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Concurrent systemic antibiotics at catheter insertion and intravascular catheter-related infection in the ICU: a post hoc analysis using individual data from five large RCTs

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Abstract:

Objectives: Data on the impact of systemic antibiotics at the time of catheter insertion are scarce. Therefore, we assessed the association between coincident antibiotic administration at insertion and short-term catheter-related infections.

Methods: We used individual data gathered from five large, randomized, controlled ICU trials. We analyzed adult patients who required arterial, short-term central venous or dialysis catheter insertion in the ICU. The effect of antibiotics at insertion on major catheter-related infection (MCRI), catheter-related bloodstream infection (CRBSI) and colonization was estimated using multivariate marginal Cox and propensity score models.

Results: We included 10,269 patients and 18,743 catheters from 36 ICUs. Antibiotic use was ongoing at the time of 11,361 (60.6%) catheter insertions. After adjusting for well-known risk factors for intravascular catheter infection, we observed a similar risk for MCRI (HR 0.83, 95% CI 0.62-1.10, $p=0.19$) and CRBSI (HR 0.85, 95% CI 0.60-1.22, $p=0.38$) between the antibiotic and no-antibiotic groups. A confirmatory analysis using propensity score showed consistent results. No specific antibiotic subclasses reduced the risk of MCRI. Non-fermenting Gram-negative bacilli were more frequently observed in the antibiotic group.

Conclusions: Ongoing antibiotic administration at the time of catheter insertion was not associated with a decrease risk of catheter-related infections and should not be administered for preventing such infections. Our results bring new insights to antimicrobial stewardship in critically ill patients and may direct empirical antimicrobial therapy if MCRI is suspected.

Introduction

Short-term intravascular catheters are essential in the care of critically ill patients. Central venous catheter (CVC) are frequently used in European intensive care units (ICUs) and ICU-acquired bloodstream infections are catheter-related in almost half of cases [1]. Additionally, intravascular catheter-related infections are associated with increased morbidity and mortality [2].

The role of prophylactic systemic antibiotics at the time of catheter insertion remains the subject of ongoing debate. In long-term catheters of oncologic patients, flushing and locking long-term CVCs with a combined antibiotic and heparin solution significantly decreases risk of Gram-positive catheter-related infection [3]. Use of prophylactic antibiotics at the time of dialysis catheter insertion significantly reduces risk of catheter-related infections and bacteremia [4]. A meta-analysis including three relatively small studies concluded that the routine use of prophylactic systemic antibiotics in neonates during the full period of CVC maintenance reduced the rate of “proven” or “suspected” septicemia and of clinical sepsis [5].

The role of systemic antibiotic prophylaxis in adults with short-term intravascular catheters remains unresolved and the literature shows conflicting results [6-9]. We performed a *post-hoc* analysis using high-quality, individual data gathered from five large randomized, controlled trials (RCTs) [10-14] to determine the association between coincident systemic antibiotic at insertion and short-term intravascular catheter-related infections in critically ill patients.

Material and Methods

Design and data sources

We performed a *post-hoc* analysis using individual patient data from five large RCTs (DRESSING1, DRESSING2, ELVIS, CLEAN and 3SITES) [10-14]. The definitions and inclusion criteria were similar among all these RCTs. Therefore, we merged the five study databases. The objectives of the five studies were similar: to evaluate the effect of specific prevention measures on the risk of intravascular catheter complications. Briefly, the DRESSING1 study assessed the effect of chlorhexidine-gluconate (CHG) sponge for preventing catheter-related infections [10]. The DRESSING2 study evaluated the effect of CHG gel-dressing for catheter-related infections prevention [11]. The ELVIS trial evaluated the risk of infection with or without ethanol lock among short-term dialysis catheters [12]. The impact of skin antisepsis with 2% CHG compared to povidone iodine-alcohol [PVI] on intravascular catheter-related infections was investigated in the CLEAN study [13]. The 3SITES study evaluated differences in infectious and mechanical complications between the subclavian, jugular and femoral insertion sites [14]. CHG-sponges, CHG-gel dressing, CHG-skin antisepsis and the subclavian vein insertion site decreased the risk of catheter infection[10, 11, 14]. The study interventions were not blinded to the ICU staff nor to the investigators. They were blinded to the microbiologists who processed the blood and catheter cultures and to the adjudication committee. The five RCTs were approved by the national ethic committees.

Patients

Adult patients (≥ 18 years) were recruited from 2006 to 2014 in ICU in France as soon as they required an arterial catheter (AC), a CVC or a short-term dialysis catheter (DC) insertion [10-14]. Patients underwent follow-up until 48 hours after ICU discharge [10-13], ICU discharge [14] or death [10-14].

Catheters

This *post hoc* analysis investigated individual data from short-term catheters included in the five RCTs. All short-term catheters were managed in the same way and complied with national recommendations (*i.e.*, French Haute Autorité de Santé checklist) [15], which are similar to U.S.

(Centers for Disease Control and Prevention) recommendations [16]: 1) maximal sterile barrier precautions were used (surgical hand antisepsis; large sterile drape; mask, cap, sterile gloves, and gown); 2) the site of insertion was selected according to the randomization scheme [14] or at the physician's discretion [10-13]; 3) CHG or PVI was utilized for skin antisepsis at catheter insertion and during dressing changes according to the randomization scheme [13] or at the physician's discretion [10-12, 14]; 4) standard or impregnated-dressings were changed 24h after insertion and then every 3 or 7 days according to randomization scheme or standard practices in each ICU [10-14]. Soiled, wet or leaking dressings were immediately removed and changed. Antibiotic- or antiseptic-impregnated catheters were not included in the five RCTs. Most importantly, antibiotics were administered at the physician's discretion and this variable was routinely collected in all studies (*i.e.*, in the 48h before the insertion). Of note, the reason for antibiotic use was not known (*e.g.*, treatment of a known infection or prophylaxis). The physicians caring for each patient decided independently to remove catheter.

Outcomes and definitions

French and U.S. definitions were used [17, 18]. A catheter culture yielding ≥ 1000 cfu/mL was required for defining catheter tip colonization [19]. Catheter-related bloodstream infection (CRBSI) was a combination of 1) ≥ 1 positive peripheral blood culture sampled after >48h of catheter maintenance or within 48h after removal; 2) the identification of the same microorganism from the positive catheter tip culture, or a blood culture differential time-to positivity of ≥ 2 h [11, 13] (*i.e.*, time growth difference between catheter-drawn blood culture and peripherally-drawn blood cultures) [20]; and 3) no other source of bacteremia or fungemia other than the catheter. Positive blood culture with coagulase-negative staphylococci (CoNS) were considered if the same pulsotype (*i.e.*, the clonality was checked) was identified from the isolates recovered from the catheter tip and blood culture [11]. Alternatively, the same microorganism that colonized the catheter tip was identified in >1 separate peripheral blood cultures [10, 12-14]. Catheter-related clinical sepsis without bloodstream infection (BSI) was a combination of abnormal temperature ($\leq 36.5^{\circ}\text{C}$ or $\geq 38.5^{\circ}\text{C}$), positive catheter tip culture, purulence at the insertion site, or resolution of clinical sepsis after catheter removal, and no apparent infectious source other than the catheter. Major catheter-related infection (MCRI) was defined as

either catheter-related clinical sepsis without BSI or a CRBSI. Of note, MCRI is a moderate to good surrogate endpoint for CRBSI [21]. We performed an exploratory analysis for the following antibiotic groups which were routinely collected in four studies [10-13]: beta-lactam, beta-lactam with activity against *Pseudomonas* spp, antibiotics against only Gram-positive microorganisms (*i.e.*, glycopeptide, linezolid or lincosamide), aminoglycoside/quinolone/trimethoprim-sulfamethoxazole, and others.

Statistics

Patient and catheter characteristics are described as median (interquartile range) or number (percent), as appropriate.

The statistical plan had three steps: 1) To evaluate the association between antibiotics at insertion and MCRI, CRBSI and colonization using multivariate Cox models; 2) to perform a secondary analysis using a propensity score model; 3) and to explore if a specific antibiotic subgroup was associated with a reduction of MCRI.

We performed “marginal” Cox models, which considered a possible clustering effect of multiple catheters per patient [22], and we stratified by ICU. Data were censored at 28 days after catheter insertion. A hazard ratio (HR, representing the daily risk for infection during the catheter maintenance) was derived: a HR <1 indicated a decreased risk for antibiotics at insertion. This model considers the intra-cluster dependency (*i.e.*, more than one catheter per patient), using robust sandwich covariance estimates (PROC PHREG of SAS) [23]. The proportionality of hazard risk for antibiotic at insertion was tested using Martingale residuals. HR for MCRI, CRBSI and colonization were evaluated by univariate and multivariate analysis. The variable “antibiotic at insertion” was forced in the multivariate models and the following clinically relevant variables were used as adjustment factors (*i.e.*, well-known risk factors for intravascular catheter infections): SAPS II, experience of the operator, insertion site, catheter type (*i.e.*, AC, CVC or short-term dialysis catheter), skin antisepsis, CHG-impregnated dressing, heparin during catheter insertion, vasopressor and mechanical ventilation at insertion. Moreover, we performed additional analyses using propensity score models (see electronic supplementary material [ESM]).

149 In the exploratory analysis, we used, instead of a binary variable (antibiotics *vs* without antibiotics),
150 the categorical variable “antibiotic subgroups” in order to describe the individual infectious risk for the
151 different antibiotic subgroups.

152 Tests were considered significant with a $p < 0.05$. We performed all analyses using R (version 3.5.3)
153 and SAS (version 9.4; SAS Institute, Cary, NC).

154 See the ESM for further details on methods and statistical analysis.

155

Results

Patients and catheters:

Between 2006 and 2014, 10,269 patients and 18,743 (9,641 CVCs, 6,373 ACs and 2,729 DCs) catheters were included in 36 ICUs (Figure 1). Median age was 64 years (interquartile range [IQR] 52.9, 74.8) and 3,704 (36.1%) patients were female (Table 1). The SAPS II at admission was 54 (41, 69) and 1,952 (19%) patients were immunosuppressed. Senior operators (>50 procedures) placed 7,075 (37.7%) catheters and 7,186 (38.3%) catheters were inserted at the femoral site. CHG for skin disinfection was used in 8,416 (44.9%) catheters and CHG-impregnated dressings were used in 4,061 catheters (21.7%).

Antibiotics were administered at catheter insertion in 11,361 (60.6%) catheters, predominantly consisting of beta-lactam antibiotics (8,344, 54.9%, Table E1 in ESM). MCRI, CRBSI and catheter colonization were observed in 241 (1.3%), 151 (0.8%) and 1,514 (8.1%) episodes, respectively. The proportionality of hazards assumption was violated for catheter colonization ($p < 0.0001$), but respected for MCRI ($p = 0.51$) and CRBSI ($p = 0.81$).

MCRI and antibiotic type:

Among catheters without MCRI, antibiotics were administered during 11,211 (60.6%) catheter insertions, whereas among catheters with MCRI, 150 (62.2%) received an antibiotic at insertion. In the univariate Cox model analysis, the MCRI risk was similar for the antibiotic and no-antibiotic group (HR 0.82, 95% confidence interval [CI] 0.62-1.09, $p = 0.18$, Figure 2 and Table E2 ESM). After adjusting for well-known risk factors for intravascular infection, we found similar results (HR for antibiotics 0.83, 95% CI 0.62-1.10, $p = 0.19$, Figure 2 and Table E2 ESM). A confirmatory analysis using IPTW also showed similar results (HR for antibiotics 0.82, 95% CI 0.61-1.09, $p = 0.17$). No specific antibiotic subgroup reduced the risk for MCRI: beta-lactam antibiotics or other groups of antibiotics with Gram-positive antimicrobial activity exhibited a HR of 0.83 (95%CI 0.57-1.21, $p = 0.34$) and 0.86 (95%CI 0.55-1.36, $p = 0.52$, Figure E2 ESM), respectively. However, the distribution of microorganisms associated with MCRI was significantly different between the two groups

($p < 0.0001$). Non-fermenting Gram-negative bacilli were more frequently observed in the antibiotic group (21.1% versus without antibiotics 5.7%, 0.0053). In >85% of cases non-fermenting Gram-negative were *Pseudomonas* MCRI. *S. aureus* was more frequently detected in the group without antibiotics (Table 2).

CRBSI risk:

Among catheters without CRBSI, Antibiotics were administered at insertion for 11,266 (60.6%) catheters; whereas among catheters with CRBSI, 95 (62.9%) received an antibiotic at insertion. In the univariate Cox model analysis, the CRBSI risk was similar for antibiotics compared to group without antibiotics (HR 0.84, 95% CI 0.59-1.21, $p = 0.34$, Figure 2 and Table E3 ESM). After adjusting for risk factors for intravascular catheter infection, we found similar results (HR for antibiotics 0.85, 95% CI 0.60-1.22, $p = 0.38$, Figure 2 and Table E3 ESM). A confirmatory analysis using IPTW revealed similar results (HR for antibiotics 0.86, 95% CI 0.60-1.24, $p = 0.43$).

Catheter colonization risk

Among catheters without colonization, Antibiotics were administered at insertion for 10,505 (61%) catheters, whereas among colonized catheters, 856 (56.5%) received an antibiotic at insertion. In the univariate Cox model analysis, catheter colonization risk was significantly decreased in the antibiotic group (HR 0.67, 95% CI 0.6-0.75, $p < 0.0001$, Figure 2 and Table E4 ESM). After adjusting for risk factors for intravascular infection, we found similar results with a reduced risk for the antibiotic group (HR 0.67, 95% CI 0.60-0.75, $p < 0.0001$, Figure 2). After introducing a time-dependent variable, the HR was 0.53 (95% CI 0.45-0.63, $p < 0.0001$) in the first 7 days and 0.81 (95% CI 0.70-0.93, $p = 0.0039$) after >7 days of catheter maintenance (Table E4 ESM).

Discussion

Using high-quality, individual data from five RCTs, we demonstrated that the daily hazard ratio of MCRI and CRBSI was similar regardless of whether or not antibiotics were administered at catheter insertion. Moreover, no specific antibiotic subgroup significantly reduced the subsequent risk of catheter infection. However, antibiotics administered at insertion did decrease risk of catheter colonization.

Data in the literature regarding the role of antibiotic administration during short-term catheter insertion are scant and, to our knowledge, no RCT on this topic is currently planned. Only a limited number of studies assessed the association between antibiotics administration and infectious risk related to short-term catheters in critically ill patients. The post-hoc analysis of the first RCT illustrated that systemic antibiotics were an independent protective factor regarding infectious complications [6]. Of note, the definition “infectious complications” included either CRBSI, MCRI, or catheter colonization [6]. In a second prospective study including eight ICUs and 8,593 CVCs, the absence of antibiotics administration within 48 hours of insertion was a risk factor for CVC-associated BSIs [7]. The third study was an observational study with 179 patients which revealed that extending routine perioperative antibiotic prophylaxis until all intravascular catheters had been removed did not influence rates of intravascular catheter colonization [8]. The last study found that antibiotic administered at the time of catheter insertion was associated with a reduced CVC colonization in a multivariate model [9]. Most of these studies were published prior to 2010 and may be less relevant today due to the widespread adoption of recommendations for prevention of catheter infections [24]. Indeed, intravascular catheter bundles have changed the landscape of risk factors associated with intravascular catheter infections in critically ill patients [25]. In an environment of consistent catheter care representing the largest dataset ever assembled, we found that coincident systemic antibiotic administration at catheter insertion was not associated with decreased risk of infection. Our data were supported by different statistical models and support the fact that antibiotics at catheter insertion should not be administered for preventing intravascular catheter infections when such catheters are inserted. Our data also has relevance for antibiotic stewardship programs [26].

Although antibiotic administration at insertion significantly reduced catheter colonization, colonization does not represent a reliable outcome for clinical trials [21]. However, catheter colonization is required to meet the gold standard definition of CRBSI [18] and, therefore, in patients with concurrent antibiotic at insertion, the diagnosis of CRBSI may be difficult.

Our study has an important clinical implication: we found that non-fermenting Gram-negative bacilli were more frequently observed in the group that received antibiotics, whereas *S. aureus* was more frequently observed in the group without antibiotic administration. This data may direct empirical antimicrobial therapy if CRBSI is suspected after catheter insertion.

We acknowledge several limitations. First, we conducted an observational study: the patients were not randomized according to the antimicrobial therapy and unmeasured factors may persist and cause residual confounding. However, we presented data that were prospectively collected by trained investigators in the field of catheter-related infections and we corrected for several confounders. Second, no information on reason (*e.g.*, treatment of a known infection or prophylaxis) of antimicrobial administration or antibiotic duration was available. It is conceivable that a longer duration of antibiotic therapy may reduce the risk of infection. However, as mentioned above, a prior study did not demonstrate any difference in infectious risk between a prolonged *versus* short antimicrobial prophylactic course [8]. Third, we described a large cohort designed to investigate the impact of several prevention measures, and interactions may have occurred among the various study groups. However, our statistical analyses considered these potential drawbacks. Fourth, we found that antibiotics significantly reduced catheter tip colonization. This result should be interpreted with caution: catheter colonization was demonstrated to be unsuitable to establish definite patient-oriented benefit or harm for a specific treatment [21]. However, it is possible that yield of MCRI and CRBSI (*i.e.*, definitions partially using catheter tip colonization) can be reduced since antibiotics appeared to decrease catheter tip colonization. Finally, the five studies were conducted in French ICUs, which may limit the generalizability of our results.

The analysis of five large RCTs involving over 10,000 ICU patients with more than 18,000 catheters demonstrated that ongoing antibiotic administration at the time of catheter insertion was not associated

with decreased risk of subsequent catheter-related infections. These findings may suggest that antibiotics at catheter insertion did not prevent short-term intravascular catheter infections and represents an additional point of intervention for antibiotic stewardship programs in critically ill patients.

Transparency declaration

Conflicts of interest. The authors have disclosed that they do not have conflict of interest. Dr. Timsit received fees for lectures to MSD, Pfizer, 3M and Biomerieux; he received research grants from Astellas, 3M, MSD, and Pfizer; and he participated to advisory boards of Bayer Pharma, Nabriva, 3M, MSD, and Pfizer. Dr. Lucet received research grants from Anios; and fees for lectures for 3M, Pfizer MSD. Dr. Mimoz received fees for lectures for 3M and Becton, Dickinson and Company ; he received research grants from BD. LM has served as a consultant for Citius Pharmaceuticals, Marvao Medical, Leonard-Meron Biosciences, Destiny Pharma, and Nobio. Dr. Souweine reports personal fees from SANOFI, personal fees from MSD, non-financial support from TTM BARD, personal fees from MSD.

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Contributions. NB, SR and JFT designed the study. OM, LM, NM, JPM, JCL, JJP and JFT collected the data. NB, AL, JFT and SR did the statistical analysis. NB, AL, SR, JJP and JFT analyzed and interpreted the data. NB, LM, NM and JFT drafted the manuscript. All authors critically reviewed the manuscript and approved the final report.

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Figure legends

Figure 1: Flow-chart.

Legends. ICU: Intensive care unit. MCRI: Major catheter-related infection. CRBSI: Catheter-related bloodstream infection. CVC: Central venous catheter. AC: Arterial catheter. DC: Short-term dialysis catheter.

Figure 2: Unadjusted and adjusted risk for MCRI, CRBSI and colonization for catheters with antibiotics (vs without antibiotics).

Legend. Univariable (unadjusted results) and multivariable (adjusted results) Cox models were used. *The risk proportionality was not respected for colonization. We demonstrated a global effect of adjusted colonization risk for antibiotic administration. However, after introducing a time-dependent variable, the HR was 0.53 (95% CI 0.45-0.63, $p < 0.0001$) in the first 7 days and 0.81 (95% CI 0.70-0.93, $p = 0.0039$) after >7 days of catheter maintenance (please see Table E4 in the ESM).

Tables

Table 1: Patient and catheter characteristics.

Patients		Total n=10,269	Without antibiotics n=4,403	With Antibiotics n=5,866
Age		64 [52.9 ; 74.8]	63 [51 ; 74]	63 [51 ; 74]
Sex	Male	6,565 (63.9)	3,863 (65.9)	2,702 (61.4)
SAPS II at ICU admission		54 [41 ; 69]	56 [42 ; 71]	52 [39 ; 67]
Diabetes mellitus		1,206 (11.7)	710 (12.1)	496 (11.3)
Respiratory failure		768 (7.5)	453 (7.7)	315 (7.2)
Chronic kidney disease		631 (6.1)	370 (6.3)	261 (5.9)
Immunosuppression		1,952 (19)	1,312 (22.4)	640 (14.5)
Catheters		Total (n=18,743)	n=7,382	n=11,361
Heparin at catheter insertion		6,216 (33.2)	2,440 (33.1)	3,776 (33.2)
Experience of the operator	<50 procedures	11,668 (62.3)	4,376 (59.3)	7,292 (64.2)
	≥50 procedures	7,075 (37.7)	3,006 (40.7)	4,069 (35.8)
Insertion site	Jugular	4,164 (22.2)	1,511 (20.5)	2,653 (23.4)

	Subclavian	3,276 (17.5)	1,393 (18.9)	1,883 (16.6)
	Femoral	7,186 (38.3)	2,763 (37.4)	4,423 (38.9)
	Radial	4,117 (22)	1,715 (23.2)	2,402 (21.1)
Catheter type	Arterial catheter	6,373 (34)	2,625 (35.6)	3,748 (33)
	Central venous catheter	9,641 (51.4)	3,982 (53.9)	5,659 (49.8)
	Short-term dialysis catheter	2,729 (14.6)	775 (10.5)	1,954 (17.2)
Skin antisepsis	CHG	8,416 (44.9)	3,320 (45)	5,096 (44.9)
	Non-CHG	10,327 (55.1)	4,062 (55)	6,265 (55.1)
Dressing type	CHG-impregnated	4,061 (21.7)	1,608 (21.8)	2,453 (21.6)
Mechanical ventilation at insertion		14,401 (76.8)	5,257 (71.2)	9,144 (80.5)
Vasopressor at insertion		10,537 (56.2)	3,613 (48.9)	6,924 (60.9)
Reason for catheter removal: no longer needed		6,582 (35.1)	2,614 (35.4)	3,968 (34.9)
Reason for catheter removal: suspected infection		2,492 (13.3)	885 (12)	1,607 (14.1)
Antibiotic at catheter insertion		11,361 (60.6)	0 (0)	11,361 (100)
MCRI		241 (1.3)	91 (1.2)	150 (1.3)
CRBSI		151 (0.8)	56 (0.8)	95 (0.8)
Colonization		1514 (8.1)	658 (8.9)	856 (7.5)

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388 Data are expressed as n (%) or median [IQR], as appropriate. Legends. SAPS: Simplified Acute Physiology Score. ICU:
389 Intensive care unit. IQR: Interquartile range. CVC: Central venous catheter. CHG: Chlorhexidine gluconate. MCRI: Major
390 catheter-related infection. CRBSI: Catheter-related bloodstream infection.

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394 **Table 2: Distribution of microorganisms among MCRI and CRBSI**

	Without antibiotic	With Antibiotic	p-value*
MCRI	n=91	n=150	
CoNS	24 (26.4)	34 (22.7)	0.51
<i>S. aureus</i>	22 (24.2)	8 (5.3)	<.0001
Enterococci	2 (2.2)	3 (2)	0.999
Enterobacteriaceae	19 (20.9)	35 (23.3)	0.66
Fungi	1 (1.1)	11 (7.3)	0.034
Polymicrobial	11 (12.1)	21 (14)	0.67
Non-fermenting Gram-negative bacilli	7 (7.7)	32 (21.3)	0.0053
Other Gram-negative bacilli	1 (1.1)	0 (0)	0.38
Other Gram-positive bacilli	1 (1.1)	0 (0)	0.38
CRBSI	n=56	n=95	
CoNS	11 (19.6)	18 (18.9)	0.92
<i>S. aureus</i>	18 (32.1)	7 (7.4)	<0.0001
Enterococci	1 (1.8)	1 (1.1)	0.999
Enterobacteriaceae	10 (17.9)	24 (25.3)	0.29
Fungi	1 (1.8)	6 (6.3)	0.26
Polymicrobial	8 (14.3)	15 (15.8)	0.80

Non-fermenting Gram-negative bacilli	3 (5.4)	19 (20)	0.016
Other Gram-negative bacilli	1 (1.1)	0 (0)	0.378

395 Legends. *Chi square or Fisher tests as appropriate. Data are expressed as n (%). MCRI: Major catheter-related infection.
396 CRBSI: Catheter-related bloodstream infection. CoNS: Coagulase-negative Staphylococci. *p-values were calculated for this
397 categorical variable with Fisher test.

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