

Central venous catheter-related blood stream infections in a neonatal care unit

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doi: 10.3396/IJIC.v9i3.026.13

Abstract

The aim of this study was to detect the rate of catheter-related bloodstream infection (CRBSI) in NICU of Mansoura University Children's Hospital and to focus on possible predictors of infection. A cross sectional comparative study was performed to detect the rate of CRBSI among neonates with central vascular catheters during the period between January 2009 and April 2012. Then, a nested case control study done among CRBSI cases and central vascular catheters none infected as a control group to detect predictors associated with their occurrence. Blood samples were collected from 111 neonates clinically suspected of septicemia and had inserted venous line. Central, peripheral blood and catheter tip cultures were done for each case.

CRBSI was confirmed in 69 cases as central blood culture count was more than 3 folds of peripheral blood culture count. Catheter tip culture showed more than 10³ CFU/ml per catheter of the same organisms. Low birth weight, age below 7 days, prematurity, mechanical ventilation, TPN administration and prolonged catheter stay were predictors of CRBSI. Logistic regression of the studied predictors showed that birth weight, TPN administration and length of central venous catheter stay were significant predictors of CRBSI. CRBSI is a common problem in NICU. Predictors of CRBSI included low birth weight, prematurity and mechanical ventilation. Potential use of TPN, prolonged catheter stay and low birth weight are independent predictors for CRBSI.

Keywords: Catheterization, central venous; Intensive care units, neonatal; Cross infection; Catheter-related infections

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Introduction

Health care-associated blood stream infections (HABSI) among infants hospitalized in the neonatal intensive care unit (NICU) are a leading cause of morbidity and mortality. Neonatal health care associated infections are often related to the use of central venous catheters (CVC) which are necessary to administer intravenous fluids and medications.¹

Catheter-related blood stream infection (CRBSI) is categorized into septic, exit site, and tunnel infections. Infection is diagnosed on the basis of local inflammation, purulence, fever, and leukocytosis. Lack of localizing signs and debilitation among patients with central lines attribute to difficulty to diagnose septic infections.²

Although the risk of death from CRBSI is low, infection of intravascular devices is today's leading cause of nosocomial bacteremia.^{3,4,5} Fever is the most common clinical sign. Others include chills associated with catheter flushing.⁶ CRBSI can be diagnosed when colony counts are at least 3-times higher in cultures of blood obtained via the CVC than in cultures of blood taken from a peripheral vein.⁷

If the CVC is removed for suspected CRBSI, the catheter tip should be submitted for culture. The port reservoir contents from removed subcutaneous port should be cultured. If the organisms present in either culture have also been isolated from a percutaneously obtained blood culture, CRBSI is confirmed.⁷ This study aimed to detect the rate of CRBSI and its possible predictors in the NICU.

Subjects & Methods

Study design

This is a cross sectional comparative study carried out to detect rate of CRBSI among neonates with CVC. Then, a nested case control study was done among CRBSI cases and CVC non infected as a control group to detect the predictors associated with their occurrence including sex, weight at birth, total parenteral nutrition (TPN), neonatal age at catheter insertion, weeks of gestation, length of catheter stay, number of previously inserted CVC and mechanical ventilation. Stepwise logistic regression model were

then fit using predictors significant in the bivariate analyses. The National Health Safety Network (NHSN) definition and reporting of CRBSI was applied.¹

Study population and Inclusion criteria

This study was conducted in the NICU (22 incubators), of Mansoura University Children's Hospital (MUCH) in conjunction with Microbiology Diagnostics Infection Control Unit (MDICU) in Medical Microbiology and Immunology Department in Mansoura Faculty of Medicine starting from January 2009 until April 2012. The study enrolled neonates with CVC. Blood samples from clinically suspected septicemic patients were submitted for diagnosis of CRBSI.

History and physical examination were recorded using a standardized form with special concern for evidence of risk factors. Written consent from the parents precede enrollment in the study. The study was approved by the institutional review board of MUCH.

Methodology

Catheters insertion technique

Percutaneous central venous catheterization including peripherally inserted central catheters (PICC line) or umbilical venous catheters were placed in neonates for long-term venous access for intravenous fluids, particularly parenteral nutrition. PICC lines were preferentially used in low birth weight infants. The operator and staff assisting with catheter insertion wore a surgical mask, perform a surgical hand wash with povidone-iodine containing soap (Isobetadine, Asta Medica, Brussels, Belgium) wore a sterile gown and sterile gloves. Percutaneous placement of a CVC was performed at the bedside by the neonatologist under strict aseptic conditions. After local skin disinfection with a solution of povidone-iodine solution and 0.5% chlorhexidine in 70% isopropanol (Hibitane solution, Zeneca), the introducer needle is inserted into a vein e.g. basilic, greater saphenous, external jugular or subclavian vein then the catheter is threaded and advanced the predetermined distance for central venous positioning. The catheter tip is positioned at the junction of the vena cava and right atrium, as confirmed by radiography.⁸

In neonates who had umbilical venous catheters, a 3.5 or 5 French catheter was inserted in the umbilical vein, advanced through the ductus venosus into the inferior vena cava and its position verified by x-ray.⁸ The catheters were left in place until no longer needed or until a complication such as bacteremia, venous thrombosis or catheter malfunction occurred.

Sample collection and processing

When CRBSI was suspected, the catheter hub was cleaned with alcohol and allowed to dry to minimize blood culture contamination; 1-2 ml of blood was drawn from lumen of CVC for quantitative blood culture by the pour plate method on nutrient agar plates after serial dilution. Colonies were formed on the top of the agar as well as in the agar, those on top, were larger but all colonies on and in the agar were counted. Plates that had between 30 - 300 colonies in and on the agar were selected as those give the best statistical representation of the number of bacteria in the undiluted sample. Quantitative culture was reported according to the following equation CFU/ml = CFU/plate x dilution factor.

Simultaneous quantitative peripheral blood culture from a fresh venipuncture was done taking all aseptic precautions. Media used for subculture included chocolate agar, 5% sheep blood agar and MacConkey's agar (Oxoid, UK).

After removal, the tip of the CVC was sent for culture. and inoculated agar plates were incubated at 37°C for up to 48 hours Results were reported as positive if $\geq 10^3$ CFU / ml of broth cultures per catheter were counted on the agar plate.

Microbial identification

Full identification up to species level was done by Gram stained film, colony characters, and biochemical reactions. API 20E and API 20 non E (bioMerieux, Marcy l'Etoile, France) was used to confirm the identity of Gram negative isolates. While culture characters, catalase, coagulase and API 20 Staph were used to identify Gram positive isolates.

Antimicrobial Susceptibility Tests

Susceptibility tests were performed using the Kirby-Bauer disc diffusion method on the surface of Muller-

Hinton agar plates (Oxoid, UK) following National Committee for Clinical Laboratory Standards (NCCLS) guidelines.⁹

Plasmid extraction

Cases proven to be CRBSI, Plasmid extraction was carried out to ensure that they have the same identity of those isolated from peripheral blood culture. Briefly one and half ml of broth culture of the organism was centrifuged at 12,000 rpm for 30 seconds at 4°C. Then, the bacterial pellet was resuspended in 100µl of ice cold solution I [50 mM glucose, 25 mM TrisCL (pH 8.0), 10 mM EDTA (pH 8.0)] and vigorously vortexed. Two hundred µl of freshly prepared solution II [0.2 NaOH in 1% SDS] were added and inverted rapidly five times and stored on ice for 5 minutes. Then, one hundred and fifty µl of ice cold solution III [3M K+ acetate in 11.5% glacial acetic acid] were added and vortexed for 10 seconds then stored on ice for 3-5 minutes. Next, supernatant was collected after centrifugation at 12,000 rpm for 5 minutes at 4°C. Two volumes of ethanol were added, vortexed and left at room temperature for 2 minutes. The tubes were centrifuged at 12,000 rpm for 5 minutes at 4°C. After removal of the supernatant, pellets were rinsed with 1 ml of 70% ethanol then the products were visualized under ultraviolet light after electrophoresis on 2% agarose gel stained with ethidium bromide. The plasmid pattern and size con were compared with standard molecular weight marker.¹⁰

Statistical analysis

Analysis of data was undertaken using SPSS (statistical package for social science) version 16. Variables were presented as number and percentage. Chi-square test was used for comparison between groups. Significant predictors on bivariate analysis were entered into a logistic regression model using forward Wald method to predict the independent predictors of infection. Odds ratio (OR) and confidence interval (95% CI) were calculated. The significance were adopted when $p < 0.05$.

Results

Over the period of this study, 1314 neonates admitted to NICU unit of whom, 293 (22.3 %) had one CVC line inserted, including 192 (65.5%) umbilical venous catheters, 77 (26.7%) CVC and 24 (8.2%)

PICC lines. Blood samples were collected from 111 neonates suspected to have septicemia, CRBSI was detected in 69 (23.5%) patients guided by culture and identification. The overall infection rate for CRBSI was 21.4 per 1,000 CVC days commonly caused by CoNs (n = 41), *K. pneumoniae* (n = 25), *S.aureus* (n = 3), *E. cloacae* (n = 2) and *P. aeruginosa* (n = 1). Mixed CoNs, *S. aureus*, and *Enterococcus* were detected in 2 cases.

CoNS and *S. aureus* that were isolated from blood samples through the CVC shared 100% sensitivity to vancomycin while *Klebsiella* isolates were only sensitive to imipenem (93.4%). *Enterobacter* isolates showed best sensitivity to meropenem (100%)

followed by ciprofloxacin (88.9%). *Pseudomonas* were most susceptible to imipenem (98.2%) followed by ceftazidime (88%) and gentamycin (64.7%).

CRBSI was confirmed in 69 cases. Catheter tip culture showed more than 10^3 CFU / ml per catheter of the same organisms. Further confirmation by biotyping, resistogram and plasmid typing were done. Three clinically suspected septicaemic cases with positive culture results were excluded from the study, two cases did not match diagnostic criteria for CRBSI. The remaining case was positive only by catheter tip culture. All cultures from the remaining 39 clinically suspected cases were negative.

Table I. Predictors of catheter-related versus non catheter-related BSI

Risk factors	CRBSI (n = 69)	Non-CRBSI (control) (n = 224)	P
Sex:			
Male	41 (59.4%)	118 (48.8%)	0.077
Female	28 (40.6%)	124 (51.2%)	
Birth weight:			
≥ 1500 g	13 (18.8%)	153 (63.2%)	0.0001
< 1500 g	56 (81.2%)	89 (36.8%)	
TPN:			
YES	59 (85.5%)	108 (55.4%)	< 0.001
NO	10 (14.5%)	134 (44.6%)	
Neonatal age:			
< 7 days	38 (55.1%)	101 (41.7%)	0.034
≥ 7 days	31 (44.9%)	141 (58.3%)	
Weeks of gestation:			
< 34 weeks	66 (95.7%)	107 (44.2%)	< 0.001
≥ 34 weeks	3 (4.3%)	135 (55.8%)	
Length of catheter stay:			
≥ 3 days	54 (78.3%)	69 (28.5%)	< 0.001
< 3 days	15 (21.7%)	173 (71.5%)	
Previously inserted CVC:			
Yes	20 (29%)	56 (23.1%)	0.20
No	49 (71%)	186 (76.9%)	
Mechanical ventilation:			
Yes	41 (59.4%)	108 (44.6%)	0.04
No	28 (40.6%)	134 (55.4%)	

CRBSI: Catheter-related blood stream infection

CVC: Central venous catheter

TPN: Total parenteral nutrition

Table II. Logistic regression model for risk factors

	B	Significance	OR	95.0% C.I.for EXP(B)	
				Lower	Upper
Weight	-3.631	< 0.001	0.026	0.009	0.081
TPN	-1.326	0.012	0.265	0.095	0.744
Length of CVC insertion	-3.480	< 0.001	0.031	0.011	0.090
Constant	3.274	< 0.001	6.409		

Model $\chi^2 = 22.17$, $P < 0.01$

This model predicts 91%

Neonates with CRBSI were more likely to be VLBW, aged below 7 days, premature, mechanically ventilated, on TPN, and had a longer catheter stay when compared with those without BSI. The risk of BSI did not differ by gender or previous catheterization (table I).

Logistic regression of the studied predictors showed that birth weight, TPN infusion and length of CVC stay were still significant predictors of CRBSI (table II).

Discussion

CVC is mandatory in the critically ill child including VLBW (VLBW), infants with short-gut syndrome, children with cancer, and those with chronic diseases such as cystic fibrosis and hemophilia.¹¹ Complications with CVC are relatively common and result in increased morbidity, hospitalization, and costs.¹²

Throughout the period of the 40 months study, a total of 69 positive blood cultures were proven to be related to the inserted CVC at a percentage of 23.5% and 21.4 per 1,000 CVC days. These results were concordant with the data of other publications.¹³⁻¹⁷ This was in contrast, to the data reported in the NHSN report in which the CRBSI ranged from 3.1–6.4 per 1,000 CVC days.¹⁸

This high rate could be related to increased number of VLBW of our studied group who needed frequent handling and mechanical ventilation. Moreover, underlying patient condition, frequent changes in nurses which lead to lack of regularity of following the written guidelines for access and care of central

venous catheters, or the physical environment have shared to this high rate.^{17, 19}

There is a wide range of disparity in the infection rates in different studies which may depend on unit-associated factors such as size and settings, patient-associated factors such as type of illness and its severity and catheter-associated factors such as type of catheter, site of insertion and conditions under which the catheter was located.²⁰ Stover *et al.* reported great inconsistency in the blood stream infections rates from 23 US hospitals ranging from 0.0 to 18.5/1000 catheter-days.¹⁵ Richard *et al.* examined BSI in the USA and found that blood stream infection in 61 PICUs to be the most common nosocomial infection with a rate ranging from 0.0 to 20/1000 catheter-days.²¹

In one study, CRBSI; only central venous catheters type was detected at a rate of 9.3 infections per 1,000 catheter days which is lower than our reported rate.²² Another prospective study of 226 neonates who had PICCs in NICU between January 2006 and June 2009, the PICC infection rate was 17 per 1000 catheter-days.²³ This could be explained by that, the CRBSI were not categorized according to type of catheters in this study.

In another report, the incidence of CRBSI was classified according to the neonatal birth weight to be 11 per 1000 catheter-days and 4 per 1000 catheter-days in babies weighing less than 1 k and in those more than 2.5 kg, respectively.²⁴

CoNs (59.4%) were the most common pathogen isolated from positive cultures as has been reported by other authors.^{19,25} The high frequency of this organism in CRBSI is due to its ability to adhere to the exterior surface of the catheter and formation of biofilm and slime layer which protects them from phagocytosis and antibiotics.¹⁴ Furthermore, the presence of lipid emulsion in the infusate has been linked to CoNS bacteremia.²⁶

An alarming point in this study is the emergence of higher incidence of *Klebsiella* (36.2%) among the organisms causing CRBSI than other previously mentioned data.^{17,23,27} The most common pathogens of bacterial sepsis differ in various parts of the world and health settings. This high incidence could be due to the fact that *Klebsiella* is a major pathogen in our NICU.

In the study carried in NICU in MUCH, *Klebsiella* was the commonest organism (46.2%) isolated from blood stream infected cases.²⁸ Also Rizk *et al.* found that *Klebsiella* was the most frequent pathogen isolated in MUCH accounting for 17.0% of the total nosocomial isolates.²⁹ Another study was done in MUCH pediatric ICU revealed that *Klebsiella* was the commonest isolated nosocomial organism.³⁰ In addition, Badr and Shouman found that *Klebsiella* was responsible for nearly 50% of neonatal sepsis in MUCH NICU.³¹ Moreover, *Klebsiella* was found to be the commonest isolate among admitted neonates in the same NICU representing 39.2%.³²

Hospitalized neonates are often colonized with *Klebsiella*, *Enterobacter*, and *Citrobacter* species at high rates when compared with babies at home in whom *Escherichia coli* is the main bowel flora. The risk of stool colonization with these species is increased with over three days of antibiotic use and with length of hospital stay, 60% being colonized by day 15 and over 90% by day 30. It was found that colonized babies are the commonest reported source of infection with gut colonization as the major reservoir.²⁸

An approach to eradicate potentially disease-producing micro-organisms from the oropharynx and gastrointestinal tract of intensive care unit (ICU) patients is selective decontamination of the digestive tract, therefore decreasing the incidence of nosocomial

sepsis. A lower cost one is to consider that all babies are colonized and that strict attention to hand washing is routinely encouraged.²⁸ Gut decontamination strategies for prevention of septicemia may be needed.³³

The knowledge about specific risks could allow neonatologist to identify infants at high risk of sepsis and early management. Factors reported to increase the incidence of CRBSI include low birth weight, age below than 7 days, prematurity, number of CVC days, mechanical ventilation and infusion of TPN.^{14,28,34} Previous catheterization was not a significant factor of CRBSI in this study.

In the logistic regression model, birth weight, the duration of catheters in place and those who received TPN remained significant predictors for CRBSI. Mechanical ventilation, age of infection and gestational age were not significant predictors of CRBSI in this model.

Subhani *et al.* postulated that a higher infection rate in VLBW neonates could reflect functional immaturity of the immune system.³⁵ Besides, our results seem to agree with the findings of Gaynes *et al.*, who noted a positive correlation between overall nosocomial infection rates and a measure of device utilization.³⁶ This could be explained by the relation between prolonged catheters stay and the higher risk of skin colonization which is associated with an increased risk of CRBSI.³⁷ Moreover, TPN need prolongs the duration of CVC stay.¹³ Shouman *et al.* found that the use of full dose intralipids in TPN decreases the rate of blood stream infection clearance compared to restricted dose of intralipids to 1 g/kg/d. Furthermore, TPN adversely affects phagocytosis in neutrophils and increases epithelial permeability.³⁸⁻⁴⁰

Central venous blood passes through reticuloendothelial cells in the lung reaching the peripheral vein which lead to much less concentration of microorganisms in peripheral blood than the catheter blood. This explains exclusion of two cases that do not fulfill this criterion. On the other hand, the barred third case could be explained by the possibility of catheter tip contamination during removal.⁴¹

Limitations to this study are that we did not evaluate several possible confounders such as underlying host factors, antibiotics, crowding, understaffing or severity of illness. Also, surveillance cultures of neonates or the environment were not performed in this study, due to cost and reliability. Finally, we did not categorize the CRBSI rate in our neonatal unit per catheter type.

In summary, this study confirmed that the predictors of CVC infections included low birth weight, prematurity and mechanical ventilation for neonates with HCABSI. This study further elucidated the potential use of TPN, prolonged catheter stay in neonates and low birth weight as independent predictors for CRBSI. Preventive strategies as gut decontamination and limiting the use of invasive devices should be encouraged to minimize BSI in neonates in our NICU.

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