considerably. It is difficult to compare departments in developed

countries to those in developing countries as they have a completely different patient profile. The type of patient seen by the ID departments in most of the above articles cannot be generalised to SA as they are conducted in high-income countries that do not face the burden of HIV that SA does. The burden of HIV impacts significantly on the reasons for ID consultation, the diagnoses, the demographics and risk factors seen in patients in SA in general. It is therefore important to review ID departments and services in a context that is relevant to the developing world in order to draw appropriate conclusions.

In the following descriptive review, I would like to investigate the type of patient and conditions that an ID department typically see in a South African tertiary institution. I hope to illuminate frequently encountered infectious diseases, how they manifest and how often ID services are requested. Using this information, one can create awareness of the infectious diseases specialty and the importance that they can have in patient care. Education regarding the scope of services provided would hopefully increase appropriate referrals and decrease those that are inappropriate.

1.3 STUDY AIMS AND OBJECTIVES

1.3.1 AIMS

To do a descriptive review of infectious diseases consultations in a South African tertiary hospital over a six-month period.

1.3.2 OBJECTIVES

To audit an infectious diseases consultation database retrospectively, looking particularly at:

- Male to female ratio

- Length of stay of a patient in hospital prior to ID consultation

- HIV status

- The CD4 count of HIV positive patients

- Reason for ID consultation

- Infectious diagnoses

- Non-infectious co-morbidities

- Number of deaths per 100 consultations

- Number of hospital admissions requiring an ID consultation per month

- Association between length of stay prior to ID consultation and outcome

1.4 METHODS

1.4.1 STUDY DESIGN

This is a retrospective descriptive review of all formal ID consultations requested during a period of 6 months. (October 2015 to March 2016)

1.4.2 STUDY POPULATION

All consecutive, inpatient infectious diseases consultations will be captured retrospectively on a computerised database by the medical registrar or medical officer performing the consultation. Only formal bedside consultations will be included and telephonic or informal consults will be excluded, as will incomplete entries onto the database. Incomplete entries are defined as those that don't include the patients' demographics and all of the relevant study variables analysed in this review. Repeat consults by the ID team during a patient's same admission will not be recorded as additional consultations. During the period of October 2015 to March 2016, 749 formal consultations were performed and entered onto the database. This data will be reviewed.

1.4.2.1 SETTING

Helen Joseph Hospital is located in Johannesburg, South Africa. Helen Joseph Hospital is a 500-bed academic hospital affiliated with the University of the Witwatersrand. It is a tertiary hospital and includes all major adult specialties apart from obstetrics and gynaecology. The infectious diseases department, during the study period, consisted of one full time ID specialist physician, an ID fellow, two

medical registrars and a medical officer. There is no specific ID ward and therefore the department works on a consultation basis.

1.4.2.2 STUDY VARIABLES

Variables to be collected are: Patient sex; time period between hospital admission and ID consultation; the reason for the ID consultation; the main infectious diagnoses; the non-infectious comorbidities; HIV status; CD4 count if the patient is HIV positive and patient outcome. Outcome is defined as either death (the patient demised during the period of consultation) or discharge (the patient was still alive at the time of discharge from ID services). The CD4 count (cells/mm^3) will be recorded as an absolute number and then analysed after being sorted into three categories. The categories were chosen as less than 100, between 100 and 500 and greater than 500. The cut off of 100 was chosen as this implies a patient is at risk for specific opportunistic infections that rarely occur otherwise. The cut off of 500 was chosen as this was the CD4 threshold at which the South African state sector recommended the initiation of ART at the time of the study.

1.4.2.3 DATA SOURCES

The date of admission and ID consultation were derived from the patient files and the formal consultation request form submitted to the ID department. The reason for consult was recorded by the infectious diseases doctor who entered the data. Diagnoses were derived from confirmatory microbiological, histological or radiological investigations. Empiric diagnoses not confirmed by these investigations were made by specialist physicians in the relevant medical field. Non-infectious comorbidities

were obtained from patient history mainly or by the above special investigations if they were diagnosed on the current admission. The HIV status was determined by 4th generation enzyme-linked immunosorbent assay (ELISA) and if equivocal an HIV viral load or polymerase chain reaction (PCR) was performed. All microbiological, pathological and serological investigations were performed by the National Health Laboratory Services (NHLS).

The number of hospital admissions per month will be obtained from Helen Joseph Hospital's statistics department.

1.5 STATISTICAL ANALYSIS

Data will be entered onto a spreadsheet using Microsoft Excel. Descriptive analysis of the data will be carried out with the assistance of a statistician. Categorical variables will be summarised by frequency and percentage tabulation. Continuous variables will be summarised by the mean, standard deviation, median and interquartile range. Data analysis will be carried out using SAS (version 9.4 for Windows). The 5% significance level will be used, in other words, p-values <0.05 indicate significant associations.

1.6 **ETHICS**

No personal identification details of patients will be revealed in this study. Patients' will receive a participant number when entered onto the data collection sheet. No privacy interests of the patients were affected. Ethical clearance was obtained from the University of the Witwatersrand Human Research Ethics Committee on 6 May 2016.

1.7 TIMELINE

	Jan 2016	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Literature Review												
Preparing protocol												
Protocol assessment												
Ethics application												
Collecting data												
Data analysis												
Writing up thesis												

1.8 FUNDING

The only expense currently is photocopying and this will be self-funded. This is a retrospective study and therefore I don't expect any unforeseen expenses. If something does arise this will be self-funded.

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CHAPTER 2: SUBMISSIBLE ARTICLE

Title: Infectious diseases consultations at a South African academic hospital: A six-month review of inpatient consultations

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Conflicts of interest: None

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Abstract

Background

The infectious diseases (ID) department is becoming increasingly valuable in an era of evolving antimicrobial resistance and an enlarging immunocompromised population. To date, there has been little evaluation of the infectious diseases consultation services in South African hospitals.

Methods

A review of ID inpatient consultations was performed over a period of six months at Helen Joseph Hospital, a South African tertiary hospital. Data from each consultation was recorded on a computerised database and analysed.

Results

A total of 749 ID consultations were reviewed representing an average of 4.8% of hospital admissions. The most common reasons for consultation were for initiation of antiretroviral therapy (ART) (27.8%), lipoarabinomannan antigen (LAM) testing (24.8%) and change of ART (21.6%). Of all patients reviewed, 93.3% were human immunodeficiency virus (HIV) positive and the median CD4 count was 52 cell/mm^3.

The infectious diagnoses (excluding HIV) that were most frequently encountered were pulmonary and abdominal tuberculosis (TB) and acute gastroenteritis. When all subcategories of TB infection were combined, 42.9% of patients reviewed were found to be infected with TB. The most common non-infectious co-morbidities were acute kidney injury, hypertension and diabetes mellitus.

Conclusion

The ID department sees a high volume of cases. HIV, TB and their management dominate the workload and the patient disease profile. Non-infectious comorbidities were infrequent in this population, possibly due to the relatively young median age. Due to the large numbers of HIV- and TB-related cases, only a small proportion of the inpatient ID service was devoted to antibiotic stewardship, infection prevention and control, and the spectrum of cases seen more frequently by ID departments in the developed world.

Introduction

Infectious Diseases (ID) is a subspecialty of internal medicine that is relatively new in South African medicine since the specialty had its first graduates only in 2004 [1]. The value of a physician specially trained in infectious diseases and the management thereof is becoming increasingly apparent in an era of greater antimicrobial resistance and increasing numbers of immunocompromised patients. Specialist ID consultation has been shown to decrease mortality, improve patient outcomes and reduce expenditure on care [2-6].

Antimicrobial resistance threatens the ability to manage common infectious diseases and this has been exacerbated by the paucity of new antimicrobial agents. These two factors underpin the urgent need for antibiotic stewardship. In this regard, ID specialist intervention improves the appropriateness of the antibiotic prescribed, the dose and the duration. As such these specialists are in the vanguard of antibiotic stewardship programs [3-6]. Pulcini et al. reviewed 31 studies from around the world evaluating the effect that ID specialists had on antimicrobial prescriptions in hospitals [4]. The appropriateness of the antibiotics prescribed was improved in almost all of the studies reviewed across a range of diseases, clinical settings and types of antimicrobials used.

Aside from increased resistance to antibiotics, ID specialists are becoming more relevant as the principal therapists of an increasing population of immunocompromised patients. This is of particular importance in South Africa where although according to Stats SA, in 2015 11,2% of the South African population was human immunodeficiency virus (HIV) positive, the average life expectancy of South

Africans had risen to 62 years. This increase in life expectancy is in part due to a decrease in the number of deaths due to the acquired immune deficiency syndrome (AIDS), primarily due to the increased use of antiretroviral therapy (ART) [7, 8]. As the HIV positive population lives longer new medical challenges arise, increasing the need for specialists in this field [9].

In addition to an aging HIV population there are still a large number of HIV positive patients not yet on ART who are presenting to healthcare facilities at a late stage of their illness with infections, opportunistic or otherwise [10]. This frequently represents significant diagnostic difficulty as they may have more than one disease process or may present atypically. Managing this type of patient is often complex involving the initial diagnosis and therapy, the initiation of ART and monitoring for drug interactions and side effects. The management of the patient with HIV requires specialist knowledge and training for which the ID specialist is eminently qualified.

In many South African hospitals, ID specialist input is mainly in the form of bedside consultations, as typically there is no dedicated ID ward. This makes evaluation of the role of ID specialists more difficult. To date there is a paucity of information on the spectrum of patients and problems that South African ID departments encounter. This review may assist in highlighting the type of patient typically referred, it may also indicate areas that need further attention or improvement and define where further education is necessary. As South Africa has a unique patient population, particularly in relation to the developed world, this review may cast further light on the current state of infectious diseases in a developing country.

Aim

To do a retrospective review of infectious diseases consultations in a South African tertiary hospital over a six-month period.

Methods

The site of the review is the Helen Joseph Hospital (HJH) located in Johannesburg, South Africa. The Helen Joseph Hospital is a tertiary academic hospital affiliated with the University of the Witwatersrand. During the study period, the infectious diseases department consisted of one full time ID specialist physician, an ID fellow, two medical registrars and a medical officer. There is no specific ID ward and therefore the department works on a consultation basis.

From October 2015, all consecutive, inpatient infectious diseases consultations were captured on a computerised database by the medical registrar or medical officer performing the consultation. All consultations performed by the ID department over a six-month period (October 2015-March 2016) were analysed. Consultation details recorded were: Patient sex; age; time period between hospital admission and ID consultation; the reason for the ID consultation; HIV status; CD4 count if the patient was HIV positive; the main infectious diagnoses; the non-infectious comorbidities and patient outcome. Outcome was defined as death (the patient demised during the period of consultation) or discharge (the patient was still alive at the time of discharge from ID services). The CD4 count was recorded as an absolute number as well as sorted into three categories (<=100; 101-500; >500). The cut off of 100 cells/mm^3 was chosen as this implies a patient is at risk for specific opportunistic infections that rarely occur otherwise. The cut off of 500 cells/mm^3 was chosen as this was the

number at which South Africa initiated ART during the review period, this has since changed. Only formal bedside consultations were included and telephonic or informal consults were excluded. Repeat visits by the ID team during a patient's admission were not recorded as additional consultations.

Data analysis included the previously mentioned consultation details. Categorical variables were summarised by frequency and percentage tabulation. Continuous variables were summarised by the mean, standard deviation, median and interquartile range. In addition, the number of deaths per 100 consultations and the number of total hospital admissions requiring an ID consultation per month were calculated. Lastly, an attempt to associate a patient's length of stay (<=10d vs. >10d) with outcome was made, controlling for HIV status/CD4 count category; number of infectious diagnoses (0-1 vs. more than 1) and number of non-infectious diagnoses (0 vs. 1 or more). Analysis was performed using SAS (version 9.4 for Windows). P-values <0.05 indicate significant associations.

Results

During the 6-month study period a total of 15472 patients were admitted to HJH. (January-March 2016) (table 1). Of these, 749 (4.3%) were seen by ID as inpatient consultations. There was a statistically significant increase in the number of consultations from the start to the end of the review. The median percentage of admissions seen was 4.95% (95% Confidence interval (CI) 4.12-5.77) These inpatient consultations were analysed: The study group consisted of 50.9% males and 49.1% females. The male to female ratio was 1.04. The median age of patients was 38.8 years (interquartile range (IQR) 32.8-47.0). The median length of stay of a

patient prior to an ID consultation was 6 days (IQR 3-9 d; range 0-114 d) and 19.6% of the patients received the ID consultation after more than 10 days (figure 1). There was no significant association between length of stay prior to consultation and patient outcome, given the other variables in the model (odds ratio (OR) 1.24; 95% CI 0.63-2.42). The most common reasons for consultation were ART initiation (27.8%), lipoarabinomannan antigen (LAM) testing (24.8%), and ART change (21.6%) (Figure 2). Of those patients with a known HIV status (n=741), 93.3% (n=691) were HIV-positive. Within these 691 patients, the median CD4 count was 52 cells/mm^3 (IQR 15-54; range 0-1125) (n=682; 1.3% missing data). (figure 3) When CD4 counts were categorised, the majority of patients (65.5%) had CD4 counts of 100 cells/mm^3 or less (figure 4). In terms of diagnoses, 91.7% of the patients had at least one infectious diagnosis (excluding HIV), while 51.9% had at least one non-infectious diagnosis (figure 5). Patients had predominantly one (45.4%) or two (30.2%) infectious diagnoses in addition to HIV. There was a portion of patients (12%) with three infectious diagnoses made during the admission. (Figure 6) The most common infectious diagnoses were pulmonary tuberculosis (TB) followed by acute gastroenteritis, abdominal TB; virological failure on ART and a drug induced liver injury. (Figure 7) When combining all subcategories of TB infection, a total of 42.9% of patients were infected with TB. Acute kidney injury was the most common non-infectious diagnosis followed by hypertension, diabetes mellitus, non-AIDS-defining malignancy and chronic kidney disease. (figure 8). Of the patients seen, 59 (7.9%) died while the ID team was still in attendance. More than one infectious diagnosis increased the odds of death, compared to no or one infectious diagnosis, given the other variables in the model. (OR 2.00; 95% CI 1.11-3.60). One or more non-infectious diagnoses increased the odds of death, compared to no non-infectious diagnosis, given the other variables in the model. (OR 2.27; 95% CI 1.25-4.11).

Discussion

South Africa (SA) is still the epicenter of the HIV epidemic. This creates a disease and patient profile that is very different from that found in developed countries [11]. This review has described the experiences and role of the infectious diseases specialist in a tertiary hospital in South Africa. It has demonstrated the complexity of the patients consulted and the impact that an ID physician can have on patient care. To my knowledge this review, together with one other performed at Groote Schuur hospital in Cape Town by Pandie et al. provide the only available data on the functioning of South African ID units [12].

The HJH ID unit sees 4.8% of total hospital admissions, which is significantly greater than that of hospitals outside of SA. This may be attributed to the hospital policy that all patients initiating ART must have an ID consultation, however, even after these patients were excluded, 3.7% of all admissions still required a consultation. Other reasons to consider are the possibility that there is a higher proportion of infectious diagnoses among total admissions to HJH or that in general, patients that are admitted may be sicker. As most of the patients seen by the ID unit were HIV positive with relatively low CD4 counts, this is a plausible explanation. Another reason for the number of consults could be the perception that the ID unit could be of assistance in accelerating or facilitating access to certain investigations, which may aid diagnosis, and expedite discharge.

In this study there was a statistically significant increase in the number of consultations requested from the start to end of the review that was not accounted for by changes in hospital admissions. One explanation for this could be improved data

collection over time, as the implementation of the database and the start of the review coincided. As medical registrars and medical officers responsible for data capturing became more familiar with the process, they may have seen the benefits and become more involved. Alternatively, the ID department may have gradually been receiving more referrals over the study period.

Of the total number of patients seen, 93.3% were HIV positive. Two thirds of these had CD4 counts of less than 100 cells/mm^3. The median CD4 count of all HIV positive individuals was 52 cells/mm^3. This is striking as it shows that patients are still presenting to health care facilities at an advanced stage of their illness despite increased availability of ART initiation centers in South Africa. This is not, however, isolated to the HJH ID unit: The review by Pandie et al. found that 80% of patients seen by the ID unit at Groote Schuur Hospital were HIV positive with a median CD4 of 128cells/mm^3 [12]. An editorial commentary by Ford et al. stated that the current European consensus definition of late presenters is a patient with "a CD4 cell count of <350 cells/mm^3 or an AIDS diagnosis within 6 months of HIV diagnosis". As such, the vast majority of patients initiating ART in sub-Saharan Africa are late presenters and caring for these sick patients constituted a significant portion of the workload of the ID specialist [10].

The most common reason for ID consultation in this review was for ART initiation (27.8%). As stated above this is, in part, due to the policy at HJH requiring that all ART must be initiated by a member of the ID department. However, another factor contributing to this is that most of these patients were eligible for ART initiation as at the time of the review ART were only initiated at CD4 counts ≤ 500 cells/mm^3.

Assistance with changing ART, for a variety of reasons, closely followed ART initiation as the third most common reason for consultation. This data clearly reflects the HIV burden experienced in South Africa and emphasizes the complexities of management of these patients, and as such often needing the assistance of a specialist [13].

The complexity of these patients, contrary to the principle espoused in Occam's razor (that "Plurality must not be posited without necessity") was exaggerated by the fact that most patients were found to have multiple diagnoses, both infectious and non-infectious in nature [14]. Excluding the HIV positivity, 45.4% of the patients in this review had one, 30.2% had two and 12% three distinct and active infectious diagnoses. Just less than half of the patients had at least one infectious diagnosis (excluding HIV) together with one non-infectious co-morbidity. HIV infected individuals are at an increased risk for acquiring diseases historically associated with advanced age and half of the patients in this review had at least one non-infectious co-morbidity. Acute kidney injury was diagnosed in 25% and chronic kidney disease was the fifth most common co-morbidity. This data suggests that there is a heightened risk of kidney disease among South Africans with advanced HIV infection in keeping with current literature. Thereafter the most prevalent non-infectious diagnoses were hypertension, diabetes mellitus (DM) and all forms of malignancy [15]. There is conflicting evidence as to whether HIV is an independent risk factor for developing DM, but certain complications associated with DM can be seen more commonly in HIV positive patients [16-18]. HIV is changing the assumption that a single diagnosis, infectious or otherwise, can alone explain the clinical picture, especially at very low CD4 counts. Failure of the treating physician to recognize this

is likely to result in inadequate medical management and the failure of the patient to respond to medical care.

The HIV epidemic has brought with it an explosion of tuberculosis. TB was the most common diagnosis amongst HIV positive and seronegative patients in the review by Pandie et al [12]. The review by Meintjes et al. reported that the most common admission diagnosis amongst HIV positive individuals at a South African district hospital was TB, and it was also the most common cause of death [19]. Similarly, the most frequent infectious diagnosis made in this review aside from HIV, was TB. When all forms of TB were taken as a collective, 42.9% of patients seen by the ID unit had this diagnosis. Interestingly the second most frequent reason for a consult was to gain access to the test for the mycobacterial lipoarabinomannan antigen, a urine-based investigation which assists in the diagnosis of disseminated TB, the use of which is controlled by the ID department at HJH. The test is restricted as it is not freely available in the government sector and therefore is in limited supply. It is further restricted to HIV infected individuals with low CD4 counts in whom it is most sensitive and in whom the diagnosis cannot be made in any other way [20]. The fact that it is the second most common reason for consultation illustrates how frequently the diagnosis of tuberculosis is suspected in our patient population and how difficult it can be to make a definitive diagnosis in the presence of immune compromise [21].

Aside from HIV and TB, the ID unit at HJH assists with antibiotic prescriptions, which is a more traditional area of ID expertise particularly in the developed world. Assistance with antimicrobial choice was the fifth most common reason for requesting a consultation, and the infectious diagnoses most frequently encountered

were acute gastroenteritis, community acquired pneumonia and bacteremia of unknown aetiology.

There were 7.9 deaths per 100 consultations during the review period. More than one infectious diagnosis (excluding the diagnosis of HIV) increased the odds of death, compared to no or one infectious diagnosis. In terms of non-infectious diagnoses one or more also increased the odds of death, relative to those without.

Limitations of this review include the fact that a number of different people were responsible for entering the data. There was no way to assess if all consultations were entered into the database and as such there may have been some for which data was not recorded. This review did not include informal or telephonic consultations, which also contribute to the workload of the ID department. Another aspect that is not generally considered and adding to the workload, are the follow up visits of patients known to the department, which are not documented. Patients were followed up until hospital discharge, demise, recovery or to a point where it was felt that the department could no longer offer any assistance. The latter may have been due to a particularly poor prognosis where care was considered to be futile, which may have led to an underestimation of the overall mortality. Finally, the data available did not allow for an analysis of the cost effectiveness of an ID consultation.

In summary, sick HIV patients are still coming to medical attention with significant morbidity and mortality. Although TB is always the clinician's number one concern it is not the only one. Practitioners need to look for other diagnoses in the patient that do not get better on TB treatment. Although these sick patients require ART this is

only part of the story. Achieving the UNAIDS goal of the eradication of HIV by 2030 cannot be met only by supplying ARVs. The epidemic in Africa demands improvements in all facets of HIV management if this goal is ever to be met. The fact that the ID unit is so frequently requested to assist in these areas reflects the overall complexity of these cases such that specific expertise is required beyond that of the general practitioner or even the specialist physician. The ID physicians are best qualified to manage these patients and to educate their colleagues in the intricacies of care particularly with advanced HIV. Although this specialty is a relative newcomer, this study and others have proven the worth of the discipline.

Table 1. Monthly infectious diseases consultations as a percentage of total hospital admissions at Helen Joseph Hospital

Month	Total admissions	ID consultations	% ID consultations
Oct-15	3232	117	3.6
Nov-15	2998	130	4.3
Dec-15	2570	119	4.6
Jan-16	2199	119	5.4
Feb-16	2309	152	6.6
Mar-16	2164	112	5.2
Total	**15472**	**749**	**4.8**

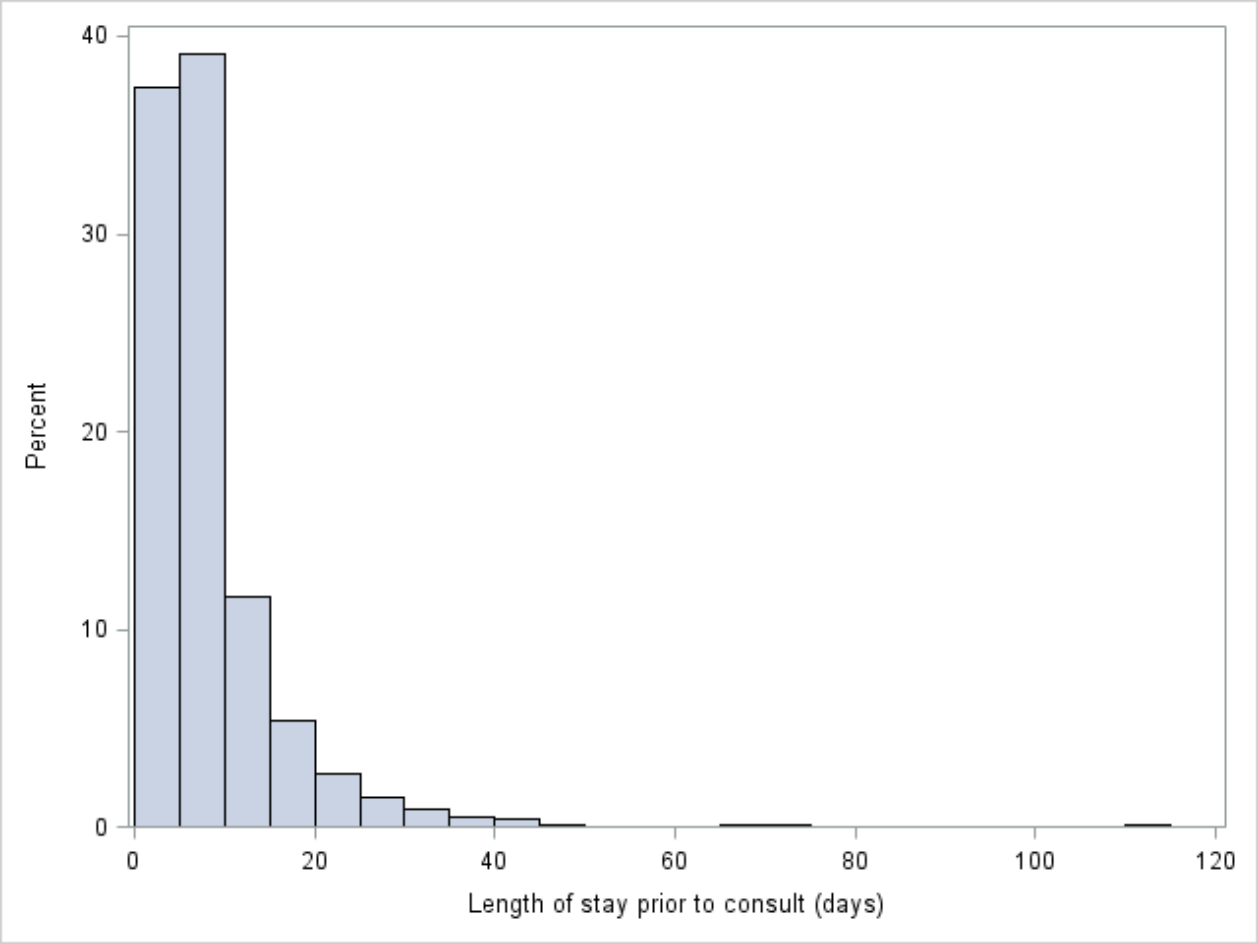


Figure 1. Length of hospital stay prior to an ID consultation

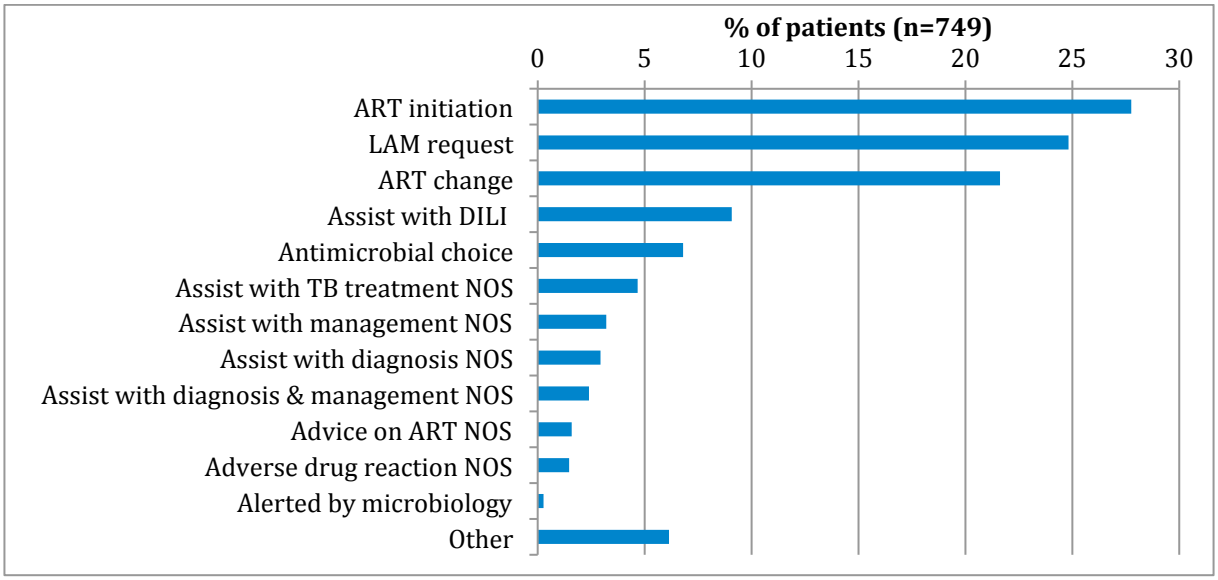


Figure 2. Reason for ID consultation

ART= antiretroviral therapy; LAM= lipoarabinomannan antigen test; DILI=drug induced liver injury (related to an infectious process); TB=tuberculosis NOS= not otherwise specified

***Note that the percentages do not sum to 100% as some patients had multiple reasons for consultation**

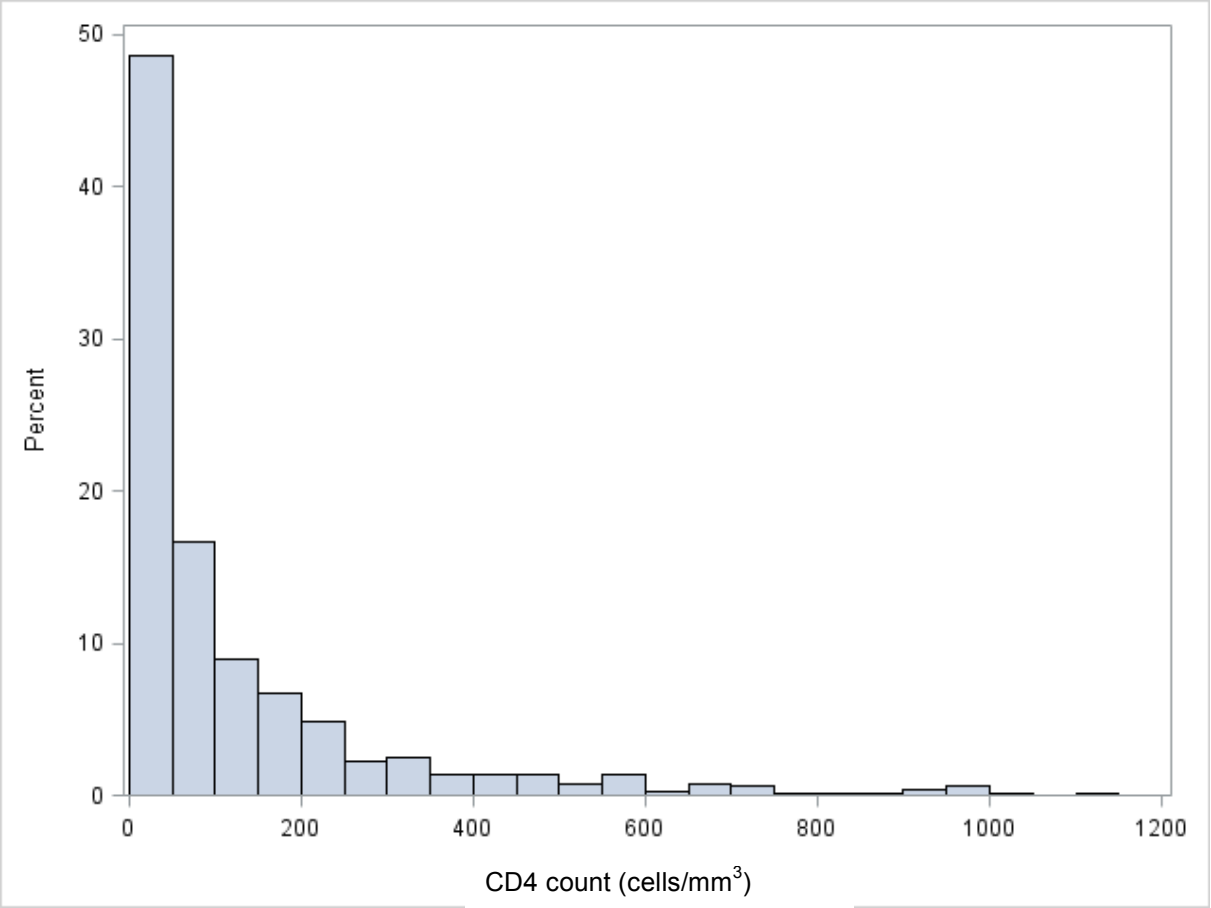


Figure 3. CD4 count (cells/mm^3) of HIV positive patients

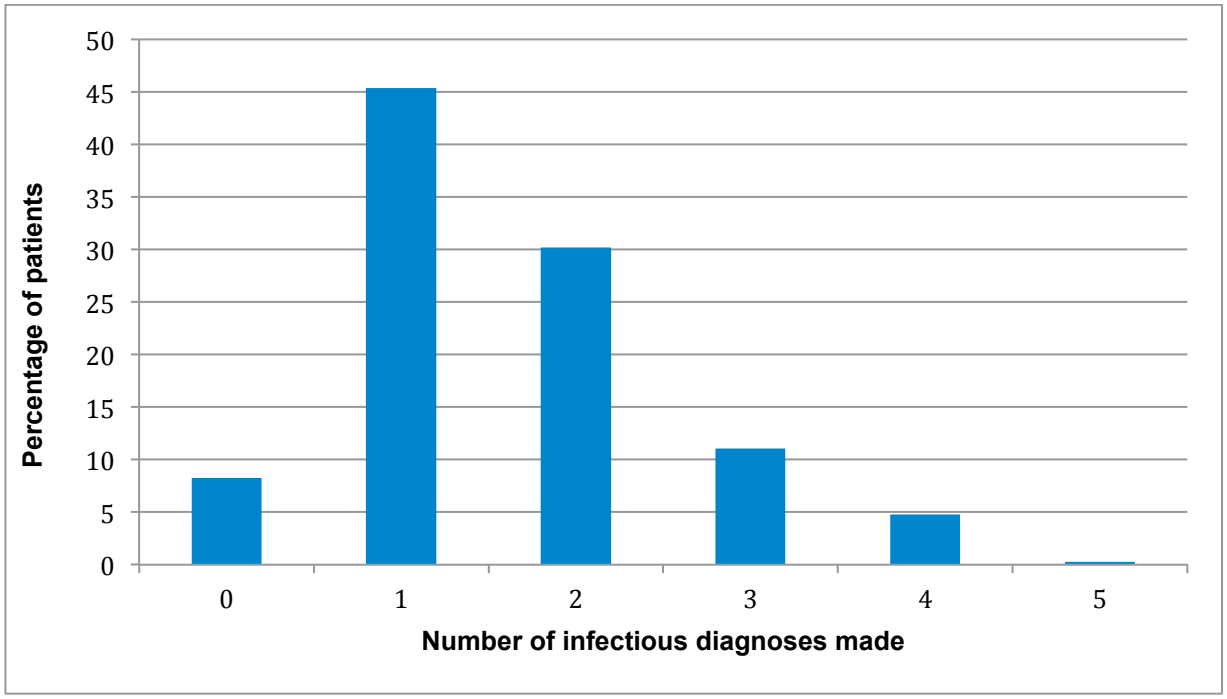


Figure 4. Number of infectious diagnoses made in individual patients

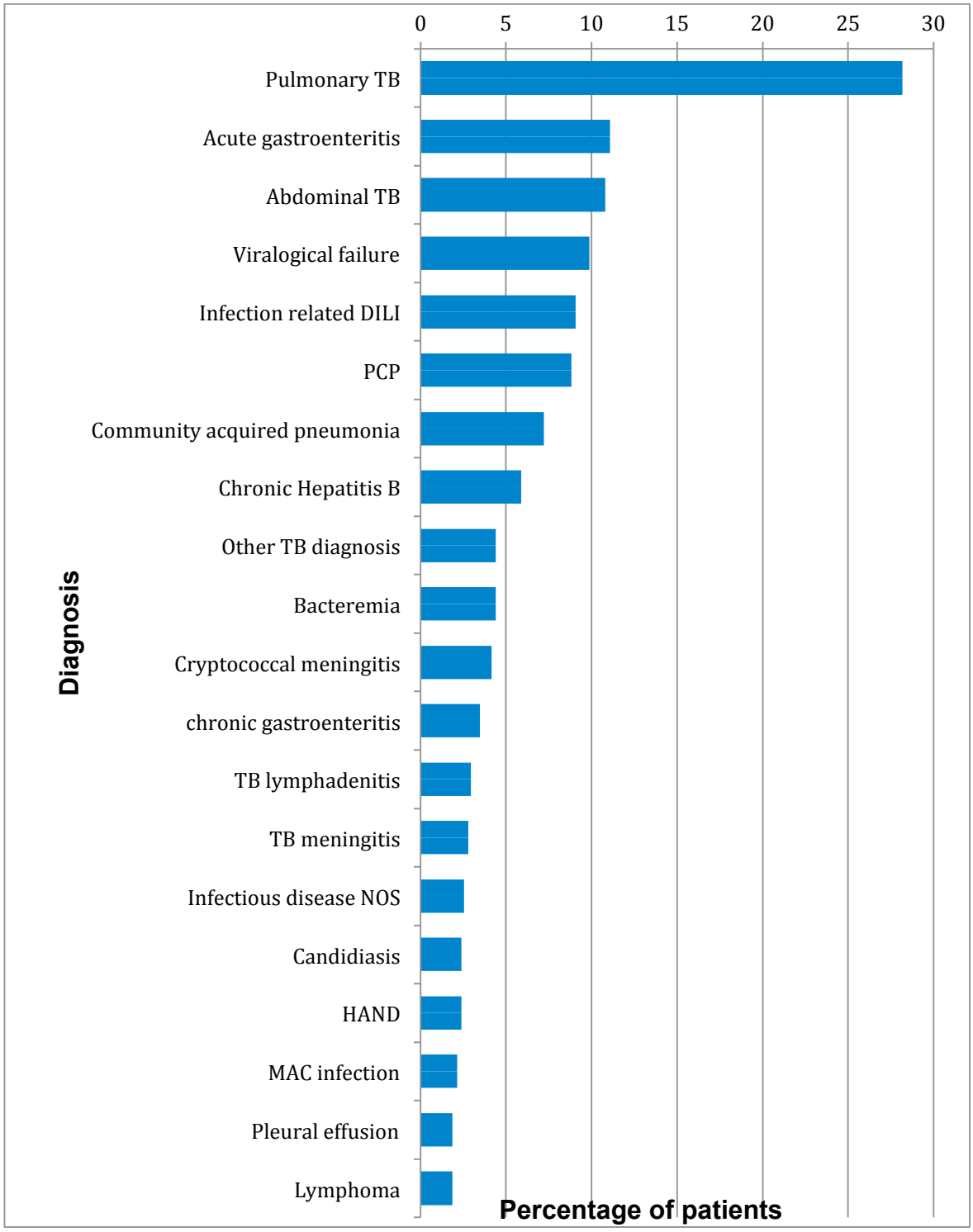


Figure 5. Top 20 Infectious diagnoses made in patients consulted, excluding HIV

TB= tuberculosis; DILI=drug induced liver injury (related to an infectious process); PCP=Pneumocystis jirovecii pneumonia; NOS=not otherwise specified; HAND=HIV associated neurocognitive disorder; MAC= Mycobacterium avium complex

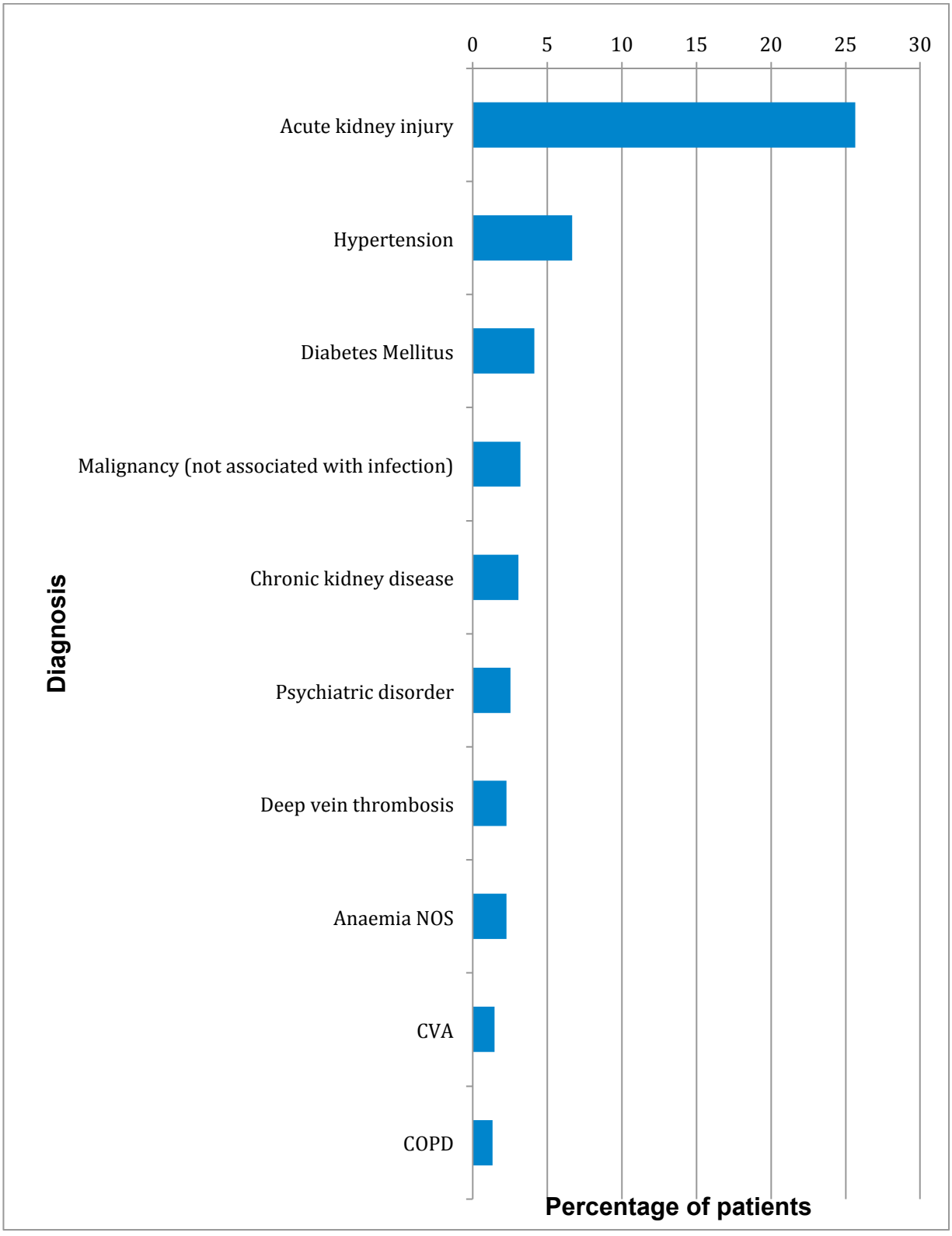


Figure 6. Top 10 non-infectious co-morbidities

NOS= not otherwise specified; CVA= cerebrovascular accident; COPD= chronic obstructive pulmonary disease

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CHAPTER 3: APPENDICES

3.1 Data collection sheet

APPENDIX A: DATA COLLECTION SHEET									
Participent_code	SEX	stay_ prior_to_consult_in_days	HIV_status	CD4_range	Actua_ CD4	Reason_for_consult	Infectious_Diagnosis	non-infectious_comorbidity	Pt_outcome
1									
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5									
6									
7									
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3.2 Ethics Clearance

R14/49 Dr Lauren Richards

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160486

NAME: (Principal Investigator)	Dr Lauren Richards
DEPARTMENT:	Internal Medicine Helen Joseph Academic Hospital Division of Infectious Diseases
PROJECT TITLE:	Infectious Diseases Consultations at a South African Academic Hospital: A Six-Month Review of Inpatient Consutations
DATE CONSIDERED:	06/05/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Prudence Ive
APPROVED BY:	Professor P. Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	12/05/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004,10th floor, Senate House/2nd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the the conditions under which I am/we are authorised 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 resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially review in April and will therefore be due in the month of April each year.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

3.3 Research Committee Permission Letter

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

Helen Joseph Hospital
Enquiries: Dr. M. Mukansi
Chairperson of the HJH Ethics and Research Committee
Tell: 011 489 0352
Fax: 011 489 1038/0355
Email: murimisi.mukansi@wits.ac.za

25 February 2016

To whom it may concern

SUBJECT: **HELEN JOSEPH HOSPITAL RESEARCH COMMITTEE**
Protocol Title: Infectious Diseases Consultations at a South African Academic Hospital: a six-month review of inpatient

Protocol Ref No: student number 0604623E
Ethics Clearance: Pending
Principal Investigator: Lauren Richards
Department: Medicine

Committee Recommendations
Approval provisional, awaiting ethic clearance

Thank you in anticipation

Dr. M. Mukansi
Chairperson of the HJH Ethics and Research Committee

GAUTENG PROVINCIAL GOVERNMENT
26 -02- 2016

3.4 Turnitin Originality Report

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