Acinetobacter baumannii Infections in the Paediatric Intensive Care Unit of a tertiary hospital in South Africa

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Declaration

I, Deveshni Reddy, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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1. Protocol

1.1 Abstract

Acinetobacter baumannii (*A. baumannii)* is now increasingly recognised as an important cause of nosocomial infections in paediatric intensive care unit (PICU) patients, particularly in developing countries, where it contributes significantly to morbidity and mortality. Furthermore, it has been documented that emerging antimicrobial resistance patterns complicate antibiotic choice in these patients. At present, more paediatric data is needed regarding these infections.

This is a retrospective case-control study that aims to document the demographic data and relevant clinical details of patients in whom *A. baumannii* was cultured, either from blood or respiratory specimens (thus including both infections and colonisation), in the PICU at Red Cross War Memorial Children's Hospital (RCWMCH) during 2010.

Secondary objectives include comparing these patients with those in whom *A. baumannii* was not cultured and determining which isolates were causing infection and which were colonisers. In addition; of the isolates regarded as infections, documenting the antimicrobial sensitivities and resistance of the organisms cultured, determining whether infections were late or early onset and determining whether specific bed numbers were consistently involved.

1.2 Background

The Acinetobacter genus consists of a group of non-fermenting, aerobic Gram-negative cocco-bacilli, normally found in soil and fresh water (1).

This species, in particular *Acinetobacter baumannii*, has been increasingly recognised as an important cause of nosocomial infections, particularly in an intensive care unit (ICU) setting (2,3,4,5).

In addition, recent studies have shown an increase in antimicrobial resistance in isolates from ICU patients (4,6). This poses a serious dilemma with regard to therapeutic antibiotic choice in severely ill patients. Outbreaks of carbapenem-resistant strains of *Acinetobacter baumannii* have been reported in diverse geographical areas such as America, Europe, Far East and India (7).

The majority of studies conducted about *A. baumannii* infections in ICU patients have been in adults; however *A. baumannii* has also been implicated as the main cause of paediatric nosocomial pneumonia in studies from South Africa and Brazil, both developing countries with different patient profiles to that of PICU's in developed countries (8,9,10).

A South African study conducted in Durban in 2000 demonstrated the emergence of a multi-drug resistant Acinetobacter species during outbreaks in both the NICU and PICU at King Edward Hospital (3). It was a case-defined, descriptive study of two outbreaks that occurred over two eight-week periods in 1999 in both ICU's – 23 patients were studied altogether. Molecular typing of the isolates suggested patient-to-patient spread and the associated mortality rate was 56.5%. No comparisons were made between those who developed infections and those who did not.

A retrospective case-control study was conducted in a PICU in Greece in 2006, regarding the acquisition of imipenem-resistant *A. baumannii* (2). It was also a small study with 26 cases and 52 controls. Demographic variables, co-morbid conditions, clinical picture at admission, invasive procedures and use of antimicrobials were analysed as potential risk factors. Multivariate analysis revealed aminoglycoside use and length of stay in ICU as independent risk factors for acquisition of imipenem-resistant *A. baumannii*.

1.3 Study objectives

1.3.1 Primary objective

a. To describe the demographic and clinical features of patients from whom *A. baumannii* was isolated over a period of 1 calendar year.

1.3.2 Secondary objectives

a. To compare the features of patients in whom *A. baumannii* was cultured and those in whom it was not; in terms of demographics, mortality, duration of PICU stay, duration of invasive positive pressure ventilation (IPPV), and severity of illness on admission to ICU as determined by the Paediatric Index Mortality Score 2 (PIM2).

b. To determine which isolates were causing infection and which were colonisers.
c. To compare the features of patients who were infected with *A. baumannii* with those who were colonised.
d. Of the patients infected with *A. baumannii*:
    I. To determine when, relative to ICU admission, *A. baumannii* was first isolated in patients.
    II. To describe the resistance and sensitivity patterns of the organisms.
    III. To determine if the same bed spaces were consistently associated with patients infected with *A. baumannii*.

1.4 Study Design

This is a retrospective case-control study focused on patients in the PICU at RCWMCH, in whom *A. baumannii* was isolated during the period 1 January 2010 to 31 December 2010.

1.5 Methodology

1.5.1 Study population

The PICU at RCWMCH is a 20-bed unit, which serves as a tertiary referral centre for a large proportion of the Western Cape. It also provides a tertiary ICU service to areas in the Eastern Cape.

The cases will consist of patients admitted to the PICU at RCWMCH during the period 1 January 2010 to 31 December 2010, from whom *A. baumannii* was isolated either from blood or respiratory specimens (tracheal aspirates, bronchoalveolar lavage). These will include both patients infected with *A. baumannii* and those colonised.

Cases in whom *A. baumannii* was cultured from blood, will be considered infected. In the cases that *A. baumannii* was cultured from respiratory specimens, clinical notes will be reviewed to determine if there were other features correlating with a new infection at the time of culture i.e. rising septic markers (white cell count, procalcitonin levels etc.), temperature spikes, increased ventilator requirements, Clinical Pulmonary Infection Score (appendix) suggestive of infection.

In order to quantify resistance, cultured organisms will be grouped according to their resistance profiles i.e. fully susceptible to all classes of antibiotics, resistant to 1 class only, resistant to 2 classes, resistant to >2 classes.

Controls will be patients admitted to the ICU during the same time period, from whom *A. baumannii* was not cultured. The controls will be matched to the cases in a 1:1 ratio, based on the chronological order of admissions i.e. one sequential admission prior to or after the admission of the case patient.

1.5.2 Study procedures

All isolates of *Acinetobacter baumannii* from respiratory or blood specimens will be identified from the data of the National Health Laboratory Service (NHLS), over the period 1 January 2010 to 31 December 2010. These patients will be included in the study as cases. The information available from this database would include the age, sex, date of birth of the subject, as well as the date on which the specimen was taken and the nature of the clinical specimen (blood, tracheal aspirate, bronchoalveolar lavage). Antimicrobial sensitivity of the organism cultured will also be obtained from the same database. Re-admissions to the PICU will not be included as separate cases.

This data will be linked to patient data via the PICU database. Information regarding the date of admission to ICU, duration of PICU stay, duration of IPPV, mortality, PIM2 score on admission and the bed space occupied by the patient will be obtained from the PICU database, which logs all the clinical and demographic details of all admissions to ICU. This database is updated on a daily basis by the consultants. Any additional information regarding a patient's condition, if unavailable from the PICU database, will be obtained from the patient's folder.

1.5.3 Statistical analysis

All the information about both cases and controls collected from the two databases will be entered on a Microsoft Excel spreadsheet and then analysed using STATISTICA (data analysis software system).

Normally distributed continuous variables will be reported as mean (standard deviation). Non-normally distributed continuous variables will be reported as median (interquartile range). Categorical variables will be compared by t test. Risk ratios and confidence intervals will be calculated using standard formulae. Adjusted odds ratios will be modelled using logistic regression.

1.6 Ethics

As this is a retrospective study, no additional tests or procedures will be conducted on the study patients.

Patients enrolled in the study will be allocated a study number and thus their confidentiality will be protected. No reference will be made to any patient in any research output arising from this study, which could lead to their identification.

1.7 Dissemination of results

Results of the study and the final dissertation will be presented to the School of Child and Adolescent Health Research Committee for evaluation. Results will be presented at a content-relevant congress and submitted for publication in a peer-reviewed journal.

1.8 References

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2. Literature review

2.1 Objective of the literature review

The objective of this study is to describe the clinical and demographic features and outcomes of patients from whom *Acinetobacter baumannii (A. baumannii)* was isolated from blood or respiratory specimens, whilst admitted in the Paediatric Intensive Care Unit (PICU) at Red Cross War Memorial Children's Hospital (RCWMCH) in Cape Town, South Africa during 2010.

The modified Clinical Pulmonary Infection Score (CPIS), made up of several clinical parameters has been used to identify ventilator associated pneumonia (VAP) in other studies conducted in the PICU at RCWMCH (1,2). We aim to distinguish between infection and colonisation in cases with positive cultures from respiratory specimens by using the CPIS.

Finally, the features of those from whom the organism was cultured will be compared with a control group from who it was not. A comparison will also be made between those infected with the organism and those colonised.

Acinetobacter baumannii is a gram negative cocco-bacillus that is ubiquitous in nature and can survive for prolonged periods of time in water and on various surfaces (3). It is being reported with increasing frequency in hospital settings and outbreaks may occur due to widespread environmental contamination and breaches in implementation of infection control policies. The organism has also demonstrated the ability to develop resistance to a wide range of antimicrobial agents (3).

A. baumannii has been reported as a common cause of nosocomial infections in adult ICU settings (3,4,5). More recently it has been reported to also cause nosocomial infections, especially VAP, in PICU settings (2,6,7). This seems to be the case in both developed and developing countries. However, there remains a paucity of data concerning this organism in the PICU population worldwide and more specifically in South Africa. The vast majority of studies are still conducted in adult ICU's.

Nosocomial infections exponentially increase costs both in monetary terms and in terms of health resource allocation. In a resource limited setting, such as ours, it becomes even more important to identify potentially modifiable factors in order to decrease the number of nosocomial infections and save time, money and lives.

The main aim of this literature review is to describe the prevalence, clinical features and impact of *Acinetobacter baumannii* infections in a PICU setting.

2.2 Literature search strategy

An internet search using PubMed was undertaken. Key words used in the search were *Acinetobacter baumannii* AND Paediatric Intensive Care Unit.

This search led to 60 articles.

Abstracts were scanned for the most relevant articles for inclusion in this review.

Inclusion criteria for studies were:

1. Human studies in English.
2. Studies conducted in paediatric ICU's.
3. Studies describing demographic and clinical details of PICU patients from whom Acinetobacter was cultured.

Studies that were excluded were those conducted in adult ICU's or neonatal ICU's only, with no mention of a PICU population. Studies conducted in paediatric populations in general paediatric wards were excluded unless they included data from the PICU population as well. Studies that focused on basic molecular microbiological factors without describing any patient characteristics were excluded.

There was no time limit set on publication of studies, but more recent and larger studies were favoured when the most relevant literature was selected.

After applying the above criteria 10 articles were selected for inclusion in this review, 3 of which are South African studies and 7 of which were conducted elsewhere in the world.

2.3 Literature

2.3.1 South African studies

2.3.1.1 Studies conducted in the RCWMCH PICU

Morrow et al 2012 (1)

This was a prospective observational partially randomised clinical study done in the RCWMCH PICU, investigating the effect of closed-system suctioning on the frequency of VAP. All infants and children ventilated for >24hrs were eligible for inclusion. VAP was defined as a noscomial lower respiratory tract infection (LRTI) occurring in mechanically ventilated patients ≥48 hrs after initiation of ventilatory support. It compared closed system suctioning to open endotracheal suctioning on the frequency of VAP. The suctioning system was randomised monthly. Demographic, clinical and laboratory data were recorded.

A CPIS was calculated for all ventilated patients on a daily basis and cut-off points were determined in order to define VAP. Two hundred and fifty patients in 263 PICU admissions were included in the study. Fifty nine patients developed VAP with a calculated rate of 45.1 infections per 1000 ventilator days.

VAP was also shown to be associated with an increased length of PICU and hospital stays. Although VAP was not found to predict crude mortality on multivariate analysis, the risk-adjusted mortality was greater in those who did develop VAP. The most commonly isolated organisms from respiratory specimens were *Acinetobacter baumannii* and *Klebsiella pneumoniae*. Viral pathogens were not looked for. Closed-system suctioning did not impact on the frequency of VAP or patient outcome in this study.

This article is important for inclusion in this literature review as it confirmed the presence of VAP in the RCWMCH PICU, and found *A. baumannii* to be strongly associated with the development of VAP. It also highlighted the serious consequences of VAP in terms of prolonged length of PICU and hospital stay, thus re-inforcing the need for more research into this topic.

Morrow et al 2009 (2)

In this study the primary objective was to obtain preliminary prevalence, aetiological and outcome data on RCWMCH PICU patients with VAP. This study also highlighted the use of the CPIS in the identification of VAP in PICU patients. The medical and laboratory data of all those patients who had non-bronchoscopic bronchoalveolar lavage (BAL) specimens taken between January 2004 and September 2005 as part of their standard care, was reviewed.

VAP was defined as a new organism (bacterial, viral or fungal) detected on BAL as well as a modified CPIS of ≥ 5. *A. baumannii* was the most common organism identified in patients with VAP (33.9% of VAP cases). It was shown to be nosocomially acquired in all cases. The majority of patients (55/63) with VAP developed it between 2 and 4 days post intubation. The median length of PICU stay in patients with VAP was shown to be significantly longer than those without VAP. The risk-adjusted mortality was also higher in the group of patients with VAP.

Due to the retrospective nature of the data collection, causality between the organism and VAP could not be established but a definite association was shown to exist. Again, VAP was shown to be associated with a longer PICU stay and a higher risk adjusted mortality.

2.3.1.2 Other South African studies

Jeena et al 2001 (8)

This was a study conducted in both the neonatal ICU (NICU) and PICU of a tertiary hospital in Durban, South Africa. It was a case-defined descriptive study of two outbreaks of multi-drug-resistant (MDR) *Acinetobacter anitratus (A. anitratus)* that occurred during different time periods during 1999 in the NICU and PICU of King Edward VIII Hospital. This PICU was a 12 bed unit which was divided into a ‘neonatal’ section (6 beds for those patients <5kg or <3 months) and a paediatric section (6 beds).

This article was included in the literature review because it was conducted in South Africa and documents PICU data separately from the NICU data. Even though the organism was not *Acinetobacter baumannii* it does belong to the same genus and shows many similarities in terms of infectivity and host susceptibility.

Twenty three infants under 2 months of age acquired MDR *A. anitratus* during the two outbreaks. Eighteen of these patients were in the 'neonatal' section of the PICU and the other five patients were in the NICU. There were no cases of infection in the older group of children in the PICU.

The organism was isolated from endotracheal aspirates in all 23 cases. Blood cultures isolated the same organism in 7 cases. All 23 cases showed clinical deterioration at the time the organism was isolated, either in terms of radiological deterioration, abnormal laboratory parameters or temperature abnormalities. Infection was associated with a 56.5% mortality.

Although the organism was cultured from various items of equipment in the NICU and PICU (table surfaces, ventilator dials etc.), susceptibilty patterns were different from the infecting organism.

In this study younger patients appeared to be more susceptible to nosocomial infections with the Acinetobacter genus. It also showed an association with a poorer outcome and a higher mortality in NICU and PICU patients infected with Acinetobacter.

2.3.2 Non-South African studies

Hu et al 2010 (9)

This was a systematic review of the literature up to December 2008 for reports of invasive Acinetobacter infections in children. All studies providing information on the clinical course and outcome of one or more cases of Acinetobacter infection, defined as the organism being isolated from a normally sterile site (thus excluding culture from respiratory specimens), in children up to the age of 18 years were included in the review. Reports only describing colonisation with the organism were excluded.

One hundred and one studies were included. They were divided into outbreaks (believed by study authors to be epidemiologically linked), case series (2 or more cases not believed to have a common source) and case reports (individuals). Eighteen of the included studies documented possible outbreaks, 33 were case series and 49 were case reports.

The vast majority of the suspected outbreaks (16/18) were in NICU settings involving either bacteraemia or meningitis. Identification of the source of the outbreaks was seldom established. Attributable mortality in the cases series and outbreaks combined was 14.5%. Outbreaks occurred in geographically diverse areas such as Asia, Europe, South America and Africa. A variety of Acinetobacter species were implicated. *A. baumannii* was the offending organism in 6 studies. Typing of isolates was only done in 1 study. The source of the outbreak was proven in 1 study. The majority of these patients had bloodstream infections. Meningitis was the second most common infection. Eleven studies reported deaths attributable to Acinetobacter and the mortality varied from 0% to 44%.

The case series dated as far back as 1953. There were 33 studies included in this review. The majority occurred in India, Slovakia and the United States. The number of patients per case series was very variable (from 1 to 138). Only 1 study was from a PICU, the others being from NICU's, neurosurgical ICU's and paediatric wards. *A. baumannii* was implicated in 13 of the 33 studies. Twenty four studies reported on patients being 5 years and younger. There was equal distribution between males and females. Twenty studies reported mortality directly attributable to Acinetobacter infection. This varied from 0% to 83%.

The case reports included 49 studies, the majority of which were from the developed world. These reports included unusual presentations of Acinetobacter infection eg. skin abscesses, osteomyelitis etc.

This review article highlighted the wide range of clinical presentations which infection with Acinetobacter can cause and that *A. baumannii* has been associated with outbreaks in at least 6 studies. The Acinetobacter genus seems to be prevalent in both developed and developing countries as is evident from the diverse geographical areas named in this study.

The patients most commonly infected with the organism appeared to be younger (neonates) and sicker (ICU patients). The most common infections in this review was either bacteraemia or meningitis. A shortcoming of this study is that VAP caused by Acinetobacter was not reported on owing to the fact that the diagnosis is based on culture of the organism from respiratory specimens, which was not considered an acceptable means of diagnosing infection in this study.

Balkhy et al 2012 (10)

This was a retrospective study conducted in a tertiary hospital in Saudi Arabia. The medical records of all children under 12 years of age with positive cultures for Acinetobacter species between October 2001 and December 2007 were reviewed. The objective of the study was to describe the epidemiology of Acinetobacter species hospital acquired infections (HAI's) and colonisation among inpatients.

Patients who had community acquired infections or those who were outpatients at the time of positive culture were excluded from the study. The National Healthcare Safety Network's definition was used to identify HAI's (11). Isolates were also classified according to whether they were multi-drug resistant (MDR) or not. MDR Acinetobacter species were defined as those organisms showing resistance to three or more of the commonly used antimicrobial classes of drugs, according to microbiological susceptibility testing.

Patients included in the study were thus divided into three groups viz. those who had MDR Acinetobacter HAI's, those who had antibiotic susceptible Acinetobacter HAI's and those who did not fulfill the definition for HAI (these were classified as colonised, regardless of whether the organism cultured was MDR or not).

Clinical data such as demographics, length of hospital stay and admission diagnosis was extrapolated from medical records of the patients. Outcome measures evaluated for each patient included length of hospital stay, length of stay after positive culture, whether ICU admission was required, length of ICU stay and in-hospital mortality within 14 days of positive culture.

One hundred and five patients were included in the study out of a potential 175 who had positive clinical cultures for Acinetobacter. Thirty seven patients were colonised, 23 had HAI's with MDR Acinetobacter and 45 had HAI's with susceptible Acinetobacter. Comparisons were made between the two groups infected with the organism (Table 1), and then between the MDR Acinetobacter infected group and the colonised group (Table 2).

Table 1. Comparison between MDR Acinetobacter group and antibiotic susceptible Acinetobacter group

Patient characteristics	**MDR *Acinetobacter* infections (n=23)**	**Antibiotic susceptible *Acinetobacter* infections (n=45)**	**p-value**
Mean age years (SD)	5.3 (4.0)	1.8 (3.5)	0.0004
Female	12 (52.2%)	23 (51.1%)	0.93
Reason for admission			
Burns	12 (52.2%)	1 (2.2%)	
Cardiac disease	3 (13%)	23 (51.1%)	0.002
Infection type			
VAP	8 (34.8%)	12 (26.7%)	
Central line associated bloodstream infection	6 (26.1%)	12 (26.7%)	
Bloodstream infection not associated with central lines	3 (13%)	12 (26.7%)	
Admitted to PICU	21 (91.3%)	34 (75.6%)	0.12
Infection acquired in PICU	15 (65.2%)	28 (62.2%)	0.81
Length of PICU stay (mean(SD))	32.9 (30.4)	37.4 (52)	0.72
Length of PICU stay till first positive culture	10.3 (10)	8.8 (44.6)	0.86
Total length of hospital stay	52. 4 (34.6)	58.5 (50.5)	0.61
Mortality for infections acquired in PICU	7 (46.7%)	8 (28.6%)	0.23
Overall mortality	9 (39.1%)	12 (26.7%)	0.29

Table 2. Comparison between MDR Acinetobacter group and colonised group

Patient characteristics	MDR *Acinetobacter* infections (n=23)	*Acinetobacter* colonised patients (n=37)	p value
Mean age years (SD)	5.3 (4.0)	2.7 (3.6)	0.01
Female	12 (52.2%)	14 (37.8%)	0.28
Reason for admission			
Burns	12 (52.2%)	4 (10.8%)	
Cardiac disease	3 (13%)	16 (43.2%)	0.01
Admitted to PICU	21 (91.3%)	26 (70.3%)	0.06
Organism acquired in PICU	15 (65.2%)	16 (43.2%)	0.1
Length of PICU stay (mean(SD))	32.9 (30.4)	32 (31)	0.92
Length of PICU stay till first positive culture	10.3 (10)	28.8 (66.7)	0.2
Total length of hospital stay	52. 4 (34.6)	49.8 (56.5)	0.84
Mortality for organisms acquired in PICU	7 (46.7%)	2 (12.5%)	0.01
Overall mortality	9 (39.1%)	4 (10.8%)	0.02

Of significance is that the patients with MDR Acinetobacter HAI's were older than both colonised patients and those infected with antibiotic susceptible organisms. Burns was the most common reason for admission in the MDR group and VAP was the most common HAI caused by MDR Acinetobacter. The total length of hospital stay and the length of ICU stay was similar across all groups. The majority of HAI's were acquired in an ICU setting. More than 70% of the MDR isolates were resistant to aminoglycosides, quinolones and 3rd generation cephalosporins. MDR Acinetobacter infection was associated with a higher mortality when compared to the colonised group.

A substantial number of patients from whom the organism was cultured were colonised and studies have shown that colonisation may precede infection in certain patients (12,13). A third of the isolates were MDR and a significant number of these children were shown to have received inappropriate empiric antibiotic therapy. Although the mortality in these children was double that in children who received appropriate antibiotic therapy for the MDR Acinetobacter, it was not statistically significant.

The limitations of this study included it's retrospective nature and thus the inability to identify risk factors for Acinetobacter infection or colonisation. The Acinetobacter species were not subdivided therefore we do not know the role *Acinetobacter baumannii* specifically played.

Katragkou et al 2006 (14)

This study was a retrospective case-control study to determine risk factors for the acquisition of imipenem-resistant *Acinetobacter baumannii* (IRAB) in the PICU population of a tertiary hospital in Greece. Cases comprised of children admitted to the PICU between July 2001 and December 2003 in whom IRAB was isolated from any clinical specimen and thus included both colonised and infected patients. The cases were matched to the controls in a 2:1 ratio according to chronological order of admission.

Patients admitted to ICU for <4 days were excluded. Readmissions were not analysed as separate patients. Data was collected retrospectively and consisted of demographic details, preceding hospitalisation history, severity of illness on admission, underlying diseases or co-morbidities, use of mechanical ventilation and invasive devices or procedures. Antimicrobial exposure was also documented over 2 periods viz. 15 days and 30 days prior to discharge (controls) or isolation of IRAB (cases).

Over the study period there were 423 PICU admissions, and IRAB was isolated from 26 of them. A total of 84 *A. baumannii* isolates were recovered. There was no significant difference in the monthly incidence of cases. IRAB was isolated from respiratory specimens in 37% of cases. Other sites included blood (26%), CSF (7%), urine (4%), pleural effusion and catheter tips (26%).

There was no significant difference between cases and controls in terms of gender, birth weight, location before admission, PRISM III score, prior ICU stay, hospitilisation during the past year, mortality rate or co-morbidities. No significant differences were present in terms of admission diagnosis.

Cases were older than controls at admission. Cases appeared to stay significantly longer in the PICU than controls, and were exposed to beta lactam antibiotics and aminoglycosides for longer than controls. On univariate and multivariate analysis the 2 independent risk factors for the isolation of IRAB were found to be time at risk (defined as duration from the date of PICU admission to the date of IRAB acquisition) and duration of aminoglycoside use 15 days prior to isolation of IRAB.

The results of this study will be comparable to our study due to the similar methodology used and outcomes determined. This study highlighted the association between a longer duration of PICU stay and the isolation of IRAB. Prior exposure to certain classes of antibiotics has been associated with drug-resistant *A. baumannii* isolates (3,4). In this study an association was found with prior use of aminoglycosides. A limitation of this study is the failure to distinguish between patients infected with *A. baumannii* and those merely colonised by it.

Ebenezer et al 2011 (7)

This was a short study describing an outbreak of MDR *A. baumannii* induced VAP in a PICU in India. The outbreak occurred between September and October 2008. *Acinetobacter baumannii* was isolated from clinical specimens including non-bronchoscopic BAL specimens. Possible sources of the organism were then investigated.

During the study period 73 patients were admitted to the PICU, of which 43 (59%) required ventilatory support. *A. baumannii* was cultured from 6 BAL specimens. All these patients had shown clinical deterioration and were suspected of having VAP when the BAL specimens were taken. All the isolates were multi-drug resistant. The patients in the study were young with a mean age of 4.5 months.

Samples were analysed from oxygen humidifying chambers, ventilator humidifiers and thermometer solutions. Swabs were also taken from ventilator tubing suction devices and other surfaces in the PICU. Seven of the 12 water samples from the oxygen humidifying chambers grew *A. baumannii*. These isolates were similar to the isolates from the patients with regard to antibiotic susceptibility.

The sterilisation and cleaning practices of the respiratory equipment were reviewed and found to be suboptimal. New cleaning and maintenance practices were put into place and the outbreak was controlled thereafter.

This study was conducted in a developing country with a similar patient profile to ours. It highlighted the importance of reviewing infection control practices when dealing with *A. baumannii*. The organism can grow in the water of various respiratory equipment in ICU settings and thus place critically ill patients at risk of nosocomial infections.

Chang et al 2007 (15)

This was a retrospective study describing the clinical characteristics and outcomes of paediatric patients colonised or infected with MDR *A. baumannii* (MDRAB) in a tertiary hospital in Taiwan. MDRAB were defined as those organisms not susceptible to aminoglycosides, cephalosporins, carbapenems and ciprofloxacin. Positive clinical specimen cultures for MDRAB taken from the PICU's, NICU and general paediatric wards were looked at from April 2000 till December 2005 and patient records subsequently reviewed.

A total of 205 isolates of MDRAB were obtained from 52 paediatric patients during the study period. Forty three (82.7%) of these patients were in ICU during the time the organism was isolated. The clinical data recorded included demographic characteristics, underlying disease, length of ICU stay, whether mechanical ventilation was required and antibiotic usage before and after culture of the organism (Table 3).

The majority of the isolates (75%) were from respiratory specimens and almost 10% of isolates from sterile sites like blood, ascites and catheter tips. Patients who had positive cultures from respiratory specimens were reviewed for signs of pneumonia and if these were not present they were considered colonised. Mortality was deemed related to MDRAB if no other pathogen was identified at the time of bacteraemia. Thirty one (59.6%) patients were considered to be infected with MDRAB. There were 22 deaths (42.3%) and 6 of these were directly attributable to MDRAB sepsis.

Table 3. Characteristics and outcomes of patients with MDR *A. baumannii* isolation

Patient Characteristics	**n = 52**
Male:Female	1.00:1.08
Mean age (range)	6 years (3 days-27 years)
Mean duration of ICU stay in days (range)	58.2 (0-201)
Underlying diseases	
Haematological or Oncological diseases	15 (29%)
Neurological disorders	12 (23%)
Cyanotic congenital heart disease	10 (19%)
Gastrointestinal disease	3 (5.8%)
Infectious diseases	2 (3.8%)
Neonatal disorders	6 (11.5%0
Received mechanical ventilation	48 (92.3%)
Neutropaenia	14 (26.9%)
Major surgery	17 (32.7%)
Broad spectrum antibiotic usage prior to isolation of *A. baumannii*	46 (88.5%)
Mortality	22 (42.3%)

Most patients were exposed to broad spectrum antibiotics prior to the isolation of MDRAB and had required ICU admission and mechanical ventilation. Infection with MDRAB was associated with a prolonged ICU stay. This has been shown in previous studies as well (1,2,14).

Hong et al 2012 (16)

This study described an outbreak of IRAB in a PICU in Korea. Twenty positive cultures for IRAB from January 2010 to February 2011 were obtained and the clinical and demographic details of the patients documented. Active surveillance was performed and the environmental sources looked for.

Thirteen of the 20 were determined to be infected due to clinical deterioration at the time of culture and the fulfillment of Centers for Disease Control and Prevention (CDC) criteria for nosocomial infections (17). Of these 13, 10 had bacteraemia and 3 had pneumonia. The mean age of the patients was 6 years and the mean duration of ICU stay before a positive culture was 25 days. The mean total length of ICU stay was 67 days.

The underlying diseases of the infected patients were haemato-oncological diseases, diaphragmatic hernias, complex congenital heart disease and gastrointestinal diseases. Death thought to be directly attributable to the IRAB infection occurred in 85% (11/13) of the infected patients with the mean interval between infection and death being 5.3 days.

Thirty eight environmental samples were collected for analysis and 4 samples taken from a single sink and water tap in the PICU cultured IRAB. The sink was found to be shallow with a water overflow problem resulting in lots of towels being placed around the sink. Active surveillance was performed from December 2010 to June 2011. The sink was replaced and 11 weeks after active surveillance there were no positive cultures for IRAB from either patients or the environmental samples.

This study found pneumonia and blood stream infection to be the commonest diagnoses in patients with nosocomial IRAB infection. IRAB infection was associated with a prolonged ICU stay and a high mortality rate. It re-inforced the importance of looking for environmental sources of *A. baumannii* and the successful implementation of infection control measures and active surveillance in controlling an outbreak.

Ozdemir et al 2011 (6)

In this study conducted in a PICU in Turkey, the medical records of children who cultured *A. baumannii* between January and December 2008 were reviewed and clinical characteristics and outcomes recorded. Of the 203 patients admitted to the PICU during this period, 15 patients were found to have nosocomial infections with *A. baumannii* according to CDC criteria fulfillment (18).

The mean age of infected patients was 55.5 months. There was no significant difference in gender. The leading diagnoses were VAP (10/15 patients), catheter related blood stream infections (4/15) and VAP associated with meningitis (1 patient). The mean length of ICU stay was significantly longer in infected patients when compared with uninfected patients.

Frequently observed risk factors included mechanical ventilation, central venous catheters, urinary catheters and broad spectrum antibiotic usage. The most common underlying diseases were neuromuscular disorders and malignancies. The majority of the isolates were multi-drug resistant. The mortality rate was higher in the infected patients than the uninfected patients but this was not significant. The majority of deaths also occurred in patients with underlying malignancies which could have been the direct cause of death.

This study described an association between *A. baumannii* acquisition and a longer PICU stay and the predominance of multi drug resistant strains of the organism. Bloodstream infections and VAP were the commonest sites of infection. The impact of infection on mortality could not be clearly defined due to the underlying illnesses of a large number of the infected patients.

2.4 Conclusion

The works cited in this literature review highlight the fact that *Acinetobacter baumannii* has become a formidable pathogen in PICU settings throughout the world. The organism also displays the ability to develop drug resistance to a number of commercially available antimicrobial agents making treatment options and drug choices problematic. The objective of this literature review was to find any studies describing *A. baumannii* infections in a PICU population, which could serve as a comparison to the results of our study.

A number of recent and relevant studies have been quoted. They are from a wide range of different geographical areas and population subtypes. Not all studies distinguished between infection and colonisation with the organism and due to the retrospective nature of most of the studies, risk factors for Acinetobacter acquisition could not really be determined. However these studies described a number of associations between acquisition of the organism and patient outcomes and this will provide a useful comparison to our own data set.

Results of individual studies done in the last 10 years which describe the clinical characteristics and outcomes of patients from whom Acinetobacter was isolated have been summarised below (Table 4).

Table 4. Summary of study results

Patient characteristics	Katragkou et al (14)	Balkhy et al (10)	Ozdemir et al (6)	Hong et al (16)	Chang et al (15)	Ebenezer et al (7)
N	26	23	15	13	52	6
Age in years	7.6	5.3	4.6	6	6	4.5 months
Male gender	15 (57.7%)	11 (47.8%)	6 (40%)	6 (46%)	M:F = 1.00:1.008	-
Length of PICU stay in days mean (range)	70.6 ± 13.6	32.9 ± 30.4	65.5 ± 48.7	67 (11-144)	58.2 (0-201)	-
Length of PICU stay until organism isolated	30.5 ± 6.9	10.3 (10)	32.1 ± 47.8	25 (3-70)	-	-
Total length of hospital stay	-	52. 4 (34.6)	-	-	-	-
Mortality	7 (27%)	7 (46.7%)	5 (33.3%)	11 (85%)	22 (42.3%)	1 (16.7%)
Organism isolated from respiratory specimens	37%	8 (34.8%)	11 (64.7%)	3 (23%)	19 (36.5%)	6 (100%)
Organism isolated from blood	26%	9 (39%)	5 (29.4%)	10 (77%)	8 (15%)	-
Organism isolated from CSF	7%	0	1 (5.9%)	0	0	
Organism isolated from urine	4%	2 (8.7%)	-	0	2 (3.8%)	
Organism isolated from other sites (wounds. conjunctivitis etc	26%	3 (13%)	-	0	1 (1.9%)	
Diagnosis at admission						
Infectious disease	7 (26.9%)	-	-	-	2 (3.8%)	6 (100%)
Haemato-oncological disease	-	-	4 (26.7%)	8 (62%)	15 (29%)	-
Cardiac disease	-	3 (13%)	2 (13.3%)	1 (8%)	10 (19%)	-
Gastrointestinal disease	-	-	-	2 (15%)	3 (5.8%)	-
Neurological disease	-	-	6 (40%)	-	12 (23%)	-
Burns	3 (11.5%)	12 (52.2%)	-	-	-	-
Trauma	6 (23.1%)	-	-	-	-	-
Received mechanical ventilation	26 (100%)	-	14 (93.3%)	13 (100%)	48 (92.3%)	6 (100%)

The age of patients from whom Acinetobacter was isolated varied between studies. Jeena et al (8), Hu et al (9) and Ebenezer et al (7) all described young children (neonates and infants) from whom the organism was cultured, however the majority of the patients described in table 4 were older children.

There was no significant gender difference among patients who isolated the organism in any of the studies reviewed. Most studies were conducted in a PICU setting but even in the 3 studies that were not, most patients were admitted to PICU during the time the organism was isolated (9,10,15).

Acinetobacter isolation was associated with a prolonged PICU and hospital stay in most studies (6,14,15,16). The organism was most commonly isolated from respiratory and blood specimens with the majority of positive cultures being from respiratory specimens i.e BAL's and TA's (6,7,8,14,15). Hu et al described bloodstream infections as being the commonest source of Acinetobacter isolation, however VAP was not reported on in this study (9). Almost all patients from whom Acinetobacter was isolated received mechanical ventilation (6,7,8,14,15,16) and VAP was the commonest nosocomial infection caused by Acinetobacter in 4 studies (6,7,10,16).

Most organisms cultured exhibited multi-drug resistance to antibiotics which would form part of second or third line regimens for nosocomial cover in many hospitals (6,7,10,14,15,16). The reason for admission to ICU varied widely among patients, however in 2 studies most patients had an underlying haemato-oncological disease when admitted (15,16) and in another, burns was the commonest reason for admission (10). Interestingly not many patients were admitted with infectious diseases except in the study by Ebenezer et al (7). This will provide an interesting comparison to the results of our study where most of our patients are admitted to the PICU with infections (2).

The direct impact of Acinetobacter acquisition on mortality was inconclusive in some studies due to the serious nature of some of the patient's underlying diseases (6). Other studies did show a definite association between higher mortality rates and Acinetobacter isolation (8,16).

This literature review has helped define the characteristics and outcomes of patients who acquire Acinetobacter in PICU's around the world. It will be useful to compare these findings and associations to the data from our own study, in which the patients have a different demographic profile and different underlying diseases requiring PICU admission.

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3. Journal article

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3.1 Abstract

Objectives: To describe and compare characteristics and outcomes of patients colonised or infected with *Acinetobacter baumannii* to a control group.

Design: Retrospective case-control study.

Setting: A 20-bed paediatric intensive care unit (PICU) in a tertiary paediatric hospital.

Patients: Patients admitted to PICU between January and December 2010: cases with positive blood or respiratory *A. baumannii* culture; controls without *A. baumannii* isolation.

Measurements and Main Results: Clinical, demographic and laboratory data were extracted from folders and clinical databases. Cases with positive blood cultures or clinical pulmonary infection score (CPIS) of > 6 were considered infected, the remainder colonised. *A. baumannii* was isolated in 194 patients, 95% from respiratory specimens. 107 patients were colonised, 61 infected and 26 unknown. 88.7%, 80.9%, 77.3%, and 75.3% of isolates were aminoglycoside, penicillin with beta lactamase, cephalosporin and carbapenem resistant respectively. Admission weight and risk of mortality (PIM2) in cases vs. controls was 6 (3.5 – 10kg) vs. 7.9 (3.9 – 13kg) ($P = 0.02$) and 0.08 (0.05 – 0.16) vs. 0.06 (0.02 – 0.17) ($P = 0.002$). 88.1% of cases and 72% of controls were emergency admissions ($P = 0.0001$). Median length of PICU stay in cases vs. controls was 10 vs. 2 days ($P < 0.0001$); and 12 vs. 9 days in patients infected vs. colonised with *A. baumannii* ($P = 0.02$). Median duration of ventilation was 9 vs. 1 day in cases vs. controls ($P < 0.0001$); and 10 vs. 7 days in infected vs. colonised patients ($P = 0.04$). Mortality was not different between cases and controls or infected vs. colonised patients.

Conclusion: *A. baumannii* acquisition was associated with a longer duration of PICU stay and mechanical ventilation. Cases were sicker on admission, weighed less and were more likely to be admitted as an emergency rather than electively. Most organisms cultured were multi drug resistant.

3.2 Introduction

Acinetobacter baumannii (*A. baumannii)* is a gram negative cocco-bacillus normally found in soil and fresh water. It is a resilient organism that can survive for prolonged periods of time on hospital equipment and the hands of health care workers and can contribute significantly to nosocomial infections (1,2). It has also been shown to cause outbreaks in paediatric intensive care unit (PICU) settings (1,3,4).

A. baumannii has the ability to develop resistance to multiple antibiotics using numerous mechanisms (2). There have been reports of multi drug resistant (MDR) Acinetobacter species in PICU's around the world including South Africa (4,5,6,7,8,9). *A. baumannii* has become recognised as a formidable pathogen in PICU and adult ICU settings, causing a variety of nosocomial infections such as ventilator associated pneumonia (VAP) and bloodstream infections (3,4,6,10), and in some instances significantly contributing to the mortality of these vulnerable patients (4,11).

A number of studies looking at the impact of *A. baumannii* in the ICU setting have been conducted in adult ICU's (10,11). Few studies conducted in PICU settings regarding Acinetobacter infections have been in Africa (9). Studies conducted in PICU's elsewhere in the world have shown an association between Acinetobacter acquisition and an increased length of PICU and hospital stay (4,5,6,8). Most isolates in these studies were multi-drug resistant (MDR) organisms (3,4,5,6,7,8).

In this study site, it has previously been shown that *A. baumannii* contributes significantly to nosocomial infection especially VAP, where it was the most common causative organism (12,13).

Our PICU patient profile differs from other countries due to the high burden of infectious diseases requiring PICU admission; young age; and high prevalence of comorbid conditions, including HIV infection (13). Knowing that our patients have a different profile in terms of demographics and underlying illnesses, this study was conducted in the PICU of Red Cross War Memorial Children's Hospital (RCWMCH) in Cape Town, South Africa.

3.3 Materials and Methods

We aimed to compare characteristics and outcomes of patients who cultured *A. baumannii* from blood and respiratory specimens and those who did not; and to evaluate the impact of *A. baumannii* infection versus colonisation.

Ethical approval for this study was obtained from the University of Cape Town's Human Research Ethics Committee (HREC:REF 580/2011).

This was a retrospective case-control study conducted in the PICU at RCWMCH, in Cape Town, South Africa. This is a 20 bed tertiary unit, which serves a large population including areas throughout the Western Cape and some areas in the Eastern Cape. There were approximately 1265 admissions to the PICU during 2010. The PICU admissions were both elective admissions and emergencies, and included post surgical patients (cardiac surgery, neurosurgery and general surgery) as well as medical admissions.

The National Health Laboratory Services (NHLS) database was reviewed for all positive cultures of *A. baumannii* from the PICU during the period January to December 2010. Only blood cultures and respiratory specimens were taken into consideration for the purposes of this study. The respiratory specimens were non-bronchoscopic bronchoalveolar lavages (BAL), tracheal aspirates (TA) and nasopharyngeal aspirates (NPA).

Patients were included in the study as cases if they had a positive blood or respiratory specimen culture. Readmissions were not regarded as separate cases and only the first positive culture was taken into account. Controls were regarded as patients in the PICU at the same time as the cases, but who did not culture the organism. The PICU database, which stores all demographic and clinical admission data, was reviewed and controls were matched to cases in a 1:1 ratio, with the control being the next sequential admission after the case.

Cases and controls were assigned a patient number to protect confidentiality and the folders of all cases were reviewed. Clinical and laboratory data at the time of the positive culture was collected from the patient folders and a clinical pulmonary infection score (CPIS) (12) was calculated in those who had positive respiratory cultures.

The calculation of the CPIS took into account any clinical features and laboratory parameters that would suggest new infection viz. temperature spikes, rise in white cell count, presence of purulent secretions and increasing oxygen requirements as well as new infiltrates on chest radiograph. All cases with either a positive blood culture, or a positive respiratory specimen culture and a CPIS of > 6 were regarded as infected with *A. baumannii*. Those cases with a CPIS ≤ 6 were regarded as colonised. Patients with a CPIS of > 6 more than 48 hours after starting ventilation were considered to have VAP. All data collected was entered onto an Excel spreadsheet.

3.3.1 Statistical analysis

Continuous variables were tested for normality using Shapiro Wilks W test. Data were not normally distributed and are therefore presented throughout this paper as median (interquartile range, IQR), unless otherwise stated. Categorical variables are presented as proportions (%). Comparisons of continuous variables were performed using Mann Whitney U tests and proportions were compared using chi-squared or Yates corrected chi square tests where cell values were <10. A p value of < 0.05 was considered statistically significant. STATISTICA (data analysis software system), version 11 (StatSoft, Inc. (2012); USA) was used for analysis.

3.4 Results

There were a total of 323 positive blood and respiratory cultures for *A. baumannii* during 2010. Once duplicates were removed and readmissions excluded, a total of 194 patient folders were reviewed. Clinical information about the control group was obtained from the PICU database. All further results relate to the 194 cases and 194 controls. Unless otherwise stated, all data are presented as median (interquartile range).

Ten (5.2%) positive cultures were from blood specimens, the other 184 were from respiratory specimens: 91 (46.9%) from tracheal aspirates (TA), 92 (47.4%) from non-bronchoscopic bronchoalveolar lavage specimens (BAL) and 1 (0.5%) from a nasopharyngeal aspirate (NPA) (Figure 1). The median number of days from PICU admission till the first positive culture was obtained was 3.0 (1.0-7.0).

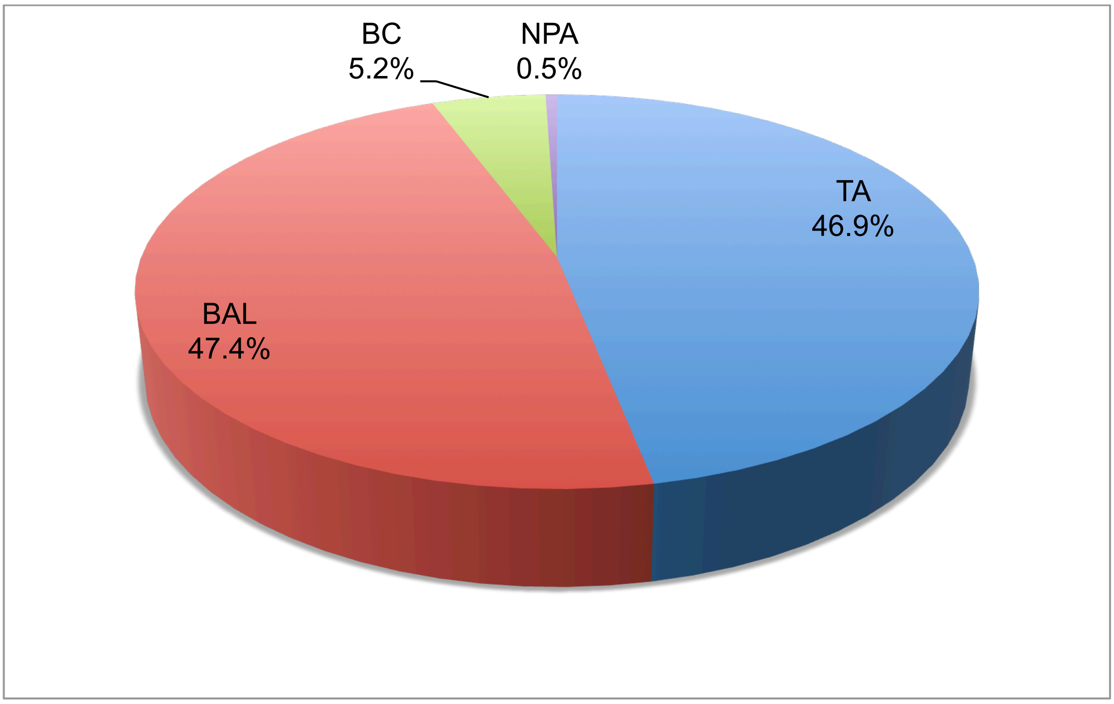

Figure 1.

There was no significant difference in terms of age or gender when comparing the cases with the controls. Cases were found to weigh significantly less on admission and had a significantly higher PIM2 score on admission than the control group (Table 1). Even though cases weighed less than controls on admission, when nutritional status was compared between the two groups based on growth charts and z-score calculations, no significant differences were found (Table 2).

Cases were more likely to have been admitted as emergencies than as elective admissions in comparison to the control group. The reasons for admission varied and some patients had multiple diagnoses. The most common reasons for admission were sepsis, pneumonia, gastroenteritis, congenital and acquired heart disease (these included both emergency and elective admissions) and neurological disease (status epilepticus and seizures). A significantly higher number of cases were admitted with a diagnosis of pneumonia and traumatic brain injuries than controls (Table 1).

Significantly more cases received mechanical ventilation in PICU compared to the control group (p < 0.0001*)*. The durations of PICU stay and mechanical ventilation were significantly longer in the case group (p < 0.0001*)* but there was no difference in mortality between the groups (Table 1).

Table 1. Admission characteristics and outcomes of cases versus controls

Patient characteristics	Cases n=194	Controls n=194	p
Gender male:female	107:87	119:75	0.2
Age in months	5.6 (2.3 – 18.8)	8.4 (2.5 – 37.9)	0.07
Admission weight in kg	6.0 (3.5 – 10.0)	7.9 (3.9 – 13.0)	**0.02**
PIM2	0.0842 (0.0491-0.1679)	0.0572 (0.0170-0.1664)	**0.002**
Emergency admission	171 (88.1%)	140 (72.2%)	**0.0001**
Reason for admission n (%)			
Sepsis	25 (12.9%)	16 (8.2%)	0.1
Pneumonia	82 (42.3%)	42 (21.6%)	**<0.0001**
Gastroenteritis	18 (9.3%)	19 (9.8%)	0.9
Cardiac Disease	50 (25.8%)	45 (23.2%)	0.55
Neurological Disease	19 (9.8%)	18 (9.3%)	0.9
Traumatic brain injury	13 (6.7%)	1 (0.5%)	**0.003**
Burns and other trauma	11 (5.7%)	13 (6.7%)	0.7
Other	15 (7.7%)	20 (10.3%)	0.4

Upper airway obstruction	8 (4.1%)	13 (6.7%)	0.4
Toxins	2 (1.0%)	1 (0.5%)	1.0
Duration of PICU stay (days)	10.0 (7.0 – 18.0)	2.0 (1.0 – 5.0)	**<0.0001**
Received mechanical ventilation n (%)	193 (99.5%)	157 (81%)	**<0.0001**
Duration of mechanical ventilation (days)	9.0 (5.0 – 15.0)	1.0 (0.0 – 3.0)	**<0.0001**
Mortality	18 (9.3%)	19 (9.8%)	0.9

Data are presented as median (IQR) unless otherwise stated. PIM2, paediatric index of mortality score.

Table 2. Nutritional status of cases versus controls

Nutritional status	**Cases n=194**	**Controls n = 194**	**p**
Normal[a]	110	112	0.9
Moderate malnutrition[a]	26	24	0.9
Severe malnutrition[a]	55	51	0.7
Underweight for age[b]	2	3	1
Overweight for age[b]	1	4	0.4

[a] Calculated using World Health Organisation Z score charts (2007)

[b] Calculated using Centre for Chronic Disease prevention and Health promotion (CDC) percentile charts (2000)

After calculation of the CPIS in the cases with positive respiratory specimen cultures (184); 61 were found to be infected, 107 were colonised and 26 could not be determined due to missing data.

When comparing the infected group with the colonised group there were no significant differences in terms of age, gender, admission weight, admission risk of mortality (PIM2) scores or the proportion of emergency versus elective admission to the PICU. The infected group did have a significantly longer duration of stay in the PICU than the colonised group (*p* =0.02*)* and was also mechanically ventilated for significantly longer than the colonised group (*p* =0.04*)* (Table 3).

Table 3. Characteristics and Outcomes of those infected versus colonised with *A. baumannii* (n=168)

Patient characteristics	**Infected n=61**	**Colonised n=107**	**p**
Gender male:female	37:24	57:50	0.35
Age (months)	4.1 (2.5 – 14.0)	5.6 (2.1 – 18.8)	0.35
Admission weight (kg)	5.6 (3.5 – 8.0)	6.2 (3.7 – 10.0)	0.4
PIM2	0.0939 (0.0562 – 0.1997)	0.0799 (0.0420 – 0.1761)	0.2
Emergency admission	52 (85.2%)	95 (88.8%)	0.7
Days post ICU admission organism first isolated	3 (1-7)	3 (1 – 6)	0.6
Aminoglycoside resistant	52 (85.2%)	97 (90.7%)	0.4
Peninicillins with beta lactamase resistant	49 (80.3%)	86 (80.4%)	0.99
Carbapenem resistant	44 (72.1%)	80 (74.8%)	0.7
Colistin resistant	0	1 (0.9%)	0.8
Duration of PICU stay (days)	12.0 (7.0 – 19.0)	9.0 (6.0 – 14.0)	**0.02**

Duration of mechanical ventilation (days	10.0 (6.0 – 15.0)	7.0 (4.0 – 14.0)	**0.04**
Mortality	7 (11.5%)	11 (10.3%)	0.99

Antibiotic resistance patterns (Figure 2)

Of the 194 cases from whom *A. baumannii* was cultured 172 organisms were resistant to aminoglycosides (88.7%), 157 were resistant to penicillins with a beta lactamase inhibitor (80.9%), 150 were cephalosporin resistant (77.3%), and 146 were resistant to carbapenems (75.3%). One cultured organism was colistin resistant.

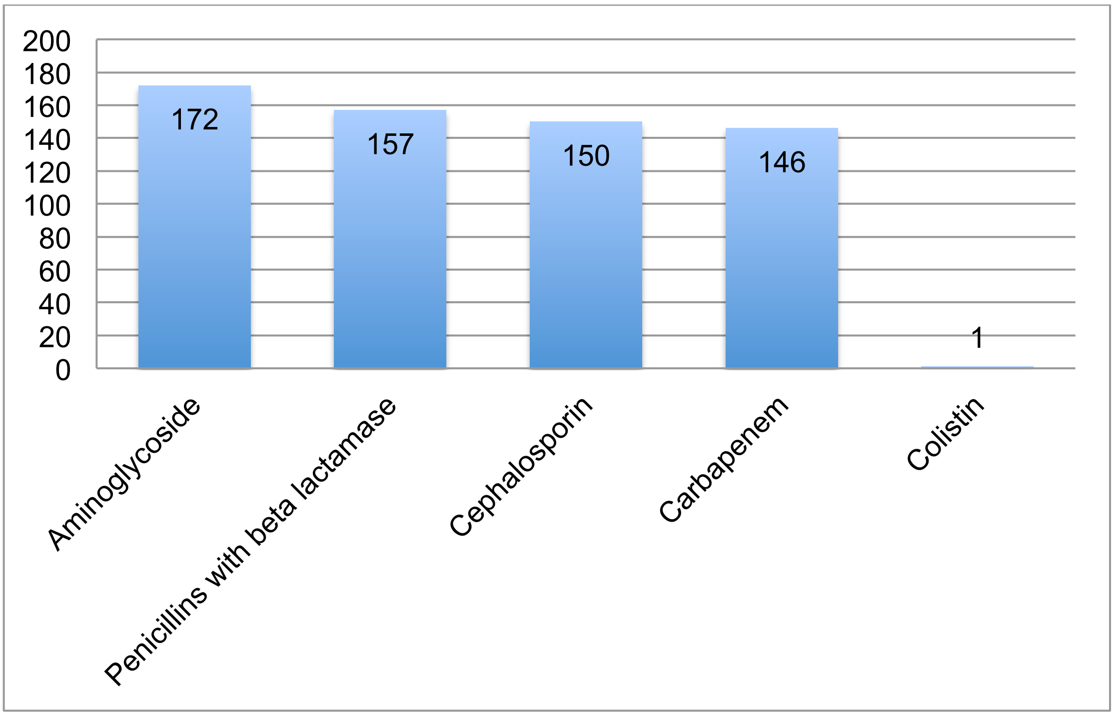

Figure 2. Number of resistant organisms isolated per antibiotic group

Seasonal Variation (Figure 3)

No significant difference was found with regard to seasonal variation, although there appeared to be more positive cultures in the winter months (June) as compared to summer (February). This would be in keeping with the increase in the number of respiratory illnesses normally seen during winter months.

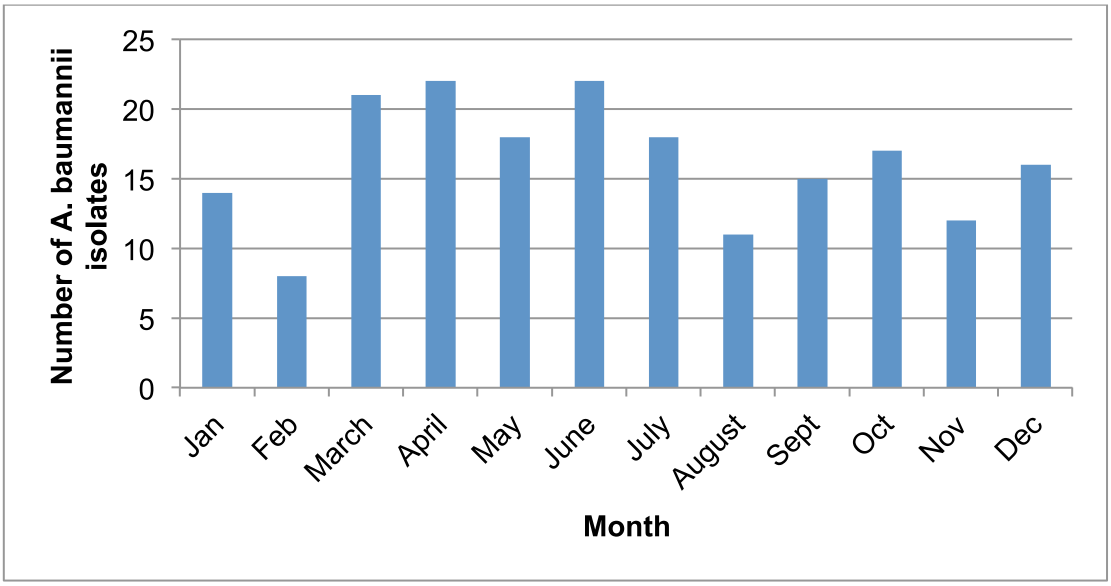

Figure 3.

3.5 Discussion

No studies have been done in the last 10 years specifically describing *Acinetobacter baumannii* infections in a South African PICU population. This is the first study in South Africa to describe the characteristics of patients in the PICU from whom the organism was cultured from blood or respiratory specimens, and attempt to distinguish between colonisation and infection in these patients.

Although some work has been done with regard to this in other units around the world, our study population is different to other paediatric ICU populations due to our high HIV prevalence and significant burden of infectious disease (13). During the period of the study, standard infection control practices were implemented in the RCWMCH PICU.

Risk factors for *A. baumannii* acquisition in an adult ICU setting have been described in the literature (10,11,14). Prior use of broad-spectrum antibiotics, mechanical ventilation, ICU admission and length of ICU and hospital stay have all been described as risk factors for the isolation of MDR *A. baumannii* in adult ICU patients (10,11,14).

In a PICU population in Greece Katragkou et al (8) described time at risk (defined as duration from the date of PICU admission to the date of isolation of the organism) and duration of aminoglycoside use 15 days prior to organism isolation, as the two independent risk factors for acquiring imipenem resistant *A. baumannii* (IRAB).

The age of children from whom Acinetobacter was isolated, varied in the literature with some studies reporting neonates and infants being more commonly affected (1,3,9) and other studies describing the isolation of the organism in older children (4,5,6,7,8). In our study we found no significant difference in the age of the cases versus the controls, however overall our study population comprised younger children. There was no significant difference in gender between the cases and controls, which is consistent with findings in other studies (4,5,6,7,8).

The admission weight of the cases in our study was significantly less than that of the controls (p =0.02) and it was initially thought that this might reflect that cases were malnourished compared to controls. However when the weights were plotted on growth carts and z scores compared, no significant differences were found in nutritional status between the groups. No differences in weight between cases and controls have been reported in other studies (8).

Stratification of illness severity on admission to PICU was not reported on in other studies except for one, which found no difference between cases and controls (8). This is in contrast to our findings in which cases were sicker on admission to PICU compared with the control group (p =0.002). Some adult ICU studies reported that a higher Acute Physiology and Chronic Health Evaluation (APACHE) score on admission, which reflected severity of illness, was associated with an increased risk of *A. baumannii* infection (11,15).

Almost all the cases received mechanical ventilation during their stay in the PICU, whereas only 81% of controls received mechanical ventilation (p <0.0001). This is consistent with most paediatric studies in which 92% -100% of patients who isolated Acinetobacter required mechanical ventilation prior to the organism being isolated (3,4,5,6,8).

Although we only took into account positive blood and respiratory specimen cultures for the purposes of this study, in other studies where all clinical specimens positive for Acinetobacter were taken into consideration, the majority of organisms were still isolated from respiratory specimens (3,5,6,8,9). VAP was the commonest nosocomial infection caused by Acinetobacter in a number of studies (3,4,6,7). Our study findings were consistent with this with the majority of positive cultures being from respiratory specimens (95%).

The median length of PICU stay until the first positive culture of the organism was three days in our study, which is much shorter than that reported in other studies of between 10,3 and 32,1 days (4,6,7,8). This suggests that patients were exposed to the organism early in their admission to PICU.

The reasons for PICU admission in our study were primarily for the management of infectious diseases such as pneumonia, sepsis and gastroenteritis. This is very different to the patient profile in other studies where fewer patients were admitted with infectious diseases and more had underlying haemato-oncological diseases (4,5,6), burns (7), cardiac disease (4,5,6,7) or neurological diseases (5,6). A significantly higher number of patients with admission diagnoses of pneumonia or traumatic brain injury were in the case group as compared to the control group in our study. Patients with traumatic brain injury tend to have a longer PICU stay and this could make them more susceptible to *A. baumannii* infection.

The length of PICU stay in patients from whom Acinetobacter has been isolated is prolonged and this has been shown in our study (p <0.0001) and in other studies as well (4,5,6,7,8). Considering the case group was sicker on admission and owing to the retrospective nature of this study it is difficult to determine whether the *A. baumannii* acquisition was the cause of the prolonged PICU stay and duration of mechanical ventilation, or whether the prolonged period of mechanical ventilation and PICU stay made patients more susceptible to acquisition of the organism.

Calculation of the modified CPIS in the cases with positive cultures from respiratory specimens was used to determine which isolates were causing infection and which were merely colonisers. The use of the modified or simplified CPIS in diagnosing VAP in children has been validated (16) and used in other studies (12,13). A CPIS of > 6 has been shown to have a 93% sensitivity and a 100% specificity in the diagnosis of pneumonia when compared to the Centres for Disease Control (CDC) criteria in the same setting (16).

Of the cases in whom we could calculate a CPIS (168) most (64%) were colonised with *A. baumannii* rather than infected. Some adult studies have suggested that prior colonisation with the organism increases the likelihood of developing infection (11). It is unclear how many patients in our study who were colonised with *A. baumannii* went on to develop infections as only data regarding the first positive culture result was collected. Those infected with the organism had a prolonged PICU stay (p =0.02) and were ventilated for longer (p =0.04) than those colonised.

Most organisms cultured displayed antimicrobial resistance to a variety of commercially available antibiotics, which is consistent with findings in other studies (3,4,5,6,7,8). Prior use of carbapenems and 3rd generation cephalosporins have been associated with an increased risk for the acquisition of multidrug resistant *A. baumannii* (10,11,14) in adults and Katragkou et al (8) reported prior aminoglycoside use as an independent risk factor for acquisition of imipenem-resistant *A. baumannii* in children. The RCWMCH PICU enforces strict antibiotic restriction policies and carbapenems, quinolones and colistin are never used as first or second line antibiotic regimens and usually require consultant clearance before initiation.

Some studies did show a definite association between higher mortality rates and Acinetobacter isolation (4,9) whereas most were inconclusive. We found no significant difference in mortality between the cases and controls in our study.

Seasonal variation in the distribution of infection with Acinetobacter has been reported in the past (15). We found no significant seasonal variation in this study although there did appear to be an upward trend in the number of positive cultures toward the winter months.

Respiratory specimens are not routinely collected in the PICU unless clinically indicated e.g. if there is a clinical deterioration in the patient's condition, increasing ventilatory requirements or new infiltrates on chest X-ray and suspected new infection. This means that some controls will not have had respiratory specimens collected at all and we have no way of knowing whether they were colonised by *A. baumannii* or not. This constitutes a limitation of this study.

Another limitation of this study is that data regarding HIV infection in both cases and controls was not collected. Considering that HIV infection contributes to the comorbidities of patients admitted to the PICU at RCWMCH (13), it would be interesting to determine if there is an association between HIV infection and the acquisition of *A. baumannii.* This is recommended for future studies looking at *A. baumannii* infections in this PICU.

As with any non-randomised selection of study participants there is always potential for bias. The controls in this study were selected as the sequential admission after a case from the PICU database. This method was used despite its shortcomings in order to ensure that the cases and controls were admitted to the PICU during a similar time period so that exposure to the organism was similar. For future studies it is recommended that a randomised method for selection of study participants be used so as to eliminate any potential bias.

Ebenezer et al (3) and Hong et al (4) reported isolating the organism from environmental samples like sinks, ventilator tubing and ventilator humidifiers during outbreaks of *A. baumannii* infections in PICU patients. Due to the retrospective nature of this study we were unable to obtain samples from potential environmental sources like the ventilator circuits in the PICU.

3.6 Conclusion

This study is the first study looking at *A. baumannii* infections and colonisation in a PICU in South Africa. Although infection was not found to be associated with an increase in mortality it was associated with a longer PICU stay and duration of ventilation. The findings of this study suggest that the sicker, smaller (weigh less) children who require mechanical ventilation in PICU may be at increased risk for acquisition of the organism.

3.7 References

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4. Appendices

4.1. Diagnostic criteria for ventilator- associated pneumonia (Morrow et al, 2012)

PARAMETER	CPIS RANGE	CPIS SCORE
Temperature (°C)	36.5-38.4	0
	38.5-39.0	1
	<36.0 or >39.0	2
Leukocyte count ($X\ 10^9/l$)	4.0-11	0
	≤3.9 ≥11.1 and absence of band forms; or ≥ 11.1 ≤17.0 and no differentiation done	1
	≥11.1 with band forms on differentiation or no differentiation done and leukocytes ≥17.1	2
Chest radiography	No CXR taken or no infiltrate	0
	Diffuse or patchy infiltrate	1
	Localised infiltrate	2
Pulmonary secretions	Absent or minimal	0
	Present and nonpurulent	1
	Present and purulent	2
PaO_2 (mmHg)/FiO_2	>240	0
	≤ 240	2
Organism isolated on BAL	No or Not Done	0
	Yes	2

CPIS- clinical pulmonary infection score;

BAL- non-bronchoscopic bronchoalveolar lavage

4.2. Data capture form: cases

Patient Number	
Gender	Male: Female:
Date of birth (dd/mm/yy)	
PICU Admission weight (kg)	
Specimen	Blood/ TA/ BAL/ NPA
Date of PICU admission (dd/mm/yy)	
Date of PICU discharge / Death (dd/mm/yy)	
Date specimen taken (dd/mm/yy)	
Date of intubation (dd/mm/yy)	
Date of extubation (dd/mm/yy)	
Reason for PICU admission	
Emergency/Elective admission	Emergency: Elective:
Bed Space	
Mortality	Died: Alive:
PIM2 score	

4.3. Data capture form: controls

Patient Number	
Gender	Male: Female:
Date of birth (dd/mm/yy)	
PICU admission weight (kg)	
Date of PICU admission (dd/mm/yy)	
Date of PICU discharge / Death (dd/mm/yy)	
Date of intubation (dd/mm/yy)	
Date of extubation (dd/mm/yy)	
Reason for PICU admission	
Emergency/Elective admission	Emergency: Elective:
Mortality	Died: Alive:
PIM2 score	

4.4. CPIS calculation: cases with positive respiratory specimens

Patient Number: *Date specimen taken:* *CPIS score:*

PARAMETER	**CPIS RANGE**	**CPIS SCORE**
Temperature (°C)	36.5-38.4	0
	38.5-39.0	1
	<36.0 or >39.0	2
Leukocyte count (X 10^9/l)	4.0-11	0
	≤3.9 ≥11.1 and absence of band forms; or ≥ 11.1 ≤17.0 and no differentiation done	1
	≥11.1 with band forms on differentiation or no differentiation done and leukocytes ≥17.1	2
Chest radiography	No CXR taken or no infiltrate	0
	Diffuse or patchy infiltrate	1
	Localised infiltrate	2
Pulmonary secretions	Absent or minimal	0
	Present and nonpurulent	1
	Present and purulent	2
PaO_2 (mmHg)/FiO_2	>240	0
	≤ 240	2
Organism isolated on BAL	No or Not Done	0
	Yes	2

4.5. Ethics approval

UNIVERSITY OF CAPE TOWN

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23 December 2011

HREC REF: 580/2011

Dr D Reddy,
Paediatric Medicine
Red Cross War Memorial Children's Hospital

Dear Dr Reddy,

PROJECT TITLE: ACINETOBACTER INFECTIONS IN THE PAEDIATRIC INTENSIVE CARE UNIT OF A TERTIARY HOSPITAL IN SOUTH AFRICA

Thank you for submitting your new study to the Faculty of Health Sciences Human Research Ethics Committee

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

Approval is granted until 15 January 2013

Please submit an annual progress report (FHS016) if the research continues beyond the expiry date. Please submit a brief summary of findings if you complete the study within the approval period so that we can close our file (FHS010).

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

Please quote the HREC. REF in all your correspondence.

Yours sincerely

PROFESSOR MARC BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.