Central line-associated bloodstream infections in a resource-limited South African neonatal intensive care unit

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Declaration

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own original work, that I am the author thereof and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

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Abstract

Background: The rate of central line-associated bloodstream infection (CLABSI) in South African public sector neonatal intensive care units (NICU) is unknown. Tygerberg Children's Hospital (TCH) introduced a neonatal CLABSI surveillance and prevention programme in August 2012.

Objectives: To describe CLABSI events and identify risk factors for development of CLABSI in a resource-limited NICU.

Methods: A retrospective case-control study was conducted using prospectively collected NICU CLABSI events matched to four randomly selected controls, sampled from the NICU registry between 9 August 2012 and 31 July 2014. Clinical data and laboratory records were reviewed to identify possible risk factors using stepwise forward logistic regression analysis.

Results: Seven hundred and six central lines were inserted in 530 neonates during the first two years of the programme. Nineteen CLABSI events were identified with a CLABSI rate of 5.9/1000 line days. CLABSI cases were of lower gestational age (28 vs 34 weeks; p=0.003), lower median birth weight (1170g vs 1975g; p=0.014), had longer catheter dwell times (> 4 days) (OR 5.1 [95% CI 1.0-25.4]; p=0.04) and were more likely to have surgery during their NICU stay (OR 3.5 [95% CI 1.26-10]; p=0.01). Significant risk factors for CLABSI were length of stay > 30 days (OR 20.7 [95% CI 2.1-203.2]; p=0.009) and central line insertion in the operating theatre (OR 8.1; [95% CI 1.2-54.7]; p=0.03). Gram-negative pathogens predominated (12/22; 54%), with most isolates 10/12 (83%) exhibiting multi-drug resistance.

Conclusion: The TCH NICU CLABSI rate is similar to that reported from resource-limited settings but far exceeds that of high-income countries. Prolonged NICU stay and central line insertion in the operating theatre were important risk factors for CLABSI development. Intensified neonatal staff training regarding CLABSI maintenance bundle elements and hand hygiene is key to reducing CLABSI rates.

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Abbreviations

CLABSI = Central line-associated bloodstream infection

NICU = Neonatal intensive care unit

TCH = Tygerberg Children's Hospital

HAI = Healthcare-associated infections

LMIC = Low-middle income countries

ICU = Intensive care unit

TPN = Total parenteral nutrition

INICC = International Nosocomial Infection Control Consortium

NHSN = National Healthcare Safety Network

CDC = Centres for Disease Control and Prevention

UVC = Umbilical venous catheter

PICC = Peripherally inserted central catheter

CVC = Central venous catheter

LC-BSI = Laboratory confirmed bloodstream infection

HIV = Human Immunodeficiency Virus

PCR = Polymerase chain reaction

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Introduction

In most low-resource settings, surveillance of healthcare-associated infection (HAI) is limited or non-existent. A meta-analysis of HAI in low-middle income countries (LMIC) reported infection rates double that of developed countries, and a tripling of HAI rates in intensive care units (ICU).(1) Central line-associated bloodstream infections (CLABSI) are a type of device-associated HAI mainly encountered in the ICU setting, resulting in longer hospital stay and higher costs.(2-3) Data on CLABSI rates in LMIC is scant, particularly from NICU settings.

The use of central lines in NICU is often unavoidable with lines used for administration of intravenous fluids, blood products, inotropes, antibiotics and total parenteral nutrition (TPN). Even without the use of invasive devices, hospitalized neonates are at increased risk of infection owing to prematurity, poor skin integrity and prolonged hospitalisation.(4) Resource-limited countries contributing data to the International Nosocomial Infection Control Consortium (INICC) (3,5) report NICU CLABSI rates 3 to 4-fold higher than those documented by the United States National Health Surveillance System (NHSN).(6-7)

In high-income country NICU's, CLABSI rates declined dramatically following widespread implementation of central line bundles.(8-10) A CLABSI bundle is a strategy for insertion and maintenance of central lines, which includes several evidence-based best practices implemented simultaneously.(11-12) Central line care bundle elements include: hand hygiene, optimal catheter site selection, maximal barrier precautions at insertion, chlorhexidine skin antisepsis**,** daily review of line necessity, sterile line access, use of closed needleless intravascular catheter systems and ensuring the line dressing stays clean and intact.(11-12)

Reductions in NICU CLABSI rates have been achieved in developing countries (13-14), but data from African NICU's is extremely limited.(5,15) Our study reports the first CLABSI surveillance programme data from a public sector NICU in South Africa and aims to identify risk factors for CLABSI in this setting.

Methods

Study setting

Tygerberg Hospital is a public sector teaching hospital in Cape Town, South Africa. The neonatal service provides care to both inborn babies and neonates referred in from surrounding clinics and hospitals. Approximately 7800 babies were born per year in 2012 and 2013: 40% were low birth weight (<2500g), 13% were very low birth weight (<1500g) and 6% were extremely low birth weight (<1000g) infants.(16) The neonatal service includes the NICU with 8 intensive care beds and 4 high-care beds, as well as 112 ward beds. In the year 2013 the NICU had 491 admissions and the wards 5265.(16)

Indications for central line insertion in the NICU include requirement for TPN and/or inotropes, as well as neonates who require intravenous fluids and/or antibiotics where peripheral intravenous access is not possible or difficult to obtain. Umbilical venous catheters (UVC's) and peripherally inserted central catheters (PICC's) are first and second choice central lines and are inserted by paediatric registrars or medical officers. Central venous catheters (CVC's) and broviac lines are inserted in patients who have difficult intravenous access or where attempts at other central lines have failed and/or in post-surgical patients who need TPN. Broviac lines are inserted by the paediatric surgical team and CVC's are inserted by either the paediatric surgery or anaesthetic team.

The TCH NICU CLABSI surveillance and prevention program was implemented on 9 August 2012 with the aims of determining baseline CLABSI rates through prospective surveillance and reducing CLABSI events through use of central line insertion and maintenance bundles.

Study design

The prospectively compiled NICU central line register was used to identify cases and controls. All cases within the two year study period (9 August 2012 - 31 July 2014) were included, with 4 randomly selected controls per CLABSI event. Research randomizer (a computer programme that generates random numbers) (17) was used to select 4 controls for each CLABSI case, matching only for the year of the programme i.e. 9 August 2012 - 31 July 2013 or 1 August 2013 - 31 July 2014.

Hospital and laboratory records for the cases and controls were retrospectively reviewed. If a "control" folder was not available or the information in the folder was incomplete,

the next randomly selected folder number was used. Information obtained from the folders for both cases and controls included: patient demographics, details of their NICU stay and central line information. Additional information was obtained for all CLABSI cases: weight closest to CLABSI event onset, number of CLABSI's per patient, date of CLABSI event, pathogen isolated and antibiotic susceptibility; antibiotics used prior to and after CLABSI diagnosis; white cell count, platelet count, haemoglobin and C-reactive protein result 48-72 hours prior to CLABSI and 24-48 hours after CLABSI.

All positive cultures from catheter tips submitted from the NICU during the study period and all blood culture results of babies who died or were transferred to other neonatal wards with central lines in situ were evaluated for possible missed CLABSI cases. Umbilical arterial lines were excluded from this study because surveillance of these lines was not part of the programme initially and none of the CLABSI cases were attributed to arterial lines. The CLABSI register was the primary data source used to determine total patients and central line days in order to calculate the CLABSI rate.

Definitions

The US Centres for Disease Control and Prevention (CDC)/NHSN 2014 definitions for HAI were used.(18) CLABSI is defined as a laboratory confirmed bloodstream infection (LC-BSI) in a patient with a central line in situ for at least two calendar days (where line insertion is day 1). It is still considered a CLABSI if a LC-BSI occurred within one day of line removal. The definition for HAI and LC-BSI must be met before the definition of CLABSI can be applied and other HAI must be excluded. The CLABSI rate per 1000 central line days is calculated by dividing the number of CLABSI by the number of central line days and multiplying the result by 1000. Line days are the total number of days of exposure to central venous catheters by all patients in the selected population and time period. Definitions of multidrug-resistance applied from Magiorakos et al (19) were used to report on the antibiotic-susceptibility profile of pathogens. Mangram et al's (20) wound classification was used to classify the wounds of all the study participants that underwent surgery.

Statistical Analysis

Normally distributed data was described using means and standard deviations; non-parametric data was described with medians and interquartile ranges. The Chi-square test

was used to compare demographics of CLABSI cases vs controls; a p-value <0.05 was considered statistically significant. Stepwise forward logistic regression analysis was performed to identify risk factors for CLABSI reporting odds ratios and 95% confidence intervals.

Ethical Approval

Approval of the study (including a waiver of individual informed consent) was obtained from the Health Research Ethics Committee at Stellenbosch University (S14/07/153).

Results

Fourteen CLABSI episodes were documented in the CLABSI register. One CLABSI episode was excluded from the study because it did not meet the CLABSI definition as per CDC/NHSN 2014 guidelines. An additional six "missed" CLABSI episodes were added following review of laboratory and hospital records, yielding a total of 19 CLABSI events for which 76 controls were selected (a total of 95 study patients). The NICU CLABSI surveillance registers documented insertion of 706 central lines into 530 neonates during the first two years of the programme (a total of 3187 central line days). Nineteen CLABSI episodes in 17 patients were identified, yielding a CLABSI rate of 5.9/1000 line days. The demographics of the study population are summarised in Table 1.

Nine of the CLABSI cases had medical indications for admission: hyaline membrane disease (3), meconium aspiration syndrome (2), presumed nosocomial sepsis (2), congenital cytomegalovirus infection (1) and pulmonary haemorrhage (1). Eight patients that had undergone abdominal surgery during their current or previous NICU admission developed CLABSI episodes (10/19; 53%); including one surgical baby admitted to NICU for 107 days who experienced three CLABSI events with different pathogens on three separate lines. Of the eight babies who underwent surgery, five had a wound class of III/ IV (contaminated or dirty) (20). Comparison of septic markers 48 hours prior to and at/within 24 hours after the CLABSI event confirmed the possibility of sepsis with a decrease in white cell count, platelets and/or raised C-reactive protein. Of the five neonates who demised (26.3%), three deaths were directly attributed to the CLABSI event, one to necrotizing enterocolitis and one to congenital abnormalities. The babies that died from CLABSI were of very low birth weight (<1500g), premature, had medical

indications for NICU admission and died within 48 hours of CLABSI diagnosis. The catheter dwell times in NICU and time to CLABSI onset after insertion of different central line types are summarised in Table 2.

Of the 19 CLABSI events, 16 were mono-microbial and 3 were poly-microbial with 2 pathogens each (a total of 22 laboratory-confirmed pathogens). Gram-negative organisms predominated (12/22; 54%) followed by Gram-positives (5/22; 23%) and fungi (5/22; 23%). Antimicrobial susceptibility testing was performed on all isolates. Gram-negatives exhibited high rates of antimicrobial resistance: 6/7 *A. baumannii* were multidrug-resistant and 4/5 *K. pneumoniae* produced extended-spectrum beta-lactamases (Table 2). Fungi isolated were *Candida albicans* (3), *Candida parapsilosis* (1) (all fluconazole susceptible) and *Candida krusei* (1) susceptible to amphotericin B and voriconazole. For 14/19 CLABSI events, patients were receiving antibiotics for other indications prior to the development of CLABSI. A change in the antimicrobial treatment was made in 16/19 (84%) patients who showed clinical deterioration or had a change in their septic markers, while awaiting blood culture results. After results of antimicrobial susceptibility testing were available: 9 patients required a change in treatment, 4 had therapy targeted to the pathogen isolated, 1 had an antimicrobial agent added, 1 remained on broad-spectrum antibiotics for suspected Gram-negative sepsis, another had incomplete notes. Three babies died before susceptibility testing results were available.

Two-thirds of the cohort were premature with a lower median gestational age and birth weight among the cases (28 vs 34 weeks; p=0.003 and 1170g vs 1975g; p=0.014). The median length of stay in NICU was 7 days but significantly longer in neonates who developed CLABSI (26 vs 5 days; p=<0.001). Both groups had a greater proportion of male infants. Human immunodeficiency virus (HIV) exposure rates were similar between cases and controls; of the five HIV-exposed neonates who developed CLABSI, all tested HIV polymerase chain reaction (PCR) negative within the first two weeks of life. Seven controls were HIV-exposed, but had an unknown HIV-PCR result. The predominant line types used were UVC's (58%) and PICC's (24%). Broviac lines (3%) and CVC's (15%) were less frequently used, and almost exclusively inserted in the operating theatre (all 3 Broviac lines and 3/4 CVC's). Infection rates of lines inserted in NICU were significantly lower than that of lines inserted in the operating theatre (12/78 [15%] vs

7/15[41%]; p=0.012). Only 3 Broviac lines were inserted over the 2-year study period and all 3 developed CLABSI.

Table 3 lists the factors associated with the development of CLABSI. In the stepwise forward logistic analysis, significant risk factors included insertion of central line in the operating theatre (OR 8.1; [95% CI 1.2-54.7]; p=0.03) and length of NICU stay > 30 days (OR 20.7 [95% CI 2.1-203.2]; p=0.009).

Discussion

The CLABSI rate of 5.9/1000 lines in our NICU is similar to that reported from other LMIC but much higher than CLABSI rates in high-income settings. Limited resources, understaffing, overcrowding and the high rate of premature and low birth weight babies probably contributed to our high CLABSI rate. In this setting, CLABSI cases occurred more commonly in babies of lower gestational age, lower birth weight, those undergoing surgical procedures and patients with catheter dwell time exceeding 4 days.

A patient with a central line, who was admitted to NICU for longer than 30 consecutive days, was 20 times more likely to develop a CLABSI event, than patients with shorter NICU stays. This result remained significant in multivariate analysis, although the confidence interval was very wide. The wide confidence level can be attributed to the small number of cases. We postulate that the increased risk associated with CLABSI and long NICU stay may be due to increased risk of bacterial colonisation in critically-ill patients with complicated and/or multi-system disease (21,22).

In our setting, central lines inserted in the operating theatre (Broviac and CVC's) had an 8-fold increased risk of CLABSI compared with lines inserted in NICU. The increased risk could arise during the insertion and/or the maintenance of these lines. CLABSI events related to insertion factors usually develop within 48-72 hours of line insertion, suggesting that line maintenance issues were more likely responsible for Broviac and CVC CLABSI's (median time to infection onset of 20 and 7 days respectively). Insertion of Broviac's and CVC's are also technically more difficult and often inserted in patients with difficult venous access, or where attempts at inserting other central line types have failed. In addition, these lines were more likely to be used for TPN, possibly contributing

to infection risk. Another notable difference is that central line insertion checklists are routinely completed for lines inserted in NICU, but not for lines inserted in theatre. In light of these findings, the insertion bundle checklist should be implemented in theatre and education of all staff involved in maintenance of surgically inserted lines (not only NICU staff) undertaken. Central lines increase the risk of bloodstream infection (21,23) and known risk factors for CLABSI include administration of TPN (21-23,25), frequent manipulation of the line (26), open vascular systems (27,28), not using needleless connections (12) and the use of multiple access ports.(12) Conflicting data exist on which type of central line is associated with the highest risk for CLABSI.(23,29,30). Prolonged catheter dwell time is confirmed to increase infection risk in UVC's (31), conflicting data exist for PICC's (29,30,32) and data in Broviac lines and CVC's in neonates are lacking.

In our study nearly 80% of neonates who experienced CLABSI events were premature and half required surgery. Although surgery during NICU stay and catheter dwell time in NICU was not significant in the multivariate analysis, an association was found in the univariate analysis. The limited data available for neonates undergoing surgery suggest that premature infants, those with stomas and patients with multiple surgical interventions are at highest risk of developing a CLABSI.(33) Coffin et al developed a definition for CLABSI in neonates with presumed mucosal barrier injury due to gastrointestinal conditions (including abdominal surgery) noting that this group were at increased risk of recurrent CLABSI.(34)

Our study did not confirm TPN administration as a significant risk factor for CLABSI but we were unable to compare the duration of TPN administration in the cases versus controls. Surgery during NICU, catheter dwell time and prolonged stay in NICU could all be risk factors related to a specific group of patients requiring long-term TPN. Future research is required to evaluate these factors and the cost effectiveness of establishing a TPN unit for babies who are infection free but require long-term central lines for TPN.

The pathogens isolated were predominantly antibiotic-resistant Gram-negatives, in keeping with findings of a prior study of bloodstream infections in TCH NICU by Morkel et al.(35) The high rate of antimicrobial-resistance highlights the importance of our CLABSI surveillance and prevention programme and the need for continued antibiotic stewardship.

Study limitations included: a small number of cases making it difficult to extrapolate findings to the larger population, an unknown baseline CLABSI rate prior to implementing the CLABSI programme and the retrospective collection of clinical data for the controls. This study did not specifically evaluate adherence to specific maintenance bundle elements (including number of access ports, use of needless connectors and accessing central lines in a sterile manner). Other important CLABSI prevention strategies not explored in this study include daily assessment of the need for a central line, prevention of prematurity and promotion of early enteral feeding. Although the NICU had established a CLABSI registry, we identified 6 missed CLABSI events, suggesting a need for improved surveillance methods.

Despite these limitations, this study is (to our knowledge) the first study to establish CLABSI rates and risk factors in a South African public sector NICU. The establishment of a baseline CLABSI rate has assisted us with setting targets for the programme, assessing the impact of interventions and benchmarking ourselves against other similar NICU's. LMIC are faced with unique challenges such as staff shortages, high patient turnover and limited resources, making prevention of HAI's like CLABSI very difficult. Support from management and ongoing in-service training of all staff involved in the insertion and maintenance of central lines in neonates is vital to sustain and improve our CLABSI prevention and surveillance programme. Other resource-limited NICU's can benefit from our experience in implementing a CLABSI surveillance and prevention programme.

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Table 1: Characteristics of the study population (n=95)

Variable assessed	Number (%) unless specified (n=95)	Cases (n=19)	Controls (n=76)	p-value
Gestational age (weeks), median (IQR)	33 (28-38)	28 (27-36)	34 (30-39)	0.003
Gestational age premature (< 37 weeks)	66 (69)	15 (79)	51 (67)	0.316
Birth weight (gram), median (IQR)	1670 (1130-2765)	1170 (960-2120)	1975 (1170-2838)	0.014
Length of stay in NICU (days), median (IQR)	7 (4-15)	26 (12-83)	5 (4-10)	<0.001
* Catheter dwell time in NICU < 4 days 4-8 Days > 8 days	 36 (38) 39 (41) 20 (21)	 2 (11) 9 (47) 8 (42)	 34 (45) 30 (39) 12 (16)	0.007
Gender (male)	61 (64)	13 (68)	48 (63)	0.669
HIV-exposed	21 (22)	5 (26)	16 (21)	0.621
* Type of central line UVC PICC CVC Broviac	 55 (58) 23 (24) 14 (15) 3 (3)	 6 (32) 6 (32) 4 (21) 3 (15)	 49 (65) 17 (22) 10 (13) 0 (0)	0.001
* Insertion venue NICU Theatre Neonatal ward	 82 (86) 8 (8) 5 (5)	 12 (63) 6 (32) 1 (5)	 70 (92) 2 (3) 4 (5)	0.001
Respiratory support in NICU	86 (91)	18 (95)	68 (89)	0.480

Inotropes in NICU	43 (45)	11 (58)	32 (42)	0.216
TPN via central line	72 (76)	16 (84)	56 (74)	0.338
Surgery during NICU stay	28 (29)	10 (53)	18 (24)	0.013
Final outcome (survived)	75 (79)	14 (74)	61 (80)	0.529

CLABSI = central line-associated bloodstream infection; n = number; SD = standard deviation; IQR = interquartile range; NICU = neonatal intensive care unit; LOS = length of stay; UVC = umbilical venous catheter; PICC = peripherally inserted central catheter; CVC = central venous catheter; TPN = total parenteral nutrition. *For cells with <5 observations the Fishers exact test was used; for cells with >5 observations the Chi square test was used.

Table 2: Characteristics of CLABSI episodes (n=19)

Total number of cases*, n	19
Time to CLABSI after line insertion(days), median (IQR)	
UVC	2 (2-4)
PICC	9 (6-13)
CVC	7 (6-10)
Broviac	20 (19-35)
Weight closest to CLABSI (gram), median (IQR)	1400 (1029-2510)
Catheter dwell time in NICU, median (IQR)	
All line types	8 (14-18)
UVC	4 (3-5)
PICC	13 (8-13)
CVC	8 (8-11)
Broviac	22 (21-36)
Pathogens causing CLABSI (n = 22)	
Gram-positive organisms (Total), n (%)	5 (23)
Staphylococcus aureus	1 (5)
Coagulase negative Staphylococci	2 (9)
Enterococcus faecalis	2 (9)
Gram-negative organisms (Total), n (%)	12 (54)
Klebsiella pneumoniae	5 (22)
Acinetobacter baumannii	7 (32)
Yeasts (Total), n (%)	5 (23)
Candida albicans	3 (13)
Candida krusei	1(5)
Candida parapsilosis	1(5)

CLABSI = central line-associated bloodstream infection; n = number; IQR = interquartile range; UVC = umbilical venous catheter; PICC = peripherally inserted central catheter; CVC = central venous catheter

Table 3: Risk factors for CLABSI

Variable	Unadjusted Analysis			Adjusted Analysis		
	OR	**95%CI**	**p-value**	**OR**	**95%CI**	**p-value**
Length of stay						
< 7 days (reference)	1			1		
7-29 days	3.5	0.9-14.4	0.07	2.3	0.47-11.2	0.30
> 30 days	27.3	5.1-146.3	**<0.001**	20.7	2.1-203.2	**0.009**
Insertion venue						
NICU (reference)	1		**0.001**	1		
Theatre	17.5	3.1-97.1	0.74	8.1	1.2-54.7	**0.03**
Ward	1.5	0.15-14.2		2.9	0.2-42.2	0.437
Catheter dwell time						
0-3 (reference)	1					
4-8	5.1	1.0-25.4	**0.04**			
>8	11.3	2.1-61.0	**0.005**			
Surgery during NICU stay						
Any surgery performed	3.5	1.26-10	0.01			
Birth weight						
2500 (reference)	1					
<1000	5.2	1.0-26.1	**0.04**			
1000-1499	3.7	0.9-15.8	0.07			
1500-2499	1.5	0.3-8.1	0.65			

CLABSI = central line-associated bloodstream infection; NICU = neonatal intensive care unit; OR = odds ratio; 95%CI = 95% Confidence interval

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