

Significance of the isolation of *Staphylococcus aureus* from a central venous catheter tip in the absence of concomitant bacteremia: a clinical approach

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Abstract The optimal approach following the isolation of *Staphylococcus aureus* from an intravascular catheter tip in the absence of concomitant bacteremia remains unclear. We aimed to determine the rate of delayed complications in these patients. We performed a retrospective observational study (during the period 2002–2012) including patients with a catheter tip culture yielding *S. aureus*. Patients were followed up for ≥ 6 months. The primary endpoint was the occurrence of delayed staphylococcal complications (either bacteremia and/or metastatic distant infections). A total of 113 patients were included (75 % male, median age 61 years): 46 and 67 with negative and positive blood cultures, respectively. We found a lower rate of delayed staphylococcal complications in cases with no bacteremia within 48 h since catheter removal than in cases of confirmed *S. aureus* catheter-related bacteremia (0.0 % vs. 25.4 %; p -value < 0.001). In the group without bacteremia, there was a subgroup of 15 patients (32.6 %) who did not receive antimicrobial treatment. Again, delayed complications occurred less commonly in this subgroup of patients without bacteremia (0.0 % vs. 25.4 %; p -

value = 0.033). In contrast to patients with *S. aureus* catheter-related bacteremia, no delayed infectious complications were observed in patients with an isolated catheter tip culture yielding *S. aureus* and negative blood cultures within 48 h of catheter removal. Futures studies are needed to assess if the therapeutic approach could be different for this group of patients.

Introduction

As opposed to *Staphylococcus aureus* catheter-related bacteremia (CRB), a situation in which the indication for at least 14 days of antibiotic therapy is well established, the appropriate attitude following the isolation of *S. aureus* from a central venous catheter (CVC) tip culture in the absence of concomitant bacteremia remains uncertain [1]. This clinical scenario has been acknowledged as an unresolved issue in current guidelines of catheter-related infections [1]. Among other concerns, the wide range of time frames arbitrarily selected for establishing that the “simultaneous” blood cultures (BCs) drawn at the time of CVC removal were negative—a critical point in order to evaluate the clinical significance of this scenario—limits the interpretation of previous studies [2–6]. We propose a more pragmatic, bedside approach by comparing the rate of complications after the isolation of *S. aureus* from a CVC tip culture with negative BCs obtained within a 48-h interval to that observed in episodes of *S. aureus* CRB.

Materials and methods

Study design and setting

The study was developed in the University Hospital “12 de Octubre” (Madrid, Spain) and was approved by the local

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Ethics Committee. We retrospectively reviewed all CVC and peripherally inserted central catheter (PICC) tip cultures positive for *S. aureus* between January 2002 and December 2012 identified in the computerized database of the Department of Microbiology. This database was used to determine whether simultaneous BCs (i.e., drawn from 48 h before to 48 h after CVC removal) had also been obtained. Patients' charts were reviewed to assess the development of infection-related complications (i.e., isolation of *S. aureus* from follow-up BCs or other sterile sites) during the following 6 months.

The decision to remove the CVC and to order tip culture had to be made due to the clinical suspicion of CRB based on the presence of fever and/or signs of infection at the catheter exit site (induration, erythema, warmth, pain, tenderness, and/or purulent exudate) [1]. Patients in which the CVC was removed in the absence of a clinically suspected CRB or in which no BCs were drawn within 48 h since the catheter withdrawal were excluded. The decision to initiate antibiotic therapy was made by the attending clinician.

Study groups

Patients with a CVC tip culture positive for *S. aureus* were classified in two groups according to the results of BCs drawn within 48 h since the catheter removal. Group 1 included those in which the BCs yielded *S. aureus* with identical antimicrobial susceptibility profile and no alternative source of infection, thus fulfilling the diagnostic criteria for CRB [1]. Group 2 included those patients in which the BCs obtained within the above-mentioned 48-h interval were negative for *S. aureus*.

Study endpoint

The study endpoint was a composite of delayed bacteremia (i.e., detected after the first 48 h from CVC removal) and/or other complications that could be attributed to the hematogenous spread of the *S. aureus* strain isolated in the CVC tip (identical antimicrobial susceptibility profile). The latter diagnosis included septic arthritis, osteomyelitis, soft tissue abscess, infective endocarditis, septic thrombophlebitis, septic pulmonary embolism, or septic endophthalmitis.

Microbiological procedures and study definitions

Catheters tips were processed using the roll-plate semiquantitative method described by Maki et al. [7] and results were considered positive when the culture yielded ≥ 15 colony-forming units (CFUs). The prognosis of the underlying disease was classified according to the McCabe–Jackson score [8]. Immunosuppressive therapy was defined as the use of corticosteroids (prednisone ≥ 5 mg daily or equivalent dose for >2 weeks) or other immunosuppressive drugs in the previous 6 months. Antibiotic therapy was deemed appropriate if

the prescription was initiated within the first 48 h after CVC removal, the regimen administered was in vitro active against the isolated *S. aureus*, and it was administered during ≥ 72 h.

Statistical analysis

Quantitative data are shown as the mean \pm standard deviation (SD) or the median with interquartile ranges (IQRs). Qualitative variables are expressed as absolute and relative frequencies. Categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate, whereas the Mann–Whitney *U*-test was applied for continuous variables. All the significance tests were two-tailed. Statistical analysis was performed using SPSS, version 15.0 (Statistical Package for the Social Sciences, Inc., Chicago, IL).

Results

We identified 137 patients with a CVC tip culture positive for *S. aureus* during the study period. Twenty-four of them (17.5 %) were excluded because no BCs had been obtained within 48 h since catheter removal, resulting in 113 evaluable patients: 67 (59.3 %) had concomitant bacteremia and, therefore, were diagnosed with *S. aureus* CRB (Group 1); the remaining 46 patients (40.7 %) had either sterile BCs ($n = 38$) or a concomitant bacteremia due to a microorganism other than *S. aureus* (coagulase-negative staphylococci in five cases, Enterobacteriaceae in two cases and *Enterococcus* spp. in one case) (Group 2). Their baseline characteristics, clinical and microbiological data, and outcome are summarized in Table 1.

The study endpoint was significantly more frequent in Group 1 than in Group 2 (25.4 % [17/67] vs. 0.0 % [0/46]; p -value < 0.001). *Staphylococcus aureus* bacteremia beyond the first 48 h from CVC removal occurred in 14 patients and hematogenous dissemination in six (including septic arthritis [four cases], septic pulmonary embolism [two cases], and infective endocarditis, cerebral abscess, splenic abscess, and septic endophthalmitis [one case each]).

Antimicrobial treatment was more commonly administered in patients within Group 1 than Group 2 (85.1 % [57/67] vs. 67.4 % [31/46]; p -value = 0.026). Since the receipt of antistaphylococcal therapy could at least partially justify the absence of complications in Group 2, we performed a further comparison restricted to 15 patients (32.6 %) that did not receive antistaphylococcal antimicrobial treatment following CVC removal. This subgroup was comparable in terms of baseline and clinical and microbiological characteristics to those patients in Group 2 in which antistaphylococcal antibiotic therapy was administered, except for a non-significant trend towards a lesser frequency of immunosuppressant therapy (0 % vs. 16.1 %; p -value = 0.157), and a lower frequency

Table 1 Patients with a CVC tip culture positive for *Staphylococcus aureus*

	All patients (<i>n</i> = 113)	Group 1 (BC ^g positive for <i>S. aureus</i>) (<i>n</i> = 67)	Group 2 (BC ^g negative for <i>S. aureus</i>) (<i>n</i> = 46)	<i>p</i> -Value ^a	Patients in Group 2 that received antibiotic therapy ^b (<i>n</i> = 31)	Patients in Group 2 that did not receive antibiotic therapy ^b (<i>n</i> = 15)	<i>p</i> -Value ^c
Baseline characteristics							
Male gender (<i>n</i> [%])	85 (75.2)	54 (80.6)	29 (63.0)	0.038	19 (61.3)	10 (66.7)	0.199
Age, years (median [IQR])	61 (49–73)	62 (51–73)	60 (45–73)	0.335	63 (41–76)	55 (49–65)	0.252
Diabetes (<i>n</i> [%])	27 (23.9)	13 (19.4)	14 (30.4)	0.187	7 (22.6)	7 (46.7)	0.034
Chronic renal failure (<i>n</i> [%])	31 (27.4)	23 (34.3)	8 (17.4)	0.047	5 (16.1)	3 (20.0)	0.224
Hemodialysis (<i>n</i> [%])	12 (10.6)	8 (11.9)	4 (8.7)	0.759	1 (3.2)	3 (20.0)	0.414
Solid organ malignancy (<i>n</i> [%])	51 (45.1)	33 (49.2)	19 (41.3)	0.446	12 (38.7)	7 (46.7)	0.856
Hematologic malignancy (<i>n</i> [%])	6 (5.3)	2 (2.9)	4 (8.7)	0.222	3 (9.7)	1 (6.7)	0.459
McCabe–Jackson score 1 (<i>n</i> [%]) ^d	23 (20.7)	19 (29.2)	4 (8.7)	0.009	2 (6.5)	2 (13.3)	0.331
Neutropenia (<0.5 × 10 ⁹ /L) (<i>n</i> [%])	3 (2.6)	2 (2.9)	1 (2.2)	1.000	0 (0.0)	1 (7.7)	0.435
HIV infection (<i>n</i> [%])	1 (0.9)	0 (0.0)	1 (2.2)	0.407	1 (3.2)	0 (0.0)	–
Immunosuppressive therapy (<i>n</i> [%])	12 (10.6)	7 (10.4)	5 (10.9)	1.000	5 (16.1)	0 (0.0)	0.340
Solid organ transplantation (<i>n</i> [%])	6 (5.3)	5 (7.5)	1 (2.2)	0.398	1 (3.2)	0 (0.0)	0.577
Prosthetic device (<i>n</i> [%])	13 (11.5)	9 (13.4)	4 (8.7)	0.555	1 (3.2)	3 (20.0)	0.686
Clinical and microbiological characteristics							
Methicillin-resistant <i>S. aureus</i> (<i>n</i> [%])	31 (27.4)	18 (26.8)	13 (28.3)	1.000	10 (32.3)	3 (20.0)	0.749
PICC (<i>n</i> [%])	11 (9.7)	6 (8.9)	5 (10.9)	0.774	4 (12.9)	1 (6.7)	1.000
Leukocyte count (× 10 ⁹ /L) (median [IQR])	10.7 (7.6–13.9)	9.6 (7.3–13.1)	12.7 (9.3–17.4)	0.713	12.8 (8.6–18.7)	11.3 (10.0–15.0)	0.235
Temperature ≥38.0 °C (<i>n</i> [%])	100 (88.5)	60 (89.6)	40 (86.9)	0.671	29 (93.5)	11 (73.3)	0.110
Local signs of thrombophlebitis (<i>n</i> [%])	39 (34.5)	29 (43.3)	10 (21.7)	0.018	8 (26.7%)	1 (6.7)	0.008
Treatment and endpoint							
Appropriate antibiotic therapy (<i>n</i> [%])	84 (74.3)	57 (85.1) ^f	31 (67.4)	0.026	31 (100)	0 (0.0)	–
Delayed <i>S. aureus</i> bacteremia and/ or hematogenous dissemination (<i>n</i> [%])	17 (15.0)	17 (25.4)	0 (0.0)	<0.001	0 (0.0)	0 (0.0)	0.033
Delayed <i>S. aureus</i> bacteremia (<i>n</i> [%])	14 (12.5)	14 (20.9)	0 (0.0)	0.001	0 (0.0)	0 (0.0)	0.062
Delayed hematogenous dissemination (<i>n</i> [%]) ^e	6 (5.3)	6 (9.0)	0 (0.0)	0.080	0 (0.0)	0 (0.0)	0.334
Death by any cause 6 months after removal of the catheter	21 (18.6)	14 (20.9)	7 (15.2)	0.446	6 (19.4)	1 (6.7)	0.283

CVC Central venous catheter; HIV human immunodeficiency virus; IQR interquartile range; PICC peripherally inserted central catheter; SD standard deviation

^a *p*-Values refer to the comparison between Group 1 and Group 2

^b Patients in Group 2 that did not receive appropriate antibiotic therapy (i.e., antistaphylococcal therapy within the first 48 h after CVC removal)

^c *p*-Values refer to the comparison between Group 1 and those patients in Group 2 that did not receive antibiotic therapy

^d Patients with a disease leading to death in a few months

^e Three patients with delayed hematogenous dissemination did not present with delayed staphylococcal bacteremia

^f Nine patients did not receive antibiotics within the first 48 h after CVC removal; one case due to methicillin-resistant *S. aureus* was empirically treated with piperacillin–tazobactam

^g Blood cultures taken within 48 h since catheter removal

of fever (73.3 % vs. 93.5 %; *p*-value = 0.078) and local inflammatory signs (6.7 % vs. 25.8 %; *p*-value = 0.235) (Table 1). Again, the study endpoint occurred more commonly in Group 1 than in this subgroup of patients (25.4 % [17/67] vs. 0.0 % [0/15]; *p*-value = 0.033) (Table 1).

Among cases in whom no BCs had been taken within 48 h since catheter removal (*n* = 26), there were 17 (65.3 %) patients who were febrile at the moment of catheter removal and 7 (34.7 %) that were not. Delayed complications happened in 4 patients (16.7 %), all of them belonging to the group of febrile patients (4/17 [23.5 %]).

Discussion

Our experience emphasizes the absolute necessity of always drawing BCs in any patient with suspected CRB. The need to draw BCs in this situation is emphasized by the 23.5 % rate of complications among febrile patients of our study with positive culture of the CVC tip in whom BCs around the CVC removal were not taken. This approach was retrospectively considered inadequate and this group was not analyzed more in depth. In contrast, the culture of an intravascular catheter tip in the absence of clinical suspicion of CRB is not

recommended by guidelines [1] and, therefore, such cases were also excluded from the analysis in our study.

Our results should be only extrapolated to patients with clinical suspicion of CRB. In our study, no patient with a CVC tip culture yielding *S. aureus* and BCs (drawn within 48 h since the catheter removal) negative for this microorganism had subsequent staphylococcal complications during the 6-month follow-up. This observation also applies for the subgroup of patients that did not receive antistaphylococcal antibiotic therapy following the CVC removal. These findings are in contrast to those of the control cohort of patients with confirmed CRB due to *S. aureus* and who presented a significantly higher rate of delayed complications.

The decision to withdraw the CVC was made in all the analyzed patients due to the concurrent presence of symptoms or signs suggestive of infection (i.e., fever or inflammatory signs at the catheter exit site). As referred, the results of the BC drawn at the time of catheter withdrawal [1] will have a deep impact on the therapeutic management and on the risk of further complications. Indeed, the isolation of *S. aureus* in the bloodstream should lead to a complete course of antistaphylococcal therapy. According to our results, the approach to patients in which this microorganism is not recovered from BCs taken at the time of catheter removal cannot be directly extrapolated from those with *S. aureus* CRB. The beginning of empirical antimicrobial therapy while awaiting the results of BCs is mandatory, but our findings challenge the pertinence of considering both groups as equivalent when deciding on the definitive treatment.

Other authors have previously addressed this issue [2–6, 9]. However, most studies were designed from a microbiological rather than clinical perspective. For instance, the isolation of *S. aureus* in BCs obtained as soon as the second day after CVC removal was considered as a “delayed” complication in the studies by Ekkelenkamp et al. [2], Zafar et al. [6], and Hetem et al. [3]. Such a brief interval would suggest more a postponed diagnosis of CRB than a genuine, late complication derived from the tip colonization. In our opinion, the 48-h threshold used in the present study is more realistic. On the other hand, the analyses by Ruhe and Menon [5] and Muñoz et al. [4] included patients lacking concomitant BCs. The study by Park et al. [9] has a design similar to ours, although these authors grouped infections due to different bacteria, did not take into account the occurrence of late pyogenic complications, and did not include a comparative group. Two-thirds of the 58 patients with *S. aureus* in the CVC tip culture were given antibiotic therapy, and only two of them developed subsequent bacteremia (at 3 and 9 days after CVC removal, respectively) [9].

The major limitation of our study is the low number of patients analyzed, thus diminishing the statistical power to detect the occurrence of late complications. Moreover, the

administration of antistaphylococcal antibiotic therapy in Group 2 was not random but based on clinician’s criteria, and, therefore, remains susceptible to confounding bias.

In conclusion, we have analyzed a cohort of patients in which the CVC was removed due to clinical suspicion of infection and whose tip culture yielded *S. aureus* in the absence of concomitant bacteremia. Our findings provide further evidence that such a scenario should be distinguished from that of *S. aureus* CRB, as the rate of delayed attributable complications was negligible. Prospective studies are necessary to assess if both groups deserve different therapeutic approaches.

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Compliance with ethical standards

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Conflict of interest The authors declare not to have any conflict of interest.

Ethical approval and informed consent This is an observational retrospective study. Informed consent was not needed.

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