Complications of Central Venous Access Devices: A Systematic Review

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abstract

CONTEXT: The failure and complications of central venous access devices (CVADs) result in interrupted medical treatment, morbidity, and mortality for the patient. The resulting insertion of a new CVAD further contributes to risk and consumes extra resources.

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

DATA SOURCES: Central Register of Controlled Trials, PubMed, and Cumulative Index to Nursing and Allied Health databases were systematically searched up 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 10 years. CVAD failure was defined as CVAD loss of function before the completion of necessary treatment, and complications were defined as CVAD-associated bloodstream infection, CVAD local infection, dislodgement, occlusion, thrombosis, and breakage.

DATA EXTRACTION: Data were independently extracted and critiqued for quality by 2 authors.

RESULTS: Seventy-four cohort studies met the inclusion criteria, with mixed quality of reporting and methods. Overall, 25% of CVADs failed before completion of therapy (95% confidence interval [CI] 20.9%–29.2%) at a rate of 1.97 per 1000 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 1000 catheter days in umbilical catheters (28.6 per 1000 catheter days [95% CI 17.4–39.8]). Totally implanted devices had the lowest rate of failure per 1000 catheter days (0.15 [95% CI 0.09–0.20]).

LIMITATIONS: The inclusion of nonrandomized and noncomparator studies may have affected the robustness of the research.

CONCLUSIONS: CVAD failure and complications in pediatrics are a significant burden on the health care system internationally.

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Ms Ullman conceptualized and designed the study, carried out the initial analysis, and drafted the initial manuscript; Ms Marsh assisted with the acquisition of data and critically reviewed the manuscript; Mr Mihala carried out the subsequent analysis; Drs Cooke and Rickard assisted with the conception and design of the study; Mr Mihala and Drs Cooke and Rickard assisted with the interpretation of the data and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Worldwide, millions of central venous access devices (CVADs) are used in health care facilities to provide supportive and interventional therapies during acute and chronic illness. Within pediatrics, the therapies that CVADs facilitate are diverse, varying from lifelong 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]

A range of CVADs are available. Health care professionals choose a CVAD on the basis of the predicted duration of clinical necessity (short, medium, or long term), risk of adverse outcomes, treatment requirements (eg, hemodialysis), frequency of use, and vein availability. Traditionally, nontunneled and umbilical CVADs have been recommended for short-term use (7 to 10 days),[4–6] peripherally inserted central catheters (PICCs) for short- to medium-term use (4 weeks to 6 months),[4,6] and tunneled CVADs and totally implantable catheters for long-term use (months to 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, or removal.

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 health care 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, theater time, monitoring devices, and radiologic 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 had, the more complex the procedure becomes, as CVAD failures can result in venous damage and insufficiency.[12] Even after successful CVAD insertion, many mechanisms may result in CVAD failure or complications, many of which are considered preventable.[14,15]

CVADs place patients at risk for local and systemic infectious complications, including local site infection (eg, 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, 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 worldwide, with an estimated 41 000 occurring in US 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 BSIs have an attributable cost of between US$5821 and $60 536 per event[22–24] and frequently result in device failure.

Because 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, as a result of drag from multiple heavy infusion tubes, catching on environmental structures (eg, 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, or catheter tip thrombus or the catheter tip being positioned 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 cause malfunction only 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 CVAD types.

METHODS

The study used standard methods for systematic review and is reported in accordance with 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]: (1) cohort design (prospective or retrospective)[2]; (2) study participants aged 0 to 18 years[3]; and (3) failure and/or complications of CVADs included as outcome measures[4] and reported as outcomes per PICCs, umbilical catheters, nontunneled percutaneous CVADs, hemodialysis (HD) catheters, tunneled CVADs, or totally implantable CVADs. The review was limited to observational studies 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 the patient's underlying condition. We excluded studies if they were not written in English and were >10 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 before the completion of necessary treatment.[27–29] The secondary outcomes were CVAD complications after successful CVAD insertion. These were as follows: (1) CVAD-associated BSI: minimum definition of a laboratory-confirmed BSI that is not secondary to an infection at another body site, with a CVAD in place for >2 days[20]; (2) CVAD-associated thrombosis: development of thrombosed vessel (partial or complete) at the CVAD site diagnosed via ultrasound[30]; (3) occlusion or blockage: as defined by study investigators, including partial and full blockage of the CVAD lumen or lumens, irrespective of occlusion treatment[30]; (4) dislodgement or migration: as defined by study investigators, including partial, complete, and accidental removal resulting 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, including a visible split in CVAD 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 investigators, including exit, entrance, and tunnel infections and phlebitis.[5]

Search Strategy and Study Selection

The Cochrane Central Register of Controlled Trials (the Cochrane Library), US National Library of Medicine National Institutes of Health (PubMed), and Cumulative Index to Nursing and Allied Health databases were systematically and independently searched on January 27, 2015. Medical subject headings were developed by a health care 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 2 independent investigators (AJU, NM) using a standardized data extraction form. Study data were extracted regarding the number of patients, catheters, patient population, CVAD type, study method, frequency of CVAD failures and complications, catheter days, and country of origin. For studies with missing data (eg, CVAD catheter days), the study authors were contacted via e-mail if possible.

Statistical Methods

Because only cohort studies were included, descriptive statistics have been used to provide summative information of the study population and results. Score confidence intervals (CIs) 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 by using inverse variance, with the DerSimonian and Laird method, per 1000 catheter days and 95% CI. Heterogeneity (between studies) was assessed by using the I^2 measure, categorized as low (<25%), moderate (25% to 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 <.05. Extreme or obviously incorrect data were rechecked 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 CVAD 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 1000 catheter days, and 95% CI, where possible.

Risk of Bias Assessment and Sensitivity Analyses

In accordance with the Meta-analysis of Observational Studies in Epidemiology guidelines,[26] study quality was assessed by examination of key components of an included study's design, in comparison with an overall score. Based on elements of the 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 proportions, IR per 1000 catheter days, and 95% CI per CVAD 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 because they included both adult and pediatric participants,[35,36] reported intraoperative CVAD complications,[11,37–39] did not provide separate outcome data per CVAD 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.

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] 3 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 ages 0 to 17 years and required treatment of oncologic or hematologic conditions, support during intensive care admission, or central access for hemodialysis, postsurgical, or general infusion therapy or parenteral nutrition. Table 1 describes the populations and CVAD types described in the included studies.

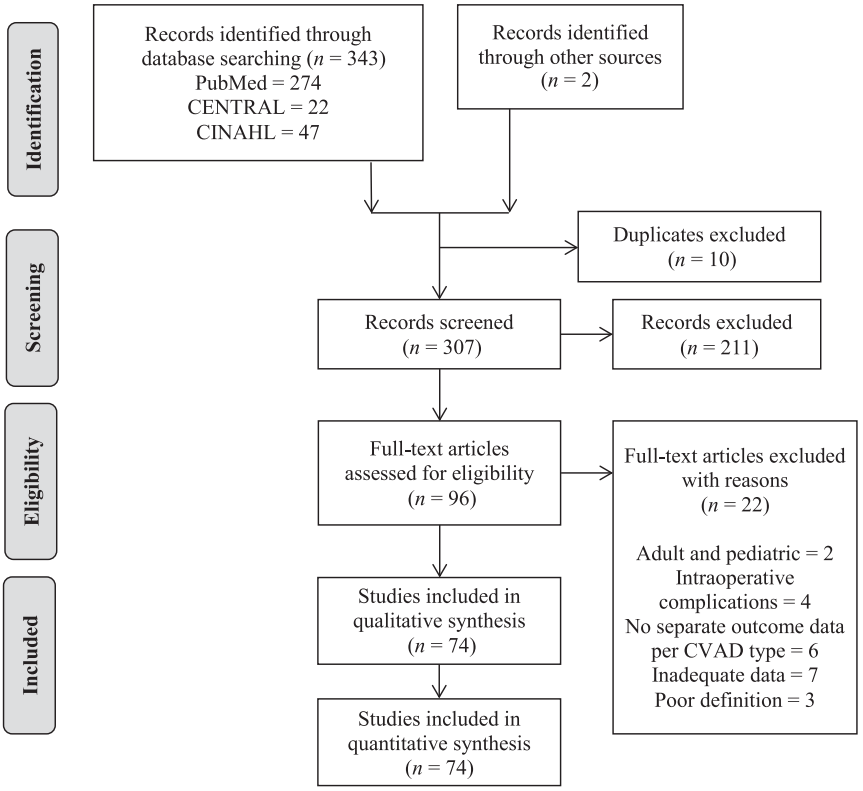

FIGURE 1
PRISMA flow chart of study selection.

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 in the review. Two studies[30,116] provided combined "all-type" infection or mechanical failure outcomes, instead of providing separated local and systemic infection, occlusion, and dislodgement data. These data also were 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 1000 catheter days.

Synthesis of Results

CVAD Failure

Table 2 reports the overall pooled proportion and IR of CVAD failure and complications across CVAD types. Supplemental Figures 2 and 3 report the individual and pooled proportions and IRs of CVAD failure across CVAD types. Overall, 25% (95% CI 20.9%–29.2%) of pediatric CVADs failed before completion of therapy, with an IR of 1.97 per 1000 catheter days (95% CI 1.71–2.23; 60 studies; 16 859 CVADs; 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% to 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 1000 catheter days (28.6 [95% CI 17.4–39.8]), with 2 studies and 1 study, respectively (426 CVADs;

TABLE 1 Studies Included, With Patient Population and CVAD Type

CVAD Type	NICU	PICU	Hematology/ Oncology	General Pediatrics	Outpatients (Including Gastroenterological Failure)	Total
PICC	16	—	6	8	3	33
Umbilical	5	—	—	1	—	6
Nontunneled, percutaneous	3	5	—	2	—	10
Hemodialysis	—	—	—	4	4	8
Tunneled, partially implanted	—	1	13	5	1	20
Totally implantable	—	—	19	4	1	24
Total	24	6	38	24	9	

—, none.

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 1000 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 1000 catheter days (0.15 [95% CI 0.09–0.20]; 819 022 catheter days). Because of a lack of data, the rate of CVAD failure per 1000 catheter days for nontunneled, percutaneous CVADs could not be estimated.

CVAD Complications

Table 2 and Supplemental Figures 4 and 5 report the individual and pooled proportions and IRs per 1000 catheter days of CVAD-associated BSI, stratified by CVAD type. Overall, 10.3% (95% CI 8.9%–11.6%; I^2 = 95.0%; 75 studies; 31 933 CVADs) of pediatric CVADs developed a CVAD-associated BSI, with an IR of 1.63 per 1000 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 BSIs (19.9% [95% CI 12.6%–27.2%]; 1992 CVADs), whereas umbilical catheters had the highest pooled IR per 1000 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%]; 1485 CVADs), but PICCs had the highest pooled IR per 1000 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%]; 1827 catheter days), with umbilical catheters having the highest IR per 1000 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 1000 catheter days (2.0% [95% CI 0.1%–5.1%], 1902 CVADs; 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%]; 2179 CVADs).

Subgroup Analyses

The results of the subgroup analyses describing the pooled proportions and IRs of CVAD failure per 1000 catheter days across study populations are shown in Table 3. Due to availability of data, subgroup analyses were carried out only 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 1000 catheter days was significantly ($P < .001$) 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 ($P = .007$) lower proportions of failure (24.5% [95% CI 16.9%–32.8%]) in comparison with inpatient facilities (35.1% [95% CI 27.3%–43.2%]). Comparatively, tunneled CVADs that were managed in outpatient facilities had significantly ($P = .016$) higher proportions of failure (37.8% [95% CI 17.0%–61.3%]) than those managed in inpatient facilities (12.6% [95% CI 8.5%–17.3%]).

Sensitivity Analyses

Table 4 describes the results of sensitivity analyses comparing pooled proportions and IRs of CVAD failure across study methods. The majority of studies reporting CVAD failure used retrospective methods (73.6% of studies; 64.8% of CVADs; 78.9% of catheter days). Overall IRs of failure were not different between prospective and retrospective studies. There was a significant difference between study types in reported proportions of failure of nontunneled devices (prospective, 22.4% [95% CI 20.0%–25.0%]; retrospective, 8.8% [95% CI 1.2%–21.2%]; $P = .046$). Sensitivity analyses could not be undertaken for HD catheters, as all included studies used retrospective study methods.

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 1 in 4 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 before the completion of therapy in 11% to 30% of cases, with a pooled incidence failure rate of 12 to 29 per 1000 catheter days. This high rate of pediatric umbilical catheter and PICC failure is also evident in reported rates of catheter-associated

TABLE 2 Proportions and Incidence Rates of CVAD Complications Across Device Type in Included Studies

Event and CVAD Type	Proportion of Complications					Incidence Rates of Complications per 1000 Catheter Days				
	Studies	CVADs	Outcomes	Pooled %	95% CI	Studies	Catheter Days	Outcomes	Pooled IR	95% CI
Failure										
All	60	16 859	4121	25.0[d,e,g]	20.9–29.2	37	1 282 332	2370	1.97[d,e,g]	1.71–2.23
PICC	23	10 163	2771	30.1[d,e]	24.4–36.1	17	241 019	2006	12.43[d,e]	9.98–14.89
Umbilical	2	426	41	11.0[d,e]	0.7–30.2	1	979	28	28.60[e]	17.44–39.77
Nontunneled	2	1126	248	16.7[c,e]	6.1–30.9	0	—	—	—	—
HD	4	323	124	46.4[d,e]	29.6–63.6	2	53 828	86	1.57[b,e]	1.16–1.99
Tunneled	10	1501	424	29.2[d,e]	15.9–44.6	6	167 484	123	0.86[d,e]	0.41–1.32
Totally implanted	19	3320	493	15.8[d,e]	9.4–23.5	10	819 022	127	0.15[c,e]	0.09–0.20
CVAD-associated BSI										
All	75	31 933	2899	10.3[d,e,h]	8.9–11.6	50	1 338 756	2164	1.63[d,e,g]	1.40–1.86
PICC	27	16 428	1081	8.6[d,e]	7.0–10.2	22	363 208	861	3.06[d,e]	2.39–3.72
Umbilical	6	498	60	8.7[d,e]	1.5–15.9	1	979	33	33.7[e]	21.64–45.78
Nontunneled	10	11 020	1028	8.7[d,e]	3.6–13.8	7	144 885	887	5.86[d,e]	3.38–8.34
HD	4	323	31	10.4[b,e]	3.7–17.0	2	53 828	23	0.41[a,e]	0.22–0.60
Tunneled	13	1992	413	19.9[d,e]	12.6–27.2	8	188 807	189	1.13[d,e]	0.65–1.61
Totally implanted	15	1672	286	15.9[d,e]	10.2–21.7	10	587 049	171	0.28[d,e]	0.14–0.42
Thrombosis										
All	53	15 979	471	1.7[d,e,h]	0.8–2.8	30	1 168 248	153	0.08[c,e,h]	0.04–0.11
PICC	16	8482	317	2.1[d,e]	0.5–4.7	12	226 931	61	0.17[c,e]	0.06–0.29
Umbilical	3	402	12	3.7[d,f]	0.0–12.2	0	—	—	—	—
Nontunneled	4	1370	23	3.7[d,e]	0.0–11.1	2	7689	13	9.06[d,f]	0.00–28.4
HD	3	264	7	2.9[d,f]	0.0–12.8	1	30 936	2	0.07[f]	0.00–0.18
Tunneled	12	3019	42	0.6[b,e]	0.2–1.2	7	335 689	20	0.04[b,e]	0.01–0.07
Totally implanted	15	2442	70	1.9[d,e]	0.1–4.9	8	567 003	57	0.06[d,]	0.01–0.12
Occlusion/blockage										
All	53	15 344	1321	7.4[d,e,h]	5.5–9.6	32	698 836	823	1.06[d,e,g]	0.85–1.27
PICC	23	9786	837	8.2[d,e]	5.9–10.9	18	269 774	543	2.21[d,e]	1.66–2.77
Umbilical	3	472	2	0.2[a,f]	0.0–1.2	1	979	0	0.00[f]	0.00–1.88
Nontunneled	2	1126	118	8.0[c,e]	2.7–15.5	0	—	—	—	—
HD	2	233	17	11.1[d,e]	0.0–34.8	1	30 936	8	0.26[d,e]	0.06–0.46
Tunneled	10	1485	227	12.1[d,e]	0.4–23.5	7	280 516	216	0.85[d,e]	0.48–1.23
Totally implanted	13	2242	120	5.0[d,e]	1.5–9.9	5	116 631	56	0.30[d,e]	0.04–0.57
Dislodgement/migration										
All	39	9784	686	4.7[d,e,h]	3.2–6.4	23	645 611	437	0.43[d,e,g]	0.30–0.56
PICC	14	5389	389	5.4[d,e]	3.3–8.0	11	203 619	383	1.42[d,e]	0.70–2.14
Umbilical	1	140	4	2.9[e]	0.6–6.4	1	979	4	4.09[e]	0.0–8.76
Nontunneled	2	1126	91	3.5[d,f]	0.0–15.2	0	—	—	—	—
HD	3	264	14	8.8[d,e]	0.1–26.0	1	30 936	3	0.10[f]	0.00–0.23
Tunneled	8	963	89	7.0[d,e]	1.7–15.0	5	154 725	41	0.24[d,e]	0.03–0.46
Totally implanted	11	1902	99	2.0[d,e]	0.1–5.2	5	256 962	6	0.02[a,f]	0.00–0.04
Breakage/rupture										
All	45	12 092	313	1.6[d,e,g]	0.9–2.5	29	841 359	240	0.14[d,e,g]	0.08–0.19
PICC	19	8154	279	3.9[d,e]	2.5–5.5	15	226 990	218	0.88[d,e]	0.51–1.26
Umbilical	1	140	0	0.0[f]	0.0–1.2	1	979	0	0.00[f]	0.00–1.88
Nontunneled	1	34	3	8.8[e]	1.2–21.2	0	—	—	—	—
HD	3	264	2	0.5[c,f]	0.0–5.3	1	30 936	0	0.00[f]	0.00–0.06
Tunneled	8	963	21	1.1[c,e]	0.0–3.1	5	154 725	18	0.08[c,f]	0.00–0.17
Totally implanted	13	2179	8	0.0[a,f]	0.0–0.0	7	427 729	4	0.01[a,f]	0.00–0.02
Local infection/phlebitis										
All	39	8217	404	3.1[d,e,g]	2.0–4.4	28	900 192	304	0.19[d,e,g]	0.12–0.26
PICC	15	4191	220	4.5[c,e]	3.3–5.8	13	176 590	219	1.32[d,e]	0.85–1.79
Umbilical	1	140	9	6.4[e]	2.9–11.2	1	979	9	9.19[e]	2.57–15.82
Nontunneled	2	259	0	0.0[b,f]	0.0–0.4	1	7303	0	0.00[f]	0.00–0.25
HD	2	233	3	0.9[a,f]	0.0–2.9	1	30 936	3	0.10[f]	0.00–0.23
Tunneled	9	1827	113	4.8[d,e]	1.4–9.6	5	154 725	64	0.38[d,e]	0.10–0.65
Totally implanted	10	1567	59	1.5[d,e]	0.0–4.5	7	529 659	9	0.01[a,f]	0.00–0.02

Heterogeneity of studies [a]negligible, [b]low, [c]moderate, or [d]high.
Effect-size test [e]significant or [f]nonsignificant.
Test for heterogeneity between subgroups [g]significant or [h]nonsignificant.

TABLE 3 Subgroup Analyses: Proportions and Incidence Rates of CVAD Failure per Device Across Study Populations

CVAD Type and Study Population	Proportion of Failure					Incidence Rates of Failure per 1000 Catheter Days				
	Studies	CVAD	Outcomes	Pooled %	95% CI	Studies	Catheter Days	Outcomes	Pooled IR	95% CI
PICC										
Neonates	11	4521	1472	35.4[d,e]	25.0–46.6	8	29 744	700	25.87[d,e]	21.23–30.52
Pediatrics	11	4138	894	25.0[d,e]	18.2–32.5	9	146 824	881	5.64[d,e]	3.18–8.09
Pooled	22	8596	2346	30.2[d,e,h]	23.9–36.9	17	176 568	1581	13.06[d,e,g]	10.39–15.73
Oncology/hematology	4	357	119	30.0[d,e]	15.2–47.3	3	54 285	114	2.54[d,e]	0.55–4.53
All others	19	9743	2652	30.1[d,e]	23.9–36.7	15	186 734	1892	15.80[d,e]	12.44–19.15
Pooled	23	10 163	2791	30.1[d,e,h]	24.4–36.1	18	241 019	2006	12.43[d,e,h]	9.98–14.89
Outpatients	32	3673	748	24.5[d,e]	16.9–32.8	7	128 133	743	5.04[d,e]	2.28–7.80
Inpatients	19	6399	2035	35.1[d,e]	27.3–43.2	11	112 886	1263	19.91[d,e]	15.15–24.67
Pooled	51	10 072	2783	31.3[d,e,h]	25.4–37.4	18	241 019	2006	12.43[d,e,g]	9.98–14.89
Tunneled										
Oncology/hematology	8	1410	395	31.1[d,e]	15.8–48.9	5	166 068	122	0.88[d,e]	0.41–1.34
All others	2	91	29	21.3[d,e]	0.3–57.5	1	1416	1	0.71[f]	0.00–2.67
Pooled	11	1501	424	29.2[d,e,h]	15.9–44.6	6	167 484	123	0.87[d,e,h]	0.41–1.32
Outpatients	6	1058	347	37.8[d,e]	17.0–61.3	3	94 901	74	1.20[d,e]	0.30–2.10
Inpatients	1	223	28	12.6[e]	8.5–17.3	1	51 839	28	0.54[e]	0.33–0.75
Pooled	7	1281	375	33.6[d,e,g]	16.1–53.8	4	146 740	102	0.84d[e,h]	0.32–1.35
Totally implanted										
Oncology/hematology	17	2694	361	15.2[d,e]	8.1–23.9	10	819 022	127	0.15[c,e]	0.09–0.20
All others	2	626	132	21.1[b,e]	17.9–24.4	0	—	—	—	—
Pooled	18	3320	493	15.8[d,e,h]	9.4–23.5	10	819 022	127	0.15[c,e]	0.09–0.20

Heterogeneity of studies [a]negligible, [b]low, [c]moderate, or [d]high.
Effect-size test [e]significant or [f]nonsignificant.
Test for heterogeneity between subgroups [g]significant or [h]nonsignificant. —, none.

BSI, occlusion, dislodgement, and local infection/phlebitis. There is no previous umbilical catheter meta-analysis to benchmark these results, and only small studies are 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 need 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] Although the insertion of totally implanted and other tunneled CVADs requires the skills and resources of an experienced surgeon and an operating theater, fatal complications from cardiac tamponade and major vessel injury are rare.[10] It may be that, because of lower rates of failure and complications, the cost-effectiveness of totally implanted devices is superior to that of other CVAD types for some population groups. Randomized controlled trials (RCTs) studying comparative clinical and cost-effectiveness of totally implanted devices, compared with other intravascular device types in suitable populations (eg, 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 depend on 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 and the Centers for Disease Control and Prevention has been solely on CVAD-associated BSI, and generally in the ICU setting. However, our data demonstrate 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 on clinical suspicion of thrombosis, rather than routine imaging, significantly underestimating the true proportion/rate of CVAD-related thrombosis. These mechanical complications also

TABLE 4 Sensitivity Analyses: Proportions and Incidence Rates of CVAD Failure per Device Reported in Prospective and Retrospective Studies

CVAD Type and Study Method	Proportion of Failure					Incidence Rate of Failure per 1000 Catheter Days				
	Studies	CVAD	Outcomes	Pooled %	95% CI	Studies	Catheter Days	Outcomes	Pooled IR	95% CI
PICC										
Retrospective	17	6609	1876	28.3[d,e]	21.1–36.1	14	157 350	1272	12.49[d,e]	9.69–15.30
Prospective	6	3554	915	35.1[d,e]	23.8–47.4	4	83 669	734	13.17[d,e]	5.10–21.25
Pooled	23	10 163	2791	30.1[d,e,h]	24.4–36.1	18	241 019	2006	12.43[d,e,h]	9.98–14.89
Nontunneled										
Retrospective	1	34	3	8.8[e]	1.2–21.2	0	—	—	—	—
Prospective	1	1092	245	22.4[e]	20.0–25.0	0	—	—	—	—
Pooled	2	1126	248	16.7[c,e,g]	6.1–30.9	0	—	—	—	—
Tunneled										
Retrospective	7	1110	291	30.6[d,e]	15.4–48.4	4	129 538	96	1.08[d,e]	0.40–1.75
Prospective	3	391	133	26.1[d,e]	1.6–65.0	2	37 946	27	0.68[d,e]	0.04–1.32
Pooled	10	1501	424	29.2[d,e,h]	15.9–44.6	6	167 484	123	0.87[d,e,h]	0.41–1.32
Totally implanted										
Retrospective	14	2547	420	15.0[d,e]	9.9–20.9	8	681 196	117	0.17[c,e]	0.10–0.24
Prospective	5	773	73	18.7[d,e]	0.0–54.7	2	137 826	10	0.06[a,e]	0.02–0.11
Pooled	19	3320	493	15.8[d,e,h]	9.4–23.5	10	819 022	127	0.15[c,e,h]	0.09–0.20

Heterogeneity of studies [a]negligible, [b]low, [c]moderate, or [d]high.
Effect-size test [e]significant or [f]nonsignificant.
Test for heterogeneity between subgroups [g]significant or [h]nonsignificant. —, data not available.

result in an interruption to necessary treatment and the insertion of new CVADs 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 on patient age. The variation was most evident in comparisons involving PICCs, where neonates had a significantly higher rate of failure ($P <$ .001) than the remaining pediatric population, with a failure rate of 25.5 per 1000 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 (<1500 g) or extremely low birth weight (<1000 g) and are at greatest risk for failure and 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 CVADs in pediatrics are necessary to provide benchmarking targets and inform practice innovations. Meta-synthesis of the 2 studies reporting nontunneled CVAD failure showed a failure proportion of 16.7%; however, no studies reported an estimation of catheter days. In accordance with previous international focus, the majority of nontunneled CVAD studies that reported CVAD complications reported only CVAD-associated BSI. The failure and complications associated with HD and umbilical catheters were also inadequately reported, with only 6 studies of 749 CVADs available. Considering the prevalence and importance of umbilical, HD, and nontunneled CVADs within pediatric health care management, reliable measurement of their failure and complications is essential. Additionally, although multiple cohort studies described the failure of PICCs and totally implanted devices, the majority used retrospective methods, 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 1000 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 expose the patient to more or less risk of complications. Second, the unavoidable heterogeneity of the populations in the included studies may have affected 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 who require CVADs. This heterogeneity needs to be recognized before applying the results to local individual health care institutions. Third, although our review was limited to include studies ≤10 years old, 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 overestimate the

burden of device failure in 2015. Finally, whereas 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 with another.
Future updates of this review may also consider inclusion of the "standard care" arms of RCTs that have evaluated various interventions.

Comparison With Other Studies

No previous systematic review in pediatrics has examined 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. Although primarily focused on describing strategies to prevent and treat CVAD complications, their systematic review reported an overall incidence of CVAD failure of >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.

CONCLUSIONS AND FUTURE RESEARCH

International health care institutions have highlighted the significance of CVAD failure associated with BSI. This systematic review has described the broader, multifocal rate of CVAD failure and complications across CVAD types in pediatrics within the international health care community. As context, from the 82 US hospitals reporting to the National Healthcare Safety Network in 2013, >2.7 million CVAD catheter days in the pediatric and neonatal population were registered.[134] Applying the rate of failure described in our study, 5457 pediatric and neonatal CVADs in US hospitals failed before completion of treatment in 1 year alone. These failures place a massive economic and physical burden on the US health care 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.

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ABBREVIATIONS

BSI: bloodstream infection
CI: confidence interval
CVAD: central venous access device
HD: hemodialysis
IR: incidence rate
PICC: peripherally inserted central catheter
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT: randomized controlled trial

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