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Should non-bacteraemic patients with a colonized catheter receive antimicrobial therapy?

V. De Egea[a], M. Guembe[a,*], A. Rodríguez-Borlado[a], M.J. Pérez-Granda[b,c], C. Sánchez-Carrillo[a], E. Bouza[a,b,d]

[a] Department of Clinical Microbiology and Infectious Diseases, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria del Hospital Gregorio Marañón, Madrid, Spain
[b] Red Española de Investigación en Patología Infecciosa (REIPI), RD06/0008/1025, Spain
[c] Cardiac Surgery Postoperative Care Unit, H. G. U. Gregorio Marañón, Madrid, Spain
[d] Universidad Complutense, Madrid, Spain

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ABSTRACT

Objectives: The impact of antimicrobial therapy on the outcomes of patients with colonized catheters and no bacteraemia has not been assessed. This study assessed whether targeted antibiotic therapy is related to a poor outcome in patients with positive cultures of blood drawn through a non-tunnelled central venous catheter (CVC) and without concomitant bacteraemia.
Methods: This was a retrospective study involving adult patients with positive blood cultures drawn through a CVC and negative peripheral vein blood cultures. Patients were classified into two groups: those with clinical improvement and those with a poor outcome. These two groups were compared. The outcome was considered poor in the presence of one or more of the following: death, bacteraemia or other infection due to the same microorganism, and evidence of catheter-related bloodstream infection.
Results: A total of 100 patients were included (31 with a poor outcome). The only independent predictors of a poor outcome were a McCabe and Jackson score of 1–2 and a median APACHE score of 5. No association was found between the use of targeted antimicrobial therapy and a poor outcome when its effect was adjusted for the rest of the variables.
Conclusions: This study showed that antimicrobial therapy was not associated with a poor outcome in non-bacteraemic patients with positive blood cultures drawn through a CVC.

Introduction

Catheter-related bloodstream infection (CRBSI) is a major nosocomial disease occurring by extra- or intraluminal route, depending on the duration that the catheter is in place. Those catheters that are inserted for a short period of time (<7 days) are usually colonized extraluminally (skin), and those catheters that are inserted for a long period of time (>7 days) are usually colonized intraluminally (contamination of the hubs) (Mermel et al., 2009; Kumar et al., 2013; Ramritu et al., 2008). Therefore, the diagnosis of catheter colonization can be made without catheter withdrawal using conservative diagnostic methods, such as the differential time to positivity, which has proven useful in various populations (Mermel et al., 2009; Guembe et al., 2010; Bouza et al., 2007; Chen et al., 2009; Freeman et al., 2013; Garcia et al., 2012; Park et al., 2014; Seifert et al., 2003). This approach requires blood cultures to be obtained simultaneously from all catheter lumens and from a peripheral vein, so that an episode of CRBSI is confirmed when the same microorganisms recovered from the lumen blood grow at least 2 h before those recovered from peripheral blood. However, sometimes only blood drawn through the catheter yields positive cultures, in which case the catheter is considered to be colonized.

The clinical significance of colonization of non-tunnelled central venous catheters (CVCs) in patients with no concomitant bacteraemia has not been properly assessed, and the decision of whether to start antimicrobial therapy in this situation is controversial (Guembe et al., 2014; Ruhe and Menon, 2006;

* Corresponding author at: Servicio de Microbiología Clínica y Enfermedades Infecciosas, Hospital General Universitario Gregorio Marañón, C/ Dr. Esquerdo, 46, 28007 Madrid, Spain. Tel.: +34 91 586 84 53; Fax: +34 91 586 87 67.
E-mail addresses: Vivi_de_egea@hotmail.com (V. De Egea), mariaguembe@hotmail.com (M. Guembe), anabelborlado@yahoo.es (A. Rodríguez-Borlado), massus@hotmail.es (M.J. Pérez-Granda), cscarrillo@salud.madrid.org (C. Sánchez-Carrillo), ebouza@micorb.net (E. Bouza).

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Ekkelenkamp et al., 2008; Perez-Parra et al., 2009; Mrozek et al., 2011; Park et al., 2010; Perez-Parra et al., 2011; Munoz et al., 2012; Peacock et al., 1998; Leenders et al., 2011; van Eck van der Sluijs et al., 2012; Hetem et al., 2011). This issue remains unresolved in current clinical guidelines (Mermel et al., 2009; Mermel et al., 2001).

The objective of this study was to assess whether targeted antibiotic therapy is a protector factor or a risk factor for having a poor outcome in patients with colonized CVCs and without concomitant bacteraemia.

Methods

Setting

The study hospital is a 1550-bed general teaching institution, with approximately 50 000 admissions per year. The hospital provides all of the services of a general teaching hospital.

Design

This was an observational retrospective cohort study that included all adult patients admitted to the institution between January 2010 and December 2012 with positive cultures of blood drawn through a non-tunnelled CVC and a negative peripheral blood culture. Patients could not have had bacteraemia during the previous month. Children under 16 years old and patients with oncological and haematological conditions were excluded. Patients were identified and analyzed by reviewing the microbiology databases and medical records (Figure 1).

For the patient follow-up, clinical data from the patient records and hospital databases were reviewed at least until discharge, as well as survivors for up to 1 year.

Patients were classified into two groups according to the clinical outcome: good outcome or poor outcome. The outcome was considered poor in the presence of one or more of the following variables during the year after culture: death, bacteraemia or any other infection due to the same microorganism isolated in blood from a catheter, or evidence of CRBSI. The two groups were compared in order to analyze risk factors for a poor outcome, including the influence of targeted antimicrobial therapy for catheter colonization as the most important variable.

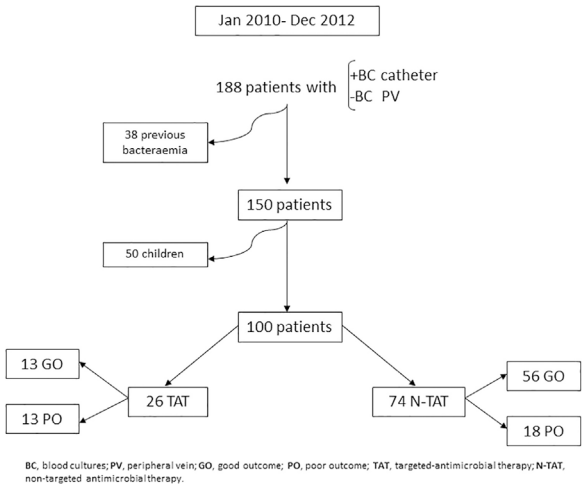

Figure 1. Flow chart of patient inclusion.

Clinical data collection

Patient characteristics were recorded using a pre-established protocol and included age, sex, intensive care unit (ICU) admission, neutropenia, surgical procedure, recent parenteral nutrition, endocarditis, defined daily doses (DDDs), antibiotic treatment, other infections, underlying diseases, comorbidity factors, severity of illness scores such as APACHE II, and the maximum severity reached before the catheter was shown to be colonized. Microbiological data from blood cultures and data on antimicrobial therapy and end-points (mortality, bacteraemia, and CRBSI) were also recorded.

Laboratory procedures

Blood cultures were processed following routine methods using a semi-automated culture detector (Bactec 9240, Bactec Plus Aerobic/F; Becton Dickinson Microbiology Systems, Maryland, DE, USA). The microorganisms recovered were fully identified using standard microbiological methods.

Definitions

Targeted antimicrobial therapy after catheter colonization was considered adequate when an oral or parenteral antimicrobial agent was active in vitro against the microorganism causing catheter colonization.

Statistical analysis

Normally distributed continuous variables were compared using the *t*-test; non-normally distributed variables were compared using the Mann–Whitney test, median test, or Kruskal–Wallis test. Categorical variables were evaluated using the Chi-square test or two-tailed Fisher's exact test.

Values for continuous variables were expressed as the mean and standard deviation (SD), or median and interquartile range (IQR); values for categorical variables were expressed as percentages, with a 95% confidence interval (95% CI) when applicable. A two-tailed test was used to determine statistical significance, which was set at $p < 0.05$.

Multivariate analysis was used to identify independent prognostic factors including those variables that showed a statistically significant difference between the two groups on univariate analysis. This analysis was performed using binary logistic regression and incorporated variables found to be significant (p-value of <0.1) on univariate testing. The statistical analysis was performed using PASW Statistics for Windows version 18.0 (SPSS Inc., Chicago, IL, USA).

Ethics

The local ethics committee of the Hospital General Universitario Gregorio Marañón approved the study. The study was exempted from the need for participant written or verbal informed consent given its retrospective nature.

Results

A total 100 patients were identified during the study period. Their median age was 61.5 years (IQR 50.6–73.3 years). Clinical and demographic data are summarized in Table 1.

According to the study definition, 69 patients had a good outcome and 31 a poor outcome. Overall, 26 patients received targeted antibiotic treatment after CVC colonization, 18.8% in the good outcome group and 41.9% in the poor outcome group

Table 1
Clinical and demographic characteristics of the patients according to the clinical outcome.

Variable	All patients ($N = 100$), n (%)	Good outcome ($n = 69$), n (%)	Poor outcome ($n = 31$), n (%)	p-Value
Age (years), median (IQR)	61.5 (50.6–73.3)	60.5 (48.9–71.9)	65.3 (52.7–75.6)	0.17
Sex				0.64
Male	55 (55.0)	39 (56.5)	16 (51.6)	
Female	45 (45.0)	30 (43.5)	15 (48.4)	
Non-fatal underlying disease (McCabe criteria)	63 (63.0)	53 (76.8)	10 (41.9)	<0.001
Comorbidity index (Charlson criteria), median (IQR)	3.0 (2.0–6.0)	3.0 (2.0–6.0)	3.0 (1.0–6.0)	0.32
APACHE score, median (IQR)	5.0 (2.0–6.0)	3.0 (2.0–6.0)	6.0 (4.0–10.0)	<0.001
Admission to the intensive care unit	44 (44.0)	25 (36.2)	19 (61.3)	0.02
Neutropenia	8 (8.0)	5 (7.2)	3 (9.7)	0.67
Surgical procedure	44 (44.0)	30 (43.5)	14 (45.2)	0.87
Previous episode of bacteraemia caused by a different microorganism	2 (2.0)	1 (1.4)	1 (3.2)	0.55
Recent parenteral nutrition	37 (37.0)	21 (30.4)	16 (51.6)	0.04
Recent chronic renal failure	19 (19.0)	13 (18.8)	6 (19.4)	0.95
Recent previous antibiotic treatment	62 (62.0)	38 (55.1)	24 (77.4)	0.03
Targeted antibiotic treatment after catheter colonization	26 (26.0)	13 (18.8)	13 (41.9)	0.01
DDDs of antibiotics after catheter colonization, median (IQR)	13.0 (7.0–23.7)	10.0 (7.0–25.09)	14.0 (7.2–38.0)	0.45
Endocarditis	1 (1.0)	0 (0)	1 (3.2)	0.13
Infection at another site with the same microorganism	6 (6.0)	0 (0)	6 (19.4)	<0.001
CRBSI after catheter colonization with the same microorganisms	5 (5.0)	0 (0)	5 (16.1)	0.01

IQR, interquartile range; DDDs, defined daily doses; CRBSI, catheter-related bloodstream infection.

($p = 0.01$). A difference between the two groups in the median (IQR) DDD was also found: 21 (10.8–37.1) in the good outcome group vs. 20.3 (8.3–51.5) in the poor outcome group. In the good outcome group, 36.2% of the patients had to be admitted to the ICU compared to 61.3% in the poor outcome group ($p = 0.02$) (Table 1). Regarding episodes of CRBSI after catheter colonization, 16.1% of the patients with a poor outcome developed a CRBSI ($p = 0.01$) (Table 1).

The following variables were included in the multivariate analysis: McCabe score (<3), APACHE II score, ICU admission, targeted antimicrobial therapy after catheter colonization, use of parenteral nutrition, and previous antimicrobial therapy. The only independent predictors of a poor outcome were a McCabe score of 1–2 and a median APACHE score of 5. Moreover, although ICU admission was not an independent predictor of a poor outcome ($p = 0.05$), it was associated with a 2.9-times greater risk of a poor outcome.

The multivariate analysis did not reveal an association between the use of antimicrobial therapy and a poor outcome when its effect was adjusted for the remaining variables (odds ratio 1.61, 95% CI 0.51–5.09; $p = 0.41$).

The distribution of microorganisms in colonized CVCs of patients with a good outcome and a poor outcome was as follows: Gram-positive, 93.8% vs. 81.8% ($p = 0.013$); Gram-negative, 5.0% vs. 13.6% ($p = 0.58$); and yeasts, 1.3–4.5% (Table 2).

Discussion

The study data showed that giving targeted antimicrobial therapy to a non-bacteraemic patient with a colonized catheter was not associated with having a good or poor outcome.

The issue of whether to start antimicrobial therapy in patients with a colonized catheter and negative blood cultures remains unresolved in the international guidelines (Mermel et al., 2009; Mermel et al., 2001). Several authors have reported contradictory data on whether to start antimicrobial therapy in colonized catheters based on the presence of subsequent bacteraemia and aetiology. In the case of *Staphylococcus aureus*, the present authors recently found that late CRBSI was present in 4.1% of colonized catheters and that this was significantly associated with the presence of methicillin-resistant *S. aureus*. These findings were consistent with those of Ruhe et al. and

Table 2
Distribution of microorganisms isolated from colonized catheters in patients with good and poor outcomes.

Microorganism	Overall ($N = 124$), n (%)	Good outcome ($n = 80$), n (%)	Poor outcome ($n = 44$), n (%)	p-Value
Gram-positive	111 (89.5)	75 (93.8)	36 (81.8)	0.013
Staphylococcus epidermidis	85 (68.5)	60 (75.0)	25 (56.8)	
Enterococcus faecalis	4 (3.2)	0 (0.0)	4 (9.1)	
Enterococcus faecium	6 (4.8)	2 (2.5)	4 (9.1)	
Staphylococcus aureus	2 (1.6)	1 (1.3)	1 (2.3)	
Streptococcus viridans	2 (1.6)	2 (2.5)	0 (0.0)	
Other Gram-positive	12 (9.7)	10 (12.5)	2 (4.5)	
Gram-negative	10 (8.1)	4 (5.0)	6 (13.6)	0.58
Klebsiella pneumoniae	4 (3.2)	2 (2.5)	2 (4.5)	
Ochrobactrum anthropi	1 (0.8)	0 (0.0)	1 (2.3)	
Pseudomonas aeruginosa	1 (0.8)	0 (0.0)	1 (2.3)	
Escherichia coli	2 (1.6)	1 (1.3)	1 (2.3)	
FGNB	1 (0.8)	0 (0.0)	1 (2.3)	
NFGNB	1 (0.8)	1 (1.3)	0 (0.0)	
Yeasts	3 (2.4)	1 (1.3)	2 (4.5)	NA
Candida albicans	3 (2.4)	1 (1.3)	2 (4.5)	

FGNB, fermented Gram-negative bacilli; NFGNB, non-fermented Gram-negative bacilli; NA.

Peacock et al., who reported subsequent *S. aureus* bacteraemia in 12% and 72% of patients with a colonized catheter, respectively (Guembe et al., 2014; Ruhe and Menon, 2006; Peacock et al., 1998). In general, early initiation of antibiotic therapy for patients whose intravenous catheters are colonized by *S. aureus* has been shown to prevent subsequent *S. aureus* bacteraemia (Ekkelenkamp et al., 2008; Hetem et al., 2011). However, Muñoz et al. suggested that antimicrobial therapy does not seem justified in the absence of signs and symptoms of ongoing infection in patients with central vascular catheter tips colonized by *S. aureus* (Munoz et al., 2012).

In the case of Gram-negative bacteria, pre-emptive antibiotic treatment could be beneficial in high-risk patients with Gram-negative microorganisms cultured from arterial intravenous catheters (van Eck van der Sluijs et al., 2012).

For *Candida sp*, similar data were found by Leenders et al., who reported a 12% frequency of subsequent candidaemia in catheters colonized by *Candida sp* (Leenders et al., 2011). However, Muñoz et al. suggested that antifungal therapy does not have a significant influence on clinical outcomes in non-neutropenic critically ill patients with no concomitant candidaemia and CVC tips colonized by *Candida sp* (Perez-Parra et al., 2009).

In the present study, blood drawn through the catheter was analyzed and not cultures of withdrawn catheter tips. However, targeted antimicrobial therapy was present in 80% (4/5) of patients with CRBSI, thus supporting the findings that antimicrobial therapy does not have a positive impact on patient outcomes. Park et al. performed the only similar study based on blood culture results, although the catheters analyzed were long-term Hickman catheters. The authors reported an overall incidence of subsequent bloodstream infection of 8.0% in patients with positive catheter blood cultures and negative peripheral blood cultures, and showed that inappropriate empiric antibiotic therapy was associated with subsequent bloodstream infection (Park et al., 2010).

Regarding the differences between the two groups (good outcome and poor outcome) according to the colonizing microorganisms, it was found that patients with a good outcome had significantly more catheters colonized with Gram-positive bacteria, which may be due to coagulase-negative staphylococci. This could be explained by the fact that patients with a worse follow-up (poor outcome) could be those with catheters colonized by Gram-negative bacteria or yeasts, which are microorganisms that are more difficult to eradicate.

The main limitation of this study is the small sample size. A sample size of 250 patients would have been required to obtain statistically significant differences in the main variable (targeted antimicrobial therapy after catheter colonization: odds ratio 1.61, 95% CI 0.51–5.09; $p = 0.41$) with a power of 83%. However, the study was stopped at the moment when the main end point showed statistical significance as, in the univariate analysis, targeted antibiotic therapy was associated with a significant increase in poor outcome. Moreover, long-term CVCs were not included and the catheter indwelling time was not assessed. Therefore, case–control studies should be performed in the future. Nevertheless, this appears to be the first retrospective non-aetiology-related study based on indwelling catheters analyzing the impact of antimicrobial therapy.

In conclusion, not giving antimicrobial treatment for a colonized non-tunnelled CVC in patients without bacteraemia may not be associated with a poor outcome.

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Conflict of interest

The authors declare no conflicts of interest.

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