Appendix: *Recommendations for Prevention and Control of Infections in Neonatal Intensive Care Unit Patients: Central Line-associated Blood Stream Infections*

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A. Search Strategies and Results

A.1. Guideline Search Strategies (April 2011)

Table 1 **Guideline Search of** MEDLINE

#	Search History	Results
1	As outlined below	61

Table 2 Guideline Search of American Academy of Pediatrics (AAP)

#	Search History	Results
1	Browsed http://aap.org	31

A.2. Primary Study Search Strategies: Central Line-associated Bloodstream Infections (CLABSI) (May 5, 2021)

Table 3 Primary Search of MEDLINE: CLABSI

#	Search History	Results
1	exp Intensive Care Units, Neonatal/ or exp Intensive Care, Neonatal/	17500
2	exp Infant, Newborn/	609494
3	1 or 2	610861
4	exp Catheters, Indwelling/	19234
5	exp Catheterization, Central Venous/ or exp Catheterization, Peripheral/	24828
6	exp Umbilical Arteries/ or exp Umbilical Veins/	17948
7	4 and 6	157
8	5 and 6	303
9	4 or 5	39634
10	7 or 8	402
11	PICC.mp.	974
12	Broviac.mp.	364
13	9 or 10 or 11 or 12	40041
14	exp Infection Control/	61617
15	exp Cross Infection/ or exp Catheter-Related Infections/	60971
16	exp Infusions, Intravenous/ae, mo [Adverse Effects, Mortality]	1143
17	exp Injections, Intravenous/ae, co, mo [Adverse Effects, Complications, Mortality]	1300

18	16 or 17	2409
19	14 or 15 or 18	112730
20	3 and 13 and 19	425
21	limit 20 to (English language and humans)	385
22	exp Bacteremia/	28376
23	19 or 22	137107
24	3 and 13 and 23	490
25	limit 24 to (English language and humans)	442
26	21 or 25	442
27	limit 26 to yr="2012 -Current"	150

Table 4 Primary Search of EMBASE: CLABSI

#	Search History	Results
1	Exp newborn intensive care/ or exp newborn/	385215
2	Exp indwelling catheter/ or exp central venous catheter/ or exp catheterization/	162190
3	Exp umbilical artery catheter/ or exp umbilical artery catheterization/	389
4	Exp umbilical vein/	12348
5	2 and 4	342
6	2 or 3 or 5	162291
7	Exp infection control/ or exp hospital infection/ or exp cross infection/	130845
8	Exp bloodstream infection/ or exp catheter infection/	23173
9	7 or 8	149431
10	1 and 6 and 9	658
11	Limit 10 to (English language and humans and embase)	411

Table 5 Primary Search of Cochrane Library: CLABSI

#	Search History	Results
1	MeSH descriptor Intensive Care, Neonatal explode all trees	120
2	MeSH descriptor Intensive Care Units, Neonatal explode all trees	84
3	MeSH descriptor Infant, Newborn explode all trees	153
4	1 or 2 or 3	206
5	MeSH descriptor Catheters, Indwelling explode all trees	46

6	MeSH descriptor Catheterization, Central Venous explode all trees	59
7	MeSH descriptor Catheterization, Peripheral explode all trees	52
8	5 or 6 or 7	91
9	MeSH descriptor Umbilical Arteries explode all trees	9
10	MeSH descriptor Umbilical Veins explode all trees	11
11	9 or 10	16
12	8 and 11	2
13	8 or 12	91
14	4 and 13	19

Table 6 Primary Search of CINAHL: CLABSI

#	Search History	Results
1	(MH "Infant, Newborn+") or (MH "Intensive Care, Neonatal+") or (MH "Intensive Care Units, Neonatal")	78909
2	MH "Central Venous Catheters+"	2595
3	(MH "Catheterization, Peripheral+") or (MH "Catheterization, Central Venous+")	4398
4	(MH "Umbilical Arteries") or (MH "Umbilical Veins")	707
5	2 or 3	6420
6	4 and 5	39
7	5 or 6	6420
8	MH "Infection Control+"	46282
9	(MH "Cross Infection+") or (MH "Catheter-Related Infections")	23582
10	MH "Bacteremia"	3178
11	(MH "Infusions, Intravenous/AE") or (MH "Infusions, Parenteral/AE")	246
12	8 or 9 or 10 or 11	61658
13	1 and 7 and 12	215
14	Limit 13 to (English language and human; exclude MEDLINE records)	206

A.3. Primary Study Search Strategies: Central Line-associated Bloodstream Infections and Chlorhexidine (May 5, 2021)

Table 7 CLABSI and Chlorhexidine Search Strategy for MEDLINE

#	Search History	Results

1	exp Intensive Care Units, Neonatal/ or exp Intensive Care, Neonatal/	17500
2	exp Infant, Newborn/	609494
3	1 or 2	610861
4	exp Catheters, Indwelling/	19234
5	exp Catheterization, Central Venous/ or exp Catheterization, Peripheral/	24828
6	PICC.mp.	974
7	Broviac.mp.	364
8	4 or 5 or 6 or 7	40041
9	exp Infection Control/	61617
10	exp Cross Infection/ or exp Catheter-Related Infections/	60971
11	exp Infusions, Intravenous/ae, mo [Adverse Effects, Mortality]	1143
12	exp Injections, Intravenous/ae, co, mo [Adverse Effects, Complications, Mortality]	1300
13	exp Bacteremia/	28376
14	9 or 10 or 11 or 12 or 13	137107
15	Chlorhexidine.mp. or exp Chlorhexidine/	11575
16	3 and 15	326
17	15 and 8 and 14	290
18	16 or 17	590
19	limit 18 to (English language and humans)	535

Table 8 Primary Search of EMBASE: CLABSI and Chlorhexidine

#	Search History	Results
1	Exp newborn intensive care/ or exp newborn/	385215
2	Exp indwelling catheter/ or exp central venous catheter/ or exp catheterization/	162190
3	Exp umbilical artery catheter/ or exp umbilical artery catheterization/	389
4	2 or 3	162291
5	Exp infection control/ or exp hospital infection/ or exp cross infection/	130845
6	Exp bloodstream infection/ or exp catheter infection/	23173
7	5 or 6	149431
8	4 and 7	9679
9	Exp chlorhexidine/ or chlorhexidine	17183

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10	1 and 9	420
11	8 and 9	852
12	10 or 11	1224
13	Limit 12 to (English language and humans and embase)	744

Table 9 Search of the Cochrane Library: CLABSI and Chlorhexidine

#	Search History	Results
1	MeSH descriptor Intensive Care, Neonatal explode all trees	120
2	MeSH descriptor Intensive Care Units, Neonatal explode all trees	84
3	MeSH descriptor Infant, Newborn explode all trees	153
4	1 or 2 or 3	206
5	MeSH descriptor Catheters, Indwelling explode all trees	46
6	MeSH descriptor Catheterization, Central Venous explode all trees	59
7	MeSH descriptor Catheterization, Peripheral explode all trees	52
8	5 or 6 or 7	91
9	MeSH descriptor Umbilical Arteries explode all trees	9
10	MeSH descriptor Umbilical Veins explode all trees	11
11	9 or 10	16
12	8 and 11	2
13	8 or 12	91
14	4 and 13	19
15	MeSH descriptor Chlorhexidine explode all trees	88
16	13 and 15	11
17	4 and 15	8
18	16 or 17	12

B. Study Exclusion Criteria

Criteria for excluding studies from the literature review are:

1. Not relevant to key question

2. Not primary research
3. Meeting abstract only
4. No full text available
5. Not in English
6. No NICU patients included in study
7. Mixed patient population without NICU patient subgroups
8. Methods paper on HAI surveillance only
9. Descriptive epidemiology study only
10. Studies examining only non-modifiable risk factors for infection
11. Studies that do not provide a clear description of intervention and statistical analysis comparing time points before and after N<10 NICU patients with Outcome Definitions of interest (does not apply to studies evaluating severe adverse events such as death or permanent disfiguration)
12. Study only examining treatments of CLABSI
13. Study only examining catheter removal for documented CLABSIs
14. Study only examining peripheral IVs (note: this does not include Midline or PICCs)
15. Study with only endocarditis as a reported clinical outcome

C. Evidence Review

C.1. Non-sterile Gloves

Question 1. In NICU patients requiring a central line catheter, does the use of non-sterile gloves after hand hygiene compared with hand hygiene alone prior to every patient contact prevent CLABSI?

Table 10 The Summary of Evidence for Using Non-Sterile Gloves After Hand Hygiene vs. Hand Hygiene Alone Prior to Every Patient Contact to Prevent CLABSI

Outcome	Findings	Quantity and Type of Evidence (Sample Size)	GRADE of Evidence for Outcome (Limitations of the Evidence)
CLABSI*	• One single center RCT compared non-sterile glove use after hand hygiene with hand hygiene alone prior to every patient contact and found no difference in CLABSI rate (1.9 vs. 1.7, Rate Ratio: 0.90 (95% CI: 0.22-3.61), p = 0.88).	1 RCT N=120 lines[1]	Moderate • Imprecision: only one study
Possible CLABSI*	• One single center RCT compared non-sterile glove use after hand hygiene with hand hygiene alone prior to every patient contact and reported a decrease in possible CLABSI rate (9.4 vs. 3.4, Rate Ratio: 0.36 (95% CI: 0.16-0.81), p = 0.01).	1 RCT N=120 lines[1]	Moderate • Imprecision: only one study
BSI*	• One single center RCT compared non-sterile glove use after hand hygiene with hand hygiene alone prior to every patient contact and found no difference in BSI incidence (20/60 (33%) vs 14/60 (23%), difference in proportion: -10% (95% CI: -26 to 6), p = 0.22).	1 RCT N=120 lines[1]	Moderate • Imprecision: only one study
Gram Positive BSI	• One single center RCT compared non-sterile glove use after hand hygiene with hand hygiene alone prior to every patient contact and reported a reduction in gram positive BSI incidence (19/60 [32%] vs. 9/60 [15%], Difference in proportion: -17% (95% CI: -31 to -1), p = 0.03).	1 RCT N=120[1] lines[1]	Moderate • Imprecision: only one study
Gram Negative BSI	• One single center RCT compared non-sterile glove use after hand hygiene with hand hygiene alone prior to every patient contact and found no difference in gram negative BSI incidence (3/60 (5%) vs. 5/60 (8%), Difference in proportion: 3% (95% CI: -7 to 14), p = 0.46).	1 RCT N=120[1] lines[1]	Moderate • Imprecision: only one study

Table 11 Extracted Information for Non-Sterile Gloves After Hand Hygiene to Prevent CLABSI

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
Author: Kaufman[1] **Year:** 2014 **Study Design:** Randomized control trial **Risk of Bias:** Moderate	**Number of Patients:** N=120 Randomized N=124 **Number of Lines:** 120 lines **Setting:** NICU **Location:** US **Dates:** December 2008-June 2011	**Intervention:** n=60 Group A: Glove use + HH • Non-sterile glove use after hand hygiene (HH) prior to all contact with the patient, inside the bed area, and with all central and peripheral venous catheters	**Outcome Definitions:** CLABSI: Centers for Disease Control and Prevention definition (2008) Possible CLABSI: detection of ≥1 blood cultures of any organism, and the presence of a central line within 72 hours in the absence of another source of infection	**Primary Outcomes:** CLABSI rate per 1000-line days: • Glove use + HH: 1.7 • HH Only: 1.9 • Ratio: 0.90 (95% CI: 0.22-3.61) • p = 0.88 CLABSI, n/N (%): • Glove use + HH: 4/60 (6.7%) • HH only: 4/60 (6.7%)

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
	• 4-week minimum intervention duration after birth; extended if infant required intravenous access (peripheral or central), or if line was removed and then subsequently needed **Inclusion Criteria:** All inborn or outborn [preterm] infants admitted to the University NICU were eligible for the study if they had a birth weight <1000g or gestational age <29 weeks and were <8 days old **Exclusion Criteria:** NR	• Signs were placed on a stand at the bedside of all enrolled patients (with a box of gloves) indicating group assignment and protocol. **Control/Comparison:** **Pre-intervention:** n=60 Group B: HH only • Hand hygiene (HH) alone prior to all patient, bed, and/or catheter [all central and peripheral venous catheters] contact **Device/agent:** NA **Monitoring intervention:** Hand hygiene compliance **Standard preventive measures:** • All healthcare professionals followed the 5 moments of hand hygiene from the World Health Organization guidelines for hand hygiene in healthcare, used non-sterile gloves for contact with body fluids, used sterile gloves for aseptic procedures • For both groups, non-sterile gloves were used when accessing arterial lines • CLABSI bundle for placement, maintenance, and removal of catheters • Fluconazole prophylaxis for all infants who weighed <1000g at birth	Symptomatic BSIs: growth in ≥1 blood culture and treated Late-onset invasive infection: > 72 hours after birth, ≥ 1 episodes per patient of a BSI, urinary tract infection, meningitis, and/or NEC associated with clinical signs, and symptoms of infection and treated with antimicrobials Blood (BSI), urine (UTI), cerebrospinal fluid (CSF) infections: growth of bacteria or fungi from ≥ 1 cultures Central line (CL) days: days with umbilical venous line, peripherally inserted central catheter, or surgical central venous line Contact with catheter: whenever there was central and peripheral venous catheter contact and when making or breaking a connection with the hub when: (1) giving medications or flush, (2) changing tubing, (3) accessing an injection port, and (4) adding a device Hand hygiene: using alcohol hand rub or washing hands with antimicrobial soap (e.g., 2% chlorhexidine gluconate) Presence of NEC: stage II or greater. **Sampling /Testing strategy:** Blood and urine cultures **Other notes:** None	• p = NR Possible CLABSI rate per 1000-line days: • Glove use + HH: 3.4 • HH Only: 9.4 • Ratio: 0.36 (95% CI: 0.16-0.81) • p = 0.01 Possible CLABSI, n/N (%): • Glove use + HH: 8/60 (13.3%) • HH Only: 20/60 (33.3%) • p = NR BSI (≥ 1), n/N (%): • Glove use + HH: 14/60 (23%) • HH only: 20/60 (33%) • Difference in proportion: -10% (95% CI: -26 to 6) • p = 0.22 BSI (gram-positive), n/N (%): • Glove use + HH: 9/60 (15%) • HH only: 19/60 (32%) • Difference in proportion: -17% (95% CI: -31 to -1) • p = 0.03 BSI (gram-negative), n/N (%): • Glove use + HH: 5/60 (8%) • HH only: 3/60 (5%) • Difference in proportion: 3% (95% CI: -7 to 14) • p = 0.46 BSI rate per 100 study days: • Glove use + HH: 17 • HH only: 23 • Risk Ratio: 0.63% (95% CI: 0.34 to 1.18%) • p = 0.15 Late on-set infection (any BSI, UTI, CSF, or NEC), n/N (%): • Glove use + HH: 19/60 (32%)

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
		and/or had a gestational age <28 weeks, or any infant with necrotizing enterocolitis (NEC) or gastroschisis • Antibiotic stewardship including limited use of third- and fourth-generation cephalosporins and carbapenems • Limited use of postnatal corticosteroids, histamineH2 receptor blockers, and proton pump inhibitors • Weekly changing of all nasogastric and orogastric tubes • All patients with NEC were placed in contact isolation in which gowns and non-sterile gloves were used while patients were receiving antimicrobials. • Auditing of compliance performed throughout the study		• HH only: 27/60 (45%) • Difference in proportion: -12% (-28 to 6%) • p = 0.13 Any infection rate per 100 study days: • Glove use + HH: 27 • HH only: 35 • Risk Ratio: 0.67% (95% CI: 0.41 to 1.10%) • p = 0.12 **Topic-specific outcomes:** Central line days / patient days (%): • Glove use + HH: 2,374/5,323 (44.6%) • HH only: 2,125/5,303 (40.1%) • p = 0.43 Hand hygiene compliance, observed monthly (%): • 2,675/3,385 (79%) **Adverse events:** NR

Table 12 Risk of Bias of Randomized Controlled Trials on Using Non-Sterile Gloves After Hand Hygiene

	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
Kaufman 2014[1]	✓	✓			✓		✓	✓		✓	Moderate

C.2. Central Line Type

Key Question 2: In NICU patients requiring central venous catheters, does the use of one central line catheter type, compared with another, prevent CLABSI?

Table 13 The Summary of Evidence on UVC vs. Peripheral Catheters to Prevent CLABSI

Outcome	Findings	Quantity and Type of Evidence and Sample Size	GRADE of Evidence for Outcome and Limitations of the Evidence
CLABSI*	• One observational study[2] reported a two-fold increase in the risk of CLABSI for UVCs compared with PICCs in a multivariable analysis (aHR 1.00 vs. 0.51 (95% CI: 0.40 – 0.66)). • Two observational studies suggested no difference in the incidence of CLABSI when comparing UVC and PICCS. • One observational study[3] reported no difference in the incidence of catheter removal for CLABSI for UVCs compared to PICCs (15% vs 19%, p = NR). This result may have been confounded by shorter dwell time for UVCs compared with PICCs (6.9±2.7 vs 10.2±5.2, p <0.001). • One observational study[4] found no difference in the rate of CLABSI for UVC compared with PICCs (P = 0.952)	3 OBS n= 3985 lines[2] n=203 lines[3] n = 71 lines[4]	Very Low • Inconsistency: studies reporting different results
Catheter-associated BSI*	• One observational study reported no difference in the risk developing a CA-BSI per when comparing PICCs and UVCs (Adjusted IRR:1.18 (95% CI: 0.59–2.34); p = 64).	1 OBS n=540 lines[5]	Very Low • Imprecision: only one study
Late Onset Sepsis*	• One observational study reported no difference the risk of developing a CA-BSI per when comparing PICCs and UVCs (Adjusted IRR: 1.06 (0.64–1.75); p = 82).	1 OBS n=540 lines[5]	Very Low • Imprecision: only one study
Adverse Events	• Two observational studies noted no difference in adverse events associated with both UVCs and PICCs including obstruction, extravasation, dislocation, and leakage.	2 OBS n=203 lines[3] n = 71 lines[4]	Very Low • Imprecision: only one study

Table 14 The Summary of Evidence for the Efficacy of All Catheter Types to Prevent CLABSI

Outcome	Findings	Quantity and Type of Evidence and Sample Size	GRADE of Evidence for Outcome and Limitations of the Evidence
CLABSI*	• One observational study[6] found a higher incidence of CLABSI for tunneled catheters, PICC, and CVCs when compared with UVCs (p = 0.001); however in multivariable analysis, central line insertion in the operating theater (including CVCs and tunneled catheters) was a significant risk factor for CLABSI (OR 8.1 (95% CI 1.2 – 54.7); p = 0.03. • One large multicenter observational study[7] found the incidence of CLABSI for tunneled catheters was 2.4 times as high as the CLABSI incidence for PICCs (p<0.001). The accompanying median dwell time was shorter for PICCS than it was for tunneled catheters. • One observational study[8] reported a higher rate of CLABSI for PICCs than for extended dwell peripheral intravenous catheters (EPIV) (0 vs. 0.68/ 1000 days; p = NR) • One observational study[9] found no difference in the incidence of UAC, UVC, short duration venous catheter, PICC, and tunneled catheters (P =0.816).	4 OBS n=95 lines[6] n=15,567 lines[7] n = 400 lines[9] n = 2,828 patients[8]	Very Low • Inconsistency: studies reported different results

Outcome	Findings	Quantity and Type of Evidence and Sample Size	GRADE of Evidence for Outcome and Limitations of the Evidence
Catheter associated-BSI*	• One observational study (de Brito 2010) reported a higher rate of catheter associated BSI for PICCs than for other catheters (including UVC, intracaths, and phlebotomy catheters) (p<0.01).	1 OBS n = 461[10]	Very Low • Imprecision: only one study, wide confidence intervals
Nosocomial BSI*	• One observational study reported higher infection rates associated with percutaneous venous and tunneled catheters compared with UVCs (Crude RR: 1, p<0.05).	1 OBS n=19,507 infants[11]	Very Low • Imprecision: only one study
Nosocomial Sepsis*	• One observational study reported higher sepsis incidence associated with tunneled and percutaneous catheters compared with umbilical catheters (p<0.0001).	1 OBS n=3,107 lines[12]	Very Low • Imprecision: only one study
Infiltration	• One observational study found higher rates of infiltration associated with PICCs compared with UAC, UVC, short duration venous catheter, and tunneled catheters (IR: 12.4 CLABSI/ 1000 days).	1 OBS n = 400 lines[9]	Very Low • Imprecision: only one study
Adverse events	• One observational study reported a higher rate of obstruction, peritonitis, and premature ventricular contractions in infants with PICCs compared with EPIVs, however infants with EPIVs received a higher incidence of hyaluronidase treated IV fluid extravasation.	1 OBS n = 2,828 patients[8]	Very Low • Imprecision: only one study

Table 15 Extracted Information on Central Line Type

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
Author: Konstantinidi[4] **Year:** 2019 **Study Design:** Cohort study **Risk of Bias:** Moderate	**Number of patients:** N = 71 VLBW **Number of lines:** N=71 **Setting:** Tertiary NICU **Location:** Greece **Dates:** 18 months (NR when) **Inclusion Criteria:** (1) Birth weight below 1500 g and gestational age < 32 weeks. Gestational age was defined by strict criteria, prioritizing menstrual dating confirmed by early ultrasound. (2) Insertion of CVC (UVC or PICC) in our NICU. **Exclusion Criteria:** (1) Catheter removal within 24 h following insertion because of inappropriate line tip	**Study Groups:** Group A: n= 34 PICC (Because UVC insertion failed during first 3 days of life) • Insertion was performed during the morning shift by a trained group of neonatologists and nurses. The same group was also responsible for infant monitoring and catheter removal. Group B: n= 37 UVC only, no PICC insertion UVC access (with single-lumen umbilical catheters) of • The inferior vena cava was performed by a group of trained neonatologists within the incubator, under sterile conditions.	**Outcome Definitions:** CLABSI: CDC definition: Presence of bacteria in a single blood culture (for organism not commonly present on the skin), or in two or more blood cultures (for organisms commonly present on the skin), obtained from a symptomatic infant either within 48 h after a central catheter insertion or within a 48-h period following catheter removal, and not related to an infection at another site Probable but unproven sepsis: Either clinical signs (aggravated clinical status presenting with apnea, hyperthermia or hypothermia, tachycardia or bradycardia, hypotension, hyperglycemia), and/or on laboratory findings (elevated C-reactive protein along with two of the following: Immature/mature white blood cell ratio > 0.2, low (<100,000) platelet count, neutrophils white blood cell	**Primary Outcomes:** CLABSI Rate/ 1000 line days: • PICC: 2.28 • UVC: 2.59 • p = 0.952 CLABSI Incidence: • PICC: 1/34 (2.9%) • UVC: 1/37 (2.7%) • p = 0.952 **Topic-specific outcomes:** Catheter dwell time mean±SD (days) • PICC: 11.91 ± 6.93 • UVC: 10.43±5.38 • p = 0.152 **Adverse events:** NR Obstruction, n/N (%) • PICC: 1/34 (2.9%) • UVC: 0 Local edema +skin irritation, n/N (%) • PICC: 2/34 (5.88 %) • UVC: 0

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
	position, as the complication rate was expected to be low due to the short indwelling time; (2) CVC insertion in another center, because of possible differences or incomplete data regarding the insertion procedure that might affect the complication rate; (3) congenital abnormality; and (4) necrotizing enterocolitis (NEC) Bell stage II or III, during the first five days of life.	**Device/agent:** Catheter type **Standard preventive measures:** • Choice of catheter was based on protocol. • In VLBWs infants scheduled for a long NICU hospitalization, the preferred option was catheter insertion in the umbilical vein on the first or second day of life. In case the first UVC insertion attempt in the inferior vena cava failed or in case of early UVC catheter removal due to various reasons, a PICC insertion was performed, usually after the third day of life. • Skin antiseptic preparation included cleansing the site three times with a cotton swab remoistened with povidone-iodine 10%. To avoid prolonged exposure to iodine, skin sites disinfected with povidone-iodine were wiped with sterile normal saline solution after 60 s until all antiseptic stains were removed. • The distal edge of the catheter was disinfected with a 0.5% chlorhexidine/alcohol 70% solution at least three	count of <1500 without positive blood culture, and being defined as a systemic condition resulting from an adverse reaction to the presence of an infectious agent that was neither present nor incubating at the time of admission to the hospital **Sampling /Testing strategy:** Whenever a neonate presented with clinical signs or symptoms of sepsis, blood culture was performed prior to antibiotic therapy initiation. Blood specimens were collected through peripheral venipuncture, on separate occasions: from at least two separate blood draws on the same or consecutive calendar days, or two separate site preparations (decontamination steps) performed during specimen collection. No blood specimens were drawn through **Other notes:** None	Skin irritation, n/N (%) • PICC: 1/34 (2.9 %) • UVC: 0

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
		times daily, according to the instructions of the Infectious Diseases Committee of Hospital		
Author: Chenoweth[8] **Year:** 2018 **Study Design:** Prospective cohort study **Risk of Bias:** Moderate	**Number of patients:** N = 2,828 **Number of lines:** N= NR **Setting:** Level III NICU **Location:** USA **Dates:** August 2012 – December 2016 **Inclusion Criteria:** All neonates who were 32 weeks of gestation or older and weighed 1500 g or more at birth with EPIV catheter, PICC, and/or PIV catheter placements. **Exclusion Criteria:** NR	**Study Groups:** All PIV: 2,828 EPIV: n=432 • Neonates who are 32 weeks of gestation or more and weighing 1500g or more at birth with difficult or limited venous access that is likely to be required up to 4 weeks. • Excluded: Neonates requiring fluid greater than dextrose 12.5% concentration, total parenteral nutrition osmolarity greater than 900 mOsm/L, and/or medications that are administrated via central catheters. PICC: n=202 • PICC Group inclusion criteria: NR **Device/agent:** Catheter type **Standard preventive measures:** Implemented a CLABSI	**Outcome Definitions:** CLABSI: NR Complications: NR **Sampling /Testing strategy:** None **Other notes:** None	**Primary Outcomes:** CLABSI rate/ 1,000 line days • EPIV: 0 • PICC: 0.68 • p = NA **Topic-specific outcomes:** Catheter dwell time, mean (SD), days • EPIV 4.0 (2.3) • PICC: 7.31 (4.4) • p < 0.001 **Adverse events:** Incidence of hyaluronidase treated IV fluid extravasation, % • EPIV: 1.2 • PIV: 3.9 • p = 0.004 Premature ventricular contractions, rate/ 1000 catheter days • EPIV: 0 • PICC: 0.68 • p = NA Superior vena cava obstruction, rate/ 1000 catheter days • EPIV: 0 • PICC: 0.68 • p = NA Peritonitis rate/ 1000 catheter days • EPIV: 0 • PICC: 0.68 • P = NA Success rate (%) • EPIV: 71.1

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
				• PICC: 83.6 • p = 0.001

Author:
Geldenhuys[6]
 	
Year: 2017
 	
Study Design:
Retrospective case control study
 	
Risk of Bias:
Low
	Number of patients:
	N = 95
	Number of lines: N=95
	
	Cases were significantly younger in GA than control, and had longer lengths of stay
	
	Setting: NICU and NICU wards
	
	Location: South Africa
	
	Dates: August 9, 2012 – July 31, 2014
	
	Inclusion Criteria:
	• All cases within the 2-year study period
	• 4 randomly selected controls per CLABSI event were included.
	• Central line insertion requirements include:
	  • Neonates who need TPN and/or inotropes
	  • neonates who require intravenous fluids and/or antibiotics where peripheral intravenous access is not possible or difficult to obtain
	
	Exclusion Criteria:
	Umbilical arterial lines
		Case:
		CLABSI n=19
		
		Control:
		Non-CLABSI n=76
		• 4 random controls were selected for each case
		
		Device/agent: Catheter type
		
		Standard preventive measures:
		• Implemented a CLABSI surveillance program, and insertion and maintenance bundles at start of study (no baseline data)
		• UVCs and PICCs are inserted by pediatric registrars or medical officers
		• CVCs and Tunneled lines are inserted in patients in whom intravenous access is difficult, where attempts at insertion of other central lines have failed, and/or in post-surgical patients who need TPN.
		• Tunneled lines are inserted by the pediatric surgical team and CVCs by either the pediatric surgery or anesthetic team.
			Outcome Definitions:
			HAI: CDC/NHSN 2014 definition used
			
			CLABSI:
			• Laboratory-confirmed bloodstream infection (LC-BSI) in a patient with a central line in situ for at least 2 calendar days (where line insertion is day 1).
			• LC-BSI occurred within 1 day of line removal
			• The definitions for HAI and LC-BSI must be met before the definition of CLABSI can be applied, and other HAI must be excluded.
			
			CLABSI rate per 1000 central line days is calculated by dividing the number of CLABSIs by the number of central line days and multiplying the result by 1000.
			CLABSI bundle: strategy for insertion and maintenance of central lines, which includes several evidence-based best practices implemented simultaneously
			Line days: total number of days of exposure to central venous catheters by all patients in the selected population and time period
			Adverse events: NA
			
			Sampling /Testing strategy: Blood cultures
			
			Other notes:
			• Gram-negative pathogens were (54%) dominant pathogens and half the premature infants had surgery (stoma repairs)
				Primary Outcomes:
				CLABSI Rate (overall):
				• 5.9/1 000 line days
				CLABSI Incidence:
				• UVC: 6/55 (10.9%)
				• PICC: 6/23 (26%)
				• CVC: 4/14 (28%)
				• Tunneled: 3/3 (100%) (3 tunneled lines inserted in 2-year period and all 3 developed CLABSI)
				• p = 0.001
				
				CLABSI Incidence by insertion setting:
				• NICU: 12/82 (14.6%)
				• Theatre: 6/8 (75%)
				• Neonatal Ward: 1/5: (20%)
				• p = 0.001
				• OR: 8.1 (95% CI 1.2 – 54.7)
				• p = 0.03
				
				Topic-specific outcomes:
				Catheter dwell time in NICU (incidence) Overall p = 0.007
				< 4 days
				• Case: 2/19 (11%)
				• Control: 34/76 (45%)
				4 - 8 days
				• Case: 9/19 (47%)
				• Control: 30/76 (39%)
				> 8 days
				• Case: 8/19 (42%)
				• Control: 12/76 (16%)
				
				Time to CLABSI after line insertion (median IQR)
				• UVC: 2 days (2-4)
				• PICC: 9 days (6-13)
				• CVC: 7 days (6-10)
				• Tunneled: 20 (19-35)
				
				Catheter dwell time in NICU for CLABSI, (median IQR)

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
				• All line types: 8 days (14-18) • UVC: 4 days (3-5) • PICC: 13 days (8-13) • CVC: 8 days (8-11) • Tunneled: 22 days (21-36) **Adverse events:** NR Attributable Mortality: • 3/5 (60%)
Author: Sanderson[2] **Year:** 2017 **Study Design:** Retrospective cohort study **Risk of Bias:** Low	**Number of patients:** • UVC only: 1392 • PICC only: 1317 • UVC & PICCs: 1276 **Number of Lines:** • UVC only: 1392 • PICC only: 1317 • UVC & PICCs: 1276 **Setting:** Tertiary NICUs (n =10) **Location:** Australia **Dates:** January 1, 2007 – December 31, 2009 **Inclusion Criteria:** All infants: • Born within study period • Admitted to one of 10 NICUs • with UVC or PICC inserted • with 1st CVC insertion for ≥ 4 h • 1 or more CVCs inserted throughout admission during study period **Exclusion Criteria:** • CLABSIs occurring within the first 48 hours of life	**Study Groups:** UVC only (n=2668) PICCs only (n = 3332) **Device/agent:** Catheter type **Standard preventive measures:** NR	**Outcome Definitions:** CLABSI: • (CDC, 2016) late onset sepsis (LOS) with positive blood culture taken after the first 48 h of a CVC being in situ • (NSW Health criteria, 2008) 48 h of CVC removal • CLABSI episodes were assigned to the CVC in situ according to this 48 h post-insertion or post-removal cut-off criteria if there were overlaps of CVC. Incidence of CLABSI: number of episodes / 1000 catheter-days and number of episodes / 1000 catheters inserted. Early onset sepsis (EOS): positive blood culture in an infant taken within the first 48 hours of life and a clinical picture consistent with sepsis. Late onset sepsis (LOS): positive blood culture, clinical symptoms, and signs of sepsis and clinician decision to treat with antibiotics for ≥ 5 days, including coagulase-negative staphylococci (CoNS) in the Australian neonatal population, (consistent with the definitions used by NICHD Network, Vermont Oxford	**Primary Outcome:** CLABSI Multivariable hazard ratio, aHR (95% CI) • UVCs:1.00 • PICCs: 0.51 (0.40 – 0.66) • p = NR CLABSI rate per 1000 days • UVCs: 9.88 CLABSI / 1000 days • PICCs: 9.09 CLABSI/ 1000 days • p = NR CLABSI incidence (% of catheter) • UVCs: 116/ 2668 (4.3%) • PICCs: 287/ 3332 (8.6%) • p < 0.01 **Topic-specific outcomes:** Catheter days to CLABSI median, (IQR) • UVCs: 5.3 days (3.6, 7.3) • PICCs: 8.1 days (5.2, 12.5) • p < 0.01 **Adverse events** NA

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
			Neonatal Network and the Canadian Neonatal Network) Causative pathogen: organism cultured in the first episode of CLABSI of any CVC Adverse events: NA **Sampling /Testing strategy:** Blood cultures **Other notes:** • Time to first CLABSI episode was used if there were multiple CLABSI episodes in the same CVC. The primary outcome was the first CLABSI in a UVC or PICC.	
Author: Soares[9] **Year:** 2017 **Study Design:** Retrospective cohort study **Risk of Bias:** Low	**Number of patients:** N = 240 **Number of lines:** N= 400 central lines **Setting:** Level III NICU, in a regional hospital **Location:** Portugal **Dates:** July 1, 2014 – June 31, 2016 **Inclusion Criteria:** • Admitted to NICU during study period who had a central line placed **Exclusion Criteria:** • Neonates in NICU for less than 3 days • Neonates with central lines inserted and removed same day	**Study Groups:** Patients with infectious central line complications n= 51 Patients without infectious central line complications n= 189 **Standard preventive measures:** • Radiograph obtained after the last repositioning for CTP evaluation • Central lines were removed due to elective (end of therapy, discharge or death) or non-elective reasons • Catheter removal because of CLABSI is only required if clinical deterioration after starting antibiotherapy or	**Outcome Definitions:** Infectious complications: CLABSI: (CDC 2008 NHSN criteria) a primary bloodstream infection in a patient with a central line at the time or within 48-h period before the onset of sepsis clinical signs, without another identifiable infection source and with a positive blood culture, collected when possible from central line. Line days to infection: number of days from line placement to onset of sepsis signs CLABSI mortality: considered if cases whose autopsy report referred to it Central venous catheters (UVC, PICC, Tunneled, and short duration venous catheter (SDVC)): central if the tip was located at superior vena cava (SVC), inferior vena cava (IVC), or at SVC/IVC-right atrium junction and non-central if located elsewhere	**Primary Outcomes:** CLABSI Rate (overall): 12.4 CLABSI/ 1000 days CLABSI Incidence (Overall): 48/240 (20%) Infectious complications • UACs: 3/55 (5.5%) • UVC: 6/84 (7.1%) • Tunneled: 3/22 (13.6%) • SDVC: 9/57 (15.8%) • PICC: 30/182 (16.5%) • p = 0.816 **Topic-specific outcomes:** Length of catheter stay, (min-max) • UACs: 6 (2-28) • UVC: 5 (2-18) • Tunneled: 16 (4-94) • SDVC: 11 (2-37) • PICC: 10 (2-46) • p < 0.001 **Adverse events** Mortality rate: • CLABSI related: 21.4%

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
		persisting or relapsing bacteremia. • Tip culture follows central line removal	Length of catheter stay: the number of days the line stayed in the patient Central line utilization ratio: the number of catheter-days divided by the number of patient-days. **Adverse events:** Mechanical complications: occlusion, breakage, external leaking, infiltration, vasospasm, bleeding, phlebitis, exteriorization, pneumothorax, pericardial and pleural effusion, and cardiac tamponade Catheter related thromboembolism: catheter occlusion due to the presence of a thrombus; confirmed by echocardiography or ultrasonography. Occlusion: inability to infuse through a line or inability to flush it External leaking: a collection of intravenous fluid under the catheter dressing Infiltration: fluid extravasation into soft tissues and diagnosed by the inability to infuse fluid associated with swelling in the region of the catheter tip Phlebitis: inflammation tracking along the path of a non-occluded venous catheter expressed as tenderness, erythema, and/or induration at the surrounding area of the insertion site. Exteriorization: migration of the catheter until its tip surfaces Pleural or pericardial effusion: the escape of fluid from blood vessels and its collection, respectively, in pleural or pericardial space **Sampling /Testing strategy:** Blood cultures	Type of complications Mechanical • UACs: 5/55 (9.1%) • UVC: 6/84 (7.1%) • Tunneled: 7/22 (31.8%) • SDVC: 9/57 (15.8%) • PICC: 45/182 (24.7%) • p = 0.816 Infiltration • UACs: 0/55 (0%) • UVC: 0/84 (0%) • Tunneled: 2/22 (9.1%) • SDVC: 1/57 (1.8%) • PICC: 28/182 (15.4%) • p = 0.003 Rate of non-elective removals • UACs: 7/55 (13.0%) • UVC: 9/84 (11.7%) • Tunneled: 7/22 (46.7%) • SDVC: 11/57 (19.6%) • PICC: 62/182 (39.5%) • p < 0.001

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
			Other notes: • Time to first CLABSI episode was used if there were multiple CLABSI episodes in the same CVC. The primary outcome was the first CLABSI in a UVC or PICC.	
Author: Greenberg[7] **Year:** 2015 **Study Design:** Retrospective cohort study **Risk of Bias:** Low	**Number of patients:** N = 13,327 **Number of lines**: N = 15,567 **Setting:** Multicenter NICU (141 NICUs; 13 states) **Location:** USA **Dates:** September 2011 – August 2013 **Inclusion Criteria:** • Infant with PICCs or tunneled catheters obtained from NCLABSI database during study dates **Exclusion Criteria:** • Central lines inserted and removed within the first 2 days • Positive blood cultures occurring within 2 days of line placement	**Study Groups:** Tunneled catheters (n = 1116) PICCs (n = 14,451/15,567; 93%) **Device/agent:** Catheter type **Standard preventive measures:** Participating sites adopted a central catheter insertion and maintenance bundle which included: • Hygiene for insertion • Daily assessment of line need • A recommendation to remove central lines when infants achieved 120 mL/kg per day of enteral feedings • Techniques for sterile dressing changes and catheter access • Antibiotic practices were not standardized between the sites	**Outcome Definitions:** CLABSI: NHSN 2008 definition. • Positive blood culture for a recognized pathogen not related to an infection at another site • Systemic signs and symptoms of infection and isolation of the same organism from ≥ 2 blood cultures drawn on separate occasions. CLABSI attribution: • If a single catheter had multiple associated positive blood cultures (occurred on 12 occasions), only the first positive blood culture was included in the analysis. • If a CLABSI occurred in the presence of multiple catheters (this occurred on 3 occasions), the CLABSI was attributed to both catheters. Dwell time: number of days from line insertion until either line removal or day of CLABSI. The day of line insertion was defined as line day 1; weeks of dwell time were categorized into 7-day periods starting on line day 3 (week 1 = line days 3–9, week 2 = line days 10–16, etc.). Adverse events: NR **Sampling /Testing strategy:** Blood cultures **Other notes:** None	**Primary Outcome:** CLABSI Incidence • Tunneled catheters: 39/1116 (3.5%) • PICCs: 199/ 14,451 (1.4%) • p <0.001 CLABSI Rate • 0.93 CLABSI / 1000 catheter days CLABSI by dwell time (highest) Week 1 • Tunneled catheters: 5/1116 (0.4%) • PICCs: 82/14,451 (0.6%) Week 2 • Tunneled catheters: 5/969 (0.5%) HR: 1.3 (0.4 – 4.4) • PICCs: 56/8250 (0.7%); HR 1.2 (0.9 – 1.7) Week 3 • Tunneled catheters: 3/748 (0.4%) HR: 1.0 (0.2 – 4.4) • PICCs: 31/4061 (0.8%); HR 1.3 (0.8 – 1.9) Week 4 • Tunneled catheters: 2/580 (0.3%) HR: 0.9 (0.2 – 4.7) • PICCs: 5/2209 (0.2%); HR 0.4 (0.1 – 0.9) Week 5 • Tunneled catheters: 23/452 (0.7%) HR: 1.8 (0.4 – 7.6) • PICCs: 7/1290 (0.5%); HR 0.9 (0.4– 1.9) Week 6 • Tunneled catheters: 4/355 (1.1%) HR: 3.2 (0.8 – 12.0) • PICCs: 7/765 (0.9%); HR 1.5 (0.7– 3.2) Week 7 • Tunneled catheters: 4/280 (1.4%); HR 4.0 (1.1-15.4)

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
				• PICCs: 4/453 (0.9%); HR 1.4 (0.5-4.0) Week 8 • Tunneled catheters: 1/288 (0.4%); HR 1.3 (0.1-20.3) • PICCs: 2/183 (1.1%); HR 1.5 (0.4-6.3) Week 9 • Tunneled catheters: 3/178 (1.7%) • PICCs: 2/183 (1.1%) Week 9 • Tunneled catheters: 1/151 (0.7%); HR: 2.0 (0.2-17.7) • PICCs: 0/125 (0) **Topic-specific outcomes:** Catheter dwell time median, (IQR) • Tunneled catheters: 24.5 d (14-45) • PICCs: 11 d (7-18) • p < 0.001 **Adverse events:** NR

Author: Shalabi[5]
 	
Year: 2015
 	
Study Design: Retrospective matched cohort study
 	
Risk of Bias: Low
	Number of patients:
	N=540
	PICC only: N = 180
	
	UVC only: n=180
	UVC + PICC: n=180
	
	Setting: tertiary level NICU
	
	Location: Canada
	
	Dates: January 1, 2010 – December 31, 2013
	
	Inclusion Criteria:
	• Preterm infants born at less than 30 weeks' gestational age
	• Admitted to CNN NICUs within study period
	• Received either a UVC or PICC on the first day after birth (day 1) as their venous access
	• MATCHING
	• Because a small number of infants were expected in the PICC group, eligible infants were first for that group.
	• Once the infants in the PICC group were identified, the UVC and UVC + PICC groups were formed by randomly selecting infants from the pool of eligible infants by matching 1:1 for gestational age in weeks, gender, and birth weight 6 100 g.
	
	Exclusion Criteria:
	• Infants who had a major congenital anomaly
		Study Groups:
		UVC only (n=180)
		• Infants who received a UVC on day 1 and did not receive any other central venous access
		
		PICC only (n=180)
		
		• Infants who received a PICC on day 1 and never received a UVC
		
		UVC + PICC (n=180)
		• Infants who received a UVC on day 1 that remained in place for a minimum of 4 days followed by placement of a PICC.
		
		Device/agent: Catheter type
		
		Standard preventive measures:
		• Patients with multiple episodes of infections were counted once.
		• A patient was identified as having a second episode of infection only after 7 days of treatment with the appropriate antibiotic for the previous episode
			Outcome Definitions:
			CABSI: presence of bacteria or fungus in 1 or more blood cultures obtained from a symptomatic infant after 2 days of placement of a central catheter or within a 48-hour period after catheter removal.
			• Did not mandate the need for 2 blood cultures or a blood culture to be drawn from the catheter for diagnosis of CABSI.
			• Did not include cultures from the catheter tip in the definition of CABSI
			• A patient who had a UVC removed and a PICC inserted on the same day and then developed an infection within 2 days was counted as CABSI associated with UVC and not PICC.
			
			Incidence was calculated per 1000 catheter days and as raw incidence
			
			Rate of any LOS: presence of bacteria or fungus in 1 or more blood cultures from a symptomatic infant
			
			Adverse events: NR
			
			Sampling /Testing strategy: Blood cultures
			
			Other notes:
			• Clinical practice of removing UVCs by 5 to 7 days after birth, whereas PICCs are removed mostly when not needed or when complications occur
				Primary Outcomes:
				CABSI Rate: CABSI / 1000 catheter days
				• UVC: 7.8
				• PICC: 9.3
				• UVC + PICC: 8.2
				• PICC vs UVC: P = 0.60
				  • Adj Incident Rate: 1.18 (0.59-2.34)
				  • p = 0.64
				• PICC vs UVC + PICC: p = 0.55
				  • Adj Incident Rate: 1.33 (0.83-2.15)
				  • p = 0.23
				• UVC vs UVC + PICC: p = 0.89
				  • Adj Incident Rate: 1.13 (0.59-2.16)
				  • p = 0.71
				
				CABSI Incidence, n (%)
				• UVC: 12/180 (7%)
				• PICC: 28/180 (15%)
				• UVC + PICC: 37/180 (21%)
				• PICC vs UVC: P < 0.01
				• PICC vs UVC + PICC: p = 0.22
				• UVC vs UVC + PICC: p < 0.01
				
				LOS (Late Onset Sepsis)
				Rate: / 1000 catheter days
				• UVC: 13.7
				• PICC: 13.3
				• UVC + PICC: 9.3
				• PICC vs UVC: P = 0.89
				  • Adj Incident Rate: 1.06 (0.64-1.75)
				  • p = 0.82
				• PICC vs UVC + PICC: p = 0.05
				  • Adj Incident Rate: 1.73 (1.15-2.60)
				  • p <0.01
				• UVC vs UVC + PICC: p = 0.12
				  • Adj Incident Rate: 1.63 (0.97-2.76)
				  • p = 0.06
				Incidence, n (%)
				• UVC: 21/180 (12%)
				• PICC: 40/180 (22%)
				• UVC + PICC: 42/180 (23%)
				• PICC vs UVC: P < 0.01
				• PICC vs UVC + PICC: p = 0.80

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
	• Infants who were moribund on admission • Had early onset sepsis • Did not receive a central catheter on day 1			• UVC vs UVC + PICC: p < 0.01 **Topic-specific outcomes:** Catheter days • UVC: 1532 days • PICC: 3012 days • UVC + PICC: 4515 days • p = NA Duration of UVC, median (IQR), d • UVC: 8 (6-10) • PICC: NA • UVC + PICC: 7 (5-9) • PICC vs UVC: p = NA • PICC vs UVC + PICC: p = NA • UVC vs UVC + PICC: p < 0.01 Duration of PICC, median (IQR), d • UVC: NA • PICC: 13 (9-19) • UVC + PICC: 13 (8-22) • PICC vs UVC: p = NA • PICC vs UVC + PICC: p = 0.49 • UVC vs UVC + PICC: p = NA **Adverse events**: NR
Author: Arnts[3] **Year:** 2014 **Study Design:** Retrospective observational study **Risk of Bias:** Low	**Number of patients:** N = 232 **Number of lines:** N= 203 CVCs **Setting:** Level III NICU **Location:** NR **Dates:** 16-month period 2005-2006 **Inclusion Criteria:** • Gestational age between 24 and 42 weeks	**Study Groups:** **UVCs:** n=140 UVCs UVCs are typically inserted in the umbilical vein in the first 2 days postpartum. Insertion technique: • Inserted under aseptic conditions by trained neonatologists, nurse practitioners, and resident physicians, all of whom follow a standardized protocol outlining the insertion practices.	**Outcome Definitions:** CLABSI: CDC definition: patients < 1 year old, laboratory-confirmed bloodstream infection with UVC or PICC in place for a minimum of 2 days or in place on the day of event or the day before 4 Laboratory-confirmed BSI: • Criterion 1- one or more positive blood cultures with the exception of skin micro-organisms, not related to another source • Criterion 2- Clinical signs of sepsis (especially for patients < 1 year old) and two or more positive blood cultures drawn on separate occasions with the same micro-	**Primary Outcomes:** CLABSI: Total rate = 20.5 per 1000 CVC days Total incidence = 13/203 (16.3%) Incidence: • UVC: 21/140 (15%) • PICC: 12/63 (19%) • p = NR **CDC CLABSI—Laboratory-confirmed BSI (Criteria 1 and 2)** Total rate = 8 per 1000 CVC days Total incidence = 20/203 (9.8%) Incidence • UVC: 6/140 (4.3%) • PICC: 7/63 (11.1%) • p = NR

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
	• CVC (UVC or PICC) inserted in ward **Exclusion Criteria:** • Catheter removed within 24 hours after insertion. • CVC inserted in another center. • Underwent extracorporeal membrane oxygenation (ECMO) treatment UE	• Catheter is fixed with a suture through the umbilical jelly. • A second fixation of the catheter with plaster on the abdominal wall using a neo-bridge construction is generally performed for additional safety **PICCs:** n=63 PICCs inserted via the Seldinger technique. • PICCs are inserted by trained neonatologists under maximum aseptic conditions in the NICU. • After insertion, the catheter is covered at the insertion site by a sterile transparent film dressing. **Device/agent:** Catheter site and catheter type **Standard preventive measures:** • The insertion site (not the skin) was disinfected with a 0.5% chlorhexidine/ alcohol 70% solution twice daily to conform with hospital policy. • The catheter insertion site was examined by trained NICU nurses every 2 hours for signs of inflammation or leakage as a standard of care. • The entire drip system for all CVCs was replaced every 96 hours by NICU	organism (including skin micro-organisms) and no other infection source Criterion satisfied within a timeframe that did not exceed a gap of 1 day Clinical sepsis: Criterion 3- clinical signs of sepsis (criterion 2) but no or one positive blood culture (only skin micro-organisms), with no infection source other than a CVC (in-situ or removed in 24 hours) and a medical reason to initiate sepsis treatment **Adverse events:** Obstruction: difficulty or inability to flush the catheter or inability to administer fluid in 3 seconds Dislocation: NR Leakage: NR Extravasation/perforation: NR **Sampling /Testing strategy:** After CVC removal, a tip culture was not routinely performed, except when the CVC was removed due to clinical signs of sepsis. A tip culture was followed by a blood culture when possible. **Other notes:** NA	**Clinical sepsis (Criterion 3):** Total rate = 12.4 per 1000 CVC days Total incidence = 20/203 (9.8%) Incidence • UVC: 15/140 (10.7%) • PICC: 5/63 (7.9%) • p = NR **Topic-specific outcomes:** CVC indwelling time (days): • UVC: 6.9±2.7 • PICC: 10.2±5.2 • p < 0.001 **Adverse events** Obstruction: • Total rate = 3.1 per 1000 CVC days • Total incidence: 5/203 (2.5%) • UVC: 0/140 (0%) • PICC: 5/63 (7.9%) • p = NR Dislocation: • Total rate = 2.5 per 1000 CVC days • Total incidence: 4/203 (2.0%) • UVC: 4/140 (2.9%) • PICC: 0/63 (0%) • p = NR Leakage: • Total rate = 2.5 per 1000 CVC days • Total incidence: 4/203 (2.0%) • UVC: 3/140 (2.1%) • PICC: 1/63 (1.6%) • p = NR Extravasation/perforation: • Total rate = 1.2 per 1000 CVC days • Total incidence: 2/203 (1.0%) • UVC: 0/140 (0%) • PICC: 2/63 (3.2%)

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
		nurses as a standard of care. • All CVCs used were single-lumen CVCs.		• p = NR
Author: de Brito[10] **Year:** 2010 **Study Design:** Prospective cohort study **Risk of Bias:** High	**Population:** N= 318 patients N=v461 CVCs **Setting:** 1 NICU, University Hospital **Location:** Brazil **Dates:** April 2006 – April 2008 **Inclusion Criteria:** Neonates with at least one CVC placed for >24h, followed up via NHSN. **Exclusion Criteria:** NR	**Study Groups:** UVC: n=33 PICC: n=20 Phlebotomy: n=24 Intracath: n=7 **Device/agent:** Catheter type **Standard preventive measures:** Catheters removed when no longer required for patient care, when the patient experienced an adverse event, or when catheter exchange was necessary. Catheters removed under aseptic conditions.	**Outcome Definitions:** Laboratory-confirmed BSI: isolation of recognized pathogens from blood culture that were not related to infection at another site, with > 38°C fever and with clinical signs of sepsis including apnea, temperature instability, lethargy, feeding intolerance, worsening respiratory distress or hemodynamic instability. Catheter tip colonization: absence of infection signs at the catheter insertion site and microorganism's growth≥103 CFU/mL of the catheter's tips (by quantitative culture). CVC-related BSI: presence of clinical signs for sepsis and positive hemoculture with the same microorganism present on the catheter tip (by quantitative culture) and clinical and microbiological absence of any other source of infection. CVC-associated BSI: bacteremia (isolation of the same organism with identical antibiograms from the blood drawn from peripheral veins and CVC), clinical manifestations sepsis, defervescence after removal of implicated catheter, but without laboratory confirmation of CVC colonization. Incidence density: number of infectious episodes starting during exposure to a specific type of catheter/ number of days of a specific CVC presence times 1000. **Sampling /Testing strategy:** Blood cultures **Other notes:** None	**Primary Outcomes:** CVC-associated BSI rate/ 1000 catheter days • UVC: 1.7 • PICC: 6.0 • Phlebotomy: 3.5 • Intracath: 1.9 • PICC vs. other catheters: Higher proportion observed in PICC: p<0.01 CVC-related BSI rate/ 1000 catheter days • UVC: 1.0 • PICC: 0.6 • Phlebotomy: 0.4 • Intracath: 0 **Topic-specific outcomes:** Dwell time, median, days • UVC: 5.3 • PICC: 13.6 • Phlebotomy: 15.2 • Intracath: 14.8 • UVC vs. other catheters: p = 0.02 **Adverse events:** NR

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
Author: Chien[11] **Year:** 2002 **Study Design:** Prospective cohort study **Risk of Bias:** Low	**Number of patients:** N= 19, 507 **Number of lines:** N = 19,507 **Setting:** 17 NICUs – Level III NICU **Location:** Canada **Dates:** January 1996 – October 1997 **Inclusion Criteria:** • CVC use: umbilical venous catheter; percutaneously inserted long catheter or spaghetti catheter; surgically placed Tunneled catheter. **Exclusion Criteria:** Viral infection	**Study Groups:** Umbilical venous catheter: n = 126 patients Percutaneous catheter: n = 322 patients Tunneled catheter: n = 115 patients **Device/agent:** Catheter type **Standard preventive measures:** NR	**Outcome Definitions:** Nosocomial blood stream infection: one or more positive single organism blood cultures obtained after 48 h of life in an infant with clinical suspicion of infection. • To differentiate between nosocomial and primary (maternal origin) infections, the infant blood culture isolates were required to be different from maternal isolates or to occur at least 7 days after a treated positive blood culture obtained during the first 48 hours of life Infection episode: a positive culture occurring at least 7 days after a previous treated positive culture or if the culture isolates were different from the previous culture. At risk period for CVC-related nosocomial BSI: the period from insertion of a CVC until removal of CVC or patient discharge, whichever was shorter. Not at-risk period: the length of NICU stay minus the at-risk period. CVC-related nosocomial BSI: All positive blood cultures occurring during the at-risk periods Not CVC-related nosocomial BSI: Positive blood cultures occurring during the not at-risk periods Adverse Events NR **Sampling /Testing strategy:** Blood cultures **Other notes:** None	**Primary Outcomes:** There was significant variation between hospitals in CVC-related infections even after adjusting for significant patient characteristics. Nosocomial BSI: Incidence: 6.1%; Rate: (Incidence/ 1000 Patient Days) • No CVC: 2.9/ 1000 patient days • Crude RR: 1 • UVC: 7.2 / 1000 Patient Days • Percutaneous catheter: 13.1 / 1000 Patient Days • Tunneled catheter: 12.1 / 1000 Patient Days Crude RR • UVC: 2.5 (2.1-3.1) • Percutaneous catheter: 4.6 (4.1-5.3) • Tunneled catheter: 4.3 (3.6-5.2) • $p < 0.05$ aRR for BSI: • UVC: 2.0 (1.7–2.5) • Percutaneous catheter: 3.5 (3.0–4.0) • Tunneled catheter: 3.1 (2.5–3.8) **Topic-specific outcomes:** Median duration of CVC Use (days) • UVC: 4 ± 8.9 • Percutaneous catheter: 10 ± 10.9 • Tunneled catheter: 16 ± 19.1 Interhospital variation (range) • UVC: 1.9% - 60.3% • Percutaneous catheter: 0.2% - 48.1% • Tunneled catheter: 0% - 20.5% **Adverse events** NR
Author: Bhandari[12]	**Number of patients:** N=2091	**Study Groups:** • UA: n = 1699	**Outcome Definitions:**	**Primary Outcomes:** Nosocomial sepsis:

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
Year: 1997 **Study Design:** Prospective cohort study **Risk of Bias:** Moderate	**Number of lines:** N=2091 CVCs **Setting:** 2 NICUs, 1 University Hospital & 1 Regional Hospital **Location:** USA **Dates:** NICU 1: November 11, 1987 - December 31, 1993 NICU 2: January 1, 1989 - December 31, 1993 **Inclusion Criteria:** • All neonates admitted to NICUs during respective study periods • One or more vascular catheters simultaneously or sequentially placed umbilical artery (UA), Umbilical venous (UV), central venous Tunneled (CV), percutaneously placed central venous (PC), or peripheral artery (PA). **Exclusion Criteria:** NR	• UV: n = 617 • CV: n = 294 • C: n = 308 • PA: n = 189 **Device/agent:** Catheter type **Standard preventive measures:** • UA and UV were placed either by the physicians or the neonatal nurse practitioners (NNP) at both NICUs • Central venous tunneled catheters (CV) were placed by the same group of pediatric surgeons • Peripheral arterial catheters were placed by physicians/ NNPs. • Percutaneous central venous placements were done exclusively by the NNPs using a standard protocol: sterile technique and site prep with povidone iodine at both units. • Catheter maintenance was done per nursing protocols at both hospitals: sterile dressing and IV tubing changes. • All lines had heparin infusions.	Nosocomial sepsis: Presence of clinical signs of infection, initiation of anti-microbial therapy and positive blood cultures obtained from a peripheral site or via the catheter after the third postnatal day. **Sampling /Testing strategy:** Blood/catheter tip culture. **Adverse Events:** NA **Other notes:** • Incidence of infection by comparing different catheter types. • To define an association between the duration of catheter use, type, and nosocomial sepsis, the incidence of positive blood cultures from time of insertion of catheter until 3 days after removal was analyzed for a consecutive population subset over 2.5 years at NICU 2 (Jan 7, 91- Dec 31, 1993.	Incidence, n (%) • UA: 179/1699 (10.5%) • UV: 81/617 (13.1%) • Tunneled: 99/294 (33.8%) • PC: 96/308 (31.2%) • PAC: 35/189 (18.5%) • $p < 0.0001$ Incidence by NICU (%) • NICU 1: 9.9% • NICU 2: 10.7% CVC-associated infection incidence, n (%) • CV: 17/112 (15.2%) • PC: 4/79 (5.1%) • $p < 0.05$ **Topic-specific outcomes:** (refer to Table 4 for duration of use by 1-3 days, 4-7 days, 8-14 days, and ≥15 days) • Less duration of use highest for UVC • Greater duration of use highest for UVC and CVC **Adverse events:** NA

Table 16 Risk of Bias of Two Group Studies on Catheter Types

Author Year	All study groups derived from similar source/reference populations	Attrition not significantly different across study groups	Measure of exposure is valid	Measure of outcome is valid	Investigator blinded or were outcomes well-defined and objective to endpoint assessment	Potential confounders identified	Statistical adjustment for potential confounders done	Funding source(s) disclosed and no obvious conflict of interest	Overall Risk of Bias
Arnts 2014[3]	✓		✓	✓	✓	✓	✓	✓	Low
De Brito 2010[10]	✓		✓	✓	✓	✓			Moderate
Bhandari 1997[12]	✓		✓	✓	✓	✓			Moderate
Chenoweth 2018[8]	✓	✓	✓	✓				✓	Moderate
Chien 2002[11]	✓		✓	✓	✓	✓	✓	✓	Low
Geldenhuys 2017[6]	✓		✓	✓	✓	✓	✓	✓	Low
Greenburg 2015[7]	✓		✓	✓	✓	✓	✓	✓	Low
Konstantinidi 2019[4]	✓	✓	✓	✓				✓	Moderate
Sanderson 2017[2]	✓		✓	✓	✓	✓		✓	Low
Shalabi 2015[5]	✓		✓	✓	✓	✓		✓	Low
Soares 2017[9]	✓	NO	✓	✓	✓	✓		✓	Low

C.3. Central Line Insertion Site

Key Question 3: In NICU patients requiring central venous catheters, does the use of one central line catheter insertion site, compared with another, prevent CLABSI?

Table 17 Summary of Findings on Central Line Sites to Prevent CLABSI: PICC Placement in Femoral vs. Non-Femoral Sites

Outcome	Findings	Quantity and Type of Evidence and Sample Size	GRADE of Evidence for Outcome and Limitations of the Evidence
Catheter-related sepsis*	• Two observational studies[13, 14] conducted in the same NICU population over a slightly different time period found that use of a PICC at a femoral sites was associated with a higher incidence of CRS than at non-femoral sites (N= 518 PICCs)[13] (54/240 (22.5%) vs: 34/278 (12.2%); P = 0.002)[13] or was a significant risk factor for CRS (10400).[14]	2 OBS N= 518 lines[13] N= 808 lines[14]	Very Low • Imprecision: only one study

Outcome	Findings	Quantity and Type of Evidence and Sample Size	GRADE of Evidence for Outcome and Limitations of the Evidence
Adverse events	• One observational study[14] found no difference between groups. • One observational study[13] found that patients with non-femoral central lines were more likely to experience phlebitis, catheter site inflammation, or early removal of the central line.	2 OBS[13, 1413, 1413, 1413, 1413, 1413, 1413, 1413, 14] N= 518 lines[13] N= 808 lines[14]	Very Low • Inconsistency: inconsistent results across studies

Table 18 Summary of Findings on Central Line Sites to Prevent CLABSI: CVC Placement in Jugular vs. Subclavian vs. Femoral Sites

Outcome	Findings	Quantity and Type of Evidence and Sample Size	GRADE of Evidence for Outcome and Limitations of the Evidence
CLABSI*	• One case control study[15] reported a significant increase in the odds of internal jugular placement among NICU patients with CLABSI with internal jugular placements [OR: 2.7 (95% CI: 1.5 – 5.1); p = 0.001], and no difference in the proportion of subclavian, saphenous, external jugular, or brachial placement among NICU patients with CLABSI. • One cohort study[16] examining tunneled CVCs reported no difference in the incidence of CLABSI when comparing lines placed in the femoral sites and those placed in the subclavian sites [p = 1.0)	2 OBS n = 179 lines[15] n = 601 lines[16]	Low
Catheter-associated Infection*	• One observational study[17] found that the use of subclavian sites was associated with a lower rate of catheter-associated infections compared with the jugular vein for implanted catheters in NICU patients with surgically-implanted CVCs. (p<0.01).	1 OBS n = 236 lines[17]	Very Low • Imprecision: only one study
Catheter-related sepsis*	• One observational study[18] found that the use of femoral sites was associated with a lower rate of catheter-related sepsis when compared with sites in the neck including jugular and subclavian sites for long-term, tunneled catheters in NICU patients. (p = 0.032).	1 OBS n = 137 lines[18]	Very Low • Imprecision: only one study • Study Quality: study at high risk of bias

Table 19 Summary of Findings on the Efficacy of Central Line Site to Prevent CLABSI: CVC Placement in Upper vs. Lower Extremities

Outcome	Findings	Quantity and Type of Evidence and Sample Size	GRADE of Evidence for Outcome and Limitations of the Evidence
CLABSI*	• Two cohort studies[19, 20] reported no significant difference in CLABSI incidence or rates between insertion sites (Adjusted OR: 1.23 (95% CI: 0.58-2.60); p = 0.57) [19] or [p = 0.941].[20] • One case control study reported a significant increase in the proportion of upper limb insertions among NICU patients with CLABSI than among those who did not have a CLABSI (p = 0.01), and no difference in the proportion of lower limb placements among NICU patients with and without CLABSI.	3 OBS n = 1,104 lines[19] n = 365 lines[20] n = 179 lines[15]	Low
Catheter related-BSI*	• One observational study[21] reported no significant difference in CRBSI incidence between insertion sites (UE: 43/370 (11.6%) vs LE: 10/107 (9.3%)).	1 OBS n = 477 lines[21]	Very Low • Imprecision: only one study
Sepsis*	• One observational study[20] reported no difference in the proportion of sepsis for PICCs inserted in upper and lower extremities in NICU patients (p = 0.941)	1 OBS N= 365 lines[20]	Very Low • Imprecision: only one study

Outcome	Findings	Quantity and Type of Evidence and Sample Size	GRADE of Evidence for Outcome and Limitations of the Evidence
Presumed Sepsis*	• One observational study[22] reported no significant difference between insertion sites (UE: 31 (8.3) vs LE: 18 (7.1) p = 0.6006).	1 OBS n = 626 lines[22]	Very Low • Imprecision: only one study
Adverse Events	• The upper extremity insertion site was associated with a greater risk for infiltration, [19] cholestasis,[21] effusion, and dislodgement,[20] and a shorter time to first complication.[21] • No significant difference was reported between groups for thrombus,[20] phlebitis,[19, 21, 22] occlusion,[19-21] clotting,[22] and edema.[22]	4 OBS n = 1,104 lines[19] n = 477 lines[21] n = 626 lines[22] N= 365 lines[20]	Low

Table 20 Extracted Information on Central Line Sites

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
Author: Elmekkawi[20] **Year:** 2019 **Study Design:** Retrospective cohort **Risk of Bias:** Low	**Number of patients:** N = 365 **Number of lines:** N=365 PICC lines **Setting:** NICU at quaternary children's hospital **Location:** Canada **Dates:** January 2005 – August 2010 **Inclusion Criteria:** • Neonates who had PICC lines placed in the NICU **Exclusion Criteria:** • Lines inserted by interventional radiology • Patients that were transferred out of the NICU with a PICC *in situ*, or died with a line *in situ* • PICCS that were malpositioned on the insertion X-ray	**Study Groups:** UE PICCS: n=138 Via basilic, cephalic, median cubital, or axillary veins LE PICCs: n=227 Via greater saphenous vein, lesser saphenous vein, dorsal venous arch, or popliteal vein **Device/agent:** Catheter site **Standard preventive measures:** • Majority of PICCs were inserted by specialized PICC nurses • Catheter choice and insertion site were guided by operator preference and vein availability • Procedure was performed at the bedside and ultrasound guidance was not used • Post insertion X-rays were taken with the shoulder abducted at 30 degrees for UE PICCs and	**Outcome Definitions:** Sepsis during the line: blood culture taken a minimum of 24 hours after catheter insertion and a maximum of 48 hours after catheter removal was positive **Adverse events:** Mortality: death Mechanical: occlusion or leaking Interstitial: NR Pleural or pericardial effusion: NR Phlebitis: NR Thrombus: NR **Sampling /Testing strategy:** Blood cultures **Other notes:** None	Sepsis during the line: Incidence, n (%) • UE: 18/138 (13.0%) • LE: 29/227 (12.8%) • p = 0.941 Coagulase-negative staphylococcus incidence, n (%) • UE: 12/138 (8.7%) • LE: 17/227 (7.5%) *S. aureus* incidence, n (%) • UE: 1/138 (0.7%) • LE: 1/227 (0.4%) Group *B streptococcus* incidence, n (%) • UE: 0/138 (0%) • LE: 1/227 (0.4%) Enterococcus incidence, n (%) • UE: 0/138 (0%) • LE: 1/227 (0.4%) Klebsiella incidence, n (%) • UE: 1/138 (0.7%) • LE: 3/227 (1.3%) *E. coli* incidence, n (%) • UE: 2/138 (1.4%) • LE: 1/227 (0.4%) Enterobacter incidence, n(%) • UE: 1/138 (0.7%) • LE: 2/227 (0.9%) *S. marcescens* incidence, n (%)

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
	that could not be used for infusion and removed immediately post X-ray • PICCs removed within 24 hours of insertion for malposition	the hips in 'frog' position for LE PICCs • A repeat X-ray to confirm final tip position was done if the catheter was pulled by more than 1 cm • The routine unit practice was to remove non-central PICCs within 24 hours of insertion		• UE: 0/138 (0%) • LE: 2/227 (0.9%) Proteus incidence, n (%) • UE: 1/138 (0.7%) • LE: 0/227 (0%) **Topic-specific outcomes:** Duration of catheter median, days (IQR) • UE: 17 days (8-27) • LE: 16 days (9-30) **Adverse events** Mortality, n (%) • UE: 7/138 (5.1%) • LE: 14/227 (6.2%) • p = 0.818 Mechanical (occlusion or leaking), n (%) • UE: 14/138 (10.1%) • LE: 28/227 (12.3%) Interstitial, n (%) • UE: 3/138 (2.2%) • LE: 3/227 (1.3%) Pleural or pericardial effusion, n (%) • UE: 3/138 (2.2%) • LE: 0/227 (0%) Phlebitis, n (%) • UE: 1/138 (0.7%) • LE: 10/227 (4.4%) Thrombus, n (%) • UE: 0/138 (0%) • LE: 1/227 (0.4%)
Author: Garcia[15] **Year:** 2019 **Study Design:** Nested case-control **Risk of Bias:** Low	**Number of patients:** N = 179 patients **Number of lines:** N=179 lines **Setting:** Third-care level NICU **Location:** Mexico	**Case**: CLABSI: n=74 **Control**: Non-CLABSI: n=105 **Device/agent:** Catheter site; double lumen catheter	**Outcome Definitions:** CLABSI: CDC 2018 definition • Patient ≤1 year of age has at least one of the following signs or symptoms: fever (>38.0°C), hypothermia (<36.0°C), apnea, or bradycardia, and • Organism(s) identified in blood is (are) not related to an infection at another site, and	**Primary Outcomes:** Placement site of CVC: Internal jugular, n/N (%) • OR: 2.7 (95% CI: 1.5-5.1); P = 0.001 • Case: 43/74 (58.1%) • Control: 35/105 (33.3%) • p = 0.001 Subclavian (percutaneous insertion), n/N (%) • Case: 17/74 (23%)

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
	Dates: January 2014 – December 2015 **Inclusion Criteria:** • Patients with installation of a CVC during their hospital stay at the NICU were included • Patients with first CVC installation and those with CVC duration ≥48 hours • Cases were neonates diagnosed with CLABSI • Controls were those neonates with a CVC during the same period but who did not develop a CLABSI **Exclusion Criteria:** Patients who had a catheter installed in another hospital	**Standard preventive measures:** NR	• The same common commensal is identified by a culture or non-culture based microbiologic testing method, from two or more blood specimens collected on separate occasions **Adverse events:** CLABSI-related mortality: a death directly related to the infection which occurred during active infection event and no other underlying cause of fatal outcome was present **Sampling /Testing strategy:** • Two-set of blood cultures were obtained in patients with a suspected infection • Disinfection with 2% iodine-povidone were performed • One peripheral blood culture was obtained along with a catheter-drawn blood culture **Other notes:** None	• Control: 27/105 (25.7%) • p = 0.67 Saphenous, n/N (%) • Case: 7/74 (9.5%) • Control: 16/105 (15.2%) • p = 0.25 External jugular, n/N (%) • Case: 4/74 (5.4%) • Control: 7/105 (6.7%) • p = 0.98 Upper limb, n/N (%) • Case: 1/74 (1.3%) • Control: 12/105 (11.4%) • p = 0.01 Brachial, n/N (%) • Case: 1/74 (1.3%) • Control: 5/105 (4.8%) • p = 0.21 Lower limb, n/N (%) • Case: 1/74 (1.3%) • Control: 3/105 (2.8%) • p = 0.64 Double-lumen catheter: • OR: 10.0 (95% CI: 2.3-44.3); P = 0.0001 • Case: 72/74 (97.3%) • Control: 82/105 (78.1%) **Topic-specific outcomes:** CVC indwelling total time >21 days, n/N (%): • OR: 2.9 (95% CI: 1.5-5.4); P = 0.001 • Case: 37/74 (50.0%) • Control: 27/105 (25.7%) **Adverse events** CLABSI-related mortality, n/N (%) • Case: 5/74 (6.8%) • Control: NR
Author: Litz[16]	**Number of patients:** N = 601	**Study Groups:** T-CVC: n=134	**Outcome Definitions:** CLABSI: CDC 2015 definition	**Primary Outcomes:** CLABSI

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
Year: 2017 **Study Design:** Retrospective cohort **Risk of Bias:** Low	**Number of lines:** N=601 lines **Setting:** NICU **Location:** USA **Dates:** November 2008 – October 2015 **Inclusion Criteria:** • Patients in the NICU who had T-CVCs placed between November 2008 – October 2015 or PICCs placed between July 20014 – October 2015 **Exclusion Criteria:** Patients who died or were discharged with a central venous catheter and those who were not yet discharged were excluded	PICC: n=467 **Device/agent:** Catheter type and site **Standard preventive measures:** • PICC lines are the preferred modality of vascular access in neonates and T-CVCs are typically placed in long-term access is needed or alternative vascular access is unable to be obtained • PICCs are placed and removed by a dedicated NICU vascular access team comprised of trained nurses, nurse practitioners, and physicians • T-CVCs are placed by surgeons and removed by surgical nurse practitioners, fellows, or attendings • Daily chlorhexidine gluconate treatments for patients >36 weeks and >1000g • Routine tubing and sterile cap changed every 96 hours or 24 hours for lines running lipids, propofol, or blood products • Heparinized intravenous fluid at a minimal rate (1ml/h) to maintain patency in idle lines	Line utilization ratio: the number of central line days divided by the number of patient days **Adverse events:** Line complications: mechanical (broke, infiltrated occluded), local concerns (erythema, swelling, phlebitis), malposition/ migration, or other (pleural effusion, arrhythmia, deep venous thrombosis) **Sampling /Testing strategy:** • NR **Other notes:** None	Incidence, n/N (%): • T-CVC: 14/134 (10.2%) • PICC: 10/467 (2.1%) • p = NR Incidence, % • T-CVC placed in femoral or saphenous vein: 8.5% • T-CVC placed in subclavian or jugular vein: 10.8% • p = 1.0 Incidence, rate/ 1000 line days • OR: 0.50 (95% CI: 0.11-2.22); P = 0.55 • In use T-CVC: 2.2 • Idle T-CVC: 1.1 • p = NR Incidence, rate/ 1000 line days • OR: 0.50 (95% CI: 0.11-2.22); P = 0.55 • In use PICC: 1.3 • Idle PICC: 0 • p = NR **Topic-specific outcomes:** Line utilization ratio • T-CVC: 0.52 • PICC: 0.27 • p <0.001 **Adverse events** Line complications, n/N (%) • T-CVC: 9/134 (6%) • PICC: 32/467 (6.8%) • p = NR

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
		Daily discussion of the need for a central line on rounds		
Author: Bashir **Year:** 2016[19] **Study Design:** Retrospective cohort study **Risk of Bias:** Low	**Number of patients:** N = 827 patients **Number of lines:** N=1104 PICC lines **Setting:** Tertiary NICU **Location:** Canada **Dates:** January 1, 2006 – December 31, 2010 **Inclusion Criteria:** • All preterm infants (age < 37 complete weeks) • 1st time PICCs inserted during study period **Exclusion Criteria:** • Infants with incomplete PICC data • PICCs inserted from sites other than upper or lower extremity • Neonates who were transferred out to other hospitals with an indwelling catheter and who did not return the final data	**Study Groups:** UE PICCs: n=593 Via cephalic and basilica veins LE PICCs: n=234 Via saphenous veins **Device/agent:** Catheter site **Standard preventive measures:** • Data from first time PICC used if more than one PICC placed during hospital stay • PICC lines were placed at the baby's bedside, under sterile conditions, by a dedicated team of transport nurses, neonatal physicians, and nurse practitioners • Site of insertion was selected at the discretion of the inserter based on the accessibility of veins. • During the study period, single lumen catheter 20–30 cm long with an introducer cannulae. • After the catheter was inserted, catheter tip position was confirmed by radiograph with the limbs in standard resting position, and repeat radiographs were taken if there was a manipulation.	**Outcome Definitions:** CLABSI: (CDC) • Confirmed primary bloodstream infection with one of following clinical signs of infection (fever, hypothermia, apnea, or bradycardia) • Presence of central catheter at the time of or within 48 hours before the onset of the infection Incidence of CLABSI: infection episodes per 1000 catheter days **Adverse events:** Mechanical complications considered present if there was a line infiltration, occlusion, phlebitis, and dislodgement, resulting in removal of PICC • Line infiltration: extravasation of fluid into soft tissue around the region of the catheter tip. • Line occlusion: inability to infuse fluid • Phlebitis: presence of a linear red streak developing along the superficial veins from the catheter insertion site. • Dislodgement: NR **Sampling /Testing strategy:** • Blood cultures **Other notes:** NA	**Primary Outcomes:** CLABSI: aOR: 1.23 (95% CI: 0.58-2.60); P = 0.57 Rate/ 1000-line days • UE: 4.7 • LE: 3.3 • p = NR Incidence, n (%) • UE: 35/593 (5.9%) • LE: 10/234 (4.2%) • p = 0.35 **Topic-specific outcomes:** Duration of catheter median, days (IQR) • UE: 10 days (6-15) • LE: 10.5 days (5-17) • p = 0.81 **Adverse events** Infiltration, n (%) • UE: 89/593 (15%) • LE: 15/234 (6.4%) • p = 0.001 UE vs LE, n (%) • Right: 56/320 (17.5%) vs 14/152 (9.2%) • Left: 33/273 (12%) vs 1/82 (1.2%) • p < 0.001 Adjusted OR: 2.41 (95% CI: 1.36-4.29); P = 0.003 Occlusion, n (%) • UE: 52/593 (8.7%) • LE: 31/234 (13.2%) • p = 0.054 UE vs LE, n (%) • Right: 21/320 (6.5%) vs 23/152 (15.1%) • Left: 31/273 (11.3%) vs 8/82 (9.7%) • p = 0.02 • Adjusted OR: 0.68 (95% CI: 0.41-1.10); P = 0.12 Phlebitis, n (%) • UE: 21/593 (3.5%) • LE: 9/234 (3.8%)

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
		• Optimal placement for UE: catheter tip lying beyond midclavicular area and up to 1 cm at the junction of right atrium and superior vena cava • Optimal placement for LE: catheter tip located in the inferior vena cava below the diaphragm • Heparin was infused in all PICCs as per standard unit policy. • All catheters were removed either after completion of intravenous therapy or prematurely if they developed complications.		• p = 0.83 UE vs LE, n (%) • Right: 12/320 (3.7%) vs 6/152 (3.9%) • Left: 9/273 (3.3%) vs 3/82 (3.6%) • p = 0.98 Adjusted OR: 0.88 (95% CI: 0.39-1.98); P = 0.76 Dislodgement incidence, n (%) • UE: 1/593 (0.1%) • LE: 0/234 (0%) • p = 0.63 UE vs LE incidence, n (%) • Right: 1/320 (0.31%) vs 0/152 (0%) • Left: 0/273 (0%) vs 0/82 (0%) • p = 0.66
Author: Wrightson **Year:** 2013[22] **Study Design:** Retrospective cohort **Risk of Bias:** Low	**Number of patients:** N = 559 **Number of lines:** N= 626 PICCs After Exclusion: N = 528 patients N = 655 PICCs Excluded n=29 **Setting:** Level III NICU **Location:** USA **Dates:** January 1, 2004 – December 31, 2009 **Inclusion Criteria:** • All PICCs placed in the NICU during the timeframe	**Study Groups:** Upper extremities N=374 PICCs (59.7%) For an upper extremity vein, the ideal tip location is in the superior vena cava at T2-T4 resting just above the right atrium. (NANN PICC guidelines) • Axillary 62 (16.6%) • Basilic 119 (31.8) • Cephalic 186 (49.7%) • Unspecified 7 (1.9%) Lower extremities N=252 PICCs (40.3%) For lower extremity veins, the tip should be in the inferior vena cava (IVC) at the level of the diaphragm, outside the heart. (NANN PICC guidelines)	**Outcome Definitions:** CLABSI: CDC definition Presumed sepsis: collective term for PICCs removed for suspected sepsis or positive blood cultures **Adverse Events:** Nonelective removal: unresolvable PICC complication leading to removal of the PICC prior to the completion of therapy for which the PICC was initially placed (leaking, clotting, presumed sepsis, positive blood cultures, catheter contamination, thrombosis, edema, phlebitis, pleural effusion, cardiac tamponade, central tip required, broken catheter, dislodgement, or malposition.) Clotted: NR Leaking: NR Edema/infiltrated: NR	**Primary Outcomes:** CLABSI: • CLABSI incidence/ PICCs removed for presumed sepsis: 28/50 (56%) • CLABSI Rate for PICCs removed because of confirmed sepsis: 2.86/ 1000 catheter days Presumed sepsis, n (%) • Incidence: 50/626 (8%) • UE: 31 (8.3) • LE: 18 (7.1) • p = 0.6006 PICCs removed for any complication Central Tip vs Non-central Tip • UE: 73 (72%) vs 29 (28%) • p = 0.0001 • LE: 50 (94%) vs 3(6%) • p = 0.7 **Topic-specific outcomes:** PICC dwell time, range (mean ± SD; median): • UE: 0-160 days (15 ± 13; 13) • LE: 0-76 days (16 ± 11.6; 13.5)

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
	• Central and non-central veins **Exclusion Criteria:** • Incomplete data • Neonate transfer with the PICC indwelling	**Device/agent:** Catheter site **Standard preventive measures:** • None of the study infants had concurrent PICCs • Under the supervision of the neonatologists and the clinical nurse specialist, a team of specially trained nurses has inserted and maintained PICCs at the study hospital NICU since 1999. On rare occasions, when a PICC team inserter was not available or was unsuccessful at the insertion, PICCs were placed by a physician.	**Sampling /Testing strategy:** Culture **Other notes:** • No PICC complications contributed directly to a neonate's death. • 2% chlorhexidine gluconate for skin antisepsis was implemented during the study period. Authors do not note when, and note it was only for infants weighing >1200 g or older than 2 weeks. Authors note "its impact on the sepsis rates during the study period is unknown."	• p = 0.2038 **Adverse events** Phlebitis, n (%) • UE: 4 (1.1) • LE: 5 (2) • p = 0.4958 Clotted, n (%) • UE: 20 (5.4) • LE: 16 (6.4) • p = 0.5976 Leaking, n (%) • UE: 16 (4.3) • LE: 4 (1.6) • p = 0.0605 Edema/infiltrated, n (%) • UE: 15 (4) • LE: 5 (2) • p = 0.1574
Author: Tsai **Year:** 2011[14] **Study Design:** Retrospective cohort study **Risk of Bias:** Low	**Number of patients:** N = 534 **Number of lines:** N= 808 Percutaneously inserted CVCs **Setting:** Level III NICU **Location:** Taiwan **Dates:** January 2004 – December 2007 **Inclusion Criteria:** • Premature infants with BW ≤ 1500g **Exclusion Criteria:** • Early death unrelated to PICC insertion • No PICC needed	**Study Groups:** Old type n=518 Percutaneously inserted CVCs (334 patients) Non-femoral n= 278 (190 patients) Femoral n = 240 (183 infants) • Old type Percutaneously inserted CVCs used before June 2006— single lumen silicone catheter with an introduction cannula New type n= 290 Percutaneously inserted CVCs in 200 infants	**Outcome Definitions:** Catheter-related sepsis (CRS): culture confirmed; at least 1 positive culture of blood obtained from a peripheral vein, clinical features consistent with bloodstream infection, no other site of infection, and a PICC in place for at least 3 days. **Adverse events:** Phlebitis: a linear red streak developed along the superficial veins from the insertion site; can be culture negative; patients with both inflammation and phlebitis categorized as phlebitis Thrombosis: leg swelling with or without poor perfusion developed Catheter site inflammation: local site inflammation with no pathogen identified	**Primary Outcomes:** Catheter-related complications: 271/534 (50.7%) patients experienced 368 total catheter-related complications Catheter-related sepsis Incidence: 134/368 (36.4%) • Old Peripheral CVC: 88/518 (16.9%) • New Peripheral CVC: 46/290 (15.9%) • p = 0.680 Rate • Old Percutaneous CVC: 8.8 cases per 1,000 catheter-days • New Percutaneous CVC: 9.9 cases per 1,000 catheter-days • p = 0.121 PICC with CRS by Percutaneous CVC site (recalculated by CDC to show infections per site, instead of site infections per all infections)

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
	• Detailed records unavailable	Non-femoral n= 120 in 114 infants Femoral n = 170 in 111 infants) • New type Percutaneously inserted CVCs used since July 2006 due to hospital policy change – single lumen silicone catheter with a stiffening stylet and an Excalibur introducer **Device/agent:** Catheter site and catheter type **Standard preventive measures:** • Peripheral CVC usually placed by a nursing specialist who had worked in this field for more than 15 years. • Residents or clinical neonatologist fellows followed a standardized insertion procedure under supervision. • All Percutaneous CVC were inserted through a peripheral vein; Tip location confirmed to be in a central vein • The Percutaneous CVC were advanced or retreated if needed, after a follow-up chest radiograph was taken. • Standardized procedure for the insertion and continuous care of the Percutaneous CVC,	and it was diagnosed in the presence of lymphangitis, purulence, or at least 2 signs of inflammation (erythema, tenderness, increased warmth, or induration); can be culture negative Cholestasis: direct bilirubin level ≥ 1.5 mg/dL Occlusion of the PICC: diagnosis only if it happened under standard practice and was excluded if it occurred because of misconduct Rupture: completely broken Percutaneous CVC rather than simple leakage Extravasation: dislodgement of a PICC Leakage: NR Pericardial effusion: NR **Sampling /Testing strategy:** • When clinical symptoms and signs developed, a single blood sample culture was obtained peripherally (never through the Peripheral CVC), and empiric antibiotic therapy was administered. Usually 1 mL (at least 0.5 mL) of blood was taken for each culture **Other notes:** • The principle of site selection did not change when authors substituted new-type Peripheral CVC for the old type. • In this paper, the authors define PICC as percutaneously inserted central catheter not peripherally inserted central catheter. Catheters are inserted into the greater and lesser saphenous veins of the lower	• Femoral: 83/410 (20.2%) • Non-femoral: 51/398 (21.8%) • p = NR • Adjusted OR for Femoral Placement: 1.53 (1.07 – 2.25) • p = 0.044 PICC with CRS by Percutaneous CVC type • Old Percutaneous CVCs: 88/518 (17.0%) • New Percutaneous CVC: 46/290 (15.9%) • p = NR • Adjusted OR for New Percutaneous CVC: 1.18 (0.76 – 1.83) • p = 0.462 Suspected sepsis Incidence: • Old Percutaneous CVC: 28/518 (5.4%) • New Percutaneous CVC: 17/290 (5.9%) • p = 0.786 **Topic-specific outcomes:** Duration of indwelling PICC (days): • Old Percutaneous CVC: 21.0 (11.0-29.0) • New Percutaneous CVC: 16.0 (6.75 – 25.0) • p < 0.001 **Adverse events** Noninfectious complications Percutaneous CVC without CRS by PICC site • Femoral: 95/410 (23.2%) • Non-femoral: 139/398 (34.9%) • p = NR • Adjusted OR (femoral): 0.76 (0.51– 1.15) • p = 0.197 Percutaneous CVC without CRS by PICC type • Old Percutaneous CVC: 135/518 (26.0%) • New Percutaneous CVC: 99/290 (34.1%) • p = NR • Adjusted OR (new type): 1.13 (0.74 – 1.71) • p = 0.573 Phlebitis • Old Percutaneous CVC: 31/518 (6.0%)

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
		regardless of the insertion site. • After successful insertion, 10% povidone-iodine containing alcohol (75%) was applied to the insertion site, normal saline used to decolorize, and the area was covered by a transparent dressing ("Tegaderm"). • Nurses checked the insertion site frequently and changed the dressing every 3 days. • The Percutaneous CVC lines were not impregnated with antibacterial or antiseptic agents and antibiotic lock prophylaxis was not used.	extremities, basilic veins or cephalic veins of the upper extremities, and femoral veins and the tip end in a central vein	• New Percutaneous CVC: 9/290 (3.1%) • p = 0.072 Thrombosis • Old Percutaneous CVC: 2/518 (0.8%) • New Percutaneous CVC: 0/290 (0%) • p = 0.214 Catheter site inflammation • Old Percutaneous CVC: 36/518 (6.9%) • New Percutaneous CVC: 31/290 (10.7%) • p = 0.064 Cholestasis • Old Percutaneous CVC: 88/518 (26.3%) • New Percutaneous CVC: 50/290 (25.0%) • p = 0.739 Occlusion • Old PICCs: 37/518 (7.1%) • New PICCs: 24/290 (8.3%) • p = 0.559 Rupture • Old PICCs: 13/518 (2.5%) • New PICCs: 13/290 (4.5%) • p = 0.127 Extravasation • Old PICCs: 8/518 (1.5%) • New PICCs: 13/290 (4.5%) • p = 0.012 Leakage • Old PICCs: 8/518 (1.5%) • New PICCs: 8/290 (2.8%) • p = 0.235 Pericardial effusion • Old PICCs: 0/518 (0%) • New PICCs: 1/290 (0.34%) • p = 0.359
Author: Tsai **Year:** 2009[13] **Study Design** Retrospective cohort study **Risk of Bias**	**Number of patients:** N = 334 **Number of lines:** N= 518 Percutaneously Inserted CVC **Setting:** Level III NICU	**Study Groups:** Femoral: N = 183 Patients N = 240 Percutaneously Inserted CVCs Non-femoral: N = 190 patients N= 278 Percutaneously Inserted CVCs	**Outcome Definitions:** Catheter-related sepsis (CRS): culture confirmed; at least 1 positive culture of blood obtained from a peripheral vein, clinical features consistent with bloodstream infection, no other site of infection, and a PICC in place for at least 5 days.	**Primary Outcomes:** Catheter related sepsis. Incidence • Femoral: 54/240 (22.5%) • Non-femoral: 34/278 (12.2%) • p = 0.002 Rate • Femoral: 10.9/1000 catheter days

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
Moderate	**Location:** Taiwan **Dates:** January 2004 – June 2006 **Inclusion Criteria:** • Premature infants with BW < 1500g **Exclusion Criteria:** • Early death unrelated to Percutaneously Inserted CVCs insertion • No Percutaneously Inserted CVCs needed • Detailed records unavailable	**Device/agent:** Catheter type **Standard preventive measures:** • All Percutaneously Inserted CVCs were single lumen silicone catheters with an introduction cannula. • Percutaneously Inserted CVCs usually placed by a nursing specialist who had worked in this field for more than 15 years. • Residents or a clinical neonatologist fellow would perform and follow a standardized procedure under supervision. • Authors used a standardized procedure for the insertion and continuous care of the PICC, regardless of the insertion site. • After successful insertion, 10% povidone-iodine containing alcohol (75%) was applied to the insertion site, normal saline used to decolorize, and the area was covered by a transparent dressing ("Tegaderm"). • Nurses checked the insertion site frequently and changed the dressing every 3 days. • The PICC lines were not impregnated with	**Adverse events:** Phlebitis: a linear red streak developed along the superficial veins from the insertion site; can be culture negative; patients with both inflammation and phlebitis categorized as phlebitis Thrombosis: leg swelling with or without poor perfusion developed Catheter site inflammation: diagnosed in the presence of lymphangitis, purulence, or at least 2 signs of inflammation (erythema, tenderness, increased warmth, or induration); can be culture negative Cholestasis: direct bilirubin level ≥ 1.5 mg/dL Occlusion of the Percutaneously Inserted CVCs: diagnosis only if it happened under standard practice and was excluded if it occurred because of malpractice Rupture: completely broken Percutaneously Inserted CVCs rather than simple leakage Extravasation: dislodgement of a Percutaneously Inserted CVCs Leakage: NR **Sampling /Testing strategy:** • When clinical symptoms and signs developed, a single blood sample culture was obtained peripherally (never through the Percutaneously Inserted CVCs), and empiric antibiotic therapy was administered. Usually 1 mL (at least 0.5 mL) of blood was taken for each culture **Other notes:** • In this paper, the authors define PICC as percutaneously inserted central catheter not peripherally inserted central catheter. Here a Percutaneously Inserted CVCs is a CVC in the femoral vein both centrally and	• Non-femoral: 6.8/1000 catheter days • p = 0.012 Insertion of PICCs at femoral sites •OR:1.91 (95% CI, 1.17–3.12,) • p = 0.010) **Topic-specific outcomes:** Duration of indwelling PICC, d (mean ± SD) • Femoral: 20.7 ± 8.9 • Non-femoral: 17.0 ± 9.3 • p < 0.001 **Adverse events** Phlebitis • Femoral: 0/240 (0%) • Non-femoral: 29/278 (9.3%) • p < 0.001 Thrombosis • Femoral: 2/240 (0.8%) • Non-femoral: 0/278 (0%) • p = 0.214 Catheter site inflammation • Femoral: 6/240 (2.5%) • Non-femoral: 30/278 (13.3%) • p < 0001 Cholestasis • Femoral: 49240 (26.7%) • Non-femoral: 56/278 (29.4%) • p = 0.861 Occlusion • Femoral: 18/240 (7.5%) • Non-femoral: 19/278 (6.8%) • p = 0.769 Rupture • Femoral: 8/240 (3.3%) • Non-femoral: 5/278 (1.5%) • p = 0.265 Extravasation • Femoral: 5/240 (2.1%) • Non-femoral: 3/278 (1.5%) • p = 0.481 Leakage • Femoral: 4/240 (1.7%)

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
		antibacterial or antiseptic agents and antibiotic lock prophylaxis was not used. • The confirmation of catheter-related complications and the decisions for the removal of a PICC, either elective or due to complications were made by the attending neonatologists, or senior residents on duty.	peripherally inserted in inserted catheters where the tip terminated in central veins other than the femoral vein. • Peripheral sites other than femoral veins were preferred over femoral sites. Femoral venous cannulation was performed when all other peripheral vascular accesses failed. • For those with need for early removal, the second PICC line was usually placed at least 3 days after the condition for early removal was resolved.	• Non-femoral: 4/278 (2.3%) • p = 0.555
Author: Hoang **Year:** 2008[21] **Study Design** Retrospective cohort study **Risk of Bias** Low	**Number of patients:** N = 396 **Number of lines:** N= 477 PICCs **Setting:** Level III NICU **Location:** USA **Dates:** June 2002-June 2006 **Inclusion Criteria:** NR **Exclusion Criteria:** Neonates with • Liver dysfunction • Inborn errors of metabolism Liver dysfunction: direct hyperbilirubinemia (serum direct bilirubin of >2.0 mg/dL) and high alanine aminotransferase and alanine aminotransferase levels.	**Study Groups:** Upper extremity group: n= 370 PICCs of 183 infants Lower extremity group: n=107 PICCs of 190 infants **Device/agent:** Catheter site **Standard preventive measures:** • Indications for a PICC are determined by the attending neonatologists • PICCs are placed by specialized nursing teams supervised by the neonatologists • No patient had 2 PICCs at the same time. Heparin routinely added to PICC.	**Outcome Definitions:** Catheter related bloodstream infection (CRBSI): [CDC guidelines] positive culture of an intravascular catheter with the same species as from ≥1 peripheral blood culture. For culture, ≥ 1.0 mL of blood was procured from both a peripheral site and the central lines **Adverse events:** Mechanical complications were determined whenever dislodgement of a PICC occurred. • Phlebitis: a physicochemical or mechanical complication not related to a proven infection. • Cholestasis & renal insufficiency: elevated direct bilirubin ≥ 2 mg/dL and maximum serum creatinine level of ≥ 1.6 mg/dL, respectively. • Catheter occlusion: pump occlusion or inability to flush and/or withdraw from the PICC and the cause to be related to thrombotic event. • Leakage: construed as fluid extravasation and/or pleural or pericardial effusion. **Sampling /Testing strategy:**	**Primary Outcomes:** CRBSI: Rate; infections/ 1000 catheter days • UE: 7.1 • LE: 4.8 • p = NS Incidence, n (%) • UE: 43/370 (11.6%) • LE: 10/107 (9.3%) • p = NS Coagulase-negative Staphylococcus incidence, n (%) • UE: 37/43 (86.0%) • LE: 5/10 (50.0%) • p <0.05 **Topic-specific outcomes:** Duration of PICC, median (IQR), d • UE: 13.0 (8.0-22.0) • LE: 16.0 (11.0-26.8) • p <0.004 **Adverse events:** Phlebitis, n (%): • UE: 21/370 (5.7%) • LE: 6/107 (5.6%) • p = NS Cholestasis, n (%):

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
			• For culture, ≥1.0 mL of blood was procured from both a peripheral site and the central lines. **Other notes:** • Lower extremity PICCs were inserted because of failure to insert PICCs in the upper extremity, or it was the primary selection site	• UE: 112/370 (30%) • LE: 25/107 (21.5%) • p < 0.05 Occlusion, n (%): • UE: 25/370 (6.7%) • LE: 8/107 (7.5%) • p = NS Leakage, n (%): • UE: 25/370 (6.7%) • LE: 3/107 (2.8%) • p = NS Time to first complication, median (IQR) d: • UE: 9.0 (4.0–18.0) • LE: 15.0 (9.5–22.0) • p = 0.050
Author: Breschan **Year:** 2007[17] **Study Design** Retrospective cohort study **Risk of Bias** Low	**Number of patients:** N= 236 **Number of lines:** N = CVCs **Setting:** NICU **Location:** Austria **Dates:** 1998- 2006 **Inclusion Criteria:** • Neonates who received a CVC placed percutaneously in either the internal jugular or the subclavian vein while undergoing abdominal or thoracic noncardiac surgery. • Comprised babies who underwent major surgery during their first 28 days of life or, if born prematurely, until 28 days had	**Study Groups:** Internal jugular- group I: N= 129 internal jugular venous catheters among 103 patients Subclavian- group 2: n=107 subclavian venous catheters among 84 neonates **Device/agent:** Catheter site **Standard preventive measures:** Catheter type • Standard: 2-French single-lumen catheter • Baby > 1.9 kg: 2-French single lumen or 4-French double lumen catheter inserted • All CVCs inserted in the operating room during general anesthesia before surgery. • Insertion was performed by three anesthesiologists	**Outcome Definitions:** Catheter associated infection (CAI) diagnosis was made in patients who developed signs of infection (fever [<38˚C], hypothermia [<36.5 ˚C], leukocytosis or leukopenia, apnea, or bradycardia) with no other clinically apparent site of infection. Suspected infection: If the tip culture was found to be negative after catheter removal, the diagnosis was reversed to suspected catheter infection retrospectively. **Adverse events:** Clinical obstruction: NR Clinical thrombosis: NR Clinical dislocation: NR Pneumothorax: NR Hemothorax: NR **Sampling /Testing strategy:**	**Primary Outcomes:** Catheter associated infections: Incidence, n (%): • Group I: 20/129 (15.5%); 95% CI: 0.09-0.23 • Group S: 5/107 (4.7%); 95% CI: 0.01-0.11 • P < 0.01 • Observed RR = 3.29 • Cox Proportion Hazard Model Suspected infection: Incidence, n (%): • Group I: 7/129 (5.4%); 95% CI: 0.02-0.12 • Group S: 4/107 (3.7%); 95% CI: 0.01-0.1 • p = 0.38 Catheter associated + Suspected infection: Incidence, n (%): • Group I: 27/129 (20.9%); 95% CI: 0.14-0.29 • Group S: 9/107 (8.4%); 95% CI: 0.03-0.15 • p < 0.01 **Topic-specific outcomes:** Length of catheterization in relation to BW**:** • Group I: Median: 10 • Group S: Median: 10 **Adverse events:** Clinical obstruction: • Group I: 8/129 (6.2%); 95% CI: 0.027-0.12

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
	elapsed from the calculated birth date. • Babies weighing <4.6 kg at time of operation. • Availability of patient's tip culture after CVC removal. **Exclusion Criteria:** If percutaneous catheter implantation was unsuccessful in patients	experienced in central venous line placement in infants. • The vein selected for cannulation was determined by the attending anesthesiologist. • Aseptic technique used during all insertions: use of sterile gloves, drapes, gowns, and facemasks. • Patient's skin disinfected by rubbing the site of insertion with sterile gauze soaked in a solution of 2% chlorhexidine in 70% alcohol and was allowed to dry. • Specific catheters were fixed by stitches; No tunneling was performed. • Exit site of the CVC covered by an occlusive dressing unless the baby's weight was less than 1 kg, then Steristrips were used. • Any manipulations on the catheters were performed by NICU nurses following a standardized protocol. • Proper catheter tip positioning in the superior caval vein was confirmed by x-ray. • Postoperatively all babies were cared for in the (NICU) or intermediate care unit	• The catheter tips were taken under sterile conditions to the microbiology laboratory where they were plated on 5% horse blood agar. **Other notes:** Infants in Group I (internal jugular insertion site) were of younger gestational age and lower birthweight than infants in Group II (subclavian insertion site). Cox Regression analysis for association wit with Catheter-associated infection over time: • Study group (insertion site): p = 0.002 • Weight: p = 0.075 • Post-conceptual age: p = 0.931	• Group S: 1/107 (0.9%); 95% CI: 0.0002-0.05 • p < 0.05 Clinical thrombosis: • Group I: 1/129 (0.7%); 95% CI: 0.002-0.04 • Group S: 2/107 (1.8%); 95% CI: 0.002-0.06 • p = 0.43 Clinical dislocation: • Group I: 1/129 (0.7%); 95% CI: 0.0002-0.04 • Group S: NR • p = 0.54 Pneumothorax: • Group I: 2 • Group S: 1 • p = NR Hemothorax: • Group I: 1 • Group S: 0 • p = NR

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
		for neonates; Both units were managed by the same team of doctors and nurses who had all been trained in neonatal intensive care medicine. • Any manipulations on the catheters were performed by the NICU nurses following a standardized protocol. • Three-way stopcocks connecting the hub with the intravenous sets were changed every 48 h, or even 24 h when used for total parenteral nutrition administration. • Stopcocks and hubs were disinfected with a solution of 2% chlorhexidine in 70% isopropyl alcohol using a sterile swab immediately before and after each manipulation and wrapped in sterile gauze dressing. • Babies weighing less than 1 kg received a low dose of vancomycin prophylactically until the CVC was in place		
Author: Vegunta[18] **Year:** 2005 **Study Design** Retrospective cohort study **Risk of Bias** High	**Number of patients:** N = 126 **Number of lines:** N = 137 tunneled catheters **Setting:** NICU **Location:** USA	**Study Groups:** Neck site group: n=88 CVCs implanted in NICU • L/R Subclavian vein • L/R Internal jugular vein • R external jugular vein • R internal jugular vein Groin site group:	**Outcome Definitions:** Catheter infection NR Line sepsis/ Catheter-related sepsis: definition NR **Adverse events:** Dislodgement: NR Pleural/pericardial complication: NR	**Primary Outcome:** Catheter infection: Incidence, n (%): • Neck: 11/88 (12.5%) • Groin: 1/49 (2%) • p = 0.032 Catheter-related sepsis: Rate per 1000 catheter days • Neck: 5.8

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
	Dates: June 1998-February 2003 **Inclusion Criteria:** • Infants requiring single lumen tunneled catheter during study period **Exclusion Criteria:** NR	n=49 CVCs implanted in NICU • L/R Long saphenous vein **Device/agent:** Catheter site **Standard preventive measures:** Catheter type • Single lumen 2.7F tunneled catheters used in all neonates • 3.5F percutaneous introducer sets were used for subclavian placement. • Neck lines mostly performed in operating room (OR), placed under general anesthesia. • Groin lines were performed predominantly in NICU • Babies ≥ 1500 g had attempts at percutaneous subclavian access; failing which, ipsilateral internal or external jugular vein was accessed by cut down. No patient in this study population had 2 tunneled catheters concurrently.	Clotted catheter: NR Leak from tunnel: NR **Sampling /Testing strategy:** • Line sepsis was confirmed with cultures, and salvage was attempted by treating appropriate antibiotics. **Other notes:** • Infants in the "groin site" group were significantly younger, and of lower birthweight and gestational age than infants in the "neck site" group. • There were no catheter related deaths in this study.	• Groin: 0.7 • p = 0.032 **Topic-specific outcomes:** Catheter live days (mean ± 1 SD) • Neck: 21.6 (23.8) • Groin: 30.5 (45) • p = 0.105 **Adverse events:** Total complications (including infections) Incidence, n (%): • Neck: 26/88 (29.5%) • Groin: 4/49 (8.2%)) • p = 0.005 Rate per 1000 catheter days: • Neck: 13.7 • Groin: 2.67 • p = 0.005 Dislodgement/Accidental removal, n (%): • Neck: 9/88 (10.2%) • Groin: 0/49 (0%)) • p = 0.050 Pleural/ pericardial complications, n (%): • Neck: 4/88 (4.5%) • Groin: 0/49 (0%)) Clotted catheter, n (%): • Neck: 0/88 (0%) • Groin: 3/49 (6.1%)) Leak from tunnel, n (%): • Neck: 2/88 (2.3%) • Groin: 0/49 (0%)

Table 21 Risk of Bias of Two Group Studies on Catheter Sites

Author Year	All study groups derived from similar source/reference populations	Attrition not significantly different across study groups	Measure of exposure is valid	Measure of outcome is valid	Investigator blinded or were outcomes well-defined and objective to endpoint assessment	Potential confounders identified	Statistical adjustment for potential confounders done	Funding source(s) disclosed and no obvious conflict of interest	Overall Risk of Bias
Bashir 2016[19]	✓		✓	✓	✓	✓	✓	✓	Low
Breschan 2007[17]	✓		✓	✓	✓	✓	✓		Low
Elmekkawi 2019[20]	✓	✓	✓	✓	✓	✓		✓	Low
Garcia 2019[15]	✓	✓	✓	✓	✓	✓	✓	✓	Low
Hoang 2008[21]	✓		✓	✓	✓	✓		✓	Low
Litz 2017[16]	✓	✓	✓	✓	✓	✓			Low
Tsai 2011[14]	✓		✓	✓	✓	✓	✓	✓	Low
Tsai 2009[13]	✓		✓	✓	✓	✓			Moderate
Vegunta 2005[18]	✓		✓	NO	NO	✓			High
Wrightson 2013[22]	✓		✓	✓	✓	✓		✓	Low

C.4. Number of Catheter Lumens

Key Question 4. In NICU patients requiring umbilical venous catheters, does the use of single-lumen, compared with double-lumen, umbilical venous catheters prevent CLABSI in NICU patients?

Table 22 Summary of Findings on the Number of Umbilical Venous Catheter Lumens to Prevent CLABSI

Outcome	Findings	Quantity and Type of Evidence and Sample Size	GRADE of Evidence for Outcome and Limitations of the Evidence
CLABSI*	• Two observational studies reported an increase in CLABSI is associated with an increasing number of lumens. • One cohort study[23] examining 2,017 UVCs reported an increase in the adjusted risk of CLABSI in patients who had lines with two lumens compared to lines with one lumen (aOR: 2.7 (95% CI: 1.1-6.8); P = 0.04)	2 OBS n = 4,052 lines[23] n= 250 lines[15]	Low

Outcome	Findings	Quantity and Type of Evidence and Sample Size	GRADE of Evidence for Outcome and Limitations of the Evidence
	• One case control study[15] reported a large increase in the adjusted odds of CLABSI in patients with double lumen catheters compared with patients with single lumen catheters, however confidence intervals were wide [OR: 5.8 (95% CI: 1.2 – 30.0); p = 0.03]		
Catheter Sepsis*	• One RCT[24] found that no infections were reported in either group.	1 RCT n=43 lines[24]	Low • Imprecision: only one study, low number of events

Table 23 Extracted Information on the Number of Umbilical Venous Catheter Lumens

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
Author: Levit[23] **Year:** 2020 **Study Design:** Cohort **Risk of Bias:** Low	**Number of patients:** N = 2676 patients **Number of lines:** N= 4052 lines **Setting:** Level IV NICU **Location:** USA **Dates:** January 1, 2008 – May 31, 2018 **Inclusion Criteria:** • Any infant admitted to the NICU who had a UAC, UVC, or both successfully placed (i.e., catheter tip in the desired, central location) **Exclusion Criteria:** • NR	**Study Groups:** UAC: n=2035 UVC: n=2017 Double lumen: n=679 Single lumen: n=3373 **Device/agent:** Catheter type; Number of lumens **Standard preventive measures:** • UC insertion is a sterile, bedside procedure typically performed by advanced practice providers, pediatric interns and residents, and neonatal-perinatal medicine fellows • Double-lumen catheter insertion is based solely on anticipated need • UVCs used for infusion of intravenous fluids, parenteral nutrition and lipids and continuous medication infusions; may be used for infusion of	**Outcome Definitions:** CLABSI: CDC/NHSN definition, and if no other source was identified and if the UC was still indwelling or had been removed within 48 hours of the onset of infection **Adverse events:** Complications: break/rupture, occlusion, catheter tip malposition, poor perfusion to lower extremity, CLABSI, thrombus, or effusion **Sampling /Testing strategy:** NR **Other notes:** Only the first instance of a complication within a neonate was considered in the analyses.	**Primary Outcomes:** CLABSI: Incidence, n/N (%) • UAC: 2/2035 (0.1%) • UVC: 19/2017 (0.9%) UVC: Adjusted incidence rate ratio/ 1000 central-line days: (adjusted for infant's sex, gestational age, and birthweight) • aIRR: 2.7 (95% CI: 1.1-6.8); P = 0.04 Adjusted rate/ 100 catheter days • Double lumen UVC: 2.0 • Single lumen UVC: 0.7 Cumulative incidence of UVC-related CLABSI: • First week of life: <1% • At day 14: 3.6% • At day 18: 16.5% **Topic-specific outcomes:** Mean dwell time, days (range) • UAC: 5.5 days (1-22) • UVC: 7.6 days (1-21) • p = NR **Adverse events** All complications:

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
		intermittent medications and blood products • Blood is not typically withdrawn from a UVC • UACs used predominantly blood pressure monitoring but may be used for infusion of intravenous fluids, parenteral nutrition and lipids • Confirmation of UC placement is via thoracoabdominal radiograph • Routine, scheduled reconfirmation of UC location is not performed • Heparin at a concentration of 1 U ml^{-1} of fluid is infused continuously through all central line lumens • Central line tubing utilized for parenteral nutrition, intralipids, and/or blood products is changed every 24 hours • Tubing utilized only for dextrose containing fluids is changed every 96 hours • An assessment of the continued need for central access is typically made at day 5-7 of use		Adjusted incidence rate ratio/ 1000 central-line days • IRR for any UAC associated complication: 0.3 (95% CI: 0.2-0.4) Adjusted UAC complication rate/ 1000 days: • UAC: 4.6 • UVC: 17.6 • p = NR Incidence, n/N (%) • UAC: 51/2035 (2.5%) • UVC: 269/2017 (13.3%) • p = NR Adjusted rate/ 1000 central-line days • Double lumen UVC: 17.2 • Single lumen UVC: 15.9 • p = 0.23 Complications excluding catheter malposition: Adjusted rate/ 1000 central-line days • aIRR: 2.3 (95% CI: 1.2-4.6); P = 0.02 • Double lumen UVC: 3.8 • Single lumen UVC: 1.6 Adjusted incidence rate ratio/ 1000 central-line days • IRR: 1.6 (95% CI: 1.02-2.5) Adjusted rate: • UAC: 3.9 • UVC: 2.4 • p = NR
Author: Garcia[15] **Year:** 2019 **Study Design:** Nested case-control	**Number of patients:** N = 179 patients **Number of lines:** N=179 lines **Setting:** Third-care level NICU	**Case**: CLABSI: n=74 **Control**: Non-CLABSI: n=105 **Device/agent:** Catheter site; double lumen catheter	**Outcome Definitions:** CLABSI: CDC 2018 definition • Patient ≤1 year of age has at least one of the following signs or symptoms: fever (>38.0°C), hypothermia (<36.0°C), apnea, or bradycardia, and	**Primary Outcomes:** Placement site of CVC: Internal jugular, n/N (%) • OR: 2.7 (95% CI: 1.5-5.1); P = 0.001 • Case: 43/74 (58.1%) • Control: 35/105 (33.3%) • p = 0.001 Subclavian (percutaneous insertion), n/N (%)

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
Risk of Bias: Low	**Location:** Mexico **Dates:** January 2014 – December 2015 **Inclusion Criteria:** • Patients with installation of a CVC during their hospital stay at the NICU were included • Patients with first CVC installation and those with CVC duration ≥48 hours • Cases were neonates diagnosed with CLABSI • Controls were those neonates with a CVC during the same period but who did not develop a CLABSI **Exclusion Criteria:** Patients who had a catheter installed in another hospital	**Standard preventive measures:** NR	• Organism(s) identified in blood is (are) not related to an infection at another site, and • The same common commensal is identified by a culture or non-culture based microbiologic testing method, from two or more blood specimens collected on separate occasions **Adverse events:** CLABSI-related mortality: a death directly related to the infection which occurred during active infection event and no other underlying cause of fatal outcome was present **Sampling /Testing strategy:** • Two-set of blood cultures were obtained in patients with a suspected infection • Disinfection with 2% iodine-povidone were performed • One peripheral blood culture was obtained along with a catheter-drawn blood culture **Other notes:** None	• Case: 17/74 (23%) • Control: 27/105 (25.7%) • p = 0.67 Saphenous, n/N (%) • Case: 7/74 (9.5%) • Control: 16/105 (15.2%) • p = 0.25 External jugular, n/N (%) • Case: 4/74 (5.4%) • Control: 7/105 (6.7%) • p = 0.98 Upper limb, n/N (%) • Case: 1/74 (1.3%) • Control: 12/105 (11.4%) • p = 0.01 Brachial, n/N (%) • Case: 1/74 (1.3%) • Control: 5/105 (4.8%) • p = 0.21 Lower limb, n/N (%) • Case: 1/74 (1.3%) • Control: 3/105 (2.8%) • p = 0.64 Double-lumen catheter: • OR: 10.0 (95% CI: 2.3-44.3); P = 0.0001 • Case: 72/74 (97.3%) • Control: 82/105 (78.1%) **Topic-specific outcomes:** CVC indwelling total time >21 days, n/N (%): • OR: 2.9 (95% CI: 1.5-5.4); P = 0.001 • Case: 37/74 (50.0%) • Control: 27/105 (25.7%) **Adverse events** CLABSI-related mortality, n/N (%) • Case: 5/74 (6.8%) Control: NR
Author: Khilnani[24]	**Number of patients:** N = 43	**Study Groups:**	**Outcome Definitions:**	**Primary Outcomes:** **Catheter related sepsis, n (%):**

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
Year: 1991 **Study Design:** RCT **Risk of Bias:** High	**Number of lines:** N = 43 **Setting:** Neonatal ICU **Location:** USA **Dates:** NR **Inclusion Criteria:** Critically ill neonates requiring an umbilical venous catheter Indications for umbilical venous catheter included hemodynamic instability resulting from severe birth asphyxia, respiratory distress syndrome, sepsis/pneumonia, meconium aspiration syndrome, or congenital heart disease. **Exclusion Criteria:** NR	Double lumen umbilical venous catheter: n=23 Single lumen umbilical venous catheter: n=20 **Device/agent:** single or double lumen catheter **Monitoring intervention:** **Standard preventive measures:** • A standard umbilical venous catheter insertion technique was used. Single and double lumen 5-Fr radiopaque polyurethane umbilical venous catheters were used. • Central venous pressure (CVP) was monitored in patients when the catheter tip was at the inferior vena cava-right atrial junction Both lumens of the double lumen umbilical venous catheters were used at all times for the infusion of fluids and medications. Heparin (0.5 U/mL) was used in all fluids infused via the single or the double lumen umbilical venous catheters, regardless of type of fluid infused.	Catheter related sepsis: two "positive" blood cultures for the same organism obtained at least 24 hours after umbilical venous catheter insertion. **Sampling /Testing strategy:** Catheter tips were also cultured when catheters were removed due to suspected catheter-related sepsis. **Other notes:** None	Double Lumen: 0/23 Single lumen: 0/20 **Topic-specific outcomes:** Duration of catheterization, mean days (SD): Double lumen: 2.9 (±2.0) Single lumen: 3 (± 1.2) p = NR Number of additional IV catheters needed, mean catheters (SD): Double lumen: 0.8 (±0.1) Single lumen: 2.3 (± 0.8) p<0.05 **Adverse events** Leak around the catheter site, n (%): Double lumen: 0/23 (0) Single lumen: 1/20 (5) p = NR Occlusion of one lumen, n (%): Double lumen: 1/23 Single lumen: 0/20 p = NR Other mechanical problems: None observed Difficulty with catheter insertion: None observed

Table 24 Risk of Bias for Randomized Controlled Trials on Number of Catheter Lumens

Author 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
Khilnani 1991[24]	✓						✓	✓	✓	✓	High

Table 25 Risk of Bias for Two Group Studies on Number of Catheter Lumens

Author Year	Were patients randomly assigned to the study's groups?	For non-randomized trials, did the study employ any other methods to enhance group comparability such as matching, stratification, or statistical methods to adjust for baseline differences?	Did patients in different study groups have similar levels of performance on the outcome of interest and other important factors at the time they were assigned to groups?	Did the study enroll all suitable patients or consecutive suitable patients within a time period?	Was the comparison of interest prospectively planned?	Were the two groups treated/ evaluated concurrently?	Was the study blinded or double-blinded?	Was the funding for this study derived from a source that would not benefit financially from results in a particular direction?	Risk of Bias
Garcia 2019[15]	✓	✓	✓	✓	✓	✓	✓	✓	Low
Levit 2020[23]	✓	✓	✓	✓	✓	✓	✓		Low

C.5. Skin Antisepsis for Catheter Insertion and Maintenance

Key Question 5: In NICU patients requiring skin antisepsis for catheter insertion and maintenance, does alcoholic chlorhexidine, compared with alcoholic povidone-iodine, prevent CLABSI?

Table 26 Summary of Findings on the Use of 2% Alcoholic CHG vs. 10% PI for Catheter Insertion and Maintenance

Outcome	Findings	Quantity and Type of Evidence (Sample Size)	GRADE of Evidence for Outcome (Limitations of the Evidence)
CRBSI*	• 1 multicenter RCT[25] using 2% CHG in alcohol base vs 10% PI suggested catheter related blood stream infections did not occur in either group.	1 RCT n= 48 lines[25]	Very Low • Indirect: study not conducted in current standard of care, • Imprecision: only one study
CABSI*	• 1 multicenter RCT[25] using 2% CHG in alcohol base vs 10% PI suggested no difference in catheter associated blood stream infections: 1/24 (4%) vs. 1/24 (4%); p = 0.99.	1 RCT n= 48 lines[25]	Very Low • Indirect: study not conducted in current standard of care • Imprecision: only one study

Outcome	Findings	Quantity and Type of Evidence (Sample Size)	GRADE of Evidence for Outcome (Limitations of the Evidence)
Presumed BSI*	• 1 multicenter RCT[25] using 2% CHG in alcohol base vs 10% PI suggested no difference between BSI rates: 4/24 (17%) vs. 4/24 (17%); p = 0.99.	1 RCT n= 48 lines[25]	Very low • Indirect: study not conducted in current standard of care • Imprecision: only one study
Septicemia*	• 1 multicenter RCT[25] using 2% CHG in alcohol base vs 10% PI reported septicemia rates to be similar among groups: 7/24 (29%) vs. 9/24 (38%); p = 0.54.	1 RCT n= 48 lines[25]	Very low • Indirect: study not conducted in current standard of care • Imprecision: only one study
Chlorhexidine gluconate absorption	• 1 multicenter RCT[25] reported an increase in CHG absorption following the first and second dressing change for the infants whose absorption level was 13-100 ng mL-1 during catheterization: 6/7 (85.7%).	1 RCT n= 48 lines[25]	Very ow • Indirect: study not conducted in current standard of care • Imprecision: only one study
Product-related Adverse Events	• 1 multicenter RCT[25] (Garland 2009) using 2% CHG in alcohol base vs 10% PI reported 2% CHG was not associated with an increased risk of contact dermatitis when compared to control group.	1 RCT n=48 lines[25]	Very low • Indirect: study not conducted in current standard of care, • Imprecision: only one study

Table 27 Extracted Information on the Use of Chlorhexidine Skin Antiseptic

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
Author: Garland[25] **Year:** 2009 **Study Design:** RCT **Risk of Bias:** Moderate **Intervention Bucket:** Skin prep/ skin cleansing/ absorption/ CRBSI, BSI, septicemia	**Number of patients:** N = 48 **Number of lines:** N = 48 **Setting:** five Level III NICUs, two community hospitals, 3 university teaching hospitals **Location:** USA **Dates:** 2005-2007 **Inclusion Criteria:** • Parental informed consent • Critically ill neonates at least 7 days old - <2 months of age who required a PICC • Weight > 1500g	**Intervention** n= 24 2% chlorhexidine gluconate (CHG) in an alcohol-based solution • PICC sites cleansed with ampoules containing 3mL of 2% CHG • All peripheral intravenous catheter sites were cleansed with CHG ampules containing 0.67 mL of 2% CHG. **Control** n=24 10% povidone-iodine (PI) **Standard preventive measures:** • Neonates were block randomized to one of two treatment groups	**Outcome Definitions:** CRBSI: a BSI in which there was concordance between organisms grown from the blood and catheter tip CABSI: Not defined BSI without a source: positive peripheral blood culture during time of catheterization or within 24 h of catheter removal, clinical signs and symptoms of a BSI, antibiotic therapy for ≥ 7 days and no other documented primary site of infection Presumed BSI: signs and symptoms of sepsis with a negative blood culture Septicemia: Blood culture drawn while PICC in situ	**Primary Outcomes:** CRBSI, n (%): • CHG: 0/24 (0%) • PI: 0/24 (0%) Catheter-associated BSI, n (%): • CHG: 1/24 (4%) • PI: 1/24 (4%) • p = 0.99 BSI incidence, n (%): • CHG: 2.8/ 1000 catheter days • PI: 3.0/ 1000 catheter days • p = 0.96 Presumed BSI, n (%): • CHG: 4/24 (17%) • PI: 4/24 (17%) • p = 0.99 Septicemia, n (%):

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
	Exclusion Criteria: • ≥ 60 days of age at enrollment • Catheterization ≤ 48 h • Prior discharge home • Conditions of altered skin integrity	• Insertion sites cleansed with appropriate antiseptic before catheter placement • Site dressed with polyurethane dressing changed weekly while catheter remained in situ. • Same antiseptic was used to re-cleansed site with each dressing change • All peripheral intravenous catheter sites were cleansed with the same antiseptic used for PICC insertion • All catheters were placed using standard sterile techniques with wide barriers • Catheter removal decisions made independently by primary care team • Catheter sites (PICC and peripheral) inspected daily for the presence and severity of contact dermatitis by a study nurse using a dermatitis severity scale	Severe contact dermatitis: dermatitis score of ≥ 2 Absorption: Not defined **Sampling /Testing strategy:** • Dermatitis assessment inspected daily at catheter sites by study nurse using dermatitis severity scale • Peripheral blood cultures performed at discretion of primary care team in neonates with signs of sepsis • Blood CHG concentrations determined using liquid chromatography with tandem mass spectrometry following catheter placement, just before the first dressing change and immediately after the first dressing change **Other notes:** Absorption section of study ended early. Only 10 neonates had concentration measured	• CHG: 7/24 (29%) • PI: 9/24 (38%) • p = 0.54 **Topic-specific outcomes:** NR **Adverse Events:** Dermatitis: Cutaneous disinfection with 2% CHG was not associated with an increased risk of contact dermatitis when compared to cutaneous scrub with PI. CHG Absorption > 10 ng mL^{-1} after 1st application of antisepsis • 5/10 (50%) 13-100 ng mL^{-1} during catheterization • 7/10 (70%) Increased following 1st and 2nd dressing change • 6/7 (85.7%) 100 ng mL^{-1} after 3rd dressing change • 1/10 (10%)

Table 28 Risk of Bias for Randomized Controlled Trials Using Chlorhexidine Skin Antiseptics

Author 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 2009[25]	✓	✓	NO		✓					✓	Moderate

C.6. Chlorhexidine Bathing

Key Question 6. In NICU patients requiring central venous catheters, does chlorhexidine bathing, compared with no bathing or bathing with placebo, prevent CLABSI?

Table 29 Summary of Findings on Bathing with 2% CHG Cloths vs. Placebo or No Bathing to Prevent CLABSI

Outcome	Findings	Quantity and Type of Evidence (Sample Size)	GRADE of Evidence for Outcome (Limitations of the Evidence)

CLABSI*	• 1 observational study[26] using 2% CHG washcloths for bathing vs no cleansing suggested there was a significant decrease in CLABSI rate per 1000 central line days: 4.28 vs 8.64; Adjusted IRR by weight = 0.49 (95CI: 0.36-0.68); p = 0.0000.
	• 1 observational study[27] using 2% CHG-impregnated cloths for routine bathing vs mild soap in NICU patients suggested bathing with CHG-impregnated cloths is associated with a clinically meaningful reduction in CLABSI rates per 1000 CVC days: 2.32 (1.06-4.40) vs 6.17 (4.77-7.85) p = NR (text states NS).
	  • Infants > 1000g: 1.28 vs 4.92; Crude IRR= 0.26 (95% CI: 0.07-0.72), p = NR
	  • Infants ≤ 1000g, aged ≥28 days: 5.73 vs 8.97; Crude IRR=0.79 (95% CI: 0.15-2.60), p = NR
	  • Neonates ≤ 1000g, aged < 28 days: no CHG received during baseline and intervention periods and showed no difference: 8.62 vs 8.57; Crude IRR=1.01 (95% CI: 0.10-5.62); Adjusted IRR by weight = 0.86 (95% CI: 0.17-4.44), p = NR
		2 OBS
		n= 4,243 patients[26]
		n=790 patients[27]
			Low

Lab-confirmed sepsis*	• One observational study[56] reported a reduction in the hazard of lab-confirmed sepsis when comparing patients who received a CHG bath with those who did not, however this reduction did not achieve statistical significance in the analysis for either the intervention period [0.48 (95% CI: 0.24 – 0.95); p = 0.035], but not when analyzing the combined intervention and implementation period [HR: 0.58 (95% CI: 0.31 – 0.11); p = 0.10]	1 OBS n = 1,233 patients[56]	Very Low • Imprecision: only one study
Culture-negative sepsis*	• One observational study[56] reported a reduction in the hazard of culture-negative sepsis when comparing patients who received a CHG bath with those who did not. This reduction did not achieve statistical significance for the intervention period [HR: 1.17 (95% CI: 0.81 – 1.69); p = 0.39] or the combined intervention and implementation period [HR: HR: 1.08 (95% CI: 0.77 – 1.51); p = 0.66]	1 OBS n = 1,233 patients[56]	Very Low • Imprecision: only one study
Product-related Adverse Events	• 1 observational study[26] using 2% CHG washcloths for bathing vs no cleansing reported no local or systemic adverse events. • 1 observational study[27] using 2% CHG-impregnated cloths for bathing vs mild soap reported no events of dermatitis or adverse events during intervention period.	2 OBS [26, 27] n = 4,243 patients [26] n = 790 patients[27]	Very Low • Imprecision: small number of events

Table 30 Summary of Findings on a Single Bath with 0.25% CHX Cloths vs. Saline Impregnated Cloths vs. No Cleansing to Prevent CLABSI

Outcome	Findings	Quantity and Type of Evidence (Sample Size)	GRADE of Evidence for Outcome (Limitations of the Evidence)
Culture positive sepsis	• 1 single-center RCT[28] comparing the use of 0.25% free CHX impregnated washcloths vs saline impregnated washcloths or no cleansing suggested there was no difference in the incidence of culture positive sepsis in the first seven days of life among the three groups comparing different agents for use in a single bath: 1/20 (5%) vs. 2/20 (10%) vs. 2/20 (10%); p = 0.53.	1 RCT N = 60 patients[28]	Low • Imprecision: only one study
Clinical sepsis	• 1 single-center RCT[28] comparing the use of 0.25% free CHX impregnated washcloths vs saline impregnated washcloths or no cleansing suggested there was no difference in the incidence of clinical sepsis in the first seven days of life between the three groups: 2/20 (10%) vs. 3/20 (15%) vs 1/20 (5%); p = 0.41.	1 RCT N = 60 patients[28]	Low • Imprecision: only one study
Hypothermia	• 1 single-center RCT[28] comparing the use of 0.25% free CHX impregnated washcloths vs saline impregnated washcloths or no cleansing reported no instances of moderate hypothermia (<36.0°C); and no difference in instances of mild hypothermia/ cold stress (36.0° - 36.4 1°C) at 30 mins: (2/20 (10%) vs 2/20 (10%) vs 0/20 (0%)).	1 RCT N = 60 patients[28]	Low • Imprecision: only one study
Product-related Adverse Events	• 1 single-center RCT[28] of NICU comparing the use of 0.25% free CHX impregnated washcloths vs saline impregnated washcloths vs no cleansing reported none of the infants had skin erythema, fissuring, or crusting.	1 RCT N = 60 patients[28]	Low • Imprecision: only one study

Table 31 Extracted Information on Chlorhexidine Bathing

Study Information	Population and Setting	Intervention/ Study Groups	Definitions L	Results
Author: Westling[56] **Year:** 2020 **Study Design:** Prospective Cohort **Risk of Bias:** Low	**Number of patients:** N = 1,233 **Number of lines:** N = NR **Setting:** NICU **Location:** Zambia **Dates:** NR **Inclusion Criteria:** • Infants ≥1.5 kg infants admitted to the study NICU during the implementation and intervention periods **Exclusion Criteria:** Infants:	**Study Groups:** CHG Bathing: n = 864 Implementation period: n = 28 Intervention period: n = 836 • Infants ≥1.5kg who received a CHG bath within three days of NICU admission, and weekly thereafter. CHG was diluted with sterile water **No Bathing:** n = 369 Implementation period: n = 170 Intervention period: n = 199 • Infants who did not receive a bath	**Outcome Definitions:** *Laboratory confirmed sepsis with pathogen:* the day on which a blood culture that grew a pathogenic organism was drawn, *Culture-negative sepsis:* the day on which a blood culture that did not grow any organism was drawn *All-cause mortality* prior to NICU discharge *Suspected sepsis:* the day on which a blood culture was taken (regardless of culture results) *Laboratory-confirmed sepsis with contaminant organism* **Sampling /Testing strategy:** • Blood cultures **Other notes:** None	**Primary Outcomes:** *Intervention period only* Lab-confirmed Sepsis HR: 0.48 (95% CI: 0.24 – 0.95); p = 0.035 Culture-negative Sepsis HR: 1.17 (95% CI: 0.81 – 1.69); p = 0.39 Death HR: 0.83 (95% CI: 0.56 – 1.23); p = 0.35 *Intervention & implementation period only* Lab-confirmed Sepsis HR: 0.58 (95% CI: 0.31 – 0.11); p = 0.10 Culture-negative Sepsis HR: 1.08 (95% CI: 0.77 – 1.51); p = 0.66 Death HR: 0.94 (95% CI: 0.64 – 1.38); p = 0.75

Study Information	Population and Setting	Intervention/ Study Groups	Definitions L	Results
	• Born outside the facility • From the baseline period • <1.5 kg. • With suspected sepsis on the day of admission	**Device:** bath with 2% aqueous CHG **Standard preventive measures:** • (1) IPC training; • (2) Locally manufactured alcohol hand rub; • (3) Daily IPC reminders via short messaging service (SMS); • (4) Enhanced routine cleaning of the environment including potential reservoirs of infection (such as sinks and suction machines) with a focus on daily cleaning of high touch surfaces and moving from clean to dirty		**Topic-specific outcomes:** NR **Adverse events:** There were no reports of local or systemic adverse events due to the use of CHG baths in the study period.
Author: Cleves[26] **Year:** 2018 **Study Design:** Retrospective, quasi-experimental study **Risk of Bias:** Low	**Number of patients:** N = 4,243 **Number of lines:** N = 4,243 **Setting:** Tertiary care hospital with NICU **Location:** Columbia (South America) **Dates:** January 2012 – February 2017 **Inclusion Criteria:** • NR **Exclusion Criteria:** • NR	**Intervention:** n= 1662 new central lines inserted July 2014- February 2017 • July 2014, Chlorhexidine gluconate (CHG) baths implemented in NICU by Infection Committee • CHG baths performed by NICU nurses using 2 antiseptic body cleansing washcloths with 2% CHG in a non-alcohol and non-alkaline base—one cloth for upper limbs, neck, thorax, back and armpits –the other cloth used for inferior limbs, gluteus and groin	**Outcome Definitions:** CLABSI: bloodstream infection confirmed by two blood cultures in a patient with a central line in place for > 2 calendar days, with ≥1 of the following symptoms: fever (body temperature >38°C), hypothermia (body temperature <36°C), apnea or bradycardia. CLABSI ratio: number of central line infections/ 1000 central line days. Patient-days: number of days since birth Incidence rate ratio (IRR): ND **Sampling /Testing strategy:** • Blood cultures **Other notes:** None	**Primary Outcomes:** CLABSI incidence, n (%): • CHG bath: 65 • No CHG bath: 75 CLABSI rate / 1000 central line days • CHG bath: 4.28 • No CHG bath: 8.64 • Global IRR = 0.49 (95% CI: 0.35-0.70) • Adjusted IRR by weight= 0.49 (95CI: 0.36-0.68) • p = 0.0000 Handwashing adherence found to be: • Intervention (CHG bath): 86.5% • Pre-intervention (No CHG bath): 91.8% **Topic-specific outcomes:** NR

Study Information	Population and Setting	Intervention/ Study Groups	Definitions L	Results
		• Neonates with BW > 1000g started daily skin cleansing on 2nd day after birth • Neonates with BW < 1000g started biweekly skin cleansing on 7th day after birth **Control:** n=1246 new central lines inserted January 2012 - June 2014 • Skin disinfection performed before insertion of all central lines and for catheter care every seven days or when necessary, with 2% CHG and 70% alcohol solution **Standard preventive measures:** NR		**Adverse events:** There were no reports of local or systemic adverse events due to the use of CHG baths in the study period.
Author: Quach[27] **Year:** 2014 **Study Design:** Retrospective cohort study **Risk of Bias:** Low **Intervention Bucket:** CHG bathing	**Number of patients:** N=790 **Number of lines:** N = 790 **Setting:** Level III NICU in a tertiary care pediatric hospital **Location:** Canada **Dates:** April 1, 2009 – March 31, 2013 **Inclusion Criteria:** • All infants with a CVC admitted to NICU during study period **Exclusion Criteria:** NR	**Study Groups:** **Intervention:** n= 195 >35weeks gestation: 144/195 (74%) After April 1, 2012 • Infants with central venous catheter (CVC) and a BW > 1000g bathed with 2% chlorhexidine gluconate (CHG) impregnated cloth daily • Use of CHG for insertion and dressing change remained unchanged (same as baseline) as well as bathing frequency with the substitution of CHG for the agent	**Outcome Definitions:** Primary bloodstream infections: same as 2009 American National Healthcare Safety Network definition CLABSI cases: same as 2009.American National Healthcare Safety Network definition until April 1, 2013, the need for the CVC to have been in place for ≥ 48 hours before CLABSI onset was added to definition Central lines: intravenous catheters that ended at or near the heart or in a great vessel. Number of patient-days: total number of days that patients spent in the NICU Number of CVC-days: total number of days of exposure to at least 1 CVC and was collected daily	**Primary Outcomes:** CLABSI (incidence) • Total = 75 • Baseline = 46 • Intervention: 9 Total CLABSI rates/ 1000 CVC-days 95% CI) • Baseline (pooled): 6.17 (4.77-7.85) • Intervention: 2.32 (1.06-4.40) • Adjusted IRR = 0.86 (95% CI: 0.63-1.16) • p = NR (text states NS) Pooled CLABSI rates/ 1000 CVC-days by CHG use (# CLABSIs / annual CVC days) Pooled CHG-bathed infants (separated by BW and Age) • Baseline: 6.0 • Intervention: 1.92 • Crude IRR: 0.30 (95% CI: 0.12-0.70)

Study Information	Population and Setting	Intervention/ Study Groups	Definitions L	Results
		• Infants with BW ≤ 1000g bathed with mild soap until day of life 28, then 2% CHG-impregnated cloths used (also used as subgroup comparator—mild soap used during time not eligible for CHG bath) • Nurses used 2 CHG wipes per infant per bath • Clinical care protocols similar for all infants in the NICU. **Control:** n= 595 Baseline Period: Before April 1, 2012 • Infants with BW ≤ 1000g at gestational age (GA) ≤ 28 weeks & chronological age (CA) <28 days bathed twice a week with mild soap and used 2% aqueous CHG for CVC insertion and dressing change (also used as subgroup comparator—Not eligible for CHG bath) • Infants with BW ≤ 1000g at GA ≤ 28 weeks & CA ≥28 days bathed twice a week with mild soap and used 0.5% alcoholic CHG in 70% alcohol for CVC insertion and dressing change • Infants with BW ≤ 1000g at GA 29-35 weeks & CA ≥28 days bathed every other day with mild soap and used 0.5% alcoholic CHG in 70% alcohol for	<u>CLABSI rates per 1,000 CVC-days by year</u>: CLABSI episodes divided by number of central line–days times 1,000 <u>Incidence rate ratios (IRRs)</u>: compare CLABSIs/1,000 CVC-days during the baseline (2009–2012) and intervention (2012–2013) periods **Sampling /Testing strategy:** NR **Other notes:** None	• Adjusted IRR (for BW): 0.33 (95% CI: 0.15 – 0.73) BW >1000g, Age=NR (CHG group) • Baseline (pooled): 4.92 (36/7323) • Intervention: 1.28 (4/3126) • Crude IRR= 0.26 (95% CI: 0.07-0.72) BW ≤1000g, Age ≥28 days (CHG group) • Baseline (pooled): 8.97 (24/2677) • Intervention: 5.73 (3/524) • Crude IRR: 0.79 (95% CI: 0.15-2.60) BW ≤1000g, age <28 days (Non-CHG group) No CHG bathing during baseline and intervention periods • Baseline (poled): 8.57 (6/700) • Intervention: 8.62 (2/232) • Crude IRR= 1.01 (95% CI: 0.10-5.62) • Adjusted IRR (for BW) = 0.86 (95% CI: 0.17-4.44) **Topic-specific outcomes:** NR **<u>Adverse events:</u>** "No dermatitis or adverse events reported during the 2012-2013 period."

Study Information	Population and Setting	Intervention/ Study Groups	Definitions L	Results
		CVC insertion and dressing change • Infants with BW > 1000g at GA 29-35 weeks & CA of all ages (days) bathed every other day with mild soap and used 0.5% alcoholic CHG in 70% alcohol for CVC insertion and dressing change • Infants with BW > 1000g at GA >35 weeks & CA of ages (days) bathed daily with mild soap and used 0.5% alcoholic CHG in 70% alcohol for CVC insertion and dressing change **Standard preventive measures:** • During study period, CHG used for skin antisepsis prior CVC insertion and for dressing change on all neonates		
Author: Sankar[28] **Year:** 2009 **Study Design:** RCT **Risk of Bias:** Low **Intervention Bucket:** bath/ skin colonization/ Sepsis	**Number of patients:** N = 60 **Number of lines:** N = 60 **Setting:** Level III NICU **Location:** India **Dates:** August 2005 – February 2006 **Inclusion Criteria:** • Preterm infants of 28-36 weeks of gestation with birthweights between 1001-2000g admitted to ICU/Postnatal ward	**Intervention:** n= 20 in each Group A: n=20 cleansing with wipes containing 0.25% free CHX (.44% CHdG) Group B: n=20 Cleansing with wipes containing 0% CHX (Saline cleansing) • Wipes placed in sealed plastic packages containing 6 of a given type • Infants' skin wiped from neck to sole in 5 steps by	**Outcome Definitions:** • Primary outcome variables were (a) skin condition score at 24 h, days 3 and 7 (b) skin temperature at 30 min, 1 and 6 h, and (c) colonization rates of the axilla and the groin at 24 and 72 h after intervention. • Secondary Outcome Definitions included the incidence of clinical and culture positive sepsis in the first week of life. • Culture positive sepsis: infants with symptoms and/or signs suggestive of sepsis and a positive blood culture (with known pathogens and coagulase negative staphylococcus)	**Primary Outcomes:** Culture positive sepsis • CHX: 1/20 (5%) • Saline: 2/20 (10%) • No cleansing: 2/20 (10%) • p = 0.53 Clinical sepsis • CHX: 2/20 (10%) • Saline: 3/20 (15%) • No cleansing: 1/20 (5%) • p = 0.41 **Topic Specific Outcomes:** **Adverse Events:** Skin condition

Study Information	Population and Setting	Intervention/ Study Groups	Definitions L	Results
	• Informed written consent from 1 parent **Exclusion Criteria:** Infants with one minute Apgar score <4, hemodynamic instability, congenital malformations, generalized skin disorder and who needed respiratory support (continuous positive airway pressure and/or intermittent mandatory ventilation)	trained staff/resident- 1 wipe for each step with the 6th used as a spare **Control** n=20 Group C: n=20 No skin cleansing **Standard preventive measures:** • Infants randomized within 1-3 hours of age and stratified into two strata based on birth weight: 1501-2000g and 1001 to 1500g • Those who carried out the intervention and investigators were blinded • All the infants were monitored until the end of the first week of life for features of sepsis • Skin condition assessed by observing skin on abdomen and dorsum of hands/feet for drying, erythema, fissuring, scaling etc. using a 9 point grading scale adopted by Darmstadt et al. from Lane et al.	• Clinical sepsis: infants with negative cultures but with positive sepsis screen (as per the unit protocol) • Cold stress: defined as per standard definitions; Temperature of 36.0-36.4°C • Hypothermia: defined as per standard definitions. **Sampling /Testing strategy:** • Clinical thermometer measured skin temperature—kept in the axilla for 3 min. **Other notes:** None	• None of the infants had skin erythema/ fissuring/ crusting. Median skin condition scores of the three groups were identical at 24, 72, and 168 hours after intervention. Skin temperature: Axillary temperature (°C) Mean skin temperature (sd) Baseline • CHX: 36.6 (0.13) • Saline: 36.6 (0.13) • No cleansing: 36.6 (0.16) • p = 0.78 30 mins • CHX: 36.6 (0.20) • Saline: 36.6 (0.12) • No cleansing: 36.7 (0.24) • p = 0.46 1 hour • CHX: 36.6 (0.13) • Saline: 36.6 (0.08) • No cleansing: 36.7 (0.14) • p = 0.46 6 hours • CHX: 36.7 (0.12) • Saline: 36.7 (0.07) • No cleansing: 36.7 (0.11) • p = 0.66 Incidences of hypothermia No instances of hypothermia (<36°) in any group. Incidence of cold stress No infant had cold stress at 1 and 6 hours. 30 mins • CHX: 2/20 (10%) • Saline: 2/20 (10%) • No cleansing: 0 (0%) • p = 0.34 **Adverse Events:** NR

Table 32 Risk of Bias of Randomized Controlled Trials on Chlorhexidine Bathing

Author 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
Sankar 2009[28]	✓	✓	✓	✓	✓	✓					Low

Table 33 Risk of Bias of Two Group Studies on Chlorhexidine Bathing

Author Year	All study groups derived from similar source/ reference populations	Attrition not significantly different across study groups	Measure of exposure is valid	Measure of outcome is valid	Investigator blinded to endpoint assessment or outcomes are objective	Potential confounders identified	Statistical adjustment for potential confounders done	Funding source(s) disclosed and no obvious conflict of interest	Overall Risk of Bias
Cleves 2018[26]	✓	✓	✓	✓		✓		✓	Low
Quach 2014[27]	✓	✓	✓	✓		✓	✓	✓	Low
Westling 2020[56]	✓	✓	✓	✓				✓	Low

C.7. Catheter Hub Manipulation

Key Question 7: In NICU patients with central line catheters does minimizing the number of times central line hubs are accessed prevent CLABSI?

Table 34 Summary of Findings on Catheter Manipulation to Prevent CLABSI in NICU Patients

Outcome	Findings	Quantity and Type of Evidence (Sample Size)	GRADE of Evidence for Outcome (Limitations of the Evidence)
Catheter-associated bloodstream infection	• 1 single-center observational study[29] reported catheter hub manipulations that required disinfection, disconnection, or drawing blood through central line were associated with an increased risk of infection (OR: 1.2; 95% CI: 1.1 – 1.3).	1 OBS n=357 lines[29]	Low • Imprecision: Only one study

Table 35 Extracted Information on Catheter Manipulation

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
Authors: Mahieu[29]	**Number of patients:** N=223 **Number of lines:**	**C:** n=357 Catheters	**Outcome Definitions:**	**Primary Outcomes:** CABSI incidence per catheter, n (%):

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
Year: 2001 **Study Design:** Prospective cohort study **Risk of Bias:** Low	N=357 **Setting:** Neonatal ICU **Location:** Belgium **Dates:** November 1, 1993-October 31, 1994 **Inclusion Criteria:** All neonates with one or more central venous catheters admitted to the NICU. **Exclusion Criteria:** NR	**Device/agent:** NA **Monitoring intervention:** NA **Standard preventive measures**: • Aseptic technique: An aseptic technique was used during insertion and repositioning; this included surgical scrubbing with 4% chlorhexidine, sterile gloves, drapes, gowns, and facemasks. • Skin cleaning: Before inserting a catheter, the skin was cleaned with a solution of 2% chlorhexidine in 70% isopropyl alcohol. • The exit-site of non-umbilical central venous catheters was covered with a sterile gauze help in place by an occlusive transparent dressing. • The exit-site of umbilical lines remained uncovered and was cleaned thrice daily with a solution of 2% chlorhexidine in 70% isopropyl alcohol prior to the application of a powder containing virginiamycin. • Line maintenance: Three-way stopcocks connecting the hub with the IV sets changed every 48 hours	Catheter associated bloodstream infection (CABSI): 1) Primary bloodstream infection according to the CDC surveillance definition: a) recognized pathogen isolated from blood culture or a skin contaminant isolated from two blood cultures drawn on separate occasions, b) one of following clinical signs of infection (fever >38°C, hypothermia <37°C, apnea or bradycardia) and 2) Central venous catheter present at the time the blood culture was obtained. Catheter manipulations were stratified according to the type of manipulation: (1) Disinfection (catheter hub and/or exit site), (2) connection of an infusion line to the catheter (glucose solution, parenteral nutrition solution, continuous intravenous (IV) medication (3) administration of IV drugs in shot (heparin, antibiotics, other), (4) transfusions (plasma, packed red blood cells, platelets), (5) manipulation of the calibrated fluid chamber (addition of electrolytes, hypertonic glucose) and finally, (6) blood drawings through the central line Adverse events: NR **Sampling /Testing strategy:** Swabs were taken from the catheter exit site and hub at the time of sepsis evaluation as well at catheter removal in those catheters not associated with infection.	• CABSI: 17/357 (4.8%) • No CABSI: 340/357 (95.2%) • p = NR **Topic-specific outcomes:** Catheter duration, mean days (SD): • CABSI: 20.1 (17.5) • No CABSI 9.2 (6.8) • p < 0.001 Disinfection of catheter exit-site, mean no. of catheter manipulations (SD): • CABSI: 5.5 (13.2) • No CABSI 12.6 (13.3) • p < 0.001 Disinfection of catheter hub, mean no. of catheter manipulations (SD): • CABSI: 18.2 (16.2) • No CABSI: 7.6 (7.0) • p < 0.001 Administration of glucose solutions, mean no. of catheter manipulations (SD): • CABSI: 4.7 (6.3) • No CABSI: 2.7 (3.1) • p = 0.14 Administration of parenteral nutrition, mean no. of catheter manipulations (SD): • CABSI: 12.2 (16.1) • No CABS: 4.3 (6.7) • p < 0.05 (=0.02) Administration of continuous IV drugs, mean no. of catheter manipulations (SD): • CABSI: 7.1 (6.4) • No CABSI: 2.8 (5.7) • p < 0.05 (<0.001) Administration of antibiotics, mean no. of catheter manipulations (SD): • CABSI: 11.6 (17.6)

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
		or every 24 hours when used for TPN administration. The stopcocks and hubs were disinfected with a homemade solution 2% chlorhexidine in 70% isopropyl alcohol using a sterile swab immediately before and after each manipulation and wrapped in sterile gauze dressing. • Gloves and masks were not used during catheter manipulation, but hands were disinfected with 70% isopropyl alcohol before and after each catheter manipulation. • Catheters were flushed with heparinized saline daily at the tie of IV set change. In arterial lines, a continuous infusion of a heparinized solution was used to control patency. • Antibiotics: not used prophylactically but only for treatment of suspected infections. • Administration of blood products: No blood products were administered through the CVC	A culture was taken from the skin catheter junction with another sterile cotton swab after removal of the dressing. **Other notes:** None	• No CABSI: 4.6 (8.2) • p = 0.05 Administration of heparin solution, mean no. of catheter manipulations (SD): • CABSI: 7.8 (15.1) • No CABSI: 3.1 (6.4) • p = 0.10 Administration of other IV drugs as bolus, mean no. of catheter manipulations (SD): • CABSI: 10.7 (16.8) • No CABSI: 3.9 (6.9) • p = 0.11 Transfusions, mean no. of catheter manipulations (SD): • CABSI: 0 (0) • No CABSI: 0.4 (3.9) • p = “No association” Fluid chamber manipulation, mean no. of catheter manipulations (SD): • CABSI: 0.6 (1.1) • No CABSI: 0.8 (1.9) • p = “No association” Blood drawing of blood gases, mean no. of catheter manipulations (SD): • CABSI: 12.8 (23.5) • No CABSI: 5.0 (11.9) • p < 0.05 (= 0.02) Blood drawing of others, mean no. of catheter manipulations (SD): • CABSI: 3.2 (5.3) • No CABSI: 1.3 (2.9) • p < 0.05 (= 0.02) Number of manipulations, mean no. (SD): • CABSI: 70.7/100.4 (70.4) • No CABSI: 28.7/107.9 (26.6) • p < 0.001

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
				Manipulation-related risk factors significantly associated with CLABSI: Multivariable analysis Disinfection of the catheter hub: OR: 1.2 (95% CI: 1.1-1.3); SE: 0; p = 0.002 Blood sampling/drawing (other than blood gases): OR: 1.4 (95% CI: 1.1-1.8); SE: 0; p = 0.009 1-7 blood samples: OR: 1.04 (95% CI: 0.33-3.27); p = 0.95 8-14 blood samples: OR: 5.82 (95% CI: 1.53-22.63); p = 0.006 >14 blood samples: OR: 8.4 (95% CI: 0-67.1); p = 0.036 Risk of CLABSI increased with number of blood samples taken through the central line Heparinization: OR: 0.9 (95% CI: 0.8-1.0); SE: 0; p = 0.047 Antisepsis of exit-site: OR: 0.9 (95% CI: 0.8-1.0); SE: 0; p = 0.014 **Adverse events:** NR

Table 36 Risk of Bias for Two Group Studies on Catheter Hub Manipulation

Author Year	All study groups derived from similar source/reference populations	Attrition not significantly different across study groups	Measure of exposure is valid	Measure of outcome is valid	Investigator blinded or were outcomes well-defined and objective to endpoint assessment	Potential confounders identified	Statistical adjustment for potential confounders done	Funding source(s) disclosed and no obvious conflict of interest	Overall Risk of Bias
Mahieu 2001[29]	✓	✓	✓	✓	✓	✓	✓		Low

C.8. Central Line Antimicrobial Locks

Key Question 8: In NICU patients with central line catheters, does the use of central line antimicrobial locks, compared with standard of care, prevent CLABSI?

Table 37 Summary of Findings on Antimicrobial Locks vs. Standard of Care to Prevent CLABSI

Outcome	Findings	Quantity and Type of Evidence	GRADE of Evidence for Outcome and Limitations of the Evidence
Catheter –related bloodstream infection*	Three RCTs found the use of antimicrobial lock prophylaxis was associated with a reduced risk for CR-BSI. Each study used a different antibiotic agent and a different lock protocol. • One study[30] found the use of Amikacin-heparin locks for 20 minutes two times a day was associated with reduced risk for definite CR-BSI. OR: 0.27 (95% CI: 0.16 – 0.87); p<0.001 • One study[31] found the use of Fucidic acid-heparin locks once per day for 30-60 minutes was associated with reduced risk for CR-BSI. RR: 0.09 (95% CI: 0.01 – 0.72); p<0.01 • One study[32] found the use of Vancomycin-heparin locks for 20 minutes in neonates who were being fed primarily by parenteral hyperalimentation and for 60 minutes when enteral feeding exceeded 20 mL/kg/day was associated with reduced risk for CR-BSI OR: 0.05 (95% CI: 0.003 – 0.95); p = 0.05*	3 RCT n=103[31] n=85[32] n=83[30]	Moderate • Indirectness: studies not conducted in current standard of care
Suspected/ probable bloodstream infection	• Three studies reported no difference in suspected or probable CR-BSI with any type of antimicrobial catheter lock	3 RCT n=103[31] n=85[32] n=83[30]	Moderate • Indirectness: studies not conducted in current standard of care
Hypoglycemia	• One study[32] reported an increase in hypoglycemia with use of heparin saline infusions (p = 0.03) • Two studies[30, 31] reported that antimicrobial catheter locks were not associated with increased risk for hypoglycemia	3 RCT n=103[31] n=85[32] n=83[30]	Moderate • Indirectness: studies not conducted in current standard of care
Antimicrobial resistance	• Two studies reported no incidences of resistance to the antimicrobial used in the lock protocol were detected.	2 RCT n=85[32] n=83[30]	Low • Indirectness: studies not conducted in current standard of care • Imprecision: low number of events

Table 38 Extracted Information on Central Line Antimicrobial Locks

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
Author: Seliem[30] **Year:** 2010 **Study design:** RCT **Risk of bias:** Low	**Number of patients:** N=83 **Number of lines:** N = 83 **Setting:** Level III Neonatal ICU **Location:** Egypt **Dates:** February 2007-February 2008	**Intervention group B: n=41** Amikacin-heparinized saline lock for 20 minutes 2x/ day **Control group A: n=42** Heparinized-normal saline lock for 20 minutes 2x/ day **Device/agent:** Amikacin **Monitoring intervention:** NR	**Outcome Definitions:** Definite Catheter related bloodstream infection: When a positive peripheral blood culture (through venous puncture) concomitant with positive blood culture withdrawn from the catheter or catheter tip cultures grew the same species in the presence of clinical manifestations of sepsis without apparent source of bloodstream infection rather than UVC.	**Primary Outcome:** Definite catheter-related bloodstream infection, n (%): • Amikacin Lock 3/41 (7.3%) • No Lock: 11/42 (26.2%) • RR: 0.27 (95% CI: 0.16 – 0.87); • p < 0.001 Probable catheter-related bloodstream infection, n (%): • Amikacin Lock 1/41 (2.4%

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
	Inclusion Criteria: All neonates (term and preterm) admitted to the unit and were expected to require a UVC for at least 48 hours. **Exclusion Criteria:** Neonates with indwelling UVCs for more than 24 hours without a lock technique and those who have received systemic antibiotic therapy or were transferred to other hospitals in the first day of life.	**Standard preventive measures:** Maximum sterile barriers including use of sterile gloves, gown, cap, mask, and a large sterile drape. The umbilical stump and surrounding skin area of at least 5 cm radius were disinfected with 10% povidone iodine prior to catheter insertion. The umbilical stump was cleansed routinely on a daily basis with 70% alcohol. The intravenous tubing was changed every 24 hours using strict sterile technique. Catheter hubs were cleansed with 70% alcohol whenever hubs were accessed. Catheters removed whenever their use was deemed unnecessary.	Probable CR-BSI: Considered when the positive peripheral blood culture and positive blood culture withdrawn from the catheter grew different species. If there were positive cultures from the blood withdrawn from the catheter or catheter tip while peripheral blood culture was sterile in presence of clinical manifestations of infection. Bloodstream infection (BSI) without a source: Positive peripheral blood culture with clinical manifestations of sepsis and negative blood culture withdrawn from the catheter or tip culture. Hypoglycemia: defined as a bedside whole-blood glucose concentration <45 mg/dL **Sampling /Testing strategy:** All study subjects had a culture taken after 48 hours for early detection of catheter contamination and on the 5th and 10th days. When the UVC was removed, the catheter hubs and distal 5 cm of each catheter were cultured semi-quantitatively. Surveillance rectal and axillary cultures were obtained at study entry and at the time of catheter removal. If sepsis was suspected, two blood cultures were obtained (peripheral and central) and a culture from the catheter hub was performed. Susceptibility of bacterial isolates to amikacin was tested for growth on amikacin-containing agar. Evidence of growth indicated resistance. For amikacin group only: serum concentrations of amikacin were measured with fluorescence polarization immunoassay technology	• No Lock: 1/42 (2.3%) • RR: 1.01 (95% CI: 0.8 – 1.1); • p = 0.9 Total Definite and probable catheter-related bloodstream infection, n (%): • Amikacin Lock 4/41 (9.7%) • No Lock: 12/42 (28.5%) • RR: 0.34 (95% CI: 0.02 – 0.65); • p = 0.01 BSI without a source, n (%): • Amikacin Lock 2/41 (4.9%) • No Lock (saline heparin): 2/42 (4.8%) • RR: 1.02 (95% CI: 0.76 – 1.12); • p = 0.97 All BSI, n (%): • Amikacin Lock 6/41 (14.6%) • No Lock (saline heparin): 14/42 33.3%) • RR: Relative Risk: 0.43 (95% CI: 0.12 – 0.61); • p = 0.02 **Topic-specific outcomes:** Duration of catheter, days, mean (SD) • Amikacin Lock 11.6 (2.1) • No Lock (saline heparin):10.3 (3.6) • Standardized Mean Difference: -0.44 (95% CI: -0.88 - -0.004) • p = 0.048* **Adverse events** Mortality, n (%): • Amikacin Lock 4/41 (9.8%) • No Lock (saline heparin): 8/42 (19.0%) Hypoglycemic episodes, n (%): • Amikacin Lock 5/41 (12.2%) • No Lock (saline heparin): 8/42 (19.0%) • p = 0.27 Portal or IVC thrombosis: None observed

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
			Other notes: None	Amikacin resistance: None of the positive cultures grew microorganisms resistant to amikacin and there were no amikacin-resistant microorganisms detected in any skin or rectal surveillance cultures in either group.
Author: Filippi[31] **Year:** 2007 **Study design:** RCT **Risk of bias:** Moderate	**Number of patients:** N = 103 **Number of lines:** N = 103 **Setting:** Neonatal ICU **Location:** Italy **Dates:** July 2004 – Nov. 2005 **Inclusion Criteria:** All admitted neonates who required a nonmedicated CVC for ≥24 hrs. **Exclusion Criteria:** Neonates with medicated CVCs and neonates who had CVCs removed within 24 hrs. or were transferred to other hospitals or died in the first day of life.	**Study Groups** **Intervention group A: N=50** Fusidic acid-heparin lock for 30–60 mins, once per day **Control group C: n=53** Heparin-normal saline lock for 30–60 mins, once per day **Device/agent:** Fusidic acid **Monitoring intervention:** NA **Standard preventive measures:** Catheters were inserted with sterile technique. Skin surface surrounding the insertion point was disinfected with 10% povidone-iodine. A transparent polyurethane dressing was used to cover the insertion site. Intravenous tubing was changed daily, and catheter hubs were cleansed with 2% chlorhexidine every time they were accessed.	**Outcome Definitions:** Definite catheter related bloodstream infection: considered as one positive blood culture in a neonate with CVC, with concordant colonization of catheter hub or tip, clinical manifestations of infection, and no other apparent source for bloodstream infection except CVC. Suspected CR-BSI: positive culture of catheter hub or tip, clinical manifestations of infection, and no other apparent source for bloodstream infection except CVC, with negative or not concordant blood culture. Colonization: positive culture of catheter hub or tip with neither concordant blood culture nor clinical signs of infection. Non catheter related sepsis: positive blood culture with clinical manifestations of infection but negative culture of catheter hub or tip. Hypoglycemia: >180 or <40 mg/dL **Sampling /Testing strategy:** In both groups, cultures of aspired fluid were taken every 2 days before lock administration for early detection of catheter contamination. If any clinical sign of CR-BSI was present, two blood cultures were obtained (1 ml specimen from peripheral vein, 0.5 ml specimen from the catheter) and a culture was performed from the catheter hub. In case	**Primary Outcomes:** Definite catheter-related bloodstream infection • Fusidic acid lock: 1/50 (2%) • Heparin saline: 11/53 (20.8%) • Relative Risk: 0.09 (95% CI: 0.01 – 0.72); • p < 0.01 Suspected catheter-related bloodstream infection • Fusidic acid lock: 2/50 (4%) • Heparin saline: 2/53 (3.8%) • Relative Risk: 1.06 (95% CI: 0.16 – 7.24); • p = NS Total Catheter-related bloodstream infection rate/ 1000 catheter days • Fusidic acid lock: 6.6 • Heparin saline: 24.9 • Relative Risk: 0.28 (95% CI: 0.13 – 0.60); • p < 0.01 Colonization • Fusidic acid lock: 3/50 (6%) • Heparin saline: 2/53 (4%) • Relative Risk: 1.59 (95% CI: 0.28 – 9.12); • p = NS Non-catheter-related bloodstream infection • Fusidic acid lock: 4/50 (8%) • Heparin saline: 4/53 (7.5%) • Relative Risk: 1.06 (95% CI: 0.28 – 4.01); • p = NS **Topic-specific outcomes:** Total catheter days • Fusidic acid lock: 456 • Heparin saline: 522 • p = NS

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
			the CVC was removed, hubs and tip (3-4 cm, distal part) were cultured. **Other notes:** None	**Adverse events** Mortality • Fusidic acid lock: 13/50 (26%) (0 with CR-BSI) • Heparin saline: 11/53 (20.75%) (4 with CR-BSI) Treatment-related adverse events: None observed Phototherapy, n • Fusidic acid lock: 34/50 (68%) • Heparin saline: 35/53 (66.0%) • Relative Risk: 1.03 (95% CI: 0.77 - 1.38) Phototherapy, days, mean (±SD) • Fusidic acid lock: 3.1±1.9 • Heparin saline: 2.6±1.3 Jaundice • Fusidic acid lock: 33/50 (66%) • Heparin saline: 33/53 (62.3%) • Relative Risk: 1.03 (95% CI: 0.77 - 1.38) Leukopenia**:** No cases observed Thrombocytopenia**:** No cases observed Sideroblastic anemia: No cases observed Hypoglycemia: No cases observed
Author: Garland[32] **Year:** 2006 **Study design:** RCT **Risk of bias:** Low	**Number of patients:** N = 85 **Number of lines:** N = 85 **Setting:** Level III Neonatal ICU **Location:** USA **Dates:** May 2000- May 2001 **Inclusion Criteria:** All neonates who were admitted to the unit and would require a catheter	**Study Groups:** **Intervention group: n=42** Vancomycin-heparin saline lock solution for 20 minutes in neonates who were being fed primarily by parenteral hyperalimentation and for 60 minutes when enteral feeding exceeded 20 mL/kg/day **Control group:** n=43 Heparin normal saline lock solution for 20 minutes in neonates who were being fed	**Outcome Definitions:** Definite Catheter related bloodstream infection: a positive peripheral blood culture with concordant colonization of the catheter hub or catheter tip. Probable CR-BSI: Defined by either (1) a positive peripheral blood culture for coagulase negative staphylococci, with concordant colonization of the catheter hub or hub tip, but DNA subtyping was not done or (2) a blood culture through the catheter was positive (peripheral culture sterile or	**Infections:** Definite catheter-related bloodstream infection, n(%): • Vancomycin lock: 0/42 • Heparin saline: 8/43 (18.6%) • Relative Risk: 0.41 (95% CI: 0.08 – 2.00); p = 0.006 • OR: 0.05 (95% CI: 0.003 – 0.95); • p = 0.05* Probable catheter-related bloodstream infection, n (%): • Vancomycin lock: 2/42 (4.8%) • Heparin saline: 5/43 (11.6%)

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
	(newly placed PICC) for at least 48 hours. **Exclusion Criteria:** NR	primarily by parenteral hyperalimentation and for 60 minutes when enteral feeding exceeded 20 mL/kg/day **Device/agent:** NR **Monitoring intervention:** NR **Standard preventive measures:** Catheters were inserted percutaneously by staff neonatologists using maximal sterile barriers, including a sterile mask, cap, gloves and gown, and a large sterile drape. Insertion sites were disinfected with 10% povidone-iodine, and catheters were dressed with a polyurethane film dressing. Catheter sites were cleansed and redressed on a weekly basis or as needed if the dressing became loose or the site wet. Intravenous tubing was changed every 3 days when used for hyperalimentation and every 24 hours when used for intralipid therapy. Needless access ports were not used during the trial. Catheter hubs were cleansed with alcohol whenever the hub was accessed.	not done) for the same organism recovered from the catheter hub or tip, with clonal concordance confirmed by DNA subtyping when the blood culture grew coagulase-negative staphylococci <u>Bloodstream infection (BSI) without a source</u>: Defined by a positive peripheral or line blood culture and no other identifiable primary site of infection. Neonates were treated with at least 7 days of systemic antibiotic therapy. Cultures of the catheter were negative or, when positive, showed colonization with a strain or strains different from those recovered from the blood culture. **Adverse events** <u>Hypoglycemia</u>: defined as a bedside whole-blood glucose concentration <40 mg/dL **Sampling /Testing strategy:** Surveillance rectal and axillary cultures were obtained at study entry and at time of catheter removal. Gram-positive bacterial isolates that were recovered from catheter insertion sites, catheter cultures, or blood cultures were also tested for resistance to vancomycin. Microorganisms that showed growth on vancomycin-containing agar were considered resistant. When infants showed signs suspicious for sepsis, blood cultures were obtained: a 1-mL specimen drawn by percutaneous venipuncture and at least 0.5 mL drawn through the infant's catheter; the catheter hub was also cultured, using a premoistened sterile cotton swab. Catheters were removed at the discretion of the attending neonatologist. At that time, a 1-cm x	• Relative Risk: 0.41 (95% CI: 0.08 – 2.00); • p = 0.43 Catheter-related bloodstream infection rate/ 1000 catheter days • Vancomycin lock: 2.3 • Heparin saline: 17.8 • Relative Risk: 0.13 (95% CI: 0.01 – 0.57); • p = 0.004 BSI without a source<u>, n (%):</u> • Vancomycin lock: 5/42 (11.9%) • Heparin saline: 5/43 (11.6%) • Relative Risk: 1.02 (0.32-3.28); • p = 0 .97 **Topic-specific outcomes:** NR **<u>Adverse events</u>** <u>Patients with organ systems affected</u>: None observed <u>Hypoglycemia, n (%):</u> • Vancomycin lock: 8/42 (19.0%) • Heparin saline: 18/43 (41.9%) • p = 0.03 <u>Colonization by vancomycin-resistant gram positive bacteria</u>: None observed <u>Minimum inhibitory concentration of gram positive isolates from skin, catheter or blood >2 ug/mL</u>: None observed <u>Detectable blood vancomycin level >2 µg/mL</u> • Vancomycin lock: 1/42 (2.4%) • Heparin saline: 0/43

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
			1-cm area of skin surrounding the catheter, the catheter hub, and the distal 5 cm of the catheter each were cultured semi quantitatively. **Other notes:** None	

Table 39 Risk of Bias for Randomized Controlled Trials on Central Line Antimicrobial Locks

Author 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
Seliem 2010[30]	✓	✓			✓		✓			✓	Moderate
Filippi 2007[31]	✓						✓				High
Garland 2005[32]	✓		✓		✓	✓	✓	✓		✓	Low

C.9. Optimal Umbilical Arterial and Venous Catheter Dwell Time

Key Question 9 In NICU patients requiring an umbilical catheter, what is the optimal duration of umbilical artery and umbilical venous catheters to prevent CLABSI?

Table 40 Summary of Findings on the Optimal Duration of Umbilical Catheters Prior to Prevent CLABSI

Outcome	Findings	Quantity and Type of Evidence and Sample Size	GRADE of Evidence for Outcome and Limitations of the Evidence

CLABSI*	• Three observational studies[2, 23, 33] found that longer use of umbilical catheter was associated with an increased risk for CLABSI, at seven days of life.
	  • One observational study[33] found an increase in the odds of developing a CLABSI for UVCs in situ >7 days (OR: 5.48 (95% CI: 1.18-25.50); p = 0.03).
	  • One observational study[34] implemented a QI initiative directing providers to increase the dwell time of UVCs from the average of 5 days to 7 days prior to inserting a PICC and found no increase in UVC-associated CLABSI (IRR 1.13 (95% confidence interval 0.469–2.332) P = 0.92) with a 37.5% reduction in replacement with PICCs.
	  • One observational study[23] suggested the cumulative incidence of CLABSI increases with increasing UVC dwell time. Cumulative incidence was <1% in the first week of life, 3.6% at day 14, and 16.5% at day 18.
		4 OBS
		n=986 lines[33]
		n=6,000 lines[2]
		n=201 lines[34]
		n=4,052 lines[23]
			Low

Outcome	Findings	Quantity and Type of Evidence and Sample Size	GRADE of Evidence for Outcome and Limitations of the Evidence
	One observational study[2] suggested CLABSI rates increased beyond 4 days (UVC: 116/2668 (4.3%) vs PICC: 287/ 3332 (8.6%) p<0.01). For UVCs that were removed, there was more than five times the risk of CLABSI on days 6-7 than on days 4-5. However, this was not reported as statistically significant. UVCs replaced with PICCs before 4 days were associated with a trend of reduced CLABSI in the first PICC, compared with UVCs replaced on or after 4 days. After adjusting for gestational age, this trend continued but no longer reached statistical significance.		
Catheter-related infection*	• One RCT study[35] found the use of umbilical catheter for up to 28 days was associated with higher rate of infections when compared with UVC dwell times of 7-10 days, but the difference was not statistically significant (OR: 1.66; 95% CI: 0.79 – 3.48; p = 0.18).	1 RCT n=210 lines[35]	Moderate • Imprecision: only one study
Sepsis*	• One observational study[12] found the incidence of sepsis was higher in umbilical artery catheters in situ for ≥8 days when compared with those in situ for ≤7 days. (13.6% vs. 1.3%; p<0.0001). This study noted an increase in the incidence of sepsis in UVCs in situ for 4-7 days when compared with those in situ for 1-3 days but the UVC numbers were insufficient for valid statistical analysis.	1 OBS n=2,316 lines[12]	Very Low • Imprecision: only one study
Adverse Events	• One RCT study[35] found there was no difference in adverse events between UVCs left in situ for up to 28 days compared with UVCs in situ for 7-10 days. Adverse events included thrombosis, mortality, arrhythmia, embolus, hemorrhage, and pleural effusion • One observational study[23] reported a decrease in the rate of adverse events for UVCs compared with UVCs [IRR: 0.3 (95% CI: 0.2-0.4)]	1 RCT n=210 lines[35] 1 OBS n = 4,052 lines[23]	Moderate • Inconsistency

Table 41 Summary of Findings on the Optimal Duration of Umbilical Artery Catheter for Removal to Prevent CLABSI

Outcome	Findings	Quantity and Type of Evidence and Sample Size	GRADE of Evidence for Outcome and Limitations of the Evidence
CLABSI*	• One observational study[23] reported two CLABSI for 2,035 UAC lines. No conclusions can be drawn about the impact of duration on CLABSI risk.	1 OBS n = 4,052 lines[23]	Very Low • Imprecision: only one study
Sepsis*	• One observational study[12] found the incidence of sepsis was higher in umbilical artery catheters in situ for ≥8 days when compared with those in situ for ≤7 days. (13.6% vs. 1.3%; p<0.0001).	1 OBS[12] n=1,699 lines	Very Low • Imprecision: only one study
Adverse Events	• One observational study[23] reviewed data on 2,035 UAC lines and reported an increase in adverse events with increasing dwell time for UACs. The incidence of complications was 2.5% by day 5, 4.3% by day 10, and 37% by day 20. The most common adverse events were breakage/ rupture (20%), occlusion (10%), and catheter tip malposition (10%).	1 OBS n = 4,052 lines[23]	Very Low • Imprecision: only one study

Table 42 Summary of Findings on the Optimal Duration Prior to Removal of Umbilical Venous Catheters to Prevent CLABSI

Outcome	Findings	Quantity and Type of Evidence and Sample Size	GRADE of Evidence for Outcome and Limitations of the Evidence
CLABSI*	• One observational study[2] suggested CLABSI rates increased beyond 4 days (UVC: 116/2668 (4.3%) vs PICC: 287/ 3332 (8.6%) p<0.01). For UVCs that were removed, there was more than five times the risk of CLABSI on days 6-7 than on days 4-5. However, this was not reported as statistically significant. • One observational study[34] implemented a QI directing providers to increase the dwell time of UVCs from the average of 5 days to 7 days prior to inserting a PICC and found no increase in UVC-associated CLABSI (IRR 1.13 (95% confidence interval 0.469–2.332;) P = 0.92) with a 37.5% reduction in replacement with PICCs.	2 OBS n = 1,392 lines[2] n = 201 lines[34]	Very Low • Consistency: Inconsistent results across studies • Imprecision: only one study, low number of events
Sepsis*	• One observational study[12] found an increase in the incidence of sepsis in UVCs in situ for 4-7 days when compared with those in situ for 1-3 days but the UVC numbers were insufficient for valid statistical analysis (p<0.0001).	1 OBS n = 2,316 lines[12]	Very Low • Imprecision: only one study, low number of events

Table 43 Summary of Findings on the Optimal Duration Umbilical Venous Catheter for Replacement with a Long-term Catheter to Prevent CLABSI

Outcome	Findings	Quantity and Type of Evidence and Sample Size	GRADE of Evidence for Outcome and Limitations of the Evidence

CLABSI*	• Two observational studies[2, 33] found that longer use of umbilical catheter prior to replacement with a PICC was associated with an increased risk for CLABSI.
	  • One observational study[33] found an increase in the odds of developing a CLABSI for UVCs in situ >7 days (OR: 5.48 (95% CI: 1.18-25.50); p = 0.03).
	  • One observational study[2] found that the HR of CLABSI increased beyond 3-4 days of dwell time, and the risk doubled every 2 days thereafter if the UVC was followed by PICC insertion (UVC: 116/2668 (4.3%) vs PICC: 287/ 3332 (8.6%) p<0.01).
	• One observational study[34] implemented a QI directing providers to increase the dwell time of UVCs from the average of 5 days to 7 days prior to inserting a PICC and found no increase in UVC-associated CLABSI (IRR 1.13 (95% CI: 0.469–2.332); P = 0.92) with a 37.5% reduction in replacement with PICCs.
		3 OBS
		n = 986 lines[33]
		n = 6,000 lines[2]
		n = 201 lines[34]
			Low

Catheter-related infection*	• One RCT study[35] found the use of umbilical catheter for up to 28 days was associated with higher rate of infections when compared with UVC in place for 7-10 days prior to replacement with a PICC, but the difference was not statistically significant (OR: 1.66 (95% CI: 0.79 – 3.48); p = 0.18).	1 RCT n = 210 lines[35]	Moderate • Imprecision: only one study
Adverse Events	• One RCT study[35] found there was no difference in adverse events between UVCs left in situ for up to 28 days compared with UVCs in situ for 7-10 days. Adverse events included thrombosis, mortality, arrhythmia, embolus, hemorrhage, and pleural effusion.	1 RCT n = 210 lines[35]	Moderate • Imprecision: only one study

Table 44 Extracted Information on Umbilical Catheter Dwell Time

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
Author: Levit[23] **Year:** 2020 **Study Design:** Cohort **Risk of Bias:** Low	**Number of patients:** N = 2,676 patients **Number of lines:** N= 4,052 lines **Setting:** Level IV NICU **Location:** USA **Dates:** June 1, 2008 – May 31, 2018 **Inclusion Criteria:** • Any infant admitted to the NICU who had a UAC, UVC, or both successfully placed (i.e., catheter tip in the desired, central location) **Exclusion Criteria:** • NR	**Study Groups:** UAC: n=2035 UVC: n=2017 Double lumen: n=679 Single lumen: n=3373 **Device/agent:** Catheter type; double-lumen catheter **Standard preventive measures:** • UC insertion is a sterile, bedside procedure typically performed by advanced practice providers, pediatric interns and residents, and neonatal-perinatal medicine fellows • Double-lumen catheter insertion is based solely on anticipated need • Blood is not typically withdrawn from a UVC • Confirmation of UC placement is via thoracoabdominal radiograph • Routine, scheduled reconfirmation of UC location is not performed • Heparin at a concentration of 1 U ml^{-1} of fluid is infused continuously through all central line lumens • Central line tubing utilized for parenteral nutrition, intralipids, and/or blood products is changed every 24 hours • Tubing utilized only for dextrose containing fluids is changed every 96 hours • An assessment of the continued need for central access is typically made at day 5-7 of use	**Outcome Definitions:** BSI: CDC/NHSN definition CLABSI: if no other source was identified and if the UC was still indwelling or had been removed within 48 hours of the onset of infection **Adverse events:** Complications: break/rupture, occlusion, catheter tip malposition, poor perfusion to lower extremity, CLABSI, thrombus, or effusion **Sampling /Testing strategy:** NR **Other notes:** authors concluded the risk of CLABSI was low at day 14 even though the risk increased to 3 times the risk of the first week of life.	**Primary Outcomes:** CLABSI: Adjusted rate/ 1000 central-line days: • aRR: 2.7 (95% CI: 1.1-6.8); P = 0.04 • Double lumen UVC: 2.0 • Single lumen UVC: 0.7 Cumulative incidence of UVC-related CLABSI • In the first week: <1% • at day 14: 3.6% • At day 18: 16.5% BSI: Incidence, n/N (%) • UAC: 2/2035 (0.1%) • UVC: 19/2017 (0.9%) **Topic-specific outcomes:** Mean dwell time, days (range) • UAC: 5.5 days (1-22) • UVC: 7.6 days (1-21) **Adverse events** All complications: Adjusted rate/ 1000 central-line days • IRR: 0.3 (95% CI: 0.2-0.4) • UAC: 4.6 • UVC: 17.6 • p = NR Incidence, n/N (%) • UAC: 51/2035 (2.5%) • UVC: 269/2017 (13.3%) • p = NR Adjusted rate/ 1000 central-line days • Double lumen UVC: 17.2 • Single lumen UVC: 15.9 • p = 0.23 Complications excluding catheter malposition: Adjusted rate/ 1000 central-line days • aIRR: 2.3 (95% CI: 1.2-4.6); p = 0.02

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
				• Double lumen UVC: 3.8 • Single lumen UVC: 1.6 Adjusted rate/ 1000 central-line days • IRR: 1.6 (95% CI: 1.02-2.5) • UAC: 3.9 • UVC: 2.4 • p = NR
Author: Sanderson[2] **Year:** 2017 **Study Design:** Multicenter retrospective cohort **Risk of Bias:** Low	**Number of patients:** N= 3985 **Number of lines:** N = 6000 • UVC: 2668 • PICC: 3332 Total catheter days: 43, 302 • Baseline characteristics were significantly different between groups: including Gestational age, birth weight, congenital anomaly, PPROM, respiratory distress, cesarean delivery, major surgery, mortality, perinatal asphyxia/ trauma, age at first insertion, duration of CVC **Setting:** Multicenter: 10 NICUs in 10 hospitals **Location:** Australia **Dates:** January 1, 2007 – December 31, 2009 **Inclusion Criteria:** All infants born during the study dates admitted to 1	**Study groups:** UVC only: n=1392 UVC only: n=1317 UVC and PICC: n=1276 **Standard preventive measures**: NR	**Outcome Definitions:** First CLABSI**:** CDC 2016 definition and consistent with and within 48 hours of CVC removal (consistent with NSW criteria). CLABSI assigned to CVC in situ. Repeated organism isolates w/in 14 days of LOS diagnosis is not considered new LOS. Early onset sepsis (EOS): positive blood culture in an infant taken within the first 48 h of life and a clinical picture consistent with sepsis. Late onset sepsis (LOS): a positive blood culture, clinical symptoms, and signs of sepsis and clinician decision to treat with antibiotics for 5 days (including CoNS) **Sampling /Testing strategy:** Blood/catheter tip culture. **Other notes:** None	**Primary Outcome:** CLABSI: Incidence: n (%) • UVC: 116/2668 (4.3%) • PICC: 287/ 3332 (8.6%) • p < 0.01 Rate: n/ 1000 catheter days • UVC: 9.88 • PICC: 9.09 • UVC CLABSI rate: increased beyond 4days, and by days 6-7 had more than 5 times the risk (IRR: 5.85 (1.18-28.96) of CLABSI than on days 45. **Topic-specific Outcomes:** Dwell time: • "The hazard ratio (HR) of UVC and PICC diverged beyond the 3-4 days dwell time. UVC had a higher HR and earlier rise than PICC." • "the incremental CLABSI rate increase was highest in UVCs of infants with UVC+PICC, which almost doubled every 2-3 days between days 2 and 7 (14, 27, and 45 per 1000 line-days respectively) and continued to rise with increasing duration, peaking at 85 per 1000 line-days at days 10 and 11." • "the hazard function for CLABSI showed that the group with early PICC insertion (before day 4) had a trend of lower HR." **Adverse events:** Mortality w/in 14 days of CLABSI (%LOS deaths) • UVC: 8/1392 (61.3%) • PICC: 1/1317 (16.0%) • UVC+PICC: 11276 (5.0%) • p < 0.001

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
	of 10 NICUs with one or more UVCs or PICCs inserted. **Exclusion Criteria:** NR			
Author: Vachharajani[34] **Year:** 2017 **Study Design:** Uncontrolled before-after **Risk of Bias:** Moderate	**Number of patients:** N = 201 **Number of lines:** N = 201 **Setting**: NICU, University Hospital **Location:** USA **Dates:** Jan 1, 2012 – June 30, 2014 **Inclusion Criteria:** uncomplicated NICU patients without congenital anomalies with GA>27 wks. or >1000g at birth, extubated by 3 days of age and on enteral feeds by 2 – 3 days of age **Exclusion Criteria:** babies who died within a week following redirection of care. Neonates with abdominal wall defects, congenital heart defect, congenital diaphragmatic hernia, spontaneous intestinal perforation, neonates requiring >7d antibiotic therapy.	**Study groups:** Post-QI1: Jan 1, 20014 – March 30, 2014: introduction of QI initiative including questionnaire, staff education, and standardization of feeding protocol: Feeding GL for preterm infants: BW≤1000g • Starting volume: 10ml/kg • Advance volume: 10ml/kg during morning rounds • When to fortify: 60-100ml/kg BW≥1000g • Starting volume: 20ml/kg • Advance volume: 20ml/kg during morning rounds • When to fortify: 80-100ml/kg Questionnaire implemented to encourage providers to consider leaving the existing UVC in situ if neonate met criteria. Encourage provider to remove UVC and insert PICC after day 7 if neonate not tolerating 60-70ml/kg/ day of feeds by 5-6 days of age. Post QI2: April 1, 2014 – June 30, 2014 Pre-QI: Jan 1, 2012 – December 31, 2013 baseline **Standard preventive measures**: NR	**Outcome Definitions:** CLABSI & UVC-associated CLABSI: not defined **Sampling /Testing strategy:** NR. **Other notes:** None	**Primary Outcomes:** CLABSI: • Pre-QI: 1 (in situ 8 days) • QI: 2 (in situ for 7 & 10 days) UVC-associated CLABSI QI to Pre-QI: • IRR 1.13 (95% CI 0.469 – 2.332); p = 0.92 **Topic-specific outcomes:** NR <u>UVC> 7days</u> • PRE-QI: 23/86 (27%) • QI1: 42/115 (36.5%) • p = 0.045 **Adverse events:** NR
Author: Butler-O'Hara[33] **Year:** 2012	**Number of patients:** N = 986 **Number of lines:** N = 986	**Patient Groups:** Pre-intervention Jan – Oct 2006 Post-intervention: After November 2006	**Outcome Definitions:** CLABSI: infant was considered to have a CLABSI when one of these two criteria were met: (1) the infant had a recognized	**Primary Outcomes:** CLABSI: Multiple logistic regression model: • Year (2006, 2007 vs 2008, 2009) 4.10 (1.29-13.0); p = 0.02

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
Study Design: Uncontrolled before after study (Retrospective cohort) **Risk of Bias:** Moderate	**Setting:** Neonatal ICU **Location:** USA **Dates:** January 1, 2006 – December 31, 2009 **Inclusion Criteria:** All infants for whom UVC was placed as part of routine care. **Exclusion Criteria:** NR	Infants >7 days UVC group: n=448 • Infants in this group were smaller and had lower gestational age at birth. Infants ≤ 7 days UVC group: n=536 Assess impact of evidence based catheter insertion and maintenance bundle. Multi intervention: November 2006 All providers in NICU in contact with central catheters received education, evidence-based checklists for UVC and PICC insertions, dressing changes, and care and maintenance of UVC and PICC during solution changes. PICC Team: dedicated 4 hours/day exclusively to catheter care and maintenance and changing of central catheter solutions. Team not responsible for umbilical venous or arterial catheter care or fluid changes. Provided care for most but not all days each month. Parenteral nutrition solutions for PICCs were changed once daily. Team used procedure carts specifically for PICC care and maintenance. used a closed medication administration system and adhered to strict evidence-based practices for solution changes and catheter care. hand hygiene and maintained aseptic technique when changing all intravenous tubing and when entering the catheter, including scrubbing the catheter hub with povidone-iodine. catheter-tubing changes using a standardized intravenous tubing setup and changed according to a written unit policy. Insertion site inspected for signs	pathogen cultured from one or more culture sites and the organism cultured from the blood was not related to an infection at another site; and (2) the infant had symptoms (eg, fever, hypotension) and positive laboratory results not related to an infection at another site and a common skin contaminant (eg, coagulase-negative staphylococcus) was cultured from two or more blood cultures drawn on separate occasions. **Sampling /Testing strategy:** Blood and catheter tip cultures performed. **Other notes:** None	• Birthweight, kg 0.20 (0.02-1.71); p = 0.14 • Gestational age, weeks 0.92 (0.70-1.20); p = 0.52 • UVC in place >7 days 5.48 (1.18-25.50); p = 0.03 • Initial antibiotics >3 days 0.28 (0.10-0.76); p = 0.01 CLABSI Rate/ 1000 days & HR (95% CI) and duration of CVC ≤7 days • UVC: 1.0; 1 • PICC: 6.1: 1 8-10 days: • UVC: 5.4; 5 (0.98 – 51.00) • PICC: 1.4; 0.2 (0.02 – 1.60) 11-14 days: • UVC: 21; 20 (5 – 185) • PICC: 3.8; 0.6 (0.2 – 3.1) >14 days: • UVC: 32, 31 (4 – 368) • PICC: 9.2; 1.5 (0.6 – 5.8) **Topic-specific outcomes:** None **Adverse events:** NR

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
		of infection and dressing integrity. PICC care done by assistant buddy system. **Standard preventive measures**: UVC Placement care: care of the umbilical site included use of betadine for cord preparation before catheter placement. No triple dye applied to any umbilical cord that required a UVC. Either a single- or double lumen catheter was inserted in sterile conditions. A second assistant or ‘‘buddy’’ was assigned and dedicated to placement of the UVC. Care of the catheters was standardized, with use of evidence-based bundled care and a series of procedural checklists. Catheters were sutured in place in the umbilical cord, and tape was then used to secure the catheter to the infant’s abdomen. The clinical team (not the PICC team) was responsible for changing the fluids of the umbilical arterial and venous catheters. At the completion of the procedure, a procedural checklist was completed indicating use of sterile technique from the start of the procedure until the final placement and suture of the catheter. PICC insertion/care: Placement of the PICC was performed in sterile conditions. Povidone-iodine solution swabbed 360 degrees surrounding the chosen insertion site. Either a 25- or 30-cm catheter with a 24-gauge introducer needle was inserted in the infant’s brachial, axillary, saphenous, or external jugular vein. Dressings were assessed hourly and changed when loss of adhesiveness, drainage at the site, or the dressing		

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
		became too restrictive. A ''second assistant'' or ''buddy'' was available for PICC insertion, dressing changes and maintenance. Dedicated team of performed all dressing changes and catheter manipulations. Checklists were used for PICC insertion, catheter dressing changes, and care and maintenance of the PICC during solution changes.		
Author: Butler O'Hara[35] **Year:** 2006 **Study Design:** RCT **Risk of Bias:** Low	**Number of patients:** N=210 **Number of lines:** N = 210 **Setting:** Neonatal ICU **Location:** Boston, Massachusetts, USA **Dates:** July 1998 - February 2004 **Inclusion Criteria:** Infants with birth weights ≤1250 g who had a UVC placed on NICU admission. Infants born at <24 weeks' gestation or <500 g at birth, but attending neonatologist was first consulted and had to provide approval. **Exclusion Criteria:** Infants who required a UVC for exchange transfusion, infants with gastrointestinal abnormalities including gastroschisis and omphalocele, or infants with congenital heart	**Patient Groups:** Long term (n=104) UVC was replaced when the catheter was no longer needed or by 28 days at the latest. UVC replaced with PCVCs Short term: (n=106) The umbilical venous catheter remained in place up to 7 to 10 days of age. If central access was necessary beyond day 10, PCVC placement was attempted beginning at day 7 to assure successful placement by day 10. **Standard preventive measures:** • Both infusion and flush solutions contained heparin (1.0 IU/ml for infants >1000 g and 0.5 IU/ml for infants ≤1000g or on total parenteral nutrition. • Catheters sutured in place into the umbilical cord, and tape was then used to secure the catheter to the infant's abdomen. • Placement of PCVC performed under sterile conditions, and care of catheters was standardized. • The catheter and the proximal portion of the extension set were secured to the skin by using a sterile, transparent, occlusive dressing.	**Outcome Definitions:** Catheter related infection: defined infection while a catheter (UVC or PCVC) was in place. Each infant was counted only once as having a catheter infection during the study regardless of future blood-culture results. **Sampling /Testing strategy:** All infants who had a sepsis workup performed during the study period (until 28 days or until catheter removal, whichever came first) had simultaneous quantitative peripheral and catheter blood cultures performed. **Other notes:** None	**Primary Outcomes:** Catheter related infection rate/ 1000 catheter days: • Long term: 11.5 • Short term: 7.4 Catheter-related infection Incidence: • Long term: 21/104 • Short term: 14/106 • OR: 1.66 (95% CI: 0.79 – 3.48); p = 0.17 • p = 0.18 **Topic-specific outcomes:** Catheter duration before infection, days, median: • Long term: 14.0 • Short term: 11.5 • p = 0.35 **Adverse events (n)** Thromboses: • Long term: 7 • Short term: 4 Pericardial effusions • Long term: 10 • Short term: 11 NEC (Bell's 40 stage 2 or above) • Long term: 11 • Short term:7 Mortality: • Long term: 7 • Short term: 8

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
	disease with intracardiac shunting.	• Solution infusing through the PCVC contained heparin (at the same concentrations as for UVC) and ran at a minimum rate of 1.0 ml/hour. • Sterile gloves were worn during all solution changes. • Intravenous tubing was secured well to the skin but did not occlude any part of the dressing. • Dressing integrity was assessed routinely and documented. Dressings were changed when there was loss of adhesiveness or drainage at the site or when they became too restrictive.		Arrhythmia • Long term: 1 • Short term: 0 Embolus • None observed Hemorrhage • None observed Pleural effusion • None observed Liver disease (one-year follow-up) • Long term: 1 • Short term: 0 Broken catheter • None observed Catheters removed due to mechanical complications • Long term: 27/181 • Short term: 27/210
Author: Bhandari[12] **Year:** 1997 **Study Design:** Prospective cohort study **Risk of Bias:** High	**Number of patients:** N = 2091 **Number of lines:** N = 2091 **Setting:** 2 NICUs, 1 at a University Hospital, 1 at a regional hospital **Location:** USA **Dates:** Regional Hospital November 11, 1987 - December 31, 1993 University Hospital: January 1, 1989 - December 31, 1993 **Inclusion Criteria:** All neonates admitted to the 2 hospital NICUs if one or more vascular catheter was simultaneously or sequentially placed:	**Patient groups:** Patients: n = 2091 **Standard preventive measures**: • UA and UV were placed either by the physicians or the neonatal nurse practitioners (NNP) at both the NICUs. • Tunneled CVs (Broviac) were placed by pediatric surgeons • Percutaneous central venous placements were done exclusively by the NNPs using a standard protocol (sterile technique and site preparation with povidone iodine) • Some PCVs placed as "long peripheral" lines rather than as central lines for technical reasons. • Catheter maintenance was done per nursing protocols at both hospitals: sterile dressing and IV tubing changes. • Peripheral arterial catheters were placed by physicians/NNPs • All lines had heparin infusions.	**Outcome Definitions:** Nosocomial sepsis: Presence of clinical signs of infection, initiation of anti-microbial therapy and a positive blood culture obtained from a peripheral site or via the catheter after the third postnatal day. Association between duration of catheter use, type, and nosocomial sepsis at University hospital: the incidence of positive blood cultures from time of insertion of catheter until 3 days after removal was analyzed for a consecutive population subset over 2.5 years Infants with bacteremia: - And >1 catheter simultaneously: each	**Primary Outcomes:** Total Nosocomial Sepsis: % infected was significantly different for each catheter type: P<0.0001 Umbilical artery • Infected: 179/1699 (10.5%) • Non-infected: 1520/ (89.5%) Umbilical venous: • Infected: 81/617 (13.1%) • Non-infected: 536/617 (86.9%) Central Venous • Infected: 99/294 (33.5%) • Non-infected: 194/294 (66.2%) Percutaneous Catheter • Infected: 96/308 (31.2%) • Non-infected: 212/308 (68.8%) Peripheral Artery • Infected: 35/189 (18.5%) • Non-infected: 154/189 (71.5%) Nosocomial Sepsis and Dwell Time: n (%) Umbilical artery • 1-3 days: 1/207 (0.5%) • 4-7 days: 4/175 (2.3%) • 8-14 days: 7/62 (11.3%) • ≥15 days: 4/19 (21.1%)

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
	umbilical artery (UA), Umbilical venous (UV), central venous Broviac (CV), percutaneously placed central venous (PC), or peripheral artery (PA). **Exclusion Criteria:** NR		catheter was included in analysis for association - And >1 catheter sequentially: the last catheter place was assigned the infection. - 1/3 of infants with CV or PC compared 10-18% of infants with other catheter types. **Sampling /Testing strategy:** Blood/catheter tip culture. **Other notes:** Incidence of infection by comparing different catheter types.	• ≥8 days: 13.6% • ≤7 days: 1.3% • p < 0.0001 Umbilical venous: • 1-3 days: 1/129 (0.8%) • 4-7 days: 4/58 (6.9%) • 8-14 days: 3/52 (5.8%) • ≥15 days: 1/5 (20.0%) Central Venous • 1-3 days: 0/4 (0%) • 4-7 days: 1/6 (16.7%) • 8-14 days: 2/30 (6.7%) • ≥15 days: 14/72 (19.4%) Percutaneous Catheter • 1-3 days: 0/12 (0%) • 4-7 days: 0/13 (0%) • 8-14 days: 1/27 (3.7%) • ≥15 days: 3/27 (11.1%) Peripheral Artery • 1-3 days: 1/30 (3.3%) • 4-7 days: 0/27 (0%) • 8-14 days: 1/9 (11.1%) • ≥15 days: 0/3 (0%) **Topic-specific outcomes:** NR **Adverse events:** NR

Table 45 Risk of Bias for Randomized Controlled Trials on Umbilical Catheter Dwell Times

Author 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
Butler O' Hara 2006[35]	✓	✓			✓		✓	✓	✓	✓	Low

Table 46 Risk of Bias for Two Group Studies on Umbilical Catheter Dwell Times

Author Year	Were patients randomly assigned to the study's groups?	For non-randomized trials, did the study employ any other methods to enhance group comparability such as matching, stratification, or statistical methods to adjust for baseline differences?	Did patients in different study groups have similar levels of performance on the outcome of interest and other important factors at the time they were assigned to groups?	Did the study enroll all suitable patients or consecutive suitable patients within a time period?	Was the comparison of interest prospectively planned?	Were the two groups treated/ evaluated concurrently?	Was the study blinded or double-blinded?	Was the funding for this study derived from a source that would not benefit financially from results in a particular direction?	Risk of Bias
Levit 2020[23]	✓	✓	✓	✓	✓	✓	✓		Low

Table 47 Risk of Bias for Single Group Studies on Umbilical Catheter Dwell Times

Author Year	Did the study enroll all suitable patients or consecutive suitable patients within a time period?	Was the study prospectively planned?	Were independent or blinded assessors used to assess subjective Outcome Definitions, or were the Outcome Definitions objective?	Was the funding for this study derived from a source that would not benefit financially from results in a particular direction?	Risk of Bias
Bhandari 1997[12]	✓		✓		High
Sanderson 2017[2]	✓		✓	✓	Moderate
Vachharajani 2017[34]	✓		✓	✓	Moderate

Table 48 Risk of Bias for Two Group Studies on Umbilical Catheter Dwell Times

Author Year	Were patients randomly assigned to the study's groups?	For non-randomized trials, did the study employ any other methods to enhance group comparability such as matching, stratification, or statistical methods to adjust for baseline differences?	Did patients in different study groups have similar levels of performance on the outcome of interest and other important factors at the time they were assigned to groups?	Did the study enroll all suitable patients or consecutive suitable patients within a time period?	Was the comparison of interest prospectively planned?	Were the two groups treated/ evaluated concurrently?	Was the study blinded or double-blinded?	Was the funding for this study derived from a source that would not benefit financially from results in a particular direction?	Risk of Bias
Butler-O'Hara 2012[33]		✓	✓	✓	✓	✓			Moderate

C.10. Optimal Peripherally Inserted Central Catheter Dwell Time

Key Question 10. What is the optimal duration for peripherally inserted central catheters to prevent CLABSI in NICU patients?

Table 49 Summary of Findings on Peripherally Inserted Central Catheter Dwell Times to Prevent CLABSI

Outcome	Findings	Quantity and Type of Evidence	GRADE of Evidence for Outcome and Limitations of the Evidence

CLABSI*	• Three observational studies[2, 36, 37] reported increasing risk of CLABSI with increasing PICC dwell time, but no clear inflection point for PICC removal or replacement to reduce CLABSI risk.
	  • One observational study[2] found that increasing dwell time was associated with increased risk of CLABSI for PICCs, but reported no clear inflection point for PICC removal or replacement.
	  • One observational study[36] reported the risk of CLABSIs increased during the 2 weeks after PICC insertion and then remained elevated until PICC removal but data did not point to a clear inflection point beyond which infection increases.
	  • One observational study[37] reported an increase in CLABSI risk of 14% per day between catheter days 1-18, and of 33% per day from days 35 through 60.
	• One observational study[7] reported that compared with the risk of CLABSI in week 1, no other week was associated with increased risk of CLABSI for PICCs suggesting no clear optimal PICC dwell time to reduce CLABSI risk.
		4 OBS
		n=3332 PICCS[2]
		n=4797 PICCS[36]
		n=683 PICCS[37]
		n=14,451 PICCS[7]
			Low

Catheter-related BSI*	• One observational study[38] reported increasing dwell time was a significant factor for the odds of developing CRBSI (p<0.01), however the optimal timing for removal of a PICC could not be determined. • One observational study[39] reported that for each week of PICC duration, the trend was for an increasing rate over time; however, this did not reach significance (p = 0.09) and dwell time was not a predictor of the odds of developing CR-BSI. (OR: 1.19 (0.91–1.57); p = 0.212). Almost all PICCs in this study were removed within 2 weeks after insertion. • One observational study[40] found no difference in the mean dwell time between infected and non-infected patients. (p = 0.6064).	3 OBS N=412 PICCS[38] N=946 PICCS[39] N=63 PICCS[40]	Low
Catheter –related sepsis*	• One observational study[41] found the odds of developing CRS was 3 times higher if the catheter was in place for ≥9 days (OR: 3.1 (95% CI: 1.64-5.87); p<0.01).	1 OBS n=294 PICCS[41]	Very Low • Imprecision: only one study

Table 50 Extracted Information on Peripherally Central Catheter Dwell Time

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
Author: Sanderson[2] **Year:** 2017	**Number of patients:** N = 3,985 **Number of lines:** n=6,000 • UVC: 2,668	**Patient group:** UVC only: n=1,392 UVC only: n=1,317 UVC and PICC: n=1,276	**Outcome Definitions:** First CLABSI**:** CDC 2016 definition and consistent with and within 48 hours of CVC removal (consistent with NSW Health criteria*). CLABSI assigned to CVC in situ. Repeated organism isolates w/in 14 days of LOS diagnosis is not considered new LOS.	**Primary Outcomes:** CLABSI: Incidence: n (%) • UVC: 116/2668 (4.3%) • PICC: 287/ 3332 (8.6%)

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
Study Design: Multicenter retrospective cohort **Risk of Bias:** Low	• PICC: 3,332 Total catheter days: 43, 302 • Baseline characteristics were significantly different among groups (UVC only [group 1], PICC only [group 2], UVC and PICC [group 3]): including gestational age, birthweight, congenital anomaly, PPROM, respiratory distress, cesarean delivery, major surgery, mortality, perinatal asphyxia/ trauma, age at first insertion, duration of CVC **Setting:** Multicenter: 10 NICUs in 10 hospitals **Location:** Australia	**Standard preventive measures**: NR	* available at: http://www.cec.health.nsw.gov.au/data/assets/pdf_file/0009/258372/hai-manual.pdf Early onset sepsis (EOS): positive blood culture in an infant taken within the first 48 hrs. of life and a clinical picture consistent with sepsis. Late onset sepsis (LOS): a positive blood culture, clinical symptoms, and signs of sepsis and clinician decision to treat with antibiotics for ≥5 days (including CoNS) Incidence of CLABSI: expressed as number of episodes per 1,000 catheter-days and number of episodes per 1,000 catheters inserted PPROM: prolonged premature rupture of membranes IRR: incidence rate ratio **Sampling /Testing strategy:** Blood/catheter tip culture. **Other notes:** None	• p < 0.01 Rate: n/ 1,000 catheter days • UVC: 9.88 • PICC: 9.09 • UVC CLABSI rate: increased beyond 4 days, and by days 6-7 group 1 [UVC only] had more than five times the risk (IRR: 5.85 (CI: 1.18-28.96) of CLABSI than on days 45. Dwell time: • "The hazard ratio (HR) of UVC and PICC diverged beyond the 3-4 days dwell time. UVC had a higher HR and earlier rise than PICC." • "the incremental CLABSI rate increase was highest in UVCs of infants with UVC+PICC, which almost doubled every 2-3 days between days 2 and 7 (14, 27, and 45 per 1,000 line-days respectively) and continued to rise with increasing duration, peaking at 85 per 1,000 line-days at days 10 and 11." • "the hazard function for CLABSI showed that the group with early PICC insertion (before day 4) had a trend of lower HR." **Topic-specific outcomes:** NR **Adverse events:** Mortality w/in 14 days of CLABSI (% LOS deaths) • UVC: 8/1,392 (61.3%) • PICC: 1/1,317 (16.0%) • UVC+PICC: 1/1,276 (5.0%) • p < 0.001

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
	Dates: January 1, 2007 – December 31, 2009 **Inclusion Criteria:** All infants born during the study dates admitted to 1 of 10 NICUs with one or more UVCs or PICCs inserted. **Exclusion Criteria:** NR			
Author: Greenberg[7] **Year:** 2015 **Study Design:** retrospective cohort study **Risk of Bias:** Low	**Number of infants:** N = 13,327 **Number of lines:** N = 15,567 Catheter days: N = 256,088 **Setting:** Multicenter NICU (141 NICUs; 13 states) **Location:** USA **Dates:** September 2011 – August 2013 **Inclusion Criteria:** • Infant with PICCs or tunneled catheters obtained from NCLABSI database during study dates	**Patient group:** N = 13,327 NICU infants Tunneled catheters (n= 1,116/15,567; 7.2 %)) PICCs (n = 14,451/15,567; 93%) **Device/agent:** Catheter type **Standard preventive measures:** Participating sites adopted a central catheter insertion and maintenance bundle which included: • Hygiene for insertion • Daily assessment of line need • A recommendation to remove central lines when infants achieved 120 mL/kg per day of enteral feedings • techniques for sterile dressing changes and catheter access.	**Outcome Definitions:** CLABSI: NHSN 2008 definition. • Positive blood culture for a recognized pathogen not related to an infection at another site • Diagnosis of CLABSI required systemic signs and symptoms of infection and isolation of the same organism from ≥ 2 blood cultures drawn on separate occasions. CLABSI attribution: • If a single catheter had multiple associated positive blood cultures (occurred on 12 occasions), only the first positive blood culture was included in the analysis. • If a CLABSI occurred in the presence of multiple catheters (this occurred on 3 occasions), the CLABSI was attributed to both catheters. Dwell time: number of days from line insertion until either line removal or day of CLABSI. The day of line insertion was defined as line day 1; weeks of dwell time were categorized into 7-day periods starting on line day 3 (week 1 = line days 3–9, week 2 = line days 10–16, etc.). Adverse events: NR **Sampling /Testing strategy:** Blood cultures **Other notes:** HR: hazard ratio	**Primary Outcomes:** CLABSI: Incidence • Tunneled catheters: 39/1,116 (3.5%) • PICCs: 199/ 14,451 (1.4%) • p <0.001 Rate • 0.93 CLABSI / 1,000 catheter days Effect of dwell time on CLABSI Week 1 • Tunneled catheters: 5/1,116 (0.4%) • HR (95% CI:) reference • PICCs: 82/14,451 (0.6%) • HR (95% CI): reference Week 2 • Tunneled: 5/969 (0.5%) HR: 1.3 (0.4 – 4.4) • PICCs: 56/8,250 (0.7%) • HR 1.2 (95% CI: 0.9 – 1.7) Week 3 • Tunneled: 3/748 (0.4%) HR: 1.0 (0.2 – 4.4) • PICCs: 31/4,061 (0.8%); HR 1.3 (0.8 – 1.9) Week 4 • Tunneled: 2/580 (0.3%) HR: 0.9 (0.2 – 4.7) • PICCs: 5/2,209 (0.2%); HR 0.4 (0.1 – 0.9) Week 5 • Tunneled: 3/452 (0.7%) HR: 1.8 (0.4 – 7.6) • PICCs: 7/1,290 (0.5%); HR 0.9 (0.4– 1.9)

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
	Exclusion Criteria: • Central lines inserted and removed within the first 2 days • Positive blood cultures occurring within 2 days of line placement	• Antibiotic practices were not standardized between the sites.		Week 6 • Tunneled: 4/355 (1.1%) HR: 3.2 (0.8 – 12.0) • PICCs: 7/765 (0.9%); HR 1.5 (0.7– 3.2) Week 7 • Tunneled: 4/280 (1.4%); HR 4.0 (1.1-15.4) • PICCs: 4/453 (0.9%); HR 1.4 (0.5-4.0) Week 8 • Tunneled: 1/288 (0.4%); HR 1.3 (0.1-11.4) • PICCs: 3/278 (1.1%); HR 1.6 (0.5-5.2) Week 9 • Tunneled: 3/178 (1.7%); HR: 4.7 (1.1-20.3) • PICCs: 2/183 (1.1%); HR: 1.5 (0.4-6.3) Week 10 • Tunneled: 1/151 (0.7%); HR: 2.0 (0.2-17.7) • PICCs: 0/125 (0) **Topic-specific outcomes:** Catheter dwell time median, (IQR) • Tunneled catheters: 24.5 d (14-45) • PICCs: 11 d (7-18) • p < 0.001 **Adverse events:** NR
Author: Rangel[40] **Year:** 2014 **Study Design:** Retrospective cohort study **Risk of Bias:** Moderate	**Number of patients:** N = 63 **Number of lines:** N = 63 **Setting:** NICU, 1 university hospital **Location:** Brazil **Dates:** January 2009 - December 2010 **Inclusion Criteria:** NICU newborns weighing	**Patient group:** N = 63 **Standard preventive measures**: • A protocol for the insertion and maintenance of PICC lines, • A routine for recording procedures undertaken with the PICC by the nursing professionals in a surveillance form for intravascular devices filed in the medical records, • A technical body trained and	**Outcome Definitions:** Catheter-related Infection: categorized as positive or negative according to the result of the blood culture **Sampling /Testing strategy:** Blood culture. **Other notes:** None	**Primary Outcomes:** Catheter-related infection: Positive Blood Culture: 16/63 (25.40**%)** **Topic-specific outcomes:** Indwell Time mean (SD), days • Catheter-related infection: 10.69 (± 6.322) • No infection: 9.88 (± 4.87) • p = 0.6064 **Adverse events:** NR

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
	500 - 1,499 g, born in the institution between January 2009 - December 2010, with a record of having had a PICC line in that period. **Exclusion Criteria:** NICU newborns with congenital malformations, diagnosis of infection prior to the implantation of the PICC, who were suspected of primary bloodstream infection (BSI) or who were transferred due to any situation were excluded from the study.	empowered for the use of this type of protocol.		
Author: Milstone[36] **Year:** 2013 **Study Design:** Retrospective cohort **Risk of Bias:** Moderate	**Number of patients:** N = 3,967 **Number of lines:** N = 4,797 PICCs Number of catheter days: N = 89,946 **Setting:** multicenter; NICU (8), university hospitals **Location:** USA	**Patient group:** N= 3,967 **Standard preventive measures**: • Trained infection preventionists performed prospective surveillance to monitor positive blood cultures in patients with indwelling catheters by using laboratory databases and infection surveillance support systems	**Outcome Definitions:** PICC dwell time: days from PICC insertion until either PICC removal or the date of CLABSI, whichever was earlier. PICC-associated CLABSI: CDC 2008 NHSN definition of CLABSI occurring in a PICC "two or more blood cultures drawn on separate occasions" for common skin commensal bacteria (i.e., coagulase negative staphylococci **Sampling /Testing strategy:** Blood/catheter tip culture. **Other notes:** IRR: incidence rate ratio	**Primary Outcomes:** Catheter-related sepsis: PICC-associated CLABSI, incidence, n/N (%): 149/4,797 (3.1%) PICC-associated CLABSI incidence rate/1,000 days: 1.66 Time from PICC insertion to CLABSI, median (range), days: 18 (1–166) CLABSI Incidence rate/ 1,000 catheter days (95% CI) • 1-10d: 1.05 (95% CI: 0.77–1.41) • 11-20d: 1.98 (95% CI: 1.44–2.66) • 21-30d: 2.07 (95% CI: 1.31–3.11) • 31-40d: 2.47 (95% CI: 1.38–4.07) • 41-50d: 1.73 (95% CI: 0.63–3.76) • 51-60d: 2.95 (95% CI: 1.08–6.41)

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
	Dates: January 1, 2005- June 30, 2010 **Inclusion Criteria:** Neonates who had a PICC inserted in a NICU during the study dates. **Exclusion Criteria:** NR		Median PICC dwell time of 14 days; 25% remained in place for ≥ 23 days	• >60d: 3.31 (95% CI: 1.65–5.92) • "PICCs w/ dwell time of 8 - 13 days, 14 – 22 d, and ≥23 days each had an increased risk of infection compared w/ PICCs in place for ≤7 days" (p <0.05). • "there is no clear inflection point after which the daily risk of CLABSIs increases" **Topic-specific outcomes:** PICC dwell times, n (%) • ≤7 d:1,096 (22.9) • 8–13 d: 1,289 (26.8) • 14–22 d: 1,129 (23.6) • ≥23 d 1,283 (26.7) Univariate analysis: Catheter dwell time: CLABSI (%), unadjusted IRR (95% CI); p • ≤7 d: 25 (16.6%), 1.0 (reference) • 8–13 d: 32 (21.2%), 2.02 (1.21–3.38); p = 0.007 • 14–22 d: 39(25.8%), 3.27 (2.04–5.24); p < 0.001 • ≥23 d: 55(36.4%), 2.71 (1.71–4.27); p < 0.001 **Adverse events:** NR
Author: Ohki[39] **Year:** 2013 **Study Design:** Prospective cohort study **Risk of Bias:** Moderate	**Population:** N = 946 **Number of lines:** N = 946 **Setting:** Multicenter NICU (19) **Location:** Japan **Dates:** February 2005 - March 2007. **Inclusion Criteria:** Neonates >21 weeks of gestational age,	**Patient group:** N=946 Number of lines: n=946 PICCs **Standard preventive measures**: Institution insertion practices were classified into three groups: 1) Those with MBP (i.e., cap, mask, sterile gown, sterile gloves, and large sterile drapes: MBP group), 2) Those with standard barrier precautions (i.e., sterile gloves and small	**Outcome Definitions:** CR-BSI: one of the following signs or symptoms: fever (>38°C), hypothermia (<36°C), apnea, or bradycardia, plus at least one positive blood culture from a patient with a PICC, without an infection at another site. PICC- associated BSI: if the line was in use during the preceding 48 hr. period. Extremely low-birthweight (ELBW): birthweight <1000 g Very low-birthweight (VLBW): birthweight <1500 g, PCE/CT: determined by ultrasonography. Pleural effusion/ascites: identified on ultrasonography or standard radiography. Catheter removal difficulties: inability to remove the catheter after local warming or local massage, and requirement for procedures such as guidewire re-insertion or surgical removal.	**Primary Outcomes:** Catheter-related BSI: Duration of PICC (per each 1 week) Multivariate analysis: • OR: 1.19 (95% CI: 0.91–1.57) • p = 0.212 **Topic-specific outcomes:** NR **Adverse events:** NR

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
	weighing >400 g at birth, and without lethal congenital anomalies or major chromosomal abnormalities. **Exclusion Criteria:** Patients transported from study institutions with a PICC in situ	sterile drape: SBP group), and 3) Those that conducted the procedure similarly to peripheral line placement (i.e., without preparing a sterile field, the operator pulls the catheter from the vinyl sheath with small sterile forceps, and inserts it from the introducer needle without touching the PICC: non-PICC group)	Symptomatic catheter-related thrombosis: thrombosis seen on venography or ultrasonography and associated with clinical symptoms. Asymptomatic catheter-related thrombosis: excluded from analysis because routine ultrasonography was conducted at only two institutes. **Sampling /Testing strategy:** Blood culture. **Other notes:** None	
Author: Njere[41] **Year:** 2011 **Study Design:** Prospective cohort **Risk of Bias:** Moderate	**Number of Patients:** N = 218 **Number of lines:** N = 294 **Setting:** Neonatal ICU; tertiary referral hospital **Location:** UK **Dates:** January 2006 to June 2009 **Inclusion Criteria:** Neonates who had PICCS for parenteral nutrition and venous access. **Exclusion Criteria:** Incomplete data on Neonate	**Patient group:** N=218 Number of lines: n=294 PICC lines **Standard preventive measures**: Insertion: Aseptic technique: use of sterile set, theater gowns, gloves, drapes, catheters, and other equipment. Use of masks and caps was not considered an essential part of aseptic technique. Skin prep: chlorhexidine gluconate 0.05% and allowed to dry. Catheter care: • Run saline when not in use (not heparinized) • Catheters accessed after washing hands, donning sterile gloves, cleaning connector hubs with .05% CHG, and allowing to dry.	**Outcome Definitions:** Catheter-related sepsis: positive blood cultures (peripheral/central) and/or a positive tip culture after removal in the presence of a clinical suspicion of line sepsis. Sepsis: in the presence of a catheter, the patient developed temperature instability, tachypnea, apnea, lethargy, and abdominal distension, a rising C-reactive protein, or nonspecific factors. PICC line infection: positive peripheral or central blood culture or a positive catheter tip culture after removal in the presence of clinical signs of catheter-related sepsis **Sampling /Testing strategy:** Blood/catheter tip culture. **Other notes:** None CONS: coagulase-negative staphylococcus	**Primary Outcomes:** Catheter-related sepsis: Rate/ 1,000 catheter days: 17 (21%) Odds of infection: Catheter in situ ≥9 days: OR: 3.1 (95% CI: 1.64-5.87); p<0.01 • Multivariable analysis included dwell time, incubator vs. open crib, catheter type, previous infected line, number of previous lines, attempts at insertion & gestational age. • Only significant predictor: of PICC line infection: dwell time ≥9 days **Topic-specific outcomes:** CONS isolated from blood culture: 55/62 (89%). **Adverse events:** Reasons for catheter removal Possible infection: 77/ (20.2%) Leakage/extravasation: 45/294 (15.3%) Blocked: 4/ (1.4%)

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
		• Secured with Steristrips and occlusive transparent dressings Dressing replacement: removed if loose and new dressing reapplied. Tubing Change: every 24hrs when parenteral nutrition bags changed		
Author: Hsu[38] **Year:** 2010 **Study Design:** Retrospective cohort study **Risk of Bias:** Moderate	**Number of patients:** N = 275 **Number of lines:** N = 275 **Setting:** Neonatal ICU **Location:** Taiwan **Dates:** January 2005 to December 2006 **Inclusion Criteria:** Very low birthweight (VLBW) infants admitted to the NICU with a percutaneously inserted catheter inserted into a central vein **Exclusion Criteria:** percutaneous catheters inserted into non-central veins	**Patient group:** N=275 VLBW infants PICCs: n=412 PICC lines **Standard preventive measures**: Insertion: • Under sterile environment by nursing specialist or residents/fellows under supervision • Vein selected by those who performed catheter insertion and peripheral veins preferred over femoral vein. • Skin disinfection: rubbing the site of insertion with sterile gauze soaked in a solution of 10% PI containing 75% alcohol. The same disinfectant applied to insertion site after successful insertion; saline used to decolorize and covered by transparent dressing. Maintenance:	**Outcome Definitions:** CRBSI: At least one positive blood culture obtained from a peripheral vein, the presence of clinical features consistent with bloodstream infection in the presence of a PICC in position, and no other site of infection. Phlebitis: when a linear red streak developed along the superficial veins from the insertion site. Thrombosis: suspected when leg swelling with or without poor perfusion developed. Catheter site inflammation: diagnosed in the presence of lymphangitis, purulence, or at least two signs of inflammation (erythema, tenderness, increased warmth, or induration). Cholestasis: direct bilirubin ≥ 1.5 mg/dL. Rupture: completely broken PICCs, rather than simple leakage. Extravasation: dislodgement of PICC. Time to complication: calculated from day of insertion to day recognition of any catheter-related complication. **Sampling /Testing strategy:** Blood culture. **Other notes:** No bacterial pathogens were identified from blood cultures for both phlebitis and catheter site inflammation.	**Primary Outcomes:** CRBSI: • Episodes: 67/412 (16.3%) • Rate/ 1000 catheter days: 8.3 • Time from placement to CRBSI: 16.4 ± 8.4 days Multivariable logistic regression including Dwell time, insertion site, birthweight, gestational age, weight. • Duration of PICC: p<0.01 (Area under curve 0.68) • Femoral insertion site: OR: 1.76, 95% CI: 1.01-3.07; p < 0.045 Univariate analysis: Duration of PICC, days; case no/total no, incidence (%) • ≤10 days: 6/92; 6.2%) (reference) • 11-20 days: 10/98, 10.2%); RR: 1.72, 95% CI: 0.60-4.94 • ≥21: days: 51/217 (23.5%) RR: 4.66, 95% CI: 1.93-11.28 Site of insertion, incidence (%) • Non-femoral: 30/241 (12.4%) • Femoral: 37/171 (21.6%) **Topic-specific outcomes:** NR **Adverse events:** incidence, n/N (%); rate/1000 catheter days • Phlebitis: 25/412 (6.1%); 3.1/1,000 catheter days • Thrombosis: 1/412 (0.2%); 0.12/1,000 catheter days • Catheter site inflammation: 28/412 (6.8%); 3.5/1000 catheter days • Leakage: 7/412 (1.7%); 0.9/1,000 catheter days • Rupture: 10/412 (2.4%); 1.2/1,000 catheter days • Extravasation: 4/412 (1.0%); 0.5/1,000 catheter days

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
		• Manipulations performed using standard protocol by NICU nurses. • Decision for PICC removal made by neonatologist or senior resident; phlebitis, catheter fracture, extravasation, thrombosis and catheter site inflammation were definitive indications for removal and infected catheters always removed with positive cultures or infant unresponsive to IV antibiotics		• Occlusion: 32/412 (7.8%); 4.0/1,000 catheter days
Author: Sengupta[37] **Year:** 2010 **Study Design:** Retrospective cohort study **Risk of Bias:** Moderate	**Population:** N= 683 PICC lines = 953 **Setting:** NICU at tertiary care hospital **Location:** US **Dates:** Jan 1, 2006-Dec 31, 2008 **Inclusion Criteria**: Eligible patients had a PICC inserted in the NICU between Jan 1, 2006-Dec 31, 2008. In patients	**Patient group:** N = 683 NICU patients with PICC PICC lines: 917/953 eligible for analysis **Standard preventive measures**: PICCs placed by designated trained nurse or physicians Standard protocol followed re insertion and maintenance practices As part of a quality improvement initiative to reduce CLABSI, hospital epidemiology and infection control dept. monitors development of bacteremia in patients	**Outcome Definitions:** CLABSI: CDC/NHSN 2002 Guideline definition PICC: peripherally inserted central venous catheter that terminates at or close to the heart or in 1 of the great vessels and is used for infusion, withdrawal of blood, or hemodynamic monitoring PICC associated CLABSI: primary bloodstream infection in a patient admitted to the NICU for > 48 hrs. before the onset of infection that met the NHSN criteria for CLABSI PICC follow-up time(duration): days from line insertion until 1 of the following: 1) date of CLABSI, 2) termination of the PICC, or 3) administrative censoring at discharge from the NICU Only the first CLABSI was included for a patient who had multiple CLABSIs from the same PICC **Sampling /Testing strategy:** Blood culture	**Primary Outcomes:** CLABSI: Incidence/ PICC n/N (%): 21/683 (3.1%) CLABSI Incidence (over study period): 2.01/1,000 catheter days; (95% CI: 1.24-3.06) PICC associated CLABSI **Topic-specific Outcomes:** PICC duration: (interval, no. of events, incidence) 1-10 days = 6; 1.08/1,000 catheter days 11-20 days = 8; 2.77/1,000 catheter days 21-30 days = 4; 2.7/1,000 catheter days 31-40 days = 0 41-50 days = 1; 2.29/1,000 catheter days 51-60 days = 2; 7.78/1,000 catheter days Univariate analysis of PICC as risk factor for CLABSI: (days since PICC insertion, IRR, 95% CI) < 19 days: IRR = 1.15 (1.05-1.26) p < 0.01 19-35 days: IRR = 0.80 (0.67-0.96) p = 0.02

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
	with multiple PICCs, only the first was included in analysis **Exclusion criteria**: PICCs terminated the same day inserted and PICCs removed within 48 hrs. of NICU admission excluded		**Other notes:** None	> 35 days: IRR = 1.32 (1.12-1.55) p = < 0.01 Multivariable analysis of PICC as risk factor for CLABSI: (days since PICC insertion, IRR, 95% CI) < 19 days: IRR = 1.14 (1.04-1.25) p = < 0.01 19-35 days: IRR = 0.80 (0.66-0.96) p = 0.02 > 35 days: IRR = 1.33 (1.12-1.57) p = < 0.01 **Adverse Events:** NR

Table 51 Risk of Bias for Two Group Studies on Percutaneous Central Catheter Dwell Times

Author Year	Were patients randomly assigned to the study's groups?	For non-randomized trials, did the study employ any other methods to enhance group comparability such as matching, stratification, or statistical methods to adjust for baseline differences?	Did patients in different study groups have similar levels of performance on the outcome of interest and other important factors at the time they were assigned to groups?	Did the study enroll all suitable patients or consecutive suitable patients within a time period?	Was the comparison of interest prospectively planned?	Were the two groups treated/ evaluated concurrently?	Was the study blinded or double-blinded?	Was the funding for this study derived from a source that would not benefit financially from results in a particular direction?	Risk of Bias
Greenburg 2015[7]	✓		✓	✓	✓	✓	✓	✓	Low
Sanderson 2017[2]	✓		✓	✓	✓	✓		✓	Low

Table 52 Risk of Bias for Single Group Studies on Percutaneous Central Catheter Dwell Times

Author Year	Did the study enroll all suitable patients or consecutive suitable patients within a time period?	Was the study prospectively planned?	Were independent or blinded assessors used to assess subjective Outcome Definitions, or were the Outcome Definitions objective?	Was the funding for this study derived from a source that would not benefit financially from results in a particular direction?	Risk of Bias
Hsu 2010[38]	✓		✓		Moderate
Milstone 2013[36]	✓		✓		Moderate
Njere 2011[41]	✓		✓		Moderate
Ohki 2013[39]	✓	✓	✓		Moderate
Rangel 2014[40]	✓	✓	✓		Moderate
Sengupta 2010[37]	✓		✓		Moderate

C.11. Dedicated Catheter Care Team

Key Question 11. In NICU patients requiring central catheters, does the use of dedicated catheter care teams compared with standard of care, prevent CLABSI?

Table 53 Summary of Findings for a Dedicated Percutaneous Inserted Central Catheter Care Team vs. Standard of Care to Prevent CLABSI

Outcome	Findings	Quantity and Type of Evidence (Sample Size)	GRADE of Evidence for Outcome (Limitations of the Evidence)
CLABSI*	• 1 single center OBS study[42] implemented a central line maintenance team in the NICU and reported a significant decrease in overall CLABSI rates comparing pre- and post-line team rates [11.6 vs. 4.0 per 1000 catheter days, P<0.001].	1 OBS n=NR lines[42]	Very Low • Imprecision: only one study
CRBSI*	• 1 single center OBS study[43] implementing dedicated vascular access team in NICU reported no difference in CRBSI rates for all indwelling lines [23/100 (23%) vs. 24/100 (24%); p = 0.868]; however, a duration stratification analysis revealed a 49% reduction in CRBSI for indwelling PICC lines ≥30 days: 39/47 (83%), p = 0.0407; no difference for indwelling lines <30 days: short (0-3 days): 2/47 (4.3%), p = NS; intermediate (4-29 days): 6/47 (12.8%), p = NS.	1 OBS[44] n=200 lines[43]	Very Low • Imprecision: only one study

Table 54 Extracted Information on a Dedicated Percutaneous Inserted Central Catheter Care Team

Study Information	Population and Setting	Intervention/ Study Group	Definitions	Results
Author: Holzmann-Pazgal[42] **Year:** 2012 **Study Design:** Before-after study **Risk of Bias:** Moderate	**Number of patients:** N = NR **Number of lines:** N = NR **Setting:** Level III to III NICU **Location:** US **Dates:** December 2006 – September 2010 **Inclusion Criteria:** NR **Exclusion Criteria:** NR	**Intervention:** **Catheter care team:** Recruitment: Sixteen bedside nurses and seventeen neonatal transport nurses Education & Training: intensive education repeated on evidence-based practices for central line management already in place in the unit. Training utilized standardized written protocols developed by infection control and NICU nursing leadership that formalized established guidelines for performance maintenance Line maintenance: tubing changes, dressing changes, and accessing of central lines for blood draws or medication administration. Every member of the line team had to learn proper procedures and techniques for line maintenance,	**Outcome Definitions** CLABSI • CDC-2004 National Healthcare Safety Network (NHSN) definitions. Definition changed 2008 **Sampling /Testing strategy:** NR **Other notes:** None	**Primary Outcomes:** CLABSI, rate/ 1000 line day (after correcting for NHSN definition change and excluding skin contaminants): • Pre-intervention: 11.6 • Intervention: 4.0 • p < 0.001 Weight-specific CLABSI, rate/ 1000 line days: <750g • Pre-intervention: 15.6 • Intervention: 6.1 • p = 0.012 751-1000g • Pre-intervention: 9.7 • Intervention: 5.3 • p = 0.095 1001-1500g

		perform the procedure while being observed by a trainer and be checked off upon satisfactory demonstration of competence. March 2008, the line team took over performance of all tubing changes, accessing of central lines for blood draws and all dressing changes. Line team members worked in teams of two to perform dressing changes and tubing changes. Only members of the line team could perform these functions on any central line. October 2009: line team took over medication administration through central lines, however in **Control:** Pre-Intervention: December 2006 – March 2008, baseline **Device/agent:** Central care team **Monitoring intervention:** NA **Standard preventive measures:** NR		• Pre-intervention: 12.8 • Intervention: 3.2 • p = 0.001 1501-2500g • Pre-intervention: 9.8 • Intervention: 2.1 • p = 0.001 >2500g • Pre-intervention: 9.5 • Intervention: 2.5 • p < 0.001 **Topic-specific outcomes:** NR **Adverse events:** NR
Author: Taylor[43] **Year:** 2011 **Study Design:** Prospective cohort **Risk of Bias:** Low	**Number of patients:** N = 200 **Number of lines:** N = 200 **Setting:** Level IIIC NICU **Location:** US **Dates:** Pre-intervention: March 1, 2005-March 31, 2006; Post-intervention (PICC team): June 22, 2006-July 9, 2007 **Inclusion Criteria:** All extremely low birth weight infants (≤1000g) admitted to a level IIIC	**Intervention:** **PICC team:** n = 100 April 14, 2006 Percutaneously inserted central catheters (PICC) team established that included neonatal nurse practitioners, neonatology fellows, NICU transport nurses, and selected NICU bedside nurses. Policies established for early patient identification for line placement, regular surveillance of line site and dressing integrity, and tracking of complications Standardized training developed according to national guidelines to	**Outcome Definitions** Catheter-related bloodstream infection (CRBSI): • Positive blood culture with recognized pathogen, or • positive blood culture with common skin contaminant or positive antigen test on blood and temperature instability (>100.4˚C), hypotension, apnea or bradycardia, and • Signs and symptoms with positive laboratory results not related to infection at another site (e.g., necrotizing enterocolitis) Short duration: central lines between 0-3 days	**Primary Outcomes:** CRBSI, n/N (%): • Pre-intervention: 23/100 (23%) • Intervention: 24/100 (24%) • p = 0.868 Survival analysis (attributable to CRBSI): • Hazard ratio: 0.48 (95% CI: 0.25-0.91) • p = 0.025 CRBSI, patients with short central line duration (0-3 days), n/N (%): • 2/47 (4.3%)

	Exclusion Criteria: Infants born in the 2-week period when the PICC team was being formulated.	improve aseptic precautions, promote best practice, and to minimize variability in technique among team members. A formalized system developed for tracking weekly, and as necessary dressing changes for all and lines, including chlorhexidine patches PICC dressing changes and line assessments performed weekly; daily line changes are the responsibility of the bedside registered nurse. **Control:** Pre-intervention: n=100 Incoming neonatology fellows, transport nurses, and neonatal nurse practitioners would receive bedside training for PICC placement by their senior peers. Dressing changes would be performed by fellows, transport nurses, and nurse practitioners on an as needed basis, with the goal of once per week. Patients needing PICC lines identified when bedside nurse would approach the medical team for intravenous access or when it was noted that an umbilical line needed to be replaced (14-day maximum). Documentation of PICC placement or removal was done via a free-text procedure note in the medical record. No set system for documentation or tracking of dressing changes, although date of last dressing change was kept in a log	Intermediate duration: central lines between 4-29 days **Sampling /Testing strategy:** Blood cultures performed. **Other notes:** It is acknowledged that some infants in the control group were exposed toward the end of their hospitalization to the benefits of the PICC team if they were still hospitalized after the PICC team was established. However, given the direction of these differences, it is most likely that any such effect would have led to an underestimation of the intervention-related reduction in CRBSI risk. April 2005 Adopted the closed medication system	CRBSI, patients with intermediate central line duration (4-29 days), n/N (%): • 6/47 (12.8%) CRBSI, patients with highest central line duration (≥30 days), n/N (%): • 39/47(83%) • 49% reduction • p = 0.0407 **Topic-specific outcomes:** Time to CRBSI, median (range): • Pre-intervention: 30 (5-70) • Intervention: 35 (1-82) • p = 0.360 Central line days, median (range): • Pre-intervention: 7 (0-100) • Intervention: 18 (1-141) • p = 0.009 **Adverse events:** Mortality (not attributable to CRBSI), n/N (%): Pre-intervention: 15/100 (15%) Intervention: 27/100 (27%) p = 0.056

		maintained by the on-service neonatology fellow. March 2006 Didactic and clinical training to improve aseptic precautions, promote “best practice,” and minimize variability to technique among team members were completed (continued an ongoing basis for new members). After a 2-hr. didactic training session, new team members demonstrated proficiency by completing PICC insertions and dress changes under the guidance of a preceptor. **Device/agent:** NA **Monitoring intervention:** NA **Standard preventive measures:** Sterile prep for PICC placement was done with full sterile gown, mask, gloves and 10% iodine solution. Dressing changes were done with mask and sterile gloves, using 2% chlorhexidine swabs. Dressing changes included replacement of chlorhexidine dressing for infants older than 30 days or 32 weeks.		

Table 55 Risk of Bias for Two Group Studies on a Dedicated Percutaneous Inserted Central Catheter Care Team

Author Year	All study groups derived from similar source/reference populations	Attrition not significantly different across study groups	Measure of exposure is valid	Measure of outcome is valid	Investigator blinded or were outcomes well-defined and objective to endpoint assessment	Potential confounders identified	Statistical adjustment for potential confounders done	Funding source(s) disclosed and no obvious conflict of interest	Overall Risk of Bias
Holzmann-Pazcal 2012[42]	✓		✓	✓		✓			Moderate
Taylor 2011[43]	✓	✓	✓	✓	✓	✓	✓		Low

C.12. Central Line Insertion and Maintenance Bundles

Question 12. In NICU patients that are the optimal elements of central line insertion and maintenance bundles to prevent CLABSI?

Table 56 Summary of Findings on Insertion and Maintenance Bundles vs. Standard of Care to Prevent CLABSI

Outcome	Findings	Quantity and Type of Evidence (Sample Size)	GRADE of Evidence for Outcome (Limitations of the Evidence)
CLABSI*	• Three observational studies[45-47] reported a reduction of CLABSI rate.	3 OBS N=NR[45] N=NR[46] N=NR[47]	Low
Healthcare Personnel Bundle Compliance*	• Three observational studies[45-47] reported increases in compliance with bundle elements.	1 OBS[45] N=NR N=NR[46] N=NR[47]	Low

Table 57 Extracted Information for Central Venous Catheter Insertion and Maintenance Bundles

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
Author: Balla[47] **Year:** 2018 **Study Design:** Interrupted time series	**Number of patients:** N = 229 **Number of lines:** N = 229 **Setting:** NICU	**Patient Groups:** n=229 **Number of lines:** n=229 Baseline: n = 54 • 3 months Intervention: n = 175 • 12 months	**Outcome Definitions:** BSI: A laboratory-confirmed bloodstream infection that was not secondary to an infection at another site. CLABSI: A primary BSI in a patient that had a central line within the 48-hour period before the development of the BSI was considered CLABSI.	**Primary Outcomes** CLABSI rate per 1000-line days • Baseline: 31.74 • Phase 1: 18.58 • Phase 2: 3.73 • Phase 3: 3.53

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
Risk of Bias:	**Location:** USA **Dates:** June 2015 – August 2016 **Inclusion Criteria:** All patients (aged 0 months to 21 years) admitted to the hospital who received a central line, as defined by the NHSN, comprised the study population. The NHSN defines a central line as an intravascular catheter that terminates at or close to the heart or 1 of the great vessels and is used for infusion, withdrawal of blood, or hemodynamic monitoring. **Exclusion Criteria:** Exclusion of a patient from the study occurred only if the patient had received a central line before admission and developed a bloodstream infection within 48 hours of admission with supporting clinical or laboratory evidence of an infection at the time of admission. This exclusion criterion is	Surveillance • Denominator data collection: A monthly roster for denominator data collection displayed on the QI board was successful. • Audits of the denominator data were performed on 5 random days per month to verify the accuracy. Hand hygiene: • Change in HH policy: revised from routine hand wash to hand rub. Education & training: • All the HCPs were educated about HH through posters, regular classes and one to one communication. Performance & Feedback • Sharing data regularly during monthly ward meetings, giving feedback both group and individualized, including personnel from all levels of care in the team Compliance assessment: • The compliance with HH was studied with the help of audits, which found that the main problem was duration of hand	Compliance Indicators: The process indicators were based on hand hygiene (30 audits per month) and central line care audits (10 audits per month). • If all the steps of hand hygiene including the six core steps and the duration were correctly performed, it was considered 'overall compliant to HH'. • Central line bundle: The central line care audits focused on insertion practices (number of central lines inserted by eligible Healthcare Personnel (HCP), checklist analysis) and maintenance practices (breaks in circuit, 2 HCP handling the central line, scrubbing the hub for 15 seconds, 2% chlorhexidine used for scrub, use of single lumen central line and needleless connectors). Compliance: Random auditing of at least 10% of lines on each unit by staff nurse CLABSI-prevention champions ensured bundle compliance and evaluated necessity of the line. **Sampling /Testing strategy:** NR **Other notes:** None	BSI rate per 1000-line days • Baseline: 7.3 • Phase 1: 4.6 • Phase 2: 4.2 • Phase 3: 2.3 Mortality • Baseline: 2.9% • Intervention: 1.7% **Topic-specific outcomes:** Compliance with maintenance bundle (%) • Baseline: NA • Phase 1: 59% • Phase 2: 68.2%% • Phase 3: 66.7% **Adverse events:** NR

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
	in line with NHSN definitions issued by the Centers for Disease Control and Prevention (CDC). Blood cultures that were positive on admission and those reported as contaminants were not included.	hygiene. The successful PDSA cycle was to do the hand rub by the clock for 20-30 seconds. It was ensured that a clock with a second hand was easily visible from each bed of the unit. Designated HCP for insertion: • Only those HCPs certified by the QI team (those who had assisted five central line insertions) were privileged to place the central line. A senior nurse or doctor supervised the process of insertion using a checklist and any deviation from the policy was noted and stopped promptly. Initially • Insertion had to be a 2-person job Insertion Checklist: • Required but elements not reported Maintenance bundle: • Central line card displayed on infant warmer to document the need of line daily and number of circuit breaks;		

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
		• Break in circuit – 2 HCP job; • Scrub the hub – 2% chlorhexidine for 15 seconds Removal bundle • Review the need every day and remove as soon as possible. **Control/Comparison:** NA **Device/agent:** NA **Monitoring intervention:** Insertion and maintenance compliance **Standard preventive measures:** NR		

Author: Savage[46]
 	
Year: 2018
 	
Study Design: Interrupted time series
 	
Risk of Bias: Moderate
	Number of patients: N = NR
	Number of lines: N = NR
	
	Setting: NICU
	
	Location: USA
	
	Dates: 2006-2014
	
	Inclusion Criteria: All patients (aged 0 months to 21 years) admitted to the hospital who received a central line, as defined by the NHSN, comprised the study population. The NHSN
		Patient Groups: n=NR
		Number of lines: n=NR
		Study Periods:
		• Preintervention: 2006 - 2008
		• Peri-intervention: 2008 - 2011
		• Post-intervention: February 2011 - December 2012
		• 2nd Peri-intervention: 2013 - 2014
		
		Hospital-wide CLABSI Bundle implemented June 2008 - 2011
		First peri-intervention period
		2008
			Outcome Definitions:
			CLABSI: NR
			Compliance: Random auditing of at least 10% of lines on each unit by staff nurse CLABSI-prevention champions ensured bundle compliance and evaluated necessity of the line.
			
			Sampling /Testing strategy: NR
			
			Other notes: Authors conducted a root cause investigations utilizing the event-specific focus groups as well as a special focus group aimed at identifying common potential causes. Through this process they identified that the NICU was failing to consistently clean and disinfect patient positioning devices on a daily and as-needed basis. The focus groups also identified that wrist and hand jewelry, and hair not kept up and away from the face by staff were potential sources of bacteria. Family and staff noncompliance with hand
				Primary Outcomes
				NICU CLABSI rate per 1000-line days ± SD; p-value = compared with preintervention period)):
				• Preintervention period: 4.84 ± 1.16
				• Peri-intervention period: 2.20 ± 1.11;
				  • p = 0.003
				• Post-intervention period: 0.41 ± 1.30
				  • p < 0.001
				• 2nd Peri-intervention period: 0.79 ± 1.27
				  • p < 0.001
				
				NICU VLBW CLABSI rate per 1000-line days ± SD; p-value = compared with preintervention period)):
				• Pre-intervention period: 7.55 ± 2.23
				• Peri-intervention period: 3.41 ± 2.12
				  • p = 0.020
				• Post-intervention period: 0.72 ± 2.49
				  • p < 0.001

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
	defines a central line as an intravascular catheter that terminates at or close to the heart or 1 of the great vessels and is used for infusion, withdrawal of blood, or hemodynamic monitoring. **Exclusion Criteria:** Exclusion of a patient from the study occurred only if the patient had received a central line before admission and developed a bloodstream infection within 48 hours of admission with supporting clinical or laboratory evidence of an infection at the time of admission. This exclusion criterion is in line with NHSN definitions issued by the Centers for Disease Control and Prevention (CDC).	• CHG gluconate scrub of administration set hub at every access (15-s scrub, 3-s dry) • Neutral displacement needleless connector on all central lines • Aseptic administration tubing change policy initiated 2009 • Adoption of silver antimicrobial IV patch at insertion site • Central line maintenance bundle for changing administration set tubing initiated • Administration set changes required to have disinfected table, sterile kit, hat, mask, sterile cover gown, and sterile gloves 2010 • 2-person Broviac dressing and administration set line changes in the NICU to prevent patient contamination of line • Implementation of focus groups to determine root cause of CLABSI events • Maintenance bundle updated to include: Aseptic technique for	hygiene principles, especially after cellular telephone use, and lack of coordination with respiratory therapy and lab blood collection to minimize central line accesses potentially contributed to the increase in CLABSIs.	• 2nd Peri-intervention period: 1.00 ± 2.44 • p < 0.001 NICU NLBW CLABSI rate per 1000-line days ± SD; p-value = compared with preintervention period)): • Preintervention period: 1.95 ± 0.96 • Peri-intervention period: 0.84 ± 0.91 • p = 0.232 • Post-intervention period: 0.01 ± 1.07 • p = 0.021 • 2nd Peri-intervention period: 0.66 ± 1.05 • p = 0.180 CLABSI rate per 1000-line days, (n/N): • Preintervention period: 5.14 (45/8763) • SIR: 1.78; p<0.05 • Peri-intervention period: 2.18 (21/9622) • SIR: 1.30 • Post-intervention period: 0.36 (2/5562) • SIR: 0.29; p<0.05 • 2nd Peri-intervention period: 0.87 (5/5730) • SIR: 0.78 **Topic-specific outcomes:** Compliance for entire Hospital • 2013 and 2016: 94% - 99%. Compliance to the maintenance bundle, • 2015: 79% • 2016: 91% Reasons for compliance deviation: • Improper documentation of line necessity • Late dressing changes, or • Administration set tubing changes **Adverse events:** NR

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
		all line interactions and standardized dressing change protocol • PICU and medical floors: 24-h administration sets and needleless component changes for lipids and blood product and 96 h for nonlipids • NICU: 96-h administration set tubing change for all fluids/solutions except lipids and blood draws. Lines used for lipids and blood draws remain at 24-h change • Administration set hub/access site cap change after each blood draw in all units except NICU: • Disinfection of patient area at each shift in NICU and PICU, disinfection includes all items used in the immediate area of the patient, such as bed (including linen), bedside table, overbed tables, IV pump, feeding pumps, diaper scales, and bedside supply cabinets 2011 • Closed system for UAC in NICU (Figure S1)		

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
		Second peri-intervention period 2013 • Monthly rotation and terminal cleaning of bedside supply cabinets in NICU to ensure • Cleanliness of supplies and cabinets used with long-term-stay infants. PICU cleans and • Disinfects cabinet at least monthly and at discharge • NICU dressing changed when loose, wet, or compromised; all other units maintain 7-d dressing change • Umbilical cord cleaned with CHG before and after line removal • Exposed PICC lines removed after another line established. No manipulation of line to insert back under skin 2014 • CHG daily body wipe for children older than age 2 mo in PICU following SPS • Recommendations. Daily linen changes re-emphasized The unit time out included checking patient identification and announcing the procedure, the type of		

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results

		line to be inserted, and the site of line insertion
		• All supplies required available at bedside before insertion
		• Inserter and assistant use maximal sterile barrier precautions (i.e., mask, cap, gown, sterile gloves, and full body drape)
		• Face mask worn by those within 3 feet of sterile field
		• Perform skin antisepsis with povidone-iodine, CHG, or alcohol
		• Skin preparation agent completely dry at time of first skin puncture
		• Procedure stopped if anyone notes sterility compromised
		
		Catheter maintenance checklist:
		• Volume of infant feedings in mL/kg per day
		  • Central lines be discontinued when an infant's enteral feedings reached 120 mL/kg per day
		• Daily assessment of catheter need:
		  • "Do we need the line today?"
		  • "If there was no line in place today, would we place one?"		

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results

		• Dressing integrity and site cleanliness assessed (daily at minimum)
		• Dressing and site care if dressing change performed
		• Site cleansed with an appropriate solution (povidone-iodine, CHG, or alcohol)
		• Cleansing solution allowed to air-dry completely
		• Use of a closed system: closed system maintained for infusion, blood draws, and medication administration; closed system is one in which entries are made through needleless connectors or hubs that have been disinfected before use
		• For all catheter entries/access
		  • Scrub needleless connector or hub using friction with alcohol or CHG for ≥15 seconds
		  • Allow surface of connector or hub to dry before entry
		  • Staff wear clean gloves when accessing or entering catheter (if not using closed system)		

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results
		Control/Comparison: NA **Device/agent:** NA **Monitoring intervention:** Insertion and maintenance compliance **Standard preventive measures:** NR		
Author: Fisher[45] **Year:** 2013 **Study Design:** Prospective cohort study **Risk of Bias:** Moderate	**Number of patients:** N=NR **Number of lines:** N=NR **Setting:** 13 NICUs **Location:** USA **Dates:** Pre-intervention (NHSN data, 10/13 NICUs): January 2008-September 2009 Intervention (NHSN data, 13/13 NICUs): October 2009-June 2010 Post-intervention: One quarter after intervention, and one year later, July-September 2011 **Inclusion Criteria:** Perinatal Quality Collaborative of North Carolina (PQCNC) invited all hospitals in the state	**Patient Groups:** n=NR **Number of lines:** n=1308 Catheter insertion checklist: • Perform hand hygiene before insertion • Unit time out before procedure • The unit time out included checking patient identification and announcing the procedure, the type of line to be inserted, and the site of line All supplies required available insertion • At bedside before insertion • Inserter and assistant use maximal sterile barrier precautions (i.e., mask, cap, gown, sterile gloves, and full body drape) • Face mask worn by those within 3 feet of sterile field	**Outcome Definitions:** CLABSI: used the Centers for Disease Control and Prevention, National Healthcare Safety Network definition (June 2008, available at https://doi.org/10.1016/j.ajic.2008.03.002) Process measures: elements of the insertion and maintenance bundles **Sampling /Testing strategy:** NR **Other notes:** No baseline data for process measures Compliance measures were limited to 9 points. Statistical process control (SPC) guidelines suggest a minimum of 12 data points to determine significant changes in control limits on the basis of trends of $7 points, but that would not limit our ability to detect signals of change and draw conclusions. Baseline data from 10/13 reported sites; 3/13 level II sites reported no infections based on NHSN criteria from January 2008 through September 2009	**Primary Outcomes** CLABSI rate per 1000-line days, adjusted mean rate: • Pre-intervention: 3.94 • Post-intervention (through July 2010): 1.16 • Reduction rate: 71% • p = 0.01 CLABSI, n: Intervention: 57 CLABSI rate per 1000-line days, quarterly (values estimated from fig 3): January 2008: 4.6 April 2008: 5.2 July 2008: 3.1 October 2008: 4.0 January 2009: 3.3 April 2009: 5.1 July 2009: 3.8 October 2009: 2.2 January 2010: 2.0 April 2010: 1.1 July 2010: 0.9 July 2011: 0.5 12/13 NICUs showed a reduction in CLABSI rates **Topic-specific outcomes:**

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results

	with a NICU and on-site neonatologist to join PQCNC CLABSI
	
	Exclusion Criteria: NR
		• Perform skin antisepsis with povidone-iodine, CHG, or alcohol
		• Skin preparation agent completely dry at time of first skin puncture
		• Procedure stopped if anyone notes sterility compromised
		
		Catheter maintenance checklist:
		• Volume of infant feedings in mL/kg per day
		  • Central lines be discontinued when an infant's enteral feedings reached 120 mL/kg per day
		• Daily assessment of catheter need:
		  • "Do we need the line today?"
		  • "If there was no line in place today, would we place one?"
		• Dressing integrity and site cleanliness assessed (daily at minimum)
		• Dressing and site care if dressing change performed
		  • Site cleansed with an appropriate solution (povidone-iodine, CHG, or alcohol)
		  • Cleansing solution allowed to air-dry completely
				Catheter days
				Intervention: 30,587
				
				Insertion compliance, %:
				• Baseline: 76
				• Peaked: 93
				
				Insertion compliance, %, monthly (estimated from Figure):
				October 2009: 76
				November 2009: 73
				December 2009: 87
				
				January 2010: 92
				February 2010: 90
				March 2010: 93
				April 2010: 92
				May 2010: 88
				June 2010: 80
				
				Maintenance compliance, %:
				• Baseline: 32
				• Peaked: 56
				
				Maintenance compliance, %, monthly (estimated from Figure):
				October 2009: 32
				November 2009: 40
				December 2009: 39
				
				January 2010: 38
				February 2010: 34
				March 2010: 34
				April 2010: 35
				May 2010: 56
				June 2010: 46
				
				Adverse events: NR

Study Information	Population and Setting	Intervention/ Study Groups	Definitions	Results

		• Use of a closed system: closed system maintained for infusion, blood draws, and medication administration; closed system is one in which entries are made through needleless connectors or hubs that have been disinfected before use
		• For all catheter entries/access
		  • Scrub needleless connector or hub using friction with alcohol or CHG for ≥15 seconds
		  • Allow surface of connector or hub to dry before entry
		  • Staff wear clean gloves when accessing or entering catheter (if not using closed system)
		
		Control/Comparison: NA
		
		Device/agent: NA
		
		Monitoring intervention: Insertion and maintenance compliance
		
		Standard preventive measures: NR		

Table 58 Risk of Bias for Two Group Studies on Central Venous Catheter Insertion and Maintenance Bundles

Author Year	All study groups derived from similar source/reference populations	Attrition not significantly different across study groups	Measure of exposure is valid	Measure of outcome is valid	Investigator blinded or were outcomes well-defined and objective to endpoint assessment	Potential confounders identified	Statistical adjustment for potential confounders done	Funding source(s) disclosed and no obvious conflict of interest	Overall Risk of Bias
Balla 2018[47]	✓	✓	✓	✓				✓	Moderate
Fisher 2013[45]	✓		✓	✓	✓			✓	Moderate
Savage 2018[46]	✓	✓	✓	✓	✓			✓	Moderate

C.13. Prophylactic Antimicrobial Administration

Key Question 13: In NICU patients requiring central venous catheters, what is the efficacy of prophylactic antimicrobials, compared with standard of care, to prevent CLABSI?

Table 59 Summary of Findings on Prophylactic Amoxicillin vs. No Prophylactic Amoxicillin to Prevent CLABSI

Outcome	Findings	Quantity and Type of Evidence	GRADE of Evidence for Outcome and Limitations of the Evidence
Proven septicemia*	• One RCT[48] found no difference was reported in proven septicemia (OR: 0.24; 95% CI: 0.01 – 5.37; p = 0.37).	1 RCT N=148 patients[48]	Moderate • Imprecision: only one study
Suspected septicemia	• One RCT[48] found no difference in suspected septicemia (OR: 0.47; 95% CI: 0.11 – 1.94; p = 0.29).	1 RCT N=148 patients[48]	Moderate • Imprecision: only one study
Thrombotic complications	• One RCT[48] found thrombotic complications were reported in 9% of patients administered prophylactic amoxicillin, and 3% of the control group.	1 RCT N=148 patients[48]	Moderate • Imprecision: only one study
Amoxicillin resistance	• One RCT[48] found one incidence of amoxicillin resistant Staphylococcus epidermidis in the control group. • One RCT[48] found no decrease in amoxicillin susceptibility during the study period when compared with before the study period (47% vs. 42%), however susceptibility patterns after the study period were not reported.	1 RCT N=148 patients[48]	Moderate • Imprecision: only one study

Table 60 Summary of Findings on Prophylactic Vancomycin vs. No Prophylactic Vancomycin to Prevent CLABSI

Outcome	Findings	Quantity and Type of Evidence	GRADE of Evidence for Outcome and Limitations of the Evidence
CONS catheter- related sepsis*	• A reduction was seen in the incidence of CONS Catheter related sepsis (0/41 vs. 8/52 (15%); p = 0.004).	1 RCT[49] N=93	Moderate • Imprecision: only one study

Outcome	Findings	Quantity and Type of Evidence	GRADE of Evidence for Outcome and Limitations of the Evidence
Laboratory confirmed BSI*	• No difference was seen in the incidence of Laboratory Confirmed BSI in patients with peripheral CVCs for a period of prophylactic vancomycin compared with a period with no prophylaxis. (42/153 (27.4%) vs. 32/141 (22.7%); p = NS). • This study reported an increase in the incidence of CONS BSI in patients with PCVCs when administered prophylactic vancomycin: 10/153 (6.5%) vs. 0/141 (0); P = 0.002).	1 OBS[50] N=294	Very Low • Study Quality: high risk of bias • Imprecision: only one study
Gram-positive infections	• The use of prophylactic vancomycin for infants with central venous catheters was associated with reduced incidence of gram-positive infections (26/85 (31%) vs. 26/61 (43%); p<0.05).	1 OBS[51] N=141	Very Low • Study Quality: high risk of bias • Imprecision: only one study
Gram-negative infections	• One observational study[51] found the use of prophylactic vancomycin for infants with central venous catheters was associated with reduced incidence of gram-negative infections (19/85 (22%) vs. 21/61 (34%); p<0.05).	1 OBS n=146 lines[51]	Very Low • Study Quality: high risk of bias • Imprecision: only one study
Total amount of vancomycin administered	• One observational study[50] found that discontinuing prophylactic vancomycin resulted in fewer infants being exposed, but a larger total amount of vancomycin was administered for treatment of infection in the post-prophylactic period.	1 OBS n=294 lines[50]	Very Low • Imprecision: only one study
Vancomycin Resistance	• One RCT[49] reported no incidences of vancomycin resistance during the study, CONS susceptibility patterns did not change during study, and Vancomycin resistant strains of CONS were not detected during study. • One observational study[51] reported no incidences of vancomycin resistance were observed during the study period; however two years following the study, four cases of CONS resistance to vancomycin appeared.	1 RCT N=93 lines[49] 1 OBS n=146 lines[51]	Moderate • Imprecision: low number of events

Table 61 Extracted Information on Prophylactic Antimicrobials

Study Information	Population and Setting	Intervention/ Study Group	Definitions	Results
Author: Harms[48] **Year:** 1995 **Study Design:** RCT **Risk of Bias:** Moderate	**Number of Patients:** N=148 **Number of lines:** N = 148 **Setting:** Neonatal ICU, University Hospital **Location:** Germany **Dates:** August 1990 - November 1992 **Inclusion Criteria:** neonates with successful central venous catheter insertion. CVC insertion	**Intervention:** n=75 Amoxicillin prophylaxis: 100mg/kg/ day in 3 doses, until catheter was removed. **Control:** n=73 No prophylactic antibiotics. **Device/agent:** Amoxicillin **Standard preventive measures:** • Catheters inserted by a member of the medical staff using aseptic technique with infant in the incubator.	**Outcome Definitions:** Proven Septicemia: Clinical signs (e.g., apnea, bradycardia, instability of temperature, feeding problems, circulatory changes, lethargy), suspect lab findings (CRP >0.6 mg/dl; I/T ratio >0.16), and cultures reveal identical bacterial growth of the line tip and the blood. Suspected septicemia: Clinical signs and laboratory findings present but no bacterial growth was identified in the culture of the blood specimen taken from the peripheral vein.	**Primary Outcomes:** **CLABSI:** Proven septicemia, n (%) • Amoxicillin: 0/75 (0) • No Amoxicillin: 2/73 (2.7%) • Amoxicillin resistant: 1/2 (50%) • OR: 0.24 (95% CI: 0.01 – 5.37); • p = 0.37 Suspected septicemia, n (%): • Amoxicillin: 3/75 (4.0%) • No Amoxicillin: 6/75 (8.2%) • OR: 0.47 (95% CI: 0.11 – 1.94); • p = 0.29 Topic-specific outcomes:

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	was performed if peripheral venous access was difficult and the anticipated period of parenteral nutrition was longer than 10 days. Only initially inserted catheters were included in the analysis. **Exclusion Criteria:** NR	• One unit of heparin added to each ml of the infusate. • Blood products not administered through the catheter. Lines used to withdraw blood. • Entire administration set, including all connectors, changed daily. • Hub of the catheter and connecting pieces wrapped in sterile gauze. • Catheters removed when no longer needed or when signs of serious infection, blockage or dislodgement occurred. Antibiotic therapy: • Uniform regimen of abx therapy prescribed for all infants admitted to unit. • Neonates with a history of infection, respiratory distress, clinical signs of infection, or suspect laboratory findings received combination intravenous amoxicillin and gentamicin therapy after blood culture specimens, tracheal aspirates, and skin swabs had been taken • >90% of low birth weight or preterm neonates received antibiotic treatment initially. • Treatment stopped after 48 - 72 hours if: cultures remained sterile, markers of inflammation were within the normal range, and no clinical signs of infection. • In infants randomly assigned to receive prophylactic antibiotic treatment with amoxicillin, only the aminoglycoside was discontinued.	Mechanical complications: Clotting of catheter or dislodgement **Sampling /Testing strategy:** • A drop of fluid from the connecting hub was collected twice a week for bacteriologic examination. • Catheter tip removed cut off and placed immediately in nutrient broth for culture. **Other notes:** Every 10 infants, the study was evaluated. Decision to stop or continue depended on indication of superiority of amoxicillin treatment or if superiority could not be proved.	Duration of catheterization, median, days (25^{th} to 75^{th} percentiles): • Amoxicillin: 15 (10-23) • No amoxicillin: 15 (12-25) **Adverse events** Antibiotic susceptibility of all isolated microorganisms (in vitro): • During study period: 47% • Before study period: 42% Thrombotic complications, n (%): • Amoxicillin: 7/75 (9.3%) • No amoxicillin: 2/73 (2.7%) • p = NR . Mechanical complications, n (%): • Amoxicillin: 3/75 (4.0%) • No amoxicillin: 4/73 (5.5%) • p = NR Thrombocytopenia <150, n (%): • Amoxicillin: 7/75 (9.3%) • No amoxicillin: 9/73 (12.3%) • p = NR CRP >0.6 mg/dl, n (%): • Amoxicillin: 8/75 (10.6%) • No amoxicillin: 10/73 (13.6%) • p = NR I/T ratio >0.16, n (%): • Amoxicillin: 14/75 (18.6%) • No amoxicillin: 16/73 (21.9%) • p = NR Additional antibiotics, n (%): • Amoxicillin: 20/75 (26.7%) • No amoxicillin: 18/73 (24.7%) • p = NR

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		• If infants had signs of nosocomial infection, they received cefotaxime or ceftazidime and netilmicin, amikacin, or tobramycin. • Other abx (e.g., vancomycin) administered according to the susceptibility of the isolated organism.		
Author: Spafford[49] **Year:** 1994 **Study Design:** Prospective, double blind RCT **Risk of Bias:** Low	**Number of patients:** N = 70 **Number of lines:** N = 93 **Setting:** Neonatal ICU, Regional Hospital **Location:** USA **Dates:** April 1991- June 1992 **Inclusion Criteria:** All infants admitted to the NICU in whom a CVC was inserted. (general care for infants weighing <1000g included insertion of a CVC on day 3 or 4 to improve overall nutrition.) **Exclusion Criteria:** Broviac, Hickman or umbilical venous catheters were not included as study catheters and were not used in conjunction with a CVC. Infants with renal dysfunction.	**Intervention:** n=35 patients; n=41 catheters • TPN with 25 µg/ml Vancomycin **Control:** n=35 patients; N=52 catheters • TPN only **Device/agent:** Vancomycin **Standard preventive measures:** • Catheters placed under sterile conditions. • Catheters were inserted only after a negative blood culture finding had been obtained, and there was no evidence of an acute infection • Insertion site covered with a clear bio-occlusive dressing that was changed only if necessary. • All infants given empiric treatment with ampicillin and gentamicin at birth. • These antimicrobial agents were continued until culture results were confirmed negative at 48 hours after birth. • TPN solution infused over 24h • Ampicillin and gentamicin used during periods of suspected sepsis, for 48 hours pending results of cultures. If a positive culture, then appropriate	**Outcome Definitions:** Catheter related sepsis: When the culture of the CVC specimen contained at least 10 times the concentration of the same pathogen isolated from the peripheral sample. • Infants examined for sepsis when they had temperature instability, increased oxygen or ventilator requirements, increased number or severity of episodes of apnea or bradycardia, feeding intolerance, lethargy, or blood pressure instability. If sepsis suspected, blood specimens obtained from peripheral vein and through CVC **Sampling /Testing strategy:** • If sepsis was suspected, blood culture specimens obtained from a peripheral vein and drawn through the CVC were obtained. • On removal, catheters were sent to the microbiology laboratory for culture of catheter specimens to determine colonization. • Concentrations of blood urea nitrogen were measured each week to assess renal function. Vancomycin concentrations	**Primary Outcomes:** CONS Catheter related sepsis, No. of catheters, n (%): • Vancomycin: 0/41 (0) • No vancomycin: 8/52 (15%) • p = 0.004 Non-CONS Catheter related sepsis, No. of catheters, n (%): • Vancomycin: 1/41 (2.4%) • No vancomycin: 5/52 (9.6%) • p = NR Topic-specific outcomes: Duration of catheterization, mean days (±SE): • Vancomycin: 18.7 (±5.4) • No vancomycin: 17.3 (±2.5) • p = NS Adverse events Antibiotic resistance: CONS susceptibility patterns: did not change during study Vancomycin resistant strains of CONS: not detected during study BUN, mmol/L (mg/dl): • Vancomycin: 6.5 (18.2) • No vancomycin: 6.5 (18.2) • p = NS Creatinine, µmol/L (mg/dl): • Vancomycin: 80 (0.9) • No vancomycin: 88 (1.0) • p = NR (noted not different)

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		antimicrobial therapy continued for 10 days. • Vancomycin administered only for culture-proven positive infections	measured weekly. Brain-stem auditory evoked responses were obtained before discharge to determine possible vancomycin-induced ototoxic effects. **Other notes:** Majority of catheters inserted at 48-96 h of age to provide concentrated TPN solution.	Mortality, n: • Vancomycin: 5/35 (sepsis: 0) • No vancomycin: 9/35 (sepsis: 4/9, none attributable to CVC) • p = NR
Author: Elhassan[50] **Year:** 2004 **Study Design:** Uncontrolled before after (Retrospective Cohort) **Risk of Bias:** High	**Number of patients:** N = 294 **Number of lines:** N = 294 **Setting:** Neonatal ICU, Tertiary Care Hospital **Location:** USA **Dates:** June 1, 1997 – September 31, 2000: • Period I: June 1, 1997 - December 31, 1998 • Period II: April 1, 1999 - September 31, 2000 **Inclusion Criteria:** Neonates admitted to the NICU during the study periods and had a PCVC inserted during their stay. Infants with UVC placed before PCVC. **Exclusion Criteria:** Infants with surgically placed catheters (Broviac or Hickman) or femoral.	**Patient Groups:** **Period I:** n= 153 patients; n=193 catheters • Prophylactic Vancomycin in Hyperalimentation solutions (HAL) **Period II:** n=141 patients; n=178 catheters • No Prophylactic Vancomycin, **Device/agent:** Vancomycin **Standard preventive measures:** • PCVCs inserted in the NICU percutaneously through a needle or under direct visualization of the vein through a cutdown technique. • No change in catheter management technique between study periods	**Outcome Definitions:** Nosocomial laboratory confirmed blood stream infections (LC-BSI): if a (+) blood culture was collected beyond 3 days of age and the patients satisfied Criterion I, or IIa or IIb and positive lab results are not related to an infection at another site. • Criterion I- Patient has a recognized pathogen cultured from one or more blood cultures, and the organisms cultured from blood are not related to an infection at another site. • Criterion II- Patient age <1 year has at least one of the following signs or symptoms: fever >100.4°F, hypothermia <98.6°F, apnea or bradycardia and at least one of the following: • Criterion IIa- common skin contaminants cultured from two or more blood cultures drawn on separate occasions; • Criterion IIb- common skin contaminants cultured from at least one blood culture from a patient with an intravenous catheter, and the physician	**Primary Outcomes:** LC-BSI, total no. of positive blood cultures; n (%): • Period I (proph): 52/153 (34.0%) • Period II (no proph): 64/141 (45.3%) • p = 0.0457 Group A (with PCVC), LC-BSI, total no. of positive blood cultures; n (%): • Period I (proph): 42/153 (27.4%) • Period II (no proph): 32/141 (22.7%) • p = NS Group B (no PCVC), LC-BSI, total no. of positive blood cultures; n (%): • Period I (proph): 10/153 (6.5%) • Period II (no proph): 26/141 (18.4%) • p = 0.0019 **Topic-specific outcomes:** Duration of catheterization, mean days (SD): • Period I (proph): 22.1 (±19.2) • Period II (no proph): 20.8 (±15.4) • p = NS Patients given Prophylactic Vancomycin, n: • Period I (proph): 151/153 • Period II (no proph): 0/141 • p = NR Amount of vancomycin administered, mean (g): • Period I (proph): 5.85 • Period II (no proph): 0 • p = NR

Study Information	Population and Setting	Intervention/ Study Group	Definitions	Results
			institutes appropriate antimicrobial therapy; and signs and symptoms with positive laboratory results are not related to an infection at another site. **Group A:** With PCVC in place **Group B**: Without PCVC in place. Cultures collected before PCVC insertion or up to 7 days after PCVC removal Effect of continuous vancomycin prophylaxis evaluated through HAL on: 1) total count and longevity of PCVCs and 2) the total vancomycin exposure in the two periods. **Sampling /Testing strategy:** Blood cultures. **Other notes:** None	Total number and rate of patients who received vancomycin treatment, n (%): • Period I (proph): 29/153 (18.9%) • Period II (no proph): 43/141 (30.4%) • p = 0.0215 Vancomycin treatment for Proven LC-BSI, n (%): • Period I (proph): 14/153 (9.1%) • Period II (no proph): 24/141 (17.0%) • p = 0.0025 Amount of vancomycin administered, for Proven LC-BSI mean (g) • Period I (proph): 2.72 • Period II (no proph): 10.0 • p = NS Vancomycin treatment for Suspected Infection n, (%) • Period I (proph): 15/153 (9.8%) • Period II (no proph): 19/141 (13.5%) • p = NS Amount of vancomycin administered for Suspected Infection, n (g) • Period I (proph): 2.35 • Period II (no proph): 4.29 • p = NS **Adverse events** LC-BSI by organism, no. of positive blood cultures; n (%): Coagulase-negative Staphylococcus, n (%): • Period I (proph): 19/153 (12.4%) • Period II (no proph): 31/141 (21.9%) • p = 0.0291 Group A, n (%): • Period I (proph): 16/153 (10.4%) • Period II (no proph): 25/141 (17.7%) • p = NS Group B, n (%): • Period I (proph): 3/153 (2.0%) • Period II (no proph): 6/141 (4.2%) • p = NS Other gram-positive organisms • Period I (proph): 7/153 (4.6%) • Period II (no proph): 14/141 (9.9%) • p = NS

Study Information	Population and Setting	Intervention/ Study Group	Definitions	Results
				Group A, n (%): • Period I (proph): 7/153 (4.5%) • Period II (no proph): 8/141 (5.7%) • p = NS Group B, n (%): • Period I (proph): 0/153 (0) • Period II (no proph): 6/141 (4.2%) • p = 0.0099 Gram-negative organisms • Period I (proph): 15/153 (9.8%) • Period II (no proph): 9/141 (6.4%) • p = NS Group A, n (%): • Period I (proph): 10/153 (6.5%) • Period II (no proph): 0/141 (0) • p = 0.002 Group B, n (%): • Period I (proph): 5/153 (3.3%) • Period II (no proph): 9/141 (6.4%) • p = NS Fungal organisms • Period I (proph): 11/153 (7.2%) • Period II (no proph): 10/141 (7.1%) • p = NS Group A, n (%): • Period I (proph): 9/153 (5.9%) • Period II (no proph): 5/141 (3.5%) • p = NS Group B, n (%): • Period I (proph): 2/153 (1.3%) • Period II (no proph): 5/141 (3.5%) • p = NS
Author: Ocete[51] **Year:** 1998 **Study Design:** Non-	**Number of patients:** N = 146 • No differences between the two groups in terms of gestational age, weight, risk factors on admittance or duration of assisted respiration.	**Intervention:** n= 85 Prophylactic Vancomycin at 25 µg/mL through catheter **Control:** n= 61 No Prophylactic Vancomycin **Device/agent:** Vancomycin	**Outcome Definitions:** Infection: with presence of at least two clinical symptoms (bad perfusion, apnea, respiratory distress, digestive, neurological, or urinary disorders) in the absence of any other evidence cause of the clinical alteration.	**Primary Outcomes:** Infections, n [numerator calculated by CDC] (%): Negative coagulase staphylococci (NCS) • Vancomycin: 19/85 (22%) • No vancomycin: 21/61 (34%) • p < 0.05 Gram positive • Vancomycin: 26/85 (31%) • No vancomycin: 26/61 (43%)

Study Information	Population and Setting	Intervention/ Study Group	Definitions	Results
Randomized Control Study **Risk of Bias:** High	• Intervention group contained a higher number of newborns with assisted respiration (p<0.01). **Number of lines:** N = 146 **Setting:** Neonatal ICU, university hospital **Location:** Spain **Dates:** Control: September 10, 1993 - September 9, 1994 Intervention: September 10, 1994 - September 9, 1995 **Inclusion Criteria:** Newborns admitted to the NICU requiring central catheters (umbilical artery, umbilical vein and/or silastic) during the study periods for both groups. **Exclusion Criteria:** NR	**Standard preventive measures:** Umbilical and silicone catheters inserted using sterile technique with povidone iodine applied to all connections. Umbilical catheters fitted by doctor and Silicone catheters fitted by nurse.	**Sampling /Testing strategy:** Central and peripheral cultures were performed. **Other notes:** None	• p < 0.05 Gram negative • Vancomycin: 19/85 (22%) • No vancomycin: 20/61 (33%) • p = NS Fungus • Vancomycin: 6/85 (7%) • No vancomycin: 6/61 (10%) • p = NS **Topic-specific outcomes:** Duration of catheterization, mean days (SD): • Vancomycin: 9.20 (±9.15) • No vancomycin: 9.36 (±13.35) • p = NS **Adverse events** Antibiotic resistance: • No resistance to vancomycin observed during the study period. • Two years following the study, four cases of NCS resistance to vancomycin appeared.

Table 62 Risk of Bias for Randomized Controlled Trials on Prophylactic Antimicrobials

Author 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
Harms 1995[48]	✓	✓					✓	✓	✓		Moderate
Spafford 1994[49]	✓	✓	✓	✓	✓	✓	✓	✓	✓		Low

Table 63 Risk of Bias for Two Group Studies on Prophylactic Antimicrobials

Author Year	Were patients randomly assigned to the study's groups?	For non-randomized trials, did the study employ any other methods to enhance group comparability such as matching, stratification, or statistical methods to adjust for baseline differences?	Did patients in different study groups have similar levels of performance on the outcome of interest and other important factors at the time they were assigned to groups?	Did the study enroll all suitable patients or consecutive suitable patients within a time period?	Was the comparison of interest prospectively planned?	Were the two groups treated/ evaluated concurrently?	Was the study blinded or double-blinded?	Was the funding for this study derived from a source that would not benefit financially from results in a particular direction?	Risk of Bias
Elhassan 2004[50]			✓	✓					High
Ocete 1998[51]			✓	✓	✓				High

C.14. Prophylactic Anticoagulant Administration

Key Question 14: In NICU patients requiring central venous catheters, what is the efficacy of prophylactic anticoagulant infusions, compared with standard of care, to prevent CLABSI?

Table 64 Summary of Findings on Prophylactic Heparin + TPN or dextrose vs. TPN or dextrose to Prevent CLABSI

Outcome	Findings	Quantity and Type of Evidence	GRADE of Evidence for Outcome and Limitations of the Evidence
Catheter-related sepsis (CRS) or definite CRS*	• Four RCTs[52-55] found no difference in the incidence of catheter-related sepsis or definite CRS when comparing the use of prophylactic heparin with no heparin.	4 RCT[52-55] N=210 patients N=66 patients N=201 patients N=239 patients	High
Definite or probable CRS*	• One RCT study found no difference in the incidence definite or probable CRS when comparing the use of heparin with no heparin. [9/102 vs. 16/108; RR: 0.60 (95% CI: 0.28 – 1.26); p = 0.18].	1 RCT[52] N=210 patients	Moderate • Imprecision: only one study
Septicemia*	• One RCT study found no difference in the incidence of septicemia when comparing the use of heparin with no heparin. [7/35 (20.0%) vs. 9/31 (29.0%); RR: 0.7 (95% CI: 0.3-1.6); p = NR].	1 RCT[55] N=239 patients	Moderate • Imprecision: only one study
Occlusion	• Two RCT studies[52, 53] found no difference in the incidence of occlusion with the use of heparin compared with no heparin [5/102 vs. 3/108; RR: 1.76 (95% CI: 0.48-6.56); p = 0.42] & [5/35 (14.3%) vs. 7/31 (22.6%); RR: 0.6 (95% CI: 0.2-1.8); p = NR]. • Two RCT studies[54, 55] found heparin was associated with significant reduction in occlusion (23/118 (19.5%) vs. No heparin: 55/121 (45.5%); RR: 3.44 (95% CI: 1.92-6.44); p<0.05 (=0.0001)] & [6/100 vs. 31/101; RR: 0.20 (95% CI: 0.09-0.42); p<0.05 (=0.001)].	4 RCT[52-55] N=210 patients N=66 patients N=239 patients N=201 patients	Moderate • Consistency: inconsistent results
Intraventricular hemorrhage	• Three RCT studies[52-54] reported no difference in the incidence of intraventricular hemorrhage with the implementation of prophylactic anticoagulant.	3 RCT[52-54] N=210 patients N=66 patients N=201 patients	High

Table 65 Extracted Information on Anticoagulant Infusion

Study Information	Population and Setting	Intervention	Definitions	Results
Author: Birch[52] **Year:** 2010 **Study Design:** Prospective double blind RCT **Risk of Bias:** Low	**Number of patients:** N = 210 **Number of lines:** N = 210 **Setting:** Tertiary Neonatal ICU **Location:** New Zealand **Dates:** March 2004-October 2007 **Inclusion Criteria:** Infants requiring a long line for TPN as judged by the clinical team **Exclusion Criteria:** Any previous long line successfully inserted and utilized	**Intervention:** n=102 Heparin plus TPN **Control:** n=108 TPN without heparin **Device/agent:** Heparin **Monitoring intervention:** **Standard preventive measures:** • Long lines were inserted according to current unit practice using an aseptic technique and all lines were secured using medical adhesive and covered with non-adhesive dressing. • Choice of catheter was determined by the inserting physician. Following insertion, the lines were either attached directly to a bag of TPN or to an infusion of normal saline while waiting for the confirmation of the position of the line.	**Outcome Definitions:** Catheter related sepsis (CRS): A positive blood culture growing CONS, Staphylococcus aureus, Acinetobacter species or Candida. Definite CRS: Two positive blood cultures with the same organism taken from two separate sites within 72 hours of each other. Probable CRS: Single positive blood culture and a peak C-reactive protein level greater than 9 mg/l recorded from 24 h before to 72 h after the positive culture was drawn. Possible CRS: Single positive blood culture without elevation of C-reactive protein. Bacteremia with organisms not commonly associated with line sepsis: a single positive blood culture with the following organisms: streptococcal species, Gram-negative organisms and enterococci. Two or more blood cultures positive for the same organism and less than 7 days apart were considered to be the same single bacteremia episode. Positive blood culture: any blood culture growing one or more organism drawn from insertion of the long line to 24 hours after the line was removed. Intraventricular hemorrhage (IVH) progression: an increase on either side from grade 0–2 to grade 3–4	**Primary Outcomes:** Definite catheter related sepsis, n: • Heparin: 3/102 • No heparin: 10/108 • RR: 0.32 (95% CI: 0.1-1.03) • p = 0.06 Rates of definite catheter related sepsis/1000 days catheter in situ, n: • Heparin: 2.3 • No heparin: 6.8 • RR: 0.34 (95% CI: 0.09-1.24) • p = 0.09 Probable catheter related sepsis, n: • Heparin: 6/102 • No heparin: 6/108 • RR: 1.06 (95% CI: 0.37-3.03) • p = 0.92 Possible catheter related sepsis, n: • Heparin: 6/102 • No heparin: 13/108 • RR: 0.49 (95% CI: 0.2-1.19) • p = 0.12 Any CRS (definite, probable, possible), n: • Heparin: 15/102 • No heparin: 28/108 • RR: 0.57 (95% CI: 0.32-0.98) • p<0.05 (=0.04) Rate: any episodes of CRS/1000 days catheter in situ, n: • Heparin: 12.3 • No heparin: 20.3 • RR: 0.61 (95% CI: 0.33-1.11) • p = 0.10 Definite or probable CRS, n:

Study Information	Population and Setting	Intervention	Definitions	Results
			between the 'worst initial IVH' and the 'worst post-trial IVH'. **Sampling /Testing strategy:** Blood cultures **Other notes:** None	• Heparin: 9/102 • No heparin: 16/108 • RR: 0.60 (95% CI: 0.28 – 1.26) • p = 0.18 Bacteremia with organisms not commonly associated with line sepsis, episodes: • Heparin: 1 • No heparin: 0 • p = NR **Topic-specific outcomes:** Duration of catheter patency, mean days (SD): • Heparin: 12.9 (±9.8) • No heparin: 13.7 (±12.4) • p = 0.93 **Adverse events:** Occlusion, n: • Heparin: 5/102 • No heparin: 3/108 • RR: 1.76 (95% CI: 0.48-6.56) • p = 0.42 Extravasation, n: • Heparin: 4/102 • No heparin: 8/108 • RR: 0.53 (95% CI: 0.17-1.6) • p = 0.28 IVH Progression, n: • Heparin: 2/102 • No heparin: 7/108 • RR: 0.3 (95% CI: 0.07 - 1.24) • p = 0.11 Non-catheter-related sepsis, n: • Heparin: 1/102 • No heparin: 0/108 • p = NR Mortality, n: • Heparin: 0/102

Study Information	Population and Setting	Intervention	Definitions	Results
				• No heparin: 1/108 • p = NR Bleeding diatheses: None observed Thrombocytopenia: None observed
Author: Uslu[55] **Year:** 2010 **Study design:** Prospective double blind RCT **Risk of Bias:** Low	**Number of patients:** N = 239 **Number of lines:** N = 239 **Setting:** Neonatal ICU **Location:** Turkey **Dates:** February 1, 2007-October 31, 2008 **Inclusion Criteria:** All neonates admitted to the NICU who had required a peripherally inserted percutaneous central venous catheter (PCVC) as determined by the attending neonatologist. **Exclusion Criteria:** Neonates with bleeding tendencies, grade 3 to 4 intraventricular hemorrhage, recent suspected or confirmed sepsis (within 48 h of initiation of antibiotic therapy), thrombocytopenia (<100,000 mm^{-3}), disseminated intravascular coagulation, arrhythmia, and congenital malformations. Additionally, patients with uncertain viability	**Intervention group:** n=118 Heparin plus TPN **Control group:** n=121 TPN without heparin **Device/agent:** Heparin **Monitoring intervention:** **Standard preventive measures:** • Catheters were placed by using a sterile technique. Catheter type and place of insertion were determined by the physician's choice. • Catheters were stabilized and secured with a transparent medical film dressing, which was not changed unless it became polluted or slack.	**Outcome Definitions:** Catheter related sepsis: Clinical signs of sepsis was associated with a positive peripheral blood culture and positive catheter culture of the same organism. Duration of catheter: Number of days between insertion and removal. Catheter removal: signs of local or systemic infection, phlebitis, extravasation, blockage, breakage and leakage of catheter, accidental removal, death, and if neonate reached close to full enteral feeds Catheter occlusion: the inability of infusing fluids through the catheter due to blockage Thrombosis: a thrombus along the catheter line detected by inspection after removal of the catheter Phlebitis: inspection as swelling, hyperemia and change in skin color associated with an inflamed vein **Sampling /Testing strategy:** Bacterial cultures were obtained from catheters and flushing solutions. In case of suspicion of septicemia, blood culture was obtained. **Other notes:** None	**Primary Outcomes:** Catheter related sepsis, n (%): • Heparin: 2/118 (1.7) • No heparin: 4/121 (3.3) • p = 0.68 Septicemia, n (%): • Heparin: 5/118 (4.2) • No heparin: 4/121 (3.3) • p = 0.74 **Topic-specific outcomes:** Duration of catheter patency, days: • Heparin: 12.4 (±4.5) • No heparin: 9.7 (±4.0) • p < 0.05 (=0.0001) **Adverse events:** Occlusion, n (%): • Heparin: 23/118 (19.5) • No heparin: 55/121 (45.5) • RR: 3.44 (95% CI: 1.92-6.44) • p < 0.05 (=0.0001) Thrombosis, n (%): • Heparin: 2/118 (1.7) • No heparin: 5/121 (4.1) • p = 0.25 Phlebitis, n (%): • Heparin: 10/118 (8.4) • No heparin: 10/121 (8.3) • p = 0.12

Study Information	Population and Setting	Intervention	Definitions	Results
	(determined by neonatologist), need for use of heparin (umbilical arterial catheter), and a prolonged activated partial thromboplastin time (aPTT) (>74 s for preterm infants and >51 s for term infants)			Thrombocytopenia, n: • Heparin: 2/118 • No heparin: 1/121 • p = NR aPTT >100s, n: • Heparin: 1/118 • No heparin: 0/121 • p = NR Bleeding tendencies, n: • Heparin: 1/118 • No heparin: 1/121 • p = NR Intracranial hemorrhage, n (%): • Heparin: 19/118 (16.1) • No heparin: 21/121 (17.4) • p = 0.93 Intracranial hemorrhage after PCVC removal, n (%): • Heparin: 21/118 (17.8) • No heparin: 23/121 (19.0) • p = 0.80 Arrythmia after PCVC removal, n (%): • Heparin: 1/118 (0.8) • No heparin: 1/121 (0.8) • p = 0.80 Mortality, n (%): • Heparin: 6/118 (5.1) • No heparin: 6/121 (4.8) • p = 0.79 Other (e.g., breakage, leakage, accidental withdrawal), n (%): • Heparin: 3/118 (2.5) • No heparin: 4/121 (3.2) • p = 1
Author: Shah[54]	**Number of patients:** N = 201	**Intervention:** n=100	**Outcome Definitions:**	**Primary Outcomes:** Catheter related sepsis, n:

Study Information	Population and Setting	Intervention	Definitions	Results
Year: 2007 **Study Design:** Prospective double blind RCT **Risk of Bias:** Low	**Number of lines:** N = 201 **Setting:** Four tertiary care Neonatal ICUs **Location:** Canada **Dates:** November 2002-November 2005 **Inclusion Criteria:** All neonates requiring peripherally placed percutaneous central venous catheters (PCVC) access as judged by the clinical team **Exclusion Criteria:** Neonates who had grade ¾ intraventricular hemorrhage, recent onset of presumed or confirmed sepsis (within 48 hours of initiation of antimicrobial therapy), bleeding diathesis, disseminated intravascular coagulation, thrombocytopenia, arrhythmia, or preexisting liver disease.	Heparin: 10% or 5% dextrose with heparin **Control:** n=101 No heparin: 10% or 5% dextrose **Device/agent:** Heparin **Monitoring intervention:** **Standard preventive measures:** • All PCVCs were placed by using sterile technique as per similar standards in each NICU. • Catheters were flushed by normal saline before insertion, and the extension tubing was connected to the PCVC hub. • Catheters were secured by transparent occlusive dressing that was not changed unless it was soiled or loose	Catheter related sepsis: Symptoms and signs suggestive of sepsis with a positive blood culture obtained from catheter fluid and a normally sterile site (blood urine, or cerebrospinal fluid) for the same organism. Catheter occlusion: the inability to infuse fluid Duration of catheter use: time between insertion and removal (elective or because of complications) of the catheter in hours. Thrombosis: the detection of a thrombus along the catheter path **Sampling /Testing strategy:** NR **Other notes:** None	• Heparin: 5/100 • No heparin: 2/101 • p = 0.243 Suspected catheter-related sepsis, n: • Heparin: 5/100 • No heparin: 4/101 • OR: 1.28 (95% CI: 0.33-4.90) • p = 0.722 **Topic-specific outcomes:** Duration of catheter patency, mean hours (SD): • Heparin: 267 (±196) • No heparin: 233 (±194) • p = 0.220 Duration of catheter patency, median (range): • Heparin218 (6-1095) heparin • No heparin: 188 (3-1176) • p = NR Duration of catheter usability, n: • p < 0.05; Hazard ratio: 0.53 (95% CI: 0.35-0.81) **Adverse events:** Reasons for non-elective catheter removal Occlusion, n: • Heparin: 6/100 • No heparin: 31/101 • RR: 0.20 (95% CI: 0.09-0.42) • p < 0.05 (=0.001) Non occlusive thrombosis, n: • Heparin:18/100 • No heparin: 18/101 • p = NR Intraventricular hemorrhage: • None observed HIT thrombocytopenia, n: • Heparin: 1/100 • No heparin: 0/101 • p = NR Bleeding:

Study Information	Population and Setting	Intervention	Definitions	Results
				• None observed Leakage, n: • Heparin: 6/100 • No heparin: 2/101 • p = 0.145 Extravasation, n: • Heparin: 8/100 • No heparin: 14/101 • p = 0.183 Other reasons for non-elective catheter removal, n: • Heparin: 7/100 • No heparin: 6/101 • p = 0.760
Author: Kamala[53] **Year:** 2002 **Study Design:** Prospective double-blind RCT **Risk of Bias:** Low	**Number of patients:** N = 66 **Number of lines:** N = 66 **Setting:** Neonatal ICU **Location:** Malaysia **Dates:** August 1,1999-August 31, 2000 **Inclusion Criteria:** All neonates admitted to the NICU who had Peripherally or percutaneously inserted central venous catheters (PICCs) inserted subsequently for the purpose of receiving TPN. **Exclusion Criteria:** Neonates with clinical evidence of bleeding tendencies, severe IVH of grade 3 or 4; platelet counts <100 x $10^9 1^{-1}$ and/or prolonged activated partial thromboplastin time (APTT more than 51 sec for term infants of gestation ≥37	**Intervention group:** n=35 Heparin plus TPN **Control group:** n=31 TPN no heparin **Device/agent:** Heparin **Monitoring intervention:** **Standard preventive measures:** • The TPN fluids used in both groups of infants were prepared under sterile conditions by the pharmacist. • Catheters were inserted percutaneously from a sterile protective conduit through either a 21 or 19 gauge winged needle.	**Outcome Definitions:** Catheter related sepsis: Present in neonates manifesting clinical signs of sepsis associated with a positive catheter-tip culture and a positive peripheral blood culture of the same bacterial organism. Septicemia: Diagnosed when infants developed clinical signs of sepsis associated with a positive blood culture, irrespective of the catheter tip culture result. Duration of catheter patency: the number of days for which the PICC remained functioning in-situ, and upon removal there was no evidence of blockage. Hyperbilirubinemia: Diagnosed as being present when any infant's serum bilirubin level rose higher than normal **Sampling /Testing strategy:** Specimens of blood was collected from each infant for measurement of bilirubin, triglyceride, APTT and platelet count before insertion of catheter and again on days 4 and 8 with PICC in situ, or on	**Primary Outcomes:** Catheter related sepsis, n (%): • Heparin:1/35 (2.9) • No heparin: 1/31 (3.2) • RR: 0.9 (95% CI: 0.06-13.6) • p = NR Septicemia, n (%): • Heparin: 7/35 (20.0) • No heparin: 9/31 (29.0) • RR: 0.7 (95% CI: 0.3-1.6) • p = NR **Topic-specific outcomes:** Duration of PICC in situ, mean days (SD): • Heparin: 10.8 (±6.7) • No heparin: 9.3 (5.1) • 95% CI difference between means: -4.4-1.4 • p = NR **Adverse events** Blocked catheter/ Occlusion, n (%): • Heparin: 5/35 (14.3) • No heparin: 7/31 (22.6) • RR: 0.6 (95% CI: 0.2-1.8) • p = NR Intraventricular hemorrhage, n (%): • Heparin: 4/23 (17.4)

Study Information	Population and Setting	Intervention	Definitions	Results
	weeks, or more than 74 sec for preterm infants of gestation <37 weeks.		removal of the PICC if the catheter was to be removed before day 4. Catheter blockage was diagnosed when unable to infuse TPN fluid readily through the catheter while in situ and detection of clots in the PICC after removal from the infants. If clot was detected upon removal, the catheter tip and aseptically collected solution were sent for bacterial culture. A specimen of blood for bacterial culture was obtained from the peripheral vein of an infant whenever attending doctor suspected septicemia. Cranial ultrasonography was carried out before, 1 week after commencement and upon completion of TPN. **Other notes:** None	• No heparin: 4/20 (20.0) • RR: 0.9 (95% CI: 0.3-3.00) • p = NR Peak serum bilirubin level, mean µmol 1^{-1} (SD): • Heparin: 199 (±65) • No heparin: 230 (±71) • 95% CI difference between means: -1.4-63.8 • p = NR Peak serum triglyceride level, mean mmol 1^{-1} (SD): • Heparin: 2.3 (±1.5) • No heparin: 1.9 (±1.4) • 95% CI difference between means: -1.2-0.3 • p = NR Peak duration of activated partial thromboplastin time (APTT), mean sec (SD): • Heparin: 61.1 (±30.8) • No heparin: 66.8±36.8 • 95% CI difference between means: -11.8-23.3 • p = NR Lowest platelet count, $x10^{9}1^{-1}$: • Heparin: 172 (±109) • No heparin: 156 (±101) • 95% CI difference between means: -66.6-35.2 • p = NR Phlebitis, n (%): • Heparin: 3/35 (8.6) • No heparin: 6/31 (19.4) • RR: 0.4 (95% CI: 0.1-1.6) • p = NR Bleeding, n: • Heparin: 2/35 • No heparin: 4/31 • p = NR Thrombocytopenia, n: • Heparin: 3/35

Study Information	Population and Setting	Intervention	Definitions	Results
				• No heparin: 4/31 • p = NR Mortality, n (%): • Heparin: 4/35 (11.4) • No heparin: 6/31 (19.4) • RR: 0.6 (95% CI: 0.2 - 1.9) • p = NR

Table 66 Risk of Bias for Randomized Controlled Trials on Anticoagulant Infusion

Author 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
Birch 2010[52]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	Low
Uslu 2010[55]	✓		✓	✓	✓	✓	✓		✓		Moderate
Shah 2007[54]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	Low
Kamala 2002[53]	✓		✓	✓	✓	✓	✓	✓	✓	✓	Low

D. Evaluation of Study-level Risk of Bias

D.1. Randomized Controlled Trial Checklist

1. Described as randomized
2. Randomization appropriately performed
3. Described as double-blind
4. Outcome assessor blinded
5. Study participant blinded
6. Investigator blinded
7. Attrition described
8. Attrition smaller than 10-15% of assigned patients
9. Attrition appropriately analyzed
10. Funding source(s) disclosed and no obvious conflict of interest

D.2. Observational Study Checklist

1. Were all study groups derived from similar source/ reference populations?
2. Was attrition not significantly different across study groups?
3. Was the measure of exposure valid?
4. Was the measure of outcome valid?
5. Were investigators blinded to endpoint assessment or are the Outcome Definitions objective?
6. Were potential confounders identified?
7. Were statistical adjustments done for potential confounders?
8. Were funding source(s) disclosed and no obvious conflict of interest?

D.3. Descriptive Study Checklist

1. Did the study enroll all suitable patients or consecutive suitable patients within a time period?
2. Was the study prospectively planned?
3. Were independent or blinded assessors used to assess subjective Outcome Definitions?
4. Was the study's funding derived from a source that would not benefit financially from results in a particular direction?

D.4. Rating for Overall Risk of Bias

- The risk of Bias was rated as follows:
    - Observational studies:
        - High Risk of Bias: studies with ≤ 50% of checklist items reported
        - Moderate Risk of Bias: studies with > 50% and < 75% of checklist items reported
        - Low Risk of Bias: studies with ≥ 75% of checklist items reported
    - Descriptive Studies
        - High Risk of Bias: studies with ≤ 50% of checklist items reported
        - Moderate Risk of Bias: studies with > 50% of checklist items reported

D.5. Aggregate Risk of Bias

- When the risk of bias was rated as "High" for ≥75% of studies making up the evidence base for a given outcome, one point was deducted for Study Quality in the GRADE table.

E. HICPAC Recommendation Categorization Scheme (2019)

Table 67 Strength of Recommendations

Strength	Definition	Implied Obligation	Language
Recommendation	A Recommendation means that we are confident that the benefits of the recommended approach clearly exceed the harms (or, in the case of a negative recommendation, that the harms clearly exceed the benefits). In general, Recommendations should be supported by high- to moderate-quality evidence. In some circumstances, however, Recommendations may be made based on lesser evidence or even expert opinion when high-quality evidence is impossible to obtain, and the anticipated benefits strongly outweigh the harms or when then Recommendation is required by federal law.	A Recommendation implies that healthcare personnel/healthcare facilities "should" implement the recommended approach unless a clear and compelling rationale for an alternative approach is present.	The wording of the Recommendation should specify the setting and population to which the Recommendation applies (eg, adult patients in intensive care unit settings). • Action verbs, eg, use, perform, maintain, replace • Should, should not • Recommend/ is recommended, recommend against/ is not recommended • Is indicated/ is not indicated
Conditional Recommendation	A Conditional Recommendation means that we have determined that the benefits of the recommended approach are likely to exceed the harms (or, in the case of a negative recommendation, that the harms are likely to exceed the benefits). Conditional Recommendations may be supported by either low-, moderate- or high-quality evidence when: • there is high-quality evidence, but the benefit/harm balance is not clearly tipped in one direction • the evidence is weak enough to cast doubt on whether the recommendation will consistently lead to benefit	A Conditional Recommendation implies that healthcare facilities/ personnel "could," or could "consider" implementing the recommended approach. The degree of appropriateness may vary depending on the benefit vs. harm balance for the specific setting.	The wording of the Conditional Recommendation should specify the setting and population to which the Conditional Recommendation applies when relevant, including: – select settings (eg, during outbreaks) – select environments (eg, ICUs) – select populations (eg, neonates, transplant patients).

Strength	Definition	Implied Obligation	Language
	• the likelihood of benefit for a specific patient population or clinical situation is extrapolated from relatively high-quality evidence demonstrating impact on other patient populations or in other clinical situations (eg, evidence obtained during outbreaks used to support probable benefit during endemic periods) • the impact of the specific intervention is difficult to disentangle from the impact of other simultaneously implemented interventions (eg, studies evaluating "bundled" practices) • there appears to be benefit based on available evidence, but the benefit/harm balance may change with further research • benefit is most likely if the intervention is used as a supplemental measure in addition to basic practices		• Consider • Could • May/ may consider
No Recommendation	No Recommendation is made when there is both a lack of pertinent evidence and an unclear balance between benefits and harms.	n/a	"No recommendation can be made regarding"

Table 68 Justification for Choice of Recommendation Strength

Components	What to include	Comments
Supporting Evidence	List the number and type(s) of available evidence used.	eg, " … 10 observational studies"
Level of Confidence in the Evidence	Level of confidence is low/moderate/high (See Table 3).	eg, "The level of confidence in this evidence is low, as observational studies are at increased risk of bias"
Benefits	List the favorable changes in Outcome Definitions that would likely occur if the Recommendation were followed.	Be explicit, clear about pros/cons
Risks and Harms	List the adverse events or other unfavorable Outcome Definitions that may occur if the Recommendation were followed.	Be explicit, clear about pros/cons
Resource Use	Describe (if applicable) direct costs, opportunity costs, material or human resources requirements, facility needs, etc, that may be associated with following the Recommendation.	HICPAC does not perform its own cost analyses and is not obliged to address cost if analyses are not available and no useful statements can be made. State clearly if information on resource use is lacking.
Benefit-Harm Assessment	Classify as "preponderance of benefit over harm" (or vice versa) or a "balance of benefit and harm." Description of this balance can be from the individual patient perspective, the societal perspective, or both.	Recommendations are possible when clear benefit is not offset by important harms or costs (or vice versa); conversely, when the benefit is small or offset by important adverse factors, the balance between benefit and harm prevents a Recommendation.
Value Judgments	Summarize value judgments used by the group in creating the Recommendation; if none were involved, state "none."	Translating evidence into action often involves value judgments, which include guiding principles, ethical considerations, or other beliefs and priorities. Stating them clearly helps users understand their influence on interpreting objective evidence.
Intentional Vagueness	State reasons for any intentional vagueness in the Recommendation; if none was intended, state "none."	Recommendations should be clear and specific, but if the group chooses to be vague, acknowledging their reasoning clearly promotes transparency. Reasons for vagueness may include insufficient evidence; inability to achieve consensus among panel regarding evidence quality, anticipated benefits/harms, or interpretation of evidence; legal considerations; economic reasons; ethical/religious issues.

Components	What to include	Comments
Exceptions	List situations or circumstances in which the Recommendation should not be applied.	

Table 69 Aggregate Level of Confidence in Effect Estimate*

High	Highly confident that the true effect lies close to that of the estimated size and direction of the effect. For example, confidence in the evidence is rated as "High" when there are multiple studies with no major limitations, there are consistent findings, and the summary estimate has a narrow confidence interval.
Moderate	The true effect is likely to be close to the estimated size and direction of the effect, but there is a possibility that it is substantially different. For example, confidence in the evidence is rated as "Moderate" when there are only a few studies and some have limitations but not major flaws, there is some variation between study results, or the confidence interval of the summary estimate is wide.
Low	The true effect may be substantially different from the estimated size and direction of the effect. For example, confidence in the evidence is rated as "Low" when supporting studies have major flaws, there is important variation between study results, the confidence interval of the summary estimate is very wide, or there are no rigorous studies.

*Based on Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) and the Canadian Task Force on Preventive Health Care

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G. Acronyms and Abbreviations

Acronym	Expansion
*	Critical outcome by which decisions are made
BSI	Bloodstream Infection
CDC	Centers for Disease Control and Prevention
CRBSI	Catheter-Related Bloodstream Infection
CLABSI	Central Line-Associated Bloodstream Infection
CHG	Chlorhexidine Gluconate
CoNS	Coagulase-Negative Staphylococci
DES	Descriptive Study
FDA	Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HHS	(United States Department of) Health and Human Services
HICPAC	Healthcare Infection Control Practices Advisory Committee
IV	Intravenous
MRSA	Methicillin-Resistant Staphylococcus aureus
MSSA	Methicillin-Sensitive Staphylococcus aureus
NICU	Neonatal Intensive Care Unit
OBS	Observational Study
PICC	Peripherally Inserted Central Catheter
PCR	Polymerase Chain Reaction
PI	Povidone Iodine
QI	Quality Improvement
RCT	Randomized Controlled Trial
S. aureus	Staphylococcus aureus
TAP	Targeted Assessment for Prevention
UAC	Umbilical Arterial Catheter

Acronym	Expansion
UVC	Umbilical Venous Catheter
VLBW	Very Low Birthweight