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ORIGINAL

Treatment of positive catheter tip culture without bloodstream infections in critically ill patients. A case-cohort study from the OUTCOMEREA network

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Abstract

Purpose: This study aimed to evaluate the impact on subsequent infections and mortality of an adequate antimicrobial therapy within 48 h after catheter removal in intensive care unit (ICU) patients with positive catheter tip culture.

Methods: We performed a retrospective analysis of prospectively collected data from 29 centers of the OUTCOMEREA network. We developed a propensity score (PS) for adequate antimicrobial treatment, based on expert opinion of 45 attending physicians. We conducted a 1:1 case-cohort study matched on the PS score of being adequately treated. A PS-matched subdistribution hazard model was used for detecting subsequent infections and a PS-matched Cox model was used to evaluate the impact of antibiotic therapy on mortality.

Results: We included 427 patients with a catheter tip culture positive with potentially pathogenic microorganisms. We matched 150 patients with an adequate antimicrobial therapy with 150 controls. In the matched population, 30 (10%) subsequent infections were observed and 62 patients died within 30 days. Using subdistribution hazard models, the daily risk to develop subsequent infection up to Day-30 was similar between treated and non-treated groups (subdistribution hazard ratio [sHR] 1.08, 95% confidence interval [CI] 0.62–1.89, $p = 0.78$). Using Cox proportional hazard models, the 30-day mortality risk was similar between treated and non-treated groups (HR 0.89, 95% CI 0.45–1.74, $p = 0.73$).

Conclusions: Antimicrobial therapy was not associated with decreased risk of subsequent infection or death in short-term catheter tip colonization in critically ill patients. Antibiotics may be unnecessary for positive catheter tip cultures.

Keywords: Catheter tip, Catheter-related bloodstream infections, Mortality, Critically ill, Positive catheter tip cultures

Introduction

More than 50% of patients in intensive care units (ICUs) have a central venous catheter (CVC), and the mean device infection-adjusted rate in critically ill patients varies from 0.87 to 4.82 central line-associated bloodstream infections episodes per 1000 CVC-day depending on countries of detection [1–3]. Catheter-associated

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bloodstream infections were associated with a substantially increased attributable mortality [4–6] and an additional 15 days of ICU length-of-stay [7]. Colonization of central catheters in the ICU is a frequent phenomenon, affecting more than 8% of intravascular catheter [8], depending on the study. Colonization is not sufficient by itself to define catheter infection but is classically considered as an acceptable surrogate for catheter infection, although poorly correlated with catheter-related infections [9]. Since CVC colonization is the first step of CVC infection, it is likely that CVC colonization predisposes to catheter-related bloodstream infections (CRBSIs) [10]. Therefore, CVC removal is recommended as soon as the CVC is no longer needed to prevent both CVC colonization and infection [11]. To date, there is no uniform approach to the management of colonized catheters, and the consequences in terms of bacteremic or non-bacteremic subsequent infections following catheter removal remain controversial in the literature [12]. In 2009, the Infectious Disease Society of America (IDSA) highlighted the importance of this subject and the need to guide healthcare professionals in initiating an appropriate response to this issue [13].

Up to now, the conclusions of published studies on this topic are limited, because they are (i) heterogeneous, (ii) mostly monocentric and observational, and (iii) mostly describe a single pathogen [10]. A recent national microbiological surveillance study including more than 15,000 positive catheter tips showed that several microorganisms (i.e., *Serratia marcescens, Pseudomonas aeruginosa, Staphylococcus aureus* and *Candida albicans)* were associated with an increased risk of subsequent bacteremia [14]. However, due to the retrospective nature of this study without access to clinical data, the role of systemic antibiotic treatment in adults with colonized CVC remains unresolved.

Therefore, we aimed to evaluate the role of systemic antibiotic therapy in patients with a colonized catheter tip with potentially pathogenic microorganisms, assessing the occurrence of bacteremic or non-bacteremic subsequent infections. Preliminary results of this manuscript have been presented at the European Congress of Clinical Microbiology and Infectious Diseases (ECCMID Barcelona, Spain, 27–30 April 2024) [15].

Take-home message

Adequate antimicrobial therapy was not associated with decreased risk of subsequent infection or death in short-term catheter tip colonization in critically ill patients.

These findings could significantly impact future management strategies when addressing positive catheter tip cultures in critically ill patients.

Materials and methods

Study design and data sources

We conducted a matched case-cohort study using the OUTCOMEREA prospective database which has been maintained since 1997 by a total of 32 ICUs in France, comprising 18 in university hospitals. The methodology implemented for data collection and quality control has been described in detail elsewhere [18]. The database protocol was submitted to the Institutional Review Board of the Clermont-Ferrand University Hospital (Clermont-Ferrand, France) which waived the need for informed consent (IRB no. 5891). The OUTCOMEREA database was approved by the French Advisory Committee for Data Processing in Health Research (CCTIRS) and registered by the French National Informatics and Liberty Commission (CNIL, registration no. 8999262), in compliance with French law on electronic data sources. The methods and results of this study are exposed according to the STROBE guidelines [16].

Study population

We included patients from 1st January 1997 to 31st December 2021. Patients were enrolled for the current study if they had a positive quantitative intravascular catheter tip culture, with at least one potentially pathogenic microorganism. Potentially pathogenic microorganisms included *S. aureus*, *Streptococcus* spp., *Enterococcus* spp., *Enterobacterales*, *P. aeruginosa*, *Acinetobacter* spp., and *Candida* spp. Of note, *S. aureus*, *P. aeruginosa*, *A. baumannii*, other non-fermentative Gram-negative bacteria and *Candida* spp. were classified as high-risk microorganisms for subsequent infections.

Coagulase-negative staphylococci (except *Staphylococcus lugdunensis*), *Neisseria* spp., *Corynebacterium* spp. (except *Corynebacterium* JK), *Bacillus* spp., unspecified Gram-positive cocci were not included. Patients with central venous catheters (CVCs), short-term dialysis catheters and arterial catheters were included. Only the first positive catheter tip culture was considered in this study. Patients with positive blood cultures with a potentially pathogenic microorganism also identified on the catheter tip culture within 48 h before and 48 h after catheter removal (i.e., CRBSI) were excluded. Moreover, patients who died within the first 48 h after catheter removal were also excluded. The follow-up period was 30 days after catheter removal in the ICU.

Definitions, variables of interest and outcomes

Data were extracted from the OUTCOMEREA records of all patients whose intravascular catheters were included in the study and fully reviewed to retrieve demographic,

clinical and laboratory data. All study data were obtained from patient files, and no additional tests were performed for the purpose of the current study. The following variables were extracted: severity of illness defined at ICU admission using the Simplified Acute Physiology Score (SAPS) II, age, sex, type of intravascular catheter, duration of catheterization, underlying disease and comorbid conditions, data on mechanical ventilation, duration of hospital stay, symptoms of systemic inflammatory response syndrome (SIRS), immunosuppressive therapy, diagnosis of vessel thrombosis, and characteristics at ICU discharge. For each positive catheter tip culture, we collected data on antimicrobial drugs including type of antibiotic used, duration and day of initiation of antibiotics, organ dysfunction and organ failure defined as Sequential Organ Failure Assessment (SOFA).

Positive intravascular catheter tip culture was defined as a positive quantitative device tip culture showing at least one microorganism yielded ≥ 1000 cfu/ml by vortexing or sonication [17–19].

Our variable of interest was an adequate antimicrobial therapy within 48 h after intravascular catheter removal. An adequate antimicrobial therapy was defined as a therapy with at least one antimicrobial with in vitro activity for the microorganism, with adequacy of antimicrobial selection, dosing and administration carefully reviewed for all potentially pathogenic microorganisms by three experts (JRZ, BS and JFT).

Our primary outcome was *subsequent infection* between 48 h and 30 days after intravascular catheter removal. The 30-day cutoff was chosen based on pathophysiological reasoning, suggesting that it is less likely for a subsequent infection with the same microorganism to be linked to a catheter tip beyond 30 days after its removal. Subsequent infections were defined as infections with the same potentially pathogenic microorganisms detected in the catheter tip culture. Concordance between the microorganism detected in the catheter tip culture and subsequent infections was based on phenotypic microbiological characteristics and the results of antibiotic susceptibility testing (i.e., identical species and antibiogram). The concordance was established by two independent blinded experts (JRZ and BS) who classified these episodes according to infection definitions. In case of disagreement, the opinion of a third expert (JFT) was sought. Infections were classified as subsequent bloodstream infections, surgical site infections (SSI), hospital-acquired pneumonia and urinary tract infection according to European Centre for Disease Prevention and Control (ECDC) definitions. Subsequent infections were assessed at day 30. Our secondary outcomes were 15-day subsequent infections, 15-day mortality and 30-day mortality.

Statistical analysis

Characteristics of patients were described as median (interquartile range) or count (percent) for qualitative and quantitative variables, respectively. Patients receiving an adequate antimicrobial therapy within 48 h were matched with patients without an adequate antimicrobial therapy within 48 h. We performed a propensity score Greedy matching (5 to 1) to select our treated and non-treated patients. We performed a survey with 45 experts to select the most important variables that should be associated with a high antimicrobial treatment probability and included in the propensity score (supplementary methods, eTables 1 and 2). After consultation of 45 experts, the following confounding and prognostic covariates were included in the propensity score: presence of sepsis or septic shock, temperature > 38.5 °C, high SOFA at intravascular catheter removal, time spent in the ICU before intravascular catheter removal, immunosuppression, presence of vascular thrombosis within the first 48 h after intravascular catheter removal, decrease in temperature > 0.5 °C after intravascular catheter removal, and microorganism identified (*S. aureus*, *P. aeruginosa*, *Candida* spp., *Streptococcus* spp., *Enterococcus* spp., *Acinetobacter* spp.). A logistic regression using these variables was performed to develop the propensity score. To assess the quality of matching, we computed standardized mean differences (SMD) for each variable. The risk of developing subsequent infections (at day 30 and day 15) for patients treated within 48 h (*versus* non-treated patients) was then estimated using Cox proportional subdistribution hazard (Fine and Gray) models stratifying by matched pairs [20]. These models considered mortality as competing event. Proportionality of hazard risk was tested graphically. Further sensitivity analyses for subsequent infections were conducted in patients with catheter tip colonization with high-risk microorganisms or patients with sepsis. To assess 15- and 30-day mortality, we used similar methods, but proportional Cox models were performed without considering competing events. P values < 0.05 were considered to be significant. Statistical analyses were performed using SAS 9.4 (Cary, North Carolina, USA).

Results

Unmatched and matched patients

From 15,233 patients with intravascular catheter of the OUTCOMEREA database, we identified 1199 positive intravascular catheter tip cultures; of them, 478 were excluded because they were due to non-potentially pathogenic microorganisms. Moreover, 93 were not first episodes of positive intravascular catheter tip cultures and were, therefore, excluded. Finally, 146 and 55 episodes

were excluded because they were associated with concurrent bacteremia and because the patients died within the first 48 h after the positive catheter tip culture, respectively (Fig. 1), leading to a set of 427 patients.

Forty-four percent of these patients (189/427) received an adequate antimicrobial therapy within 48 h after intravascular catheter removal. Overall, 501 microorganisms were identified (eTable 3). The logistic regression model used to develop the propensity score is illustrated in eTable 4 and showed an acceptable calibration and discrimination (AUC [Area Under The Curve] ROC [Receiver Operating Characteristics] 0.675, Hosmer–Lemeshow p value = 0.25). Finally, based on the propensity score, 150 patients with an

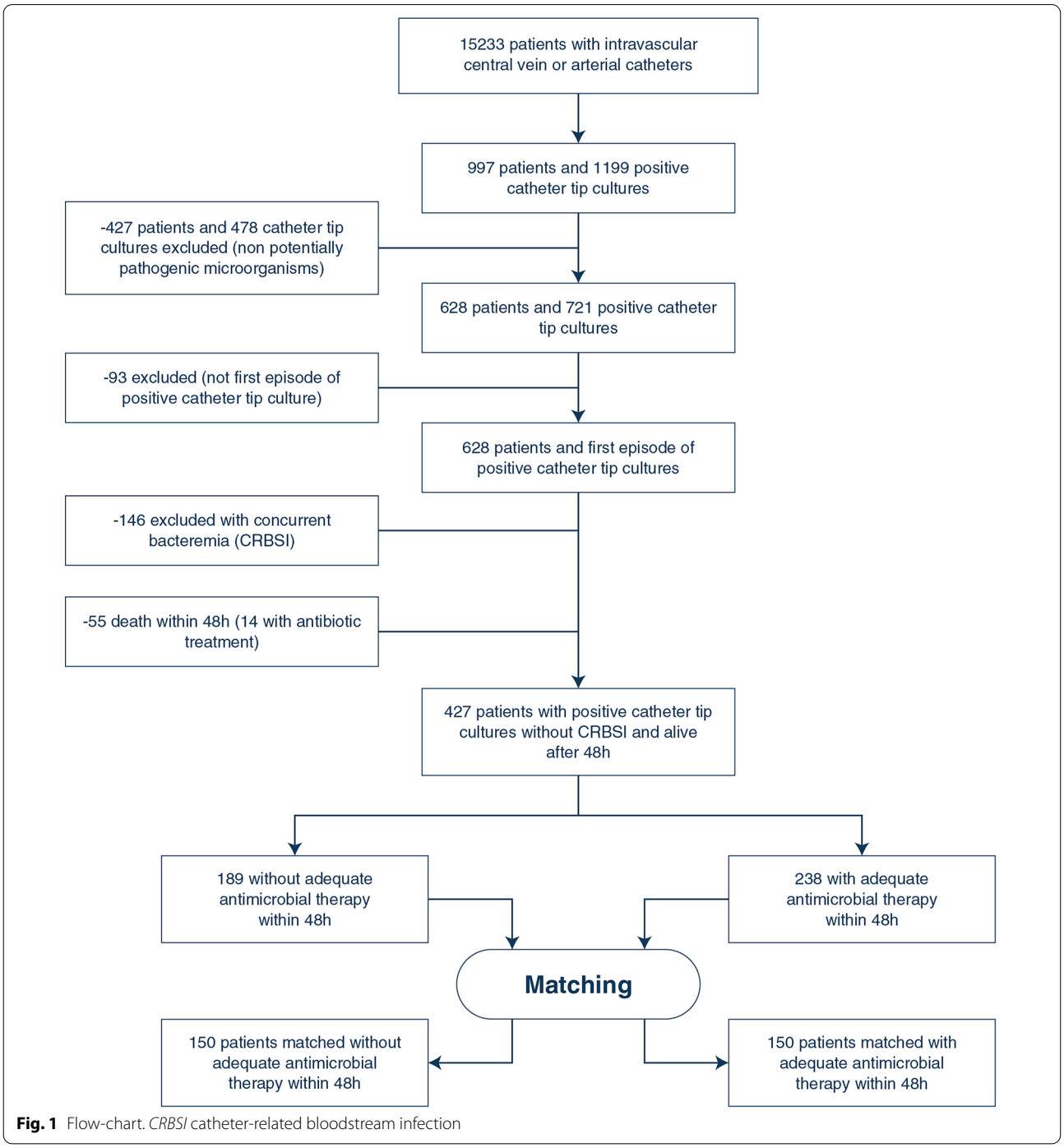

Fig. 1 Flow-chart. *CRBSI* catheter-related bloodstream infection

adequate antimicrobial therapy within 48 h were matched with 150 controls according to the predefined criteria (Table 1, eFigure 1). The matching process was adequate as shown in Table 1 and eFigures 1–2. The characteristics of unmatched and matched cohorts are shown in Table 1.

In the matched population, the median age was 68 (interquartile range [IQR] 53; 77) and 62.1% ($n=182$) of patients were male. At the time of positive catheter tip culture, median SOFA score was 5. Patients with sepsis and septic shock were 139 (46.4%) and 39 (13%), respectively. Of note, among the 150 matched patients without antimicrobial within 48 h, 55 (36.7%) received an adequate therapy after a median delay of 4 (IQR 3; 6) days.

Subsequent infections

In the matched population, 30 (10%) subsequent infections were observed, with 15 in the treated and 15 in the non-treated group, after a median delay of 5.5 days (IQR 3; 7). Bacteremia ($n=8$) and pneumonia ($n=15$) were the most frequently observed subsequent infections. The median time between positive catheter tip culture and subsequent infection was 3 days (IQR 2; 7) in the treated and 6 days (IQR 3; 9) in the non-treated group. The cumulative risk of subsequent infection in matched patients with and without adequate therapy is illustrated in Fig. 2. Microorganisms identified in subsequent infections are illustrated in eTable 5.

Using subdistribution hazard models, the daily risk to develop subsequent infection up to Day-30 was similar

Table 1 Description of unmatched and matched patients with and without adequate antimicrobial therapy within 48 h

	Overall ($n=427$)			Matched ($n=300$)		
	Adequate treatment < 48 h	No adequate treatment < 48 h	SMD	Adequate treatment < 48 h	No adequate treatment < 48 h	SMD
Characteristics	$n=238$	$n=189$		$n=150$	$n=150$	
Age, *n* (%)	69 [54; 77]	67 [53; 76]	0.0742	69 [55; 77]	67 [53; 75]	0.0809
Male, *n* (%)	142 (59,7)	123 (65,1)	0.112	87 (58)	95 (63.3)	0.1093
Immunosuppression, *n* (%)	56 (23.5)	18 (9.5)	0.384	19 (12.7)	18 (12)	0.0203
SAPS II on admission Median [IQR]	48 [36; 60]	49 [38; 65]	0.0813	48 [36; 61]	47 [37; 65]	0.017
At catheter tip colonization time						
SOFA score Median [IQR]	5 [3; 8]	6 [3; 8]	0.0185	5 [3; 8]	5.5 [3; 9]	0.0338
Corticosteroids, *n* (%)	114 (47.9)	87 (46)	0.0374	77 (51.3)	74 (49.3)	0.04
Presence of sepsis, *n* (%)	116 (48.7)	88 (46.6)	0.0436	69 (46)	70 (46.7)	0.0134
Presence of septic shock, *n* (%)	40 (16.8)	25 (13.2)	0.1003	21 (14)	18 (12)	0.0595
Intravascular prosthesis *n* (%)	7 (2.9)	8 (4.2)	0.0695	5 (3.3)	8 (5.3)	0.0983
Time spent in the ICU before catheter removal Median [IQR]	9 [4; 15]	12 [6; 20]	0.2287	10.5 [5; 18]	12 [6; 21]	0.0968
Temperature > 38.5°, *n* (%)	70 (29.4)	28 (14.8)	0.3573	26 (17.3)	26 (17.3)	< 0.0001
Thrombosis within the first 48-h catheter removal, *n* (%)	2 (0.8)	3 (1.6)	0.0683	1 (0.7)	1 (0.7)	0.0000
Decrease temperature > 0.5 °C after catheter removal, *n* (%)	61 (25.6)	37 (19.6)	0.1451	29 (19.3)	28 (18.7)	< 0.0001
Microorganism						
S. aureus	44 (18.5)	15 (7.9)	0.3154	13 (8.7)	15 (10)	0.0458
P. aeruginosa	50 (21)	49 (25.9)	0.1162	37 (24.7)	36 (24)	0.0155
Candida spp.	7 (2.9)	7 (3.7)	0.0426	5 (3.3)	6 (4)	0.0355
Streptococcus spp.	10 (4.2)	3 (1.6)	0.1564	1 (0.7)	3 (2)	0.1164
Enterococcus spp.	35 (14.7)	37 (19.6)	0.1295	29 (19.3)	30 (20)	0.0168
Acinetobacter spp.	7 (2.9)	9 (4.8)	0.0947	7 (4.7)	5 (3.3)	0.0681
Outcomes						
Subsequent infections (day 30), *n* (%)	25 (10.5)	18 (9.5)		15 (10)	15 (10)	
Subsequent infections (day 15), *n* (%)	25 (10.5)	17 (9)		15 (10)	14 (9.3)	
Mortality (day 30), *n* (%)	54 (22.7)	36 (19)		33 (22)	29 (19.3)	
Mortality (day 15), *n* (%)	40 (16.8)	24 (12.7)		25 (16.7)	20 (13.3)	
1-Year mortality, *n* (%)	122 (51.3)	92 (48.7)		75 (50)	70 (46.7)	

For quantitative variables, log-linearity was checked. For variables included in the propensity score or our outcomes, no missing values were observed

SMD standardized mean differences, *SOFA* sepsis-related organ failure assessment, *SAPS* Simplified Acute Physiology Score

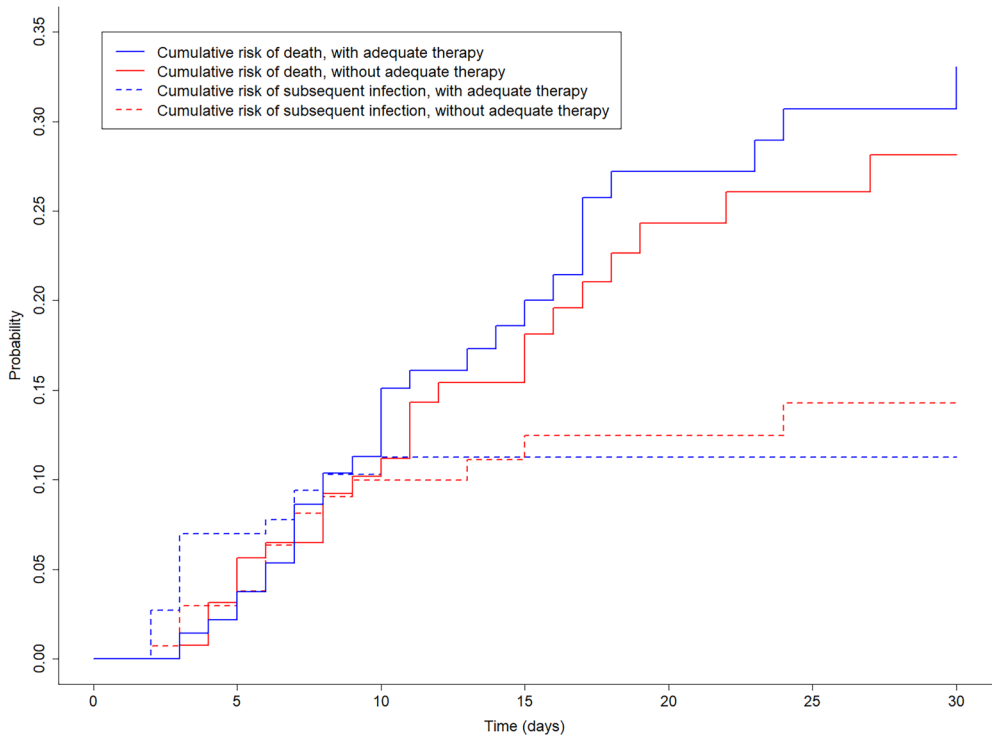

Fig. 2 Cumulative risk of subsequent infection and death in matched patients with and without adequate therapy within 48 h

between treated and non-treated groups (sHR 1.08, 95% CI [confidence interval] 0.62–1.89, $p=0.78$, Fig. 3, eTable 6). Sensitivity analyses including only patients with positive catheter tip with high-risk microorganism (sHR 2.33, 95% CI 0.83–6.54, $p=0.11$) or only with sepsis (sHR 0.83, 95% CI 0.46–1.51, $p=0.55$) showed similar results. Using proportional subdistribution hazards models, the daily risk to develop subsequent infection up to Day-15 was similar between treated and non-treated groups (sHR 1.18, 95% CI 0.67–2.09, $p=0.57$, eTable 6).

Mortality

In the matched population, 62 patients died within 30 days (Table 1), with 33 (22%) in the treated group and 29 (19.3%) in the non-treated group. Using Cox proportional hazard models, the 30-day mortality risk was similar between treated and non-treated groups (HR 0.89, 95% CI 0.45–1.74, $p=0.73$, Fig. 3, eTable 6). Sensitivity analyses including only patients with positive catheter tip with high-risk microorganism (HR 1.22, 95% CI 0.51–1.95, $p=0.66$) or with sepsis (HR 1.20, 95% CI 0.61–2.38, $p=0.60$) showed similar results. We observed similar results using 15-day mortality as an outcome (Fig. 3, eTable 6).

Discussion

In a large multicentre database including more than 400 patients with a positive catheter tip without concurrent bloodstream infection, we found that adequate systemic antibiotic therapy did not decrease the risk of subsequent infection with the same microorganism or death. Results were similar for high-risk microorganisms (e.g., *S. aureus*) and for patients with sepsis. To the best of our knowledge, it is the largest study exploring this research question.

Several studies suggested that the percentage of catheter with positive quantitative tip culture is correlated with the percentage of CRBSI [9, 18, 21], however, only 17% of patients with positive catheter tip culture has a CRBSI [9]. The decision to perform catheter tip culture is only recommended when infection is suspected [13]. On one hand, infection is frequently suspected in the ICU when the catheter is removed because critically ill patients often present fever, hypothermia or sepsis signs [12, 22, 23]. On the other hand, neither suspicion of infection as the cause of removal nor pathological temperature at removal increased the probability of diagnosing CRBSI.

Concomitant bloodstream infection (BSI) seems to be more frequent and had a higher risk of mortality compared to subsequent BSI [24]. Indeed, Guembe et al., in a large study based on microbiology lab results, showed

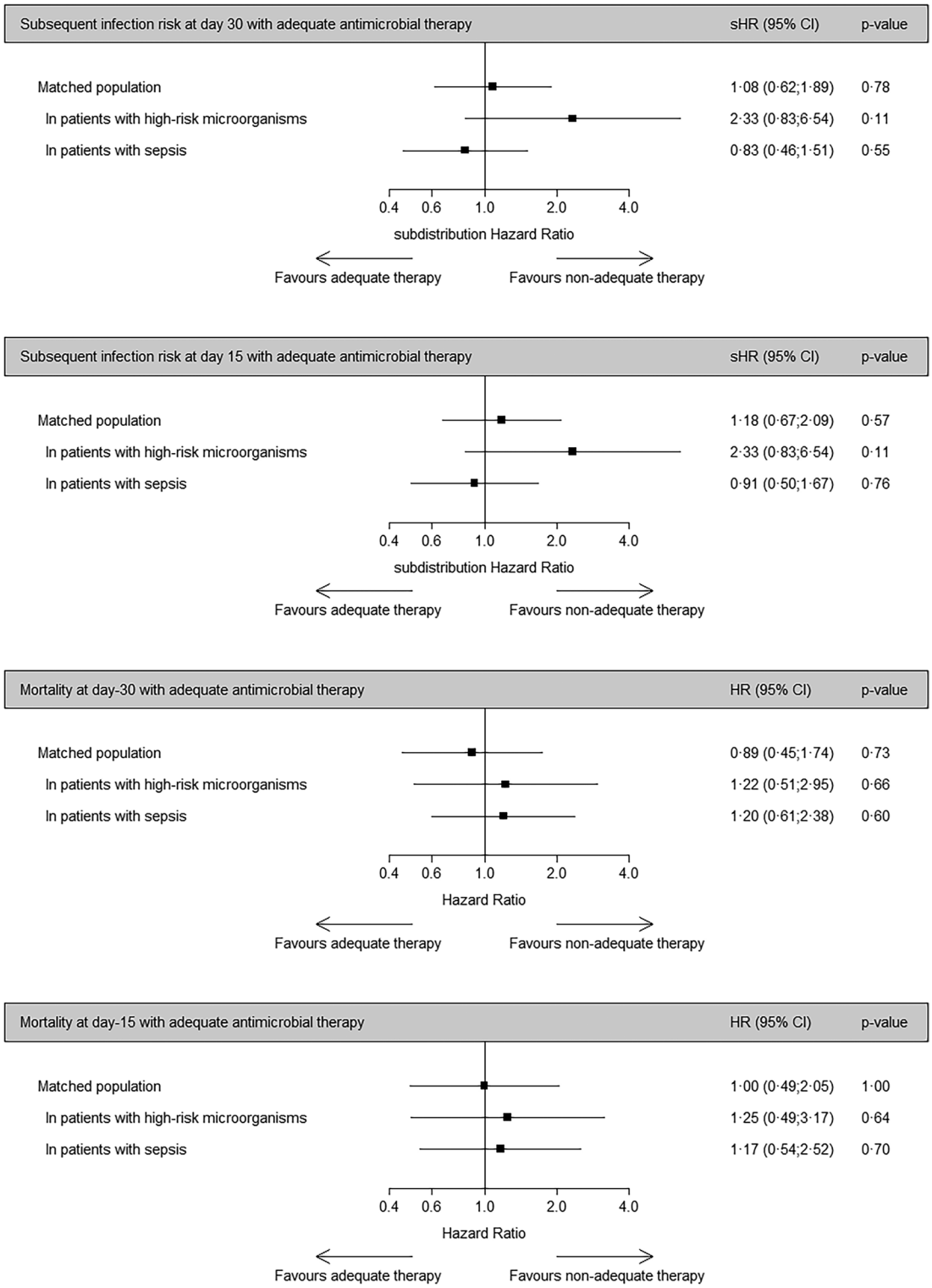

Fig. 3 Subsequent infection and mortality risk for patients treated with and without adequate therapy within 48 h after catheter removal. *HR* hazard ratio, *sHR* subdistribution hazard ratio, *CI* confidence interval

that concomitant positive blood cultures were observed in 23% of cases [24]. A similar multicentre laboratory-based study from Switzerland showed that the prevalence of CRBSI was 17% [14]. In addition, the prevalence of subsequent BSI was rare ranging from 1.8% (2.8% if coagulase-negative Staphylococci were excluded) [14] and 4.3% [24]. In cohort studies including clinical data and specifically focused on isolated positive catheter tip culture, the risk of subsequent bloodstream infection varied from 1.3 to 53%, with *S. aureus, Candida* spp. and non-fermentative Gram-negative bacteria carrying the highest risk [12, 14, 24–32]. Previous corticosteroid therapy, permanent intravascular prosthesis, underlying immune disease, cancer, the presence of venous thrombosis and acquisition in the ICU setting were associated with a higher likelihood of subsequent BSI [33, 34].

Based on the results of an expert consultation, a large panel of attending physicians and experts selected several of these factors and others (e.g., organ failure and the presence of shock) as determinants for starting antimicrobial therapy in the presence of colonized catheter tip. Our matching strategy was able to balance these factors between treated and untreated patients.

The impact of antimicrobial therapy in decreasing the risk of subsequent infection was evaluated in several studies with conflicting results [12]. On one hand, several studies showed that antimicrobial therapy for positive catheter tip culture could have a positive impact on subsequent infections. For *S. aureus*-positive tip cultures, cohort studies [25, 26, 35] showed that antibiotic therapy decrease the risk of subsequent BSI. In the Ekkelenkamp et al. study the risk of subsequent BSI for *S. aureus*-positive catheter tip culture was 24% and early antimicrobial therapy significantly reduced the risk [27]. However, the authors did not assess if blood cultures were systematically drawn within 48 h and may have missed several cases of CRBSI. Similar results were observed for *A. baumannii* and for *P. aeruginosa*-positive catheter tip culture in single-center studies [30, 32].

On the other hand, several studies showed less impact of antimicrobial therapy on subsequent infections in patients with positive catheter tip with *S. aureus*, *Candida* spp. and Gram-negative microorganisms [28, 31, 36, 37]. To our knowledge, no large multicentre study investigated the impact of antimicrobial treatment of positive catheter tip cultures on mortality. Our results suggested that antimicrobial treatment may be unnecessary for patients with positive catheter tips with high-risk microorganisms but without concomitant positive blood cultures. This finding could contribute to antimicrobial stewardship efforts, potentially reducing antibiotic overuse in critically ill patients.

Our study has several limitations. First, information bias may have influenced the results. In the available articles, the reason for culturing catheter tip was not detailed. We made a specific effort, considering all patient characteristics upon ICU admission and their clinical status at the time of catheter tip removal. However, it is important to note that local signs or symptoms of infection, such as purulence or pain, were neither recorded nor considered in the matching process. Moreover, reasons for catheter removal were not routinely collected. While local signs have been linked to an increased likelihood of CRBSI, they have never been reported as a risk factor for subsequent infections [23]. Other unmeasured confounders may also have been overlooked. Second, patients were not monitored for new infections after discharge from the ICU. In studies conducted outside the ICU, the follow-up duration was longer, potentially explaining for the higher risk of subsequent infections. Third, *S. aureus*, the only microorganism for which a reduced risk of subsequent infection with antimicrobial treatment was observed in several articles, represented only 10% of the cases in our cohort. Therefore, it is conceivable that our study was underpowered to detect an increased risk of poor outcome without therapy for a specific microorganism. In this context, we observed a higher risk of subsequent infections, although it did not reach statistical significance, when considering only high-risk microorganisms. However, our study population included only microorganisms which showed a priori an increased risk for subsequent infections and excluded low-risk microorganisms (e.g., coagulase-negative Staphylococci). Fourth, patients who died in the first 48 h were excluded from the analysis because they were not exposed to antibiotics. We could not exclude that this cohort represented an extreme of the unfavorable association between the exposure and our secondary outcome. Finally, we evaluated only the impact of early treatment of positive catheter tips without assessing the impact of a delayed antimicrobial therapy that may influence the occurrence of subsequent infections. An additional post hoc analysis including patients who received an adequate therapy between 48 and 96 h or without an adequate treatment within the first 96 h showed similar results (supplementary material).

Conclusions

Using a large multicentre cohort, we showed that early antimicrobial therapy was not associated with decreased risk of subsequent infection or death in short-term catheter tip colonization in critically ill patients. Antibiotics may be probably avoided for positive catheter tip cultures.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1007/s00134-024-07498-1.

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Author contributions
NB, JRZ, SR, BS and JFT designed and conceptualized the study. All the other coauthors acquired the data in their ICUs. SR, NB and JFT did the statistical analysis. SR performed the data curation. NB, SR and JFT analyzed and interpreted the data. NB, JRZ and JFT drafted the manuscript. All the authors critically reviewed the manuscript and approved the final report.

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Availability of data and material
The datasets used and/or analyzed during the current study are available from the OUTCOMEREA organization on reasonable request.

Declarations

Conflicts of interest
J-FT reported advisory boards participation for Merck, Gilead, Beckton-Dickinson, Pfizer, Shionogi, Roche diagnostic, Advanz Pharma, research grants from Merck, Pfizer, Thermofischer. MD received support from the "Société de

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Ethics approval
The database protocol was submitted to the Institutional Review Board of the Clermont-Ferrand University Hospital (Clermont-Ferrand, France) which waived the need for informed consent (IRB no. 5891). The OUTCOMEREA database was approved by the French Advisory Committee for Data Processing in Health Research (CCTIRS) and registered by the French National Informatics and Liberty Commission (CNIL, registration no. 8999262), in compliance with French law on electronic data sources.

Consent for publication
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