

Research Article

Diagnosis of CLABSI from Blood and Needleless Connector Cultures in Patients with Acute Leukemia: a Prospective Cohort Study

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Abstract

Background: Global guidelines defining the procedure for collection of blood cultures (BC) are still unclear (especially number of samples and the procedure itself).

Purpose: The aim of this study is to evaluate the management of the collection of BC and needleless connector (NC) cultures to study the impact on the diagnosis of CLABSI.

Methods: A single-center prospective cohort study was performed, including all consecutive cases of first event febrile neutropenia that occurred in Acute Leukemia patients using a central venous catheter (Hickman[®]), since April 15th 2018 to October 15th 2018.

Results: Ninety-six hospital admissions along with 1235 hospital days and 1172 CVC-days were analyzed. A total of 38 cultures (BC and CVC-line) including 76 NCs were studied. The gram negative bacteria was the most representative microorganism reported in the CVC-line, $p < 0.05$. No gram negative bacteria was reported in the NC. All BCs were negative in the presence of NC colonization events. No positivity risk between CVC-lines was found [RR 1.292, 95% CI, 0.639 to 1.960].

Conclusion: Our study suggests that: 1) NCs should be removed prior to drawing blood for culture testing; 2) Paired BCs should be obtained in every catheter lumen and peripheral blood; 3) A 72-hour period substitution for NCs is useful to control the microbiological interconnection risk between the CVC-line and NCs.

Keywords: CLABSI; CRBSI; Acute Leukemia; Needleless Connector; Blood Cultures

Introduction

Infections are one of the most important causes of morbidity and mortality in immunosuppressed patients, namely haematology oncology patients. Patients with Acute Leukemia (AL) have a higher risk of neutropenia due to Chemotherapy Treatments (CT) and to malignancy itself. Multiple chemotherapy cycles and high transfusion rates are known predisposing risk factors that, associated with antibiotic resistant bacteria, increase the incidence and prevalence of Bloodstream Infections (BSI) [1].

Aiming for a safe and efficient chemotherapy regimen, the use of central venous catheters (CVC) increased in the 1980s; however, this resulted in reports of higher numbers of nosocomial infections. Along with CVCs, the use of needleless systems to access the catheter

is a major recommendation, with the split septum valve preferred over mechanical valves due to the associated infection risk [2]. In addition, we now know that many nosocomial pathogens can persist on inanimate surfaces for weeks or even months [ex: *E. Coli* (1.5h to 16 months); *Klebsiella pneumoniae* (2h to >30 months); *Pseudomonas aeruginosa* (6h to 16 months); or *Staphylococcus aureus* (7 days to 7 months)], being the *Staphylococcus spp* considered the most representative [3]. If colonization progresses and clinical infection occurs, it is recommended that blood cultures should be obtained and empirical antibiotics started immediately.⁴ If the infection source is identified as the CVC, it is defined a Catheter-Related Bloodstream Infection (CRBSI) [2].

In neutropenic patients, the natural host defense against local flora is reduced, enhancing a direct invasion across the colonic mucosa,

predisposing patients to BSI. Infection due to Mucosal Barrier Injury (MBI) microorganisms (ex: viridians group, *Streptococci*, *Enterococci spp.*, *E. coli*, *Klebsiella* and *Enterobacter spp.*) is common [4]. Taking into account the potential sources for bacterial contamination [5], the hematogenous seeding from distant sites increases the infection risk in this special population where central-line associated bloodstream infection (CLABSI) is frequently reported [2].

Global guidelines defining the procedure for collection of blood cultures are still unclear. Blood collection of CVC-line and peripheral blood are consensual, but the number of samples and the procedure itself are still undefined [4–8].

The aim of this study is to evaluate the management of the collection of blood cultures (BC) and needleless connector (NC) cultures to study the impact on the diagnosis of CLABSI.

Material and Methods

Selection and Description of Participants

A single-center prospective cohort study was performed, including all consecutive cases of first event febrile neutropenia that occurred in AL patients using a central venous catheter (Hickman[®] type, double lumen, 7 French) for more than 72h, undergoing Chemotherapy Treatment (CT) or aplasia support, since April 15th 2018 to October 15th 2018.

Patients older than 18 years old, with newly diagnosed or relapsed acute leukemia, admitted for CT or iatrogenic aplasia support were included.

Data concerning patients' background was prospective collected. Baseline demographic data was collected on the CVC placement day and the assessment was encompassed in every hospital admission.

Central-line devices management and culture procedure

Only the first BC episode during the hospital admission was analyzed. No concurrent antibiotic was used before BC episode. For every first BC episode, samples were collected first from a peripheral vein (PV), followed by the CVC line no more than five minutes apart (to reduce DTP results bias) [1,7]. The NCs were removed before collecting BC samples [1,6–7]. The BC procedure is performed by one nurse alone. BC samples were collected (with a minimum of 5 ml of blood, when possible) into BACTED PLUS Aerobic/F[®] vials [9] and the NCs were inserted in a sterile container for sample collection. Positive cultures were automatically analyzed by COS Biomérieux; incubation (24 hours, 37 °C) was performed. Mass spectrophotometry (Microflex – Bruker) was used for microorganism identification. The NCs were withdrawn and cultured in a liquid medium (Brain-heart-infusion Becton-Dickinson).

A NC external film surface swab rubbed was also performed. The NC microorganism lumen growth was reported when positive recoveries observed between 1 and < 15 colony-forming units (CFU). When BCs were collected, an insertion site swab was rubbed on the surface of 1–2 cm around the catheter insertion site.

Central-line Infections and neutropenia definitions

CLABSI and CRBSI rates were calculated, considering BCs yielding an organism (positive culture in PV and at least one CVC-line) per 1000 CVC-days. In the presence of a positive DTP, CRBSI was considered [2]. Also, it was considered localized catheter colonization if microorganism growth ≥ 15 CFU in the absence of positive blood results.[2] Neutropenia was considered as the absolute neutrophil count (ANC) less than 500/ μ L or ANC less than 1000/ μ L and predicted decline to 500/ μ L or less over the next 48 hours [4].

Technical Department Information

A 20-bed unit, distributed along eight double rooms and four single rooms, all equipped with positive pressure ventilation and HEPA filters. Only patients with a diagnosis of hematological malignancy are admitted to the department.

The management of CVCs follows the CDC (2011) guidelines [2]. Double lumen Hickman[®] type catheters (Vygon SA) are usually inserted (7 French, lumen 1 = 0.6 mm and lumen 2 = 1.0 mm). No antibiotic prophylaxis is given.

Specific CVC management in our unit includes the use of 2% chlorhexidine in 70% isopropyl alcohol solution for NC disinfection (considering 15" disinfection of NC hubs) [10] (neutral split septum needleless connector Bionecteur[®]), either in the stand-alone presentation or in a double lumen configuration (Octopus[®]) [11]. The CVC-flushing interval time in the CVC-lines was performed every 72-hours. Sodium heparin 20 IU/ml (Fibrilin[®]) is used for CVC-lock. Push-pause and positive pressure techniques always were performed using syringes 10 mL volume or higher. [1]

Data Analysis

Data analysis was conducted using IBM SPSS Statistics for Windows (SPSS Inc., Version 24.0). A continuous variable was reported by median and range. Categorical variables were reported as frequency and percentages. Normality tests reported a sample without normal distribution; therefore, hypothesis tests were analyzed by non-parametric tests. Relative Risk was performed by confidence intervals of 95%. A *p* value of ≤ 0.05 was determined to be statistically significant.

Ethics

The study was approved by the Ethics Committee (CES IPO: 104/018) of the Portuguese Institute of Oncology (Porto) in April 12th, 2018. Informed consent was waived for the included patients.

Results

A total of 21 patients diagnosed with AL were included: median age of 49 years [range, 75 to 22]; 15 (71.4%) female patients. Ninety-six hospital admissions [median 4, range 11 to 1] along with 1235 hospital days [median 10, range 44 to 3] and 1172 CVC-days [median 10, range 44 to 3] were analyzed.

A total of 38 cultures (BC, CVC-line and NC) were analyzed (Table I). Neutropenia was reported in 27/38 events (71.1%). BSI was only

observed in neutropenic patients [BSI 2 (28.6%); CLABSI 5 (71.4%) (4.26/1000 CVC-days)]. No CRBSI was reported. One fungus in the bloodstream was discovered and documented.

The microbiological recovery (Table II) reported *E.Coli* as the most representative microorganism in peripheral blood and

in the catheter lumen; *S. epidermidis* was the most representative microorganism in the NCs. The gram negative bacteria was the most representative microorganism reported in the CVC-line, $p < 0.05$. MBI microorganisms were observed in 60% of CLABSIs. No positive insertion site swipe was observed.

Table 1. Microbiological Results

| | Peripheral Vein | 1.0 mm CVC-line | 0.6 mm CVC-line | NC Lumen | NC Surface |
|--|----------------------|---------------------|---------------------|---|----------------|
| 1 | E. coli | | | | |
| 2 | P. aeruginosa | P. aeruginosa | | | |
| 3 | | | | | S. epidermidis |
| 4 | | | | S. epidermidis + Corynebacterium | |
| 5 | E. coli | E. coli | E. coli | | |
| 6 | | | | S. epidermidis | S. epidermidis |
| 7 | | | | S. hominis | |
| 8 | | | | S. epidermidis | S. epidermidis |
| 9 | | E. coli | | | |
| 10 | E. coli | E. coli | E. coli | S. epidermidis | S. epidermidis |
| 11 | | | | S. haemolyticus | |
| 12 | Missing | K. pneumoniae | K. pneumoniae | | |
| 13 | | E. coli | | | |
| 14 | E.coli | E. coli | E. coli | Missing | Missing |
| 15 | | | | S. epidermidis* | |
| 16 | Strep. dysgalactiae | Strep. dysgalactiae | Strep. dysgalactiae | Strep. dysgalactiae* + S. epidermidis* + Bacillus cereus* | |
| 17 | | | | S. epidermidis* | |
| 18 | | | | S. hominis* | |
| 19 | | | | S. hominis* | |
| 20 | | | | S. epidermidis | |
| 21 | Geotrichum capitatum | | | | |
| n=38 (17 negative); * Microbiological Growth | | | | | |

Needleless Connector Assessment

Overall, 76 NCs were studied. Thirteen positive samples were obtained [8 (≥ 15 CFU) and 5 (< 15 CFU)].

In two cases, the CVC-line and the NC were positive at the same time; one case showed different microorganisms in the devices [gram

negative bacteria *E. Coli* (CVC-line) and gram positive bacteria *S. Epidermidis* (NC)]; the other case showed the same microorganism in both samples [gram positive bacteria *Strep dysgalactiae*] from the NC and the CVC-line [1/13 (7.6%)]. No gram negative bacteria was reported in the NC.

Table 2. Microorganisms Recovered

| Microorganisms | Total n (%) |
|----------------------|-----------------|
| Gram - | |
| E. coli | 6 (31.5)* |
| K. pneumoniae | 1 (5.3)* |
| P. aeruginosa | 1 (5.3)* |
| Gram + | |
| Strep. dysgalactiae | 1 (5.3)* |
| S. epidermidis | 6 (31.5)** |
| S. hominis | 1 (5.3)** |
| S. haemolyticus | 1 (5.3)** |
| Corynebacterium | 1 (5.3)** |
| Fungi | |
| Geotrichum capitatum | 1 (5.3)* |
| Total | 19 (100) |
| *PV/CVC ; **NC | |

S. Epidermidis was the only microorganism observed in the external NC surface. No different microbiological species between the lumen and surface of the NC were identified, being both NC lumen and surface positive at the same time in 3 (37.5%) cases. No colonization risk by the same microorganisms between the lumen and surface of the NC was observed [RR 2.000, 95% CI, 0.899 to 4.452].

Positive catheter and/or peripheral BCs when the NC was negative were reported in 7/59 (11.8%) cases. All BCs were negative in the presence of NC colonization events.

CVC-lines Positivity Reports

Considering CVC-lines positivity, the 1.0 mm CVC lumen was the most representative, being reported in 8 (61.5%) cases, always associated with CLABSI identification.

The 0.6 mm CVC-line was never positive alone, being always associated with the 1.0 mm CVC-line positivity. However, the 1.0 mm CVC-line was identified in more 37.5% reports (3 cases) than the 0.6 mm CVC-line. No positivity risk between 1.0 mm and 0.6 mm CVC-lines was found [RR 1.292, 95% CI, 0.639 to 1.960]. No positive risk was found for the association with the CVC-line condition (open/closed) [RR 1.339, 95% CI, 0.582 to 3.083].

Discussion

Several studies have been published regarding the assessment of bloodstream and CVC infections. However, the management of the BC collection procedure associated with central line devices remains unclear. Y Siegman-Igra and colleagues (1996) [12] published in the actual reference guidelines of the National Comprehensive Cancer Network in the Prevention and Treatment of Cancer-Related Infections (“*Diagnosis of Vascular Catheter-related bloodstream infection: a meta-analysis*”). The authors reported that the use of

semiquantitative catheter segment culture is considered the less expensive test for the microbiology laboratory to perform, reporting less accuracy than the quantitative methods (pooled sensitivity and specificity above 90%). Considering long-term tunneled catheters, the hospital costs associated with the semiquantitative method is high, with the paired quantitative method considered the most accurate of BC methods, reporting a labor-intensive process involved. Gaur Aditya and colleagues (2003) [13] published “*The difference in time to detection as a simple method to differentiate CRBSI or non-CRBSI in pediatric immunocompromised patients*”, concluding that paired CVC and PV BCs, using DTP, is a useful test to distinguish CRBSI from non-CRBSI in that specific population.

Cultures Procedure and number of sets

The NCCN recommendations present three options to obtain BCs in neutropenic patients: 1. one set obtained peripherally and one from a CVC; 2. both sets can be obtained peripherally; 3. both sets can be obtained through the CVC [4]. This suggests that the first and third options are prone to false positives (reporting BSI when the correct diagnosis is CLABSI) or false negatives (when the correct diagnosis is colonization). In the case of CVCs with more than one line, colonization could be present and not identified when only one CVC-line sample is recovered, reducing the probability of finding a positive report by at least 50%. Our study does not allow us to suggest a specific CVC-line to analyze because no risk was found between the CVC-line positivity (1.0 mm versus 0.6 mm). Martinez and colleagues (2017) [7], in their thesis publication “*Central-line associated bloodstream infection rates and blood cultures collection assessment in Acute Leukemia patients: retrospective cohort study*”, reported the analyses of 105 BCs in neutropenic patients, suggesting that a false CLABSI negative could be identified in one-third of CLABSIs reported in their research. Besides, Martinez and colleagues reported the 1.0 mm CVC-line positivity in 12 (92.3%) cases when CLABSI was identified (PV and 0.6 mm CVC-line positive reported in 1 (4.7%) observations), suggesting that if BCs were collected from one of the negative CVC-lines and the positive PV was identified, BSI could be diagnosed in place of CLABSI.[7] Similar reports were found by Planes and colleagues in 2016 [14] suggesting that one-third of CRBSI diagnoses could be missed if BCs were not collected from all CVC lumens. Our study reported positivity in PV and concomitant CVC-lines (1.0 mm and 0.6 mm CVC-lines) in five cases, not being reported CLABSI or colonization events only including PV and/or 0.6 mm CVC-line positivity. However, considering the first option in the NCCN recommendation, if only one set is collected from the CVC-line, the real source of the infection (CRBSI) cannot be studied, being CLABSI reported in place of CRBSI, affecting the clinical and educational decision. On the other hand, Herrera-Guerra and colleagues (2015) [8] suggested a pooled multiple-lumen BC collection; however, our study reported colonization events of one CVC-line alone. In consequence, the BC method suggested could be considered a diagnosis bias regarding the posterior clinical decision taken (e.g., antimicrobial-lock).

Needless Connectors and CLABSI prediction

The study suggests Gram positive bacteria as the most representative microorganism recovered from the NCs, being

identified only once in the CVC-line. Guembe and colleagues (2016) [15] in their publication “*Assessment of central venous catheter colonization using surveillance culture of withdrawn connectors and insertion site skin reported*”, suggested that the NCs could be used as an alternative diagnostic method to hub cultures in intensive care units. It was also referred that their results could not be immediately extrapolated to populations other than ICU patients and the results should be used with prudence to maintain, remove or change a CVC-line undergoing CRBSI suspicion. However, immunosuppression in intensive care unit patients in oncology hospitals is plausible and could affect the microbiological results associated with MBI microorganisms. In consequence, it could be possible to recover MBI microorganisms in the CVC-line and other species in the NC lumen, as shown in our study. Our population, the AL patients (special neutropenic and CLABSI risk population) [1] reported high rates of MBI microorganisms without associated NC cultures (especially with high gram positive bacteria reports). In consequence, NCs should be removed prior to drawing blood for culture testing; in order to reduce the incidence of false positives such the Infusion Nurses Society recommends [2]. Indeed, in our study the NC (that is removed in all BC events) shows no interference with the clinical decision taken, regardless of CVC-line results, in most cases empirical.

NC management and substitution

The Guidelines for the Prevention of Intravascular Catheter-Related Infections published by the CDC in 2011 [2] recommended the replacement of NCs and the administration sets no more frequently than 72–96 hours (category II). Mauro Pittiruti and colleagues published in 2016 [16] the “*Evidence-based criteria for the choice and the clinical used of the most appropriate lock solutions for central venous catheters (excluding dialysis catheters): a GAVeCeLT consensus*”, suggesting the use of neutral or positive pressure displacements, being the risk of occlusion related to inappropriate policies of flushing and/or CVC-line or NC use. However, the infection risk associated with positive pressure devices is documented; being the split septum neutral device recommended, especially in high infection risk populations [1]. The specific procedure performed by our department: 1) the 72-hour period substitution for NCs and administration sets; 2) NC and administration sets substitution in every BC collection (supported by the theoretical rationale, based on the attempt to remove the possible device infection source at the BC collection moment), could suggest that 72-hour interval time for NC substitution is useful to control the microbiological interconnection risk between the CVC-line and NCs [7]. However, future clinical trials are required.

Potential directions of the study and limitations

The study reports 3 potential limitations: First, this is a single population study, and our suggestions may not applicable to low infection risk populations; however, the oncology-hematology clinical research in this field is scarce and more studies are strongly recommended [17]. Second, this study includes a small number of patients but this is a population that have multiple hospital admissions by patient, being the study event (CLABSI) frequently reported [1]. Third, the process of clinical cultures “in vivo” from blood and NC collection could be influence by the patient symptomatology. Our

study reported two missing cultures: 1) the venipuncture procedure missed in a patient undergoing chills; 2) A sample of NC was not processed by human lapse (without microbiological study) associated with the complex CVC-management in a patient undergoing septicemic shock.

On the other side, the homogeneity of the sample could be considered an advantage, being reduced the bias observed in the central elements related to effectiveness of CVC clinical research (product, practice and patient), frequently reported in multicenter studies [18]. Several studies does not report CVC-management dynamics based on the use of chlorohexidine 2% NC hub disinfection 15”, CVC-flushing frequency report, positive pressure and push-pause techniques [19]; being the quality of the research limited to the product. The authors can conclude that the future clinical research in this field should relate to the CVC and NC management associated practice.

Conclusion

Our study suggests that: 1) NCs should be removed prior to drawing blood for culture testing; 2) Paired BCs should be obtained in every catheter lumen and peripheral blood; 3) A 72-hour period substitution for NCs is useful to control the microbiological interconnection risk between the CVC-line and NCs.

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