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Original Article

Diagnosis of central venous catheter-related bloodstream infection without catheter removal: A prospective observational study

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ARTICLE INFO

Article history:

Received 29 July 2013

Accepted 6 August 2013

Available online 16 December 2013

Keywords:

Catheter related sepsis

Central venous catheter

CRBSI

ABSTRACT

Background: Catheter-related bloodstream infections (CRBSI) resulting from bacterial colonisation of an intravascular catheter are the leading cause of nosocomially acquired sepsis contributing significantly towards in-hospital morbidity and mortality. Suspicion of central venous CRBSI leads frequently to catheter withdrawal but not all infection requires the catheter to be withdrawn; therefore, diagnosis of central venous CRBSI without catheter withdrawal is a necessity.

Methods: The study was prospectively performed in a cohort of adult patients who had short term central venous catheter use. The samples collected from each patients included, skin swab from insertion site, swab from catheter hub, paired blood samples from catheter and from the peripheral vein for quantitative blood culture collected within 15 min of each other and catheter-tip sample by cutting off the tip (distal 5-cm segment). All samples were processed immediately.

Results: 50 episodes of clinical sepsis involving 100 patients occurred in the study population. 28 of the episodes were confirmed as CR-BSI (56%). Blood culture from the central venous catheter had the highest sensitivity (71.43%) and the greatest negative predictive value (86.67%). However, the peripheral blood culture was most specific and had the highest positive predictive value (specificity 75%; positive predictive value 50%). The most accurate technique was differential quantitative blood cultures (accuracy 72%), followed by semiquantitative superficial cultures (accuracy 68%), although there were no statistically significant differences between values.

Conclusion: We recommend combining semiquantitative cultures and peripheral blood cultures to screen for CR-BSI, leaving differential quantitative blood cultures as a confirmatory and more specific technique.

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<http://dx.doi.org/10.1016/j.mjafi.2013.08.001>

Introduction

Catheter-related bloodstream infections (CRBSI) resulting from bacterial colonisation of an intravascular catheter are a significant clinical problem, magnified in recent years by the increasing use of intravascular catheters in intensive care units (ICUs). In particular, central venous catheter-related infections are a common cause of bacteraemia and sepsis. Central venous catheters can cause bloodstream infection by three routes i.e. intraluminal, extraluminal, and haematogenous.^{1,2} The symptoms and signs of catheter-related infection may be localised to the insertion site or track of a tunnelled device. Alternatively, manifestations may be systemic and possibly complicated by bacteraemia.³ Suspicion of central venous catheter-related bloodstream infection leads frequently to unnecessary catheter withdrawal and reinsertion of a new CVC at a different site often in a patient with many comorbid conditions resulting in increased morbidity to patient and loss of time and effort of the intensivist. Confirmation of central venous catheter-related bloodstream infection requires identification of the same microorganism in pure culture (single isolate) recovered from blood and catheter tips. Furthermore, not all central venous catheter-related bloodstream infections require the catheter to be withdrawn; therefore, diagnosis of central venous catheter-related bloodstream infection without catheter withdrawal is necessary.^{4,6} This study was aimed to develop a standardized protocol by using three conservative methods for determining presence of central venous catheter-related bloodstream infection.

Material and methods

This prospective study was conducted after approval of the Institutional ethical committee in an intensive care unit of a tertiary care health facility between 2007 and 2010. All patients with central venous catheter inserted for >48 h having clinical suspicion of sepsis were included in the study.^{5,6} Patients with neutropenia and blood disorders were excluded from the study. No antibiotic coated catheters were used in the intensive care unit during the study period. Case patients were included only once. Demographic data such as age, sex, underlying disease, duration of hospitalization, duration of intensive care unit stay, type of catheter, number of catheter lumens, insertion sites and indwelling time were recorded on a predecided proforma.

CR-BSI was defined as the presence of bacteremia or fungemia in a patient with clinical manifestations of infection and no other apparent source of bloodstream infection (with the exception of the catheter). A catheter-tip culture positive for the same microorganism by the roll-plate technique was also required as a reference in order to determine the accuracy of the conservative methods. Significant colonization of the catheter tip was defined as a positive semiquantitative catheter culture by the roll-plate method, when a ≥ 15 colony-forming unit was cultured from the catheter tip.⁷

The following samples were collected from each patient. (1) Superficial swab from insertion site: A 3 cm area of skin swabbing around the insertion site (obtained by lifting the

dressings and rubbing the area around the insertion site (in a 3-cm radius) with a cotton swab wet with sterile saline). (2) Swab from catheter hub: A similarly wet cotton swab sample of each catheter hub for semiquantitative culture. (3) Paired blood samples: A 10 ml blood sample from the hub of catheter for quantitative blood culture and 10 ml blood sample from the peripheral vein for quantitative blood culture both taken within 15 min of each other. After withdrawing blood samples central venous catheter were withdrawn. The catheter-tip sample was taken after scrubbing the skin surrounding the insertion site with 2% chlorhexidine or betadine and cutting off the tip (distal 5-cm segment) using sterile scissors into a sterile container. All samples were dispatched to microbiology lab immediately.

Superficial swabs were streaked all over the blood agar plate and colony count more than 15 cfu was considered significant. The catheter was processed by roll plate on blood agar plate technique for semiquantitative culture while all swabs were processed on both Blood agar and MacConkey agar. The plates were incubated aerobically for 72 h at 37 °C, and the number of colonies recovered was counted only for the catheter roll plate. Blood cultures were collected in BHI (Brain Heart Infusion) broth and processed quantitatively according to routine methods. The microorganisms recovered were fully identified by standard microbiological methods. Superficial cultures (cultures of skin) were given cognizance only if the organism/one of the organisms isolated from the swab culture was the same as the microorganism isolated from the roll plate/blood cultures and the Roll plate culture of the catheter tip was considered to be positive only if isolated in pure culture and when the same microorganism was isolated from peripheral blood. Quantitative blood cultures were defined as positive when the number of colony-forming units of bacteria or yeasts isolated per milliliter of catheter-drawn blood were at least 5 times greater than that of blood obtained from a peripheral vein. Significant colonization of the catheter tip was defined as a positive semiquantitative catheter culture by the roll-plate method, when ≥ 15 colony-forming units were cultured from the catheter tip.

CR-BSI and non-CR-BSI groups were compared using a 2-tailed Fisher's exact test for proportions (qualitative variables) or a 2-tailed Student's *t* test for means (quantitative variables). We obtained the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the different diagnostic techniques, compared with the reference technique. All values were calculated with a 95% Confidence Interval following an exact binomial distribution. To compare sensitivities, specificities, and accuracies, we used the 2-tailed McNemar's test for paired samples. Predictive values were evaluated by 2-tailed Fisher's exact test. For the comparisons, $P < 0.05$ was considered to be statistically significant. Data was analyzed using the software package, SP Version 10.0.

Results

A total of 119 patients with clinical suspicion of sepsis and central venous catheter inserted for >48 h were enrolled in the study. The demographic profile of the patients in two groups is

shown in Table 1. Of these, 19 patients were excluded from the study, because the sample set was not complete. Therefore, 100 patients were included in the study. A total of 50 episodes of positive blood cultures of one or the other sample taken occurred in the study population. After analysis, 28 of the episodes were confirmed as CR-BSI (56%). 22 episodes that were not confirmed as CRBSI were either bloodstream infections that were not catheter-related or involved catheter-tip colonization only (with no microorganisms isolated from the peripheral blood samples), and the remainder 50 were cases with negative peripheral blood culture results and non-colonised catheters.

Of the 28 cases of CR-BSI included in the analysis, 26 were monomicrobial infections, and 2 were polymicrobial infection (Table 2). Of the significant microorganisms, 5 (17.86%) were gram-positive bacteria, whereas the others were gram-negative bacteria (23; 82.14%). There were 2 deaths in patient with CRBSI (7.1%) and nil in non-CRBSI group.

Table 3 shows a comparison of the validity values from the 3 conservative techniques for the diagnosis of CR-BSI. Culture of blood from the central catheter proved to be the most sensitive technique (sensitivity, 71.43%) with the greatest negative predictive value (negative predictive value 86.67%). However, the culture of blood from peripheral site was most specific (specificity 75%) with highest positive predictive value (positive predictive value 50%). Overall, the most accurate technique was differential quantitative blood cultures (accuracy, 72%), followed by semiquantitative roll plate cultures (accuracy, 68%), although there were no statistically significant differences between values.

Discussion

CR-BSIs are the main cause of nosocomially acquired sepsis, but they are particularly prevalent among patients admitted to the ICU. Incidence density of sepsis ranges from 3.9 to 30 episodes of CR-BSI per 1000 days of central venous catheter

Table 2 – Microorganism in catheter-related bloodstream infection.

Microorganism	No of cases	Percentage
Coagulase +ve staphylococci	2	7.14
Coagulase –ve staphylococci	3	10.71
Non-fermenter, Gram-Negative Bacteria (<i>Pseudomonas aeruginosa</i> , <i>Acinetobacter baumannii</i>)	21 ^a	75
Gram –ve, Fermenter, <i>Klebsiella pneumoniae</i>	2	7.14
Total	28	100

^a 2 were polymicrobial (only dominant species with greater CFU counted).

use, and mortality associated with CRBSI is estimated to be 9%–43%.^{1,8} In this study mortality associated with CRBSI was found to be 7.1%. It is common practice in many ICUs to remove all central venous catheters from patients with sepsis, but on many occasions, watchful waiting is a prudent approach, and many cases can be empirically managed without immediate catheter withdrawal provided rapid and reliable laboratory support exists.^{9,10} In addition, 80% of catheter tips cultured in microbiology laboratories are found to be sterile.^{3,10,11}

The most commonly reported techniques for assessing the catheter tip without catheter removal (i.e. conservative techniques) include the so-called superficial roll plate cultures, the differential colony counts between peripheral blood and blood obtained from the catheter hubs, and—more recently—differential time to positivity.¹⁰

The first prospective study comparing 3 techniques for the diagnosis of CR-BSI without catheter withdrawal involving patients without blood disorders or neutropenia who had central venous catheters and were hospitalized in the intensive care unit was conducted by Bouza et al² and has recommended combining semiquantitative superficial roll plate cultures and peripheral vein blood cultures to screen for CR-

Table 1 – Demographic and clinical data for patients with suspected catheter-related bloodstream infection (CR-BSI).

Variable	Patients with CR-BSI (n = 28)	Patients without CR-BSI (n = 72)	All patients (n = 100)	T value/chi-square value ^a	P value
Age (years)	50.64 ± 12.08	46.86 ± 15.96	—	0.90	>0.05
Male sex	16 (57.14%)	42 (58.33%)	58%	0.01 ^a	>0.05
ICU stay (days)	11.04 ± 5.09	10.28 ± 6.31	—	0.44	>0.05
Duration of catheter use (days)	6.93 ± 3.88	5.06 ± 2.47	—	1.68	>0.05
Catheter insertion site					
IJV	12 (42.8%)	34 (47.2%)	46	0.15 ^a	>0.05
Subclavian vein	16 (57.2%)	38 (52.8%)	54		>0.05
Lumens					
Double	24 (85.7%)	54 (75%)	78	1.35 ^a	>0.05
Triple	4 (14.3%)	18 (25%)	22		>0.05
TLC > 12,000 cumm	10 (35.71%)	13 (18.05%)	23	3.54 ^a	>0.05
TLC (cumm)	10,500 ± 2720.57	9058.33 ± 2792.23	—	1.67	>0.05
Fever present	26 (92.8%)	38 (52.77%)	64	14.06 ^a	<0.0001
Afebrile after 24 h	20 (71.43%)	36 (28.57%)	56	3.75 ^a	<0.05

Values are mean ± SD or number of patients (%); IJV = Internal Jugular vein; TLC = Total Leukocyte Count.

^a Chi-square values.

Table 3 – Comparison of the validity values from the 3 conservative techniques for the diagnosis of CR-BSI.

	Blood CVC port	Blood peripheral	Superficial culture
Sensitivity	71.43% (63–81)	64.29% (55–75)	71.43% (63–81)
Specificity	72.22% (63–82)	75% (67–84)	66.67% (57–77)
PPV	50% (40–61)	50% (40–61)	45.45% (36–56)
NPV	86.67% (80–94)	84.38% (77–92)	85.71% (77–94)
Accuracy	72%	72%	68%
Chi-square value	16.01	13.5	11.87
P value	P < 0.0001	P < 0.0001	P < 0.001

PPV = Positive Predictive Value; NPV = Negative Predictive Value; Values in bracket are 95% Confidence Interval.

BSI, leaving differential quantitative blood cultures as a confirmatory and more specific technique. No statistically significant differences in accuracy were detected among the techniques. The classic reference method to confirm CR-BSI consists of the concomitant isolation of the same microorganism from blood samples and the catheter tip. Unfortunately, this requires catheter withdrawal and culture of the catheter tip, which, as we have mentioned, is frequently premature and unnecessary.

In our study all central venous catheters were inserted under maximum sterile barrier precautions¹² by anaesthesiologist/intensivist experienced in the procedure following the guidelines as per central line bundle.¹³ In patients with bloodstream infection, the hub is frequently the source of CR-BSI, and negative hub and skin culture results almost rule out catheter colonization and CRBSI.^{14,15} In the present study, sterile quantitative cultures of the blood from the central venous catheter port and periphery had a negative predictive value of 86.67% and 84.38% for the catheter origin of a bloodstream episode. The differential in quantitative bacteremia between blood samples obtained through the catheter hubs and peripheral blood samples is currently accepted as a confirmatory criterion for CR-BSI. However, the technique is tedious, requires handling of blood samples by laboratory personnel, involves frequent contamination, and is expensive.

Time to positivity and length of lag period are strongly related to the concentration of bacteria inoculated. Rijnders et al¹⁶ did not find differences in median differential time to positivity between patients with CR-BSI and patients without CR-BSI, and they rejected the differential time to positivity as being of no use for the diagnosis of CR-BSI. In a meta-analysis that evaluated the diagnosis of vascular CR-BSI, paired quantitative blood cultures were the most accurate test for the diagnosis of CR-BSI.⁹ However, most other methods that were studied showed acceptable sensitivity and specificity (75% for both) and negative predictive value (99%). The positive predictive value of all tests increased greatly with high pretest clinical probability. In our series, the higher negative predictive value of peripheral blood and superficial cultures (84.38% and 85.71%), were statistically significant. However, CVC blood cultures represented the best specificity and negative predictive value in the diagnosis of CR-BSI (72.22% and 86.67% respectively).

In this study, CRBSI and Non-CRBSI pts had similar length of stay in ICU and duration of catheter in situ was also same suggesting CRBSI is not dependant on duration of stay or days

of catheter in situ.¹⁷ There was no statistical difference in the CRBSI incidence with respect to either the site of catheter placement (Internal Jugular Vein or Subclavian. Since femoral route was not used for CVC insertion in any of the patients, we are not able to comment on the same.) or the number of lumens in our study.^{17,18}

In our study we found association of fever in pts with CRBSI to be significant and also patients became afebrile 24 h after removal of catheter. Defervescence of sepsis after removal of culture-positive central venous catheters (CVCs) has been advocated for diagnosis of catheter-related bloodstream infection (CRBSI) even without positive blood culture.¹⁹ However, most studies report CRBSI incidence only when blood cultures and CVC tip are positive (standard definition).

Our results suggest that the negative predictive value for each of the 3 tests that we compared is very high and that they each allow us to rule out catheter colonization and CR-BSI. The need incubate blood cultures immediately after withdrawal is another drawback of this technique but was overcome in our case by the placement of an incubator in the ICU (Medical) where inoculated BHI Bottles were incubated till sent to the laboratory the next morning. Mention of date and time of withdrawal on the form prevented any perceived delay of processing of the samples. Limitations of this study were that incidence could not be reported in infection per 1000 catheter days which is required to establish the causal relationship and the odds of acquiring CRBSI attributable to various risk factors. The greatest aim of all the trials to diagnose CRBSI is to lessen the unnecessary catheter withdrawal and lower the economy burden on the institute, we did not analyse the cost effectiveness of conservative diagnosis as compared to cost involved in changing of the catheter.²⁰

Conclusion

Conservative methods to assess catheter-tip colonization or CRBSI are an important advancement and include paired quantitative blood cultures, differential time to positivity, roll plate cultures of superficial skin surrounding the portal of entry and catheter hubs, Acridine Orange staining and Gram staining. The ease of performance, low cost, and wide availability of the techniques lead us to recommend combining semiquantitative superficial cultures and peripheral blood cultures to screen for CR-BSI, leaving differential quantitative blood cultures as a confirmatory and more specific technique.

Conflicts of interest

All authors have none to declare.

REFERENCES

1. Safdar N, Maki DG. The pathogenesis of catheter-related bloodstream infection with noncuffed short-term central venous catheters. *Intensive Care Med.* 2004;30:62–67.
2. Bouza E, Alvarado N, Alcalá L, et al. A randomized and prospective study of 3 procedures for the diagnosis of catheter-related bloodstream infection without catheter withdrawal. *Clin Infect Dis.* 2007;44:820–826.
3. Hocking Graham. Central venous access and monitoring. *Update Anaesth.* 2000;12:1–6.
4. Fortun J, Perez-Molina JA, Asensio A, et al. Semiquantitative culture of subcutaneous segment for conservative diagnosis of intravascular catheter-related infection. *JPEN J Parenter Enteral Nutr.* 2000;24:210–214.
5. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest.* 1992;101:1644–1655.
6. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock. *Intensive Care Med.* 2008;34:17–60 (And *Crit Care Med* 2008;36(1):296–327).
7. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2009;49:1–45.
8. National Nosocomial Infections Surveillance (NNIS) System report, data summary from January 1990–May 1999, issued June 1999. *Am J Infect Control.* 1999;27(6):520–532.
9. Mohr-O'Hara C, Weinstein MP, Michael-Miller J. Manual and automated systems for detection and identification of microorganisms. In: Murray PR, Baron EJ, Jorgensen JH, Tenover FC, Tenover FC, eds. *Manual of Clinical Microbiology*. 8th ed. Will Behington, DC: American Society for Microbiology; 2003:185–207.
10. Blot F, Schmidt E, Nitenberg G, et al. Earlier positivity of central venous versus peripheral-blood cultures is highly predictive of catheter related sepsis. *J Clin Microbiol.* 1998;36:105–109.
11. Blot F, Nitenberg G, Chachaty E, et al. Diagnosis of catheter-related bacteremia: a prospective comparison of the time to positivity of hub blood versus peripheral-blood cultures. *Lancet.* 1999;354:1071–1077.
12. Raad II, Hohn DC, Gilbreath J, et al. Prevention of central venous catheter-related infections by using maximal sterile barrier precautions during insertion. *Infect Control Hosp Epidemiol.* 1994;15:231–238.
13. Abe C, Zack J, Lewis AR, Vanderveen T. Zero tolerance: Curbing catheter-related blood stream infections. *Patient Saf Qual Healthc.* 2007;4(6):14–18.
14. Mijlčević V, Suljagić V, Jovanović B, Gligorićević J, Jovanović S, Mazić N. Risk factors for the appearance of central venous catheters colonization. *Vojnosanit Pregl.* 2007 Nov;64(11):760–764.
15. Zingg W, Cartier-Fässler V, Walder B. Central venous catheter-associated infections. *Best Pract Res Clin Anaesthesiol.* 2008 Sep;22(3):407–421.
16. Rijnders BJ, Verwaest C, Peetermans WE, et al. Difference in time to positivity of hub-blood versus no hub-blood cultures is not useful for the diagnosis of catheter-related bloodstream infection in critically ill patients. *Crit Care Med.* 2001;29:1399–1403.
17. Centers for Disease Control and Prevention. *Guidelines for the Prevention of Intravascular Catheter-related Infections*; 2011. www.cdc.gov/hicpac/BSI/BSI-guidelines-2011.html. Accessed 26.06.11.
18. Farkas JC, Liu N, Bleriot JP, Chevret S, Goldstein FW, Carlet J. Single- versus triple-lumen central catheter-related sepsis: a prospective randomized study in a critically ill population. *Am J Med.* 1992;93:277–282.
19. Walshe CM, Boner KS, Bourke J, Hone R, Phelan D. Diagnosis of catheter-related bloodstream infection in a total parenteral nutrition population: inclusion of sepsis defervescence after removal of culture-positive central venous catheter. *J Hosp Infect.* 2010 Oct;76(2):119–123 [Epub 2010 Jun 16].
20. Warren DK, Quadir WW, Hollenbeak CS, Elward AM, Cox MJ, Fraser VJ. Attributable cost of catheter-associated bloodstream infections among intensive care patients in a nonteaching hospital. *Crit Care Med.* 2006;34:2084–2089.