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CLINICAL APPLICATION OF
DIFFERENTIAL TIME TO POSITIVITY OF
BLOOD CULTURES AS A DIAGNOSTIC
METHOD FOR CATHETER-RELATED
BLOODSTREAM INFECTION



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iii. Abstract:

Clinical suspicion of catheter-related bloodstream infection (CR-BSI) usually requires catheter withdrawal. The definitive diagnosis confirms CR-BSI in only 15 to 25% of withdrawn catheters. Differential time to positivity (DTP) of blood cultures is an accurate method of diagnosing CR-BSI without catheter withdrawal. The aim of this study is to prove the usefulness of DTP in comparison with a standard method.

We performed a prospective randomized study in 133 patients admitted to the ICU who required a central venous device. 56 patients were randomized to one of the diagnostic methods as soon as CR-BSI was suspected.

There was no difference in morbidity and mortality between the two groups avoiding unnecessary catheter withdrawal in 70% in the DTP group.

iv. Resum:

La sospita de bacterièmia relacionada a catèter (BRC) necessita la retirada d'aquest, confirmant-se a posteriori només en un 15-25%. La diferència en el temps de positivització d'hemocultius (DTP) ha demostrat ser un mètode fiable per el diagnòstic de BRC evitant la retirada del catèter. Amb la intenció de comprovar la utilitat clínica de la DTP, l'hem comparada amb un mètode diagnòstic estàndard.

Hem inclòs 133 pacients ingressats a una unitat de cures intensives portadors de catèters venosos centrals. 56 pacients s'han aleatoritzats. No hem trobat diferències significatives en quant a morbi-mortalitat en els 2 grups havent evitat 70% de retirada innecessària de catèters en el grup de DTP.

CERTIFICAT DEL DIRECTOR O CO-DIRECTOR DEL TREBALL DE RECERCA

Antoni Artigas Raventós, Professor del Departament de Medicina de la Universitat Autònoma de Barcelona, Director del Centre de Crítics del Hospital de Sabadell.

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FA CONSTAR,

que el treball titulat **CLINICAL APPLICATION OF DIFFERENTIAL TIME TO POSITIVITY OF BLOOD CULTURES AS A DIAGNOSTIC METHOD FOR CATHETER-RELATED BLOODSTREAM INFECTION** ha estat realitzat sota la meua direcció pel llicenciat **Caroline Sabatier**, trobant-se en condicions de poder ser presentat com a treball d'investigació de 12 crèdits, dins el programa de doctorat en Medicina Interna/Diagnòstic per la Imatge (curs 2009-2010), a la convocatòria de juny.

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CLINICAL APPLICATION OF DIFFERENTIAL TIME TO POSITIVITY OF BLOOD CULTURES AS A DIAGNOSTIC METHOD FOR CATHETER-RELATED BLOODSTREAM INFECTION

INTRODUCTION

Catheter-related bloodstream infections (CR-BSI) are the most common type of nosocomial bloodstream infections; they increase length of stay and morbidity, thus resulting in higher healthcare costs [a].

Central venous devices are very common in the management of patients admitted to critical care units. Clinical suspicion of CR-BSI often requires catheter withdrawal and replacement, because standard techniques can only confirm CR-BSI retrospectively by showing that blood cultures and catheter tip cultures are positive for the same pathogen. CR-BSI is confirmed in only 15% to 25% of catheters withdrawn for suspicion of CR-BSI [b].

Consequently, a reliable diagnostic method that does not require catheter withdrawal would be useful.

Several diagnostic methods that do not require catheter withdrawal have been tested in recent years. The accuracy of one such technique, the differential time to positivity (DTP) of blood cultures, has been validated by our group and others [c-e]. We aimed to compare the usefulness and the safety of the DTP method, with those of a standard method requiring catheter removal in routine clinical practice in critically ill patients.

MATERIAL & METHODS

STUDY DESIGN

We conducted a prospective randomized trial assigning patients to a strategy involving either a standard diagnostic method of CR-BSI requiring catheter withdrawal or the DTP method.

We aimed to determine whether the DTP method lowered morbidity and costs by avoiding unnecessary catheter exchange and whether delays in catheter withdrawal in DTP were associated with increased morbi-mortality. The primary outcome measure was morbidity due to catheter exchange; secondary outcome measures were morbidity due to delayed catheter withdrawal and reduction in number of catheters.

The study was performed in a medical-surgical ICU during a 20-month period (July 2007-Feb 2009). Patients were randomly assigned to a diagnostic method as soon as CR-BSI was suspected. The clinical team who assessed the patient was aware of the assignment, and the patient remained in the assigned group throughout the ICU stay.

ETHICS

The hospital's Ethics Committee approved the study. Patients or their families provided informed written consent on admission to the ICU. Patients remained anonymous.

PATIENTS

All patients admitted to the ICU who require a short-term central venous catheter were eligible. The exclusion criteria were a) hemodynamic instability

(systolic blood pressure-TAS- < 90 mmHg or decrease ≥ 40 mmHg, mean arterial pressure-TAM- < 60 mmHg or the need for vasoactive drugs or an increase > 5 mcg/kg/min of dopamine or dobutamine, or > 0.25 mcg/Kg/min norepinephrine in the last 12h) at the moment of suspicion of CR-BSI, b) immunodeficiency, c) endovascular device carriers, d) positive blood cultures in the previous 72h, or e) inclusion in other experimental studies. We also excluded pulmonary artery catheters, long-term catheters, and catheters with local signs of infection.

The attending medical team suspected CR-BSI when clinical symptoms of infection (fever, leukocytosis, increased in C-reactive protein -CRP- levels) were present in patients with catheters in place for more than 96h in whom other sources of infection were ruled out.

At the time of CR-BSI suspicion, patients were randomly assigned to either the standard diagnostic method, or DTP. We used a restricted randomization protocol with blocks of 4 patients to ensure that sequential patients were distributed equally between groups.

INTERVENTIONS

- Group 1: Standard management (Quantitative or semi-quantitative catheter-tip culture)

Two serial blood samples (10 ml each) from a peripheral vein obtained 30 minutes apart were cultured in aerobic (5 ml) and anaerobic (5 ml) media.

The suspected catheters were withdrawn and the tip (3 -5 cm) was processed for quantitative or semiquantitative cultures. Positivity was defined as the growth of 10^3 colony-forming units (CFU) per catheter segment according to

modified Cleri method for quantitative cultures [f] and as 15 CFU per segment for semiquantitative cultures according to Maki's method [g].

Cases were considered CR-BSI when the microorganism isolated in a positive peripheral blood culture was identical in species and antibiogram to that isolated in the catheter-tip culture by either the quantitative or the semiquantitative method.

Cases were considered catheter colonization when blood cultures were negative but the catheter-tip cultures were positive by either the quantitative or semiquantitative culture method. Cases were considered non-catheter-related bloodstream infection (Non-CR-BSI) when catheter-tip culture was negative or the pathogen isolated in a positive peripheral blood culture was different from the one isolated in the catheter-tip culture.

- Group 2: DTP- Alternative management

Two peripheral vein blood samples and a catheter hub blood sample were simultaneously cultured. Times to positivity of all the blood cultures were automatically registered (BacT/ALERT; bioMerieux, Durham, North Carolina, USA). Cases were considered CR-BSI when all cultures were positive for the same micro-organism, identical in species and antibiogram, and DTP \geq 120 min. Cases were considered colonization when the pathogen isolated in a positive hub-blood culture was different from the one isolated in peripheral blood cultures or when peripheral blood cultures were negative. Cases were considered non-CR-BSI was considered when peripheral blood cultures were positive and the hub-blood culture was negative for the same pathogen or positive for the same pathogen but the differential time to positivity of the cultures was $<$ 120 minutes.

When patients developed hemodynamic instability after blood cultures or polymicrobials cultures, the catheters were removed. Furthermore, in patients in whom signs of sepsis persisted after 72 h of negative cultures, the medical team decided in consensus whether to remove catheters on a case-by-case basis.

STATISTICAL ANALYSIS

We carried out a descriptive study of all variables, expressing results in means and standard deviations for quantitative variables and frequencies and percentages for qualitative variables.

The two groups were compared using chi-square tests for qualitative variables and T-Student's t-test for quantitative variables: clinical and microbiological data, rates of CR-BSI, unnecessary catheter removals, and complications due to new puncture and to delay in catheter removal. All *P* variables were based on two-tailed tests (level of significance, $P < 0.05$).

RESULTS

We included 133 of the 654 patients with a CVC in the ICU during the study period. Most (323=62%) of the 521 patients initially excluded, were not included because they remained in the ICU for a short time and their catheters were in place for less than 96h and thus, no CR-BSI were suspected (Figure 1).

Of the 133 patients initially included, CR-BSI were suspected in 54 patients and 2 of these were excluded from the analysis (one because of errors in sample collection and the other because of lost data). Thus, 26 were randomized to each group. There were no differences in age, sex, severity, or number of catheters days between the two groups (77% males, 59 years \pm 19, APACHE II 22 \pm 10, 10.7 \pm 3.3 respectively) Table 1.

In the standard group, we analyzed 37 suspected episodes of CR-BSI involving 58 catheters; 6 episodes were confirmed as CR-BSI and 5 episodes were classified as catheter colonization.

In the DTP group, we analyzed 26 suspected episodes of CR-BSI involving 41 catheters; 5 episodes were confirmed as CR-BSI and 4 episodes were classified as catheter colonization.

In cases of confirmed CR-BSI, there were no differences in the evolution of inflammatory parameters during the 24h-48h after initiating the diagnostic work-up for suspected CR-BSI between patients in the DTP group, in whom the catheter was not removed immediately upon suspicion: CRP (0.4 ± 6 vs 0.8 ± 3 $p=0.86$), leukocytosis (1405 ± 2105 vs 1201 ± 2090 $p=0.94$), change in body temperature (0.33 ± 0.8 vs 0.84 ± 0.7 $p=0.27$). Likewise, no differences in the use of vasoactive drugs were observed (NA 0.01 ± 0.03 vs 0.05 ± 0.1 $p=0.6$). No catheters of the DTP group were removed because of hemodynamic instability following blood cultures collection or polymicrobial cultures.

In the standard group, all catheters ($n=58$ - 100%) were removed immediately when CR-BSI was suspected; whereas in the DTP group, 13 catheters (32%) were removed when the CR-BSI was confirmed and 10 more (24%) in patients with negative blood cultures and persistent signs of sepsis 72h after initiating the diagnosis work-up for CR-BSI. Thus, 18 catheters (43.9%) were maintained in the DTP group.

No major complications due to new punctures to replace catheters were noted in the standard group (Table 2).

The micro-organisms isolated in cases of CR-BSI were *S. epidermidis* (n=4), *Pseudomonas aeruginosa* (n=2), *S. aureus* (n=1), MRSA (n=1), *Enterobacter cloacae* (n=1) (Table 3).

DISCUSSION

To our knowledge, this is the first randomized prospective study that compares a diagnostic method of CR-BSI that does not require catheter removal with a standard method that requires catheter withdrawal in short-term catheters.

Most hospitals cannot afford to do quantitative blood cultures but they will be able to use the differential time to positivity of qualitative blood samples.

The latest guidelines from the Infectious Diseases Society of America (IDSA) for the diagnosis and management of intravascular catheter-related infection consider the differential time to positivity method reliable (level of evidence All). This level of evidence was supported by two references.

The first is a meta-analysis of 8 prospective studies published by Safdar et al. in 2005; however, but only 2 of these studies were limited to short-term catheters in patients in general ICUs [h]. The second is a study by Raad et al. that found high sensitivity (81%) and specificity (92%) for DTP compared with the gold-standard of catheter-tip culture plus quantitative blood culture in cancer patients[d]. Recent studies provide more evidence for the reliability of the DTP method [c, e].

CR-BSIs are the main cause of nosocomial bloodstream infection in patients admitted to the ICU. The incidence ranges from 3 to 5 episodes per 1000 days of central venous catheters in place. The incidence density of CR-BSI in our ICU during the study period was 2.67 episodes per1000 days of central venous catheters in place. This low incidence can be explained by the implementation, during the same period, of a multi-intervention protocol to reduce CR-BSI in the ICU [i] consisting of hand washing, using full-barrier

precautions during the insertion of central venous catheters, cleaning the skin with chlorhexidine, avoiding the femoral site if possible, and removing unnecessary catheters.

Even with this low incidence, we found no differences CR-BSI and colonization rates were not different between the groups. In the standard group, 6 of 37 suspected episodes of CR-BSI (16.2%) were confirmed, while in the DTP group 5 of 26 (19.2%) suspected episodes were confirmed.

The reason fewer episodes were suspected in the DTP group is probably because of the need of removal after 72h in case of negative blood cultures and persistent septic signs.

In the standard group all catheters (n=58-100%) were replaced immediately when CR-BSI was suspected. In contrast, in the DTP group only 23 catheters (66%) were removed: 13 when CR-BSI was diagnosed (i.e., when blood cultures became positive, 24h after CR-BSI was suspected) and 10 more (24%) when removed after 72h because of persistent septic signs but, all tips were cultured signs of sepsis persisted 72h after CR-BSI was suspected. Nevertheless, the tips of the catheters in these 10 patients were cultured and none were positive. Thus, 18 catheters (44%) remained in place and 10 more (34%) could have been safely kept in place.

These percentages are similar to those in the series published by Rello et al. [b], where 71% of the catheters from patients with suspected CR-BSI were sterile.

Our study has some limitations. First, the slow recruitment, mainly due to the short stay in ICU and to the implementation of a complete intervention protocol to reduce CR-BSI, resulted in a small sample. This protocol required staff to

review all catheters daily to determine whether they were absolutely or whether they could be removed. The second limitation is that this study took place in a single center where central venous catheterization was protocolized and the management of suspected CR-BSI was very strict. Suspicious catheters were always replaced by new puncture, never exchanged over a guidewire; thus, it may not be possible to extrapolate our results to other centers where the management is different. Finally, the third limitation is that randomization was not blinded, so we cannot rule out possible bias due to special care to one group or the other of randomized patients.

CONCLUSIONS

As CR-BSI and colonization rates were not different between groups, DTP made it possible to maintain many catheters that would have been removed if the standard method had been used.

The DTP method obviates unnecessary catheter withdrawal. Delay in catheter removal in cases of CR-BSI did not result in increased morbidity. On the other hand, we did not observe any complications due to new catheter insertion.

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Figure 1. Flow diagram

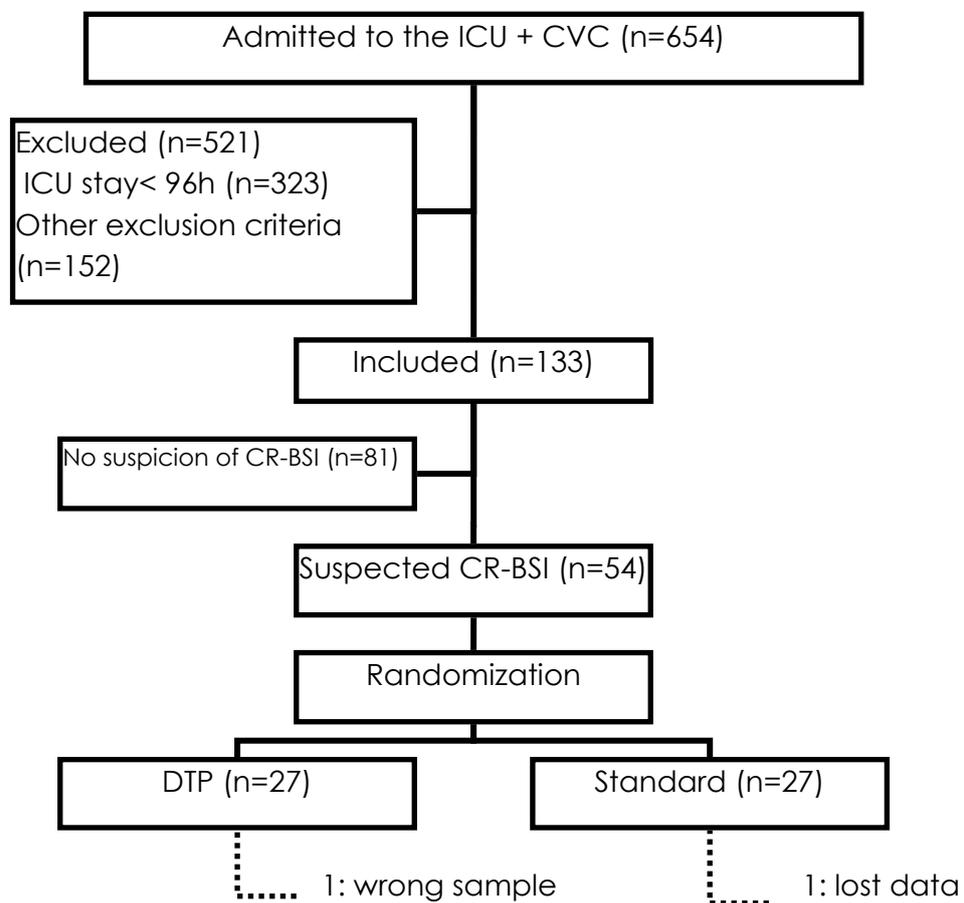


Table 1. Characteristics of patients and catheters.

	Standard	DTP	P
Gender ♂	19	21	0.75
Age (years)	61.8±18.5	57.1±18.7	0.64
APACHE II	20±9	19,3±7.5	0.88
Catheter days	11.2±2.9	10.2±3.7	0.78

Table 2. Results

	STANDARD	DTP	P
Patients	26	26	
Suspected CR-BSI episodes	37	26	
CR-BSI	6 (16.2% of suspected)	5 (19.2% of suspected)	0.98
Colonization	5 (13.5% of suspected)	4 (11.5% of suspected)	0.88
Catheters studied	58	41	
Catheters removed	58 (100% catheters)	13 (32% cath.) at diag. 10 (24%) persistent septic signs	< 0.001
Cat. related to CR-BSI or Colonization	19 (32% catheters)	13 (32% catheters)	1
Catheters maintained	0	18 (43.9% catheters)	<0.001
Complications	0	0	

Table 3. Microbiology

