



TITLE: Peripherally Inserted Central Catheters (PICCs) for Adult and Pediatric Patients: A Review of Clinical Evidence

DATE: 5 April 2013

CONTEXT AND POLICY ISSUES

Peripherally inserted central catheters (PICCs) are central lines that are inserted into the one of the large veins of the upper extremities, with the catheter tip placed in the distal superior vena cava, to provide prolonged central venous access.¹ PICCs have a number of uses in both the inpatient and outpatient setting, including medication administration such as chemotherapy or antibiotics, and administration of parenteral nutrition.¹ PICC lines can also be used to provide venous blood samples, thereby reducing the number of venipunctures.¹

While generally safe, there are potential complications associated with PICC lines. Complications associated with the use of PICCs include central line-associated bloodstream infection (CLABSI), line occlusion, phlebitis, and venous thrombosis (both superficial and deep).¹⁻³ Although these complications are relatively rare, given the frequency of use of PICC lines in individuals of all ages for a number of different conditions, it is likely that clinicians will encounter complication associated with PICCs in their patients.³

A number of strategies have been proposed to minimize the occurrence of complications associated with PICCs. Some strategies include antimicrobial-impregnated PICCs for prevention of CLABSI,⁴ and differences in catheter valve technology (that is, valved catheters may prevent catheter occlusion by preventing reflux of blood into the catheter relative to non-valved catheters) and catheter flushing agents to potentially reduce catheter occlusion and line infection.⁵ It is unclear, however, whether these strategies truly have an impact on reducing complications in those with a PICC line, and if they do, whether the reduction in complications is experienced similarly by all age groups.

The purpose of this report is to determine the clinical evidence for use of chlorhexidine impregnated PICCs compared to non-chlorhexidine impregnated PICCs, valved versus non-valved PICCs, and saline versus heparin for non-valved catheters with neutral displacement caps (that is, neutral pressure for fluid movement into the catheter lumen) in adult and pediatric populations.

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RESEARCH QUESTIONS

1. What is the clinical evidence for chlorhexidine impregnated or coated peripherally inserted catheters (PICCs) versus non-chlorhexidine PICCs in adult and pediatric populations?
2. What is the clinical evidence for valved versus non-valved PICCs for adult and pediatric inpatient or outpatient populations?
3. What is the clinical evidence for the use of saline versus heparin for non-valved (open-end) catheters with neutral displacement caps for adult and pediatric populations?

KEY FINDINGS

No evidence was found reporting the clinical evidence of using chlorhexidine-impregnated or coated PICCs compared to non-chlorhexidine PICCs. One study found no difference in terms of frequency of occlusion in adult ICU patients who had a valved versus a non-valved PICC line. Use of normal saline was associated with a longer duration of patency compared with heparin in neonates. No difference was found in terms of patency, occlusion, pain, burning, and swelling in pediatric patients in those who received heparin compared to those who received normal saline.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including Pubmed, The Cochrane Library (2013, Issue 2), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No methodological filters were applied. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2008 and March 7, 2013.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications for relevancy, and evaluated the relevant full-text publications for the final article selection based on the criteria listed in Table 1.

Table 1: Selection Criteria

Population	Questions 1, 2 and 3: Adult and pediatric populations, inpatient and outpatient populations
Intervention	Question 1: Chlorhexidine impregnated or coated PICCs Question 2: Valved PICCs Question 3: Heparin
Comparator	Question 1: Non-chlorhexidine impregnated or coated PICCs Question 2: Non-valved PICCs Question 3: Saline

Outcomes	Question 1: Risk of infection/ infection rate, allergic reactions/ allergy, thrombosis Question 2: Infection rate, air embolus, bleeding, occlusion/blockage Question 3: occlusion, infection rate/ risk of infection
Study Designs	Health technology assessments (HTA), systematic reviews (SR), meta-analyses (MA), randomized controlled trials (RCTs), and non-randomized studies

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, if they were duplicate publications, or were published prior to January 1, 2008.

Critical Appraisal of Individual Studies

The Downs and Black checklist⁶ was used to critically appraise the randomized controlled trials and observational studies included in this report. Summary scores were not calculated for the included studies, rather, a review of the strengths and limitations of each included study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search identified 365 citations, with an additional five citations identified from the grey literature. After screening of the abstracts, 19 potentially relevant studies were identified for full-text review.

A total of three studies were included in this review, one study that addressed PICC valve technology,⁷ and two studies that addressed heparin compared with normal saline flushes.^{8,9} No studies were identified in the literature search comparing chlorhexidine-impregnated or coated PICCs relative to non-chlorhexidine-coated PICCs and risk of infection.

The PRISMA flowchart provides the details of the study selection process (Appendix 1).

Summary of Study Characteristics

Details on study design, critical appraisal, and study findings are located in Appendices 2, 3, and 4, respectively.

Study Design

A single site randomized controlled trial evaluated valved versus non-valved PICC lines.⁷ One single site randomized controlled trial,⁸ and one single site observational before/after study were identified that compared heparin to normal saline.⁹

Country of Origin

The study that evaluated PICC line valve technology originated from the United Kingdom,⁷ whereas both studies that evaluated heparin compared to normal saline originated from the United States.^{8,9}

Patient Population

The study that evaluated valved and non-valved PICCs included adults admitted to an intensive care unit (ICU).⁷ For the comparison of heparin to normal saline, the study populations were pediatric patients admitted to a pediatric hospital (unit not specified)⁸ and neonates admitted to a neonatal intensive care unit.⁹

Interventions and Comparators

The study that evaluated valve technology compared three types of dual lumen PICCs, including the Cook Medical non-valved Turbo-Flo PICC, the Bard Groshong valved PICC, and the Navilyst Medical Vaxcel PICC with pressure activated safety valve (PASV).⁷ Each type of PICC was compared to one another.

Two studies evaluated heparin as the intervention and normal saline as the comparator. The dose of heparin in the pediatric study was 10 units (1 mL), in addition to 2 mL of normal saline for a total volume of 3 mL administered three times daily, and this was compared with 3 mL of normal saline administered three times daily in patients with a capped pediatric peripheral intravenous catheter.⁸ The dose of heparin in the neonatal study was 4 units (0.4 mL) administered every four hours, and the comparator group received 0.4 mL of normal saline every four hours in neonates using an intravenous lock.⁹

Clinical Outcomes

The primary outcome of the valve versus no valve study was to evaluate the number of occlusions per type of PICC line.⁷ The secondary outcomes included total urokinase dose required to unblock occlusions per PICC line, and the mean dose of urokinase per occlusion per PICC line.⁷

Regarding heparin compared to normal saline, outcomes evaluated in the pediatric study included patency, redness, swelling, clotting, bruising, leakage, and patient pain and burning after each flush.⁸ The neonatal study evaluated duration of patency, occlusion, and adverse events due to heparin including cerebral hemorrhage, thrombocytopenia, and thrombosis.⁹

Summary of Critical Appraisal

What is the clinical evidence for valved versus non-valved PICCs for adult and pediatric inpatient or outpatient populations?

Strengths of the study included the randomized assignment of the type of PICC line, a clear description of each PICC line included in the study, clear definitions of the outcomes of occlusion and urokinase use, clear description of the baseline characteristics of the study participants, and no losses to follow up.⁷ The major limitation of this study was the fact that the study was likely underpowered to detect a difference between the types of PICC lines. This was because the study was powered to detect an absolute risk reduction of 20%, which required 300

total participants (100 in each group), however, study personnel were only able to randomize 102 patients in total because the study was discontinued early due to four episodes of hemolysis in patients who received the Navilyst PASV PICC.⁷ Other limitations included lack of blinding of staff and study personnel (although outcomes were objective, so this may not have impacted results), lack of reporting on the process for randomization, and the restricted inclusion of adults admitted to ICU, making it unclear whether the results of the study are generalizable to other populations.⁷

What is the clinical evidence for the use of saline versus heparin for non-valved (open-end) catheters with neutral displacement caps for adult and pediatric populations?

Strengths of the first study included random assignment of heparin and normal saline, and clear description of the intervention (heparin), comparator (normal saline), and characteristics of patients included in the study.⁸ No losses to follow up reported in the study.⁸ The major limitation of this study was the lack of blinding of staff and study personnel, especially given that many of the outcomes being evaluated were subjective without a standard definition provided (redness, swelling, pain, and burning).⁸ In addition, the process for randomization was not reported, a sample size calculation was not completed, making it unclear whether the study was large enough to detect clinically important differences, and the study evaluated children only (average age 6.5 years), therefore results are not generalizable to infants or adults.⁸

Strengths of the second study were the description of the patients included in the study, as well as clear descriptions of the intervention and comparator.⁹ In addition, study investigators adjusted for potential confounding variables including birth weight, gestational age, and location of catheter (upper or lower extremity).⁹ Limitations of the study included lack of randomization to heparin or normal saline. The outcome information was collected during a retrospective chart review, and as a result, it is unclear if adverse events were documented differently before and after switching heparin to saline.⁹ In addition, a power calculation was not completed, therefore it is unclear whether the study was large enough to detect a difference between the two interventions.⁹ Also, it was unclear whether hospital practices changed during the before/after period, which could impact safety and effectiveness results.⁹ Lastly, the study included neonates admitted to NICU only, therefore it is unclear whether the results of the study are generalizable to other populations.⁹

Summary of Findings

What is the clinical evidence for chlorhexidine impregnated or coated peripherally inserted catheters (PICCs) versus non-chlorhexidine PICCs in adult and pediatric populations?

No studies were identified from the literature search that addressed this question.

What is the clinical evidence for valved versus non-valved PICCs for adult and pediatric inpatient or outpatient populations?

One study was identified that compared catheter occlusion rates between three types of dual lumen PICC lines: open ended non-valved (Cook), Groshong valve, and PASV valve.⁷ The study investigators evaluated the frequency of occlusion in each type of PICC line as the primary study outcome, and total and average dose of urokinase required to clear occlusions from each line.⁷ The overall frequency of occlusion in the study population was 76 per 1000 catheter days.⁷ The study authors found no statistically significant difference in number of

occluded lines between the three types: 13/35 (38%) for the non-valved line, 13/34 (38%) for the valved Groshong line, and 9/33 (27%) for the PASV valve line.⁷ Also, no statistical difference between lines was found in terms of total or average urokinase dose for occlusions.⁷ It must be noted, however, that the study was stopped early because 4/33 (12.1%) of people who had the PASV valve line developed hemolysis, compared to none in the other two groups.⁷

What is the clinical evidence for the use of saline versus heparin for non-valved (open-end) catheters with neutral displacement caps for adult and pediatric populations?

In the study conducted in the pediatric population, no statistical difference was found for occurrence of redness, swelling, blood in catheter, bruising, leakage, pain, burning, clotting, or infiltration in children randomized to heparin (1 unit) compared to those randomized to normal saline.⁸ Pain and burning were the most common negative effects reported by both groups.⁸ A total of 34.4% of children randomized to heparin reported pain after the flush, and 34.4% reported burning, compared to 26.7% and 23.3% of the children randomized to normal saline, respectively.⁸ These comparisons were not statistically different between groups.⁸

When comparing duration of patency in neonates, the neonates who received normal saline had a statistically significantly longer duration of patency (54.45 hours) compared to the neonates who received heparin (0.4 units) (40.98 hours, $P = 0.02$).⁹ No difference was found in terms of frequency of occlusion, however. Lastly, no adverse events including cerebral hemorrhage, thrombocytopenia, and thrombosis were noted in the neonates who received heparin.⁹

Limitations

There are limitations in the currently available evidence that must be noted. There was no evidence identified from the literature search that addressed the use of chlorhexidine-impregnated PICCs relative to non-chlorhexidine-impregnated PICCs for any clinical outcome. Only one study was identified that compared valve and non-valve technology and rate of occlusion. Two studies were identified that compared heparin to normal saline, but it was unclear whether the intravenous lines were non-valved or whether they had neutral displacement caps. In addition, one study utilized a before after study design, and it was unclear whether practice changes during the study time frame had an impact on the study results. Also, the studies included in this report had small sample sizes (62 to 102 patients) making it difficult to draw conclusions based on the study results, as it was unclear whether the studies had the power necessary to detect a statistical difference. Lastly, the studies evaluated restrictive populations, including adults in ICU, pediatrics, and neonates in NICU, limiting the generalizability of the study results.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

No studies were identified from the literature search that compared chlorhexidine coated PICCs to non-chlorhexidine coated PICCs. It should be noted, however, that the Healthcare Infection Control Practices Advisory Committee (HICPAC) 2011 guidelines for the prevention of intravascular catheter-related infections recommend to “Use a chlorhexidine/silver sulfadiazine or minocycline/rifampin-impregnated central vascular catheter in patients whose catheter is expected to remain in place > 5 days if, after successful implementation of a comprehensive strategy to reduce rates of central line-associated bloodstream infection (CLABSI), the CLABSI rate is not decreasing.”¹⁰ The HICPAC states that a comprehensive strategy to reduce CLABSI rates should include at least three components: “educating persons who insert and maintain

catheters, use of maximal sterile barrier precautions, and a > 0.5% chlorhexidine preparation with alcohol for skin antisepsis during central vascular catheter insertion.”¹⁰ These recommendations were based on randomized controlled trial and systematic review evidence published from 1997 to 2005.¹¹⁻¹⁵

Based on the limited evidence included in this review, PICC lines with a valve compared to no valve did not seem to impact the frequency of occlusion in the adult ICU population. While normal saline was associated with a longer duration of patency relative to heparin in neonates, no difference was found in terms of patency, pain, bruising, and swelling in pediatric patients who received heparin compared to those who received normal saline. More research with larger sample sizes and broader populations are needed to clearly identify whether valve technology impacts patient outcomes, and whether heparin or normal saline is the preferred solution for non-valved catheters with neutral displacement caps for adult and pediatric populations.

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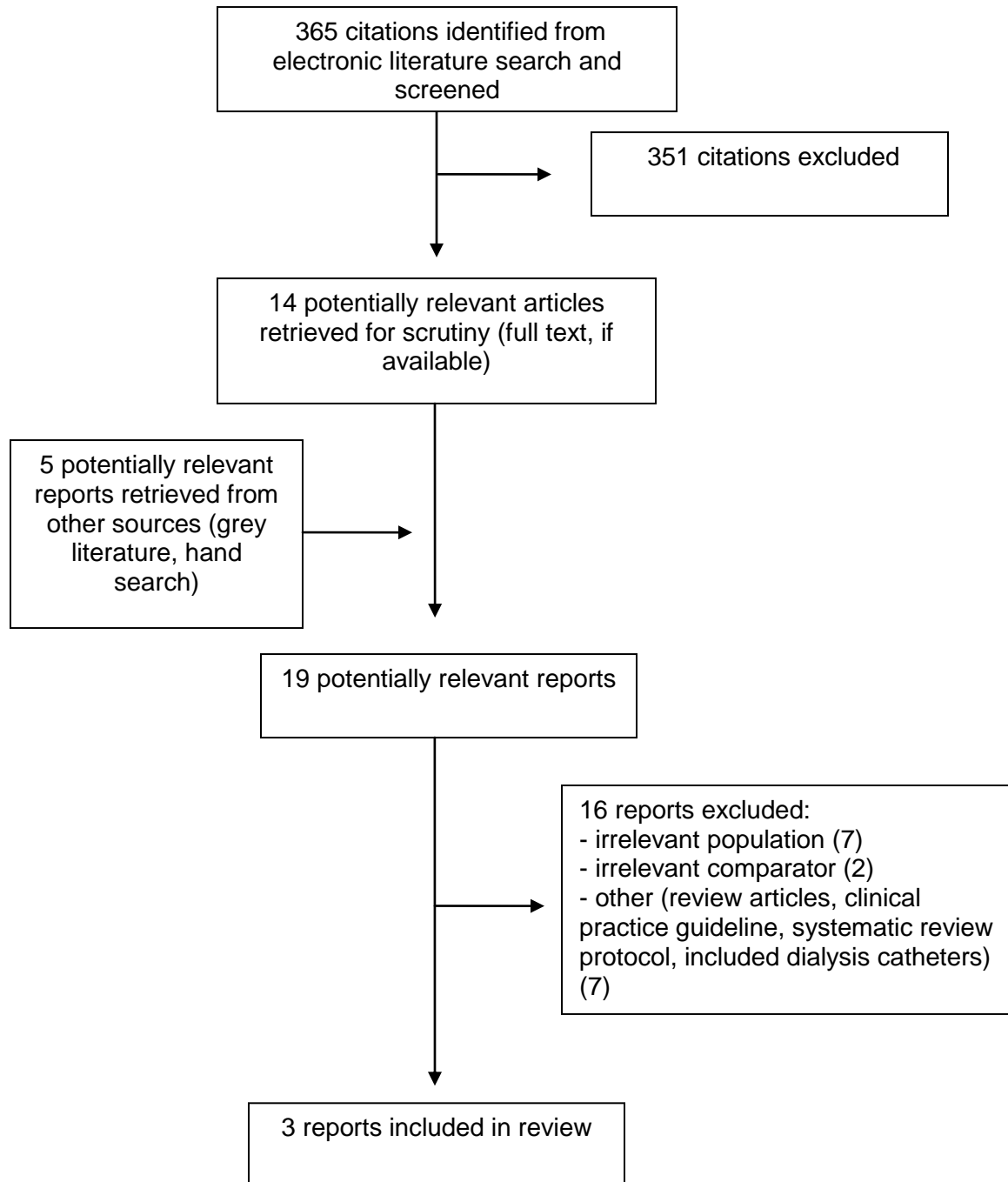
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APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Studies

First Author, Publication Year, Country	Study Design and Length	Patient Characteristics	Intervention	Comparator	Clinical Outcomes Measured
Question 1: Chlorhexidine versus non-chlorhexidine impregnated or coated PICCs					
No evidence identified					
Question 2: Valved versus non-valved PICCs					
Johnston, 2012, United Kingdom ⁷	RCT Length not reported, but study was discontinued early due to four episodes of hemolysis in the individuals randomized to the Navilyst Medical Vaxcel PICC with PASV	Included patients admitted to ICU only Age ≥ 18 years (average age 57.6 years) 52.9% males	n = 34 Cook medical non-valved Turbo-Flo PICC n = 34 Bard Groshong valved PICC n = 33 Navilyst Medical Vaxcel PICC with PASV	PICCs compared to one another	Primary outcome: occlusion rate Secondary outcomes: total urokinase dose; average urokinase dose per occlusion
Question 3: Saline versus heparin for non-valved (open-end) catheters with neutral displacement caps					
Randomized controlled trial					
White, 2011, United States ⁸	RCT Duration of study was not reported	Pediatric patients with CPP IV catheters (unclear whether they were valved or non-valved, or whether a neutral displacement cap was used) Average age 6.5 years (5.5 years in heparin group; 7.5 in normal saline group)	n = 32 heparin (10 units/1mL) plus 2mL normal saline for a total of 3mL volume, flushed three times daily	n = 30 normal saline (3mL), flushed three times daily	Patency, redness, swelling, clotting, bruising, leakage, patient pain and burning after each flush

First Author, Publication Year, Country	Study Design and Length	Patient Characteristics	Intervention	Comparator	Clinical Outcomes Measured
		Most had a 22 gauge (55.7%) or 24 gauge (41.0%) catheter			
Observational study design					
Cook, 2011, United States ⁹	Before/after study Length: data collected 3 months before and 3 months after switch to normal saline locks	Neonates admitted to NICU (average post-conception age 36.1 weeks Catheters were 24 gauge, ¾ inch in length (unclear whether they were valved or non-valved, or whether a neutral displacement cap was used)	n = 34 heparinized saline (4 units/0.4mL every 4 hours)	n = 36 normal saline (0.4mL every 4 hours)	Duration of patency, occlusion, and adverse effects from heparin (cerebral hemorrhage, thrombocytopenia, thrombosis)

CPP: capped pediatric peripheral; ICU: intensive care unit; IV: intravenous; NICU: neonatal intensive care unit; PASV: pressure activated safety valve; PICC: peripherally inserted central catheter; RCT: randomized controlled trial

APPENDIX 3: Critical Appraisal of Included Studies

First Author, Publication Year	Strengths	Limitations
Question 1: Chlorhexidine versus non-chlorhexidine impregnated or coated PICCs		
No evidence identified		
Question 2: Valved versus non-valved PICCs		
Johnston, 2012 ⁷	<ul style="list-style-type: none"> Interventions were clearly described. PICC insertion was standardized across the three intervention groups. Outcomes of occlusion and urokinase use were clearly predefined. Baseline characteristics of the study participants were clearly described. No losses to follow up. 	<ul style="list-style-type: none"> Process for randomization was not reported. Staff and study personnel were not blinded to treatment group. The study was powered to detect an absolute risk reduction of 20%, which required 300 total participants (100 in each group). The study only randomized 102 patients in total because the study was discontinued early due to four episodes of hemolysis in patients who received the Navilyst PASV PICC. As a result, it is likely the study is underpowered to detect a difference between the interventions. Study included adults admitted to ICU only, therefore it is unclear whether the results of the study are generalizable to other populations.
Question 3: Saline versus heparin for non-valved (open-end) catheters with neutral displacement caps		
Randomized controlled trial		
White, 2011 ⁸	<ul style="list-style-type: none"> Random assignment of heparin and normal saline. Characteristics of patients included in the study were clearly described. Intervention and comparator were clearly described. Main findings of the study were clearly described. No losses to follow up. 	<ul style="list-style-type: none"> Process for randomization was not reported. Staff and study personnel were not blinded to treatment group. No sample size calculation completed, therefore it is unclear whether the study was large enough to detect a difference. Some outcomes were subjective (pain, burning) and it is unclear how this information was gathered from the study participants. Evaluated children only, therefore results are not generalizable to infants or adults.
Observational study design		
Cook, 2011 ⁹	<ul style="list-style-type: none"> Characteristics of patients included in the study were 	<ul style="list-style-type: none"> Participants were not randomized to heparin or normal saline.

First Author, Publication Year	Strengths	Limitations
	<p>clearly described.</p> <ul style="list-style-type: none"> • Intervention and comparator were clearly described. • No losses to follow up. • Study authors adjusted for potential confounding variables including birth weight, gestational age, and location of catheter (upper or lower extremity). 	<ul style="list-style-type: none"> • Outcome results were collected by a chart review – unclear if adverse events were documented differently before and after switching heparin to saline. • Staff and study personnel were not blinded to treatment group. • No sample size calculation completed, therefore it is unclear whether the study was large enough to detect a difference. • Study included neonates admitted to NICU only, therefore it is unclear whether the results of the study are generalizable to other populations.

NICU: neonatal intensive care unit; PASV: pressure activated safety valve; PICC: peripherally inserted central catheter

APPENDIX 4: Results of Included Studies

First Author, Publication Year	Main Study Findings	Authors' Conclusions
Question 1: Chlorhexidine versus non-chlorhexidine impregnated or coated PICCs		
No evidence identified		
Question 2: Valved versus non-valved PICCs		
Johnston, 2012 ⁷	<ul style="list-style-type: none"> Overall, 76 occlusions per 1000 catheter days (95% CI: 61 – 95). No significant difference found for occlusion rates at any time during the study period: <ul style="list-style-type: none"> Cook: 13/34 (38%) Groshong: 13/34 (38%) PASV: 9/33 (27%) No statistical difference found in total dose of urokinase used to treat occlusions or mean urokinase dose per PICC occlusion. 	<ul style="list-style-type: none"> “Our randomized pragmatic study in intensive care patients failed to show any significant difference in occlusion rate between valved PICCs (Groshong and PASV) and an open ended non-valved PICC (Cook).” – page 4 “Our conclusion that there are no differences in occlusion rate between the different valve technologies may represent a lack of statistical power to detect clinically relevant differences because we did not recruit the entire number of patients specified by the power calculation.” – page 5
Question 3: Saline versus heparin for non-valved (open-end) catheters with neutral displacement caps		
Randomized controlled trial		
White, 2011 ⁸	<ul style="list-style-type: none"> No statistically significant difference in redness, swelling, blood in catheter, bruising, leakage, pain, burning, clotting, or infiltration in children randomized to heparin compared to those randomized to normal saline. Most common negative effects in both groups were pain (34.4% in those who received heparin; 26.7% in those who received normal saline) and burning (34.4% in those who received heparin; 23.3% in those who received normal saline) 	<ul style="list-style-type: none"> “Based on the lack of statistically significant differences in negative effects of either heparin or normal saline, it appears that the 2 flushing solutions provide similar results.” – page 267 “This lack of difference supported previous research that normal saline used to flush CPP IV catheters was as effective as, and more cost-effective than, heparin.” – page 268

First Author, Publication Year	Main Study Findings	Authors' Conclusions
Observational study design		
Cook, 2011 ⁹	<ul style="list-style-type: none"> • Duration of patency was significantly longer in neonates who received normal saline (54.45 hours) compared to neonates who received heparin (40.98 hours) (p = 0.02). • No significant difference in occlusion (5 catheters in the heparin group; 6 catheters in the normal saline group). • No noted adverse effects due to heparin. 	<ul style="list-style-type: none"> • “While the sample size was small, it was found that the NS-flushed catheters remained patent on an average of 13 hours longer than the HS-flushed catheters.” – page 215 • “Further study is indicated that would corroborate or refute these findings since there were no studies that found NS-flushed catheters to last longer than HS flushes. While the results should be viewed with a sense of caution due to small sample size, the outcomes were encouraging.” – page 215

CI: confidence interval; CPP: capped pediatric peripheral; HS: heparinized saline; IV: intravenous; NS: normal saline; PASV: pressure activated safety valve; PICC: peripherally inserted central catheter