Vascular catheter infections: time to get technical

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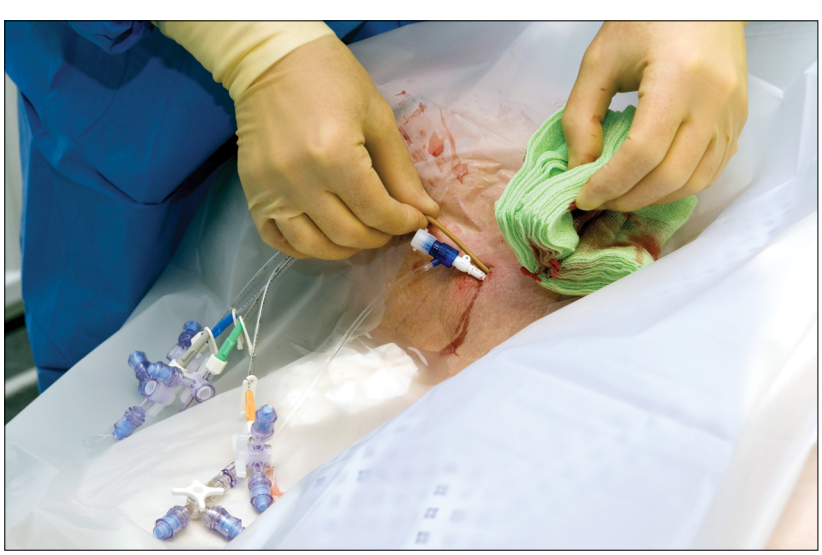
Catheter-related bloodstream infections were once viewed as an inescapable consequence of providing care to critically ill patients. It was not until the beginning of the 21st century that a conceptual model identified both technical and socioadaptive strategies to prevent this outcome.[1] Key among technical factors were processes such as skin disinfection with chlorhexidine and use of large drapes at the time of insertion to prevent catheter contamination. Conversely, socioadaptive factors were focused on behavioural aspects such as adhering to proper hand hygiene, nurse-led halts if parts of sterile insertion were not followed, and targeting of unit-specific culture to increase compliance. Although closely intertwined, combining technical and socioadaptive factors within a bundle of best practices has substantially reduced catheter-related bloodstream infections in the past decade.[2]

But which elements of this bundle are most responsible for reducing catheter infections? This question is not merely a point of academic debate, but one that has important clinical and policy ramifications. For example, empowering nurses to stop physicians if hand hygiene before catheter insertion is not performed or specific sterile technique is not followed requires changes in social norms and organisational culture. Such initiatives are difficult and might distract from more efficient preventive measures if not effective. Alternatively, if a technical factor such as chlorhexidine is most responsible for reductions in bloodstream infection, then implementation of a chlorhexidine-only skin antisepsis strategy is relatively straightforward and less likely to meet resistance.[3]

The powerful ability of chlorhexidine to reduce a wide range of health-care-associated infections is well known.[4,5] Although a meta-analysis reported superiority of chlorhexidine over povidone iodine to prevent catheter infections, available data were limited by differences in definitions of catheter-related infection and use of varying concentrations of chlorhexidine or alcohol.[6] Isolation of the active ingredient responsible for prevention of vascular catheter infections has therefore been difficult.[3] In *The Lancet*, Olivier Mimoz and colleagues[7] report the results of a randomised controlled trial to compare 2% chlorhexidine–alcohol with 5% povidone iodine–alcohol for skin antisepsis (with or without scrubbing of the skin) to prevent catheter infection. Results of this methodologically rigorous investigation involving 1181 patients in 11 French intensive-care units across a number of vascular devices and outcomes were clear: compared with povidone iodine–alcohol, chlorhexidine–alcohol significantly reduced catheter-related infections (hazard ratio [HR] 0·15, 95% CI 0·05–0·41). Findings favouring chlorhexidine–alcohol also extended to catheter colonisation, often the prelude to infection (HR 0·18, 95% CI 0·13–0·24).

These data inform clinical practice in several ways. First, results suggest that chlorhexidine–alcohol is superior to alcohol containing povidone iodine. Notably, although infection was not significantly reduced for central venous catheters, the point-estimate trended towards benefit and the wide 95% CI supports lack of statistical power for these devices (HR 0·54, 95% CI 0·16–1·56). Second, chlorhexidine was effective despite low baseline rates of catheter infection across participating sites, suggesting that the goal of zero rates of catheter infection is not only plausible, but also feasible. Third, in an era of modern antiseptics, separately scrubbing the skin before inserting lines seems ineffective; thus, such practice should no longer be used.

Despite these important take-away messages, questions remain. First, although the number of skin reactions associated with chlorhexidine was low



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(27 [3%] patients), they were increased compared with povidone (seven [1%] patients) and these outcomes are problematic when advocating for a chlorhexidine-only approach. Further study should be done to predict who will develop such events and how best to manage them. Second, only commercially available, fixed combinations of alcoholic–chlorhexidine or povidone iodine were tested; generalising findings to other formulations of povidone iodine or different solutions of chlorhexidine might thus be premature. Relatedly, whether the benefits attributable to chlorhexidine are mediated by the alcohol component, a minimum inhibitory concentration of chlorhexidine, or interplay of both substances on the skin is unknown and remains a topic of intense debate.[8] Third, peripherally inserted central catheters were not included in this study, despite being increasingly prevalent. Because dwell times, bacterial density, and care practices in the upper arm set these devices apart from others, studies that include peripherally inserted central catheters are needed.[9]

Mimoz and colleagues[7] provide strong evidence to support the technical intervention of alcoholic chlorhexidine as a powerful way to reduce vascular catheter infections. Although use of chlorhexidine has grown in the USA,[10] this is not the case in all nations and work to understand and overcome barriers is needed.[11] This study should also prompt the infection-prevention community to reflect on how best to prevent other health-care-associated infections. For example, current efforts to prevent catheter-associated urinary tract infection and *Clostridium difficile* mainly focus on socioadaptive elements such as removal of indwelling catheters or avoidance of unnecessary antimicrobial use. Given the absence of a straightforward technical solution to prevent these infections, socioadaptive elements are necessary but have met limited success. Indeed, changes in clinician behaviour or organisational culture to reduce infection is far more complex than swapping out one skin disinfectant for another.[12] Thus, although a key technical solution (chlorhexidine–alcohol) should become the standard of care to prevent vascular catheter infections, now might be a good time to consider getting even more technical to prevent other health-care-associated infections.

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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

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Summary

Background Intravascular-catheter-related infections are frequent life-threatening events in health care, but incidence can be decreased by improvements in the quality of care. Optimisation of skin antisepsis is essential to prevent short-term catheter-related infections. We hypothesised that chlorhexidine–alcohol would be more effective than povidone iodine–alcohol as a skin antiseptic to prevent intravascular-catheter-related infections.

Methods In this open-label, randomised controlled trial with a two-by-two factorial design, we enrolled consecutive adults (age ≥18 years) admitted to one of 11 French intensive-care units and requiring at least one of central-venous, haemodialysis, or arterial catheters. Before catheter insertion, we randomly assigned (1:1:1:1) patients via a secure web-based random-number generator (permuted blocks of eight, stratified by centre) to have all intravascular catheters prepared with 2% chlorhexidine–70% isopropyl alcohol (chlorhexidine–alcohol) or 5% povidone iodine–69% ethanol (povidone iodine–alcohol), with or without scrubbing of the skin with detergent before antiseptic application. Physicians and nurses were not masked to group assignment but microbiologists and outcome assessors were. The primary outcome was the incidence of catheter-related infections with chlorhexidine–alcohol versus povidone iodine–alcohol in the intention-to-treat population. This study is registered with ClinicalTrials.gov, number NCT01629550 and is closed to new participants.

Findings Between Oct 26, 2012, and Feb 12, 2014, 2546 patients were eligible to participate in the study. We randomly assigned 1181 patients (2547 catheters) to chlorhexidine–alcohol (594 patients with scrubbing, 587 without) and 1168 (2612 catheters) to povidone iodine–alcohol (580 patients with scrubbing, 588 without). Chlorhexidine–alcohol was associated with lower incidence of catheter-related infections (0·28 *vs* 1·77 per 1000 catheter-days with povidone iodine–alcohol; hazard ratio 0·15, 95% CI 0·05–0·41; p=0·0002). Scrubbing was not associated with a significant difference in catheter colonisation (p=0·3877). No systemic adverse events were reported, but severe skin reactions occurred more frequently in those assigned to chlorhexidine–alcohol (27 [3%] patients *vs* seven [1%] with povidone iodine–alcohol; p=0·0017) and led to chlorhexidine discontinuation in two patients.

Interpretation For skin antisepsis, chlorhexidine–alcohol provides greater protection against short-term catheter-related infections than does povidone iodine–alcohol and should be included in all bundles for prevention of intravascular catheter-related infections.

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Introduction

Catheter-related bloodstream infections are common infections in health care settings that are associated with high mortality.[1] Skin at the insertion site and the catheter hub or connector are the main sources of pathogens for infection, with skin the main source when catheters are placed for a shorter duration of time and the hub or connector being the main source in longer timeframes.[2] Therefore, optimum skin antisepsis is crucial during short-term catheter insertion and maintenance. Alcohol has the greatest immediate efficacy, with 70% isopropyl alcohol being microbiologically superior to 69% ethanol, but does not have persistency on skin.[3] The action of chlorhexidine or povidone iodine is slower, less profound, and chlorhexidine has substantial persistency on skin.[4–6] Use of chlorhexidine–alcohol at chlorhexidine concentrations higher than 0·5% has been advocated as the first-line solution for catheter insertion-site antisepsis in USA[7] and English[8] guidelines because it combines the immediate microbicidal activity of alcohol and the persistent (residual) activity on skin of chlorhexidine. However, the authors of these recommendations point

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See Online for appendix

Research in context

Evidence before this study

In their 2011 guidelines for the prevention of intravascular catheter-related infections, the US Centers for Disease Control and Prevention stated that substances for skin preparation before catheter insertion was an unresolved issue. Although evidence was accumulating for use of chlorhexidine for skin preparation before catheter insertion, the higher clinical efficacy of chlorhexidine reported in studies could not be attributed to the chlorhexidine alone, but rather to the combination of chlorhexidine with alcohol, when compared with aqueous povidone iodine. Chlorhexidine in alcohol and povidone iodine in alcohol had not been compared head to head in a large-scale trial. The bactericidal efficacy of povidone iodine might be compromised by the presence of skin biomaterials, with possible partial inactivation of the antiseptic agent and so whether scrubbing before skin antisepsis before surgery should be done was also debated.

Added value of this study

We did a multicentre randomised controlled trial in 11 intensive care units in which all patients due to receive a central venous catheter, arterial catheter, or haemodialysis catheter were enrolled to receive skin preparation with 2% chlorhexidine–70% isopropyl alcohol or 5% povidone iodine–69% ethanol, both preceded or not by skin scrubbing, for antisepsis. Patients assigned to receive the chlorhexidine–alcohol combination had fewer catheter-related infections and catheter-related bloodstream infections compared with those assigned to receive the povidone iodine–alcohol combination. Skin scrubbing before skin antisepsis did not reduce the incidence of catheter colonisation.

Implications of all the available evidence

Chlorhexidine–alcohol combination should now be the standard of skin preparation before catheter insertion. Scrubbing of the skin with detergent should not. Whether the combination should be used for skin preparation before surgery remains to be established, as do the optimum concentration of chlorhexidine and type and concentration of alcohol to be combined with chlorhexidine.

out that few head-to-head comparisons of chlorhexidine and povidone iodine in alcoholic formulations are available and that a large-scale randomised trial would be helpful. French guidelines[9] recommend an alcoholic formulation of either chlorhexidine or povidone iodine in this setting with no advantage of one product over the other.

Scrubbing of the skin with antiseptic detergent before application of an antiseptic solution decreases the amount of bacteria and (potentially antiseptic-inhibiting) protein-rich biomaterials on the skin.[10] The recommendations of US Centers for Disease Control and Prevention (CDC) do not provide advice on cleansing the skin before application of antiseptic.[7] No large randomised trials have tested skin cleansing with a detergent before antisepsis.

We hypothesised that application of 2% chlorhexidine–70% isopropyl alcohol (chlorhexidine–alcohol) was more effective than 5% povidone iodine–69% ethanol (povidone iodine–alcohol) to prevent short-term catheter-related infections. We also hypothesised that scrubbing of the skin with an antiseptic detergent before antiseptic application would not reduce catheter colonisation compared with application of antiseptic alone.

Methods

Study design and participants

We did an open-label, multicentre, randomised, controlled, two-by-two factorial design study. The study protocol has been published previously.[11] We recruited patients in 11 French intensive-care units in five university hospitals and one general hospital. Five intensive-care units were medical, five surgical, and one medical–surgical. We enrolled consecutive adult patients (≥18 years) who required at least one of an arterial, haemodialysis, or central venous catheter for 48 h or longer unless they had known intolerance, hypersensitivity, or contraindication to any trial drug; were likely to die within 48 h after admission; needed a catheter coated with antimicrobial agents; or had previously been enrolled in this trial. We obtained written informed consent before study inclusion from competent patients and at competence recovery from incompetent patients, according to French law. The study was approved by the ethics committee of the Poitiers University Hospital, France, based on French guidelines for prevention of catheter-related infection.[9]

Randomisation and masking

A statistician not involved in either screening patients or assessing outcomes provided a computer-generator number list. Randomisation was done through a secure web-based randomisation system and stratified by centre. We randomly assigned (1:1:1:1) patients in permuted blocks of eight to one of the four treatment groups based on skin preparation procedures (chlorhexidine–alcohol or povidone iodine–alcohol, with administration preceded by skin scrubbing with an antiseptic detergent [two-step procedure] or administration with no scrubbing [one-step procedure]). Masking of the participants and staff in the intensive-care units was not feasible because the study antiseptics had different colours and formulations. However, microbiologists who tested the catheters and blood samples, the four outcome assessors, and the statisticians were all masked to group assignment.

Procedures

All study centres were required to follow French recommendations, similar to CDC recommendations, for catheter insertion and care.[7] For each patient, all intravascular catheters needed for standard care were inserted and maintained in the same way with either 2% (weight/volume [w/v]) chlorhexidine and 70% (v/v) isopropyl alcohol (ChloraPrep, CareFusion, Voisins le Bretonneux, France) or 5% (w/v) povidone iodine and 69% (v/v) ethanol (Betadine alcoolique, MEDA Pharma SAS, Paris, France), with (two-step procedure) or without (one-step procedure) scrubbing with an antiseptic detergent (4% [w/v] chlorhexidine, Hibiscrub, Molnlycke Health Care, Wasquehal, France, or 4% [w/v] povidone iodine, Betadine Scrub, MEDA Pharma, respectively). The same assigned antiseptic procedure was used at each dressing change.

In the one-step procedure, the physician who inserted the catheter disinfected the skin using maximal barrier precautions. The antiseptic was applied by moving back and forth (chlorhexidine–alcohol) or by circular movements (povidone iodine–alcohol) for at least 30 s, starting at the catheter insertion site and then extending to the entire work area. Large sterile drapes were applied once the work area was dry. The catheter was then inserted without any further application of antiseptic. In the two-step procedure, the work area was scrubbed by a nurse using sterile gauze soaked with antiseptic detergent and applied by circular movements for at least 15 s, rinsed with sterile water, and dried with sterile gauze. Study antiseptic was then applied, followed by large sterile drapes, and the physician inserted the catheter using maximal barrier precautions as described for the one-step procedure.

After insertion, the catheters were dressed with semi-permeable transparent dressing. In each unit, the same catheter and dressing types were used throughout the study. Catheter insertion sites were inspected daily for signs of infection by attending nurses not masked to the antiseptic group. Dressings were changed 24 h after catheter insertion and then every 3–7 days according to standard practice in each intensive-care unit. Leaking, soiled, or wet dressings were changed immediately. Manipulation of lines and three-way stopcocks was done with gauze moistened with the same antiseptic used for catheter insertion. Use was not allowed of antiseptic-containing dressings, topical antimicrobial ointments, antimicrobial filters, and line locks. Blood sampling through the central venous line was also not allowed.

A poster showing how to carry out skin preparation and kits containing all the products required to prepare the skin in each randomisation group were available in each patient's room to avoid misuse of antiseptics. Before study initiation, the health-care providers attended training sessions designed to homogenise skin preparation practices across units. An independent clinical research assistant was available at each participating hospital to help with data collection and to monitor the conduct of the study.

Patients were monitored until 48 h after discharge from intensive-care. Catheters were removed if no longer needed, usually before discharge from the unit or when a catheter-related infection was suspected. Catheter tips were cultured with a simplified quantitative broth dilution technique.[12] In patients who needed use of the catheter after discharge, paired blood samples were drawn simultaneously via the catheter hub and from a peripheral venous site for determination of the differential time to positivity.[13] We evaluated skin colonisation before catheter removal by pressing a sterilised nutritive trypticase-soy agar plate containing antiseptic neutralising agents (Count-tact, 3P Pack+, Biomérieux, Crapone, France) on the skin for 10 s. The plates were then sent to the local microbiology laboratory of their respective hospital and cultured for 48 h. The number of colony-forming units (CFUs) per agar plate was counted as has been previously done.[14,15] We routinely obtained sets of aerobic and anaerobic blood cultures in patients with fever (body temperature ≥38·5°C), hypothermia (≤36·5°C), or other symptoms such as chills (a sensation of cold, with convulsive shaking of the body) or sudden shock (systolic blood pressure <90 mm Hg or decrease of 40 mm Hg or more in systolic pressure compared with baseline in patients with arterial hypertension), and when a catheter-related infection was suspected.

When a catheter-tip culture or a blood culture sampled 48 h before or after catheter removal tested positive, or when a catheter-tip was not cultured and no blood culture was drawn for determination of the differential time to positivity before catheter removal, two assessors masked to the group assignment independently reviewed the case-report form and classified the catheter infection status according to the accepted definitions.[14,15] Disagreements between the two assessors were resolved by consensus conference among the four outcome assessors.

We defined catheter colonisation as a quantitative catheter-tip culture eluate in broth showing at least one microorganism in a concentration of at least 1000 CFU per mL. We defined catheter-related sepsis without bacteraemia as a combination of: fever (body temperature ≥38·5°C) or hypothermia (body temperature ≤36·5°C); catheter colonisation; resolution of fever or hypothermia within 48 h after catheter removal and without any change in antimicrobial therapy, or with presence of pus at the catheter insertion site; and no other source of infection identified. We defined catheter-related bloodstream infection (CR-BSI) as a combination of: fever (body temperature ≥38·5°C) or hypothermia (body temperature ≤36·5°C); one or more positive peripheral blood cultures drawn 48 h before or after catheter withdrawal; isolation of the same organism (same species and same susceptibility pattern) from the colonised catheter or from the catheter insertion site, or a blood culture differential time-to-positivity of 2 h or more; and no apparent source of bacteraemia other than the catheter. In patients with bacteraemia due to

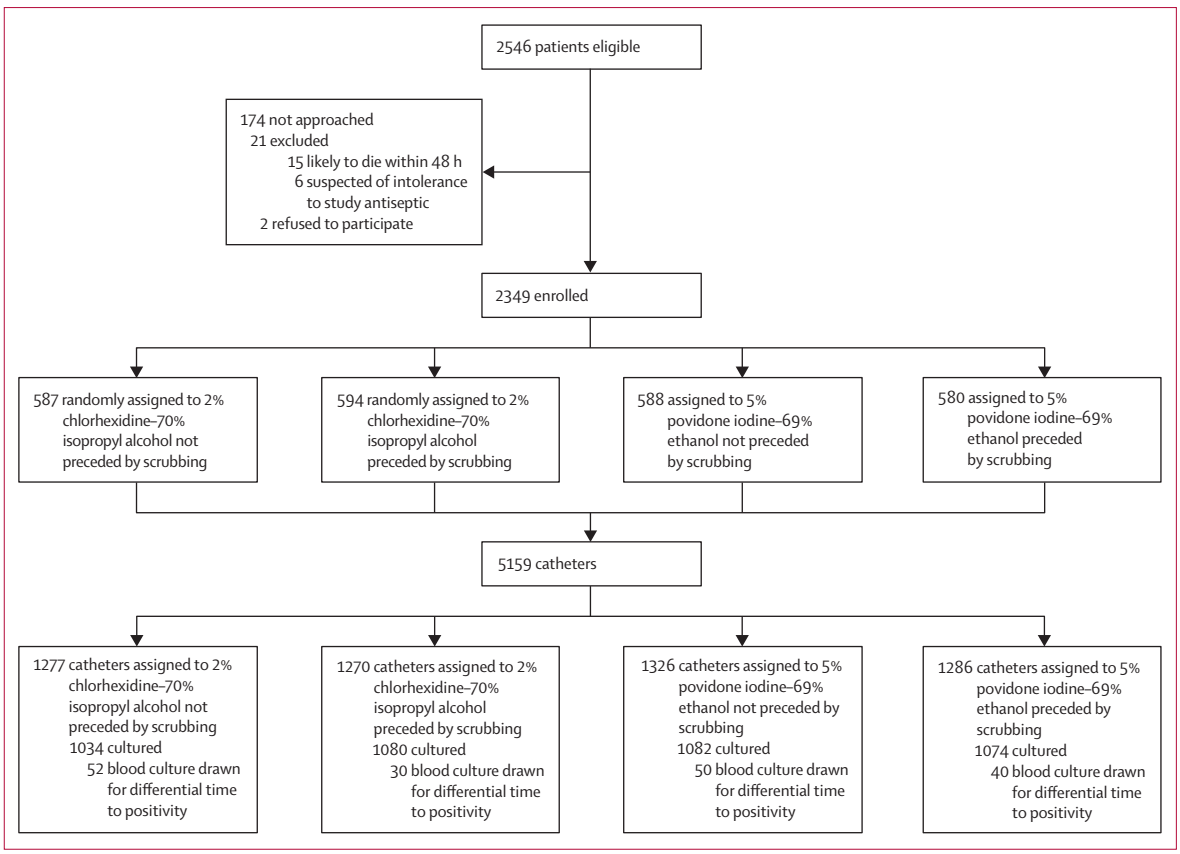

Figure 1: **Trial profile**

coagulase-negative staphylococci, at least two positive cultures from separate blood samples were required. Catheter-related infections were either catheter-related sepsis without bacteraemia or CR-BSI.

Non-cultured catheters were classified as associated with catheter-related sepsis or CR-BSI in case of sepsis with or without bacteraemia and no detectable source other than the catheter, colonised in cases of a blood culture test from the catheter hub positive for bacteria other than coagulase-negative staphylococci and no other detectable source of bacteraemia, and sterile otherwise.

Outcomes

The primary outcome was the incidence of catheter-related infections in patients assigned to chlorhexidine–alcohol versus incidence in those assigned to povidone iodine–alcohol as the skin antiseptic. The main secondary outcome was the incidence of catheter colonisation with the two-step versus the one-step procedure. Catheter colonisation, a precursor to catheter-related infection, was used for the scrubbing outcome because it is a more sensitive criterion that is likely to detect smaller differences between treatment groups.[4,6] Additional prespecified outcomes were CR-BSI, skin insertion-site colonisation at catheter removal, mortality during stay in the intensive-care unit, length of intensive-care unit stay, and safety outcomes including skin status at each dressing change and at catheter removal, assessed using the International Contact Dermatitis Research Group scale,[16] between groups (chlorhexidine–alcohol *vs* povidone iodine–alcohol or two-step *vs* the one-step procedure). Cost for skin disinfection procedures and cost of catheter-related infections were estimated in 2014€ according to French guidance for cost and economic evaluations.[17]

Statistical analysis

Based on the findings of two previous studies showing a 52–59% reduction in the risk of CR-BSI with use of chlorhexidine–alcohol instead of povidone iodine–alcohol,[4,18] we hypothesised that use of chlorhexidine–alcohol would decrease the incidence of catheter-related infection by 50% compared with povidone iodine–alcohol. We assumed a 5% incidence of catheter-related infections with povidone iodine–alcohol. On the basis of data from previous studies,[14,15] we hypothesised that each patient would have at least two catheters inserted. We used an intraclass correlation within patients of 0·02, a two-sided α risk of 5%, and power of 80% to compute sample size. With our hypotheses, 2256 evaluable patients (more than 4512 catheters) were needed to take into account the interaction between antiseptic efficacy and skin scrubbing.

	Entire population (n=2349)	Antiseptic groups		One-step or two-step groups	
		Chlorhexidine–alcohol group (n=1181)	Povidone iodine–alcohol group (n=1168)	Non-scrubbing group (n=1175)	Scrubbing group (n=1174)
Age (years)	64 (53–74)	64 (53–74)	64 (53–73)	64 (53–73)	64 (53–75)
Men	1484 (63%)	740 (63%)	744 (64%)	739 (63%)	745 (64%)
At least one chronic disease	825 (35%)	428 (36%)	397 (34%)	420 (36%)	405 (34%)
Immune deficiency	141 (6%)	82 (7%)	59 (5%)	69 (6%)	72 (6%)
Haematological malignancy	133 (6%)	69 (6%)	64 (5%)	68 (6%)	65 (6%)
Metastatic cancer	132 (6%)	63 (5%)	69 (6%)	70 (6%)	62 (5%)
SAPS II score at admission	51 (38–66)	52 (38–67)	49 (37–64·5)	49 (37–65)	52 (38–66)
SOFA score at admission	9 (6–11)	9 (6–12)	8 (6–11)	9 (6–12)	9 (6–11)
Admission category					
Medical	1717 (73%)	849 (72%)	868 (74%)	862 (73%)	855 (73%)
Scheduled surgery	172 (7%)	93 (8%)	79 (7%)	86 (7%)	86 (7%)
Emergency surgery	460 (20%)	239 (20%)	221 (19%)	227 (19%)	233 (20%)
Main reason for ICU admission					
Septic shock	460 (20%)	251 (21%)	209 (18%)	219 (19%)	241 (21%)
Cardiogenic shock	150 (6%)	69 (6%)	81 (7%)	69 (6%)	81 (7%)
De-novo respiratory failure	669 (28%)	308 (26%)	361 (31%)	340 (29%)	329 (28%)
Coma	222 (9%)	107 (9%)	115 (10%)	118 (10%)	104 (9%)
Trauma	142 (6%)	65 (6%)	77 (7%)	70 (6%)	72 (6%)
Mechanical ventilation	1663 (71%)	826 (70%)	837 (72%)	830 (71%)	833 (71)
ICU stay length (days)	8 (4–18)	8 (4–16)	8 (4–18)	8 (4–18)	8 (4–16)
ICU deaths	677 (29%)	338 (29%)	339 (29%)	347 (30%)	330 (28%)
Hospital deaths	793 (34%)	400 (34%)	393 (34%)	410 (35%)	383 (33%)

Data are median (IQR) or n (%). SAPS II=Simplified Acute Physiology Score II.[20] SOFA=Sequential Organ Failure Assessment.[21] ICU=intensive care unit.

Table 1: **Patient characteristics**

Data were analysed on an intention-to-treat basis. No interim analysis was planned. Demographic data were described as number and percentage or median and IQR and compared with the χ^2 test or Mann-Whitney test, as appropriate. We assessed antiseptic efficacy (catheter colonisation, catheter-related infection, and CR-BSI) with a marginal Cox model stratified by centre and adjusted for covariates that were significantly imbalanced between groups. This model took into account the censored nature of the data and the intracluster (within-patient) dependency (more than one catheter per patient), using a robust sandwich covariance matrix.[19] A potential interaction between scrubbing and antiseptic application was first sought by forcing the interaction term into the final model. In the case of absence of significant interaction, interaction terms were not included in the reported results but results were systematically adjusted on the other intervention (ie, scrubbing or not for comparison between antiseptic agents; chlorhexidine–alcohol use or not for comparison between one-step and two-step procedures). We calculated hazard ratios (HR) and 95% CIs, as well as incidence density and Kaplan-Meier estimates. We compared the number of CFUs recovered from skin cultures between groups with the Mann-Whitney test. Tests were two-tailed and unadjusted for multiple comparisons. Analyses were done with SAS version 9.4 and R software. This study is registered with ClinicalTrials.gov, number NCT01629550 and is closed to new participants.

Role of the funding source

The University Hospital of Poitiers, France, sponsored the study. CareFusion, the manufacturer of the 2% chlorhexidine–alcohol antiseptic solution used in this study, provided an unrestricted grant. Neither the sponsor nor CareFusion had a role in the trial initiation, study design, choice of antiseptic products, data collection, data analysis, data interpretation, writing of the report, or the decision to submit. The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Oct 26, 2012, and Feb 12, 2014, 2546 patients were eligible to participate in the study; we enrolled 2349 (figure 1). 1181 patients (2547 catheters) were randomly allocated to chlorhexidine–alcohol (594 patients with scrubbing, 587 without) and 1168 (2612 catheters) to povidone iodine–alcohol (580 patients with scrubbing, 588 without; tables 1 and 2).

	Entire population (n=5159)	Antiseptic groups		One-step or two-step groups	
		Chlorhexidine–alcohol group (n=2547)	Povidone iodine–alcohol group (n=2612)	Non-scrubbing group (n=2603)	Scrubbing group (n=2556)
Time in place (days)	6 (3–11)	6 (3–11)	6 (3–11)	7 (4–11)	6 (3–11)
Experience of the operator					
<50 procedures	3656 (71%)	1786 (70%)	1870 (72%)	1902 (73%)	1754 (69%)
≥50 procedures	1503 (29%)	761 (30%)	742 (28%)	701 (27%)	802 (31%)
Arterial catheter	2446 (47%)	1189 (47%)	1257 (48%)	1226 (47%)	1220 (48%)
Femoral	775/2446 (32%)	383/1189 (32%)	392/1257 (31%)	386/1226 (31%)	389/1220 (32%)
Radial	1671/2446 (68%)	806/1189 (68%)	865/1257 (69%)	840/1226 (69%)	831/1220 (68%)
Venous catheter	2155 (42%)	1052 (41%)	1103 (42%)	1096 (42%)	1059 (41%)
Jugular	843/2155 (39%)	414/1052 (39%)	429/1103 (39%)	446/1096 (41%)	397/1059 (37%)
Subclavian	739/2155 (34%)	354/1052 (34%)	385/1103 (35%)	356/1096 (32%)	383/1059 (36%)
Femoral	573/2155 (27%)	284/1052 (27%)	289/1103 (26%)	294/1096 (27%)	279/1059 (26%)
Haemodialysis catheter	558 (11%)	306 (12%)	252 (10%)	281 (11%)	277 (11%)
Jugular	244/558 (44%)	136/306 (44%)	108/252 (43%)	126/281 (45%)	118/277 (43%)
Subclavian	12/558 (2%)	7/306 (2%)	5/252 (2%)	5/281 (2%)	7/277 (3%)
Femoral	302/558 (54%)	163/306 (53%)	139/252 (55%)	150/281 (53%)	152/277 (55%)
Antimicrobial administration during catheter insertion	3097 (60%)	1538 (61%)	1559 (60%)	1542 (59%)	1555 (61%)
Use of lipids	966 (19%)	470 (19%)	496 (19%)	508 (20%)	458 (18%)
Use of heparin	3733 (72%)	1851 (73%)	1882 (72%)	1880 (72%)	1853 (72%)
Transport with catheter in place					
No	2974 (58%)	1437 (56%)	1537 (59%)	1454 (56%)	1520 (60%)
Once	1288 (25%)	646 (25%)	642 (25%)	672 (26%)	616 (24%)
Twice	533 (10%)	266 (10%)	267 (10%)	278 (11%)	255 (10%)
More than twice	364 (7%)	198 (8%)	166 (6%)	199 (8%)	165 (6%)
Packed red blood cells transfused	890 (17%)	434 (17%)	456 (17%)	470 (18%)	420 (16%)
Number of dressing changes per catheter	2 (1–5)	2 (1–5)	2 (1–5)	2 (1–5)	2 (1–4)
Local signs at catheter removal					
Normal	4172 (81%)	2114 (83%)	2058 (79%)	2113 (81%)	2059 (81%)
Redness	681 (13%)	295 (12)	386 (15%)	332 (13%)	349 (14%)
Bleeding	243 (5%)	117 (5%)	126 (5%)	126 (5%)	117 (5%)
Non-purulent discharge	96 (2%)	44 (2%)	52 (2%)	48 (2%)	48 (2%)
Purulent discharge	52 (1%)	17 (1%)	35 (1%)	29 (1%)	23 (1%)
Catheter removal for suspected infection	635 (12%)	255 (10%)	380 (15%)	324 (12%)	311 (12%)

Data are median (IQR), n (%), or n/N (%).

Table 2: **Characteristics of the catheters**

We cultured or did culturing to determine the differential time to positivity before catheter removal for 4442 (86%) of the 5159 catheters. We reviewed masked case report forms of patients with a positive catheter-tip culture (n=815), a positive blood culture sampled 48 h before or after catheter removal (n=281), or a non-cultured catheter (n=717) to classify the catheter infection status. Of these, 56 were considered debatable and submitted to the four assessors. The assessors were in complete agreement for 31 catheters and reached a consensus after discussion for the remaining 25 catheters (catheter-related infection in two cases, CR-BSI in one case, and no infection in 22 cases).

There was no significant interaction between the two study interventions (one-step *vs* two-step scrubbing procedure and antiseptic agent) and incidence of catheter colonisation (p=0·8887), catheter-related infection (p=0·1740), and CR-BSI (p=0·1645). Ie, the results for comparison between the two antiseptics were not affected by the type of procedure (one-step *vs* two-step) and the results for comparison between one-step and two-step procedures were also not affected by the type of antiseptic chosen. We therefore analysed both study interventions by fitting separate models.

Incidence of catheter-related infection in patients assigned to chlorhexidine–alcohol was 0·28 per 1000 catheter-days (six infections) compared with

1·77 per 1000 catheter-days (39 infections) in those assigned to povidone iodine–alcohol (HR 0·15, 95% CI 0·05–0·41; p=0·0002; figure 2). The chlorhexidine–alcohol group had significantly fewer CR-BSIs (0·28 *vs* 1·32 per 1000 catheter-days; 0·21, 0·07–0·59; p=0·003) and fewer colonised catheters (3·34 *vs* 18·74 per 1000 catheter-days; 0·18, 0·13–0·24; p<0·0001), with similar effects on Gram-negative and Gram-positive organisms (appendix). The effects were not significantly affected by admission category, baseline Simplified Acute Physiology Score (SAPS) II, type of catheter, catheter insertion site (appendix) or when only cultured catheter cases were included in the analysis (appendix). However, for central venous catheters, the higher efficacy of chlorhexidine–alcohol compared with povidone iodine–alcohol skin preparation was significant only for colonisation and not for catheter-related infection and CR-BSI (appendix). Use of povidone iodine-alcohol instead of chlorhexidine-alcohol did not significantly affect length of stay or mortality for patients in intensive-care units (0·3 days [95% CI –0·4 to 0·7] and 0·4% [–3·3 to 4·1], respectively) or mortality for those in hospital (0·3% [–3·5 to 4·1]; table 1).

The incidences of catheter colonisation (11·56 and 10·75 per 1000 catheter-days, respectively; HR 1·10, 95% CI 0·89–1·35; p=0·3877), catheter-related infection (1·09 *vs* 0·99 per 1000 catheter-days, respectively; 1·03, 0·57–1·88; p=0·9131), and CR-BSI (0·77 *vs* 0·85 per 1000 catheter-days, respectively; 0·86, 0·44–1·67; p=0·6494) did not significantly differ between patients given the one-step and the two-step procedure. Number of days in intensive-care and mortality also did not significantly differ between patients assigned to the one-step procedure and those assigned to skin scrubbing in the two-step procedure (increase in ICU stay of 0·6 days [95% CI –0·1 to 1·0], mortality in intensive care of 1·4% [–2·3 to 5·1], and of mortality in hospital of 2·3% [–1·5 to 6·1]; table 1).

We did Count-Tact cultures at removal of 3657 (71%) catheters. Tests were negative in 1125 (31%) cases (appendix). Bacterial growth was more common in patients with colonisation (n=383 [94%]; p<0·0001), catheter-related infection (n=35 [95%]; p=0·0006), or CR-BSI (n=26 [93%]; p=0·0023) than in patients with non-colonised catheters (n=2123 [65%]). Median Count-Tact colony counts were significantly lower in catheters from patients assigned to chlorhexidine–alcohol than in those from patients assigned to povidone iodine–alcohol (4 CFU [IQR 0–50] *vs* 41 CFU [1 to >100], respectively; p<0·0001). Median colony counts did not significantly differ for between catheters from patients assigned to the one-step and two-step procedures (14 CFU [0 to >100] *vs* 12 CFU [0 to >100], respectively, p=0·9112).

No systemic adverse reactions to chlorhexidine–alcohol or povidone iodine–alcohol occurred. Skin reactions were more frequent with chlorhexidine–alcohol than with povidone iodine–alcohol (p=0·0110; appendix). Severe skin reactions occurred in 27 (3%) patients

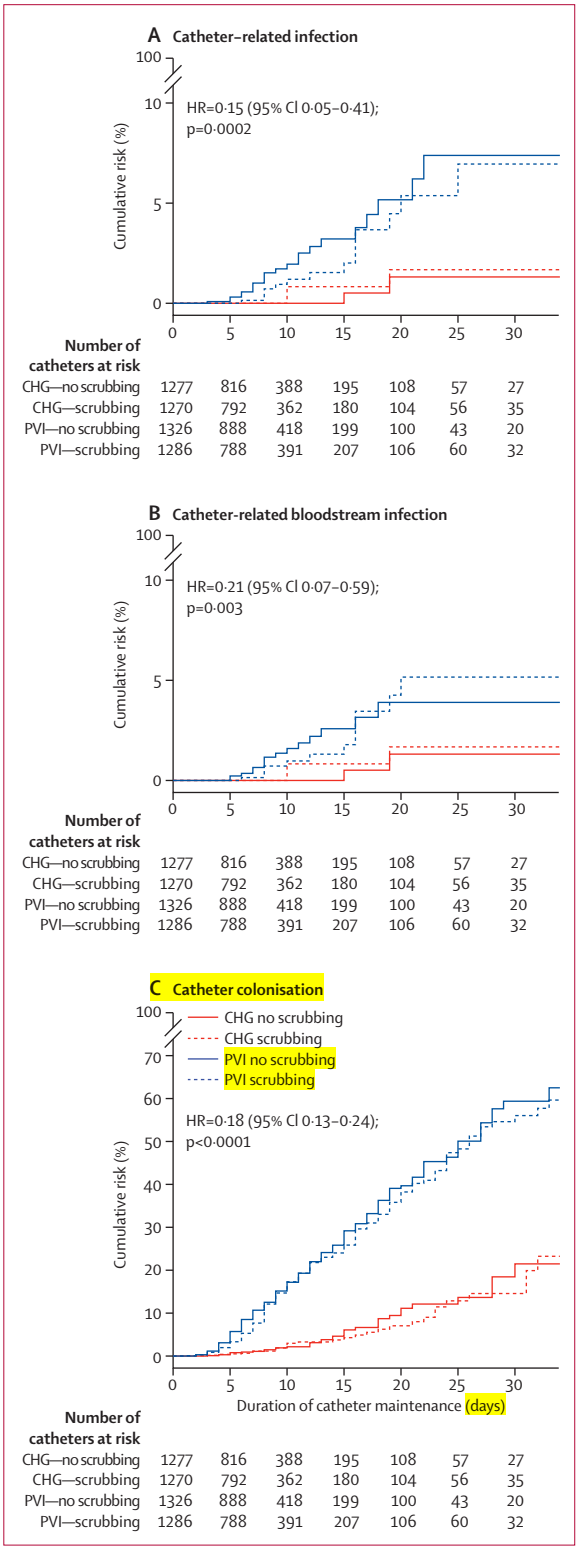

***Figure 2*: Cumulative risk of catheter-related infection (A), catheter-related bloodstream infection (B), and catheter colonisation (C) by treatment group**
HR for chlorhexidine group versus povidone iodine group. CHG=chlorhexidine–alcohol. PVI=povidone iodine–alcohol. HR=hazard ratio.

assigned to chlorhexidine–alcohol and in seven (1%) assigned to povidone iodine–alcohol (p=0·0017; appendix). Two patients in the chlorhexidine group had their treatment discontinued for intolerance. The first was a very ill patient with acute graft-versus-host disease and fragile skin. The second patient developed superficial skin ulcerations under the dressing leading to the suspicion of allergy to chlorhexidine; allergy testing 4 months later ruled out this diagnosis. The exact cause remains unknown, but the patient was found to be highly allergic to nickel, a metal used to make some catheters. The incidence of skin reactions was not different between the one-step and two-step procedures (p=0·9554). No specific intervention apart from antiseptic discontinuation was needed to manage these complications. Skin lesions resolved after catheter removal.

We estimated use of chlorhexidine–alcohol instead of povidone iodine–alcohol prevented one catheter-related infection for each 78 (95% CI 25–311) catheters left in place for a mean of 8 days. Resources for both skin disinfection strategies were the same except for the cost of each antiseptic solution (chlorhexidine–alcohol €1·25 for each dressing [mean cost in study €2·90 per patient]; povidone iodine–alcohol: €1·5, one unit for 8 days) and cost of gauzes (€0·01 for each dressing) in the povidone iodine-alcohol group. Therefore, the cost of prevention of one episode of catheter-related infection with chlorhexidine–alcohol use was €227 (€74–€912). This extra cost compared favourably with the cost of one catheter-related infection measured previously by our group in similar patients with microcosting techniques in 2007 and corrected for inflation from 2007 to 2014 at €19 583.[22] A cost analysis study will be done and published elsewhere.

Discussion

Use of 2% chlorhexidine–alcohol for skin antisepsis was associated with six-fold decreases in the incidences of catheter-related infection and catheter colonisation and a five-fold decrease in the incidence of CR-BSI, compared with 5% povidone iodine–alcohol. Skin scrubbing before antiseptic application was not associated with a further decrease in catheter colonisation. Adverse skin reactions were rare but more common with chlorhexidine–alcohol than with povidone iodine–alcohol.

Previous studies that compared chlorhexidine and povidone iodine for skin antisepsis during catheter insertion and maintenance used formulations with or without alcohol, and their results are therefore difficult to compare. Two single-centre studies compared a mixture of 0·25% chlorhexidine, 0·025% benzalkonium, and 4% benzylic alcohol to 5% povidone iodine–alcohol for insertion-site care of central venous catheters in patients in intensive-care units.[4,18] Both studies reported significant decreases in catheter colonisation with the chlorhexidine-based formulation. However, both studies had several drawbacks, including their design, use of a mixture of three compounds in the chlorhexidine group, and insufficient statistical power to show a significant effect on catheter-related infections. All these drawbacks are major limitations to the general applicability of their findings. Our study confirms the superiority of chlorhexidine–alcohol compared with povidone iodine–alcohol and warrants recommendation of chlorhexidine–alcohol as the preferred antiseptic for intravascular catheter insertion and care. The superiority of alcoholic solutions compared with aqueous solutions has been shown elsewhere.[23]

The superiority of chlorhexidine–alcohol over povidone iodine–alcohol was not affected by the type of admission (medical *vs* surgical), the patients' severity, the type of catheter, or the insertion site, and it extended to both Gram-positive and Gram-negative microorganisms (appendix). However, with central venous catheters, the difference was significant only for colonisation and not for catheter-related infection and CR-BSI, which might be attributed to insufficient power for subgroup analysis in the study. Although both antiseptic solutions possess broad-spectrum antimicrobial activity, the better clinical protection provided by chlorhexidine–alcohol is probably linked to the long-term antimicrobial suppressive activity, which is mainly due to the power of chlorhexidine and the inactivation of povidone iodine by blood and other protein-rich biomaterials present on skin,[24] even though the latter point was recently challenged.[25] In keeping with these theories, our skin cultures from catheter insertion sites showed larger bacterial concentration decreases with chlorhexidine–alcohol than with povidone iodine–alcohol.

With neither of the two antiseptic solutions did previous scrubbing with an antiseptic detergent further decrease catheter colonisation, catheter-related infections, or CR-BSI. These findings are in agreement with studies done in surgery that indicate that skin antisepsis preceded by skin scrubbing is not superior to skin antisepsis alone.[26]

The findings showing benefit for chlorhexidine–alcohol in our study were obtained in intensive-care units with a low baseline incidence of catheter-related infection, as observed in the povidone iodine–alcohol group. This low baseline incidence occurred in a population of high-risk patients in intensive-care units, as shown by their high severity scores at admission, the large proportion of ventilated patients, and a high mortality rate. The low incidence of infections can be ascribed to the extensive use of recommended preventive measures, including maximal barrier precautions.

Adverse events with both antiseptic solutions were rare. Severe skin reactions occurred in 3% of patients assigned to chlorhexidine–alcohol, a proportion comparable with those reported with chlorhexidine dressings[14] and chlorhexidine sponges[15] in similar patients in the intensive-care unit. The proportion of patients with reactions was smaller in those assigned to povidone iodine–alcohol. Severe skin reactions require

early recognition followed by immediate cessation of the antiseptic at fault. No systemic reactions occurred in our study.

Our study has several limitations. First, masking was not feasible, because the two antiseptic solutions differed in colour and formulation. However, the microbiologists who did skin and catheter cultures were unaware of treatment allocation. Most importantly, all suspected cases of catheter-related infections were reviewed by masked independent assessors based on detailed pre-established definitions. Therefore, we do not believe that absence of masking of patients and clinicians has caused a bias in the assessment of main outcomes. Second, the possible effect of differences in the antiseptic types and concentrations (including the alcoholic component) in the study solutions or application methods could not be assessed. However, the antiseptics were used in their commercially available formulations and as recommended by their manufacturers. Further studies are necessary to determine the optimum concentration of chlorhexidine and type and concentration of alcohol to be combined with chlorhexidine. Third, adhesion to the study protocol was not regularly checked by formal audits. However, the health-care providers attended training sessions designed to homogenise skin preparation practices across units before start of the study and independent clinical research assistants were available at each participating hospital to monitor the conduct of the study. Fourth, potential additive value through the use of the same antiseptic product for hub decontamination could not be measured. However, it is routine practice to use the same antiseptic for skin and hub disinfection. Finally, no significant effect on mortality or length of stay was observed according to the antiseptic agent or procedure used, but our study was probably underpowered to detect a significant difference for these outcomes. Further studies with an appropriate design are needed to explore these issues.

Our randomised study is the largest so far to compare chlorhexidine–alcohol and povidone iodine–alcohol in prevention of intravascular catheter-related infections in intensive-care units. Moreover, it was a multicentre study with a mix of medical and surgical units. Nearly all eligible patients were included and, before study initiation, all participating units were already routinely applying measures recommended by the CDC to prevent catheter-related infections. Therefore, our results can be reasonably generalised to severely ill patients in intensive-care units who are expected to require a short-term central venous or arterial catheter. Whether these results can be extended to catheters remaining in place for longer periods of time, such as peripherally inserted devices, needs further studies. The extra cost of chlorhexidine use compared favourably with the cost of one catheter-related infection measured previously by our group in similar patients and so seems cost efficient.

Contributors
OM obtained funding. OM, J-CL, AL and J-FT designed the study; recruited the participating sites; were responsible for the study execution, data collection, and data analysis; wrote the manuscript, and decided in consultation with the other authors to submit the paper for publication. OM, TK, JP, BS, VG, AM, LB, SL, SA, AF, FW, NA, and DB made substantial contributions to patient recruitment and data collection. SR and J-FT did the statistical analysis.

Declaration of interests
OM received research grants, lecture, and consultancy fees from CareFusion. JF-T received research grants from CareFusion. JC-L has received lecture fees from CareFusion. All other authors have no competing interests.

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