JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Prevalence, antimicrobial susceptibility profiles and case fatality rates of *Acinetobacter Baumannii* sepsis in a neonatal unit

Reenu Thomas[1], Jeannette Wadula[2], Sharona Seetharam[2], Sithembiso Velaphi[1]

[1] Department of Paediatrics, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
[2] Department of Clinical Microbiology and Infectious Diseases, School of Pathology, Faculty of Health Sciences, University of the Witwatersrand and the National Health Laboratory Services, Johannesburg, South Africa

Abstract

Introduction: The burden of sepsis in neonates due to *Acinetobacter baumannii (A. baumannii)* in developing countries is not well reported. The objective of this study was to determine prevalence of culture confirmed sepsis due to *A. baumannii*, antimicrobial susceptibility and case-fatality rates (CFR) due to this organism.

Methodology: A retrospective review of medical and laboratory records of neonates admitted to a tertiary government hospital from a developing country was conducted. Records of neonates with positive microbiological cultures from blood or cerebrospinal fluid due to *A. baumannii* were reviewed for demographic characteristics, clinical presentation, laboratory findings, antibiotic susceptibility and outcome at hospital discharge.

Results: There were 399 isolates of *A. baumannii* cultured from sterile sites, with a prevalence of 4.3/1000 live births or 22.8/1000 admissions, accounting for 13% of all culture confirmed sepsis. Majority of neonates were preterm (91%) with a mean gestational age and birth weight of 30 weeks and 1400 grams respectively. Antimicrobial susceptibility of isolates was 64% to cephalosporins, 21% to aminoglycosides and 17% were extremely-drug resistant (XDR), only susceptible to colistin. The CFR was 32%. Factors associated with mortality were presence of a central venous catheter prior to onset of sepsis (49% vs 31%, $p = 0.03$); need for mechanical ventilation (62% vs 36%, $p = 0.005$) and inotropic support (57% vs 17%, $p < 0.001$).

Conclusions: *A. baumannii* is a significant pathogen causing sepsis in neonates, with 17% of them being XDR. It is associated with high CFR. These findings highlight the need for strict enforcement of infection control and antibiotic stewardship practices.

Key words: *Acinetobacter sepsis*; neonates; extremely-drug resistant; colistin, epidemiology.

J Infect Dev Ctries 2018; 12(4):211-219. doi:10.3855/jidc.9543

(Received 26 June 2017 – Accepted 05 March 2018)

Introduction

Infection is one of the major causes of neonatal mortality in developing countries [1-4]. Premature neonates are at high risk of infection due to underdeveloped innate immunity, fragile skin and lack of protective maternal antibodies. The increasing survival of these premature babies has led to an increase in duration of hospital stay, rendering them at risk for nosocomial infections, with the reported incidence of nosocomial infections ranging from 7%-24% of admitted preterm infants [5-7]. Neonatal nosocomial infections have been shown to increase the risk of mortality as well as neuro-developmental and growth impairment [8-10].

A. baumannii has recently emerged as a nosocomial pathogen responsible for numerous hospital outbreaks [11-13]. *A. baumannii* are aerobic gram-negative cocco-bacilli, which have the ability to survive in the hospital environment for prolonged periods [14-19]. The main concern with *A. baumanni* is its ability to accumulate mechanisms of antimicrobial resistance rapidly, leading to multi-drug resistance. *A. baumanni* has acquired resistance to various classes of antimicrobials including penicillins, aminoglycosides, cephalosporins, fluoroquinolones and carbapenems [12-14,20-22]. The polymyxins, such as colistin/colistimethate sodium, have been used for the treatment of *A. baumannii* that are resistant to multiple classes of antibiotics, however emerging resistance to colistin has been reported, and is of great concern [23].

Risk factors identified for the development of *A. baumannii* infection include prematurity, very-low-birth-weight, postnatal age <7 days, mechanical ventilation, use of central venous catheters, as well as

prior broad spectrum antibiotic use [12,13]. The mortality rates associated with *A. baumannii* infections in neonates range from 14% to 80% [12,13,19,24]. Number of reports on epidemiology of *A. baumannii* in neonates are often from developed countries yet nosocomial sepsis is more common in developing countries. The objectives of this study were to determine characteristics of patients infected with *A. baumannii*, its antibiotic susceptibilities, case fatality rates and factors associated with mortality from a tertiary government hospital with high patient load and limited resources, based in a developing country.

Methodology

Study design and population

This was a retrospective descriptive study of babies admitted in the neonatal unit with culture confirmed *A. baumannii*, from blood and/ or cerebrospinal fluid, during the study period 1st October 2007 to 31st October 2011.

Study setting

Chris Hani Baragwanath Academic Hospital (CHBAH) lies on the outskirts of Soweto, Johannesburg, South Africa. It is the referral hospital for all clinics in Soweto, and surrounding areas. It provides free maternal and child-care to an urban, middle-income and low-income population. The hospital conducts approximately 23,000 of the 32,000 annual births in Soweto. All babies less than 1800 grams as well as any baby with an indication for admission is admitted to the neonatal unit. The neonatal unit at CHBAH is a 179 bedded unit consisting of an 18 bedded Level IIIB intensive care unit, a 42 bedded high care nursery, a 100 bedded neonatal ward, and a 19 bedded kangaroo mother care (KMC) ward. All admitted patients with signs suggestive of infection have bloods taken for a full blood count (FBC), blood culture, and c-reactive protein (CRP). Blood culture bottles (BacT/ALERT PF bottle, BioMerieux Inc., Durham, NC, USA) are collected from the wards every hour and taken to the CHBAH microbiology laboratory. The microbiology laboratory uses an automated continuous monitoring blood culture system (BacT/Alert system, BioMerieux, Marcy l'Etoile, France). If bacterial growth is detected, a Gram stain is performed and the sample sub-cultured onto appropriate media and incubated overnight. Further identification and antimicrobial susceptibility is performed using either the Kirby-Baeur method or the automated system, Microscan, Siemens, USA and interpreted according to the Clinical Laboratory Standards Institute standards (2007 – 2011) [25].

Study procedures

Hospital files of infants with *A. baumannii,* cultured on blood and/or cerebrospinal fluid (CSF), were retrieved. A diagnosis of *A. baumannii* blood stream infection (BSI) or *A. baumannii* meningitis was made if the infant presented with new clinical signs or abnormal laboratory findings suggestive of sepsis and had culture confirmed *A. baumannii* on blood and/or CSF respectively, taken at the time of sepsis work-up [26, 27]. Common signs suggestive of infection for which a sepsis work-up was done included signs as reported by Weber *et al*. [26]. Multiple blood and/or CSF cultures yielding the same organism from the same patient within 72 hours of each other was considered to be a single infection. Antibiotic susceptibilities of *A. baumannii* isolates were retrieved from the laboratory database. *Acinetobacter baumannii* was considered to be multi-drug resistant when the isolate was not susceptible to at least one agent in 3 or more antimicrobial categories, and a subset of these were defined as extremely-drug resistant (XDR) when the organism was resistant to at least one agent in all antibiotics categories except one, namely the polymyxins [28]. Very low birth weight was defined as a birth weight less than 1500 grams. Case fatality rate was defined as mortality within 7 days of onset of sepsis, attributable to *A. baumannii* infection. Patient's demographics, clinical management, laboratory findings, and antibiotic susceptibilities were compared between those who died and those who survived. The approval to conduct this study was obtained from the University of the Witwatersrand Human Research Ethics Committee.

Data Collection

Prenatal factors such as patient demographics and maternal human immunodeficiency virus (HIV) status were collected. Postnatal factors obtained included birth weight and age of the baby at the onset of *A. baumannii* sepsis, any surgical/ invasive procedures prior to the onset of sepsis, need for mechanical ventilation, need for inotropic support as well as death or survival within 7 days of diagnosis of the infection. Use of central venous catheters and total parenteral nutrition for 48 hours or more at the time of onset of sepsis was also recorded [29]. Clinical signs and laboratory findings namely FBC and CRP at the time of diagnosis of sepsis were also collected.

Data analysis

Data were captured onto Microsoft Office Excel 2010 and analyzed using Statistica version 12 (StatSoft Inc., Tulsa, USA). Means and standard deviations were used to describe continuous variables with normal distribution, and medians and ranges were used to describe continuous variables that were not normally distributed. Frequencies and proportions were used to describe categorical variables. In comparing the susceptible to extremely-drug resistant or survivors to non-survivors, the Student t-test was used when comparing parametric data, while Mann-Whitney U test was used to compare non-parametric data and the Pearson Chi-square test was used to compare categorical variables. Antibiotic susceptibility trends over the years were analyzed using the Chi-square trend test, using 2×5 contingency tables. Differences between the two groups were considered to be statistically significant when the p-value was less than 0.05.

Results

During the study period, there were 93527 live births in the hospital and 17501 admissions to the neonatal unit. There were 399 patients with *A. baumannii* isolated from blood and/or CSF, resulting in an overall prevalence of 4.3 per 1000 live births and 22.8 per 1000 admissions. *A. baumannii* accounted for 13% of the 3005 bacterial and fungal isolates identified over this 4-year period. Of the 399 isolates, 379 had susceptibility data available for analysis (95%) and only 155 files could be retrieved for analysis of clinical data (39%).

Maternal and neonatal characteristics of those who had their records reviewed (n = 155) are shown in Table 1. Ninety-one percent (91%) of the infants were born preterm, with a mean gestational age of 30.5 weeks. Of these, the majority (87%) was of gestational age of less than 34 weeks. The mean birth weight was 1401 grams, with 72% of the infants being very low birth weight. The median age at onset of sepsis was 6 days. Twenty-four percent (24%) of patients presented within the first 3 days of life (defined as early onset sepsis) and the rest presented as late onset sepsis [30,31]. The most common clinical presentation at the time of assessment for infection was respiratory distress, which was present in 22% of all cases. On laboratory findings majority of patients had a normal white cell count, 29% had leucopenia (white cell count < 5×10^9/L) and 47% had thrombocytopenia (platelet count below 150×10^9/L) (Table 2). Seventy-eight (50%) infants had an elevated CRP (> 10 mg/L).

Table 1. Baseline characteristics and interventions before onset of sepsis; (N = 155).

Stratification	Number	Percent
Human immunodeficiency virus exposed*		
Yes	49	32
No	103	66
Gestational age (in weeks) *		
< 28	29	19
28 - 34	105	69
35 - 37	6	4
> 37	13	8
Birth weight (in grams)		
< 1000	38	24
1000 - 1499	74	48
1500 - 2499	28	18
≥ 2500	15	10
Male sex	83	54
Apgar score		
1 minute	7 (5 - 8) †	-
5 minutes	9 (7 - 10) †	-
Interventions before or at onset of sepsis		
Central venous catheter	56	36
Parenteral nutrition	51	33
Surgery	14	9
Mechanical ventilation	17	11

* - Human immunodeficiency virus exposure and gestational age not recorded in 3 and 2 patients respectively; † - Median (25^{th} - 75^{th} percentile).

Table 2. Clinical presentation, laboratory markers and outcome (N = 155).

Stratification	Number	Percent
Age at onset of sepsis		
Early-onset sepsis (≤ 72 hours of life)	37	24
Late-onset sepsis (> 72 hours of life)	118	76
Clinical presentation		
Respiratory distress	34	22
Apnea	28	18
Abdominal distension	26	17
Large gastric aspirates	17	11
Hyperglycemia	12	8
White cell count ($\times 10^9$/L)		
< 5	45	29
5.0 - 25.0	87	56
> 25.0	11	7
Unknown	12	8
Platelet count ($\times 10^9$/L)		
< 100	56	36
100 - 150	17	11
> 150	69	45
Unknown	13	8
C-reactive protein (mg/L)		
< 10.0	61	40
10.0 - 20.0	14	9
> 20	64	41
Unknown	16	10
Site of positive culture		
Blood only	145	94
Cerebrospinal fluid only	3	2
Blood and cerebrospinal fluid	7	4
Required mechanical ventilation due to sepsis	60	43
Required inotropes due to sepsis	45	29
Outcome		
Died	49	32
Survived	106	68

*Refers to patients who were not already on ventilatory support (N = 138).

Table 3. Susceptibility profiles of *Acinetobacter baumannii* isolates.

Year	All	2007	2008	2009	2010	2011	
Number infected	**379**	**23**	**105**	**90**	**91**	**70**	**p -value**
Cephalosporins							
Ceftazidime, n (%)	216 (57)	11 (48)	63 (60)	49 (54)	47 (52)	46 (66)	
Cefepime, n (%)	160 (42)	13 (57)	63 (60)	57 (63)	14 (15)	13 (19)	
Combined, n (%)	242 (64)	13 (57)	70 (67)	63 (70)	48 (53)	48 (69)	0.095
Aminoglycosides							
Tobramycin, n (%)	66 (17)	8 (35)	20 (19)	12 (13)	16 (18)	10 (14)	
Amikacin, n (%)	19 (5)	0 (0)	7 (67)	4 (4)	4 (4)	4 (6)	
Gentamicin, n (%)	2 (1)	1 (4)	1 (1)	0 (0)	0 (0)	0 (0)	
Combined, n (%)	81 (21)	8 (35)	26 (25)	14 (16)	20 (22)	13 (19)	0.254
Carbapenems							
Meropenem, n (%)	11 (3)	0 (0)	6 (6)	1 (1)	0 (0)	4 (6)	
Imipenem, n (%)	6 (2)	0 (0)	5 (5)	0 (0)	0 (0)	1 (1)	
Combined, n (%)	15 (4)	0 (0)	10 (10)	1 (1)	0 (0)	4 (6)	0.003
Piperacillin-Tazobactam, n (%)	24 (6)	1 (4)	17 (16)	3 (3)	2 (2)	1 (1)	< 0.001
Ciprofloxacin, n (%)	27 (7)	2 (9)	3 (3)	1 (1)	10 (11)	11 (16)	0.001
Colistin only, n (%)	64 (17)	3 (13)	18 (17)	14 (16)	18 (20)	11 (16)	0.914

Thirty-three percent of patients had received parenteral nutrition, and 36% had a central line in situ prior to the onset of infection and 17 (11%) developed sepsis whilst on mechanical ventilation. Of the remaining hundred and thirty-eight (89%) patients, sixty (43%) required ventilation subsequent to the onset of infection. Forty-five (29%) of the patients required some form of inotropic support. The mean duration of treatment was 8 days and the mean length of hospital stay was 29 days. The case fatality rate was 32%.

Antibiotic susceptibilities

As part of the antimicrobial susceptibility testing, the cephalosporins tested included cefepime and ceftazidime, the aminoglycosides tested included gentamicin, amikacin and tobramycin and the carbapenems tested included meropenem and imipenem. Of the 399 isolates with *A. baumannii*, 379 had data on antimicrobial susceptibilities (Table 3). Two hundred and fourty two (64%) of the 379 isolates were susceptible to cephalosporins (57% to ceftazidime and 42% to cefepime), 81 (21%) were susceptible to aminoglycosides (17% to tobramycin, 5% to amikacin and 1% to gentamicin), 28 (7%) were susceptible to ciprofloxacin, 24 (6%) were susceptible to piperacillin-tazobactam and 4% were susceptible to carbapenems (3% to meropenem and 2% to imipenem). Sixty-four (17%) were resistant to all classes of antibiotics (XDR) except to colistin. Compared to other groups of antimicrobials, most of the isolates remained susceptible to cephalosporins over the study period (64% vs 4-21% for other antibiotics; p = 0.03). Resistance to antibiotics remained high and over the study period there was no significant change in susceptibility profiles to the cephalosporins (p = 0.095) and the aminoglycosides (p = 0.254). However, there was a significant decrease in susceptibility to the carbapenems (p = 0.003) and piperacillin-tazobactam (p < 0.001). Susceptibility to ciprofloxacin increased over the years (p = 0.001). The proportion of isolates that were only susceptible to colistin (XDR) remained consistently high over the four-year period ranging from 13 to 20% (p = 0.914).

Characteristics of babies infected with susceptible isolates compared to those infected with extremely-drug resistant isolates

Among the 155 files retrieved for analysis, susceptibility results were available for 153 isolates. One hundred and thirty-two patients (86%) were infected with susceptible isolates and 21 were infected with XDR isolates (14%). There were no significant differences in baseline characteristics between the 2 groups (Table 4). Hyperglycemia was seen more frequently in the XDR group compared to the susceptible group (25% vs 5%; p = 0.003). There were no cases of *A. baumannii* meningitis in the XDR group, compared with 7% in the susceptible group (p = 0.048; Table 5).

Table 4. Comparing baseline characteristics and interventions before onset of sepsis between susceptible and extremely drug resistant (XDR) isolates.

Stratification	**Susceptible (N = 132)**	**XDR (N = 21)**	**p-value**
	n (%)	**n (%)**	
Human immunodeficiency virus exposed*	40 (31)	8 (38)	0.52
Gestational age (in weeks) *			**0.45**
< 28	26 (20)	3 (14)	
28 - 34	88 (68)	15 (71)	
35 - 37	4 (3)	2 (10)	
> 37	12 (9)	1 (5)	
Birth weight (in grams)			**0.95**
< 1000	32 (24)	5 (24)	
1000 - 1499	62 (47)	11 (52)	
1500 - 2499	25 (19)	3 (14)	
≥ 2500	13 (10)	2 (10)	
Male sex	**70 (53)**	**11 (52)**	**0.96**
Apgar score			
1 minute	7 (5 - 8) †	5 (4 - 8) †	0.05
5 minutes	9 (4 - 10) †	8 (5 - 10) †	0.77
Interventions before or at onset of sepsis*			
Central venous catheter	44 (34)	10 (48)	0.22
Parenteral nutrition	45 (35)	6 (29)	0.59
Surgery	13 (10)	1 (5)	0.45

*- Missing variables: Human immunodeficiency virus exposure and gestational age in 3 and 2 patients respectively; †- Median (25^{th} - 75^{th} percentile).

Table 5. Comparing clinical characteristics between susceptible and XDR isolates.

Stratification	Susceptible	XDR	p-value
	N = 132	N = 21	
	n (%)	n (%)	
Age at onset of sepsis			**0.22**
Early-onset sepsis	28 (21)	7 (33)	
Late-onset sepsis	104 (79)	14 (67)	
Clinical presentation *	N = 129	N = 20	
Respiratory distress	27 (21)	6 (30)	0.36
Apnea	27 (21)	1 (5)	0.09
Abdominal distension	24 (19)	2 (10)	0.35
Large gastric aspirates	16 (12)	1 (5)	0.33
Hyperglycemia	7 (5)	5 (25)	< 0.01
Site of positive culture			**0.05**
Blood only	122 (93)	21 (100)	
Cerebrospinal fluid only	7 (5)	0 (0)	
Both sites	3 (2)	0 (0)	
Required mechanical ventilation due to sepsis †	53/119 (45)	7/18 (39)	0.65
Requiring inotropes	40 (30)	4 (19)	0.29
Died *	41/128 (32)	6/21 (29)	0.75

Table 6. Comparing characteristics between survivors and non-survivors.

Stratification	Survivors	Non-survivors	p-value
	N = 102	N = 49	
	n (%)	n (%)	
Exposed to human immunodeficiency virus *	31 (30)	17 (36)	0.48
Gestational age *			**0.45**
< 28	17 (17)	11 (23)	
28 - 34	69 (68)	34 (71)	
35 - 37	5 (5)	1 (2)	
> 37	10 (10)	2 (4)	
Birth weight			**0.06**
< 1000	20 (20)	18 (37)	
1000 - 1499	49 (48)	23 (47)	
1500 - 2499	21 (21)	6 (12)	
≥ 2500	12 (12)	2 (4)	
Male sex	55 (54)	28 (57)	0.71
Apgar score			
1 minute	7 (5 - 8) ł	6 (5 - 8) ł	0.19
5 minutes	9 (8 - 10) ł	8 (7 - 9) ł	0.02
Interventions before onset of sepsis*			
Central venous catheter	31 (31)	24 (49)	0.03
Parenteral nutrition	32 (32)	16 (33)	0.90
Surgery	10 (10)	3 (6)	0.45
Requiring mechanical ventilation †	33/92 (36)	26/42 (62)	0.005
Requiring inotropes	17 (17)	28 (57)	<0.01
Extremely drug resistant	15 (15)	6 (13)	0.75

*- Missing numbers: for human immunodeficiency virus exposure- 2 non-survivors; for gestational age - 2 (1-survivor, 1- non-survivor); for interventions before or at onset of sepsis: Central venous catheter- 1 for survivor, parenteral nutrition- 1 for survivor; ł- Median (25^{th} - 75^{th} percentile); †- Among babies who were not already on ventilatory support (n = 92 for survivors; n = 42 for non-survivors).

Outcome

Of the 155 cases, outcome data were available for 151 babies. There were 102 survivors and 49 deaths within 7 days after onset of infection with a case fatality rate of 32%. There were no statistically significant differences in case fatality rates between babies with XDR *A. baumannii* (29%) and those with susceptible *A. baumannii* (32%) (p = 0.75). Similarly, there were no statistically significant differences in case fatality rates of babies with isolates that were resistant compared to isolates that were susceptible to the cephalosporins (p = 0.895), the aminoglycosides (p = 1.00) and the carbapenems (p = 0.504).

Comparison of characteristics between survivors and non-survivors

There were no significant differences in gestational age, birth weight, and HIV exposure between survivors and non-survivors. The median 5 minute Apgar score was significantly lower in the non-survivors. There were significantly more babies with central venous lines prior to the onset of sepsis in the group that died compared to the group that survived (49% vs 31%; p = 0.03). There was no significant difference in mortality between babies who developed sepsis while on ventilator support compared to those not ventilated (41% vs 31%; p = 0.41). In the group of babies who were not on a ventilator at the time of sepsis onset, a greater number among the babies who died required ventilator support (62% vs 36%, p = 0.005) subsequent to infection compared to those who survived. Among the babies who died a greater number required inotropic support (57% vs 17%, p < 0.001) compared to those who survived (Table 6).

Discussion

This study reports on some of the epidemiologic features of infections caused by *A. baumannii* in a neonatal unit from a tertiary public hospital in a developing country.

The proportion of neonates infected with *A. baumannii*, among those with positive blood cultures, in this study is high compared to that in other neonatal intensive care units from both developed and developing countries, which reported rates ranging from 0.2 – 14.1% [8,32-34]. However, this is lower than the reported prevalence of 21% in a recent South African study [35]. Preterm and very low birth weight infants were mostly affected, in keeping with previous studies looking at associated risk factors [12,13,34]. Use of total parenteral nutrition and central venous lines prior to the onset of sepsis was high, at 33% and 36% respectively. The use of central venous catheters has been shown in previous studies to be associated with an increased risk of *A. baumannii* infection [12,13,34]. Although 76% of infections were acquired after 3 days of life, it is of concern that 24% of the time the infection was presumably acquired before 72 hours suggesting maternal acquisition. [30]. In a retrospective study conducted in India, *A. baumannii* accounted for 14.4% of early onset neonatal sepsis [36]. In this study, the most common clinical presentation at the onset of infection was related to the respiratory system (respiratory distress and apneas), followed by gastrointestinal (abdominal distension and aspirates). Of note, is that a high proportion of the patients' required mechanical ventilation (43%) and inotropic support (29%). Laboratory markers of infection that were suggestive of sepsis in these patients included a high mean CRP, leukopenia and thrombocytopenia.

The degree of extreme-drug resistance of the *A. baumannii* isolates is very concerning, with 17% of isolates being only susceptible to colistin. The majority of isolates were susceptible to cephalosporins (64%), followed by the aminoglycosides (21%). Among the cephalosporins majority were susceptible to ceftazidime and among the aminoglycosides majority were susceptible to tobramycin. Carbapenem resistance was high. *Acinetobacter baumannii* possesses their own chromosomally encoded OXA β-lactamases; OXA-48 has been shown to have activity against penicillins and carbapenems but is unique in that it spares the cephalosporins [37]. This could explain why many of the carbapenem resistant isolates were susceptible to the cephalosporins.

Resistance patterns remained mostly unchanged over the years. Most of the isolates remained susceptible to cephalosporins compared to other groups of antimicrobials. Susceptibility to carbapenems and piperacillin-tazobactam declined over the years, while that of ciprofloxacin increased. The rates of extreme-drug resistance remained consistently high over the years. High rates of extreme-drug resistance to *A. baumannii* have been shown in many studies [11-14,22]. A recent South African study has also demonstrated a high rate of extreme-drug resistance (71%) among *A. baumannii* isolates [35]. These findings highlight the need for proper infection control and antibiotic stewardship practices. Infection control measures should focus on hand hygiene and adherence to other infection prevention and control (IPC) guidelines. Enforcement of continuing antibiotic stewardship practices will prevent selection of resistant strains of *A. baumannii,* and hence reduce the

prevalence of extreme-drug resistance. These practices include early discontinuation of empiric antibiotic therapy and appropriate use and duration of antibiotics in blood culture confirmed infections. Regular IPC audits should be carried out in the unit, feedback should be given to the healthcare providers and measures to improve infection control and antibiotic stewardship practices should be implemented accordingly.

There were no significant differences between the baseline characteristics and mortality of patients with extremely-drug resistant and susceptible *A. baumannii*. This is not in keeping with other studies, which have shown a strong association between mortality and extremely-drug resistant *A. baumannii* [12,34,38]. Our inability to demonstrate a difference may be explained by the smaller proportion of patients with extremely-drug resistant *A. baumannii* in our cohort compared to the studies that reported an association between mortality and drug resistance.

Mortality attributable to *A. baumannii* sepsis was high, at 32%, higher than the reported mortality of 22% from a previous South African study [19]. The reported mortality rates from other studies range from 14% - 80% [12,13,23,34]. Comparing baseline characteristics of survivors to non-survivors, not surprisingly, the need for mechanical ventilation and inotropic support was significantly higher in babies that died, suggesting that this was a sicker group of infants who in most instances required ventilator and inotropic support, most likely secondary to septic shock, prior to their demise. This highlights the need for ventilator and inotropic support as poor prognostic signs. In addition, more babies who died had a central venous line placement compared to babies that survived. The presence of central venous lines has been shown to increase the risk of *A. baumannii* infection, but as far as we know, has not been shown to be associated with increased mortality. Unfortunately, due to the retrospective nature of this study we were not able to determine if the central lines were removed from the patients after confirmation of the *A. baumannii* sepsis. Leaving a central line in situ in an infected neonate may result in colonization of the line with the offending organism, resulting in inadequate therapeutic clearance of the infection, which may inadvertently affect outcome. Infection control measures should therefore also target reduction in the use and duration of central venous catheters in this susceptible population.

This study has several limitations. This was a retrospective record review. Although susceptibility patterns could be retrieved on majority of the cases (95%), only 39% of the hospital files could be retrieved for analysis. Although the sample size is small, to our knowledge, this study represents one of the largest numbers of studied patients with *A. baumannii* sepsis.

Conclusion

In conclusion, the prevalence and proportion of infections due to *A. baumannii* reported in this study is high. Of major concern is the high rate of extreme-drug resistance as well as case fatality. This highlights the need for strict enforcement of infection control and antibiotic stewardship practices. This study also highlights the need for continuous surveillance programs as well as the need for ongoing research, preferably prospective in nature, in order to accurately document the incidence of nosocomial infections and resistance patterns.

Acknowledgements

Dr. Kebashni Thandrayen for her assistance in the statistical analysis.

References

1. Hyder AA, Wali SA, McGuckin J (2003) The burden of disease from neonatal mortality: a review of South Asia and Sub-Saharan Africa. BJOG 110: 894-901.
2. Stoll BJ (2006). Neonatal infections: A global perspective. In Remington JS, Klein JO, editors. Infectious diseases of the fetus and newborn infant. 6th edition. Philadelphia: WB Saunders Company. 27 -57.
3. Nannan N, Dorrington RE, Laubscher R, Zinyakatira N, Prinsloo M, Darikwa TB, Matzopoulos R, Bradshaw D (2012) Under 5 mortality statistics in South Africa: Shedding some light on the trends and causes 1997-2007. South African Medical Research Council. Available: www.mrc.ac.za/sites/default/files/files/2017-05-26/MortalityStatisticsSA.pdf. Accessed 9 April 2014.
4. Baltimore RS (1998) Neonatal Nosocomial Infections. Semin Perinatol 22: 25-32.
5. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, Lemons JA, Donovan EF, Stark AR, Tyson JE, Oh W, Bauer CR, Korones SB, Shankaran S, Laptook AR, Stevenson DK, Papile LA, Poole WK (2002) Late onset sepsis in very low birth weight neonates: The experience of the NICHD Neonatal Research Network. Pediatrics 110: 285-291.
6. Aly H, Herson V, Duncan A, Herr J, Bender J, Patel K, El-Mohandes AA (2005) Is bloodstream infection preventable among premature infants? A tale of two cities. Pediatrics 115: 1513-1518.
7. Aziz K, McMillan DD, Andrews W, Pendray M, Qui Z, Karuri S, Lee SK (2005) Variations in rates of nosocomial infection among Canadian Neonatal Intensive Care Units may be practice related. BMC Pediatrics 5: 22.
8. Tsai MH, Hsu JF, Chu SM, Lien R, Huang HR, Chiang MC, Fu RH, Lee CW, Huang YC (2014) Incidence, clinical characteristics and risk factors for adverse outcome in neonates with late onset neonatal sepsis. Pediatr Infect Dis J 33: 7 – 13.
9. Stoll BJ, Hansen NI, Adams-Chapman I, Fanaroff AA, Hintz SR, Vohr B, Higgins RD (2004) Neurodevelopmental and

growth impairment among extremely low birth weight infants with neonatal infection. JAMA 292: 2357-2365.
10. Mitha A, Foix-L'Helias L, Arnaud C, Marret S, Vieux R, Aujard Y, Thiriez G, Larroque B, Cambonie G, Burguet A, Boileau P, Rozé JC, Kaminski M, Truffert P, Ancel PY (2013) Neonatal infection and 5 year neurodevelopmental outcomes of very preterm infants. Pediatrics 132: 372-380.
11. Simmonds A, Munoz J, Aquero-Rosenfeld M, Carbonaro C, Montecalvo M, Clones B, La Gamma EF (2009) Outbreak of *Acinetobacter* infection in extremely low birth weight neonates. Pediatr Infect Dis J 28: 210-214.
12. Al Jarousha AM, El Jadba AH, Al Afifi AS, El Qouqa IA (2009) Nosocomial multi-drug resistant *Acinetobacter baumannii* in the neonatal intensive care unit in Gaza city, Palestine. Int J Infect Dis 13: 623-628.
13. Touati A, Achour W, Cherif A, Hmida HB, Afif FB, Jabnoun S, Khrouf N, Hassen AB (2009) Outbreak of *Acinetobacter baumannii* in a neonatal intensive care unit: Antimicrobial and genotype analysis. Ann Epidemiol 19: 372-378.
14. Hanlon GW (2005) The emergence of multidrug resistant *Acinetobacter baumannii* species: A major concern in the hospital setting. Lett Appl Microbiol 41: 375-378.
15. Fournier PE, Richet H (2006) The epidemiology and control of *Acinetobacter baumannii* in health care facilities. Clin Infect Dis 42: 692-699.
16. Wendt C, Dietze B, Dietz E, Ruden H (1997) Survival of *Acinetobacter baumannii* on dry surfaces. J Clin Microbiol 35: 1394-1397.
17. Catalano M, Quelle LS, Jeric PE, Di Martino A, Maimone SM (1999) Survival of *Acinetobacter baumannii* on bed rails during an outbreak and during sporadic cases. J Hosp Infect 42: 27-35.
18. Denton M, Wilcox MH, Parnell P, Green D, Keer V, Hawkey PM, Evans I, Murphy P (2004) Role of environmental cleaning in controlling an outbreak of *Acinetobacter baumannii* in a neurological intensive care unit. J Hosp Infect 56: 106-110.
19. Pillay T, Pillay DG, Adhikary M, Pillay A, Sturm AW (1999) An outbreak of neonatal infection with *Acinetobacter* linked to contaminated suction catheters. J Hosp Infect 43: 299-304.
20. Abbo A, Navon-Venezia S, Hammer-Muntz O, Krichali T, Siegman-Igra Y, Carmeli Y (2005) Multidrug resistant *Acinetobacter baumannii*. Emerg Infect Dis 11: 22-29.
21. Karlowsky JA, Draghi DC, Jones ME, Thornsberry C, Friedland IR, Sahm DF (2003) Surveillance for antimicrobial susceptibility among clinical isolates of Pseudomonas Aureginosa and *Acinetobacter baumannii* from hospitalized patients in the United States, 1998-2001. Antimicrob Agents Chemother 47: 1681-1688.
22. Turton JF, Kaufmann ME, Warner M, Coelho J, Dijkshoorn L, van der Reijden T, Pitt TL (2004) A prevalent multi-resistant clone of *Acinetobacter baumannii* in South East England. J Hosp Infect 58: 170-179.
23. Giamarellou H (2016) Epidemiology of infections caused by polymyxin-resistant pathogens. Int J Antimicrob Agents 48: 614-621
24. Von Dolinger De Brito D, Oliveira EJ, Abdallah VO, da Costa Darini AL, Filho PP (2005) An outbreak of *Acinetobacter baumannii* septicemia in a Neonatal Intensive Care Unit of a University Hospital in Brazil. Braz J Infect Dis 9: 301-309.
25. Clinical and Laboratory Standard Institute (CLSI) (2007) Performance standards for antimicrobial susceptibility testing, 17th informational supplement. CLSI document M100-S17 (ISBN 1-56238-625-5).
26. Weber MW, Carlin JB, Gatchalian S, Lehmann D, Muhe L, Mulholland K (2003) Predictors of neonatal sepsis in developing countries. Pediatr Infect Dis J 22: 711 – 716.
27. Margolis P, Mulholland KE, Harrell F, Gove S (1999) Clinical prediction of serious bacterial infections in young infants in developing countries. Pediatr Infect Dis J 18 Suppl 10: 23- 31.
28. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG (2012) Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance Clin Microbiol Infect 18: 268–281.
29. O'Grady NP, Alexander M, Dellinger E, Gerberding JL, Heard SO, Maki DG et al (2002) Guidelines for the prevention of intravenous catheter-related infections. Pediatrics 110: 1 – 24.
30. Shane AL, Sánchez PJ, Stoll BJ (2017). Neonatal Sepsis. Lancet 390: 1770–80
31. Dong Y, Speer C (2015) Late-onset neonatal sepsis: recent developments. Arch Dis Child Fetal Neonatal Ed 100: F257-263.
32. Bas AY, Demirel N, Zenciroglu A, Gol N, Tanir G (2010) Nosocomial bloodstream infections in a neonatal intensive care unit in Ankara, turkey. Turkish J Pediatr 52: 464-470.
33. Zakariya BP, Bhat V, Harish BN, Arun Babu T, Joseph NM (2011) Neonatal sepsis in a tertiary hospital in South India: Bacteriological profile and antibiotic sensitivity pattern. Indian J Pediatrics 78: 413-417.
34. Thatrimontrichai A, Apisarnthanarak A, Chanvitan P, Janjindamai W, Dissaneevate S, Maneelil G (2013) Risk factors and outcomes of carbapenem-resistant *Acinetobacter baumannii* bacteremia in a neonatal intensive care unit: A case control study. Pediatric Inf Dis J 32: 140-145.
35. Morkel G, Bekker A, Marais BJ, Kirsten G, Van Wyk J, Dramowski A (2014) Bloodstream infections and antimicrobial resistance patterns in a South African neonatal intensive care unit. Paediatr Int Child Health 34: 108-114.
36. Bhat YR, Lewis LE, Vandana KE (2011) Bacterial isolates of early onset neonatal sepsis and their antibiotic susceptibility pattern between 1998 and 2004: an audit from a center in India. Ital J Pediatr 37: 32.
37. Evans BA, Amyes SG (2014) OXA β-Lactamases. Clin Microbiol Rev 27: 241–263.
38. Sheng WH, Liao CH, Lauderdale TL, Ko WC, Chen YS, Liu JW, Lau YJ, Wang LH, Liu KS, Tsai TY, Lin SY, Hsu MS, Hsu LY, Chang SC (2010) A multicenter study of risk factors and outcome of hospitalized patients with infections due to carbapenem-resistant Acinetobacter baumannii. Int J Infect Dis 14: 764-769

Corresponding author
Reenu Thomas
Department of Paediatrics, Metabolic Unit
Chris Hani Baragwanath Academic Hospital
P. O. Bertsham, 2013
Johannesburg, South Africa
Phone: +27-82-929-6310
Fax: +27-11-938-9074
Email: Reenu.Thomas@wits.ac.za

Conflict of interests: No conflict of interests is declared.