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Strydom, Magdel

2022

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BACTERIA ISOLATED FROM THE AIRWAYS OF PATIENTS PRESENTING WITH AN ACUTE EXACERBATION OF NON-CYSTIC FIBROSIS BRONCHIECTASIS: A PROSPECTIVE STUDY

AUGUST 2018 – AUGUST 2019

MAGDEL STRYDOM

A research report submitted to the Faculty of Health Sciences,

University of Witwatersrand, Johannesburg, in partial fulfillment of

the requirements for the degree of Master of Medicine in the branch

of Internal Medicine

Johannesburg ,2022

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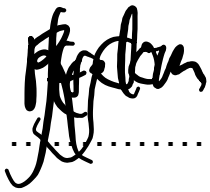
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I. Declaration

I, Magdel Strydom, do hereby declare that this research report is my unaided work. It is being submitted for the degree of Master of Medicine in the branch of Internal Medicine. This research report is submitted in the submissible format (with my protocol and an extended literature review) as recognized by the Faculty of Health Sciences. I further declare that this work has not been submitted for any other examination or degree at this or any other University.



……..

The 28th of January 2022.

II. Dedication

To the amazing people on the Wits Internal Medicine Circuit, for their support, encouragement, motivation, and tremendous kindness. Without them this would not have been possible.

Dr A Ingratta

Dr N Diana

Dr J Nel

III. Presentations originating from this research

No presentations has been generated from this research.

IV. Ethical considerations

Permission for this prospective study was obtained from Dr A Black (Head of Department, Pulmonology, Helen Joseph Hospital), Dr Z Bayat (Head of Internal Medicine, Helen Joseph Hospital), Dr M Mukansi (Chairperson of Helen Joseph Hospital Ethic and Research Committee) and the Human Research Ethics Committee of the University of Witwatersrand (clearance number – M180555).

V. Acknowledgements

The support and assistance of the following persons in preparation of this research report is gratefully acknowledged:

- Dr Andrew Black – for guidance as supervisor of this study, review of the prepared manuscript and constant availability, support and encouragement.

- Dr Jeremy Nel – for the availability to join as co-supervisor, assistance, guidance and review of the prepared manuscript.

- Dr Faith Moyo – for her expert assistance with statistics.

- Dr Kapila Hari – for the guidance and review of the prepared manuscripts

- Dr Nina Diana, Dr Argentina Ingratta, Prof Adam Mahomed and Dr Zaheer Bayat – for always encouraging me to go further and believing in me.

VI. Abstract

Background:

There is little information available on the precipitating bacteria in acute exacerbation of bronchiectasis in developing countries. The Standard treatment guidelines and essential medicine list for South Africa's[1], recommendations for treating acute exacerbation of bronchiectasis relies on data from non-developing countries, which may not reflect the South African situation. Therefore a study was preformed to identify the most common bacteria occuring in our setting and determine the appropriateness of the current recommended empiric antibiotic choices. Empiric therapy that is currently based on the Guidelines for non-cystic fibrosis Bronchiectais published in 2010 by *Thorax*, an International journal on respiratory medicine.[2]

Objective*:*

1. Identify and document the frequency of bacteria cultured from the sputum samples of patients presenting with acute exacerbation of non-cystic fibrosis bronchiectasis at the Helen Joseph Hospital.
2. Determine the appropriateness of current standard treatment guidelines' first line antibiotic choices for the bacteria cultured in our patients that present with acute exacerbation of non-cystic fibrosis bronchiectasis.

Methods:

A prospective cohort study of 81 patients that presented with acute exacerbation of non-cystic fibrosis bronchiectasis. The diagnosis of bronchiectasis was suspected on a combination of clinical manifestations and chest radiography. Where possible definite diagnosis or confirmation of suspected diagnosis was made by HRCT. Patients was classified as definite or suspected bronchiectasis, if outpatient HRCT was still pending.

Three sputum samples were collected on admission from these patients. The sputum samples were obtained prior to the initiation of antibiotics. The samples were tested

for Tuberculosis using Gene Expert, Acid-Fast Bacillus microscopy and culture. A Bartlett score and bacterial microscopy, culture and sensitivity was also performed. (These investigations are part of the normal standard of care as described in the National Department of Health Standard Treatment Guidelines and Essential medicine list.[1])

Results:

A pathogenic bacteria was isolated in only 30% of cases. The most common bacteria cultured from the sputum samples of patients presenting with acute exacerbation of non-cystic fibrosis bronchiectasis were *Haemophilus influenzae (7.4%), Pseudomonas aeruginosa (4.9%), Klebsiella pneumoniae (3.7%), Escherichia coli (1.2%) and Acinetobacter baumannii* (1.2%). Of the subjects 7.4% had *Mycobacterium tuberculosis isolated from their sputum.*
The 60% of the pathogenic bacteria isolated were sensitive to the first line antimicrobials recommended.

Conclusion:

The most common bacteria cultured from the sputum samples of patients presenting with acute exacerbation of non-cystic fibrosis bronchiectasis at the Helen Joseph Hospital is comparable to previous studies done in developed countries.[3,5,22]
Since our yield of positive cultures was lower then that obtained in other studies, there will definetly be value in re-attempting this study on a larger scale.

The results suggest that the current South African treatment guidelines are appropriate for the treatment of acute exacerbation of bronchiectasis in our setting, as more then 60% of the pathogenic bacteria was sensitive to the fist line antimicrobial.

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IX. Nomenclature

ABPA	Allergic bronchopulmonary aspergillosis
AE	Acute exacerbation
AFB	Acid-fast Bacillus
AIDS	Acquired immunodeficiency syndrome
ARV	Antiviral Drug
COVID-19	Coronavirus disease 2019
CT	Computed tomography
CXR	Chest X-ray
ENaC	Epithelial sodium channel
EPTB	Extra-pulmonary tuberculosis
GXP	Gene Expert
HIV	Human immunodeficiency virus
HJH	Helen Joseph Hospital
HRCT	High-resolution computed tomography
IgE	Immunoglobulin E
MCS	Microscopy, Culture, Sensitivity
MMed	Master of Medicine
NCF	Non-cystic fibrosis
NHLS	National Health Laboratory Service
NHRD	National Health Research Database
PTB	Pulmonary tuberculosis
TB	Tuberculosis
WITS	University of the Witwatersrand

Chapter 1: PROTOCOL WITH EXTENDED LITERATURE REVIEW

1.1 Introduction

Current non-cystic fibrosis bronchiectasis'(NCF) management is guided by the Standard Treatment Guidelines and Essential Medicine List for South Africa[1], which is based on the guidelines for non-cystic fibrosis bronchiectais published in 2010 by *Thorax*, an international journal on respiratory medicine.[2] Amoxicillin/clavulanic acid or clarithromycin (in patients who are allergic to penicillin) are recommended as first line therapy while waiting for the sputum results.[1] These drugs have broad coverage, but do not cover Pseudomonas *aeruginosa*, an organism associated with worse outcomes.[3]

Most of the documented literature on the suitability of empiric antibiotic cover in patients with an acute exacerbation of non-cystic fibrosis bronchiectasis are based on experiences in developed countries. . The data guiding the use of empiric antibiotics in our setting is limited.

1.1.1 Justification for the study

This study will give us better knowledge about the precipitating organisms that cause acute exacerbation in NCF bronchiectasis. Better understanding of this, will help us to adequately treat our patients.

1.2 Bronchiectasis

1.2.1 Definitions

1.2.1.1 Definition of Bronchiectasis

Bronchiectasis is defined as a chronic suppurative pulmonary disease that is characterized by irreversible, pathological dilatation of the small and medium sized bronchi.[4,5] The dilated bronchi frequently contain thick, purulent material, and the more peripheral airways are often occluded by secretions or obliterated and replaced by fibrous tissue.[5,6]

Bronchiectasis can either be diffuse, involving a widespread area of the distal airways, or focal, only involving a limited area or region of the airways.[6]

Due to the high morbidity and mortality of the disease, there is a renewed interest in bronchiectasis, for the purpose of understanding the aetiology, progression and correct treatment of the disease. [7,8]

1.2.1.2 Definition of Acute exacerbation of non-cystic fibrosis Bronchiectasis

The British Thoracic Society defines exacerbation as an increase in at least three of the following respiratory symptoms:

- Cough
- Increase in sputum volume, production, or purulence in sputum.
- Change in sputum viscosity with or without wheezes
- Haemoptysis
- Increased Dyspnoea
- Chest pain

And/ or systemic complains, such as fever, and new infiltrates on chest radiography.[2,4]

1.2.2 Epidemiology

The prevalence of bronchiectasis is not completely known, but most likely varies between different countries.[5,6] Very little data is available of the prevalence of bronchiectasis in South Africa. Given the high prevalence of tuberculosis in our

country[9] (tuberculosis is a risk factor for bronchiectasis)[10], we can argue that South Africa theoretically should have a high incidence of post-infective bronchiectasis[10,11]. Information obtained from independent analyses of ICD codes from two different United States databases showed an increase in prevalence. .[2,4,12] The incidence increased with age and peaked between 80-84 years.[6,13] Approximately two-thirds of patients are women.[2,4,6,13]

Patients with bronchiectasis add a signifianct burden to the healthcare resources, due to an increased number of hospital admissions, clinic visits and expensive investigations. [13]

1.2.3 Pathophysiology

Bronchiectasis is not a disease in its own right, but rather the consequense of a vicious cycle of inflammation, bacterial colonisation and infection.[14] Colonisation of the airways with micro-organisms that cannot be expelled due to different underlying diseases, leads to infection and an inflammory response.[14] The host's response, together with secreted bacterial toxins, cause additional damage (hypersecretion, injury to the respiratory epithelium and impaired mucociliary clearance), which in turn further weakens local resistance.[6,14-16]

The inflammatory response induces epithelial injury, largely as a result of mediators released from neutrophils. [6,14-18] As protection against infection is compromised, the dilated airways become more susceptible to colonization and growth of bacteria.[6,14-16] Thus, reinforcement of the vicious cycle can result, with inflammation producing airway damage, impaired clearance of microorganisms, and further infection.[2,6,14,19]

1.2.4 Aetiology

Various causes for bronchiectasis have been identified in previous studies and are listed in table 1.1 below. [20-22] In 2000 Patreur and colleagues found that even after a rigorous evaluation 53% of casees remained idiopathic.[22] They found post-infective bronchiectasis to be the most common cause of non-cystic fibrosis bronchiectasis.[22]

Table 1.1[20-23]

Category and causes of non-cystic fibrosis bronchiectasis	
Category	**CAUSES**
Post infectious	Viral Bacterial Fungal Atypical Mycobacteria
Immunodeficiency	*Primary* Hypogamma-globulinaemia Congenital agamma-globulinaemia Hyper IgE syndrome *Secondary* Chemotherapy or immuno-suppressive therapy HIV/AIDS Cancer (eg, chronic lymphatic leukaemia)
Auto immune disease / Auto-inflammatory conditions	Rheumatoid arthiritis Sjogren's syndrome Systemic lupus erythematosus Ulcerative colitis or Chron's disease
Congenital conditions	Scoliosis Marfan syndrome Tracheobronchomalacia Williams-Campbell Syndrome Pulmonary sequestration Primary Ciliary dyskinesia Alpha1-antitrypsin deficiency Defective ENaC protein
Asthma	
Allergic bronchopulmonary aspergillosis	
Obstruction	Tumour Foreign object Lymphadenopathy
Aspiration	
Idiopathic	
Other	Yellow nail syndrome Amyloidosis Young's syndrome

1.2.4.1 Post-infective Causes

Several pulmonary infections can cause bronchiectasis.[6,10,20-23] Traditionally, epidemic diseases such as pertussis, measles and tuberculosis have been a major cause of bronchiectasis. This has decreased due to effective vaccination programs and antituberculosis therapy.[24]. In China, several studies have indicated a shift in aetiology from pertussis, measles and tuberculosis to bacterial, mycoplasmal and viral pneumonia during the last 50 years.[24]

The incidence of *Mycobacterium tuberculosis* infections annually is over 9 million.[9]
In developmenting countries tuberculosis is still a dominant cause of bronchiectaisis.[10]
A previous south African study showed obstrutive airway disease in up to 68% of patients with a previous history of pulmonary tuberculosis.[25]

Pulmonary infections that have been implicated, are gram-negative organism (*P. aeruginosa, H. influenzae*), other atypical mycobacteria and viral infections (Paramyxovirus, adenovirus and influenza A/B).[26] There has been a case report documenting severe bronchiectasis in a previously healthy indivuals post Coronavirus disease 2019(COVID-19) infection.[27] Further studies will be of value to see the extent of this complication.

1.2.4.2 HIV and Bronchiectasis

Numerous insults can eventualy lead to bronchiectasis, including recurrent pulmonary infections, chronic aspiration, and congenital or acquired immunode- ficiency syndromes.[28] HIV is associated with an increased risk of tuberculosis, and recurrent viral and bacterial pulmonary infections.[28] However, some data suggest that HIV predisposes to bronchiectasis inde- pendent of infection, likely because of HIV-mediated defects in innate immunity and accompanying airway neutrophilic inflammation.[30]

1.2.5 Diagnosis

Bronchiectasis should be considered in patients that present with a chronic, productive cough[2-4,6,8,9], especially in young, non-smoking patients.[6] Shortness of breath, fatigue and upper respiratory tract symptoms are also commonly present in these patients.[2-4,6,8,9]

Suspicious, but nondiagnostic chest radiographic findings include linear atelectasis, dilated and thickened airways (ie, tram or parallel lines, ring shadows on cross section) and irregular peripheral opacities that may represent mucopurulent plugs.[31]

For definitive diagnosis the gold standard is high resolution computer tomography (HRCT),[2,5,32] which typically shows

(1) Increase in bronchial diameter (signet ring sign).

(2) Lack of tapering of the bronchi.

(3) Increased visibility of small airways in the subpleural region.[32]

Currently bronchiectasis is classified according to the degree of bronchial dilitation, the severity of the bronchiolar obliteration and the number of lobes involved.[33] Three degrees of severity have been described.

The first degree is cylindrical bronchiectasis, with minimal dilatation and smooth and regular outlines.

The second degree is varicose bronchiectasis, the outline is irregular and moderate dilatation of bronchi.

Finally, the third degree is saccular or cystic bronchiectasis, which is progressive dilatation towards the periphery.[32]

The modified reiff score is based on the number of lobes involved.[33] The scoring system of Bhalla et al. is used for the evaluation of the severity of bronchiectasis on HRCT.[33] Bronchiectasis is present when the internal luminal diameter is slightly greater than the adjacent blood vessel, and peribronchial thickening is present when the wall thickness is equal to or larger than the diameter of the adjacent vessel.[32]

It is also of importance to remember that some HRCT changes may be reversible and acute exacerbations should be noted. Shah et al found that airfluid levels, mucus plugging, centrilobular nodules and peribronchial thickening were potentially reversible

findings in symptomatic patients with bronchiectasis[32] Diagnosis of bronchiectasis on imaging should always be investigated further for the underlying cause.[2,4,6]

1.2.6 Microbiome

1.2.6.1 Microbiome in stable and acute exacerbation of bronchiectasis

It is necessary to understand the lung microbiome encountered in patients with bronchiectasis, as it adds to the complexity of treating these patients and understanding how to entepret the results obtained from sputum culture specimens.[35]

It is important to compare the organisms identified in stable patients with NCF bronchiectasis, with those cultured in patients that present with exacerbations.[36,37] Numerous aerobic and anaerobic bacteria have been cultured from the sputa of stable patients.[34,35] The most common organisms cultured were *Haemophilus influenzae, Streptococcus penumoniae, Pseudomonas aeruginosa and , Moxarella catarrhalis*.[36] In adults with acute exacerbation of NCF bronchiectasis, he most common organisms isolated were *Haemophilus influenza* (most common)*, Moxarella catarrhalis, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus pneumoniae* and normal bacterial flora/no growth.[2,4,35,37]There is a high concordance between the organisms cultured in stable patients and in those patients with a non-pneumonia exacerbation.[35] The concordance between organisms cultured in stable patients and pneumonia related exacerbations it is not as high as with non-pneumonia exacerbation.[35] This is particularly important, because we tend to not distinguish between Pneumonia and non-pneumonia exacerbations.[35]

Another interesting feature from the study by Tunney et al. is that there was no significant change in the organism load cultured pre- and post treatment.[38] This is important, as repeated cultures in patients that clinically respond to the treatment of choice might lead to unneccasarily prolonging or escalation of antimicrobals.[37] The contrary is also true, in that a patient not responding to treatment but culturing the same organisms and sensitivity as the initial sample, might need to be covered for an atypical organism or resistant organism.[38]

1.6.2.2 HIV and the possible alteration in the respiratory tract microbiome

Recent studies have shown that, without ART, HIV infection alters the airway microbiome with certain bacetria such as *Tropheryma whipplei, Prevotella* and *Veilonella* that may contribute to airway inflammation.[39] Effective ART appears to reverse these changes. We have very limited data on how this will effect the pathogenic bacteria cultured in acute exacerbation of NCF bronchiectasis and if it will significanty alter our treatment strategies.[39]

1.6.3 Management

Management principles fall into the following modalities:[2]

- Preventative
- Identifiying and treatment of underlying cause
- Education
- Airway clearance
    - Exercise and physiothetapy
- Treatment of exacerbation
    - Antibiotic drug therapy
    - Bronchodilation and anti-inflammotary
- Surgical management
- Management of complications

1.6.3.2 Prevention

Preventative strageties in the treatment of acute exacerbations of bronciectasis forms a big part of our approach to acute exacerbations..[2] As repeated exacerbations reinforce the viscous cycle descriped in the pathophysiology.[2,6]. Two important preventative strageties are teaching patients adequate airway clearance techniques and routine vaccinations.[36] It is essential to involve respiratory physiotherapists to educate and teach individuals with bronchiectasis airway clearance techniques and if

appropriate to give advice on adjuncts (exercise or oral/inhaled theraphy) that might assist in enhancing their chosen airway clearance technique.[36]

There are no randomised controlled trials evaluating the impact of annual influenza vaccination on respiratory exacerbations and pulmonary decline in adults with bronchiectasis. Potential benefits of influenza vaccination is derived from studies of patients with chronic obstructive pulmonary disease.[36]
There is limited evidence supporting the use of 23 valent pneumococcal vaccine to prevent exacerbations of bronchiectasis. A metanylasis of random control trials supported the use of 23 valent pneumococcal vaccine I reducing the rate of all causes pneumonia.[36]

1.6.3.3 Antibiotic therapy in exacerbations

The aim will be to limit disease progression, through identifying and treating acute infective exacerbations early on with appropriate anti-microbials.[2,4,36] Thus it is of paramount importance to know which organisms are commonly the cause of acute exacerbations, so that the condition can be treated accordingly.[2,35,36]

As mentioned the most common organisms cultured were *Haemophilus influenzae, Streptococcus penumoniae, Pseudomonas aeruginosa and , Moxarella catarrhalis*.[36]
The treatment approach at our facility for patients presenting with an exacerbation is in line with published guidelines.[1,2] The first line of treatment, while waiting for the sputum culture, is amoxicillin/clavilanic acid or clarithromycin (in patients that are penicillin-allergic).[1] This combination covers the organisms most commonly cultured, but not P. aeruginosa, an organism associated with worse outcomes.[3]

Most of the documented literature on the suitability of empiric antibiotic cover in patients with an acute exacerbation of NCF bronchiectasis is based on experiences from developed countries. The data guiding the use of empiric antibiotics in our setting is limited.[1,2]

1.6.3.4 The goal of bronchiectasis management

The following is the main goals when treating bronchiectasis:[2]

- Prevent disease progression
- Maintain and improve pulmonary function
- Reduce exacerbations
- Improve quality of life

1.7 Aim and Objectives

1.7.2 Aims

To document the bacteria cultured in patients who present to Helen Joseph Hospital with acute exacerbations of non-cystic fibrosis bronchiectasis.

1.7.3 Objectives

1. To identify the common bacteria cultured from the sputum samples of patients presenting with acute exacerbations of non-cystic fibrosis bronchiectasis at the Helen Joseph Hospital.
2. Determine if the current standard treatment guidelines' first line antibiotic therapy is appropriate for the bacteria cultured in our patients presenting with acute exacerbations of non-cystic fibrosis bronchiectasis.

1.8 Study Design and Methodology

1.8.2 Study Design

This will be a prospective cohort study.

1.8.3 Study Setting

The study will take place in Helen Joseph Hospital, a tertiary public hospital in Johannesburg, South Africa. All patients presenting with acute exacerbation of non-cystic fibrosis bronchiectasis will be referred to the pulmonology registrar.

1.8.4 Study Population

The study population will be composed of all patients aged 18 and older admitted to Helen Joseph Hospital with acute exacerbation of non-cystic fibrosis bronchiectasis.
The diagnosis of bronchiectasis will be based on a combination of clinical manifestations, chest radiography and HRCT of the chest. [4]
Suspected bronchiectasis criteria will be the following.

- Patients with a chronic cough most days of the week, production of mucopurulent and tenacious sputum most days of the week for months to years, and a history of exacerbations. Particularly partients with relevant associated risk factors.[2]
- Chest radiograph: Suspicious, but nondiagnostic radiographic findings include linear atelectasis, dilated and thickened airways (ie, tram or parallel lines, ring shadows on cross section) and irregular peripheral opacities that may represent mucopurulent plugs.[28]

Definite diagnosis or confirmation of suspected diagnosis will be made by HRCT.[2,4]

Patients with known cystic fibrosis will be excluded from the study.

1.8.5 Methods of assessment or Measurement

Three sputum samples will be taken on admission from all the patients presenting with acute exacerbation of non-cystic fibrosis bronchiectasis. Sputum samples will be obtained prior to the initiation of antibiotics. All the samples will be sent to the National Health Laboratory Service (NHLS). The samples will be tested for tuberculosis using GeneXpert, microscopy for acid-fast bacilli and culture. A Bartlett score and bacterial microscopy, culture and sensitivity will also be performed. These investigations are part of the normal standard of care as described in the National Department of Health Standard Treatment Guidelines.[1]

The researcher will advise the attending doctor of any results that may change or impact on patient management.

1.8.6 Outcome measures

The primary outcome of this study is toto identify the common bacteria cultured in our study population.

The second outcome will give us more information about the correct empiric treatment that needs to be given, and if the standard treatment guidelines are sufficient.

1.9 Data Collection

- After obtaining approval from the Ethics Committee of the Faculty of Health Sciences to conduct this study, WITS, and the superintendent of Helen Joseph Hospital, the research will be registered on the National Health Research Database (NHRD), and this prospective study will be commenced over a period of 12 months.
- Patients presenting to Helen Joseph hospital with acute exacerbation of non-cystic fibrosis bronchiectasis during this time, will be identified by the admitting registrar and referred to the registrar working in pulmonology at the time. The researcher will also ask the registrars that are rotating through Helen Joseph Hospital to inform her of any such cases.

- Any patient aged18 years and older, fulfilling the criteria for acute exacerbation of bronchiectasis, as previously defined, will be referred to the researcher and pulmonology registrar.
- The study will be presented to the consultants working at Helen Joseph Hospital, requesting their assistance in identifying patients who will qualify for the study.
- During this period, the researcher will put in a special request to rotate, to try to have most of her rotations at Helen Joseph Hospital, so as to be able to help with the data collection.
- Patients will be assessed for the following:
    - Severity according to the CURB 65 score
    - Possible etiology of bronchiectasis
    - Possible Trigger of acute exacerbation
    - Sex and age of the patient
    - HIV status
    - Previous PTB
    - Smoker or non-smoker
- Three sputum samples will be sent to NHLS for MCS, AFB and mycobacterial culture and GXP respectively. The sputum will be collected prior to the initiation of antibiotic therapy.

1.10 Statistical analysis

Data will be captured on the data sheet (appendix A3), transferred to an Excel spreadsheet and accuracy will be verified before statistical analysis. The organisms cultured will be analyzed and, where possible, stratified. Results will be summarized

as medians for numerical variables, or frequencies and percentages for categorical variables.

1.11 Ethics

Data collection will only start after approval has been obtained from the Ethics Committee of the Faculty of Health Sciences of the University of the Witwatersrand, and the superintendent of Helen Joseph Hospital. Clearance number – M180555 (appendix B)

Consent will be obtained from the identified patients. Data collected will be anonymized and completed**.** Confidentiality will be maintained at all times. All data will be kept in a secure location and the names and file numbers will be assigned a number on a restricted access Excel document.

1.12 Study Limitations

1) We are relying on colleagues to inform us, when a patient presented with acute exacerbation of bronchiectasis. It is possible that not all patients that presents will be referred to us.
2) Bronchiectasis will be suspected with a relevant history, clinical examination and chest X-ray. All the patients will assessed by the pulmonology department. As the gold standard for diagnosis of bronchiectasis is HRCT[4], there is a possibility that some of the patients will be wrongly diagnosed at the time of presentation and on review of further investigations done as an outpatient, the diagnosis might change. A diagnosis of bronchiectasis may be difficult in patients presenting to us for the first time with acute infective symptoms. Also, there might be patients presenting with acute exacerbation of bronchiectasis that are missed by admitting doctors.
3) Studies have shown that sputum samples sensitivity and specificity vary substantially in different settings and the 2007 IDSA/ATS consensus guidelines recognise the limitations of sputum Gram stain and culture.[2]
4) We will only looked at bacterial organisms cultured as the cause for the acute exacerbation and not atypical bacteria, viral infections or other triggers.[40]

5) As the study will only include patients presenting to the Helen Joseph Hospital, a secondary/tertiary hospital, there is likely to be a bias in that we will be 'excluding' patient who present with mild disease to primary care clinics and level one hospitals.

1.13 Timing

Gant Chart showing the timeline of the study:

2018	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec
Literature Review												
Preparing Protocol												
Protocol Assessment												
Ethics Application												
Data Collection												
Data Analysis												

2019	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec
Data Collection												
Data Analysis												

2020	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec
Data Analysis												
Write Up												

2021	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec
Write Up												
Request to add a supervisor												
Nomination of examinaer												
Submit for marking												
Corrections and resubmittion												

1.14 Funding

Study expenses were self-funded, and these costs included stationary, printing and transport. Courses offered by the University to assist with knowledge on data analysis and writing up of the thesis were attended.

1.16 References

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Chapter 2: SUBMISSIBLE ARTICLE

TITLE: BACTERIA ISOLATED FROM THE AIRWAYS OF PATIENTS PRESENTING WITH AN ACUTE EXACERBATION OF NON-CYSTIC FIBROSIS BRONCHIECTASIS: A PROSPECTIVE STUDY

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Short title: Bacteria cultured form the airways of patients presenting with Acute Exacerbation of Bronchiectasis.

Conflict of Interest: Nil

Keywords: Bacteria,, Acute Exacerbation of Bronchiectasis

Word count: 5118

Abstract word count: 416

Abstract

Background:

There is little information available on the precipitating bacteria in acute exacerbation of bronchiectasis in developing countries. The Standard treatment guidelines and essential medicine list for South Africa's[24], recommendations for treating acute exacerbation of bronchiectasis relies on data from non-developing countries, which may not reflect the South African situation. Therefore a study was preformed to identify the most common bacteria occuring in our setting and determine the appropriateness of the current recommended empiric antibiotic choices. Empiric therapy that is currently based on the Guidelines for non-cystic fibrosis Bronchiectais published in 2010 by *Thorax*, an International journal on respiratory medicine.[18]

Objective*:*

1. Identify and document the frequency of bacteria cultured from the sputum samples of patients presenting with acute exacerbation of non-cystic fibrosis bronchiectasis at the Helen Joseph Hospital.
2. Determine the appropriateness of current standard treatment guidelines' first line antibiotic choices for the bacteria cultured in our patients that present with acute exacerbation of non-cystic fibrosis bronchiectasis.

Methods:

A prospective cohort study of 81 patients that presented with acute exacerbation of non-cystic fibrosis bronchiectasis. The diagnosis of bronchiectasis was suspected on a combination of clinical manifestations and chest radiography. Where possible definite diagnosis or confirmation of suspected diagnosis was made by High Resolution Computed Tomography (HRCT). Patients was classified as definite or suspected bronchiectasis, if outpatient HRCT was still pending.

Three sputum samples were collected on admission from these patients. The sputum samples were obtained prior to the initiation of antibiotics. The samples were tested

for Tuberculosis using Gene Expert, Acid-Fast Bacillus microscopy and culture. A Bartlett score and bacterial microscopy, culture and sensitivity was also performed. (These investigations are part of the normal standard of care as described in the National Department of Health Standard Treatment Guidelines and Essential medicine list.[24])

Results:

A pathogenic bacteria was isolated in only 30% of cases. The most common bacteria cultured from the sputum samples of patients presenting with acute exacerbation of non-cystic fibrosis bronchiectasis were *Haemophilus influenzae (7.4%), Pseudomonas aeruginosa (4.9%), Klebsiella pneumoniae (3.7%), Escherichia coli (1.2%) and Acinetobacter baumannii* (1.2%). Of the subjects 74% had *Mycobacterium tuberculosis* isolated from their sputum.
The majority (60%) of the pathogenic bacteria isolated were sensitive to the first line antimicrobials recommended.

Conclusion:

The most common bacteria cultured from the sputum samples of patients presenting with acute exacerbation of non-cystic fibrosis bronchiectasis at the Helen Joseph Hospital are comparable to studies done in developed countries.[3,6,23]
Since our yield of positive cultures was lower than that obtained in other studies, there will be value in repeating this study on a larger scale.

The results suggest that the current South African treatment guidelines are appropriate for the treatment of acute exacerbation of bronchiectasis in our setting, as more then 60% of the pathogenic bacteria were sensitive to the fist line antimicrobial prescribed.

Introduction

Bronchiectasis is defined as a chronic suppurative pulmonary disease that is characterized by irreversible, pathological dilatation of the small and medium sized bronchi.[1,2] The dilated bronchi frequently contain thick, purulent material, and the more peripheral airways are often occluded by secretions or obliterated and replaced by fibrous tissue.[3,4]

The British Thoracic Society defines an exacerbation of bronchiectasis as an increase in at least three of the following respiratory symptoms:

- Cough
- Increase in sputum volume, production, or purulence in sputum.
- Change in sputum viscosity with or without wheezes
- Haemoptysis
- Increased Dyspnoea
- Chest pain

and/ or systemic complains, such as fever, and new infiltrates on chest radiography.[2,5]

The prevalence of bronchiectasis is not well described.[3,4] Information obtained from independent analyses from two American databases showed an increase in prevalence over a 7 year period from 2000-2007.[2,3,6] This analysis revealed an increase in incidence with age and a higher prevalence amongst women.[6] Patients with bronchiectasis add a signifianct burden to the healthcare resources, due to an increased number of hospital admissions, clinic visits and expensive investigations.[7]

Bronchiectasis is not a disease in its own right, but rather the consequense of a vicious cycle of inflammation, bacterial colonisation and infection.[8] Colonisation of the airways with micro-organisms that cannot be expelled due to different underlying diseases, leads to infection and inflammory response.[8.] The host's response, together with

secreted bacterial toxins, cause additional damage (hypersecretion, injury to the respiratory epithelium and impaired mucociliary clearance), which in turn further weakens local resistance.[3,9-13] The inflammatory response induces epithelial injury, largely as a result of mediators released from neutrophils.[9-13] As protection against infection is compromised, the dilated airways become more susceptible to colonization and growth of bacteria.[3,9-14] Thus, reinforcement of the vicious cycle can result, with inflammation producing airway damage, impaired clearance of microorganisms, and further infection.[8]

Bronchiectasis should be considered in patients that present with a chronic, productive cough,[1,2,4] especially in young, non-smoking patients.[4] Shortness of breath, fatigue and upper respiratory tract symptoms are also commonly present in these patients.[2,4] Suspicious, but nondiagnostic chest radiographic findings include linear atelectasis, dilated and thickened airways (ie, tram or parallel lines, ring shadows on cross section) and irregular peripheral opacities that may represent mucopurulent plugs.[15]
The Gold standard for diagnosis is HRCT on these patients,[3,4,16] which typically shows (1) Increase in bronchial diameter (signet ring sign). (2) Lack of tapering of the bronchi. (3) Increased visibility of small airways in the subpleural region.[17]
Some HRCT changes may be reversible and acute exacerbations should be noted.[17]
A diagnosis of bronchiectasis based on imaging should always be investigated further for the underlying cause.[2]

The aim in managing these patients is to limit disease progression, therefore we need to identify and treat acute infective exacerbations early on with the appropriate anti-microbials.[1,2,18] It is of paramount importance to know which bacteria are commonly implicated in acute exacerbations, so that we can treat the condition accordingly.[2,18-23] Studies previously done in adult patients with non cystic fibrosis (NCF) bronchiestasis have shown the commonest organisms cultured are *H. influenza* (most common)*, Moxarella catarrhalis, Pseudomonas aeruginosa, Staphylococcus aureus and, Streptococcus pneumoniae*.[1,2,18,20] King et al. correlated clinical features with organisms identified and concluded that *Pseudomonas aeruginosa was associated with more severe disease.*[1]

Our institution treatment guidelines for the treatment of exacerbations is in line with published recommendations.[2,18,24] These guidelines are based on data obtained in developed countries.[2,18] There is minimal data on the adequacy of our empiric antibiotic recommendations, and this study aims to assist in acquiring data relevant to our setting.

Methods

This study was a prospective cohort study done at Helen Joseph Hospital, a tertiary public hospital in Johannesburg, South Africa. The study evaluated patients that presented with an acute exacerbation of bronchiectasis. The data was collected over a time period of one year, from August 2018 to August 2019. The study population comprised of adults (above the age of 18 years) that presented with acute exacerbation of NCF bronchiectasis.

Bronchiectasis was suspected in patients with: relevant associated risk factors; a chronic cough most days of the week; production of mucopurulent and tenacious sputum most days of the week for months to years, and a history of exacerbations.[2,16,19] Suspicious radiographic findings included linear atelectasis, dilated and thickened airways (ie, tram or parallel lines, ring shadows on cross section) and irregular peripheral opacities that may represent mucopurulent plugs.[15]

Definite diagnosis was made by HRCT.

Patients with cystic fibrosis were excluded from the study.

Due to limited resources, patients with a clear history of previous pulmonary tuberculosis, clinical examination and CXR findings consistent with a diagnosis of bronchiectasis did not have confirmatory HRCT of the chest done as an inpatient. These patients were followed-up at the pulmonology outpatient department and referred for a HRCT. Patients that did not have a confirmatory HRCT were classified as suspected bronchiectasis.

Expectorated sputum samples were collected on admission from all patients and sent to the National Health Laboratory Service (NHLS). All samples were collected prior to the initiation of antimicrobial therapy. The samples were tested for tuberculosis using

Genexpert, microscopy for acid-fast bacilli and culture. A Bartlett score and bacterial microscopy, culture and sensitivity were also performed. (These investigations are part of the normal standard of care as described in the National Department of Health Standard Treatment Guidelines.[24])

This study was approved by the University of Witwatersrand Medical Human Research Ethics Committee (Ethics clearance number - M180555).

Measurements

Demographic, clinical information, as well biochemical and microbiological laboratory parameters and radiographic investigations were collected from each of the patient's file. The presence or absence of co-morbidities as well as a history of previous lung pathologies and previous exacerbations was noted. Additional information was gathered on how the diagnosis of bronchiectasis was made.

These patients were seen and assessed by the pulmonology team in order to assure that the correct diagnosis was made.

Statistical analysis

All samples collected from patients were included in the analysis. Some patients had multiple exacerbations during the study period and therefore had multiple samples. Data were entered onto an Excel spreadsheet, version 2016 (Microsoft, USA). Data were summarised using proportions and percentage for categorical variables, mean and SD for normally distributed continuous variables and median and inter-quartile range (IQR) for non-normal continuous variables. The Fisher's exact test was used for categorical variables and paired T-tests for comparison of means. Differences were statistically significant when the p-value was <0.05.

Results

Eighty-eight patients with non-CF bronchiectasis presented to HJH with an acute exacerbation episode during the study period. Seven patients were excluded from the study four patients did not provide consent for enrolment into the study and in three patients the sputum specimens were lost (Figure 1).

A total of eighty-one patients were included in this study, demographic data are shown in Table 2.1. The mean (SD) age of the group was 49.2 (14.8) years, the majority of the patients were male (55.6%) and most patients were of African descent (84%). Forty-three of the eighty-one subjects had a history of smoking, 19 were still smoking at the time of presentation and only 3 reported smoking additional drugs, e.g. marijuana. The majority (65 patients) in this cohort were classified as having post-infective bronchiectasis, as 65 patients reported to have had previous tuberculosis. (Table 2.2) Nine individuals had no history of previous tuberculosis but did report a history of previous severe pneumonia. Four had a previous diagnosis of Chronic Obstructive Pulmonary Disease. Seven of the eighty-one patients had no history or known precipitating factor for their bronchiectasis, with a negative work-up and thus classified as idiopathic.

Of the forty-five subjects that were HIV reactive, we only obtained CD4 count on 40 of these subjects and viral loads on 36 subjects.

The median CD4 count and viral load were 93 cells/μL (range 37.5-411.0) and 631 copies/ml (range 20 – 68 050) respectively.

Pathogenic organisms were found in 31% of the HIV-reactive group, of which only two sputum cultures were positive for *Mycobacterium tuberculosis*.

In forty-four of the eighty-one subjects' the diagnosis of bronchiectasis was confirmed on a HRCT and in thirty-seven the diagnosis was suspected on chest radiography, clinical assessment and a history of previous pulmonary tuberculosis or previous severe pneumonia. The subjects were divided into two groups, the forty-four subjects that had a HRCT of the chest were classified as definite bronchiectasis. The remaining thirty-seven subjects that did not have their confirmatory HRCT yet were classified as suspected bronchiectasis. Twenty-seven of the thirty-seven subjects in the suspected

group had a clear history of previous pulmonary tuberculosis. A further seven had a history of severe pneumonia, that preceded the history of a chronic cough. Only three patients in the suspected group had no clear history that might allude to the cause of their bronchiectasis. All three of these patients had a localised area on their CXR that was thought to be suggestive of focal bronchiectasis.

Three sputum samples were collected on admission from sixty-seven of the subjects and send for microscopy, culture and sensitivity, GeneXpert and TB culture, in fourteen subjects, tuberculosis cultures were not received and two subjects had no GeneXpert or TB culture logged.

Pathogenic organisms were identified in 30% of the samples. The most commonly isolated organisms were *Haemophilus influenzae (7.4%), Mycobacterium tuberculosis* (7.4%)*, Candida albicans (6.2%), Pseudomonas aeruginosa (4.9%) and Klebsiella pneumoniae(3.7%)* The remaining *3.7%* comprised *of Escherichia coli, Acinetobacter baumannii* and *Aspergillus fumigata.*

In the definite bronchiectasis group, 76% showed normal flora, with only 23% culturing specific organisms. The distribution of organisms was as follow: *Haemophilus influenzae (6.8%), Mycobacterium tuberculosis* (6.8%)*, Candida albicans (4.5%), Pseudomonas aeruginosa (4.5%), and other organisms (2.3%). Klebsiella pneumoniae* was not cultured in this group.

In the suspected bronchiectasis group, 65% showed normal flora, with 35% showing positive cultures. Organisms cultured included *Haemophilus Influenzae (8.1%), Klebsiella Pneumoniae (8.1%), Mycobacterium tuberculosis* (5.4%)*, Candida albicans (5.4%), Pseudomonas aeruginosa (5.4%), and other organisms (2.3%). (Figure 3)*

All cultures that grew *Haemophilus influenza* were sensitive to ampicillin/amoxicillin. *Pseudomonas aeruginosa* was predominately sensitive to piperacillin/tazobactum, with only 25% sensitive to ceftazidime and cefepime. Two-thirds of the *Klebsiella pneumonia* cultures were sensitive to Amoxicillin-clavulanic acid, a third was sensitive to Cefepime. (Figure 2 andTable 3)

Mycobacterium tuberculosis was one of the most common organisms isolated in this cohort of patients. Two patients had positive tuberculosis GeneXpert results, but contaminated tuberculosis cultures. There results were not added to our statistics as active infection was not confirmed. Mycobacterium tuberculosis was found in both the suspected and definite bronchiectasis groups. Positive cultures were 6.8% and 5.4% respectively in the two groups. The patients in the definite bronchiectasis group, that cultured Mycobacterium tuberculosis, had HRCTs prior to this acute exacerbation episode. Also of note was that all of them had previous sputum cultures on the system that excluded active *Mycobacterium tuberculosis* as a pathogenic organism of their previous acute exacerbation episodes.

In the suspected bronchiectasis group, we unfortunately did not have prior HRCTs. All the patients had a relevant history of recurrent lower respiratory tract infections over the last few years. They also had previous sputum cultures that excluded active pulmonary tuberculosis, during the mentioned episodes. The majority of *Mycobacterium tuberculosis* cultured were sensitive to Rifampicin, with only 17% of the culture indeterminate and no multi-resistant strains. Among the HIV-reactive group, positive cultures for *Mycobacterium tuberculosis* were seen in 4.4%.

Discussion

The objectives of this study were to identify the most common bacteria cultured from the sputum samples of patients presenting with acute exacerbation of NCF bronchiectasis to Helen Joseph Hospital and the appropriateness of our current empiric antibiotic choices. Unfortunately, our sputum culture yield was low (30%). This low yield could in part be attributed to the quality of sputum specimens submitted. This low figure is however, in keeping with the sputum culture positivity rate in a Taiwanese study of patients with bronchiectasis. Their culture yield was 17.9%.[25]

Haemophilus influenzae was the most common organism cultured in both the definite (6.8%) and suspected bronchiectasis groups (8.1%). The presence of haemophilus species in patients with bronchiectasis has been well documented.[26]

Mycobacterium tuberculosis was one of the most common organisms isolated in this cohort of patients, consistent with the high prevalence of tuberculosis in South Africa.[27] Pulmonary tuberculosis is not commonly described in acute exacerbations of NCF bronchiectasis, but there is some literature describing the presence of *Mycobacterium tuberculosis* in acute exacerbations.[28] Our findings are consistent with those of Dhar et al.[29] Their study was conducted in India, a low-middle income country, similar to South Africa. In their cohort of 2195 patients with confirmed bronchiectasis, 6.4% had active tuberculosis.[29] In the definite bronchiectasis group, three patients had *Mycobacterium tuberculosis* isolated. It is of note that all three of these patients had HRCT done a few years prior to this admission, thereby confirming the diagnosis of bronchiectasis and implicating *Mycobacterium tuberculosis* as the cause for the acute exacerbation. Patients with underlying lung disease are at a greater risk of contracting pulmonary tuberculosis.[30] Three patients in the suspected bronchiectasis group had *Mycobacterium tuberculosis* isolated. The parenchymal changes may well have been due to active tuberculosis rather than pre-existing bronchiectasis. All three of these patients had a history of recurrent pulmonary infections, requiring hospital admission and multiple sputum samples submitted to the NHLS lab. None of the sputum samples submitted in the preceding years isolated *Mycobacterium tuberculosis*.

There was no statistical difference between HIV-infected and HIV-uninfected patients when comparing the number of positive and negative bacterial cultures, or the type of organisms cultured.

Of note is that *Candida albicans* was the third most common organism isolated in our cohort of patients. Primary pneumonia caused by a *Candida species* is extremely rare, and the results here suggest oropharyngeal colonization, rather than the organism being a true cause of the exacerbation.[31] In one study it was shown that *Candida albicans* are frequently isolated in patients with non-CF bronchiectasis, and is was associated with long-term antibiotics.[31] In our patients that isolated *Candida albicans* there were no association with HIV status of the patient or the severity of the exacerbation.

Previous studies have shown high organism loads in stable patients.[19,20] In our sputum samples that cultured normal flora, almost one third (32%) had Bartlett scores of 0 and

less. The poor quality of our sputum samples can account for the low yield of pathogenic bacteria cultured. It is important to note that we cannot always presume that the organisms cultured in these patients is responsible for the exacerbation.[21] We should distinguish between patients that present with a pneumonia related exacerbation versus non-pneumonia related exacerbations.[21]

Sixty per cent of the organisms cultured were sensitive to either ampicillin/amoxicillin or amoxicillin-clavulanic acid. The Standard Treatment Guidelines recommend this combination as empiric therapy in exacerbations of bronchiectasis.[24]

Study limitations

Unfortunately, there are several limitations to this study. Firstly, we were relying on colleagues to inform us of appropriate patients, and it is possible that not all patients that presented were referred to us. Some patients may not have been included due to an incorrect diagnosis.

Secondly, only 54% of the patients had a definitive diagnosis based on HRCT. In the remainder of the cohort the diagnosis was suspected based on one or more of the following criteria: a previous history of tuberculosis infection, clinical examination, and chest X-ray. All the patients were evaluated by the pulmonology department.

Thirdly, studies have shown that sputum samples sensitivity and specificity vary substantially in different settings and the 2007 IDSA/ATS consensus guidelines recognise the limitations of sputum Gram stain and culture.[32] Not all sputum samples collected were of an adequate quality, and by the time the microscopy results were reported the patients already received a few doses of antibiotics. So further samples could not be obtained.

Fourthly, we looked predominantly at typical bacterial causes for the exacerbations and did not exclude viral triggered exacerbations or atypical bacteria.

We could have very likely cultured organisms that colonised the airways of these patient and were not the cause of the exacerbation.[33]

Lastly, we only included patients that presented to Helen Joseph Hospital, a secondary/tertiary hospital, thus excluding patients who presented with mild disease to the primary care clinics and hospitals.
Lastly, we only patients that presented to Helen Joseph Hospital, a secondary/tertiary hospital form part of the study population. Likely missing most of the patient who presented with only mild disease to the primary clinics and hospitals.

Conclusion

The most common bacteria cultured from the sputum samples of patients presenting with acute exacerbation of non-cystic fibrosis bronchiectasis at the Helen Joseph Hospital, were *Haemophilus influenzae (7.4%), Pseudomonas aeruginosa (4.9%), Klebsiella pneumoniae (3.7%), Escherichia coli (1.2%) and Acinetobacter baumannii* (1,2%). This is comparable to studies done in developed countries.

Our findings suggest that current empiric antimicrobials that will cover over 60% of the pathogenic bacteria that we identified and are therefore adequate. The guidelines suggest strategies that cover the four main goals in the treatment of bronchiectasis and should be adhered to.[18]

There is still much for us to learn and discover in the treatment and prevention of acute exacerbation of non-cystic fibrosis bronchiectasis, especially concerning the airway microbiota in these patients and further studies to explore this are necessary.

Figure 2.1: A Flow diagram describing creation of analytical dataset

A Flow diagram describing creation of analytical dataset

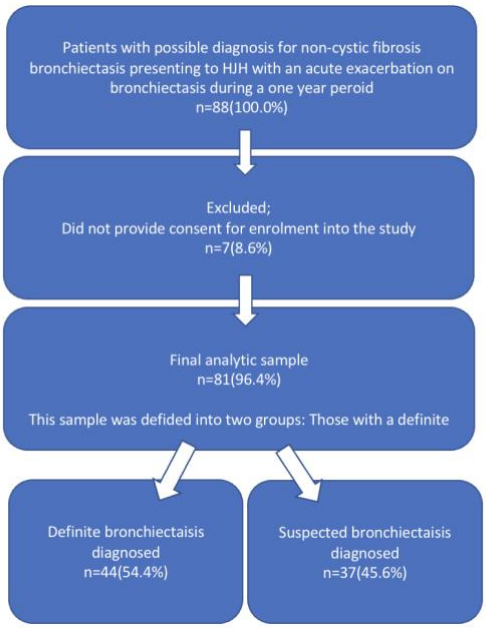


Table 2.1: Socio-demographic data of patients

Socio-demographic Characteristic	N (%)	Socio-demographic Characteristic	N (%)
Age (Years)		**Smoking status (Ever)**	
Mean (SD)	*49.2 (14.8)*	**Non smoker**	38 (46.9%)
<30	9 (11.1%)	**Smoker**	43 (53.1%)
30-<40	15 (18.5%)	**Substance smoked**	
40-<50	16 (19.8%)	**Cigarettes**	40 (93.0%)
≥50	41 (50.6%)	**Cigarettes and marijuana**	3 (7.0%)
Sex		**Smoking pack years**	
Male	45 (55.6%)	**0-4**	15 (34.9%)
Female	36 (44.4%)	**5-9**	8 (18.6%)
Race		**10-14**	17 (39.5%)
African	68 (84.0%)	**≥15**	3 (7.0%)
Other	13 (16.0%)	**Current smoking status**	
Employment history		**Stopped smoking**	24 (55.8%)
Unemployed	31 (38.3%)	**Current smoker**	19 (44.2%)
Employed	50 (61.7%)		

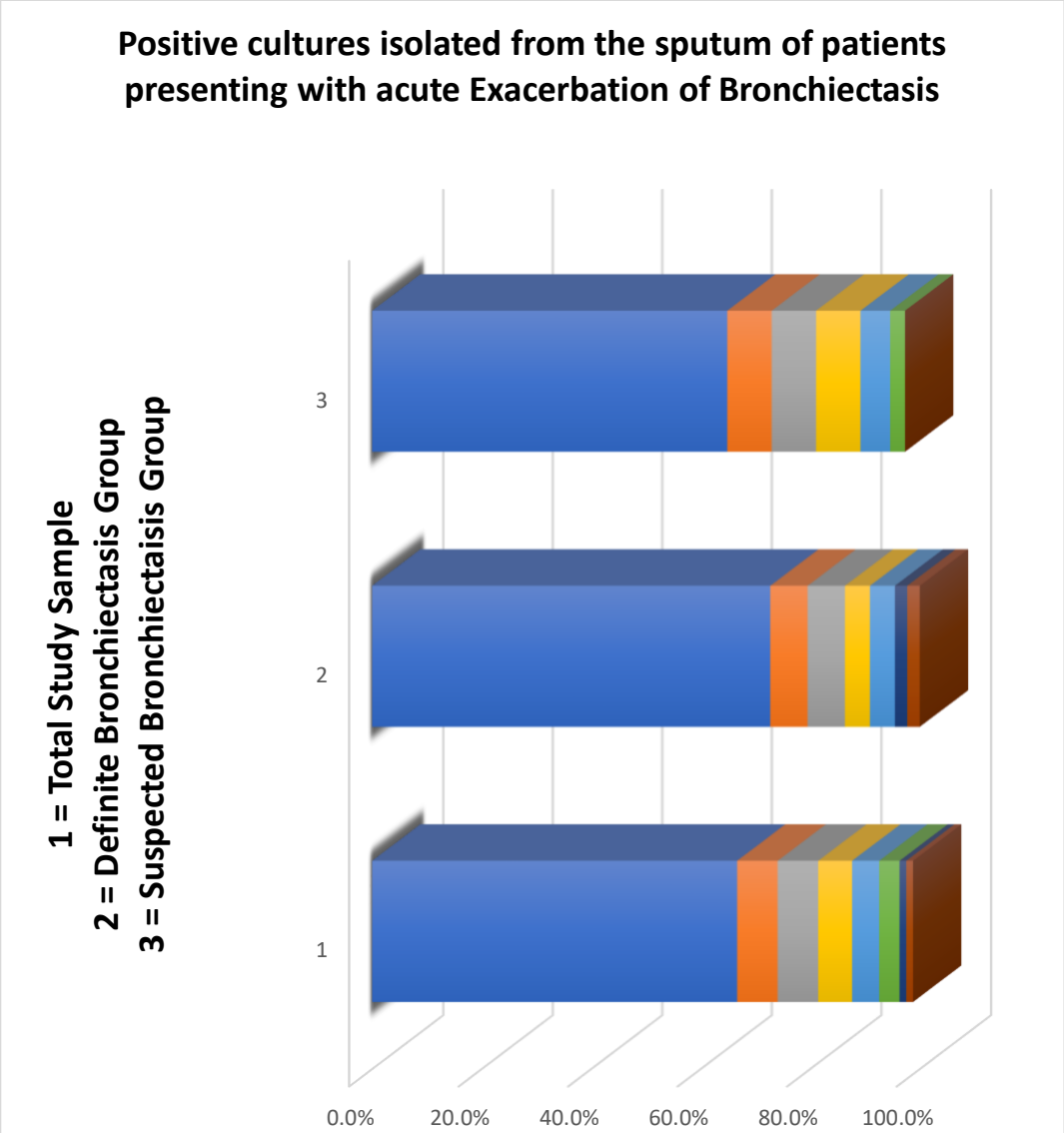
Abbreviation (s): SD, standard deviation

Table 2.2: Clinical characteristics of patients

Clinical Charactaristics	N (%)	Clinical Charactaristics	N (%)
HIV status		**Previous TB diagnosis made (according to patients history)**	
HIV negative	36 (44.4%)	**Chest x ray**	11 (16.9%)
HIV positive	45 (55.6%)	**Clinically suspected**	10 (15.4%)
CD4 count (cells/ µL)		**Sputum**	43 (66.2%)
Median (IQR)	*93.0 (37.5-411.0)*	**Unknown**	1 (1.5%)
<200	23 (51.1%)	**Previous history of severe pneumonia**	
200-<350	6 (13.3%)	**No**	25 (32.0%)
≥350	11 (24.4%)	**Yes**	53 (68.0%)
Unknown	5 (11.1%)	**Bronchiectasis Staging* (MMRC Score)**	
Viral load (copies/mL)		**Moderate**	19 (23.5%)
Median (IQR)	*631 (20- 68 050)*	**Severe**	61 (75.3%)
<50	14 (31.1%)	**Unknown**	1 (1.2%)
50-<1 000	6 (13.3%)	**Bronchiectasis diagnosis based on**	
≥1 000	16 (35.6%)	**CT**	44 (54.3%)
Unknown	9 (20.0%)	**CXR and Clinical**	37 (45.7%)
TB history			
No TB	16 (19.8%)		
Had TB	65 (80.3%)		
Site of TB			
Pulmonary TB	65 (100.0%)		

Abbreviation (s): QR, interquartile range; mL, millilitre; TB, tuberculosis; mMRC,-modified Medical Research Counsil Dysnpnea score; *moderate disease= MMRC score <2.0, severe disease= MMRC score ≥2.0;

Figure 2.2: Organisms isolated from the sputum cultures of patients in both the definite bronchiectasis and the bronchiectasis groups

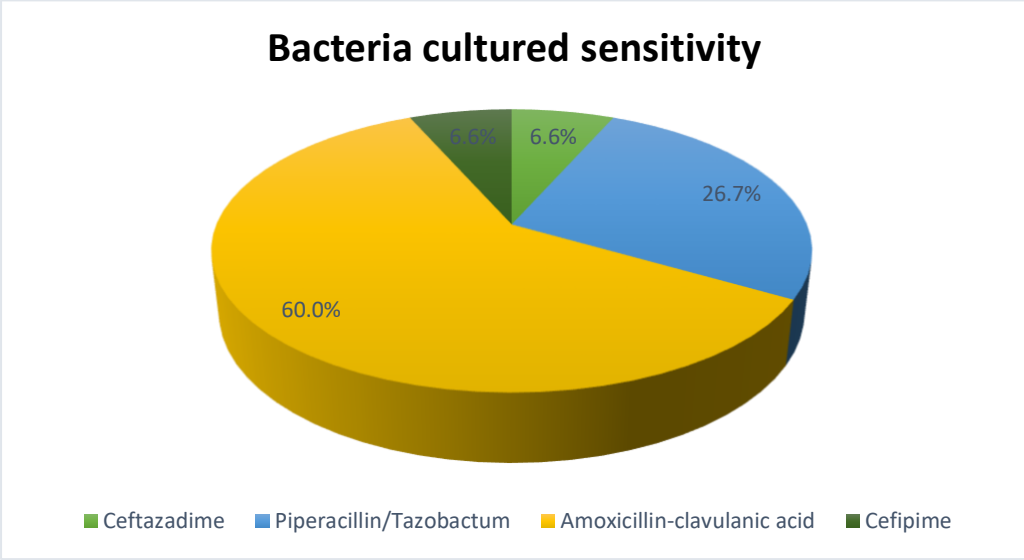


	1	2	3
Normal flora	66.7%	72.7%	64.9%
Haemophilus Influenza	7.4%	6.8%	8.1%
Mycobacterium Tuberculosis	7.4%	6.8%	8.1%
Candida Albicans	6.2%	4.5%	8.1%
Pseudomonas Aergunosa	4.9%	4.5%	5.4%
Klebsiella Pneumoniae	3.7%	0.0%	2.7%
Eshericia Coli	1.2%	2.3%	0.0%
Acinetobacter Baumannii	1.2%	2.3%	0.0%

Table 2.3: The Sensitivity of the Bacteria cultured

	Sensitivity of organisms Cultured	
	Total Study Sample	
Organisms	**Sensitivity**	**Number of cultures**
Haemophilus Influenza	Ampicillin/Amoxicillin	6
Pseudomonas Aergunosa	Ceftazadime	1
Pseudomonas Aergunosa	Piperacillin/Tazobactum	3
Klebsiella Pneumoniae	Amoxicillin-clavulanic acid	2
Klebsiella Pneumoniae	Cefipime	1
Eshericia Coli	Amoxicillin-clavulanic acid	1
Acinetobacter Baumannii	Piperacillin/Tazobactum	1

Figure 2.3: The cultured bacteria's overall sensitivity to specific antibiotics



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Chapter 3: Appendixes

Appendix A1: Patient consent form

Faculty of Health Sciences

University of the Witwatersrand

Study title: Bacteria isolated from the airways of patient presenting with an acute exacerbation of non-cystic fibrosis bronchiectasis : A prospective study

This consent form and data collected will be stored by the researcher for a period of two years post publication of results, or for 6 years if there is no publication.
If you have any questions about the study feel free to contact me at 011 489 1011 / 072 581 6667.
If you have any questions or complaints about the research process you may contact Human research Ethics Committee admin office at 011 717 1234.

My name is Dr Magdel Strydom and I am conducting a research study for my MMed qualification in internal medicine at the University at Witwatersrand. Your doctor suspects that you may have damaged lungs and that you now have an infection in your lungs. You are therefore being asked to take part in this research study looking at the types of bacteria that causes infections in damaged lungs.

Please read this form carefully before agreeing to take part in the study. If you have any questions or concerns, please feel free to contact me. (If you would like, someone can read this form to you)

What the study is about: We would like to determine the type of bacteria that causes lung infections in damaged lungs (Bronchiectasis).

What we will ask you to do: If you agree to take part in this study, the results from your tests completed at the hospital (for example bloods including HIV results, sputum and X-rays) will be used to better understand the causes of this infection.

Risks involved for participating in the study: There are no risks. We will simply use the data already obtained from your tests.

Benefits for participating in the study: There are no direct benefits for the participant. However, it will contribute significantly to the Health Care Professional's understanding of lung infections and will therefore help to improve the treatment provided to the community in future.

Your answers will be confidential: All of your results and the records of this study will be kept private. In any sort of report that is published, your name will not be mentioned and no information will be included that can make it possible to identify you. Research records will be kept in a locked file cabinet; only the researchers will have access to the records. After two years the data will be destroyed if a publication comes out of the study; in no publication emerges, the data will be destroyed after six years.

Taking part is voluntary: Taking part in this study is completely voluntary. If you decide not to take part, it will not affect your current or future treatment. If you decide to take part, you are free to withdraw at any time, without having to give any reason.

Statement of Consent: I have read the Study Information Sheet, or had it read to me. I was given the opportunity to ask questions about the study and have received answers to any questions I asked. I consent to take part in the study.

Participant's Signature _____

Printed name of participant _____ Date _____

Signature of person obtaining consent _____

Printed name of person obtaining consent _____ Date _____

Appendix A2: Patient Information sheet

Faculty of Health Sciences

University of the Witwatersrand

Study title: Bacteria isolated from the airways of patient presenting with an acute exacerbation of non-cystic fibrosis bronchiectasis : A prospective study.

My name is Dr Magdel Strydom and I am conducting a research study for my MMed qualification in internal medicine at the University at Witwatersrand. Your doctor suspects that you may have damaged lungs and that you now have an infection in your lungs. You are therefore being asked to take part in this research study looking at the types of bacteria that causes infections in damaged lungs.

Please read this form carefully before agreeing to take part in the study. If you have any questions or concerns, please feel free to contact me. (If you would like, someone can read this form to you)

What the study is about: We would like to determine the type of bacteria that causes lung infections in damaged lungs (Bronchiectasis).

What we will ask you to do: If you agree to take part in this study, the results from your tests completed at the hospital (for example bloods including HIV results, sputum and X-rays) will be used to better understand the causes of this infection.

Risks involved for participating in the study: There are no risks. We will simply use the data already obtained from your tests.

Benefits for participating in the study: There are no direct benefits for the participant. However, it will contribute significantly to the Health Care Professional's

understanding of lung infections and will therefore help to improve the treatment provided to the community in future.

Your answers will be confidential: All of your results and the records of this study will be kept private. In any sort of report that is published, your name will not be mentioned and no information will be included that can make it possible to identify you. Research records will be kept in a locked file cabinet; only the researchers will have access to the records. After two years the data will be destroyed if a publication comes out of the study; in no publication emerges, the data will be destroyed after six years.

Taking part is voluntary: Taking part in this study is completely voluntary. If you decide not to take part, it will not affect your current or future treatment. If you decide to take part, you are free to withdraw at any time, without having to give any reason.

If you have any questions about any aspect of the study, please feel free to contact me, Dr Magdel Strydom, at any time on telephone numbers 011 489 1011 or 072 581 6667, or my Supervisor, Dr Andrew Black, on e-mail address Andrew.Black@wits.ac.za.

This study has been approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg ("Committee"). A principal function of this Committee is to safeguard the rights and dignity of all human subjects who agree to participate in a research project and the integrity of the research.
If you have any concern over the way the study is being conducted, please contact the Chairperson of this Committee who is Professor Clement Penny, who may be contacted on telephone number 011 717 2301, or by e-mail on Clement.Penny@wits.ac.za. The telephone numbers for the Committee secretariat are 011 717 2700/1234 and the e-mail addresses are Zanele.Ndlovu@wits.ac.za and Rhulani.Mukansi@wits.ac.za

Thank you for reading this Study Information Sheet.

Appendix A3: Data Collection Sheet

Faculty of Health Sciences

University of the Witwatersrand

Research project name: Bacteria Isolated from the airways of patient presenting with an acute exacerbation of non-cystic fibrosis bronchiectasis: A prospective study

Questionnaire

1. **Demograpic details**

Study number: _____

Hospital number: _____

Age: _____

Sex: Male ☐ Female ☐

Ethnicity: Caucasian ☐ African ☐ Indian ☐ Other ☐

Occupational History: _____

2. **Medical History:**

Smoking History: Yes ☐ No ☐

If Yes

Still smoking: Yes☐ No ☐

Cigarettes ☐ Marijuana ☐ other ☐

Pack Years: 0-4☐ 5-9 ☐ 10-14 ☐ >15 ☐

RVD status: Reactive ☐ Non-reactive ☐

If Reactive

Year Diagnosed _____

On ARV's Yes☐ No ☐

CD4 Count _____ Viral Load _____

Previous TB: Yes ☐ No ☐

If Yes

Site: Pulmonary ☐ EPTB ☐

Diagnosis based on Sputum ☐ CXR ☐ Emperic ☐

Previous Severe Pneumonia (Requiring hospital admission) Yes ☐ No ☐

3. Bronchiectasis

Diagnosis of Bronchiectasis based on: CXR ☐ CT ☐ Clinical ☐

Year patient first presented with symptoms _____

Amount of AE per Year: _____

MMRC:

Current admission

Severity of Exacerbation: C ☐ U ☐ R ☐ B ☐ 65 ☐

Sample barcodes:

MCS _____

GXP _____

TB Culture _____

Thank You.

Appendix B: HREC Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr M Strydom

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M180555

NAME: (Principal Investigator)	Dr M Strydom
DEPARTMENT:	School of Clinical Medicine Department of Medicine Division of Internal Medicine Helen Joseph Hospital
PROJECT TITLE:	Bacteria isolated from the airways of patients presenting with an acute exacerbation of bronchiectasis: A prospective study
DATE CONSIDERED:	25/05/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr A Black
APPROVED BY:	Professor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	31/08/2018

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 on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/We fully understand 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**. When a funder requires annual re-certification, the application date will be one year after the date of the meeting when the study was initially reviewed. In this case, the study was initially reviewed in **May** and will therefore reports and re-certification will be due early in the month of **May** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix C:Plagiarism Report

Turnitin Originality Report

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