Review

Effect of chlorhexidine bathing on colonization or infection with *Acinetobacter baumannii:* a systematic review and meta-analysis

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SUMMARY

Healthcare-associated infections (HAIs) caused by multi-drug-resistant Gram-negative bacteria (MDRGNB) have increased prevalence in intensive care units (ICUs). A common strategy to prevent HAIs is bathing patients with chlorhexidine gluconate (CHG). However, the effectiveness of CHG bathing against multidrug-resistant *Acinetobacter baumannii* (MDRAB) is still controversial. The aim of this study was to perform a systematic review and meta-analysis of the effectiveness of CHG bathing on A*cinetobacter baumannii* colonization and infection in the ICU setting. A systematic literature search of PubMed, EMBASE, Web of Science and CINAHL was performed from inception through to June 2018. Randomized controlled trials (RCTs), pre-post studies, or interrupted time series (ITS) studies were included. The numbers of patients with/without colonization or infection of *A. baumannii* in the experimental or control groups were extracted from each study. Quality assessment was performed by the related instruments of National Institute of Health. Pooled risk ratios (RRs) were calculated using the random-effects model. One RCT and 12 pre-post or ITS studies comprising 18,217 patients were included, of which 8069 were in the CHG bathing arm and 9051 in the control arm. CHG bathing was associated with a reduced colonization of *A. baumannii* (RR, 0.66; 95% confidence interval: 0.57—0.77; $P<0.001$). Chlorhexidine at 4% showed a better effect than 2% chlorhexidine (meta-regression $P=0.044$). CHG bathing was associated with a non-significant reduction of infection (pooled RR 0.41, 95% CI: 0.13—1.25). This study suggests that CHG bathing significantly reduces colonization of *A. baumannii* in the ICU setting. However, more trials are needed to confirm whether CHG bathing can reduce infections with *A. baumannii*.

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Introduction

Healthcare-associated infections (HAIs) caused by multi-drug-resistant Gram-negative bacteria (MDRGNB) continue to increase in frequency and to become a serious threat in intensive care units (ICUs) globally [1–3]. Among Gram-negative bacteria, multi-drug-resistant (MDR) strains of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* have emerged as being of particularly serious concern due to their high mortality rate and treatment difficulties [4–7]. According to a previous study, *A. baumannii* related HAIs have been estimated to cost hospitals more than 30,000 USD per infection on average [8].

A. baumannii is a common cause of bloodstream infections in ICUs. The pathogen can live on the skin of humans, especially at tracheostomy sites and on open wounds [9]. Skin colonization with *A. baumannii* may then be related to contamination of vascular catheters such as central venous or arterial origin [10]. Studies have also reported lower respiratory tract infections and urinary tract infections as possible sources of *A. baumannii* bloodstream infections [11]. Risk factors for *A. baumannii* infection include previous use of broad-spectrum antibiotics, catheter insertion, longer duration of ventilation, and longer periods of hospitalization [12–14].

Cross-transmission between ICU patients is also a major determinant of MDR *A. baumannii* (MDRAB) acquisition [15]. In order to reduce MDR bacterial colonization and infection, a plethora of strategies have been developed, including hand hygiene among healthcare personnel, contact precautions, antimicrobial stewardship, environmental cleaning, decolonizing bathing and source control. It has been shown that a multi-modal strategy is more effective in reducing MDRGNB spread compared with a single strategy alone [16].

Chlorhexidine gluconate (CHG) bathing in ICU settings has been proven to be beneficial in preventing catheter colonization and catheter-related bloodstream infections [17]. The efficacy of daily CHG bathing among ICU patients in reducing the acquisition of drug-resistant Gram-positive cocci, such as meticillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE), has been demonstrated in a multi-centre trial [18]. However, the effectiveness of CHG bathing against *A. baumannii*, and especially MDRAB, is still controversial. To solve this ongoing issue, this study aimed to conduct a systematic review and meta-analysis to assess the benefit of CHG bathing on reducing *A. baumannii*, and especially MDRAB, colonization and infection rates, especially those with multi-drug resistance. This study investigated whether CHG bathing, compared with usual care, significantly decreases the rates of HAIs in adult ICUs.

Materials and methods

Data sources and search strategy

A systematic literature search was performed through medical literature databases including PubMed, EMBASE, Web of Science and CINAHL, published up until July 2018. PubMed was searched by combining four separate queries composed of medical subject heading (MeSH) terms and title/abstract keywords for the three topics described above, along with a query starting with 'NOT' to exclude inappropriate studies and article types. A similar search strategy was repeated in EMBASE, Web of Science and CINAHL. In addition, manual searches of the reference lists of included papers were undertaken for potential studies that met the inclusion criteria. The detailed information of keywords combinations is shown in Supplementary Table SI.

Study selection

Inclusion and exclusion criteria

Two authors (C.Y.F., C.H.L.) independently screened articles for inclusion. Studies were included if all of the following conditions were met: adults comprised over 50% of the enrolled patients in the study; the study was conducted in at least one ICU; the study applied CHG bathing as one of the interventions; the outcome(s) were either colonization or infection rates; and the study was a randomized controlled trial, an interrupted time series study, or a pre-post comparative study analysis. Review articles, studies of non-adult populations, non-ICU-based studies or studies not reporting the relevant outcomes were excluded. Any discrepancies between reviewers as to which articles merited inclusion were resolved by a consensus meeting of three authors (C.Y.F., C.H.L., C.C.L). The study selection process is summarized in Figure 1.

Data extraction

The following data were extracted: first author, country, year of publication, study design, ICU type, number of beds, type of *A. baumannii*, total number of patients, total patient-days, concentration of CHG, medium used for bathing, definition of outcome, and types of hospital acquired infection. When necessary, authors were contacted for additional data or confirmation of results. If the authors did not reply but the data were available on previously published meta-analyses, the data was extracted from those meta-analyses.

Quality assessment and risk of bias

Quality assessment by two authors (C.Y.F., H.P.W.) using the Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group, and Quality Assessment of Controlled Intervention Studies [19]. Two of the 12 criteria regarding blinding (question 8) and follow-up (question 9) were removed for our study design (Supplementary Table SII). Blinding was not applicable because it was obvious to the nurses whether CHG was used, and none of our included studies used it. Follow-up after discharge is not of interest for this study. Studies were classified as low quality (fewer than 3 points), moderate quality (3–6 points), or high quality (more than 6 points). Randomized controlled trials were assessed using Quality Assessment of Controlled Intervention Studies [19]. Studies were classified as low quality (fewer than 5 points), moderate quality (5–9 points), or high quality (more than 9 points) (Supplementary Table SIII). The criteria for every question are listed in Supplementary Tables SIV and SV.

Statistical analysis

Pooled risk ratios (RRs) and 95% confidence intervals (CIs) were summarized for the effect size of CHG bathing

113 citations identified from literature search, 22 from PubMed, 55 from Embase, 24 from Web of science and 12 from CINAHL database

→ 46 citations excluded due to overlap

→ 50 citations excluded based on screening of titles and abstracts using pre-defined criteria

← 3 relevant citations identified from reference lists and other databases

20 potentially relevant articles identified for further review

→ 7 citations excluded after full-text review
2 antimicrobial susceptibility
2 no available outcomes
2 no separate outcomes for AB
1 lack original numbers of outcome

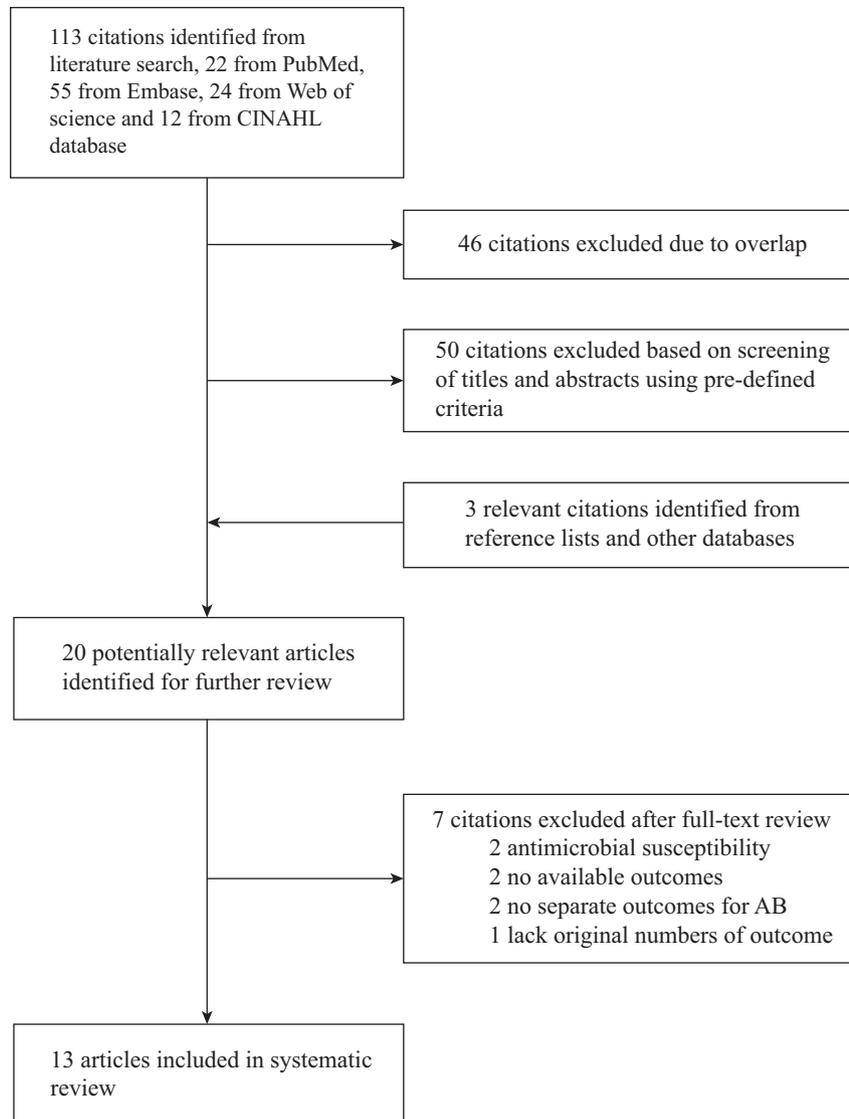| |
|---|
| 13 articles included in systematic review |

Figure 1. Selection of articles for systemic review. AB, *Acinetobacter baumannii*.

on the prevention of MDRAB colonization or infection using the random effect model by the DerSimonian and Laird method, and the heterogeneity was quantified with the I^2 statistic. To identify potential statistical outliers, Galbraith plots were created to visualize the impact of individual studies on the overall homogeneity test statistic. To explore whether there was an interaction between specific study characteristics and the outcome of interest, meta-regression analyses were performed. Even when the meta-regression result was not statistically significant, a subgroup analysis was conducted when a study characteristic was clinically relevant. Effects size was estimated for each pre-defined patient group. The presence and the effect of publication bias was examined using a combination of the Begg and Egger's tests. Statistical analyses were performed using Stata 13 (StataCorp Inc. College Station, TX, USA). The metan, metabias, galbr, and metareg commands were used for meta-analytic procedures. *P*-values <0.05 were considered statistically significant.

Results

Study selection

Our search criteria identified 113 studies. After excluding 46 overlapping citations, 67 articles were included for title and abstract screening. An additional three articles were included from related systematic reviews and meta-analyses. After title and abstract screening, 20 articles were deemed eligible for full-text review. After full-text review, 13 articles remained eligible for final analysis, including one randomized control trial, seven interrupted time series studies, and five pre-post comparison studies. The detailed inclusion/exclusion process is shown in Figure 1.

Study characteristics

The 13 studies were performed in different types of ICUs, including medical [10,20–26], surgical [24,26–29], one mixed medical–surgical [24], one anaesthetic [26] and one unknown

type of ICU [30]. Daily CHG bathing was used in most studies — two performed weekday bathing [23,27] and one performed weekly bathing [26]. In two studies by Popovich *et al.*, additional bathing was allowed if the nurse thought it was necessary. CHG at 2% was used in 10 studies, while the study by Borer *et al.* [10] and Robustillo-Rodela *et al.* [30] used 4% CHG for bathing. The media for bathing included sponges, douches, wipes and washcloths. In Borer *et al.* [10] 4% CHG was kept on the skin for at least 2 min before it was washed away by warm tap water. In all studies, the area above the neck was excluded from CHG bathing to avoid exposure to mucosal membranes of the mouth, eyes and ears. The summary of study characteristics is listed in Supplementary Table SVI.

Quality assessment

Assessment of study quality is shown in Supplementary Table SII (pre-post comparison observational studies) and Supplementary Table SIII (randomized controlled trials). One pre-post comparison study was considered moderate in quality because most of the details were not provided, whilst the rest of the studies were rated as high quality. The randomized controlled trial by Boonyasiri *et al.* [21] scored more than 9, but it was considered poor quality because of fatal flaws in which the differential dropout rates were higher than 15% in both arms.

Effect of CHG bathing on colonization of drug-resistant A. baumannii

The primary outcome was the colonization rate of *A. baumannii*. CHG bathing was associated with a reduced

drug-resistant *A. baumannii* colonization rate, with a pooled RR of 0.46 (95% Cl: 0.28—0.76) (Figure 2). After excluding two outlier studies ([23,27]) on Galbraith plot (Supplementary Figure S1), results remained significant (odds ratio (OR) 0.40, 95% CI: 0.24—0.64) (Figure 3). The secondary outcome was MDRAB infection, including urinary tract infections, ventilator-associated pneumonia and bloodstream infections. CHG bathing was associated with a non-significant reduction in *A. baumannii* infection, with a random-effects pooled RR of 0.41 (95% CI: 0.13—1.25). The outcome estimates are summarized in Table I and Figure 4.

Subgroup analysis

CHG is available either in 2% or 4% concentrations, and as a liquid or as commercial impregnated wipes. To compare the efficacy of the concentrations and methods of administration, a subgroup analysis was performed. No direct comparison was made between 2% or 4% CHG, but pooled effect estimates showed bathing with 4% CHG (OR 0.03, 95% CI: 0.004—0.23) was more effective than 2% CHG (OR 0.57, 95% CI: 0.36—0.91). Meta-regression analysis showed a significant difference between the effects of two concentrations of CHG bathing ($P=0.044$). Bathing with a cloth (OR 0.39, 95% CI: 0.23—0.67) or disposable wipes (OR 0.53, 95% CI: 0.14—2.08) did not show different colonization rates for *A. baumannii* ($P=0.716$). Whether the intervention was single measure or bundle care is a potential confounding factor in our study, and the meta-regression analysis showed no difference between these two groups ($P=0.916$). Whether the study was set up in an epidemiologic outbreak of *A. baumannii* colonization or not was
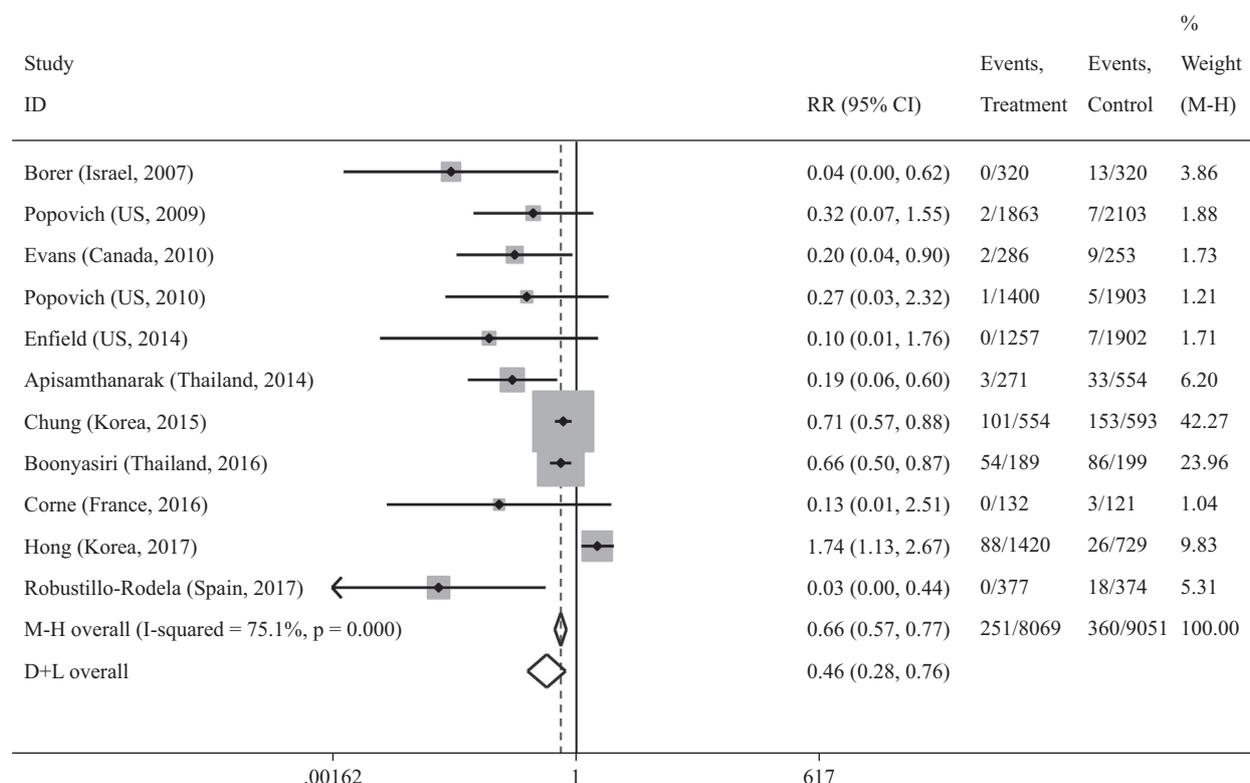
Study ID	RR (95% CI)	Events, Treatment	Events, Control	% Weight (M-H)
Borer (Israel, 2007)	0.04 (0.00, 0.62)	0/320	13/320	3.86
Popovich (US, 2009)	0.32 (0.07, 1.55)	2/1863	7/2103	1.88
Evans (Canada, 2010)	0.20 (0.04, 0.90)	2/286	9/253	1.73
Popovich (US, 2010)	0.27 (0.03, 2.32)	1/1400	5/1903	1.21
Enfield (US, 2014)	0.10 (0.01, 1.76)	0/1257	7/1902	1.71
Apisamthanarak (Thailand, 2014)	0.19 (0.06, 0.60)	3/271	33/554	6.20
Chung (Korea, 2015)	0.71 (0.57, 0.88)	101/554	153/593	42.27
Boonyasiri (Thailand, 2016)	0.66 (0.50, 0.87)	54/189	86/199	23.96
Corne (France, 2016)	0.13 (0.01, 2.51)	0/132	3/121	1.04
Hong (Korea, 2017)	1.74 (1.13, 2.67)	88/1420	26/729	9.83
Robustillo-Rodela (Spain, 2017)	0.03 (0.00, 0.44)	0/377	18/374	5.31
M-H overall (I-squared = 75.1%, p = 0.000)	0.66 (0.57, 0.77)	251/8069	360/9051	100.00
D+L overall	0.46 (0.28, 0.76)			

Figure 2. Random effects meta-analysis of the effects of chlorhexidine bathing on colonization of *Acinetobacter baumannii* in intensive care unit patients: overall analysis. CI, confidence interval; RR, risk ratio.
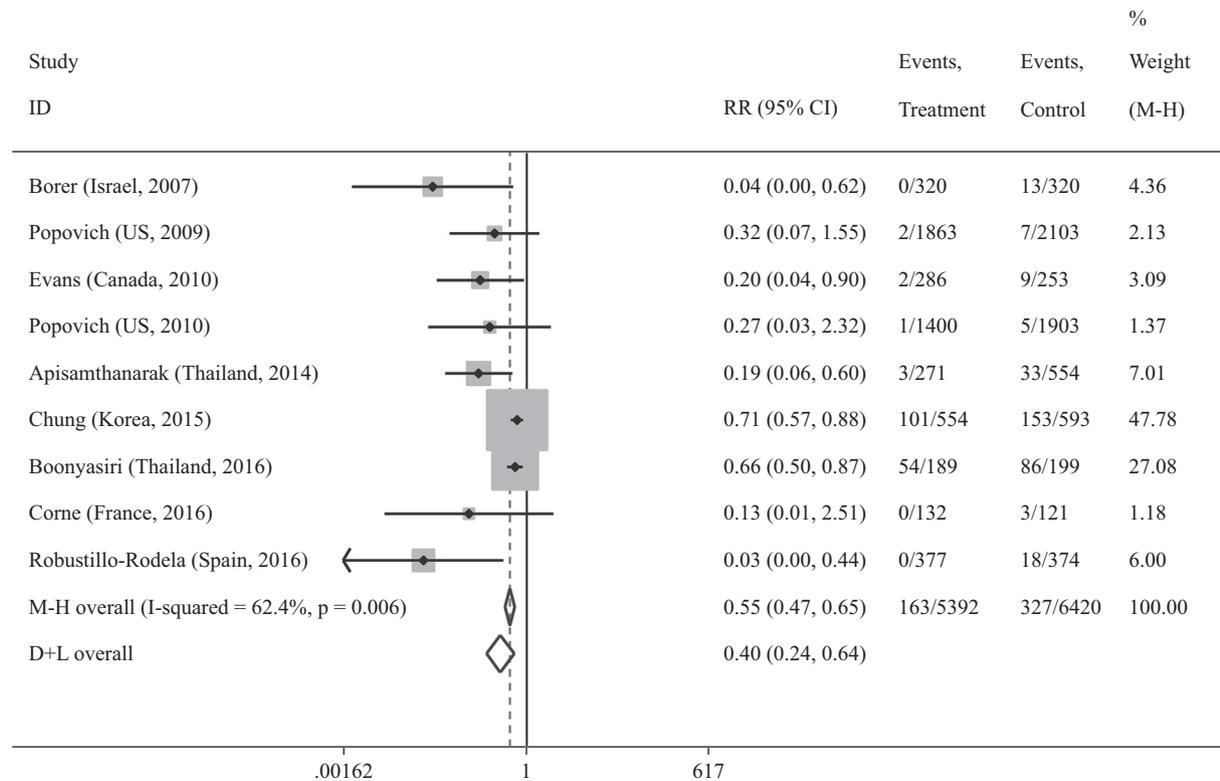
Study ID	RR (95% CI)	Events, Treatment	Events, Control	% Weight (M-H)
Borer (Israel, 2007)	0.04 (0.00, 0.62)	0/320	13/320	4.36
Popovich (US, 2009)	0.32 (0.07, 1.55)	2/1863	7/2103	2.13
Evans (Canada, 2010)	0.20 (0.04, 0.90)	2/286	9/253	3.09
Popovich (US, 2010)	0.27 (0.03, 2.32)	1/1400	5/1903	1.37
Apisamthanarak (Thailand, 2014)	0.19 (0.06, 0.60)	3/271	33/554	7.01
Chung (Korea, 2015)	0.71 (0.57, 0.88)	101/554	153/593	47.78
Boonyasiri (Thailand, 2016)	0.66 (0.50, 0.87)	54/189	86/199	27.08
Corne (France, 2016)	0.13 (0.01, 2.51)	0/132	3/121	1.18
Robustillo-Rodela (Spain, 2016)	0.03 (0.00, 0.44)	0/377	18/374	6.00
M-H overall (I-squared = 62.4%, p = 0.006)	0.55 (0.47, 0.65)	163/5392	327/6420	100.00
D+L overall	0.40 (0.24, 0.64)			

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Figure 3. Random effects meta-analysis of the effects of chlorhexidine bathing on colonization of *Acinetobacter baumannii* in intensive care unit patients: excluding two outliers. CI, confidence interval; RR, risk ratio.

also analysed. The effect of a CHG bathing programme in an outbreak period (OR 0.21, 95% CI: 0.01–5.22) was not better than in a non-outbreak period (OR 0.47, 95% CI: 0.31–0.72, P=0.075). CHG bathing was equally effective in the medical ICUs (OR 0.54, 95% CI: 0.32–0.91) and surgical ICUs (OR 0.19, 95% CI: 0.06–0.61, P=0.433).

Heterogeneity analysis and publication bias

The heterogeneity of the effect estimates for *A. baumannii* colonization reduction as quantified by I^2 was 75.1% in all studies, and 62.4% after two statistical outliers were removed ([23,27]). There was no evidence of publication bias as the funnel plot was symmetrical (Supplementary Figure S2) and the P-values for Begg and Egger's were >0.05 (Supplementary Table SVII).

Discussion

This meta-analysis comprising 13 studies with 18,217 patients presented a summary of the estimated benefits of CHG bathing to prevent *A. baumannii* colonization and infection in ICUs. The results show that CHG bathing decreases the risk of *A. baumannii* colonization, regardless of different study designs, medium of CHG bathing, types of ICU settings, or whether implemented in the MDRAB outbreak periods or not. Compared with patients who did not received CHG bathing, patients receiving CHG bathing were associated with an approximately 34% reduction in the colonization rate. Moreover, 4% CHG had better efficacy than 2%. Due to the limited number of studies reporting infection outcomes, the effect of

CHG bathing on the *A. baumannii* infection rate remains unclear.

Previous meta-analyses have confirmed the benefits of CHG bathing to reduce central-line-associated bloodstream infections with MRSA and VRE [31–33]. Currently, the only meta-analysis discussing the prevention of MDRGNB infection concluded that a multiple-strategy method including antibiotic stewardship, CHG bathing, and environmental cleaning is the best means of preventing infection [16]. However, there is no analysis addressing the effectiveness of CHG bathing exclusively in reducing *A. baumannii* colonization or infection. *Acinetobacter* spp. are natural inhabitants of human skin, but the most important nosocomial pathogen, *A. baumannii,* is rarely found on the skin of healthy people or patients in the general ward [34]. While *A. baumannii* is frequently found in the ICU [35], the natural reservoir of the organism in the acute medical setting remains unknown.

Daily CHG bathing was shown to reduce the development of hospital-acquired infection of MDR pathogens including MRSA and VRE [36]. A meta-analysis in 2018 revealed an association between CHG bathing and the decreased colonization rate but not the infection rate of VRE [37]. Xiao *et al.* suggested that this discrepancy was due to very few studies actually measuring infection rate [37]. This challenge extends to this meta-analysis as well, because only four studies provided data for *A. baumannii* infection [10,24,26,28]. Additionally, three of these studies [26,28,29] included surgical patients and CHG bathing is of limited effect in surgical site infections [38]. Despite the non-significant effect of CHG bathing on MDRAB infection demonstrated in this meta-analysis, CHG bathing is still recommended to control nosocomial infection by

Table I
Summary of subgroup analysis of chlorhexidine bathing on the incidence of *Acinetobacter baumannii* colonization

Category	Number of studies	Summary estimate (95% CI)	I^2	Meta-regression P
Overall	11	0.46 (0.28–0.76)	75.1%	NA
Outlier removed	9	0.40 (0.24–0.64)	62.4%	0.007
Design factors				
Pre-post design	10	0.52 (0.32–0.87)	73.9%	NA
Intervention				
2% chlorhexidine bathing	9	0.57 (0.36–0.91)	72.8%	0.044
4% chlorhexidine bathing	2	0.03 (0.004–0.23)	0.0%	0.044
Bathing with cloth	7	0.39 (0.23–0.67)	70.7%	0.716
Bathing with disposable wipe	4	0.53 (0.14–2.08)	67.2%	0.716
Single measure intervention	8	0.71 (0.58–0.87)	75.8%	0.916
Bundle care intervention	3	0.13 (0.04–0.40)	34.8%	0.916
Comparison period				
Involved an outbreak period	3	0.21 (0.01–5.22)	86.4%	0.075
Not involved an outbreak period	8	0.47 (0.31–0.72)	53.0%	0.075
Settings				
MICU	8	0.54 (0.32–0.91)	79.6%	0.433
SIGU	3	0.19 (0.06–0.61)	0.0%	0.433

CI, confidence interval; NA, not available; SIGU, Surgical intensive care unit; MICU, Medical intensive care unit

A. baumannii. The proportion of body sites colonized by MDRAB is a major risk factor for infection with the same pathogen [39–41]. Therefore, skin decolonization is an important preventative measure. Furthermore, environmental contamination has also been shown to play a role in the spread of MDRAB [16,42,43]. Another study suggested that environmental cleaning should be implemented as part of multi-strategy infection control in the ICU [16]. There is sufficient evidence to recommend daily CHG bathing of ICU patients for the prevention of MDRAB.

Most studies that were included carried out CHG bathing on a daily basis, though a previous study demonstrated that CHG has at least 48 h of antimicrobial activity on human skin [44]. Swan *et al.* stated that CHG bathing every other day could decrease the infection rate in the surgical ICU [45]. Hitherto, no study has directly compared different frequencies of CHG bathing on the prevention of hospital-acquired infections. It must be considered that pathogens may develop into more virulent strains under intermittent or prolonged exposure to CHG. Future studies should focus on investigating the efficacy
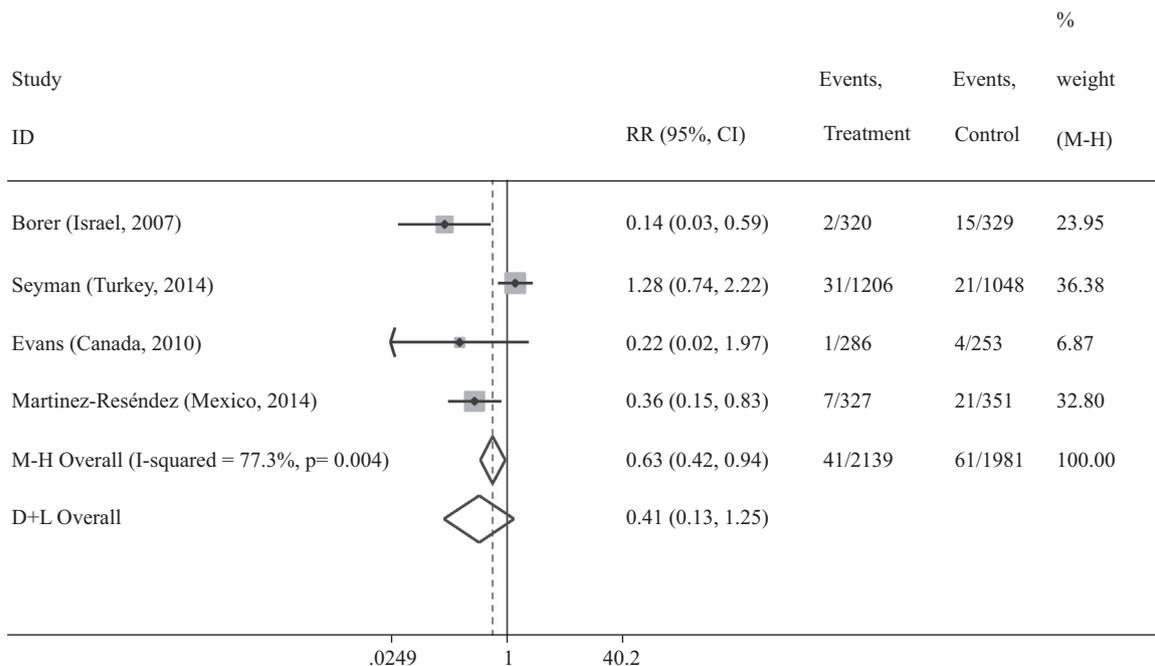

Figure 4. Random effects meta-analysis of the effects of chlorhexidine bathing on hospital-acquired *Acinetobacter baumannii* infection. CI, confidence interval; RR, risk ratio.

of various frequency of CHG bathing and the potential for the development of CHG-resistant strains.

This study is the first meta-analysis to try to confirm the effect of CHG bathing on *A. baumannii* colonization and infection. A comprehensive search of not only PubMed, EMBASE and Web of Science was performed, but nursing and allied health databases such as CINAHL were also searched, covering most of the studies related to the topic. Currently, there is no standard tool of quality assessment for interrupted-time series and pre-post study, but this study applied a novel tool published recently by the National Institute of Health. Meta-regression was also performed to identify the potential source of heterogeneity between studies. There are some limitations in this study. High heterogeneity was observed in this meta-analysis. Heterogeneity may reflect true differences in background incidence of *A. baumannii* colonization, transmission dynamics of *A. baumannii*, variable frequency and medium in application of CHG bathing, different definitions of MDRAB and the distribution of effect modifiers such as age, case mix of ICU. Some published trials were excluded that were unable to be pooled in the meta-analysis because of missing original data. Some of the included studies were interrupted-time series. The statistical method for pooling the results of interrupted-time series has not yet been developed. The before-and-after RR for meta-analysis was calculated. However, this may not capture the change in trend of *A. baumannii* colonization. Although most of the included studies were high-quality pre-post studies, the inherent trend bias could not be totally excluded by this study design. Well-designed multi-centre pragmatic randomized controlled trials are needed to show the real-world effectiveness [46].

In conclusion, this meta-analysis has shown that CHG bathing decreases A. baumannii colonization in ICU patients. The heterogeneity in study designs and settings highlights the need for well-designed randomized controlled studies to confirm these findings and verify the effectiveness of CHG bathing in reducing A. baumannii infection. Given the low risk of CHG bathing, it can be recommended as a measure to reduce A. baumannii colonization before a confirmatory trial is available.

Author contributions

C.C.L. had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. C.C.L. was responsible for study concept and design, analysis and interpretation of data. C.Y.F., S.P.W. and C.H.H. were responsible for acquisition of data. C.C.L., W.T.L. and T.C.H. performed the statistical analysis. C.Y.F. and C.C.L. were responsible for drafting of the manuscript. W.T.L., C.H.L., S.P.W., S.C.C. and C.C.L. were responsible for critical revision of the manuscript for important intellectual content. C.C.L. supervised the study.

Conflict of interest statement
The authors declare that no competing interests exist.

Appendix A. Supplementary data

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.jhin.2019.08.004.

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