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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Central Venous Access Devices (CVADs) and Peripherally Inserted Central Catheters (PICCs) for Adult and Pediatric Patients: A Review of Clinical Effectiveness and Safety

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Context and Policy Issues

Central venous access devices (CVADs) or central venous catheters (CVCs) are devices that are inserted into the body through a vein to enable the administration of fluids, blood products, medication and other therapies to the bloodstream. CVADs can be inserted into the subclavian or jugular vein (implanted ports, tunneled catheters), or can be inserted into one of the peripheral veins of the upper extremities, called peripherally inserted central catheters (PICCs).[1]

While generally safe, CVADs can be associated with complications such as catheter occlusion or rupture, venous thrombosis, and bloodstream infection.[1] A number of strategies have been used to minimize the occurrence of CVAD- and PICC-associated complications such as antimicrobial-impregnated lines for prevention of infection, or addition of a valve (valved catheters) to prevent occlusion by preventing reflux of blood into the catheter.[2] Flushing the catheters with saline or heparin – an agent with anticoagulant activity - have been used to reduce clot formation and occlusion of the catheters.

This Rapid Response report is an update of the previous CADTH reports which found no difference in terms of frequency of occlusion in patients who had a valved versus a non-valved PICCs, and similar patency between heparin and saline use for CVCs.[3,4] This report aims to review the evidence on the clinical effectiveness of valved versus non-valved PICCs, and saline versus heparin flushing in the maintenance of CVADs patency and reduction of complications.

Research Questions

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

2. What is the clinical evidence for the use of saline versus heparin for flushing of any central venous access devices (CVADs) for adult and pediatric populations?

Key Findings

Limited evidence from one RCT showed that there was no difference between valved and non-valved peripherally inserted central catheters (PICCs) in the incidence of occlusion of the catheters or PICC-related blood stream infection and complications.

A meta-analysis on data from 10 RCTs showed that in general heparin saline and normal saline had similar efficacy in maintaining the patency of central venous catheters, but patency with heparin use is statistically better than normal saline when placement was 30 days or less. Differences between heparin and saline use in secondary outcomes such as heparin-induced thrombocytopenia, hemorrhage, central venous thrombosis and catheter-related bloodstream infection were not statistically significant.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, 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 filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2012 and March 29, 2017.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult and pediatric populations, inpatient and outpatient populations
Intervention	Valved PICCs Saline flush for CVADs
Comparator	Non-valved PICCs Heparin flush for CVADs
Outcomes	Infection rate, air embolus, bleeding, occlusion/blockage Occlusion, infection rate/ risk of infection
Study Designs	Heath technology assessments, systematic reviews (SRs), meta-analyses, randomized controlled trials (RCTs), non-RCTs.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2012. Studies included in the selected systematic reviews were also excluded.

Critical Appraisal of Individual Studies

The included clinical study and SR were assessed using the Downs and Black[5] and AMSTAR[6] checklists, respectively. Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described, narratively.

Summary of Evidence

Quantity of Research Available

A total of 133 citations were identified in the literature search. Following screening of titles and abstracts, 114 citations were excluded and 19 potentially relevant reports

from the electronic search were retrieved for full-text review. No potentially relevant publication was retrieved from the grey literature search. Of these potentially relevant articles, 17 publications were excluded for various reasons, while two publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Characteristics of the included studies are detailed in Appendix 2.

The 2014 study comparing valved to non-valved PICCs is a randomized controlled trial conducted in Italy.[7] It included 180 adult oncologic patients randomized to three groups: PICCs with a Solo-2 proximal valve (Bard); PICCs with a PASV (Pressure Activated Safety Valve) proximal valve (Navilyst); and non-valved PICCs (Medcomp). The primary outcome was incidence of occlusion of the catheters. Secondary outcomes were PICC-related blood stream infection and complications (obstruction, rupture).

The 2017 study comparing heparin saline to normal saline for maintaining the patency of CVCs is a systematic review/meta-analysis conducted in China.[8] It included 10 RCTs (7875 subjects) with average duration of follow-up from 1 to 400 days, concentrations of heparin from 10 IU/ml to 5000 IU/ml, and average patient age from 5.1 to 68.43 years. The primary outcome was patency of CVCs (risk of occlusion). Secondary outcomes were heparin-induced thrombocytopenia, hemorrhage, central venous thrombosis, catheter-related blood stream infection.

Summary of Critical Appraisal

Details of the critical appraisal of the included studies are presented in Appendix 3.

The included study[7] was a randomized controlled trial. It described clearly the hypothesis, method of selection from source population and representation**,** main outcomes, interventions, patient characteristics, and main findings. The study had sufficient power to detect a clinically important effect. Estimates of random variability and actual probability values were not provided.

The included systematic review[8] provided an a priori design**,** had duplicate independent study selection and data extraction procedures in place, performed a comprehensive literature search, provided a list of included studies and study characteristics, conducted publication bias and quality assessment of included studies which was used in formulating conclusions. The SR included studies with a wide range of follow-up periods and anticoagulant concentrations that may have affected the findings; this clinical heterogeneity may not justify pooling data from the studies. Conflict of interest was stated. A list of excluded studies was not provided.

Summary of Findings

The main findings of the included studies are presented in Appendix 4.

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

An RCT compared valved to non-valved PICCs on 180 adult oncologic patients[7] randomized to three groups: PICCs with Solo-2 proximal valve; PICCs with PASV (Pressure Activated Safety Valve) proximal valve; and non-valved PICCs. Mean PICC days were 56, 64 and 65 for the Solo valve group, PASV group and the no-valve group, respectively. The primary outcome was incidence of occlusion of the catheters. Secondary outcomes were PICC-related blood stream infection and complications (obstruction, rupture).

No complications were found at insertion. There were no PICC-related bloodstream infections or dislocations in any group. There were five cases of transient occlusion which were evenly distributed among the groups, and one case of irreversible occlusion in the Solo valve group. There were four episodes of asymptomatic peripheral venous thrombosis which were evenly distributed among the groups and one episode of symptomatic, severe central vein thrombosis in the PASV group. Difficulties with gravity infusion were reported in 31% of PICCs in the Solo valve group (19/61), in 65% of PASV group (39/60) and 0% in the no-valve group. Three PICCs in the Solo valve group were complicated by rupture of the intravascular tract during pump infusion. Five PICCs were removed because of complications, four in the Solo valve group (one obstruction; three ruptures) and one in the PASV group (central venous thrombosis). *P* values were not reported in any outcomes. The authors concluded that there were no clinical advantages of valved vs non-valved PICCs.

What is the clinical evidence for the use of saline versus heparin for flushing of any central venous access devices (CVADs) for adult and pediatric populations?

A systematic review/meta-analysis compared heparin saline to normal saline for maintaining the patency of CVCs.[8] It included 10 RCTs (7875 subjects) with average duration of follow-up from 1 to 400 days, concentrations of heparin from 10 IU/ml to 5000 IU/ml, average age from 5.1 to 68.43 years. The primary outcome was patency of CVCs (risk of occlusion). Secondary outcomes were heparin-induced thrombocytopenia, hemorrhage, central venous thrombosis, catheter-related blood stream infection.

In general, the risk of occlusion for heparin or saline use was similar (relative risk [RR]: 1.21; 95% confidence interval [CI] 0.91 to 1.61; *P* = 0.186). Differences between heparin and saline use in secondary outcomes such as heparin-induced thrombocytopenia, haemorrhage, central venous thrombosis and catheter-related bloodstream infection were not statistically significant. Subgroup analyses in patients with short vs long term CVC placement found no statistical difference between heparin and saline use for maintenance of catheter patency in patients with a long-term placement (>30 days). Normal saline however lead to a 1.5 times higher risk of occlusion in patients with CVC placement ≤30 days than heparin (RR: 1.52; 95% CI 1.02 to 2.27; *P* = 0.041). The authors concluded that in general, heparin is not superior to normal saline in reducing CVC occlusion, but heparin use is statistically better than normal saline when CVC placement was less than 30 days.

Limitations

Statistical significance between the differences in outcomes was not reported in the included RCT. The SR included studies with a wide range of follow-up periods and

anticoagulant concentrations that may have affected the findings due to clinical and methodological heterogeneities.

Conclusions and Implications for Decision or Policy Making

Limited evidence showed that there was no difference between valved and non-valved PICCs in the incidence of occlusion of the catheters or PICC-related blood stream infection and complications (obstruction, rupture). Meta-analysis from data from 10 RCTs showed that, in general, heparin saline and normal saline had similar efficacy in maintaining the patency of CVCs, but patency with heparin use is statistically better than normal saline when placement was 30 days or less. Differences between heparin and saline use in secondary outcomes such as heparin-induced thrombocytopenia, hemorrhage, central venous thrombosis and catheter-related bloodstream infection were not statistically significant. The findings from this review are in agreement with previous CADTH reports which also found no difference in terms of frequency of occlusion in patients who had a valved versus a non-valved PICCs, and similar patency between heparin and saline use for CVCs, though the previous report did not have information specific to the <30 day subgroup.[3,4]

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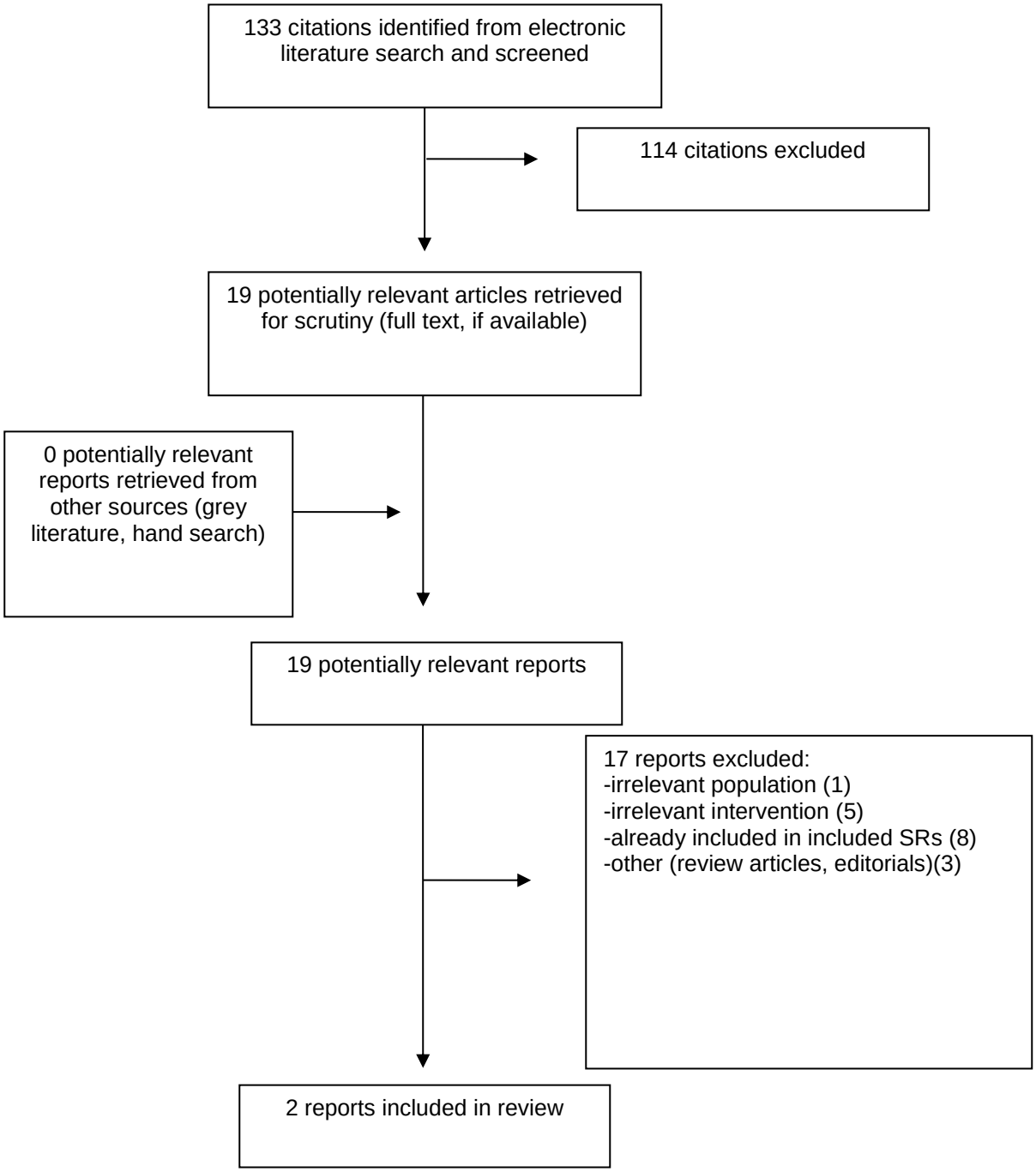
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table A1: Characteristics of Included Clinical Study

First Author, Year, Country	Study Design Study Objectives	Interventions/ Comparators	Patients	Main Outcomes
Pittiruti,[7] 2014, Italy	RCT "Few randomized studies have investigated the impact of valved and non-valved power-injectable peripherally inserted central catheters (PICCs) in terms of incidence of occlusion, infection, malfunction and venous thrombosis" (p 519)	PICCs with Solo-2 proximal valve (Bard) PICCs with PASV (Pressure Activated Safety Valve) proximal valve (Navilyst) Non-valved PICCs (Medcomp)	188 patients. Mean PICC days were 56, 64 and 65 for the Solo valve group, PASV group and the no valve group, respectively *"We enrolled exclusively adult oncologic patients candidate to the insertion of a 4Fr single-lumen PICC for intermittent infusion of chemotherapy drugs for a period not exceeding 4 months"* (p 520)	Primary outcomes: Incidence of occlusion and malfunction of the catheters Secondary outcomes: PICC-related blood stream infection Complications (obstruction, rupture)

PICCs = peripherally inserted central catheters; RCT = randomized controlled trial

Table A2: Characteristics of Included Systematic Review

First Author, Year, Country	Objectives Literature Search Strategy	Inclusion Criteria	Exclusion Criteria	Number of studies included Main Outcomes
Zhong,[8] 2017, China	"The aim of this systematic review and meta-analysis was to assess the efficacy of NS versus HS in the maintenance of the patency of CVCs in adult patients" (p 1) "We systematically searched PubMed, Embase and the Cochrane library databases from the inception to 28 September 2016, using the following terms: "Sodium Chloride", "Saline Solution, Hypertonic", "NaCl", "Heparin", "Catheterization, Central Venous", "Randomized Controlled Trial", etc. (Additional file 3). There was no restriction on language" (p 2)	"Only clinical randomized controlled trials (RCTs) of NS flushing vs flushing with HS solution in adults were included" (p 2)	"Exclusion criteria were (1) age <18 years, and (2) case reports, letters, reviews, case-control studies and cohort studies, or non-human studies" (p 2)	10 RCTs (7875 subjects) Primary outcomes: Patency of CVCs (risk of occlusion) Secondary outcomes: Heparin-induced thrombocytopenia, hemorrhage, central venous thrombosis, catheter-related blood stream infection

Appendix 3: Critical Appraisal of Included Publications

Table A3: Strengths and Limitations of Clinical Studies using Downs and Black[5]

Strengths	Limitations
Pittiruti[7]	
• Randomized controlled trial • hypothesis clearly described • method of selection from source population and representation described • main outcomes, interventions, patient characteristics, and main findings clearly described • study had sufficient power to detect a clinically important effect	• estimates of random variability and actual probability values not provided

Table A4: Strengths and Limitations of Clinical Systematic Reviews using AMSTAR[6]

Strengths	Limitations
Zhong[8]	
• a priori design provided • independent studies selection and data extraction procedure in place • comprehensive literature search performed • list of included studies, studies characteristics provided • quality assessment of included studies provided and used in formulating conclusions • assessment of publication bias performed • conflict of interest stated	• list of excluded studies not provided

Appendix 4: Main Study Findings and Author's Conclusions

Table A4: Summary of Findings of Included Studies

<table>
<tr><th>Main Study Findings</th><th>Author's Conclusion</th></tr>
<tr><td colspan="2">Pittiruti,[7] 2014</td></tr>
<tr><td>

Primary outcomes

	Solo Valve (n =61)	PASV (n = 60)	No valve (n = 59)
Irreversible occlusions	1	0	0
Irreversible occlusions	2	1	2
PWO	1	0	1
Difficulty with gravity infusion	19 (31%)	39 (65%)	0
Removed for occlusion	1	0	0

Secondary outcomes

	Solo Valve (n =61)	PASV (n = 60)	No valve (n = 59)
Infection (CRBSI)	0	0	0
Symptomatic Thrombosis	0	1	0
Asymptomatic Thrombosis	2	1	1
Dislocation	0	0	0
Intravascular rupture	3	0	0
Removal due to rupture	3	0	0

</td><td>

"We found no clinical advantages of valved vs. non-valved PICCs" (p 519)

</td></tr>
<tr><td colspan="2">Zhong,[8] 2017</td></tr>
<tr><td>

Quality assessment: the majority (80%) of the included studies had low risk of bias.

Publication bias: there was a risk of publication bias (funnel plot)

Primary outcomes(number of patients; Relative risk RR; 95% CI)

Risk of occlusion with saline use vs heparin use saline(n = 7875)
RR: 1,21 (95% CI 0.91 to 1.61) *P* = 0.186
Risk of occlusion is similar between normal saline and heparin use.

Secondary outcomes (number of patients; Relative risk RR; 95% CI)

Heparin-induced thrombocytopenia (n = 1263)
RR: 1.33 (95% CI 0.09 to 18.54) *P* = 0.834

Haemorrhage (n = 439)
RR, 0.75; 95% CI 0.32 to 1.74; *P*= 0.501)

Central venous thrombosis (n = 1512)
RR: 0.81 (95% CI 0.50 to 1.31) *P* = 0.381)

</td><td>

"Based on the results of this meta-analysis, HS is not superior to NS in reducing CVCs occlusion. But in the short term, the use of HS is slightly superior to NS for flushing catheters from a statistical point of view" (p 1)

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</table>

Table A4: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion
CRBSI (n = 1630) RR: 0.84 (95% CI 0.11 to 6.71) *P* = 0.871 **Subgroup analysis** Risk of occlusion with saline use vs heparin use (number of patients; Relative risk RR; 95% CI) Catheter placement > 30 days(n = 6589) RR: 0.97 (95% CI 0.76 to 1.23) *P*= 0.796) Normal saline and heparin are similar in risk of occlusion. Catheter placement ≤ 30 days(n = 1286) RR: 1.52 (95% CI 1.02 to 2.27) *P* =0.041) Normal saline use increased the risk of occlusion by 1.5 times as compared to heparin.	

CRBSI = Catheter-related blood stream infection; PASV = Pressure Activated Safety Valve; PICCs = peripherally inserted central valves; PWO = Partial withdrawal occlusion