REVIEW ARTICLE

Impact of Oral Chlorhexidine on Bloodstream Infection in Critically Ill Patients: Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Objectives: **Oropharyngeal overgrowth of microorganisms in the critically ill is a risk factor for lower respiratory tract infection and subsequent invasion of the bloodstream. Oral chlorhexidine has been used to prevent pneumonia, but its effect on bloodstream infection never has been assessed in meta-analyses. The authors explored the effect of oral chlorhexidine on the incidence of bloodstream infection, the causative microorganism, and on all-cause mortality in critically ill patients.**

Design: **Systematic review and meta-analysis of published studies.**

Setting: **Intensive care unit.**

Participants: **The study comprised critically ill patients receiving oral chlorhexidine (test group) and placebo or standard oral care (control group).**

Interventions: **PubMed and the Cochrane Register of Controlled Trials were searched. Odds ratios (ORs) were pooled using the random-effects model.**

Measurements and Main Results: **Five studies including 1,655 patients (832 chlorhexidine and 823 control patients) were identified. The majority of information was from studies at low or unclear risk bias; 1 study was at high risk of bias. Bloodstream infection and mortality were not reduced significantly by chlorhexidine (OR 0.74; 95% confidence interval [CI] 0.37-1.50 and OR 0.69; 95% CI 0.31-1.53, respectively). In the subgroup of surgical, mainly cardiac, patients, chlorhexidine reduced bloodstream infection (OR 0.47; 95% CI 0.22-0.97). Chlorhexidine did not affect any microorganism significantly.**

Conclusion: **In critically ill patients, oropharyngeal chlorhexidine did not reduce bloodstream infection and mortality significantly and did not affect any microorganism involved. The presence of a high risk of bias in 1 study and unclear risk of bias in others may have affected the robustness of these findings.**

BLOODSTREAM INFECTION (BSI) is one of the most frequent infections in critically ill patients requiring treatment in the intensive care unit (ICU).[1] The incidence is between 5 and 19 per 1,000 patient days, and BSI is associated with increased mortality and costs.[2]

Apart from catheter-related BSI, the main sources of BSI are internal organs (eg, lungs, bladder, and the gut).[3,4] Overgrowth of potentially pathogenic microorganisms (PPMs) in the patient's oropharynx is the major risk factor for lower respiratory tract infections and of subsequent invasion from the lungs into the bloodstream.[4–6] Bacteremia is an independent risk factor for mortality in nosocomial pneumonia.[6] Microorganisms causing infection of the bladder may be responsible for subsequent blood invasion.[4,7] Moreover, gut overgrowth promotes translocation of bacteria into the systemic circulation.[8–10] Finally, a substantial number of catheter-related BSIs may be due to skin microorganisms.[4]

About half of BSIs are caused by Gram-positive bacteria, 40% are caused by aerobic Gram-negative bacilli (AGNB), and the remaining are polymicrobial or due to yeasts.[4] BSI can be due to both normal and abnormal PPMs. "Normal" potential pathogens (eg, *Streptococcus pneumoniae,* methicillin-sensitive *Staphylococcus aureus, Haemophilus influenzae*, and *Escherichia coli)* are carried by previously healthy individuals and may cause early lower respiratory tract infection and subsequent BSI due to an acute event requiring ICU admission.[4] "Abnormal" potential pathogens, including both AGNB and methicillin-resistant *S. aureus*, are uncommon in healthy people and generally cause late BSI.[4]

Chlorhexidine is an antiseptic agent active against Gram-positive and Gram-negative bacteria, facultative anaerobes and aerobes, and yeasts.[11] In the last decade, decontamination of the oropharynx with chlorhexidine has become a standard practice for the prevention of lower respiratory tract infection in ICU patients receiving mechanical ventilation.[12] This mainly is due to the results of several studies and systematic reviews showing a reduction of lower respiratory tract infection and ventilator-associated pneumonia of about 30% to 40%.[13–16] However, the efficacy of oral hygiene with chlorhexidine on BSI has not yet been explored in a systematic review.

The authors undertook a systematic review and meta-analysis to assess the effectiveness of oral chlorhexidine in

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the control of BSI in critically ill patients, to identify the causative microorganism, and to evaluate the effect on all-cause mortality.

METHODS

Search Strategy

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.[17] The authors searched PubMed and the Cochrane Register of Controlled Trials for randomized controlled trials (RCTs) published until December 2015 with no language restriction. Search terms were chlorhexidine, oral care, oral hygiene, oral health, oral rinse, oral decontamination, mouthwashes, bloodstream infection, bacteremia, lower airway (respiratory tract) infection, nosocomial pneumonia, ventilator-associated pneumonia, hospital-acquired pneumonia, dental plaque, with the search limits of "clinical trial" and "humans" (Supplementary Material 1). The references of articles and published meta-analyses were cross-checked. Three investigators (LS, HKFvS, WIW) independently performed the search and screened titles and abstracts. RCTs were analyzed based on the full text using a standardized data extraction form.

Selection Criteria

Inclusion and exclusion criteria were determined before abstracts and articles were reviewed. All RCTs with usable information on BSI were included. In the included randomized trials, critically ill patients received oral chlorhexidine in the test group and patients in the control group received placebo or different oral care products. RCTs using oropharyngeal antibiotics or probiotics and RCTs including cancer, neutropenic, and bone marrow transplant patients were excluded.

Data Extraction

Three investigators independently retrieved and compared the sets of data from each trial. Any disagreement was resolved by discussion. The following data were sought: author, publication year, population included, description of the intervention and the control arms, randomization and allocation concealment, blinding, handling of dropouts and withdrawals, number of patients included, number of patients with BSI, number of patients with the microorganism causing BSI (individual microorganism, Gram-positive and Gram-negative microorganisms, "normal" and "abnormal" flora), and total mortality. PPMs causing BSI were classified with the Gram staining technique which differentiates Gram-positive from Gram-negative bacteria, and the method using the distinction between "normal" and "abnormal" microorganisms described elsewhere.[18]

Quality Assessment

Two investigators (NT, DFZ) assessed the quality of the studies using the Cochrane Collaboration risk-of-bias tool.[19]

Statistical Analysis

The primary endpoints were the number of patients with BSI and all-cause mortality; the secondary endpoint was the microorganism involved. The following subgroup analyses of the primary endpoints were determined a priori: (1) adequate or inadequate randomization/allocation (smaller treatment effect in concealed allocation); (2) blinding (smaller treatment effect in blinded studies); (3) chlorhexidine concentration (smaller

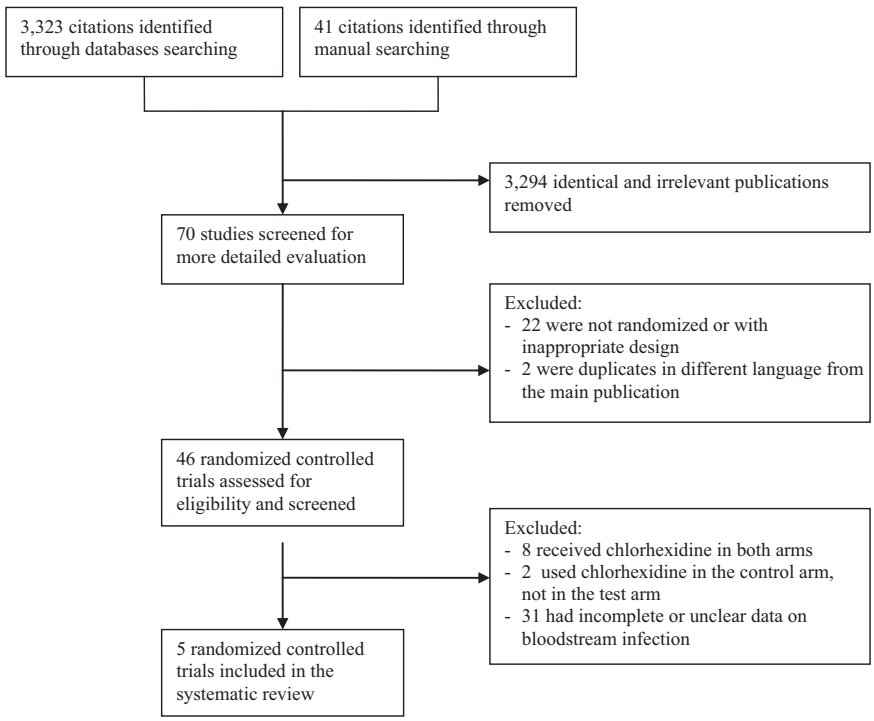

Fig 1. Flow diagram of the search strategy.