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Do antibiotics administered at the time of central venous catheter removal interfere with the evaluation of colonization?

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Abstract *Objective:* Catheter colonization is commonly used as an end point in studies on central venous catheter (CVC) infections. This study aimed at comparing the rates of catheter colonization in patients according to the administration of antibiotics at removal. *Design:* Prospective study over a 5-year period. All patients with a CVC removed without suspicion of CVC infection were included. *Setting:* An adult medical/surgical intensive care unit at a university teaching hospital. *Patients:* A total of 472 patients with CVC inserted for a mean CVC duration of 6.0 ± 3.7 days were included. *Methods:* Antibiotics at removal was defined as antibiotics administered within 48 h before CVC removal, and CVC colonization as catheter tip culture yielding $\geq 10^3$ colony-forming units per milliliter. *Interventions:* None. *Measurements and results:* Of 472 patients, 302 (64%) were receiving antibiotics at removal. The number of CVC colonizations per number of CVCs inserted was 4.7% (22 of 472) and the number of CVC colonizations per 1000 CVC days was 8.0. Administration of antibiotics at removal was associated with a lower risk of CVC colonization. Irrespective of CVC duration, CVC colonization rate differed between patients with or without antibiotics at removal (Kaplan–Meier test, $p = 0.04$). *Conclusions:* The proportion of patients with antibiotics at time of removal should be taken into account when interpreting the results of surveys and trials using the quantitative CVC tip culture to define CVC colonization as an end point.

Keywords Nosocomial infections · Antibiotics · Central venous catheter

Introduction

Numerous infection-control interventions have been developed to prevent CVC-related bloodstream infection; of these, CVC-related infection surveys and trials designed to measure the impact of hospital practice or new strategies are key elements in the development and evaluation of CVC-related infection policies.

Since CVC-related bloodstream infection is a rare event, most authors consider a quantitative CVC tip culture yielding $\geq 10^3$ colony-forming units per milliliter as a suitable surrogate marker for CVC-related bac-

teremia [1, 2]; however, antibiotics administered at the time of microbiological sampling may inhibit the growth of bacteria potentially present in the samples. Whether antibiotics at CVC removal have a major impact on the results of CVC cultures is unknown. If they do, the findings of studies giving CVC culture results of patients irrespective of systemic antibiotic administration at the time of CVC removal are questionable.

The aim of the present work was to evaluate specifically the impact of antibiotics at CVC removal on the rate of CVC colonization.

Methods

Study population

This prospective study was performed in a nine-bed medical/surgical intensive care unit (ICU) at the university hospital of Clermont-Ferrand, France. From 1 September 2000 to 8 August 2005 all patients admitted to the ICU for more than 48 h and with a CVC in place during ICU stay were eligible. The patients were included in the study if they met the following criteria: CVC inserted and removed in the ICU; CVC duration $\geq$ 48 h, and CVC removed either because CVC was no longer needed or because of the death of the patient. To reduce the bias due to antibiotics administered for a suspected CVC infection on the results of CVC cultures, the patients with CVC removed while exhibiting local signs of CVC infection or suspicion of systemic CVC infection were not included. Only the first CVC inserted in the ICU was taken into account for inclusion in the study.

Data collection

For all eligible patients, demographics, the characteristics of catheterization, and the antibiotics within 48 h before insertion and before removal were collected.

Central venous catheterization

Polyurethane single- or multi-lumen CVCs with no antibiotic or antiseptic properties were inserted using strict sterile precautions according to a previously published standard protocol [3]. The CVCs were not tunneled and no guidewire assisted change of CVCs was used. In our unit, the CVCs were not changed after a fixed insertion time but removed when they were no longer needed, when the patient was suspected of systemic CVC infection, or because of death of the patient. The study and the consent policy were approved by the Ethics Committee of the hospital.

Microbiology

The CVCs were removed under aseptic conditions according to our standard protocol. The skin surrounding the insertion site was carefully disinfected with an alcoholic solution of 0.5% chlorhexidine before CVC removal. A 5-cm distal segment (tip) was collected in sterile containers for all catheters. All catheter tips were sent to the microbiology laboratory in a sterile tube for quantitative culture. The CVC tip was cultured as follows [4]: 1 ml of brain-heart broth was dripped on the tip and the tube was sonicated and vortexed; 0.1 ml of the suspension was then plated on blood agar. Standard micro-

biological methods were used to identify the colonizing organisms.

Definitions

Local CVC infection was defined by the presence of pus at the insertion site. The suspicion of systemic CVC infection was defined by one or more of the following criteria: temperature of $< 36°C$; temperature of $\geq 38.3°C$ with or without chill or sepsis or septic shock in a patient with no other obvious focus of infection. The CVC colonization was defined by a CVC tip culture yielding $\geq 10^3$ colony-forming units per milliliter. The CVC-related bacteremia was defined as the isolation of the same phenotypic microorganism from both peripheral blood culture and catheter-tip culture growing $\geq 10^3$ cfu/ml when there was no other overt source of the bacteremia except the catheter. The comparability of microorganisms was based on speciation and antibiotic susceptibility profile. Antibiotics at removal refers to antibiotics administered within 48 h before CVC removal.

Statistical analysis

The aim of the study was not to assess the diagnostic accuracy of the quantitative CVC tip culture as a surrogate of CVC-related infection. The primary end point for the study was risk for CVC colonization according to antibiotics at removal. The CVC colonization rate was expressed using cumulative incidence (number of CVC colonizations per number of CVC inserted) and incidence density (number of CVC colonizations per 1000 CVC days). The variables associated with CVC colonization in univariate analysis were determined using chi-square test or Fischer's exact test when necessary for categorical variables and by Mann–Whitney test for continuous variables. Multivariate logistic regression analysis was performed, with colonization being the dependent variable and the variables found in the univariate analysis for CVC colonization with a p-value lower than 0.05 being the independent variables. The Kaplan–Meier test was used to compare the risk for CVC colonization according to catheter duration with regard to antibiotics at removal. Two-tailed p-values of less than 0.05 were considered to indicate statistical significance. Analyses were performed using SAS (SAS Institute, Cary, N.C.).

Results

The study included 472 patients, 279 men and 193 women (Table 1). The mean number of antibiotics administered at removal was 1.85 ± 0.98. Antibiotics were infused through the CVC in 245 of the 302 patients who were receiving

Table 1 Characteristics of the 472 patients and of their catheterization. *Antibiotics*, antibiotics administered within 48 h before central venous catheter removal; *SAPS II*, Simplified Acute Physiology Score II; *CVC*, central venous catheter; *ICU*, intensive care unit

	Overall Population ($n = 472$)	Antibiotics Yes ($n = 302$)	No ($n = 170$)	Significance (p)
SAPS II (mean ± SD)	53 ± 24	56 ± 23	47 ± 24	< 0.001
Mechanical ventilation[a]	376 (80)	259 (86)	117 (69)	< 0.001
Renal replacement therapy[b]	151 (32)	102 (34)	49 (29)	0.032
Insertion site				0.61
Internal jugular	253 (52)	159 (52)	84 (49)	
Subclavian	111 (24)	72 (24)	39 (23)	
Femoral	118 (25)	71 (24)	47 (28)	
CVC placed by a senior physician	329 (70)	207 (69)	122 (72)	0.53
CVC placed in emergency	42 (9)	28 (9)	14 (8)	0.84
Cause of CVC removal				0.01
No longer needed	356 (75)	216 (72)	140 (82)	
Death of the patient	116 (25)	86 (28)	30 (18)	
CVC duration (days, mean ± SD)	6.0 ± 3.7	5.7 ± 3.3	6.5 ± 4.3	0.09
ICU length of stay (days, mean ± SD)	10.3 ± 10.1	10.7 ± 11.1	9.7 ± 8.0	0.94
ICU mortality	150 (32)	112 (37)	38 (22)	0.002

Numbers in parentheses are percentages
[a] Either invasive or non-invasive
[b] During central venous catheterization

them at removal. In 143 of 302 patients with antibiotics at removal, the antibiotics were administered throughout the catheterization period.

The cumulative incidence of CVC colonization was 4.7% (22 of 472) and the incidence density was 8.0 per 1000 days of CVC use. In univariate analysis, antibiotics at removal was the only variable associated with CVC colonization at a p-value < 0.05 (Table 2), and therefore no multivariate model was performed. Among the patients with antibiotics at removal there was no difference in the incidence rate of CVC colonization between those whose antibiotics at removal were administered throughout the catheterization period and the others (5 of 159 vs. 3 of 143, $p = 0.72$). Figure 1 shows an actuarial survival curve for CVC colonization. The Kaplan–Meier test demonstrated that the difference in the risk of CVC colonization with regard to antibiotics at removal was observed regardless of the catheter duration ($p = 0.037$). Similar results were observed in the subgroup of 356 patients who had their CVC removed because it was no longer needed ($p = 0.033$). During the study period, 170 eligible patients were not included because of CVC removal for a suspicion of CVC infection. When the data of these patients were combined with the data of the 472 included patients, similar results were observed. Antibiotics at removal was the independent risk factor associated with CVC colonization: OR = 0.49; 95% CI = 0.24 – 0.98 ($p = 0.04$; data not shown).

A total of 24 etiologic organisms were isolated in the 22 CVC colonizations. They were mainly Gram-positive cocci with a predominance of coagulase-negative staphylococci (Table 3). In patients on antibiotics at removal, the etiologic organisms of CVC colonization were resistant to the antibiotics in 5 of 8 cases.

In 1 patient with CVC removed because of death while exhibiting no sign of infection, both peripheral blood cultures and CVC tip culture yielded methicillin-resistant *Staphylococcus aureus*. Since there was only one CVC-related bacteremia, we cannot draw any meaningful conclusion concerning the impact of antibiotics at removal on CVC-related bacteremia.

Discussion

The CVC colonization is widely used as a primary end point in numerous studies on CVC infections [5–8]. The potential impact of antibiotics at removal on the rate of colonization of CVCs has not been fully assessed in clinical studies [9–15]. Our work is the first to specifically focus on this topic. Our results show that when CVCs are removed without suspicion of CVC infection, antibiotics at time of CVC removal interfere with the evaluation of CVC colonization, when CVC colonization is defined by a quantitative catheter-tip culture threshold $> 10^3$ ufc/ml. Our findings are not able to show whether antibiotics at removal have an impact on CVC colonization when CVC colonization is defined by the roll-tip culture. Our study cannot determine whether CVC culture yielding $< 10^3$ colony-forming units per milliliter corresponded to true-negative tests, i.e. the CVC were actually not colonized, or whether antibiotic use led to negative tests even in the presence of CVC colonization. Such a study would require another definition of CVC colonization that

Table 2 Factors associated with catheter colonization (univariate analysis). *SAPS II*, Simplified Acute Physiology Score II; *CVC*, central venous catheter; *ICU*, intensive care unit

	CVC colonization Yes ($n=22$)	No ($n=450$)	Significance (p)
SAPS II (Mean ± SD)	48.5 ± 29.5	53.3 ± 23.5	0.17
Mechanical ventilation[a]	17 (77.3%)	359 (79.8%)	0.79
Renal replacement therapy[b]	4 (18.2%)	147 (32.7%)	0.15
Time between admission and insertion (days, mean ± SD)	0.5 ± 0.5	0.7 ± 1.8	0.17
Insertion site between the three insertion sites			0.44
Internal jugular site	10 (45.5%)	233 (51.8%)	
Subclavian site	4 (18.2%)	107 (23.8%)	
Femoral site	8 (36.3%)	110 (24.4%)	
No. of CVC lumens between all lumens			0.14
Single	1 (4.6%)	17 (3.8%)	
Double	3 (13.6%)	18 (4.0%)	
Triple	17 (77.2%)	361 (80.2%)	
Quadruple	1 (4.6%)	54 (12.0%)	
CVC placed by a senior physician	17 (77.3%)	312 (69.3%)	0.43
CVC placed in an emergency	1 (4.5%)	41 (9.1%)	0.71
Antibiotics within 48 h before CVC insertion	12 (54.5%)	260 (57.8%)	0.76
Antibiotics within 48 h before CVC removal	8 (34.6%)	294 (65.3%)	0.006
Other intravascular lines during CVC catheterization	18 (81.8%)	372 (82.7%)	0.92
Cause of CVC removal			0.19
CVC no longer needed	14 (63.6%)	342 (76.0)	
Death of the patient	8 (36.4%)	108 (24.0)	
CVC duration (days, mean ± SD)	6.4 ± 3.5	6.0 ± 3.7	0.46

Numbers in parentheses are percentages
[a] Either invasive or non-invasive
[b] During central venous catheterization

Fig. 1 Proportion of central venous catheters (*CVC*) free of colonization

Proportion of central venous catheters free from catheter colonization
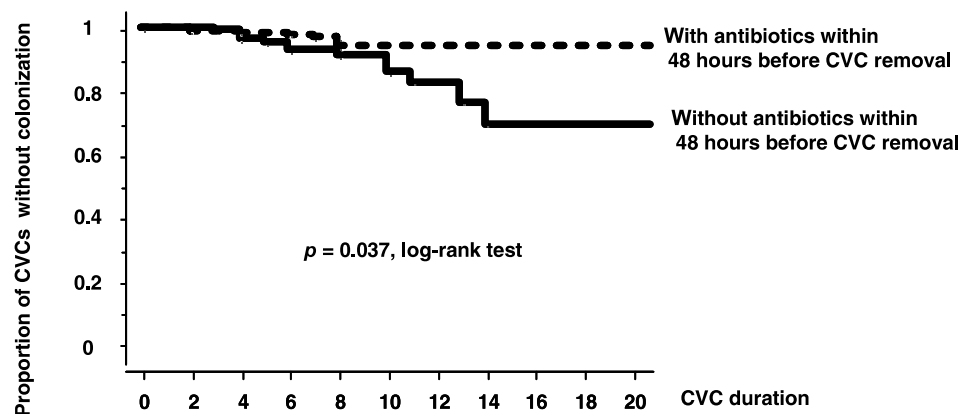
	0	2	4	6	8	10	12	14	16	18	20
No-antibiotics*	170	128	81	55	34	19	11	07	05	02	
Antibiotics*	302	214	141	70	30	15	08	05	03	02	

CVC, central venous catheter; *, within 48 hours before CVC removal

Table 3 Micro-organisms isolated from colonized central venous catheters according to the presence or absence of antibiotics administered within 48 h before catheter removal

Micro-organism	No antibiotics[a]	Antibiotics[a]
Number	16	8
Cocci Gram positive	9	5
Coagulase-negative staphylococci	7	4
Staphylococcus aureus	1	0
Enterococci	1	0
Other streptococci	0	1
Gram-negative bacteria	7	3
Enterobacter sp.	2	2
Pseudomonas aeruginosa	2	0
Escherichia coli	1	1
Proteus mirabilis	2	0
Yeasts	0	0

[a] Antibiotics administered within 48 h before catheter removal

does not take into account the results of CVC cultures. The mechanisms by which antibiotics inhibit bacterial growth are speculative and the methods we used are unable to clarify this point.

To circumvent the bias due to the relationship between antibiotic administration for a suspicion of CVC infection and the subsequent results of CVC cultures, the patients with suspected CVC infection were excluded from the study. This renders questionable the translation of the results to this subpopulation; however, similar results were observed in the secondary analysis combining both patients with CVC removed with and without a suspicion of CVC infection suggesting that our results are extrapolated to all CVC removed when the quantitative culture is used to define CVC colonization.

We are aware that the present study has limitations. Firstly, the patients were not randomized to have antibiotics at removal, but conducting such an ideal study would not have been clinically feasible. Secondly, the inclusion in the study of the patients with CVC removal because of death could represent another potential bias in the interpretation of the results, since it would have been difficult to firmly rule out that CVC removal in this setting was unrelated to a suspicion of CVC infection; however, after excluding the CVCs removed because of death of the patients, we found similar results concerning the negative impact of antibiotics at removal on the occurrence of CVC colonization. Thirdly, we did not systematically record the indication for antibiotic treatment and the date of antibiotic introduction. Interestingly, among the patients receiving antibiotics at CVC removal, the frequency of CVC colonization was not different between the 145 whose antibiotics at removal had been administered throughout the catheterization period and the 159 whose antibiotics at removal had been introduced during catheterization. Fourthly, we took into account in the analysis only the antibiotics administered within 48 h before CVC removal. We cannot exclude that in some cases antibiotics previously administered but with a very long plasmatic half-life may have been present in the patient and therefore had an impact on the results of the quantitative CVC tip cultures.

Conclusion

In studies using the CVC quantitative culture tip to define CVC colonization, antibiotics at removal should be taken into account either when comparing the results of CVC colonization as benchmarks for quality management or as a surrogate of CVC infection for the evaluation of new preventive strategies in the field of CVC infection.

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