Chlorhexidine for meatal cleaning in reducing catheter-associated urinary tract infections: a multicentre stepped-wedge randomised controlled trial

Oyebola Fasugba, Allen C Cheng, Victoria Gregory, Nicholas Graves, Jane Koerner, Peter Collignon, Anne Gardner, Brett G Mitchell

Summary

Background Evidence for the benefits of antiseptic meatal cleaning in reducing catheter-associated urinary tract infection (UTI) is inconclusive. We assessed the efficacy of 0·1% chlorhexidine solution compared with normal saline for meatal cleaning before urinary catheter insertion in reducing the incidence of catheter-associated asymptomatic bacteriuria and UTI.

Methods A cross-sectional, stepped-wedge, open-label, randomised controlled trial was undertaken in Australian hospitals. Eligible hospitals were Australian public and private hospitals, with an intensive care unit and more than 30 000 hospital admissions per year. Hospitals were randomly assigned to an intervention crossover date using a computer-generated randomisation system. Crossover dates occurred every 8 weeks; during the first 8 weeks of the study, no hospitals were exposed to the intervention (control phase), after which each hospital sequentially crossed over from the control to the intervention every 8 weeks. Patients requiring a urinary cathetwer were potentially eligible for inclusion in this hospital-wide study. Participants were excluded if they were younger than 2 years, had a medical reason preventing the use of the chlorhexidine, had the catheter inserted in theatre, did not have the catheter insertion date documented, required in-and-out or suprapubic catheterisation, had symptoms and signs suggestive of UTI at the time of catheter insertion, or were currently undergoing treatment for UTI. The intervention was the use of 0·1% chlorhexidine solution for meatal cleaning before urinary catheterisation with 0·9% normal saline used in the control phase. Masking of hospitals was not possible because it was not feasible to mask staff administering the intervention. The co-primary outcomes were the number of cases of catheter-associated asymptomatic bacteriuria and UTI per 100 catheter-days and were assessed within 7 days of catheter insertion in the intention-to-treat population. This trial is registered with Australian New Zealand Clinical Trials Registry, number ACTRN12617000373370.

Findings 21 hospitals were assessed for eligibility between Jan 5, 2017, and May 1, 2017; of these, three were successfully enrolled and randomised to one of three intervention crossover dates. 1642 participants in these hospitals were included in the study between Aug 1, 2017, and March 12, 2018, 697 (42%) in the control phase and 945 (58%) in the intervention period. In the control period, 13 catheter-associated UTI and 29 catheter-associated asymptomatic bacteriuria events in 2889 catheter-days (0·45 catheter-associated UTI cases and 1·00 catheter-associated asymptomatic bacteriuria cases per 100 catheter-days) were recorded compared with four catheter-associated UTI and 16 catheter-associated asymptomatic bacteriuria events in 2338 catheter-days (0·17 catheter-associated UTI cases and 0·68 catheter-associated asymptomatic bacteriuria cases per 100 catheter-days) during the intervention period. The intervention was associated with a 74% reduction in the incidence of catheter-associated asymptomatic bacteriuria (incident rate ratio 0·26, 95% CI 0·08–0·86, p=0·026), and a 94% decrease in the incidence of catheter-associated UTI (0·06, 95% CI 0·01–0·32, p=0·00080). There were no reported adverse events.

Interpretation The use of chlorhexidine solution for meatal cleaning before catheter insertion decreased the incidence of catheter-associated asymptomatic bacteriuria and UTI and has the potential to improve patient safety.

Funding HCF Research Foundation.

Lancet Infect Dis 2019

Published Online
April 12, 2019
http://dx.doi.org/10.1016/S1473-3099(18)30736-9

See Online/Comment
http://dx.doi.org/10.1016/S1473-3099(18)30758-8

Nursing Research Institute, Australian Catholic University & St Vincent's Health Australia, Sydney, NSW, Australia (O Fasugba PhD); **Lifestyle Research Centre, Avondale College of Higher Education, Cooranbong, NSW, Australia** (O Fasugba); **School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia** (Prof A C Cheng PhD); **Infectious Prevention and Healthcare Epidemiology Unit, Alfred Hospital, Melbourne, VIC, Australia** (Prof A C Cheng); **Faculty of Arts, Nursing and Theology, Avondale College of Higher Education, Wahroonga, NSW, Australia** (V Gregory MSc, Prof B G Mitchell PhD); **Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, QLD, Australia** (Prof N Graves PhD); **School of Nursing, Midwifery and Paramedicine Australian Catholic University, Watson, ACT, Australia** (J Koerner PhD); **Australian Capital Territory Pathology, Canberra Hospital and Health Services, Yamba Drive, Garran, ACT, Australia** (Prof P Collignon PhD); **Medical School, Australian National University, Acton, ACT, Australia** (Prof P Collignon); **School of Public Health and Social Work, Queensland University of Technology, Brisbane, QLD, Australia** (A Gardner PhD); **and School of Nursing and Midwifery, University of Newcastle, Newcastle, NSW, Australia** (Prof B G Mitchell)

Introduction

Urinary tract infections (UTIs) are a common health-care-associated infection and a large proportion of these are associated with the high usage of indwelling urinary catheters.[1] Bacteriuria due to urinary catheterisation can represent colonisation (catheter-associated asymptomatic bacteriuria) or symptomatic infection (catheter-associated UTI).[2] The proportion of hospitalised patients that receive a urinary catheter is high and ranges from 18% in the UK, 24% in the USA, to 26% in Australia.[3–5] A large point-prevalence study in the USA done in 183 hospitals, identified that catheter-associated UTIs account for 8·7% of all health-care-associated infections.[5] Catheter-associated UTIs pose substantial health and economic implications for patients and the health-care system by prolonging hospital stay[6] and increasing the risk of

Correspondence to:
Prof Brett G Mitchell, Faculty of Arts, Nursing and Theology, Avondale College of Higher Education, Wahroonga, NSW 2076, Australia
brett.mitchell@avondale.edu.au

Research in context

Evidence before this study

Catheter-associated urinary tract infection (UTI) is a leading preventable cause of health-care-associated infection. Current international infection-control guidelines identify that the benefit of antiseptic meatal cleaning before urinary catheter insertion in reducing catheter-associated UTI remains unresolved. We searched the Cochrane Library, PubMed, Embase, CINAHL, MEDLINE, Joanna Briggs Institute EBP database, Ovid, Science Direct, EBSCO, Scopus, Academic Search Complete, and Health Source from inception to December, 2015, to identify randomised controlled trials and quasi-experimental studies that evaluated the use of an antiseptic, antibacterial, or non-medicated product for meatal cleaning before urinary catheterisation and during catheter use. We used different combinations of the following search terms: "urinary catheter", "urinary tract infection", "meatal cleaning", "peri-urethral cleaning", "antiseptic", "antimicrobial", "antibacterial", "antibiotic", "topical", and "bundle intervention". 14 relevant studies were identified: three quasi-experimental studies and 11 randomised controlled trials. Two studies compared povidone-iodine with routine meatal care (removal of debris from the catheter during bathing), three studies compared povidone-iodine with soap and water, two studies compared chlorhexidine with water, four studies compared an antibacterial agent with routine meatal care, one study compared povidone-iodine with saline, one study compared povidone-iodine with water, and one study compared green soap with routine meatal care. All studies were included in a meta-analysis which showed no difference in the incidence of catheter-associated UTI between antiseptic and non-antiseptic products. However, 64% of the studies were assessed to have a high risk of bias. An updated search of PubMed was undertaken on Aug 21, 2018, and one additional randomised controlled trial was identified. This trial included 122 paediatric patients in an intensive care unit and found no significant differences in catheter-associated UTI incidence when comparing sterile water, povidone-iodine, and chlorhexidine for periurethral cleaning before urinary catheterisation.

Added value of this study

To the best of our knowledge, this is the largest published multicentre randomised controlled trial to assess the efficacy of using 0·1% chlorhexidine solution compared with 0·9% normal saline for meatal cleaning before urinary catheterisation, in reducing catheter-associated asymptomatic bacteriuria and UTI. The use of chlorhexidine was associated with a 74% reduction in the incidence of catheter-associated asymptomatic bacteriuria (incidence rate ratio 0·26, 95% CI 0·08–0·86; p=0·026), and a 94% decrease in the incidence of catheter-associated UTI (0·06, 0·01–0·32; p=0·00080) in all three participating hospitals with no detection of blood-stream infection during the overall study period.

Implications of all the available evidence

Catheter-associated UTI has substantial health and economic implications for patients and the health-care system; hence, strategies to reduce this infection are warranted. Our study suggests that 0·1% chlorhexidine solution might be an effective antiseptic meatal-cleaning product before urinary catheterisation in preventing catheter-associated asymptomatic bacteriuria and UTI with the potential to improve safety for hospitalised patients.

antimicrobial resistance.[1] Despite implementation of multiple infection control strategies such as appropriate urinary catheter use, aseptic insertion, and maintenance—including the timely removal of catheters—catheter-associated UTIs remain problematic.[7] While evidence suggests that reducing catheter use is the most effective way to reduce catheter-associated asymptomatic bacteriuria and catheter-associated UTIs,[2] some patients will unavoidably require a catheter as part of their management in hospital. Hence, investigation of other strategies to reduce these infections is warranted.

A potential strategy to decrease catheter-associated UTI risk is cleaning of the urethral meatus before catheterisation. This approach aims to decrease bacterial colonisation around the area thereby limiting the introduction of opportunistic bacteria into the urinary tract during catheter insertion.[8] Current national and international guidelines differ in their recommendations on the choice of product for meatal cleaning, which are based on evidence from low quality studies or expert opinion.[9,10] The UK epic3 guideline[10] recommends the use of normal saline for cleaning the urethral meatus before catheter insertion while the US Healthcare Infection Control Practices Advisory Committee guideline[9] provides no recommendation, stating that issue remains unresolved with a call for further research on the use of antiseptic solutions. Evidence from our preliminary systematic review and meta-analysis[11] showed that the benefits of antiseptic meatal cleaning in reducing catheter-associated UTIs remains inconclusive, emphasising the need for a rigorously done and adequately powered randomised controlled study. We therefore aimed to evaluate the efficacy of using chlorhexidine in meatal cleaning before catheter insertion for the prevention of catheter-associated asymptomatic bacteriuria and UTI.

Methods

Study design and participants

We undertook a cross-sectional, stepped-wedge, open-label, randomised controlled trial (RCT) in three Australian hospitals over a 32-week period from Aug 1, 2017, to March 12, 2018. The protocol for this study has been previously published.[12] The stepped-wedge design was chosen for its feasibility. It also enabled each hospital

to act as its own control, removing the potential for confounders such as variations in hospital size and casemix and differences between public and private hospitals.

Eligible hospitals were Australian public and private hospitals, with an intensive care unit and more than 30 000 hospital admissions per year. A purposive sampling method (non-probability sampling) was used. Hospitals that met the eligibility criteria were approached by the research team to determine their interest in participating. Of those hospitals who were approached, the first three hospitals to agree to participate were included in the study.

All hospitalised patients requiring a urinary catheter were potentially eligible for inclusion in this hospital-wide study. Participants were excluded if they were younger than 2 years, had an allergy, had contraindication or other medical reason preventing the use of the chlorhexidine, had the catheter inserted in the theatre, did not have the catheter insertion date documented, required in-and-out or suprapubic catheterisation, had symptoms and signs suggestive of UTI at the time of catheter insertion, or were undergoing treatment for UTI.

This trial was approved by the Avondale College of Higher Education Human Research Ethics Committee (HREC; approval number 2017:03), the Australian Capital Territory Health HREC (approval number ETH.4.17.083), and the Adventist HealthCare Limited HREC (approval number 2017–018). Site-specific hospital-level consent was granted by the relevant HRECs with a waiver of individual patient consent.

Randomisation and masking

Hospitals were randomly assigned to one of three dates to cross over to the intervention, which occurred once every 8 weeks over the trial duration of 32 weeks. Randomisation was done independently by an investigator not involved in assessment or delivery of the intervention using a computer-generated randomisation system. During the first 8 weeks of the study, no hospitals were exposed to the intervention (control phase), after which each hospital sequentially crossed over from the control to the intervention every 8 weeks beginning from Sept 26, 2017, for hospital A. Hospital B crossed over to the intervention on Nov 21, 2017, and hospital C crossed over on Jan 16, 2018. Masking of hospitals was not possible because it was not feasible to mask staff administering the intervention. Before study commencement, randomisation allocation was unmasked and revealed to hospitals by the project manager.

Procedures

The intervention was the use of 0·1% chlorhexidine solution for meatal cleaning before urinary catheterisation. The meatal area was cleaned with 0·9% normal saline in the control phase. Clinical staff at participating hospitals were responsible for cleaning the meatal area of participants before urinary catheter insertion. The procedure did not differ from usual clinical practice.

Before commencement of the intervention, hospital staff were provided with information about the study. Ward posters, information leaflets, and branded promotional material were also used to raise awareness about the intervention. To prevent the effect of confounding on the trial results, no additional education was given on catheter insertion and management practices and staff were expected to follow the hospital's usual practice. Only information about the change of meatal cleaning product was provided. To prevent the potential confounding effect of antiseptic-containing lubricants used during the catheterisation process, the lubricating product remained constant in each hospital during both control and intervention periods. No lubricant in any hospital contained chlorhexidine. The type of lubricant used was checked before the commencement of the study and during the study.

Chlorhexidine was not readily available for staff to use during the control phase. During the intervention phase, chlorhexidine was incorporated into existing catheter procedure packs and trial information stickers were attached to the packs. A temporary amendment to hospital procedural documentation was implemented and an insert for internal communications was provided.

Participants who received a urinary catheter were identified prospectively and followed up during the trial period for 7 days after catheter insertion and for 48 h after catheter removal or discharge, depending on which occurred first. The decision to collect a catheter urine specimen for culture was made by the treating physician. There was no change in the urine culture collection process during this study, at any hospital. Study investigators worked alongside hospitals to assist staff with implementation of the intervention by using hospital data collection and reporting systems already in place.

Data were collected by hospital personnel from participants' medical records and recorded in a purpose-designed spreadsheet. Demographic and clinical data abstracted included hospital number, age, sex, admission date, UTI symptoms or signs, comorbidities, catheter insertion date and time, designation of person inserting catheter, and catheter type and size. Data on UTI symptoms and signs were used to differentiate between catheter-associated asymptomatic bacteriuria and UTI. Denominator data on the number of catheter-days over the trial period was collected at each hospital during both control and intervention periods. The number of catheter-days for each participant included in the study was estimated from the catheter insertion and removal dates. Data on the primary and secondary outcomes were obtained from the hospitals' microbiology laboratory database.

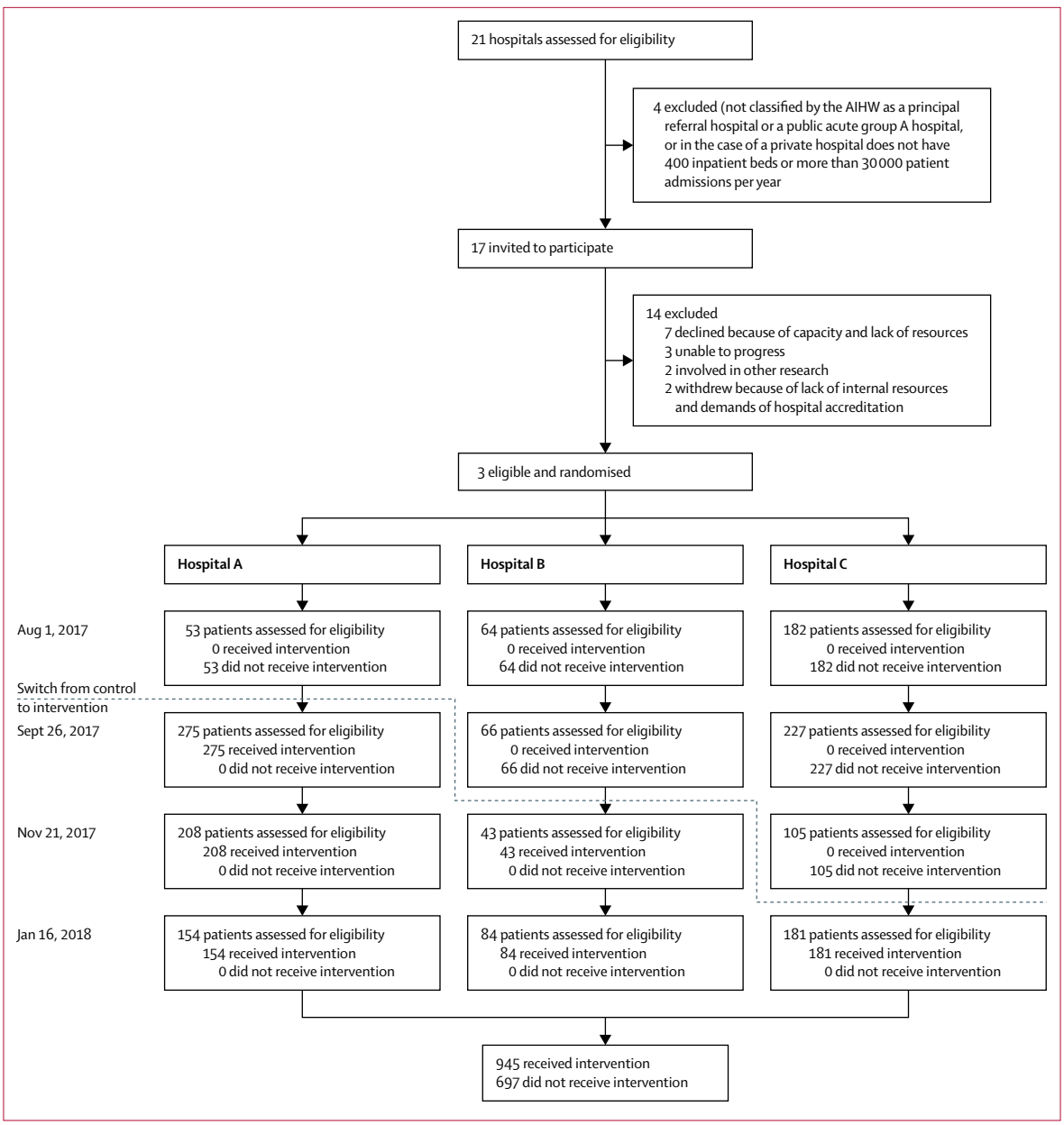

Figure 1: **Trial profile**
AIHW=Australian Institute of Health and Welfare.

Outcomes

The primary outcomes were the weekly number of cases of catheter-associated asymptomatic bacteriuria and UTI per 100 catheter-days and were assessed within 7 days of catheter insertion. Catheter-associated asymptomatic bacteriuria was defined as the presence of at least 10^5 colony forming units (cfu) per mL of one bacterial species or two in a single catheter urine specimen in a participant without symptoms compatible with UTI.[2] We considered any sample with more than two species as a contaminant and therefore they were not considered as a case of catheter-associated asymptomatic bacteriuria. Catheter-associated UTI was defined following the National Healthcare Safety Network criteria,[13,14] according to which a patient must meet all of three criteria. First, the patient had an indwelling urinary catheter that had been in place for more than 2 days on the date of event (day of device placement is day 1) and was either present for any portion of the calendar day on the date of event or removed the day before the date of event. Second, the patient has at least one of these signs or symptoms: fever (>38·0°C), suprapubic tenderness, costovertebral angle pain or tenderness, urinary urgency, urinary frequency, and

	Total (n=1642)	Control period				Intervention period			
		Hospital A (n=53)	Hospital B (n=130)	Hospital C (n=514)	Total control (n=697)	Hospital A (n=637)	Hospital B (n=127)	Hospital C (n=181)	Total intervention (n=945)
Median age, years (IQR)	69 (38–82)	79 (68–86)	72 (64–81)	80 (70–88)	78 (69–87)	35 (30–56)	73 (60–84)	82 (70–89)	50 (32–76)
Sex									
Female	949 (58%)	27 (51%)	52 (40%)	250 (49%)	329 (47%)	477 (75%)	65 (51%)	78 (43%)	620 (66%)
Male	693 (42%)	26 (49%)	78 (60%)	264 (51%)	368 (53%)	160 (25%)	62 (49%)	103 (57%)	325 (34%)
Comorbidities									
Cancer	327 (20%)	9 (17%)	32 (25%)	160 (31%)	201 (29%)	42 (7%)	24 (19%)	60 (33%)	126 (13%)
Diabetes	229 (14%)	2 (4%)	34 (26%)	89 (17%)	125 (18%)	43 (7%)	29 (23%)	32 (18%)	104 (11%)
Liver disease	63 (4%)	2 (4%)	9 (7%)	29 (6%)	40 (6%)	10 (2%)	6 (5%)	7 (4%)	20 (2%)

Data are median (IQR) or n (%).

Table 1: **Baseline characteristics by study period and hospital**

dysuria. Finally, the patient has a urine culture with no more than two species of organisms identified, at least one of which is a bacterium with a colony count of 10^5 cfu/mL or more.

The secondary outcome was the number of bloodstream infection (BSI) cases associated with a UTI and was defined according to National Healthcare Safety Network surveillance definitions.[13] A participant must meet the definition for catheter-associated UTI and have at least one organism from the blood specimen that matches an organism identified in the urine specimen that is used as an element to meet the catheter-associated UTI criterion. The blood specimen must have been collected during the secondary BSI attribution period when the urinary catheter was in place.

Data on primary and secondary outcomes and on any adverse events were collected at each participating hospital and reported and analysed centrally.

Statistical analysis

Our study was powered to detect a 20% reduction in the incidence of catheter-associated asymptomatic bacteriuria and UTI individually with 80% power, two-sided type I error of 5%, and intracluster correlation coefficient of 0·05 as described in the protocol.[12] The power calculation used the stepped-wedge sample size formula from Hussey and Hughes.[15] On the basis of estimates calculated before the study, a minimum of 2640 patients was necessary for our analyses to have this statistical power.

A Poisson regression model was used to estimate the effect of the intervention on the outcome. In this regression, the weekly number of events (catheter-associated asymptomatic bacteriuria, catheter-associated UTI, and BSI) was the dependent variable, with hospital, study week, and intervention as independent variables, and the number of catheter-days per week as the exposure. The effect of the intervention was modelled as the change in incidence following the switch from control to intervention, reported as an incidence rate ratio (IRR; estimate, 95% CI); because of the small number of sites, interactions between intervention and hospital and between intervention and time were not considered. We calculated SEs using the robust estimator to account for clustering at the hospital level.

On the basis of post-hoc exploratory analysis, we did two sensitivity analyses. The first sensitivity analysis excluded hospital A because of the wide age distribution of patients in that hospital. The second sensitivity analysis used a logistic regression model with catheter-associated asymptomatic bacteriuria or UTI as the dependent variable, and intervention phase, age, and sex as independent variables. This model was done on individual participant data and accounted for clustering at the hospital level (and, therefore, sub-hospital levels, including ward) using the robust estimator. The effect of the intervention in this sensitivity analysis was quantified as odds ratio (OR; 95% CI). All analyses were done with Stata version 15.1. Analysis was by intention to treat and included all eligible hospitalised patients requiring a urinary catheter. In the primary analysis, the unit of analysis was by month and hospital. The sensitivity analysis was a patient-level analysis so confounding by patient-level factors could be accounted for.

This trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12617000373370.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

21 hospitals were initially considered for this study and assessed for eligibility. 17 eligible hospitals were invited to participate with recruitment occurring between Jan 5, 2017, and May 1, 2017. 14 (82%) hospitals were excluded (figure 1). Three hospitals were successfully

	Control period			Intervention period			Poisson regression	
	Number of patients	Catheter days	Number (incidence*)	Number of patients	Catheter days	Number (incidence*)	IRR (95% CI)	p value
CA-ASB								
Hospital A	53	254	8 (3·15)	637	1327	11 (0·82)	1 (reference)	..
Hospital B	130	552	5 (0·91)	127	418	2 (0·48)	0·35 (0·12–1·03)	0·056
Hospital C	514	2093	16 (0·76)	181	593	3 (0·49)	0·27 (0·09–0·78)	0·015
Total	697	2889	29 (1·00)	945	2338	16 (0·68)	..	..
CAUTI								
Hospital A	53	236	3 (1·18)	637	1345	4 (0·30)	1 (reference)	..
Hospital B	130	552	2 (0·36)	127	418	0 (0·00)	0·17 (0·04–0·73)	0·018
Hospital C	514	2068	8 (0·38)	181	618	0 (0·00)	0·14 (0·04–0·51)	0·0026
Total	697	2856	13 (0·45)	945	2381	4 (0·17)	..	..

There were no cases of the secondary outcome (bloodstream infections secondary to a urinary tract infection) in any hospital in either group of the study. CA-ASB=catheter-associated asymptomatic bacteriuria. CAUTI=catheter-associated urinary tract infection. IRR=incidence rate ratio. *per 100 catheter days.

Table 2: **Number and incidence of CA-ASB and CAUTI, stratified by study period and hospital**

See Online for appendix

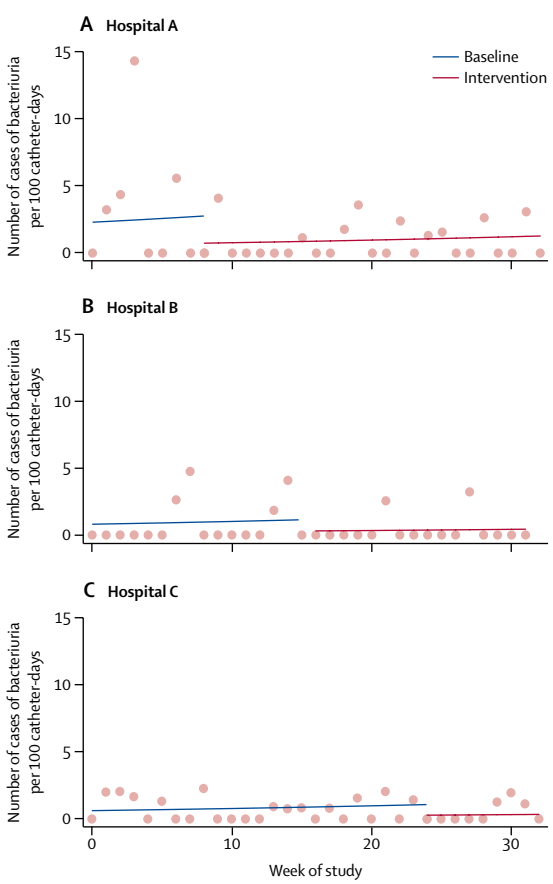

Figure 2: **Incidence of catheter-associated asymptomatic bacteriuria during intervention and control periods, stratified by hospital**

enrolled in the study and randomised in July 2017 to one of three intervention crossover dates. Two of the three hospitals in our study are publicly funded, the other being privately funded. Additional information on the governance, casemix of hospital patients, and services provided are detailed in the appendix.

1642 participants in these hospitals were included in the study, 697 (42%) in the control phase and 945 (58%) in the intervention period.

The median age of participants in the control period was 78 years (IQR 69–87) and 50 years (32–76) in the intervention period. Overall, 949 (58%) participants were female (table 1). Catheter insertion varied over the study period (appendix). For most participants, removal of the catheter was the reason for censoring follow-up in both control (363 [52%] of 697 participants) and intervention (751 [79%] of 945 participants) periods.

There were 29 cases of catheter-associated asymptomatic bacteriuria, equating to 1·00 cases per 100 catheter-days, in the control period and 16 cases, or 0·68 per 100 catheter-days, during the intervention. The number of cases of catheter-associated UTI also reduced from 13 (0·45 per 100 catheter-days) to four (0·17 per 100 catheter-days; table 2).

The use of chlorhexidine was associated with a 74% reduction in the incidence of catheter-associated asymptomatic bacteriuria (IRR 0·26, 95% CI 0·08–0·86; p=0·026). There was a 94% decrease in the incidence of catheter-associated UTI (0·06, 0·01–0·32; p=0·00080). A reduction in both catheter-associated asymptomatic bacteriuria and UTI was identified in all three participating hospitals (figure 2; figure 3).

There were no cases of a BSI associated with a UTI in the control or intervention periods.

After exploratory analysis of the data, we noted that there was a large difference in the age distribution of participants at hospital A, which was not reported at hospitals B and C (appendix). To determine whether the observed results could be confounded by this difference, we did two sensitivity analyses. In the first sensitivity analysis, which excluded hospital A, the intervention significantly reduced the risk of catheter-associated UTI (IRR is undefined as it is zero in the post-intervention

period; p<0·0001; appendix). There were no catheter-associated UTI reported at hospitals B and C during the intervention period. In this analysis, a non-significant reduction in the risk of catheter-associated asymptomatic bacteriuria was observed (IRR 0·48, 95% CI 0·14–1·63, p=0·241; appendix).

In the second sensitivity analysis, a logistic regression model was done. After adjusting for age, sex, and clustering by hospital, the use of chlorhexidine was associated with a significantly reduced risk of catheter-associated asymptomatic bacteriuria (OR 0·42, 95%CI 0·33–0·53; p<0·0001) and of catheter-associated UTI (0·17, 0·05–0·55; p=0·0031; appendix).

There were no adverse events reported as a result of or associated with the intervention. There were no adverse events in either the control or intervention phase of the study. The study team were not advised of any participant excluded from the study as a result of a known allergy.

Discussion

To our knowledge, this is the first multicentre RCT comparing the efficacy of 0·1% chlorhexidine solution and 0·9% normal saline solution for meatal cleaning before urinary catheterisation in preventing catheter-associated asymptomatic bacteriuria and UTI. We found a significant reduction in the incidence of catheter-associated asymptomatic bacteriuria and UTI in the intervention period with no detection of BSI during the overall study period.

The findings are noteworthy and suggest that the 0·1% chlorhexidine solution might be an effective antiseptic meatal cleaning product before urinary catheterisation in preventing catheter-associated asymptomatic bacteriuria and UTI. Health-care associated bacteriuria, including catheter-associated asymptomatic bacteriuria and UTI are costly, with estimates suggesting that attributable costs for a catheter-associated UTI in the USA is over US$1000 per patient, for excess costs related to additional diagnostics, medications, and Medicare.[16] We intend to also undertake a cost-effectiveness analysis of our intervention. Although less than a quarter of patients with catheter-associated asymptomatic bacteriuria develops symptomatic UTI,[17] the excess costs, increased length of stay in hospital, and antimicrobial use for treatment, coupled with the frequency of these infections, provide a strong rationale to prevent its occurrence.[6,16,18]

Our findings contrast with previous RCTs that assessed the effect of chlorhexidine on catheter-associated asymptomatic bacteriuria and UTI. Although these single site RCTs[19,20] found that the use of chlorhexidine did not decrease the incidence of bacteriuria or UTI, important limitations were noted. The study by Webster and colleagues[19] comprised 436 young obstetric patients. In the study by Düzkaya and colleagues,[21] the sample included 122 paediatric patients in intensive care units and the absence of a power analysis to calculate the required sample size is identified as a major

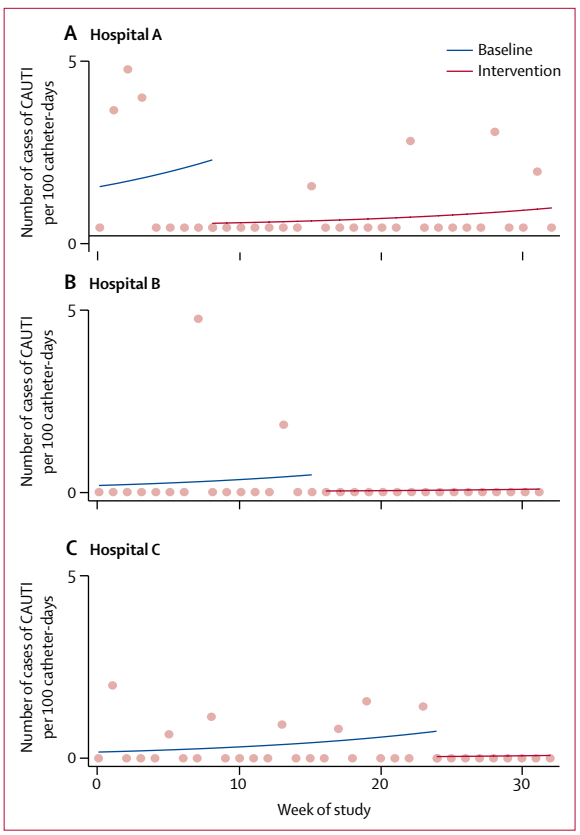

Figure 3: **Incidence of CAUTI during control and intervention periods, stratified by hospital**
CAUTI=catheter-associated urinary tract infection.

methodological flaw. Carapeti and colleagues[20] included only 156 pre-operative general surgical patients in their study, also with no sample size estimation reported. Furthermore, this study[20] assessed the effect of two different urethral catheterisation techniques—sterile versus non-sterile—in which chlorhexidine was included as a component within the solution used for cleaning patients' meatal area before catheterisation. The potential effect of chlorhexidine could therefore have been overshadowed by other aspects of the intervention being investigated. Additionally, the small sample size in these studies might also have been insufficient to detect a significant difference even if it existed. Our study has benefited from the inclusion of three large but diverse hospitals, in addition to appropriate sample size.

In support of our findings, a cluster RCT[22] of 74 adult intensive care units in the USA, aimed to investigate the effect of three interventions on the incidence of bacteriuria. Findings from this study[22] suggest that the use of a universal decolonisation strategy involving the use of daily chlorhexidine baths resulted in a 26% reduction in bacteriuria in male participants when compared with the targeted decolonisation, screening, and isolation strategies. In particular, patients randomly assigned to

this strategy received 2% nasal mupirocin antibiotic ointment, in addition to daily baths with 2% no-rinse chlorhexidine-impregnated cloths for their entire stay in the intensive care unit. Staff were instructed to cleanse the perineal area and urinary catheter as part of the chlorhexidine bathing procedure.[22] While this US-based study[22] only found a significant effect in male participants, the potential beneficial effect of chlorhexidine in reducing catheter-associated asymptomatic bacteriuria was shown.

The active concentrations for chlorhexidine vary from 0·1% to 4%. When combined with alcohols, the presence of two active components might create an enhanced antiseptic effect.[23] Although evidence supports chlorhexidine plus alcohol over chlorhexidine-only solutions in preventing some health-care-associated infections,[23] there are no published data available specifically for catheter-associated UTI. Furthermore, the use of an alcohol-based solution on the meatal area could be uncomfortable and therefore unacceptable from a patient's perspective.

Evidence shows that patients with catheter-associated asymptomatic bacteriuria are inappropriately treated with antimicrobials despite guidelines recommending otherwise.[2,24] This inappropriate antimicrobial use is exacerbated by the fact that patients with indwelling urinary catheters often have other comorbidities which might require treatment with antimicrobials.[25] Catheterised patients are therefore under intense antimicrobial pressure, which can lead to the isolation of antimicrobial resistant bacteria from their urine, and subsequent use of antimicrobials.[25] Hence, reducing the incidence of catheter-associated asymptomatic bacteriuria, even without development of catheter-associated UTI, has the potential to decrease inappropriate antimicrobial use. The impact of reducing the incidence of catheter-associated asymptomatic bacteriuria should not be underestimated, given that the proportion of inpatients who receive an indwelling urinary catheter is between 18% and 26%.[3,4] Our study findings highlight the potential for a preventive strategy in catheter-associated asymptomatic bacteriuria development with the use of 0·1% chlorhexidine solution for meatal cleaning before urinary catheterisation. This preventive strategy is especially important given the global increase in multidrug resistant urinary pathogens.[1]

We found no occurrence of hospital-acquired BSI secondary to catheter-associated asymptomatic bacteriuria or UTI during the study. While bacteriuria is considered a prerequisite for urosepsis[26] and the presence of an indwelling catheter is recognised as a risk factor for bacteraemia,[27] the risk of BSI has been shown to be higher from catheter-associated UTI than catheter-associated asymptomatic bacteriuria,[28] with a prevalence of catheter-associated bacteraemic UTI of up to 15% reported in previous studies.[26] However, the prevalence of hospital-acquired BSI secondary to catheter-associated UTI has generally tended to be low.[17]

Our study has limitations. The difference in the age distribution of participants in hospital A by comparison with hospitals B and C was unexpected. We did investigate this further with hospital A. The timing of the control period for hospital A was close to Christmas. During this time, there appeared to be fewer obstetric gynaecological procedures undertaken than in the intervention period. Patients in this cohort are generally much younger. We would also expect patients in this casemix to have more catheters. For these reasons, in addition to hospital A having the longest intervention period, we saw a difference in age. Hospital A was also the largest hospital in our study. While there was potential for this to skew the study findings, the sensitivity analysis, accounting for age and sex, found similar results to the original analysis, suggesting that our primary analysis finding remains valid. Although this was a hospital-wide study, it was not feasible to include patients who had a catheter inserted in a surgical theatre . For pragmatic reasons, the intervention could be implemented more easily and consistently in other clinical areas. Despite the sample size being attained, the potential for selection bias cannot be excluded. Selection bias was also likely to occur from the discretionary urine testing which was based on the treating physician, thereby limiting the generalisability of the findings. A focus on catheter-associated UTI prevention, albeit just through a change of product, might have inadvertently caused a Hawthorne effect—that is, more attention on correct catheter insertion techniques. However, staff were only provided information about the change of meatal cleaning product. There was no education provided on catheter insertion and management practices. Since we did not collect data on the antimicrobial use of participants, we could have underestimated the prevalence of bacteriuria as antimicrobials could reduce catheter-associated asymptomatic bacteriuria. The inability to mask staff who administered the intervention might have affected the meatal cleaning procedure and the subsequently measured incidence of catheter-associated asymptomatic bacteriuria. Nonetheless, a stepped-wedge design should account for this issue, given hospitals act as their own control.[29]

Despite these limitations, our study is the largest trial to date (three hospitals; 1642 participants) to assess the efficacy of using 0·1% chlorhexidine solution, compared with 0·9% normal saline, for meatal cleaning before urinary catheter insertion, in reducing the incidence of catheter-associated asymptomatic bacteriuria and UTI. Reductions in catheter-associated asymptomatic bacteriuria and UTI were identified in all three hospitals, despite differences in their governance, funding, size, and geographical location. Our trial is strengthened by using a stepped-wedge design which removed the potential for confounders such as variations in casemix. The relatively short study inclusion period also removed the potential for confounders as much as possible. We ensured a clear distinction was made between catheter-associated asymptomatic bacteriuria and UTI using additional data on UTI symptoms and signs from partici-

pants' medical records. This distinction is an added strength for our study as previous studies have not made it.

Our pragmatic study, assessed against the PRagmatic Explanatory Continuum Indicator Summary (appendix), can easily be implemented in hospitals internationally. Given the size of the reduction in UTI identified, we believe the use of chlorhexidine for meatal cleaning has the potential to improve safety for hospitalised patients. Any reduction in catheter-associated asymptomatic bacteriuria, although not infection, should be welcomed, as it has the potential to reduce inappropriate antimicrobial use. We encourage an update of existing systematic reviews that inform international guidelines for the prevention and control of catheter-associated UTI, in addition to local hospital policies.

Contributors

All authors designed the study. BGM is the chief investigator for the study. BGM and VG were responsible for study administration and management, and all authors were involved in ongoing implementation. ACC analysed the data. OF, ACC, NG, JK, PC, AG, and BGM interpreted the data. OF and BGM wrote the first draft of the manuscript. ACC, VG, NG, JK, PC, and AG revised the draft critically for important intellectual content. All authors read and approved the final manuscript.

Declaration of interests

We declare no competing interests.

Data sharing

Individual de-identified participant data that underlie the results reported in this Article are subject to ethics and privacy restrictions. The conditions of ethics approval do not allow us to distribute or make available these data directly to other parties. However, the study protocol is freely available online for researchers to access. Applications for data access should be made by contacting the chief investigator and corresponding author BGM, Avondale College of Higher Education. Researchers must have their study protocol approved by the relevant human research ethics committee.

Acknowledgments

This study was funded by a competitive grant supported by the HCF Research Foundation. Cash support from Avondale College of Higher Education was also provided. We thank and acknowledge the staff of the infection prevention and control departments of participating hospitals. In particular, we wish to thank Vicki Denyer, Robyn Masters, Andrea Menzies, Wendy Beckingham, Jayne O'Connor, Holly Dodd, and Laisa Kulavere.

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