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A Comparison of the Effectiveness of Using Heparinised Saline versus 0.9% Sodium Chloride to Prevent Central Venous Catheter Occlusion in People with a Totally Implantable Venous Access Device (TIVAD's): A Systematic Review

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Abstract

Historically in the UK, unfractionated heparin (heparinised saline), has been used to reduce the occlusion rate of central venous catheters (CVCs) used for renal dialysis. This practice was carried across to other CVC's, including totally implantable venous access devices (TIVAD's). However, heparin use carries risks such as infection, thrombocytopenia, bleeding and interactions with other drugs. The aim of this systematic review was to determine the effectiveness of heparinised saline versus 0.9% sodium chloride to prevent TIVAD occlusion in people with cystic fibrosis (CF). We included 6 databases and 4 trial registry platforms. Due to a lack of studies within the CF population, participants of included studies were people with a TIVAD and applicability to the CF population was reviewed. The primary outcome measure was catheter occlusion rate. Eight studies were included, four RCTs, three retrospective non-randomised trials and one observational study. Statistical pooling and subgroup analysis was not possible. All eight of the studies concluded there was no statistically significant difference in occlusion rates and that heparin was not superior to 0.9% sodium chloride. Secondary outcomes showed no statistical difference in line infection rates or complications. There was one incident of heparin induced thrombocytopenia. Our review found no reliable evidence that 0.9% sodium chloride is inferior to heparinised saline in the maintenance of TIVAD patency. In view of the risks associated, 0.9% sodium chloride offers a potentially safer, equally effective, cost saving alternative.

Keywords

Cystic Fibrosis, Heparin, 0.9% Sodium Chloride, TIVAD, Port, Occlusion

1. Introduction

Totally implantable venous access device (TIVAD) were introduced in the late 1970's to aid the long-term administration of intravenous therapies such as chemotherapeutic agents, antibiotics, and total parental nutrition [1]. They are used in both children and adults across a variety of diseases, however most commonly in oncology, cystic fibrosis (CF) and those requiring total parental nutrition (TPN). The number of people with TIVADs in the UK is not well documented, with most studies focusing on small cohorts in differing disease groups. The use of TIVAD's in people with CF was first documented in 1986 [2]. The largest study to date, conducted in 2004, focused on the follow up of 452 people with CF having a TIVAD inserted [3]. This study found that complication rates in people with CF compared favorably to other populations studied, and that occlusion (21%) was in fact lower than reported in patients with malignant disease or sickle cell disease, echoed by Royle *et al.,* study where occlusion occurred in 20% of people with CF [4].

With increased knowledge of its structure and properties, the second half of the century saw the use of unfractionated heparins in the use of prevention of venous thrombosis and central venous catheter (CVC) occlusion in renal dialysis. When CVCs, including TIVAD's, were used for other indications, the practice of using unfractionated heparinised saline was carried across [5] [6]. Heparin inhibits blood coagulation by binding to protease inhibitor antithrombin, inactivating the protease factors of the coagulation cascade. Heparin inhibits the actions of thrombin, preventing it from cleaving fibrinogen and so inhibiting the formation of fibrin. However, heparin is not a thrombolytic, so does not digest fibrin which has already formed [7]. The use of heparin does not come without risks. It is associated with the promotion of biofilms, which increases the risk of a bloodstream infection [8]-[12]. Studies have found that biofilms quickly develop once a CVC is inserted and bacteria in this biofilm can be very difficult to eradicate without line removal [8]-[13]. Due to the morbidity and mortality associated with catheter related bloodstream infections (CRBI's) they are of significant concern for people requiring CVC's [13] [14]. This is of particular importance in recent years due to the increasing rates of CRBI's nationally and growing resistance to the antimicrobials used to treat them [8] [10] [15] [16]. The European Society for Clinical Nutrition and Metabolism no longer recommends heparinised saline in CVCs used for parenteral nutrition (TPN), due to the increased risk of catheter-related bloodstream infections [17].

A further associated risk is heparin induced thrombocytopenia (HIT), a severe life and limb-threatening complication in which the immune system causes platelets to clot in the presence of heparin, resulting in low platelet levels. 1–5% of peo-

ple administered heparin in any form or dose will develop HIT with thrombocytopenia [18], with unfractionated heparin having a ~10-fold greater risk of HIT than low molecular weight heparin [19] [20]. Even administration at low doses, such as those used to flush CVCs, can lead to antibody formation or HIT itself [21]-[25].

In addition to this risk, there have been cases of unintentional systemic anticoagulation when using heparin flushing for CVC's maintenance, particularly in children [26]-[30].

Furthermore, heparin, which is negatively charged, may be physically incompatible with positively charged medications, such as aminoglycoside antibiotics. If they are mixed during infusion then precipitation may occur, although the evidence base for guidelines recommending avoidance of mixing is limited [31] [32].

A further consideration, as heparin is derived from porcine products (pig intestinal mucosa), its use in some religious faiths, vegans and vegetarians, requires additional consideration and informed consent must be obtained. Religious leaders only accept the use of these products if there is no alternative drug and the treatment is considered life prolonging [33] [34].

As a consequence of adverse incidents, including dosing errors and HIT, in 2008, the National Patient Saftey Agency (NPSA) recommended minismising the use of heparin flush solutions in all CVCs and discontinuing its use in any peripheral intravenous catheters [35]. A Cochrane review concluded there was insufficient evidence to determine the effects of intermittent flushing of heparin versus normal saline to prevent occlusion in long term central venous catheters in infants and children as their review only found three trials, with a total of 245 participants [36]. However, pediatric guidelines state that, in the absence of convincing prospective pediatric studies, prophylaxis use of heparin for CVC occlusion prevention is not recommended in children [37] [38]. A Cochrane review in 2013, which included papers from a variety of adult settings with mixed line type and duration, concluded that 0.9% saline had comparable efficacy to heparinised saline and offered a cost saving [39]. A further consensus document, collaborated by expert review of systematically collected evidence across mixed adult cohorts and settings, also concluded 0.9% saline was as appropriate as heparinised saline [40]. Despite these reports a survey of national CF centers in the UK [41] in 2017 highlighted that the majority of centers had not changed practice in line with the recommendations [35] [39]. Of the centers surveyed, 90% use heparinised saline after intra-venous (IV) antibiotics administered through a totally implantable venous access device (TIVAD); 70% use heparinised saline after intravenous antibiotics administered through a peripherally inserted central catheter (PICC/midline); and 100% use heparinised saline as a 4 - 6 weekly TIVAD lock. Informal discussion with these centers revealed perseverance with historical practice rather than resistance to change [41]. The study also highlighted a reluctance to rely on the evidence as the reviews omitted papers with people with CF and did not include long term CVCs, particularly TIVADs [39]. Despite further evidence supporting

the use of 0.9% sodium chloride in place of heparinised saline in mixed line type studies [42]-[44], including a further systematic review in children [45], and European CF guidelines stating there is no clear evidence to support the use of anticoagulants in TIVAD's [46], practice within CF has remained unchanged. A TIVAD specific review in 2021 yielded limited studies [47]. Therefore, in view of possible risks associated with heparin use and ongoing research in this area, the aim of the systematic review was to assess the effectiveness of 0.9% sodium chloride versus heparinised saline to prevent TIVAD occlusion, and to discuss whether such research was applicable to the CF population.

2. Methods

2.1. Design

A systematic review protocol was prospectively written and published on the PROSPERO register (ref 147317). This systematic review is structured and reported according to the PRISMA guidelines [48].

2.2. Eligibility Criteria

Our original intention had been to focus only on those with CF however, due to the lack of studies within this population, it was necessary to include people with a TIVAD who have other conditions, predominately oncological. People with cancer and those with CF are both at increased risk of intravascular thrombosis. In those with CF this is due to inflammation and impaired clotting due to vitamin K deficiency [49] [50]. In those with cancer, the increased risk is due to inflammation, pro-thrombotic substances and blood vessel damage caused by cancer and its treatment [51] [52]. Those immunosuppressed by cancer treatments will be at greater risk of line infection [53]. The applicability of results between different populations is discussed in greater depth in the results section.

Why this final review differs from the proposal registered on PROSPERO

The original inclusion criteria of any CVCs over 3 months in duration was discarded as during the review evidence showed significant variations in line care and treatment from that of TIVAD's, and it was therefore felt this data was not transferable.

Age restrictions were also removed from the original proposal as data suggesting heparin use and occlusions rates in paediatrics differed from adults lacked validity and were not supported by wider evidence [36].

There was a further deviation from protocol due to accessibility of the JBI system and GRADE assessment of bias. CASP was used as an alternative.

2.3. Information Sources

The databases used in this review were: MEDLINE, CINAHL, BNI, AMED, EMBASE and the Cochrane Library. Registers: PROSPERO was also included. The search for unpublished studies included: the World Health Organization International Clinical Trials Registry Platform, the Cochrane Central Register of Con-

trolled Trials (CENTRAL) and ClinicalTrials.gov. Only studies published in the English language were considered for inclusion. No publication date restrictions were applied.

2.4. Search Strategy

The search strategy used both MeSH terms and keywords. The articles were searched using the keywords heparin, heparinised, central venous catheter, central venous access device, CVAD, venous access device, totally implantable venous access device, catheterisation peripheral, Implantable venous access device, IVAD, port, 0.9% sodium chloride, normal saline, saline solution (see Table 1). The searches were conducted by CW and JML.

Table 1. Search strategy.

	Search Term
1	Heparin
2	"HEPARIN/OR LOW-MOLECULAR WEIGHT"
3	Heperani*
4	1 OR 2 OR 3
5	"Central Venous Catheters"
6	CVC
7	"Central Venous Access Device"
8	CVAD
9	Catheterisation, Central
10	"Implantable venous access device"
11	IVAD
12	"Totally implantable venous access device"
13	TIVAD
14	port-a-cath.
15	port
16	5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15
17	"0.9% Sodium Chloride"
18	"normal saline"
19	"Saline solution"
20	17 OR 18 OR 19
21	4 AND 16 AND 20

2.5. Study Selection

Both experimental and quasi-experimental study designs were considered, includ-

ing randomized controlled trials, non-randomized controlled trials, before-and-after studies, and interrupted time-series studies. In addition, observational studies, including prospective and retrospective cohort studies, case-control studies and cross-sectional studies were considered for inclusion. This review also considered descriptive observational study designs, including case series, individual case reports and descriptive cross-sectional studies for inclusion. Studies in both adults and paediatrics are included in this review.

2.6. Outcomes

The outcome measures considered were: Catheter occlusion rate (defined as the inability to infuse fluids) and line replacement/manipulation. Additional outcomes included: Infection; central venous catheter-related thrombosis; abnormal coagulation profile; allergic reaction to heparin; heparin-induced thrombocytopenia, haemorrhage and mortality.

2.7. Data Collection Process

The studies retrieved during the searches were screened for relevance, and those identified as being potentially eligible for inclusion were fully assessed against the inclusion/exclusion criteria. Data were extracted from the papers by two independent reviewers (CW and JML). The data included the interventions, populations, study methods and outcomes of significance to the review question and specific objectives. Disagreements were discussed and solved with a third reviewer (DDD). Missing data were requested from authors.

2.8. Risk of Bias in Individual Studies

Risk of bias was assessed by CW and JML using Critical Appraisal Skills Programme (CASP) randomised control trial and cohort study checklists [54] [55].

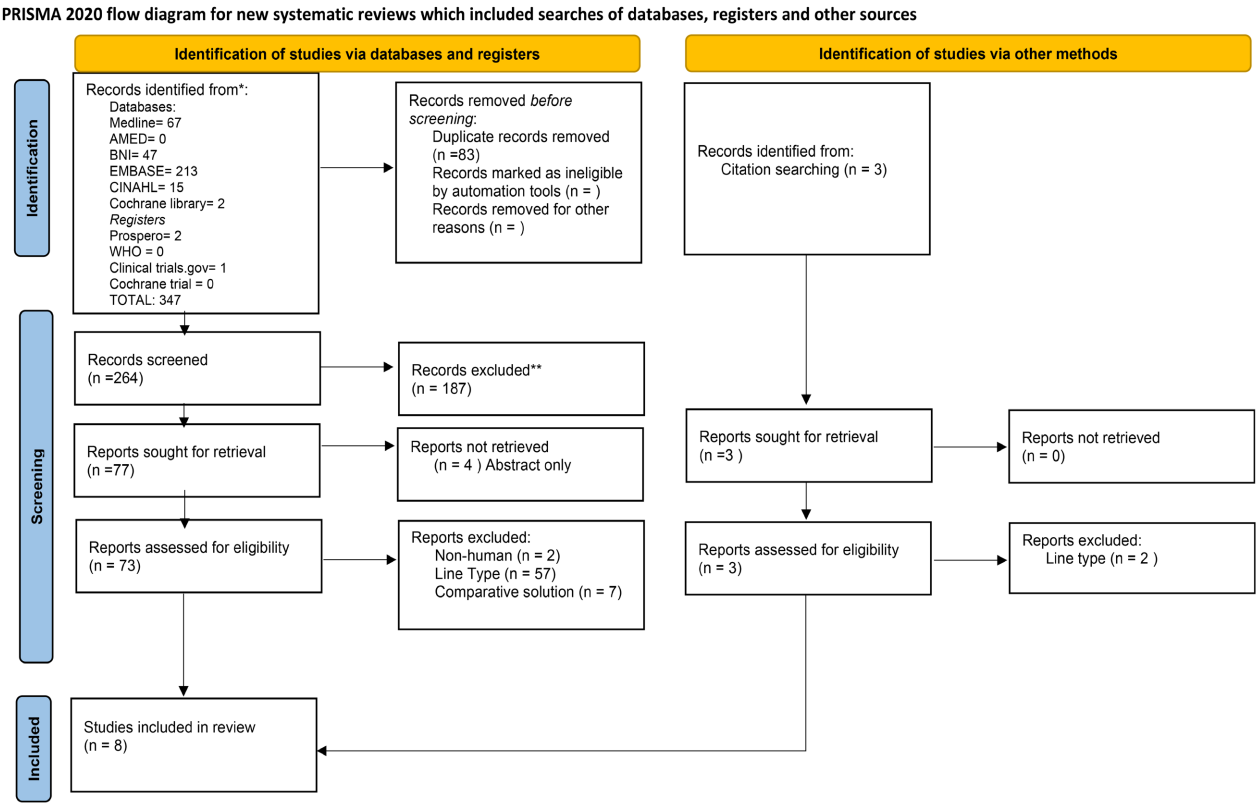
2.9. Synthesis of Results

Statistical pooling and subgroup analysis was not possible due to the differing interventions and heterogeneity of the studies. Therefore, findings are presented in narrative form including tables to aid data presentation.

3. Results

3.1. Study Selection

Database searches revealed 347 articles and 3 from citation searching (**Figure 1**). After removing duplicates (n = 83), 264 titles and abstracts were reviewed in the screening phase, and 187 articles were removed. 4 were abstract only, leaving 76 articles (n = 73 search, n = 3 citation searching) for full-text assessment in the eligibility phase. We excluded 68 articles based on the study design; non-human; line type; comparative diluent; unable to abstract data (**Figure 1**). The systematic review included 8 articles [56]-[63].



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Figure 1. Systematic review Flowchart Results.

3.2. Study Characteristics

Of the final eight papers retrieved, three papers were retrospective non-randomised trials [56] [59] [60], one was a descriptive observational study (before-and-after) [61], and four were randomised controlled trials (RCT) [57] [58] [62] [63] (see **Table 2**). All papers compared the use of 0.9% sodium chloride with heparinised saline in TIVADs, however dose and volumes varied. Occlusion rate was the primary outcome measure for all papers, methods to assess this also varied. All papers were set in oncology. Ullman was able to provide TIVAD data from their study, the extracted data is included in this review [62].

Study size varied from 22 to 862 participants, with a total number of 3221 study participants.

All papers were within cancer care, with average participant age ranging from 5 - 62.7 years. Primary outcome for all papers was occlusion, however this was defined and assessed differently in each study. Meta-analysis was not possible due to heterogeneity of interventions and outcome assessments.

3.3. Risk of Bias within Studies

Overall risk of bias was moderate, with the main limitation for all studies being reporting of blinding/blinding and each group receiving the same care.

Table 2. Study characteristics.

Author/ Country/Year	Type	Area	Participants	Av age	Disease type	Control	Intervention	F/U Duration (days)	Primary Outcome	Secondary Outcome
Bertoglio *et al.*, Italy, 2012 [56]	RNRT	Onc.	313/297	divided age groups > 60 <60	Cancer	10 mL 0.9% SC	10 mL 0.9% SC + 500 u HS (?volume)	413 days (med)	Irreversible occlusion, was defined by the failure of 3 different consecutive attempts to restore catheter patency	catheter-related infection, local infection, catheter rupture, or skin erosion
Goosen *et al.,* Belgium, 2013 [57]	RCT	Onc.	404/398	55.8	Cancer	10 - 20 ml 0.9% SC	10 - 20 ml 0.9% SC + 3 ml HS (100 u/ml)	180	Withdrawal occlusion at access (*i.e.* inability to aspirate blood while injection is easy)	Catheter-related bacteraemia within 180 days, duration of catheter
Dal Molin *et al.,* Italy, 2015 [58]	RCT	Onc.	203/212	62.7	Cancer	20 ml 0.9% SC + 5 ml 0.9% SC	20 ml 0.9% SC + 5 ml HS (50 u/ml)	231	Withdrawal occlusion, defined when fluids can be flushed freely but blood cannot be withdrawn - total occlusion, defined as impossibility to flush and draw blood	Catheter infection, thrombus, extravasation
Brito *et al.,* Brazil, 2018 [59]	RNRT	Onc.	592/270	53	Cancer	1.5 ml 0.9% SC	1.5 ml saline solution 0.9% containing HS at a concentration of 100 IU/ml	399	Occlusion (absence of flow and reflux), (2) reflux dysfunction (normal flow without reflux), and (3) flow dysfunction (abnormal flow and abnormal reflux).	
Egnatios & Gloria, USA, 2021 [60]	RNRT	Onc.	37/37 (same pts)	62.3	Cancer	HS 500 u ?volume	?10 ml 0.9%SC	60	Occlusion rates determined by alteplase orders	
Hoffman & Fischer-Cartlidge, USA, 2022 [61]	Observational study	Onc.	?	?	Cancer	0.9% SC ?volume	10 mL of 0.9% SC + 500 u HS ?volume	365	Alteplase usage	
Ullman, Amanda J*et al.* Australia, 2022 [62]	RCT	Onc.	11-Nov	5	Cancer Paeds	0.9% SC 10 ml	HS 100 U/mL; 2 ml	42	Occlusive events, described proportionally and per 1000 catheter days, and assessed using the Catheter Injection and aspiration classification system	Use of thrombolytic agents, CVAD fracture,27 venous thrombosis, CABSI, medication error, and differences in direct healthcare costs.
Pelegan *et al.* USA, 2022 [63]	RCT	Onc.	222/214	59.2	Cancer	20ml SC + 5 ml of HS (100 units/ml)	20ml SC	365	Occurrence of first complete occlusion. Occurrence of first partial occlusion. Frequency with which alteplase (CathFlo) has to be utilised to resolve an occlusion	Central Line-Associated Blood Stream Infection (CLABSI) Develops complication related to HS HIT Other HS allergy

Key: RCT - Randomised control trial, RNRT - Retrospective randomised control trial, Onc - Oncology, SC - 0.9% sodium chloride, HS - Heparinised saline, Med - median.

Flushing volumes varied in four of the eight studies heparinised saline was in addition to a 0.9% sodium chloride flush, resulting in an increased total volume [56] [57] [62] [63]. Evidence suggest this reduces the risk of occlusion [64]. Two papers [60] [61] did not state volumes. Two Papers [58] [59] maintained consistent volumes in both groups, however one study [59] used 1.5ml, which challenges the validity of techniques as pulsatile flushing would be difficult to achieve at low volumes.

Education/training

Six of the eight studies [56]-[58] [60] [62] [63] discussed staff training and flush delivery with standardisation across the groups. Two studies [59] [61] omitted this information.

The risk of bias in the included studies is summarized in Table 3 and Table 4.

Table 3. CASP critical appraisal skills programme RCT checklist.

	Goosen	Molin	Ullman	Pelegan
Did the study address a clearly focused research question?	Y	Y	Y	Y
Was the assignment of participants to interventions randomised?	Y	Y	Y	Y
Were all participants who entered the study accounted for at its conclusion	Y	Y	Y	?
Were the participants "blind" to intervention they were given	?	Y	Y	Y
Were the investigators "blind" to the intervention they were giving to participants?	?	Y	Y	?
Were the people assessing/analysing outcome/s "blinded"?	?	?	N	N
Were the study groups similar at the start of the randomised controlled trial?	Y	Y	Y	Y
Apart from the experimental intervention, did each study group receive the same level of care (that is, were they treated equally)?	N	Y	Y	Y
Were the effects of intervention reported comprehensively?	Y	Y	Y	Y
Was the precision of the estimate of the intervention or treatment effect reported?	Y	Y	Y	N
Do the benefits of the experimental intervention outweigh the harms and costs?	Y	N	Y	Y
Can the results be applied to your local population/in your context?	Y	Y	Y	Y
Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?	Y	Y	Y	Y

Table 4. CASP critical appraisal skills programme cohort study checklist.

	Bertoglio	Egnatios	Brito	Hoffman
Did the study address a clearly focused research question?	Y	Y	Y	Y
Was the cohort recruited in an acceptable way?	Y	Y	N	?
Was the exposure accurately managed to minimise bias?	N	N	N	?
Was the outcome accurately managed to minimise bias?	Y	N	N	?
Have the authors identified all confounding factors	Y	N	N	N
Have they taken account of confounding factors in the design and/or analysis?	Y	N	N	N
Was the follow up complete?	Y	Y	Y	?
Was the follow up long enough?	Y	N	Y	Y
What are the results of the study?				

Continued

How precise are the results?	Y	Y	Y	?
Do you believe the results?	Y	Y	Y	?
Can the results be applied to your local population/in your context?	Y	Y	Y	Y
Do the results of this study fit with others available evidence?	Y	Y	Y	Y
What are the implications for practice?				

3.4. Synthesis of Results

Bertoglio, *et al.* reported irreversible occlusion rate of 6.2% in both groups [56].

Goosen, *et al.* reported an incidence of primary outcome (easy injection, impossible aspiration) of 3.70% (95% CI 2.91% - 4.69%) and 3.92% (95% CI 3.09% - 4.96%) in the 0.9% sodium chloride and heparin groups respectively [57].

Dal Molin, *et al.* reported an occlusion rate (withdrawal or total) of 4.71% (95% CI: 1.86%; 7.56%) in the heparin group and 7.39% (95% CI: 3.79%; 10.99%) in the 0.9% sodium chloride group (no statistical significance) [58].

Brito, *et al.* reported occlusion rate of 2.96% in the heparinised saline group and 1.35% in the 0.9% sodium chloride ($p = 0.11$). There was 1 case of flow dysfunction in the heparin group (0.37%) and 4 cases in the 0.9% sodium chloride group (0.68%) (no statistical significance) [59].

Egnatios and Gloria reported the mean (95% CI) model-based estimated percentage of alteplase orders per access was 1.29% for heparin and 2.64% (CI:1.08; 6.46) for 0.9% sodium chloride ($p = 0.317$) [60].

Ullman (extracted TIVAD data) reported no occlusions in either group [62].

Pelgen, *et al.* reported (2.3%) of participants had a first complete occlusion within 12 months in the heparinised saline group and 1.9% in the 0.9% sodium chloride group (no statistical significance). Partial occlusion within 12 months in the heparinised saline group was 17.6% and 25.7% in the 0.9% sodium chloride group (no statistical significance) [63].

Hoffman and Fischer-Cartlidge reported alteplase use 6 months pre-implementation, compared with 6 months after they stopped using heparinised saline [61]. Alteplase use was used as a proxy for line occlusion. No significant difference was observed between groups at 6 months (1.2% in the 0.9% sodium chloride group vs 0.9% in the heparinised saline group; $p = 0.13$). They reported additional data in the body of the paper, with further analyses at 12 months and subgroup analysis by "IVAD count" and "visit type". Although there was only a minor rise in alteplase use between 6 and 12 months (from 1.2% to 1.3%), they include a table which indicates some of their subgroups showed statistically significant differences. We approached the authors of this study but were unable to obtain additional details of their methodology, of the statistical tests they had used, or source data to corroborate their analysis. Their control, pre-implementation, data was obtained early during the Covid pandemic (from May 2020), and the authors report a significant change in the frequency with which IVADs were flushed. Hoffman and Fischer-Cartlidge [61] attributed the differences observed in their additional anal-

yses between 6 to 12 months to an influx of new staff and lack of training in correct flushing procedures (specifically a change in their practice of pulsatile flushing, which itself is thought to reduce the frequency of line occlusion [64]), rather than to removal of heparin from their flush solution. Furthermore, the authors of this study have continued to use 0.9% saline [personal correspondence]. They did not revert to using heparinised saline, demonstrating their confidence that any differences demonstrated in their additional analyses were due to factors other than the removal of heparin from routine use.

All eight studies concluded that 0.9% sodium chloride was not statistically inferior to heparin [56]-[63].

Intervention

Six of the eight studies discussed standardisation of staff training and flush delivery [56]-[58] [60] [62] [63]. Two papers [58] [59] maintained the same total volumes in both groups, two papers [60] [61] omitted the information from their study, in the remaining four studies the total volumes varied [56] [57] [62] [63].

The importance of flush technique to promote turbulence to clear the internal lumen of the catheter and prevent occlusion was evidenced in Vigier *et al* qualitative *in vitro* study. They demonstrated that flushing with an unsteady flow (push-pause technique) resulted in a significant reduction of solid deposits within a line, compared to flushing with a laminar flow rate [64].

Positive pressure flush has also demonstrated reduced occlusion rates as this prevents blood reflux back into the catheter. First documented in 1987, Shearer defined the technique as withdrawing the syringe from the injection site while still exerting pressure on the syringe [65]. This can also be achieved by clamping the catheter while injecting. Technologies including positive displacement connectors, syringes with a plunger rod design or valves integrated in catheters mimic this effect [66].

TIVAD Duration

Three studies [59]-[61] omitted information about TIVAD duration. Three studies [56]-[58] consisted of newly inserted TIVAD's, with standardised insertion techniques. Two studies included dwell time prior to study start [62] [63].

The risk of TIVAD complication increases with duration [67]-[69]. Oncology patients often have TIVAD's for duration of treatment, with 42.2% of patients having their TIVAD removed as it was no longer needed [67]. People with CF often have long TIVAD durations (6-4440 days) and evidence suggests they are only removed due to complication [3] [4], however, with the recent introduction of cystic fibrosis transmembrane conductance regulator (CFTR) modifiers leading to a decrease in intravenous antibiotic demand, removing as 'no longer required' may become more common practice in the CF cohort.

Cohort Age

Mean cohort age in five of the studies was >50. One study [61] omitted the data. One study [62] was paediatric with a mean cohort age of 5 years old. One study [56] divided the cohort to <60 and >60.

Other therapies-total parental nutrition (TPN) and Anticoagulation

One study excluded patients on anticoagulation therapy. One study [59] excluded those that had received IV anticoagulation. Six studies [56]-[58] [61]-[63] omitted information relating to anticoagulation therapy. One paper [60] included those on anticoagulation, and although their sample consisted of the same patients across both groups, they did not specify if therapy was delivered across both time periods.

One paper [56] included those on TPN and assessed this in secondary outcomes, concluding that, in line with other studies, the use of TPN increases occlusion risk in TIVAD's [70]. One study [57] referred to flushes post TPN but did not include further details in the cohort statistics or data analysis. One study [58] excluded those receiving TPN. Five studies [59]-[63] omitted information relating to TPN use. TPN is not routinely required within CF, if needed a secondary line would be used [71].

Complications

One patient within one study developed HIT [57], one study reporting HIT as a secondary outcome did not report any cases [63]. The remaining studies did not include this data [56] [58]-[62] (**Table 5**).

Table 5. CRBI rates.

Study author	0.9% Sodium Chloride Group	Heparinised Saline Group
Bertoglio, *et al.* [56]	5.7% (18)	5.4% (16)
Goosen, *et al.* [57]	0.5% (2)	1.5% (6)
Dal Molin, *et al.* [58]	0% (0)	0.47% (1)
Ullman, *et al.* (extracted data) [62]	9% (1)	0% (0)
Brito, *et al.* [59]	No CRBI data reported	
Egnatios and Gloria [60]		
Hoffman and Fischer-Cartlidge [61]		
Pelegan, *et al.* [63]		

Of the four papers that included CRBI data, none reached statistical significance (**Table 6**).

Table 6. Risk/benefits of heparin use.

Benefits	Risks
Potential reduction in line occlusion (not observed) [44] [45] [47] [56]-[63]	HIT, HITTS [56]-[63]
	Allergic reactions [56] [57] [59]-[63]
	Drug incompatibility [57] [59]
	Possible systemic Anticoagulation [56] [57] [60] [62]
	Possible promotion of biofilms/CRBSI [56]-[63]
	Production methods-pig intestinal Mucosa [33] [34]

Due to the associated complication, costs and impact for patients of both HIT and CRBI, data collection is of significant importance, highlighting a need for further studies focusing on complication rates.

4. Discussion

This systematic review aimed to provide clarity on the rate of line occlusions and complications when 0.9% sodium chloride is used in place of heparinised saline in people with cystic fibrosis with TIVADs. We identified no studies in this this population, so extended the review to include all people with TIVADs. The data indicate that heparinised saline is not superior with regard to maintenance of line patency. Its use is associated with additional cost. There are insufficient data to draw conclusions regarding differences in any other adverse event associated with the use of 0.9% sodium chloride or heparinised saline. This review considers the type of flush solution used; it does not consider the optimal interval between flushes, flushing volume, or optimal technique for flushing.

Are these results applicable to different patient populations? Some have theorised that advancing patient age is associated with an increase rate of thrombotic events, attributable to increases in fibrinogen and coagulation proteins [70] [72]. One of the studies [56] divided the cohort to <60 and >60 and demonstrated a hazard ratio for total occlusion of 1.0 for the <60 group and 1.18 for the >60 group. Although these data are not statistically significant, if this hypothesis were correct, one would expect a reduced risk of line thrombosis in the CF cohort due to a mean lower cohort age than observed in oncology cohorts. Reduced occlusion rates seen in the Munik and Royal study may support this theory [3] [4].

How might heparin be beneficial? Various mechanisms of line obstruction are observed [73]: 1) catheters may stop working due to occlusion by thrombosis within the line (intraluminal occlusion); 2) thrombosis may occur within the vein, but outside the catheter, as a consequence of endothelial damage caused by the catheter; 3) a "fibrin tail" or flap may form, extending away from the tip of the catheter, which does not affect infusion through the catheter, but is drawn back and occludes the catheter during attempts at aspiration; 4) a more extensive "fibrin sheath" is formed around, and encases the tip of the line. They probably form as a reaction to endothelial injury where the tip contacts and injures the vein wall. They can develop as early as 24 hours post line insertion and increase to cover the catheter within a week [68] [74]. The prevalence of fibrin sheaths increases with dwell time [75]. Heparin is an anticoagulant which inhibits the actions of thrombin, preventing the formation of fibrin. However, it is not a thrombolytic, so it will not digest fibrin which has already formed [7].

Heparin has a 60 to 90 minutes half-life in the blood, with limited data to support effectiveness once diluted in saline and in a vascular device [56] [76]. Its half-life is a consequence of enzymatic rather than physical degradation, so it will persist in the lumen of a TIVAD/CVC if not exposed to blood. This persistence may be observed clinically by the prolongation of APTT clotting test when an earlier

heparin lock has not been adequately flushed from a line before blood samples are taken. Paradoxically, this might mean that if exposed to blood, heparin will be digested and disappear; if no blood is present, the heparin will persist but not be needed. Therefore, the value of using a heparin lock might be greater if the line has been used previously to take blood, where some coagulation factors or platelets might remain within the lumen of an inadequately flushed line. No study considered this factor.

While it is possible that intraluminal heparin might reduce the risk of occlusion due to intraluminal thrombosis, it is less plausible it would influence the other types of occlusion due to thrombosis or fibrin outside the line. In the Munik study of 452 TIVADs [3], although occlusion type was not determined, line salvage was attempted with urokinase. This medication, would treat intraluminal thrombosis and, as a thrombolytic, be more effective than heparin against the other causes of occlusion, such as fibrin sheaths [68]. However, in this study, only 23% of blocked catheters could be salvaged by urokinase, suggesting that intraluminal thrombosis is the cause of a minority of line occlusions.

How might the use of heparin be disadvantageous?

Statistical significance was not seen in CRBI rates in the included papers, however this has been demonstrated in wider studies [8]-[13].

Both line occlusion and infection can cause distress for patients, exposing them to additional risks from interventions to reopen/replace the line and could result in delays in treatment while venous access is determined. This can have longer-term complications and costs associated. The 2 studies [60] [61] that included cost analysis both demonstrated a cost saving from stopping the use of heparin. However, both only looked at the cost of medications and omitted additional costs associated with line occlusion/infection.

The volume of heparin dose used in TIVAD care, in both oncology and CF centres, varies greatly [77] [78], lacking the individualised dosing according to TIVAD catheter volume, as is recommended [46] [78] [79]. Although not reported in the included papers, it is important to recognise the heightened risk of increased bleeding caused by unintentional systemic anticoagulation in the CF patient group [26]-[30]. The UK National CF Registry details that 165 (2.5%) adults with cystic fibrosis reported hemoptysis at annual review in 2024 [71]. While less prevalent in the paediatric population (<5 children) [71], this risk of unintentional anticoagulation is higher due to the greater variability in size of the patient/catheter volume. Bleeding events are not only distressing for patients but also lead to a greater treatment burden, more complications, and higher associated costs [8]-[11] [15].

Of the two studies which included HIT as an outcome measure (612 participants), only one case of HIT was reported [57] [63]. This is significantly lower than expected with the quoted 1% - 5% for unfractionated heparin, however as HIT usually occurs within 5 to 14 days of receiving heparin, participants in these papers may have been preselected as not having HIT by virtue of previous heparin exposure [80]. A limited search yielded no data or case studies of incidents of HIT

within the CF population. Additional consideration/caution should be given to those with no previous heparin exposure-for example younger patients who generally have not received heparin as prophylaxis for thromboembolic disease (due to an unfavourable risk: benefit analysis), in whom flushing a new TIVAD with heparin may indeed carry a 1% - 5% risk of HIT [18].

Alternatives to heparin? The historical inclusion of anticoagulants in line lock solutions led to consideration of the use of alternatives to heparin. Of these, citrate shows the greatest success in reducing infection rates compared to heparin [8]-[16]. There are suggestions that low dose antibiotics used alongside anticoagulants may reduce line infection rates, but the addition of another drug further increases costs and introduces extra risks, including the possibility of increased antibiotic resistance [8] [10] [15] [16].

We believe that the comparator arm in future studies of novel lock solutions should be 0.9% sodium chloride control, rather than heparinised saline, due to the latter's potential to increase risk of line infection and other complications. Further analysis of alternative lock solutions falls outside the scope of this review.

The way forward? The task of flushing TIVADs is performed almost exclusively by nursing staff. Prescription of flush solutions is performed increasingly by non-medical prescribers [81] [82]. Both those administering and those prescribing a medication are accountable and have a responsibility to undertake evidence-based practice [83]-[86].

In 2012, the UK National Institute of Clinical Excellence recommended use of heparinised saline be discontinued in CVCs [35]. Non-medical prescribers tend to exercise greater caution—ensuring sound knowledge, accurate dosing, and a strong evidence base—when prescribing medications [87] [88], which should result in more professionals questioning the continued use of heparinised saline in TIVADs.

5. Limitations

This review was limited by the low number of studies in this area, particularly in pediatrics/younger cohorts. Papers were restricted to English language, which may have limited results further.

6. Conclusions

Evidence suggests that 0.9% sodium chloride is not inferior to heparin in the maintenance of TIVADs. Although there was no statistically significant difference in safety, wider research demonstrates the importance of risks associated with heparin use.

Ongoing research assessing occlusion and complications rates is of importance to monitor the long-term effect in this cohort of patients, particularly in pediatric cohorts where less data is available. The potential benefit in the subgroup of patients whose TIVAD has been used for blood sampling is worth specific consideration.

Historical practice, "what we have always done", can be hard to change. There is a natural tendency to preserve the status quo, to require a higher level of evidence to justify a change than to continue current practice. If CVCs/TIVADs had always been flushed with 0.9% sodium chloride the evidence of potential harm, the additional cost and lack of evidence of benefit would stop clinicians from starting to use heparinised saline. With the situation reversed, we still need to ask, "Does the evidence support the continued use of heparinised saline?" While further research would strengthen this conclusion, we believe there is sufficient evidence available now, to justify a change to this historical practice.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Niederhuber, J.E., Ensminger, W., Gyves, J.W., Liepman, M., Doan, K. and Cozzi, E. (1982) Totally Implanted Venous and Arterial Access System to Replace External Catheters in Cancer Treatment. *Surgery*, **92**, 706-712.

[2] Pattison, J. and Heaf, D.P. (1986) Totally Implantable Vascular Access in Treatment of Cystic Fibrosis. *The Lancet*, **327**, Article No. 799. https://doi.org/10.1016/s0140-6736(86)91806-4

[3] Munck, A., Malbezin, S., Bloch, J., Gerardin, M., Lebourgeois, M., Derelle, J., *et al.* (2004) Follow-Up of 452 Totally Implantable Vascular Devices in Cystic Fibrosis Patients. *European Respiratory Journal*, **23**, 430-434. https://doi.org/10.1183/09031936.04.00052504

[4] Royle, T.J., Davies, R.E. and Gannon, M.X. (2008) Totally Implantable Venous Access Devices—20 Years' Experience of Implantation in Cystic Fibrosis Patients. *The Annals of The Royal College of Surgeons of England*, **90**, 679-684. https://doi.org/10.1308/003588408x321684

[5] Murea, M., Geary, R.L., Davis, R.P. and Moossavi, S. (2019) Vascular Access for Hemodialysis: A Perpetual Challenge. *Seminars in Dialysis*, **32**, 527-534. https://doi.org/10.1111/sdi.12828

[6] Goodall, K.T., Chooi, C.C. and Gallus, A.S. (1980) Heparin Stability: Effects of Diluent, Heparin Activity, Container, and pH. *Journal of Clinical Pathology*, **33**, 1206-1211. https://doi.org/10.1136/jcp.33.12.1206

[7] Hirsh, J., Anand, S.S., Halperin, J.L. and Fuster, V. (2001) Mechanism of Action and Pharmacology of Unfractionated Heparin. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **21**, 1094-1096. https://doi.org/10.1161/hq0701.093686

[8] Handrup, M.M., Møller, J.K. and Schrøder, H. (2013) Central Venous Catheters and Catheter Locks in Children with Cancer: A Prospective Randomized Trial of Taurolidine versus Heparin. *Pediatric Blood & Cancer*, **60**, 1292-1298. https://doi.org/10.1002/pbc.24482

[9] Power, A., Duncan, N., Singh, S.K., Brown, W., Dalby, E., Edwards, C., *et al*. (2009) Sodium Citrate versus Heparin Catheter Locks for Cuffed Central Venous Catheters: A Single-Center Randomized Controlled Trial. *American Journal of Kidney Diseases*, **53**, 1034-1041. https://doi.org/10.1053/j.ajkd.2009.01.259

[10] Weijmer, M.C. (2002) Superior Antimicrobial Activity of Trisodium Citrate over Heparin for Catheter Locking. *Nephrology Dialysis Transplantation*, **17**, 2189-2195. https://doi.org/10.1093/ndt/17.12.2189

[11] Vanholder, R., Canaud, B., Fluck, R., Jadoul, M., Labriola, L., Marti-Monros, A., Tordoir, J. and Van Biesen, W. (2010) Diagnosis, Prevention and Treatment of Haemodialysis Catheter-Related Bloodstream Infections (CRBSI): A Position Statement of European Renal Best Practice (ERBP), *NDT Plus*, **3**, 234-246. https://doi.org/10.1093/ndtplus/sfq041

[12] Sanders, J., Pithie, A., Ganly, P., Surgenor, L., Wilson, R., Merriman, E., *et al*. (2008) A Prospective Double-Blind Randomized Trial Comparing Intraluminal Ethanol with Heparinized Saline for the Prevention of Catheter-Associated Bloodstream Infection in Immunosuppressed Haematology Patients. *Journal of Antimicrobial Chemotherapy*, **62**, 809-815. https://doi.org/10.1093/jac/dkn284

[13] Pironi, L., Arends, J., Bozzetti, F., Cuerda, C., Gillanders, L., Jeppesen, P.B., *et al*. (2016) ESPEN Guidelines on Chronic Intestinal Failure in Adults. *Clinical Nutrition*, **35**, 247-307. https://doi.org/10.1016/j.clnu.2016.01.020

[14] Lal, S., Chadwick, P., Nightingale, J. for the British Intestinal Failure Alliance Committee of BAPEN (2018) British Intestinal Failure Alliance (BIFA) Recommendation. Management of Catheter Related Blood Stream Infections (CRBSIs) Diagnosis. Management of Catheter Related Blood Stream Infections (CRBSIs).

[15] Chu, H., Brind, J., Tomar, R. and Hill, S. (2012) Significant Reduction in Central Venous Catheter-Related Bloodstream Infections in Children on HPN after Starting Treatment with Taurolidine Line Lock. *Journal of Pediatric Gastroenterology and Nutrition*, **55**, 403-407. https://doi.org/10.1097/mpg.0b013e31825bb0ae

[16] Zhao, Y., Li, Z., Zhang, L., Yang, J., Yang, Y., Tang, Y., *et al*. (2014) Citrate versus Heparin Lock for Hemodialysis Catheters: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *American Journal of Kidney Diseases*, **63**, 479-490. https://doi.org/10.1053/j.ajkd.2013.08.016

[17] Pironi, L., Boeykens, K., Bozzetti, F., Joly, F., Klek, S., Lal, S., *et al*. (2023) ESPEN Practical Guideline: Home Parenteral Nutrition. *Clinical Nutrition*, **42**, 411-430. https://doi.org/10.1016/j.clnu.2022.12.003

[18] Kelton, J.G. (2002) Heparin-Induced Thrombocytopenia: An Overview. *Blood Reviews*, **16**, 77-80. https://doi.org/10.1054/blre.2001.0189

[19] Lindhoff-Last, E., Nakov, R., Misselwitz, F., Breddin, H. and Bauersachs, R. (2002) Incidence and Clinical Relevance of Heparin-Induced Antibodies in Patients with Deep Vein Thrombosis Treated with Unfractionated or Low-Molecular-Weight Heparin. *British Journal of Haematology*, **118**, 1137-1142. https://doi.org/10.1046/j.1365-2141.2002.03687.x

[20] Arachchillage, D.J., Thachil, J., Anderson, J.A.M., Baker, P., Poles, A., Kitchen, S., *et al*. (2023) Diagnosis and Management of Heparin-Induced Thrombocytopenia: Third Edition. *British Journal of Haematology*, **204**, 459-475.

https://doi.org/10.1111/bjh.19180

[21] Warkentin, T.E., Ling, E., Ho, A. and Sheppard, J.I. (1998) "Incidental" Unfractionated Heparin (UFH) vs Normal Saline (NS) Flushes for Intraoperative Invasive Catheters and the Frequency of Formation of Heparin-Induced Thrombocytopenia IgG Antibodies (HIT-IgG): A Randomized, Controlled Trial. *Blood*, **92**, 91b.

[22] Brushwood, D.B. (1992) Hospital Liable for Allergic Reaction to Heparin Used in Injection Flush. *American Journal of Health-System Pharmacy*, **49**, 1491-1492. https://doi.org/10.1093/ajhp/49.6.1491

[23] Heeger, P.S. and Backstrom, J.T. (1986) Heparin Flushes and Thrombocytopenia. *Annals of Internal Medicine*, **105**, 143-143. https://doi.org/10.7326/0003-4819-105-1-143_1

[24] Rice, L. and Jackson, D. (1981) Can Heparin Cause Clotting? *Heart Lung*, **10**, 331-335.

[25] McNulty, I., Katz, E. and Kim, K.Y. (2005) Thrombocytopenia Following Heparin Flush. *Progress in Cardiovascular Nursing*, **20**, 143-147. https://doi.org/10.1111/j.0889-7204.2005.04693.x

[26] Lersch, C., Kotowa, W., Fung, S. and Janssen, D. (2004) Prophylaxis of Port System-Associated Thromboses in Advanced Oncology Patients Using Heparin Flushing. *Journal of Cancer Research and Clinical Oncology*, **130**, 235-241. https://doi.org/10.1007/s00432-003-0528-5

[27] Passannante, A. and Macik, B.G. (1988) Case Report: The Heparin Flush Syndrome: A Cause of Iatrogenic Hemorrhage. *The American Journal of the Medical Sciences*, **296**, 71-73. https://doi.org/10.1097/00000441-198807000-00014

[28] Moritz, M.L., Vats, A. and Ellis, D. (2003) Systemic Anticoagulation and Bleeding in Children with Hemodialysis Catheters. *Pediatric Nephrology*, **18**, 68-70. https://doi.org/10.1007/s00467-002-0983-2

[29] Morgan, S.K., Grush, O.C. and Jernigan, D. (1989) Unexplained Bleeding Associated with Central Venous Catheter Care. *American Journal of Pediatric Hematology/Oncology*, **11**, 447-449.

[30] Lambert, C., Deneys, V., Pothen, D., Vermylen, C. and Hermans, C. (2006) Inadvertent Anticoagulation of a Haemophiliac Child with Routine Line Flushing. *Haemophilia*, **12**, 548-550. https://doi.org/10.1111/j.1365-2516.2006.01294.x

[31] Neering, I.R. and Brewer, G.N. (1986) On the Interaction between Heparin and Some Aminoglycoside Antibiotics. *Journal of Biological Physics*, **14**, 99-103. https://doi.org/10.1007/bf01857746

[32] Medscape (n.d.). Heparin Dosing, Indications, Interactions, Adverse Effects, and More. https://reference.medscape.com/drug/calciparine-monoparin-heparin-342169#0

[33] Eriksson, A., Burcharth, J. and Rosenberg, J. (2013) Animal Derived Products May Conflict with Religious Patients' Beliefs. *BMC Medical Ethics*, **14**, Article No. 48. https://doi.org/10.1186/1472-6939-14-48

[34] Harding, S., Williams, L., Smith, N., Soomro, D.e.S., Allawi, S., Singh, K., *et al.* (2023) Animal-Derived Medicinal Products: Community Representatives' Views of Their Use. *Future Healthcare Journal*, **10**, 291-295. https://doi.org/10.7861/fhj.2023-0005

[35] National Patient Saftey Agency (NPSA) (2008) Heparin Flush-Rapid Response Repo. https://webarchive.nationalarchives.gov.uk/ukgwa/20180501163616/http:/www.nrls.npsa.nhs.uk/resources/type/alerts/?entryid45=59892&p=3

[36] Pelland-Marcotte, M., Amiri, N., Avila, M.L. and Brandão, L.R. (2020) Low Molecular Weight Heparin for Prevention of Central Venous Catheter-Related Thrombosis in Children. *Cochrane Database of Systematic Reviews*, **2020**, CD005982. https://doi.org/10.1002/14651858.cd005982.pub3

[37] Chalmers, E., Ganesen, V., Liesner, R., Maroo, S., Nokes, T., Saunders, D., *et al*. (2011) Guideline on the Investigation, Management and Prevention of Venous Thrombosis in Children. *British Journal of Haematology*, **154**, 196-207. https://doi.org/10.1111/j.1365-2141.2010.08543.x

[38] Monagle, P., Chan, A.K.C., Goldenberg, N.A., Ichord, R.N., Journeycake, J.M., Nowak-Göttl, U., *et al*. (2012) Antithrombotic Therapy in Neonates and Children: Antithrombotic Therapy and Prevention of Thrombosis, 9th Edition: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*, **141**, e737S-e801S. https://doi.org/10.1378/chest.11-2308

[39] López-Briz, E., Ruiz Garcia, V., Cabello, J.B., Bort-Marti, S., Carbonell Sanchis, R. and Burls, A. (2014) Heparin versus 0.9% Sodium Chloride Intermittent Flushing for Prevention of Occlusion in Central Venous Catheters in Adults. *Cochrane Database of Systematic Reviews*, **10**, CD008462. https://doi.org/10.1002/14651858.cd008462.pub2

[40] Pittiruti, M., Bertoglio, S., Scoppettuolo, G., Biffi, R., Lamperti, M., Dal Molin, A., *et al*. (2016) Evidence-Based Criteria for the Choice and the Clinical Use of the Most Appropriate Lock Solutions for Central Venous Catheters (Excluding Dialysis Catheters): A GAVeCeLT Consensus. *The Journal of Vascular Access*, **17**, 453-464. https://doi.org/10.5301/jva.5000576

[41] Whitton, C.L. and Derry, D.D. (2017) 380 Practising Evidence-Based Medicine? Using Heparinised Saline to Flush Central Lines? *Journal of Cystic Fibrosis*, **16**, S158-S159. https://doi.org/10.1016/s1569-1993(17)30710-5

[42] López-Briz, E., Ruiz Garcia, V., Cabello, J.B., Bort-Martí, S. and Carbonell Sanchis, R. (2022) Heparin versus 0.9% Sodium Chloride Locking for Prevention of Occlusion in Central Venous Catheters in Adults. *Cochrane Database of Systematic Reviews*, **2022**, CD008462. https://doi.org/10.1002/14651858.cd008462.pub4

[43] Sharma, S.K., Mudgal, S.K., Gaur, R., Sharma, R., Sharma, M. and Thakur, K. (2019) Heparin Flush vs. Normal Saline Flush to Maintain the Patency of Central Venous Catheter among Adult Patients: A Systematic Review and Meta-Analysis. *Journal of Family Medicine and Primary Care*, **8**, 2779-2792. https://doi.org/10.4103/jfmpc.jfmpc_669_19

[44] Santomauro, I., Campani, D., Tiozzo, V., Barletta, B., Scotti, L., Barisone, M., *et al*. (2022) Heparin versus Normal Saline Locking for Prevention of Occlusion, Catheter-Related Infections and Thrombosis in Central Venous Catheter in Adults: Overview of Systematic Reviews. *The Journal of Vascular Access*, **25**, 1741-1748. https://doi.org/10.1177/11297298221103201

[45] Semerci, R., Bingöl, H., Bay Büyükkapu, S., Kudubes, A.A., Bektaş, M. and Kebudi, R. (2023) Comparison of Heparin and Saline for Prevention of Central Venous Catheter Occlusion in Pediatric Oncology: A Systematic Review and Meta-Analysis. *Seminars in Oncology Nursing*, **39**, Article ID: 151426. https://doi.org/10.1016/j.soncn.2023.151426

[46] European Cystic Fibrosis Society (2020) Optimizing Pharmaceutical Care in Cystic Fibrosis.

[47] Wu, X.H., Chen, L.C., Liu, G.L., Zhang, T.T. and Chen, X.S. (2021) Heparin versus 0.9% Saline Solution to Maintain Patency of Totally Implanted Venous Access Ports

in Cancer Patients: A Systematic Review and Meta-Analysis. *International Journal of Nursing Practice*, **27**, e12913. https://doi.org/10.1111/ijn.12913

[48] Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D. (2021) The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews. *BMJ*, **372**, n71. http://www.prisma-statement.org/

[49] Rickles, F.R. and Levine, M.N. (2001) Epidemiology of Thrombosis in Cancer. *Acta Haematologica*, **106**, 6-12. https://doi.org/10.1159/000046583

[50] Esmon, C.T. (2003) Inflammation and Thrombosis. *Journal of Thrombosis and Haemostasis*, **1**, 1343-1348. https://doi.org/10.1046/j.1538-7836.2003.00261.x

[51] Horsted, F., West, J. and Grainge, M.J. (2012) Risk of Venous Thromboembolism in Patients with Cancer: A Systematic Review and Meta-Analysis. *PLOS Medicine*, **9**, e1001275. https://doi.org/10.1371/journal.pmed.1001275

[52] Takemoto, C.M. (2011) Venous Thromboembolism in Cystic Fibrosis. *Pediatric Pulmonology*, **47**, 105-112. https://doi.org/10.1002/ppul.21566

[53] Belloni, S., Caruso, R., Cattani, D., Mandelli, G., Donizetti, D., Mazzoleni, B., *et al.* (2022) Occurrence Rate and Risk Factors for Long-Term Central Line-Associated Bloodstream Infections in Patients with Cancer: A Systematic Review. *Worldviews on Evidence-Based Nursing*, **19**, 100-111. https://doi.org/10.1111/wvn.12574

[54] CASP Critical Appraisal Skills Programme (2018) CASP Randomised Control Trial Checklist.

[55] Critical Appraisal Skills Programme (2018) CASP Cohort Study Checklist.

[56] Bertoglio, S., Solari, N., Meszaros, P., Vassallo, F., Bonvento, M., Pastorino, S., *et al.* (2012) Efficacy of Normal Saline versus Heparinized Saline Solution for Locking Catheters of Totally Implantable Long-Term Central Vascular Access Devices in Adult Cancer Patients. *Cancer Nursing*, **35**, E35-E42. https://doi.org/10.1097/ncc.0b013e31823312b1

[57] Goossens, G.A., Jérôme, M., Janssens, C., Peetermans, W.E., Fieuws, S., Moons, P., *et al.* (2013) Comparing Normal Saline versus Diluted Heparin to Lock Non-Valved Totally Implantable Venous Access Devices in Cancer Patients: A Randomised, Non-Inferiority, Open Trial. *Annals of Oncology*, **24**, 1892-1899. https://doi.org/10.1093/annonc/mdt114

[58] Dal Molin, A., Clerico, M., Baccini, M., Guerretta, L., Sartorello, B. and Rasero, L. (2015) Normal Saline versus Heparin Solution to Lock Totally Implanted Venous Access Devices: Results from a Multicenter Randomized Trial. *European Journal of Oncology Nursing*, **19**, 638-643. https://doi.org/10.1016/j.ejon.2015.04.001

[59] Brito, A.R.d.O., Nishinari, K., Saad, P.F., Saad, K.R., Pereira, M.A.T., Emídio, S.C.D., *et al.* (2018) Comparison between Saline Solution Containing Heparin versus Saline Solution in the Lock of Totally Implantable Catheters. *Annals of Vascular Surgery*, **47**, 85-89. https://doi.org/10.1016/j.avsg.2017.09.015

[60] Egnatios, D. and Gloria, C. (2021) Implanted Port Patency: Comparing Heparin and Normal Saline. *Clinical Journal of Oncology Nursing*, **25**, 169-173. https://doi.org/10.1188/21.cjon.169-173

[61] Hoffman, M. and Fischer-Cartlidge, E. (2022) Implementation of an Evidence-Based Practice Change Removing Heparin from Implanted Vascular Access Devices. *Journal of Infusion Nursing*, **45**, 258-263. https://doi.org/10.1097/nan.0000000000000482

[62] Ullman, A.J., Edwards, R., Walker, R., Roy, J., Paton, A., Rickard, C.M., *et al.* (2022) Routine Catheter Lock Solutions in Pediatric Cancer Care: A Pilot Randomized Controlled Trial of Heparin vs Saline. *Cancer Nursing*, **45**, 438-446.

https://doi.org/10.1097/ncc.0000000000001053

[63] Pelegan, S., Singeltary, B., Blau, R., Swango, M., Barker, R. (2022) Maintaining Patency in Implanted Port Catheters Clinical Trial.gov. NCT02354118 TriHealth Inc.

[64] Vigier, J.P., Merckx, J., Coquin, J.Y., Flaud, P. and Guiffant, G. (2005) The Use of a Hydrodynamic Bench for Experimental Simulation of Flushing Venous Catheters: Impact on the Technique. *Revue Européenne de Technologie Biomédicale*, **26**, 147-149. https://doi.org/10.1016/j.rbmret.2005.03.001

[65] Shearer, J. (1987) Normal Saline Flush versus Dilute Heparin Flush. National Intravenous Therapy Association, 425-427.

[66] Lapalu, J., Losser, M., Albert, O., Levert, H., Villiers, S., Faure, P., *et al*. (2010) Totally Implantable Port Management: Impact of Positive Pressure during Needle Withdrawal on Catheter Tip Occlusion (an Experimental Study). *The Journal of Vascular Access*, **11**, 46-51. https://doi.org/10.1177/112972981001100110

[67] Tumay, L.V. and Guner, O.S. (2020) Availability of Totally Implantable Venous Access Devices in Cancer Patients Is High in the Long Term: A Seven-Year Follow-Up Study. *Supportive Care in Cancer*, **29**, 3531-3538. https://doi.org/10.1007/s00520-020-05871-6

[68] Crain, M.R., Horton, M.G. and Mewissen, M.W. (1998) Fibrin Sheaths Complicating Central Venous Catheters. *American Journal of Roentgenology*, **171**, 341-346. https://doi.org/10.2214/ajr.171.2.9694448

[69] Matusik, P.S., Łoboda, P., Krzanowska, K., Popiela, T.J., Heba, G. and Pawlik, W. (2020) Presence of Retained Calcified Fibrin Sheath after Central Venous Catheter Removal: A Systematic Literature Review. *The Journal of Vascular Access*, **23**, 644-652. https://doi.org/10.1177/1129729820969328

[70] Liu, L., Liu, Z., Wang, J., Cheng, M., Xie, Y., Wang, W., *et al*. (2023) Exploring Risk Factors for Totally Implantable Venous Access Devices (TIVADs)-Related Thrombotic Occlusion in the Off-Treatment Period. *Scientific Reports*, **13**, Article No. 10767. https://doi.org/10.1038/s41598-023-37902-7

[71] The Cystic Fibrosis Trust (2025) UK Cystic Fibrosis Registry 2024 Annual Data Report.

[72] Yi, X., Chen, J., Li, J., Feng, L., Wang, Y., Zhu, J., *et al*. (2013) Risk Factors Associated with PICC-Related Upper Extremity Venous Thrombosis in Cancer Patients. *Journal of Clinical Nursing*, **23**, 837-843. https://doi.org/10.1111/jocn.12227

[73] Jonker, M.A., Osterby, K.R., Vermeulen, L.C., Kleppin, S.M. and Kudsk, K.A. (2010) Does Low-Dose Heparin Maintain Central Venous Access Device Patency? *Journal of Parenteral and Enteral Nutrition*, **34**, 444-449. https://doi.org/10.1177/0148607110362082

[74] Mayo, D.J. (2000) Current Treatment Options for Catheter-Related Thrombosis. *Journal of Vascular Access Devices*, **5**, 10-20. https://doi.org/10.2309/108300800775897980

[75] Hemker, H.C. (2016) A Century of Heparin: Past, Present and Future. *Journal of Thrombosis and Haemostasis*, **14**, 2329-2338. https://doi.org/10.1111/jth.13555

[76] Linkins, L.A., Dans, A.L. and Moores, L.K. (2012) Treatment and Prevention of Heparin Induced Thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th Edition American College of Chest Physicians Evidence-Based Clinical Guidelines. *Chest*, **141**, 495S-530S.

[77] Oliveira, F.J.G.d., Rodrigues, A.B., Ramos, I.C. and Caetano, J.Á. (2020) Dosage of Heparin for Patency of the Totally Implanted Central Venous Catheter in Cancer

Patients. *Revista Latino-Americana de Enfermagem*, **28**, e3304. https://doi.org/10.1590/1518-8345.3326.3304

[78] Mele, R., Spoletini, G., Shaw, N.J., Swarbrooke, J.G., Clifton, I.J. and Peckham, D.G. (2025) P475 a Review of Use and Maintenance of Totally Implantable Venous Access Devices in People with Cystic Fibrosis. *Journal of Cystic Fibrosis*, **24**, S218. https://doi.org/10.1016/j.jcf.2025.03.1358

[79] Nickel, B., Gorski, L., Kleidon, T., Kyes, A., DeVries, M., Keogh, S., *et al.* (2024) Infusion Therapy Standards of Practice, 9th Edition. *Journal of Infusion Nursing*, **47**, S1-S285. https://doi.org/10.1097/nan.0000000000000532

[80] Nicolas, D., Nicolas, S., Hodgens, A. and Reed, M. (2025) Heparin-Induced Thrombocytopenia. StatPearls Publishing.

[81] Department of Health (2000) The NHS Plan: A Plan for Investment, a Plan for Reform. Home Office.

[82] Department of Health (2006) Improving Patients Access to Medicine: A Guide to Implementing Nurse and Pharmacist Prescribing within the NHS in England. Home Office.

[83] Department of Health (1968) Medicines Act 1968. http://www.legislation.gov.uk/ukpga/1968/67

[84] Nursing and Midwifery Council (2015) The Code: Professional Standards of Practice and Behaviour for Nurses and Midwives. NMC.

[85] Department of Health (2006) Standards for Better Health. hhttps://data.parliament.uk/DepositedPapers/Files/DEP2008-1907/DEP2008-1907.pdf

[86] NHS England and NHS Improvement (2020) Leading the Acceleration of Evidence into Practice: A Guide for Executive Nurses.

[87] Funnell, F., Minns, K. and Reeves, K. (2014) Comparing Nurses' and Doctors' Prescribing Habits. *Nursing Times*, **110**, 12-14.

[88] McIntosh, T., Stewart, D., Forbes-McKay, K., McCaig, D. and Cunningham, S. (2016) Influences on Prescribing Decision-Making among Non-Medical Prescribers in the United Kingdom: Systematic Review. *Family Practice*, **33**, 572-579. https://doi.org/10.1093/fampra/cmw085