

ORIGINAL



# Short-term dialysis catheter versus central venous catheter infections in ICU patients: a post hoc analysis of individual data of 4 multi-centric randomized trials

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## Abstract

**Purpose:** Little is known on catheter-related infections associated with short-term dialysis catheters (DC). Recommendations for infection prevention are mostly derived from those related to central venous catheters (CVC). A comparison of infectious risk of DCs and CVCs would be instrumental for improving infection control prevention strategies. This study aimed to describe differences in infectious risk between DC and CVC.

**Methods:** We used individual data from 4 multicenter randomized controlled trials in intensive care units (ICUs) that evaluated various prevention strategies regarding colonization, major catheter-related infections (MCRI) and catheter-related bloodstream infections (CR-BSI). We selected only catheters with non-chlorhexidine gluconate impregnated dressings. A marginal Cox model for clustered data was used for the evaluation of the daily hazard rate for catheter-tip colonization, MCRI and CR-BSI.

**Results:** We included 3029 patients and 4148 catheters (31,547 catheter-days) which comprised 1872 DCs and 2276 CVCs. After adjustment on confounders, we identified an increased risk in DC compared to CVC for colonization (HR 1.45, 95% CI 1.03–2.04,  $p = 0.04$ ) and for MCRI (HR 2.97, 95% CI 1.03–8.51,  $p = 0.04$ ) in the first 7 days of catheter maintenance. The daily hazard rate for colonization and MCRI was generally higher for DC in the first catheter-days, whereas it was similar between DC and CVC for longer catheterizations.

**Conclusions:** The daily risk of colonization and MCRI was significantly higher in DC compared to CVC within the first 7 days of catheter maintenance. Targeted prevention strategies for DC should mostly focus on the period following the insertion.

**Keywords:** Catheter, Dialysis catheter, Central venous catheter, ICU, Infection, Colonization

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## Introduction

Infections related to short-term catheters are frequent in the intensive care unit (ICU) setting, although they can be substantially reduced with adequate prevention strategies [1, 2]. International guidelines and studies investigating infections associated with short-term catheters mostly focused on central venous catheters (CVCs) [2–7]. In the ICU, vascular access for renal replacement therapy (RRT) for acute kidney injury is usually granted by means of a large-bore short-term dual-lumen catheter (DC) inserted in a central vein [8]. Few studies investigated infections associated with short-term DCs and recommendations for their prevention are scarce [8–11]. On one hand, extrapolating the DC data regarding catheter-related infections (CRIs) from long-term dialysis patients is debatable, as procedures applied in dialysis centers and in ICU differ in terms of patient populations, catheter types, modalities and catheter duration [8]. On the other hand, data on the epidemiology of standard CVCs cannot be extrapolated to DCs, as the latter differ substantially from CVCs in design and use (e.g., other lumens, different use with frequent hub disconnections, and other insertion sites) [8]. However, most information and recommendations on DC prevention measures are based on data on the use of CVCs in the ICU [9, 11]. A comparison of infectious risk of DCs and CVCs when the same infection control measures are used for the insertion and maintenance of the two catheters would be a step toward defining and targeting infection control prevention strategies. However, only three limited studies have directly evaluated the differences in the infection risk between DCs and CVCs [12–14]. The present study aimed (1) to describe the differences in the infection risk between DCs and CVCs, and (2) to assess whether the duration of DC or CVC placement influences this risk of infection. We used the data gathered for four large randomized controlled trials (RCTs) for which an extensive prospective high-quality data collection at catheter insertion and catheter removal was performed [15–18].

## Methods

### Study design

This study used the databases of four longitudinal RCTs: DRESSING1 [15], DRESSING2 [16], ELVIS [17] and CLEAN [18] for conducting a post hoc analysis. The similarities among all these studies with regards to definitions and inclusion criteria allowed to merge the databases. Their objectives were also similar: to evaluate the effect of specific prevention strategies on the colonization and infection of intravascular catheters in ICU. The studies were not blinded to ICU staff or the investigators but to the microbiologists who processed the samples of skin

### Take-home message

The risk of infection is higher for short-term dialysis catheters than CVC, especially within the first seven catheter-days.  
Targeted prevention strategies for short-term dialysis catheters should focus on the period following the insertion.

and catheter for cultures, and to the adjudication committee [15–18]. All studies were approved by the national ethics committee.

### Study patients

The patients were recruited from 2006 [15] to 2014 [18] in various ICUs in France. For the current study, only patients from ICUs which recruited both DCs and CVCs during one (i.e., CLEAN) or more studies were included in the final analysis. Patients were included if they required a catheterization with an expected duration of use longer than 48 h. The characteristics of patients were similar across studies, except the ELVIS trial which included only patients requiring acute RRT [15–18]. Patients underwent follow-up until 48 h after ICU discharge.

### Study catheters

This post hoc analysis evaluated data from patients with short-term dialysis catheter (DC) and/or central venous catheter (CVC) included in the four studies. As chlorhexidine gluconate-impregnated dressings were tested only on CVCs and not on DCs, and showed a reduced infection rate, patients with chlorhexidine gluconate-sponges or -dressing catheters were excluded from the analysis. Moreover, as the subclavian access for DC placement is rarely used for fear of vein stenosis, patients with CVCs or DCs inserted in the subclavian vein were excluded. All DCs and CVCs in a given patient were managed in the same way. Indeed, all study centers complied with the French recommendations for catheter insertion and care, which are similar to CDC recommendations [2]. Catheters were removed if no longer needed, in the case of dysfunction or thrombosis, or if a CRI was suspected. Catheter tips were cultured using quantitative culture technique [19, 20]. Moreover, in three studies (1911 catheters), skin colonization was evaluated using semi-quantitative insertion-site cultures: the insertion site was sampled immediately before catheter removal [15, 16, 18]. Because the size of the counting surface was different across studies, we created a semi-quantitative variable with sterile, low-grade colonization, and high-grade colonization according to the median of quantitative cultures obtained in each study.

### Definitions and evaluation criteria

According to French and American guidelines [21, 22], the following definitions were used. Catheter colonization was defined as a quantitative catheter tip culture yielding  $\geq 1000$  colony-forming units/mL. A catheter-related clinical sepsis without bloodstream infection (BSI) was a combination of body temperature ( $\geq 38.5$  °C or  $\leq 36.5$  °C), catheter colonization, pus at the insertion site, or resolution of clinical sepsis after catheter removal, and the absence of any other infectious focus. A catheter-related bloodstream infection (CR-BSI) was a combination of (1) one or more positive peripheral blood cultures sampled 48 h before or after catheter removal; (2) isolation of the same organism (same species and same susceptibility pattern) from the colonized catheter or from the catheter insertion site, or a blood culture differential time-to positivity of 2 h or more [23]; and (3) no apparent source of bacteremia other than the catheter. If a patient had a positive blood culture for coagulase-negative *Staphylococci* (CoNS), the same pulsotype from the strains recovered from the catheter and blood culture was required for a diagnosis of CR-BSI [15–17]. Alternatively, at least two positive cultures with CoNS from separate blood samples were required [18]. A major catheter-related infection (MCRI) was defined as either a catheter-related clinical sepsis without BSI or a CR-BSI. For patients without any catheter cultures, a blinded adjudication committee determined whether a MCRI was present; sepsis or BSI were classified as catheter-related when there was no other detectable cause of sepsis with or without BSI.

### Statistical analysis

Characteristics of patients and catheters were described as count (percent) or median (interquartile range) for qualitative and quantitative variables, respectively, and were compared between catheters groups using Chi-square, Fisher or Mann–Whitney tests, as appropriate.

The statistical plan had three steps: (1) the identification of the risk differences in catheter colonization, MCRI and CR-BSI between DC and CVC and to describe the daily risk of infection according to the duration of catheterization; and the conduct of (2) confirmatory and (3) additional explanatory analyses for specific subgroup of catheters.

We used a marginal Cox model for clustered data (PROC PHREG of SAS), to take into account a possible clustering effect of multiple catheters per patient. This model takes into account the censored nature of the data and possible intra-cluster dependence using a robust sandwich covariate estimate. Analyses were stratified by ICU and data were censored at 28 days since catheter

insertion. Hazard risk for catheter colonization, MCRI and CR-BSI was evaluated by univariate and multivariate analyses. The variable “catheter type” (DC vs. CVC) was forced in our multivariate models and the other variables showing significance in the univariate analysis were used as adjustment factors. The choice of adjustment variables was based on the results of the univariate analysis and refined by including clinically relevant variables and excluding redundant ones. The proportionality of hazard (PH) risks for catheter type was tested using Martingale residuals. We planned to introduce a time-dependent covariate in case of failure of PH. The graphical of daily risk of dialysis catheter-tip colonization, MCRI and CR-BSI was illustrated using the hazard rate function from right-censored data using kernel-based methods [24].

Confirmatory subgroup analyses were performed according to the duration of catheter maintenance ( $\leq 7$  days and  $>7$  days) and insertion site (femoral and jugular). Moreover, for patients with at least one CVC and one DC (resulting in a matched comparison), a sensitivity analysis was performed.

We conducted additional analyses to evaluate the differences of the skin cultures at catheter removal and microorganisms’ distribution between DC and CVC. Moreover, we compared the colonization risk between CVCs and DCs in patients whom information on the mode of first RRT (continuous renal replacement therapy [CRRT] or intermittent hemodialysis [IHD]) during the first 7 days of catheterization was available (786 DCs). Among DC, differences in mean dialysis time per day were calculated according to the duration of catheter maintenance ( $\leq 7$  days and  $>7$  days).

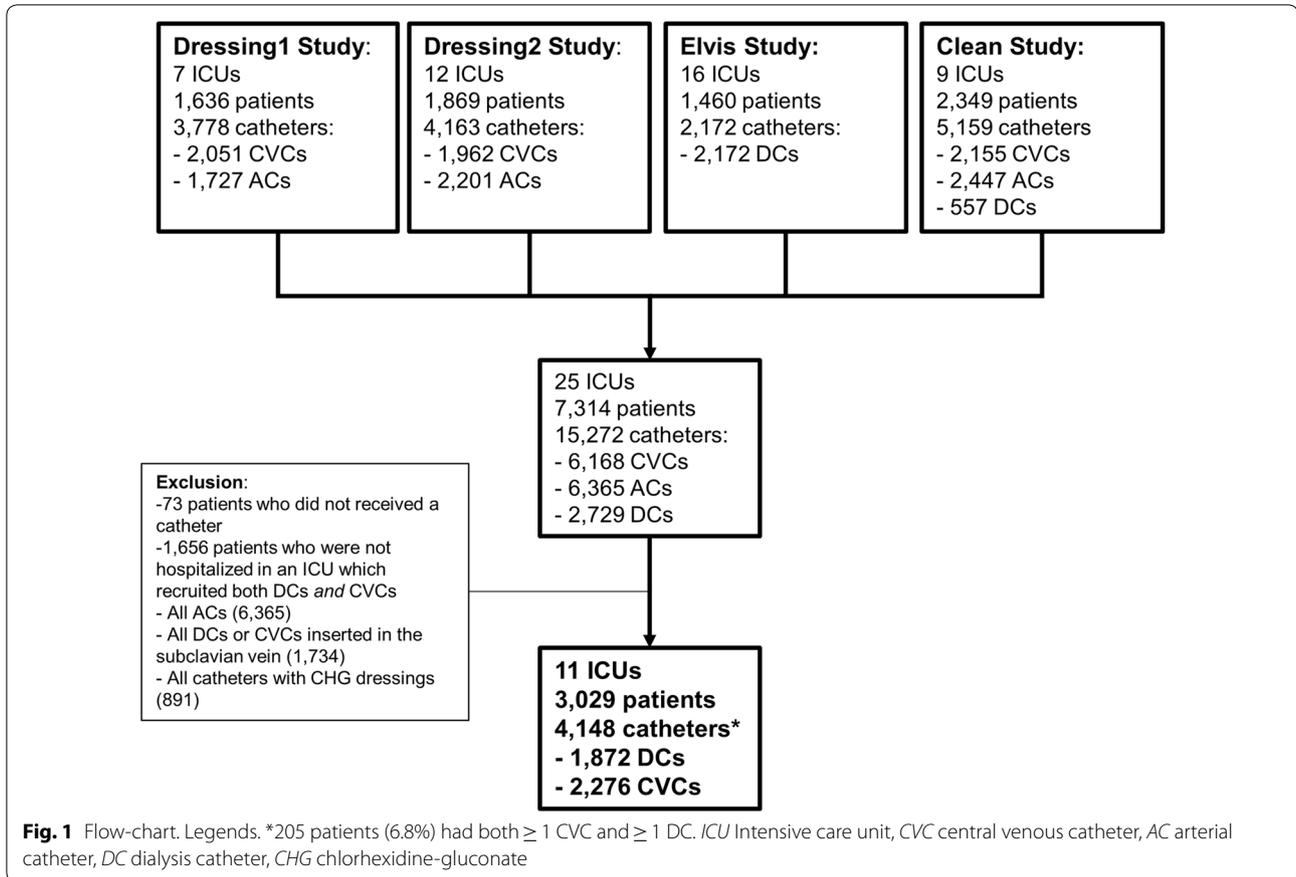
Tests were two-tailed, with  $p < 0.05$  being considered significant. All analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC). For more detailed information on Materials and methods, see the Electronic Supplementary Material (ESM).

## Results

### Patients and catheters

A total of 3029 patients with at least one DC and/or CVC were included by 11 ICUs in this study (Fig. 1); 1406 (46%) from the CLEAN study, 884 (29%) from the ELVIS study, 380 (13%) from the DRESSING1 study and 359 (12%) from the DRESSING2 study. A total of 4148 catheters and 31,547 catheter-days were analyzed; 205 patients (6.7%) had at least one DC and one CVC (537 catheters). Characteristics of the patients and catheters are described in Tables 1 and 2.

The incidence density per 1000 catheter-days was 13.3 for colonization (10.1% of the total number of catheters, 420 events), 2.0 for MCRI (1.5%, 64) and 1.4 for CR-BSI (1.1%, 45).



There were 2276 CVCs and 1872 DCs. In the CVC group, the patients had less comorbidities (63%) and their SAPS II at study inclusion was significantly lower (54, IQR [41; 68]) than patients with DCs. DCs were placed later during the hospitalization (median on 3rd ICU day), were most frequently inserted in the femoral vein (63%), and these patients received frequently antibiotics at insertion. In addition, the skin antiseptics was different according to the catheter type.

The proportionality of hazard was not respected for colonization ( $p=0.002$ ), marginally respected for MCRI ( $p=0.055$ ) and respected for CR-BSI ( $p=0.12$ ).

#### Catheter colonization

The incidence density was 13.0/1000 catheter-days for DCs and 13.6/1000 for CVC. In the univariate Cox model analysis (see ESM, Table E1), the infection risk was similar for DCs compared to CVCs (HR 0.88, CI 95% 0.71–1.09,  $p=0.24$ ). As shown in Fig. E1, the instantaneous hazard of catheter-tip colonization was higher in the first days of catheter maintenance among DCs and appeared to be higher for CVCs later. Using multivariate marginal Cox model with a time-dependent variable and after

adjustment on confounders, DCs were associated with an increased risk for colonization compared to CVCs within the first 7 days (1.45, 1.03–2.04,  $p=0.04$ , Table E2), whereas no significant differences between DCs and CVCs were observed after 7 days (0.82, 0.59–1.15,  $p=0.25$ , Table E2). In the subgroup analysis including only catheters with  $\leq 7$  days maintenance (2558 catheters), the colonization risk was still increased for DC (1.41, 0.99–2.02,  $p=0.06$ ). In the subgroup with  $>7$  days of catheter maintenance (1590 catheters), the risk of colonization of DC was not significantly different (Fig. 2 and Table E2). The analysis of patients with at least both one DC and one CVC showed similar trends (DC: HR 1.44, 0.93–2.24,  $p=0.10$ , Table E3).

#### Major catheter-related infection

The incidence density of MCRI per 1000 catheter-days was 2.6 for DCs and 1.6 for CVC. DC showed similar infectious risk compared to CVC (HR 1.34, 95% CI 0.81–2.21,  $p=0.26$ , Table E4) in the univariate analysis. Using graphical methods, the instantaneous hazard of MCRI was higher in the first days of catheterization for DCs (Fig. E1). In the multivariate marginal Cox model, DCs

**Table 1 Patient's characteristics**

Characteristic	Patients with CVC* (n = 1716)	Patients with DC* (n = 1108)	p value
Sex			
Female	601 (35)	437 (39.4)	0.02
Male	1115 (65)	671 (60.6)	
Age (years)	64 [53; 75]	66 [56; 75]	<0.01
Admission category			
Medical	1343 (78.3)	926 (83.6)	<0.01
Scheduled surgery	94 (5.5)	73 (6.6)	
Emergency surgery	279 (16.3)	109 (9.8)	
Main reason for ICU admission			
Septic shock	377 (22)	292 (26.4)	<0.01
Cardiac shock	155 (9)	111 (10)	
Renal insufficiency	58 (3.4)	237 (21.4)	
Coma	181 (10.5)	58 (5.2)	
De novo respiratory failure	284 (16.6)	136 (12.3)	
Other shock	506 (29.5)	218 (19.7)	
Other reason	155 (9)	56 (5.1)	
Comorbidities			
No comorbidity	1088 (63.4)	355 (32)	<0.01
AIDS	46 (2.7)	33 (3)	0.64
Renal insufficiency	81 (4.7)	103 (9.3)	<0.01
Chronic heart failure	113 (6.6)	101 (9.1)	0.01
Diabetes	119 (6.9)	140 (12.6)	<0.01
Chronic respiratory failure	106 (6.2)	27 (2.4)	<0.01
Immunosuppression or solid organ transplant	156 (9.1)	116 (10.5)	0.23
Hematologic neoplasia or metastatic cancer	181 (10.5)	156 (14.1)	<0.01
SAPS II score at admission	54 [41; 68]	61 [47; 78]	<0.01
SOFA score at admission	9 [7, 12]	15 [11, 19]	<0.01
Mechanical ventilation at inclusion	1309 (76.3)	751 (67.8)	<0.01
Mechanical ventilation with PEEP $\geq$ 6 cm H <sub>2</sub> O at inclusion	641 (37.4)	452 (40.8)	0.07
Vasopressor at inclusion	1178 (68.6)	701 (63.3)	<0.01
In-ICU mortality	567 (33)	458 (41.3)	<0.01
In-hospital mortality	695 (40.5)	516 (46.6)	<0.01

Data are median [IQR] or n (%)

IQR interquartile range, CVC central venous catheter, DC dialysis catheter, AIDS acquired immunodeficiency syndrome, PEEP positive end-expiratory pressure, SAPS II simplified acute physiology score II, SOFA sequential organ failure assessment, ICU intensive care unit

\*The total number of patients included in this study was 3029; 205 patients had both CVC and DC and were not included in the data set illustrated in this table (2824 patients)

tended to increase the risk for MCRI compared to CVCs (1.26, 0.73–2.19,  $p=0.41$ , Table E5). Interestingly, when including only catheters with  $\leq 7$  days maintenance, we observed a significantly increased infection risk for DCs (2.97, 1.03–8.51,  $p=0.04$ , Fig. 2). Similar trends were observed if jugular and femoral catheters were separately analyzed (supplementary results, ESM).

#### Catheter-related bloodstream infections

The incidence density of CR-BSI per 1000 catheter-days was 1.5 for DCs and 1.3 for CVCs. In the multivariate

analysis, DCs tended to be associated with an increased risk of CR-BSI compared to CVCs (HR 1.26, 95% CI 0.73–2.19,  $p=0.41$ , Fig. 2 and Tables E6–E7).

#### Additional analyses

##### Skin colonization at removal

The skin at catheter removal was significantly more often sterile for CVC than DC ( $p<0.01$ , Table 3). The difference was larger within the first 7 days of catheter maintenance.

**Table 2 Catheter's characteristics**

Characteristic	CVC (n = 2276)	DC (n = 1872)	p value
Duration of catheter in place	6 [3, 10]	6 [3; 9]	< 0.01
Time from ICU admission to catheter insertion	1 [1; 4]	3 [1; 10]	< 0.01
Experience of the operator			
< 50 procedures	1537 (67.5)	1281 (68.4)	0.54
≥ 50 procedures	739 (32.5)	591 (31.6)	
Insertion site			
Left jugular	399 (17.5)	214 (11.4)	< 0.01
Right jugular	804 (35.3)	478 (25.5)	
Femoral	1073 (47.1)	1180 (63)	
Ultrasound guidance*	792 (45)	236 (44.4)	0.80
Skin antisepsis			
No CHG	1191 (52.3)	781 (41.7)	< 0.01
CHG 2%	698 (30.7)	297 (15.9)	
CHG < 2%	387 (17)	794 (42.4)	
Mechanical ventilation at insertion	1697 (74.6)	1319 (70.5)	< 0.01
Vasopressor at insertion	1260 (55.4)	1194 (63.8)	< 0.01
Antibiotics at insertion	1436 (63.1)	1334 (71.3)	< 0.01
Reason for removal			
Became useless	691 (30.4)	510 (27.2)	0.03
Suspicion of infection	318 (14)	198 (10.6)	< 0.01
Death	561 (24.6)	476 (25.4)	0.56
Local signs at catheter removal			
Redness at removal	235 (10.3)	104 (5.6)	< 0.01
No skin lesion at removal	1778 (78.1)	1580 (84.4)	< 0.01
Colonization	243 (10.7)	177 (9.5)	0.19
MCRI	29 (1.3)	35 (1.9)	0.12

Data are median [IQR] or n (%)

CVC central venous catheter, DC dialysis catheter, ICU Intensive care Unit, CHG chlorhexidine-gluconate, MCRI major catheter-related infection

\*The ultrasound guidance variable was available only for 2292 catheters

### Microorganisms

CoNS were more frequently associated with DCs, whereas polymicrobial flora characterized CVC colonization (Table E8). The distribution of microorganisms associated with CR-BSI was similar between DCs and CVCs.

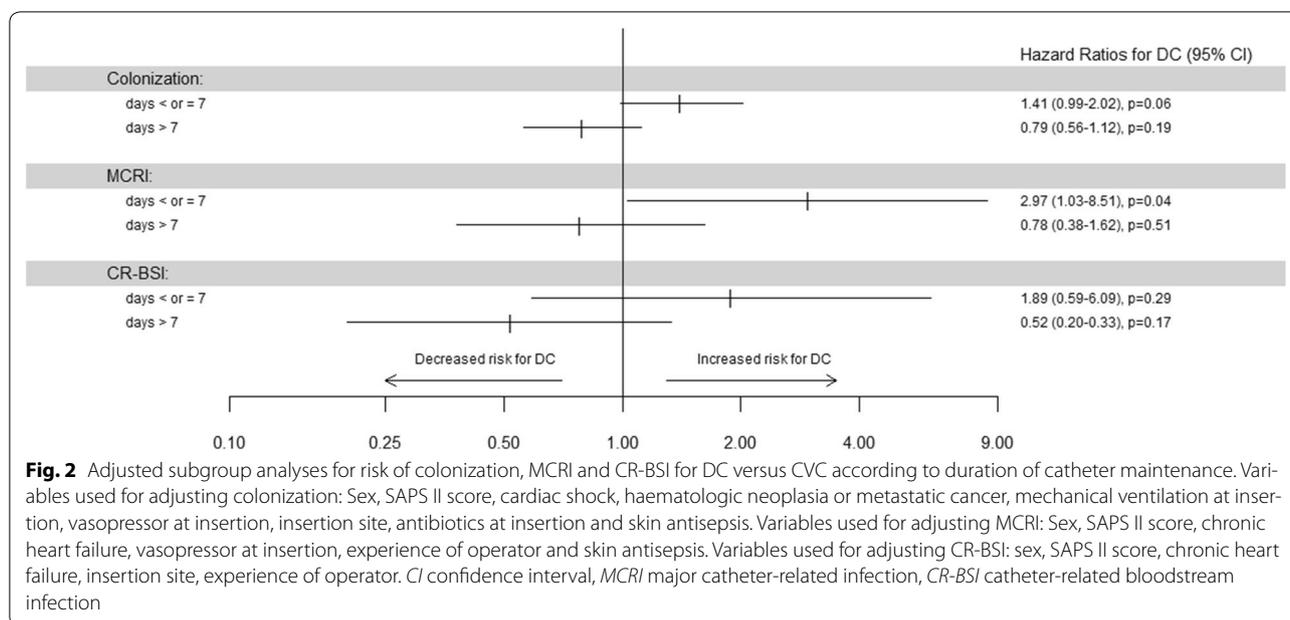
### Mode of first RRT and duration of dialysis

The risk of catheter tip colonization at removal was similar between catheters used for CRRT (HR 1.08, 95% CI 0.53–2.21;  $p=0.83$ ) versus catheters used for IHD as a first dialysis (1.24, 0.74–2.08,  $p=0.41$ ), and did not differ from the CVC group ( $p=0.69$ , Table E9). Overall, the mean dialysis duration was 4 h (h) and 48 min (min) per day for the first 7 days of catheter maintenance, compared to 2 h and 58 min per day after 7 days of catheter maintenance ( $p<0.01$ ). For more detailed information on results, see the ESM.

### Discussion

Through high-quality data from four multi-centric RCTs and after correction for other confounders, this post hoc analysis showed that daily hazard rates of colonization and MCRI for DCs were higher than those for CVCs. This finding was explained by an increased risk of infection for DCs within the first 7 days of catheter maintenance.

Few studies have worked out the differences between DCs and CVCs. In a systematic review in 2006, Maki et al. postulated that the use of short-term hemodialysis catheters was associated with an increased risk of infection [25]. However, this review 1) reported very high DC-related BSI rates, likely due to studies performed in the era before infection preventive bundles were implemented in routine, and 2) did not perform a direct comparison between DCs and CVCs. To our knowledge, only three limited studies directly assessed the infection risk in both DCs and CVCs [12–14]. All these studies showed that the infection risk related to DCs placed in critically



**Table 3 Skin colonization at catheter removal (main group and subgroup analyses)**

variable	CVC (n = 1548)	DC (n = 363)	p value*
All			
Sterile	233 (15.1)	4 (1.1)	<0.01
Low-grade colonization	666 (43)	234 (64.5)	
High-grade colonization	649 (41.9)	125 (34.4)	
≤ 7 days			
Sterile	158 (17.2)	2 (0.9)	<0.01
Low-grade colonization	426 (46.4)	150 (70.1)	
High-grade colonization	335 (36.5)	62 (29)	
>7 days			
Sterile	75 (11.9)	2 (1.3)	<0.01
Low-grade colonization	240 (38.2)	84 (56.4)	
High-grade colonization	314 (49.9)	63 (42.3)	

In 1911 catheters skin cultures were performed

DC dialysis catheter, CVC central venous catheter

\*Fisher exact test was performed

ill patients was similar to that of CVCs and remained unchanged with time [12–14]. Of note, due to the small numbers of patients included, the sole outcome considered was the colonization [12–14].

We found that DCs were associated with an increased risk for colonization and MCRI compared to CVCs. Subgroup analyses illustrated that the infection risk was significantly increased within the first 7 days after the catheter placement and was not influenced by the mode of RRT or the insertion site (supplementary discussion,

ESM). Moreover, skin colonization at catheter removal occurred more frequently for DCs and was greater in the first 7 catheter-days.

Debate still exists regarding the major route whereby microorganisms infect DCs, an extraluminal route arising from skin at the catheter insertion site or an intraluminal route emanating from the catheter hub [26]. In our study, the increase in the hazard of colonization and MCRI during the first 7 days with DC was associated with an increased skin colonization around the catheter insertion site. These findings suggest that the extraluminal route should be considered the main mechanism of DC infection. Indeed, the risk for catheter infections may be related to the density of local skin flora [27–29]. Our study also showed that the median duration of RRT per day was longer during the first 7 days of catheter maintenance than after. Although frequent manipulations during DC use may predispose the intraluminal route to DC colonization or infection [9] and therefore have partially influenced our results, a reasonable explanation for the early augmented risk for DC is that the significantly longer duration of dialysis time during the first 7 catheter-days may expose DCs to higher external and environmental contamination.

Our results provided a rational explanation for the negative results of two RCTs which tested ethanol lock (i.e., targeting the intraluminal route) for preventing catheter-related infections [17, 30]. A single-center study targeting the intraluminal route with citrate lock and including 78 ICU DC patients failed to demonstrate a reduction of CR-BSI [31]. A quasi-experimental study including two

historical cohorts matched on a propensity score compared the standard of care (either saline solution or heparin lock solution) with citrate lock, and found a reduction of the rate of dialysis catheter-tip colonization but not of CR-BSI in the treatment group [32]. In light of these considerations, we believe that the extraluminal route plays the predominant role in the pathogenesis of DC infections (supplementary discussion, ESM) and, therefore, our findings may substantially influence future prevention cares for DC. Importantly, targeted prevention strategies should focus on the first week after the catheter insertion. For example, the introduction of chlorhexidine-gluconate dressing in the first 7 days for DC may be worth. To our knowledge, the impact of chlorhexidine-gluconate dressings on short-term dialysis catheter infections was not evaluated.

Our study has several limitations. First, it was an observational study, and unmeasured factors may persist and cause residual confounding. However, we presented high-quality exhaustive data that were prospectively collected by trained investigators and study monitors during all RCTs. Second, we identified an increased risk for MCRI and colonization, but not for CR-BSI. The rate of CR-BSI was low, and our study may still be insufficiently powered to illustrate differences between DC and CVC, despite the very large population included. Third, for some subgroups analyses, we used the catheter colonization as endpoint because of the low MCRI and CR-BSI rate. However, colonization has been shown to reliably correlate with CR-BSI, which is the gold standard [33]. Fourth, only the CLEAN trial recruited both DC and CVC. We cannot exclude an increased heterogeneity between catheters included in the other trials. To mitigate this bias, only ICUs which recruited both DC and CVC were included in the current analysis. Finally, we described a large database designed to investigate the impact of certain prevention measures, and interactions may have occurred among the various study groups. However, our statistical analyses considered these potential drawbacks or excluded certain patients assigned to a specific treatment group.

## Conclusion

Using the largest data set ever collected from large multicentric RCTs conducted with consistent catheter care, we showed that the infection risk was higher for DC than CVC within the first 7 catheter days. Targeted prevention strategies for DC should focus on this short period following catheter insertion.

## Electronic supplementary material

The online version of this article (<https://doi.org/10.1007/s00134-019-05812-w>) contains supplementary material, which is available to authorized users.

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## Author contributions

All authors contributed to the study conception and design. Material preparation and analysis were performed by NB, SR and J-FT. The first draft of the manuscript was written by NB and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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## Compliance with ethical standards

## Conflicts of interest

The authors have disclosed that they do not have conflict of interest. JFT received fees for lectures to 3M, MSD, Pfizer, and Biomerieux. JFT received research grants from Astellas, 3M, MSD, and Pfizer. JFT participated to advisory boards of 3M, MSD, Bayer Pharma, Nabriva, and Pfizer. NB is currently receiving a Post.doc Mobility grant from the Swiss National Science Foundation (Grant Number: P400PM\_183865) and a grant from the Bangerter-Rhyner Foundation. JCL received fees for lectures for 3M, Pfizer MSD, and research grants from Anios. OM received fees for lectures for 3M and BD. OM received research grants from BD.

## Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

## Informed consent

Informed consent was obtained from all individual participants included in the study and whose decision-making capacity was intact.

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