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THE PREVALENCE AND MANAGEMENT OF RIFAMPICIN-RESISTANT TUBERCULOSIS AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

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

Johannesburg, 2017

DECLARATION

I, Rajiv Manhar Narsing declare that this research report is my own work. I am submitting this research report for the degree Master of Medicine (in the published format with my protocol and extended literature review) 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 this or any other University.

Signature: _____

Signed at: _____

Date: _____

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Mr. Honest Muchabaiwa (Master of Science in Statistics), for his input regarding data interpretation and statistical analysis.

And finally I would like to thank my wife and my family, for their continued support, encouragement and patience.

OUTCOME OF MY WORK

The final results of this research report was published in *The South African Respiratory Journal*, Volume 23, No. 2, June 2017, under the title "The prevalence and management of rifampicin-resistant tuberculosis among adults at Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa".

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Abstract

Background. Early effective management of drug-resistant tuberculosis (TB) is important for the patient, and for infection control. The Xpert MTB/RIF (Cepheid, USA) assay detects *Mycobacterium tuberculosis* DNA and the presence of rifampicin resistance.

Objective. To assess the prevalence and initial management of rifampicin-resistant pulmonary TB (PTB), confirmed by the Xpert MTB/RIF assay, in hospitalised adult patients.

Methods. This retrospective descriptive study assessed adult patients from March 2011 to February 2013. Data was obtained from the National Health Laboratory Service database and patient records. Management comprised the submission of additional confirmatory sputum tests, initiation of appropriate anti-TB drug therapy, patient isolation, and proper referral.

Results. The prevalence of rifampicin resistance was 10.6% (*n*=77) of 729 positive assays. The initial management was assessed for the 70 patients with complete records. However of these 70 patients, 12 patients had been discharged and 5 patients had died prior to receiving their results. The management of the total cohort and of the 53 remaining inpatients were analysed separately. The overall confirmatory sputum submission rates were 76%, 60%, 60% and 26% for TB microscopy, Line Probe Assay, TB culture, and drug-susceptibility testing, respectively, and 87%, 72%, 68% and 30%,

respectively for the 53 remaining patients. Overall, 33% of patients received appropriate anti-TB treatment, 50% were isolated, and 49% were appropriately referred. For the 53 remaining patients, 43% received appropriate drug treatment, 66% were isolated, 64% were appropriately referred, and 19% were not referred. The inpatient mortality rate was 19%.

Conclusions. Rifampicin-resistant TB prevalence in-hospital was more than double the national rate. The initial management of patients with rifampicin-resistant PTB was substandard. Submission of paired sputum samples and educating healthcare professionals and healthcare users are of paramount importance to improve the management of drug-resistant TB.

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LIST OF ABBREVIATIONS

AFB	Acid Fast Bacilli
ART	Anti-Retroviral therapy
CD4	Cluster of Differentiation 4
CHBAH	Chris Hani Baragwanath Academic Hospital
DNA	Deoxyribonucleic Aid
DST	Drug Susceptibility Testing
GXP	GeneXpert
HIV	Human Immunodeficiency Virus
INH	Isoniazid
LPA	Line Probe Assay
MDR-TB	Multi Drug Resistant tuberculosis
MTB	*Mycobacterium tuberculosis*
NHLS	National Health Laboratory Service
PTB	Pulmonary tuberculosis
RIF	Rifampicin
RMR	Rifampicin Mono Resistance
TB	Tuberculosis
WHO	World Health Organization

CHAPTER ONE – PROTOCOL AND EXTENDED LITERATURE REVIEW

1.1 INTRODUCTION AND BACKGROUND:

Pulmonary tuberculosis causes an enormous burden of disease worldwide. There were an estimated 8.7 million new cases of tuberculosis in 2011 with 1.4 million deaths [1], in keeping with approximately 9 million new cases in 2013 [2]. Geographically the major burden of disease remained concentrated in Asia, which made up 56% of cases, followed by Africa with 29% of new cases. South Africa ranked amongst the top 6 countries in the world as having the largest number of incident cases [2]. The causative organism, *Mycobacterium tuberculosis* (MTB) has been successfully treated with anti-mycobacterial agents for many years. The four first-line drug agents used to treat tuberculosis are isoniazid (INH), rifampicin (RIF), ethambutol (ETH) and pyrazinamide (PZA). The emergence of drug resistant tuberculosis in recent years has complicated the management of the disease. Multi-drug resistant tuberculosis (MDR-TB) is defined as resistance to the two most effective first-line drugs, namely isoniazid and rifampicin [3]. Of the new tuberculosis cases reported in 2013, there were approximately 480 000 cases of MDR-TB. It is estimated that 3.5% of the new TB cases were due to MDR-TB infections, whereas 20.5% of MDR-TB cases had a history of being treated for previous tuberculosis [2,4].

1.2 PATTERNS OF DRUG RESISTANCE

Since the discovery of microbes and the development of drug therapy to treat them,

organisms have developed ways to counteract drug therapy. Organisms undergo mutations in their deoxyribonucleotide acid (DNA) structure to change their structure and function so that previous effective chemicals are rendered useless. This is the principal by which drug resistance develops. Some examples of these include alterations of the organism's cell wall to halt penetration of the substances into the organism, the production of efflux pumps to remove any active compounds that may have entered into the organism and the production of enzymes that directly inhibit or break down the active drug formulation [5]. Mutations can occur in different ways. The simplest form is that of a point mutation; this is a single nucleic acid amendment in the organism's DNA strand. This alteration in the organism's DNA sequence, leads to a variation in the type of protein synthesized, thereby altering the primary structure or function of the organism. These alterations promote resistance to drug agents. The development of drug-resistant tuberculosis is a result of spontaneous point mutations [5]. This affects resistance to one drug agent. The development of MDR-TB, results as a consequence of repeated mutations at different regions of the organism's DNA [5,6]. The specific genetic mutations related to the development of drug-resistant tuberculosis are now identifiable and are tested for using specific genomic testing.

Resistance to rifampicin (RIF) usually occurs due to point mutations in the *rpoB* gene [3,7,8]. The *rpoB* gene consists of 81 base pairs or 27 codons (codon 507-533). Roughly 95% RIF resistant TB is related to mutations occurring in this region [3,9]. Almost all of the mutations are a result of amino acid substitutions, with a few exceptions, which are a result of amino acid deletions [9]. Rifampicin inhibits the organism's transcription process, by targeting a subunit of the mycobacterial DNA-dependent RNA polymerase

[3].

Resistance to isoniazid (INH) may occur at one of three main sites. It may occur at either the *katG* gene region, *inhA* gene region or the *ahpC-oxyR* intergenic region [3,7]. Mutations that occur at the *katG* gene results in the inability of the organism to activate the isoniazid pro-drug and mutations that occur at the *inhA* gene alters the binding site for INH [3]. Majority of INH-resistant strains are found to have mutations in codon 315 of the *katG* gene or ribosomal binding site [7]. Approximately 13 - 18% of INH-resistance are due to mutations in the *ahpC-oxyR* intergenic region [7]. INH mono-resistance accounts for about 5% of mono-drug resistant tuberculosis in Western Europe [6]. The mutations responsible for the different drug mutations occur at different sites on the mycobacterial DNA. Rifampicin mono-resistance (RMR) is less common than isoniazid mono-resistance and is more likely to be found in patients who are HIV positive and have a previous history of pulmonary tuberculosis [10]. RIF-resistance is considered a marker for MDR-TB because it is thought that the majority of isolates resistant to rifampicin are also resistant to INH [3]. It was found that RIF-resistant INH-susceptible isolates are more likely to be susceptible to other anti-tuberculosis drugs, both first-line drugs (ethambutol, pyrazinamide) and second-line drugs (aminoglycosides, fluoroquinolones, ethionamide, capreomycin), when compared to MDR-TB isolates [11]. Thus patients with RMR are likely to have better outcomes when treated with the conventional anti-tuberculosis drugs, compared to those with MDR-TB.

Risk factors related to the development of drug resistance include, previous exposure to tuberculosis [6,10,12,13], incomplete treatment regimens, non-compliance [14] and Human Immunodeficiency Virus (HIV) co-infection [6,10]. Other factors influencing the

development of drug-resistant tuberculosis are poorly coordinated management strategies from healthcare institutions, inadequate guidelines, poor patient compliance, social barriers, patient access to care, availability of adequate medication and co-infections (e.g. HIV) [15].

1.3 THE ROLE OF XPERT MTB/RIF (GENEXPERT) ASSAY

The conventional technique for detecting pulmonary tuberculosis makes use of sputum smear microscopy. The sputum sample obtained from the patient is smeared onto a glass slide and then stained using a special staining technique. The stained slide is then examined under a microscope to identify acid-fast TB bacilli. Smear microscopy is a relatively cheap technique and can be obtained fairly quickly. This method can be used in resource-limited settings [16] provided there is adequately trained laboratory staff. The disadvantages of microscopy are, it does not differentiate the type of mycobacterium that is identified (that is, if it is *Mycobacterium tuberculosis* or nontuberculous mycobacterium (NTM) such as *Mycobacterium avium complex*, *M.abscessus, M.kansasii, etc.)* and it does not provide any information regarding drug susceptibility. For culture and susceptibility testing to be performed, a second sputum sample needs to be submitted, which leads to further costs and a delay in diagnosis. Studies indicate that patients who have tuberculosis confirmed on sputum culture, may not have acid-fast bacilli (AFB) visualized on sputum microscopy [17,18]. These smear-negative culture-positive patients, which accounted for up to 17% of cases in one study [17] and 33% of cases in a study from a high prevalence-setting [18], would have remained undiagnosed and therefore untreated whilst transmitting the resistant strain of TB. Therefore rapid and

accurate detection of TB cases and earlier detection of MDR-TB are part of the WHO global priorities [1]. The WHO introduced the Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) in December 2010. The introduction of the genetic based assay was to rapidly and accurately diagnose TB, as well as determine its susceptibility to one of the most effective first line medications, rifampicin [1]. The assay makes use of real time polymerase chain reaction (PCR) techniques to amplify mycobacterial DNA. The Xpert MTB/RIF assay is designed specifically to identify to MTB DNA. The assay uses nucleic acid hybridization probes that are labeled with a colored fluorophore which correspond to a specific target sequence within the *rpoB* gene of MTB DNA [19]. If present, the DNA sample is assessed for the presence of mutations in the *rpoB* gene. If mutations are discovered which are consistent with those promoting resistance [9], then the sample will be marked as being 'Rifampicin-Resistant'. If the sample detects MTB DNA without any mutations in the *rpoB* gene region conferring resistance, then the sample will be marked as 'Rifampicin-Susceptible'. Finally if MTB DNA is not detected then it will be labeled as such. The simplicity of this test aids in rapid diagnosis of patients with MTB infection, as well as providing the added benefit of initiating appropriate drug therapy timeously. This in turn, leads to favorable outcomes for the patient as well as cost savings [20].

The Xpert MTB/RIF assay makes use of PCR in a closed system, which is then interpreted by a single instrument device. It excludes the need for any additional laboratory equipment or personnel, as well as providing a quicker result than offered by AFB culture or drug susceptibility testing (DST) [4]. The accuracy of the Xpert MTB/RIF assay in detecting rifampicin resistance has been reported as having a

sensitivity range from 86% - 100% and a specificity range of 95% - 100% in smear-positive cases [3]. These values have been proven to be accurate in studies that evaluated the effectiveness and accuracy of the Xpert MTB/RIF assay. A sensitivity of 95% and specificity of 94% was found in a study conducted by Theron et al. [18] in patients with smear positive sputum. The sensitivity of the Xpert MTB/RIF assay for smear negative sputum patients was 55% [18]. Steingart et al. [21] demonstrated 95% sensitivity and 98% specificity in smear positive sputum in their study, and 67% sensitivity in smear negative sputum. A recent South African study, demonstrated that the Xpert MTB/RIF outperformed many other diagnostic tests (AFB smear microscopy, Hain Lifescience, LightCycler Mycobacterium Detection, liquid culture) when comparing the time taken and sensitivities of the respective assays [22]. The average time taken to yield results is 1 day with the *Xpert MTB/RIF* compared to an average of 20 days with the line probe assay (LPA) and an average duration of 106 days for DST [19]. The rapid turn around time related to this assay allows for rapid diagnosis and earlier treatment initiation. This in turn has positive effects on patient outcomes and costs related to treatment. The costs of treating MDR-TB are substantially higher than treating drug-susceptible TB [23,24]. Considering the value gained for the cost of implementation, the ease of use, the rapidity of results and the accuracy of the assay in sputum smear positive disease, the Xpert MTB/RIF has proven to be an effective diagnostic tool for tuberculosis and related resistance.

1.4 MANAGEMENT AND MORTALITY OF DRUG RESISTANT TUBERCULOSIS

Appropriate management of patients with drug resistant tuberculosis is essential, once the diagnosis has been confirmed. In high-income countries management usually includes early isolation and appropriate chemotherapy [25]. In resource-limited settings, isolation facilities are usually reserved for patients with MDR-TB. The standard 6-month chemotherapy course used for drug susceptible TB includes, a 2-month 'intensive phase' which consists of rifampicin, isoniazid, ethambutol and pyrazinamide and a 4-month 'continuation phase' consisting of rifampicin and isoniazid only. This drug regimen has proven to be effective for drug-susceptible TB. RIF and INH remain two of the most efficacious chemotherapeutic agents against MTB. Unfortunately the most effective combination needed to treat MDR-TB still needs to be researched [26]. Patients with MDR-TB (which includes both RIF and INH resistance) can no longer use INH, whereas patients with RMR still have INH added to their treatment regimen. Guidelines released by the South African Department of Health in 2011 [27] provide an approach to confirm and treat patients with drug resistant pulmonary tuberculosis. The recommendations are that dedicated MDR-TB units manage all MDR-TB patients or that management can be continued by community trained health care workers in an appropriate infection controlled environment [27]. The diagnosis must be confirmed by submitting specimens for AFB microscopy, AFB culture, LPA and DST. Treatment should then be reviewed following laboratory confirmation [27]. The standardized regimen recommended to treat MDR-TB in 2011 consisted of a 6-month intensive phase, which comprises of five drugs taken at least six times per week during the injectable phase [27]. The drugs used in the intensive phase are a second line injectable (e.g. kanamycin or amikacin), a fluroquinolone (e.g. moxifloxacin), ethionamide, terizidone and pyrazinamide. It is

followed by the continuation phase, which consists of four drugs taken at least six times per week for a period of 18 months [27]. The 4 drugs are moxifloxacin, ethionamide, terizidone and pyrazinamide. Ethambutol may be used as a sixth drug agent in the intensive phase, but should be reserved for patients in areas with a low prevalence to ethambutol-resistance and for patients who have never been exposed to this agent [27]. The use of combination of 5 agents in the treatment of MDR-TB has been shown to be effective [28]. The use of multiple agents allows for different areas of the mycobacterium to be targeted and increases the likelihood of killing the bacillus.

The cost of treating patients with MDR-TB in South Africa is significantly higher than for patients with drug susceptible TB [23,26]. A study conducted in the Western Cape demonstrated that treating MDR-TB costs 26 times more than treating drug susceptible TB [26]. The costs calculated were approximately $192 to treat a patient with smear positive drug sensitive TB. This was compared to the costs of $5 930 and $14 348 to treat a patient with MDR-TB as an outpatient or as an inpatient respectively [26]. The increased costs were attributed to drug expenditure and the increased cost of hospitalized MDR-TB patients [24,26]. The suggestion of a decentralized approach compared to hospitalization and inpatient management may help alleviate the costs related to treat MDR-TB [28], though this may not be feasible.

Effective management of drug resistant TB requires an effort that is focused around the patient. This initiative should be shared between the health care provider and the patient. A previous study done at CHBAH showed that 21% of patients that were referred to local clinics for continuation of treatment had defaulted [29]. After interviewing patients that were traced and re-educating them, one third still did not attend [29]. This demonstrates

that 1 out of 15 patients that are diagnosed with TB will not follow up for appropriate treatment despite being educated about the disease. Previous negative experiences at a particular clinic and the stigma attached to HIV/AIDS association with TB are possible explanations for the poor follow-up at local clinics [29]. Ebonwu et al. [30] showed that after being diagnosed with MDR-TB, 37% of patients were not initiated on appropriate treatment. The reasons stated were because patients died or could not be traced [30]. Being lost to follow up was the most important factor, in the failure of referral of patients diagnosed with drug resistant TB to specialist care in a 2013 Gauteng study [31]. These factors appear to be common setbacks within the South African setting and therefore it is essential to have the commitment of both patients and health care professionals to help prevent the transmission of this disease and improve the morbidity and mortality.

In 2013, there were 1.5 million deaths reported due to TB and approximately 210 000 deaths worldwide due to MDR-TB [2]. Mortality rates reported amongst patients with drug-resistant TB are 16% [4], 19% [29] and 11.5% [31]. According to the 2011 global cohort of MDR-TB patients, only 48% were successfully treated. There was a 16% mortality rate and 12% were not cured despite receiving adequate treatment [4]. The multiple risk factors that contribute to the increased MDR-TB mortality rate include lower education level, greater number of previous TB episodes, history of diabetes mellitus and HIV co-infection [32]. HIV co-infection remains an independent risk factor for increased mortality [4,32]. The presence of a lower CD4 count (particularly <200/µl) and resistance to multiple anti-tuberculosis drugs have been identified as additional risk factors [4,33].

1.5 DRUG RESISTANT TUBERCULOSIS AND HIV CO-INFECTION

In 2013, it was estimated that there were approximately 480 000 new cases of drug resistant tuberculosis worldwide [4], with over 15 000 cases in South Africa [34]. HIV incidence in sub-Saharan Africa is amongst the highest in the world. In 2010, it was estimated that 64% of the global population infected with HIV were living in sub-Saharan Africa [35]. The presence of HIV in patients co-infected with TB is more likely to have rapid progression of active TB disease when compared to HIV negative individuals [36]. Furthermore patients with HIV have a higher likelihood of MDR-TB than HIV negative patients [36]. The incidence of HIV co-infection and tuberculosis is the highest in the African region, with about 80% of cases being co-infected [2]. In Sub-Saharan Africa it was estimated that there was a 70% co-infection rate of drug-resistant tuberculosis and HIV [2,39]. A study conducted in Kwa-Zulu Natal in 2012, showed a 92% co-infection rate of MDR-TB and HIV [33], whereas a study from the United States of America, showed an 81% prevalence of rifampicin mono-resistance (RMR) and HIV co-infection [10]. The significance of these patients who are co-infected are related to the challenges posed by coexistence of the two diseases, as well as those if affected by either alone. The difficulties are related to the clinical presentation of the patient. Patients may present with sputum smear negative disease yet have active drug resistant tuberculosis [14], or present with features of an immune reconstitution inflammatory syndrome after the initiation of anti-retroviral therapy (ART) [34]. Other challenges related to management include, malabsorption of drugs due to enteropathy caused by HIV, the shared drug toxicities in terms of drug metabolism and excretion by the liver and kidney and drug-drug interactions between ART and anti-tuberculosis treatment

[10,34]. Patients with drug-resistant TB and HIV co-infection have poorer survival outcomes. The mortality rate amongst patients with MDR-TB and HIV co-infection are higher than in HIV negative patients with MDR-TB [7]. Lower cluster of differentiation 4 (CD4) counts, particularly if below 200 cells/μl are associated with higher mortality rates amongst patients who are co-infected [33,37]. A systematic review demonstrated that HIV co-infection itself was positively and significantly associated with MDR-TB [38]. The guideline recommendation for HIV co-infected patients that are currently not on ART, is that ART to be commenced as soon as possible, preferably within the first month of drug-resistant treatment, irrespective of CD4 count [27].

1.6 STUDY OBJECTIVES

The study objectives are:

1. To describe the prevalence of rifampicin-resistant pulmonary tuberculosis that was confirmed by Xpert MTB/RIF assay between the period of 01 March 2011 and 28 February 2013 at Chris Hani Baragwanath Academic Hospital (CHBAH).
2. To describe the management (drug therapy, confirmatory tests, isolation and appropriate referral) of rifampicin-resistant cases at CHBAH during this period.
3. To describe patient characteristics including, patient demographics, prevalence of HIV co-infection, previous pulmonary tuberculosis infection and treatment completion, time taken to obtain the Xpert MTB/RIF assay result and inpatient mortality rate.

1.7 RESEARCH METHODOLOGY

1.7.1 Study design:

The research design was a retrospective cross-sectional descriptive study, which assessed patients with rifampicin-resistant pulmonary tuberculosis confirmed on Xpert MTB/RIF assay and if adequate management was instituted, in correlation to the national guidelines (Appendix 3.1).

This retrospective study made use of information that had been recorded previously. The data was collaborated to describe averages and percentage trends during the period under investigation. This study was a descriptive study and made use of descriptive statistics to calculate the results.

Patients that tested positive for rifampicin resistance had their inpatient files reviewed and relevant data extracted from their files. A data collection sheet (Appendix 3.2) was used to record patient demographics, HIV status, CD4 count, anti-retroviral therapy, previous exposure to TB, previous treatment completion, additional investigative tests done, appropriate drug therapy instituted, appropriate isolation and referral and finally inpatient hospital death. The data sheet was designed to extract data relevant to this study and results were entered onto an excel spreadsheet for interpretation.

1.7.2 Study Population

The population sample included all adult patients, over the age of 14 years, who presented with rifampicin-resistant pulmonary tuberculosis diagnosed by the Xpert MTB/RIF assay during a two-year period. The period under review was between 01 March 2011 and 28 February 2013.

1.7.3 Sample size

After applying the relevant exclusion criteria, the sample size consisted of 70 patients over the 24-month period. Of the positive Xpert MTB/RIF assays that were submitted between 01 March 2011 and 28 February 2013, 729 assays fit the inclusion criteria. Of these assays 77 were positive for rifampicin-resistance. Seven patients' records could not be traced and therefore were excluded from the final cohort of 70.

1.7.4 Inclusion and exclusion criteria:

Inclusion criteria

- A rifampicin-resistance positive result on the Xpert MTB/RIF assay during 01 March 2011 and 28 February 2013. The total number of positive Xpert MTB/RIF assays was used to calculate the prevalence.
- Patients that presented to the adult medical wards or outpatient clinics at CHBAH.

Exclusion criteria

- Patients under the age of 14 years.
- Tests submitted from an outside health care institution or community clinic

1.7.5 Variables:

There were multiple variables reviewed in this study. These included the patient demographics, including age and gender, the patients' HIV status, their respective CD4 count where available and whether the patient had started anti-retroviral therapy. The

patients' pulmonary tuberculosis history was recorded. This included current or previous infection, treatment initiated and completion of treatment. Current management of the patient after the diagnosis was made, specifically the drug therapy initiated, sputum samples submitted for appropriate confirmatory tests (i.e. AFB microscopy, LPA, AFB culture and DST). Based on the results from the relevant tests, the resistance patterns were determined in the study population. The allocation of appropriate isolation measures, referral processes and inpatient mortality was recorded as part of the patient's management. These variables were obtained from inpatient records at CHBAH. As the study was a retrospective review of inpatients' files, the reliability and validity was dependent on the quality of the records kept. This process required scrutinizing the available records for the required information. The results of the Xpert MTB/RIF assays were obtained from the National Health Laboratory Service (NHLS) database. Other results including the patients HIV status and CD4 count were obtained from the NHLS database, as well as patient records. The TB care center was approached regarding details of notification and referral for those not available in patient records.

1.8 DATA ANALYSIS:

Data was collected from the NHLS database, regarding all patients whose sputum was tested using the Xpert MTB/RIF assay. The total number of patients (RIF-sensitive and RIF-resistant) diagnosed with tuberculosis on the Xpert MTB/RIF assay during this period was used to determine the prevalence of rifampicin-resistance.

The Xpert MTB/RIF assay uses molecular techniques to amplify DNA and genetic resistance based on the DNA that has been amplified [7]. It provides a final result either

as ‘rifampicin-resistant’ organism, ‘rifampicin-sensitive’ organism or which ‘no mycobacterial DNA has been detected’. All positive rifampicin-resistant results were compared to the overall positive Xpert MTB/RIF assays performed and analyzed to determine the prevalence of drug-resistant tuberculosis in this population. The patterns of resistance were calculated on the data available regarding INH resistance from the LPA assays. Patients’ records were reviewed and data recorded on the data collection sheet. The information obtained from the NHLS and data sheet was then presented on an excel spreadsheet and with the assistance of a statistician, the data was analyzed. Descriptive statistical methods are used to interpret this data and the IBM SPSS Statistics program was used for data analysis.

1.9 LIMITATIONS:

The limitations of the study include, 40% of patients had no designated resistance pattern due to insufficient sputum specimen submission. The study population under review only relates to tertiary level hospitalized patients in a limited geographical area. The study provided the prevalence and management at the initiation of treatment. It does not include the outcomes relating to continuation, completion or rate of default. The failure of complete record tracing was another limiting factor.

1.10 ETHICAL CONSIDERATIONS:

The Human Research Ethics Committee at the University of the Witwatersrand granted ethics clearance on the 25 October 2013, with the clearance certificate number M131033 (Appendix 3.3). Permission from the Medical Advisory Committee (Appendix 3.4) at

Chris Hani Baragwanath Academic Hospital was granted to conduct research at the hospital and permission to access patients' records. The National Manager of Academic Affairs and Research at the National Health Laboratory Service (NHLS) granted permission to access their result database (Appendix 3.5). The study conducted was a retrospective descriptive analysis based on laboratory results and patient records. There were no personal interactions with any of the participants and participants remained completely anonymous throughout the data collection stage. Participants were randomly assigned a study number in numerical order and the researcher alone gathered all information from the participant files. Anonymity was assured throughout the study and no informed consent was sought. This study did not involve any drug interventions and was conducted according to good clinical practice and in accordance with ethical principals for medical research [39].

1.11 BUDGET AND FUNDING:

No additional funding was required.

1.12 TIMING

	Apr - May 2013		Jun '13	Jul - Aug 2013		Sep – Nov 2013			Dec '13 - Jan '14		Feb – Oct 2014	
Literature review												
Preparing protocol												
Protocol assessment												

Ethics application												
Collecting data												
Data analysis												
Writing up												

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CHAPTER TWO – PUBLISHED ARTICLE

Title: *The prevalence and management of rifampicin-resistant tuberculosis among adults at Chris Hani Baragwanath Academic Hospital*

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Abstract

Background. Early effective management of drug-resistant tuberculosis (TB) is important for the patient, and for infection control. The Xpert MTB/RIF (Cepheid, USA) assay detects *Mycobacterium tuberculosis* DNA and the presence of rifampicin resistance.

Objective. To assess the prevalence and initial management of rifampicin-resistant pulmonary TB (PTB), confirmed by the Xpert MTB/RIF assay, in hospitalised adult patients.

Methods. This retrospective descriptive study assessed adult patients from March 2011 to February 2013. Data was obtained from the National Health Laboratory Service database and patient records. Management comprised the submission of additional confirmatory sputum tests, initiation of appropriate anti-TB drug therapy, patient isolation, and proper referral.

Results. The prevalence of rifampicin resistance was 10.6% (*n*=77) of 729 positive assays. The initial management was assessed for the 70 patients with complete records. However of these 70 patients, 12 patients had been discharged and 5 patients had died prior to receiving their results. The management of the total cohort and of the 53 remaining inpatients were analysed separately. The overall confirmatory sputum submission rates were 76%, 60%, 60% and 26% for TB microscopy, Line Probe Assay, TB culture, and drug-susceptibility testing, respectively, and 87%, 72%, 68% and 30%,

respectively for the 53 remaining patients. Overall, 33% of patients received appropriate anti-TB treatment, 50% were isolated, and 49% were appropriately referred. For the 53 remaining patients, 43% received appropriate drug treatment, 66% were isolated, 64% were appropriately referred, and 19% were not referred. The inpatient mortality rate was 19%.

Conclusions. Rifampicin-resistant TB prevalence in-hospital was more than double the national rate. The initial management of patients with rifampicin-resistant PTB was substandard. Submission of paired sputum samples and educating healthcare professionals and healthcare users are of paramount importance to improve the management of drug-resistant TB.

Introduction

Tuberculosis (TB) causes a significant burden of disease worldwide, with approximately 9.6 million cases and 1.5 million deaths in 2014.[1] South Africa is ranked amongst the top 6 countries in the world as having the largest number of incident cases.[1,2] *Mycobacterium tuberculosis (MTB)* is the organism responsible for tuberculosis infection and has been treated successfully for many decades. The emergence of drug-resistant tuberculosis has complicated the management of the disease. Multi-drug resistant tuberculosis (MDR-TB) is defined as resistance to the two most effective first-line drugs, isoniazid (INH) and rifampicin (RIF).[3] Of the new tuberculosis cases reported in 2013 and 2014, there were approximately 480 000 cases of MDR-TB annually,[1,2,4] with an estimated 6900 cases in South Africa in 2014.[4] It was estimated that 3.3% of new TB cases were due to MDR-TB, whereas 20% of previously treated tuberculosis cases had presented with MDR-TB in 2014.[1] Risk factors for the development of MDR-TB include previous exposure to anti-tuberculosis treatment, incomplete treatment regimens, poor patient compliance, lack of availability of adequate medication, co-infection with Human Immunodeficiency Virus (HIV), social barriers, lack of patient access to care, poorly coordinated management strategies from healthcare institutions and inadequate guidelines.[5-11]

In 2013, there were an estimated 2.1 million new HIV infections globally and 1,5 million new infections in the World Health Organization (WHO) African region.[12] Patients who are co-infected with HIV and TB are more likely to have rapid progression of active TB disease, have a higher likelihood of MDR-TB and higher mortality.[4,13-17] The incidence

of HIV co-infection and tuberculosis is the highest in the African region, with about 80% of cases being co-infected.[2] In Sub-Saharan Africa there was an estimated 70% co-infection rate of drug-resistant tuberculosis and HIV.[2,14] Gandhi et al [18] demonstrated a 92% co-infection rate of MDR-TB and HIV in KwaZulu Natal province.

Resistance to RIF usually occurs due to point mutations of the *rpoB* gene,[3,19-20] with more than 95% of mutations responsible for the development of RIF resistance in this gene region.[3,21] In regions with a high probability of MDR-TB, such as sub-Saharan Africa, rifampicin resistance can be used as a reliable indicator for MDR-TB.[22] The WHO has endorsed the use of molecular testing for the rapid diagnosis of tuberculosis and drug resistance.[23] The Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) assay has been approved for use since December 2010. The Xpert MTB/RIF assay detects MTB Deoxyribonucleic Acid (DNA) and the presence of RIF resistance.[23] Studies reviewing the effectiveness of the Xpert MTB/RIF assay found a sensitivity of 95% and specificities of 94% - 98% with smear positive sputum and sensitivities of 55% and 67% in smear negative sputum.[24-25] The rapid result is an advantage when compared to the lengthier duration of conventional drug susceptibility testing (DST).[26]

In 2011, the South African Department of Health released guidelines for the management of drug-resistant tuberculosis.[27] Following the result of RIF-resistant MTB on the Xpert MTB/RIF assay, MDR-TB treatment should be initiated, confirmatory sputum specimens submitted, patients should be isolated and appropriately referred. Treatment should then be reviewed following laboratory confirmation of drug susceptibility.[27] A combination

of 5 effective chemotherapeutic agents are recommended for the treatment of MDR-TB.[28] These include a fluoroquinolone (moxifloxacin or ofloxacin), a 2nd line aminoglycoside (kanamycin or amikacin), pyrazinamide, ethionamide and terizidone.[27] Commitment from both patient and health care professional is essential to effectively treat TB and drug-resistance in the community. Local studies have shown that patient compliance, delay in initiation of treatment, loss to follow-up, poor contact tracing and early mortality still remain hindering factors in current treatment strategies.[29-31] Ebonwu et al.[30] found that only 63% of patients were initiated on MDR-TB treatment in Gauteng province in 2011.

Objective

To describe the prevalence and initial management of patients with rifampicin-resistant pulmonary tuberculosis (PTB) diagnosed by the Xpert MTB/RIF assay in adult hospitalized patients.

Methods

Study setting

Chris Hani Baragwanath Academic Hospital (CHBAH) is a tertiary level hospital with 702 adult medical beds, which serves the community of Soweto and surrounding areas.

Study design

This retrospective descriptive study, based on record review, assessed adult patients with RIF-resistant pulmonary tuberculosis confirmed on Xpert MTB/RIF assay during a 2-year period from March 2011 to February 2013. The National Health Laboratory Service (NHLS) provided a list of all patients with a positive Xpert MTB/RIF assay result. Patients included in the study were older than 14 years and 1 day and were admitted to adult medical wards at CHBAH.

The prevalence of rifampicin resistance was calculated by dividing the number of positive rifampicin-resistant Xpert MTB/RIF assays by the total number of positive Xpert MTB/RIF assays (i.e. rifampicin-sensitive and rifampicin-resistant) submitted by adult patients at CHBAH during the 2-year period. Rifampicin resistance was further subdivided into MDR-TB (resistance to both rifampicin and isoniazid), RMR (resistance to rifampicin only) and unclassified (patients without confirmatory test submission). The management of patients was assessed based on submission of the confirmatory sputum samples (LPA, TB microscopy, TB culture and DST), appropriate drug therapy (a fluoroquinolone: moxifloxacin or ofloxacin, a 2nd line aminoglycoside: kanamycin or amikacin, pyrazinamide, ethionamide and terizidone), adequate isolation of patients with confirmed RIF-resistance and referral to a designated drug resistant TB care centre.

Data collection

A list of patients that were over the age of 14 years and had RIF-resistant MTB confirmed by an Xpert MTB/RIF assay, was compiled and their records were obtained from the CHBAH's record department. Data from the NHLS database and the TB care center at CHBAH was obtained to support information obtained from the patients'

hospital records. For patients with confirmed RIF-resistance on MTB/RIF assay, a name search was performed on the NHLS database to obtain all confirmatory sputum samples that were submitted. The data collection sheet used for the study recorded patient demographics, HIV status, cluster of differentiation 4 (CD4) count, anti-retroviral therapy (ART), previous TB exposure, previous TB treatment completion, current anti-tuberculosis drug treatment, the time taken for the MTB/RIF assay result, the submission and results of additional TB susceptibility tests, isolation of the patient, appropriate referral and hospital outcome. The data was then collated and entered on an Excel worksheet.

Ethical approval

Permission to conduct this study was granted by the Human Research Ethics Committee at the University of the Witwatersrand (M131033) and the Medical Advisory Committee at CHBAH. The National Manager of Academic Affairs and Research at the NHLS granted permission to access their result database.

Results

Prevalence of rifampicin resistant tuberculosis

Of the 729 positive Xpert MTB/RIF assays submitted, 77 were positive for RIF-resistance. The prevalence of RIF-resistant PTB among patients who presented to CHBAH between March 2011 and February 2013 was 10.6%. Seven patients' files could not be traced and therefore are not included in further analysis. Of the 70 patients, 22 (31.4%) had RMR tuberculosis, 19 (27.1%) patients had MDR-TB and 29 (41.4%)

patients had no other confirmatory test submitted and therefore the pattern of drug resistance could not be established.

Demographic characteristics, HIV co-infection and TB history (Table 1)

Thirty-four patients (49%) were female. The mean (SD) age was 36 (10.2) years. Among 66 patients with known HIV-serostatus, 58 (83%) patients were HIV infected and 8 (11%) patients were HIV non-infected. Amongst the 51 (88%) patients who had their CD4 cell counts recorded, the mean CD4 cell count was 91/µl. The median CD4 cell count was 43/µl (IQR 15 – 160). Thirty-two (55%) HIV positive patients were on ART prior to admission. Forty-one (59%) patients had a history of previous tuberculosis among whom 11 (26.8%) patients had more than one episode of TB. Four (9.8%) patients admitted to not completing their prescribed treatment regimen previously. Twenty-six (37%) patients were being treated for susceptible pulmonary tuberculosis at the time of hospitalization.

Management

Of the 70 patients with RIF-resistant TB, 12 (17%) patients had been discharged and 5 (7%) patients had died. Therefore 53 (75.7%) patients were still in hospital when their Xpert MTB/RIF result was obtained. Results of management outcomes will be presented for the total 70 patients in the cohort and the subgroup of patients who received their results in hospital.

Additional susceptibility testing (Table 2)

It took on average 3.36 days (range: 1-10 days) from the date of admission to obtain the Xpert MTB/RIF result. Overall 42 (60%) patients had the LPA test submitted, to differentiate between MDR-TB and RMR-TB. Of the sputum samples submitted, 53 (76%) and 42 (60%) patients had submitted sputum specimens for TB microscopy and TB culture respectively. Eighteen (26%) patients had submitted sputum for DST. Of the 53 patients who received results in hospital, 38 (72%) patients had the LPA test, 46 (87%) and 36 (68%) patients had a TB microscopy and TB culture sent respectively and 16 (30%) patients had a DST requested. Twenty (29%) patients of the overall cohort had no further sputum tests requested.

Drug therapy (Table 2)

Of the anti-tuberculosis drug therapy that was provided to patients, 23 were initiated on appropriate treatment for MDR-TB, representing 33% of the total cohort and 43% of the 53 patients remaining. Thirty-nine patients were kept on treatment for drug-susceptible TB.

Isolation, referral and outcome (Table 2)

It took an average of 4 days to isolate patients. The median duration of hospital stay was 11 days (IQR 6 – 18). Thirty-five patients were isolated, comprising 50% of the cohort and 66% of the remaining 53 patients. Appropriate referral was carried out for 34 patients, constituting 49% of the cohort and 64% of the 53 remaining patients.

Of the other 36 patients, 10 (14%) patients were not appropriately referred, 12 (17%) patients were discharged before their result became available, 1 (1.4%) absconded and 13 (19%) patients died in hospital.

Discussion

Study of the initial inpatient management of patients diagnosed with RIF-resistant pulmonary TB is important for 2 main reasons. Firstly, for the patient's benefit, it measures the time to diagnosis after hospitalization, the submission of further sputum tests to define the extent of resistance to anti-tuberculosis drugs, early initiation of guideline-recommended therapy and referral for supervision and management. Secondly, for the purpose of infection control to protect other patients and health care workers, it investigates patient isolation and initiation of effective treatment. Knowing the prevalence of RIF-resistant TB can strengthen the case for effective infection control in a given population.

The prevalence of RIF-resistance during the 2-year period was 10.6%. This is more than double the rate of 4.6% found in a national survey conducted in South Africa during the period 2012-2014.[32] The prevalence of RMR (3.02%) exceeded that of MDR-TB (2.60%), but the unclassified group (3.97%) was the largest due to a lack of submission of confirmatory tests. Since CHBAH is a referral center for patients with complicated and non-resolving disease processes, it could be expected that the prevalence rates would be higher than the national average. The prevalence rate of RMR has doubled in new TB cases nationally since 2002[32] and in the Western Cape province.[33] Risk factors for the increase in prevalence were advanced HIV infection and previous TB treatment.[33]

The recommended management strategy of confirmed RIF-resistant TB includes submission of confirmatory tests, initiation of MDR-TB therapy, isolation and referral to

an appropriate health facility to continue management.[27,] The confirmatory tests include sputum samples sent for TB microscopy and culture, LPA and DST. Overall our study revealed that 76%, 60%, 60% and 26% of TB microscopy, TB culture, LPA and DST samples were respectively submitted. A likely reason for the disjuncture between rates of submission for culture and DST is that the laboratory form requires the clinician to request DST separately from culture, whereas many clinicians assume that susceptibility will be performed automatically. Two factors that may have contributed negatively to the overall results were patients who were discharged (17%) or had died (7%) before their result had become available. After considering these 2 factors, 72% patients had the LPA test, 68% patients had the TB culture sent and 30% patients had the DST requested, which still demonstrates a substantial deficiency in the submission of confirmatory tests despite having a confirmed result on MTB/RIF assay. In Zimbabwe the submission rate of sputum for culture and drug susceptibility testing at 2 health care centers was 70%, of which only half reached the laboratory and were processed.[34] Possible explanations for our results are that patients may have been transferred to the referral center before a confirmatory specimen was submitted, the patient may no longer have been expectorating sputum or the attending doctor may have not known the recommended protocol. Premature discharging of patients is a result of limited hospital beds and a high patient demand at our center.[29] Patient tracing and continued surveillance would ensure these patients receive the diagnosis and appropriate medical treatment despite being discharged early. Educating health care workers and encouraging sputum sample collection immediately after obtaining the result, can improve the confirmatory tests submission and thus ensure accurate diagnosis and treatment. A better solution would be to send paired

samples whereby the laboratory would retain the second sputum samples for the supplementary and confirmatory tests, which would be triggered once the MTB/RIF assay detects rifampicin-resistance.

A fundamental part of managing drug-resistant TB is the correct combination of therapeutic drugs. At the time of the study being conducted, the 5 essential drugs used during the intensive phase to treat MDR-TB were kanamycin or amikacin, moxifloxacin, ethionamide, terizidone or cycloserine and pyrazinamide.[27] In our high-prevalence setting, the presence of rifampicin resistance may be used as a surrogate for MDR-TB, however due to the recent studies displaying an increase in RMR prevalence [32-33], this may no longer be true. Nonetheless each of the 70 patients from our study should have been initiated on MDR-TB treatment. The study revealed that less than half of the patients received appropriate drug treatment in hospital. Of the patients who were inadequately treated, 89% were kept on treatment for drug susceptible TB. The regimen may not have been changed due to the patient being prematurely discharged (17%) or dying (7%) before their result became available, or possibly due to the patient being rapidly transferred to a dedicated center for drug-resistant TB management. Inadequate knowledge of the appropriate drug regimen by the treating doctors may have accounted for the reluctance to amend treatment. It is imperative that all health care providers that are faced with the challenge of tuberculosis and drug-resistance on a day-to-day basis become familiar with the appropriate drug resistant treatment regimen.

It took an average of 3.36 days from the day of admission to confirm the presence of rifampicin-resistance pulmonary tuberculosis. The Xpert MTB/RIF assay was introduced for use as a point of care rapid diagnostic assay in poor rural areas. Its use in the tertiary level hospital revealed a longer duration before obtaining the result, which is contrary to the intended rapid use of the assay. A delay in obtaining the result leads to a delay in appropriate treatment and exposure of the hospital population to drug resistant organisms. Possible explanations include a delay in obtaining a sputum sample from the patient, delays in transport, registration, or processing of the specimen by the laboratory and sputum samples that may be lost in transit.[34] A contemporary investigation of the time to obtaining a result will be of benefit. After taking in account patients who were discharged or had died before their result became available, 66% of the remaining 53 patients were isolated with a mean time of 4 days after being admitted. The time taken to isolation corresponds to the duration of time taken to obtain the MTB/RIF assay result. Appropriately isolating patients with drug resistant TB whilst awaiting referral will decrease the risk of further transmission in the hospital setting. Many hospitals have a limited number of isolation facilities, which are typically reserved for patients with a high clinical suspicion for or confirmed drug-resistant TB.

Appropriate referral forms an essential part of the management of drug resistant TB. The referral center will ensure that patients will have the correct confirmatory tests submitted and will review the results, will prescribe correct drug therapy and will have adequate stock of drugs, will screen for HIV and initiate and manage ART, will monitor progress with resubmission of sputum specimens for testing to assess treatment success, will

manage adverse drug reactions and will have access to allied health care providers to discuss dietary advice, to manage psychological issues and to perform hearing tests for those on aminoglycosides. Of the 53 patients who received their results in hospital, 64% were appropriately referred, while 14% were not referred, with the remainder dying in hospital and with 1 absconsion.

The mortality rate was 19% which is comparable to the global estimate of 16% amongst patients with MDR-TB[4] and a local study[29] that demonstrated an inpatient mortality rate of 19% amongst patients diagnosed with pulmonary TB. A delay in obtaining the diagnosis, inappropriate drug therapy and advanced HIV disease may have contributed to the overall mortality.

The prevalence of HIV and any rifampicin-resistant TB co-infection in this cohort was 83%, which is in keeping with global comparisons of 70%-80% [2,14] and corresponds with the high levels found in sub-Saharan Africa. Ghandhi et al.[18] demonstrated a rate of 92% with MDR-TB and HIV co-infection. A majority of patients had advanced immunosuppression.

Study limitations

Due to the lack of submission of the follow up LPA and DST tests, a considerable proportion (40%) of the study population could not be assigned a specific resistance pattern. Although the NHLS system was searched by name for evidence of follow-up testing, the retrospective nature of the study did not allow us to trace patients who had not

submitted tests, in order to ascertain details of further testing and appropriate care. The study design allowed for the description of prevalence and initial management at the beginning of the treatment program. It did not incorporate patients' adherence to treatment, adverse reactions and long-term outcomes. The study only reviewed a single health care facility and therefore the results only pertain to a limited geographical area and may not be fully representative of other regions. The adequacy of records and untraceable records was another limitation to the study. The quality of information recorded within the inpatient hospital files was sufficient in most instances.

Conclusion

In conclusion, the study results revealed >10% prevalence rate of RIF-resistant pulmonary TB. The study demonstrated that overall management (including confirmatory tests, appropriate drug therapy, isolation and referral) of patients with rifampicin-resistant pulmonary TB was substandard and there are multiple areas that need to be improved upon. Submission of paired sputum samples and storage by the laboratory may improve the diagnostic yield of drug resistant TB. Educating health care professionals regarding initial management and therapeutic regimens is of paramount importance to help control the scourge of this treatable disease.

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Table 1. Prevalence of TB and baseline characteristics of study cohort (*N*=70)	
	n* (%)
Prevalence	
RMR	22 (3.02)
MDR-TB	19 (2.60)
Unclassified	29 (3.97)
Baseline characteristics	
Female	34 (49)
Age (years), mean (SD)	36 (10.2)
HIV-positive	58 (83)
CD4 cell count (cells/μL), median (IQR)	43 (15 – 160)
CD4 cell count <100 cells/μL	37 (73)
ART	32 (55)
Previous history of TB infection	41 (59)
Discharged before results available	12 (17)
Time to obtain Xpert MTB/RIF assay result (days), mean (SD)	3.36 (2.28)
Duration of hospitalisation (days), median (IQR)	11 [6 - 18]
Inpatient mortality	13 (19)
TB = tuberculosis; RMR = rifampicin mono-resistance; MDR-TB = multi-drug resistant tuberculosis; SD = standard deviation; CD4 = XX; ART = antiretroviral therapy; IQR = interquartile range; MTB/RIF = XX. *Unless otherwise specified.	

Table 2. Management outcomes for study cohort (*N*=70) and remaining inpatients (*N*=53)*		
	***n* (%)**	
Outcome	**Study cohort (*N*=70)**	**Inpatients (*N*=53)**
LPA	42 (60)	38 (72)
DST	18 (26)	16 (30)
TB Culture	42 (60)	36 (68)
TB Microscopy	53 (76)	46 (87)
No additional testing	20 (29)	11 (21)
Adequate drug treatment	23 (33)	23 (43)
Patients isolated	35 (50)	35 (66)
Patients appropriately referred	34 (49)	34 (64)
LPA = line probe assay; DST = drug susceptibility testing; TB = tuberculosis. *Management outcomes of 70 patients with rifampicin-resistant TB and the 53 patients still hospitalised on receipt of results.		

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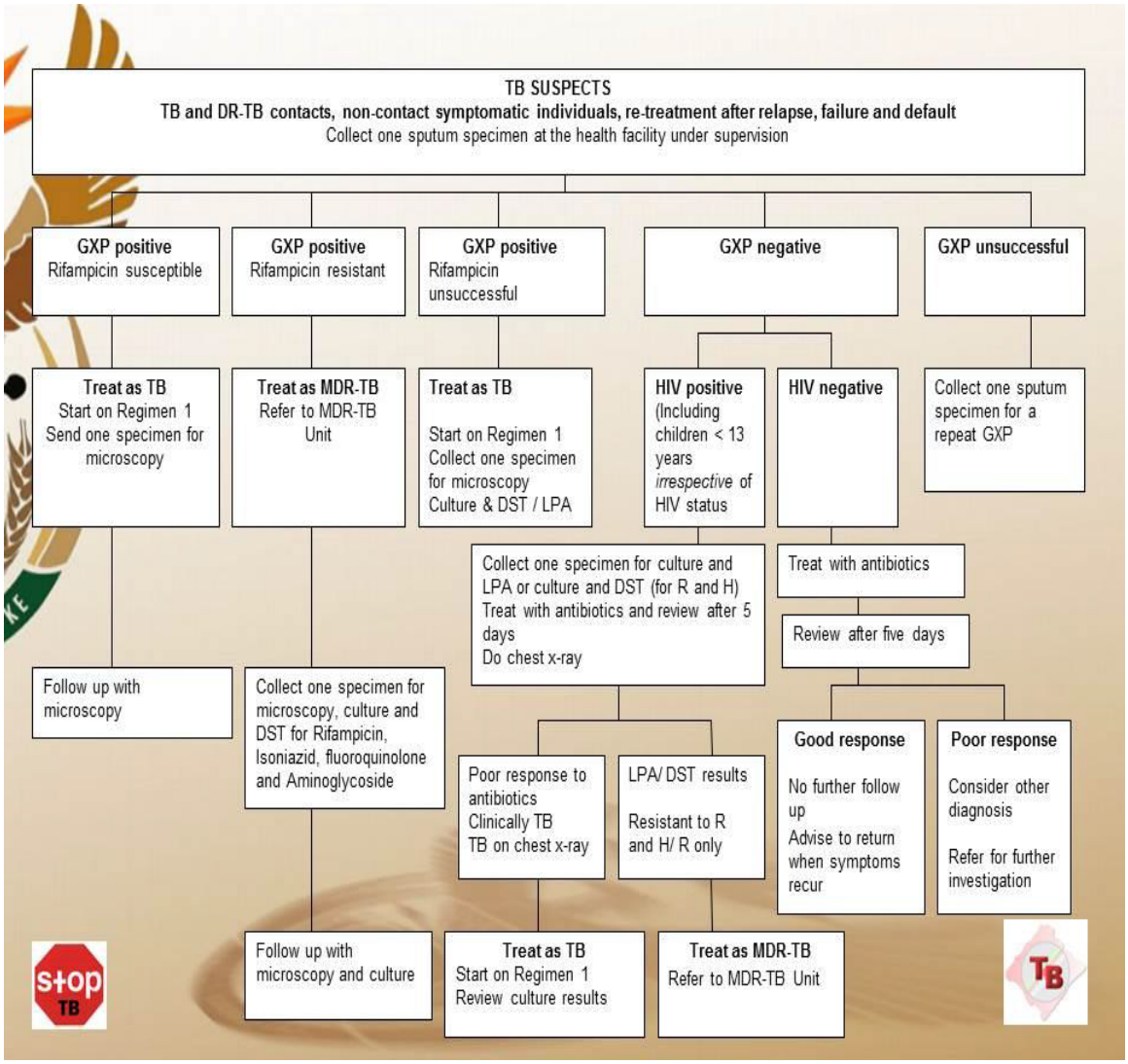
CHAPTER THREE – APPENDICES

3.1 National guidelines for the management of drug-resistant tuberculosis 2011



3.2 Data collection sheet

DATA SHEET (STUDY NUMBER:)

DEMOGRAPHICS

AGE: _____
GENDER: MALE FEMALE

HIV CO-INFECTION

HIV STATUS: POSITIVE NEGATIVE UNKNOWN
CD4 COUNT: _____ UNKNOWN
VIRAL LOAD: _____ UNKNOWN
ANTI-RETROVIRALS: YES NO
STARTED ON THIS ADMISSION: YES NO

TUBERCULOSIS HISTORY

PREVIOUS TB: YES NO
NUMBER OF PREVIOUS EPISODES: 1 EPISODE > 1 EPISODE (__)
DATE OF PREVIOUS EPISODE/S: _____
DURATION OF TREATMENT: 6 MONTHS > 6 MONTHS
SITE: PULMONARY OTHER
TREATMENT COMPLETION: YES NO
REASON FOR DEFAULTING: _____

INVESTIGATIONS

DURATION OF GENEXPERT RESULT: _____
SPUTUM AFB SMEAR POSITIVE: YES NO UNKNOWN
LINE PROBE ASSAY SUBMITTED: YES NO
AFB CULTURE AND SENSITIVITY: YES NO
DRUG SENSITIVITY TESTING (DST): YES NO

INITIAL DRUG TREATMENT

RIFAMPICIN	
ISONIAZID	
ETHAMBUTOL	
PYRAZINAMIDE	
AMIKACIN / KANAMYCIN	
MOXIFLOXACIN / OFLOXACIN	
TERIZIDONE / CYCLOSERINE	
ETHIONAMIDE	
OTHER:	

MANAGEMENT (AFTER CONFIRMATION)

	Y / N	SENSITIVE	RESISTANT
RIFAMPICIN			**X**
ISONIAZID			
ETHAMBUTOL			
PYRAZINAMIDE			
AMIKACIN / KANAMYCIN			
MOXIFLOXACIN / OFLOXACIN			
TERIZIDONE / CYCLOSERINE			
ETHIONAMIDE			
OTHER:			

ISOLATION: YES NO
NO. OF DAYS BEFORE ISOLATION: _____
APPROPRIATELY REFERRED: YES NO
PLACE: SOUTHRAND HJH SIZWE
DIAGNOSIS MADE AS: INPATIENT OUTPATIENT
DATE OF ADMISSION: _____
DATE OF DISCHARGE: _____
DEATH: NO YES (DATE:_____)

3.3 Human Research Ethics Committee clearance certificate

R14/49 Dr Rajiv Narsing

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M131033

NAME: (Principal Investigator)	Dr Rajiv Narsing
DEPARTMENT:	Internal Medicine Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	The Prevalence and Management of Rifampicin-Resistant Tuberculosis at Chris Hani Baragwanath Academic Hospital
DATE CONSIDERED:	25/10/2013
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Alan Karstaedt
APPROVED BY:	Professor A Dhai, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	25/10/2013 (Initial Approval)12/12/2014 (Recertified)

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 Secretary in Room 10004, 10th floor, Senate House, University.
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 resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

3.4 Medical advisory committee permission letter

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 3rd October 2013

TITLE OF PROJECT: The Prevalence and Management of Rifampicin-Resistant Tuberculosis at Chris Hani Baragwanath Academic Hospital

UNIVERSITY: Witwatersrand

Principal Investigator: Dr R M NARSING

Department: Medicine

Permission Head Department (where research conducted): **Yes Dr Alan Karstaedt**

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Academic Hospital. The CEO / management of Chris Hani Baragwanath Academic Hospital is accordingly informed and the study is subject to:-

- Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.
- The Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- The MAC will be informed of any serious adverse events as soon as they occur
- Permission is granted for the duration of the Ethics Committee Approval.

.....
Recommended
(On behalf of the MAC)
Date: 3/10/2013

.....
Approved/Not Approved
Hospital Management
Date: 04/10/13

3

3.5 National Health Laboratory Service approval letter

NATIONAL HEALTH LABORATORY SERVICE

Academic Affairs and Research
Modderfontein Road, Sandringham, 2031
Tel: +27 (0)11 386 6142
Fax: +27 (0)11 386 6296
Email: babatyi.kgokong@nhls.ac.za
Web: www.nhls.ac.za

06 January 2015

Applicant: Dr Rajiv Narsing
Institution: University of the Witwatersrand
Department: Medical Sciences
Contact Number: 084 458 5663
Email: RAJ4065@yahoo.com

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

Your application to undertake a research project "**The Prevalence and Management of Rifampicin-Resistance Tuberculosis at Chris Hani Baragwaneth Academic Hospital**" 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 to conduct the proposed study as outlined in the submitted application.

Please note that the 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.

- Full Updated Ethics clearance have been obtained from an approved local Ethics Committee and sent as proof.
- Processes are discussed with the laboratory manager and/or the Business Manager and/or the Unit Manager 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.
- A final report of the research study and any published paper resulting from this study are submitted and addresses 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. Any data related queries may be directed to Sue Candy, Manager NHLS Corporate Data Warehouse, Tel: (011) 386 6036 Email: sue.candy@nhls.ac.za

Yours sincerely,

Dr Babatyi Malope-Kgokong
National Manager: Academic Affairs and Research

Chairperson: Prof Algonda Perez Deputy Chairperson: Dr Fazel Randera Interim CEO: Ms Joyce Mogale
Physical Address: 1 Modderfontein Road, Sandringham, Johannesburg, South Africa Postal Address: Private Bag X8, Sandringham, 2131, South Africa
Tel: +27 (0) 11 386 6000/ 0860 00 NHLS(6457) www.nhls.ac.za
Practice number: 5200296

3.6 Permission letter from the publisher

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Dr R M Narsing
Division of Pulmonology, Department of Internal Medicine
Chris Hani Baragwanath Academic Hopsital
Johannesburg
raj4065@yahoo.com

Wednesday, 02 August 2017

Dear Dr Narsing,

Re: Your paper published in the South African Respiratory Journal

Authors: R M Narsing, A S Karstaedt, F Sahid

Title (SARJ 151): The prevalence and management of rifampicin-resistant tuberculosis among adults at Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa

https://doi.org/10.7196/SARJ.2017.v23i2.151

I hereby confirm that the above detailed paper was published in the South African Respiratory Journal and the author retains full rights to use the paper for academic purposes.

Yours sincerely

Hannah Kikaya
CEO and Publisher
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ORIGINAL RESEARCH

The prevalence and management of rifampicin-resistant tuberculosis among adults at Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa

R M Narsing,[1,3] MB BCh, FCP; **A S Karstaedt**,[2,3] MB BCh, MMed; **F Sahid**,[2,3] MB BCh, FCP

[1] *Division of Pulmonology, Department of Internal Medicine, Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa*
[2] *Division of Infectious Diseases, Department of Internal Medicine, Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa*
[3] *School of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa.*

***Corresponding author**: R M Narsing (raj4065@yahoo.com)*

Background. Early effective management of drug-resistant tuberculosis (TB) is important for the patient, and for infection control. The Xpert MTB/RIF (Cepheid, USA) assay detects *Mycobacterium tuberculosis* DNA and the presence of rifampicin resistance.
Objective. To assess the prevalence and initial management of rifampicin-resistant pulmonary TB (PTB), confirmed by the Xpert MTB/RIF assay, in hospitalised adult patients.
Methods. This retrospective descriptive study assessed adult patients from March 2011 to February 2013. Data was obtained from the National Health Laboratory Service database and patient records. Management comprised the submission of additional confirmatory sputum tests, initiation of appropriate anti-TB drug therapy, patient isolation, and proper referral.
Results. The prevalence of rifampicin resistance was 10.6% (*n*=77) of 729 positive assays. The initial management was assessed for 70 patients with complete records. However, of these 70 patients, 12 patients had been discharged and 5 patients had died prior to receiving their results. The management of the total cohort, and of the 53 remaining inpatients, was analysed separately. The overall confirmatory sputum submission rates were 76%, 60%, 60% and 26% for TB microscopy, Line Probe Assay, TB culture, and drug-susceptibility testing, respectively, and 87%, 72%, 68% and 30%, respectively for the 53 remaining patients. Overall, 33% of patients received appropriate anti-TB treatment, 50% were isolated, and 49% were appropriately referred. For the 53 remaining patients, 43% received appropriate drug treatment, 66% were isolated, 64% were appropriately referred, and 19% were not referred. The inpatient mortality rate was 19%.
Conclusions. Rifampicin-resistant TB prevalence in-hospital was more than double the national rate. The initial management of patients with rifampicin-resistant PTB was substandard. Submission of paired sputum samples and educating healthcare professionals and healthcare users are of paramount importance to improve the management of drug-resistant TB.

S Afr Respir J 2017;23(2):30-34. DOI:10.7196/SARJ.2017.v23i2.151

Tuberculosis (TB) causes a significant burden of disease worldwide, with ~9.6 million cases and 1.5 million deaths in 2014.[1] South Africa (SA) is ranked among the top six countries in the world as having the largest number of incident cases.[1,2] *Mycobacterium tuberculosis* (MTB) is the organism responsible for TB infection and has been treated successfully for many decades. The emergence of drug-resistant TB has complicated the management of the disease. Multi-drug-resistant tuberculosis (MDR-TB) is defined as resistance to the two most effective first-line drugs, isoniazid (INH) and rifampicin (RIF).[3] Of the new TB cases reported in 2013 and 2014, there were ~480 000 cases of MDR-TB annually,[1,2,4] with an estimated 6 900 cases in SA in 2014.[4] It was estimated that 3.3% of new TB cases were due to MDR-TB, whereas 20% of previously treated TB cases had presented with MDR-TB in 2014.[1] Risk factors for the development of MDR-TB include previous exposure to anti-TB treatment, incomplete treatment regimens, poor patient compliance, lack of availability of adequate medication, co-infection with HIV, social barriers, lack of patient access to care, poorly coordinated management strategies from healthcare institutions and inadequate guidelines.[5-11]

In 2013, there were an estimated 2.1 million new HIV infections globally and 1.5 million new infections in the World Health Organization (WHO) African region.[12] Patients who are co-infected with HIV and TB are more likely to have rapid progression to active TB disease, have a higher likelihood of MDR-TB, and higher mortality.[4,13-17] The incidence of HIV co-infection and TB is the highest in the African region, with about 80% of cases being co-infected.[2] In sub-Saharan Africa there was an estimated 70% co-infection rate of drug-resistant TB and HIV.[2,14] Gandhi *et al.*[18] demonstrated a 92% co-infection rate of MDR-TB and HIV in KwaZulu-Natal Province, SA.

Resistance to RIF usually occurs due to point mutations of the *rpoB* gene,[3,19,20] with more than 95% of mutations responsible for the development of RIF resistance occurring in this gene.[3,21] In regions with a high probability of MDR-TB, such as sub-Saharan Africa, RIF resistance can be used as a reliable indicator for MDR-TB.[22] The WHO has endorsed the use of molecular testing for the rapid diagnosis of TB and drug resistance.[23] The Xpert MTB/RIF (Cepheid, USA) assay has been approved for use since December 2010. The assay detects MTB DNA and the presence of RIF resistance.[23] Studies reviewing the effectiveness of the Xpert MTB/RIF assay found a sensitivity of 95% and specificities of 94 - 98% with smear-positive sputum and sensitivities of 55% and 67% in smear-negative sputum.[24,25] The rapid

result is an advantage when compared to the lengthier duration of conventional drug susceptibility testing (DST).[26]

In 2011, the SA Department of Health released guidelines for the management of drug-resistant TB.[27] Following the result of RIF-resistant MTB on the Xpert MTB/RIF assay, MDR-TB treatment should be initiated, confirmatory sputum specimens submitted, patients should be isolated and appropriately referred. Treatment should then be reviewed following laboratory confirmation of drug susceptibility.[27] A combination of five effective chemotherapeutic agents are recommended for the treatment of MDR-TB.[28] These include a fluoroquinolone (moxifloxacin or ofloxacin), a second-line aminoglycoside (kanamycin or amikacin), pyrazinamide, ethionamide and terizidone.[27] Commitment from both the patient and the healthcare professional is essential to treat TB and drug-resistance effectively in affected communities. Local studies have shown that patient compliance, delay in initiation of treatment, loss to follow-up, poor contact tracing, and early mortality still remain hindering factors in current treatment strategies.[29-31] Ebonwu *et al.*[30] found that only 63% of patients were initiated on MDR-TB treatment in Gauteng Province in 2011.

This study aimed to describe the prevalence and initial management of hospitalised adult patients with RIF-resistant pulmonary TB (PTB), as diagnosed by the Xpert MTB/RIF .

Methods

Study setting

Chris Hani Baragwanath Academic Hospital (CHBAH) is a tertiary-level hospital with 702 adult medical beds that serves the community of Soweto and surrounding areas.

Study design

This retrospective descriptive study, based on record review, assessed adult patients with RIF-resistant PTB during a two-year period from March 2011 to February 2013. The National Health Laboratory Service (NHLS) provided a list of all patients with a positive Xpert MTB/RIF assay result. Patients included in the study were older than 14 years and were admitted to the adult medical wards at CHBAH.

The prevalence of RIF resistance was calculated by dividing the number of positive RIF-resistant Xpert MTB/RIF assays by the total number of positive Xpert MTB/RIF assays (i.e. RIF-sensitive and RIF-resistant) submitted by adult patients at CHBAH during the 2-year period. RIF resistance was further subdivided into MDR-TB (resistance to both RIF and INH), RMR (resistance to RIF only) and unclassified (patients without confirmatory test submission). The management of patients was assessed based on submission of the confirmatory sputum samples (line probe assay (LPA), TB microscopy, TB culture, and DST), appropriate drug therapy (a fluoroquinolone, such as moxifloxacin or ofloxacin, a second-line aminoglycoside, such as kanamycin or amikacin, pyrazinamide, ethionamide, and terizidone), adequate isolation of patients with confirmed RIF-resistance, and referral to a designated drug-resistant TB care centre.

Data collection

A list of patients who were >14 years old, and had RIF-resistant MTB confirmed by an Xpert MTB/RIF assay, was compiled and their records were obtained from the CHBAH's records department. Data from the NHLS database and the TB care centre at CHBAH were obtained to support information obtained from the patients' hospital records. For patients with confirmed RIF-resistance, a name search was performed on the NHLS database to obtain all confirmatory sputum samples that were submitted. The data collection sheet used for the study recorded patient demographics, HIV status, CD4 count, antiretroviral therapy (ART), previous TB exposure, previous TB treatment completion, current anti-TB drug treatment, the time taken to obtain the MTB/RIF assay result, the submission and results of additional TB susceptibility tests, isolation of the patient, appropriate referral and hospital outcome. The data were then collated and entered on an Excel worksheet.

Permission to conduct this study was granted by the Human Research Ethics Committee at the University of the Witwatersrand (ref. no. M131033) and the Medical Advisory Committee at CHBAH. The National Manager of Academic Affairs and Research at the NHLS granted permission to access their result database.

Results

Prevalence of RIF-resistant TB

Of the 729 positive Xpert MTB/RIF assays submitted, 77 were positive for RIF resistance. The prevalence of RIF-resistant PTB among patients who presented to CHBAH between March 2011 and February 2013, was 10.6%. Seven patients' files could not be traced and therefore they were not included in further analysis. Of the 70 patients, 22 (31.4%) had RMR-TB, 19 (27.1%) had MDR-TB, and 29 (41.4%) patients had no other confirmatory test submitted and therefore the pattern of drug resistance could not be established.

Demographic characteristics, HIV co-infection and TB history

Thirty-four patients (49%) were female. The mean (SD) age was 36 (10.2) years. Among 66 patients with known HIV-serostatus, 58 (83%) patients were HIV-positive and 8 (11%) patients were HIV-negative. Among the 51 (88%) patients who had their CD4 cell counts recorded, the mean CD4 cell count was 91 cells/μL. The median CD4 cell count was 43 cells/μL (interquartile range (IQR) 15 - 160). Thirty-two (55%) HIV-positive patients were on ART prior to admission. Forty-one (59%) patients had a history of previous TB, among whom 11 (26.8%) patients had more than one episode of TB. Four (9.8%) patients admitted to not completing their prescribed treatment regimen previously. Twenty-six (37%) patients were being treated for susceptible PTB at the time of hospitalisation (Table 1).

Management

Of the 70 patients with RIF-resistant TB, 12 (17%) patients had been discharged and 5 (7%) patients had died. Therefore 53 (75.7%) patients were still in hospital when their Xpert MTB/RIF result was obtained. Table 2 displays the results of the management outcomes for the total cohort (*N*=70) and the subgroup (*N*=53) of patients who received their results in hospital.

Additional susceptibility testing

It took on average 3.36 days (range: 1 - 10 days) from the date of admission to obtain the Xpert MTB/RIF result (Table 2). Overall, 42 (60%) patients had the LPA test submitted, to differentiate

Table 1. Prevalence of TB and baseline characteristics of study cohort (*N*=70)

	n (%)*
Prevalence	
RMR	22 (3.02)
MDR-TB	19 (2.60)
Unclassified	29 (3.97)
Baseline characteristics	
Female	34 (49)
Age (years), mean (SD)	36 (10.2)
HIV-positive	58 (83)
CD4 cell count (cells/μL), median (IQR)	43 (15 - 160)
CD4 cell count <100 cells/μL	37 (73)
ART	32 (55)
Previous history of TB infection	41 (59)
Discharged before results available	12 (17)
Time to obtain Xpert MTB/RIF assay result (days), mean (SD)	3.36 (2.28)
Duration of hospitalisation (days), median (IQR)	11 (6 - 18)
Inpatient mortality	13 (19)

TB = tuberculosis; RMR = rifampicin mono-resistance; MDR-TB = multi-drug resistant tuberculosis; SD = standard deviation; ART = antiretroviral therapy; IQR = interquartile range; MTB/RIF = rifampicin-resistant *Mycobacterium tuberculosis*.
*Unless otherwise specified.

Table 2. Management outcomes for study cohort (*N*=70) and remaining inpatients (*N*=53)*

	n (%)	
Outcome	**Study cohort (*N*=70)**	**Inpatients (*N*=53)**
LPA	42 (60)	38 (72)
DST	18 (26)	16 (30)
TB culture	42 (60)	36 (68)
TB microscopy	53 (76)	46 (87)
No additional testing	20 (29)	11 (21)
Adequate drug treatment	23 (33)	23 (43)
Patients isolated	35 (50)	35 (66)
Patients appropriately referred	34 (49)	34 (64)

LPA = line probe assay; DST = drug susceptibility testing; TB = tuberculosis.

*Management outcomes of 70 patients with rifampicin-resistant TB and the 53 patients still hospitalised on receipt of results.

between MDR-TB and RMR-TB. Of the sputum samples submitted, 53 (76%) and 42 (60%) patients had submitted sputum specimens for TB microscopy and TB culture, respectively. Eighteen (26%) patients had submitted sputum samples for DST. Of the 53 patients who received results in hospital, 38 (72%) patients had the LPA test, 46 (87%) and 36 (68%) patients had a TB microscopy and TB culture sent, respectively. DSTs were requested for 16 (30%) patients. Twenty (29%) patients of the overall cohort had no further sputum tests requested.

Drug therapy

Of the anti-TB drug therapy that was provided to patients, 23 were initiated on appropriate treatment for MDR-TB, representing 33% of the total cohort and 43% of the 53 remaining inpatients (Table 2). Thirty-nine patients were kept on treatment for drug-susceptible TB.

Isolation, referral and outcome

It took an average of 4 days to isolate patients. The median duration of hospitalisation was 11 days (IQR 6 - 18). Half of the patients in the study cohort and 66% of the inpatients were isolated, respectively. Appropriate referral was carried out for 34 patients, constituting 49% of the cohort and 64% of the 53 remaining patients.

Of the other 36 patients, 10 (14%) patients were not appropriately referred, 12 (17%) patients were discharged before their result became available, 1 (1.4%) absconded, and 13 (19%) patients died in hospital.

Discussion

Study of the initial inpatient management of patients diagnosed with RIF-resistant PTB is important for two main reasons. Firstly, for the patient's benefit, it measures the time to diagnosis after hospitalisation, the submission of further sputum tests to define the extent of resistance to anti-TB drugs, early initiation of guideline-recommended therapy, and referral for supervision and management. Secondly, for the purpose of infection control to protect other patients and healthcare workers, it investigates patient isolation and initiation of effective treatment. Knowing the prevalence of RIF-resistant TB can strengthen the case for effective infection control in a given population.

The prevalence of RIF-resistance during the 2-year period was 10.6%. This was more than double the rate of 4.6% found in a national survey conducted in SA during the period 2012 - 2014.[32] The prevalence of RMR (3.02%) exceeded that of MDR-TB (2.60%), but the unclassified group (3.97%) was the largest due to a lack of submission of confirmatory tests. Since CHBAH is a referral centre for patients with complicated and non-resolving disease processes, it could be expected that the prevalence rates would be higher than the national average. The prevalence rate of RMR has doubled in new TB cases nationally, and in the Western Cape Province, since 2002.[32,33] Risk factors for the increase in prevalence were advanced HIV infection and previous TB treatment.[33]

The recommended management strategy of confirmed RIF-resistant TB includes submission of confirmatory tests, initiation of MDR-TB therapy, isolation, and referral to an appropriate health facility to continue management.[27] The confirmatory tests include sputum samples sent for TB microscopy and culture, LPA, and DST. Overall, our study revealed that 76%, 60%, 60% and 26% of TB microscopy, TB culture, LPA and DST samples were submitted, respectively. A likely reason for the disjuncture between rates of submission for culture and DST is that the laboratory form requires the clinician to request DST separately from culture submissions, whereas many clinicians assume that susceptibility tests would be performed automatically. Two factors that may have contributed negatively to the overall results were patients who were discharged (17%) or had died (7%) before their result had become available. After these two

factors had been taken into consideration, 72% had the LPA test, 68% had the TB culture submitted, and 30% had the DST requested, which still demonstrates a substantial deficiency in the submission of confirmatory tests despite having a confirmed result on MTB/RIF assay. In Zimbabwe, the submission rate of sputum samples for culture and DST at two healthcare centres was 70%, of which only half reached the laboratory and were processed.[34] Possible explanations for our results are that patients may have been transferred to the referral centre before a confirmatory specimen was submitted, the patient may no longer have been expectorating sputum, or the attending doctor may not have known the recommended protocol. Premature discharging of patients is a direct result of limited hospital beds and a high patient demand at our centre.[29] Patient tracing and continued surveillance would ensure that these patients receive the diagnosis and appropriate medical treatment, despite being discharged early. Educating healthcare workers and encouraging sputum sample collection immediately after obtaining the result, can improve the rate of confirmatory tests submission and thus ensure accurate diagnosis and treatment. A better solution would be to send paired samples, whereby the laboratory would retain the second sputum sample for the supplementary and confirmatory tests, which would be triggered once the MTB/RIF assay detects RIF resistance.

A fundamental part of managing drug-resistant TB is the correct combination of therapeutic drugs. At the time of the study being conducted, the five essential drugs used during the intensive phase to treat MDR-TB were kanamycin or amikacin, moxifloxacin, ethionamide, terizidone, or cycloserine and pyrazinamide.[27] In our high-prevalence setting, the presence of RIF resistance may be used as a surrogate for MDR-TB; however due to the recent studies displaying an increase in RMR prevalence, [32-33] this may no longer be true. Nonetheless, each of the 70 patients from our study should have been initiated on MDR-TB treatment. The study revealed that <50% of the patients received appropriate drug treatment in hospital. Of the patients who were inadequately treated, 89% were kept on treatment for drug-susceptible TB. The regimen may not have been changed due to the patient being prematurely discharged (17%) or dying (7%) before their result became available, or possibly due to the patient being rapidly transferred to a dedicated centre for drug-resistant TB management. Inadequate knowledge of the appropriate drug regimen by the treating doctors may have accounted for the reluctance to amend treatment. It is imperative that all healthcare providers that are faced with the challenge of TB and drug-resistance on a day-to-day basis become familiar with the appropriate drug-resistant treatment regimen.

It took an average of 3.36 days from the day of admission to confirm the presence of RIF-resistant PTB. The Xpert MTB/RIF assay was introduced for use as a point-of-care, rapid diagnostic assay in poor rural areas. Its use in the tertiary level hospital revealed a longer duration before obtaining the result, which was contrary to the intended rapid use of the assay. A delay in obtaining the result leads to a delay in appropriate treatment, and exposure of the hospital population to drug-resistant organisms. Possible explanations include a delay in obtaining a sputum sample from the patient, delays in transport, registration, or processing of the specimen by the laboratory, and sputum samples that may be lost in transit.[34] A contemporary investigation of the time to obtaining a result would be beneficial. After patients who were discharged or had died before their result became available were taken into account, 66% of the remaining 53 patients were isolated with a mean time of 4 days after being admitted. The time taken to isolation corresponds to the duration of time taken to obtain the MTB/RIF assay result. Appropriately isolating patients with drug-resistant TB, while awaiting referral, will decrease the risk of further transmission in the hospital setting. Many hospitals have a limited number of isolation facilities, which are typically reserved for patients with a high clinical suspicion for, or confirmed, drug-resistant TB.

Appropriate referral forms an essential part of the management of drug-resistant TB. The referral centre will: ensure that patients have the correct confirmatory tests submitted and will review the results; prescribe correct drug therapy and will have adequate stock of drugs; screen for HIV and initiate and manage ART; monitor progress with resubmission of sputum specimens for testing to assess treatment success; manage adverse drug reactions; and have access to allied healthcare providers to discuss dietary advice, to manage psychological issues, and to perform hearing tests for those on aminoglycosides. Of the 53 patients who received their results in hospital, 64% were appropriately referred, while 14% were not referred, with the remainder dying in hospital, and a single case absconded.

The mortality rate was 19%, which was comparable with the global estimate of 16% among patients with MDR-TB[4] and a local study[29] that demonstrated an inpatient mortality rate of 19% among patients diagnosed with PTB. A delay in obtaining the diagnosis, inappropriate drug therapy, and advanced HIV disease may have contributed to the overall mortality.

The prevalence of HIV and any RIF-resistant TB co-infection in this cohort was 83%, which is in keeping with global comparisons of 70 - 80%,[2,14] and corresponds with the high levels found in sub-Saharan Africa. Ghandhi *et al.*[18] demonstrated a rate of 92% with MDR-TB and HIV co-infection. Most of the patients had advanced immunosuppression.

Study limitations

Owing to the lack of submission of the follow-up LPA and DST tests, a considerable proportion (40%) of the study population could not be assigned a specific resistance pattern. Although the NHLS system was searched by name for evidence of follow-up testing, the retrospective nature of the study did not allow us to trace patients who had not submitted tests, to ascertain details of further testing and appropriate care. Although the study design allowed for the description of prevalence and initial management at the beginning of the treatment programme, it did not incorporate patients' adherence to treatment, adverse reactions, and long-term outcomes. The study only reviewed a single healthcare facility and therefore the results only pertain to a limited geographical area, which may not be fully representative of other regions in SA. The adequacy of records and untraceable records was another limitation to the study. The quality of information recorded within the inpatient hospital files was sufficient in most instances.

Conclusion

In conclusion, our results revealed that the prevalence of RIF-resistant PTB in our setting was >10%. The study also showed that the overall management (including confirmatory tests, appropriate drug therapy, isolation, and referral) of patients with RIF-resistant

PTB was substandard and there are multiple areas that need to be improved upon. Submission of paired sputum samples and storage by the laboratory may improve the diagnostic yield of drug-resistant TB. Educating healthcare professionals regarding initial management and therapeutic regimens is of paramount importance to help control the scourge of this treatable disease.

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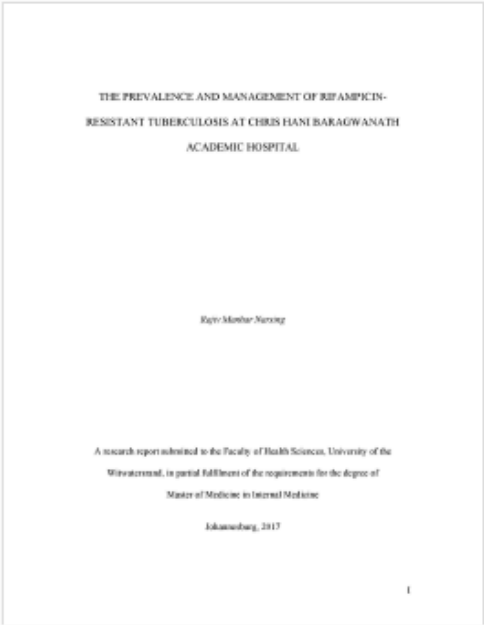

THE PREVALENCE AND MANAGEMENT OF RIFAMPICIN-
RESISTANT TUBERCULOSIS AT CHRIS HANI BARAGWANATH
ACADEMIC HOSPITAL

Rajiv Manhar Narsing

A research report submitted to the Faculty of Health Sciences, University of the
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Master of Medicine in Internal Medicine

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