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Perumal, Craig Ashley

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THE CLINICAL PROFILE OF PATIENTS WITH ACINETOBACTER BAUMANNII BACTEREMIA AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

Craig Ashley Perumal

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

Johannesburg, 2021

DECLARATION

I, Dr Craig Ashley Perumal, declare that this Research Report is my own, unaided work. It is being submitted for the degree of Master of Medicine in Internal Medicine (in the submissible format with my protocol and extended literature review) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



_____

…28th…Day of…June….2021 in Johannesburg

ACKNOWLEDGEMENTS

I would like to thank God for his help and strength, my wife, daughters and parents for their love and support. I would also like to thank Prof Menezes and Dr Wadula for their patience and guidance.

ABSTRACT

Introduction

Within the last twenty years *Acinetobacter baumannii* has emerged as a particularly problematic pathogen, owing largely to its aptitude for acquiring and developing resistance mechanisms. Whilst infections of the lower respiratory tract, urinary tract and soft tissue may occur out of hospital, *A.baumannii* bacteraemia (ABB) is an exclusively nosocomial phenomenon, with most studies highlighting its penchant for the intensive care environment.

Aim

This study aims to determine the proportion, clinical profile and clinical outcome of patients with ABB.

Method

This was a single-centre retrospective review at Chris Hani Baragwanath Academic Hospital (CHBAH) from January 2013 to December 2015. Data was accessed from the National Health Laboratory Service (NHLS). Blood cultures positive for *A.baumannii* were retrieved and patients' files accessed at the medical records department. A data sheet was used to record patient, antibiotic, antibiogram and outcome details. Patients included were 18 years or older, admitted to any ward, and had a blood culture taken during the study period that was positive for *A.baumannii*. Patients excluded were those with polymicrobial positive blood cultures and those with missing or incomplete clinical records.

Results

A total of 104 ABB episodes were yielded from 3418 positive blood cultures. The study sample contained a significant number of episodes from the

medical wards (*n*=52; 50%). More episodes were obtained from male patients (*n*=55; 52.9%). The mean age was 47 years (SD 17.29). There were 56 deaths (53.8%). Older age was associated with mortality (p=0.03). Even though human immunodeficiency virus (HIV) was the commonest co-morbidity (*n*=45; 43.3%), diabetes mellitus was the only co-morbidity associated with mortality (p=0.01). Hypo-/hyperthermia was the only clinical sign associated with mortality (p=0.04). Multi-drug resistance was the commonest resistance phenotype (*n*=72; 69.2%), but was not associated with mortality (p=0.17).

Conclusion

ABB is a clinically significant disease in general medical wards in addition to ICU, with a considerable rate of mortality. Diabetes mellitus, older age and hypo-/hyperthermia confer an increased risk for mortality whilst HIV does not.

Key words: *Acinetobacter baumannii,* bacteraemia, resistance phenotype

(Count: 325 words)

TABLE OF CONTENTS

DECLARATION ii

ACKNOWLEDGEMENTS iii

ABSTRACT iv

LIST OF TABLES viii

ABBREVIATIONS ix

CHAPTER 1 – PROTOCOL WITH EXTENDED LITERATURE REVIEW 1

Introduction *1*

Epidemiology *1*

Risk Factors *3*

Clinical Presentation *3*

A.baumannii Bacteremia in HIV patients *4*

Treatment and Resistance Phenotypes *5*

Prognosis *7*

Role of this Study *8*

Aims *8*

Objectives *9*

Methods *9*

Study Design 9

Study Setting 9

Study Population 9

Sample Selection 10

Sample Size Calculation 10

Data Collection 10

Data Analysis 11

Ethics *12*

Funding *12*

Timing *12*

Potential Limitations *13*

References *13*

CHAPTER 2 – SUBMISSABLE ARTICLE 19

CHAPTER 3 – APPENDICES 37

***Appendix A – Data Collection Sheet*.....41**

Appendix B – Ethics Clearance Certificate 42

Appendix C – Turn-It-In Originality Report.....43

Appendix D – Plagiarism Declaration 44

LIST OF TABLES

CHAPTER 2 – SUBMISSABLE ARTICLE

Table 1: Baseline Characteristics……..……...28

Table 2: Clinical Characteristics……29

Table 3: Resistance Phenotype and Treatment Choice……...30

Table 4: Antibiotic Susceptibility……31

Table 5: Patient Characteristics and Death Outcome……...32

Table 6: Antibiotic Susceptibility, Resistance Phenotype and Death Outcome……33

ABBREVIATIONS

A.baumannii	*Acinetobacter baumannii*
ABB	*Acinetobacter baumannii* bacteremia
ARV	anti-retroviral therapy
CHBAH	Chris Hani Baragwanath Academic Hospital
CD4	cluster of differentiation type 4 positive T-cells
CDW	Corporate Data Warehouse
CRAB	carbapenem-resistant *Acinetobacter baumannii*
DNA	deoxyribonucleic acid
ETA	endotracheal aspirate
HREC	Human Research Ethics Committee
HIV	human immunodeficiency virus
IALCH	Inkosi Albert Luthuli Central Hospital
ICU	intensive care unit
MDR	multi-drug resistant
NHLS	National Health Laboratory Service
STATA 16	Statistics and Data version 16.0
PDR	pan-drug resistant
UNAIDS	Joint United Nations Programme on HIV/AIDS
USA	United States of America
XDR	extensively-drug resistant

CHAPTER 1 – PROTOCOL WITH EXTENDED LITERATURE REVIEW

Introduction

Acinetobacter baumannii belongs to a group of Gram negative, non-fermenting, oxidase negative coccobacilli. This bacterium is innately resistant to many antibiotic groups, with horizontal transfer of deoxyribonucleic acid (DNA) now being recognized as a major contributor to this resistance.[1] *A.baumannii* has been shown to survive for months on surfaces and equipment (perpetuated by biofilm formation), making it an ideal candidate for nosocomial infections and placing it in the ideal location to develop resistant clones.[1]

Whilst previously regarded as an occasional respiratory pathogen, this organism has proven itself to be one of the six most predominant multi-drug resistant opportunistic nosocomial pathogens across the planet.[2] It is currently estimated that *A.baumannii* infection is responsible for two percent of all healthcare associated infections in Europe and the United States with 1 000 000 cases occurring yearly worldwide.[3]

Epidemiology

In addition to naturally inhabiting water and soil, the epidemiology of *A.baumannii* includes its associations with war zones, tropical climates, natural disasters, healthcare-associated outbreaks and community-acquired pneumonias.[2,4]

Acinetobacter species are commonly colonisers, which can lead to community acquired infections.[5] *A.baumannii* bacteraemia (ABB) however, is isolated to

the hospital environment, hospital outbreaks being caused by both epidemic and sporadic strains.[6] Within the hospital environment bacteraemia accounts for 10 to 30% of all episodes from which *A.baumannii* is isolated.[7] Environmental contamination, patient colonization/infection, and colonized healthcare workers form potential reservoirs for bacteraemia and outbreaks.[7,8] Whilst medical and surgical wards both report outbreaks, intensive care units (ICU) are the most affected.[7] Both nosocomial infection and bacteraemia seem to increase during summer months, temperature and humidity likely both playing a role.[9] A 2019 systematic review and meta-analyses of *A.baumannii* infection across Europe, Africa and the Eastern Mediterranean showed incidence of hospital-acquired *A.baumannii* to be between 0.85 and 5.6 cases per 1000 patients.[10]

The incidence of ABB seems to vary between epidemic and non-epidemic years (3 per 1000 admissions to 17 per 1000 admissions) and varies between institutions.[8,11]

A seven-year retrospective study at the Inkosi Albert Luthuli Central Hospital (IALCH) in Durban, South Africa, determined the prevalence of *A.baumannii* isolated on culture to be between 0.9% and 2.4% from all episodes, with between 155 to 453 episodes per year (2656 total episodes).[12] This study further separated patients into ‘sepsis’ (44%, n=1147) and ‘colonized’ (56%, n=1479) groups. Of these ‘sepsis’ group patients, 46% (540 patients) had isolation of *A.baumannii* on blood culture.

Risk Factors

ABB is associated with in-patient care, especially in units with sicker patients who have had invasive procedures (arterial/central venous lines, intubation, urinary catheterization, etc.).[6] Additionally, colonization with *A.baumannii* is an important source for potential invasive bacteraemia as well as patient-to-patient spread of infection.[13,14] Cancer patients receiving immunosuppressive treatment are at increased risk of *A.baumannii* infection that may eventually result in sepsis.[5]

Risk factors for ABB in ICU patients from a study in 2001 included immunosuppression, respiratory failure, unscheduled admission, previous sepsis, prior antimicrobial therapy and invasive procedures.[15,16]

A 2019 study highlighted numerous risk factors for acquiring multi-drug resistant (MDR) ABB including: longer hospital stay; ICU admission; mechanical ventilation; emergency surgery; invasive procedures; renal replacement therapy; and previous exposure to beta-lactam/beta-lactamase inhibitors, corticosteroids and carbapenems.[17]

Clinical Presentation

A.baumannii infection can manifest as pneumonia (often ventilator associated), meningitis, peritonitis, endocarditis or urinary and skin infections.[3] Clinical manifestations of the bacteraemia itself are non-specific and include a transitory maculopapular rash involving the palms and soles, and necrotic lesions of the soft tissue and skin.[7] Common sources of bacteremia are respiratory infections and intravascular catheters, with urinary tract infections, surgical wounds and burns being less common.[6,8] In 2010, a

multi-centre surveillance study in the United States of America (USA) showed the majority of clinical isolates of *A.baumannii* cultured from the respiratory tract (57.6%), followed by bacteraemia and soft tissue infections (23.9% and 9.1% respectively).[18] This order mirrors the results of a 2013 study conducted in an ICU at a regional hospital in Durban, South Africa, on *Acinetobacter* species, showing the largest proportion of positive cultures (36%) were retrieved from endotracheal aspirates (ETA) followed by blood(13%), although the majority of these patients (59%) were assessed as being colonized rather than infected.[19] A Moroccan study from 2016 shows a similar picture.[20] The IALCH study however showed the highest number (46%) isolated from blood cultures and 27-38%, ETA.[12]

A.baumannii Bacteremia in HIV patients

In the South African context, it is important to consider the role of human immunodeficiency virus (HIV) on mortality in patients with ABB, given the high HIV disease burden in this country. In an ICU-focused study from 2012 at Groote Schuur Hospital in Cape Town, South Africa, Ntusi *et al* found a statistically greater risk of death in patients co-infected with HIV having a cluster of differentiation type 4 positive T-cell (CD4) count below 200 cells/mm^3.[21] *A.baumannii* infection/colonisation was also found to be more likely in HIV-positive patients.[21] A 2018 study from Shanghai, China showed *A.baumannii* incidence to be 17.4 per 100 person years in HIV patients, which is higher than that of the general population.[22] This study found a 28-day survival rate that was lower in HIV patients with *A.baumannii* infection

requiring mechanical ventilation, though CD4 count and anti-retroviral (ARV) usage had no significant association.[22]

Treatment and Resistance Phenotypes

The *Acinetobacter* species has evolved into MDR and extensively-drug resistant (XDR) phenotypes over the past 20 years, with the Infectious Disease Society of America declaring *Acinetobacter* species to be amongst the six antimicrobial-resistant pathogens causing high mortality and morbidity.[5] The increase in MDR and XDR phenotypes worldwide has put pressure on current infection control and management options.[5]

ABB utilizes multiple strategies to evade and defeat the bodies complement and phagocytic mechanisms.[15] Paramount in these resistance mechanisms are the capsule and lipopolysaccharide layers, and protease, beta-lactamase and carbapenamase production.[23] Advances in chromosome genotyping have also allowed scientists to appreciate the role of horizontal gene transfer via transposons, plasmids and pathogenicity islands in resistance mechanisms.[5,23]

Definitions for resistance phenotypes that will be used in this study are those suggested by Magiorakos *et al*[24]:

Multi-drug Resistant (MDR): The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories.

Extensively-Drug Resistant (XDR): The isolate is non-susceptible to at least 1 agent in almost all antimicrobial categories but susceptible to all of the agents in a maximum of 2 antimicrobial categories.

Pan-drug Resistant (PDR): Non-susceptible to all antimicrobial agents listed.

First-line treatment options for susceptible *A.baumannii* infection include broad-spectrum cephalosporins (e.g., ceftazidime or cefepime), a combination beta-lactam/beta-lactamase inhibitor, or a carbapenem (e.g., meropenem, imipenem). Amikacin has been the most actively utilised aminoglycoside used locally in the treatment of MDR phenotypes but there has been increasing resistance in the last few years.[5] Contributing to this resistance is the fact that amikacin is normally used in combination with piperacillin-tazobactam as second line therapy for systemic infections in many local facilities.[5] A surveillance study evaluating antimicrobial resistance over a 2-year period (2016-2017) in the South African private and public sector noted a significant increase in resistance of *A.baumannii* to aminoglycosides and carbapenems in the public sector, and to imipenem in particular in the private sector.[5] Imipenem-resistant isolates were recognised in the 1990's, these isolates also being resistant to the cephalosporin and penicillin classes, with or without aminoglycoside and fluoroquinolone resistance.[1] The carbapenem-resistant clones that have emerged seems to have permanently replaced the carbapenem-susceptible clones.[25] Carbapenem-resistant *A.baumannii* (CRAB) infection poses a serious challenge to treatment due to the limited therapeutic options, resulting in these patients have twice the mortality rate of patients with carbapenem-susceptible *A.baumannii*.[25,26] Carbapenem resistance has now placed increased reliance on colistin for even MDR phenotypes.[27] For XDR phenotypes, tigecycline and/or colistin remain standard therapy alone or in combination with other antibiotics, though there is an increasing number of cases showing resistance to these agents as well.[28] Studies comparing treatment with colistin and/or tigecycline in

combination with either sulbactam, carbapenems, sulbactam-ampicillin or rifampin, in XDR cases show varying results in prospective and retrospective trials conducted thus far.[29,30] A 2017 study in Western Cape, South Africa, showed that colistin resistance was clonal in origin and only recently acquired.[27]

From Pretoria, South Africa, a study from 2008 showed resistance to imipenem (59%), meropenem (63%), gentamycin (58%), cefepime (62%), amikacin (5%), ciprofloxacin (65%), ceftazidime (45%), piperacillin-tazobactam (60%), and no resistance to colistin.[31] The IALCH study showed 99% susceptibility to colistin with 1% of samples in both the colonized and sepsis groups being PDR.[12] Inherent to colistin are its poor pharmacokinetics, neurotoxicity, neuromuscular blockage and nephrotoxicity, while tigecycline remains difficult to access in the South African public healthcare system.

Prognosis

Studies have shown that severity of disease, underlying malignancies, neutropenia and carbapenem resistance correlated with a higher mortality from ABB.[3] Mortality is not clear; one recent study showed crude mortality to be between 17% and 52%, but it is difficult to determine if this is purely a result of ABB or of the co-morbid illnesses these patients often have.[7] A 2014 meta-analysis showed *A.baumannii* infection had an overall mortality of 33% although this cannot be extrapolated to include ABB.[26] A 2019 study evaluating risk factors for acquisition and mortality from MDR ABB showed mortality for all cases (MDR as well as non-MDR) to be 46.4% amongst 338

patients.[17] In this same study MDR ABB patients had longer hospital stay and poorer outcomes compared to patients with non-MDR ABB, the factors influencing mortality in these patients were old age and bacteremia secondary to pneumonia.[17]

In a meta-analysis exclusively on CRAB, pooled mortality from CRAB bacteremia was 56.3%, with chronic liver disease, chronic kidney failure, septic shock, neutropenia, steroid therapy, immunosuppressant use and inappropriate antimicrobial therapy found to be significant risk factors for mortality.[25]

Despite the prognostic uncertainty, it should be noted that studies have shown that 25-30% of patients with ABB develop septic shock, with disseminated intravascular coagulopathy being another common feature.[6,7] Zhang *et al* validated a model predicting mortality from *A.baumannii* infection which implicated infection source, carbapenem resistance, hypo-albuminemia and mechanical ventilation as independent risk factors for death.[3]

Role of this Study

This study may attempt to describe risk factors associated with mortality amongst patients with ABB in our setting, allowing for more appropriate management of these patients.

Aims

This study aims to determine the proportion, clinical profile and clinical outcome of patients with ABB.

Objectives

1. To determine the proportion of patients with ABB.
2. To describe the demographic and clinical characteristics of patients with ABB.
3. To determine the risk factors for mortality in patients with ABB.
4. To determine the resistance phenotype and antibiotic choice in patients with ABB.
5. To evaluate the outcome of HIV positive patients with ABB.

Methods

Study Design

This is a single-centre retrospective review.

Study Setting

The study will be based at Chris Hani Baragwanath Academic Hospital (CHBAH) in Soweto, Johannesburg. CHBAH is the third largest hospital in the world, with approximately 3200 beds. Every year, the hospital registers about 500 000 outpatient and 150 000 inpatient cases. The majority of patients admitted to CHBAH reside within Soweto, a township with a population of more than 1.3 million people, the majority of which are from low to middle income social groups.

Study Population

- Inclusion Criteria
    1. Adults >18 years

2. Admission to ICU, Medical, and non-Medical wards
3. One *A.baumannii* positive blood culture taken within the study period.

- Exclusion Criteria
  1. Patients with blood culture specimens isolating *A.baumannii* in a polymicrobial culture.
  2. Patients with missing or incomplete clinical records.

Sample Selection

All adult patients admitted with the above criteria from 01/01/2013 to 31/12/2015 will be included in the study.

Sample Size Calculation

A convenience sampling method will be used. Approximately 52 bacteremic episodes for *A.baumannii* are isolated per year, therefore the sample size will be approximately 150 patients.

Data Collection

Data will be accessed from the blood culture database at the National Health Laboratory Service (NHLS) at CHBAH as well as the Corporate Data Warehouse (CDW). Positive blood cultures meeting above inclusion and exclusion criteria will be recorded and patient information (name and hospital number) will be used to apply for access to the relevant patients' files at the medical records department. Patient identifiers will remain confidential. Patients' files will be used in conjunction with a data sheet (**Appendix A**) to

record patient, antibiotic, antibiogram and outcome details. The data sheet will include: date of admission, age, gender, department admitted to (Medical, Surgical, Obstetrics & Gynaecology, Psychiatry, ICU), blood culture result, features of sepsis, co-morbidities, risk factors (invasive procedures, immunosuppression, unscheduled admission, prior sepsis, respiratory failure, prior antibiotic usage), choice of antibiotic, duration of stay, and outcome (death vs. discharge). Patient admission data over the given time period will also be accessed via the hospital administrative department.

Data Analysis

The information obtained from the data sheets will be entered on an Excel® spreadsheet. Data will then be exported onto Stata Version 14® (Stata Corp USA) statistical software for further analysis.

The baseline and clinical characteristics of all patients will be described. Categorical variables will be presented as percentages and with appropriate charts. Continuous variables will be reported as mean (with standard deviation), if normally distributed, or median (with interquartile range) if not normally distributed. Categorical variables (HIV status, etc.) will be compared using the Pearson's Chi-square. Antibiotic choice will be assessed with percentages and appropriate charts. A univariate model of the association between death, and other clinical and treatment parameters will also be conducted. A statistically significant level will be set at a confidence interval of 95% (P-value <0.05).

Ethics

Ethics approval will be obtained from the Wits Human Research Ethics Committee (HREC) (Medical). Permission for the use of patient's records will be gained from the Clinical Head of the Department of Internal Medicine and the Chief Executive Officer/Superintendent of CHBAH. Neither patient names or hospital numbers will be recorded. Patient identifiers will be kept confidential.

Funding

Any costs associated with the research will be self-funded.

Timing

	April – May 2017	June – Sep 2017	Oct 2017 - Feb 2018	Mar – Sep 2018	Oct 2018 - Dec 2019	Jan 2020 - Sep 2020	Oct 2020 – Mar 2021
Literature Review	■						
Protocol Preparation		■					
Protocol Assessment			■				
Ethics Application				■			
Data Collection					■		
Data Analysis						■	
Writeup							■

Potential Limitations

In interpretation of the results, due consideration will be made to sampling bias and limitations on generalization of our findings.

As this is a retrospective review, we will be relying on competent record keeping at the study facility. Incomplete/inaccurate records may influence findings despite adequate measures being taken to minimize inaccuracies. This includes note keeping as well as test results accessed through the NHLS. As this is a single-centre study, our findings may not reflect results from other centres conducting similar research.

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CHAPTER 2 – SUBMISSABLE ARTICLE

Title: The Clinical Profile of Patients with *Acinetobacter Baumannii* Bacteremia at Chris Hani Baragwanath Academic Hospital

Authors:

CA Perumal [1,3]

C Menezes [1,3]

J Wadula [2,3]

Affiliations:

[1] Department of Internal Medicine, Chris Hani Baragwanath Academic Hospital

[2] Department of Clinical Microbiology and Infectious Diseases, Chris Hani Baragwanath Academic Hospital, National Health Laboratory Services, Johannesburg, South Africa

[3] Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

Conflict of interest: None

Keywords: *Acinetobacter baumannii*, bacteremia, resistance phenotype

Corresponding author:

Craig Perumal, e-mail: craigash85@hotmail.com, telephone: +27795230532

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ABSTRACT

Introduction

Within the last 20 years *Acinetobacter baumannii* has emerged as a particularly problematic pathogen, owing largely to its aptitude for acquiring and developing resistance mechanisms. Whilst infections of the lower respiratory tract, urinary tract and soft tissue may occur out of hospital, *A.baumannii* bacteraemia (ABB) is an exclusively nosocomial phenomenon, with most studies highlighting its penchant for the intensive care environment.

Aim

This study aims to determine the proportion, clinical profile and clinical outcome of patients with ABB.

Method

This was a single-centre retrospective review at Chris Hani Baragwanath Academic Hospital (CHBAH) from January 2013 to December 2015. Data was accessed from the National Health Laboratory Service (NHLS). Blood cultures positive for *A.baumannii* were retrieved and patients' files accessed at the medical records department. A data sheet was used to record patient, antibiotic, antibiogram and outcome details. Patients included were 18 years or older, admitted to any ward, and had a blood culture taken during the study period that was positive for *A.baumannii*. Patients excluded were those with polymicrobial positive blood cultures and those with missing or incomplete clinical records.

Results

A total of 104 ABB episodes were yielded from 3418 positive blood cultures. The study sample contained a significant number of episodes from the

medical wards (*n*=52; 50%). More episodes were obtained from male patients (*n*=55; 52.9%). The mean age was 47 years (SD 17.29). There were 56 deaths (53.8%). Older age was associated with mortality (p=0.03). Even though human immunodeficiency virus (HIV) was the commonest co-morbidity (*n*=45; 43.3%), diabetes mellitus was the only co-morbidity associated with mortality (p=0.01). Hypo-/hyperthermia was the only clinical sign associated with mortality (p=0.04). Multi-drug resistance was the commonest resistance phenotype (*n*=72; 69.2%), but was not associated with mortality (p=0.17).

Conclusion

ABB is a clinically significant disease in general medical wards in addition to ICU, with a considerable rate of mortality. Diabetes mellitus, older age and hypo-/hyperthermia confer an increased risk for mortality whilst HIV does not.

Key words: *Acinetobacter baumannii,* bacteraemia, resistance phenotype

(Count: 325 words)

Introduction

Acinetobacter species has evolved from an occasional respiratory pathogen, to being declared one of the 6 most important antimicrobial-resistant pathogens causing high morbidity and mortality, largely as a result of the emergence of multi-drug resistant (MDR) and extensively-drug resistant (XDR) clones in the last 10 years.[1,2]

Acinetobacter baumannii can be a coloniser, occasionally resulting in community acquired infections, but *A.baumannii* bacteremia (ABB) is exclusive to the hospital environment.[2–5] The incidence of ABB varies between epidemic and non-epidemic years (3 per 1000 admissions to 17 per 1000 admissions), between institutions, between seasons and between intensive care units (ICU) and non-ICU wards.[6–9] As a proportion of all positive *A.baumannii* cultures, international studies reveal that ABB accounts for between 10% and 30%.[6,10] A 2016 study in Durban, South Africa, found *A.baumannii* isolated on blood culture to be 46% of all positive *A.baumannii* cultures.[4]

Resistance to antimicrobials is common with *A.baumannii* infection.[11] Increased reliance on carbapenem antibiotics for the management of MDR phenotypes has resulted in strains of carbapenem-resistant *A.baumannii* (CRAB) being reported globally.[11] A 2019 surveillance study in South Africa found decreasing susceptibility to both carbapenems and aminoglycosides in the public and private sectors.[12]

Overall risk factors for acquiring ABB include immunosuppression, respiratory failure, unscheduled admission, previous sepsis, previous antimicrobial therapy and invasive procedures.[13]

Studies have found difficulty in determining actual mortality relating to ABB; a 2002 study showed crude mortality to be between 17% and 52% but it is uncertain whether this is related to the *A.baumannii* infection itself or the serious co-morbid illness these patients often have when *A.baumannii* is cultured.[6] A study investigating risk factors influencing death from ABB has highlighted severity of disease, underlying malignancies, neutropenia and carbapenem resistance to be significantly associated with an increased mortality.[14] A 2012 study in Cape Town found there to be a statistically greater risk of mortality in patients who were co-infected with human immuno-deficiency virus (HIV) with a cluster of differentiation type 4 positive T-cell (CD4) below 200 cells/mm^3.[3] Other studies evaluating MDR ABB and CRAB infections found mortality-related risk factors to be old age, bacteremia secondary to pneumonia, chronic liver disease, chronic kidney disease, septic shock, neutropenia, steroid therapy, immunosuppressant use and inappropriate antimicrobial therapy.[15,16]

This study aimed to determine the clinical profile of patients with *A.baumannii* bacteremia, in addition to drug susceptibility, association with HIV, and patient outcomes.

Patients and Methods

This was a single-centre retrospective review of patients with *A.baumannii* bacteraemia at Chris Hani Baragwanath Academic Hospital (CHBAH) from January 2013 to December 2015. CHBAH is the third largest hospital in the world, based in Soweto, Johannesburg, with approximately 3200 beds.[17]

Data was accessed from the blood culture database at the National Health Laboratory Service (NHLS) at CHBAH as well as the Corporate Data Warehouse (CDW). Blood cultures positive for *A.baumannii* were recorded and patient information (name and hospital number) was used to apply for access to the relevant patients' files at the medical records department. Patient identifiers remained confidential. Patients' files were used in conjunction with a data sheet to record patient, antibiotic, antibiogram and outcome details. The data sheet included: date of admission, age, gender, department admitted to (Medical, Surgical, Obstetrics & Gynaecology, Psychiatry, ICU), blood culture result, features of sepsis, co-morbidities, risk factors (invasive procedures, immunosuppression, unscheduled admission, prior sepsis, respiratory failure, prior antibiotic usage), choice of antibiotic, duration of stay and outcome (death vs. discharge). Antibiotic susceptibility was determined and antibiotic choice was assessed as 'appropriate' (if episode was susceptible to selected choice of antibiotic), 'inappropriate' (if episode was resistant to selected choice of antibiotic), 'not treated' (if a clinical judgment was made to not treat the episode result) or 'not documented' (if no documentation was made regarding choice of antibiotic).

Definitions for resistance that were used in this study are as follows:

Multidrug-Resistant (MDR): The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories.

Extensively Drug-Resistant (XDR): The isolate is non-susceptible to at least 1 agent in almost all antimicrobial categories but susceptible to all of the agents in a maximum of 2 antimicrobial categories.

Pan drug-Resistant (PDR): Non-susceptible to all antimicrobial agents listed.[18]

Patient admission data over the given time period was accessed via the hospital administrative department.

Patients included in the study were: 18 years or older; admitted to ICU, Medical, and non-Medical wards; had a blood culture taken within the study period that was positive for *A.baumannii*. Patients that were excluded from the study were: patients with blood culture specimens isolating *A.baumannii* in a polymicrobial culture; patients who had missing or incomplete clinical records.

The study was approved by the Human Research Ethics Committee (Medical), University of the Witwatersrand (approval no. M180339).

Statistical Analysis

The information obtained from the data sheets was entered on an Excel® spreadsheet. Data was then exported onto Stata Version 16 ® (Statistics and Data Corp USA) statistical software for further analysis.

The baseline and clinical characteristics of all patients was described. Categorical variables were presented as percentages and with appropriate tables. Continuous variables were reported as mean (standard deviation), if normally distributed, or median (interquartile range) if not normally distributed. Categorical variables (HIV status, etc.) were compared using the Pearson's Chi-square. Antibiotic susceptibility was determined and represented with percentages and appropriate tables. A univariate model of the association between death, and other clinical and treatment parameters was also

conducted. A statistically significant level was set at a confidence interval of 95% (P value<0.05).

Results

Proportion of patients with ABB

The NHLS recorded a total of 3418 positive bacteremic episodes over the study period, of which *A.baumannii* was detected in 240 of these, giving a proportion of 7%. From these 240 episodes, complete clinical records of 104 patients were evaluated.

Clinical profile of patients with ABB

The patients in this study had a mean age of 47 years (SD,17.29). There was a predominance of male patients (*n*=55; 52.9%). Most patients were admitted to the medical ward (*n*=52; 50%), followed by surgical wards (*n*=26; 25%) and ICU (*n*=23; 22.1%). The duration of stay had a median of 23 days (IQR, 24.75).

The specific co-morbidities seen in this study were hypertension, diabetes mellitus, chronic kidney disease and HIV. Of these, HIV was the commonest medical co-morbidity (*n*=45, 43.3%).

Of the risk factors assessed for acquiring ABB, more than two thirds of patients underwent invasive procedures (*n*=74; 71.2%). One patient was documented to have received chronic immunosuppressive treatment for an underlying co-morbidity (1%). A small number of patients (*n*=16; 15.4%) warranted mechanical ventilation for respiratory failure. Just under half the patients (*n*=48; 46.2%) had documented antibiotic use prior to ABB being

diagnosed. Only a small number of patients (*n*=7; 6.7%) were admitted for elective procedures, and as a result unscheduled admission was the commonest risk factor.

Features of sepsis assessed in this study were hypo-/hyperthermia, tachycardia, tachypnoea and leukopenia/-cytosis. Of these, tachycardia was the commonest feature encountered (*n*=91; 87.5%).

These results are summarised in **Tables 1** and **2** below.

Table 1: Baseline Characteristics

	Patients with *A.baumannii* Bacteremia (*N*=104)
Age, mean years (SD)	47 (17.29)
Male	55 (52.9%)
Female	49 (47.1%)
ICU	23 (22.1%)
Medical Wards	52 (50%)
Surgical Wards	26 (25%)
Other Wards [a]	3 (2.9%)
Duration of Stay, median days (IQR)	23 (24.75)
Outcome	
Death	56 (53.8%)

[a] Psychiatry, Obstetrics and Gynaecology Wards; ICU= Intensive Care Unit; SD= standard deviation; IQR=interquartile range

Table 2: Clinical Characteristics

	Patients with *A.baumannii* Bacteremia (*N*=104)
Co-Morbidities	
Hypertension	29 (27.9%)
Diabetes Mellitus	18 (17.3%)
Chronic Kidney Disease	10 (9.6%)
HIV	45 (43.3%)
HIV (CD4 <200 cells/mm^3)	33 (31.7%)
Risk Factors [a]	
Invasive Procedure	74 (71.2%)
Immune Suppression	1 (1%)
Respiratory Failure	16 (15.4%)
Unscheduled Admission	97 (93.3%)
Prior Sepsis	12 (11.5%)
Prior Antibiotic Use	48 (46.2%)
Features of Sepsis [b]	
Hypo-/Hyperthermia (<36˚C or >38˚C)	39 (37.5%)
Tachycardia (>90 beats/min)	91 (87.5%)
Tachypnoea (>20 breaths/min)	64 (61.5%)
Leukopenia/-cytosis (White Blood Cells <4000 or >12000 cells/mm^3)	67 (64.4%)

[a] Risk Factors for *A.baumannii* bacteremia [13]; [b] Systemic Inflammatory Response Syndrome (SIRS) Criteria [19]; HIV=human immunodeficiency virus; CD4= cluster of differentiation type 4 positive T-cells

The majority of patients (n=72; 69.2%) had the resistance phenotype of MDR whilst no patients had PDR ABB. Regrettably a significant proportion of

patients (*n*=41; 39.4%) had no antibiotic choice documented. Appropriate (*n*=31; 29.8%) and inappropriate (n=30, 28.8%) antibiotic choice was fairly evenly matched, but paucity of documented treatment choices prevented further analysis (see Study Limitations below). These results are summarised in **Table 3** below.

Table 3: Resistance Phenotype and Treatment Choice

	Patients with *A.baumannii* Bacteremia (*N*=104)
Resistance Phenotype [a]	
Susceptible	6 (5.8%)
MDR	72 (69.2%)
XDR	26 (25.0%)
Antibiotic Choice	
Appropriate	31 (29.8%)
Inappropriate	30 (28.8%)
Not Treated	2 (1.9%)
Not Documented	41 (39.4%)

[a] Magiorakas *et al* [18]; MDR= Multi-drug Resistant; XDR= Extensively-drug Resistant

Antibiotic susceptibility was also determined, as outlined in **Table 4**. Piperacillin-tazobactam was found to have the lowest susceptibility (*n*=7; 6.7%). The carbapenem group also encountered low susceptibilities for imipenem (*n*=12; 11.5%) and meropenem (*n*=13; 12.5%). Fortunately, colistin

remained completely susceptible. Apart from colistin, tobramycin had the highest susceptibility (*n*=77; 74.0%).

Table 4: Antibiotic Susceptibility

	Patients with *A.baumannii* Bacteremia (*N*=104)
	Susceptibility
Imipenem	12 (11.5%)
Meropenem	13 (12.5%)
Ciprofloxacin	38 (36.5%)
Piperacillin-Tazobactam	7 (6.7%)
Tobramycin	77 (74.0%)
Gentamycin	50 (48.1%)
Amikacin	65 (62.5%)
Cefepime	8 (7.7%)
Ceftazidime	31 (29.8%)
Colistin	104 (100%)

Outcome of patients with ABB

In this study, 56 patients (53.8%) with ABB demised. Univariate assessment of all parameters was tested against the outcome of death in order to explore the significance of death from ABB. Age (p=0.03), diabetes mellitus (p=0.005), respiratory failure (p=0.003), hypo/hyperthermia (p=0.04) and leukopenia/cytosis (p=0.02), were significant on univariate assessment of death. Neither HIV status (p=0.48), nor CD4 below 200 cells/mm^3 (p=0.45)

were significantly associated with death. No resistance phenotype was significant on univariate assessment of death. The results are summarised in **Tables 5** and **6** below.

Table 5: Patient Characteristics and Death Outcome

	Patients with Death Outcome (*N*=104)		
	N	**Chi^2**	**p-value**
General			
Gender	-	3.308	0.07
Age, mean years (SD)	50 (17.17)	-	**0.03**
Ward	-	4.189	0.24
Duration of Stay, median days (IQR)	23 (24.75)	-	0.51
Medical Comorbidities			
Hypertension	18	2.087	0.35
Diabetes Mellitus	13	2.956	**0.005**
Chronic Kidney Disease	6	0.169	0.68
HIV	26	0.493	0.48
HIV (CD4<200 cells/mm^3)	15	0.584	0.45
Risk Factors [a]			
Invasive Procedure	41	0.251	0.62
Immune Suppression	1	0.866	0.35
Respiratory Failure	14	8.617	**0.003**
Unscheduled Admission	52	0.033	0.86
Prior Sepsis	6	0.081	0.78
Prior Antibiotics	26	0.004	0.95

Clinical Features of Sepsis [b]			
Hypo-/Hyperthermia (<36˚C or >38˚C)	26	4.127	**0.04**
Tachycardia (>90 beats/min)	50	0.354	0.55
Tachypnoea (>20 breaths/min)	39	3.367	0.07
Leukopenia/-cytosis (White Blood Cells <4000 or >12000 cells/mm^3)	42	5.922	**0.02**

[a] Risk Factors for *A.baumannii* bacteremia [13] ; [b] Systemic Inflammatory Response Syndrome (SIRS) Criteria [19]; SD= standard deviation; IQR= interquartile range; HIV= human immunodeficiency virus; CD4= cluster of differentiation type 4 positive T-cells

Table 6: Antibiotic Susceptibility, Resistance Phenotype and Death Outcome

	Patients with Death Outcome (*N*=104)		
	N	**Chi^2**	**p-value**
Antibiotic Susceptibility			
Imipenem	4	2.297	0.13
Meropenem	5	1.415	0.23
Ciprofloxacin	17	3.991	0.14
Piperacillin-Tazobactam	2	3.189	0.20
Tobramycin	42	0.058	0.81
Gentamycin	25	0.573	0.45
Amikacin	37	2.891	0.24
Cefepime	2	2.902	0.09
Ceftazidime	12	4.912	0.09

Colistin	56	-	-
Resistance Phenotype [a]	-	3.577	0.17

[a] Magiorakas *et al* [18]

Discussion

The hospital environment provides an ideal setting for exposure to, and establishment of, resistant *A.baumannii* infection.[6,9] Mounting evidence shows that *A.baumannii* is a cause of clinically significant disease, and not just an opportunistic pathogen as previously thought.[20]

Though, HIV was the commonest co-morbidity, both HIV and CD4 count of <200 cells/mm^3 were found not to be associated with increased mortality, in this study. Ntusi *et al* evaluated ICU-associated *A.baumannii* infection in HIV positive patients and found that predictors of *A.baumannii* infection/colonisation included younger age, female gender and CD4 count below 200 cells/mm^3, and that HIV positive patients with CD4 below 200 cells/mm^3 were more likely to have ABB.[3] That study also showed an association between CD4 count below 200 cells/mm^3 and mortality, which is in contrast to our findings. Other research indicated that *A.baumannii* infection is an independent risk factor for mortality in patients with HIV but, similar to this study, found no association between CD4 count and mortality.[21]

This study demonstrated that 53.8% of patients with ABB in our cohort demised. In addition to there being difficulty in determining attributable

mortality to ABB, it would be inaccurate to comment on mortality rate given that the majority of clinical records for the bacteremic episodes over the study period were not accessible.[6]

A study in Cape Town assessing *A.baumannii* infection in the medical ICU, showed fewer males with *A.baumannii* infection than this study, and a mean age of 39.7 years compared to a mean of 47 in this study.[22] That study however looked at all sites of infection as opposed to this study which focused only on bacteremic episodes.

Antibiotic susceptibility testing showed almost two thirds of the episodes susceptible to amikacin which mirrored a 2020 study from KwaZulu-Natal Province, South Africa.[2] A 2019 South African surveillance study noted low susceptibility to the imipenem in the private sector, a finding echoed in this study.[12] Despite reports locally and internationally of colistin resistance, this study found no resistance to colistin.[1,23] MDR *A.baumannii* was the commonest resistance phenotype in our study, in keeping with other studies but was not associated with mortality, contrary to findings in other studies.[24,25]

A study in 1990 revealed the risk factors for infection as invasive monitoring, mechanical ventilation, hyperalimentation, and number of days of invasive monitoring at the same insertion site.[7] Another study 11 years later, which investigated risk factors for nosocomial ABB, showed immunosuppression, respiratory failure, unscheduled admission, previous sepsis, previous antimicrobial therapy and invasive procedures as significant risks.[13] Although invasive procedures was a common in-patient risk in this study, respiratory failure was the only factor associated with mortality (p=0.003). Zhang *et al*

validated a model predicting mortality in *A.baumannii* infection which also identified respiratory failure (and subsequent mechanical ventilation) to be an independent risk factor for mortality. [14]

Hypo-/hyperthermia was the only clinical sign associated with mortality in our study(p=0.04), an important point to note considering a rigorous search of the literature found no similar findings in other studies.

Diabetes was the only co-morbidity associated with death (p=0.005). Diabetes is documented as one of the main underlying risk factors for *A.baumannii* sepsis and bacteraemia, with underlying hyperglycaemia and poor glycaemic control promoting morbidity and mortality.[26,27] The mortality rate due to CRAB is significantly higher in diabetic patients compared to non-diabetics.[28] Conversely, Leung *et al* confirmed previous studies which showed that hypoglycemia is associated with increased mortality in non-diabetic patients with ABB.[28]

In this study the length of stay was not significant with mortality (p=0.51); this finding is in contrast to other studies that indicate that the length of stay is a risk factor for acquiring ABB and for associated mortality.[15,24,25]

Limitations on accessibility of clinical records for this study allowed greater examination of ABB in patients outside of ICU. This is in contrast to the bulk of studies concentrating on *A.baumannii* within the ICU environment, and the prevailing theory regarding the predilection of *A.baumannii* for ICU.[3,5–7,13,22,24]

A review of the literature revealed that the bulk of research analysed *A.baumannii* infection from all sites, relatively few concentrating on bacteremia as was done in this study. This may account for some of the

perceived differences in our findings compared to other studies, in addition to the limitations of this study outlined below.

Study Limitations

The filing system at CHBAH is a manual paper-based system. The problem of missing or in-accessible files was an issue in this study, resulting in a small sample size. For the obtained files there was also some data that was not documented by the clinician in the patients' files. These constraints made comparing results from this study to other studies, difficult. To attempt overcoming this, we performed a thorough and rigorous search for as many files and as much data as possible. An additional limitation was that 41 (39.4%) patient records had no antibiotic choice documented, making it difficult to draw any conclusions regarding appropriateness of antibiotic choice.

Conclusion

This study found that ABB is a cause of clinically significant disease both within the ICU environment as well as other clinical units. In our cohort the majority of patients were from the medical wards and more than 50% of patients with ABB demised. While HIV was the commonest co-morbidity in our cohort, neither HIV nor a CD4 count below 200 cells/mm^3 were associated with an increased mortality. Increasing age and diabetes were the only co-morbidities significantly associated with death, with hypo-/hyperthermia being the only clinical sign, and respiratory failure the only risk factor. Even though our sample numbers were small, observations such as those involving HIV

were deemed to be of vital importance, especially given the high prevalence of HIV in this country. [29]

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CHAPTER 3 – APPENDICES

Appendix A – Data Collection Sheet

Data Collection Sheet

1. **Age ____**
2. **Gender**
   □ Male □ Female
3. **Date of Admission_____** **Date of Death/Discharge_____**

4. **Ward Admitted**
   □ Medical □ Psychiatry □ Obstetrics and Gynaecology
   □ ICU □ Surgical
5. **Co-Morbidities**
   □ Hypertensive □ Diabetic □ Chronic Kidney Disease
   □ HIV CD4<200 □ HIV CD4≥200
6. **Possible Source of Sepsis**
   □ Respiratory □ Urinary Tract □ Soft tissue
   □ Unknown
7. **Features of Sepsis (2 or more)**
   □ Temp >38˚C or <36˚C □ Heart Rate >90 beats per minute
   □ Respiratory rate >20 breaths per minute or $PaCO_2$ <32mmHg
   □ White Blood Cells >12 000 cells/mm^3 or <4000 cells/mm^3 or >10% immature forms
8. **Risk Factors for *A.baumannii* bacteraemia**
   □ Invasive procedures (central venous lines, arterial lines, urinary catheters, intercostal drains, endotracheal tubes)
   □ immunosuppressive drugs □ respiratory failure
   □ unscheduled admission □ prior sepsis
   □ prior antibiotic usage
9. **Resistance Pattern**
   □ Susceptible □ MDR
   □ XDR □ PDR
10. **Antibiotic choice**
    □ Imipenem □ Cefepime □ Piperacillin/Tazobactam
    □ Meropenem □ Tobramycin □ Tigecycline
    □ Ciprofloxacin □ Gentamicin □ Cefotaxime
    □ Colistin □ Amikacin □ Ceftazidime

11. **Length of Hospital Stay _____**
12. **Outcome**
    □ Discharge □ Death (*A.baumannii*-related)
    □ Death (cardiovascular-related) □ Death (respiratory-related)
    □ Death (neurologically-related) □ Death (cause not specified)

Appendix B – Ethics Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Craig Ashley Perumal

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M180339

NAME: (Principal Investigator)	Dr Craig Ashley Perumal
DEPARTMENT:	Internal Medicine Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	The Clinical Profile of Patients with Acinetobacter Baumannii Bacteremia at Chris Hani Baragwanath Academic Hospital
DATE CONSIDERED:	06/04/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Colin Menezes and Dr Jeannette Wadula
APPROVED BY:	Prof C Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	14/05/2018

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 in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. 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**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in April and will therefore be due in the month of April each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

21/08/2018
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix C – Turn-It-In Originality Report

0405053n:Craig_Perumal_MMed_FINAL_2.docx

ORIGINALITY REPORT

18%	15%	13%	5%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

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Appendix D – Plagiarism Declaration

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Craig Ashley Perumal (Student number: 0405053N) am a student registered for the degree of Master of Medicine in the academic year 2021.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: _____ Date: 28/06/2021