

Catheter-related infections in intensive care units. Closing the knowledge gap with data from four randomized trials.

Dr. med. Niccolò Buetti

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 - Main objective & implementation: four studies and merging
 - Flow-chart & cohort description

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- a) Central venous catheters versus short-term dialysis catheters
- b) Microorganisms and insertion site
- c) Local signs and catheter-related infections

1.1 BACKGROUND:

- Short-term cath intensive care u
- Central venous patients.
- One third of all resulting in abo
- Short-term dialy rates as high as

All these cathet



0.459 (95% CI, 0.381-0.554) for CLABSI

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alization duration,

Blot SI et al., CID, 2005. O'Grady NP et al., CID, 2011. Dudeck MA et al., Am j inf con, 2015. O'Horo JC et al., Crit care med, 2014. Schneider A et al., ICM, 2017. Schreiber W et al., ICHE, 2018.

1.1 BACKGROUND & PATHOGENESIS:



Extraluminal: microorganisms contaminate the catheter during the insertion and subsequently migrate further along the outer lumen of the catheter

Endoluminal: microorganisms from the hands of healthcare workers contaminating and colonizing the catheter hub during care characterize long-term catheter (?) infections

Safdar N, Maki DG., ICM, 2004.

1.2 MAIN OBJECTIVE AND IMPLEMENTATION:

- To explore determinants (risk and prognostic factors) of catheterrelated bloodstream infections.
- Creation of large data base:
 - Data from <u>four large randomized trials</u> investigating prevention measures for catheter-related infections.
 - Merging the data was facilitated by the fact that all these studies rely on the <u>same definitions</u> and <u>similar inclusion criteria</u>.
 - <u>Data quality controls</u> have been ensured by study data monitoring during the data collection and before database lock.

1.2 IMPLEMENTATION: DRESSING 1

Chlorhexidine-Impregnated Sponges and Less Frequent Dressing Changes for Prevention of Catheter-Related Infections in Critically III Adults A Randomized Controlled Trial

Context Use of a chlorhexidine gluconate-impregnated sponge (CHGIS) in intravascular catheter dressings may reduce catheter-related infections (CRIs). Changing catheter dressings every 3 days may be more frequent than necessary.

Objective To assess superiority of CHGIS dressings regarding the rate of major CRIs (clinical sepsis with or without bloodstream infection) and noninferiority (less than 3%) colonization-rate increase) of 7-day vs 3-day dressing changes.

-ral-vein Reducing Use of CHGIS dressings with intravascular catheters in the intensive care unit reduced risk of infection even when back ground infection rates were low unit reduced risk of infection even when back ground infection rates were low Design, Setting, and Patients Assessor-blind, 2×2 factorial, randomized controlled trial conducted from December 2006 through June 2008 and recruiting patients from 7 intensive care units in 3 university and 2 general hospitals in France. Patients were adults (>18 years) expected to require an arterial catheter, central-vein catheter, or both inserted for 48 hours or longer.



Tir. JF *et al.,* JAMA, 2009.

Randomized Controlled Trial of Chlorhexidine Dressing and Highly Adhesive Dressing for Preventing Catheter-related Infections in Critically III Adults **1.2 IMPLEMENTATION: DRESSING 2**

Rationale: Most vascular catheter-related infections (CRIs) occur extraluminally in patients in the intensive care unit (ICU). Chlorhexidineimpregnated and strongly adherent dressings may decrease catheter colonization and CRI rates. the ICU with intravascular catheters. Highly adhesive dressing active ters increased skin and catheter but increased skin and *Objectives*: To determine if chlorhexidine-impregnated and strongly Get-Inpregnated dressings decreased the CRI rate in pr the ICU with intravascular catheters, Highly adhesive a decreased dressing detachment but increased due and decreased dressing detachment but increased adherent dressings decrease catheter colonization and CRI rates. Methods: In a 2:1:1 assessor-masked randomized trial in patients with vascular catheters inserted for an expected duration of 48 hours or more in 12 French ICUs, we compared chlorhexidine dressings, highly Conclusions: Alargen adhesive dressings, and standard dressings from May 2010 to July 2011. Coprimary endpoints were major CRI with or without catheterrelated bloodstream infection (CR-BSI) with chlorhexidine versus nonchlorhexidine dressings and catheter colonization rate with highly adhesive nonchlorhexidine versus standard nonchlorhexidine dressings. Catheter-colonization, CR-BSIs, and skin reactions were secondary endpoints.

Timsit JF *et al.*, Am J Respir Crit Care Med, 2012.

colonization.

1.2 IMPLEMENTATION: <u>ELVIS</u>

Abstract

Rationale: Ethanol rapidly eradicated experimental biofilm. Clinical studies of ethanol lock to prevent catheter-related infections (CRIs) suggest preventive efficacy. No such studies have been done in intensive care units (ICU).

Objectives: To determine whether ethanol lock decreases the risk of major CRI in patients with short-term dialysis catheters (DCs).

Methods: A randomized, double-blind, placebo-controlled trial was performed in 16 ICUs in seven university hospitals and one general hospital in France between June 2009 and December 2011. Adults with insertion of a nontunneled, nonantimicrobial-impregnated double-lumen DC for an expected duration greater than 48 hours, to perform renal-replacement therapy or plasma exchange, were randomly allocated (1:1) to receive a 2-minute catheter lock with either 60% wt/wt ethanol solution (ethanol group) or 0.9% saline solution (control group) at the end of DC insertion and after each renal-replacement therapy or plasma exchange session. The main

Ethanol Lock and Risk of Hemodialysis Catheter Infection in Critically III Patients A Randomized Controlled Trial

outcome was major CRI defined as either catheter-related clinical sepsis without bloodstream infection or catheter-related bloodstream **Conclusions:** A 2-minute ethanol lock does not decrease the frequency of infection of DCs in ICU patients. infection during the ICU stay.

Souweine B et al., Am J Respir Crit Care Med, 2015.

1.2 IMPLEMENTATION: CLEAN

Skin antisepsis with chlorhexidine-alcohol versus povidone iodine-alcohol, with and without skin scrubbing, for prevention of intravascular-catheter-related infection (CLEAN): an open-label, multicentre, randomised, controlled, two-by-two factorial trial

Summary

Background Intravascular-catheter-related infections are frequent life-threatening events in health care, but incidence

1.3 FLOW-CHART



Footnote:

- Only patients who received a catheter were included
- Some centers were regrouped

1.3 COHORT DESCRIPTION

PATIENTS

SEX	F	2606 (36)
	Μ	4635 (64)
AGE, mean (std) / median (IQR) / min-max		<u>62 (15.8) / 64 [</u> 53 ; 74] / 18-97
ADMISSION CATEGORY	Medical	5448 (75.3)
	Planned surgery	494 (6.8)
	Urgent surgery	1295 (17.9)
ORIGIN	Emergency unit	3248 (44.9)
	Clinic unit	3086 (42.6)
	ICU	536 (7.4)
	Other	371 (5.1)
MAIN REASON FOR ICU ADMISSION	Septic shock	1572 (21.7)
	Surgery, planned	243 (3.4)
	Trauma	435 (6)
	MOF	218 (3)
	Cardiac shock	585 (8.1)
	Haemorrhagic shock	310 (4.3)
	Other shock	207 (2.9)
	Acute respiratory failure	1646 (22.7)
	Acute COPD exacerbation	140 (1.9)
	Acute kidney insufficiency	546 (7.5)
	Coma	690 (9.5)
	Continuos surveillance	647 (8.9)

1.3 COHORT DESCRIPTION

PATIENTS

No comorbidity	4246 (58.6)
HIV	162 (2.2)
Cancer	395 (5.5)
Chronic renal failure	355 (4.9)
Chronic cardiac failure	533 (7.4)
Immunosupression	424 (5.8)
Organ transplant (SOT)	276 (3.8)
Hemopathy	381 (5.3)
Diabetes	583 (8.1)
Chronic respiratory failure	376 (5.2)
VM in the first 24h	5331 (73.6)
NIV in the first 24h	1418 (19.6)
No vasopressor at inclusion	2663 (36.8)
SAPS II score, mean (std) / median	55.6 (20.9) / 54 [40 ; 70]
(IQR)	
SOFA score , mean (std) / median	10.9 (5.2) / 10 [7 ; 14]
(IQR)	
LOS hospital, mean (std) / median	35 (38.7) / 24 [12 ; 45]
(IQR)	
LOS ICU, mean (std) / median (IQR)	16.2 (20.9) / 9 [5 ; 20]
Hospital mortality	2835 (39.2)
ICU mortality	2436 (33.6)

Standard dressing

1.3 COHORT DESCRIPTION CATHETERS 9314 (61.1) Experience Junior 5924 (38.9) Senior Catheter type AC 6375 (41.7) CVC 6168 (40.4) DC 2729 (17.9) Insertion site Jugular 2876 (18.8) Subclavian 2260 (14.8) Femoral 6015 (39.4) Radial 4108 (26.9) **Right side** 9091 (59.6) No Ultrasound 7587 (83) Numbers of lumens, mean (std) / 2 (0.9) / 2 [1;3] / 1-4 median (IQR) Skin antisepsis Non-Chlorhexidine 8329 (54.5) Chlorhexidine 6943 (45.5) **CHX-Sponge** 1953 (12.8) Dressing CHX-Gel 2108 (13.8) **Tegaderm HP** 988 (6.5)

10223 (66.9)

1.3 COHORT DESCRIPTION

CATHETERS

MV at insertion	11553 (75.7)
Vasopressor at insertion	7526 (52.2)
Antimicrobial at insertion	9602 (62.9)
Lipid administration	2711 (17.8)
Heparin administration	5098 (33.4)
Packed red cells transfused	2278 (14.9)
Colonization	1236 (8.1)
CRBSI	116 (0.8)
MCRI	164 (1.1)
Catheter-days, mean (std) / median (IQR)	7 (6.5) / 5 [2 ; 9] Outcomes

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multi-centric randomized trials

and Jean-François Timsit 1.7* ()

Flow-chart and cohort description

2) Specific analyses

- c) Local signs and catheter-related inft Short-term dialysis catheter infections in ICU patients. Niccolò Buetti¹, Stéphane Ruckly¹, Jean-Christophe Lucet^{1,2}, Olivier Nimoz^{3,4,5}, Bertrand Souweine⁶ Intensive



2.2 METHODS

Patients:

- 2006 to 2014 in different ICUs in France.
- Only patients from ICU which recruited both DCs and CVCs included.

Catheters:

- <u>Only DC and CVC included (= exclusion arterial catheters)</u>.
- <u>Chlorhexidine-impregnated (CHG) dressing</u> catheters: excluded.
- DC and CVC inserted in the subclavian vein: excluded.

Statistics:

- Risk differences in <u>catheter infections (MCRI and CR-BSI)</u> and <u>colonization</u> between DC and CVC and to describe the daily risk of colonization/infection according to the <u>duration of</u> <u>catheterization</u>.
- <u>Univariate and multivariate marginal Cox</u> models for clustered data.
- Skin colonization evaluation.

2.3 PATIENTS & CATHETER SELECTION



2.4 MAIN RESULTS: COLONIZATION, MCRI and CR-BSI



2.4 MAIN RESULTS: SKIN COLONIZATION AT REMOVAL

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)			
\leq 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					

2.5 DISCUSSION



Several studies targeted the intraluminal route (i.e. lock) for preventing catheter-related infections: negative results...

CVC: main infection route \rightarrow extraluminal route **DC:** frequent manipulations during DC \rightarrow the intraluminal route predisposed to DC colonization/infection

HOWEVER OUR RESULTS...

Figure modified from Safdar N, Maki DG, ICM, 2004. Mermel LA, CID, 2011.

Souweine et al., Am J Respir Crit Care Med, 2015. Perez-Granda MJ et al., PLOS one, 2014. Hermite M et al., ICM, 2012.

2.5 DISCUSSION



Several studies targeted the intraluminal route (i.e. lock) for preventing catheter-related infections: negative results...

CVC: main infection route \rightarrow extraluminal route **DC:** frequent manipulations during DC \rightarrow the intraluminal route predisposed to DC colonization/infection

HOWEVER OUR RESULTS...

...suggested that the extraluminal route \rightarrow main mechanism of DC infection.

A) Infectious risk higher after the catheter insertion

B) DCs were associated with an increased skin colonization around the catheter insertion site

Figure modified from Safdar N, Maki DG, ICM, 2004. Mermel LA, CID, 2011.

Bouza et al., Crit Care Med, 2005

2.5 DISCUSSION

- Our findings may substantially influence future prevention cares for DC.
- Targeted prevention strategies should focus on the first week after the catheter insertion.
- Introduction of CHG dressing in the first 7 days for DC (?).

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B) MICROORGANISMS AND INSERTION SITE OBJECTIVE: to describe the epidemiology of causative microorganisms of catheter related infection and colonization accordingdered for to the insertion site. Rupp M et al., Infectious disease clinics of North America, 2018. Lorente L et al., Crit Care Med, 2007. Lorente L et al., Crit Care Med, 2008.

2.2 METHODS

Patients:

- 2006 to 2014 in different ICUs in France.

Catheters:

- all

Statistics:

- The microbiological, epidemiological, clinical and <u>microbiological</u> characteristics of the <u>colonized and infected catheters (CR-BSI)</u> compared between <u>insertion site groups</u>: Wilcoxon-, chi square- or Fisher-test.
- <u>Confirmatory analyses</u>: logistic regression models for clustered data with the response variable "non-fermenting Gram-negative bacilli".

2.3 PATIENTS & CATHETERS



2.4 RESULTS: CVCs



First exploratory analysis

polymicrobial
 Gram-positive other than Enterococci
 <u>Non-fermenting gram-negative bacilli</u>
 Fungi

Enterobacteriaceae and Enterococci

After adjustment for confounding factors: Femoral site OR for NFGN CRBSI 6.33, CI 95% 1.59-25.28, p<0.01.

Individual pathogen analysis CR-BSI

	Non-femoral	Eemoral	p-value
CONS.	11 (23.4)	10 (28.6)	0.60
Enterococci	5 (10.6)	0 (0)	0.05
S. auteus.	17 (36.2)	6 (17.1)	0.06
E. coli	1 (2.1)	1 (2.9)	0.83
Other Enterobacteriaceae	9 (19.1)	7 (20)	0.92
Non-fermenting Gram-negative bacilli	4 (8.5)	11 (31.4)	<0.01
Fungi	4 (8.5)	1 (2.9)	0.29
Other Gram-positive bacteria	0 (0)	1 (2.9)	0.24

2.4 RESULTS: Arterial catheters



First exploratory analysis

polymicrobial

Gram-positive other than Enterococci
 Non-fermenting gram-negative bacilli
 Fungi

Enterobacteriaceae and Enterococci

Individual pathogen analysis (colonization)

	Radial	Femoral	p-value
CONS	157 (56.5)	97 (49)	0.11
Enterococci	13 (4.7)	22 (11.1)	<0.01
0	17 (0.4)	0 (0)	0.40
S. aureus	17 (6.1)	6(3)	0.12
E soli	11 (4)	11 (E C)	0.44
E. COII	11 (4)	11 (0.0)	0.41
Other Enterohacteriaceae	36 (12 0)	52 (26 3)	<0.01
Other <u>Emeropacienaceae</u>	30 (12.3)	52 (20.5)	NO.01
Non-fermenting Gram-negative bacilli	33 (11.9)	40 (20.2)	0.01
	,		
Fungi	6 (2.2)	7 (3.5)	0.36
5	. ,	. ,	
Other gram-positive bacteria	31 (11.2)	11 (5.6)	0.03
Other gram-negative bacteria	5 (1.8)	3 (1.5)	0.81



2.5 DISCUSSION

Our findings may **influence the selection of empirical antibiotic therapy** with two main recommendations:

- 1) <u>Antipseudomonal antibiotics</u> should be administered together with antibiotics targeting Gram-positive microorganisms if a <u>CR-BSI</u> related to a femoral catheter is suspected.
- 2) <u>Antifungal therapy may not be indicated</u> in selected patient populations for suspected intravascular catheter infection.

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Buetti N et al., BMJ open, 2018.

C) LOCAL SIGNS AND CATHETER-RELATED

2.2 METHODS

Patients:

- 2006 to 2014 in different ICUs in France.

Catheters:

- All (with documented local signs).

Outcomes:

- <u>CRBSI</u>
- Local signs (at removal): redness, pain, non-purulent discharge, purulent discharge and ≥1 local sign

Statistics:

- Evaluate the association between CRBSI and local sign.
- Identify the risk factors for developing a specific local sign.
- Identify the <u>role of the different local signs</u> for developing CRBSI in <u>subgroup of clinically relevant populations</u>.



Cochran's Q test





2.3 PATIENTS & CATHETERS



2.3 RESULTS

	Prevalence of local sign	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Redness`(n=1633)	11.2	28.1 (20.4-37.2)	88.9 (88.4-89.4)	2.0 (1.4-2.7)	99.4 (99.2-99.5)
Pain (n=59)	0.4	1.7 (0.3-5.9)	99.6 (99.5-99.7)	3.3 (0.6-11.3)	99.2 (99.1-99.4)
Non-purulent discharge (n=251)	1.7	6.1 (2.8-11.2)	98.3 (98.1-98.5)	2.8 (1.2-5.6)	99.3 (99.1-99.4)
Purulent discharge (n=102)	0.7	11.4 (6.3-18.6)	99.4 (99.2-99.5)	12.7 (7.1-20.8)	99.3 (99.2-99.4)
≥1 local sign (n=1938)	13.3	40.4 (31.4-49.6)	86.9 (86.4-87.5)	2.4 (1.8-3.2)	99.5 (99.3-99.6)

2.3 RESULTS

	Association local signs & CRBSI	Subgroup			Odds ratios (95% CI)		
	Skin colonizat	tion at rer	noval		3.14 (2.08-4.74), p<0.01 2.73 (1.75-4.27), p<0.01	Variables indip associated wit	endently h (less) ≥1 local
Γ			without local	signs	with	≥1 local sign	
	high-grade color	nization	2158 (27.9)		582	(40)	<0.01
	low-grade coloni	zation	2214 (28.6)		411	(28.3)	
1	sterile		3373 (43.6)		461	(31.7)	
		unadjusted CRBSI			— 20.81 (11.26-38.45), p<0.01		
		adjusted CRBSI****		-	- 18.60 (9.69-35.70), p<0.01		
		>= 1 local sign			4 50 (2 00 0 50) = -0.04		
		adjusted CRBSI			4.50 (3.09-6.56), p<0.01		
		-		10			

2.3 RESULTS

	Subgroup	O	ODDS Ratio		CRBSI (n=114)	p-value	p-value heterogeneity
>	=1 local sign for all catheters		_ 	1892 (13.1)	46 (40.4)	<0.01	
	Suspicion of infection (=2,034) No suspicion of infection (=12,556)			704 (36) 1188 (9.5)	40 (51.3) 6 (16.7)	<0.01 0.15	0.97
	Pathological temperature (n=7,979) No pathological temperature (n=6,611)			954 (12.1) 938 (14.3)	31 (42.5) 15 (36.6)	<0.01 <0.01	0.27
	Catheter-days <=7 (n=9,753) Catheter-days >7 (n=4,837)		_	773 (8) 1119 (23.4)	18 (35.3) 28 (44.4)	<0.01 <0.01	0.02
	CVC (n=8,500) AC (n=6,090)		_	1041 (12.4) 851 (14)	31 (38.3) 15 (45.5)	<0.01 <0.01	0.72
	Immunosuppression (n=1,426) No immunosuppression (n=13,164)			120 (8.5) 1772 (13.6)	2 (22.2) 44 (41.9)	0.16 <0.01	0.63
	Low SOFA score (n=8,338) High SOFA score (n=6,252)		- _	1269 (15.3) 623 (10.1)	29 (48.3) 17 (31.5)	<0.01 <0.01	0.56
			1 5 10				

At least one sign was more predictive for CRBSI in the first 7 days of catheter maintenance (OR 6.30 *vs.* OR 2.61 for >7 days, p_{for heterogeneity}=0.02).

2.4 DISCUSSION

 Old study: insertion site appearance <u>was not</u> associated with catheter colonization or CVC-related bloodstream infections.

\rightarrow In contrast to our results!

• CRBSI in our cohort were due to *S. aureus* and Gram-negative bacilli: only 14% CoNS *vs* Safdar *et al.* : Table 2. Microbial profile of central venous cath-

Microoganism	n	%
CoNS	15	14.15
Staphylococcus aureus	21	19.81
Enterococci	2	1.89
Enterobacteriaceae	22	20.75
Non-fermenting gram-negative bacilli	16	15.09
Other gram-negative	1	0.94
Fungi	5	4.72
Polymicrobial CRBSI	24	22.64

Table 2. Microbial profile of central ver eter–related blood stream infections	nous cath-
Pathogen	No.
Coagulase-negative staphylococci Enterococci	27

Safdar N, Maki DG, Crit Care Med, 2002.

Enterobacter cloacae Klebsiella pneumoniae Burkholderia cepacia Candida species

2.4 DISCUSSION

Table 3: Practical clinical implications.	
Factors that independently decreased local signs at insertion site:	 Older age Severe ill patients Immunosuppression Catheter maintenance ≤7 days
Factors influencing the management of catheter	 Redness, non-purulent discharge and purulent discharge were significantly associated to CRBSI compared to pain. Local signs observed in the first 7 days are highly predictive for intravascular catheter infections. Pathological temperature, catheter type and severity of illness in the presence of local signs do not help clinician in predicting intravascular catheter infections.

NERC

niccolo.buetti@gmail.com