



Skin antiseptics 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

Olivier Mimoz, Jean-Christophe Lucet, Thomas Kerforne, Julien Pascal, Bertrand Souweine, Véronique Goudet, Alain Mercat, Lila Bouadma, Sigismund Lasocki, Serge Alfandari, Arnaud Friggeri, Florent Wallet, Nicolas Allou, Stéphane Ruckly, Dorothée Balayn, Alain Lepape, Jean-François Timsit, for the CLEAN trial investigators*

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 antiseptics 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 antiseptics, 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 antiseptics 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 antiseptics in USA⁷ and English⁸ 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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*Investigators listed in the appendix

Service d'Anesthésie et de Réanimation, CHU de Poitiers, Poitiers, France (Prof O Mimoz, T Kerforne MD, D Balayn PhD); Université de Poitiers, UFR de Médecine Pharmacie, Poitiers, France (Prof O Mimoz); INSERM U1070, Pharmacologie des Agents antinfectieux, Poitiers, France (Prof O Mimoz); AP-HP, Bichat University Hospital, Infection Control Unit, Paris, France (Prof J-C Lucet PhD); INSERM, UMR 1137—IAIE Team 5—DeSCID: Decision Sciences in Infectious Diseases, Control and Care, Paris, France (Prof J-C Lucet, L Bouadma, Prof J-F Timsit); Univ Paris Diderot, Sorbonne Paris Cité, Paris, France (Prof J-C Lucet); Service de Réanimation Adultes et Unité de Surveillance Continue, CHU Clermont Ferrand, Clermont Ferrand, France (J Pascal MD); Service de Réanimation médicale, CHU Clermont Ferrand, Clermont-Ferrand, France (Prof B Souweine PhD); Service de Réanimation Médicale, CHU de Poitiers, Poitiers, France (V Goudet MD); Département de Réanimation Médicale et Médecine Hyperbare, CHU d'Angers, Angers, France (Prof A Mercat PhD); University Paris Diderot, Sorbonne Paris Cité, Paris, France (L Bouadma PhD, Prof J-F Timsit PhD); Service de Réanimation Chirurgicale, CHU

d'Angers, Angers, France (Prof S Lasocki PhD); Service de Réanimation et Maladies infectieuses, CH de Tourcoing, Tourcoing, France (S Alfordari MD); Service d'Anesthésie et de Réanimation Médicale et Chirurgicale, CHU Lyon-Sud, Lyon, France (A Friggeri MD, F Wallet MD, A Lepape MD); Service de Réanimation Chirurgicale, Hôpital Bichat-Claude-Bernard, Paris, France (N Allou MD); and OutcomeRéa, Paris, France (S Ruckly)

Correspondence to: Prof Olivier Mimoz, Service d'Anesthésie et de Réanimation, CHU de Poitiers, Poitiers, 86021, France olivier.mimoz@chu-poitiers.fr

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 antiseptics 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 antiseptics. 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 antiseptics 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 guidelines⁹ 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 antiseptics.

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 (ChloroPrep, 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 $\geq 38.5^{\circ}\text{C}$), hypothermia ($\leq 36.5^{\circ}\text{C}$), 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 $\geq 38.5^{\circ}\text{C}$) or hypothermia (body temperature $\leq 36.5^{\circ}\text{C}$); 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 $\geq 38.5^{\circ}\text{C}$) or hypothermia (body temperature $\leq 36.5^{\circ}\text{C}$); 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

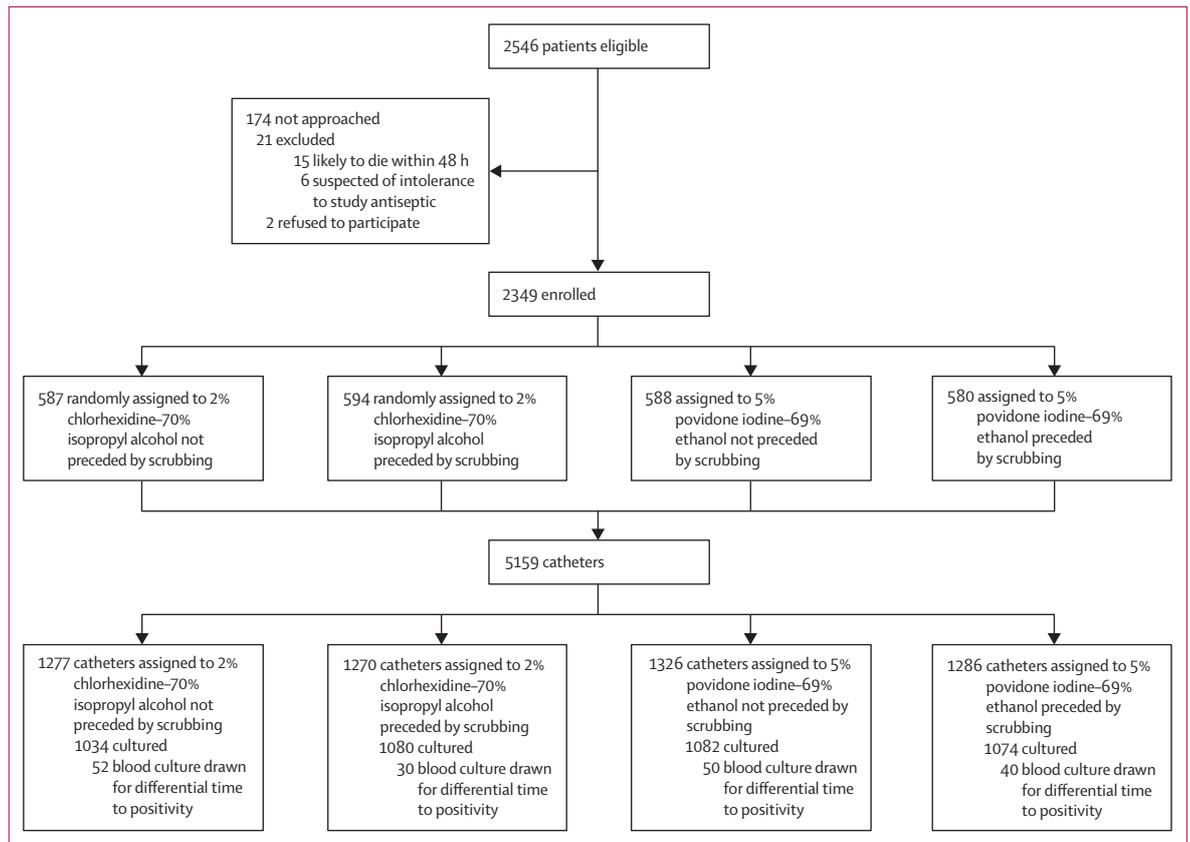


Figure 1: Trial profile

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					
Femoral	2446 (47%)	1189 (47%)	1257 (48%)	1226 (47%)	1220 (48%)
Radial	775/2446 (32%)	383/1189 (32%)	392/1257 (31%)	386/1226 (31%)	389/1220 (32%)
Venous catheter					
Jugular	1671/2446 (68%)	806/1189 (68%)	865/1257 (69%)	840/1226 (69%)	831/1220 (68%)
Subclavian	2155 (42%)	1052 (41%)	1103 (42%)	1096 (42%)	1059 (41%)
Femoral	843/2155 (39%)	414/1052 (39%)	429/1103 (39%)	446/1096 (41%)	397/1059 (37%)
Haemodialysis catheter	739/2155 (34%)	354/1052 (34%)	385/1103 (35%)	356/1096 (32%)	383/1059 (36%)
Jugular	573/2155 (27%)	284/1052 (27%)	289/1103 (26%)	294/1096 (27%)	279/1059 (26%)
Subclavian	558 (11%)	306 (12%)	252 (10%)	281 (11%)	277 (11%)
Femoral	244/558 (44%)	136/306 (44%)	108/252 (43%)	126/281 (45%)	118/277 (43%)
Antimicrobial administration during catheter insertion	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%)
Use of lipids	3097 (60%)	1538 (61%)	1559 (60%)	1542 (59%)	1555 (61%)
Use of heparin	966 (19%)	470 (19%)	496 (19%)	508 (20%)	458 (18%)
Transport with catheter in place					
No	3733 (72%)	1851 (73%)	1882 (72%)	1880 (72%)	1853 (72%)
Once	2974 (58%)	1437 (56%)	1537 (59%)	1454 (56%)	1520 (60%)
Twice	1288 (25%)	646 (25%)	642 (25%)	672 (26%)	616 (24%)
More than twice	533 (10%)	266 (10%)	267 (10%)	278 (11%)	255 (10%)
Packed red blood cells transfused	364 (7%)	198 (8%)	166 (6%)	199 (8%)	165 (6%)
Number of dressing changes per catheter	890 (17%)	434 (17%)	456 (17%)	470 (18%)	420 (16%)
Local signs at catheter removal					
Normal	2 (1–5)	2 (1–5)	2 (1–5)	2 (1–5)	2 (1–4)
Redness	4172 (81%)	2114 (83%)	2058 (79%)	2113 (81%)	2059 (81%)
Bleeding	681 (13%)	295 (12)	386 (15%)	332 (13%)	349 (14%)
Non-purulent discharge	243 (5%)	117 (5%)	126 (5%)	126 (5%)	117 (5%)
Purulent discharge	96 (2%)	44 (2%)	52 (2%)	48 (2%)	48 (2%)
Catheter removal for suspected infection	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

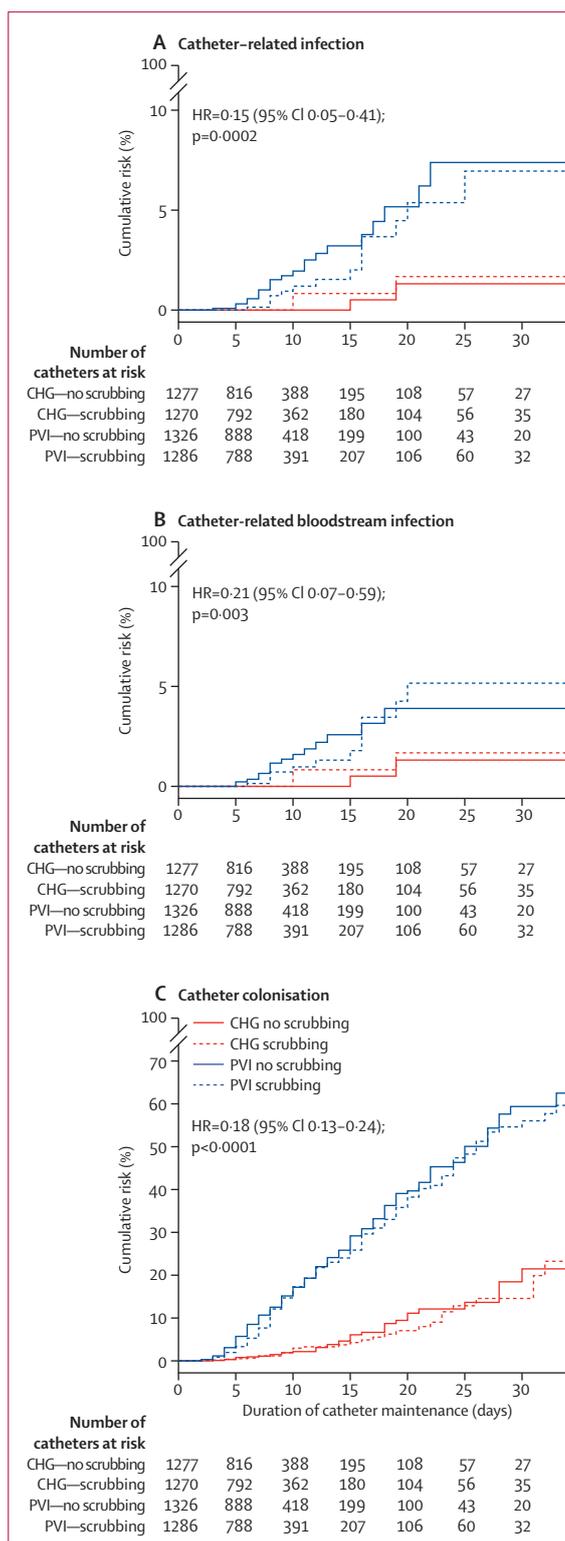


Figure 2: Cumulative risk of catheter-related infection (A), catheter-related bloodstream infection (B), and catheter colonisation (C) by treatment group

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 ($p=0\cdot0017$; 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 ($p=0\cdot9554$). 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 antiseptics 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 antiseptics 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 antiseptics preceded by skin scrubbing is not superior to skin antiseptics 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 dressings¹⁴ and chlorhexidine sponges¹⁵ 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, adherence 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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References

- 1 Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. *N Engl J Med* 2006; **355**: 2725–32.
- 2 Mermel LA. What is the predominant source of intravascular catheter infections? *Clin Infect Dis* 2011; **52**: 211–12.
- 3 Rotter M. Hand washing and hand disinfection. In: Mayhall CG, ed. *Hospital Epidemiology and Infection Control*, 3rd edn. Philadelphia: Lippincott Williams and Wilkins, 2012: 1365–83.
- 4 Mimoz O, Villemeyn S, Ragot S, et al. Chlorhexidine-based antiseptic solution vs alcohol-based povidone-iodine for central venous catheter care. *Arch Intern Med* 2007; **167**: 2066–72.
- 5 Mimoz O, Karim A, Mercat A, et al. Chlorhexidine compared with povidone-iodine as skin preparation before blood culture. A randomized, controlled trial. *Ann Intern Med* 1999; **131**: 834–37.
- 6 Mimoz O, Pieroni L, Lawrence C, et al. Prospective, randomized trial of two antiseptic solutions for prevention of central venous or arterial catheter colonization and infection in intensive care unit patients. *Crit Care Med* 1996; **24**: 1818–23.
- 7 O'Grady NP, Alexander M, Burns LA, et al. Summary of recommendations: Guidelines for the Prevention of Intravascular Catheter-related Infections. *Clin Infect Dis* 2011; **52**: 1087–99.
- 8 Loveday HP, Wilson JA, Pratt RJ, et al. Epic3: national evidence-based guidelines for preventing healthcare-associated infections in NHS hospitals in England. *J Hosp Infect* 2014; **86** (suppl 1): S1–70.
- 9 Société française d'anesthésie et de réanimation; Société de réanimation de langue française. [Prevention of hospital-acquired sepsis in intensive care unit (except cross transmission and neonate)]. *Ann Fr Anesth Reanim* 2009; **28**: 912–20.
- 10 Zamora JL, Price MF, Chuang P, Gentry LO. Inhibition of povidone-iodine's bactericidal activity by common organic substances: an experimental study. *Surgery* 1985; **98**: 25–29.
- 11 Goudet V, Timsit JF, Lucet JC, et al. Comparison of four skin preparation strategies to prevent catheter-related infection in intensive care unit (CLEAN trial): a study protocol for a randomized controlled trial. *Trials* 2013; **14**: 114.
- 12 Brun-Buisson C, Abrouk F, Legrand P, Huet Y, Larabi S, Rapin M. Diagnosis of central venous catheter-related sepsis. Critical level of quantitative tip cultures. *Arch Intern Med* 1987; **147**: 873–77.
- 13 Blot F, Nitenberg G, Chachaty E, et al. Diagnosis of catheter-related bacteraemia: a prospective comparison of the time to positivity of hub-blood versus peripheral-blood cultures. *Lancet* 1999; **354**: 1071–77.
- 14 Timsit JF, Mimoz O, Mourvillier B, et al. Randomized controlled trial of chlorhexidine dressing and highly adhesive dressing for preventing catheter-related infections in critically ill adults. *Am J Respir Crit Care Med* 2012; **186**: 1272–78.
- 15 Timsit JF, Schwebel C, Bouadma L, et al. Chlorhexidine-impregnated sponges and less frequent dressing changes for prevention of catheter-related infections in critically ill adults: a randomized controlled trial. *JAMA* 2009; **301**: 1231–41.
- 16 Fowler J Jr, Taylor J, Storrs F, et al. Gold allergy in North America. *Am J Contact Dermat* 2001; **12**: 3–5.
- 17 Haute Autorité de Santé. A methodological guide: choices in methods for economic evaluation. Paris: Department of Economics and Public Health Assessment, 2012. http://www.has-sante.fr/portail/upload/docs/application/pdf/2012-10/choices_in_methods_for_economic_evaluation.pdf (accessed Feb 17, 2015).

- 18 Girard R, Comby C, Jacques D. Alcoholic povidone-iodine or chlorhexidine-based antiseptic for the prevention of central venous catheter-related infections: in-use comparison. *J Infect Public Health* 2012; **5**: 35–42.
- 19 Lee E, Wei L, Amato D. Cox-type regression analysis for large numbers of small groups of correlated failure time observations. In: Klein JP, Goel PK, eds. *Survival analysis: State of the Art: NATO ASI Series. Datenschutz: Springer, 1992: 237–47*.
- 20 Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA* 1993; **270**: 2957–63.
- 21 Timsit JF, Fosse JP, Troche G, et al. Calibration and discrimination by daily logistic organ dysfunction scoring comparatively with daily sequential organ failure assessment scoring for predicting hospital mortality in critically ill patients. *Crit Care Med* 2002; **30**: 2003–13.
- 22 Schwebel C, Lucet JC, Vesin A, et al. Economic evaluation of chlorhexidine-impregnated sponges for preventing catheter-related infections in critically ill adults in the Dressing Study. *Crit Care Med* 2012; **40**: 11–17.
- 23 Parienti JJ, du Cheyron D, Ramakers M, et al. Alcoholic povidone-iodine to prevent central venous catheter colonization: A randomized unit-crossover study. *Crit Care Med* 2004; **32**: 708–13.
- 24 Frasca D, Dahyot-Fizelier C, Mimoz O. Prevention of central venous catheter-related infection in the intensive care unit. *Crit Care* 2010; **14**: 212.
- 25 Eardley WG, Watts SA, Clasper JC. Limb wounding and antisepsis: iodine and chlorhexidine in the early management of extremity injury. *Int J Low Extrem Wounds* 2012; **11**: 213–23.
- 26 Lefebvre A, Saliou P, Mimoz O, et al, and the French Study Group for the Pre-operative Prevention of Surgical Site Infections. Is surgical site scrubbing before painting of value? Review and meta-analysis of clinical studies. *J Hosp Infect* 2015; **89**: 28–37.