APPENDIX 1: Search Strategy and Evidence Summary Supporting the 2017 Updated Recommendations on the Use of Chlorhexidine-Impregnated Dressings for Prevention of Intravascular Catheter-Related Infections

Centers for Disease Control and Prevention

National Center for Zoonotic and Emerging Infectious Diseases

Division of Healthcare Quality Promotion

Table of Contents

Abbreviations

Abbreviation	Definition
BSI	Bloodstream infection
CABSI	Catheter-associated bloodstream infection
CFU	Colony-forming unit
C-I	Chlorhexidine-impregnated
CHG	Chlorhexidine gluconate
CI	95% confidence interval
CoNS	Coagulase-negative *Staphylococcus*
CRBSI	Catheter-related bloodstream infection
CR sepsis	Catheter-related sepsis
CVC	Central venous catheter
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HR	Hazard ratio
hr	hour
ICDRG	International Contact Dermatitis Research Group
ICU	Intensive care unit
IQR	Interquartile range
ITT	Intention to treat analysis
MBC	Minimum bactericidal concentration
NICU	Neonatal intensive care unit
NR	Not reported
NS	Not statistically significant
PCICU	Pediatric cardiac intensive care unit
PICU	Pediatric intensive care unit
PI	Povidone iodine
RCT	Randomized controlled trial
RR	Relative risk

1.0 Search Strategies and Results

Appendix Table 1: Cochrane Library Search Results (January 1, 2010–March 6, 2017)

Search	Search Terms	Results
1	Chlorhexidine and catheter	38
2	Skin antiseptic and catheter	35
3	1 or 2	56

Appendix Table 2: MEDLINE Systematic Reviews Search Results (January 1, 2010–March 6, 2017)

Search	Search Terms	Results
1	exp Chlorhexidine	7,123
2	exp Anti–infective agents, Local/ad, ae, tu, th [administration & dosage, adverse effects, therapeutic use, therapy]	42,449
3	exp catheterization, central venous/	13,301
4	exp catheters, indwelling/	17,225
5	1 or 2	45,150
6	3 or 4	27,264
7	5 and 6	466
8	limit 7 to (English language and humans)	404
9	limit 8 to (meta analysis or "review")	66
10	Limit 9 to yr=”2010-Current”	21

Appendix Table 3: MEDLINE Primary Studies Search Results (January 1, 2010–March 6, 2017)

Search	Search Terms	Results
1	exp Chlorhexidine	7,123
2	exp Anti–infective agents, Local/ad, ae, tu, th [administration & dosage, adverse effects, therapeutic use, therapy]	42,449
3	exp catheterization, central venous/	13,301
4	exp catheters, indwelling/	17,225
5	1 or 2	45,150
6	3 or 4	27,264
7	5 and 6	466
8	limit 7 to (English language and humans)	404
9	limit 8 to (clinical trial, all or clinical trial or comparative study or controlled clinical trial or randomized controlled trial)	152
10	Limit 9 yr=”2010-Current”	42

2.0 Summary of Evidence

Appendix Table 4. Strength of Evidence for Using Chlorhexidine-Impregnated (C-I) Gel Dressings or C-I Sponge under Standard Dressings vs. Using Highly Adhesive Dressing or Standard Dressing Alone among Patients Aged ≥ 18 Years with Short-term, Non-tunneled Central Venous Catheters [a].

Outcome	Findings	Quantity and Type of Evidence (Sample Size)	GRADE of Evidence for Outcome (Limitations of the Evidence)
CRBSI [b]	• 3 RCTs found that C-I dressings decreased rates of CRBSI. o 1 multicenter RCT[1] (N=1,879) of ICU patients with CVCs, arterial catheters, or both compared transparent C-I gel dressing with either highly adhesive transparent dressing alone or standard, breathable, hypoallergenic dressing alone; HR for CVCs and arterial catheters combined: 0.40 (CI: 0.19–0.87); p=0.02; HR for CVC only: 0.30 (CI: 0.10–0.92); p=0.04. The study found no difference in CRBSI rates by dressing type among patients with arterial catheters: HR: 0.51 (CI: 0.15–1.74); p=0.28. Patients in these 3 analyses may have concurrently used multiple CVCs, multiple arterial catheters, or both. o 1 multicenter RCT[2] (N=1,636) of ICU patients with CVCs, arterial catheters, or both, compared C-I sponge under semipermeable, transparent dressing with semipermeable, transparent dressing alone; HR: 0.24 (CI: 0.09–0.65); p<0.01. This study did not stratify results by catheter type. o 1 single-center RCT[3] (N=601) of hematology-oncology unit patients with chlorhexidine and silver sulfadiazine-impregnated CVC compared C-I sponge under standard, sterile, transparent wound dressing with standard, sterile, transparent wound dressing alone; RR: 0.54 (CI: 0.31–0.94); p=0.02. • 1 multicenter RCT[4] (N=306) of ICU patients with CVCs compared C-I sponge under transparent, semipermeable, polyurethane, occlusive dressing with transparent, semipermeable, polyurethane, occlusive dressing alone; found no difference in CRBSI rates by dressing type: HR: 1.65 (CI: 0.27–10.01); p=0.59.	4 RCTs[1-4] (N=4,422)	High (None)

a The overall strength of evidence for this comparison is Moderate. The overall strength of evidence for a comparison is determined by the lowest GRADE of Evidence for a Critical.

b A critical outcome

Outcome	Findings	Quantity and Type of Evidence (Sample Size)	GRADE of Evidence for Outcome (Limitations of the Evidence)
CRI[b]	• 2 large multicenter RCTs in ICUs found that use of C-I dressings decreased rates of CRI. o 1 multicenter RCT[1] (N=1,879) of ICU patients with CVCs, arterial catheters, or both compared transparent C-I gel dressing with highly adhesive transparent dressing alone or standard, breathable, hypoallergenic dressing alone; HR (arterial catheters and CVCs): 0.33 (CI: 0.17–0.62); p< 0.01; HR (for CVCs): 0.27 (CI: 0.11–0.66); p=<0.01. The study found no difference in CRI rates by dressing type among patients with arterial catheters: HR: 0.39 (CI: 0.15–1.03); p=0.06. Patients in these 3 analyses may have concurrently used multiple CVCs, multiple arterial catheters, or both. o 1 multicenter RCT[2] (N=1,636) of ICU patients with CVCs, arterial catheters, or both, compared C-I sponge under semipermeable, transparent dressing with semipermeable, transparent dressing alone; HR: 0.39 (0.16–0.93); p=0.03. This study did not stratify results by catheter type. • 2 smaller RCTs found no difference in CRI rates by dressing type. o 1 multicenter RCT[4] (N=306) of ICU patients with CVCs compared C-I sponge under transparent, semipermeable, polyurethane, occlusive dressing with transparent, semipermeable, polyurethane, occlusive dressing alone; HR: 0.65 (CI: 0.23–1.85); p=0.42. o 1 single-center RCT[5] (N=32) of ICU patients with CVCs compared C-I sponge under occlusive dressing with occlusive dressing alone; incidence (per catheter): 1/17 vs. 0/16; p=NS.	4 RCTs[1,2,4,5] (N=3,853)	Moderate (Imprecise[c])
Product-related adverse events	• 2 RCTs[1,2] of ICU patients with CVCs, arterial catheters, or both, found no systemic adverse reactions to chlorhexidine. • 1 multicenter RCT[1] (N=1,879) of ICU patients with CVCs, arterial catheters, or both, compared transparent C-I gel dressing with highly adhesive transparent dressing or standard, breathable, hypoallergenic dressing; incidence (per patient) of severe contact dermatitis: 22/938 (2.3%) vs. 5/941 (0.5%); p<0.01. Rate of abnormal ICDRG score: 2.3% vs. 1%; p<0.01 • 1 multicenter RCT[2] (N=1,525) of ICU patients with CVCs, arterial catheters, or both compared C-I sponge under semipermeable, transparent dressing with semipermeable, transparent dressing alone. Severe contact dermatitis occurred in 8 patients (10.4/patient or 5.3/1000 catheters) that required permanent removal of the C-I dressing. (Severe contact dermatitis in patients with standard dressings not reported.) Rate of abnormal ICDRG score (events/catheter): 100/6,720 (1.49%) vs. 63/5,875 (1.02%); p=0.02 • 1 multicenter RCT[4] (N=306) of ICU patients with CVCs compared C-I sponge under transparent, semipermeable, polyurethane, occlusive dressing with transparent, semipermeable, polyurethane, occlusive dressing alone; suggested all patients tolerated C-I sponge well; none were excluded due to allergy to C-I sponge.	4 RCTs[1-4] (N=4,311)	Moderate (Imprecise[d])

[b] A critical outcome

[c] Inconsistent results and inconsistent outcome definitions.

[d] Low number of events.

Outcome	Findings	Quantity and Type of Evidence (Sample Size)	GRADE of Evidence for Outcome (Limitations of the Evidence)
	• 1 single-center RCT[3] (N=601) of hematology-oncology unit patients with chlorhexidine and silver sulfadiazine-impregnated triple-lumen CVC compared C-I sponge under standard, sterile, transparent wound dressing with the standard, sterile, transparent wound dressing alone; found no product-related adverse events associated with either dressing type.		
Chlorhexidine resistance	• 1 multicenter RCT[2] (N=1,525) of ICU patients with CVCs, arterial catheters, or both compared C-I sponge under semipermeable, transparent dressing with semipermeable, transparent dressing alone; found no difference by dressing type in median minimum bactericidal concentration (MBC): 4 (IQR 4–16) vs. 4 (IQR 4–8). • 1 single-center RCT[3] (N=601) of hematology-oncology unit patients in which all patients received chlorhexidine and silver sulfadiazine impregnated CVCs compared C-I sponge under standard, sterile, transparent wound dressing with standard, sterile, transparent wound dressing alone; suggested no differences in bacterial resistance by dressing type.	2 RCTs[2,3] (N=2,126)	Low (Imprecise[e])

Appendix Table 5. Strength of Evidence for Using Chlorhexidine-Impregnated (C-I) Sponges under Standard Dressings vs. Using Standard Dressings or Gauze among Patients Aged < 18 Years with Short-term, Non-tunneled Central Venous Catheters[f].

Outcome	Findings	Quantity and Type of Evidence (Sample Size)	GRADE of Evidence for Outcome (Limitations of the Evidence)
CRBSI[b]	• 1 multicenter RCT[6] (N=705) of NICU patients with tunneled and non-tunneled CVCs compared C-I sponge under transparent polyurethane dressing with transparent polyurethane dressing alone; yielded a subanalysis of neonates with percutaneous [non-tunneled] CVCs (n=620) that found no difference in the rate of CRBSI by dressing type: RR: 1.2 (CI: 0.5–2.7); p=0.65. • 1 single-center RCT[7] (N=100) of PICU patients aged 0–18 years with non-tunneled CVCs that compared C-I gel pad dressing with sterile gauze pad; suggested no statistically significant difference in the incidence of CRBSI by dressing type: 1/50 (2%) vs. 5/50 (10%); p > 0.05.	2 RCTs[6,7] (N=720)	Very Low (Indirect,[g] Imprecise[h])
CABSI[b]	• 1 single-center RCT (N=145) of pediatric and neonatal PCICU patients with non-tunneled CVCs compared C-I sponge under semipermeable dressing with semipermeable dressing alone; suggested no difference in the proportion of patients with CABSI by dressing type: 4/74 (5.4%) vs. 3/71 (4.2%); p=1.0.	1 RCT[8] (N=145)	Low (Imprecise[i])

b A critical outcome

e Low number of events; no difference between study group

f The overall strength of evidence for this comparison is Very Low. The overall strength of evidence for a comparison is determined by the lowest GRADE of Evidence for a Critical Outcome in that comparison.

g Different skin antisepsis used for each study group.

h Wide confidence interval in one study, low power in second study.

i Underpowered; only 1 study.

Outcome	Findings	Quantity and Type of Evidence (Sample Size)	GRADE of Evidence for Outcome (Limitations of the Evidence)
BSI without a source [b]	• 1 multicenter RCT (N=705) of NICU patients with tunneled and non-tunneled CVCs that compared C-I sponge under transparent polyurethane dressing with transparent polyurethane dressing alone; yielded a subanalysis in neonates with percutaneous (non-tunneled) catheters (N=662) that suggested no difference in BSI without a source by dressing type: RR: 1.1 (0.8–1.7); p=0.44.	1 RCT[6] (N=662)	Very Low (Indirect [g], Imprecise [j])
Local catheter infection [b]	• 1 single-center RCT (N=100) of PICU patients with non-tunneled CVCs that compared C-I gel pad dressing with sterile gauze pad; suggested no statistically significant difference in the incidence of local catheter infection per patient by dressing type: 1/50 (2%) vs. 2/50 (4%); p> 0.05.	1 RCT[7] (N=100)	Low (Imprecise [i])
Product-related adverse events	• 1 multicenter RCT[6] (N=705) of NICU patients with tunneled or non-tunneled CVCs that compared C-I sponge under transparent polyurethane dressing with transparent polyurethane dressing alone; reported a higher incidence (per patient) of severe contact dermatitis among patients with sponge dressings: 19/335 (5.7%) vs. 0/370. In the C-I sponge group, 15/98 (15%) of patients weighing <1,000 grams developed dermatitis, compared with 4/237 (1.5%) of patients weighing ≥1,000 grams (p<0.01). • 1 single-center RCT[8] (N=145) of pediatric and neonatal PCICU patients with non-tunneled CVC compared C-I sponge under transparent polyurethane dressing with transparent polyurethane dressing alone; suggested a higher incidence (per patient) of local redness in patients with sponge dressings: 4/74 (5.4%) vs. 1/71 (1.4%). All intervention events occurred in neonates.	2 RCTs[6,8] (N=850)	Moderate (Imprecise [g])

Appendix Table 6. Summary of Evidence for Using Chlorhexidine-Impregnated (C-I) Dressings among Patients Aged ≥ 18 Years with Short-term, Non-tunneled Central Venous Catheters (data directly extracted from studies unless otherwise noted)

Study Features	Population and Setting	Study Groups	Outcome Definitions	Results
Timsit, 2012[1] (Extracted by: Overholt) **Risk of bias score**: Low [k] **Study objective:** To evaluate whether chlorhexidine gluconate gel dressing decreased the	**N = 1,879 patients;** 4,163 catheters (1,531 patients had CVCs, 1,666 patients had arterial catheters) [Methods did not specify if patients concurrently used more than 1 type of catheter.]; 34,339 catheter days. **Inclusion criteria:** ICU patients >18 years old and expected to require intravascular catheterization for at least 48 hrs.	**Intervention:** n= 938 patients, 2,108 catheters, transparent C-I gel dressing **Control:** n= 941 patients/2055 catheters Standard, breathable, hypoallergenic dressing: n=476 patients Highly adhesive dressing: n=465 patients **Standard care for both groups:** Insertion sites: radial artery or subclavian vein unless sites carried an increased risk of noninfectious complications (including femoral site).	**Catheter-related bloodstream infection (CRBSI):** A combination of: a. 1 or more positive peripheral blood cultures sampled immediately before or within 48 hrs after catheter removal; b. A positive quantitative catheter-tip culture (using 10^3 CFU/ml threshold when vortexing technique or 100 CFU threshold via sonication technique) for the same microorganisms(same species and susceptibility pattern) or blood culture differential time to positivity of 2 hrs or more; and	**CRBSI incidence (events/patients):** • All catheter types: 9/938 (1.0%) vs. 22/941 (2.3%); HR: 0.40 (CI: 0.19–0.87); p=0.02 **CRBSI rate (events/1,000 catheter days):** • All catheter types: 0.5/1,000 vs. 1.3/1,000 • CVCs: 0.6/1,000 vs. 1.6/1,000; HR: 0.30 (CI: 0.10–0.92); p=0.04

[j] Only 1 study; wide confidence interval.

[k] Basis of score described in Table 8.

Study Features	Population and Setting	Study Groups	Outcome Definitions	Results
rate of major catheter-related infections (CR-sepsis with or without CRBSI [defined in Outcomes column]).	**Exclusion criteria:** Patients with known allergies to chlorhexidine or transparent dressings. **Setting:** 12 ICUs in 7 university hospitals and 4 general hospitals. **Location:** France **Dates:** May 2010–July 2011 **Anticipated study power:** 80% to detect a 61% reduction in the 3% CRI rate. At least 2 catheters per patient were expected so study planned to enroll 1,888 patients (>3,776 catheters). **Follow up:** 48 hrs post ICU discharge	Maximal sterile barrier precautions: used at catheter insertion Catheters: CVC, arterial, tunneled CVC, and guidewire exchange. No antibiotic impregnated catheters were used. Single, double, and triple lumen catheters were used. Skin preparation: alcoholic PI or alcoholic CHG in accordance with standard procedure in each ICU. Skin preparation agent did not differ by study group. Dressing change: 24 hrs after insertion then every 3 or 7 days according to standard practice in ICU. Daily chlorhexidine bathing: not used in any ICU[l]	c. No other infectious focus explaining the positive blood cultures (in patients with coagulase-negative *Staphylococcus (*CoNS), the same pulse-field gel electrophoresis patterns in catheter tip and blood cultures was required for a diagnosis of CRBSI). **Major catheter-related infection (CRI):** Either catheter-related sepsis (CR-sepsis) without BSI or CRBSI CR-sepsis without BSI: combination of all of the following: a. Body temp ≥38.5°C or ≤36.5°C; b. Catheter colonization; c. Pus at insertion site or resolution of clinical sepsis after catheter removal (resolution of fever or hypothermia within 24 hrs before any change of antimicrobial therapy); and d. Absence of any other infectious focus. Sepsis or BSI was declared as CR when there was no other detectable cause of sepsis with or without BSI. Non-cultured catheters were classified as not colonized unless there was sepsis with no other detectable cause. **Systemic adverse reaction to CHG:** Not defined **Severe contact dermatitis requiring permanent discontinuation of dressings:** Not defined but confirmed by a dermatologist. Study noted: "Contact dermatitis usually occurred for a single catheter per patient and selectively affected patients with	• Arterial catheters: 0.5/1,000 vs. 1/1,000; HR: 0.51 (CI: 0.15–1.74); p=0.28 **Major CRI incidence (events/patients):** • All catheter types: 12/938 (1.3%) vs. 36/941 (3.8%); HR: 0.33 (CI: 0.17–0.62); p <0.01 **Major CRI rate (events/1,000 catheter days):** • All catheter types: 0.69/1,000 vs. 2.11/1,000 • CVCs: 0.8/1,000 vs. 2.5/1,000; • HR: 0.27 (CI: 0.11–0.66); p=<0.01 • Arterial catheters: 0.6/1,000 vs. 1.7/1,000; HR: 0.39 (CI: 0.15–1.03); p=0.06 **Systemic Reactions:** None occurred **Incidence of severe contact dermatitis requiring permanent discontinuation of dressing (events/patients):** 22/938 (2.3%) vs. 5/941 (0.5%); p<0.01 **Abnormal ICDRG score rate: (denominator unit NR):** 2.3% vs. 1%; p<0.01

[k] Basis of score described in Table 8.

[l] Information obtained via correspondence with author.

Study Features	Population and Setting	Study Groups	Outcome Definitions	Results
			multiple organ failure, subcutaneous edema, and fragile skin." **Skin conditions rated with standard scale:** The condition of the skin was described on standardized form by nurse in charge of patient at each dressing change and at catheter removal, using the International Contact Dermatitis Research Group (ICDRG) system: 1=mild redness only, 2=red and slightly thickened skin, 3= intense redness and swelling with coalesced large blisters or spreading reaction. Scores constituting "abnormal score" were not defined.	
Arvaniti, 2012[4] (Extracted by: Overholt) **Risk of bias score:** Low [k] **Study objective:** To evaluate whether chlorhexidine–impregnated sponge dressing reduced CVC-related colonization and infections with or without associated bacteremia.	**N= 306 patients;** 306 CVCs; 2,202 catheter days (not reported if tunneled or non-tunneled CVCs) **Inclusion criteria:** ICU patients over 18 years old who required a CVC for ≥3 days **Exclusion criteria**: Neutropenic patients, pregnant women, patients with expected ICU stay <3 days, patients with allergy to CHG; catheter changes over guidewire; and patients who were readmissions **Setting:** 5 general ICUs **Location:** Greece **Dates:** June 2006–May 2008 **Anticipated study power:** 80% power to detect a 50% reduction in catheter colonization rate of either study group. This would require 219 catheters per group. The study was	**Intervention:** N = 150 patients (restricted to first catheter per patient) C-I sponge under transparent, semipermeable, polyurethane, occlusive dressing placed after first 24 hrs **Control:** N = 156 patients (restricted to first catheter per patient in study) Transparent, semipermeable, polyurethane, occlusive dressing alone placed after first 24 hrs. **Standard care for both groups:** Insertion sites: internal jugular, femoral, and subclavian veins. Catheters**:** Triple lumen, polyurethane, uncoated, non-heparin-bonded CVCs Skin preparation: 10% PI Dressing change: Gauze was placed over insertion site for first 24 hrs. After this, insertion sites were covered by intervention or control group dressings. Dressings for both groups were changed for the first time 24 hrs after	**CRBSI:** For microorganisms other than CoNS: CRI plus 1 positive blood culture from peripheral venous puncture growing the same microorganism as that isolated from the catheter tip. Contaminated cultures: 1 single blood culture, or 1 of 2 or more blood cultures found positive for CoNS. For CoNS: two or more peripheral blood cultures with a minimum delay of 1 hr, testing positive for CoNS, and having the same antibiotic susceptibility profile were required. **CRI:** Positive quantitative culture (≥10^3 CFU/mL) of the catheter tip plus clinical evidence of sepsis, in the absence of additional sites of infection with the same microorganism. **Sepsis**: Temperature >38.2°C or <36.5°C or chills, leukocytes ≥10,000 or ≤4,000, or other signs of sepsis. **Product-related adverse events:** Not defined	**CRBSI incidence (events/patients):** 3/150 (2%) vs. 2/156 (1.28%);HR: 1.65 (CI: 0.27–10.01) **CRBSI rate (event/1,000 catheter days):** 2.84/1,000 vs. 1.4/1,000; p=0.59 **CRI incidence (events/patients):** 6/150 (4%) vs. 9/156 (5.77%); HR: 0.65 (CI: 0.23–1.85); p=0.42 **CRI rate (events/1,000 catheter days):** 5.69/1,000 vs. 7.83/1,000 **Product–related adverse events:** All patients tolerated the C-I dressing well. **Allergic reaction to chlorhexidine:** No patient was excluded due to allergic reaction to chlorhexidine. **Severe contact dermatitis incidence:** None

Study Features	Population and Setting	Study Groups	Outcome Definitions	Results
	stopped early due to slow recruitment **Follow Up:** Until catheter removal or transfer from the ICU to another ward if discharged from ICU with catheter in place	CVC insertion and then every 3 days or sooner if considered soiled. Daily chlorhexidine bathing: Performed in 1 of the 5 ICUs (these patients comprised approximately 40% of the study population.)[I]	**Allergic reaction to chlorhexidine:** Not defined **Severe contact dermatitis:** Not defined **Mild local redness:** Not defined	**Mild local redness incidence (events/patients)**: 1/156 (0.6%) vs. 0; this case resolved after dressing removal
Timsit, 2009[2] (Extracted by Overholt) **Risk of Bias Score:** Low [K] **Study objective:** To evaluate the respective effects of using CHG-impregnated sponge dressing and increasing the time between dressing changes in adult patients in ICU.	**N = 1,636 patients**; 3,778 arterial catheters and CVCs; 28,931 catheter-days **Inclusion criteria:** Patients older than 18 years expected to require an arterial catheter, CVC, or both inserted for 48 hrs or more. **Exclusion criteria:** Patients with a history of allergy to CHG or to transparent dressings. **Setting:** ICUs in 3 university hospitals and 2 general hospitals **Location:** France **Dates:** December 20, 2006–May 20, 2008 **Anticipated study power:** 80% to detect 60% reduction in the major CRI rate in the control group. It was hypothesized that each patient would have 2 catheters and the study planned to enroll 1,600 patients	**Intervention:** n=817 patients (in ITT analysis) C-I sponge under semipermeable, transparent dressing. This was changed after first 24 hrs **Control:** n=819 patients (in ITT analysis) Semipermeable transparent dressing alone. **Standard care for both groups:** All centers followed French guideline recommendations for catheter insertion and care. Insertion sites: CVC: jugular, subclavian, and femoral. Arterial catheters: femoral and radial Catheters: CVCs (both tunneled and percutaneous [non-tunneled]) and arterial catheters were used. No antiseptic or antibiotic impregnated CVCs used. Skin preparation: Alcoholic PI solution (5% PI in 70% alcohol) Dressing change: 24 hrs after CVC insertion, then every 3 days or 7 days, or sooner if soiled or leaking. Daily chlorhexidine bathing: None	**CRBSI:** a combination of 1. 1 or more positive peripheral blood cultures sampled immediately before or within 48 hrs after catheter removal; 2. a quantitative catheter–tip culture testing positive for the same microorganisms or a differential time to positivity of blood cultures greater than or equal to 2 hrs; and 3. no other infectious focus explaining the positive blood culture **Major CRI:** either CR sepsis without BSI or CRBSI. Catheter-related sepsis without BSI**:** combination of 1. fever (body temperature over 38.5°C) or hypothermia (body temperature below 36.5°C); 2. a catheter-tip culture yielding at least 10^3 CFUs/mL; 3. pus at the insertion site or resolution of clinical sepsis after catheter removal; and 4. absence of any other infectious focus. **Systemic adverse reactions:** Not defined **Severe contact dermatitis:** Not defined. However, suspected contact dermatitis or skin allergy was confirmed by a dermatologist.	**CRBSI incidence (events/catheters):** All catheter types: 6/1,953 (0.3%) vs. 17/1,825 (0.9%); HR: 0.24 (CI: 0.09–0.65); p<0.01 **CRBSI rate (events/1,000 catheter days):** 0.4/1,000 vs. 1.3/1,000 **Major CRI incidence (events/catheters):** All catheter types: 10/1,953 (0.5%) vs. 19/1,825 (1%); HR: 0.39 (CI: 0.16–0.93); p=0.03 **Major CRI Rate (events/1000 catheter days):** All catheter types: 0.6/1,000 vs. 1.4/1,000 Subanalysis that combined patients with either C-I dressing or standard dressings found no significant differences in CRBSI rates related to frequency of dressing changes (every 3 days vs. every 7 days). **Systemic adverse reactions to chlorhexidine:** None **Severe contact dermatitis that required removal of dressing:**

Study Features	Population and Setting	Study Groups	Outcome Definitions	Results
	Follow up: 48 hrs post-ICU discharge. Catheters were removed when no longer needed or a CRI was suspected		**Skin condition:** The condition of skin was described on a standardized form by the nurse in charge of the patient at each dressing change and at catheter removal using the International Contact Dermatitis Research Group (ICDRG) system: 1=Mild redness only, 2=red and slightly thickened skin, 3= Intense redness and swelling with coalesced large blisters or spreading reaction. Scores constituting "abnormal score" were not defined. **Chlorhexidine resistance:** Minimum bactericidal concentration (MBC) of chlorhexidine was determined for 106 strains cultured from the skin at catheter removal. Results reported as median MBC (IQR).	• 8 patients (10.4 /1,000 patients or 5.3/1,000 catheters) vs. NR • Contact dermatitis selectively affected very sick patients with multiple organ failure, subcutaneous edema, and fragile skin. **Abnormal ICDRG score rate (events/catheter):** 100/6,720 (1.49%) vs. 63/5,875 (1.02%); p=0.02 **Skin allergy to transparent adhesive dressing incidence (events/ catheters):** 1/1,953 (<0.01%) vs. 1/1,825 (<0.01%) **Median MBC of chlorhexidine (IQR):** 4 (4–8) vs. 4 (4–16); p=0.30 **MBC of chlorhexidine > 32:** 5 events/52 strains vs. 4 events/52 strains • Organisms identified: o Intervention group: *Enterococcus faecalis; Pseudomonas aeruginosa* Control group: *E. faecalis; E. faecium; Providencia stuartii.*
Ruschulte, 2009[3] (Extracted by: Overholt) **Risk of bias score:** Moderate [k] above	**N = 601 patients**; 601 non-tunneled CVCs; 9,731 catheter days **Inclusion criteria:** Hematology and oncology patients requiring a CVC for at least 5 days	**Intervention:** n=300 patients (a single catheter per patient was included) C-I sponge under transparent polyurethane dressing **Control**: n=301 patients (a single catheter per patient was included) Transparent polyurethane dressing alone **Standard care for both groups:**	**CRBSI:** Proven infection with the time to positivity method: 1 of the catheter-drawn blood cultures (taken through each lumen of the CVC) became positive at least 2 hrs earlier than the culture of a peripheral venipuncture blood draw after skin disinfection, and clinical signs and symptoms [fever (>38.0C by ear thermometer measurement), swelling, and/or hypotension; tenderness,	**CRBSI incidence (events/patients):** 19/300 (6.3%) vs. 34/301 (11.3%); RR: 0.54 (CI: 0.31–0.94); p=0.02 **CRI rate (events/1,000 catheter days):** 3.8/1,000 vs. 7.1/1,000 **Product related adverse events:** No complications of CVC

Study Features	Population and Setting	Study Groups	Outcome Definitions	Results
Study objective: To investigate the effectiveness of a chlorhexidine dressing in reducing CRI	**Exclusion criteria:** Those expected to have their CVC for less than 5 days **Setting:** 1 university hospital **Location:** Germany **Dates:** January 2004–January 2006 **Anticipated study power:** 80% power to detect a reduction in CRBSI from an estimated 6% in the control group. 707 patients were planned per group. Study reached statistical difference at second interim analysis and enrollment stopped. **Follow up:** NR	Insertion site: internal jugular vein or subclavian vein Catheters: all patients received a chlorhexidine and silver sulfadiazine-impregnated triple lumen CVC Skin preparation: alcohol spray Dressing change: weekly or after having been lifted up for inspection controls Daily chlorhexidine bathing: NR	erythema, swelling around the catheter insertion site; or elevated CRP levels suggesting infection] for which no other source than the catheter was identified. **Product-related adverse effects:** not defined **Allergic reactions:** not defined **Chlorhexidine resistance:** not defined	insertion were observed except infections **Patients excluded from study due to allergic reactions:** none **Chlorhexidine resistance:** No suspicion of bacterial resistance to chlorhexidine dressings
Roberts, 1998[5] (Extracted by Overholt) **Risk of bias score:** Moderate [k] above **Study objective:** To determine the effects of C-I sponge dressings on the rates of CVC tip and exit site infection/ colonization in an adult ICU	**N =** 32 patients and 40 CVC enrolled Data available for 33 non-tunneled CVCs **Inclusion criteria:** All patients receiving CVCs in the ICU during 7-week period **Exclusion criteria:** NR **Setting:** 1 teaching hospital ICU **Location:** West Australia **Dates:** NR	**Intervention:** n=17 catheters C-I sponge under occlusive dressing **Control**: n=16 catheters Occlusive dressing alone **Standard care for both groups:** Insertion site: NR Catheters: non-tunneled CVCs inserted over guidewire (Seldinger technique) Skin preparation: 0.5% chlorhexidine in 70% alcohol. Dressing change: dressings attended to every fifth day or as needed Daily chlorhexidine bathing: NR	**CRI:** Any infection in which the organism isolated from the CVC tip and/or exit site was the same as that isolated from a clinical isolate associated with clinical signs (elevated temperature and white cell count).	**CRI incidence (events/catheters):** 1/17 (5.9%) vs. 0/16 (0%); p=NS. In a single infection, isolates from both the catheter exit site and catheter draw were *S. epidermis* with identical antibiotic susceptibilities.

Study Features	Population and Setting	Study Groups	Outcome Definitions	Results
	Anticipated study power: 80% power to detect a 10% reduction in colonization rates (primary outcome) based on 11,000 patients **Follow up:** NR			

Appendix Table 7. Summary of Evidence for Using Chlorhexidine-Impregnated (C-I) Dressings among Patients Aged < 18 Years with Short-term, Non-tunneled Central Venous Catheters (data are directly extracted from studies unless otherwise noted)

Study Features	Population and Setting	Study Groups	Outcome Definitions	Results
Duzkaya, 2017[7] (Extracted by Dasti) **Risk of bias score:** Moderate[m] **Study objective:** To compare the efficacy of a chlorhexidine-impregnated dressing with that of a standard dressing in preventing CRBSI in children	**N = 100 patients** **Inclusion criteria:** Patients aged 1 month to 18 years old admitted to PICU; had no CRBSI at the time of hospital admission; had a CVC in place for more than 72 hours; were not receiving neuromuscular blockers; and obtained written consent to be part of the study. **Exclusion criteria:** NR **Setting:** PICU of university hospital **Location:** Istanbul, Turkey **Dates:** December 2012–January 2014 **Anticipated study power:** A minimal sample size of 61 patients would have an 80% power to detect a difference of 19% between development and absence of CRBSI at α=.05 **Follow up:** NR	**Intervention:** n=50 patients (number of catheters per patient NR) 2% C-I gel pad dressing **Control:** n=50 patients (number of catheters per patient NR) Sterile (gauze) pad **Standard care for both groups:** Insertion site: femoral, jugular, or subclavian vein Catheters: non-tunneled CVCs Skin prep: 10% PI was used for dermal antisepsis, and cleansing was maintained for 3 minutes. Dressing change: In the intervention group, 2% C-I dressings remained in situ for 7 days unless they became wet. In the control group, gauze dressings were changed daily because children's skin is more sensitive than adults' skin and frequent exposure of the catheter insertion site allowed earlier recognition of redness or changes. Chlorhexidine bathing: None	**CRBSI:** Growth of 15 CFUs or more in the catheter end. Culture and microorganisms in the two blood samples with the same antibiotic resistance patterns as the microbes in the catheter end. **Local catheter infection:** growth of 15 CFUs or more in the culture of the catheter end and findings of inflammation at the catheter insertion site in the absence of blood-borne infection	**CRBSI incidence (events/ patients):** 1/50 (2%) vs. 5/50 (10%); p>0.05 **Local catheter infection: (events/ patients):** 1/50 (2%) vs. 2/50 (4%); p>0.05

[m] Basis of score described in Table 9.

Study Features	Population and Setting	Study Groups	Outcome Definitions	Results
Levy, 2005[8] (Extracted by Overholt) **Risk of bias score:** Moderate [m] **Study objective:** To determine the efficacy and safety of the chlorhexidine gluconate-impregnated sponge for the prevention of CVC colonization and CABSI in infants and children undergoing cardiac surgery	**N = 145 patients** **Inclusion criteria:** Infants and children 0–18 years old admitted to the PCICU during the study period and required a non-tunneled CVC for >48 hrs **Exclusion criteria:** NR **Setting:** 1 children's medical center PCICU **Location:** Israel **Dates:** January 2002–March 2003 **Follow up:** NR **Anticipated study power:** 80% power to detect a 20% reduction in colonization and adverse event rates based on 70 patients in each group. CABSI was secondary study outcome.	**Intervention:** n=74 patients C-I sponge dressing under transparent polyurethane dressing **Control:** n=71 patients Transparent polyurethane dressing **Standard care for both groups:** Insertion site: Internal jugular vein Catheters: short-term, non-tunneled catheters Skin preparation: Disinfection with CHG solution for 30 seconds and allowed to dry Dressing change: Only if mechanical complications, bleeding, oozing or signs of exit site infection (redness or pus discharge) occurred. Insertion site was cleansed with CHG and covered with the same type of dressing. Daily chlorhexidine bathing: NR	**Catheter-associated bloodstream infections (CABSI):** Bacteremia without isolation of the same organism from the tip of the CVC and blood. Blood and exit site cultures were performed when clinical systemic and local signs of infection occurred **Product related adverse events:** Not defined **Local redness:** Not defined	**CABSI incidence (events/patients):** 4/74 (5.4%) vs. 3/71 (4.2%); p=1.00 **Product related adverse events:** Significant adverse events were not associated with the use of this device in this patient population. **Local redness incidence: (events/patients):** 4/74 (5.4%) vs. 1/71 (1.4%) All intervention events occurred in neonates.
Garland, 2001[6] (Extracted by Stone) **Risk of bias score:** Moderate [m] **Study objective:** To report the results of a multicenter prospective, RCT undertaken to ascertain the efficacy of a	**N = 705 neonates;** 620 percutaneous (non-tunneled) CVCs 85 Broviac (tunneled) CVCs **Inclusion criteria:** Critically ill neonates admitted to units who would likely require a CVC for at least 48 hrs where the parents gave informed consent. Amended after 9/118 (7.6%) of neonates experienced adverse reactions to the C-I dressing during the first 15 months of the study. After this, infants <26 weeks	**Intervention:** n=335 patients Skin was cleansed for at least 30 seconds with 70% isopropyl alcohol. After alcohol was allowed to dry, CVC was inserted and site was dressed with C-I sponge under transparent polyurethane dressing. Dressings were changed every 7 days **Control:** n=370 patients Skin was cleansed for at least 30 seconds with 10% aqueous PI. After PI was allowed to dry, CVC was inserted then site was dressed with transparent polyurethane dressing. **Standard care for both groups:**	**CRBSI**: clinically relevant BSI without an identifiable primary source other than a CVC colonized by the same strain grown from blood cultures. Hub cultures, if obtained, were negative for the organism grown from the blood **BSI without a source:** A positive blood culture during the time a catheter was in situ or within 24 hrs of removal; clinical signs or symptoms of a BSI within 6 hrs of the positive culture; antibiotic therapy for ≥7 days and no other documented primary site of infection; and catheter tip and hub cultures were either not colonized or colonized with organisms	**CRBSI incidence (events/percutaneous catheters):** 11/297 (3.7%) vs. 10/323 (3.1%); RR: 1.2 (CI: 0.5–2.7); p=0.68 **BSI without a source – incidence (events/percutaneous catheters):** 46/316 (14.6%) vs. 44/346 (12.7%); RR: 1.1 (CI: 0.8–1.7); p=0.49. **Adverse reaction incidence (events/patients):**

Study Features	Population and Setting	Study Groups	Outcome Definitions	Results
novel chlorhexidine gluconate impregnated dressing for the prevention of catheter colonization and CRBSI in critically ill neonates.	were enrolled only if CVC was inserted after the first week of life. **Exclusion criteria:** NR **Setting:** NICUs in 4 university hospital and 2 community hospital **Location:** USA **Dates:** June 1994–August 1997 **Anticipated study power:** 80% (α=0.05) to detect a 50% reduction in CRBSI rates from baseline of 9% risk based on 490 neonates in each group. Study stopped early due to funding and low CRBSI rate. **Follow up:** NR	Insertion sites: leg, arm, head/neck and other. Catheters: percutaneous and tunneled CVCs. 6% of catheters in each group were surgically placed. Skin preparation: different by groups. Dressing change: changed every 7 days Daily chlorhexidine bathing: none.	different from those grown from the blood • BSI signs and symptoms: an increase or decrease in the white blood cell count by $3x10^3$ per mm^2 or ≥0.15 immature neutrophils ratio on a complete blood count; new-onset apnea; glucose intolerance or hypoglycemia; metabolic acidosis; tachycardia or hypotension; mottled or ashen appearance with a normal hematocrit; and/or new onset of feeding intolerance, lethargy, or fever. **Adverse reactions**: Included severe or localized contact dermatitis, pressure necrosis and/or reactions leading to scar formation. **Severe localized contact dermatitis:** Not defined. **Pressure necrosis under C-I dressing:** Not defined.	• All neonates: 19/335 (5.7%) vs. 0; p<0.01 • Neonates <1,000g: 15/98 (15%) • Neonates ≥1,000g: 4/237 (1.5%) • p<0.01 for comparison by weight **Severe localized contact dermatitis incidence (events/patients) during first 15 months of study:** 7/118 (5.9%) of neonates with C-I dressing developed severe localized contact dermatitis • After change in protocol, there were 12/217 (5.5%) more episodes of contact dermatitis **Other adverse events under C-I dressing incidence (events/patients) during first 15 months of study:** • Pressure necrosis: 2/19 (10.5%) Scar formation: 2/19 (10.5%)

3.0 Risk of Bias Assessments of Individual Studies

Appendix Table 8. Evaluation of Risk of Bias in Studies Using Chlorhexidine-Impregnated (C-I) Dressings among Patients Aged ≥ 18 Years with Short-term, Non-tunneled Central Venous Catheters

Author Publication Year	Described as randomized	Randomization appropriately performed	Described as double–blind	Outcome assessor blinded	Study participant blinded	Investigator blinded	Attrition described	Attrition smaller than 10–15% of assigned patients	Attrition appropriately analyzed	Funding source(s) disclosed and no obvious conflict of interest	Overall Risk of Bias
Arvaniti 2012[4]	✓	✓		✓			✓	✓	✓		Low
Roberts 1998[5]	✓			✓			✓				Moderate
Ruschulte 2009[3]	✓	✓					✓	✓	✓		Low
Timsit 2009[2]	✓	✓		✓			✓	✓	✓		Low
Timsit 2012[1]	✓	✓		✓			✓	✓	✓		Low

Note: Overall risk of bias was calculated by dividing the total number of valuable trial characteristics by the total number of possible characteristics and applying these categories: ≤ 25% = high risk of bias; > 25% to ≤ 50% = moderate risk of bias; > 50% = low risk of bias.

Appendix Table 9. Evaluation of Risk of Bias in Studies Using Chlorhexidine-Impregnated (C-I) Dressings among Patients Aged < 18 Years with Short-term, Non-tunneled Central Venous Catheters

Author Publication Year	Described as randomized	Randomization appropriately performed	Described as double–blind	Outcome assessor blinded	Study participant blinded	Investigator blinded	Attrition described	Attrition smaller than 10–15% of assigned patients	Attrition appropriately analyzed	Funding source(s) disclosed and no obvious conflict of interest	Overall Risk of Bias
Garland 2001[6]	✓	✓					✓				Moderate
Levy 2005[8]	✓	✓					✓				Moderate
Duzkaya 2016[7]	✓	✓					✓	✓			Moderate

Note: Overall risk of bias was calculated by dividing the total number of valuable trial characteristics by the total number of possible characteristics and applying these categories: ≤ 25% = high risk of bias; > 25% to ≤ 50% = moderate risk of bias; > 50% = low risk of bias.

4.0 The GRADE Approach to Rating the Evidence

Appendix Table 10. Rating the Evidence for Benefit or Harm Using the GRADE Approach[9]

Type of Evidence: Starting GRADE

- RCT: High
- Observational study: Low

Criteria to Decrease GRADE

- **Study quality limitations**
  Serious (−1 GRADE) or very serious (−2 GRADE) study quality limitations determined by Risk of Bias Assessments
- **Inconsistency**
  Important inconsistency (−1 GRADE)
- **Indirectness**
  Some (−1 GRADE) or major (−2 GRADE) uncertainty about directness
- **Imprecision**
  Imprecise or sparse data (−1 GRADE)
- **Publication bias**
  High risk of bias (−1 GRADE)

Criteria to Increase GRADE

- **Strength of association**
  Strong (+1 GRADE) or very strong evidence of association (+2 GRADE)
- **Dose-response**
  Evidence of a dose-response gradient (+1 GRADE)
- **Confounding**
  Inclusion of unmeasured confounders increases the magnitude of effect (+1 GRADE)

Resulting GRADE

- High
- Moderate
- Low
- Very Low

5.0 References

1. Timsit JF, Mimoz O, Mourvillier B, et al. Randomized controlled trial of chlorhexidine dressing and highly adhesive dressing for preventing catheter-related infections in critically ill adults. *Am J Respir Crit Care Med.* 2012;186(12):1272-1278.
2. Timsit JF, Schwebel C, Bouadma L, et al. Chlorhexidine-impregnated sponges and less frequent dressing changes for prevention of catheter-related infections in critically ill adults: a randomized controlled trial. *JAMA.* 2009;301(12):1231-1241.
3. Ruschulte H, Franke M, Gastmeier P, et al. Prevention of central venous catheter related infections with chlorhexidine gluconate impregnated wound dressings: a randomized controlled trial. *Ann Hematol.* 2009;88(3):267-272.
4. Arvaniti K, Lathyris D, Clouva-Molyvdas P, et al. Comparison of Oligon catheters and chlorhexidine-impregnated sponges with standard multilumen central venous catheters for prevention of associated colonization and infections in intensive care unit patients: a multicenter, randomized, controlled study. *Crit Care Med.* 2012;40(2):420-429.
5. Roberts B, Cheung D. Biopatch--a new concept in antimicrobial dressings for invasive devices. *Aust Crit Care.* 1998;11(1):16-19.
6. Garland JS, Alex CP, Mueller CD, et al. A randomized trial comparing povidone-iodine to a chlorhexidine gluconate-impregnated dressing for prevention of central venous catheter infections in neonates. *Pediatrics.* 2001;107(6):1431-1436.
7. Duzkaya DS, Sahiner NC, Uysal G, Yakut T, Citak A. Chlorhexidine-Impregnated Dressings and Prevention of Catheter-Associated Bloodstream Infections in a Pediatric Intensive Care Unit. *Crit Care Nurse.* 2016;36(6):e1-e7.
8. Levy I, Katz J, Solter E, et al. Chlorhexidine-impregnated dressing for prevention of colonization of central venous catheters in infants and children: a randomized controlled study. *Pediatr Infect Dis J.* 2005;24(8):676-679.
9. Umscheid CA, Agarwal RK, Brennan PJ, Healthcare Infection Control Practices Advisory C. Updating the guideline development methodology of the Healthcare Infection Control Practices Advisory Committee (HICPAC). *Am J Infect Control.* 2010;38(4):264-273.