Comparison of chlorhexidine impregnated dressing and standard dressing for the prevention of central-line associated blood stream infection and colonization in Critically Ill Pediatric Patients: A Randomized Controlled Trial

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Abstract

Objective: The purpose of this study is to compare chlorhexidine gluconate (CHG)-impregnated dressing and standard dressing with respect to their effects on the frequency of central-line associated bloodstream infection (CLABSI), catheter related bloodstream infection (CRBSI), primary bloodstream infection (BSI) and catheter colonization in critically ill pediatric patients with short-term central venous catheter.

Methods: Prospective, single-center randomized controlled trial performed in pediatric intensive care unit (PICU) of a tertiary referral hospital. The patients were randomized with respect to the type of catheter fixation they had received, either with CHG-impregnated dressing or standard dressing.

Results: A total of 307 patients (151 CHG-impregnated dressing, 156 standard dressing), with 307 catheters amounting to a collective total of 4993 catheter days, were included in the study. Use of CHG impregnated dressing did not significantly decrease the incidence of CLABSI (6.36 per 1000 catheter days vs. 7.59 per 1000 catheter days; HR: 0.93, P = 0.76), CRBSI (3.82 per 1000 catheter days vs. 4.18 per 1000 catheter days; HR: 0.98, P = 0.98), primary BSI (2.54 per 1000 catheter days vs. 3.42 catheter days; HR: 0.39, P = 0.67). CHG-impregnated dressing significantly decreased the incidence of catheter colonization (3.82 per 1000 catheter days vs. 7.59 per 1000 catheter days; HR: 0.40, P = 0.04). Longer catheter time-in-place and use of blood product transfusion were found to be independently associated with CLABSI.

Conclusions: The use of CHG-impregnated dressing does not significantly decrease CLABSI incidence in critically ill pediatric patients compared to standard dressing, but it is effective in reducing catheter colonization.

Introduction

Central venous catheters (CVCs) are instruments that enable long-term vascular access and can be used for a broad range of purposes, especially in intensive care units. Common indications for CVC include their use for hemodynamic monitoring, intravenous administration of drugs, parenteral nutrition, fluids or blood products, and blood withdrawal [1, 2]. Central venous catheters are placed due to various indications in more than 50% of children admitted to pediatric intensive care units (PICUs) [3].

Despite enabling reliable and safe vascular access in critically ill patients, these devices are associated with central line-associated bloodstream infections (CLABSIs) and catheter-related bloodstream infections (CRBSIs) [4–6]. The frequency of CLABSI/CRBSI is reported to range from 0.20 to 17.6 per 1000 catheter days, and have been associated with age, catheter type, insertion site, indications, indwelling time, and underlying disease [7–10]. Higher incidence of CLABSI/CRBSI development increases antibiotic use, prolongs length of hospital stay and raises healthcare expense, as well as causing high mortality and morbidity [11–13]. Despite successful results with widespread implementation of catheter care bundles, catheter infections remain an important cause of preventable nosocomial infections in patients requiring intensive care unit management [14]. The practices proposed by catheter care bundles, which are aimed at preventing CLABSI/CRBSI development, include hand hygiene, optimal catheter site selection, daily evaluation and removal of unnecessary catheters, standardization of procedures and care, maximum

barrier precautions during the insertion process and the use of antibiotic-antiseptic-impregnated CVCs [15, 16].

Avoiding contamination that would lead to central venous catheter colonization is supposed to be the key element in decreasing the risk of catheter infections [6, 17]. The most common mechanism of catheter infections is the migration of microorganisms at the insertion site (skin) into the cutaneous catheter tract or the surface of the catheter, subsequently causing colonization of the catheter tip [6]. Therefore, effective skin antisepsis at the site of insertion and antiseptic dressing practices may prevent CRBSIs by mitigating microorganism migration that would have led to catheter colonization [18].

In recent years, the use of chlorhexidine gluconate (CHG) for catheter infection prevention has drawn interest among clinicians. Many studies have reported results with different CHG applications, such as use in cleansing, disinfection, oral care and dressing impregnation [19]. CHG-impregnated dressings provide local antimicrobial effects by constant release of CHG at the insertion site. Based on adult studies and meta-analyses, several randomized controlled trials (RCTs) have evaluated and reported the role of CHG-impregnated dressing as prophylactic measures for CRBSIs and CLABSIs, which have revealed that the use of CHG-impregnated dressing can reduce the risk for catheter colonization and CRBSI/CLABSI [18–24]. However, there are very few studies that have assessed the efficacy of CHG-impregnated dressing in limited numbers of pediatric patients, which have yielded controversial results that appear to be in conflict with adult studies [25–28]. According to the “Guidelines for the Prevention of Intravascular Catheter-Releated Infections” published by the Centers for Disease Control (CDC) and Prevention, the use of CHG-impregnated dressing is advised in those older than 18 years old; however, its use has not been advised in those younger than 18 years of age due to lack of conclusive evidence from high-quality studies evaluating the efficacy of CHG-impregnated dressing and its safety in this age group [29].

The primary aim of this study was to conduct a randomized controlled study to compare CHG-impregnated dressing and standard dressing in terms of the incidences of CLABSI, CRBSI, primary bloodstream infection (BSI) and catheter colonization in critically ill pediatric patients admitted to the PICU who had received treatment with placement of short-term non-tunneled CVC. Our secondary aim was to identify the distribution of microorganisms causing CLBASI and colonization and to determine adverse events (AEs) associated with the use of catheter dressing in this age group.

Methods

Ethics Statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by Clinical Research Ethics Committee of Istanbul Medeniyet University Goztepe Training and Research Hospital (Clinical registry registration: 2018/0203). Written informed consent was received from the parents or legal guardians of all study subjects.

Study Design

We used a single-center, randomized controlled and single-blinded study design to compare two types of transparent dressing: (i) standard dressing group: a standard breathable, hypoallergenic, transparent dressing (Tegaderm™ 1635 [8.5 x 10.5cm] or 1633 [7 × 8.5 cm] depending on patient size; 3M, Neuss, Germany), and (ii) CHG-impregnated dressing group: a CHG-gel impregnated transparent dressing (Tegaderm™ CHG 1660R [7 x 8.5 cm] or [11.5 x 8.5 cm] depending on patient size; 3M, Neuss, Germany). The laboratory microbiologist was blinded to the study groups. The two dressings were visibly different, and consequently, it was not possible to blind the patients, PICU staff or the investigators who collected data in the PICU. If a blood culture or catheter tip culture was positive, another investigator, blinded to the study groups, reviewed the medical records to determine whether or not the findings could be classified as CLABSI, CRBSI or catheter colonization.

Study Group and Randomization

From May 2018 until December 2019, we recruited pediatric patients (1 months to 18 years of age) admitted to our PICU who were expected to require short term, non-tunneled catheterization for at least 48 hours. Patients were randomly assigned to one of two dressings, both of which were being actively used as part of standard care. A researcher who had no knowledge of recruiting status–which was independently assessed by the recruiting nurse, prepared a computer-generated randomization table (1:1 ratio) that stratified patients by matching characteristics using a block size of four or eight (random).

Population and Setting

Eligibility criteria were: being aged age less than 18 years old, providing informed consent to participate in the study, and requiring the insertion of a short term non-tunneled, percutaneously inserted CVC (jugular, subclavian, or femoral) that would remain in place for greater than 48 hours during PICU admission. Patients were excluded if they: had known allergies to CHG-impregnated or standard dressing, would receive insertion of any other type of CVC device (e.g., peripherally inserted CVC, tunneled CVC), were included in the study previously, had a current BSI (positive blood culture within 48 hours), and had received CVC insertion within the 30 days prior to PICU admission. Additionally, we also excluded patients in which catheterization had not been performed by the PICU specialist, those that were discharged from the PICU with indwelling CVC, patients who received extracorporeal membrane oxygenation, and individuals in which the following events were recorded: accidental catheter removal, CVC removal before 48 hours, and death within 48 hours after CVC insertion. In the event that a patient required CVC re-insertion after the initial catheter was removed (due to any reason), only the first application was included in the study –given that any other exclusion criteria did not exclude the patient. Finally, if a patient required catheter reinsertion before the completion of the 48-hour catheter-infection monitoring of the initial application, the first catheterization was excluded from the study.

Catheters and Procedures

Before beginning the study, care bundles and checklists for catheter use and management were prepared according to various guidelines [6, 30]. The practices employed as part of the care bundle were as follows:

(i) “standards for medication administration through CVCs”, (ii) “management and replacement of infusion sets”, and (iii) “CVC exit site management”. Staff training on the care bundle and the use of checklists was conducted prior to study implementation with all nursing staff for a duration of 1 month.

The insertion of the CVC was performed according to the recommendations of CDC, and maximal sterile barrier precautions were taken by the clinician who performed the procedure (use of cap, mask, sterile gloves, large sterile drape, gown, and surgical hand antisepsis) [6]. In line with hospital policy, the CVC insertion site was cleaned with 2% CHG in 70% isopropyl alcohol (Opakjel 2–70, Istanbul, Turkey), and was allowed to dry before insertion.

Short term non-tunneled CVC sizes were based on patient weight and age. We used 4 Fr double lumen or 5.5 Fr triple lumen or 7 Fr triple lumen catheters (Alifatic polyuretane catheter, Plastimed, Seldiflex, 5 Fr – 2 Lumen / 5,5 Fr – 3 Lumen / 7 Fr – 3 Lumen, Le Plessis Bouchard, France). Antiseptic- or antibiotic-impregnated catheters were not used in any of the patients. Dressing were changed 24 hours after catheter insertion (Day 1) then every 7 days according to standard practice in our PICU. Leaking, soiled, loosened and damp dressing were changed immediately. During dressing changes, the catheter insertion site was cleaned using sterile gauze and a 2% CHG-alcohol preparation.

Patients were followed until 48 hours after PICU discharge. Removal of catheters were performed if there was no further need for catheterization, in the event that the patient had infection-related findings given that any source other than the catheter could not be identified, in the presence of findings associated with exit site infection, and discharge from the hospital or death.

Culture Assessment

When a patient was suspected to have CLABSI or CRBSI, two samples for blood culture were withdrawn simultaneously from the catheter and a peripheric vein. In the presence of recurring fever peaks, samples for blood culture were obtained in at least two separate occasions within 24 hours. If there was growth in the blood cultures, we assessed the timing of growth signals in the catheter sample and the peripheric blood sample. In patients where the catheter was scheduled for removal, two sets of blood culture samples, one from a peripheral site and one from the catheter, were obtained immediately before removal. In addition, after the skin was cleaned with 2% CHG-alcohol to prevent contamination of the catheter tip by microorganisms on the skin, the 2-cm tip of the catheter was removed and sent to the microbiology laboratory along with the blood samples. Catheter tips were cultured using a simplified quantitative dilution technique with vortex. The blood cultures were performed using an automated system (Bactec Dade Berhing, Dublin, Ireland), and the samples were monitored for seven days or until positive results for growth were observed. Microorganisms were identified by the VITEK® system (Biomerrieux, Marcy-l'Etoile, France) using identification and antibiotic susceptibility test.

Data Collection

The following patient data were collected: demographics, Pediatric Risk of Mortlitity III (PRISM III) score, % Predicted Death Rate (%PDR), primary reason for PICU admission, presence of comorbidity and/or

immunosuppression, need for mechanical ventilation (MV), steroid use, hemodialysis catheter use, renal replacement and/or plasmapheresis treatment, length of stay (LOS) at PICU, and survival.

The following data about catheter characteristics were collected: total duration of catheter days, time-in-place, catheter insertion time, transport out of the PICU with catheter in place, use of antimicrobial treatment at catheter insertion, catheterization site and lumen count, medications applied via the catheter (vasopressor, parenteral nutrition, blood product transfusion, heparin), number of dressing changes, number of unplanned dressing chan, and reasons for catheter removal. Finally, we also recorded infection-related data (CLABSI, CRBSI, primary BSI, catheter colonization and microbiological results) and catheter-related AEs.

Definitions and Outcome Measures

The primary outcome measure was the incidence of CLABSI, CRBSI, primary BSI and catheter colonization for CHG-impregnated dressing versus standard dressing. Microbiological results, and AEs were the secondary outcome criteria compared between CHG-impregnated dressing and standard dressing. These incidences were defined per 1000 catheter days. Catheter infections including CLABSI, CRBSI, primary BSI and catheter colonization were identified according to NHSN and IDSA criteria [4, 5].

Adverse events were classified as systemic and local reactions. Local AEs were described on a standardized form at each dressing change and at catheter removal by a nurse in charge of the patient. The form was based on a dermatitis scoring system developed by the International Contact Dermatitis Research Group [31]. Possible scores range from 0 to 3, categorized as mild (mild redness only), moderate (red and slightly thickened), and severe reaction (intense redness and swelling with coalesced large blisters or spreading reaction). Each value is illustrated by a corresponding standard picture for the purposes of visualization and standardization.

Statistical Analysis

Analyses were performed in the intent-to-treat population, which included all patients except those who withdrew their consent for study participation. Characteristics of patients, catheters and dressings are described as frequency and percentage (n, %) or median (interquartile range, IQR) for categorical and continuous variables, respectively, and were compared among treatment groups using the Pearson Chi-square or Mann-Whitney tests, respectively. Categorical variables were assessed by the Fisher's exact test when the expected values were < 5. Kaplan-Meier curves of the risks of CLABSI, CRBSI, primary BSI and catheter colonization were plotted for each treatment group. The design of this factorial study assumed that the two interventions did not interact. This assumption was confirmed by testing for a treatment interaction in the cox model. Heterogeneity of treatment effects was checked among various predefined patient subgroups. Logistic regression analysis was performed to determine the factors affecting CLABSI. Analyses were performed using SPSS (IBM Corp., IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY) and R Version 3.6 (R Foundation for Statistical Computing, Version 3.6; Vienna, Austria). P-values less than or equal to 0.05 were considered to demonstrate statistical significance.

Power Analysis

Post-hoc power analysis was performed using the PASS (NCSS Corp. Released 2011, Power Analysis Sample Size for Windows, Version 11.0, Utah, USA). Alpha significance level was taken as 5% (p = 0.05). The power analysis was calculated based on the frequency of CLABSI in the two groups including 151 patients with CHG-impregnated dressing and 156 patients with standard dressing. The frequency was 5.8% in the CHG-impregnated group and 7.6% in the standard dressing group. As a result of the power analysis calculated in line with these ratios, it was observed that the power of the study was 90%.

Results

Patients and Catheter Characteristics

From May 2018 to December 2019, a total of 373 patients (out of an eligible count of 430 patients) with non-tunneled CVCs who met the inclusion criteria were randomly assigned and allocated. Through the randomization procedure, a total of 185 patients were allocated to the CHG-impregnated dressing group and 188 patients were allocated to the standard dressing group. Among these, 34 patients from the CHG-impregnated dressing group and 32 from the standard dressing group were excluded according to exclusion criteria. A final total of 307 patients (151 in the CHG-impregnated dressing group, 156 in the standard dressing group) were available for inclusion in the intention-to-treat analysis with a total of 307 catheters and 4993 catheter days (Fig. 1). Patient and catheter characteristics are reported in **Table 1** and **Table 2**. The groups did not differ with regard to patient or CVC characteristics.

Ethical Considerations

Ethical committee approval was obtained from our local ethical committee. Clinical trial registration for this randomized controlled trial was done (NCT04794231).

Chg-impregnated Dressing Versus Standard Dressing

Overall CLABSI rate was 11.4% (35 events, 7.01 per 1000 catheter-days), CRBSI rate was 6.5% (20 events, 4.01 per 1000 catheter days), primary BSI rate was 4.9% (15 events, 3.00 per 1000 catheter days), and catheter colonization rate was 9.4% (29 events, 5.81 per 1000 catheter-days) (**Table 3**).

The comparison of the CHG-impregnated dressing group and the standard dressing group in terms of CLABSI, CRBSI, primary BSI and catheter colonization are detailed in **Table 3**. The CLABSI rates were 6.36 per 1000 catheter days in the CHG-impregnated dressing group and 7.59 per 1000 catheter days in the standard dressing group. The CLABSI incidence was not different between groups (HR: 0.930; 95% CI: 0.459–1.776; P = 0.767) (Fig. 2A).

The CRBSI incidences were 3.82 per 1000 catheter days in the CHG-impregnated dressing group and 4.18 per 1000 catheter days in the standard dressing group. Primary BSI rates were 2.54 per 1000 catheter days in CHG-impregnated group and 3.42 per 1000 catheter days in the standard dressing group. There was no statistically significant difference in CRBSI and primary BSI rates between the CHG-impregnated dressing

and the standard dressing groups (HR: 0.989; 95% CI: 0.405–2.415; P = 0.981 and HR: 0.799; 95% CI: 0.282–2.261; P = 0.672, respectively) (Fig. 2B and 2C).

The rate of catheter colonization was 5.9% (9 events, 3.82 per 1000 catheter-days) in the CHG-impregnated dressing group and 12.8% (20 events, 7.59 per 1000 catheter-days) in the standard dressing group. Use of CHG-impregnated dressing significantly decreased the incidence of catheter colonization (HR: 0.407; 95% CI: 0.171–0.965; P = 0.041) (Fig. 2D).

Distribution of Microorganisms in CHG-impregnated Dressing versus Standard Dressing

The distribution of microorganisms causing CLABSI and catheter colonization are depicted in **Table 4**. There were no differences between the CHG-impregnated dressing group and the standard dressing group in terms of the distribution of microorganisms causing CLABSI or catheter colonization.

When evaluated in terms of time-in-place, there was no difference between the early (< 10 days) and late periods (> 10 days) of catheterization with respect to the microorganisms causing colonization (**Table 5**). In both groups and both time periods (early and late), the most frequent microorganisms isolated in cases with CLABSI or catheter colonization were gram positive, with the majority being coagulase-negative staphylococci.

Adverse events

The distribution of AEs with respect to groups are given in **Table 6**. No systemic adverse reactions were observed in the study groups. Severe local AEs leading to permanent removal of dressing did not occur. In the CHG-impregnated dressing group, 11 local AEs (7.2 per 100 catheters) occurred, while in the standard dressing group, 7 local AEs (4.4 per 100 catheters) had occurred. The frequency of local AEs were similar in both study groups (P = 0.346).

Predictors of Increased Risk of CLABSI

We performed univariate and multivariate logistic regression analysis to assess factors that were associated with CLABSI development (**Table 7**). In logistic regression analysis, higher PRISM III score and PDR (%) at PICU admission, longer catheter time-in-place, presence of comorbidity, use of vasopressors, transfusion of blood products, and the presence of greater than 50% proportion of unplanned dressing change were found to increase the likelihood of CLABSI.

Multivariable logistic regression analysis was conducted by creating a model with significant factors identified in univariate analysis. The analysis revealed that longer catheter time-in-place (adjusted HR: 1.02; 95% CI: 1.00-1.04; P = 0.012) and blood product transfusion (HR: 3.60; 95% CI: 1.43–9.02; P = 0.006) were independently associated with CLABSI development.

Discussion

This single-blinded RCT was conducted to compare the use of CHG-impregnated dressing against standard dressing in critically ill children admitted to the PICU with regard to the prevention of CLABSI and catheter colonization. Our study showed that there were no significant differences in the incidence of CLABSI, CRBSI and primary BSI. However, CHG- impregnated dressing was found to significantly reduce the frequency of catheter colonization.

In our study, overall CLABSI frequency was found to be 7.01 per 1000 catheter days. Based on literature reviews, the incidence of CLABSI varies greatly between studies. Age, catheter type, insertion site, indwelling time, underlying disease and the development level of the country have been shown to affect CLABSI frequency which ranges from 0.20 to 17.6 per 1000 catheter days [7, 10]. The International Nosocomial Infection Control Consortium (INICC) showed that CLABSI incidence in the PICUs of lower-middle-income countries (12.2 events per 1000 catheter-days) was significantly higher compared to upper-middle-income countries (5.5 events per 1000 catheter days) [32]. The NHSN reported that CRBSI rates were 1.0–1.4 per 1000 catheter days in the adult ICUs of developed countries; whereas, in a survey conducted by INICC, the results of 36 developing countries demonstrated that CRBSI incidence was 6.8% per 1000 catheter days [33, 34]. It has been well-established that CLABSI incidence is usually higher in the pediatric population compared to the adult population [34].

The majority of studies evaluating the efficacy of CHG-impregnated dressing on CLABSI/CRBSI frequency have been conducted in the adult population. Most of these studies have demonstrated that CHG-impregnated dressing decreases the frequency of CLABSI/CRBSI in short-term non-tunneled CVCs [18–20, 22, 23, 35–37]. Timsit et al. conducted two remarkable prospective RCTs on this topic. The first study [18] showed that CHG-sponge dressings decreased CRBSI from 1.4 to 0.6 episodes per 1000 catheter-days. The second study [20] evaluated 1879 patients in which CHG-impregnated dressings achieved a decrease in CRBSI from 1.3 to 0.5 episodes per 1000 catheter-days. However, the RCT by Arvaniti et al., conducted in 2012 with the inclusion of 306 patients, did not find a reduction in CRBSI frequency with the use of CHG-impregnated dressing [21]. There are two extensive meta-analyses which have drawn most of their data from recent RCT studies focused on the effects of CHG-impregnated dressing on CLABSI/CRBSI frequency in adults. In both the 2014 study which included 9 RCTs (6067 patients), and the 2019 study which included 12 RCTs (6028 patients), it was concluded that CHG-impregnated dressing significantly reduced CRBSI frequency (relative risk: 0.57 and 0.60, respectively) [19, 24]. As a result of this extensive research, the CDC recommended the use of CHG-impregnated dressing for adults in 2017 [29].

In contrast to the wealth of data in adults, there are few studies focused on this topic in the pediatric age group [25–28, 38]. Garland et al., in their study including 705 patients managed in the neonatal intensive care unit, reported that the use of CHG-impregnated disks on the insertion site of non-tunneled catheters did not reduce CRBSI or primary BSI frequency [26]. Similar outcomes were observed by Levy et al. in 145 cardiac PICU patients and by Duzkaya et al. in 100 PICU patients [25, 28]. A recent study involving 192 pediatric patients with non-tunneled CVC reported a CLABSI incidence of 7.9 per 1000 catheter days and found no benefit with the use of CHG-impregnated dressing [38], similar to our findings. It has also been shown that CHG-impregnated dressing was not effective in reducing catheter infection frequency in tunneled long-term catheters [27].

The most common mechanism of catheter infection is considered to be the migration of microorganisms through the cutaneous catheter tract, leading to catheter colonization and subsequent catheter infection [6]. Therefore, prevention of colonization is thought to be the foremost logical step to prevent CLABSI [18]. The use of CHG-impregnated dressing has been proved to reduce catheter colonization in the adult population [18–20, 22, 23, 35–37]. In these studies, the effect of CHG-impregnated dressing on colonization frequency and CLABSI/CRBSI frequency have shown to be strongly correlated. Both of the two extensive meta-analyses have demonstrated a reduction in catheter colonization with the use of CHG-impregnated dressing (relative risk: 0.46 and 0.51, respectively) [19, 24]. The effect of CHG-impregnated dressing on catheter colonization is controversial in the pediatric age group; moreover, there is often no correlation between colonization and CLABSI frequency. The present study found that the frequency of catheter colonization was significantly reduced with CHG-impregnated dressing, similar to the studies by Gerland et al. (in neonatal intensive care) and Levy et al. (in cardiac PICU) [25, 26]. However, it is evident that the reduction in colonization frequency did not translate into positive effects in terms of CLABSI and CRBSI frequency. The studies by Duzkaya et al. and Jitrungruengnij et al. did not find any significant decrease in neither CLABSI/CRBSI frequency nor catheter colonization in their respective study groups.[28, 38] There are some explanations as to why CHG-impregnated dressing was not effective in reducing the frequency of CLABSI despite its colonization-reducing effect shown in this study. One such explanation is that the limitations in the definitions of colonization and CLABSI may lead to misdiagnosis of both conditions, which is a potential source of result heterogeneity [19]. Secondly, the risk of CRBSI for a given level of colonization may differ with regard to the coating material of different catheters. Thirdly, the presence of organisms causing colonization may have different cut-off values in order to be defined as CLABSI [39].

CHG is highly effective against gram-positive bacteria, especially those of the skin flora, and it is also moderately active against gram-negative bacteria. Therefore, it is frequently used for skin and mucosal antisepsis to reduce the frequency of hospital infections, particularly CLABSI, caused by colonization of methicillin- and vancomycin-resistant gram-positive microorganisms [40]. Our results show that the majority of cases with CLABSI and colonization were due to gram-positive bacteria, with coagulase-negative staphylococci identified as the leading cause. Similarly, gram-positive cocci are often reported as the most common agents in large cohort studies evaluating CLABSI and catheter colonization [41, 42]. In the meta-analysis by Safdar et al., which assessed the efficacy of CHG-impregnated dressing, *Staphylococcus epidermidis* was found to be the most common organism isolated, followed by *Staphylococcus aureus* and other gram-positive cocci [24]. However, the RCTs by Timsit et al. and Levy et al. have shown that gram-negative microorganisms were common in CLABSI etiology, while coagulase-negative staphylococci were common in catheter colonization. These studies also reported that the CHG-impregnated dressing did not demonstrate any significant difference from standard dressing in terms of microorganisms causing CLABSI or catheter colonization, which support our findings [18, 25].

In early CVC infections, the literature reports an increased frequency of gram-positive microorganisms, and the most widely accepted form of infection mechanism is the migration of microorganisms through the cutaneous catheter tract (extraluminal route) [6, 39]. Increased CVC time-in-place is suggested to increase the likelihood of the intraluminal route, thereby enabling a mechanism of colonization that increases the

frequency of infection with gram-negative microorganisms [39]. Based on this data, we performed comparisons with respect to CVC time-in-place. The results revealed that there was no difference between early and late catheter colonization, both of which were most commonly caused by gram-positive microorganisms. Taken together with the literature, we can feasibly suggest that the catheter maintenance procedures employed throughout our study were successful in preventing intraluminal infections with gram-negative organisms which are relatively more dangerous.

None of the studies in the literature, either in adults or children, have reported systemic AEs with CHG use, similar to our findings [18–21, 24–26, 28, 38]. Contact dermatitis in relation to CHG-impregnated dressing was the most common local AE reported in prior studies. None of the patients in the present study were found to have severe contact dermatitis. Even though mild to moderate local AE frequency was higher in the CHG-impregnated group, there was no statistical difference between the groups (events/catheters: 7.2% vs. 4.4%). Timsit et al. found that the incidence of severe contact dermatitis requiring catheter removal was higher in the CHG-impregnated dressing group compared to the standard dressing group [20]. Garland et al. reported the overall frequency of contact dermatitis to be 5.7% in their neonatal group, but found that preterm infants weighing less than 1000 grams had a frequency of 15% [26]. In another study which included PICU patients, local AE frequency was reported to be 6.8% and CHG-impregnated dressing was not found to increase AE frequency [38]. Therefore, it appears that, apart from very low-weight preterm infants, CHG-impregnated dressing can be used safely in the neonatal and pediatric age groups.

There are multiple risk factors that can be associated with CLABSI, dressing is one of the contributing factors, but it might not be the most important factor. Today, it is well-known that these factors may be relevant to the procedures, from insertion to removal of the central line, and include the type of catheter, insertion site, hand hygiene and precautions taken to reduce contamination (such as the maximal barrier approach), or they may as well be associated with patient characteristics [15, 16]. We attempted to conduct logistic regression analysis to establish the role of these factors along with treatment-dependent parameters to assess independent risk factors for CLABSI and found that longer catheter time-in-place and the transfusion of blood products were the only two variables that were associated with CLABSI risk. A previous study also demonstrated that central access duration (time-in-place), administration of parenteral nutrition and blood transfusion were risk factors for CLABSI among children in the PICU [22]. Duration of central access is recognized as a consistent risk factor for CLABSIs, and national infection prevention strategies have emphasized early removal of CVCs. It is important to note that transfusion of blood products has been identified as a risk factor for CLABSI in other previous studies [43, 44]. Potential mechanisms proposed to have a role in the development of increased risk with blood product transfusion are various, and include the possibility of immune suppression, increased frequency of CVC access and its use, and promotion of pathogen proliferation. Therefore, children with these modifiable risk factors may be identified as candidates that will require adjunctive interventions for CLABSI prevention. Although we are not able to determine the probability of CLABSI for an individual patient, we have highlighted a group of risk factors that can help identify patients who are at higher risk for CLABSI. It was noteworthy that a great number of catheter characteristics, such as insertion site, number of lumens in the catheter and presence of catheter exchange or unplanned dressing changes, were not associated with CLABSI likelihood.

Our study has several limitations. First, double-blinding was not feasible, because CHG-impregnated dressing was easily distinguishable from standard dressing due to the presence of gel. However, catheter cultures were conducted in a blinded fashion. Most importantly, independent assessors conducted a blind review of all suspected catheter infections. Another important strength is associated with the exclusion of patients who were discharged from the PICU to another ward; thus, all catheters included in the study had undergone culture analysis. However, despite reaching the highest number of patients and catheter days among PICU studies, this was a single-center study, and adult studies on this topic have frequently included greater patient numbers. Another limitation of the study pertains to the use of CHG-alcohol solutions during skin antisepsis for catheter insertion –which was a routine procedure in our center– but this approach may have reduced the frequency of infection and colonization in the standard dressing group; thereby possibly reducing the likelihood of finding statistically significant difference between the two groups. By design, this study was focused on infections related to the use of short-term non-tunneled CVC, and did not include arterial catheters or hemodialysis catheters, and therefore, cannot provide data in this context. Finally, as per the standardization of catheter care (the catheter care bundle), planned dressing change was performed every seven days in the present study. Future studies comparing planned dressing changes at intervals of 3 or 7 days may enable better analysis of infection characteristics with the use of CHG-impregnated dressing versus standard dressing.

Conclusions

The use of CHG-impregnated dressing, when compared to standard dressing, does not significantly decrease CLABSI rate in critically ill pediatric patients, but it is effective in reducing catheter colonization. In both groups and both time periods (early and late in terms of time-in-place), the most frequent microorganism was identified as coagulase-negative staphylococci, and there were no differences in terms of the distribution of microorganisms. There were no cases that developed systemic AEs or severe local AEs, while the frequency of mild to moderate local AEs were similar in both types of catheter dressing. Longer catheter time in place and the use of the blood products were identified as independent risk factors for CLABSI.

Declarations

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Author Contributions

DM: study design, statistical analysis, drafted the manuscript, and is responsible for the overall content. KZ: Study design, quality assessment, contributed to the writing of the manuscript and revised the manuscript for important intellectual content. YP: Study design, quality assessment. YS: Data extraction and quality assessment. YMN: Data extraction and quality assessment. TMO: microbiological results assessments, data extraction, and quality assessment. FN: Data extraction and quality assessment. BO: Data extraction and quality assessment. MCY: Study desing, data extraction and quality assessment. All authors have agreed on the final version of this manuscript.

Compliance with ethical standards

Conflict of interest

All authors declare no conflicts of interest.

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Tables

Table 1. Patient characteristics

Characteristics	All Patients (Intention-to-Treat) (n = 307)	CHG-impregnated dressing (n = 151)	Standard dressing (n = 156)	P
Age (year), median (IQR)	2.0 (0.8-7.9)	1.7 (0.7-6.8)	2.3 (0.9-8.5)	0.072
Male, n (%)	173 (56.4)	87 (57.6)	86 (55.1)	0.939
PRISM III Score, median (IQR)	18.0 (14.0-23.0)	19.0 (14.0-23.0)	18.0 (12.0-24.0)	0.603
% PDR, median (IQR)	25.8 (13.2-49.5)	25.8 (13.2-44.3)	25.8 (9.1-54.6)	0.682
Primary reason for PICU admission, n (%)				
Respiratory Disease / Failure	92 (30.0)	41 (27.2)	51 (32.7)	0.297
Trauma	52 (16.9)	25 (16.6)	27 (17.3)	0.782
Shock	40 (13.0)	22 (14.6)	18 (11.5)	0.527
Metabolic Disease	15 (4.9)	6 (4.0)	9 (5.8)	0.439
Liver Failure	6 (2.0)	3 (2.0)	3 (1.9)	1.000
Renal Failure	13 (4.2)	8 (5.3)	5 (3.2)	0.405
Poisoning	7 (2.3)	4 (2.6)	3 (1.9)	0.705
Central Nervous System Disease	51 (16.6)	26 (17.2)	25 (16.0)	0.889
Cardiac Disease	6 (2.0)	3 (2.0)	3 (1.9)	1.000
Malignancy	10 (3.3)	5 (3.3)	5 (3.2)	1.000
Post-operative	7 (2.3)	4 (2.6)	3 (1.9)	0.705
Others	8 (2.6)	4 (2.6)	4 (2.6)	1.000
Presence of comorbidity, n (%)	69 (22.5)	29 (19.2)	40 (25.6)	0.185
Presence of immunosuppression, n (%)	19 (6.2)	7 (4.6)	12 (7.7)	0.251
Use of parenteral steroid, n (%)	46 (15.0)	19 (12.6)	27 (17.3)	0.238
Mechanical ventilation, n (%)	202 (65.8)	98 (64.9)	104 (66.7)	0.673
Use of hemodialysis catheter, n (%)	60 (19.5)	28 (18.5)	32 (20.5)	0.606
Renal replacement treatment, n (%)	44 (14.3)	22 (14.6)	22 (14.1)	1.000

Plasmapheresis, n (%)	52 (16.9)	21 (13.9)	31 (19.9)	0.166
Length of PICU stay (days), median (IQR)	12.0 (8.0-22.0)	11.0 (7.0-19.0)	13.0 (8.0-27.0)	0.067
Death within PICU, n (%)	29 (9.4)	13 (8.6)	16 (10.3)	0.577

CHG: chlorhexidine gluconat, PRISM: pediatric risk of mortality, PDR: predictive death rate, PICU: pediatric intensive care unit,

IQR: interquartile range.

Table 2. Catheter and Treatment Characteristics

Characteristics	All Catheters (n = 307)	CHG-impregnated dressing (n = 151)	Standard dressing (n = 156)	P
Total catheter days (day)	4993	2359	2634	NA
Internal jugular vein	2904 (58.1)	1377 (58.4)	1527 (58.0)	NA
Femoral vein	1631 (32.7)	820 (34.8)	811 (30.8)	
Subclavian vein	458 (9.2)	162 (6.8)	296 (11.2)	
Time in place (days), median (IQR)	10.0 (7.0-18.0)	10.0 (6.75-15.25)	9.0 (7.0-20.5)	0.709
Catheter insertion time (days), median (IQR)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.000
Transport out of the PICU with catheter in place, n (%)				
No	207 (67.4)	103 (68.2)	104 (66.7)	0.819
Once	63 (20.5)	29 (19.2)	34 (21.8)	
More than once	37 (12.1)	19 (12.6)	18 (11.5)	
Antimicrobials at catheter insertion, n (%)	272 (88.6)	140 (92.7)	132 (84.6)	0.114
Catheterization site, n (%)				
Internal jugular vein	193 (62.9)	89 (58.9)	104 (66.7)	0.218
Femoral vein	91 (29.6)	52 (34.4)	39 (25.0)	
Subclavian vein	23 (7.5)	10 (6.7)	13 (8.3)	
No. of lumens, n (%)				
2	151 (49.2)	76 (50.3)	75 (48.1)	0.655
3	156 (50.8)	75 (49.7)	81 (51.9)	
Vasopressor use	87 (28.3)	44 (29.1)	43 (27.6)	0.900
Parenteral nutrition use	53 (17.3)	22 (14.6)	31 (19.9)	0.230
Heparin use	182 (59.3)	92 (60.9)	90 (57.7)	0.910

Blood product transfusion	159 (51.8)	82 (54.3)	77 (49.3)	0.502
No. of dressing changes per catheter, median (IQR)	3.0 (2.0-5.0)	3.0 (2.0-5.0)	3.0 (2.0-5.0)	1.000
No. of unplanned dressing changes per catheter, median (IQR)	1.0 (0.0-2.0)	1.0 (0.0-2.0)	1.0 (0.0-2.0)	1.000
Percentage of unplanned dressing change/total dressing change				
< 50%	228 (74.3)	113 (74.8)	115 (73.7)	0.796
≥ 50%	79 (25.7)	38 (25.2)	41 (26.3)	
Reasons for CVC removal, n (%)				
No longer indicated	217 (70.7)	107 (70.8)	110 (70.5)	0.973
Suspected infection[a]	51 (16.6)	25 (16.6)	26 (16.7)	
Malfunction	11 (3.6)	6 (4.0)	5 (3.2)	
Death	28 (9.1)	13 (8.6)	15 (9.6)	

[a]Suspected infection: CLABSI, NA: non-aplicable.

Table 3. Comparisons of CLABSI, CRBSI, primary BSI and catheter colonization rates in the intention-to-treat analysis group

Variable	All catheters (n = 307) 4993 catheter days	CHG-impregnated dressing (n = 151) 2359 catheter days	Standard dressing (n = 156) 2634 catheter days	HR (95% CI)	P
CLABSI rate, n (%)	35 (11.4)	15 (9.9)	20 (12.8)		
Incidence density of CLABSI (95% CI)	7.01	6.36	7.59	0.930 (0.459-1.776)	0.767
CRBSI rate, n (%)	20 (6.5)	9 (5.9)	11 (7.0)		
Incidence density of CRBSI (95% CI)	4.01	3.82	4.18	0.989 (0.405-2.415)	0.981
Primary BSI rate, n (%)	15 (4.9)	6 (3.9)	9 (5.7)		
Incidence density of BSI (95% CI)	3.00	2.54	3.42	0.799 (0.282-2.261)	0.672
Catheter colonization rate, n (%)	29 (9.4)	9 (5.9)	20 (12.8)		
Incidence density of catheter colonization (95% CI)	5.81	3.82	7.59	0.407 (0.171-0.965)	0.041

CLABSI: central line associated bloodstream infection, CRBSI: catheter related bloodstream infection, BSI: bloodstream infection, CHG: chlorhexidine gluconate, HR: hazard ratio, CI: confidence interval.

Incidence density values correspond to episodes per 1000 catheter-days.

Table 4. Distribution of microorganisms causing CLABSI and catheter colonization between study groups

Variable, n (%)	All Catheters (n = 307)	CHG-impregnated dressing (n = 151)	Standard dressing (n = 156)	P
CLABSI	35	15	20	
[a]Gram positive	29 (82.9)	12 (80.0)	17 (85.0)	1.000
Staphylococcus aureus	8 (22.9)	4 (26.7)	4 (20.0)	0.700
Coagulase-negative *staphylococcus*	23 (65.7)	9 (60.0)	14 (70.0)	0.721
Other gram-positive coccus	1 (2.9)	0 (0.0)	1 (5.0)	1.000
[a]Gram negative	9 (25.7)	4 (26.7)	5 (25.0)	1.000
Pseudomonas spp.	2 (5.7)	1 (6.7)	1 (5.0)	1.000
Enterobacter spp.	2 (5.7)	2 (13.3)	0 (0.0)	0.176
Escherichia coli	2 (5.7)	1 (6.7)	1 (5.0)	1.000
Acinetobacter baumannii	1 (2.9)	1 (6.7)	0 (0.0)	1.000
Klebsiella pneumoniae	1 (2.9)	0 (0.0)	1 (5.0)	1.000
Serratia marcescens	2 (5.7)	0 (0.0)	2 (10.0)	0.496
Fungi	2 (5.7)	0 (0.0)	2 (10.0)	0.496
Candida spp.	2 (5.7)	0 (0.0)	2 (10.0)	0.496
Catheter colonization	29	9	20	
[a]Gram positive	26 (89.7)	7 (77.8)	19 (95.0)	0.220
Staphylococcus aureus	4 (13.8)	1 (11.1)	3 (15.0)	1.000
Coagulase-negative *staphylococcus*	19 (65.5)	5 (55.6)	14 (70.0)	0.675
Other gram-positive coccus	6 (20.7)	2 (22.2)	4 (20.0)	1.000
Gram negative	4 (13.8)	2 (22.2)	2 (10.0)	0.568
Pseudomonas spp.	1 (3.4)	1 (11.1)	0 (0.0)	1.000
Enterobacter spp.	3 (10.3)	1 (11.1)	2 (10.0)	1.000

CLABSI: central line associated bloodstream infection, CHG: chlorhexidine gluconate

[a]: More than 1 microorganism recovered in some cases.

Table 5. Distribution of microorganisms by catheter days

	All Catheters (n = 307)			CHG-impregnated (n = 151)			Standard dressing (n = 156)		
Catheter days	≥10 days	<10 days	P	≥10 days	<10 days	P	≥10 days	<10 days	P
Variable									
CLABSI	29	6		13	2		16	4	
[a]Gram positive	23 (65.7)	6 (100.0)	0.561	10 (76.9)	2 (100.0)	1.000	13 (81.3)	4 (100.0)	1.000
[a]Gram negative	8 (27.6)	1 (16.7)	1.000	4 (30.8)	0 (0.0)	1.000	4 (25.0)	1 (25.0)	1.000
Fungi	2 (6.9)	0 (0.0)	1.000	0 (0.0)	0 (0.0)	NA	2 (12.5)	0 (0.0)	1.000
Catheter Colonization									
[a]Gram positive	16 (100.0)	10 (76.9)	0.078	5 (100.0)	2 (50.0)	0.167	11 (100.0)	8 (88.9)	0.450
Gram negative	1 (6.3)	3 (23.1)	0.299	0 (0.0)	2 (50.0)	0.167	1 (9.1)	1 (11.1)	1.000

CLABSI: central line associated bloodstream infection, CHG: chlorhexidine gluconate NA: not-applicable.

[a]: More than 1 microorganism recovered in some cases.

Table 6. Local adverse events

Variable	All catheters (n = 307)	CHG-impregnated dressing (n = 151)	Standard dressing (n = 156)	P
Total Local adverse event, n (%)	18 (5.8)	11 (7.2)	7 (4.4)	0.346
Mild, n (%)	14 (4.5)	8 (5.2)	6 (3.8)	0.593
Moderate, n (%)	4 (1.3)	3 (1.9)	1 (0.6)	0.317

CHG: chlorhexidine gluconate

Table 7. Univariate and multivariate logistic regression analyses for CLABSI

	Unadjusted		Adjusted	
Variable	HR (95% CI)	P	HR (95% CI)	P
Age, years	1.035 (0.971-1.103)	0.288		
< 1 year	1.0	-		
≥ 1 year	1.339 (0.522-3.439)	0.544		
PRISM III	1.050 (1.014-1.087)	0.005	1.110 (0.956-1.290)	0.171
% PDR	1.014 (1.002-1.025)	0.019	0.970 (0.924-1.019)	0.224
Time-in-place (days)	1.026 (1.011-1.042)	0.001	1.024 (1.005-1.043)	0.012
Gender				
Male	1.0	-		
Female	1.386 (0.686-2.800)	0.363		
Main Reason for PICU admission				
Liver failure	1.0	-		
Poisoning	0.333 (0.022-5.027)	0.427		
Post-operative	1.364 (0.419-4.437)	0.427		
Cardiac Disease	NA	NA		
Others	1.453 (0.433-4.878)	0.311		
Malignancy	NA	NA		
Renal Failure	0.167 (0.012-2.368)	0.186		
Metabolic Disease	0.667 (0.087-5.127)	0.697		
Shock	0.412 (0.063-2.705)	0.356		
Central Nervous System Disease	0.167 (0.023-1.207)	0.076		
Trauma	0.160 (0.022-1.158)	0.070		
Respiratory Disease / Failure	0.233 (0.038-1.434)	0.116		
Presence of comorbidity				
No	1.0	-	1.0	-
Yes	2.489 (1.195-5.184)	0.015	1.793 (0.797-4.035)	0.158
Presence of immunosuppression				
No	1.0	-		
Yes	2.314 (0.723-7.410)	0.158		

Mechanical Ventilation				
No	1.0	-		
Yes	2.276 (0.960-5.394)	0.062		
Catheter insertion site				
Subclavian vein	1.0	-		
Femoral vein	0.542 (0.168-1.745)	0.305		
Internal Jugular vein	0.586 (0.166-2.073)	0.407		
No of catheter lumens				
2	1.0	-		
3	1.120 (0.555-2.262)	0.751		
Renal replacement therapy				
No	1.0	-		
Yes	2.041 (0.861-4.838)	0.105		
Plasmapheresis				
No	1.0	-		
Yes	1.616 (0.689-3.789)	0.269		
Presence of hemodialysis catheter				
No	1.0	-		
Yes	1.581 (0.699-3.578)	0.271		
Transport with catheter				
No	1.0	-		
Yes	0.862 (0.397-1.871)	0.708		
Unplanned dressing change (%)				
< 50	1.0	-	1.0	-
≥ 50	2.835 (1.140-7.054)	0.025	2.079 (0.768-5.623)	0.150
Parenteral steroid use				
No	1.0	-		
Yes	0.960 (0.353-2.615)	0.937		
Heparin use				
No	1.0	-		

Yes	0.856 (0.423-1.734)	0.667		
Vasopressor use				
No	1.0	-	1.0	-
Yes	2.887 (1.411-5.906)	0.004	1.826 (0.786-4.244)	0.162
Blood product transfusion				
No	1.0	-	1.0	-
Yes	3.280 (1.484-7.249)	0.003	3.601 (1.437-9.023)	0.006
Antimicrobials at catheter insertion				
No	1.0	-		
Yes	1.041 (0.382-2.836)	0.937		

PRISM: pediatric risk of mortality score, PDR: predictive death rate, HR: hazard ratio, CI: confidence interval, NA: not-applicable.

Figures

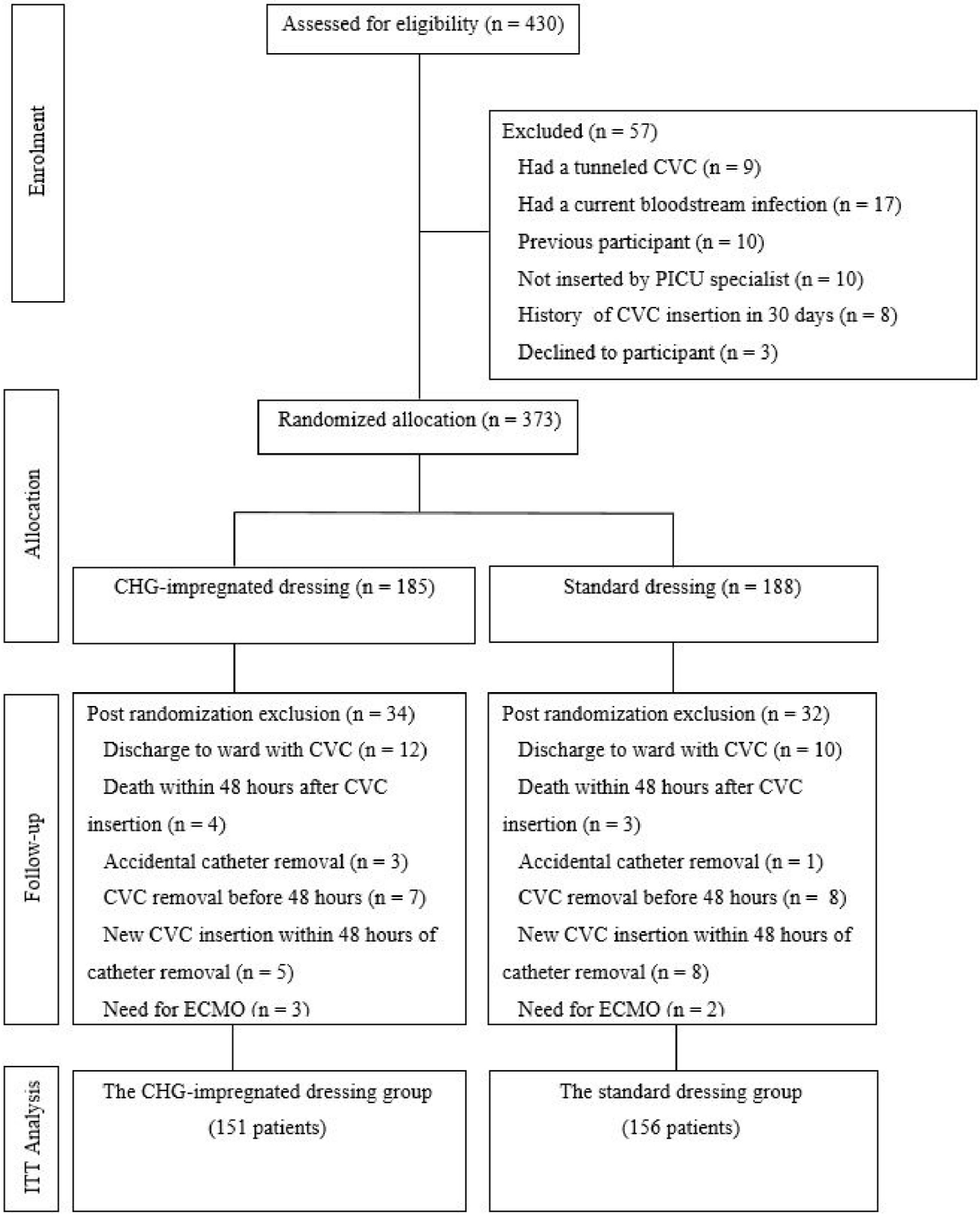

Figure 1

Flow chart of the study. CVC: central venous catheter, PICU: pediatric intensive care unit, CHG: chlorhexidine gluconat, ECMO: extra corporeal membrane oxygenation, ITT: intention-to-treat.

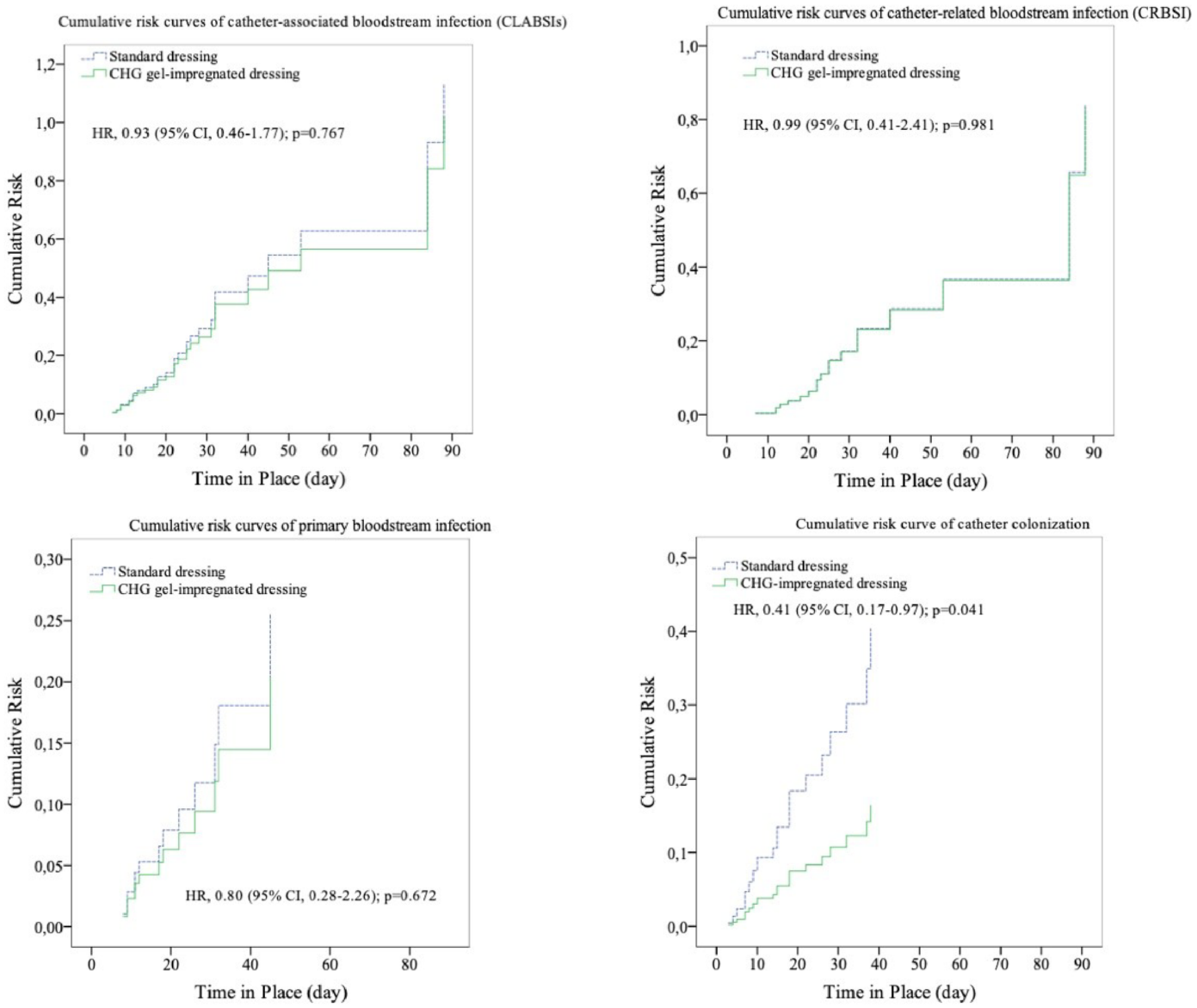

Figure 2

Cumulative risk of (A) central-line associated bloodstream infection (CLABSI), (B) catheter-related infection (CRBI), (C) primary bloodstream infection (BSI), and (D) catheter colonization with chlorhexidine (CHG)-impregnated gel dressing versus standard dressing. CI: confidence interval; HR: hazard ratio.