Daily chlorhexidine bathing to reduce bacteraemia in critically ill children: a multicentre, cluster-randomised, crossover trial

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Summary

Background Bacteraemia is an important cause of morbidity and mortality in critically ill children. Our objective was to assess whether daily bathing in chlorhexidine gluconate (CHG) compared with standard bathing practices would reduce bacteraemia in critically ill children.

Methods In an unmasked, cluster-randomised, two-period crossover trial, ten paediatric intensive-care units at five hospitals in the USA were randomly assigned a daily bathing routine for admitted patients older than 2 months, either standard bathing practices or using a cloth impregnated with 2% CHG, for a 6-month period. Units switched to the alternative bathing method for a second 6-month period. 6482 admissions were screened for eligibility. The primary outcome was an episode of bacteraemia. We did intention-to-treat (ITT) and per-protocol (PP) analyses. This study is registered with ClinicalTrials.gov (identifier NCT00549393).

Findings 1521 admitted patients were excluded because their length of stay was less than 2 days, and 14 refused to participate. 4947 admissions were eligible for analysis. In the ITT population, a non-significant reduction in incidence of bacteraemia was noted with CHG bathing (3·52 per 1000 days, 95% CI 2·64–4·61) compared with standard practices (4·93 per 1000 days, 3·91–6·15; adjusted incidence rate ratio [aIRR] 0·71, 95% CI 0·42–1·20). In the PP population, incidence of bacteraemia was lower in patients receiving CHG bathing (3·28 per 1000 days, 2·27–4·58) compared with standard practices (4·93 per 1000 days, 3·91–6·15; aIRR 0·64, 0·42–0·98). No serious study-related adverse events were recorded, and the incidence of CHG-associated skin reactions was 1·2 per 1000 days (95% CI 0·60–2·02).

Interpretation Critically ill children receiving daily CHG bathing had a lower incidence of bacteraemia compared with those receiving a standard bathing routine. Furthermore, the treatment was well tolerated.

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Introduction

Bloodstream infections are associated with substantial morbidity, mortality, and health-care costs in adults.[1] Children admitted to hospital usually have higher rates of bloodstream infections than do adults.[2] In critically ill children, primary infections have an estimated attributable cost of US$39 000 per episode[3] and associated mortality of 11–18%.[4,5] Furthermore, all positive blood cultures—including those due to commensal skin organisms such as coagulase-negative staphylococci—entail increased use of antibiotics, augmented laboratory charges, and longer hospital stays.[6–10] Although national collaborations work to reduce general bloodstream infections and those associated with the central line (CLABSI),[11–13] data are needed to address the efficacy and tolerability of novel prevention strategies in children.

Chlorhexidine gluconate (CHG) is a topical antiseptic that inhibits organism growth and reduces skin colonisation. It is used to prevent infection in many hospital settings.[14] Because bloodstream infections are sometimes caused by a patient's bacterial flora, reduction of bacteria on the skin could lessen the risk of contamination at a catheter insertion site, catheter hub, or site of peripheral blood culture. At the time this study was designed in 2006–07, findings of two studies in adults admitted to hospital suggested that daily CHG baths could decrease bloodstream infections: one was a single-centre randomised study and the other was a multicentre before-and-after intervention study.[15,16] No data were available for whether daily CHG bathing was tolerated and effective in children admitted to hospital. We assembled a collaborative of children's hospitals with large paediatric intensive-care units (ICUs) to assess whether daily CHG bathing compared with standard bathing practices would reduce bacteraemia in critically ill children. Since CHG bathing might change the local ecological environment, we designed a cluster-randomised trial, with the ICU as the unit of randomisation, to prevent contamination between treated and untreated patients.

Patients and methods

Study design

The Pediatric Scrubbing with Chlorhexidine Reduces Unwanted Bacteria (SCRUB) trial was an investigator-

initiated, unmasked, cluster-randomised, two period, crossover trial in ten ICUs at five hospitals in the USA (Johns Hopkins Hospital, Children's Hospital of Philadelphia, St Louis Children's Hospital, Seattle Children's Hospital, and Children's National Medical Center). The trial was started in February, 2008, and ended in September, 2010 (appendix p 1). Two 6-month study periods were separated by a 2-week washout. The study was designed initially to have two 5-month study periods, but fewer eligible patients were enrolled than anticipated; therefore, study periods were extended to 6 months. Study initiation was planned to be staggered.

See Online for appendix

All children admitted to every ICU were eligible for inclusion, but enrolment targeted those with an anticipated unit stay of more than 2 days. The US Food and Drug Administration (FDA) has not approved CHG for use in babies younger than 2 months. Therefore, patients were not eligible to receive CHG bathing if they were younger than 2 months of age, had an indwelling epidural or lumbar drain, had severe skin disease or burns, or had an allergy to CHG.

Characteristics and microbiology data for all patient admissions were entered at every site into a database (Microsoft Access 2007) and sent to the coordinating centre. Every site obtained institutional review board approval, and we obtained informed consent from caregivers of every admitted child (appendix p 2). This study is registered with ClinicalTrials.gov (number NCT00549393).

Randomisation and masking

We defined the ICU as the unit of randomisation. Every hospital had one control and one treatment unit during each study period. Randomisation was stratified by hospital and ICU type (cardiac and medical or surgical) to balance ICU types in the treatment group during each study period. We used a random number generator (Microsoft Excel 2007) to select assignments. The assignment was concealed from the unit until they agreed to participate. During the study period, investigators and caregivers were aware of the assignment. After study completion, when the primary outcome was assessed from submitted laboratory data, outcome assessors were masked to random allocations.

Procedures

In the control unit, patients were bathed daily with either soap and water or Comfort Bath (Sage Products, Cary, IL, USA), according to the ICU's routine practice. In the treatment unit, a 2% CHG-impregnated cloth (Sage Products; appendix p 3) was used for daily bathing of patients. The 2% CHG-impregnated cloth is not approved by the FDA for daily bathing; therefore, we undertook this study under an investigator-held investigational new drug license (IND 77 954). Children in the treatment unit who were not eligible to be bathed with CHG underwent standard bathing practices, as did all patients during the washout period. We educated bedside nurses on study bathing procedures. We measured adherence at every site by review of medical records and a study bathing log and by periodic auditing of caregivers.

Endpoints

The primary outcome of the Pediatric SCRUB trial was bacteraemia, which we defined as any single positive blood culture, including those that grew commensal skin organisms (eg, coagulase-negative staphylococci). The primary outcome measurement was incidence of bacteraemia per 1000 patient-days at risk. We chose bacteraemia as the primary outcome for several reasons: morbidity from bacteraemia is substantial in critically ill children; bacteraemia happens more frequently compared with CLABSI; and available funding might not allow capture of enough events to power CLABSI as the primary outcome. Furthermore, we included commensal skin organisms because these bacteria have a relevant effect on clinical care of children.[6,8]

Study team members, who were unaware of treatment assignments, defined distinct events of bacteraemia. We judged the first event to be any positive blood culture during the at-risk period (appendix p 4). We deemed a second event to have arisen in the same patient either when culture grew the same organism and it was established as an independent event (generally >7 days between isolates) or if a different organism was isolated from a subsequent blood culture. As sites finalised data collection, and before data were unmasked, we realised that sites were having difficulty objectively applying the initial protocol definition of a second episode of bacteraemia. Therefore, we redefined our definition of a second event as either a different organism cultured at least 7 days after the first event or the same organism cultured at least 14 days after the first event.

Antibiotic treatment of any bacteria cultured from the blood is common practice in children with catheters, but this strategy is not always done in those without catheters. Therefore, we undertook exploratory analyses after removal of commensal skin organisms in all patients and in those without catheters.

We defined the secondary outcome as primary CLABSI, using surveillance criteria from the Centers for Disease Control and Prevention's (CDC's) National Healthcare Safety Network (NHSN).[17] The secondary outcome measurement was incidence of CLABSI per 1000 catheter-days. In every hospital, infection control specialists monitored bacteraemia in children with indwelling catheters, applied NHSN criteria prospectively to identify CLABSIs, and provided a list of primary CLABSIs to the study team. These staff were not masked to study assignment. Study team members obtained catheter days with standard NHSN methods.

Additional secondary outcomes included rates of surgical-site infections and incidence of meticillin-resistant *Staphylococcus aureus* and vancomycin-resistant

enterococci. These findings will be reported in detail in subsequent reports. We ascertained adverse events as described in the appendix (p 5). Clinical care teams established whether rashes were related or unrelated to study treatment.

On June 28, 2008, the 2% CHG-impregnated washcloths were recalled because of product contamination with *Burkholderia cepacia*. All institutional review boards and the FDA were notified and two hospitals (two treatment and two control units) that had begun enrolment in the first study period were placed on hold. After product remediation and institutional review board approval, the study was restarted. The four units that were placed on study hold extended their first period end date to complete 6 months. Patients enrolled in all four units at the time of the recall were administratively censored on the recall date in the final analysis.

Statistical analysis

We estimated sample size using baseline incidence data for bacteraemia and CLABSI at every site. Detailed data were not available from every ICU to estimate the expected effect of exclusions (eg, age <2 months, length of stay ≤2 days) and variance within units. We assumed a 40% reduction in bacteraemia from available data in critically ill adults.[15,18] Since no previous data were available on which to base a design effect for clustering (ie, the statistical effect of clustering associated with a cluster-randomised trial), we included a design effect of 1·2. We estimated that 148 episodes of bacteraemia and 62 of CLABSI would be captured with ten ICUs enrolling for 12 months, and we calculated the study would have more than 80% power to detect an incidence rate ratio of 0·6 for bacteraemia and 0·45 for CLABSI comparing treatment and control, with a two-sided α of 0·05. The Johns Hopkins Biostatistics Center undertook an unplanned interim analysis at the request of the institutional review board of Seattle Children's Hospital, before the site began enrolment; no correction of the reported p value was done for this interim test.

We used two populations to assess the effect of CHG bathing. The intention-to-treat (ITT) population included all eligible admitted children age 2 months or older, except those whose caregiver refused to participate and did not consent to have protected health information gathered. The per-protocol (PP) population included all eligible admitted children age 2 months or older who received any treatment and selected admissions who were not given treatment because of defined exclusions. We included patient admissions with defined exclusions in the PP population because similar children were not identified and excluded in the control group. With our original study design, we presumed that post-randomisation informed consent for CHG bathing would be obtained for most critically ill admissions. However, because of unanticipated challenges in obtaining informed consent, we reassessed and revised our statistical plan after final collection of data but before unmasking the dataset. We compared baseline characteristics of every unit between the first and second study periods to assess distribution of potential confounders, with Wilcoxon rank-sum and χ^2 tests.[19,20] Within treatment units, children for whom consent was not received had similar baseline characteristics to those who were treated (appendix p 6). Therefore, we specified that the estimated effect of daily CHG bathing would be better reflected by the PP population, which was identified as the primary population of analysis.

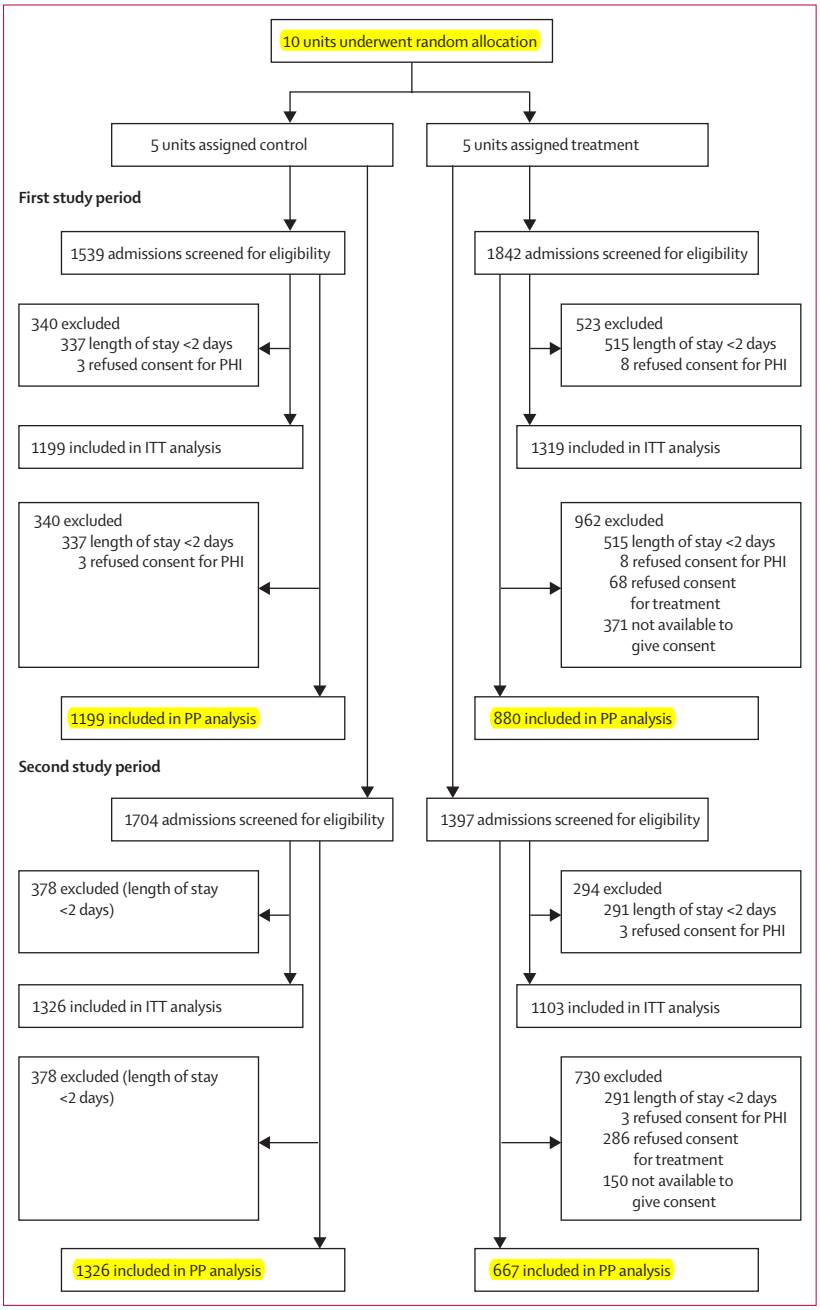

Figure 1: **Trial profile**
PHI=protected health information (including outcome data). ITT=intention to treat. PP=per protocol.

In the primary analysis, we compared incidence of bacteraemia between every unit's treatment and control periods. We used Poisson regression models to estimate adjusted incidence rate ratios (aIRRs), adjusted for unit, secular trends in infection rates over time, and characteristics of patient admissions. The period effect was not significant in any analyses. We accounted for hospital-level clustering with a robust variance estimator. We used multiple imputations to calculate missing PRISM scores at one site. Sensitivity analyses confirmed that excluding patients with missing data or including imputed results did not affect our estimate of the treatment effect. We used similar models to assess both the primary and secondary outcomes. We did a subgroup analysis to assess rates of bacteraemia in admissions with central venous catheters and an exploratory analysis to compare crude ICU mortality in treatment and control groups. All tests were two-sided with a type 1 error rate set at 0·05. We managed and analysed data with R (version 2.12)[21] and Stata (version 11.0; Stata, College Station, TX, USA).

Role of the funding source

The study was designed, undertaken, and analysed by the authors. The commercial sponsor had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The sponsor was permitted to review the manuscript. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Of 6482 admissions to ICU units who were screened for study eligibility, 4947 (76%) were enrolled and had outcome data collected, 2525 in control and 2422 in treatment units (figure 1). These patient admissions formed the ITT population. Of 2422 admissions to treatment units, 354 guardians refused consent to receive the treatment and 521 were not available to provide consent; moreover, 32 admitted children did not receive treatment. Therefore, 4072 patient admissions formed the PP population.

Key clinical and demographic characteristics were balanced between study periods (table 1). The median time at risk in the treatment and control units was 3 days (range 1–119 days and 1–183 days, respectively). 161 deaths were recorded, 88 in control units and 73 in treatment units (crude mortality 3·25%, 95% CI 2·79–3·28).

In the PP population, 113 episodes of bacteraemia were identified in 103 admissions; 34 events were in treatment

	Period 1 assignment	Patient admissions in PP population (ITT population)		Age (years)		Non-white ethnic origin		Any complex chronic condition*		Central venous catheter		PRISM III score†	
		Period 2	Period 1	Period 2	Period 1	Period 2	Period 1	Period 2	Period 1	Period 2	Period 1	Period 2	Period 1
Children's Hospital of Philadelphia													
Unit 1	Treatment	306 (306)	227 (417)	5·85 (1·55–13·40)	6·50 (2·06–14·73)	141 (46%)	73 (32%)	251 (82%)	180 (79%)	95 (31%)	77 (34%)	3 (0–8)	2 (0–5)‡
Unit 2	Control	227 (429)	342 (342)	7·64 (2·75–15·19)	5·57 (1·51–13·57)‡	86 (39%)	154 (45%)‡	177 (78%)	267 (78%)	75 (33%)	137 (40%)	3 (0–7)	2 (0–7)
Children's National Medical Center													
Unit 1	Treatment	388 (388)	156 (325)	4·61 (1·29–11·82)	2·89 (0·84–10·21)‡	318 (82%)	142 (91%)‡	303 (78%)	100 (64%)‡	155 (40%)	58 (37%)	3 (0–7)	2 (0–5)‡
Unit 2	Control	52 (68)	120 (120)	0·55 (0·34–1·92)	0·73 (0·37–2·37)	41 (79%)	85 (71%)	52 (100%)	116 (97%)	43 (83%)	80 (67%)‡	6 (3–12)	5 (1–8)
Johns Hopkins Hospital													
Unit 1	Treatment	264 (264)	150 (206)	4·49 (1·19–11·18)	3·84 (0·87–12·43)	130 (49%)	71 (47%)	219 (83%)	132 (88%)	156 (59%)	95 (63%)	8 (3–14)	8 (5–13)
Unit 2	Control	146 (208)	206 (206)	4·08 (1·35–11·93)	7·10 (1·91–13·75)	70 (48%)	109 (53%)	110 (75%)	160 (78%)	73 (50%)	103 (50%)	5 (1·5–8)	5 (2–10)
St Louis Children's Hospital													
Unit 1	Control	154 (310)	413 (413)	6·37 (1·34–13·56)	6·99 (1·91–13·67)	32 (21%)	132 (32%)‡	114 (74%)	285 (69%)	65 (42%)	178 (43%)	4 (2–10)	3 (0–7)‡
Unit 2	Treatment	152 (152)	93 (117)	2·59 (0·50–12·24)	2·73 (0·67–9·53)	33 (22%)	14 (15%)	150 (92%)	84 (90%)	125 (82%)	73 (78%)	9 (5–12)	8 (5–12)
Seattle Children's Hospital													
Unit 1	Treatment	216 (216)	254 (254)	5·92 (1·32–14·56)	6·12 (1·25–13·90)	99 (46%)	117 (46%)	171 (79%)	213 (84%)	108 (50%)	130 (51%)	3 (0–8)	3 (0–8)
Unit 2	Control	88 (88)	118 (118)	0·71 (0·39–2·43)	0·76 (0·39–3·76)	45 (51%)	57 (48%)	86 (98%)	112 (95%)	75 (85%)	98 (83%)	5 (3–10)	6 (3–10)

Data are either number of patient admissions (%) or median (IQR). Characteristics are compared for the PP population. *ICD9 codes gathered for every admitted patient.[19] †Paediatric Risk of Mortality grades severity of illness and predicts mortality in intensive-care patients.[20] ‡p<0·05 between period 2 and period 1. ITT=intention to treat. PP=per protocol.

Table 1: **Characteristics of patient admissions at every intensive-care unit, by study periods**

units and 79 in control units. The crude overall incidence of bacteraemia was 3·28 (range 0–6·53, 95% CI 2·27–4·58) in treatment units and 4·93 (0·47–9·74, 3·91–6·15) in control units (appendix p 7). In eight of ten units, the crude incidence of bacteraemia was lower during the treatment study period compared with the control study period, irrespective of whether CHG bathing was assigned in study period one or two and whether baseline rates of bacteraemia were above or below the median baseline incidence (figure 2). A child bathed with CHG had a 36% lower risk of bacteraemia versus one bathed using standard practices (aIRR 0·64, 95% CI 0·42–0·98; table 2). Most bacteraemia episodes (101/113, 89%) occurred in admissions with central venous catheters; of this group, those who were bathed with CHG had a 34% lower risk of bacteraemia (0·66, 0·47–0·94). After removing all outcome events caused by commensal skin organisms in admissions without catheters, findings of exploratory analyses showed that a child bathed with CHG had a lower risk of bacteraemia than did one bathed using standard practices (0·65, 0·44–0·95). Similarly, after removing commensal skin organisms from the outcome of all children, a child bathed with CHG had a lower risk of bacteraemia than did one bathed with standard practices (0·68, 0·39–1·22). Therefore, all treatment subgroups had reductions in risk of bacteraemia similar to the whole PP population. 17 of 103 admissions with bacteraemia died (crude ICU mortality was 16·5%, 95% CI 10·56–24·85). Overall, the crude ICU mortality was 3·49% (2·82–4·30) in children bathed with standard practices and 2·59% (2·82–4·30) in those bathed with CHG (absolute difference 0·90%, 95% CI –0·17 to 1·97; p=0·1104).

In the ITT population, 132 episodes of bacteraemia were identified in 121 patient admissions, 53 in treatment units and 79 in control units. In this population, the risk of bacteraemia did not differ between CHG bathing and standard bathing practices (aIRR 0·71, 95% CI 0·42–1·20; table 2). A child with central venous catheters admitted to the treatment unit had a 35% reduced risk of bacteraemia compared with one in the control unit (0·65, 0·44–0·97). The crude ICU mortality was 3·49% (95% CI 2·82–4·30) in admissions to control units and 3·01% (2·40–3·77) in children admitted to treatment units (absolute difference 0·48%, 95% CI –0·51 to 1·47; p=0·3416).

Of 1999 patient admissions to ICU in the PP population, 41 CLABSIs were identified in 38 admissions. 13 episodes were seen in treatment units and 28 in control units. The crude overall incidence of CLABSI was 2·20 per 1000 catheter-days (range 0–4·16, 95% CI 1·17–3·76) in treatment units and 3·00 per 1000 catheter-days (0–5·28, 2·00–4·34) in control units. The incidence of CLABSI was diminished with CHG treatment compared with control (aIRR 0·68, 95% CI 0·35–1·31; table 2). Seven of the 38 admitted children in whom a CLABSI was present died (crude ICU mortality 18·4%, 95% CI 9·22–33·42).

In the ITT population, 41 CLABSIs were identified, 13 in treatment units and 28 in control units. In this population, the risk of CLABSI did not differ between treatment and control units (aIRR 0·52, 95% CI 0·25–1·08; table 2).

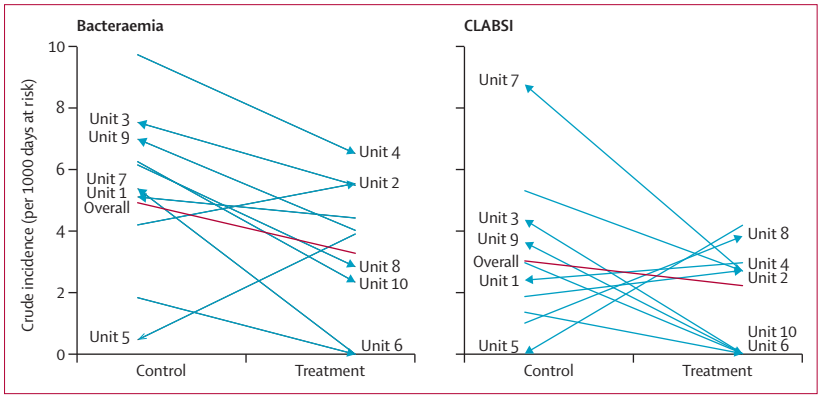

Figure 2: **Change in crude incidence of bacteraemia and CLABSI, per-protocol population**
Every line represents one unit (appendix p 7); the slope shows the change in incidence of bacteraemia or CLABSI between control and treatment study periods, and the arrow indicates the assignment change from period one to two (eg, an arrow pointing to the treatment side shows the unit assignment started as control and moved to treatment). The red line represents the overall crude incidence between control and treatment units. CLABSI=central line-associated bloodstream infection.

In the PP population, 77 of 113 episodes of bacteraemia (68%) were caused by Gram-positive organisms (table 3, appendix p 8), including 53 (47%) by coagulase-negative staphylococcus and ten (9%) by *Enterococcus* spp. The crude incidence of bacteraemia caused by Gram-positive organisms was 46% lower in treatment units compared with control units (1·93 and 3·56 per 1000 patient-days at risk, respectively; incidence rate ratio 0·54, 95% CI 0·31–0·91). No differences were noted in crude incidence of bacteraemia caused by Gram-negative organisms or yeast. Crude incidence of CLABSIs due to Gram-positive organisms did not differ between treatment and control units (0·85 and 1·60 per 1000 patient-days at risk, respectively; incidence rate ratio 0·53, 95% CI 0·15–1·52).

No serious study-related adverse events were reported. Skin reactions were seen in 69 (2%) patient admissions (appendix p 9). A greater proportion of these reactions were noted in treatment units than control (43 [3%] *vs* 26 [1%]; p<0·0001); however, the treating clinicians established that only 12 skin reactions in treatment units were related to CHG bathing. Reactions included faint macular erythaema (n=6), maculopapular erythaema (5), and dermatitis (1). The crude incidence of CHG-related skin reactions was 1·12 per 1000 days exposed (95% CI 0·06–2·02).

39 (3%) of 1547 patient admissions in the PP population who were assigned to a treatment unit withdrew. Reasons cited included: skin irritation due to CHG (n=12), skin irritation due to an underlying disorder (eg, graft-*vs*-host disease) or other drug reaction (10), no reason provided (8), did not like the smell or feel of CHG (3), had an allergic reaction (2), did not tolerate the bathing procedure (2), caregiver had concerns about chemical exposure (1), and caregiver preferred to use a lotion not compatible with CHG (1).

	Events		Crude control incidence per 1000 at-risk days (95% CI)	Crude treatment incidence per 1000 at-risk days (95% CI)	Crude absolute difference per 1000 at-risk days (95% CI)	Crude incidence rate ratio (95% CI)	Adjusted incidence rate ratio (95% CI)*	p
	Control	Treatment						
Per-protocol population								
Primary outcome (bacteraemia)	79	34	4·93 (3·91 to 6·15)	3·28 (2·27 to 4·58)	−1·66 (−3·21 to −0·11)	0·66 (0·43 to 1·00)	0·64 (0·42 to 0·98)	0·044
Bacteraemia in patients with central venous catheters	70	31	6·31 (4·92 to 7·97)	4·37 (2·97 to 6·21)	−1·94 (−4·07 to 0·19)	0·69 (0·44 to 1·07)	0·66 (0·47 to 0·94)	0·021
Secondary outcome (CLABSI)	28	13	3·00 (2·00 to 4·33)	2·20 (1·17 to 3·76)	−0·80 (−2·43 to 0·83)	0·73 (0·35 to 1·46)	0·68 (0·35 to 1·31)	0·249
Intention-to-treat population								
Primary outcome (bacteraemia)	79	53	4·93 (3·91 to 6·15)	3·52 (2·64 to 4·61)	−1·41 (−2·86 to 0·03)	0·71 (0·49 to 1·02)	0·71 (0·42 to 1·20)	0·199
Bacteraemia in patients with central venous catheters	70	43	6·31 (4·92 to 7·97)	4·36 (3·16 to 5·88)	−1·95 (−3·91 to 0·03)	0·69 (0·46 to 1·03)	0·65 (0·44 to 0·97)	0·034
Secondary outcome (CLABSI)	28	13	3·00 (2·00 to 4·33)	1·63 (0·87 to 2·79)	−1·37 (−2·79 to 0·05)	0·54 (0·26 to 1·08)	0·52 (0·25 to 1·08)	0·081

*Adjusted for presence of a central venous catheter, PRISM III score, presence of any complex chronic condition, age, period, unit, and hospital-level clustering. CLABSI=central-line associated bloodstream infection.

Table 2: **Difference in endpoints between treatment and control units**

	Bacteraemia			CLABSI		
	Treatment	Control	p	Treatment	Control	p
Gram-positive	20/34 (59%)	57/79 (72%)	0·015	5/13 (38%)	15/28 (54%)	0·212
Coagulase-negative staphylococci	15	38		2	7	
Enterococcus spp	1	9		2	6	
Staphylococcus aureus	3	4		1	2	
Other	1	6		0	0	
Gram-negative	10/34 (29%)	15/79 (19%)	0·936	4/13 (30%)	9/28 (32%)	0·578
Enterobacter cloacae	3	3		2	2	
Klebsiella spp	2	4		0	3	
Other	5	8		2	4	
Yeast	3/34 (9%)	6/79 (8%)	0·744	3/13 (23%)	3/28 (11%)	0·594
Mixed Gram-positive and Gram-negative	1 (3%)	1 (1%)	0·787	1 (8%)	1 (4%)	0·776

Data are number (%). p values are based on crude incidence rate ratios. CLABSI=central line-associated bloodstream infection.

Table 3: **Microorganisms isolated from bacteraemia and CLABSI episodes, per-protocol population**

Discussion

Findings of our study, in more than 4900 admissions to ICU, show a 36% reduction in the incidence of bacteraemia in patients receiving daily CHG bathing. Furthermore, daily CHG bathing was well tolerated in this population and could be quickly and widely implemented to prevent bacteraemia.

Large-scale interventions to decrease health care-associated infections have not generally included children (panel). During planning for this trial, early studies in adult ICU patients suggested that CHG bathing reduced bloodstream infections.[15,16] However, no data were available to assess safety and efficacy in children. In two recent systematic reviews, a reduction or possible reduction in bloodstream infections was noted with daily CHG bathing;[22,23] but, only one completed study in these reviews was a randomised trial, and none included children. Our findings support and are consistent with studies evaluating CHG bathing in critically ill adults.

In the SCRUB trial, the primary outcome of bacteraemia encompassed any positive blood culture, including those growing commensal Gram-positive skin organisms. Gram-positive commensal skin organisms cause a large proportion of bacterial bloodstream infections in children, including 21% of CLABSIs in a recent US sampling, and they frequently contaminate blood cultures.[24–26] Practice guidelines recognise that confirmation of bacteraemia or CLABSI in children is challenging: most blood cultures in paediatric patients with central venous catheters are drawn from the catheter, and usually only one culture is obtained. Therefore, many clinicians presume an infection exists and treat children empirically.[27] Most bacteraemia episodes in our study arose in children with central venous catheters, a population that is usually treated for all positive blood cultures, including those due to commensal skin organisms. The incidence of bacterial bloodstream infections due to all Gram-positive organisms was lower in children receiving CHG bathing compared with those bathed according to standard practice. The decrease in blood cultures growing coagulase-negative staphylococci (a common commensal skin organism) was pronounced, but so was the fall in blood cultures growing enterococci. Whether these reductions were attributable to prevention of Gram-positive CLABSIs, bacterial bloodstream infections, or contaminated blood cultures, eradication of Gram-positive bacteraemia episodes should have a substantial effect on patients' outcomes. Furthermore, our findings of similar crude ICU mortality in patients with CLABSI (18·4%) and bacteraemia (16·5%) support bacteraemia as an important outcome in critically ill children.

The recorded reduction in CLABSI rates in children receiving daily CHG bathing was consistent with previous reports of daily CHG bathing.[16] Although the fall was not significant in our study, all analyses showed

consistently a treatment effect of lower incidence of bacteraemia and CLABSI in children receiving CHG bathing compared with standard practice. Between planning of the study and its implementation, the predicted versus observed number of CLABSI decreased by 34%, whereas that for bacteraemia fell by only 11%. Over the past few years, several statewide and national collaborations have launched efforts and successfully reduced CLABSI rates, including a national paediatric ICU collaboration.[11–13] The sample size estimates in our study relied on CLABSI rates that preceded these national efforts. Our results showed a consistent treatment effect, but our study was not powered sufficiently to detect a significant rate reduction for these infrequent events or for mortality. Larger studies are needed to confirm our observed lower CLABSI rate and crude mortality in CHG-bathed patients.

Routine CHG bathing has not been studied previously in a paediatric population, and use of CHG has been controversial among paediatricians who remember safety issues associated with hexachlorophene.[28] CHG can cause severe skin irritation, delayed hypersensitivity, and anaphylaxis.[29] Establishing safety and tolerability data was an important component of this trial since skin sensitivity is common in this population.[30] Only 12 (1%) children bathed with CHG in this study withdrew because of CHG-related skin irritation. No severe adverse reactions arose.

Although relatively underused, especially in children, the cluster-randomised crossover design is a strength of this study. Incorporating a crossover into the design enabled us to estimate the treatment effect by comparing each unit with itself during treatment and control periods, recognising that cardiac ICUs are more similar to themselves during two periods than cardiac ICUs are to medical ICUs during the same period. Our trial included hospitals from across the USA, serving diverse patient populations. More than 4900 patient admissions to ICU were included, making our study one of the largest clinical trials in critically ill children. The treatment effect was compared within and across units, and findings showed remarkable consistency. This analytical approach enabled minimal adjustment and provided robust estimates of the reduction in bacteraemia.

A few limitations should be considered. First, only 64% of admissions to treatment units were bathed with CHG. Analysis of patients who did and did not receive CHG bathing showed similar characteristics. Therefore, we believe that the challenges we faced in obtaining informed consent for a population-based intervention did not result in biased populations. Thus, although the results in the ITT population were not significant, the treatment effect estimate (aIRR 0·71) was similar to that of the PP population (aIRR 0·66), suggesting a clinically significant and relevant result. Second, every institutional review board decided how caregivers should be informed, so in some cases, different methods were used in control and treatment units. Although this difference raises concern for selective enrolment bias, the crossover design and analysis controlled for potential unit-specific enrolment differences, and findings of reduced crude incidence of bacteraemia in the ITT population were consistent across sites. Third, no central committee was present to adjudicate CLABSIs but an infection control specialist at every site was relied on to consistently and impartially apply NHSN definitions. Although classifications can be applied differently across institutions, the crossover design dictates comparison of every unit with itself, so interinstitutional variability should not have affected our findings. Fourth, we did not capture and adjust for other possible variables associated with bacteraemia, such as presence of a peripheral intravenous catheter. Finally, the included ICUs represent academically affiliated tertiary care ICUs that serve especially sick populations. The generalisability of our findings to other settings needs further investigation.

In this large multicentre study, we have shown that a simple and easily implementable intervention decreased bacteraemia in critically ill children. In this setting, nosocomial bacteraemia costs lives and increases use of health care resources. Our study data support CHG bathing of critically ill children. Although the observed results would be further strengthened by replication in other similar studies, broad use of this intervention could reduce morbidity and costs from bacteraemia in this vulnerable and understudied population.

Panel: Research in context

Systematic review

Routine bathing of children admitted to hospital is done as a supportive care measure and is not regarded as important for prevention of health care-associated infections. Since 2007, findings of studies in adults suggest that chlorhexidine gluconate (CHG) bathing, particularly of patients who are critically ill, could reduce bloodstream infections. Derde and colleagues[22] and O'Horo and coworkers[23] systematically reviewed studies on the effect of CHG bathing to reduce bloodstream infections in adults. These reviews included one randomised controlled trial testing the effect of CHG bathing on critically ill patients; that trial was a single-centre study in adults admitted to hospital. No data are available on the efficacy of CHG bathing to reduce bloodstream infections in children admitted to hospital.

Interpretation

In this cluster-randomised trial, children underwent daily bathing with either CHG or standard procedures. Because the rate of non-consent was high in our trial, a third of eligible admissions were not bathed with CHG. Those who did receive daily CHG bathing had a 36% reduction in incidence of bacteraemia. If we include in our analysis admitted children who were eligible to receive bathing but who did not have consent to participate, the reduction in bacteraemia was not significant. However, the estimated effect of daily CHG bathing on bacteraemia was similar whether we compared all patients in the treatment group (intention-to-treat population) to controls or all patients on treatment (per-protocol population) to controls, suggesting a clinically significant and relevant result. Furthermore, CHG bathing was a safe and well tolerated procedure that could be quickly and widely implemented to prevent morbidity and costs associated with bacteraemia in this vulnerable population.

Contributors

AMM, TMP, XS, and KS had the idea for the study and designed it. AMM, SEC, AE, DMZ, XS, RO, and KS played a part in data acquisition. AMM, NGR, and DO did the statistical analysis. AMM, SEC, AE, DMZ, XS, TMP, RO, and KS supervised the study. All authors contributed to data analysis and interpretation and critically revised the manuscript. AMM had full access to all data in the study and had final responsibility for the decision to submit for publication.

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Conflicts of interest

AMM, TMP, DMZ, SEC, XS, and AE have received grant support from Sage Products. Furthermore, AMM has received grant support from BioMerieux, DMZ has received grant support from Vioguard, TMP has received grant support from Merck and is on an advisory board for Pfizer and Hospira, and XS has received grant support from Optimer Pharmaceuticals. All other authors report no conflicts of interest.

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