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Clinical Outcome of Patients with *Escherichia coli* Isolated from Catheter Lumens and/or Peripheral Blood Cultures: A Retrospective Analysis

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Abstract: Background. *Escherichia coli* commonly causes catheter-related bloodstream infection (C-RBSI) in specific populations. The differential time to positivity (DTTP) technique is the recommended conservative procedure for diagnosing C-RBSIs. **Methods**. We conducted a retrospective study of episodes in which *E. coli* was isolated from catheter lumens obtained using the DTTP technique. We analysed microbiological and clinical data based on the DTTP technique as either catheter colonization, C-RBSI, or non-C-RBSI. **Results**. We included 89 catheter blood cultures classified as follows: catheter colonization, 33.7%; C-RSBI, 9.0%; and non-C-RBSI, 57,3%. Catheter withdrawal was 15.7% without positive catheter-tip cultures. We found no statistically significant differences in catheter type, antibiotic treatment, or clinical outcome among groups, except for the frequency of catheter lock therapy or in the frequency of successful treatment. Mortality was associated with C-RBSI in only 1 patient. **Conclusion**. *E. coli* bacteremia diagnosed by the DTTP technique was non-catheter related in most patients. As the majority of the catheters were retained, *E. coli* bacteremia could not be microbiologically confirmed or ruled out as catheter related by catheter-tip culture. Future studies are needed to assess the profitability of the DTTP technique for diagnosing *E. coli* C-RBSIs..

Keywords: *Escherichia coli*; bacteremia; catheter; lock therapy; differential time to positivity; biofilm; outcome

1. Introduction

Staphylococci are the main cause of catheter-related bloodstream infection (C-RBSI). However, the Gram-negative bacillus *Escherichia coli*, which can form biofilms on the catheter surface, remains an important agent in specific populations, including patients with oncologic-haematological conditions and those undergoing haemodialysis [1–7].

The recommended conservative procedure for the diagnosis of C-RBSI is the differential time to positivity (DTTP) technique, which consists of obtaining blood cultures from catheter lumens and a peripheral vein. The presence of C-RBSI is suspected when the growth of a blood culture obtained from a catheter lumen occurs at least 2 hours before the growth of a blood culture obtained from a peripheral vein [8,9]. This process is based on the dispersion of sessile cells from the upper layer of the biofilm on the catheter surface into the bloodstream, causing C-RBSI [9,10]. Therefore, the microbial load from blood obtained through the catheter will be greater. Moreover, the appearance of persistent cells and the detachment of individual cells or microcolonies from biofilms can be difficult to diagnose and treat efficiently [11,12]. Nevertheless, the microbiological confirmation of a C-RBSI requires the growth of the same bacteria in the catheter-tip culture as in the blood culture

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obtained from a peripheral vein. This is rarely achieved, as the catheter is not always withdrawn in the context of a Gram-negative bacterial infection. So, the DTTP is recommended as a conservative diagnostic tool which can provide guidance on the origin of the bacteremia, but it is not a confirmatory technique in itself and the results should be interpreted with caution.

In some studies, the presence of high-biofilm producing strains has been associated to with worse clinical outcome [13–16]. However, there are still controversies even within the same microorganisms [17–20].

To our knowledge, there are no reported series describing the microbiological confirmation of suspected *E. coli* C-RBSIs or patient management and outcomes.

2. Materials and Methods

This retrospective study was carried out in a 1550-bed tertiary teaching hospital in Madrid (Spain) from 2020 to 2022 and included all *E. coli* infections isolated either from catheter lumens and peripheral blood cultures, or from only catheter lumens with negative peripheral blood cultures, obtained using the DTTP technique. We analyzed microbiological and clinical data.

We tested biofilm production of each strain, as a possible virulence factor associated to worse clinical outcome (which included having C-RBSI or death), with both the crystal violet (CV) assay and the tetrazolium salt (XTT) assay to quantify biomass and metabolic activity, respectively, as previously described [21]. Twenty-four hour-biofilms of *E. coli* strains isolated from blood cultures were formed onto the bottom of polystyrene well plates followed by 3 washes with phosphate buffer saline and stained separately with both CV and XTT. Experiments were performed in triplicates. The median (IQR) absorbance values for CV and XTT were obtained using a spectrophotometer at 550 nm and 492 nm, respectively [22].

2.1. Definitions

Catheter colonization (CC): positive catheter lumen blood cultures and/or positive catheter-tip culture with a negative peripheral blood culture.

C-RBSI: positive peripheral- and catheter lumen(s) blood cultures with growth of the same microorganism and a time difference between catheter lumen and peripheral blood culture of ≥2 hours and/or positive catheter-tip culture.

Non-C-RBSI: positive peripheral- and catheter lumen(s) blood culture with growth of the same microorganism, and a difference between the catheter lumen and peripheral blood culture growth of <2 hours and/or negative catheter culture.

Successful treatment: catheter maintenance and obtaining sterile control blood cultures.

2.2. Statistical Analysis

Qualitative clinical variables are expressed as numbers (percentages) and were compared using the chi-square test. Quantitative clinical variables are expressed as the mean (standard deviation) and were compared using the median test. The significance level was set at $p<0.05$. Comparisons between groups were assessed using the Kruskal–Wallis test, and a p value<0.05 indicated statistical significance. All tests were performed using SPSS Statistics for Windows, v.21.0 (IBM Corp, Armonk, New York, USA).

3. Results

We included 89 catheter blood cultures from 81 patients classified as follows: CC, 30 (33.7%); C-RSBI, 8 (9.0%); and non–C-RBSI, 51 (57.3%). There were 8 patients with two different blood culture extractions separated by at least 2 days. The percentage of catheter withdrawals was 15.7%. No positive culture results were recorded; therefore, most episodes could be classified based only on DTTP criteria. Only 1 of the 14 withdrawn catheters was from the C-RBSI group (sent for culture 4 days after DTTP blood was taken) and all 14 yielded a negative culture, which may be explained because all patients were under systemic antimicrobial therapy. Almost half of the patients had

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oncologic-haematological disease, and 40.4% had an infection at another site. We found no statistically significant differences in catheter type, antibiotic treatment, or clinical outcome between the groups, except for the catheter lock therapy rate, which was greater in the colonization and C-RBSI groups, or in the treatment success rate, which was greater in the non–C-RBSI group (**Table 1**). C-RBSI-associated mortality was recorded for only 1 patient who developed septic shock.

Table 1. Patient characteristics and outcomes after isolation of *E. coli* from catheter blood cultures obtained using the differential time-to-positivity technique.

Characteristic	Group, N (%)				p
	Total 89 (100)	**Colonization 30 (33.7)**	**C-RBSI 8 (9.0)**	**Non–C-RBSI 51 (57.3)**	
Median (IQR) age, years	64.00 (51.50-71.50)	64.00 (45.00-73.00)	66.00 (49.25-72.75)	64.00 (56.00-69.00)	0.475
Male sex	54 (60.7)	18 (60.0)	2 (25.0)	34 (66.7)	0.083
Underlying condition					
Hematologic malignancy	39 (43.8)	14 (46.7)	2 (25.0)	21 (42.0)	
Solid organ tumor	30 (33.7)	7 (23.3)	3 (37.5)	20 (40.0)	
Gastrointestinal disease	6 (6.7)	3 (10.0)	0 (0.0)	3 (6.0)	0.444
Renal disease	3 (3.4)	2 (6.7)	0 (0.0)	1 (2.0)	
Organ transplant	3 (3.4)	1 (3.3)	0 (0.0)	2 (4.0)	
Other	8 (9.0)	3 (10.0)	3 (37.5)	3 (6.0)	
Median (IQR) Charlson score	8.00 (4.00-10.00)	8.00 (2.00-10.25)	8.50 (5.25-10.75)	7.00 (4.00-10.00)	0.770
Median (IQR) APACHE II score	11 (6.25-13.00)	11.00 (6.00-12-50)	13.00 (6.75-22.5)	10.00 (7.00-13.00)	0.195
McCabe 3	60 (67.4)	23 (76.7)	3 (37.5)	34 (66.7)	0.077
Type of catheter					
Non-tunnelled CVC	5 (5.6)	3 (10.0)	0 (0.0)	2 (3.9)	
Tunnelled CVC (Hickman)	19 (21.3)	9 (30.0)	1 (12.5)	9 (17.6)	
Port	43 (48.3)	11 (36.7)	4 (50.0)	28 (54.9)	0.286
PICC	21 (23.6)	6 (20.0)	3 (37.5)	12 (23.5)	
PVC	1 (1.1)	1 (3.3)	0 (0.0)	0 (0.0)	
Median (IQR) in-hospital stay	21.00 (9.00-39.50)	23.00 (10.25-43.25)	16.00 (13.50-33.50)	18.00 (9.00-46.00)	0.238
Median (IQR) time to positivity of peripheral BC	8.95 (7.48-10.34)	NA	8.13 (7.24-9.54)	9.33 (7.57-10-4)	0.905
Median (IQR) time to positivity of catheter lumen BC	8.93 (7.09-10.40)	9.80 (7.10-11.29)	5.86 (3.60-7.45)	8.93 (7.47-10.11)	0.190
Catheter withdrawal	14 (15.7)	9 (30.0)	1 (12.5)	4 (7.8)	0.03
Catheter lock therapy	29 (32.6)	16 (53.3)	6 (75.0)	7 (13.7)	
Amikacin	28 (31.5)	15 (93.8)	6 (100)	7 (100)	<0.001
Ciprofloxacin	1 (1.1)	1 (6.3)	0 (0.0)	0 (0.0)	
Median (IQR) days of lock therapy	7.00 (4.00-10.00)	6.00 (4.25-8.50)	7.00 (4.00-14.00)	10.00 (7.00-10.00)	0.280
IV antimicrobial therapy	87 (97.8)	29 (96.7)	8 (100)	50 (98.0)	0.835
Median (IQR) days of IV antimicrobial therapy	8.00 (6.00-10.00)	7.50 (5.00-9.25)	7.50 (7.00-9.50)	8.00 (6.00-10.00)	0.724
Median (IQR) DDDs	14.00 (3.00-18.00)	15.50 (3.00-18.25)	9.50 (4.25-15.75)	14.00 (3.00-18.00)	0.894
Treatment success rate[a]	69 (69.7)	16 (53.3)	3 (37.5)	43 (84.3)	0.002

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Infection at another site	36 (40.4)	6 (20)	3 (37.5)	27 (52.9)	0.610
Abdominal	13 (14.6)	1 (3.3)	2 (25.0)	10 (19.6)	
Urinary	13 (14.6)	3 (10.0)	1 (12.5)	9 (17.6)	
Biliary tract	8 (9.0)	2 (6.7)	0 (0.0)	6 (11.8)	
Mucosal	1 (1.1)	0 (0.0)	0 (0.0)	1 (2.0)	
Perianal	1 (1.1)	0 (0.0)	0 (0.0)	1 (2.0)	
Crude mortality rate	16 (18.0)	3 (10.0)	3 (37.5)	10 (19.6)	0.1081
C-RBSI–associated mortality rate	1 (1.1)	0 (0.0)	1 (12.5)	0 (0.0)	0.006
Median (IQR) absorbance for CV assay*	0.075 (0.000-0.996)	0.060 (0.000-0.853)	0.069 (0.036-0.142)	0.094 (0.014-0.996)	0.516
Median (IQR) absorbance for XTT assay*	0.156 (0.051-0.732)	0.171 (0.053-0.534)	0.294 (0.117-0.344)	0.144 (0.051-0.732)	0.228

C-RBSI, catheter-related bloodstream infection; IQR, interquartile range; CVC, central venous catheter; PICC, peripherally inserted central catheter; PVC, peripheral venous catheter; DTTP, differential time to positivity; BC, blood culture; IV, intravenous; DDDs, defined daily dose; CV, crystal violet; XTT, tetrazolium salt. [a] Successful treatment was defined as catheter maintenance and obtaining sterile control blood cultures. * Absorbance was tested for only 72/89 strains.

As expected, in patients in whom infection was detected at another site (n=36), most *E. coli* infections were non-C-RBSI (75%), 16.7% were CC, and only 8.3% were C-RBSIs. However, among the 53 patients in whom the only presumed source of infection was the catheter, 48 (90.6%) were classified as either CC (n=24) or non-CRBSIs (n=24), and only 5 (9.4%) as C-RBSIs. The catheter was microbiologically confirmed as not being responsible for bacteremia in only 3 of 24 (12.5%) patients with *E. coli* non-C-RBSI and no other site of infection (the catheters were sent for culture, which yielded negative results in all patients). In the remaining 21 patients, the catheters were retained. The mean (SD) duration of antibiotic therapy before catheter removal in these 3 patients in whose catheter was removed was 4.67 (5.51) days. Out of the 24 patients with non-CRBSI, 16 (66.7%) had febrile neutropenia with a median (IQR) absolute neutrophil count of 0/microliter (0-0).

Regarding biofilm production, the overall median (IQR) for CV and XTT absorbance were 0.075 (0.000-0.996) and 0.156 (0.051-0.732), respectively. No statistically significant differences in biofilm production were observed between groups. In addition, the median (IQR) for CV and XTT absorbance in the 16 patients who died were 0.055 (0.035-0.170) and 0.159 (0.095-0.265) vs. 0.077 (0.042-0.148) and 0.153 (0.112-0.299) in the 73 alive patients. Therefore, no association was found between biomass (CV) or metabolic activity (XTT) and mortality (CV, p=0.739; XTT, p=0.465).

4. Discussion

E. coli bacteremia diagnosed by peripheral blood cultures obtained through the DTTP technique were not related to the catheter in most patients. However, most cases could not be microbiologically confirmed or ruled out as catheter-related by catheter culture. Although the mortality associated with *E. coli* C-RBSI was low, treatment was successful in only 37.5% of patients.

The incidence of C-RBSI caused by Gram-negative bacilli [2,7], while still low, has increased in the recent years [5,6,23], mainly among oncologic patients and those undergoing haemodialysis [1–4].

DTTP is currently the recommended technique for diagnosing C-RBSI before catheter removal [8,23–26], based on the role of biofilm dispersion in the pathogenesis and dissemination of biofilm-associated infections [27,28].

In the present study, the DTTP technique detected only 5 C-RBSI episodes in patients with *E. coli* bacteremia who exhibited no signs of infection at another site (n=29). Consequently, in the remaining 24 episodes categorized as non-C-RBSI, the DTTP technique might have been insufficient to point the catheter as the source of bacteremia. These data indicate that in *E. coli* C-RBSI episodes, preserving the catheter was not successful in most cases. Comparing the outcomes of non C-RBSI group (who had *E. coli* bacteremia without the catheter being the source of infection), who were otherwise

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comparable in terms of age, pre-existing conditions, and gender distribution, supports this statement. It is important to highlight that patients with a colonized catheter and a negative peripheral blood culture from the CC group (n=30) are also susceptible for having a catheter-related infection even with negative cultures in the peripheral vein.

In many cases, the catheter tip is not sent for culture to confirm the catheter as the source of bacteremia, as described in our study (only 15.7% of the catheters were sent for culture); or, even it is sent for culture, it yielded negative results because the patients are already under antimicrobial therapy, as we observed in our 14 patients in whom the catheter was sent for culture. Moreover, as the study was retrospective, we also were unable to assess whether the 24 patients with fever and CC were only colonized, may have a C-RBSI with blood cultures not being positive yet, or had infection at other site in addition to the catheter. Therefore, it is important to note that DTTP technique is a conservative diagnostic tool which can provide guidance on the origin of the bacteremia, but results must always be interpreted in the context of the pathogen detected and the patient's comorbidities.

Regarding the management of the patients, nearly all were treated with systemic antimicrobial therapy, and its duration was comparable between groups. Patients with C-RBSI received more antimicrobial lock therapy; however, the bacterial clearance rate in the C-RBSI group was significantly lower.

Regarding biofilm production, we demonstrated that no correlation was observed between high biofilm producing *E. coli* strains and patient outcome, as previously described by Martínez et al. [29]. In contrast, Zhang et. al reported that biofilm production was an independent risk factor of mortality for cancer patients with *E. coli* bloodstream infections [16]. So, it is needed to further assess the role of biofilm production in clinical outcome.

5. Conclusions

Despite the relatively low occurrence of *E. coli* C-RBSI (9.0%), the efficacy of treatment, relying on catheter maintenance and the attainment of negative blood cultures, was only successful in 37.5% of cases. Future investigations, incorporating catheter cultures, are imperative to confirm *E. coli* C-RBSI episodes.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by our local ethics committee (MICRO.HGUGM.2002-20).

Informed Consent Statement: Patient consent was waived due to the nature of this retrospective study and the preserved anonymity of patients.

Data Availability Statement: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Conflicts of Interest: The authors declare no conflicts of interest.

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