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ORIGINAL

EFFECT of daily antiseptic bathing with octenidine on ICU-acquired bacteremia and ICU-acquired multidrug-resistant organisms: a multicenter, cluster-randomized, double-blind, placebo-controlled, cross-over study

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Abstract

Purpose: Antiseptic bathing has garnered attention in an effort to reduce hospital-acquired infections. Previous studies have shown the efficacy of antiseptic bathing in high-risk environments, such as intensive care units (ICUs), using chlorhexidine. In this study we aimed to evaluate the effectiveness of octenidine as a potential alternative due to its established popularity and widespread use in Europe.

Methods: We compared the rates of ICU-acquired primary bacteremia and ICU-acquired multidrug-resistant organisms (MDROs) in a multicenter, cluster-randomized, double-blind, placebo-controlled, cross-over study using octenidine-impregnated and placebo washcloths. On 44 ICUs in 23 hospitals throughout Germany, we compared individual ICUs with themselves over two 12-month time periods. All data were obtained digitally via hospital information systems as individual ward-movement data and microbiological test results; both endpoints were algorithmically derived.

Results: 104,039 ICU episodes from 93,438 patients with 712,784 microbiological test results were analyzed, thereby detecting 1508 cases of ICU-acquired primary bacteremia and 1871 cases of ICU-acquired MDRO. Bathing with octenidine-impregnated washcloths prevented ICU-acquired primary bacteremia; a risk reduction of 17% was seen homogeneously across all participating ICUs (adjusted hazard ratio (HR) 0.83, 95% confidence interval (CI) [0.75; 0.92], $p = 0.0003$). This reduction affected predominantly coagulase-negative staphylococci (53%) and enterococci (17%). However, no intervention effect was seen for ICU-acquired MDROs (adjusted HR 0.98, 95% CI [0.83; 1.15]). Heterogeneity among intra-ICU intervention effects on MDRO acquisition was substantial.

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Conclusions: Antiseptic bathing with octenidine may be effective in preventing ICU-acquired primary bacteremia, particularly due to Gram-positive bacteria and common skin commensals.

Keywords: Antiseptic bathing, Octenidine, Bacteremia, Multidrug-resistant organisms, Intensive care unit

Introduction

Hospital-acquired infections (HAIs) pose a serious threat to patients and patient safety; not only do they increase morbidity and mortality [1–3], but they generate potentially avoidable high treatment costs and increase in-patient treatment time [4]. Along with well-known and widely implemented standard precautions, universal antiseptic bathing has garnered attention for its potential to reduce patients' risks of acquiring HAIs during treatment.

For patients on intensive care units (ICUs), preventing healthcare-associated bloodstream infections (HABSIs) and the acquisition of multidrug-resistant organisms (MDROs) during treatment is a top priority. Whether or not antiseptic bathing regimens can contribute meaningfully to this undertaking has been the topic of previous research: while some studies confirm the efficacy of antiseptic bathing with chlorhexidine [5–8], others do not [9, 10].

As recently as 2022, however, the Society for Healthcare Epidemiology of America (SHEA) has deemed daily antiseptic bathing with chlorhexidine for ICU patients older than 2 months of age an essential practice to prevent central line-associated bloodstream infections (CLABSIs) [11]. In addition, pre-operative antiseptic bathing with chlorhexidine has become commonplace in many hospitals to reduce rates of surgical site infection [12]. With chlorhexidine usage continually increasing despite mounting evidence suggesting developing resistance mechanisms [13–16], concrete allergic concerns and reported adverse reactions [17], the need for an effective alternative has arisen.

Widely used throughout Europe for antiseptic purposes, octenidine is a cationic substance belonging to the class of bispyridines that works against Gram-positive and Gram-negative bacteria, while also being fungicidal [18]. In vitro studies have proven octenidine's antibacterial efficacy, also suggesting a marked improvement in targeting Gram-negative bacteria when compared with chlorhexidine [19, 20]. There have been no reports of emerging resistance patterns or negative side effects for octenidine. Therefore, it harbors the potential to offer a much-needed alternative to chlorhexidine due to the above-mentioned concerns. Only a small number of studies has been conducted in which octenidine was investigated, and these either involved additional interventions or were carried out among small cohorts [21]; a thorough, large-scale investigation of octenidine as a stand-alone antiseptic option had yet to be realized.

Take-home message

Antiseptic bathing with octenidine prevents intensive care unit (ICU)-acquired primary bacteremia. Integrating octenidine-based antiseptic bathing routines as part of an infection prevention measures bundle can help to reduce nosocomial infections on ICUs.

We therefore conducted a Germany-wide study in order to evaluate antiseptic bathing with octenidine on ICUs and its effect on ICU-acquired primary bacteremia and ICU-acquired MDROs.

Methods

Study design and intervention

The EFFECT trial was a multicenter, cluster-randomized, double-blind, placebo-controlled, cross-over study in which ICUs were the units of randomization. As the risk of nosocomial infection strongly depends on ICU-specific characteristics such as the composition of the patient population, disease patterns and length of stay, an AB/BA cross-over design was used in order to compare single ICUs to themselves over a prolonged period of time based on individual patient data (see the published study protocol [22]).

To be eligible for participation, ICUs were required to have a minimum of ten beds and no restructuring plans, including no major structural and/or organizational changes, for the duration of the trial; the trial's focus on effectiveness as opposed to efficacy required that participating ICUs remained internally comparable throughout the trial's duration. In addition, individual ward-movement history and microbiological test results had to be available from the hospital and laboratory information systems (HIS/LIS) without need for extra documentation. ICUs focusing on burn patients, patients with bone marrow transplants and pediatric ICUs were excluded from participating.

Each ICU participated in two 12-month intervention periods, both preceded by a 3-month wash-out period. The wash-out period was implemented in order to neutralize probable effects of pre-existing bathing practices; the total study duration for a single ICU was 30 months (Fig. 1). The study interventions comprised using either

0.08% octenidine-impregnated or placebo washcloths (containing 0.9% 2-phenoxyethanol as a preservative agent in order to assuage the outbreak risk associated with pre-moistened, non-sterile washcloths [23, 24]) for the patients' routine washing procedure, which was conducted once daily by nursing staff and according to the manufacturer's instructions.

The washcloths were distributed to participating wards in blue and green packaging; all parties were blinded for the duration of the study and until the finalization of the analysis report. Block randomization of ICUs was used to determine in which intervention period octenidine-impregnated and placebo washcloths were used.

Adherence to the study protocol, intervention compliance and adverse effect assessment was carried out by local infection prevention and control (IPC) teams and overseen by study monitors from the Clinical Trial Centre (ZKS Leipzig) via regular, structured on-site and telephone interviews. Parameters including but not limited to MDRO screening strategies and relevant standard operating procedures (SOPs), established patient bathing methods and frequency, MDRO management, possible MDRO outbreaks, antiseptic washcloth implementation and alcohol-based hand rub usage rates were included in the monitoring process; the study monitoring comprised of a minimum of 9 visits/contacts with each participating ICU. There were no compliance issues on participating ICUs throughout the study.

Study oversight

Preceded by a scientific review process conducted via an independent advisory board, this study was financed fully by a grant from the German Research Foundation (DFG, grant number CH1525/1-2). The octenidine-impregnated and placebo washcloths were produced by Schülke & Mayr GmbH (Norderstedt, Germany). Approval of the study protocol was obtained from institutional review boards as well as data privacy officers at the participating hospitals. As the washcloths were considered a cosmetic under the European Union's regulations and data were anonymized, patients' individual informed consent was not required. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Data acquisition

EFFECT analyzed digital data from all treatment episodes on participating ICUs in the respective intervention periods. Two types of data covering the patients' comprehensive hospital stay were required: ward-movement data (timestamps for admission, ward transfers and discharge), as well as microbiological data (test results, name of bacterial genus/species, type of specimen, date of sample collection and antibiogram). Both data types were linked using the patients' admission number. After each wash-out or intervention period, data were extracted from HIS/LIS and pre-processed according to

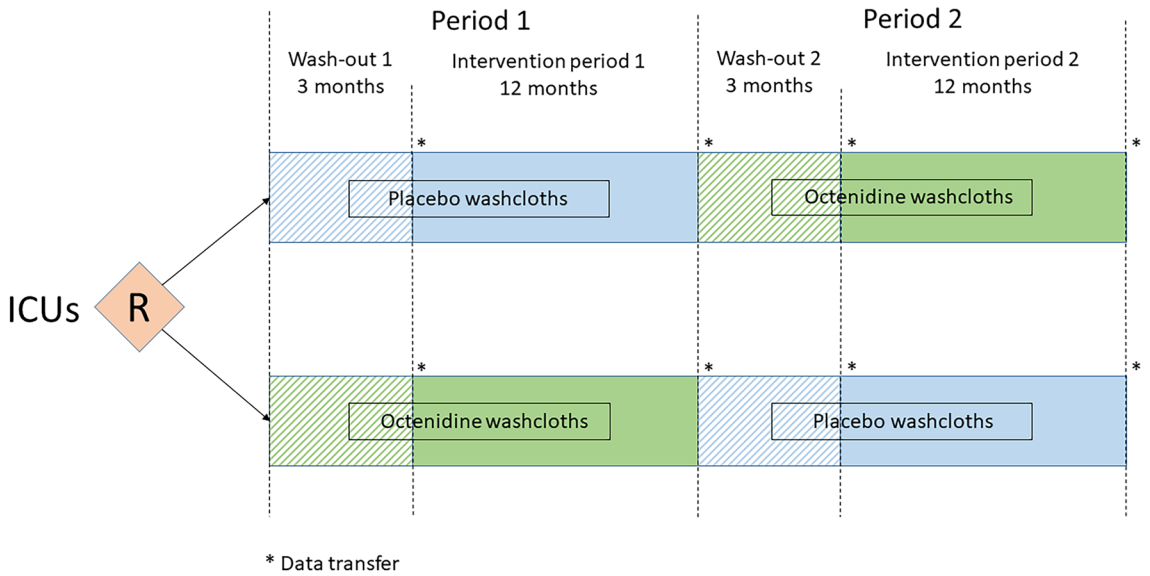

Fig. 1 Study design. The EFFECT trial was a multicenter, cluster-randomized, double-blind, placebo-controlled, cross-over study in which ICUs were the units of randomization. An AB/BA cross-over design was used in order to compare single ICUs to themselves. Each ICU participated in two 12-month intervention periods, both preceded by a 3-month wash-out period; the total study duration for a single ICU was 30 months. ICUs were randomized by starting with either green (octenidine) or blue (placebo) washcloth packages in order to average out a possible period effect. *ICU* intensive care unit

data protection regulations: admission numbers were pseudonymized, and an offset was added to all date variables. Pre-processed data were uploaded in spreadsheet format to a cloud service provided by the Clinical Trial Centre Leipzig. After each data transfer, ICUs received feedback in the form of a detailed report in order to check for plausibility. In some cases, quality checks lead to corrections.

Outcomes

EFFECT's two co-primary endpoints were ICU-acquired primary bacteremia and ICU-acquired MDROs. Secondary endpoints related to bacteremia were ICU-acquired primary bacteremia with pathogenic organisms/pathogenic, Gram-positive organisms/pathogenic, Gram-negative organisms/common commensal organisms, as well as any ICU-acquired bacteremia. Secondary endpoints related to MDRO were ICU-acquired methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE) and multidrug-resistant Gram-negative organisms (MDRGN).

These endpoints were algorithmically derived from the raw data described above in the form of time-to-detection data for individual informative episodes. Patients being treated on participating ICUs were followed from admission until discharge, thereby generating a time window in which they were considered at risk for hospital-acquired infections; these time windows, provided that they were of a certain length, were then considered informative episodes.

As HAIs are defined and monitored by the Centers for Disease Control and Prevention (CDC) National Health Safety Network (NHSN) [25], these definitions were used to generate an algorithm with which HAIs could be detected using available digital patient data. Although EFFECT's algorithm uses microbiological data to generate informative treatment episodes, the outcomes are not solely microbiological in nature; the standard CDC definition for a bloodstream event hinges upon pathogen detection. Blood cultures taken during the study's duration were clinically indicated and not conducted for screening purposes, thereby ensuring that the identified outcomes were clinically relevant. EFFECT and its algorithm, however, define a patient's time at risk for HAI acquisition slightly differently than the CDC. Analyses were, therefore, based on informative episodes on a given ICU: by definition, patients were at risk for an ICU-acquired endpoint from day three on the ICU until day two after discharge, but only if the respective endpoint event had not been documented previously.

Bacteremia is defined as detection of a pathogenic bacterial organism or a common commensal organism in a blood culture; fungi and organisms deemed exceptional by the CDC were excluded. Detection of a common commensal organism was deemed a probable contamination if there was at least one further negative blood culture within the following 2 days. We defined bacteremia as secondary if the organism found in the blood culture was also detected in other relevant clinical material during the hospital stay; all other bacteremia were considered primary.

MDROs could be detected in any clinical material submitted for microbiological analysis. During the EFFECT trial, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) changed the definitions of its susceptibility test categories [26]; the "intermediate" category (I) was redefined as "susceptible, increased exposure," causing a shift in resistance rates. What was once defined as resistant (I = R) is now defined as susceptible (I = S). We adopted the EUCAST V.9.0 definition by applying it retrospectively to the generally available antibiograms.

Statistical analysis

Primary analyses were intention-to-treat, thereby using all informative ICU episodes for the respective endpoint from all randomized ICUs according to the intervention for the respective period. The basic model for all primary and secondary endpoints is a mixed-effects Cox regression containing the study period (first or second intervention period) and the intervention (octenidine or placebo) as fixed effects; individual ICUs were incorporated as a random effect. An ICU by intervention interaction random term was added in order to model the heterogeneity of the treatment effect across ICUs.

The intervention effect was estimated as the hazard ratio (HR), along with a two-sided 95% confidence interval (CI) and a respective p value. In addition, we estimated the standard deviation, tau, of the random interaction term, which describes the heterogeneity of the treatment effect across ICUs. In order to visualize the heterogeneity of the treatment effect across ICUs, we provide forest plots based on simple, fixed-effect Cox models within each ICU (Fig. 3).

As two co-primary endpoints are investigated, we corrected for multiplicity using the Hochberg step-up procedure [27]. The overall null hypothesis "bathing with octenidine has no effect" is rejected if one of the two co-primary endpoints is significant at the level 2.5% or both at level 5%.

The cross-over design presupposes no major structural changes in ICU organization and patient population for the duration of study participation. Sensitivity analyses reflecting the rededication of select ICUs to coronavirus disease 2019 (COVID-19) wards (alongside relevant

changes in MDRO screening standards due to pandemic-related shortages) were conducted; (see electronic supplementary material, ESM, 1). Further sensitivity analyses concerned the robustness of results under variations of the endpoint definitions (see ESM 2).

Analyses were conducted with the use of the software environment for statistical computing R (version ≥ 4.1.0), using packages "coxme" and "coxphf".

Sample size calculation

Sample size calculation made use of the fact that the specified analytical model essentially corresponds to a random effect meta-analysis [28] of these ICU-specific results. The sample size was chosen to detect a risk reduction of 25% to a HR of 0.75 with a power of 90%. We conservatively assumed a baseline incidence rate of two cases of ICU-acquired events per 1000 patient days and a moderate heterogeneity in the intervention effect. We planned to recruit between 35 and 45 ICUs in order to be able to assess heterogeneity; approximately 200,000 to 225,000 patient days per year were necessary in order to observe at least 905 events in each primary endpoint [22].

Results

Between January 2017 and April 2021, 44 ICUs in 23 clinics participated in the EFFECT trial for a duration of 30 months (Fig. 1). Randomized ICUs are characterized in the supplement (ESM 1, Table S1). Figure 2 describes the available data and the process of filtering out informative episodes for the analyses. The study sites did not report any serious adverse events related to antiseptic bathing during the monitoring process.

The primary analyses of the intervention effect (Table 1) are provided in terms of cause-specific HRs from analyzing individual time-to-event data within randomized ICUs with a meta-analysis-type proportional hazard mixed-regression model. Intra-ICU HRs and the heterogeneity between ICUs are displayed in Fig. 3. Number of events, days at risk and incidence densities by treatment arm are described in Table 2 for all primary and secondary endpoints.

The analysis presented is a competing risk analysis [29, 30]. Primarily, it focuses on the cause-specific hazard function using mixed-effect Cox-regression methodology to describe treatment differences as hazard ratios.

In the presence of a competing risk,—here discharge from ICU—, this analysis cannot be visualized as an ordinary survival curve. We therefore present estimated overall hazard functions for both co-primary endpoints (ESM 1, Figures S1 A/B) in order to describe the variation of the risk with time on ICU. In addition, we present cumulative incidence functions (ESM 1, Figures S2 A/B) in order to describe the timing of the observable endpoint events.

ICU-acquired primary bacteremia

There is a significant intervention effect of octenidine bathing on the primary endpoint of ICU-acquired primary bacteremia ($p = 0.0003$). The effect size HR is estimated as 0.828 (95% CI [0.748; 0.918]). The moderate hazard reduction of approximately 17% is smaller than the effect size hypothesized (25%). The intervention effect is homogeneous across all ICUs; the scatter seen on the left side of Fig. 3 is not more than expected stochastically ($p = 0.489$).

The treatment effect of octenidine bathing to prevent primary bacteremia is similar in size for all organism types (Table 1). Note that the p values for the respective individual organism types cannot be compared among themselves, as power strongly depends on the number of observed events. In addition, the treatment effect on any type of bacteremia is similar in size to that of primary bacteremia, with an estimated HR of 0.844 (95% CI [0.779; 0.923], $p = 0.00017$). Only the octenidine effect against Gram-negative pathogenic organisms appears to be smaller, but the confidence interval is wide due to small event numbers.

ICU-acquired MDRO

There is no effect of octenidine bathing on the risk of ICU-acquired MDRO, with an estimated HR of 0.974 (95% CI [0.804; 1.18]) and $p = 0.79$. The confidence interval excludes the effect size HR = 0.75 hypothesized in study planning. This negative result equally concerns all types of MDRO, i.e., MRSA, VRE and MDRGN (Table 1).

In addition, Fig. 3 shows strong heterogeneity of observed treatment effects across ICUs ($p < 0.001$). The model estimate of the standard deviation (tau) of the random interaction term, which describes the heterogeneity of the treatment effect across ICUs, is 0.37; this is larger than the heterogeneity of the intervention effect envisaged in the study design (tau = 0.15).

Using aggregated data for $N = 88$ intervention periods, a post-hoc analysis identified at least two external factors that influence MDRO acquisition on ICUs and explain the observed heterogeneity. First, the risk of MDRO detection increases with an increased influx of MDRO carriers (ESM 1, Figure S3). Second, the risk of MDRO detection increases with heightened MDRO screening intensity (ESM 1, Figure S4).

Results reported above were stable in sensitivity analyses regarding the impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), altered screening regimens for MDROs and variations of the definition of primary bacteremia (see ESM 1).

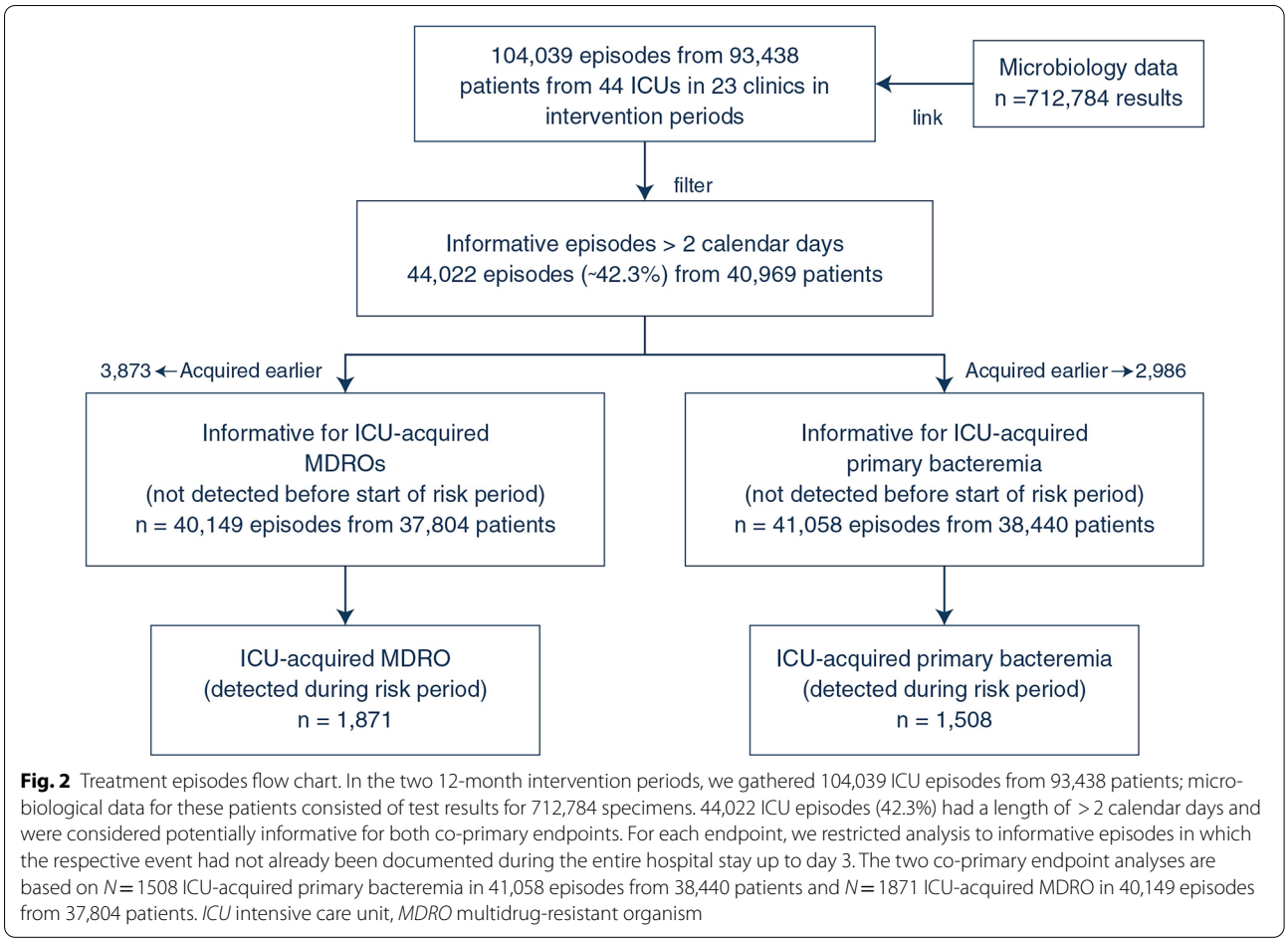

Fig. 2 Treatment episodes flow chart. In the two 12-month intervention periods, we gathered 104,039 ICU episodes from 93,438 patients; microbiological data for these patients consisted of test results for 712,784 specimens. 44,022 ICU episodes (42.3%) had a length of > 2 calendar days and were considered potentially informative for both co-primary endpoints. For each endpoint, we restricted analysis to informative episodes in which the respective event had not already been documented during the entire hospital stay up to day 3. The two co-primary endpoint analyses are based on *N* = 1508 ICU-acquired primary bacteremia in 41,058 episodes from 38,440 patients and *N* = 1871 ICU-acquired MDRO in 40,149 episodes from 37,804 patients. *ICU* intensive care unit, *MDRO* multidrug-resistant organism

Table 1 Summary of all primary and secondary endpoints

Endpoint	HR with 95% CI	*p*
ICU-acquired primary bacteremia	0.828 [0.748; 0.918]	0.0003
With pathogenic organisms	0.850 [0.710; 1.018]	0.077
With pathogenic, Gram-positive organisms	0.787 [0.634; 0.977]	0.03
With pathogenic, Gram-negative organisms	0.927 [0.686; 1.254]	0.62
With common commensal organisms	0.823 [0.727; 0.933]	0.0023
ICU-acquired MDRO	0.974 [0.804; 1.180]	0.79
With MRSA	0.946 [0.669; 1.336]	0.75
With VRE	1.021 [0.820; 1.270]	0.86
With MDRGN	1.033 [0.868; 1.228]	0.72

CI confidence interval, *HR* hazard ratio, *ICU* intensive care unit, *MDRO* multidrug-resistant organism, *MRSA* methicillin-resistant *Staphylococcus aureus*, *VRE* vancomycin-resistant enterococci, *MDRGN* multidrug-resistant Gram-negative organism

Discussion

EFFECT is the first multicenter, cluster-randomized, double-blind, placebo-controlled, cross-over study evaluating comprehensive daily bathing with octenidine on ICUs. Our results show that octenidine prevents primary bacteremia; by analyzing routine clinical data via an algorithm, clinically relevant outcomes were assessed for a large patient base. EFFECT was performed in 44 ICUs in 23 hospitals throughout Germany and therefore demonstrates that the preventive effects of antiseptic bathing with octenidine can be seen on ICUs of varying size, patient collective and treatment focus.

EFFECT did not show any preventive effect of octenidine bathing on ICU-acquired MDROs. It may be considered a limitation of the present study that any interference with clinical routine on ICUs was strictly avoided. EFFECT focused on the effectiveness of octenidine bathing as opposed to efficacy under tightly controlled circumstances. There were no preset standard operating procedures regarding MDRO screening or isolation precaution measures across participating wards; it was therefore of extreme importance that ICUs remained internally comparable throughout the trial's duration. In doing this, we showed that there is no general effectiveness of octenidine bathing on MDRO acquisition at the concentration used; we did, however, find a strong

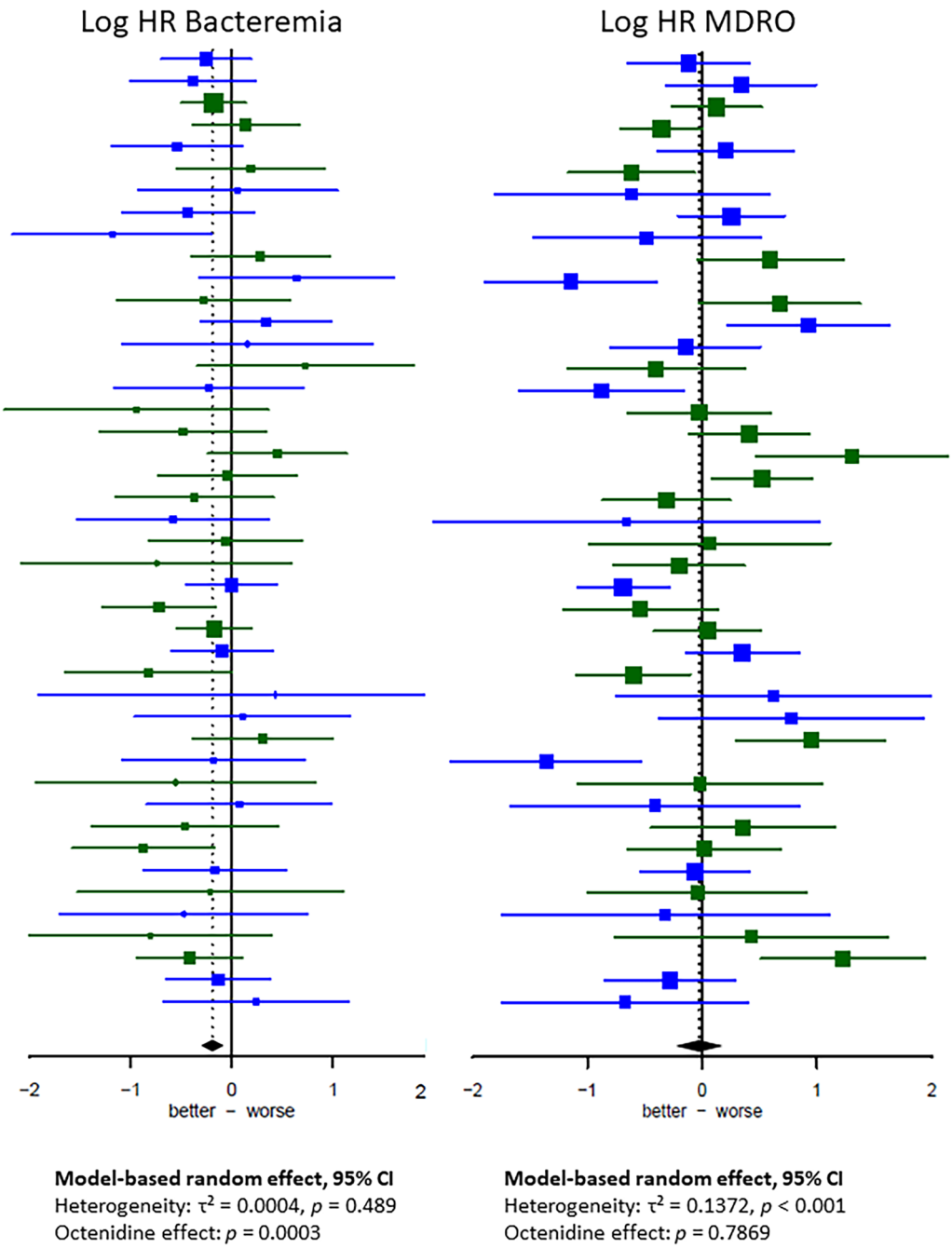

Fig. 3 Forest plots. Forest plots for each of the two co-primary endpoints visualize the heterogeneity of the treatment effect across ICUs. For each of the 44 participating ICUs, a point estimate for the intervention effect within each ICU is shown (as log HR) with 95% confidence intervals. Estimates are based on separate, simple, fixed-effect Cox models within each ICU. The color (green/blue) indicates the starting intervention to which the ICUs were randomized. The diamond-shaped summary estimates and confidence intervals are derived from the respective overall mixed-effects Cox regression model. The heterogeneity is negligible for ICU-acquired bacteremia, whereas it is substantial and clearly visible for ICU-acquired MDROs. *CI* confidence interval, *HR* hazard ratio, *MDRO* multidrug-resistant organism

heterogeneity among the intervention effects within the individual ICUs. We hypothesize that there are several externally driven, uncontrolled factors that influence the risk of MDRO acquisition on ICUs. For two of these factors, namely the influx of known MDRO carriers into the ICU and the intensity of MDRO screening, we provide evidence of marked correlation with ICU-specific incidence densities (ESM 1, Figures S3 and S4). Further

Table 2 Incidence densities for primary and secondary endpoints

Endpoint	Arm	Events	Days at risk	Incidence density/1000
ICU-acquired primary bacteremia	Octenidine	701	181,444	3.86 [3.58; 4.16]
	Placebo	807	175,275	4.60 [4.29; 4.93]
With pathogenic organisms	Octenidine	308	195,226	1.58 [1.41; 1.76]
	Placebo	351	189,226	1.85 [1.67; 2.06]
With pathogenic, Gram-positive organisms	Octenidine	207	199,442	1.04 [0.90; 1.19]
	Placebo	253	193,050	1.31 [1.16; 1.48]
With pathogenic, Gram-negative organisms	Octenidine	122	202,167	0.60 [0.50; 0.72]
	Placebo	129	197,218	0.65 [0.55; 0.77]
With common commensal organisms	Octenidine	473	191,256	2.47 [2.26; 2.70]
	Placebo	547	185,547	2.95 [2.71; 3.20]
ICU-acquired MDRO	Octenidine	935	170,994	5.47 [5.12; 5.83]
	Placebo	936	167,868	5.58 [5.23; 5.94]
MRSA	Octenidine	129	200,294	0.64 [0.54; 0.76]
	Placebo	134	195,033	0.69 [0.58; 0.81]
VRE	Octenidine	494	190,646	2.59 [2.37; 2.83]
	Placebo	517	187,155	2.76 [2.53; 3.01]
MDRGN	Octenidine	480	188,300	2.55 [2.33; 2.78]
	Placebo	430	183,863	2.34 [2.12; 2.57]

Note that the number of events and episodes in the subspecies do not add up. For an informative episode in which the patient is at risk for the specific event of interest, this particular type of event must not have been documented before day 3 on ICU. This means that, e.g., a patient known to have an MRSA on day 1 on ICU is no longer at risk for MRSA and for MRDO in general, but is still at risk for VRE and MDRGN. *ICU* intensive care unit, *MDRO* multidrug-resistant organism, *MRSA* methicillin-resistant *Staphylococcus aureus*, *VRE* vancomycin-resistant enterococci, *MDRGN* multidrug-resistant Gram-negative organism

research is required to understand the interplay of such factors.

The strengths of this study include not only its design and large size but also its approach to data acquisition. Acquiring and analyzing patient data digitally allowed for an objective, reproducible and resource-saving method to define endpoints in infection surveillance. EFFECT's unique algorithm was written specifically for the current study; the validity of its results and its conformity with the CDC's established definitions regarding HAIs was analyzed and confirmed in a separate study [31]. By eliminating third-party decision making and protocol-based surveillance methods, which have shown stark variability and volatile results [32], our results are free of inter-observer variability and provide an alternative to traditional surveillance methods.

Relating our results to the literature is difficult. Possibly pertinent publications suffer from questionable designs, e.g., quasi-experimental before-after studies without control for secular trends, small power, weak generalizability due to a limited number of participating ICUs, varying and potentially subjective endpoint definitions and a lack of comparability due to the use of combined interventions.

A recent review of studies evaluating octenidine usage shows that a majority were small, single-institution before-after studies [21]. Only one cluster-randomized, parallel-group study found that octenidine was not effective in preventing CLABSI [9] but had limited power.

How does octenidine bathing compare to bathing with chlorhexidine? A recent comprehensive meta-analysis [33] reports an effect of chlorhexidine bathing on bloodstream infections (BSI) from four studies, with an incidence rate ratio of 0.75 based on a total of 463 BSIs. EFFECT's result on primary bacteremia is in the same order of magnitude (0.83) based on 1508 events. Recently, Denkel et al. conducted a three-arm study comparing both octenidine and chlorhexidine bathing with standard care, finding that both chlorhexidine and octenidine are ineffective at preventing CLABSI. However, the study's power was insufficient [9]. With a post-hoc re-analysis incorporating pre-study data, a CLABSI-reducing effect for chlorhexidine, but not octenidine, is claimed [34]. Concerning MDRO, the aforementioned meta-analysis [33] reports a significant incidence rate ratio of 0.82 from two studies based on 497 events; our negative result is based on 1871 events.

Limitations

It may be considered a study limitation that no individual patient data, along with a lack of granularity in time reporting, results from data acquisition via algorithm. Additional study limitations include a lack of detailed reporting on background IPC measures for each

individual participating ICU, as well as having no standardized MDRO screening regimen requirements. However, these aspects were covered and controlled via study monitoring and study design respectively. The fact that the placebo washcloths contained 0.9% 2-phenoxyethanol as a preservative agent may also be considered a limitation. This was necessary to prevent the contamination with and spread of Gram-negative organisms via pre-moistened, non-sterile washcloths and had no relevant disinfecting effect according to the manufacturer.

A proper comparison of the effectiveness of octenidine and chlorhexidine bathing requires a large, well-designed, multicenter study. Further research is needed in order to compare adverse event profiles, detect newly emerging resistance patterns and assess potential changes in skin microbiome due to prolonged exposition to antiseptics, especially considering adapted concentrations of active ingredients in available products.

Conclusions

EFFECT has demonstrated that octenidine is effective at preventing primary bacteremia. The emphasis lies among Gram-positive bacteria and common skin commensals. As part of a robust bundle strategy, octenidine can serve as an additional building block in the effort to reduce nosocomial infections and enhance patient safety on ICUs.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s00134-024-07667-2.

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Author contributions

IC and DH were responsible for the trial design, NK for data collection, NK and DH for the statistical analysis. TS, NK and DH reviewed the underlying data and wrote the first draft of the manuscript. All the authors were involved in data interpretation, critical review, editing and final review of the manuscript.

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Declarations

Conflicts of interest

The author(s) declare no competing interests.

Ethics statement

This study was approved by the ethics committee at the University of Leipzig (340/16-ek). Informed consent on the patients' part was deemed unnecessary and, therefore, not required for study participation.

Data sharing

The study protocol (in German) and the statistical analysis plan are available. Study data that underlie the results reported in this article (text, tables, figures and appendices) will be shared to researchers who provide a methodologically sound and ethically approved proposal. Proposals can be submitted up to at least 36 months after article publication. Proposals should be directed to norbert.koehler@zks.uni-leipzig.de; to gain access, data requestors will need to sign a data-access agreement.

Publisher's Note

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