

Complications of Central Venous Access Devices: A Systematic Review

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Short Title: Complications of Central Venous Access Devices

Financial Disclosure Statement: The study authors have no financial relationships relevant to this article to disclose.

Funding source: This research has been undertaken as part of Ms Ullman's PhD program. She has received PhD scholarship funding from the Menzies Health Institute Queensland, NHMRC Centre of Research Excellence in Nursing and Centurion Medical Products.

Conflict of Interest Statement: Ms Ullman, Ms Marsh and Dr Rickard have received funding from CVAD dressing manufacturers (3M; Carefusion; Centurion Medical Products) but these medical products were not included within the scope of this review.

Abbreviations: BSI=bloodstream infection; CENTRAL= central register of controlled trials); CVAD= central venous access device; CINAHL= cumulative index to nursing and allied health; CI = confidence interval; HD= hemodialysis; IR= incidence rate; MeSH=Medical subject headings; MOOSE= meta-analysis of observational studies in epidemiology; PICC=peripherally inserted central catheter; PRISMA= preferred reporting items for systematic reviews and meta-analyses; STROBE= strengthening the reporting of observational studies in epidemiology.

Contributors' Statement:

Amanda J Ullman: Ms Ullman conceptualized and designed the study, carried out the initial analysis, drafted the initial manuscript, and approved the final manuscript as submitted.

Nicole Marsh: Ms Marsh assisted with the acquisition of data, critically reviewed the manuscript and approved the final manuscript as submitted.

Gabor Mihala: Mr Mihala carried out the subsequent analysis, assisted with the interpretation of the data, reviewed and revised the manuscript and approved the final manuscript as submitted.

Marie Cooke, Claire M Rickard: Drs Cooke and Rickard assisted with the conception and design of the study, interpretation of the data, reviewed and revised the manuscript, and approved the final manuscript as submitted.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Abstract:

Context: The failure and complications of central venous access device (CVAD) result in interrupted medical treatment, morbidity and mortality for the patient and the risks and resources associated with the insertion of new CVAD.

Objective: To systematically review existing evidence of the incidence of CVAD failure and complications across CVAD types within pediatrics.

Data Sources: CENTRAL, PubMed and CINAHL databases were systematically searched to January 2015.

Study Selection: Included studies were of cohort design and examined the incidence of CVAD failure and complications across CVAD type in pediatrics within the last ten years. CVAD failure was defined as CVAD loss of function prior to the completion of necessary treatment, and complications as CVAD-associated bloodstream infection, CVAD local infection, dislodgement, occlusion, thrombosis and breakage.

Data Extraction: Data were independently extracted and critiqued for quality by two authors.

Results: Seventy-four cohort studies met the inclusion criteria, with mixed quality reporting and method. Overall, 25% of CVADs failed prior to completion of therapy (95% CI 20.9%-29.2%) at a rate of 1.97 per 1,000 catheter days (95% CI 1.71-2.23). The failure per CVAD device was highest proportionally in hemodialysis catheters (46.4%, 95% CI 29.6%-63.6%); and per 1,000 catheter days in umbilical catheters (28.6 per 1,000 catheter days, 95% CI 17.4-39.8). Totally implanted devices had the lowest rate of failure per 1,000 catheter days (0.15, 95% CI 0.09-0.20).

Limitations: The inclusion of non-randomized and non-comparator studies may have affected the robustness of the research.

Conclusions: CVAD failure and complications in pediatrics is a significant burden on the healthcare system internationally.

Background

Worldwide, millions of central venous access devices (CVADs) are used in healthcare facilities to provide supportive and interventional therapies during acute and chronic illness. Within pediatrics, the therapies that CVADs facilitate are diverse, varying from the life-long administration of nutrition, to the aggressive treatment of oncological conditions.[1] Children with CVADs are already vulnerable to complications and disability because of their underlying health condition. This vulnerability to complications is worsened by the risk of adverse events associated with the insertion and management of CVADs. [2, 3]

There are a range of CVADs available, which healthcare professionals elect to insert on the basis of the predicted duration of clinical necessity (short, medium or long term), risk of adverse outcomes, treatment requirements (e.g. hemodialysis), frequency of usage and vein availability. Traditionally, non-tunneled and umbilical CVADs have been recommended for short term usage (up to 7-10 days), [4-6] peripherally inserted central catheters (PICCs) for short to medium term usage (4 weeks to 6 months), [4, 6] and tunneled CVADs and totally implantable catheters for long term usage (months / years). [6, 7] The goal for all CVADs is to provide safe and reliable vascular access to facilitate necessary treatment, without complications related to insertion, maintenance and/or removal.

CVAD failure

CVADs provide a vital contribution to each child's treatment, and their failure can result in significant harm. Each failure also places a significant burden on the healthcare system. The immediate interruption to necessary treatment results in an inability to receive prescribed chemotherapy, fluids, nutrition, antibiotics or other necessary medicines. [8, 9] CVAD reinsertions are costly, requiring highly skilled staff, large amounts of sterile and disposable equipment, theatre time, monitoring devices and radiological confirmation of placement.[10] Their insertion can result in complications including pneumothorax, arterial puncture, hemorrhage and cardiac rhythm

dysfunction [11], with overall CVAD insertion-related complications reported in 7% to 18% of CVAD insertions. [12, 13] The more CVADs a child has previously had inserted, the more complex the procedure becomes, as CVAD failures can result in venous damage and insufficiency. [12] Even after successful CVAD insertion, there are many mechanisms which may result in CVAD failure or complication, many of which are considered preventable. [14, 15]

Infectious complications

CVADs place patients at risk of local and systemic infectious complications, including local site infection (e.g. exit site) and bloodstream infection (BSI). [5, 16] The multifocal path of microbial transmission of bacteria or fungi can be as a result of skin organisms at the insertion site, contamination of the internal device hub, hematogenous seeding and/or infusate contamination. [5, 17, 18] Microbial colonization of the entry or exit site of CVADs can result in local infection. This infection is commonly caused by resident skin flora, and results in inflammation of the skin (dermatitis), subcutaneous tissue (cellulitis) or vein (phlebitis). CVAD failure related to local infection is normally due to poor response to topical therapy, tunnel infection and purulent drainage. [19]

CVAD-associated BSIs are prevalent world-wide, with an estimated 41,000 occurring in United States hospitals each year. [20] CVAD-associated BSI is associated with a prolonged hospital stay (~10 days) and an increase in the relative risk of death by 1.06 (absolute 1% attributable increase) .[21] CVAD-associated BSI have an attributable cost of between \$5,821 and \$60,536USD per event [22-24] and frequently result in device failure.

Mechanical complications

As CVADs remain partially exogenous to the body, CVAD failure may also occur as a result of dislodgement and breakage. Breakage of a CVAD is most commonly due to the use of excessive force, causing a split in the structure of the device. This may be due to drag from multiple heavy

infusion tubes, catching on environmental structures (e.g. clothing, bedrails), intentional or accidental removal by patients or the use of inappropriately small syringe size for the injection of infusates.[3]

CVAD occlusion may also result in device failure and is caused by the presence of a fibrin sheath, medication precipitate, catheter tip thrombus or position of the catheter tip against a vessel or chamber wall. [8, 25] CVAD-associated thrombosis may be as a result of fibrin deposited inside the CVADs (intraluminal thrombosis), adhering to the vein wall (mural thrombosis) or around the intravascular portion of the CVADs (fibrin sheath). [9, 25] Fibrin sheaths only cause malfunction when the sheath extends around or over the tip of the CVADs, and in many cases CVAD-associated thromboses are asymptomatic and the device continues to function. [25]

Individual studies have examined the rate and incidence rate of CVAD failure and complications in pediatrics, but an overall estimation per CVAD type throughout this population has not been established. This systematic review aims to examine the proportion and rate of CVAD failure and complications in pediatrics across CVADs type.

Methods

The study used standard methods for systematic review and is reported in accordance with MOOSE (Meta-analysis of observational studies in epidemiology) [26] where applicable.

Eligibility criteria

A systematic search for cohort studies examining failure and complications of CVADs in pediatrics was conducted. Studies were eligible for inclusion if they met predefined inclusion criteria: (1) cohort design (prospective or retrospective); (2) study participants aged 0-18 years; (3) reported the failure and / or complications of CVADs included as outcome measures (4) reported the outcomes per PICCs, umbilical catheters, non-tunneled percutaneous CVADs, hemodialysis (HD) catheters,

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tunneled CVADs or totally implantable CVADs. The review was limited to observational studies in order to describe the failure and complications statistics across CVADs in pediatrics, without confounding the description with the comparative effectiveness of various interventions. There were no restrictions placed in terms of patient underlying condition. We excluded studies if they were not written in English and were greater than ten years old, to reflect and maximize relevance to current practices.

Outcome measures

The primary outcome of the review was defined *a priori*, in accordance with landmark intravascular research, as CVAD failure prior to the completion of necessary treatment.[27-29] The secondary outcomes were CVAD complications after successful CVAD insertion. These were:

1. CVAD-associated BSI: Minimum definition of a laboratory confirmed bloodstream infection that is not secondary to an infection at another body site, with a CVAD in place for greater than two days; [20]
2. CVAD-associated thrombosis: Development of thrombosed vessel (partial or complete) at the CVADs site diagnosed via ultrasound; [30]
3. Occlusion or blockage: As defined by study investigators and included partial and full blockage of the CVAD lumen or lumens, irrespective of occlusion treatment; [30]
4. Dislodgement or migration: As defined by study investigators and included partial, complete and accidental removal which results in the CVAD tip no longer being placed in the inferior or superior vena cava;[5]
5. Breakage or rupture: As defined by study investigators and included a visible split in CVADs material diagnosed by leakage or radiographic evidence of extravasation from a portion of the CVAD into tissue; [13] and
6. Local infection and phlebitis: As defined by the study investigator and included exit, entrance, tunnel infections and phlebitis.[5]

Search strategy and study selection

The Cochrane Central Register of Controlled Trials (CENTRAL; the Cochrane Library), US National Library of Medicine National Institutes of Health (PubMed), and Cumulative Index to Nursing and Allied Health (CINAHL) databases were systematically and independently searched on the 27th of January, 2015. Medical subject headings (MeSH) were developed by a healthcare librarian and were “vascular access devices”, “central venous catheters” and “pediatrics”. Additional studies were identified through searches of bibliographies.

Data extraction and missing data

All data were extracted by two independent investigators (AU, NM), using a standardized data extraction form. Study data were extracted regarding the number of patients, catheters, patient population, CVADs type, study method, frequency of CVAD failures and complications, catheter days and country of origin. For studies with missing data (e.g. CVAD catheter days), the study authors were contacted via email where possible.

Statistical methods

As only cohort studies were included, descriptive statistics have been used to provide summative information of the study population and results. Score confidence intervals (CI) with Freeman-Tukey double arcsine transformations were calculated for individual studies where the outcome was dichotomous (failure/no failure; binomial data),^[31] and Poisson confidence intervals and standard errors were calculated for incidence rate (IR) outcomes. Pooled estimates were generated with random-effects meta-analysis, with results summarized per device type using proportion (%) and 95% CI. IR outcomes (continuous data) were pooled using inverse variance, with the DerSimonian and Laird method, per 1,000 catheter days and 95% CI. Heterogeneity (between studies) was assessed using the I^2 measure, categorized as low (<25%), moderate (25-75%) or high (>75%).

Subgroup analysis was completed with random-effects meta-regression. Subgroup analysis and tests for overall effect (null hypothesis: no treatment effect) were assessed with the P-value, categorized as significant at <0.05 level. Extreme or obviously incorrect data were re-checked for accuracy. Stata [32] was used for all analyses.

Subgroup analysis

Given the predicted heterogeneity of the study populations, subgroup analyses were planned to compare CVAD failure rates by CVADs types in populations involving: neonates and pediatrics; oncology / hematology and all others; and outpatient and inpatient managed devices. Results of the subgroup analyses are described using CVAD failure proportion, IR per 1,000 catheter days and 95% CI, where possible.

Risk of bias assessment and sensitivity analyses

In accordance with the MOOSE guidelines,[26] study quality was assessed by examination of key components of an included study's design, in comparison to an overall score. Based upon elements of the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines,[33] these design features were clarity, consistency and rigor of the outcome measures, completeness of outcome reporting and research methods. To further describe the risk of bias within the meta-analysis, sensitivity analyses were undertaken comparing CVAD failure proportion and IR per 1,000 catheter days, and 95% CI per CVADs type between retrospective and prospective studies.

Results

Systematic search results

Figure 1 describes the flow of inclusion and exclusion for the study selection, in accordance with the referred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. [34] After removal of duplicates, 307 records were identified with 96 requiring full text for review. From the full text articles, 22 were excluded as they included both adult and pediatric participants, [35, 36] reported intraoperative CVADs complications, [11, 37-39] did not provide separate outcome data per CVADs type, [7, 40-44] provided inadequate information to facilitate data extraction, [45-51] or had outcome definitions not in accordance with the review. [52-54] Seventy-four studies were assessed as meeting the inclusion criteria.

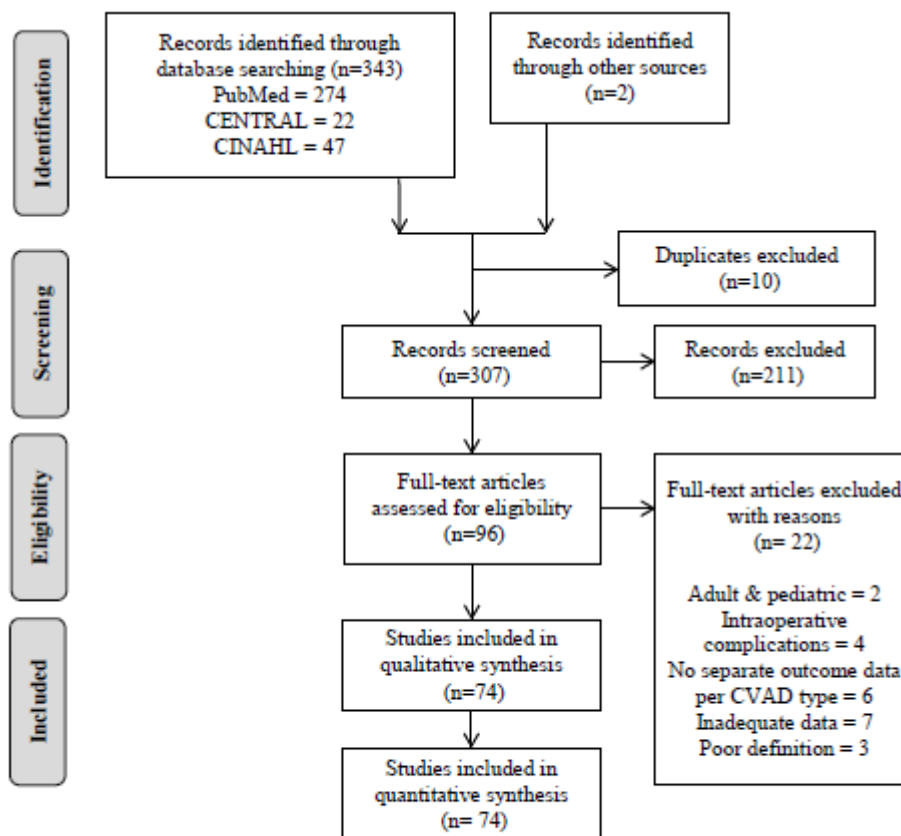


Figure 1: PRISMA flow chart of study selection

Thirty-two study authors were contacted to provide additional information regarding the research results; most commonly for the total CVAD catheter days per CVAD type. Eleven authors were able to provide the additional information,[55-65] three were unable to provide the requested data, [66-68] and 17 did not respond.[69-85]

Characteristics of included studies

The review includes 24 prospective and 50 retrospective cohort studies. These studies were undertaken in Europe, [2, 3, 30, 57-60, 66, 68, 71, 73, 75, 77, 79-81, 86-99] North America, [62-65, 67, 72, 76, 83-85, 100-114] Asia, [55, 61, 69, 70, 74, 82, 115-125] and South America. [56, 78] Included subjects were aged 0–17 years and required treatment for oncological or hematological conditions, support during intensive care admission, or central access for hemodialysis, post-surgical, general infusion therapy and parenteral nutrition. Table 1 describes the populations and CVADs types described within the included studies.

Table 1: Number of included studies with patient population and CVAD type

CVAD Type	Neonatal Intensive Care	Pediatric Intensive Care	Hematology / Oncology	General Pediatrics	Outpatients (including GE failure)	TOTAL
Peripherally inserted central catheter (PICC)	16	-	6	8	3	33
Umbilical catheters	5	-	-	1	-	6
Non-tunneled, percutaneous CVAD	3	5	-	2	-	10
Hemodialysis catheters	-	-	-	4	4	8
Tunneled, partially implanted CVAD	-	1	13	5	1	20
Totally implantable CVAD	-	-	19	4	1	24
TOTAL	24	6	38	24	9	

CVAD = Central venous access device; GE = Gastroenterological

Study qualities

The quality of the studies was mixed, with incomplete reporting of denominators of outcomes and poor outcome definition consistency to benchmarked standards evident. Twelve studies [59, 61, 66, 67, 72, 76, 82, 83, 89, 97, 105, 121] described the outcome of CVAD-associated BSI without the

clarity and rigor of benchmarked standards, which meant that their CVAD-associated BSI data were not included within the review. Two studies [30, 116] provided a combined ‘all type’ infection or mechanical failure outcomes, instead of providing separated local and systemic infection, occlusion and dislodgement data. These data were also not included in the review. We were unable to ascertain the number of catheter days in 23 studies, [66-82, 84, 85, 92, 97, 99, 122] which excluded their data from contributing to the meta-analysis reporting failure and complications per 1,000 catheter days.

Synthesis of results

CVAD failure

Table 2 reports the overall pooled proportion and IR of CVAD failure and complications across CVADs type. Figure 2 and 3 (Supplementary) report the individual and pooled proportion and IR of CVAD failure across CVADs type. Overall 25% (95% CI 20.9%-29.2%) of pediatric CVADs failed prior to completion of therapy; with an IR of 1.97 per 1,000 catheter days (95% CI 1.71-2.23; 60 studies; 16,859 CVAD; 1,282,332 catheter days). Overall heterogeneity of studies reporting proportions of failure was high ($I^2=97.1\%$), and moderate to high ($I^2= 75.0\%-97.3\%$) when examined per device group. Umbilical catheters had the lowest pooled proportion of CVAD failure (11%; 95% CI 0.7%-30.2%) and the highest pooled IR per 1,000 catheter days (28.6; 95% CI 17.4-39.8) with two and one (respectively) studies (426 CVADs; 979 catheter days) contributing to the analysis. HD catheters had the highest pooled proportion of CVAD failure (46.4%; 95% CI 29.6%-63.6%; 323 CVAD). PICCs had the second-highest pooled IR per 1,000 catheter days (12.4; 95% CI 10.0-14.9; 241,019 catheter days). Totally implanted devices had the lowest pooled IR of failure per 1,000 catheter days (0.15; 95% CI 0.09-0.20; 819,022 catheter days). Because of a lack of data, a rate of CVAD failure per 1,000 catheter days for non-tunneled, percutaneous CVADs could not be estimated.

Table 2: Proportions and incidence rates of CVAD complications across device type in included studies

CVAD type		Proportion of complications				Incidence rates of complications / 1,000 catheter days					
		Studies	CVAD	Outcomes	Pooled %	95% CI	Studies	Catheter days	Outcomes	Pooled IR	95% CI
Failure	All	60	16,859	4,121	25.0% (H,S,S)	20.9-29.2	37	1,282,332	2,370	1.97 (H,S,S)	1.71-2.23
	PICC	23	10,163	2,771	30.1% (H,S,-)	24.4-36.1	17	241,019	2,006	12.43 (H,S,-)	9.98-14.89
	Umbilical	2	426	41	11.0% (H,S,-)	0.7-30.2	1	979	28	28.60 (-,S,-)	17.44-39.77
	Non-tunneled	2	1,126	248	16.7% (M,S,-)	6.1-30.9	0	-	-	-	-
	HD	4	323	124	46.4% (H,S,-)	29.6-63.6	2	53,828	86	1.57 (L,S,-)	1.16-1.99
	Tunneled	10	1,501	424	29.2% (H,S,-)	15.9-44.6	6	167,484	123	0.86 (H,S,-)	0.41-1.32
	Totally implanted	19	3,320	493	15.8% (H,S,-)	9.4-23.5	10	819,022	127	0.15 (M,S,-)	0.09-0.20
CVAD-associated BSI	All	75	31,933	2,899	10.3% (H,S,N)	8.9-11.6	50	1,338,756	2,164	1.63 (H,S,S)	1.40-1.86
	PICC	27	16,428	1,081	8.6% (H,S,-)	7.0-10.2	22	363,208	861	3.06 (H,S,-)	2.39-3.72
	Umbilical	6	498	60	8.7% (H,S,-)	1.5-15.9	1	979	33	33.71 (-,S,-)	21.64-45.78
	Non-tunneled	10	11,020	1,028	8.7% (H,S,-)	3.6-13.8	7	144,885	887	5.86 (H,S,-)	3.38-8.34
	HD	4	323	31	10.4% (L,S,-)	3.7-17.0	2	53,828	23	0.41 (N,S,-)	0.22-0.60
	Tunneled	13	1,992	413	19.9% (H,S,-)	12.6-27.2	8	188,807	189	1.13 (H,S,-)	0.65-1.61
	Totally implanted	15	1,672	286	15.9% (H,S,-)	10.2-21.7	10	587,049	171	0.28 (H,S,-)	0.14-0.42
Thrombosis	All	53	15,979	471	1.7% (H,S,N)	0.8-2.8	30	1,168,248	153	0.08 (M,S,N)	0.04-0.11
	PICC	16	8,482	317	2.1% (H,S,-)	0.5-4.7	12	226,931	61	0.17 (M,S,-)	0.06-0.29
	Umbilical	3	402	12	3.7% (H,N,-)	0.0-12.2	0	-	-	-	-
	Non-tunneled	4	1,370	23	3.7% (H,S,-)	0.0-11.1	2	7,689	13	9.06 (H,N,-)	0.00-28.4
	HD	3	264	7	2.9% (H,N,-)	0.0-12.8	1	30,936	2	0.07 (-,N,-)	0.00-0.18
	Tunneled	12	3,019	42	0.6% (L,S,-)	0.2-1.2	7	335,689	20	0.04 (L,S,-)	0.01-0.07
	Totally implanted	15	2,442	70	1.9% (H,S,-)	0.1-4.9	8	567,003	57	0.06 (H,S,-)	0.01-0.12
Occlusion / blockage	All	53	15,344	1,321	7.4% (H,S,N)	5.5-9.6	32	698,836	823	1.06 (H,S,S)	0.88-1.27
	PICC	23	9,786	837	8.2% (H,S,-)	5.9-10.9	18	269,774	543	2.21 (H,S,-)	1.66-2.77
	Umbilical	3	472	2	0.2% (N,N,-)	0.0-1.2	1	979	0	0.00 (-,N,-)	0.00-1.88
	Non-tunneled	2	1,126	118	8.0% (M,S,-)	2.7-15.5	0	-	-	-	-
	HD	2	233	17	11.1% (H,S,-)	0.0-34.8	1	30,936	8	0.26 (H,S,-)	0.06-0.46
	Tunneled	10	1,485	227	12.1% (H,S,-)	0.4-23.5	7	280,516	216	0.85 (H,S,-)	0.48-1.23
	Totally implanted	13	2,242	120	5.0% (H,S,-)	1.5-9.9	5	116,631	56	0.30 (H,S,-)	0.04-0.57

Dislodgement / migration	All	39	9,784	686	4.7% (H,S,N)	3.2-6.4	23	645,611	437	0.43 (H,S,S)	0.30-0.56
	PICC	14	5,389	389	5.4% (H,S,-)	3.3-8.0	11	203,619	383	1.42 (H,S,-)	0.70-2.14
	Umbilical	1	140	4	2.9% (-,S,-)	0.6-6.4	1	979	4	4.09 (-,S,-)	0.0-8.76
	Non-tunneled	2	1,126	91	3.5% (H,N,-)	0.0-15.2	0	-	-	-	-
	HD	3	264	14	8.8% (H,S,-)	0.1-26.0	1	30,936	3	0.10 (-,N,-)	0.00-0.23
	Tunneled	8	963	89	7.0% (H,S,-)	1.7-15.0	5	154,725	41	0.24 (H,S,-)	0.03-0.46
	Totally implanted	11	1,902	99	2.0% (H,S,-)	0.1-5.2	5	256,962	6	0.02 (N,N,-)	0.00-0.04
Breakage / rupture	All	45	12,092	313	1.6% (H,S,S)	0.9-2.5	29	841,359	240	0.14 (H,S,S)	0.08-0.19
	PICC	19	8,154	279	3.9% (H,S,-)	2.5-5.5	15	226,990	218	0.88 (H,S,-)	0.51-1.26
	Umbilical	1	140	0	0.0% (-,N,-)	0.0-1.2	1	979	0	0.00 (-,N,-)	0.00-1.88
	Non-tunneled	1	34	3	8.8% (-,S,-)	1.2-21.2	0	-	-	-	-
	HD	3	264	2	0.5% (M,N,-)	0.0-5.3	1	30,936	0	0.00 (-,N,-)	0.00-0.06
	Tunneled	8	963	21	1.1% (M,S,-)	0.0-3.1	5	154,725	18	0.08 (M,N,-)	0.00-0.17
	Totally implanted	13	2,179	8	0.0% (N,N,-)	0.0-0.0	7	427,729	4	0.01 (N,N,-)	0.00-0.02
Local infection / phlebitis	All	39	8,217	404	3.1% (H,S,S)	2.0-4.4	28	900,192	304	0.19 (H,S,S)	0.12-0.26
	PICC	15	4,191	220	4.5% (M,S,-)	3.3-5.8	13	176,590	219	1.32 (H,S,-)	0.85-1.79
	Umbilical	1	140	9	6.4% (-,S,-)	2.9-11.2	1	979	9	9.19 (-,S,-)	2.57-15.82
	Non-tunneled	2	259	0	0.0% (L,N,-)	0.0-0.4	1	7,303	0	0.00 (-,N,-)	0.00-0.25
	HD	2	233	3	0.9% (N,N,-)	0.0-2.9	1	30,936	3	0.10 (-,N,-)	0.00-0.23
	Tunneled	9	1,827	113	4.8% (H,S,-)	1.4-9.6	5	154,725	64	0.38 (H,S,-)	0.10-0.65
	Totally implanted	10	1,567	59	1.5% (H,S,-)	0.0-4.5	7	529,659	9	0.01 (N,N,-)	0.00-0.02

BSI = Bloodstream infection; CVAD = Central venous access device; CI = Confidence interval; HD = Haemodialysis; IR = Incidence rate; PICC= Peripherally inserted central catheter; (H,S,S) etc.: first character describes heterogeneity of studies as negligible (N), low (L), moderate (M) or high (H), second describes result of effect-size test (S=significant, N=non-significant), third describes result of test for heterogeneity between sub-groups, where applicable (S=significant, N=non-significant);

CVAD complications

Table 2, Figures 4 and 5 (Supplementary) report the individual and pooled proportion and IR per 1,000 catheter days of CVAD-associated BSI, stratified by CVADs type. Overall, 10.3% (95% CI 8.9%-11.6%; $I^2=95.0\%$; 75 studies; 31,933 CVAD) of pediatric CVADs developed a CVAD-associated BSI with an IR of 1.63 per 1,000 catheter days (95% CI 1.40-1.86; $I^2=97.3\%$; 50 studies;

1,338,756 catheter days). Tunneled CVADs had the highest pooled proportion of CVAD-associated BSI (19.9%; 95% CI 12.6%-27.2%; 1,992 CVAD); while umbilical catheters had the highest pooled IR per 1,000 catheter days (IR 33.7; 95% CI 21.6-45.8; 979 catheter days).

Tunneled CVADs had the highest pooled proportion of occlusion or blockage (12.1%; 95% CI 0.4%-23.5%; 1,485 CVAD) but PICCs had the highest pooled IR per 1,000 catheter days (2.2; 95% CI 1.7-2.8; 269,774 catheter days). Tunneled CVADs had the highest proportion of local infection or phlebitis (4.8%; 95% CI 1.4-9.6; 1,827 catheter days), with umbilical catheters having the highest IR per 1,000 catheter days (9.2; 95% CI 2.6-15.8; 979 catheter days). Totally implanted devices had the lowest proportion and rate of dislodgement per 1,000 catheter days for dislodgement (2.0%, 95% CI 0.1-5.1, 1,902 CVAD; 0.02, 95%CI 0.00-0.04; 256,962 catheter days), and the lowest proportion of breakage / rupture (0.0%, 95%CI 0.0-0.0; 2,179 CVAD).

Subgroup analyses

The results of the subgroup analyses describing the pooled proportion and IR of CVAD failure per 1,000 catheter days across study populations are shown in Table 3. Due to availability of data, subgroup analyses were only carried out on PICCs (neonates and pediatrics; oncology/hematology and all others; outpatients and inpatients), tunneled CVADs (oncology/hematology and all others; outpatients and inpatients) and totally-implantable CVADs (oncology/hematology and all others). The rate of PICC failure per 1,000 catheter days was significantly ($P<0.001$) higher for neonates (IR 25.9; 95% CI 21.2-30.5) compared with pediatric patients (IR 5.6; 95% CI 3.2-8.1). PICCs managed in outpatient facilities had significantly ($P=0.007$) lower proportion of failure (24.5%; 95% CI 16.9-32.8) in comparison to inpatient facilities (35.1%; 95% CI 27.3-43.2). Comparatively tunneled CVADs which were managed in outpatients facilities had significantly ($P=0.016$) higher proportion of failure (37.8%; 95% CI 17.0-61.3) in comparison to inpatient facilities (12.6%; 95% CI 8.5-17.3).

Table 3: Subgroup analyses: Proportions and incidence rates of CVAD failure per device across study populations

CVAD type	Study population	Proportion of failure					Incidence rates of failure per 1,000 cath. days				
		Studies	CVAD	Outcomes	Pooled %	95% CI	Studies	Catheter days	Outcomes	Pooled incidence rates	95% CI
PICC	Pooled	22	8,596	2,346	30.2% (H,S,N)	23.9-36.9	17	176,568	1,581	13.06 (H,S,S)	10.39-15.73
	Neonates	11	4,521	1,472	35.4% (H,S,-)	25.0-46.6	8	29,744	700	25.87 (H,S,-)	21.23-30.52
	Paediatrics	11	4,138	894	25.0% (H,S,-)	18.2-32.5	9	146,824	881	5.64 (H,S,-)	3.18-8.09
	Pooled	23	10,163	2,791	30.1% (H,S,N)	24.4-36.1	18	241,019	2,006	12.43 (H,S,N)	9.98-14.89
	Onc/haem	4	357	119	30.0% (H,S,-)	15.2-47.3	3	54,285	114	2.54 (H,S,-)	0.55-4.53
	All others	19	9,743	2,652	30.1% (H,S,-)	23.9-36.7	15	186,734	1,892	15.80 (H,S,-)	12.44-19.15
	Pooled	51	10,072	2,783	31.3% (H,S,N)	25.4-37.4	18	241,019	2,006	12.43 (H,S,S)	9.98-14.89
Outpatients	32	3,673	748	24.5% (H,S,-)	16.9-32.8	7	128,133	743	5.04 (H,S,-)	2.28-7.80	
	Inpatients	19	6,399	2,035	35.1% (H,S,-)	27.3-43.2	11	112,886	1,263	19.91 (H,S,-)	15.15-24.67
Tunneled	Pooled	11	1,501	424	29.2% (H,S,N)	15.9-44.6	6	167,484	123	0.87 (H,S,N)	0.41-1.32
	Onc/haem	8	1,410	395	31.1% (H,S,-)	15.8-48.9	5	166,068	122	0.88 (H,S,-)	0.41-1.34
	All others	2	91	29	21.3% (H,S,-)	0.3-57.5	1	1,416	1	0.71 (-,N,-)	0.00-2.67
	Pooled	7	1,281	375	33.6% (H,S,S)	16.1-53.8	4	146,740	102	0.84 (H,S,N)	0.32-1.35
	Outpatients	6	1,058	347	37.8% (H,S,-)	17.0-61.3	3	94,901	74	1.20 (H,S,-)	0.30-2.10
Inpatients	1	223	28	12.6% (-,S,-)	8.5-17.3	1	51,839	28	0.54 (-,S,-)	0.33-0.75	
Totally implant- ted	Pooled	18	3,320	493	15.8% (H,S,N)	9.4-23.5	10	819,022	127	0.15 (M,S,-)	0.09-0.20
	Onc/haem	17	2,694	361	15.2% (H,S,-)	8.1-23.9	10	819,022	127	0.15 (M,S,-)	0.09-0.20
	All others	2	626	132	21.1% (L,S,-)	17.9-24.4	0	-	-	-	-

CVAD = Central venous access device; CI = Confidence interval; IR = Incidence rate; PICC= Peripherally inserted central catheter; onc/haem= oncology or haematology; (H,S,N) etc.: first character describes heterogeneity of studies as low (L), moderate (M) or high (H) / second describes result of effect-size test (S=significant, N=non-significant) / third describes result of test for heterogeneity between sub-groups, where applicable (S=significant, N=non-significant)

Sensitivity analyses

Table 4 describes the results of sensitivity analyses comparing pooled proportion and IR of CVAD failure across study methods. The majority of studies reporting CVAD failure were completed using retrospective methods (73.6% studies; 64.8% CVAD; 78.9% catheter days). Overall IRs of failure were not different between prospective and retrospective studies. There was significant difference between study types in reported proportions of failure of non-tunneled devices (prospective: 22.4%; 95% CI 20.0-25.0; retrospective: 8.8%; 95% CI 1.2-21.2; p=0.046). Sensitivity analyses could not be undertaken for HD catheters as all included studies used retrospective study methods.

Table 4: Sensitivity analyses: Proportions and incidence rates of CVAD failure per device reported in prospective and retrospective studies

CVAD type	Study method	Proportion of failure					Incidence rate of failure per 1,000 cath. days				
		Studies	CVAD	Outcomes	Pooled %	95% CI	Studies	Catheter days	Outcomes	Pooled incidence rate	95% CI
PICC	Pooled	23	10,163	2,791	30.1% (H,S,N)	24.4-36.1	18	241,019	2,006	12.43 (H,S,N)	9.98-14.89
	Retrospect.	17	6,609	1,876	28.3% (H,S,-)	21.1-36.1	14	157,350	1,272	12.49 (H,S,-)	9.69-15.30
	Prospective	6	3,554	915	35.1% (H,S,-)	23.8-47.4	4	83,669	734	13.17 (H,S,-)	5.10-21.25
Non-tunneled	Pooled	2	1,126	248	16.7% (M,S,S)	6.1-30.9	0	-	-	-	-
	Retrospect.	1	34	3	8.8% (-,S,-)	1.2-21.2	0	-	-	-	-
	Prospective	1	1,092	245	22.4% (-,S,-)	20.0-25.0	0	-	-	-	-
Tunneled	Pooled	10	1,501	424	29.2% (H,S,N)	15.9-44.6	6	167,484	123	0.87 (H,S,N)	0.41-1.32
	Retrospect.	7	1,110	291	30.6% (H,S,-)	15.4-48.4	4	129,538	96	1.08 (H,S,-)	0.40-1.75
	Prospective	3	391	133	26.1% (H,S,-)	1.6-65.0	2	37,946	27	0.68 (H,S,-)	0.04-1.32
Totally implant- ted	Pooled	19	3,320	493	15.8% (H,S,N)	9.4-23.5	10	819,022	127	0.15 (M,S,N)	0.09-0.20
	Retrospect.	14	2,547	420	15.0% (H,S,-)	9.9-20.9	8	681,196	117	0.17 (M,S,-)	0.10-0.24
	Prospective	5	773	73	18.7% (H,S,-)	0.0-54.7	2	137,826	10	0.06 (N,S,-)	0.02-0.11

Retrospect = retrospective; CVAD = Central venous access device; CI = Confidence interval; IR = Incidence rate; PICC= Peripherally inserted central catheter; (H,S,N) etc.: first character describes heterogeneity of studies as low (L), moderate (M) or high (H) / second describes result of effect-size test (S=significant, N=non-significant) / third describes result of test for heterogeneity between sub-groups, where applicable (S=significant, N=non-significant);

Discussion

This study has, for the first time, carefully found, critiqued and synthesized CVAD failure rates, across CVAD types and pediatric populations. The results clearly show that failure of CVADs throughout pediatrics is a substantial and significant problem, with one in four failing. This is especially prevalent within the lifespan of umbilical catheters and PICCs. These devices have been traditionally recommended for short to medium term use, [4, 6] but the PICCs and umbilical catheters described within the included studies failed prior to the completion of therapy in 11-30% of cases, with a pooled incidence failure rate of 12-29 per 1,000 catheter days. This high rate of pediatric umbilical catheter and PICC failure is also evident in reported rates of catheter-associated BSI, occlusion, dislodgement and local infection/phlebitis. There is no previous umbilical catheter meta-analysis to benchmark these results and only small studies included within this review. However our results in PICCs and recent studies by Chopra and colleagues in adults [126, 127] have demonstrated that PICCs are substantially more problematic than originally thought. The outcomes of PICCs used in clinical practice needs to be cautiously and systematically monitored. Clinicians should be made aware of the high rates of failure associated with their use, and should question whether PICCs are the suitable intravascular device for their patient group. Research needs to be undertaken to discover and evaluate innovative strategies to reduce PICC and umbilical catheter failures, through examining insertion procedures, securement devices and patency practices.

Totally implanted devices were frequently associated with the lowest pooled incidence rate of failure and complications. These devices have previously been credited with improved ease of medication administration, decreased infectious risks and improved patient quality of life.[76] While the insertion of totally implanted and other tunneled CVAD requires the skills and resources of an experienced surgeon and operating theatre, fatal complications from cardiac tamponade and major vessel injury are rare.[10] It may be that due to lower rates of failure and complications, the cost-effectiveness of totally implanted devices is superior to other CVAD types for some population groups. Randomized controlled trials (RCTs) studying comparative clinical and cost-effectiveness

of totally implanted devices, compared to other intravascular device types in suitable populations (e.g. cystic fibrosis) are urgently needed.

Given that many cases of CVAD failure and complications are thought to be avoidable,[6] the overall rate of CVAD failure and complication for children across all CVAD types appears variable, but remains unacceptably high. There are no current benchmarked targets for clinicians to compare their current rates of CVAD failure and complications, with the exception of CVAD-associated BSI in the ICU [128, 129]. Quality improvement studies have previously demonstrated a marked reduction in complication rates associated with CVAD in pediatrics and neonates, indicating that complication rates are dependent upon the care provided by multidisciplinary clinicians.[130-132] Previous international focus on the prevention of CVAD complications from organizations such as the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) has been solely focused on CVAD-associated BSI, and generally in the ICU setting. However, our data demonstrates that there is also a high rate of failure due to occlusion, thrombosis, breakage and dislodgement. The prevalence of thrombosis is likely to be higher than described, as some included studies relied upon clinical suspicion of thrombosis, rather than routine imaging, significantly underestimating the true proportion/rate of CVAD-related thrombosis. These mechanical complications also result in an interruption to necessary treatment and the insertion of new CVAD, and should be the focus of the next generation of multidisciplinary international CVAD campaigns for improvement.

The subgroup analyses demonstrated the variation in CVAD failure based upon patient age. The variation was most evident in comparisons involving PICCs, where neonates had a significantly higher rate of failure ($p < 0.001$), than the remaining pediatric population, with a failure rate of 25.5 per 1,000 catheter days. PICCs are extensively used to provide hyperosmolar solutions, inotropic medicines and parenteral nutrition within the neonatal period.[124] The neonates requiring PICCs are often very low birth weight (smaller than 1,500g at birth) or extremely low birth weight (smaller

than 1,000 g at birth), and are at greatest risk for failure and its sequelae.[60, 117] The increasing use of PICCs within the neonatal population requires caution and careful surveillance, and should be the focus of significant innovation for improvement.

Our study has demonstrated current gaps in the breadth and quality of research into pediatric CVAD failure and complications. Further prospective cohort studies estimating the rates of failure and complications of CVAD in pediatrics are necessary to provide benchmarking targets and inform practice innovations. Meta-synthesis of the two studies reporting non-tunneled CVAD failure reported a failure proportion of 16.7%, however no studies reported an estimation of catheter days. In accordance with previous international focus, the majority of non-tunneled CVAD studies which reported CVAD complications only reported CVAD-associated BSI. The failure and complications associated with HD and umbilical catheters were also inadequately reported, with only six studies of 749 CVADs available. Considering the prevalence and importance of umbilical, HD and non-tunneled CVADs within pediatric healthcare management, reliable measurement of their failure and complications are essential. Additionally, while multiple cohort studies described the failure of PICCs and totally implanted devices, the majority used retrospective methods, using less reliable means of data collection. Future descriptions of CVAD failure need to be planned prospectively, use validated definitions for outcome measures and report denominator information including catheter days.

Our study results should be interpreted in the context of some limitations. Not all study authors were able to provide the total number of catheter days, which limited their data being included in the meta-analysis per 1,000 catheter days. Such time-based analysis is the more valid way to compare CVAD complication incidence, since the different dwell times typical of the CVAD types already exposes the patient to more or less risk of complications. Secondly, the unavoidable heterogeneity of the study populations in the included studies may have impacted on the generalizability of the results, subgroup analyses were used to reduce this problem. The levels of

statistical heterogeneity of the final analyses are indicative of the heterogeneous group of pediatric patients which require CVADs. This heterogeneity needs to be recognized before applying the results to local individual healthcare institutions. Thirdly, while our review was limited to include studies up to ten years of age, many quality improvement activities have been instituted in pediatric facilities to prevent complications and failures associated with CVAD within that period. It is therefore possible that the pooled data may therefore overestimate the burden of device failure in 2015. Finally, while our study presents the association between CVAD-types and failure and complications, these results do not reflect causation. Without RCTs comparing the various CVAD types, it is impossible to assert that one CVAD type reduces complications and failure in comparison to another. Future updates of this review may also consider the inclusion of the ‘standard care’ arm of RCTs which evaluated various interventions.

Comparison with other studies

There has not been a previous systematic review undertaken in pediatrics examining the failure and complications associated with different CVADs. Landmark work by McGee and Gould [133] described the prevention, treatment and incidence of CVAD failure in the adult population. While primarily focused on describing strategies to prevent and treat CVAD complications, their systematic review reported an overall incidence of CVAD failure of greater than 15%, with mechanical complications reported in 5% to 19% of patients, and infectious complications in 5 to 26%. Our study describes a higher rate of mechanical and infectious complications which may be due to differing synthesis methodology and the underlying vulnerability and other clinical characteristics of the population studied.

Conclusion and future research

International healthcare institutions have highlighted the significance of CVAD failure associated with BSI. This systematic review has described the broader, multi-focal rate of CVAD failure and complications across CVAD type in pediatrics within the international healthcare community.

Contextually, from the 82 US hospitals reporting to the National Healthcare Safety Network in 2013, greater than 2.7 million CVAD catheter days in the pediatric and neonatal population were registered. [134] Applying the rate of failure described in our study, 5,457 pediatric and neonatal CVADs in US hospitals failed prior to completion of treatment in one year alone. These failures place a massive economic and physical burden on the US healthcare system, patients and families.

Strategies have been developed to prevent CVAD failure by focusing on different aspects of infectious and mechanical complications, and their pathogenesis. The current rate of CVAD failure in pediatrics demonstrates that further evidence-based improvements to their insertion and maintenance are necessary. This includes insertion and maintenance practices surrounding CVAD dressing and securement, needleless access devices, flushing procedures and CVAD materials. Research is required urgently to develop and apply innovative and effective solutions to prevent CVAD failure in this vulnerable pediatric group.

Acknowledgements: Thank you to all the study authors who were able to contribute additional data.

Word count: 3,988/4,000

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Figure 1: PRISMA flow chart of study selection

Supplementary Figures

Figure 2: Forest plot showing the pooled, weighted proportion of CVAD failure across CVAD type
Random effects meta-analysis showing the individual and pooled weighted proportion of CVAD failure; stratified by CVAD type

Figure 3: Forest plot showing the pooled, weighted incidence rate of CVAD failure per 1,000 catheter days across CVAD type
Inverse variance meta-analysis showing the individual and pooled incidence rate of CVAD failure per 1,000 catheter days; stratified by CVAD type

Figure 4: Forest plot showing the pooled, weighted proportion of CVAD-associated bloodstream infection across CVAD type
Random effects meta-analysis showing the individual and pooled weighted proportion of CVAD-associated bloodstream infection; stratified by CVAD type

Figure 5: Forest plot showing the pooled, weighted incidence rate of CVAD-associated bloodstream infection per 1,000 catheter days across CVAD type
Inverse variance meta-analysis showing the individual and pooled incidence rate of CVAD-associated bloodstream infection per 1,000 catheter days; stratified by CVAD type