Title: Sodium citrate locks and the risk of acute hemodialysis catheter infection among critically ill patients: A quasi-experimental study

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Running title: Citrate Locks and Catheter Infection

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ABSTRACT (253 words for 250 allowed)

Background
Critically ill patients who require renal replacement therapy (RRT) are vulnerable to catheter-related bloodstream infections (CRBSI). This study compared the risk of dialysis catheter infection according to the locking solution in the intensive care unit (ICU).

Methods
A prospective quasi-experimental study with marginal structural models (MSM) and 2:1 greedy propensity-score matching (PSM) was conducted at nine university-affiliated hospitals and three general hospitals. Five hundred ninety six critically ill patients received either saline or heparin lock solutions (SOC) from 2004-2007 in the Cathedia cohort (n=464 for MSM; n=124 for PSM) or 46.7% citrate lock from 2011-2012 in the citrate (CLock) cohort (n=132 for MSM; n=62 for PSM) to perform RRT using intermittent hemodialysis. Catheter-tip colonization and CRBSI were analyzed.

Results
The mean duration (SD) of catheterization was 7.1 days (6.1) in the SOC group and 7.0 days (5.9) in the CLock group (p=0.84). The risk of dialysis catheter-tip colonization was lower in the CLock group (20.5 versus 38.7 per 1000 catheter-days in the SOC group; hazard ratio (HR) from MSM, 0.73; 95% CI, 0.57-0.93; p<0.02). Consistent findings were found from PSM (HR, 0.46; 95% CI, 0.22-0.95; p<0.04). The risk of CRBSI was non-significantly different in the CLock group (1.1 versus 1.8 per 1000 catheter-days in the SOC group; HR from MSM, 0.48; 95% CI, 0.12-1.87; p=0.29).

Conclusions: By reducing the risk of catheter-tip colonization, citrate lock has the potential to improve hemodialysis safety in the ICU. Additional studies are warranted before the routine use of citrate locks can be recommended in the ICU.
INTRODUCTION

Critically ill patients with acute kidney injury (AKI) who require renal replacement therapy (RRT) are particularly vulnerable to nosocomial infections (1, 2). Therefore, any improvement in catheter management strategies that could delay the risk of catheter-related bloodstream infection (CRBSI) has the potential to improve patient safety (3) and reduce costs (4).

An increased understanding of the role of biofilms has added an exciting dimension and a significant challenge to device-related infection prevention. Compared with the central venous catheters used for the administration of medications, a unique feature of hemodialysis catheters is their intermittent use. In a pilot (n=78), open-label, single-center, randomized controlled trial among critically ill patients requiring RRT, Hermite et al. (5) reported a significantly longer time for central catheter-associated bloodstream infection (CLABSI) (6) to occur in the citrate locking group (20 days versus 14 days in the saline locking group; hazard ratio (HR), 2.8; 95% confidence interval (CI), 1.0-7.6; p=0.04). Of note, the incidence of CLABSI in this study (5) was >24 per 1,000 catheter-days and contrasts with the incidence of CRBSI found in the multicenter Cathedia cohort (1.9 per 1,000 catheter-days) (7) and in the study by Skofic et al. (8) conducted in the same type of patients (1.6 per 1,000 catheter-days). Whether citrate lock is more effective than saline or heparin lock in intensive care unit (ICU) settings and whether it is associated with a lower incidence of CRBSI remain unclear (9).

We hypothesized that the risk of dialysis catheter infection would be lower with the use of sodium citrate locks in the ICU. This study aimed to compare the risk of catheter-tip colonization at the time of catheter removal among patients requiring RRT according to a protocol using sodium citrate locks (CLocks) versus heparinized or saline fluids (SOC) during the interdialytic period. Secondary endpoints were catheter dysfunction, duration of catheterization, CRBSI, and ICU mortality.
METHODS

Study design, setting, and population

The CLocks cohort study was a retrospective, quasi-experimental, cohort study conducted at Caen University Hospital that enrolled all consecutive patients admitted to the ICU who required RRT between January 2011 and December 2012. Data were prospectively collected as a part of the French REA-Raisin surveillance network, which targets device-associated infections. Only adults who were undergoing their first temporary two-lumen, 14-Fr, non-tunneled, venous catheterization for intermittent hemodialysis (Arrow international, PA, United States) were included in the study.

To serve as controls, we used the patients included in the Cathedia study, which was a multicenter study involving the Caen University Hospital in addition to 8 university hospitals and 3 general hospitals. The comparison of a group of patients admitted to a single institution with a group of patients admitted to the same institution plus 11 other institutions cannot adjust for a possible center effect. Therefore, we also conducted a sensitivity analysis by restricting the control group to patients admitted to the Caen University hospital. The study was approved by the institutional review board (IRB) of the Côte de Nacre University Hospital. Informed written consent was obtained from all of the participants or their proxies. Given the retrospective and quasi-experimental nature of this analysis, no additional IRB approval was requested. Details of the dialysis catheters used in the Cathedia study were described elsewhere (7) and were consistent with those used in the CLock study. For the present analysis, we excluded patients who exclusively received continuous RRT and catheters that were not inserted first in the ICU (10).

Catheter insertion and care

Dialysis catheters were not used for drug administration and only jugular and femoral sites were used. All of the protocols used in this study to prevent catheter infection were standardized and followed the Center for Disease Control (CDC) and French recommendations (11), including the use of masks, caps, gowns, sterile gloves, sterile drapes, and catheter hub disinfection. We used 5% povidone iodine/70% ethanol
(Betadine™ Alcoolique, MEDA™ Pharma, Mérignac, France) after scrubbing the insertion site with a 4% povidone iodine detergent (Betadine™ Scrub, MEDA™ Pharma, Mérignac, France) for all dialysis catheters used in the study (12). Catheter care maintenance including cleaning the catheter hubs used 5% povidone iodine/70% ethanol (Betadine™ Alcoolique, MEDA™ Pharma, Mérignac, France). In the Cathedia and CLock cohorts, all dialysis catheters were aseptically removed and systematically sent to culture, regardless of the clinical patients’ status. Catheter colonization, as defined below, was the primary endpoint in the original Cathedia trial and an item of the French REA-Raisin surveillance network in the CLock cohort.

Protocol for hemodialysis catheter maintenance

Catheter lock with sodium citrate

In the CLock group, the locks were made by injecting 10 mL of saline and subsequently filling each branch of the catheter with citrate solution according to the manufacturer recommendation (DuraLock-C™ 46.7%, medCOMP®, Harleysville, PA, USA). Once the citrate locks were in place, catheter manipulation was forbidden until the next dialysis session, and the citrate lock was removed by aspiration before the next dialysis session in an attempt to minimize release of the solution into systemic circulation.

Standard of care

Only SOC were used to lock the dialysis catheter in the Cathedia cohort according to the practice of each center.

Endpoints

Catheter-tip colonization

The primary endpoint of this study was catheter-tip colonization, defined as cultures with \( \geq 10^3 \) colony-forming units per millimeter of growth, according to the Brun-Buisson vortex technique without neutralizing broth (7).
Catheter dysfunction, which served as the secondary endpoint in the Cathedia trial (13), was similarly defined as an inability to attain an adequate blood flow requiring catheter replacement.

**Other endpoints**

We also compared the duration of catheterization in days from the time of insertion to removal, the CRBSI incidence and all-cause ICU mortality. CRBSI was defined as catheter-tip colonization with one concordant peripheral blood culture for pathogens and two concordant peripheral blood cultures for potential skin contaminants.

**Power and statistical analysis**

The catheter-tip colonization rate in the Cathedia cohort was 24% (7). We expected a 50% reduction in the rate of catheter-tip colonization (primary endpoint) with citrate lock. Considering a two-sided alpha risk of 5%, and a sample size ratio of 4 between groups (Cathedia/CLock), a total of 103 patients in the CLock group (and 412 controls) were required to provide a statistical power of 80%.

The data were expressed as the mean ± standard deviation (SD) or median (interquartile range) and percentage depending on the nature of the variable of interest. The incidence densities were expressed as the number of events divided by the number of catheter-days. We used propensity score methods, namely marginal structural models (MSM) and 2:1 greedy propensity-score matching (PSM) to ensure that the Cathedia and Clocks populations were comparable (see Appendix). The addition of risk factors to the MSM and PSM models revealed consistent results and thus, were not shown. A hazard ratio <1 corresponded to a protective effect of CLock over SOC. In addition, MSM was used in a sensitivity analysis by restricting the Cathedia cohort to the patients admitted to the Caen University hospital only (the same institution than in the CLock cohort). We considered that
a 10% change in the effect size for the primary endpoint would denote significant confounding compared to the full Cathedia sample.

A p-value <0.05 was considered to be significant, and all p values were two-tailed without adjusting for multiple comparisons. The statistical analyses were performed using SAS statistical software, version 9.4 (SAS Institute Inc., Cary, NC, USA) and TreeAge Pro 2008 (TreeAge Software Inc., Williamstown, MA, USA).
RESULTS

Baseline characteristics

After excluding patients who never received intermittent hemodialysis, 596 consecutive patients fulfilled the inclusion criteria and were enrolled in the Cathedia-Clock study. Among these patients, 464 (77.8%) patients received SOC for dialysis catheter maintenance (saline, 34%; heparin, 66%) and 132 (22.1%) received CLocks for dialysis catheter maintenance. In the Cathedia cohort, 127/464 (27%) patients were included at the same institution than the CLock cohort (n=132). The baseline characteristics of the two cohorts are reported in Table 1; showing significant differences between the two groups.

Regarding predictors of catheter-tip colonization (Table 1), antibiotic treatment (protective), hypertension (risk factor) and diabetes (risk factor) were more frequent in the CLock group compared to the SOC group.

Unadjusted analyses

Among the 464 patients who received SOC, the overall cumulative incidence of catheter colonization was 27.6%, which corresponded to an incidence density of 38.7 per 1000 catheter-days (95% CI, 27.7-52.2). Among the 132 patients who received CLock, the overall cumulative incidence of catheter colonization was 14.4%, which corresponded to an incidence density of 20.5 per 1000 catheter-days (95% CI, 13.0-30.9). The time to colonization at the time of catheter removal was significantly longer (Figure 1A) in the CLock group than in the SOC group (HR, 0.53; 95% CI, 0.33-0.87; p<0.02).

The microbiological findings of catheter-tip colonization are shown in Table 2. Among the cases of colonization, the distributions of Gram-positive bacteria, Gram-negative bacteria, fungi, and polymicrobes were homogeneous between groups (p=0.40). The distribution of Gram-positive bacteria differed between groups (p<0.02), with a higher incidence of catheter-tip colonization of Staphylococcus epidermidis in the SOC group compared with the CLocks group.

As shown in Figure 1B, more dialysis catheters were removed due to dysfunction in the SOC group (46 [9.9%] of 464) than in the CLock group (4 [3.0%] of 132), which corresponded to a significantly longer time to dysfunction in the CLock group (HR, 0.31; 95% CI, 0.11-0.87; p<0.03).
The mean duration (SD) of catheterization was similar (p=0.84) between the CLock (7.0 days [5.9]) and SOC (7.1 days [6.1]) groups (Table 1). The overall cumulative incidence of CRBSI (Table 2) was 6 (1.3%) of 464 in the SOC group (1.8 per 1000 catheter-days) and 1 (0.8%) of 132 in the CLock group (1.1 per 1000 catheter-days) and did not significantly differ with respect to the catheter maintenance protocol (unweighted HR, 0.60; 95% CI, 0.07-4.95; p=0.64). In the ICU, the mortality rate was similar between groups (Table 1).

Propensity score analyses

The time to colonization at the time of catheter removal was significantly longer in the CLock group based on inverse probability weighting (weighted HR, 0.73; 95% CI, 0.57-0.93, p<0.02). In the sensitivity analysis, restricting the control group to patients from Caen University hospital (n=127), the time to colonization at the time of catheter removal was non-significantly longer in the CLock group based on inverse probability weighting (weighted HR, 0.76; 95% CI, 0.50-1.15, p=0.20), corresponding to an effect size modification of 4% compared to the full control group sample. As shown in Figure 2A, in the propensity-matched subgroup (n=186), the risk for colonization at the time of catheter removal was significantly higher in the SOC group (42.6 per 1000 catheter-days versus 21.6 in the CLock group; HR, 0.46; 95% CI, 0.22-0.95; p=0.04).

The time to dysfunction was also significantly longer in the CLock group based on inverse probability weighting (weighted HR, 0.29; 95% CI, 0.16-0.51; p<0.001). As shown in Figure 2B, in the propensity-matched subgroup (n=186), the time to dysfunction was not significantly higher in the SOC group (6.1 per 1000 catheter-days versus 4.3 in the CLock group; HR, 0.78; 95% CI, 0.16-3.86; p=0.76). Finally, the time to CRBSI was non-significantly different in the Clock group compared with the SOC group based on probability weighting (weighted HR, 0.48; 95% CI, 0.12-1.87; p=0.29).
DISCUSSION

Consistent with our hypothesis, the risk of dialysis catheter infection was lower with the use of sodium citrate locks in the ICU. However, the lower risk of catheter-tip colonization (38.7 versus 20.5 per 1000 catheter-days) did not translate to a significantly lower risk of CRBSI (1.8 versus 1.1 per 1000 catheter-days), possibly due to the low number of events expected with such a short indwell time. Our results support the concept of an antimicrobial catheter lock solution (14), specifically citrate, to prevent the risk of short-term catheter-associated infection risk among patients who require RRT in an ICU setting (5, 8).

The catheterization duration (7 days) reported in this study was similar to those reported in previous studies (5, 8, 15–18) ranging from 4.2 days (16) to 12.0 days (5). This short-term indwelling duration suggests that the extra-luminal route of catheter-tip colonization predominated (19). Because filling the dialysis catheter with citrate can only prevent intra-luminal colonization, it is unclear why we observed a significant reduction of catheter-tip colonization in our study. The first hypothesis is that, similar to long-term dialysis catheters (20, 21), the intra-luminal route of catheter-tip colonization may predominate for short-term dialysis catheters in the ICU population due to frequent manipulations of the catheter hub or connectors and possibly the choice of the locking solution (22). Additional studies on the dynamics of catheter colonization are warranted in this setting. However, the use of ethanol lock in the ICU did not reduce the risk of dialysis catheter (NCT00875069). The second hypothesis is that spillage of the locking solution around the intra-vascular catheter tip also affects extra-luminal catheter-tip colonization (23), despite a lower citrate concentration at the catheter-tip (24). Even when the appropriate fill volume is used, laminar flow results in the injected catheter lock streaming down the center of the lumen and the citrate solution spilling into the bloodstream (25). This finding also supports the close monitoring of calcium plasma level, even when citrate is used as a catheter locking solution.

Our ICU chose to utilize a 46.7% citrate lock solution because this medical device (DuraLock-CTM) was already approved as a catheter lock solution in Europe; nevertheless, there are other locking solutions. Although antibiotic-based lock solutions are effective in preventing CRBSI (26), the emergence of bacterial resistance could discourage their systematic use in the ICU (27). Ethanol locks could also be an attractive antimicrobial solution because of their
activity against bacteria, fungi, and biofilms (28). Importantly, several lock solutions, such as ethanol, have been associated with adverse reactions (29) or can adversely affect catheter integrity (30). Different antimicrobial agents may have synergistic antimicrobial activity (31), such as those used for skin antisepsis (12). The combination of several compounds is, therefore, a focus of research that has yielded promising results (32, 33).

The use of CLock was associated with less catheter colonization compared to SOC. This observation is consistent with the anticoagulant and antibacterial(31, 34, 35) activity across a broad spectrum of microbes. Of note, thrombosis and bacterial growth within biofilm are closely related in the physiopathology of catheter-related infections (36).

The use of CLock was also associated with less catheter dysfunction. This observation is consistent with the anticoagulant properties of citrate through the chelation of calcium. Additionally, this observation supports the higher rate of catheter dysfunction found in the saline group compared with the citrate group in a study by(35) Hermite and colleagues (5). However, the reduction of catheter dysfunction in our study did not translate into longer catheterization durations, was highly physician-dependent, and disappeared after performing propensity-score matching.

The routine use of 46.7% citrate by our experienced team as a catheter locking solution was not associated with higher mortality. However, the FDA sent out an urgent warning on April 14, 2000 reporting the risk of death when such high concentration of citrate is infusated into patients’ blood. This may be particularly relevant in the ICU population with acute renal failure and possibly acidosis, underscoring the need to close cardiac monitoring and compliance to the manufacturer recommendation.

Our study has several strengths. This study represents the third cohort (5, 8) and largest comparison employing individual data to investigate the risk of dialysis catheter infection when using citrate locking in the ICU; thus, this cohort is unique. The findings are biologically plausible and supported by in vitro (22, 28, 37) and in vivo (31, 35) studies. The effect of citrate on catheter-tip colonization was consistent in our analyses, including the propensity-score-matched sub-cohort, which mimics “post hoc” randomization by balancing the
recorded risk factors between groups. We are also aware of the limitations of the study. The study design compared CLock patients from one single institution while comparator Cathedia patients were included by this institution plus 11 other institutions, in order to increase the power of the study. Nevertheless, the sensitivity analysis showed a limited effect of confounding when the analysis was restricted to patients included by the same institution. The primary endpoint was catheter-tip culture without neutralizing broth, not CRBSI, which may limit the clinical relevance of our quasi-experimental study. Between the two time periods (2004-2007 for the Cathedia historical group and 2011-2012 for the Clock group), the effectiveness of the implementation of simple “bundle measures” to prevent the risk of CRBSI in patients admitted to the Intensive Care Units (38) could favor the CLock group, independently of the locking solution used. Maximal barrier precautions for catheter insertion and maintenance were already in use during the control period, chlorhexidine skin antisepsis was not available, avoidance of the femoral vein for vascular access is not relevant compared to jugular (7, 39) and exposure to central venous access was similar between the two periods. Moreover, the patients risk factors (2) and interventions that could increase or decrease the risk of catheter infection were prospectively monitored and standardized. Nevertheless, the possible increased use of ultrasound for catheter insertion from 2004 and 2012 as well as other unrecorded confounding factors have not been taking into account.

This study may have important implications for future research. First, the robust association between intra-luminal locking and the reduction of short-term catheter-tip colonization will aid in identifying the best composition of antimicrobial locks for use during interdialysis periods in the ICU setting (NCT01962116). Second, this strategy has the potential to reduce colonization. Particular attention should be focused on patient safety because a systemic leak of the locking solution could occur and may be masked or felt to be due to other etiologies and thus underreported.

In conclusion, citrate lock has the potential to improve acute hemodialysis safety in the ICU at reasonable cost. Additional experimental studies are required before the routine use of antimicrobial locks can be recommended for intermittent hemodialysis in the ICU setting.
References


Table 1. Baseline and follow-up characteristics according to the hemodialysis catheter maintenance protocol before and after propensity-score matching

<table>
<thead>
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<th>Baseline characteristics</th>
<th>Overall cohort before matching</th>
<th>After 2:1 propensity matching**</th>
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<tr>
<td></td>
<td>Cathedia (n=464)</td>
<td>Citrate lock (n=132)</td>
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<tr>
<td>Age, mean (SD)</td>
<td>65.0 (14.9)</td>
<td>62.3 (13.2)</td>
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<td>Gender, male</td>
<td>318 (68.5)</td>
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<td>BMI, mean (SD)</td>
<td>26.9 (5.3)</td>
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<td>APACHE II, mean (SD)</td>
<td>26.5 (9.0)</td>
<td>30.7 (10.1)</td>
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<td>273 (58.8)</td>
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<td>Immunodepression, n (%)</td>
<td>82 (17.7)</td>
<td>18 (13.6)</td>
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<td>Diabetes, n (%)</td>
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<td>61 (46.2)</td>
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<tr>
<td>Hypertension, n (%)</td>
<td>235 (46.2)</td>
<td>82 (62.1)</td>
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<tr>
<td>Jugular route, n (%)</td>
<td>226 (48.7)</td>
<td>52 (39.4)</td>
</tr>
<tr>
<td>Started with CRRT, n (%)</td>
<td>91 (19.6)</td>
<td>52 (39.4)</td>
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<tr>
<td>Propensity to receive SOC, mean (SD)</td>
<td>0.815 (0.150)</td>
<td>0.615 (0.193)</td>
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### Follow-up

<table>
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<th>Group 1 (SD)</th>
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<th>Group 4 (SD)</th>
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<td>Duration of catheterization, mean (SD)</td>
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<td>Catheter colonization, n (%)</td>
<td>128 (27.6)</td>
<td>19 (14.4)</td>
<td>42 (33.9)</td>
<td>10 (16.1)</td>
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<td>Catheter dysfunction, n (%)</td>
<td>46 (9.9)</td>
<td>4 (3.0)</td>
<td>6 (4.8)</td>
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<td>CRBSI, n (%)</td>
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<td>1 (0.8)</td>
<td>1 (0.8)</td>
<td>1 (1.6)</td>
<td>0.53</td>
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<td>ICU mortality, n (%)</td>
<td>188 (40.5)</td>
<td>45 (34.1)</td>
<td>49 (39.5)</td>
<td>18 (29.3)</td>
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* Included in the computation of the propensity score; SOC refers to standard of care (saline or heparinized locks).

** Standardized difference between groups was <10% for all baseline characteristics after propensity-score matching.

Abbreviation: SD, standard deviation; BMI, body mass index; CRBSI, Catheter-related bloodstream infection; CRRT: continuous renal replacement therapy
<table>
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<th>Overall (n=596)</th>
<th>SOC (n=464)</th>
<th>CLock (n=132)</th>
<th>P</th>
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<td>Catheter colonization n (%)</td>
<td>147 (25.7)</td>
<td>128 (27.6)</td>
<td>19 (14.4)</td>
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<td>Incidence per 1000 catheter-days</td>
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<td>38.7</td>
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<td>Microorganism characteristics, n</td>
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<tr>
<td>Fungi</td>
<td>10</td>
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<td>Polymicrobes</td>
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<td>n (%)</td>
<td>7 (1.2)</td>
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<tr>
<td>CRBSI per 1000 catheter-days</td>
<td>1.6</td>
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*p<0.02.*

*§p=0.40.*
Figure 1. Kaplan-Meier curves of time to catheter colonization at the time of catheter removal (Panel A) and at the time of dysfunction (Panel B) in the overall cohort (n=596).

Figure 2. Kaplan-Meier curves of time to catheter colonization at the time of catheter removal (Panel A) and at the time of dysfunction (Panel B) after propensity-score matching (n=186).
Acknowledgments: DdC initiated the concept of the study. JJP and DdC designed the study. SD, CD, JPM, BM, and BS collected the data. JJP performed the statistical analysis and drafted the manuscript. All of the authors were involved in the interpretation of the results and the critical revision of the manuscript. We gratefully acknowledge the dedication of the nursing and medical staff members in all of the participating centers and the generosity of the study participants and family members, without whom this study could not have been completed.

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Data Monitoring Task Force: A. Gauneau (clinical research assistant, CHU de Caen); J.J. Dutheil (clinical research assistant, CHU de Caen); E. Vastel (clinical research assistant, CHU de Caen); and F. Chaillot (administrator, CHU de Caen).

Participating Centers and Cathedia Investigators:


Centre Hospitalier Général, Saint-Malo: L. Auvray (principal investigator). All centers are located in France.
Figure 1. Kaplan-Meier curves of time to catheter colonization at the time of catheter removal (Panel A) and at the time of dysfunction (Panel B) in the overall cohort (n=596).

**Figure 1A Abbreviations:** HR, Hazard Ratio; IPWT, Inverse Probability Weighted Treatment

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<td>132</td>
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<td>Duration of catheterization, days</td>
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HR, 0.53; 95% CI, 0.33 to 0.87, P<0.02
IPWT HR, 0.73; 95% CI, 0.57 to 0.93, P<0.02
Fig. 1B

Abbreviations: HR, Hazard Ratio; IPWT, Inverse Probability Weighted Treatment

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HR, 0.31; 95% CI, 0.11 to 0.87, P<0.03
IPWT HR, 0.29; 95% CI, 0.16 to 0.51, P<0.0001
Figure 2. Kaplan-Meier curves of time to catheter colonization at the time of catheter removal (Panel A) and at the time of dysfunction (Panel B) after propensity-score matching (n=186).

Abbreviations: HR, Hazard Ratio

HR, 0.46; 95% CI, 0.22 to 0.95, P<0.04
Abbreviations: HR, Hazard Ratio

Number of subjects at risk

Standard of Care (SOC)

Citrate Lock (Clock)

Duration of catheterization, days

SOC

Clock

HR, 0.78; 95% CI, 0.16 to 3.86, P=0.76

Fig. 2B

Probability of Catheters free dysfunction