PSEUDOMONAS AERUGINOSA BLOODSTREAM INFECTION AT A TERTIARY REFERRAL HOSPITAL FOR CHILDREN

By

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DECLARATION PAGE

DECLARATION

I, Joycelyn Assimeng Dame, hereby declare that the work on which this dissertation is based is my original work and that acknowledgements have been indicated in situations where another person's work has been referenced or quoted.
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ABSTRACT

Introduction

This study describes the disease burden, clinical characteristics, antibiotic management, impact of multidrug resistance and outcome of *Pseudomonas aeruginosa* bloodstream infection (PABSI) among children admitted to a tertiary referral hospital for children in Cape Town, South Africa.

Methods

A retrospective descriptive study was conducted at a paediatric referral hospital in Cape Town, South Africa. Demographic and clinical details, antibiotic management and patient outcome information were extracted from medical and laboratory records. Antibiotic susceptibility results of identified organisms were obtained from the National Health Laboratory Service database.

Results

The overall incidence risk of PABSI was 5.4 PABSI episodes / 10,000 hospital admissions and the most common presenting feature was respiratory distress, 34/91 (37%). Overall, 69/91 (76%) of the PA isolates were susceptible to all antipseudomonal antibiotic classes evaluated. Fifty (55%) of the PABSI episodes were treated with appropriate empiric antibiotic therapy. The mortality rate was 24% and in multivariable analysis, empiric antibiotic therapy to which PA isolate was not susceptible to, infections present on admission, and not being in the intensive care unit at the time that PABSI was diagnosed were significantly associated with 14-day mortality.

Conclusion

The study provided insight into factors associated with PABSI in a tertiary hospital in Sub-Saharan Africa. Empiric antipseudomonal antibiotic therapy was associated with a decrease in 14-day mortality.

Keywords: *Pseudomonas aeruginosa* bloodstream infection, children, Sub-Saharan Africa.

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Many thanks to the patients of Red Cross War Memorial Children's Hospital, their parents and caregivers whose medical history and records were used in this study.
May God bless you all

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ABBREVIATIONS

aOR - adjusted odds ratio

BSI - bloodstream infection

CDC - Centers for Diseases Control and Prevention

CDW - Central Data Warehouse

CVAD - central venous assess device

CVP - central venous pressure

CI - confidence interval

CLSI - Clinical and Laboratory Standards Institute

DNA-PCR - deoxyribonucleic acid-polymerase chain reaction

RNA-PCR- ribonucleic acid-polymerase chain reaction

ELISA - enzyme linked immunosorbent assay

GSH - Groote Schuur Hospital

HAI - healthcare- associated infection

HIV - Human Immunodeficiency Virus

HREC - Human Research Ethics Committee

ICU - intensive care unit

IJID - International Journal of Infectious Diseases

IQR - interquartile range

IV - intravenous

IPOA - infection present on admission

MDR - multidrug- resistant

NHLS - National Health Laboratory Service

PA - *Pseudomonas aeruginosa*

PABSI - *Pseudomonas aeruginosa* bloodstream infection

PDR - pan drug-resistant

RCWMCH - Red Cross War Memorial Children's Hospital

SA	-	South Africa
SD	-	standard deviation
USA	-	United States of America
WAZ	-	weight-for-age Z score
WHO	-	World Health Organization
XDR	-	extensively drug-resistant

CHAPTER 1: INTRODUCTION

1.1 Context

Pseudomonas aeruginosa (PA) is a ubiquitous Gram-negative aerobic bacterium usually found in water, soil and plants. It grows well at 25°C to 37°C, and its ability to grow at 42°C helps distinguish it from many other *Pseudomonas* species. The features useful for identifying *Pseudomonas species* in the laboratory include a characteristic sweet, grape-like odour during culture, the elaboration of a green pigment and production of oxidase (Tang, 2014). It has an ability to form biofilm, and this enables it to persist in environmental niches such as the pipes and taps in hospitals (Streeter & Katouli, 2016). It is an important opportunistic pathogen in humans. Compared to other causes of bloodstream infection (BSI), PA occurs less frequently. Studies from South Africa and Ghana have shown that PA causes between 4 and 6.5% of Gram-negative BSI (Dramowski et al., 2015; Lochan et al., 2017; Obeng-Nkrumah et al., 2016). In some settings PA is more frequently isolated. Recent BSI studies from Finland and the USA showed that PA was responsible for 17.9% and 20.2% of all Gram-negative BSI among children, respectively (Ivády et al., 2016; Larru et al., 2016).

Pseudomonas aeruginosa typically causes healthcare-associated BSI among children with chronic or malignant diseases that are associated with impaired defence mechanisms, and among preterm infants due to their immature immune system (Logan et al., 2016; Rosanova et al., 2019; Viola et al., 2006). Physical breaches in host defences from surgical incisions and insertion of urinary or vascular catheters and endotracheal tubes predispose patients to PA bloodstream infection (PABSI) (Streeter & Katouli, 2016). In the intensive care unit (ICU), the presence of invasive devices and prolonged use of antibiotics puts patients at risk of PABSI (Kim et al., 2014). In HIV-infected children, PABSI is associated with the use of central venous catheters and may present as new pulmonary infiltrates and skin lesions (Flores et al., 1993; Roilides et al., 1992) and in cystic fibrosis, PA infection is associated with the acceleration of lung disease (Burns et al., 2001). Community-acquired PABSI may manifest in children with other immunodeficiency states including hypogammaglobulinaemia and neutropaenia (Baro et al., 2004; Johnston & Speller, 1977; Sanford et al., 2018). Community-acquired PABSI has also been reported among previously healthy, young children without underlying medical

conditions (Huang et al., 2002; Kuo et al., 2013). Neutropaenia may be associated with PA infections in immunocompetent children as a result of the production and elaboration of PA exotoxin A that leads to bone marrow suppression during the acute phase of illness (Huang et al., 2002).

The common sources of PABSI in children include the skin and soft tissue, lungs, abdomen and catheter-related or it may present without any focus (Rosanova et al., 2019; Yang et al., 2011). Ecthyma gangrenosum is a characteristic vasculitic skin lesion associated with PABSI. It results from perivascular bacterial invasion of the media and adventitia of arteries and veins with secondary ischaemic necrosis, inhibition of protein synthesis by PA exotoxin A and degradation of elastin by elastase, thus destroying the blood vessel wall support (Kanj & Sexton, 2018). The lesions commonly begin as painless red macules which rapidly evolve into areas of induration that develop into pustules and/or bullae that may occur anywhere on the body but especially on the genitalia, legs, abdomen and extremities. The lesions may become haemorrhagic as they evolve and gangrenous cellulitis may occur resulting in sharply demarcated, necrotic lesions (Viola et al., 2006). It may aid the clinician in suspecting PABSI in children without apparent underlying medical problems or reveal an undiagnosed immunodeficiency (Sanford et al., 2018). Recurrent episodes of otitis media may be a predisposing factor for PABSI in children with the risk of severe disease enhanced by the presence of fever, coagulation abnormalities, pneumonia and neutropaenia (Viola et al., 2006; Huang et al., 2002; Chuang et al., 2017). Seizures and gastrointestinal findings tend to be more common in previously healthy children with PABSI whilst fever and diarrhoea were common presenting symptoms in children with community acquired PABSI (Kuo et al., 2013; Viola et al., 2006).

The mortality of PABSI is high. In retrospective studies from Argentina and Taiwan, case-fatality rates of 30% and 35% respectively were documented (Kuo et al., 2013; Rosanova et al., 2019). Risk factors for mortality in children with PABSI include septic shock, multidrug-resistant (MDR) PA isolates, admission to an ICU, the presence of an underlying disease, pulmonary source of infection, ineffective empiric antibiotic therapy and diarrhoea as a

presenting feature (Akram et al., 2014; Grisaru-Soen et al., 2000 ; Kim et al., 2017; Rosanova et al., 2019). Conversely, among adults hospitalised at a tertiary centre in South Korea, Kim et al. demonstrated a 22.2% 14-day mortality, with delayed initiation of effective antimicrobial therapy for PABSI related to higher mortality (Kim et al., 2014).

PA is intrinsically resistant to certain beta-lactam antibiotics such as ampicillin and ceftriaxone and can acquire resistance during therapy to other antibiotics such as the carbapenems (Masuda et al., 1999; Okamoto et al., 2001). This makes the selection of empiric antibiotic therapy for suspected PABSI challenging. Carbapenems are frequently used empirically for serious infections but the growing threat of carbapenem resistance in PA may significantly decrease the efficacy of these last-resort antibiotics (Logan et al., 2016). Carbapenem-sparing antibiotic regimens such as the combination of piperacillin-tazobactam and amikacin have enhanced activity against PA because of the synergistic action of combination antibiotic therapy (Drago et al., 2004). In a multinational retrospective study (9 countries, 25 centres) involving 767 hospitalised patients with PABSI, treatment with beta-lactam monotherapy showed that the use of ceftazidime, an antipseudomonal carbapenem or piperacillin-tazobactam was not significantly associated with 30-day mortality. No significant differences between antipseudomonal antibiotics were demonstrated for clinical failure, microbiological failure, or adverse events, however the isolation of PA with new resistance to antipseudomonal drugs within 30 days, which was not apparent in the original isolate, was significantly more frequent with the use of carbapenems (Babich et al., 2020).

Generally, the major mechanisms of resistance used by PA can be classified as intrinsic, acquired and adaptive resistance. Intrinsic resistance of PA includes low outer membrane permeability, expression of efflux pumps that expel antibiotics out of the cell and the production of antibiotic-inactivating enzymes. Acquired resistance of PA can be achieved by either horizontal transfer of resistance genes between organisms or mutational changes (Breidenstein et al., 2011). Acquired resistance greatly contributes to the development of multidrug-resistant (MDR) strains, which increases the difficulty in eradicating this microorganism and leads to more cases of persistent infection and failed antibiotic therapy.

Adaptive resistance of PA involves formation of biofilm in the lungs of infected patients where the biofilm serves as a diffusion barrier to limit antibiotic access to the bacterial cells (Drenkard, 2003). The global burden of resistance among PA isolates is high. Based on the drug resistance pattern to antipseudomonal agents, PA can be described as multi-drug resistance (MDR), extensively- drug resistant (XDR) or pan-drug resistant (PDR). MDR strains are non-susceptible to at least one agent in three or more anti-microbial categories, XDR isolates are non-susceptible to at least one agent in all but two or fewer antimicrobial categories whilst PDR are non-susceptible to all agents in all antimicrobial categories (Magiorakos et al., 2012). The World Health Organization (WHO) has designated carbapenem-resistant PA as a critical pathogen that requires research and development for new and effective antibiotics (WHO, 2017) . Newer beta-lactams such as cefiderocol and imipenem-cilastatin-relebactam combination therapy have been developed for the treatment of infections caused by MDR Gram-negative organisms such as PA, but there is generally less clinical experience with them (Kazmierczak et al., 2019; Motsch et al., 2020) .

Few studies have described the prevalence of resistant PA isolates in BSI among children. In a study done at a Korean university hospital in 75 children with PABSI, the prevalence of MDR PA was 11.3%. In that study, the fatality rate was higher among children with PABSI caused by MDR isolates compared to those with non-MDR PA isolates, 57.1% versus 9.1% (Yang et al., 2011). At another teaching hospital in Korea, 36.1% of PABSI in children and adolescents with febrile neutropaenia was caused by MDR PA strains, and this was associated with a high case fatality rate (Kim et al., 2017).

While previous studies from sub-Saharan Africa have reported on the prevalence of PA in children with BSI, there are no paediatric studies providing detailed description of PABSI in children in sub-Saharan Africa. The present study was undertaken to address this knowledge gap. It describes the disease burden, clinical characteristics, antibiotic management, impact of multidrug-resistance and outcome of PABSI among children admitted to a tertiary referral hospital for children in Cape Town, South Africa. A better understanding of the clinical

epidemiology of PABSI in children at our hospital will help guide clinicians in the selection of appropriate empiric antibiotics

1.2 Ethical Considerations

The study was submitted for approval to the Departmental Research Committee, Department of Paediatrics and Child Health, University of Cape Town; Human Research Ethics Committee (HREC), Faculty of Health Sciences, University of Cape Town (Appendix 1); and the Research Committee at Red Cross War Memorial Children's Hospital (Appendix 2). The study was done in accordance with the Declaration of Helsinki. The HREC approval number is 107/2018.

The data was collected retrospectively, thus consent was not obtained from parents/legal guardians.

The data sheets included the names and hospital folder numbers of study subjects which enabled the researchers to check information from the hospital folders after data collection had been completed. Each name and hospital folder number was linked to a study number. Study numbers but not names or hospital folder numbers were entered into an electronic database for anonymous analysis and reporting.

Risk to participants

There were no risks to the patients included in the study. Data was collected retrospectively and analysed anonymously.

Benefits to the patient

There were no direct benefits to the patients included in this study

1.3 Journal for Publication- International Journal of Infectious Diseases

International Journal of Infectious Diseases (IJID) *is* a peer-reviewed, open access journal that publishes position papers, original clinical and laboratory-based research, together with reports of clinical trials, reviews, exceptional case reports. In 2018, the impact factor was 3.538. The interest areas of the *IJID* are epidemiology, clinical diagnosis, treatment, and control of infectious diseases with emphasis placed on under-resourced countries and this motivated my interest in choosing the journal. Original articles do not exceed 3500 words in length and the word count is from the introduction through to the end of the conclusion/discussion and does not include abstract, tables, figures, acknowledgements or reference list, refer Appendix 4 for the complete author guidelines.

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CHAPTER TWO: PUBLICATION-READY MANUSCRIPT

TITLE PAGE

Pseudomonas aeruginosa bloodstream infection at a tertiary referral hospital for children

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HIGHLIGHTS

- The incidence risk of *Pseudomonas aeruginosa* bloodstream infection in our setting was low.
- The majority of *Pseudomonas aeruginosa* bloodstream infections were healthcare-associated.
- 24% of the patients with *Pseudomonas aeruginosa* bloodstream infections died during hospitalisation.
- Infection present on admission and empiric antibiotics to which Pseudomonas aeruginosa isolate was not susceptible to, were associated with 14-day mortality in *Pseudomonas aeruginosa* bloodstream infection.
- Carbapenem-sparing treatment with antibiotics such as ceftazidime or piperacillin-tazobactam should be used for *Pseudomonas aeruginosa* isolates that are susceptible to these agents.

ABSTRACT

Introduction

This study describes the disease burden, clinical characteristics, antibiotic management, impact of multidrug resistance and outcome of *Pseudomonas aeruginosa* bloodstream infection (PABSI) among children admitted to a tertiary referral hospital for children in Cape Town, South Africa.

Methods

A retrospective descriptive study was conducted at a paediatric referral hospital in Cape Town, South Africa. Demographic and clinical details, antibiotic management and patient outcome information were extracted from medical and laboratory records. Antibiotic susceptibility results of identified organisms were obtained from the National Health Laboratory Service database.

Results

The overall incidence risk of PABSI was 5.4 PABSI episodes / 10,000 hospital admissions and the most common presenting feature was respiratory distress, 34/91 (37%). Overall, 69/91 (76%) of the PA isolates were susceptible to all antipseudomonal antibiotic classes evaluated. Fifty (55%) of the PABSI episodes were treated with appropriate empiric antibiotic therapy. The mortality rate was 24% and in multivariable analysis, empiric antibiotic therapy to which PA isolate was not susceptible to, infections present on admission, and not being in the intensive care unit at the time that PABSI was diagnosed were significantly associated with 14-day mortality.

Conclusion

The study provided insight into factors associated with PABSI in a tertiary hospital in Sub-Saharan Africa. Empiric antipseudomonal antibiotic therapy was associated with a decrease in 14-day mortality.

Keywords: *Pseudomonas aeruginosa* bloodstream infection, children, Sub-Saharan Africa.

BACKGROUND

Pseudomonas aeruginosa (PA) is a ubiquitous Gram-negative bacterium usually found in water, soil and plants. It is an important opportunistic pathogen in humans. Compared to other causes of bloodstream infection (BSI), PA occurs less frequently. However, studies from South Africa and Ghana have shown that PA causes between 4 and 6.5% of Gram-negative BSI (Dramowski et al., 2015; Lochan et al., 2017; Obeng-Nkrumah et al., 2016). PA typically causes healthcare-associated BSI among children with chronic or malignant diseases that are associated with impaired defence mechanisms such as neutropaenia, particularly in intensive care settings and among preterm infants with an immature immune system (Logan et al., 2016; Rosanova et al., 2019; Viola et al., 2006). Community-acquired PA bloodstream infection (PABSI) may manifest in children with other immunodeficiency states including hypogammaglobulinaemia and neutropaenia (Baro et al., 2004; Johnston & Speller, 1977; Sanford et al., 2018). Community-acquired PABSI has also been reported among previously healthy, young children without underlying medical conditions (Huang et al., 2002; Kuo et al., 2013) .

The mortality of PABSI is high. In retrospective studies from Argentina and Taiwan, case-fatality rates of 30% and 35% respectively were documented (Kuo et al., 2013; Rosanova et al., 2019). Risk factors for mortality in children with PABSI include septic shock, multidrug-resistant (MDR) PA isolates, admission to an intensive care unit (ICU), the presence of an underlying disease, a pulmonary source of infection, inappropriate empiric antibiotic therapy and diarrhoea as a presenting feature (Akram et al., 2014; Grisaru-Soen et al., 2000; Kim et al., 2017; Rosanova et al., 2019).

PA is intrinsically resistant to certain commonly used beta-lactam antibiotics such as ampicillin and ceftriaxone and can acquire resistance during therapy to other antibiotics such as the carbapenems (Masuda et al., 1999; Okamoto et al., 2001). This makes the selection of empiric antibiotic therapy for suspected PABSI challenging. The global burden of resistance among PA isolates is high. The World Health Organization (WHO) has designated carbapenem-resistant PA as a critical pathogen that requires research and development for new and effective

antibiotics (WHO, 2017). Few studies have described the prevalence of resistant PA isolates in BSI among children. In a study done at a Korean university hospital in 75 children with PABSI, the prevalence of MDR PA was 11.3%. In that study, the fatality rate was higher among children with PABSI caused by MDR isolates compared to those with non-MDR PA isolates, 57.1% versus 9.1% (Yang et al., 2011). At another teaching hospital in Korea, 36.1% of PABSI in children and adolescents with febrile neutropaenia was caused by MDR PA strains, and this was associated with a high case-fatality rate of 66.7% (Kim et al., 2017).

While previous studies from sub-Saharan Africa have reported on the prevalence of PA in children with BSI, there are no paediatric studies providing detailed description of PABSI in children in sub-Saharan Africa. The present study was undertaken to address this knowledge gap. It describes the disease burden, clinical characteristics, antibiotic management, impact of multidrug resistance and outcome of PABSI among children admitted to a tertiary referral hospital for children in Cape Town, South Africa.

METHODS

Study design, setting and inclusion/exclusion criteria

This retrospective descriptive study was conducted at Red Cross War Memorial Children's Hospital (RCWMCH), Cape Town, South Africa. This 273-bed facility serves as a referral centre for the paediatric population of the Western Cape province as well as surrounding provinces. Hospitalised children aged 0 to 14 years with culture- confirmed PABSI that was diagnosed between January 2009 and December 2017 were included in the analysis. Repeat blood cultures and insufficient information on clinical and antibiotic episodes were excluded.

Data collection

The Central Data Warehouse (CDW), housed in the information technology department of the National Health Laboratory Service (NHLS) in Johannesburg, South Africa, is a database of all laboratory investigations performed on patients treated in public sector hospitals and clinics in South Africa. The academic and research unit managing the CDW was approached to

retrieve the list of children admitted at RCWMCH with laboratory- confirmed PABSI from January 2009 until December 2017. This list was used to obtain microbiology results relating to every PABSI episode during the study period. These microbiology results were extracted from the NHLS microbiology database at Groote Schuur Hospital (GSH), Cape Town. Blood culture specimens from children admitted to RCWMCH are routinely transported to the GSH microbiology laboratory where they are processed. Clinical data relating to each PABSI episode were extracted from the patient hospital records at RCWMCH. Data collected included the patient's demographics, HIV and nutrition status, date of current hospital admission and admission in the past 30 days, and clinical information relating to the current admission such as clinical diagnosis and antibiotic usage. All microbiology and clinical data were entered in study-specific data collection sheets.

Microbiology testing

All microbiology testing was conducted at the NHLS clinical microbiology laboratory based at GSH, which is located 4.3 km from RCWMCH. Blood specimens were collected aseptically from patients either from a peripheral venepuncture or a central venous catheter. Blood was then inoculated at the bedside into an aerobic paediatric blood culture bottle. From 2009 to 2013, the BACTEC 9240 automated blood culture system (Becton Dickinson, Sparks, MD, USA) with BACTEC Plus aerobic blood culture bottles was in use. From 2013 until the end of the study period, BacT/ALERT PF Plus aerobic paediatric bottles were used along with the BacT/ALERT automated blood culture system (bioMerieux Inc., Durham, NC, USA).

At the GSH microbiology laboratory, paediatric blood culture specimens were registered and immediately incubated in the automated blood culture instrument. Once the instrument flagged positive due to detection by a light emitting diode of carbon dioxide, a Gram stain was prepared from the bottle. Bacterial identification and antibiotic susceptibility testing were performed according to the results of the Gram stain with final identification by the automated Vitek®2 system (bioMérieux, Inc., France) for the duration of the study period.

Vitek®2ID-GNB and AST-N133 cards were used for identification and susceptibility testing of Gram-negative bacilli observed on Gram stain respectively. The AST-N133 card includes the

following antibiotics: amikacin, gentamicin, ciprofloxacin, piperacillin-tazobactam, cefepime, ceftazidime, tigecycline, meropenem and imipenem. The antibiotic susceptibility testing methods and breakpoints are based on the Clinical and Laboratory Standards Institute (CLSI) of each year of the study . The breakpoints for meropenem, imipenem and piperacillin-tazobactam were revised in 2012. Changes in 2012 included an increase in the susceptibility breakpoints for piperacillin-tazobactam from ≤64/4 μg/mL to ≤16/4 μg/mL, and the introduction of a new intermediate category for piperacillin-tazobactam from 32/4 μg/mL to 64/4 μg/mL. In addition, the susceptible category breakpoints for imipenem and meropenem changed from ≤4 μg/mL to ≤2 μg/mL in 2012, while the intermediate category range changed from 8 to 4 μg/mL (CLSI, 2012). Breakpoints for all anti-pseudomonal antibiotics remained the same from 2012 until the end of the study period.

Definitions

BSI was classified as *infection present on admission* (IPOA) if PA was cultured from a blood culture specimen obtained on the day of admission to RCWMCH (calendar day 1), 2 days before admission or the calendar day after admission (calendar day 2) or *healthcare-associated infection* (HAI) if PA was isolated from a blood culture specimen obtained on or after the 3rd calendar day of admission to RCWMCH (Centers for Disease Control and Prevention (CDC), USA, 2017).

Date of onset of PABSI: The date on which the positive blood culture for PA was drawn.

Recurrent bloodstream infection: The re-isolation of PA on blood culture more than 14 days after completion of effective antibiotic therapy for the initial or previous PABSI.

Site of infection: The clinical site of infection as determined by the attending clinician.

Central venous access device (CVAD): An indwelling venous catheter that was inserted into the central venous system with the catheter tip positioned within the superior/inferior vena cava or right atrium, such as Hickman, Port-A-Cath, or central venous pressure (CVP) catheters (Dougherty, 2007)

Fever: An axillary temperature greater or equal to 38 degrees Celsius.

Anaemia: Blood haemoglobin concentration <11 g/dl (WHO, 2015).

Antipseudomonal antibiotics included gentamicin and amikacin (aminoglycosides), piperacillin (antipseudomonal penicillin), ciprofloxacin (quinolone), ceftazidime and cefepime (cephalosporins), meropenem and imipenem (carbapenems), and colistin (polymyxin).

A PA isolate was classified as (1) *multidrug-resistant (MDR)* if it was non-susceptible to at least one agent in three or more antipseudomonal antibiotic categories, (2) *extensively drug-resistant (XDR)* if it was non- susceptible to at least one agent in all but two or fewer antipseudomonal antibiotic categories, or (3) *pan drug-resistant (PDR)* if it was non-susceptible to all agents in all antipseudomonal antibiotic categories (Magiorakos et al., 2012).

Appropriate empiric antibiotic therapy: antibiotic therapy with *in vitro* activity against the PA isolate that was commenced at the onset of bloodstream infection before the antibiogram of the isolate was known.

Definitive antibiotic therapy: antibiotic therapy with *in vitro* activity against the PA isolate that was administered after the antibiogram of the isolate was known.

HIV status was classified as (1) *HIV-infected* in a child <18 months of age with a positive HIV DNA PCR result confirmed by either a quantitative HIV RNA PCR or repeat HIV DNA PCR on a separate sample, or a child ≥18 months of age with 2 positive serological test results (HIV ELISA or HIV rapid test) or a positive HIV DNA PCR result confirmed by either a HIV RNA PCR or repeat HIV DNA PCR test, (2) *HIV-uninfected* in a child with a negative HIV serological test (HIV ELISA or HIV rapid test) or a negative virological test for HIV (e.g. HIV DNA PCR) or (3) *Unknown* in a child with no history of HIV testing, no record of HIV testing in the NHLS laboratory database and whose mother's HIV status was unknown (Schneider et al., 2008).

Moderate and severe underweight were defined as weight-for-age Z-score (WAZ) between -2 and -3 standard deviations (SD) and a WAZ <-3 SD below the median WHO growth reference standards, respectively

Coagulopathy: A prothrombin time of ≥2 seconds, an activated partial thromboplastin time of ≥60 seconds or a fibrinogen level of <2 µmol/L (Dellinger et al., 2013).

Respiratory failure: the need for mechanical ventilatory support.

Renal dysfunction: a serum creatinine concentration above the normal age-related range (Boer et al., 2010; Pottel et al., 2008).

Liver dysfunction: a ≥2-fold increase of serum aspartate aminotransferase and/or serum alanine aminotransferase concentration and/or a total bilirubin in a child more than 28 days old of >70 µmol/L (Dellinger et al., 2013; Goldstein et al., 2005).

Sample size

There were no previous studies from Africa to calculate sample size and no similar study. However, we estimated a sample size using a retrospective descriptive study from Korea in children with Pseudomonas aeruginosa bacteraemia and a prevalence of 2.6% (Zhang et al., 2012). The estimated sample size was determined using the formula for a simple prevalence study.

$$n = \frac{z^2 p (1-p)}{e^2}$$

Where n= sample size

z= standard deviation at 95 % (1.96)

p= prevalence of adherence in children and adolescents

e= margin of error=5 % (0.05)

The sample size was calculated as 39. We increased this by 10% to 43 to make up for any losses.

The final estimated sample size was 45.

Statistical analysis

The data was analysed using STATA Statistical software, release 11, (College Station, Texas, USA). Incidence risk of PA-BSI was calculated per 10,000 hospital admissions. Proportions were depicted as percentages. Continuous variables were tested for normality and mean and standard deviation (SD) or median and interquartile range (IQR) used to describe the data as appropriate. The Student's t- test or Mann Whitney U test were used to compare continuous data based on their normal distribution, whilst the chi-squared, and Fisher's exact test was

used to compare categorical data. A two-sided significance level of $p<0.05$ was considered statistically significant. Predictors of 14-day mortality were explored using univariable and multivariable logistic regression analyses. The logistic regression model was built by stepwise backward selection, incorporating variables which on univariable analysis had a p value <0.20. The results of the logistic regression model were expressed as adjusted odds ratio (aOR) and 95% confidence intervals (CIs).

RESULTS

Study participants

During the study period there were 192,547 admissions to RCWMCH and 104 PABSI episodes. Analysis of the patient list and microbiology results obtained from the CDW and the NHLS clinical microbiology laboratory, GSH, respectively showed that during the study period 104 PABSI episodes occurred at RCWMCH. These episodes were used to estimate the risk of PABSI. Thirteen episodes of PABSI were excluded due to insufficient clinical and antibiotic data, thus 91 (88%) children were used in the subsequent analyses (Figure 1).

Classification and risk of *Pseudomonas aeruginosa* BSI

A total of 104 PABSI episodes was identified among 103 study participants during the study period; 69 (66%) episodes were HAIs and 35 (33%) were IPOA. There was one recurrent PABSI episode, a HAI which manifested 30 days after the initial PABSI episode. The overall incidence risk of PABSI throughout the study period was 5.4 PABSI episodes / 10,000 hospital admissions. There was a decline in annual incidence risk from 2009 until 2016 followed by a rise in 2017. This increase was mainly related to an increase in the incidence risk of HAI (Figure 2). The annual incidence risk of HAI was consistently higher than IPOA throughout the study period.

Characteristics of study participants

Table 1 describes characteristics of 91 PABSI episodes in 91 study participants, 60 (66%) episodes were HAIs and 31 (34%) were IPOA. The median time between admission and the development of PABSI in the 60 children who developed HAI was 13.5 days (IQR 7.0-28.0). The median age was 12 months (IQR 5-59) and 52% of the episodes occurred in females. There were 45/91 (50%) children under 1 year, out of which 8/45 (18%) were neonates. A higher proportion of children with HAI (38/60, 63%), experienced antibiotic exposure during the 12-month period preceding PABSI compared to children with IPOA (9/31, 29%, p=0.004). There were 13 cases of confirmed HIV infection with PABSI, 3/60 (5%) were HAI and 10/31 (32%) were IPOA. Fifteen (17%) of the children had underlying chronic illnesses other than HIV infection, that was present for at least 6 weeks duration. Eleven children had malignancies, namely, acute lymphoblastic leukaemia (3), acute myeloid leukaemia (2), lymphoma (1), neuroblastoma (1), craniopharyngioma (1) and germ cell tumour (1). Other chronic diseases included chronic lung disease (2), Fanconi anaemia (1) and aplastic anaemia (1). Children with IPOA had a significantly higher frequency of chronic diseases other than HIV, compared to those with HAI, (9/31, 29%) and (6/60, 10%) respectively, p=0.034.

Presenting features and complications of PABSI

Respiratory distress was the commonest presenting feature overall (34/91, 37%) and for HAIs (23/60, 38%) whereas diarrhoea was the commonest presenting feature for IPOA (13/31, 42%). Shock as a presenting feature was significantly more frequent among children with IPOA (9/31, 29%) than HAI (4/60, 7%), p = 0.009. Pneumonia was the most frequent site of infection, occurring in 33/91 (36%) of the PABSI episodes (Table 2).

Shock, as determined by the attending clinicians, was the commonest complication, occurring in 16/91 (18%) of the children; 11/16 (69%) required inotropic infusions. Shock, liver dysfunction and 14-day mortality were significantly more frequent complications in children with IPOA (Table 3).

Susceptibility profile of PA isolates and antibiotic therapy

Figure 2 summarises the susceptibility profile of the PA isolates during the study period. Overall, 69/91 (76%) of the PA isolates were susceptible to all antipseudomonal antibiotic categories evaluated, 12/91 (13%) isolates were MDR, 8/91 (9%) isolates were XDR and 2 (2%) isolates were PDR. The proportion of HAI isolates amongst the resistant isolates was 8/12 (67%) MDR, 7/8 (88%) XDR, and all the PDR isolates.

There were 19/91 (21%) isolates that were resistant to both imipenem and meropenem; there were an additional 2 that were resistant only to imipenem but not to meropenem i.e. a total of 21/91 (23%) isolates were resistant to imipenem. Ten meropenem-resistant isolates were susceptible to ceftazidime, (10/91; 9%), while 4/91 (4%) ceftazidime-resistant isolates were susceptible to meropenem. There were 8/91 (9%) isolates that were resistant to both ceftazidime and meropenem. Furthermore, of the 20/91 (22%) isolates resistant to gentamicin, 9/20 (45%) were susceptible to amikacin.

Fifty (55%) of the PABSI episodes were treated with appropriate empiric antibiotic therapy. A higher proportion of HAI PABSI episodes received appropriate empiric antibiotic therapy compared to IPOA PABSI episodes; 37/60 (62%) *versus* 13/31 (42%). This difference was, however, non-significant, p=0.081. Three antibiotics frequently used in empiric therapy for both HAI and IPOA were meropenem 27/91(30%), piperacillin-tazobactam 19/91(21%), amikacin 18/91 (20%). Piperacillin-tazobactam was frequently combined with amikacin for empiric therapy 18/19 (95%). There were 7/31 (23%) IPOA episodes that were treated with empiric cephalosporins therapy; 5/7 (71%) received ceftriaxone and 2/7 (29%) cefotaxime. Six (19%) of the IPOA episodes received ampicillin monotherapy as empiric antibiotic therapy and in a further 5/31 (16%) episodes, ampicillin in combination with gentamicin, to which none of the isolates were susceptible. There were 3/31 (10%) IPOA episodes that were treated with empiric piperacillin-tazobactam plus amikacin, but the isolates were resistant to both antibiotics. In 23/60 (38%) episodes of HAI that received empiric antibiotic to which PA isolate was not susceptible to, 8/23 (35%) received ertapenem which is not an antipseudomonal antibiotic, 9/23 (39%) received piperacillin-tazobactam and amikacin and 6/23 (26%) received meropenem, to which the isolates were resistant.

The mean time ± SD to effective antibiotic therapy (appropriate empiric antibiotic therapy or definitive antibiotic therapy) was 1.3 days ± 1.1. The difference in mean time to effective antibiotic therapy for HAI was 1.2 days ± 0.9 and 1.6 days ± 1.5 in IPOA, this was not significant (p = 0.112). The antibiotic most frequently used as definitive antibiotic therapy for both IPOA and HAI was meropenem. Overall, 37/91 (41%) PABSI episodes were treated with meropenem; 23 of these 37 episodes (62%) isolates were caused by isolates that were susceptible to ceftazidime. By contrast, only 18% of the PABSI episodes were treated with ceftazidime (Table 4).

Outcome

There were 69/91 (76%) PABSI episodes that were successfully treated, with the children being discharged from hospital after these episodes. Twenty-two (24%) of the children died during their hospitalisation. Most of the deaths, 17/22 (77%), occurred within 14 days of hospitalisation as a direct result of PABSI. The median time (IQR) to death of these 17 children was 1.4 (1.0–8.3) days and 11/17 (65%) of these deaths were due to IPOA. Of the 5 deaths that occurred after 14 days, the median time (IQR) to death was 22.5 (20.8-30.3) days and 3/5 (60%) had IPOA.

On multivariable analysis, empiric antibiotic therapy to which PA isolate was not susceptible to, IPOA, and not being admitted in the ICU at the time that PABSI was diagnosed were significantly associated with 14-day mortality. Multidrug-resistant, XDR or PDR isolates were not predictors of 14-day mortality (see Table 5).

DISCUSSION

This retrospective descriptive study was conducted on laboratory confirmed PABSI in children admitted to RCWMCH between 1 January 2009 and 31 December 2017. To the best of our knowledge, this is the first study from sub-Saharan Africa describing PABSI in detail among hospitalised children. The majority of the PABSI episodes, 69/104(66%) were HAIs. This is consistent with previous research that showed that PA infections are mostly healthcare-associated (Rosanova et al., 2019; Yang et al., 2011). Environmental analysis suggests that PA is found in the moist areas of hospitals such as sinks and colonises respiratory equipment in Intensive Care Units (ICUs) (Grisaru-Soen et al., 2000), highlighting the importance of good infection prevention and control practices in preventing healthcare-associated PABSI.

In addition to hospital admission, host factors are important determinants of infection. The prevalence of underlying chronic diseases and HIV infection were significantly higher in children with IPOA in this study. In these children, impaired host defence mechanisms are likely to increase the risk of PABSI as described in previous studies (Kim et al., 2017; Zhang et al., 2012). The CDC definition for IPOA used in the present study includes all infections in whom the corresponding isolates were cultured on the day of admission, 2 days before admission or the day after admission, irrespective of a recent hospitalisation. In the present study 20/31 (65%) of the PABSI episodes classified as IPOA were preceded by hospitalisation occurring within 28 days prior to the current hospitalization, suggesting that the hospital environment may have predisposed some of these children to PA colonisation, and effective IPC practices may have prevented some of these PABSI episodes.

PABSI can present with common childhood symptoms of a febrile illness such as respiratory distress, diarrhoea and discharging ears or with severe manifestations such as septic shock (Viola et al., 2006; Zhang et al., 2012). In this study, respiratory distress and diarrhoea were the commonest presenting symptoms.

Healthcare-associated infections were significantly more frequent in children who developed PABSI in the ICU, those with a central venous catheter and/or endotracheal tube, and those who had had surgery during the current admission. Patients treated in the ICU tend to be immunocompromised, require invasive procedures and may be exposed to broad-spectrum antibiotics, and in this study those who had received intravenous broad-spectrum antibiotics such as piperacillin-tazobactam or meropenem 12 months prior to the current admission had significantly more HAI than IPOA. Implementation of appropriate infection prevention and control intervention bundles and antimicrobial stewardship must be part of ICU management to decrease the incidence of HAI caused by PA.

The overall in-hospital mortality rate of 24% was lower than reported in previous paediatric studies. At a single centre in China, the overall mortality rate was 52% over a 5-year period among 36 children, with a significant association between mortality and ineffective initial antibiotic therapy (Zhang et al., 2012). In Buenos Aires, a high overall mortality of 31% was reported among 100 children over a 3-year period. The deaths were associated with admission to ICU, primary bacteraemia or multidrug-resistant isolates (Rosanova et al., 2019). The lower mortality in our study is likely to have been the result of the majority, 50/91(55%), of BSI events receiving appropriate empiric antibiotic therapy, as confirmed in the analysis of the determinants of 14-day mortality. In other studies, MDR PA and carbapenem resistance were found to be associated with mortality (Lee et al., 2017), but this was not demonstrated in our study.

At RCWMCH, the combination of piperacillin-tazobactam and amikacin is frequently used empirically when HAI is suspected. However, a carbapenem antibiotic, usually meropenem is frequently used with or without vancomycin as empiric antibiotic therapy in children with severe HAI including when septic shock is present. Of the HAI and IPOA isolates, 83% and 90% respectively, were susceptible to amikacin, whereas 58% and 61% of the HAI and IPOA isolates respectively, were susceptible to piperacillin-tazobactam. Thus, most PA isolates were susceptible to at least one antibiotic in this empiric combination.

Of 19 isolates that were resistant to meropenem, 10 remained susceptible to ceftazidime, an effective antipseudomonal antibiotic. This implies that ceftazidime can be prescribed in a subset of carbapenem-resistant PA infections, as a colistin-sparing intervention. Furthermore, the polymyxins have a narrow therapeutic window, and the major adverse effects of neurotoxicity and nephrotoxicity, makes the use of alternative agents such as ceftazidime desirable when applicable (Nation & Li, 2009).

Study limitations

Due to the retrospective study design, there were limitations in the availability and completeness of clinical and laboratory data. Additionally, information on previous antimicrobial exposure was limited to what was documented in the patient hospital records. Our sample size was small and was probably underpowered to explore risk factors associated with 14-day mortality comprehensively. Furthermore, our study did not include an appropriate control group, hence risk factors for PABSI were not evaluated. Despite these limitations, the findings do advance our understanding of PABSI in children in a sub-Saharan African context.

CONCLUSION

The study provides useful insights about PABSI at our institution. The most common presenting symptom was respiratory distress, whilst independent determinants of 14-day mortality were empiric antibiotic therapy to which PA isolate was not susceptible to, and infections present on admission to hospital. Further research is required to determine whether the presentation of PABSI, PABSI-associated mortality and the determinants of PABSI mortality differ in other parts of sub-Saharan Africa.

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We thank Ms Simone Twaku and the records department of RCWMCH for the provision of the hospital files needed for retrospective review. We acknowledge the NHLS and the Central Data Warehouse (CDW), housed in the information technology department of the National Health Laboratory Service (NHLS) in Johannesburg, for the provision of data on blood cultures and antimicrobial susceptibilities for patients from RCWMCH. We also acknowledge Dr Adelaide Masu and Ms Patti Apolles for their assistance with data entry.

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ETHICAL CONSIDERATIONS

The study was completed in accordance with the Declaration of Helsinki and approved by the Human Research Ethics Committee, Faculty of Health Sciences, University of Cape Town, reference number: HREC 107/2017 (Appendix 1). Furthermore, the hospital research committee approved the study (Appendix 2). Informed consent was not obtained from individual patients or caregivers because the data was collected retrospectively. Patient details were anonymised before data analysis.

Conflict of interest

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Joycelyn Dame collected the data from the RCWMCH patient files and the NHLS results database for the investigated cases and wrote the manuscript. Brian Eley provided guidance

on the title and objectives of the study as well as the study literature review, data analysis and manuscript development. Natalie Beylis supported manuscript writing particularly for the description of microbiology methods and assisted with retrieval of the list of blood cultures from the Central Data Warehouse in Johannesburg to identify PABSI cases. James Nuttall assisted with the study protocol and manuscript development. All authors reviewed and approved the final draft.

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FIGURES

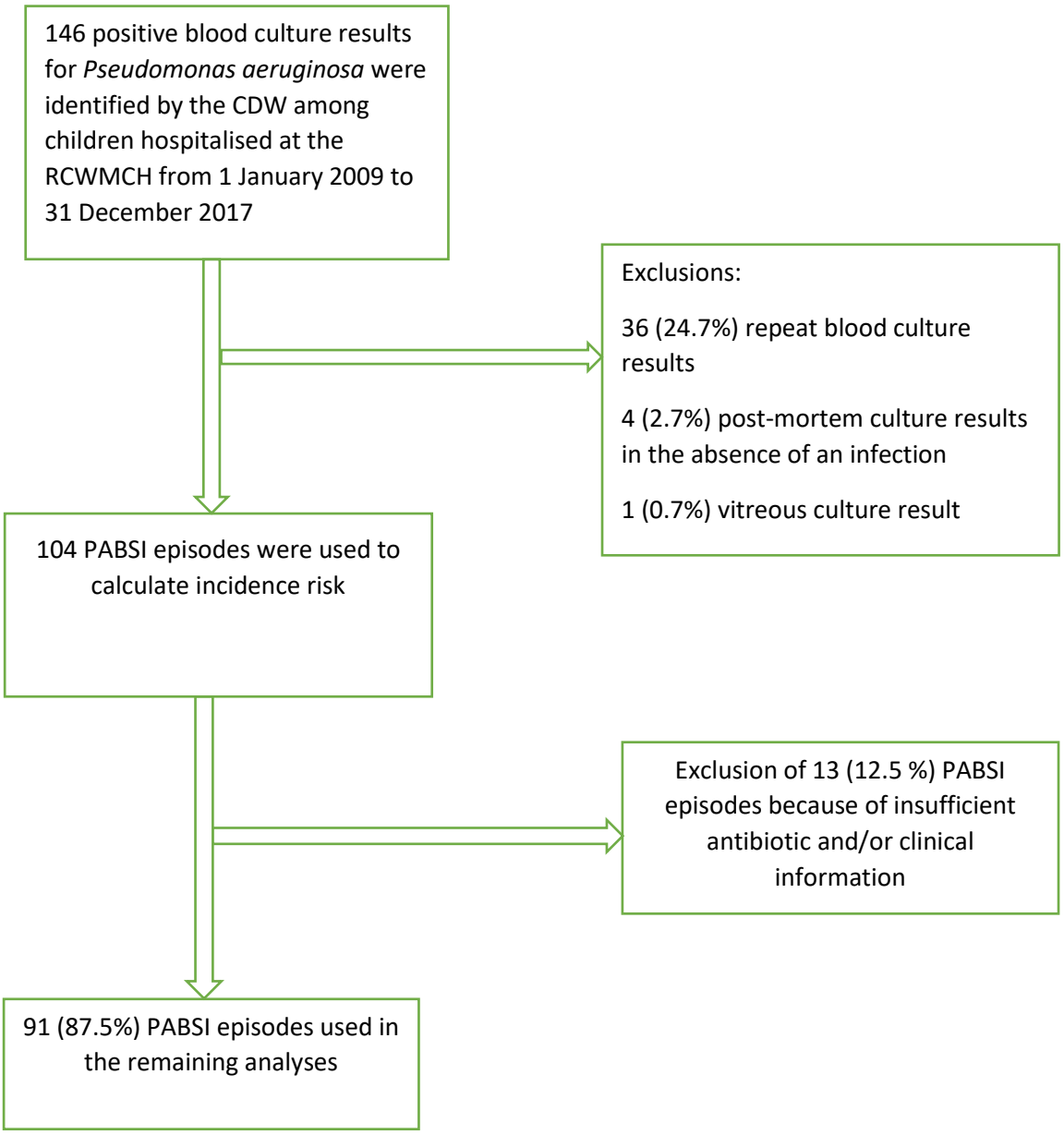

Figure 1. Selection of *Pseudomonas aeruginosa* bloodstream infection episodes for data analysis. CDW, Central Data warehouse; PABSI, *Pseudomonas aeruginosa* bloodstream infection; RCWMCH, Red Cross War Memorial Children's Hospital.

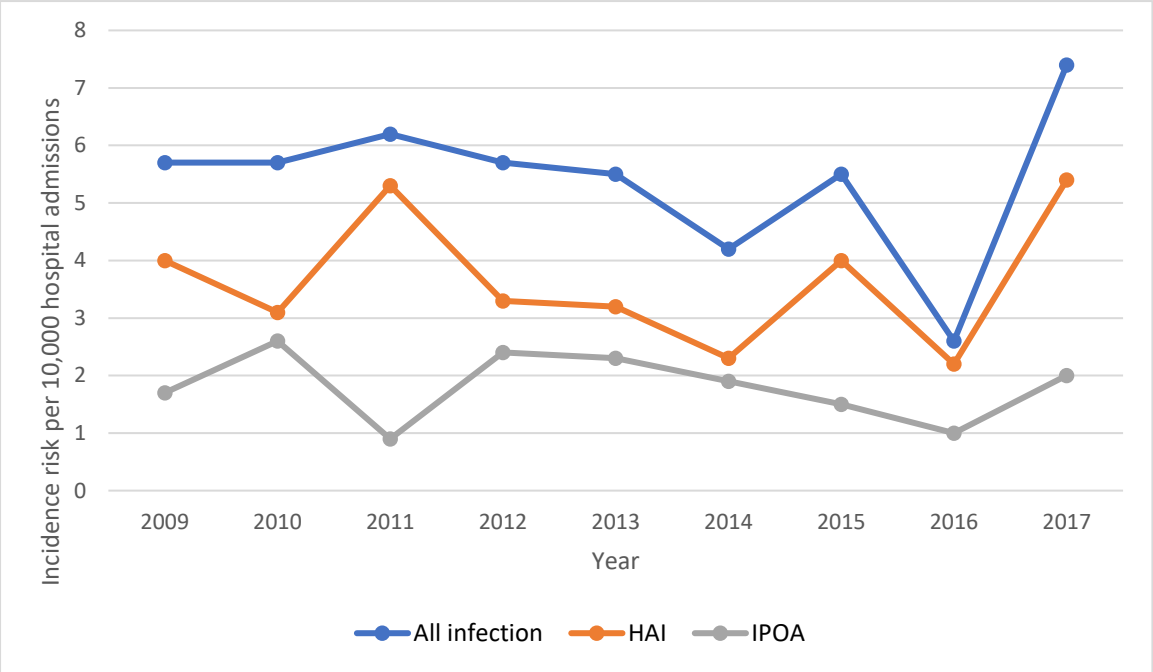

Figure 2. Annual incidence risk per 10 000 hospital admissions. HAI, healthcare-associated infection; IPOA, infection present on admission.

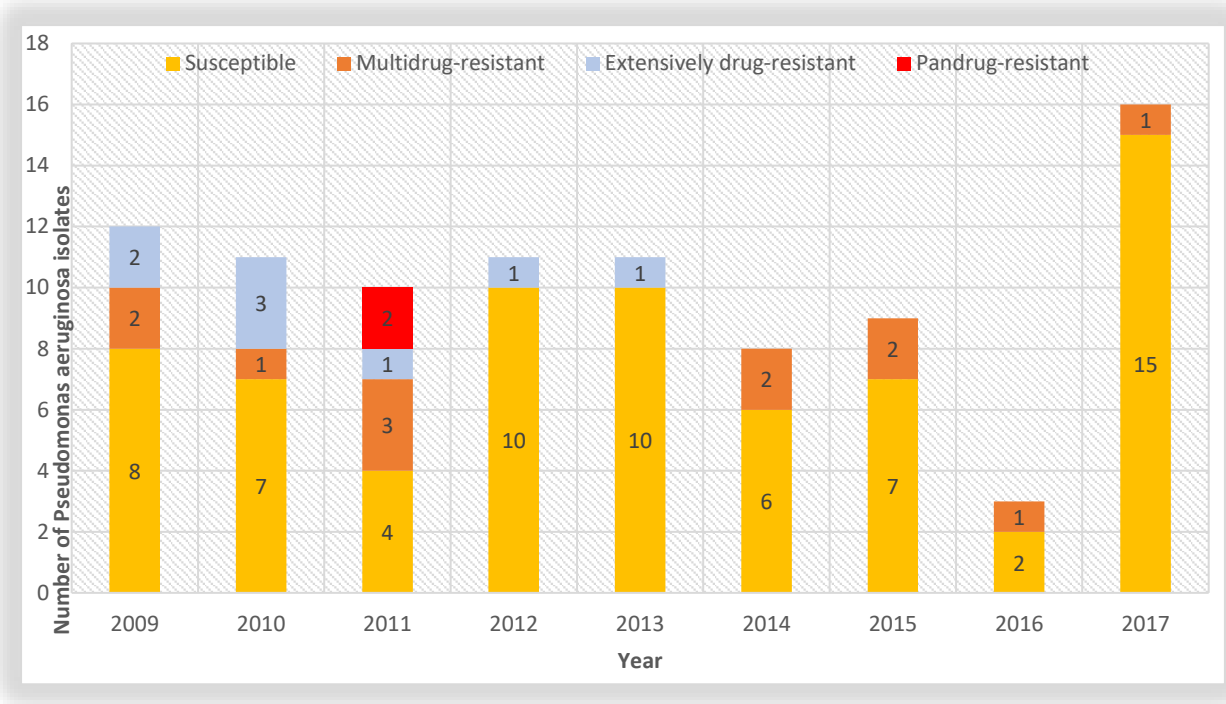

Figure 3. Annual antibiotic susceptibility profile of *Pseudomonas aeruginosa* isolates by antipseudomonal antibiotic susceptibility category, 2009-2017. M*ultidrug-resistant (MDR)*, non-susceptible to at least one agent in three or more antipseudomonal antibiotic categories; *extensively drug-resistant (XDR)*, non-susceptible to at least one agent in all but two or fewer antipseudomonal antibiotic categories; *pan drug-resistant (PDR)*, non-susceptible to all agents in all antipseudomonal antibiotic categories (Magiorakos et al., 2012).

TABLES

Table 1. Characteristics of children at the time of *Pseudomonas aeruginosa* bloodstream infection

Variable	Total N= 91	HAI N=60	IPOA N=31	P value*
Age (months) median (IQR)	12 (5-59)	10 (4.5-46)	19 (6-69)	0.065
Age category, n/N (%)				
<1 year	45 (50)	34 (57)	11 (36)	0.107
1-5 years	22 (24)	11 (18)	11 (36)	
>5 years	24 (26)	15 (25)	9 (29)	
Gender, n/N (%)				
Male	44 (48)	27 (45)	17 (56)	0.387
Female	47 (52)	33 (55)	14 (45)	
HIV status, n/N (%)				
HIV-infected	13 (14)	3 (5)	10 (32)	0.002
HIV-uninfected	51 (56)	36 (60)	15 (48)	
Unknown	27 (30)	21 (35)	6 (19)	
Weight-for-age, Z score category, n/N (%)				
Moderate underweight	9 (10)	3 (5)	6 (20)	0.008
Severe underweight	22 (25)	11 (19)	11 (37)	
Temperature in degrees Celsius				
<35^{o}C	3 (3)	1 (2)	2 (7)	0.459
>35.5-37.9^{o}C	19 (22)	12 (21)	7 (23)	
≥38.0^{o}C	65 (75)	44 (77)	21 (70)	
Anaemia	64 (70)	40 (67)	24 (77)	0.210
Hospitalisation in the 28-day period preceding the current admission, n/N (%)	47 (52)	27 (45)	20 (65)	0.121
Exposure to selective intravenous antibiotics, in the preceding 12 months, n/N (%)	47 (52)	38 (63)	9 (29)	0.004
Selective intravenous antibiotics exposure in the preceding 12 months, n/N (%)				
Gentamicin or amikacin	23 (25)	19 (32)	4 (12)	0.074
2nd to 4th generation cephalosporins	13 (14)	8 (62)	5 (39)	0.757
Piperacillin-tazobactam	12 (13)	12 (20)	0 (0)	0.005
Meropenem or ertapenem	16 (18)	15 (25)	1 (3)	0.009
Chronic diseases other than HIV infection, n/N (%)	15 (17)	6 (10)	9 (29)	0.034
Any ICU admission in this hospitalisation, n/N (%)	61 (67)	50 (83)	11 (35)	0.0001
Central venous access device *in situ*, n/N (%)	59 (55)	48 (80)	11 (36)	0.0001
Endotracheal Intubation *in situ*, n/N (%)	54 (60)	46 (77)	8 (26)	0.0001
Burn wound, n/N (%)	19 (21)	11 (18)	8 (27)	0.416
Surgery during current admission, n/N (%)	46 (51)	39 (65)	7 (23)	0.0001

*Comparison of HAI and IPOA, HAI, healthcare-associated infection; IPOA, infections present on admission; PABSI, *Pseudomonas aeruginosa* bloodstream infection; C, Celsius; ICU, intensive care unit

Table 2. Presenting clinical features of *Pseudomonas aeruginosa* bloodstream infection and site of infection

Variable	Total N=91 n/N (%)	HAI N=60 n/N (%)	IPOA N=31 n/N (%)	P value
Presenting features[a]				
Respiratory distress	34 (37)	23 (38)	11 (36)	0.487
Diarrhoea	29 (32)	16 (27)	13 (42)	0.107
Wound infection	23 (25)	18 (30)	5 (16)	0.116
Shock	13 (14)	4 (7)	9 (29)	0.009
Ecthyma gangrenosum	3 (3)	1 (2)	2 (7)	0.267
Otitis media	4 (4)	1 (2)	3 (10)	0.113
Other[b]	7 (8)	3 (5)	4 (13)	0.224
Site of infection				
No definable focus	18 (20)	12 (20)	6 (19)	1.000
Pneumonia	33 (36)	22 (37)	11 (36)	1.000
Gastrointestinal tract[c]	7 (8)	3 (5)	4 (13)	0.224
Skin & soft tissue infection	20 (22)	16 (27)	4 (13)	0.184
Line infection	8 (9)	6 (10)	2 (7)	0.711
Urosepsis	4 (4)	1 (2)	3 (10)	0.132

HAI, healthcare-associated infection; IPOA, infection present on admission; a, some patients presented with > 1 presenting feature; b, vomiting (2), renal angle tenderness (1), necrotising bowel (1), tachycardia (1), eye discharge (1), acute abdomen (1); c, gastroenteritis (4), acute appendicitis (1), acute peritonitis (2).

Table 3. Complications and outcome associated with *Pseudomonas aeruginosa* bloodstream infection

Variable	Total N=91 n/N (%)	HAI N=60 n/N (%)	IPOA N=31 n/N (%)	P value
Shock	16 (18)	7 (12)	9 (29)	0.047
Coagulopathy	10 (11)	5 (8)	5 (16)	0.300
Renal dysfunction	12 (13)	7 (12)	5 (16)	0.534
Liver dysfunction	4 (4)	0 (0)	4 (13)	0.012
Respiratory failure	11 (12)	6 (10)	5 (16)	0.500
14-day mortality	17 (19)	6 (10)	11 (36)	0.005

HAI, healthcare-associated infection; IPOA, infection present on admission

Table 4. Antibiotic susceptibility of *Pseudomonas aeruginosa* bloodstream infection isolates, and the definitive antibiotic therapy used during the study period

Antibiotic	Susceptibility of PA isolates to anti-pseudomonal antibiotics			Antibiotics used as definitive antibiotic therapy		
	HAI N=60 n/N (%)	IPOA N=31 n/N (%)	Total N=91 n/N (%)	HAI N=60 n/N (%)	IPOA N=31 n/N (%)	Total N= 91 n/N (%)
Gentamicin	43 (72)	28 (90)	71 (78)	5 (8)	2 (7)	7 (8)
Amikacin	50 (83)	28 (90)	78 (86)	10 (17)	6 (19)	16 (18)
Ciprofloxacin	42 (70)	28 (90)	70 (77)	12 (20)	7 (23)	19 (21)
Piperacillin-tazobactam	35 (58)	19 (61)	54 (59)	12 (20)	9 (29)	21 (23)
Ceftazidime	50 (83)	29 (94)	79 (87)	8 (13)	8 (26)	16 (18)
Cefepime	47 (78)	26 (84)	73 (80)	11 (18)	2 (7)	13 (14)
Meropenem	44 (73)	28 (90)	72 (79)	27 (45)	10 (32)	37 (41)
Imipenem	43 (72)	27 (87)	70 (77)	2 (3)	0 (0)	2 (2)
Colistin	-	-	-	9 (15)	-	9 (10)

PA, *Pseudomonas aeruginosa*; HAI, healthcare-associated infection; IPOA, infection present on admission

Table 5. Predictors of 14-day mortality in children with *Pseudomonas aeruginosa* bloodstream infection

Variable	Unadjusted OR (95% confidence interval)	P-value	Adjusted OR (95% confidence interval)	P value
Age category N=91				
< 1 year n= 45	1		_	
≥ 1 year n= 46	0.66 (0.23-1.93)	0.45		
Weight N=88				
Normal weight n=57	1			
Moderate or severe Underweight n=31	0.44 (0.15-1.32)	0.10	1.60 (0.330-7.803)	0.557
Admission in a health care facility 28 days prior to current hospitalisation N= 34	0.80 (0.27- 2.4)	0.79	_	
Chronic disease (excluding HIV) N=80	1.2 (0.24-6.13)	0.827	_	
HIV status N= 91				
HIV-uninfected n= 51	1			
HIV-infected n= 13	1.34 (0.32- 5.68)	0.70	_	
HIV status unknown n= 27	0.89 (0.22-3.62)	0.87		
Nature of infection N=91				
IPOA n= 31	1			
HAI n= 60	0.202 (0.066-0.619)	0.005	0.083 (0.01-0.60)	0.013
MDR, XDR or PDR isolates N=22	1.05 (0.30-3.61)	0.945	_	
Appropriate empiric antibiotic N = 50	0.19 (0.06-0.63)	0.007	0.23 (0.07-0.82)	0.023
Burn wounds N=19	2.24 (0.47-10.77)	0.315	_	
Septic shock (as a presenting feature or complication of PABSI) N=29	3.29 (1.05-10.23)	0.040	2.27 (0.41-12.55)	0.346
Anaemia N=64	1.47 (0.43-4.99)	0.540	-	
Surgery during current admission N=46	1.96 (0.64-6.0)	0.235	-	
ICU management N=30				
Patient diagnosed with PABSI whilst in the ICU n= 11	0.43 (0.15-1.25)	0.101	0.04 (0.005-0.365)	0.004
Patient requiring ICU care after PABSI diagnosis n=19	1.21 (0.399-3.670)	0.737	-	

OR, odds ratio; HAI, healthcare-associated infection; IPOA, infection present on admission; MDR, multi-drug resistant; XDR, extensively drug resistant; PDR, pan-drug resistant; PABSI, *Pseudomonas aeruginosa* bloodstream infection

APPENDICES

1. FACULTY OF HEALTH SCIENCES ETHICS APPROVAL LETTER

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: sumayah.arieffdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

12 February 2018

HREC REF: 107/2018

Prof B Eley
Department of Paediatrics & Child Health
Room 520, 5th Floor
ICH Building,
Red Cross War Memorial Children's Hospital

Dear Prof Eley

PROJECT TITLE: PSEUDOMONAS AERUGINOSA BLOODSTREAM INFECTION IN CHILDREN HOSPITALIZED AT THE RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL IN CAPE TOWN (MPhil-candidate-Dr J Dame)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 28 February 2019.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student: Dr J Dame will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.

HREC:107/2018

2. APPROVAL LETTER FROM HOSPITAL RESEARCH COMMITTEE

Dr Anita Parbhoo
Manager: Medical Services
Email: Anita.Parbhoo@Westerncape.gov.za
Tel: +27 21 658 5742 fax: +27 21 658 5166
RXH: RCC115

Prof B Eley
Red Cross War Memorial Children's Hospital

Dear Prof B Eley

APPROVAL OF RESEARCH

PROJECT TITLE: PSEUDOMONAS AERUGINOSA BLOODSTREAM INFECTION IN CHILDREN HOSPITALISED AT RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL IN CAPE TOWN

It is a pleasure to inform you that approval is hereby granted to conduct the above-mentioned study at Red Cross War Memorial Children's Hospital.

Yours sincerely,

aparbhoo

DR A PARBHOO
MANAGER: MEDICAL SERVICES
RCWMCH

08/3/18
DATE:

3. 2020 ANNUAL PROGRESS REPORT / ETHICS RENEWAL

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

HUMAN RESEARCH ETHICS COMMITTEE
15 NOV 2019
HEALTH SCIENCES FACULTY

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HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.11.2020
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	15/11/2019

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	13 November 2019		
HREC REF Number	107/2018	Current Ethics Approval was granted until	28 February 2019
Protocol title	*Pseudomonas aeruginosa* bloodstream infection in children hospitalised at Red Cross War Memorial Children's Hospital in Cape Town		
Principal Investigator	Brian Eley		
Department / Office Internal Mail Address	Room 520, 5th floor, ICH building, Red Cross War Memorial Children's Hospital, Klipfontein Road, Rondebosch, 7701		
1.1 Does this protocol receive US Federal funding?		☐ Yes	✓ No

2. Protocol status (tick ✓)

☐	Research-related activities are ongoing
✓	Data collection is complete, data analysis only

Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/registry/repository.

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval		104
Total number of records or specimens collected, reviewed or stored since last progress report		104
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	✓ Yes	☐ No

4. Signature

Signature of PI	BJE	Date	13 November 2019

4. AUTHORS INSTRUCTIONS: INTERNATIONAL JOURNAL OF INFECTIOUS DISEASES

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5: DATA COLLECTION SHEET

Biographical Information

Study No		
Folder No		
Date of Birth		
Gender	Male	Female
Admission mass (kg)		WAZ score
Admission height/length(cm)		WHZ score
Nutritional status (Z score)		
Presence of oedema	Yes	No

ADMISSIONS

Admission Status at RXH

Date of current admission to RXH		*Time of admission to RXH:*	*Ward / dept in which Blood culture was taken:*
Admission to RXH in past 28 days	*Yes/No*	*Duration*	

No of admissions to RXH in past 1 year	*Date of Admission*	*Duration of admission*
1.		
2.		
Admission to ICU in past 28 days	*Yes /No*	*Duration of admission*
Admissions to ICU in past 1 year	*Date of admission*	*Duration of admission*

Admission to other health care facilities

	Yes	*No*	*Date of admission*	*Duration of admission*
Admission during preceding 28 days				
Admission during preceding 1 year				

CLINICAL CHARACTERISTICS

HIV Infection

Patient tested for HIV	*Yes*	*No*	*Unknown*
HIV Test	*Rapid*	*PCR*	*Elisa*
Date test done			
HIV exposed	*Yes*	*No*	*Unknown*
HIV infected	*Yes*	*No*	*Unknown*
	Date	*Values*	
CD4 %/Abs(baseline) (µL)			
CD4 % /Abs (most recent)/(µL)			
Viral load (baseline)/(copies/ml)			
Viral load (most recent)/(copies/ml)			
Treatment with ART at time of blood culture	*Yes*	*No*	*Unknown*
Date of ART initiation		*Duration on ART*	

Clinical features at time of bloodstream infection

Symptoms/Signs	*Yes*	*No*	
Diarrhoea			
Shock	Hypovolemia	Cardiogenic	Septic
Ecthyma gangrenosum			
Otitis media			
Seizures			
Wound sepsis			
Respiratory distress			
Hypoxia (sats < 90^{o}C			
Other			

***Identified focus of infection at time of bloodstream infection*? Yes No**

Focus of infection	**Indicate as appropriate**
Primary bactaeremia	
Pneumonia	
Meningitis	
Osteomyelitis	
Septic Arthritis	
Catheter related blood stream infection	
Soft tissue infection	
Otitis media	

Urinary tract infection	
Other	

Temperature at time of blood stream infection /^{o}C…….

Evidence supporting an invasive infection at time of bloodstream infection

Clinical diagnosis of infection	**Yes**	***No***
Fever≥ 38^{o}		
Elevated white cell count		
Low white cell count		
Elevated C reactive protein		
Procalcitonin		
Other (specify)		

Underlying medical illness or risk factors

Medical illness /Risk factors	***Yes***	***No***	***Other information if indicated***
Chronic lung disease			
Cystic fibrosis			
HIV			
Burns			
Malnutrition			
Malignancy specify type			
Immunosuppressive therapy			
Steroid therapy (> 1 month duration)			
Permanent indwelling catheter specify type			
Intraosseous assess			
Central lines- CVP/Broviac/Hickman			
Peripheral venous catheter			
Surgical drains			
Intravenous fluid administration			
Naso/tracheal intubation			
Tracheostomy			
Urinary catheter			
Surgery during admission			
Others please state			

Investigations at time or close to bloodstream infection

Investigation	**Date/Time**	**Value**
Haemoglobin (g/dl)		
MCV (fl)		
White cell count (x 10^9 cells/L)		
Neutrophil count (x 10^9 cells/L)		
Band count		
Lymphocyte count (x 10^9cells/L)		
Platelet count (x 10^9 cells/L)		
C reactive count(mg/dL)		
Procalcitonin(µg/dL)		
Other relevant results		

DIAGNOSIS

Diagnosis during current admission

Initial diagnosis	
Additional diagnoses	
Final diagnosis	

Pseudomonas Aeruginosa Bloodstream Infection Diagnosis

Date blood culture was taken	
Time blood culture taken if available	
Date blood culture was received	
Time blood culture was received if available	

History of recurrent blood stream infection

Yes	No
Date(s) of the other episode	
Time between episodes	

Other Positive culture specimen

Site	Date	Organism(s)	Sensitivity	Resistance

ANTIBIOTICS

Antibiotic Sensitivity Profile to Pseudomonas Aeruginosa

Antibiotic	**Sensitive**	**Resistant**
Amikacin		
Tobramcyin		
Gentamicin		
Ceftazidime		
Cefepime		
Ciprofloxacin		
Levofloxacin		
Piperacillin		
Piperacillin/tazobactam		
Ticarcillin/clavulanate		
Imipenem		
Meropenem		
Other		

Antibiotic exposure in the last year

Antibiotic exposure	Yes	No	Name of drug	Duration of exposure
Carbapenems				
4th generation cephalosporin				
Fluoroquinolones				
Aminoglycosides				
Piperacillin- tazobactam				
Ticarcillin-clavulanic acid				

Empiric Antibiotic at time of/ prior to blood culture taken

Name of Antibiotic	Date and time of start	Date and time ended	Duration	Route

Empiric Antibiotic after blood culture taken if applicable

Name of Antibiotic	Date and time started	Date and time ended	Duration	Route

Definitive Antibiotics in response to blood stream infection

Antibiotic	Name	Date of start	Date ended	Duration	Route

Complications and outcome

Complications

Complications	**Yes**	**No**
Septic shock/ Inotropic Support		
DIC		
Renal failure		
Liver dysfunction		
Respiratory Failure		
Others please state.		

ICU admission *(if applicable)*

Date of admission	Total duration of admission	Reason for admission	Outcome

Hospital outcome

Discharge	Yes	No	
Date of discharge		Time of discharge	

Death	Yes	No	
Date of death		Time of death	
Cause of death			