Chlorhexidine washing in intensive care does not reduce bloodstream infections, blood culture contamination and drug-resistant microorganism acquisition: an interrupted time series analysis

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ABSTRACT

Background: Health care-associated infections are a major cause of morbidity and mortality in intensive care patients. The effect of daily washing with chlorhexidine on these infections is controversial.

Methods: Single-centre, retrospective, open-label, sequential period, interrupted time series (ITS) analysis in a 31-bed tertiary referral mixed intensive care unit (ICU), comparing daily washing with water and soap (from January 2011 to August 2013) with chlorhexidine washing (from November 2013 to December 2015), after the introduction of a unit-level policy of chlorhexidine washing. All patients in the ICU were included in the study, except: if they were under 18 years of age, if their ICU stay was less than 24 hours (to ensure that all studied patients had at least one exposure to the daily wash intervention), or if patients had a known allergy to chlorhexidine. Outcome measures included: clinically significant positive blood cultures attributable to the ICU stay; contaminated blood cultures; newly acquired multidrug-resistant microorganisms (MDRO) such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococcus (VRE) or multidrug-resistant gram-negative (MRGN) isolates attributable to ICU from clinical and screening cultures; and newly acquired *Clostridium difficile* infections (CDIs). Incidence rates of these outcomes were calculated per 1000 patient days. MDRO acquisition rates were corrected for background hospital period prevalence rates of MDRO.

Results: A total of 6634 patients were included in the study. ITS analysis showed no significant level or slope changes in any of the outcome measures after implementation of chlorhexidine washing. The incidence rate of clinically significant positive blood cultures during the chlorhexidine period compared with the water and soap period was 3.6 *v* 4.7 ($P = 0.37$); blood culture contamination rates were 11.8 *v* 9.5 ($P = 0.56$); incidence rates of new ICU-associated MDRO acquisitions were 3.22 *v* 3.69 ($P = 0.27$); incidence rates of new CDI were 2.01 *v* 0.79 ($P = 0.16$). Outcomes after adjustment for known and potential confounders were similar.

Conclusions: In this real-world, long term ICU study, implementation of a unit-level policy of daily washing with chlorhexidine impregnated cloths was not associated with a reduction in the rates of ICU-associated clinically significant positive blood cultures, blood culture contamination, newly acquired MDRO isolates, and CDIs.

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The prevention of health care-associated infections and nosocomial bloodstream infections poses a great challenge. There are around 200 000 health care-associated infections each year in Australian acute health care facilities, many of which are potentially preventable.[1] Of these health care-associated infections, especially multidrug-resistant microorganisms (MDRO) remain a concern, as they require longer and more complicated treatments than those infections caused by susceptible bacteria, with increased hospital length of stay, failure of therapy, increased morbidity and mortality and increased costs.[2-4] Patients admitted to an intensive care unit (ICU) are particularly prone to these infections because of a number of reasons. These include disease severity, critical illness-associated immunosuppression, underlying comorbidities, the use of invasive devices, the intensity of patient care, and the specific ICU environment.

In past decades, many strategies have been explored in order to prevent health care-associated infections, especially those caused by MDRO. These strategies include antimicrobial stewardship programs, improved hand hygiene, use of personal protective equipment, education of health care staff, and patient isolation.[5-7] Despite these measures, prevention of these infections remains a challenge, partly because of the difficulty in improving compliance by health care workers.[8,9]

Recently, there has been a renewed interest in the use of the antiseptic chlorhexidine gluconate as a measure to prevent infections with and transmission of MDRO in patients in the ICU.[10-15] Chlorhexidine has a bactericidal effect by means of coagulation of cytoplasm and damaging the bacterial cell membrane, and is effective against both gram-positive and gram-negative bacteria, as well as yeasts.

We investigated the effect of implementation of a policy of daily chlorhexidine washing on rates of bloodstream infections, blood culture contamination, newly acquired MDRO isolates and *Clostridium difficile* infections (CDIs). We used an

interrupted time series (ITS) design to detect whether the policy implementation had an effect significantly greater than the underlying secular trend. This is the key feature that distinguishes this method from other evaluation methods, in which observations are usually aggregated into pre-intervention and post-intervention periods, thus ignoring underlying trends during the baseline period as well as "shifts" in trend once the intervention is introduced.[16,17]

Methods

Study design

We performed a single-centre, retrospective, open-label, sequential period, ITS analysis in the ICU of the Canberra Hospital between January 2011 and December 2015. The Canberra Hospital is the Australian Capital Territory's major public hospital, with about 600 inpatient beds, providing specialist and acute care to a population of more than 500 000 people. The 31-bed mixed medical and surgical ICU admits around 2000 patients per year.

During the control period from January 2011 to August 2013, patients in the ICU were washed daily with water and soap. The chlorhexidine washing protocol was implemented in the Canberra Hospital ICU in September 2013. During the intervention period from November 2013 to December 2015, patients in the ICU were subjected to daily chlorhexidine washes. We established a 2-month wash-out period between the control and intervention period. This was based on examination of chlorhexidine product purchase data by ICU, which stabilised 2 months after implementation of the new washing protocol (supplementary Appendix, Section 1; online at cicm.org.au/Resources/Publications/Journal).

All ICU patients over the age of 18 years were eligible to be included in the study. To ensure that all studied patients had at least one exposure to the daily wash intervention, they were excluded if their ICU stay was less than 24 hours. Patients with a known allergy to chlorhexidine were also excluded from the study.

We used the SQUIRE guidelines for reporting of quality improvement initiatives, and published recommendations for methodological and reporting standards for ITS analysis.[17,18]

The study was approved by the ACT Health Human Research Ethics Committee (approval No. ETHLR.15.210), and the need for consent was waived.

Body cleansing protocol

Washing protocols were executed by registered ICU nurses with competency in this skill according to local guidelines. During both study periods, the unit-level policy stated that patients should receive their first wash within the first 24 hours after admission to the ICU. Following implementation of a new unit-level policy, 2% chlorhexidine impregnated washcloths (Teleflex Medical Australia, Sydney, NSW) were to be used according to the supplier's instructions. The policy stated that, per patient, a set consisting of six cloths was to be used to wash all body surfaces except for the face to avoid exposure of chlorhexidine to the eyes and mouth, which were to be washed with non-medicated washcloths. All washcloths were discarded after use.

Outcomes

The primary outcome of the study was the ITS analysis of 3-monthly counts of clinically significant positive blood cultures attributable to the ICU stay. Based on the concept of hospital-acquired versus community-acquired bacteraemia definitions, cultures were considered attributable to ICU if obtained from a patient between 48 hours after ICU admission and 48 hours after ICU discharge. Recurrent positive blood cultures with the same isolate during an ICU admission were excluded, except when the blood culture was classified as contamination. Positive blood cultures were assessed for clinical significance or defined as contamination by a multidisciplinary team, comprised of infection control staff and microbiologists, via a prospective bloodstream infection surveillance program according to Australian surveillance definitions (https://safetyandquality.gov.au/wp-content/uploads/2012/01/bsidefinejun05.pdf).

Secondary study outcomes were:

- ITS analysis of counts of contaminated blood cultures, obtained between 24 hours after ICU admission until ICU discharge;
- ITS analysis of newly acquired vancomycin-resistant enterococcus (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA) or multidrug-resistant gram-negative (MRGN) isolates attributable to ICU, defined as any newly acquired positive screening or clinical culture, obtained between 48 hours after ICU admission through to 48 hours after ICU discharge; and
- the incidence rate (counts per 1000 patient days) of health care facility onset *Clostridium difficile* infection (CDI) cases between 48 hours after ICU admission through to 48 hours after ICU discharge.

Screening cultures were taken in the context of routine ICU infection control screening policies. Clinical cultures were taken if the medical staff deemed this relevant due to the patient's clinical status. Positive cultures were deemed clinically significant if the patient was likely to have a clinical infection, as assessed by the clinical team's decision to institute treatment for possible or proven infection. *C. difficile* isolates were deemed clinically significant if the *C. difficile* toxin test was also positive. Definitions of MRGN organisms were in accordance with Clinical and Laboratory Standards Institute (CLSI) guidelines (online supplementary Appendix, Section 2).

Blood cultures were collected by clinical staff according to the hospital protocol. Active screening for MRSA and

VRE was performed by the ICU unit throughout both study periods. Screening cultures from the nasal mucosa and groin for MRSA and from the perianal area for VRE were obtained on ICU admission and discharge as per unit policy. Between December 2013 and April 2014, there was upscaled hospital-wide surveillance for carbapenemase-producing Enterobacteriaceae (CPE), which was not sustained in significant periods before or after this episode. Additional cultures from sites such as wounds or urine were obtained if deemed relevant by the clinical team. If screening cultures returned positive for MDRO, additional precautions were applied, including single room isolation and use of appropriate personal protective equipment.

Data collection

Clinical and demographic data on all patients were collected from the ICU clinical information system MetaVision (iMDsoft, Red Hill, Qld, Australia) and from patients' clinical records. Data including age, gender, admission source, comorbid conditions (eg, immunocompromised, hepatic disease, malignancy, insulin-dependent diabetes mellitus, chronic respiratory disease, chronic cardiovascular disease, chronic renal failure), number of ICU bed days, hospital length of stay, central venous catheter days, mechanical ventilation days, APACHE (Acute Physiology and Chronic Health Evaluation) III score and mortality rate were collected. Group definitions for comorbid conditions are shown in the online supplementary Appendix, Section 3.

Microbiological data were collected from the laboratory information system and hospital surveillance databases, including all positive and negative blood cultures, and all positive other clinical cultures and data on all surveillance (screening) cultures performed during the study periods. Hospital period prevalence rates for MRSA, VRE and MRGN were defined as the number of positive screening cultures divided by the total number of screening cultures taken in the hospital during the relevant study periods.

Statistical analyses

Comparisons of patient baseline characteristics between the control and intervention groups were performed using the χ^2 test for categorical variables and Student *t* test or Mann–Whitney U tests for the continuous variables, according to their distributions. Changes in infection proportions at the hospital level were also evaluated using a χ^2 test.

An ITS analysis was performed to evaluate changes in the number of clinically significant positive blood cultures attributable to the ICU stay, changes in the number of contaminated blood cultures, and changes in the number of newly acquired VRE, MRSA or MRGN isolates attributable to ICU.

The basic assumption in ITS is that observations from the baseline period predict where the future data points would lie in the absence of an intervention. If the intervention is associated with observations that deviate from the predicted observations, the difference represents the effect of the intervention. The effect size is expressed in terms of level change (ie, a shift observed in direct association with the intervention) and slope change (ie, a change in trend over time).[19]

To standardise the description of outcome measures, incidence rates were calculated and defined as number of events per 1000 patient days. Differences in the mean incidence of our primary and secondary outcomes were evaluated using a Poisson regression model that included consideration of patient age, sex, APACHE III score, mechanical ventilation, ICU and hospital length of stay, comorbid conditions and admission source as potential confounders. The monthly prevalence of hospital-wide clinically significant positive cultures was also included as a covariate in the model to exclude the possibility that observed changes in incidence were associated with changes in hospital-wide prevalence rates, except for analysis of CDI cases, because hospital prevalence data for CDI were not available.

All analyses were performed with the R statistical package version 2.15.2 (R foundation for Statistical Computing).

Results

Baseline characteristics

During the water and soap washing period, 4934 patients over the age of 18 years were admitted to the ICU. Of these, 1570 patients were excluded because they stayed in the ICU less than 24 hours. During the chlorhexidine washing period, 4188 patients over the age of 18 years were admitted to the ICU, and 1218 were excluded from the study because they stayed in ICU less than 24 hours. In total, 6334 ICU patients were included in the study: 3364 patients during the control washing period and 2970 during the chlorhexidine washing period. No patients were excluded because of known chlorhexidine allergy, and no patients developed anaphylaxis associated with the use of chlorhexidine. There were no significant differences in the number of ICU admissions, or the month-to-month trend in the number of ICU admissions between the two study periods (online supplementary Appendix, Table A). Compliance to the chlorhexidine washing protocol was not directly assessed, but monthly data on ICU chlorhexidine washcloth purchase indicates consistent usage following implementation of the protocol (online supplementary Appendix, Section 1).

The baseline characteristics are described in Table 1. A number of small but statistically significant differences were noted between the two groups. During the control washing period, patients were on average younger (61.1 *v* 62.6 years; $P = 0.001$), with a lower disease severity score

(mean APACHE III score on admission, 59 *v* 61; *P* = 0.003), but with a larger proportion of patients requiring mechanical ventilation (51.9% *v* 48.8%; *P* = 0.015). In addition, during the control period, more patients were immunocompromised (2.9% *v* 1.9%; *P* = 0.02), fewer patients had insulin-dependent diabetes mellitus (2.3% *v* 3.5%; *P* = 0.007), and fewer patients had chronic renal failure (2.9% *v* 4.9%; *P* = 0.0001). The median hours of central venous catheter use was 15.1 hours (interquartile range [IQR], 7.4–41.0 hours) in the control group and 9.7 hours (IQR, 5.5–35.0 hours) in the chlorhexidine group (*P* = 0.42). There were no differences in ICU and hospital mortality rates between the two groups (Table 1).

Multidrug-resistant microorganisms hospital period prevalence rates

No significant differences were found in the MRSA and VRE hospital period prevalence rates between the control and the chlorhexidine periods (Table 1). The hospital period prevalence rate of MRGN was significantly lower during the water and soap wash period compared with the chlorhexidine wash period (0.49% *v* 1.12%; *P* < 0.001).

Table 1. Baseline demographics and clinical characteristics

	Water and soap period (32 months)	Chlorhexidine period (26 months)	*P*
ICU patients	3364	2970	
Total patient days	15187	12438	
Mean monthly ICU admissions (SD)	105 ± 13	114 ± 9	0.002
Age (mean), years (SD)	61.1 ± 17.7	62.6 ± 17.3	0.001*
Sex (female)	38.4%	37.9%	0.71
Admission source			
Medical	56.6%	58.2%	0.20
Surgical	43.4%	41.8%	0.20
Cardiothoracic surgery	13.5%	15.2%	0.06
Mean APACHE III score on admission (SD)	59 ± 25.7	61 ± 25.1	0.003*
Comorbid conditions			
Immunocompromised	2.9%	1.9%	0.02*
Hepatic disease	2.4%	2.5%	0.82
Malignancy	7.6%	7.4%	0.72
IDDM	2.3%	3.5%	0.007*
Chronic respiratory disease	1.6%	1.8%	0.61
Chronic cardiovascular disease	0.7%	1.0%	0.23
Chronic renal failure	2.9%	4.9%	0.0001*
Mechanical ventilation	51.9%	48.8%	0.015*
Mean duration mechanical ventilation, hours (SD)	73.5 ± 89.6	74.5 ± 92.4	0.76
Median ICU length of stay, days (IQR)	2.58 (1.58–4.85)	2.51 (1.62–4.40)	0.43
Median hospital length of stay, days (IQR)	13.0 (7–28)	13.0 (7–27)	0.75
ICU mortality rate	7.2%	6.0%	0.06
In-hospital mortality rate	12.5%	11.1%	0.08
Hospital period prevalence rate†			
MRSA	4.08	3.89	0.52
VRE	6.63	7.03	0.29
MRGN	0.49	1.12	< 0.001*

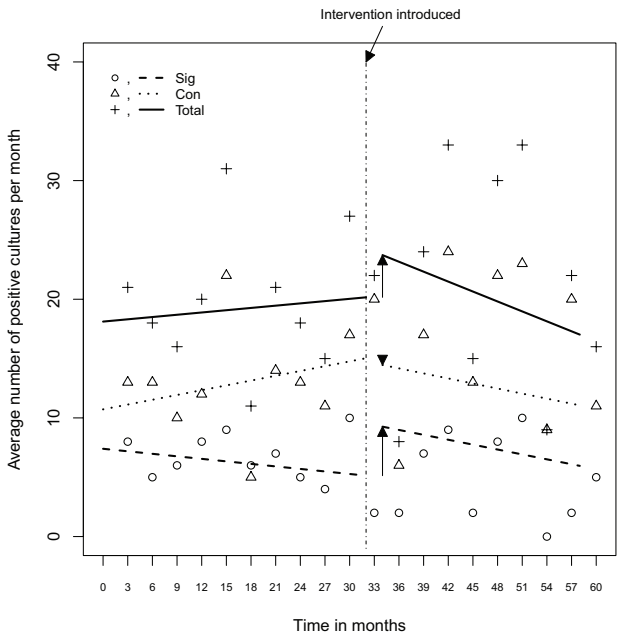
APACHE = Acute Physiology and Chronic Health Evaluation. ICU = intensive care unit. IDDM = insulin-dependent diabetes mellitus. IQR = interquartile range. MRGN = multidrug-resistant gram-negative bacteria. MRSA = methicillin-resistant *Staphylococcus aureus*. SD = standard deviation. VRE = vancomycin-resistant enterococcus. * Significant. † Hospital period prevalence rate in the Canberra Hospital, defined as the number of positive screening cultures divided by the total number of screening cultures taken in the hospital.

Table 2. Blood culture results

	Water and soap period		Chlorhexidine period		Unadjusted analysis		Adjusted analysis	
	Events	Incidence rate†	Events	Incidence rate*	Risk ratio (95% CI)	*P*	Risk ratio (95% CI)	*P*
Total blood cultures taken	1168 (100%)	76.9	1063 (100%)	85.5	1.06 (0.93–1.21)	0.41	1.06 (0.90–1.23)	0.53
Total positive blood cultures	216 (18.5%)	14.2	101 (9.5%)	8.1	0.85 (0.68–1.07)	0.17	0.80 (0.61–1.03)	0.09
Contaminants	145 (13.1%)	9.5	147 (13.8%)	11.8	0.92 (0.70–1.21)	0.56	0.86 (0.65–1.14)	0.31
Clinically significant	71 (6.1%)	4.7	45 (4.2%)	3.6	0.84 (0.58–1.22)	0.37	0.76 (0.51–1.13)	0.17
GN cultures	23 (2.0%)	1.5	13 (1.2%)	1.0	0.75 (0.38–1.49)	0.41	0.43 (0.18–1.00)	0.05
GP cultures	39 (3.3%)	2.6	26 (2.5%)	2.1	0.91 (0.72–1.16)	0.46	0.85 (0.67–1.09)	0.21
Yeast cultures	9 (1.0%)	0.6	6 (0.5%)	0.5	0.89 (0.32–2.49)	0.82	0.62 (0.20–1.94)	0.41

CI = confidence interval. GN = gram-negative bacteria. GP = gram-positive bacteria. * Adjusted values obtained by Poisson regression analysis that included consideration of patient age, sex, APACHE (Acute Physiology and Chronic Health Evaluation) III score, mechanical ventilation, intensive care unit and hospital length of stay, comorbid conditions and admission source. † The incidence rate was defined as the total number of blood cultures per 1000 patient days.

Figure 1. Interrupted time series analysis of 3-monthly positive blood cultures attributable to the intensive care unit



Sig = clinically significant. Con = contamination.

ITS analysis showed there was an increase in the month-to-month trend of the total number of MDRO cultures taken (slope change after intervention; $P = 0.005$), with an increase in the month-to-month trend of hospital-wide MDRO positive cultures (MRSA + VRE + MRGN, slope change; $P = 0.02$) (online supplementary Appendix, Table B).

Blood cultures

Table 2 and online supplementary Appendix, Table C show that there was no significant difference in the total or month-to-month trend of blood cultures taken in the ICU between the study periods.

The results of the ITS analysis of positive blood cultures attributable to the ICU is shown in Figure 1 and in the online supplementary Appendix, Table C. Before the intervention, there was no significant month-to-month change in the number of positive blood cultures (baseline trend; $P = 0.72$). After implementation of the chlorhexidine washing policy, there were no significant changes in the number of positive blood cultures (level change after intervention; $P = 0.29$). There was also no significant change after the intervention in the month-to-month trend in the number of positive blood cultures (slope change after intervention; $P = 0.29$). Similarly, there were no significant changes in the number of clinically significant blood cultures (level change; $P = 0.45$; slope change; $P = 0.69$), or in the number of contaminated blood cultures (level change; $P = 0.34$; slope change; $P = 0.24$) after the intervention.

The incidence rate of positive blood cultures during the water and soap period was 14.2/1000 patient days and 8.1/1000 patient days during the chlorhexidine period ($P = 0.17$). The overall blood culture contaminant rate and the rate of clinically significant blood cultures were not different between the study periods (Table 2). Adjustment for patient age, sex, APACHE III score, mechanical ventilation, ICU and hospital length of stay, comorbid conditions and admission source did not change these results (Table 2; adjusted analysis).

Figure 2. Interrupted time series analysis of clinically significant positive blood cultures with yeasts, gram-positive and gram-negative microorganisms attributable to the intensive care unit

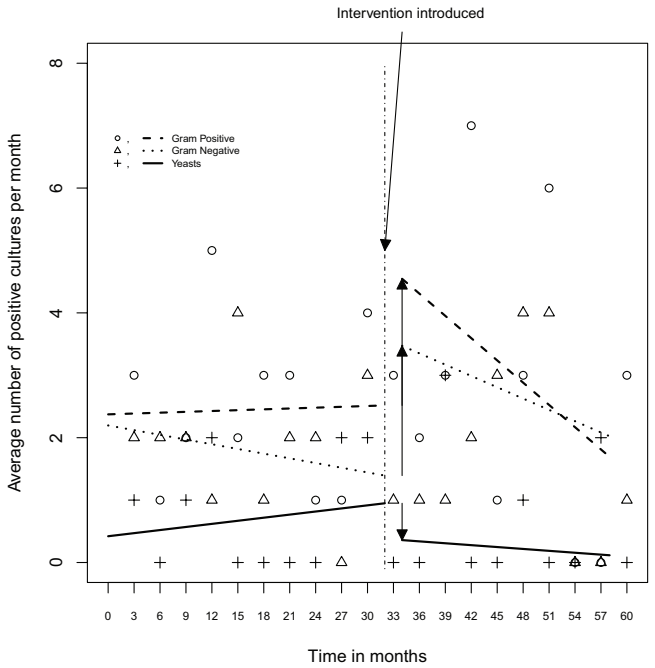
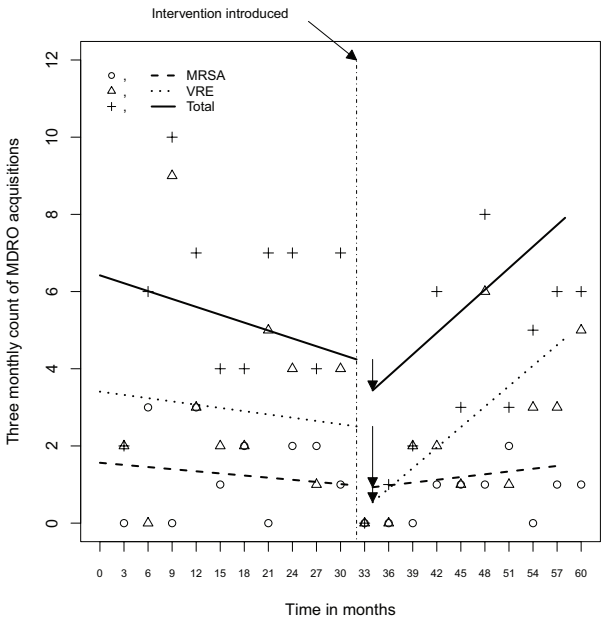


Figure 3. Interrupted time series analysis of new acquisitions with multidrug-resistant microorganisms (MDRO) in the intensive care unit



MRSA = methicillin-resistant *Staphylococcus aureus*. VRE = vancomycin-resistant enterococcus. Total depicts the sum of MRSA, VRE and multidrug-resistant gram-negative isolates.

Clinically significant positive blood cultures were divided into gram-positive bacteria, gram-negative bacteria, and yeasts (Table 2). The results of the ITS analysis of clinically significant positive blood cultures with yeasts, gram-positive and gram-negative microorganisms attributable to the ICU are shown in Figure 2 and in the online supplementary Appendix, Table D. After implementation of the policy, there were no significant changes in the number of gram-positive, gram-negative or yeast cultures (level change; $P = 0.21$; $P = 0.31$; $P = 0.93$, respectively). There was also no significant change after the intervention in the month-to-month trend in the number of gram-positive, gram-negative or yeast positive cultures (slope change; $P = 0.25$; $P = 0.67$; $P = 0.54$, respectively).

Further microbiological identification of all clinically significant blood culture isolates during the study period is shown in the online supplementary Appendix, Table E. *S. aureus* and *Enterococcus* species were the most commonly isolated pathogens during both study periods. The absolute numbers and rates per culture isolate showed no significant differences between the two study periods.

New acquisition of multidrug-resistant microorganisms in the intensive care unit

During the water and soap period, the incidence rate of new acquisitions with MDRO was 3.68/1000 patient days, compared with 3.22/1000 patient days in the chlorhexidine washing group ($P = 0.27$) (Table 3). The majority of MDRO cases were found during screening cultures.

The results of the ITS of new acquisitions with MDRO in the ICU is shown in Figure 3 and in the online supplementary Appendix, Table F. After implementation of the unit-level chlorhexidine washing policy, there were no significant changes in the number of MRSA, VRE or MRSA + VRE + MRGN positive cultures (level change; $P = 0.52$; $P = 0.19$; $P = 0.24$, respectively). There were also no significant changes in the month-to-month trend of MRSA, VRE or MRSA + VRE + MRGN positive cultures (slope change; $P = 0.47$; $P = 0.13$; $P = 0.10$, respectively).

The incidence rate of new CDI cases showed a non-significant increase during the chlorhexidine period (0.79 *v* 2.01 cases per 1000 patient days; $P = 0.16$).

Discussion

In this single-centre, retrospective, open-label, sequential period, ITS analysis, implementation of a unit-level policy of once daily washing with chlorhexidine, compared with water and soap, was not associated with a reduction in the number of clinically significant blood cultures, blood culture contamination, or ICU-associated new acquisition of MDRO.

Despite the widespread adoption and implementation of universal decolonisation techniques, such as daily chlorhexidine washing, results from the literature on efficacy

Table 3. Newly acquired screening and clinical cultures with multidrug-resistant microorganisms (MDRO) in the intensive care unit (ICU) taken between 48 hours after ICU admission and 48 hours after discharge from the ICU*

	Water and soap period		Chlorhexidine period		Unadjusted analysis		Adjusted analysis	
	Events	Incidence rate*	Events	Incidence rate†	Risk ratio (95% CI)	*P*	Risk ratio (95% CI)	*P*
New MDRO acquisitions								
Total	56 (100%)	3.69	40 (100%)	3.22	1.27 (0.83–1.93)	0.27	0.99 (0.62–1.24)	0.97
MRSA	12 (21.5%)	0.79	7 (17.5%)	0.56	0.83 (0.32–2.14)	0.70	1.23 (0.43–3.48)	0.89
VRE	32 (57.0%)	2.11	23 (57.5%)	1.85	0.95 (0.54–1.66)	0.86	0.74 (0.42–1.30)	0.29
MRGN	12 (21.5%)	0.79	10 (25.0%)	0.80	1.29 (0.55–3.02)	0.56	2.29 (0.81–6.49)	0.12
Screening cultures								
Total	40 (71.0%)	2.63	28 (70.0%)	2.25	0.92 (0.56–1.53)	0.78	0.96 (0.53–1.56)	0.87
MRSA	7 (12.5%)	0.46	4 (10.0%)	0.32	1.01 (0.85–1.19)	0.93	1.00 (0.84–1.18)	0.98
VRE	31 (55.0%)	2.04	21 (52.5%)	1.69	0.98 (0.88–1.10)	0.76	0.79 (0.57–1.09)	0.68
MRGN	2 (3.5%)	0.13	3 (7.5%)	0.24	1.00 (0.78–1.27)	0.98	1.00 (0.77–1.27)	0.98
Clinical cultures								
Total	16 (29.0%)	1.05	12 (30.0%)	0.96	1.18 (0.55–2.53)	0.67	1.19 (0.53–2.68)	0.67
MRSA	5 (9.0%)	0.33	3 (7.5%)	0.24	1.02 (0.84–1.24)	0.84	1.04 (0.85–1.26)	0.73
VRE	1 (2.0%)	0.07	2 (5.0%)	0.16	0.95 (0.70–1.30)	0.77	0.98 (0.72–1.33)	0.89
MRGN	10 (18.0%)	0.66	7 (17.5%)	0.56	1.02 (0.89–1.18)	0.74	1.03 (0.89–1.19)	0.66
Clinically Significant								
Total	12 (21.0%)	0.79	8 (20.0%)	0.64	1.01 (0.89–1.16)	0.84	1.10 (0.40–3.01)	0.85
MRSA	4 (7.0%)	0.26	1 (2.5%)	0.08	1.02 (0.80–1.30)	0.88	1.06 (0.82–1.34)	0.69
VRE	1 (2.0%)	0.07	2 (5.0%)	0.16	0.95 (0.70–1.30)	0.76	0.98 (0.72–1.33)	0.89
MRGN	7 (12.0%)	0.46	5 (12.5%)	0.40	1.03 (0.87–1.21)	0.76	1.04 (0.89–1.23)	0.61
Not clinically significant								
Total	4 (7.0%)	0.26	4 (10.0%)	0.32	1.50 (0.37–6.07)	0.60	1.29 (0.30–5.39)	0.75
MRSA	1 (2.0%)	0.07	2 (5.0%)	0.16	1.02 (0.75–1.39)	0.90	1.02 (0.75–1.39	0.90
VRE	0 (0.0%)	0.00	0 (0.0%)	0.00	na	na	na	na
MRGN	3 (5.0%)	0.20	2 (5.0%)	0.16	1.01 (0.80–1.29)	0.91	1.00 (0.78–1.28)	0.99

CI = confidence interval. MRGN = multidrug-resistant gram-negative bacteria. MRSA = methicillin-resistant *Staphylococcus aureus*. VRE = vancomycin-resistant enterococci. * Adjusted values obtained by Poisson regression analysis that included consideration of patient age, sex, APACHE (Acute Physiology and Chronic Health Evaluation) III score, mechanical ventilation, intensive care unit and hospital length of stay, comorbid conditions, admission source, and the monthly prevalence of hospital-wide positive cultures. † The incidence rate was defined as the total number of cultures per 1000 patient days.

are conflicting.[10,11,13-15,20-25] For example, in a multicentre, non-blinded, crossover trial in 7727 patients from six ICUs and bone marrow units, daily washing with chlorhexidine significantly reduced the acquisition of VRE (relative reduction, 25%) and the incidence of hospital-acquired bloodstream infection (relative reduction, 28%).[11] However, much of the reduction was explained by reduced blood culture contamination rather than actual infection rates.[26] This may still be clinically relevant because blood culture contamination may lead to unnecessary administration of antibiotics or the

ordering of more diagnostic tests, both of which may cause harm to patients. Other studies examining the effect of chlorhexidine washing on rates of contaminated blood cultures also suggest reduced rates.[20,27,28] Nevertheless, in another pragmatic, cluster, randomised, crossover study of 9340 patients admitted to five adult ICUs of a single medical centre, daily washing with chlorhexidine did not reduce the incidence of health care-associated infections, rates of blood culture contamination or clinical cultures with MDRO.[12]

We found a non-significant increase in the rate of new ICU-associated CDI cases after implementation of chlorhexidine washing. Hospital background period prevalence rates for CDI were not available. Chlorhexidine lacks sporicidal activity and is therefore not expected to be effective against *C. difficile*.[29,30]

Our study has several strengths. We studied the effects of implementation of an ICU-wide chlorhexidine washing policy in a real-world setting, which means the results are therefore likely to be more realistic, as compared with effect sizes based on randomised controlled studies, which measure the effect size of an intervention in an ideal research environment. For example, protocol compliance by nursing staff is likely to be lower in the real world than in strictly controlled study conditions, thereby influencing the measured effect of the implementation of a policy. In addition, data were collected over 5 consecutive years, resulting in a large cohort of ICU patients. This extended period may have allowed for possible effects, or lack thereof, on ICU ecological microbiology to become apparent. Importantly, we corrected for potential confounders, including for background hospital-wide period prevalence rates of MDRO. To standardise outcomes measures, incidence rates per 1000 patient days were used. Other strengths include the completeness of our dataset, and the simplicity and reproducibility of the definitions used for the various outcome measures. Our main endpoints were clinically significant blood cultures or contaminants, and we did not limit this to catheter-associated bacteraemia as other studies have done. Finally, for quasi-experimental trial designs (before and after studies), ITS analysis is the strongest design for causal inference.[31,32]

Our study also has several potential limitations, including the single-centredness and retrospective nature of the design. Despite correction for potential and known confounders, including baseline imbalances in age, disease severity, mechanical ventilation and comorbid conditions, unmeasured confounders may have caused further unbalancing of the study groups. The studied time periods had different lengths (32 *v* 26 months). Reasons for this were: the date of introduction of the ICU electronic patient data management system, the date of introduction of the chlorhexidine washing policy and the wash-out period we established on the basis of chlorhexidine purchases. However, with ITS methodology, it is acceptable to have different lengths of time periods, provided there are enough data points in each time period (a minimum of three per time period is recommended).

During the chlorhexidine washing period, hospital-wide positive MDRO cultures (MRSA, VRE and MRGN combined) increased significantly over time (slope change) compared with what would be expected, based on the observed trend before the ICU policy was implemented. The total number of MDRO cultures that were taken in the hospital also increased over this time period. This can partially be explained by the period of upscaled hospital-wide surveillance for CPE from the second until the sixth month of the chlorhexidine washing period, as described in the methods section. However, the increase in total MDRO cultures taken and new MDRO acquisitions extended to beyond this specific period of upscaled surveillance, suggesting that perhaps the level of increased surveillance was maintained at hospital-wide level.

Our study may have been underpowered to detect changes in infection and colonisation rates associated with the implementation of a unit-level policy of chlorhexidine washing. Nursing staff compliance with the chlorhexidine washing protocol was not measured, and there are no patient-level data of the extent to which the intervention was applied. Finally, we did not perform a cost–benefit analysis of the intervention, nor did we examine the effects of prolonged use of chlorhexidine on the possible emergence of chlorhexidine resistance. The latter effect is unclear and requires further research.[33]

Conclusion

In this ITS study into the effects of the implementation of a unit-level ICU policy, daily washing with chlorhexidine impregnated cloths was not associated with a reduction in the rates of ICU-associated clinically significant positive blood cultures, ICU-associated blood contaminants, and newly acquired MDRO isolates. Our findings suggest that the benefits of daily washing of critically ill patients with chlorhexidine in the real world may be limited.

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Competing interests

None declared.

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Authors' contributions

RK and ET wrote the study protocol, analysed the data and drafted the manuscript; FvH conceived and designed the study, supervised and directed the research team during the entire project, and finalised the manuscript; KD assisted in interpreting the data and contributed significantly to the manuscript; BL provided statistical analysis of the data and revised the manuscript; HR and WB collected and provided the data for the study and revised the manuscript; KK and RS provided direction to the study methodology and revised the manuscript. All authors read and approved the final manuscript for submission.

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