Intensive Care Med (2004) 30:1073–1080
DOI 10.1007/s00134-004-2212-x

ORIGINAL

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Watchful waiting versus immediate catheter removal in ICU patients with suspected catheter-related infection: a randomized trial

Received: 10 September 2003
Accepted: 29 January 2004
Published online: 4 March 2004

An editorial regarding this article can be found in the same issue (http://dx.doi.org/10.1007/s00134-004-2213-9)

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Abstract *Objective:* To find a subset of patients with suspected central venous catheter (CVC)-related infection (CRI) in whom CVC removal is not needed. *Design:* Randomized controlled trial. *Setting:* Thirty-three-bed ICU. *Patients and participants:* One hundred and forty four patients with suspected CRI in which a change of CVCs was planned were evaluated for inclusion. *Interventions:* Hemodynamically stable patients without proven bacteremia, no insertion site infection, and no intravascular foreign body were randomized to a standard-of-care group (SOC, all CVCs were changed as planned) or a watchful waiting group (WW, CVCs changed when bacteremia was subsequently confirmed or hemodynamic instability occurred). *Measurement and results:* Study groups were compared for incidence of CVC-related bloodstream infection (CR-BSI), resolution of fever, C-reactive protein, SOFA score, duration of ICU stay, and mortality. Of 144 patients with suspected CRI, 80 patients met exclusion criteria. Sixty-four were randomized. Forty-seven of 80 excluded patients were shown to be bacteremic, 20 (25%) of whom had a CR-BSI. Five of 64 (8%) included patients had a CR-BSI during their subsequent ICU stay (two in SOC and three in WW group). All 38 CVCs were changed in the SOC group versus 16 of 42 in the WW group (62% reduction, $P<0.01$). Resolution of fever, C-reactive protein, SOFA score, duration of ICU stay, and ICU mortality did not differ between SOC and WW group ($P>0.1$ for all). *Conclusions:* The use of a simple clinical algorithm permits a substantial decrease in the number of unnecessarily removed CVCs without increased morbidity.

Introduction

Clinicians working in the ICU are familiar with the everyday situation of unnecessary catheter removal for suspected catheter-related infection (CRI). The proportion of catheters removed for suspected CRI that, after the results of catheter-tip and blood cultures become available, are shown to be unnecessary varies substantially but can be as high as 91% and is probably highest in the ICU patient because unexplained fever is very frequent in the critically ill [1, 2, 3]. As Table 1 illustrates, the problem of unnecessary catheter removals seems universal and substantial. Unnecessary catheter replacement is not only a costly and time-consuming problem but every replacement increases the risk of iatrogenic complications [4].

A substantial number of catheter removals in the ICU are carried out due to unexplained signs of sepsis (mostly fever) and not for proven bacteremia of an unknown source. Hence, blood culture-dependent techniques, such as a difference in time-to-positivity and quantitative blood cultures taken through the catheter and through a peripheral puncture site, are of limited benefit when trying to prevent unnecessary catheter removal. Furthermore, the value of these blood culture-dependent techniques has been accurately validated mostly for patients with long-term CVCs and outside the ICU setting. Moreover, a

Table 1 Percentage of confirmed CRBSI (after tip culture became available) of all catheters removed for suspected CRBSI

Catheters Removed	Confirmed CRBSI	%	Reference
n=68	*n*=6	9%	[1]
n=85	*n*=19	22%	[25]
n=72	*n*=21	29%	[26]
n=50	*n*=25	50%	[27]
n=27	*n*=14	52%	[28]

significant number of patients in the ICU are on antibiotics at the time of a suspected CRI. This probably compromises blood culture-dependent techniques even further [3]. The Infectious Diseases Society of America (IDSA) guidelines for the diagnosis and treatment of CRI suggest that non-tunneled central venous catheters should not be routinely removed in patients with unexplained fever and mild to moderate disease [5]. To the best of our knowledge, no prospective clinical trial has specifically tried to explore this statement. The D-III coding (expert opinion) of this IDSA recommendation illustrates this gap in our knowledge of catheter infection.

It is clear that a better way to prevent unnecessary catheter removals would be welcome. In this study we tried to validate a clinical protocol in which central venous catheter (CVC) removal was postponed in stable patients at a presumed lower risk for catheter-related infection and clinical evolution was followed from day to day. We hoped to demonstrate that with this strategy unnecessary catheter removals could be restricted to a smaller group of patients with a higher risk of catheter-related bloodstream infection.

Methods

Inclusion/exclusion criteria

All consecutive patients with one or more short-term CVCs in place who had been electively inserted in our hospital prior to or during the ICU stay were eligible for the study whenever the treating physician planned removal of the CVC for suspected CRI. The study was conducted in a 17-bed medical ICU and a 16-bed surgical ICU of the University Hospital Gasthuisberg, Leuven, Belgium during 21 consecutive months starting 1 July 2001. In mutual agreement with the ICU physicians responsible for each department and the researchers of the study, the following exclusion criteria were chosen: 1) neutropenic patients (<500/mm^3), patients who had undergone organ transplantation during the preceding 3 months, and patients with an intravascular foreign body (e.g., pace-maker, prosthetic heart valve). These patients were excluded because of a presumed higher risk of complications when a CRI is missed; 2) haemodynamically unstable patient (with sepsis as one of the possible explanations) defined as shown in Table 2. The definitions were adapted from the definitions of severe sepsis and septic shock according to the American College of Chest Physicians [6]. These patients were excluded because the presence of severe sepsis and septic shock indicate an increased risk for morbidity and mortality; 3) suppuration or frank erythema/induration at the insertion site of the CVC. This risk factor was chosen because, although not well validated, these symptoms are thought to be predictive of catheter-related infection; 4) patients with bacteremia defined as a blood culture growing yeasts, *S. aureus*, *S. epidermidis* or gram-negative rods without a convincing other source of infection with the same germ. For typical skin flora (coagulase-negative staphylococci, *Corynebacterium* sp., *Proprionibacterium* sp.) at least two blood cultures taken at different time points were required. This risk factor was chosen because no reliable and well-validated method for the diagnosis of catheter-related bacteremia in ICU patients without removal of the catheter is available at this time; and 5) patients with a do-not-resuscitate code and patients previously included in this study were also excluded.

Arterial catheter removal was not necessary for study entry and was done at the discretion of the treating physician. In a patient with a dialysis catheter in place, removal of both the central venous catheter used for administration of drugs and fluids and the dialysis catheter had to be planned. The study was approved by the institutional review board, which waived the need for informed consent.

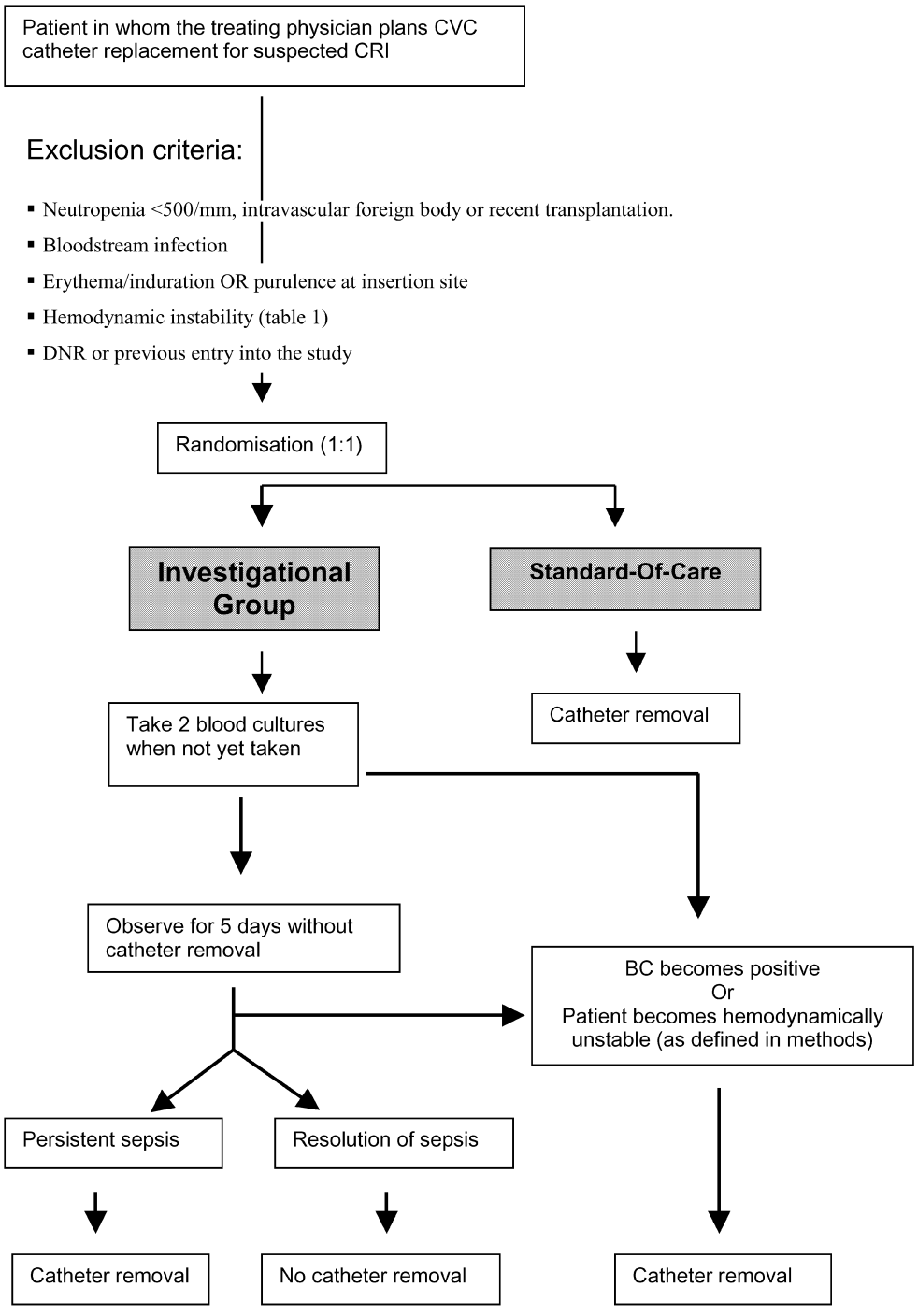
Randomization and further study design

Patients were randomized into two groups (Fig. 1). Randomization of patients was done on a 1:1 basis just before the planned catheter removal. Ten blocks of ten were used with a computer-generated random sequence of the numbers 1 through 10 for each block. An odd number meant randomization to the investigational group (from now on referred to as watchful waiting group). Patient randomization was performed 24 h a day by one investigator on call and using the printout of the randomization blocks, which were concealed under a non-transparent scratchable layer. For every subsequent randomization the non-transparent layer covering the subsequent allocation was removed. The investigator on call was systematically contacted for every patient in whom a catheter removal for suspected catheter-related infection was planned. In this way a reliable registration of all patients fulfilling exclusion criteria was also possible as this was anticipated to be crucial to evaluate the external validity of the study results. For every patient evaluated for study participation baseline data were registered [the most important of which were previous antibiotic use, parenteral or enteral nutrition, methicillin-resistant *S. aureus* (MRSA) carriage, number and insertion place and date of intravascular catheters, Acute physiology and Chronic Health Evaluation II score (APACHE II) at admission, maximum temperature during previous 48 h, and reason for suspicion of CRI].

Table 2 Definitions of clinically unstable patient as exclusion criterium

1. Systolic blood pressure <90 mmhg or reduction of 40 mmhg or more from baseline in the absence of other causes for hypotension. Mean BP <60 mmhg
2. Start of dopamine or dobutamine necessary to maintain adequate blood pressure OR increase of dose with 5 μg·kg·min over the preceding 12 h
3. Start of norepinephrine to maintain adequate blood pressure OR increase of dose with 0.25 µg·kg·min over the preceding 12 h

Fig. 1 Study design



The first group consisted of the standard-of-care group (SOC group) in which all patients underwent catheter removal as was planned by the treating physician. In patients randomized to the watchful waiting group, the catheter was removed only in the following situations: 1) patient who had become hemodynamically unstable after inclusion as defined in Table 2, but with the difference that the increase in administration of inotropics that defined hemodynamic instability was a comparison with the day of inclusion and not the preceding 12 h; 2) patients who developed bacteremia as defined above; and 3) after 5 days of observation the treating physician was allowed to change CVCs whenever in his/her opinion this was still indicated. In the watchful waiting group peripheral blood cultures (or blood cultures taken through the arterial catheter) were systematically repeated within 48 h after inclusion whenever fever persisted.

The number and degree of organ dysfunctions was scored daily using the SOFA (sequential organ failure assessment) score for the 10 days following randomization for all patients not discharged

before day 10 after randomization [7, 8]. Every effort was made to register a SOFA score at day 5 and day 10 after randomization in patients discharged from the ICU before day 10. Because arterial blood gas analysis is not routinely done after discharge from the ICU, the last SOFA score for respiration that was available was used in further assessments of SOFA score (last observation carried forward) in patients who still needed supplemental oxygen but in whom no further arterial blood gas analysis was performed after discharge from the ICU. For patients discharged and in no apparent distress without supplemental oxygen, a respiration SOFA score of 0 was scored. During the first 10 days after inclusion, antibiotic use, temperature, leukocyte count, and C-reactive protein levels were also registered daily. The duration of 10 days of observation was chosen because observing the patient for much longer (e.g., until discharge) would decrease the possibility of finding a difference in the evolution of the signs and symptoms of sepsis between groups as it is not uncommon to have more than one episode of fever or sepsis during the entire ICU hospitalization.

All CVCs that were in place at the time of randomization were cultured when removed at any time using the sonication technique [9] and reason for removal (bacteremia, unstable patient, suspected CRI persisting on day 5, unnecessary catheter, patient died, malfunction, other) was noted.

Definitions of CRI

Definitions of CRI are as follows: catheters were classified as associated with catheter-related bloodstream infection (CR-BSI), or as being colonized. CR-BSI was classified as a positive quantitative catheter-tip culture (>103 cfu/catheter) and isolation of the same phenotypic micro-organism from the catheter and peripheral venous blood (at least one positive peripheral-blood culture, except for coagulase-negative staphylococci, for which two positive blood cultures were required). Catheter-related infection was classified as probable CR-BSI when all the criteria for definite CR-BSI were fulfilled, but only hub-blood cultures were available for analysis because peripheral blood sampling was impossible. Catheter-related infection was also classified as probable CR-BSI when all the criteria for definite CR-BSI were fulfilled but the catheter-tip culture yielded a bacterial count of less than 103 cfu/catheter while patients were receiving antibiotics active against the micro-organisms recovered from the catheter. When the number of CR-BSI were analyzed, definite and probable CR-BSI were taken together. Significant colonization of the catheter was defined as a quantitative catheter-tip culture >103 cfu/catheter.

Study endpoints

The study was designed to obtain better knowledge regarding when catheter removal is unnecessary in ICU patients. As we used the exclusion criteria mentioned above, we wanted to focus on the patient with an uncertain indication for catheter removal. Incidences of CR-BSI in the excluded versus the included patients were compared. To measure the effect of immediate catheter change in the SOC-group versus the watchful waiting group the evolution of fever, C-reactive protein, leukocyte count, SOFA score, duration of hospitalization, and outcome were compared between groups. In addition, the number of CVCs removed on day 10 after inclusion (when in the watchful waiting group the treating physician had been allowed to change CVCs for five consecutive days) was compared between study groups to estimate the number of catheter changes that can be prevented when the watchful waiting policy is followed.

Statistical analysis

A two-tailed Student's *t*-test was used for the comparison of means of normally distributed data and a Mann Whitney test to compare values that were not normally distributed. Chi-square test (Fisher's exact test was appropriate) was used for analysis of data in 2×2 contingency table.

Results

In 144 patients the treating physician planned catheter removal for suspected catheter-related infection. The clinical reasons for catheter removal were (not mutually exclusive): fever in 68%, increase in inflammatory parameters (C-reactive protein, white blood cell count) in 78%, and confirmed bloodstream infection in 23%. Eighty of these 144 evaluated patients had one or more exclusion criteria. The reasons for excluding these patients are given in Table 3. Forty-seven of these 80 patients suffered from a bloodstream infection (36 of which were already diagnosed at the time of exclusion). Twenty of these 47 (43%) were catheter-related bloodstream infections (15 definite, five probable), Fig. 2.

Sixty-four patients were included into the study (32 in each group). Baseline characteristics of patients from both groups were comparable and are given in Table 4. According to protocol, all 32 patients had their CVCs removed in the SOC-group. In 12 of the 32 patients (37%) randomized to the watchful waiting group, all the CVCs in place (16 of 42) were subsequently removed between day 0 and 10 after inclusion (32/32 versus 12/32, $P<0.01$). Catheters were removed because of a diagnosis of bloodstream infection in four patients, for sepsis persisting 5 days or more after inclusion in five others, for new hemodynamic instability, catheter malfunction, and protocol violation (no predefined reason) in one patient each. In two of the patients randomized to the SOC-group, a catheter-related bloodstream infection was diagnosed (all definite). In three of the patients in the watchful waiting group a catheter-related bloodstream infection was diagnosed (all definite), two on day 1 after inclusion and one on day 14 after inclusion. Only five of the 64 (8%, CI 3–

Table 3 Reasons for excluding 80 of 144 evaluated patients (*HD* haemodynamically)

Reason for exclusion	*n*
Bloodstream infection[a]	36
HD unstable[b]	31
Inflamed/purulent insertion site	18
High risk patient[c]	12
Other[d]	4

[a] Confirmed bloostream infection as the trigger for catheter removal
[b] At time of evaluation as defined in Table 1
[c] Patient with intravascular foreign body in place (*n*=7), neutropenia (*n*=3) or recent solid organ transplantation (*n*=2)
[d] Patients that participated in the study previously

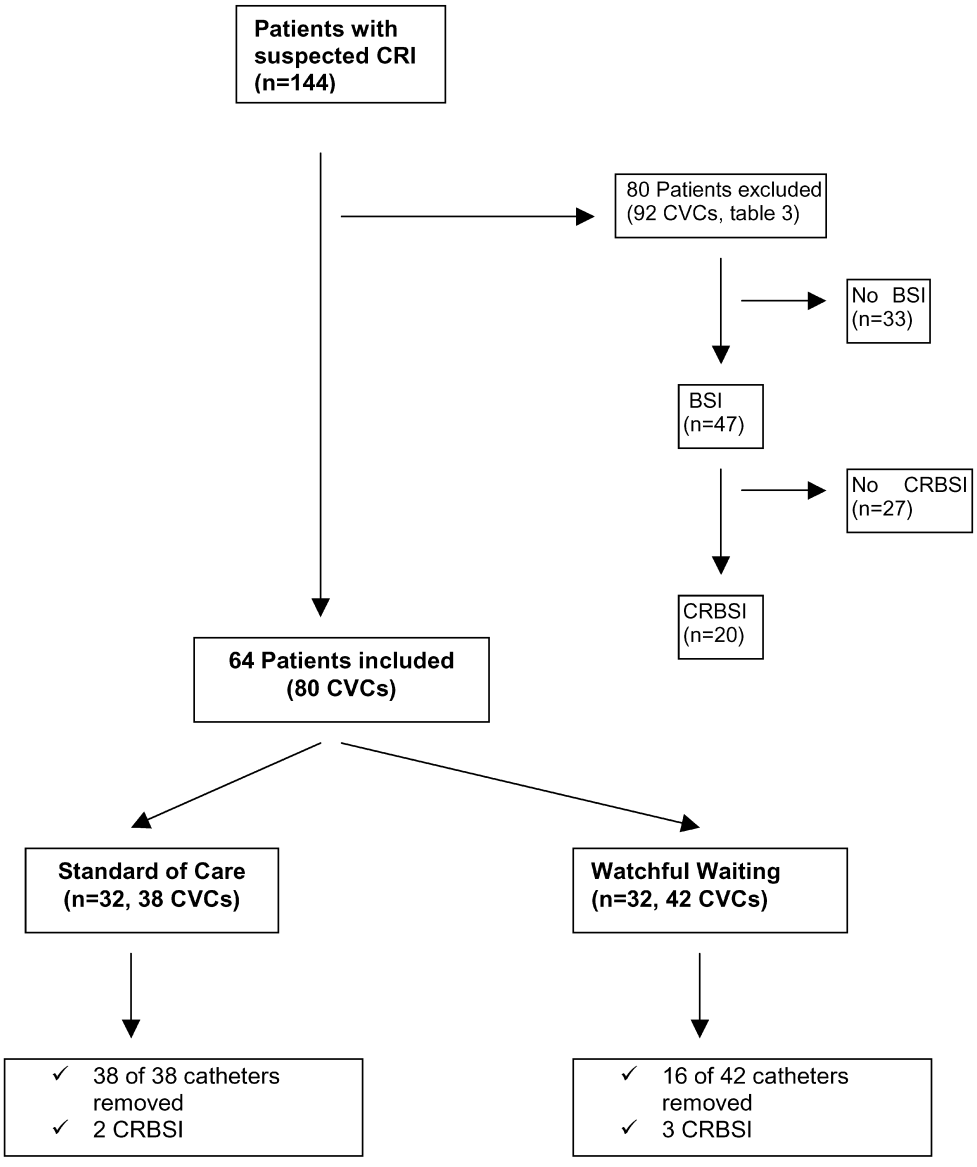


Fig. 2 Disposition of all patients evaluated for the study

17) patients included versus 20/80 (25%, CI 17–35) excluded patients had a catheter-related bloodstream infection (P=0.01). Resolution of fever, duration of hospitalization, and mortality did not differ between both groups (Table 5).

During the 10 days following inclusion antibiotic use was registered. In both groups 23 of the 32 patients were receiving antimicrobial treatment at the time of inclusion. A new antibiotic or antifungal agent was added during the 10 days following inclusion in 13 of 32 patients in the watchful waiting group and in 22 of 32 in the SOC-group (P=0.04). In addition, the total number of days that patients were receiving antibiotic treatment was not different between groups as there were 217 days (of 295 follow-up days or 74%) during which antibiotics were administered in the SOC-group versus 188 (of 251 follow-up days or 75%) in the watchful waiting group (P>0.2). These data clearly illustrate that the use of antibiotics did not increase in the watchful waiting group when compared with the SOC-group.

During the 20 months of the study the number of patients in whom the treating physician planned a catheter removal decreased significantly. During the first 10 months, a CRI was suspected in 85 patients and these patients were therefore evaluated for inclusion. This number decreased to 59 patients during the second half of the study, while the number of patients hospitalized during the first (n=704) and second (n=790) half of the study even increased slightly (85/704 versus 59/790, P=0.003).

Table 4 Baseline characteristics of randomized and excluded patients (*SOC* standard-of-care, *WW* watchful waiting, *APACHE* acute physiology and chronic health evaluation II, *SOFA* sequential organ failure assessment, *TPN* total parenteral nutrition)

Characteristic	SOC	WW	Excluded
Age (years)	56.6	61	59.7
APACHE II	20.2	20	20.3
SOFA	6.1	6.9	NA
Temperature (°C)	37.9	38.4	38.5
Sex (% males)	56%	65%	67%
% Medical ICU	75%	75%	71%
% Haemodialysis	22%	6%	22%
% TPN	75%	84%	82%

[a] Score at admission
[b] $P>0.2$ for all comparisons between the three groups except for the difference between SOC and WW ($P=0.02$) and excluded ($P<0.01$) temperature

Table 5 Outcome measures of randomized patients (*SOC* standard-of-care, *WW* watchful waiting, *CVC* central venous catheters, *CRBSI* catheter-related bloodstream infection, *T* temperature in degrees Celsius, *CRP* C-reactive protein, *SOFA* sequential organ failure assessment)

Measure	SOC	WW	
CVC changes[a]	38/38	16/42	$P<0.01$
CRBSI	2	3	$P>0.2$
Duration of Hosp.	42	34	$P>0.2$
ICU mortality	10/32	8/32	$P>0.2$
Temperature day 1	37.9	38.4	$P=0.02$
Day 5	37.6	37.6	$P>0.2$
Day 10	37.5	37.4	$P>0.2$
CRP (mg/l) day 1	128	155	$P>0.2$
Day 5	100	134	$P>0.2$
Day 10	85	104	$P=0.15$
SOFA score day 1	6.1	6.9	$P>0.2$
Day 5	5.4	6.2	$P>0.2$
Day 10	5.3	5.8	$P>0.2$

[a] Number of central venous catheters (including dialysis catheters) changed from day 1 to day 10 after inclusion

Discussion

Establishing a diagnosis of catheter-related infection based only on clinical findings is extremely difficult. This is especially true in the intensive care setting where the management of patients with unexplained new fever or sepsis is an everyday clinical problem. A broad spectrum of infectious and non-infectious etiologies can be responsible [2]. Therefore a catheter-tip culture and blood cultures are used to prove that the catheter is the source of infection. However, when the clinician makes a decision to remove the catheter purely on clinical grounds, he/she often is wrong. This is not only a costly and time-consuming problem (in the USA the estimated cost of one central venous catheter replacement was 583 dollars in 1993 [10]) but with every catheter replacement comes the risk of iatrogenic complications.

In this clinical study we tried to validate a clinical protocol, developed in agreement with the treating ICU physicians and the infectious diseases physicians, aimed at limiting unnecessary catheter removals for suspected CRI. We hoped to show that in the watchful waiting group fewer catheters than in the SOC-group would be removed with comparable evolution of signs of sepsis. In the watchful waiting group catheters were only changed when the patient became hemodynamically unstable, bacteremic or when after 5 days of observation the treating physician considered that changing the catheters would still be of diagnostic or therapeutic use. This policy led to a 62% reduction in unnecessary catheter removals when compared with the SOC-group. This more conservative approach did not influence the time to defervescence, the total amount of antibiotics used, the duration of ICU hospitalization or ICU mortality. As we hoped, in those patients excluded from the study the incidence of catheter-related bloodstream infection was significantly higher than in the randomized patients (5/64 versus 20/80, $P=0.01$) but still only 25%.

Our study has limitations. We realize that the exclusion criteria we used were not always based on hard clinical endpoint studies. The exclusion criteria were chosen during several round-table discussions with the treating intensive care physicians. This was the only way to organize a study with which all collaborating physicians felt at ease and agreed to participate. Implementation of a study which included, for instance, neutropenic patients, or patients with a prosthetic heart valve, would have been very difficult even if patients with proven bacteremia were excluded. In these patients the consequences of a missed catheter-related infection was thought to be more important than the risk of unnecessary catheter removal.

Until recently, inflammation at the insertion site was considered to be an indicator of catheter-related infection. A meticulously performed recent study in critically ill patients argues against routinely removing catheters with modest inflammation at the insertion site when no other signs of catheter-related infection are apparent [11]. Several risk factors for catheter infection have been mentioned in the literature but were not used as exclusion criteria for the study because they lack specificity for clinical use. These are sex [12], previous or current antibiotic use [12], parenteral nutrition (only conclusive data in cancer patients) [13], type of dressing [14, 15] duration of catheterization [13, 16, 17, 18], and insertion site (higher risk for jugular or femoral vein [1, 12, 16, 17, 18, 19, 20, 21].

A second limitation of our study is the lack of power to show statistical non-inferiority in hard clinical outcome measures (e.g., mortality) between the two study groups. Until now, however, the attributable mortality of CR-BSI remains unclear, as some studies did not show any attributable mortality [22, 23]. A 10% attributable mor-

tality might be a good estimate [27]. It is therefore unlikely that a study that is adequately powered for mortality will ever be performed because to show non-inferiority in comparison with a 10% attributable mortality, sample sizes would have to be extremely large.) We thus decided to use parameters of infection as surrogate endpoints. The resolution of signs and symptoms of sepsis (fever, C-reactive protein, SOFA score) was comparable between both groups and although baseline temperature was higher in the watchful waiting group than in the SOC-group (38.4 °C versus 37.9 °C, P=0.02), 10 days after inclusion the temperature had decreased to identical values (37.5 °C versus 37.4 °C).

Finally, because only 64 of 144 evaluated patients could be randomized, the observed 62% reduction of catheters removed in the watchful waiting versus the SOC-group is only valid for 45% of all patients. Some of the exclusions were for statistical reasons only (e.g., no reentry into the study allowed). Therefore, whenever this protocol is used on a routine basis in clinical practice, an estimated reduction of unnecessary catheter changes of at least 33% can be expected. New insights into the clinical predictors of CRI (e.g., the study on insertion site inflammation mentioned above) will make it possible to improve the protocol and reduce the number of catheters removed unnecessarily even more.

During the study, we observed a significant decrease in suspicion for CRI by the treating ICU physicians. This is probably the consequence of the learning effect caused by the study protocol. As the study continued, physicians might have realized that they were removing catheters too aggressively in patients with unexplained sepsis and therefore became more conservative in their approach. As a consequence the number of inclusions decreased progressively. Such a learning effect has been observed previously in a trial on the antibiotic management of suspected ventilator-associated pneumonia, which is also a difficult-to-diagnose infection in ICU patients [24].

The results of this study support the statement in the IDSA guidelines for the diagnosis and treatment of CRI that "...non-tunneled CVCs should not be routinely removed in patients with mild to moderate disease. " When confirmation of these findings in future studies follows, limiting catheter removal for suspected CRI to a subset of ICU patients will become possible. We hope that our observations will help in future clinical decision-making in the frequent clinical situation of unexplained new SIRS-sepsis in the critically ill patient.

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