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ORIGINAL ARTICLE

Vascular access in children requiring maintenance haemodialysis: a consensus document by the European Society for Paediatric Nephrology Dialysis Working Group

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ABSTRACT

Background. There are three principle forms of vascular access available for the treatment of children with end stage kidney disease (ESKD) by haemodialysis: tunnelled catheters placed in a central vein (central venous lines, CVLs), arteriovenous fistulas (AVF), and arteriovenous grafts (AVG) using prosthetic or biological material. Compared with the adult literature, there are few studies in children to provide evidence based guidelines for optimal vascular access type or its management and outcomes in children with ESKD.

Methods. The European Society for Paediatric Nephrology Dialysis Working Group (ESPN Dialysis WG) have developed recommendations for the choice of access type, pre-operative evaluation, monitoring, and prevention and management of complications of different access types in children with ESKD.

Results. For adults with ESKD on haemodialysis, the principle of "Fistula First" has been key to changing the attitude to vascular access for haemodialysis. However, data from multiple observational studies and the International Paediatric Haemodialysis Network registry suggest that CVLs are associated with a significantly higher rate of infections and access dysfunction, and need for access replacement. Despite this, AVFs are used in only ∼25% of children on haemodialysis. It is important to provide the right access for the right patient at the right time in their life-course of renal replacement therapy, with an emphasis on venous preservation at all times. While AVFs may not be suitable in the very young or those with an anticipated short dialysis course before transplantation, many paediatric studies have shown that AVFs are superior to CVLs.

Conclusions. Here we present clinical practice recommendations for AVFs and CVLs in children with ESKD. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system has been used to develop and GRADE the recommendations. In the absence of high quality evidence, the opinion of experts from the ESPN Dialysis WG is provided, but is clearly GRADE-ed as such and must be carefully considered by the treating physician, and adapted to local expertise and individual patient needs as appropriate.

Keywords: arteriovenous fistula, arteriovenous graft, central venous line, children, haemodialysis

INTRODUCTION

Paediatric vascular access is an important component in the care of a child with end-stage kidney disease (ESKD) through childhood and adolescence before ultimately entering adult health services [1, 2]. Almost all children undergoing dialysis will be considered for kidney transplantation, as this is the optimal therapy for childhood ESKD. However, once transplanted, ∼25% of children return to dialysis even before moving to adult dialysis programmes [3, 4], and some may have complex conditions that make transplant options for the foreseeable future limited. A long-term view of their potential dialysis options is essential from the start.

Perhaps due to the perceived ease and convenience of central venous lines (CVLs) for dialysis, arteriovenous fistulas (AVFs) in children have not been widely accepted. Of the 870 accesses placed in 552 children prospectively followed in the International Paediatric Haemodialysis Network (IPHN) Registry, only 26% were AVFs, with CVLs being the predominant access type in 72% [5]. Technical difficulties in forming AVFs, dialysis nursing expertise, patient concerns regarding

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puncture pain and a paucity of experience in managing complications has resulted in reluctance in considering an AVF for children with ESKD. The evidence for the benefit of AVFs over CVLs in adult dialysis programmes has been known for some time [6–10] and paediatric studies suggest similar outcomes—better quality dialysis, fewer infections, fewer access changes and less hospitalization [1, 2, 10–16]. These unfavourable outcomes may also be reduced by changing the catheter locking solutions or maintaining better CVL handling strategies [17].

We present guidance for the choice of vascular access type, preoperative evaluation, monitoring, and prevention and management of complications of different vascular access types in children with ESKD. Existing guidelines on vascular access in adults were reviewed to define the scope of the current document (Supplementary data, Table S1). We attempted to underpin any guidance by an in-depth review of evidence provided by relevant systematic reviews, randomized controlled trials (RCTs) and prospective observational studies where possible. In the absence of applicable study data, guidance is based on the consensus opinion of experts from The European Society for Paediatric Nephrology Dialysis Working Group (ESPN Dialysis WG). The guidance provided within this document was designed to provide information and assist in decision-making related to this topic. It was not intended to define a standard of care and should not be construed as one. It should not be interpreted as prescribing an exclusive course of management. These consensus statements will be audited by the ESPN Dialysis WG and revised periodically. Research recommendations are suggested.

MATERIALS AND METHODS

Overview of the guideline development group composition and task distribution

Three groups were assembled to perform different functions: a core leadership group, an external advisory panel and a review panel. The core group comprised paediatric nephrologists who are board members of the ESPN Dialysis WG. The core leadership group was responsible for defining the scope of the project, formulating the clinical questions to be addressed by the recommendations, performing a literature review, developing evidence tables, rating the quality of evidence, conducting the voting panel and drafting the manuscript. The external advisory group included two paediatric vascular access surgeons (F.C. and P.B.), an adult nephrologist (S.M.) with expertise in dialysis access, a paediatric haemodialysis nurse (L.S.), a parent representative (A.-M.W.) and a guideline development methodologist (E.V.N.) from European Renal Best Practice, the guideline development body of the ERA-EDTA. The chair and all members of the core panel had no relevant conflicts of interest. The review group comprised all members of the ESPN Dialysis WG (listed under 'Acknowledgements'). The review group were sent the draft guidance document and all evidence tables and were responsible for reviewing the evidence, confirming the certainty of the evidence and the strength of the statements, and suggesting re-wording of statements if appropriate. Comments received from all members of the review group were collated into a single document and discussed at a meeting of the core working group with inputs from the external advisory group. A final document was then compiled and circulated to the review group for their opinion.

Developing the PICO questions

Recommendations are most useful when they provide specific actionable advice on choosing between alternative approaches in particular clinical situations. With the scope of the current guidance document as a starting point, we developed clinical questions to be addressed by each statement and framed them in a searchable format. This required careful specification of the patient group (P) to whom the statement would apply; the intervention (I) being considered; the comparator (C) (which may be 'no action' or an alternative intervention); and the outcomes (O) affected by the intervention (PICO) [18].

Population covered. We focus on children <18 years of age with ESKD and those treated with chronic haemodialysis (HD).

Intervention and comparators. Different techniques of planning for, preoperative evaluation of, cannulation and monitoring of AVFs, and prevention of AVF and CVL thrombosis. Studies pertaining to technical aspects of dialysis catheters, or to surgical details of AVF formation or CVL placement were not included. Studies about uncuffed CVLs were not included as these are used for acute dialysis only. Studies that included a combined analysis of paediatric and adult data were excluded.

Outcomes addressed. This includes benefits and complications of AVFs (in particular relevance to CVLs), primary and secondary patency, access longevity, hospitalization, and patient-related outcome measures including quality of life and survival. Health economic evaluation and AVF or CVL infections were not within the remit of this document.

Literature search

We initially set out to include all systematic reviews of RCTs and individual RCTs on AVFs and CVLs in adults and children with chronic kidney disease (CKD) Stages 4 and 5D (Supplementary data, Table S3). However, the core leadership group acknowledged there is only one low-quality RCT and only a few prospective observational studies in this field. We have therefore elected to perform a wider review of the literature and include studies in the following cohorts in the following order:

(i) all systematic reviews of RCTs in adults and children (Table 1)
(ii) all RCTs in children (one available; Table 2)
(iii) all prospective observational studies in children (irrespective of number of patients or duration of study) (Table 3)
(iv) retrospective studies in children (if >20 children included; not included in Tables 1–3)
(v) data from international registries describing vascular access placement and outcomes in children on chronic dialysis (not included in Tables 1–3).

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Table 1. Systematic reviews of RCTs in adults on chronic haemodialysis

Study	No. of studies	Population	Number of AVFs/CVCs	Outcomes	Meta-analysis model	Effect measure	Results	Potential bias/limitations
Arechabala *et al.* [19]	30 studies 15 studies used antibiotic lock solutions, 21 used non-antibiotic antimicrobial lock solutions and 4 used both	Adults on HD with CVC	3392 patients	• Comparing the effects of antimicrobial (antibiotic and non-antibiotic) lock solutions with standard lock solutions for preventing catheter-related infections and catheter thrombosis • Incidence of catheter-related infections, thrombosis or both	Random effects	RR per 1000 catheter-days or 1000 dialysis sessions (95% CI)	Antimicrobial lock solutions • Probably reduces CRI (27 studies: RR 0.38; 95% CI 0.27–0.53; I^2= 54%; low certainty evidence) • Probably makes little or no difference to the risk of thrombosis (14 studies: RR 0.79; 95% CI 0.52–1.22; I^2= 83%; very low certainty evidence) • Antibiotic and the combination of both lock solutions showed that both probably reduced CRI (13 studies: RR 0.30; 95% CI 0.22–0.42; I^2= 47%) and risk of thrombosis (4 studies: RR 0.26; 95% CI 0.14–0.49; I^2= 0%), respectively • Non-antibiotic antimicrobial lock solutions probably reduced CRI (9 studies: RR 0.60; 95% CI 0.40–0.91) • Subgroup analyses showed that antibiotic (5 studies: RR 0.76; 95% CI 0.42–1.38), non-antibiotic (8 studies: RR 0.85; 95% CI 0.44–1.66) and the combination of both lock solutions (3 studies: RR 0.63; 95% CI 0.22–1.81) made little or no difference to thrombosis compared with control lock solutions	Risk of bias was low or unclear for most domains in the majority of the included studies
Kennard *et al.* [20]	8 studies	Adults on HD with CVC	580 participants	Primary outcome was be restoration of CVL patency defined as ≥300 mL/min or adequate to complete a HD session or as defined by the study authors	Random effects	RR and 95% CI for dichotomous outcomes, and mean difference (MD) and 95% CI for continuous outcomes	• Thrombolytic therapy may restore catheter function when compared with placebo (149 participants: RR 4.05; 95% CI 1.42–11.56) without an optimal dose or administration method • Physical disruption of a fibrin sheath appears to be equally efficacious as pharmaceutical thrombolytic agent (57 participants: RR 0.92; 95% CI 0.80–1.07) • Catheter patency is poor with thrombolytic agents and improved significantly by fibrin sheath stripping or catheter exchange (37 participants: MD −27.70 days; 95% CI −51.00 to −4.40) • Catheter exchange is superior to sheath disruption with respect to catheter survival (30 participants: MD 213.00 days; 95% CI 205.70–220.30)	• All studies compared different interventions • Most studies had a high risk of bias due to poor study design, broad inclusion criteria, low patient numbers and industry involvement • There is low-certainty evidence • The certainty of this evidence is reduced due to the fact that it is based on only a single study with wide confidence limits, high risk of bias and imprecision in the estimates of adverse events (149 participants: RR 2.03; 95% CI 0.38–10.73)
Al-Jaishi *et al.* [21]	61	Adults on HD	11 374 AVFs	Overall—complications of AVFs (per 1000 patient days)	Random effects	[Data below expressed as number of events per 1000 patient days (range; IQR)]	Risks of AVFs reported as shown	Marked variability in complication rates due to poor quality studies with high risk of bias, significant heterogeneity of study populations, inconsistent definitions and variable event rates (pooled summary statistic on the basis of the weighted average was not described)
			1827	Aneurysms		0.04 events (0–3.01; IQR =0.06) among 14 unique cohorts (n = 1827)		
			6439	Infections		0.11 infections (0–0.98; IQR = 0.29) among 16 unique cohorts (n = 6439)		
			2543	Steal events		0.05 events (0–0.27; IQR = 0.04) among 15 unique cohorts (n = 2543)		
			4232	Thrombotic events		0.24 events (0.07–0.71; IQR = 0.25) among 26 unique cohorts (n = 4232)		
			350	Venous hypertensive events		0.03 events 1 study only (n = 350)		

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Wang *et al.* [22]	27 studies	Adult HD patients with CVC	3003 participants	Anticoagulants compared with conventional care, which is most commonly heparin 5000 IU/mL (17 studies) Alternative anticoagulant solutions (19 studies, 2216 patients) Catheter malfunction CRB All cause mortality Systemic agents (6 studies, 664 patients) and low or no dose heparin (2 studies, 123 patients) Catheter malfunction Catheter-related bacteraemia All cause mortality Low or no dose heparin (2 studies, 123 patients) Catheter malfunction CRB All cause mortality	Random effects	RR with 95% CI RR 0.96; 95% CI 0.74–1.26, no significant effect RR 0.46; 95% CI 0.32–0.66, significant benefit RR 0.88; 95% CI 0.54–1.43, no significant effect RR 0.59; 95% CI 0.28–1.23, no significant effect RR 2.41; 95% CI 0.89–6.55, no significant effect RR 0.78; 95% CI 0.37–1.65, no significant effect RR 0.90; 95% CI 0.10–8.31, no significant effect – –	• For individual agents, rt-PA was the only locking solution shown to reduce catheter malfunction (RR 0.58; 95% CI 0.37–0.91) based on a single study • All alternative anticoagulant locking solutions, except ethanol, reduced catheter-related bacteraemia (citrate: RR 0.49; 95% CI 0.36–0.68; antibiotic: RR 0.27; 95% CI 0.11–0.70; rt-PA: RR 0.35; 95% CI 0.13–0.93; ethanol: RR 0.33; 95% CI 0.03–4.05)	Studies were mainly of low quality and underpowered with an average participant number of 75 and study duration of 6 months. The interpretation of the study evidence was further limited by the variation in tested interventions and outcome reporting
Han *et al.* [23]	Five RCTs and three CCTs	Adults on HD	916 patients	Comparison between the high-dose heparin (≥5,000 U/mL) and the low-dose (<5,000 U/mL) heparin lock Catheter thrombosis/occlusion incidence Catheter dysfunction Catheter retention time CRI incidence Incidence of bleeding related complications		RR with 95% CI RR 0.68; 95% CI 0.28–1.65, P = 0.39 RR 1.07; 95% CI 0.75–1.53, P = 0.71 MD 9.32;95% CI −6.70 to 25.35, P = 0.25) RR 1.66; 95% CI 1.01–2.73, P = 0.04). RR 3.29; 95% CI 2.19–4.94, P < 0.00001	Compared with the high-dose heparin group the low-dose heparin lock could significantly reduce the incidences of bleeding-related complications) and catheter-related infections. However, no significant differences were observed in the catheter retention time, catheter thrombosis/occlusion incidence or catheter dysfunction between the high- and low-dose heparin groups	

Continued

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Table 1. Continued

Study	No. of studies	Population	Number of AVFs/ CVCs	Outcomes	Meta-analysis model	Effect measure	Results	Potential bias/limitations
Ravani *et al.* [24]	14	Adults on HD	1393	Pre-emptive correction versus deferred correction of AVF stenosis	Fixed-effect	Mortality, hospitalizations, access thrombosis, access infections, need for CVL	Pre-emptive correction of AVF stenosis may decrease catheter use (5 RCTs; $n = 394$; IRR 0.58; 95% CI 0.35–0.98; $I^2 = 53\%$) and risk of hospital admission (3 RCTs; $n = 219$; IRR 0.54; 95% CI 0.31–0.93, $I^2 = 67\%$)	Level of evidence remains low due to risk of bias in the primary studies and a large amount of unexplained heterogeneity in the analysis with point estimates on opposite sides of the line of no effect
Tanner and Da Silva [25]	15	Adults on HD	2230	Drug treatments for AVF or AVG patency	Fixed-effect	8 drugs (aspirin, dipyridamole, warfarin, clopidogrel, sulfinpyrazone, ticlopidine, human type-I pancreatic elastase, fish oil) compared against each other or placebo in different combinations	Only ticlopidine (a platelet aggregation inhibitor) favoured active treatment (OR 0.45; 95% CI 0.25–0.82; P = 0.009) in increasing the patency of AVF or grafts in the short term	Low-quality studies with short follow-up for most. Randomization, allocation and concealment bias not clear for most studies. Incomplete outcome data for many studies
Wong *et al.* [26]	23	Adults on HD (outcomes separately analysed for in-centre versus home dialysis versus facility practices)	1601 (+2 studies with patient numbers not reported)	Buttonhole cannulation established by sharp needles versus rope ladder cannulation	Random effects	Infection risk (local and systemic), access interventions, access survival, hospitalization, pain and quality of life, mortality	• Rates of bacteraemia were higher with buttonhole cannulation • Application of mupirocin cream was associated with reduced risk of infection	Limited literature search • Largely descriptive studies with small study numbers and high level of heterogeneity • Serious methodological limitations for most outcomes (short follow-up, crossover designs, lack of parallel control groups, and use of patient-reported outcome measures that were not well validated)
Ravani *et al.* [27]	67	Adults on HD	586 337	Risk of death, infection and major cardiovascular events	Random effects	Mortality Infections Major cardiovascular events	CVC use had higher risks for all-cause mortality (RR 1.53; 95% CI 1.41–1.67) CVC use had higher risks for fatal infections (RR 2.12; 95% CI 1.79–2.52) CVC use had higher risks for cardiovascular events (RR 1.38; 95% CI 1.24–1.54)	• High risk of bias, particularly selection bias • Low-quality evidence for some studies • Short follow-up
Casey *et al*; 2008	12	Adults on HD	1570	Surveillance versus clinical monitoring	Random effects	Outcome—vascular intervention to maintain or restore patency	• Vascular interventions after an abnormal AV • access surveillance led to: • Significant reduction of the risk of access thrombosis (RR 0.53; 95% CI 0.36–0.76) • Non-significant reduction of the risk of access abandonment (RR 0.76; 95% CI 0.43–1.37)	Very low quality evidence with poor reporting of allocation concealment and blinding and high rate of loss to follow-up

CRI, catheter-related infection; CRB, catheter-related bacteraemia; IRR, incident rate ratio; CCT, controlled clinical trial; CVC, central venous catheter.

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Table 2. RCTs in children

Study	Population, gender, age	*n*	City, country	Intervention	Comparator	Duration of treatment	Results	Comments
Gittins *et al.* [28]	Children on chronic HD is 2–3 times per week Age—not reported Gender—not reported	9	Newcastle, UK	Heparin 5000 U/mL Double-blind, multiperiod cross-over experiment	Alteplase 1 mg/mL	10 weeks (one child transplanted at Week 8) Average number of treatment sessions = 29 (if dialysed 3 per week and 20 if dialysed 2 per week)	• The odds of clot forming following a heparin lock was 2.4 times greater than after alteplase (95% CI 1.4–4.0; P = 0.001) • Mean weight of clot was 1.9 times heavier (95% CI 1.5–2.4; P = 0.0005) on heparin treatment • Differences in inter-dialytic periods did not affect the probability of clot formation (P = 0.63) or its weight (P = 0.31)	• Access used for this study is not conventional practice (single lumen central lines with multiple distal side holes used for all children, 8F lines for children <10 kg, and 10F lines for larger children) • Practice of clot retrieval and weighing likely to be highly confounded • Randomization, blinding, allocation concealment not described • Cross-over design not clear • Small numbers and short follow-up leading to highly skewed data

Medline was searched using the PubMed interface through to 1 April 2018 using the search terms and strategy detailed in Supplementary data, Table S3. Limits were preset to manuscripts published in the English language, and study design limits were applied. All papers were reviewed by two independent reviewers (C.J.S. and R.S.). When there was disagreement regarding inclusion of the manuscript for this review, a third reviewer (S.B.) determined whether the manuscript was eligible. Data were extracted by at least two members of the core group, prepared in evidence tables (see Tables 1–4 and Supplementary Data) and reviewed by all members of the core group. Some studies that were outside the remit of the literature review but nevertheless contributed important information have been included in the 'Discussion' section.

Framing advice

After critically reviewing the evidence for each question, we derived statements and coded them as suggested by the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) working group (Supplementary Tables S2A and S2B). The approach is to assign separate grades for the quality of the evidence and for the strength of the recommendation [37]. The quality of evidence is graded as either high (A), moderate (B), low (C) or very low (D), and the strength of a recommendation as either level 1 (strong) or level 2 (weak or discretionary). In the absence of applicable comparative study data, we derived statements based on the opinion of experts from the ESPN Dialysis WG. We indicated the latter category by coding them as 'Ungraded'. When evidence was available only from studies conducted in adults it was downgraded for indirectness.

ADVICE FOR CLINICAL PRACTICE

1. Planning vascular access

1.1 Educate children with CKD and their carers about venous preservation, irrespective of the choice of future renal replacement therapy (RRT), and starting from their early contact with the nephrology services. (Ungraded)

1.2 Educate children with CKD Stage 4 [estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 by Schwartz formula], those with rapidly declining kidney function or those who need to start maintenance dialysis imminently about kidney failure and options for its treatment, including kidney transplantation, peritoneal dialysis (PD), HD in the home or in-centre and conservative treatment, where appropriate. (Ungraded)

1.3 We suggest referring children with CKD Stage 4 who are being prepared for future HD to a dedicated vascular access team. (Grade 2D)

Vein preservation

A child with ESKD has a lifetime of RRT ahead of them. The choice of optimal vascular access for an individual patient and determining timing of access creation are dependent on a multitude of factors that can vary widely with each patient, including demographics, comorbidities, anatomy and personal

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Table 3. Prospective observational studies of AVFs in children on chronic dialysis

Study	Age, gender, weight	*N*	City, country	Intervention/outcomes reported	Duration of follow-up	Results
Kim *et al.* [29]	15.7 ± 3.2 years 32% females	47 children (52 AVFs)	Seoul, Korea	1. Assessment of primary and secondary patency 2. Mean time to maturation	49.7 ± 39.2 years	• Primary patency 60.5, 51.4 and 47.7% at 1, 3 and 5 years, respectively; 9 cases (17.3%) of primary failure; low body weight was an independent predictor • Secondary patency 82.7, 79.2 and 79.2% at 1, 3 and 5 years, respectively • Age, body weight, AVF type, the presence of a central venous catheter, use of anticoagulation therapy and history of vascular access failure were not significantly associated with patency rates • The mean time to maturation was 10.0 ± 3.7 weeks
Shroff *et al.* [15]	Age 9.4 (IQR 3–17) years Weight 26.9 (IQR 14–67) kg	23 AVFs	London, UK	1. Outcome from a multidisciplinary vascular access clinic 2. Preoperative ultrasound mapping to determine optimal artery and vein diameter for access creation 3. AVF blood flow on 6-week maturation ultrasound scan	2 years for incident AVFs (and follow-up of prevalent AVFs)	• Maximum median vein and artery diameters of 3.0 (2–5) and 2.7 (2.0–5.3) mm, respectively • Primary maturation rate was 83% (10/12) Assisted maturation was 100%, with two patients requiring a single angioplasty • Maturation scans 6 weeks after AVF formation showed a median flow of 1277 (432–2880) mL/min • At follow-up the maximum median vein diameter was 140 (8.0–26.0) mm, and the median flow rate was 1781 (800–2971) mL/min at a median of 153 weeks after AVF formation
Almási-Sperling *et al.* [30]	Age 14 (7–17) years 55% females Weight 44.5 ± 12 kg	42 children	Erlangen, Germany	To evaluate the influence of first cannulation of AVFs on primary and secondary patency rates	123 (3–259) months	• Primary failure in 6 (14.3%) AVFs (all radiocephalic fistulas) within the first 10 days after cannulation • There was a significant decrease in primary patency when first cannulation was performed within the first 30 days after AVF creation compared with first cannulation performed after 30 days (P = 0.004). No significant difference in the outcome of primary or secondary patency when the first cannulation was performed after 45 days (P = 0.09)
Matoussevitch *et al.* [31]	Age 6–19 years Weight 43.3 ± 14.5 kg	32 AVFs in 31 children	Cologne, Germany	Outcome of AVF creation in children without indwelling CVCs	–	• 26 received a distal radiocephalic fistula, 5 a Gracz-type fistula and 1 a brachio-basilic fistula. • Primary patency 30/32 AVFs; average time to maturation and first dialysis session 45 (range: 16–191) days • 1-year primary and primary-assisted patency rates 78% and 94%, respectively

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Merouani *et al.* [32]	Age 14.7 (range 0.7–20.5 years) Weight 46 (12.5–95 kg)	78 patients	Montreal, Canada	To determine the effect of pediatric priority allocation policy for deceased-donor kidneys affected change in AVF formation rates	–	When the wait times on transplant list was significantly reduced, AVF formation rates decreased from 76% to 41% (P = 0.002)
Chand *et al.* [11]	Age 13.6 (range 4–19) years 10 females Weight range 11.8–120 kg	23 AVFs	Akron, USA	Outcomes of AVF creation Use of operating microscope ($n = 3$)		• Primary patency rate was 57% at 6 months and secondary patency rate was 100% at 1 year • The primary patency rate in the group in which microsurgery was used (3 patients) was 66% at 3 months, with a secondary patency rate of 100% at 1 year
Haricharan *et al.* [33]	Median age 14 (9–19) years 9 girls	16 patients, 18 AVFs	Birmingham, USA	Thrombosis-free survival of basilic vein transposition and brachiocephalic AVFs	2 years	• 4 AVFs thrombosed (1 brachiocephalic, 3 basilic vein transposition) and 14 AVFs did not reach the 2-year endpoint • 2-year cumulative thrombosis-free survival (assessed in 9 children) was 74% (BVT 66%; brachiocephalic fistula 83%) • 6 AVFs required additional interventions (4 percutaneous angioplasty and 2 surgical thrombectomy)
Sharathkumar *et al.* [34]	Age and weight—not available	8 AVFs (7 patients) compared with 19 AVFs (14 patients; historical control)	Ann Arbor, USA	To evaluate the effect of a primary thrombo-prophylaxis (PTP) protocol (unfractionated heparin post-operatively, followed by low molecular weight heparin until AVF maturation) on the incidence of early AVF failure due to thrombosis	1 year	• In historical group, 12 AVFs did not receive any thromboprophylaxis and 10/12 AVFs failed: 9 thromboses and 1 stenosis. In aspirin group 1/5 AVFs failed due to thrombosis • In PTP group 1/8 AVFs failed due to stenosis. Complications: • 2 AVFs developed haematoma • 1 AVF required thrombectomy • The incidence of thrombosis was less in PTP group (12.5%) when compared with no-treatment group (83%) (P < 0.05)
Chand *et al.* [35]	Age: <19 years 64% females	140 patients	Akron, USA	To determine the effect of HD access in urea clearance, anaemia management and serum albumin levels		Children on HD using an AVF or AVG had an improved outcome in relation to urea clearance patients, haemoglobin concentration and serum albumin level, compared with children with CVCs
Goldstein *et al.* [36]	Age—not mentioned Weight 47.8 ± 14.6 kg	9 children	Texas, USA	Effect of monthly ultrasound dilution (UD) measurement on early detection and management of vascular access thrombosis	2 years	• An AVF flow rate <650 mL/min/1.73 m^2 measured by UD had a 100% sensitivity and specificity for venous stenosis >50% measured by contrast venography • Prompt referral of above patients for angioplasty of the AVF reduced access thrombosis rates

BVT, basilic vein transposition; CVC, central venous catheter.

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preferences. Children, their carers and healthcare workers (doctors, nurses, phlebotomy staff) should receive education on venous preservation. The child and their carers are usually best placed to 'defend' potential fistula veins from damaging phlebotomy insults. Early dialysis education is best done in association with a play therapist who can introduce to the child and parents the concepts of dialysis, vein preservation and needling an AVF [1, 2, 13]. Wearing of Medic alert type bracelets may be helpful in preserving veins, by serving as a reminder for both the patient and healthcare professional performing phlebotomy [6]. An educational video produced by staff, patients and families is used to help patients new to dialysis understand the options for vascular access and the importance of venous preservation (https://www.youtube.com/watch? v=y_Ct6C__p18, accessed 1 December 2018).

Venipuncture above the wrist in either arm should be avoided, except in an emergency, to preserve the forearm cephalic, antecubital and upper arm veins. A pragmatic approach to balance the need for frequent blood draws versus the need for venous preservation is required, and the (presumed) non-dominant arm may be spared for later AVF creation. Using the dorsal veins of both hands needs to be emphasized.

Patient education and timely referral

The goal for the provision of optimal dialysis access is patient focused. This requires a coordinated and multidisciplinary approach in assessing and educating patients prior to their need for RRT [10, 11, 14, 15]. The team looking after children with ESKD should be familiar with the full spectrum of dialysis and transplant options so that they can guide and advise the child and their carers appropriately, keeping in mind the risks of failed transplantation and need to return to dialysis. Transplant failure [38], which is more common in adolescence [39, 40], means that children often need to return to HD before transition to adult services [3, 4], and the cycle of dialysis–transplantation–dialysis may repeat several times in the patients' lifetime. Variations in local processes (such as referral time delay for permanent access, surgical assessment for AVF prior to commencement of HD) and service delivery characteristics (such as presence of dedicated lists for vascular access surgery, venous mapping, fistula salvage and patency restoration pathways) play a major role in defining the prevalence of dialysis access types. The IPHN Registry reports that only 26% of children on maintenance HD had AVFs [5], despite a median age of 12 years, and only 5% of the population being <2 years. Adequate patient preparation and education may improve the uptake of AVFs [1, 2]. Conversion from CVL is often difficult and breaking the habit of 'staying with what you start with' requires great effort in time and persuasion [41]. In addition, a long-term CVL might be associated with central venous stenosis and it may not be possible to create an AVF in the future.

A dedicated vascular access clinic

Paediatric studies have shown that a dedicated vascular access clinic provides a focal point for education, assessment and ongoing management of children approaching ESKD as well as those on chronic HD. A vascular access clinic should ideally provide a 'one-stop' approach with a dialysis physician, a surgeon, a dialysis nurse and skilled personnel who can perform arterial and venous mapping to plan future AVF formation [10, 11, 15, 42]. The clinic serves as a hub for children and their parents to see and discuss the benefits of an AVF with the access team and other children, as well as to observe children thriving with good quality access and dialysis. Since paediatric access surgery is performed in only a small number of children, centralization of services to concentrate surgical expertise is required, which will likely improve outcomes. Improved outcomes have been reported when a skilled access surgeon and a dedicated vascular access clinic manage these cases [11]. In a prospective study in children it has been shown that after 2 years of setting up a dedicated vascular access clinic, the percentage of children dialysing via a CVL had decreased from 68% to 22% [15].

Timing of referral for vascular access

Progression to ESKD may be unpredictable. Consider referring the child for planning and assessment when the eGFR is <30 mL/min/1.73 m^2 (estimated by Schwartz formula [43]), or ESKD is estimated within the next 6–12 months [44]. It is also important to consider the underlying renal disease and the predicted rate of renal decline when considering the timing of access surgery. Sufficient time is necessary for education of the child and their parents, preoperative investigations, development of AVF maturity and any further interventions after AVF formation before it is needled. This prolonged lead-in period also allows for psychological preparation for dialysis with an AVF and helps to avoid initiating dialysis with a CVL, which may then become difficult to convert to an AVF later. While AVF maturation times of ∼2 months have been reported [5, 15], the overall process from preoperative assessment until the fistula is fully operational may require an average of 6 months in adults [6–9] and children [13, 15, 45].

2. OPTIMAL VASCULAR ACCESS IN CHILDREN

2.1 We suggest that children requiring chronic HD start with a functioning AVF where appropriate. (Grade 2C)

2.2 Reserve cuffed CVLs for very small children depending on vessel size and surgical expertise, those requiring urgent or unplanned HD, patient preference and where a short period on HD is anticipated before transplantation. (Ungraded)

2.3 There is insufficient evidence to provide recommendations on AVGs in children. (Ungraded)

Evidence and rationale

The ideal vascular access should deliver a flow rate adequate for the dialysis prescription in combination with durability and a low rate of complications [7]. A systematic review in adults on HD has indicated that compared with AVFs, the use of CVLs is associated with higher all-cause mortality [relative risk (RR) 1.53; 95% confidence interval (95% CI) 1.41–1.67], higher risks for fatal infections (RR 2.12; 95% CI 1.79–2.52) and higher risks for cardiovascular events (RR 1.38; 95% CI 1.24–1.54), adjusted for confounders [27] (Table 1). Similar complication rates have

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been reported in a more recent systematic review [21] (Table 1), but both reviews report marked variability in complication rates due to poor quality studies with high risk of bias and significant heterogeneity of study populations.

Many paediatric studies have suggested the superiority of AVFs compared with CVLs [1, 10–15, 31, 46]. Observational studies in children suggest that AVFs have better patency rates and access survival, and require fewer interventions during the entire life span of the access. In addition, lower rates of access-related sepsis, improved dialysis adequacy, and lower overall morbidity and mortality compared with CVLs is seen even after a short follow-up time [1, 10–15, 31, 35, 46], although patient numbers are small and outcome reporting is variable in most studies (Table 3). Median survival of a CVL is short compared with AVFs (0.6 versus 3.1 years, respectively) [47]. A retrospective study comparing AVF and CVL usage in the same dialysis unit indicates that poorer access survival increased infection risk and hospitalization with CVL-based HD compared with an AVF over 1 year [12]. In the 552 children followed in the IPHN Registry, infections were reported with CVLs only (1 in 26 patient-months), and required access replacement in 45% [5]. CVL dysfunction occurred in every 18 patient-months with internal jugular lines, but significantly more frequently with subclavian lines (1 in 10 patient-months) [5]. CVL placement in the subclavian vein is associated with a higher rate of central venous stenosis as discussed below. In contrast, AVF dysfunction rate occurred in every 28 patient-months, in 58% due to thrombosis, and required a new access in 44% of the cases. Primary and secondary AVF patency rates were significantly higher after 1, 2, 3 and 4 years compared with CVLs ($P < 0.0001$ for all time points). CVL use increased the need for a new access at a different side by 2-fold [5]. In addition, CVLs are the primary cause of central venous stenosis (at the site of entry into the central vein and at the catheter tip), which may compromise fistula formation in the upper limbs and increase the likelihood of superior vena cava syndrome [48, 49]. In addition, dialysis adequacy was higher [12, 15], and overall costs and frequency of hospitalization [12] lower with an AVF. Finally, children with AVFs can bathe and swim without concerns of infection risk, an important patient-related outcome measure for many.

Not every child needing chronic HD is a suitable candidate for AVF. Key factors that need to be considered are the age and size of the child, the condition of their vessels and the anticipated duration of HD before transplantation or change of dialysis modality. Using microvascular surgical techniques, AVFs can be successfully created in children weighing <10 kg [50], but most published reports are in larger children. Surgical and centre expertise for AVF creation and maintenance are critical to successful AVF maturation [51, 52]. It may be prudent to concentrate surgical and interventional radiology expertise in AVF creation and maintenance to large centres with significant HD expertise—particularly for the smaller child. Paediatric guidelines published a decade ago by Kidney Disease Outcomes Quality Initiative (KDOQI) as well as Chand and colleagues suggested that consideration should be given to placing AVFs in children weighing >20 kg who are expected to wait >1 year for a kidney transplant [7, 53]. However, as noted by Chand and co-workers, the 'perceived time' to transplantation is generally shorter than the 'actual time' to transplantation [11]. Fadrowski *et al.* indicated that mean length of time to transplantation was 163 days in a group of children in the USA with CVLs who had a transplant scheduled on initiation of HD therapy [54]. Interestingly, a Canadian study showed that when the waiting times for transplantation were significantly reduced through a paediatric priority allocation policy for deceased donor transplants, AVF formation rates significantly decreased (Table 3) [32]. Although the waiting times for kidney transplantation vary widely across European countries, an ESPN Registry report in 6454 children across 35 participating countries has shown that the median time to first kidney transplantation from start of RRT was 15 months, ranging from 6 to 17 months [55]. Given the long waiting times for transplantation in many European Union countries [56], we suggest that AVF formation is also considered for children in whom a kidney transplant is deemed unlikely within the following 6 months.

CVL use may be appropriate in certain settings, including those patients expected to receive a kidney transplant within a short time and very small children (depending on the child's weight, vessel size and surgical/centre expertise), and in the child with ESKD who 'crash lands' in need of urgent HD or when PD is anticipated in the future but cannot be started imminently. Although high-output cardiac failure after AVF formation is rarely seen in children, AVF formation in children with severe cardiac impairment needs to be considered on an individualized basis.

AVGs

An AVG is a surgically created vascular access used for chronic HD, whereby an artificial prosthetic segment—usually made of polytetrafluoroethylene—is used to connect an artery and vein. AVGs are common in adult practice, but rarely used in children in Europe [57]. A survey across European Paediatric Nephrology centres has reported that only 2 of 111 children from 13 dialysis units across Europe had an AVG [57]. In the IPHN Registry report, only 17 of the 870 (2% overall, and 7.6% of the non-CVL access) vascular accesses created over 314 patient years were AVGs, and in most cases only after failure of the AVF or CVL [5]. A retrospective study comparing 24 AVFs and 28 AVGs in 19 and 23 paediatric patients, respectively, indicated an increased risk of thrombosis, stenosis and infection with an AVG, but higher primary access failure rates with AVFs [46]. AVGs have the potential advantage of earlier use, often at 2 weeks after surgery, and sometimes immediately, depending on the type of graft used. Lower limb grafts have a significantly higher incidence of infection than those in the upper limb and may compromise future transplantation options by causing iliac vein stenoses [58]. AVGs are seldom used in children. Small-size observational data suggest superior long-term outcome with AVG as compared with CVL [5], but complication rates are much higher compared with AVF [5, 11, 45, 59]. AVGs are usually used only as a last resort or 'rescue option' for a vascular access site. In the absence of evidence and the low usage, they are not discussed further in this guidance document.

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3. PREOPERATIVE EVALUATION FOR AVF FORMATION

3.1 We suggest performing a structured history, physical examination and duplex ultrasound of upper limb arteries and veins to plan AVF creation. (Grade 2C)

3.2 We suggest performing appropriate imaging of central veins by venography, computed tomography (CT) angiography or non-contrast magnetic resonance imaging (MRI) in children in whom central venous stenosis is suspected, such as those with previous CVLs. (Grade 2D)

3.3 Avoid AVF creation in the ipsilateral arm of a central venous stenosis. (Ungraded)

Evidence and rationale

As previously mentioned, two prospective studies in children suggest that a vascular access clinic, where systematic work-up for AVF surgery is performed by a dedicated team, has higher AVF uptake rate and higher primary access patency [11, 15]. We therefore suggest the following structured approach including history, physical examination and imaging.

Physical examination is best performed in a warm and child-friendly environment, with the child well-hydrated. Careful history and examination of both arms is performed to identify any factors that may be associated with AVF failure, such as previous CVLs, repeated venipuncture of peripheral vessels, hypotension, heart failure, non-visible veins despite tourniquet application and the quality of arterial pulse, to assess for arterial occlusion or impairment of arterial flow [2, 47, 60]. Venous dilatation can be assessed by measurement of venous calibre before and after tourniquet application, and venous continuity can be assessed by manual percussion and palpation of the vessel. Previous arterial cannulation or vascular surgery may result in occlusion or stenosis of any artery. Allen's test assesses the patency of the ulnar artery—the ulnar artery is the dominant artery for circulation to the hand in >90% of individuals [61]. Hence, if the radial artery occludes in forming a radial AVF, the perfusion to the hand will not be threatened in most patients if the ulnar artery is patent.

The use of duplex ultrasound scanning is now common practice for vascular access evaluation. A poor-quality vein is the most common reason for fistula failure. The optimal venous system should have a luminal diameter of at least 2.0 mm and a length of continuity with the proximal vein without obstruction [62]. In a systematic review, Wong *et al.* identified three trials with a total of 402 adult patients. The meta-analysis showed a trend (not statistically significant) in the improvement in AVF maturation with preoperative vessel mapping [63] [odds ratio (OR) 1.96; 95% CI 0.85–4.50]. The optimum vein size is not clearly defined in the paediatric literature. However, a larger calibre vein makes way for technically easier surgery, and offers less resistance thereby encouraging greater flow and improved maturation. Where stated in the larger paediatric reviews, suitable venous vessel internal diameters range from 1.5 to 2.5 mm [2, 13, 45, 64]. In dealing with the smaller vessels of children it is important to measure the arterial diameter too, as previous arterial cannulation may compromise the artery. In adult reviews, a high brachial bifurcation, seen in up to 20% of individuals, may be associated with a higher primary failure rate [65, 66]. The 2007 European Best Practice Guidelines (EBPG) Guideline on vascular access in adults suggests a minimum internal arterial diameter of 2 mm for radial AVFs [9]; no such guidance exits in the paediatric literature.

Risk factors for central stenosis include previous CVL insertion particularly if this is associated with catheter-related blood stream infection or thrombosis. The subclavian vein is particularly prone to stenosis: an angiographic study of 100 patients dialysed either by a subclavian or internal jugular catheter (50 in each group) showed that 42% of the subclavian group had a stenosis of the subclavian/brachio-cephalic vein, compared with only 10% of the internal jugular group [67]. A similar study also indicated that 50% of patients with temporary subclavian vein catheters had strictures of their subclavian veins, whereas none of the internal jugular catheter patients had stenoses in their venous access return [68]. Clinical signs of central vein stenosis include dilated superficial veins on the chest wall and/or facial swelling that may be unilateral or bilateral.

Central vessel imaging is suggested in children who have been suspected of central venous stenosis, including those with previous CVLs, to avoid constructing access ipsilateral to a central vein occlusion. If an AVF is created it can lead to significant limb swelling, making the AVF unusable. Ultrasound may not detect central vein stenosis as it cannot directly image the brachiocephalic veins and superior vena cava, but is used in some centres as the first screening method. Imaging modalities to reliably visualize the central vessels include venography (bilateral central venograms with intravenous iodinated contrast will need to be promptly dialysed out if it is used in ESKD patients), computed tomography venography (CTV) (with iodinated contrast) or magnetic resonance venography (MRV). Compared with conventional venography, CTV is a less invasive technique that is shown to provide important information for further treatment (surgical or endovascular) in an adult study [69]. CTV was a reproducible and reliable technique for the detection of >50% stenosis or occlusion in dysfunctional AVFs [70] and showed excellent correlation with stenosis detection compared with venography [71]. Contrast-enhanced MRV have high sensitivity and specificity for the detection of central stenosis [72], but given the risk of gadolinium-induced nephrogenic systemic fibrosis, they are contra-indicated in most European centres. Non-contrast MRV, also called time-of-flight or inflow venography, that utilizes phase differences to distinguish blood from static tissue, thus avoiding contrast agents and gadolinium, is a newer technique that is shown to be useful [15].

4. SITE OF AVF PLACEMENT

4.1 Place an AVF in the non-dominant arm where possible. (Ungraded)

4.2 We suggest placing an AVF distally in the arm. (Grade 2D)

Evidence and rationale

In practice, the decision of where to form an AVF depends on a number of factors and needs to be individualized to each

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child's circumstances. Vessel anatomy, previous access history, hand dominance, intention for self-cannulation, body mass index, child or parental choice and surgical expertise should all be considered. An AVF in the non-dominant arm allows for self-needling of the AVF, easy use of the dominant arm during dialysis and also limits any potential neurovascular complications of surgery to the affected arm.

There are no randomized studies comparing different sites of AVF formation in adults or children. In adults, a meta-analysis of the secondary patency rate at 1 year for radiocephalic fistulas is 66%; however, the study-specific 1-year patency varies between 36% and 87% [73]. A prospective series in children that included mainly radiocephalic AVFs has shown excellent primary and primary-assisted patency rates of 78% and 94%, respectively (Table 3) [31]. Bourquelot's large single surgeon experience in paediatric fistula formation in 323 children suggests that better outcomes are possible, with 2-year patency of 85% in radiocephalic fistulae [64]. In addition, a distal fistula preserves proximal venous options for future fistulae, and may allow easier conversion to a more proximal fistula should the distal AVF fail.

However, primary failure and inadequate function is more common with radial AVFs than with brachial AVFs as documented in a meta-analysis in adults [73] and prospective studies in children [74]. Bourquelot's work, and also a smaller study by Chand *et al.*, recommend the use of microvascular surgical techniques and incorporating the operating microscope when forming the arteriovenous anastomosis (Table 3) [53, 75, 76]. In summary, we suggest that a single-stage cephalic-based AVF at the wrist (radiocephalic) or elbow (brachio-cephalic) is the first choice, and when this is not possible a brachio-basilic transposed AVF is the next option.

5. TIMING OF CREATION OF VASCULAR ACCESS

5.1 We suggest creating an AVF at least 3 months before its anticipated use. (Grade 2D)

Evidence and rationale

There are no RCTs in adults or children that address whether early referral to prepare for dialysis has any advantage over late referral [77]. However, several prospective cohort studies in adults and children suggest that being referred earlier to a nephrologist resulted in a reduction in mortality and hospitalization, a decreased likelihood of requiring temporary vascular access at the start of dialysis and increased likelihood of having an AVF [14, 15, 77, 78].

Paediatric practice prospective studies by Kim *et al.* [29] and Shroff *et al.* [15] have reported an average maturation time of 8–10 weeks for the majority of AVFs (Table 3). No difference in maturation time was reported between radiocephalic and brachiocephalic AVFs [15, 29]. The IPHN Registry reports a median time interval of 62 days [interquartile range (IQR) 37–134] between access placement and first fistula puncture in AVF/AVG, and this was independent of age [5]. Angioplasty to achieve assisted maturation may be required in 17–28% of AVFs in children [15, 29, 31, 33, 53], and additional time to allow for this and psychological preparation must be considered when planning the timing of vascular access surgery.

6. ASSESSMENT OF AVF MATURATION

6.1 We suggest assessing maturation 4 to 6 weeks after AVF formation by clinical examination and duplex ultrasound in order to plan the timing of AVF cannulation. (Grade 2D)

Evidence and rationale

The maturation time of an AVF can be defined as the time from creation to being ready for use for dialysis. In adult practice, multicentre prospective studies show that between 28% and 53% of AVFs fail to mature adequately [11, 15, 31, 33, 53, 64, 79, 80]. In paediatric practice, through careful assessment and preparation in a dedicated vascular access clinic, primary failure to mature rates as low as 20% are possible [12, 15]. There are no studies to suggest a single/unified protocol for assessing fistula maturation, but a pragmatic approach based on clinical and ultrasound examination has been practised in the larger paediatric series [11, 13, 15, 45].

Clinical examination should assess for the presence of a thrill, bruit, skin quality, potential needle sites and psychological readiness of the child for AVF needling. In adults with a radiocephalic AVF, KDOQI recommendations from 2006 are for fistula flow (>600 mL/min) and internal vein diameter (>6 mm) as measured by ultrasonography in combination with assessment by an experienced clinician in vascular access prior to first needling [7]. A recent guideline from the European Society for Vascular Surgery that pertains to adults on HD only does not recommend any assessment for AVF maturation. In a prospective study in children, Shroff and colleagues found similar vessel diameter and flow rates to be indicative of AVF maturation (Table 3) [15].

In children with ESKD, an average maturation time of 8–10 weeks has been reported for the majority of AVFs (Table 3) [15, 29]. Children with low blood pressure may have a 'prolonged maturation' time. Hence, if the AVF appears immature at 6 weeks post-formation, it is suggested that ultrasound and clinical assessments be performed at 6-weekly intervals in the expectation that further maturation is possible. If the fistula appears static between 6-weekly assessments, intervention such as angioplasty may then be considered [15]. Some children may require significant psychological support before the AVF can be needled.

Many variables are cited as the cause for primary fistula failure, but initial vein diameter appears to be the most important predictor of fistula maturation [81]. A paediatric study that included 83% radiocephalic AVFs also suggested that low body weight was an independent predictor of primary failure (Table 3) [29]. Although there are no publications to support this practice, most paediatric dialysis centres pay careful attention to avoiding hypotension in the early days after AVF formation, even maintaining the children in a state of controlled overhydration for a few days. For longer term self-care of the AVFs, children and their parents are instructed not to perform

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blood pressure measurements on the AVF arm, to avoid tight clothing that can restrict venous flow and to continue with physical activity but avoid sports or other activities that may cause direct trauma to the AVF. In adult practice, patients are routinely encouraged to perform hand-squeezing exercises to enhance fistula maturation. Although there is limited evidence for this practice, 5 min of squeezing a rubber ball may increase the fistula vein size by 9.3% [82].

7. AVF CANNULATION

7.1 We suggest cannulating an AVF when it has matured adequately. (Grade 2D)

7.2 Use an aseptic technique for AVF cannulation. (Ungraded)

7.3 We suggest using either rope ladder or button hole technique for AVF cannulation. (Grade 2C)

Evidence and rationale

It is suggested that the timing of first cannulation should not be earlier than 1 month after its creation. In a prospective adult study, access failure was associated with cannulation within 4 weeks of access creation [83]. In a retrospective study of 42 children, there was a significant decrease in primary patency when the first cannulation was performed within the 30 days from AVF creation compared with first cannulation performed after 30 days ($P = 0.004$), whereas no difference was seen in primary or secondary patency rates when the first cannulation was performed $\geq$45 days after AVF creation ($P = 0.09$ and $P = 0.88$ for primary and secondary patency, respectively; Table 3) [30]. The interval between AVF creation *per se* and first fistula puncture is reported to be a median of 62 (range 37–134) days in the IPHN Registry [5]. Although there is no evidence to support this practice, most centres would ensure that a highly skilled person performs the first fistula puncture, usually starting with a smaller needle size, both to increase the probability of success and also to build confidence in the child and their parents. Ultrasound-assisted cannulation may improve the cannulation rate of more difficult AVFs.

Meticulous skin preparation of the access sites using strict aseptic technique can minimize contamination and access infection and should be used for all cannulation procedures [84]. It has been shown that HD patients are more frequently nasal and skin carriers of *Staphylococcus aureus* than the general population [85]. The child is asked to wash their arm with soap and water before cannulation. The dialysis staff should wear clean gloves for cannulation [84] and clean the skin with an approved antimicrobial preparation. Studies have suggested that the buttonhole cannulation technique is associated with an increased risk of vascular access-related infections [86]. Although there are no paediatric studies comparing aseptic versus sterile techniques for cannulation of AVFs, an aseptic technique is recommended as a minimum, and dialysis facilities should have a procedural policy for patient vascular access preparation.

There are three standard techniques for access cannulation:

(i) Area puncture refers to cannulation of AVF in the same area.

(ii) Rope ladder—needle puncture sites are chosen at a defined distance from each other along the access and rotated.

(iii) Buttonhole refers to a same site where the needles are placed at each dialysis session at the same angle and depth through a previously created track with sharp needles after which blunt needles are routinely used.

The buttonhole technique has been advocated to facilitate cannulation, decrease needling pain, reduce bleeding at the end of the HD session and prevent aneurysm development. However, it is unclear how these theoretic advantages balance with potential disadvantages such as increased risk of infection, and how technique choice influences long-term AVF patency. Two systematic reviews [26, 87], including six reports of five RCTs comparing buttonhole with 'control' cannulation in AVFs, evaluated outcomes of patient survival, access survival, quality of life, needling pain, infection, bleeding during or after dialysis, and aneurysm development, but did not show a clear benefit of one cannulation technique over another. There was some evidence, albeit of low certainty, suggesting that the buttonhole technique leads to higher infection rates than rope-ladder or area cannulation. Also, there was low certainty of the evidence from the two studies to suggest that buttonhole cannulation caused less extensive aneurysm formation, but patency rates were similar.

In a cross-sectional survey of cannulation techniques in adult HD patients across 171 centres from 2009 to 2012, 65.8% used the area puncture technique, 28.2% centres used the rope ladder technique and 6% used the buttonhole technique [88]. When techniques were compared with access survival, area puncture was associated with a significantly higher rate of access failure than the rope ladder or buttonhole technique [88]. Area puncture leads to aneurysmal dilatation of the puncture areas with subsequent stenoses, thinning of the overlying skin and longer bleeding times after the needles are removed [89]. This area technique is no longer recommended.

The rope ladder technique uses the entire length of the AVF cannulation segment: at every HD session, two new puncture sites are created, avoiding previous sites. The puncture sites are rotated. It is suggested that ~5 cm distance is allowed between the tips of the arterial and venous needles, and at least 3 cm distance from the anastomosis. Thus, a long vein segment is required, which is rarely possible in children. The buttonhole technique requires repeated cannulation at exactly the same site, using the same insertion angle and the same depth of penetration every time, and ideally should be performed by the same nurse in order to establish a track. Once a track is formed with sharp needles, blunt needles can be used, following the direction and angle of the developed track [90]. RCTs regarding the potential benefits of the buttonhole technique have demonstrated reduced aneurysms and fewer haematomas but did not find a difference in pain [91, 92]. However, a recent systematic review that compared rope ladder with buttonhole cannulation techniques in adult HD patients showed that the risk of access infection was higher with the buttonhole technique, although this was reduced with application of mupirocin [26]. There was no statistical difference in cannulation pain [26]. The buttonhole

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cannulation technique may be especially appropriate for patients with a short cannulation segment. The buttonhole method cannot be recommended for all AVFs. The risks and benefits of the buttonhole cannulation technique require individual consideration, and it is important that a risk assessment is carried out in all patients. In addition, when a single person cannulates the AVF, such as children who self-cannulate or parents who cannulate AVFs, the buttonhole technique contributes to cannulation ease and extends the life expectancy of the AVF [93]. Use of local anaesthetic creams to ease the pain of AVF puncture is recommended, irrespective of the puncture technique.

The expertise of the cannulators may be as important as the cannulation technique itself. Dialysis Outcomes and Practice Patterns Study (DOPPS) data have shown that for every 20% increase in the number of experienced staff nurses (nurses who had worked in HD for >3 years) there was an 11% reduction in AVF failure (RR 0.89; $P < 0.005$) [94]. Protocols for the use of different cannulation techniques, training and troubleshooting strategies, and a continued evaluation and education of the needling technique must be developed for each centre.

8. AVF SURVEILLANCE

8.1 We suggest that a structured physical examination of AVFs is routinely performed by dialysis nurses and medical staff. (Grade 2D)

8.2 We suggest that duplex ultrasound off dialysis or haemodilution technique on dialysis of volume flow is performed 3–6 times monthly for routine surveillance of AVFs. (Grade 2D)

8.3 We suggest an urgent referral to a vascular access surgeon if AVF dysfunction or complications are detected on clinical or ultrasound examination. (Ungraded)

Evidence and rationale

The aim of AVF surveillance is early diagnosis and prevention of access dysfunction. A systematic review, including 14 RCTs, provides some evidence for the practice in adults. In 12 randomized trials, pre-emptive correction slightly reduced the risk of access thrombosis (13 RCTs; $n = 1212$; RR 0.79; 95% CI 0.65–0.97; I^2=30%), but there was a moderate degree of heterogeneity in the analysis, which could be explained by the modifying effect of access type (χ^2=10.05, df = 1, $P < 0.001$). Subgrouped, there was moderate-level evidence for an important reduction in the risk of possibly remediable failure of an AV fistula (6 RCTs; $n = 515$; RR 0.50; 95% CI 0.35–0.71; I^2=0%). In addition, pre-emptive correction may slightly reduce permanent access loss (10 RCTs; $n = 972$; RR 0.81; 95% CI 0.65–1.02), but because of high risk of bias in the included studies and the width of the CI, the level of evidence is low.

A systematic review in adults has shown that when abnormalities are detected on AVF surveillance scans, vascular intervention for the pre-emptive correction of AV access stenosis was associated with a significant reduction in the risk of access thrombosis (RR 0.79; 95% CI 0.65–0.97) but only a small non-significant reduction of the risk of access loss (RR 0.81; 95% CI 0.65–1.02; Table 3) [24]. A prospective observational study of 16 children with 18 brachial-based AVFs showed a patency rate of 74% over 2 years. Six of these AVFs were managed by angioplasty or surgical intervention to maintain their patency (Table 3) [33]. Overall, proactive monitoring of vascular access can decrease frequency of thrombosis and hospitalization [24, 95], as well as the need to revert to CVLs for dialysis access.

Monitoring consists of a full physical examination of the AVF prior to every HD session including inspection (for swelling, signs of infection, aneurysms, stenosis or haematoma), palpation (for a characteristic thrill, that will become pulsatile if there is a downstream stenosis, and typically some collapse of the vein on elevation of the arm) and auscultation (for a classic bruit that will be high pitched over a stenosis). This structured physical examination may be carried out by doctors or trained dialysis nurses [96]; an ultrasound of the AVF may be required if physical examination reveals any abnormalities. In the absence of any evidence on AVF surveillance strategies in children, an 'ABCD' approach that is shown to be effective in adult dialysis patients [96] may be considered for ongoing monitoring of AVFs:

A: Assess fistula through physical examination

B: Blood flow and change in flow from baseline—volume flow assessment by duplex ultrasound off dialysis, or by haemodilution technique on dialysis

C: Clinical problems such as difficulties in needle cannulation, or prolonged bleeding after decannulation

D: Dialysis monitoring (adequacy, venous pressure trends and recirculation)

An AVF stenosis is considered significant if there is >20% reduction in volume flow from baseline on ultrasound examination in addition with reduced dialysis adequacy or a prolonged post-dialysis bleeding time. Urgent clinical review and intervention by an experienced interventional radiologist may be necessary to optimize the long-term success of the AVF.

In a randomized controlled study in adult HD patients, Polkinghorne and colleagues assigned 137 patients dialysing via an AVF to monthly access blood flow measurements. Patients with blood flows <500 mL/min were referred for angiographic studies and AVF stenosis was twice as likely to be diagnosed as in the control group [97]. Overall, surveillance with blood flow monitoring followed by angiographic and pre-emptive angioplasty has led to the reduction of thrombosis of AVF, but such strategy has failed to show increased survival of AVF despite intervention [24].

Other techniques for AVF monitoring that have been studied include static venous pressure monitoring, dynamic venous pressure monitoring and ultrasound dilution techniques. Dynamic venous pressure monitoring was studied by Chand *et al.* but did not adequately predict access failure in paediatric HD patients when the patients are used as their own historic controls [98]. Goldstein *et al.* have described the use of an ultrasound dilution technique on a regular basis in paediatric HD patients in order to improve the life of the access (Table 3) [36]. Use of the ultrasound dilution method to monitor the access resulted in a 50% reduction in the number of patients hospitalized, and a significant reduction of costs associated with these hospitalizations. Although not an RCT, it has been

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supported by the NKF/KDOQI guidelines for paediatric vascular access [7].

Other less commonly seen complications of AVFs include steal syndrome and congestive heart failure. Steal syndrome is a possible complication of AVFs, and occurs when cardiac output is diverted from the capillary bed by the AVF causing distal ischaemia [99, 100], but it is rarely seen in children [73]. High-output cardiac failure associated with large AVFs is occasionally seen in adults [101], and although very rare in children, may require detailed cardiac assessment with a view to considering AVF volume flow reduction [102]. A retrospective study that evaluated 26 HD patients aged 4–20 years found that 2 of 14 children with wrist fistulas developed evidence of 'excessive flow' through the fistula, although the term 'excessive flow' is not well defined. In total, 23% of patients required fistula ligation, but these data have to be interpreted with caution as polytetrafluoroethylene (PTFE) grafts (present in >40%) are included in these outcome data. Limb hypertrophy associated with the hyperdynamic state of the limb with an AVF is exceedingly rare [2, 13]. There are no prospective studies in children that describe the management of the above complications. There are no studies in children that have examined the approach to the child with primary or secondary failure of the first AVF. It is likely that an individualized approach based on each patients' vascular system, experience of the vascular access surgeon and their predicted time to transplantation is required. It is not known if the correct approach might include creating another AVF (possibly more proximal to the first one), using a CVL, or exceedingly rarely considering an AVG.

9. PREVENTION OF AVF AND CVL THROMBOSIS

9A. Prevention of AVF thrombosis

9.1 We suggest that anti-platelet agents such as aspirin, ticlopidine or clopidogrel, given in the first few months after AVF creation, reduces AVF thrombosis. (Grade 2D)

Evidence and rationale

A Cochrane systematic review compared the use of eight antiplatelet agents (such as ticlodipine, aspirin, clopidogrel, etc.) in maintaining the patency of AVFs or AVGs [25] (Table 1). When the authors meta-analysed all the antiplatelet agents together as a pre-specified hypothesis that they would all have similar effects (6 RCTs; $n = 1365$; RR 0.54; 95% CI 0.39–0.74; $I^2 = 10\%$), the results indicated that antiplatelet agents seemed to reduce AV fistula thrombosis at 8 weeks, although the reliability of the evidence was compromised by risk of bias in the underlying studies and serious imprecision with a total sample size far below the optimal information size.

When sub-grouped according to the agent (ticlopidine, clopidogrel or aspirin), the summary estimates were all of similar size but with wide CIs for some, and only ticlopidine (a platelet aggregation inhibitor) favoured active treatment (OR 0.45; 95% CI 0.25–0.82) in increasing the patency of AVFs or grafts in the short term. Although the use of aspirin in the first 18 months after AVF creation may increase the risk of bleeding and affect AVF maturation, thrombophilia predisposes to AVF failure [103]. A meta-analysis of three studies for ticlopidine, which all used the same dose of treatment but with a short follow-up of only 1 month, suggests that ticlopidine may have a beneficial effect as an adjuvant treatment to increase the patency of AVFs in the short term. A small study in children that examined the use of unfractionated heparin infusion postoperatively, followed by subcutaneous low molecular weight heparin until AVF maturation in 7 children (8 AVFs), and compared outcomes with a historical control group, has shown that the incidence of thrombosis was lower when primary thromboprophylaxis was used. In this study, a historical control group treated with aspirin had 1 in 5 AVF failures due to thrombosis (Table 3) [34].

A systematic review suggests that perioperative heparin may increase AV fistula patency at 1 month but comes at a cost of increase in bleeding complications. We identified one systematic review on systemic intra-operative anticoagulation during AV access formation [104]. The review included four randomized trials that used systemic heparin during AV access creation and found the intervention may increase AV access patency, but quality of the evidence was low due to high risk of bias in the underlying studies and large imprecision of the summary effect estimate (4 RCTs; RR 0.64; 95% CI 0.37–1.09). Systemic heparin likely increased bleeding events (4 RCTs; $n = 411$; RR 7.18; 95% CI 2.4–21.4).

Anticoagulation may be particularly relevant in the youngest children or those with a pro-coagulant state, such as children with nephrotic syndrome. In the absence of evidence in children, but based on widespread and long-standing clinical practice, we suggest a pragmatic approach and the use of aspirin, at least for the first few months, after AVF formation. In addition, expert opinion suggests that maintaining adequate intravascular volume by reducing the ultrafiltration for a few HD sessions after AVF creation, and allowing permissive hypertension by adjusting antihypertensive medications may prevent early AVF thrombosis.

9B. Prevention of CVL thrombosis

9.2 We suggest that tissue plasminogen activator (t-PA) is used as a catheter locking solution to prevent catheter thrombosis. (Grade 2B)

Evidence and rationale

A number of anticoagulant solutions have been used to try and prevent CVL thrombosis. These include unfractionated heparin, low molecular weight heparin, citrate, warfarin and t-PA. As t-PA has an ability to lyse the clot once it is formed, it can be used as both a prophylactic and a therapeutic agent in the management of catheter dysfunction, with very low risk of bleeding.

A recent Cochrane review has shown that the only agent demonstrating statistically significant improvement for catheter malfunction compared with conventional care was t-PA [22], although based on a single RCT. The Pre-CLOT (Prevention of Catheter Lumen Occlusion with rt-PA versus heparin) study randomly assigned 225 adult HD patients to a catheter-locking regimen of heparin (5000 U/mL) three times per week or

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recombinant t-PA (rt-PA) (1 mg in each lumen) once per week at the mid-week session with heparin used in the other two sessions [17]. Catheter malfunction and risk of bacteraemia was significantly lower among patients receiving rt-PA once weekly compared with those treated with heparin only. This finding is consistent with those of a systematic review by Firwana *et al.* [105], which includes a paediatric study [28]. The role of other plasminogen activators such as recombinant urokinase-type plasminogen activators, although not studied in children, may be of some benefit. Cochrane and other systematic reviews also show that low-dose heparin solutions (using 1000 U/mL of unfractionated heparin) decrease the incidences of CVL infections and bleeding without influencing the incidence of catheter thrombosis [22, 23]. Unfractionated heparin solutions with higher concentrations of heparin (≥5000 IU/mL) prevent thromboses, but carry a high risk of bleeding if systemically absorbed [106]. No benefit is shown with citrate locking solutions over heparin on catheter malfunction, requirement for thrombolytic agents [22, 107] or the need for catheter removal for poor flows [107]. Studies suggest that rapid injection can cause high laminar flow in the centre of the CVL with a spilling of ∼25% of the total volume of the solution due to hydraulic effects [108]. A recent Cochrane review showed that a combination of antimicrobial and anti-thrombotic lock solutions made little or no difference to thrombosis compared with use of standard locking solutions alone (usually heparin 5000 U/mL and low/moderate dose of citrate) [19].

In children on chronic HD, a small prospective double-blinded cross-over trial of instilling either heparin 5000 U/mL or t-PA 1 mg/mL into the catheter showed that t-PA is significantly more effective than heparin in preventing clot formation (2.4 times less clot formation with t-PA than heparin and, when present, the clots were 1.9 times lighter [28] (Table 2). This study involved only nine children, had a short follow-up time of 10 weeks, did not describe methods of randomization, blinding or allocation concealment, and involved use of single-lumen lines and the practice of clot retrieval that are not considered standard practice. An observational study in children has indicated that prophylactic warfarin is safe and may improve CVL survival in children at increased risk of CVL thrombosis [109].

Although t-PA is significantly more costly than heparin, the prevention of catheter malfunction, and thus preserving vascular access, is of paramount importance for children in whom venous preservation is crucial for future dialysis.

9C. Treatment of CVL thrombosis

9.3 We suggest using t-PA as a thrombolytic agent for CVL thrombosis (Grade 2D)

Evidence and rationale

Late-onset CVL malfunction (defined as CVL malfunction >7 days after catheter insertion) reflects thrombosis and/or fibrin sheath formation and possibly infection. A Cochrane review suggests that thrombolysis, fibrin sheath disruption and over-the-wire catheter exchange are effective and appropriate therapies for restoring catheter patency in dysfunctional HD catheters in adults (Table 1) [20]. A systematic review suggests that thrombolysis with t-PA is likely to be safe and effective in some adults on chronic HD, and may be more effective than urokinase [110]. Studies in adult HD patients suggest that physical disruption of a fibrin sheath using interventional radiology techniques appears to be equally efficacious to pharmacological thrombolysis [111] and catheter exchange is superior to sheath disruption [112], but these interventions are rarely performed in children and there are no studies to support their use.

Despite limited data, t-PA is an effective thrombolytic agent in children with thrombus-related CVL occlusion [113]. Overall efficacy ranged from ∼50% to 90%, with greater efficacy generally reported with larger doses and longer dwell times [113]. In a retrospective study in children, seven cases of CVL occlusion were treated with t-PA over 2 h, and achieved catheter patency in all with blood flow rate of >200 mL/min, but re-occlusion occurred in four [114]. This study was limited by its small sample size and lack of inclusion of patients younger than 8 years.

SUMMARY OF GUIDANCE STATEMENTS

A summary of the guidance statements is provided in Table 4.

Audit recommendations

The ESPN CKD-MBD and Dialysis WGs will audit the effectiveness and safety of the recommendations within its WG. The following audit recommendations will be considered:

1. Percentage of prevalent HD children weighing >20 kg with AVFs
2. Percentage of primary AVF failure
3. Percentage of secondary AVF failure
4. The number of access revisions children on HD require before transplantation
5. Time from AVF formation to first cannulation
6. Percentage of children with CVL thrombosis
7. Management of vascular access in a child with primary or secondary failure of the first AVF
8. The usage of AVF after renal transplantation
9. The time from AVF creation to renal transplantation

These data will be collected through the IPHN Registry. The audit outcomes will be published and recommendations updated as necessary.

Research recommendations

We suggest the following research recommendations for AVF and CVL use. Recommendations for CVL use must consider the recommendations for standardized clinical trial endpoints for dialysis catheters [115].

(i) Outcomes of dedicated vascular access clinics on AVF uptake and patency in a paediatric dialysis unit
(ii) Outcomes of AVF surveillance programmes on primary and secondary AVF patency
(iii) Outcomes of different cannulation techniques on access performance, including blood flow, recirculation, access patency, thrombosis and infections
(iv) Are AVFs associated with high-output cardiac failure, when used for dialysis or after renal transplantation?

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Table 4. Summary of recommendations

	Category	Recommendation	GRADE
1.	Planning vascular access	1.1 Educate children with CKD and their carers about venous preservation, irrespective of the choice of future renal replacement therapy, and starting from their early contact with the nephrology services.	Ungraded
		1.2 Educate children with CKD Stage 4 (eGFR <30 mL/min/1.73 m^2 by Schwartz formula), those with rapidly declining kidney function, or those who need to start maintenance dialysis imminently, about kidney failure and options for its treatment, including kidney transplantation, peritoneal dialysis, HD in the home or in-centre, and conservative treatment, where appropriate.	Ungraded
		1.3 We suggest referring children with CKD Stage 4 who are being prepared for future HD to a dedicated vascular access team.	2D
2.	Optimal vascular access in children	2.1 We suggest that children requiring chronic HD start with a functioning AVF where appropriate.	2C
		2.2 Reserve cuffed CVLs for very small children depending on vessel size and surgical expertise, those requiring urgent or unplanned HD, patient preference and where a short period on HD is anticipated before transplantation.	Ungraded
		2.3 There is insufficient evidence to provide recommendations on AVGs in children.	Ungraded
3.	Preoperative evaluation for AVF formation	3.1 We suggest performing a structured history, physical examination and duplex ultrasound of upper limb arteries and veins to plan AVF creation.	2C
		3.2 We suggest performing appropriate imaging of central veins by venography, CT angiography or non-contrast MRI in children in whom central venous stenosis is suspected, such as those with previous CVLs.	2D
		3.3 Avoid AVF creation in the ipsilateral arm of a central venous stenosis.	Ungraded
4.	Site of AVF placement	4.1 Place an AVF in the non-dominant arm where possible.	Ungraded
		4.2 We suggest placing an AVF distally in the arm.	2D
5.	Timing of creation of vascular access	5.1 We suggest creating an AVF at least 3 months before its anticipated use.	2D
6.	Assessment of AVF maturation	6.1 We suggest assessing maturation 4–6 weeks after AVF formation by clinical examination and duplex ultrasound in order to plan the timing of AVF cannulation.	2D
7.	AVF cannulation	7.1 We suggest cannulating an AVF when it has matured adequately.	2D
		7.2 Use an aseptic technique for AVF cannulation.	Ungraded
		7.3 We suggest using either rope ladder or button hole technique for AVF cannulation.	2C
8.	AVF surveillance	8.1 We suggest that a structured physical examination of AVFs is routinely performed by dialysis nurses and medical staff.	2D
		8.2 We suggest that duplex ultrasound off dialysis or haemodilution technique on dialysis of volume flow is performed 3–6 times monthly for routine surveillance of AVFs.	2D
		8.3 We suggest an urgent referral to a vascular access surgeon if AVF complications are detected on clinical or ultrasound examination.	Ungraded
9.	Prevention of AVF and CVL thrombosis	9.1 We suggest that anti-platelet agents such as aspirin, ticlopidine or clopidogrel, given in the first few months after AVF creation, reduces AVF thrombosis	2D
		9.2 We suggest that t-PA is used as a catheter locking solution to prevent catheter thrombosis.	2B
		9.3 We suggest using t-PA as a thrombolytic agent for CVL thrombosis	2D

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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CONFLICT OF INTEREST STATEMENT

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