Hemodialysis in Children

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Chronic dialysis, including both hemodialysis and peritoneal dialysis, is technically feasible in children of all ages, including neonates [1]. In countries with active pediatric transplant programs, however, dialysis would not be the first choice of renal replacement therapy, as most pediatric nephrologists would aim for preemptive transplants in their patients. Despite that aim, across Europe half of patients start renal replacement therapy on peritoneal dialysis and one third on hemodialysis, and only the remainder are transplanted preemptively [2]. Some children will inevitably require a period on dialysis, such as the infant in whom dialysis may be necessary until adequate size for transplant is reached, the child needing urgent treatment because of presentation in end-stage kidney disease, and children needing native nephrectomies pre-transplant. Furthermore, only a minority of children are able to escape a period of dialysis either while waiting for their first transplant or because of subsequent graft failure. This means that overall, at any time, around 20 % of the pediatric end-stage kidney disease population is dialyzed [3, 4].

The choice of dialysis modality varies from country to country. In Europe, peritoneal dialysis is the commonest choice, with a ratio of 2:1 peritoneal dialysis to hemodialysis overall, but with an age-dependent effect such that peritoneal dialysis predominates in patients aged <5 years and hemodialysis in those aged >10 years [2]. In the USA, HD is used by 60 % of incident and prevalent patients younger than 19 years [4]. Of course, many children will need to switch modality, often from peritoneal to hemodialysis because of peritoneal membrane failure. Total numbers of children on hemodialysis throughout the world are small: for example, there are at any time approximately 70 patients less than 16 years of age in the UK [3] and 1,500 less than 19 years of age in the USA [4]. Despite regional differences in choice of dialysis modality, there are some universal rules, including avoidance of hemodialysis in the infant due to difficulties with vascular access and the use of hemodialysis when there is technique failure, intra-abdominal pathology, or social difficulties that preclude peritoneal dialysis. Because of this bias towards the use of hemodialysis in preference to peritoneal dialysis in the more complicated patient, it might be expected that outcome would be inferior in hemodialysis patients, but there is no evidence to suggest a difference either in morbidity [5] or subsequent transplant outcome [6]. There is good evidence, however, that the longer the duration of dialysis, the greater the risk of cardiovascular disease and premature death, regardless of the dialysis modality [7].

There is no prescribed GFR at which children should start dialysis. The optimum time varies between individual patients and requires assessment not only of renal function, fluid status, and biochemical abnormalities but also of well-being (both physical and psychosocial); some children can be managed extremely successfully with diet and medications and continue to remain well with good growth for prolonged periods with very poor renal function. This is particularly true for infants, in whom renal function continues to mature, and in young children with structural renal abnormalities, in whom renal function can remain stable for many years, who often continue to produce large volumes of urine. However, uremic symptoms frequently begin when the GFR falls below 15 ml/min/1.73 m^2. In the USA, registry data (USRDS) shows that the mean estimated GFR (eGFR) of 4,808 children who were initiated on dialysis was 8.2+/−4.1 ml/min/1.73 m^2; 49.6 % had an eGFR greater than 10 ml/min/1.73 m^2 and 7.3 % less than 5 ml/min/1.73 m^2 [8]. In Europe, of 938 patients younger than 18 years, eGFR at the start of renal replacement therapy was 4 mL/min/1.73 m^2 in 5 %, 4–8 mL/min/1.73 m^2 in 29 %, 8–14 mL/min/1.73 m^2 in 42 %, and >14 mL/min/1.73 m^2 in 24 % of patients [9].

Most importantly, care of children on hemodialysis requires input from a large multidisciplinary team including pediatric nephrologists, renal nurses and dieticians, transplant surgeons, urologists, interventional radiologists, anesthetists, pharmacists, play specialists, schools teachers, psychologists, and social workers, all of whom need the special skills necessary to treat such children. Availability of hospital school teachers and liaison with local schools is particularly important for children on hemodialysis who spend so much of their time at the hospital.

Many children with CKD have associated comorbidities, which can include congenital abnormalities in any of all organ systems. This amount of expertise can only be provided by bringing patients together in specialist pediatric nephrology centers sited in major cities. This inevitably means that some families have to travel long distances to obtain the best possible care for their child, placing particular social and economic stresses on the family with a child on hemodialysis.

Principles of Hemodialysis

In the normal kidney, water is removed from the blood by ultrafiltration (UF) and solutes by convection. Solutes of molecular weight below 40,000 Da are able to pass freely across the glomerular basement membrane allowing the passage of low molecular weight molecules and retention of larger molecules such as plasma proteins. The purpose of hemodialysis is to mimic the role of the kidney, removing waste products and solutes and fluids that have accumulated between dialysis sessions. The semipermeable membrane in the dialyzer allows the passage of water and small molecular weight molecules and inhibits the movement of larger molecules. Solute transfer (clearance) occurs by diffusion and convection, and water is removed by ultrafiltration.

Diffusion

Diffusion is the movement of a solute down a concentration gradient. The rate of diffusion of a solute is inversely proportional to its molecular weight and directly proportional to the temperature of the solution, in this case the dialysate. It is also affected by the electrical charge of the solute. The hemodialysis membrane itself will also affect the rate of diffusion; its permeability is a reflection of its thickness and the number of pores in it and their density, and diffusion across it will also be affected by its surface area. The transmembrane concentration gradient is maintained and maximized by high flow rates of blood and dialysate in opposite directions (countercurrent). As well as being the main mechanism for the removal of solutes, diffusion is also responsible for the replenishment of bicarbonate: as they are buffered in plasma, hydrogen ions are in low concentration and so are not readily removed by dialysis. Fluid can stagnate on either side of the dialysis membrane, and this is referred to as "unstirred" fluid, which can decrease diffusion. This can be minimized by maintaining high flow rates and by dialyzer design. Clearly, the dialysate only comes into contact with the intravascular compartment, so, although rapid equilibrium can take place with circulating solutes, predominantly intracellular solutes such as phosphate take time to move into the blood and clearance is less effective. Furthermore, protein-bound solutes will not be removed.

Ultrafiltration (UF)

Ultrafiltration is the process whereby water is moved across the membrane by convective flow down an osmotic gradient or a pressure gradient, which is created by generating a transmembrane pressure (TMP) within the dialysate compartment by the dialysis effluent pump. Large molecular weight molecules are removed better by convection than diffusion. The net rate of ultrafiltration is affected by the surface area, structure and thickness of the dialyzer, blood flow rate, and the transmembrane hydrostatic pressure and osmotic pressure.

Convection

Convection (solute drag) is the passive movement of solute "dragged" by water moving down an osmotic or pressure gradient. It is independent of the concentration gradient but is dependent on the ultrafiltration rate and the sieving properties (coefficient) of the dialyzer, i.e., if the molecular weight of the molecule is such that it is not held back and sieving does not occur, it is swept across the membrane by the ultrafiltrated water.

Mass Transfer

Removal of toxins depends on their distribution in the body compartments: those in the intravascular space will be rapidly removed, but those that are predominantly intracellular will need time to move into the intravascular space as concentration gradients change. Molecular size will also affect removal: Table 1 shows the definitions of uremic retention solutes by molecular weight and their method of removal during dialysis. Uremic retention solutes such as urea and creatinine are rapidly removed. Large numbers of biochemically active, potentially toxic "middle-sized molecules" have been identified. Many are peptides that affect many organs and may contribute to the symptoms and morbidity of uremia, such as poor appetite, anemia, inflammation, and cardiovascular disease. Well over 100 have been identified. The best known is beta-2-microglobulin, which causes dialysis-related amyloid. Recently, interest has focused on the dinucleotide polyphosphates, structural variants of angiotensin II, interleukin-18, p-cresylsulfate and the guanidines. Large pore dialyzers and hemodiafiltration may improve their removal by increasing convection. Some protein-bound middle molecules may also be toxic, one example being leptin, and are particularly difficult to remove by any dialysis technique [10]. Protein molecules may be adsorbed onto the dialyzer, depending on the nature of the dialysis membrane. A small and variable amount of protein is removed in this manner, but it does lead to an increased transmembrane pressure across the dialyzer, reduced efficacy of the dialyzer, and sometimes clotting of the filter.

The HD Machine, the HD Circuit, Dialysate, Water, and Dialyzers

The Hemodialysis Machine and Blood and Dialysate Circuits

There are two circuits, the blood circuit and the dialysate circuit, that run in opposite directions, separated by the semipermeable membrane of the dialyzer (Fig. 1). The blood circuit includes lines through which blood is pumped from the patient

Table 1 Definitions of uremic retention solutes by molecular weight (MW) and their method of removal during dialysis

Solute	Molecular weight	Example (MW)	Method of removal
Small solutes	<500	Urea (60), creatinine (113)	Diffusion
Middle molecules	300–5,000	Vitamin B_{12} (1,355)	Diffusion/convection
Low molecular weight proteins	5,000–50,000	β_2-Microglobulin (11,800)	Diffusion/convection
Large proteins	>50,000	Albumin (60,000)	Convection

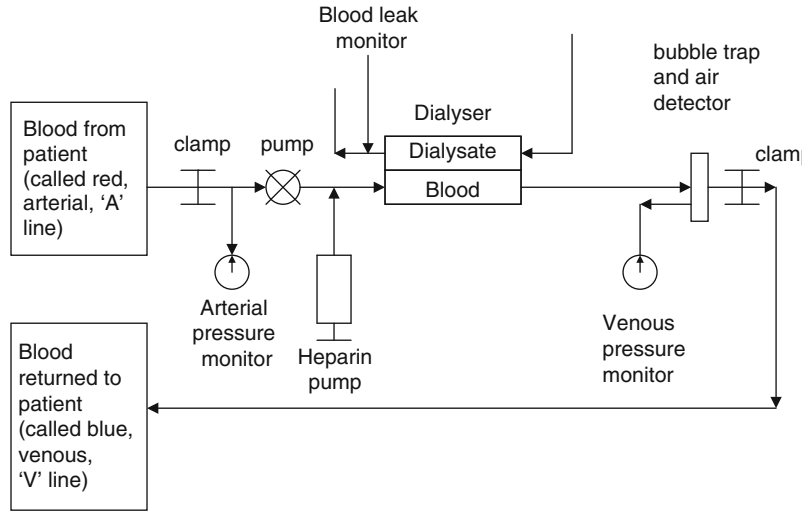

Fig. 1 The blood and dialysate circuits

to the dialyzer and then back to the patient. Conventionally, the lines taking blood from the patient are called arterial, "red" lines, and those returning blood to the patient are the venous, "blue" lines. Pressures in the blood lines are monitored in the "arterial" segment between the blood pump and the dialyzer and in the "venous" segment at the venous bubble trap and air detector, so that vascular access problems are indicated by arterial or venous pressure alarms. Low arterial pressure alarms indicate that there is an insufficient blood flow reaching the blood pump. This is commonly referred to as "sucking" and is usually a result of poor access position in the vessel. Arterial pressure between 150 and 200 mmHg limits trauma to the vascular endothelium. A low venous pressure alarm also indicates poor blood flow. A high venous pressure alarm indicates that there is an occlusion to the flow of returning blood. It is due either to poor access position, fistula stenosis, or the presence of clot formation. If an alarm is activated, the blood pump is stopped and the lines are clamped. Precise occlusion of tubing by the pump is vital in order to prevent backflow, foaming, and hemolysis. There is a separate system for delivery of anticoagulant to the blood circuit before the dialyzer. Sample ports in either side of the circuit allow blood samples to be obtained while the child is being treated.

The dialysate circuit is separated from the blood circuit by the semipermeable membrane of the dialyzer. Dialysate is run in the opposite direction to the blood to maintain the concentration gradient between the blood and the dialysate. There is a blood leak detector (to detect rupture of the dialyzer fibers with leakage of blood into the dialysate) just distal to the dialyzer. The water used for dialysis is purified to remove as many dissolved substances as possible by various filters, reverse osmosis, and absorption tanks. The dialysis machine prepares the dialysate by mixing the purified water with prescribed quantities of electrolytes and bicarbonate.

There are certain specific features that are necessary in a pediatric hemodialysis machine: it must be capable of low blood flow speeds and be able to use lines of varying blood volumes and to measure and remove very small amounts of fluid so that it can be used even in infants. A volumetric fluid removal system allows accurate fluid removal. It does this by measuring the inflow and outflow volumes from the dialyzer so that ultrafiltrate volume is measured directly, allowing the automatic calculation and application of a pressure across the dialysis membrane, the transmembrane pressure (TMP), and prescribed fluid removal throughout the dialysis session.

New machines have systems for continuous online monitoring of the hematocrit and calculated blood volume, oxygen saturation, blood pressure, and pulse and for Kt/V urea. Most new machines are able to combine diffusive and convective solute transport (hemodiafiltration [HDF]) and are able to generate ultrapure dialysate and infusion fluids "online." Two new systems, the CARPEDIEM (Cardio-Renal Pediatric Dialysis Emergency Machine) and the "NIDUS" hemodialysis machines for infants as small as 800 g, have passed efficacy and safety tests and are ready for manufacture. The CARPEDIEM can sustain dual-lumen catheters as small as 4.0–4.5 Fr and has line volumes of 27 ml; filters of $0 \cdot 075$, $0 \cdot 15$, and $0 \cdot 25$ m^2; and miniature roller pumps that can deliver flow rates of 5–50 ml/min. The UF and replacement fluid pumps run at 0–10 ml/min with UF accuracy of about 1 g and reinfusion or dialysis flow errors ranging from −8 % to 7.5 %. The NIDUS works with a single lumen catheter and has an extracorporeal circuit volume of less than 10 ml. Blood is aspirated and is then passed repeatedly through a high-flux polysulfone 0.045 m^2 hollow-fiber hemofilter before being returned to the baby. The UF capability of the circuit is 0–60 ml/h. These machines offer exciting new possibilities for the acute and chronic dialysis of very small infants [11]. New portable HD machines are also being developed. An example is the NxStage System One™. Dialysate is either available as preprepared 5-L bags or prepared by the System from tap water. This offers families the freedom of a portable machine that does not rely on plumbing of the home water supply [12].

Dialysate

Dialysate is prepared during the dialysis session. Sodium, potassium, magnesium, calcium,

chloride, dextrose, and bicarbonate are added to the purified water by the machine, and their concentrations can be varied within certain prescribed limits. They are mixed and proportionated by the dialysis machine. Standard settings are 138–140 mmol/l for sodium, 2 mmol/l for potassium, 1.25–1.75 mmol/l for calcium, and 0.5–1 mmol/l for magnesium and glucose 1 g/l. The dialysis machine monitors the electrical conductivity of the dialysis solution to ensure the correct proportion of water to concentrate is occurring before it is delivered to the hemodialyzer. Bicarbonate is used as a buffer. The bicarbonate preparation has a separate acidic component to prevent precipitation of calcium and magnesium carbonate and is added by a second proportionating pump. Inevitably with time, there will be deposition of calcium and magnesium salts, so the dialysate system needs daily decalcification. The dialysate is warmed before delivery to the dialyzer. Temperature selection is between 34.5 °C and 37.5 °C. Lower temperatures are associated with less hypotensive events, but diffusion is increased at higher temperatures. Standard dialysate flow is 500 mls/min (range 300–800 ml/min).

Water

Although water from the main supply is satisfactory for human consumption, it is not suitable for dialysis. During a standard HD session, the patient's blood is directly exposed to 120 l of water and all its potentially hazardous contaminants, including particles, dissolved substances such as ions, trace elements, organic substances, nitrogen compounds, microorganisms, and their toxins. Therefore, filters of progressively smaller sizes to remove particulate matter, activated carbon for chlorine and chloramines, and water softeners to remove calcium and magnesium must be in the water circuit before the water reaches the dialyzer. Finally, a reverse osmosis unit and/or ion exchange resin unit purifies softened filtered water before it is of a quality suitable for dialysate production by removing residual particulates, dissolved inorganic and organic substances, microorganisms, and toxins.

Table 2 European Pharmacopoeia definitions for the upper limit of water quality Ref. [13]

	Bacterial growth (cfu/mL)	Endotoxin (EU/mL)	Cytokine induction
Mains water	200	5	+
Regular water	100	0.25	+
Ultrapure	0.01	0.03	–
Sterile	10^{-6}	0.03	–

There are detailed standards for the design of the water delivery circuit and its management, and for all aspects of water purity [13]. Water quality is defined as "pure" or "ultrapure" (Table 2). "Pure" water is adequate for conventional dialysis, but ultrapure water is preferable and is essential for high-flux dialyzers, when back filtration can occur, and in high flow hemodiafiltration, when large volumes of replacement fluids are used (see below). Even very low levels of endotoxin in the water can cause cytokine-mediated inflammation which, in turn, may contribute to the increased risk for cardiovascular disease seen in patients on dialysis [14]. Water quality standards need to be maintained and regularly checked to ensure bacterial contamination and mineral content are within acceptable limits. Microbiological contamination of the delivered water should comply with published recommendations, and acceptable levels of all other recognized contaminants have also been defined [13].

The Hemodialyzer

The hemodialyzer is composed of two compartments, one for blood and one for dialysate, which are separated by the semipermeable membrane. A capillary (hollow-fiber) configuration achieves the maximal membrane surface area over which blood and dialysate make contact in a relatively low fill volume with low compliance.

The membrane can be composed of modified cellulose or a synthetic material. Unmodified cellulose membranes are the least biocompatible and

may cause activation of complement and leucocytes and a severe allergic reaction within minutes of starting dialysis. Sterilizing solutions (e.g., ethylene oxide) may also cause allergic reactions.

Each type of dialyzer has an ultrafiltration coefficient (KUf), which describes its ability to remove water. For example, a KUf of 2.0 means that 2 ml/h of UF will occur for each mmHg of TMP at a blood flow rate of 200 ml/min. KUf depends on the surface area of the dialyzer as well as its membrane characteristics. Dialyzers with KUfs of less than 10 are referred to as low flux and those with a rate of 15–60 ml/h/mmHg are called high flux. Synthetic membranes tend to be high flux.

Solute transport properties of dialysate membranes are expressed as the mass transfer-area coefficient (KoA). Dialyzers of usual efficiency (for removal of small solutes) have a KoA of 300–500; high-efficiency dialyzers may have a KoA of more than 700. Precise clearance values for creatinine, urea, vitamin B_{12}, and phosphate are given for all dialyzers in the manufacturer's specification sheet. Clearance of a solute is inversely proportional to the molecular size; most dialyzers allow the passage of solutes of up to 5–10,000 Da.

Dialyzers may be sterilized with irradiation, steam, or ethylene oxide. The latter is particularly likely to cause reactions. Priming the circuit with 1–2 l of saline to expel air and prepare the capillaries for use will also help flush out remaining ethylene oxide and other soluble compounds in the circuit, which may be toxic or cause allergic reactions at the commencement of dialysis.

Factors Affecting the Dialysis Prescription

Types of Dialysis

Conventional hemodialysis uses a low flux (small pore size) membrane and solute removal is primarily by diffusion. High-efficiency hemodialysis refers to a more rapid removal of urea, K+, and other small solutes. This is achieved by using a low flux membrane with a high efficiency (KoA) for removal of small solutes. It is also achieved by using a larger surface area membrane and a high blood flow. Because conventional dialysis is principally diffusive based, even when using high-flux dialyzers, it is limited in clearing middle-sized molecules (MW 200–20,000), which are better removed by convection.

High-flux hemodialysis utilizes high-flux (large pore size) membranes. It is more efficient in removing solutes that are substantially larger than urea (middle and large molecules such as vitamin B_{12} and beta-2-microglobulin, respectively), but may not be more efficient than conventional hemodialysis in removing small solutes. Better clearance of beta-2-microglobulin may reduce the risk of amyloidosis.

A more effective form of dialysis, particularly for the removal of higher molecular weight solutes, is to superimpose convection upon standard diffusive blood purification using hemodiafiltration. It is possible to use a high-flux hemofilter to ultrafilter up to 30 % of the blood volume passing through it. The desired volume of replacement fluid is then infused into the blood circuit. Ultrapure dialysate and infusion fluid is necessary. Care must be taken that excess fluid removal does not occur, so a volumetrically controlled machine is essential. Hemodiafiltration may be limited by blood flow rates, but is being used more in children and even in younger ones. Fluid replacement can be pre- or post-dilutional. In post-dilution HDF, the replacement fluid is infused after the dialyzer, usually into the venous bubble trap. This is the most efficient method of solute removal, but the hemoconcentration that occurs at high UF rates may cause clotting of the circuit and deposition of plasma proteins on the membrane surface, reducing clearance. Hemoconcentration is dependent on the ratio of the ultrafiltration rate to the blood flow rate (filtration fraction) and is less likely to occur with a filtration fraction of less than 30 %. In pre-dilutional HDF, the replacement fluid is infused before the dialyzer. This reduces hemoconcentration so that higher filtration rates can be achieved, but reduces the efficiency of both diffusive and convective

clearance by reducing the solute concentrations in the blood compartment.

Size of the Extracorporeal Circuit

The lines and the hemodialyzer are selected on the basis that the child can tolerate 8–10 % of their total blood volume (TBV, 80 ml/kg estimated dry weight) in the extracorporeal circuit. For example, a child weighing 10 kg has a TBV of 800 mls (10 × 80 ml); therefore, the extracorporeal circuit can be 64–80 mls. The total volume of the lines and hemodialyzer therefore must not exceed 64–80 mls. There are lines that are made in a variety of sizes by different companies. Some examples are shown in Table 3.

Lines are primed with saline. However, in the very young, even the smallest circuit may exceed the safe extracorporeal volume. In this situation, the circuit must be primed with blood. The blood is not washed back into the child at the completion of dialysis to prevent hemoconcentration. Obviously, this is not ideal because the repeated prescription of blood increases the risks of HLA sensitization, with its consequent difficulties for transplantation. This is one of the reasons for opting for peritoneal dialysis in infants.

The dialyzer is selected on the basis of its surface area and the priming volume. Roughly, the surface area should be equal to but not exceed that of the child's. At present, conventional hemodialyzer surface areas range from 0.25 m^2 up to 1.7 m^2 and above, although dialyzers for the new CARPEDIEM and NIDUS machines are much smaller [11]. The greater the surface area, the greater the clearance of water and solutes.

Table 3 Examples of the volumes of lines available for dialysis according to the size of the patient

	Venous (mls)	Arterial (mls)	Total (mls)
Mini-neonatal (<6 kg)	21	8	29
Neonatal (6–12 kg)	22	18	40
Pediatric	42	30	72
Adult	70	62	132

Frequency and Duration of Sessions

It has been a convention to dialyze for 4 h three times a week. This has evolved for economic reasons, and although it provides "adequate" dialysis, most would agree that it does not provide "optimum" dialysis. Middle-size molecules diffuse slowly into dialysis fluid, so treatment times that are less than this have a proportionately greater deleterious effect on their clearance than other molecules. This may have implications for the long-term health of dialysis patients. Indeed, increasing dialysis dose can be correlated with improved survival in large adult studies [15].

There is increasing evidence that in children too, more intensified dialysis is beneficial. Certainly, there is increased hospitalization for fluid overload and hypertension during the long break in children on three times a week hemodialysis [16]. Intensified dialysis has been reported from several pediatric centers. It can be delivered as hemodialysis or hemodiafiltration, ranging from 6 h to overnight, three to seven times per week, or short frequent sessions of 2–3 h five to seven times per week, and can be carried out in center or at home. Home hemodialysis is emerging as a feasible and safe option even for young children, who have a family member who is prepared to take on the responsibility. Intensified dialysis is particularly indicated in those with chronic fluid overload or hyperphosphatemia, because of poor growth, or for infants, whose predominantly liquid diet requires removal of relatively large fluid volumes, although it is likely to benefit all children. Reports demonstrate better phosphate and BP control, with many patients being able to come off all their medications, improved appetite and growth, and, despite increased time spent dialyzing, improved quality of life [12, 17–23].

Blood Pump Speeds

The speed at which the blood is pumped out of the child and around the circuit is calculated as the equivalent of their extracorporeal volume total (i.e., up to body weight (kg) × 8 ml/min). Thus, the 10 kg child, with an extracorporeal circuit of

64–80 mls, can have blood speeds of up to 80 ml/min. The blood pump flow rate is a very important determinant of solute clearance, allowing maximum diffusion and convection.

Estimation of Optimum Weight and Fluid Removal

The optimum weight of the child is also called the "dry" or "target" weight. The aim is to end the hemodialysis session with the child at their optimum weight, which is the weight below which the child will become symptomatically hypotensive. However, estimation of optimum weight can be difficult and needs to be reassessed at least monthly, and more often in very small children, in particular infants, to allow for growth. It can only be determined by clinical examination and careful but persistent fluid removal to achieve a normal BP after dialysis. The child who is always hypertensive is likely to be above their optimum weight; antihypertensives can usually be discarded when this is achieved. However, attainment of optimum weight with conventional three times a week dialysis can be difficult in the child who has high interdialytic weight gains requiring large UF volumes. Much better results have been obtained with daily dialysis, with most children no longer needing antihypertensives at all [12].

The amount of fluid to be removed is calculated by the weight gain since the previous session (assuming optimum weight had been achieved then), the volume of saline required for the "washback," and any fluid to be consumed during the session. The hemodialysis machine will adjust the TMP accordingly, depending on the time (in hours), and the venous pressure (which is affected by the blood speed, and peripheral resistance), to give an hourly UF rate.

The greater the TMP that is set, the greater the amount of fluid that will be removed from the child and the more likely it is that the child will feel unwell. High UF rates while diffusion is occurring are not well tolerated. To counteract this, isolated UF can be performed, in which the flow of dialysate is halted; therefore, dialysis and hence diffusion cease so that the osmolality of the intravascular space is maintained. This allows more fluid to be removed more quickly from the child and is useful when there are large volumes requiring ultrafiltration. As dialysis does not occur during isolated UF, the length of time on the dialysis machine will increase.

The amount each child will tolerate losing per hour varies, but 10 ml/kg/h is a safe starting point. Up to 600 ml/h can be removed in children weighing >40 kg who are consistently volume overloaded. No more than 5 % of body weight should be removed in one session, or 0.2 ml/kg/min. It has been shown that a decrease in blood volume of >8 % in the first 90 min or >4 % thereafter is likely to lead to hypovolemia [24].

Fluid loss (UF) can only be achieved if the fluid is in the vascular space. As the vascular space empties, refilling must occur from the other compartments, to allow ultrafiltration to continue. The child will show signs of hypovolemia if ultrafiltration (from hemodialysis or isolated UF) continues unchecked. If hypovolemia occurs, the UF rate should be decreased and the child given a drink or bolus of saline to correct hypotension, if necessary. Many patients collapse having had no prior warning of feeling unwell; therefore, close monitoring of blood pressure and other observations (including peripheral temperatures) is important during isolated UF. However, children treated with chronic hemodialysis are often able to recognize the early warning signs and can prevent such episodes.

Another way to prevent intravascular volume depletion due to slow refilling from the extravascular space is to vary the concentration of the dialysate sodium throughout the course of the session. The machine can be programmed to deliver a sodium concentration higher than that of the plasma at the beginning of the session so that sodium diffuses into the plasma and balances the change in osmolality caused by diffusive urea removal. The sodium concentration in the dialysate is then progressively reduced. This is important as leaving the patient with a high plasma sodium will stimulate thirst between sessions. Although this technique, which has been called sodium ramping, profiling, or modeling, helps intradialytic hypotension, the danger is that there

is inadequate sodium removal, hence contributing to chronic fluid overload and hypertension.

Bioimpedance and natriuretic peptides have been used to assess optimum weight, but their use is unproven in children. Newer machines are able to monitor circulating blood volume by determining changes in hematocrit or blood viscosity: Increasing values during UF mean that fluid can no longer move into the intravascular space and removal may be nearing completion.

The Electrolyte Concentrations in the Dialysate and Blood Biochemistry

Sodium – The dialysate sodium must be within 10 mmols of the child's plasma sodium to avoid disequilibrium. The sodium dialysate concentrate level can be altered on the machine within preset parameters. If it is set below that of plasma, then more sodium and therefore water will be removed, although this may cause intradialytic hypotension. Sodium modeling can improve these symptoms but may result in more salt and water retention (see above).

Potassium – The standard dialysate potassium is 1–2 mmol/l. Adjustment may be needed for children with low plasma potassium levels or in those requiring a long dialysis session, when a dialysate potassium of 3–3.5 mmol/l can be used; if the child has a very high potassium, a zero-potassium dialysate can be used for a short period of time, before reverting to the standard potassium dialysate. There is a danger of severe hypokalemia and arrhythmia if a zero potassium is used for too long. The use of serum potassium monitoring equipment (ionometer) facilitates the management of hyperkalemia.

Bicarbonate – The dialysate level can be adjusted on the machine, within preset limits. The level is usually around 35 mmol/l.

Calcium – Dialysate calcium concentrations vary between 1.25 mmol/l (which is equivalent to the blood in the normal child) and 1.75 mmol/l. Calcium concentration can be selected depending on the plasma calcium level and whether calcium influx or removal is required.

Phosphate – Clearly, there is no need for phosphate in dialysate. After an initial fall in plasma levels during the first 1–2 h, movement from the intracellular compartment is slow, so very little is removed thereafter and levels are back to 80 % of pretreatment values by 12 h post-dialysis so that dietary phosphate restriction and phosphate binders are almost always necessary. Long dialysis sessions or frequent short sessions result in the best phosphate clearance.

Urea – Care needs to be taken if serum urea levels are over 40 mmol/l (120 mg/dL) because a rapid reduction in serum levels can result in disequilibrium syndrome (see section "Complications of HD"). Mannitol can be infused continuously during hemodialysis to counteract the fall in osmolality although repeated infusions can lead to accumulation. The best way to avoid disequilibrium is to keep the dialysis session short, at less than 2 h, and to keep the absolute fall in serum osmolality low.

Creatinine – Will fall rapidly during the session as there is none in the dialysate, but it will rebound and rise linearly following the end of dialysis.

Administration of Blood Products

Albumin – A low serum albumin will result in edema and difficulty in removing excess fluid. If the child is oligoanuric, 25 % albumin should only be given when on dialysis, as the resultant fluid shifts can cause pulmonary edema. It must be given in small boluses through the arterial infusion port at the beginning of the session, to allow time for movement of fluid from the extravascular into the intravascular compartment.

Blood – Blood should only be required to prime the lines if the volume of the dialyzer and lines exceeds the safe extracorporeal circuit volume, i.e., in infants. This blood prime is not washed back into the child at the end of the session. If blood is required for the treatment of anemia, the rule of thumb is that a dose of packed red blood cells equal to 3 ml/Kg of body weight will raise the plasma hemoglobin concentration by 1 g/dL. The actual concentration of

hemoglobin in packed red blood cells, however, can vary by a considerable amount depending on the gender of the donor and the packing technique of the blood bank. The blood is infused in small boluses at the beginning of dialysis, through the arterial infusion port, so that potassium and excess plasma water will be removed.

Resulting fluid shifts with blood or albumin may lead to the need for ultrafiltration towards the end of the session.

Anticoagulation

Unfractionated heparin is the standard anticoagulant used to prevent the blood clotting in the circuit during hemodialysis. There are different protocols for administration, either by boluses, infusion, or a combination of both, all of which are based on patient weight. The commonest is to infuse it slowly and continuously throughout the session at a rate of 5–50 units/kg/h through the arterial side of the circuit. The dose can be monitored by the activated partial thromboplastin time (target 1.5–2.0) or activated clotting time (target 180–220 s), but in practice, this is rarely necessary. Some units use low molecular weight heparins, given as a bolus at the beginning of the session. The half-life of different types varies up to around 24 h. It is possible to monitor anti-Xa levels to achieve a peak of 0.4–0.6 IU/mL and <0.2 IU/ml at the end of the session or to make a clinical judgment of dose appropriateness by clotting in the circuit and bleeding after needling [25].

The circuit needs to be constantly monitored for the formation of clots. If suspected, a bolus of 50–100 ml of saline flushed through the circuit with the arterial lines clamped may reveal clot formation. Clots may form when there is slow blood flow because of access problems, a raised hematocrit, a long period of ultrafiltration as the hematocrit is raised as fluid is removed, and inadequate heparinization. If a circuit clots off completely, the blood in the lines is lost. This will not have a detrimental effect on the child, providing the extracorporeal rules have been observed. However, UF will need to be increased to remove the extra saline. The heparin dose may be increased and/or a bolus of heparin given. The venous side of the blood circuit can be changed during the session to prevent total clotting. If clotting problems persist, long-term aspirin and/or dipyridamole or warfarin treatment may need to be considered.

The heparin infusion needs to be stopped 30 min prior to the end of dialysis if a fistula is being used, to prevent bleeding after the needles have been removed. The heparin dose will need to be adjusted in the patient with abnormal clotting or low platelets. Heparin-free dialysis can be used, for example, if dialysis is taking place just before surgery. In this situation, the circuit can be primed with heparinized saline (3,000–5,000 u/l) as this will bind to the dialyzer membrane. The dialyzer must then be flushed before connecting to the patient. The dialyzer must be checked regularly for signs of clotting. High blood flows will help prevent clotting. Heparin may induce thrombocytopenia in some patients, which resolves on stopping it. Protamine may be infused after the treatment in order to bind to and inactivate unmetabolized heparin. One mgm of protamine is typically required to inactivate 100 IU of remaining heparin.

Complications of HD

Intradialytic Hypotension

The commonest complication of hemodialysis is hypotension which occurs because of the movement of fluid from the extracellular to the intracellular space due to a decrease in serum osmolality, impaired sympathetic activity, vasodilation in response to warm dialysate, and splanchnic pooling of blood while eating during dialysis. Hypotension may also be due to excessive UF requirements because of a high interdialytic salt and water intake or to the use of antihypertensive agents, although it is usual to omit the dose of antihypertensive medication on the morning before dialysis.

The treatment of hypotension includes the provision of normal saline 5 ml/kg and cessation

of UF. It is important to reassess the optimum weight in case this has been underestimated, and also the daily salt intake and fluid allowance, which may be too high so that too much fluid needs to be removed. Another cause is the use of a dialysate sodium lower than plasma, as this leads to hyponatremia in blood returning to the patient and, therefore, the movement of water into cells from the intravascular compartment. Sodium modeling (use of decreasing dialysate sodium concentration during a session; see above) to optimize vascular refilling, UF separate from dialysis, HDF. and online blood volume monitoring may help patients with recurrent hypotension. Symptoms such as nausea, vomiting, itching, pains, and cramps are also common, frequently occurring during hypotensive episodes.

Intradialytic hypotension can result in myocardial ischemia, which affects selected areas of the heart and results in regional left ventricular dysfunction that can last beyond the period of reduced perfusion. This has been given the term "myocardial stunning." Repeated stunning leads to ischemic, non-infarcted myocardium that exists in a state of contractile dysfunction, known as "myocardial hibernation." This is likely to contribute to the excess cardiovascular disease seen in patients on dialysis. Reduction of peripheral vasodilatation and therefore hemodynamic instability by the use of dialysate that is below body temperature may be able to reduce the degree of stunning during HD [26].

Disequilibrium

A less common complication is disequilibrium, which is due to the plasma urea falling more rapidly than brain cell urea with the resultant movement of water into brain cells by osmosis. It is particularly likely to occur if the plasma urea is high at the start of dialysis. It can present with headache, nausea, dizziness and progress to disorientation, seizures, and coma. Symptoms resolve spontaneously but if severe can be treated with intravenous mannitol using 1 g per 10 % of body weight.

Hemolysis

Hemolysis may occur due to overheating, contamination, or hypotonicity of dialysate, kinking of the lines, or a malfunctioning pump. Dialysis should be stopped and the potassium should be checked immediately. Hemolysis may continue for some hours. It presents with pains and nausea and a dark appearance to the venous blood.

Air Embolism

Air may enter the circuit and this is particularly likely to happen before the blood pump because the blood there is under negative pressure. Air embolism, however, is rare, as air detectors will cause the return blood lines to be clamped. One ml/kg may be fatal. Air embolism presents with seizures or coma in the upright patient and chest symptoms if recumbent. Treatment is to clamp the lines, stop the pump, put the patient head down in the left lateral position, give 100 % oxygen (to enhance nitrogen diffusion out of air bubbles), and do resuscitation as necessary. Air may need to be aspirated from the ventricle.

Anaphylaxis

An anaphylactic reaction to the dialyzer can occur at any time, but is more common after first use ("first use syndrome"). It occurs soon after the start of dialysis and disappears with dialyzer reuse and pre-dialysis rinsing. It causes hypotension (or sometimes hypertension), angioedema, pulmonary symptoms, chest and abdominal pain, vomiting, fever, urticaria, and pruritus and results from activation of plasma complement or kinin systems by the dialysis membrane or the release of noxious materials which may have contaminated the dialyzer during manufacture or the sterilization process (e.g., with ethylene oxide). Dialysis must be stopped and blood should not be returned to the patient. Normal saline for hypotension, epinephrine subcutaneously or intramuscularly (1:1,000 concentration), and/or hydrocortisone may be necessary. Symptoms may be milder, for

example, presenting with just urticaria, which can be treated with an antihistamine or hydrocortisone. The generation of complement (predominantly C3a and C5a) and bradykinin depends on pH and the negative charge on the dialyzer, so it can be made worse by giving stored blood, heparin boluses, and ACE inhibitors as they delay bradykinin breakdown. Severe reactions necessitate a change of dialyzer.

Amyloidosis

Dialysis-related amyloidosis is unusual in childhood but can occur in those who have been dialyzed for a long time. Symptoms of amyloidosis are typically first reported 7–10 years after commencing hemodialysis, although tissue accumulation of dialysis-related amyloid can be demonstrated much earlier. It is a disabling, progressive condition caused by the polymerization within tendons, synovium, and other tissues of beta-2-microglobulin, a large (molecular weight (MW) 11,600) molecule, which is released into the circulation as a result of normal cell turnover but is not excreted in renal failure and is not removed by cellulose membranes. Exposure to bioincompatible membranes may increase beta-2-microglobulin generation. HDF is a better technique to remove beta-2-microglobulin, providing around 70 % better removal than conventional HD [27].

Vascular Access

Good vascular access is crucial to the success of dialysis. The best form of access is an arteriovenous (a-v) fistula; otherwise, a catheter that is tunneled subcutaneously is used or, rarely, shunts or grafts [28]. The life of a fistula is superior to a tunneled catheter; over two thirds are still functioning after 4 years, whereas reports of the survival of tunneled catheters vary from 30 % to 85 % at 1 year [29, 30]. Vascular access problems are indicated by the arterial and venous pressure alarms. Low arterial pressure alarms indicate that there is an insufficient blood flow reaching the blood pump. This is commonly referred to as "sucking" and is usually a result of poor access position in the vessel. A low venous pressure alarm also indicates poor blood flow. A high venous pressure alarm indicates that there is an occlusion to the flow of returning blood. It is due either to poor access position, fistula stenosis, or the presence of clot formation.

Alteplase (Tissue Plasminogen Activator, TPA) can be safely used to dissolve suspected clots in the lumen of central venous catheters [31, 32]. A solution of 1 mg/ml is instilled in the dead space of the catheter and left for at least 1 h, preferably overnight or between dialysis sessions. A randomized, controlled trial has shown that Alteplase is significantly more effective than heparin in preventing clot formation in central venous hemodialysis catheters [33]. Alteplase must be completely aspirated before the catheter is next used for dialysis. This is important not only because of its anticoagulant properties but also because of its phosphate content, so that a spuriously high phosphate level can be obtained if it is not thoroughly removed before blood sampling [34].

Access Recirculation

Adequacy of dialysis may be compromised if the dialyzed blood that returns from the venous line to the circulation is directly taken back into the arterial line to the blood circuit to be re-dialyzed. This is called recirculation which can occur if the distance between the site of blood withdrawal and return is small, if there is low blood flow through a fistula, if the needles are wrongly placed, if the incorrect ports are used for dual-lumen catheters, or during single needle/lumen dialysis. Recirculation can be measured and expressed as a percentage, which should be less than 10 %. If the result is higher than this, then the fistula needs to be assessed with venography for the presence of a stenosis of the catheter has to be replaced.

The procedure for assessment of recirculation is based on the Fick principle and is typically performed by the "two needle" or "slow stop-flow" technique. Samples are taken from the

access lines 30 min after the start of dialysis and with UF turned off. Arterial (A) and venous (V) samples are obtained. The pump speed is reduced to 50 ml/min or halved, whichever is lower halved. Then, a sample is obtained from the arterial needle about 30 s later. This is considered to be the systemic (S) sample. The calculation of % recirculation is given by

$$\text{Recirculation } (\%) = \frac{S - A}{S - V} \times 100$$

Arteriovenous (a-v) Fistulae

An arteriovenous (a-v) fistula is the preferred method of vascular access in children treated with chronic hemodialysis because of the decreased risk of infection in comparison to a catheter. Catheter infection is the most important cause of vessel stenosis [35]. Preservation of vessels is particularly important in children, who have a lifetime of renal replacement therapy ahead of them. An a-v fistula can be used in children who are able to cooperate with needling; education and play therapy may enable this even in small children and those with needle phobia. Children on short-term dialysis (e.g., awaiting a living-related transplant) may elect to be dialyzed via a tunneled catheter.

A fistula is created by surgically anastomosing an artery to a vein, so that the higher pressure within the vein causes it to expand to allow large enough needles to be inserted to enable the high blood flows required for dialysis. It may be created at the wrist (radio cephalic or radio basilic) or the elbow (brachiocephalic) or by basilic vein transposition to create a brachiobasilic fistula [36]. It is preferable to start distally at the wrist to preserve more proximal vessels for future use. Clearly, the larger the vessels, the greater the chance of success, but some groups are able to operate on even very young children using microsurgery [37]. Two-stage basilic vein transposition may be preferable in small patients: a month or so after the anastomosis has been created, and at a "second stage," the arterialized vein is superficialized to make access easier [38].

The success of a fistula depends on adequate run off distal to the anastomosis. Any distal vessel stenosis will result in high venous pressures and edema of the arm. For this reason, the child who has had previous central lines will need upper limb venography to establish patency of the arm and central vessels [39]. A thrombosed subclavian vein may preclude a fistula being created in that arm as venous return may be obstructed. Balloon dilatation or stenting of the stenosis may be possible. Ultrasound examination of the proximal vessels can be misleading and should not be relied upon because collaterals may be mistaken for patent upper limb vessels, and the veins cannot be easily seen under the clavicle. It is preferable to select the nondominant arm for the fistula if at all possible.

A fistula should be created at least 6 weeks before it is needed as it takes some time to mature. Prior to surgery, the child must be well hydrated, or left at slightly above optimum weight if already on dialysis, and antihypertensives stopped to decrease the chances of clot formation due to low circulating blood volume or BP. Postoperatively, the fistula needs to be checked regularly for the presence of a thrill, which, if lost, needs to be assessed urgently as clots can be removed by catheter, surgery, or locally instilled TPA but only if this is undertaken as soon as possible [40]. Clot removal after 48 h is rarely successful in restoring flow. It is usual to increase the child's target weight for the next week or so after the surgery. Prophylactic antiplatelet doses of aspirin (1–5 mg/kg/day) may reduce the risk of clotting.

When the fistula is "mature" for use, needles should be placed proximal to the anastomosis. Fistula needles range from 15 to 17G. The arterial needle is inserted distal to the venous one, which should be as far away as possible. The arterial needle can point in either direction, but the venous needle should be towards the heart. The needle sites should be changed as repeated needling in the same place will cause weakness of the vessel wall and aneurysm formation. Anesthetic creams reduce the physical and psychological trauma associated with fistula use in children. It is also possible to use "the buttonhole technique."

Two sites (one for each needle) are selected and needles are inserted in exactly the same spots at exactly the same angle. Over 8–10 cannulations, scar tissue will form creating a tunnel at each site. The scab is then removed prior to inserting special blunt needles. This is less painful and aneurysms are less likely to form, but the risk of infection is increased.

Fistula Stenosis and Other Complications

Arterial and venous pressure alarms suggest the presence of stenosis, which can happen at any location in the blood vessel. Sites of stenosis occur where there is turbulent blood flow, which causes intimal hyperplasia of the vessel wall. The commonest location for stenosis is within a few centimeters from the anastomosis. Low blood flow and arterial pressure with "sucking" suggest stenosis at the inflow to the fistula. High venous pressure suggests stenosis more centrally. Slow blood flow through the fistula predisposes to thrombosis.

Much can be determined by clinical examination of the fistula. A palpable thrill is present if the blood flow through the fistula is >450 ml/min. In the case of a stenosis, the thrill is reduced concomitant with the reduced blood flow rate.

Doppler ultrasound studies can be used to examine flow and can be followed by tests of recirculation which if >10–15 % suggest stenosis. Arteriography is necessary to examine the arterial flow into the fistula, and a fistulogram, also using X-ray contrast, is used to demonstrate the blood flow into and out of the fistula. It is a usual practice to anticipate the formation of stenosis by screening with Doppler US every 6 months. The risk of clotting has been found to increase when flows are <650 ml/min, but the finding of a downward trend in blood flow is important. If a stenosis is >50 % of vessel diameter, it needs angioplasty, stenting, or surgical repair [41]. A stenosis at the clavipectoral junction is much harder to dilate than a basilic vein stenosis.

Other complications include ischemia of the hand or "steal syndrome," and pseudoaneurysm, due to communication of the fistula with an enclosed area of surrounding tissue. The latter may lead to prolonged bleeding and needs to be repaired. Infection of the fistula can also occur. It is also possible for the fistula to become too large with unsightly forearm veins and flows that are too high, predisposing to heart failure.

Grafts and Shunts

Grafts and shunts are rarely used in children. An artificial conduit can be inserted between an artery and vein subcutaneously (graft) where it can be needled or may be brought out externally (shunt) where the loop can be disconnected to attach to dialysis lines. Grafts and shunts are, like a-v fistulae, liable to stenosis (particularly at the anastomosis site) and to clotting. Stenosis can be suspected by the presence of a thrill, which would not normally be present. Although 1-, 3-, and 5-year survival are similar to a-v fistulae at 90 %, 50–60 %, and 40 %, respectively, the need for surgical intervention is higher in grafts [42]. They also have an increased risk over fistulae of infection, which can be difficult to eradicate. Shunts carry the further risk of disconnection and blood loss.

Tunneled Catheters

Tunneled catheters are used in children who are too young for an a-v fistula or in children who are not expected to be treated with dialysis long, e.g., when a parent is being prepared as a donor. They can be inserted so that the tip is in the right atrium using radiologic guidance [43]. The success rate is superior to non-tunneled catheters but inferior to an a-v fistula [42]. The internal jugular veins are the first choice. The presence of a catheter, particularly if it becomes infected, can lead to vessel stenosis. The subclavian vein should not be used if possible since a subclavian vein stenosis might preclude the use of that arm for future fistula formation.

The larger the gauge of the access, the faster the blood flow that can be obtained. The majority

Table 4 Catheter size and siting according to the weight of the child

Size of child	Catheter size	Siting
Neonate	5 Fr	Femoral or umbilical vein
3–6 kg	7 Fr	Internal or external jugular or femoral vein (or less preferably subclavian vein)
6–15 kg	8 Fr	
>15 kg	9 Fr	
30 kg	≥10 Fr	

of vascular access is either 7-8FG or 11FG in differing lengths (12 or 18 cm or 12–19 cm for smaller or bigger gauges, respectively) and is chosen according to the size of the child and their vessels. Some examples are shown in Table 4.

Most catheters are dual lumen, allowing a continuous flow of blood around the circuit. However, hemodialysis can also be achieved using single lumen access. In very small children, single lumen access may be more appropriate as the lumen of the catheter will be larger, and therefore, the flow that can be obtained through it is relatively greater, as flow is proportional to the fourth power of the radius. In order to obtain two directional blood flows with a single lumen line, the dialysis circuit has to be modified. This can be achieved by the double-pump method, using two blood pumps which pump alternately, or by using a single pump which pumps intermittently, using gravity to let blood flow back in to the child. Disadvantages of the single lumen catheter are that an expansion chamber is necessary in the circuit to allow for the pressure changes and this increases the volume of the blood circuit; also the superior blood flow rates are compromised by a greater degree of recirculation.

Infection in Vascular Catheters

Infection in vascular catheters may be at the exit site, in the subcutaneous tunnel, or in the catheter. The development of biofilm within the catheter makes bacterial eradication particularly difficult. Line sepsis may present as a rigor soon after starting dialysis, fever with raised CRP, or septicemic collapse. The factors increasing the risk of catheter infection include exit site and/or tunnel infection or contamination of the hub, failure of aseptic technique, frequent need to access the catheter during dialysis and long duration of use, use of non-tunneled rather than tunneled lines, immunosuppression, hypoalbuminemia, diabetes, and nasal and cutaneous colonization with *Staphylococcus aureus*. Post-dialysis heparin or alteplase into the catheter decreases infection risk by decreasing clot formation, which predisposes to infection [33].

Treatment of Catheter-Related Infection

Figure 2 demonstrates the steps in the management of exit site, tunnel, and catheter infections [44]. Exit site infection presents with erythema and tenderness within 2 cm of the exit site and discharge from the exit site itself. Great care should be taken to immobilize the catheter as far as possible as movement within the exit site encourages infection. There are different types of dressings, but there is no evidence to suggest superiority of any particular type. It is important to check for carriage of *Staphylococcus aureus*; thus, the exit should be swabbed every month, along with 3 monthly nasal swabs. *Staphylococcus aureus* carriage can be treated with topical exit site and nasal mupirocin for 5 days every month. If there are clinical signs of infection, then swabs should be taken, daily cleaning instituted, and oral antibiotics commenced. If there is no response after 4 weeks, removal of the catheter with replacement after 24–48 h is warranted.

Exit site infection can spread down the subcutaneous tunnel of the catheter, when in addition there will be tenderness, erythema and induration along the subcutaneous tract >2 cm from the exit site. A tunnel infection is much more difficult to eradicate, and may track into the blood stream, resulting in septicemia. Intravenous antibiotic therapy is warranted in that case, along with antifungal prophylaxis. If there is no response after 4 weeks, the catheter should be removed and replaced after 24–48 h.

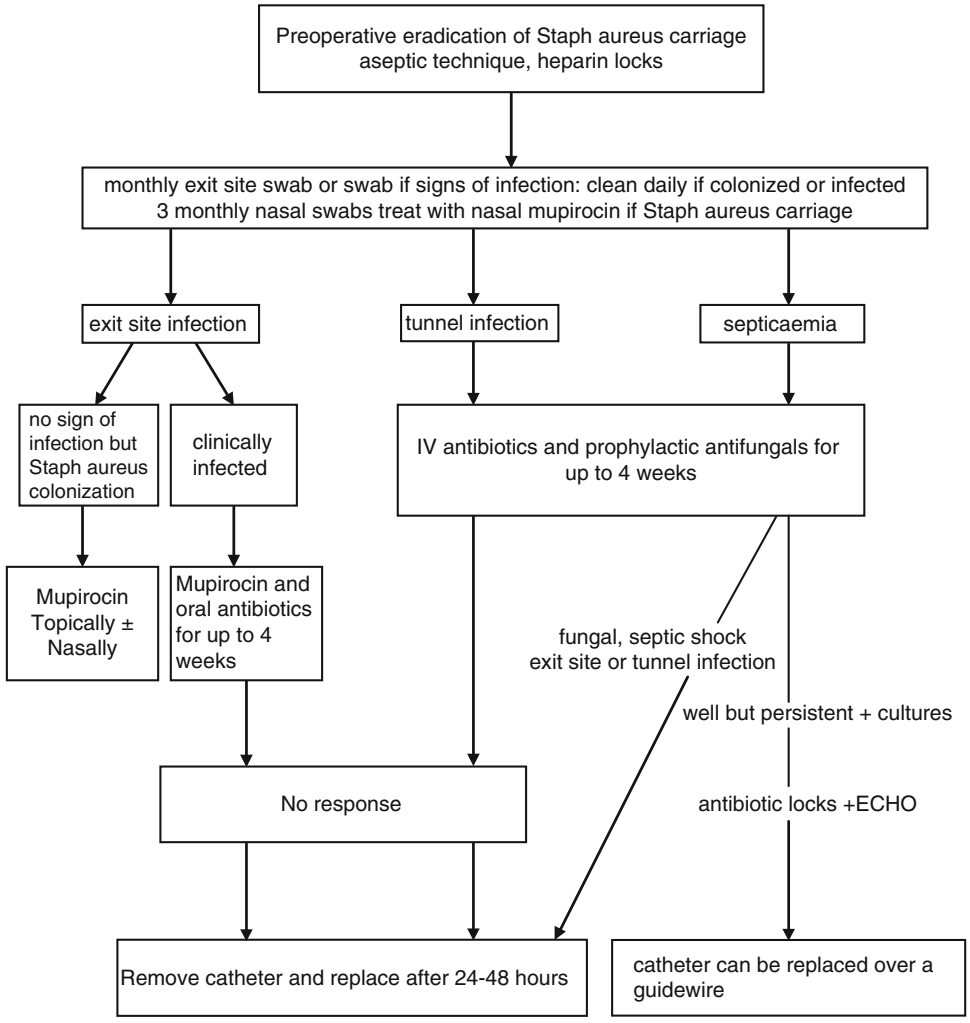

Fig. 2 Prevention and treatment of hemodialysis catheter-related infection

The catheter itself may become colonized, so that there is repeated growth of the same organism in blood drawn through the line, but without signs of sepsis. Antibiotic locks may be helpful in eradication of line colonization [45]. Antibiotic locks use an antibiotic to which the organism is sensitive and are instilled into each lumen after dialysis. The antibiotic is then removed at the start of the next dialysis session. With ongoing positive growths but no systemic symptoms, it has been shown to be safe and effective to replace the catheter over a guide wire, as long as antibiotics have been started and there is no tunnel or exit site infection [46]. This process is preferable as it means that the access point in the vessel is not lost.

The presence of septicemia, bacteremia, or fungemia with at least one positive culture of the same organism from the catheter and a peripheral vein, clinical signs of infection (fever, hypotension), no other cause of infection, and a raised C-reactive protein indicate catheter infection. Antibiotics need to be started immediately, but in the presence of septic shock, the catheter should be removed.

Treatment or septicemia is usually started with vancomycin in units with a significant incidence of MRSA. If there is severe systemic illness, two

antibiotics are used. An example could be to initially use both intravenous vancomycin and ciprofloxacin until the gram stain/culture is available, when the treatment can be modified accordingly. However, antibiotic policy will depend on local resistance patterns, which are changing, with the emergence of more resistant organisms being seen [47]. It is wise to use antifungal prophylaxis when broad-spectrum antibiotics are used. Intravenous antibiotic therapy would usually be continued for 2 weeks, but may need to be longer if there is fungal infection. If there is persistent fever, endocarditis is a possibility so an echocardiogram should be performed.

If there is septicemia, the catheter should be removed, particularly if the infection is occurring in a non-tunneled line or one that is no longer being used or if there is septic shock. If the septicemia is caused by a fungus, if the same organism is infecting the exit site or tunnel, or if there is persistence of fever after 48 h of therapy or ongoing positive blood cultures, then the chances of clearing the infection are low and again this is an indication to remove the catheter.

Dialysis Adequacy

The concept of dialysis adequacy was introduced in order to define the dialysis prescription (blood flow rate, dialyzer clearance, treatment time) required to minimize patient morbidity and mortality. Obviously, such correlations can only be made in adults, as large numbers of patients with significant complications are required for statistical analysis. However, attempts have been made to correlate adequacy with end-points such as hospitalization rates in children [48].

The clearance of urea has been selected as the basis for the calculations of dialysis adequacy, although urea represents small molecule clearance and not clearance of other larger molecules that move more slowly across the dialysis membrane. Some hemodialysis machines provide online calculation of urea clearance. Dialysis adequacy is defined as the minimum amount of urea clearance and nutritional intake that prevents adverse outcomes. The figures that have been calculated for dialysis adequacy represent a minimum acceptable level; determination and calculation of what is optimal, i.e., the dose above which no further improvement in outcome occurs, is less easy to achieve.

Urea is evenly distributed throughout the body fluid compartments. During dialysis, urea is removed from the extracellular space. However, movement from the intracellular space into the intravascular compartment occurs more slowly so that there is a difference in levels between the two compartments that persists for an hour or so after dialysis. If this difference is not taken into account in single pool calculations, then the amount of urea removed is overestimated and the dialysis dose appears greater than it is. A more accurate calculation of adequacy is obtained using a double pool model. Nutritional status is also assessed as part of the adequacy measurement. The interdialytic accumulation of urea reflects protein catabolism. Thus, in a steady state, the protein catabolic rate is equivalent to the amount of protein ingested and can be taken, therefore, as an indication of nutritional status. When calculations of dialysis adequacy use both urea clearance and patient nutritional status (i.e., urea generation rate), this is called urea kinetic modeling (UKM).

The amount of urea that is removed during a hemodialysis session is affected by the urea K_oA (urea permeability-surface area product) of the dialyzer, the treatment time, the blood flow rate, the volume of distribution of urea (V), the UF, residual renal function, and the interdialytic urea generation rate (G). The pre- and post-dialysis blood urea levels and the known values of the variables are fed into the UKM equation to obtain the calculations of V and G. These measures are then used to obtain measured urea clearance (K) and G which describe the adequacy of the treatment. Because the calculation of V and G require an iterative solution, a computer program is necessary.

The most common assessment of dialysis adequacy is Kt/V, where K is the measured urea clearance, t the treatment time, and V the measured volume of distribution. It can be calculated from the pre- and post-dialysis blood urea

concentrations, measured weight loss (UF), and duration of dialysis. For the single pool Kt/V, the blood urea can be obtained immediately after the end of the dialysis session. Although urea rises rapidly post-dialysis, it is impractical to wait to take the post-dialysis blood urea sample until after urea rebound is complete, which takes approximately 1 h. Mathematical calculations can be used to allow for the re-equilibration that determines this double pool Kt/V. Methods of standardization of post-dialysis sampling that aim to reduce variability in the timing of blood sampling are called the slow-flow and stop-flow methods. The stop dialysate flow method, when dialysate flow is stopped but the blood pump is kept running for 5 min, is the most commonly used, but gives higher results. There are several different formulae available for the calculation. Most would use the Daugirdas II formula:

$$\frac{Kt}{V} = -\ln\left(\frac{C_1}{C_0 - 0.008 * t}\right) = \left(\frac{4 - 3.5 * C_1}{C_0}\right) * \frac{UF}{W}$$

where C_0 and C_1 = pre- and post-dialysis blood urea (mg/dl), respectively, t = time (h), UF = ultrafiltration volume (Kg), and W = post-dialysis weight (Kg).

A simple but less accurate method of assessing dialysis adequacy is the urea reduction ratio (URR), which is calculated as follows:

$$\frac{\text{Pre dialysis urea} - \text{post dialysis urea}}{\text{pre dialysis urea}} \times 100\ \%$$

URR may underestimate the dose of dialysis as it does not take into account convective losses. Moreover, residual renal function is an extremely important contributor to urea clearance and should be included in all calculations of dialysis adequacy. Also, URR does not provide any assessment of nutritional status.

Measures of adequacy in children have not been defined, but consensus standards propose that they should be equal to or better than adult recommendations of a minimum Kt/V >1.2 or URR >65 % [29]. One study in children demonstrated an improvement in the risk for hospitalization up to a Kt/V of that level, but above 1.4, no further improvement occurred [48]. However, the improvement in all aspects of patient well-being with daily or frequent short hemodialysis suggests that a higher Kt/V must be better [12, 16–23].

The normalized protein catabolic rate (nPCR) can be correlated with protein intake and is more sensitive and specific than albumin as a marker of nutritional status because many processes unrelated to nutrition can affect albumin concentrations. nPCR may be useful for monitoring of nutritional status in patients receiving maintenance HD: adolescents with nPCR less than 1 g/kg/d may be at increased risk for subsequent weight loss [49].

Another important assessment of dialysis adequacy is the well-being of the patient, which can be objectively assessed in children by height and weight gain. Control of BP, anemia, acidosis, and bone disease are also part of the overall assessment of dialysis adequacy, along with hospitalization and school attendance.

Blood-Borne Viruses

Hemodialysis unit patients and staff are at risk for blood-borne viruses, particularly hepatitis B, hepatitis C, and HIV. Transmission may result from percutaneous exposure to blood or other fluids, via droplets or through contaminated equipment. Universal precautions should be followed as for all patients, and the entire dialysis circuit should be decontaminated after each use by heat or chemical disinfection. External surfaces should be wiped over between patients using a chlorine-based disinfectant.

All staff and patients should be immunized and/or show immunity to hepatitis B. It is preferable to administer the vaccine before dialysis is necessary for the best chance of a good response. The vaccine can be given at any age at intervals of 0, 1, and 6 months. An accelerated course can be used so that the third dose is given 2 months after the first dose (i.e., doses at 0, 1, and 3 months and a booster dose at 12 months). The anterolateral

thigh (intramuscular) is the preferred site in infants and young children. The deltoid muscle is the preferred site in older children. It should not be injected into the buttock as vaccine efficacy is reduced.

If the antibody level is <10 iu/L 2–3 months after the last vaccine, the course of vaccine is repeated and hepatitis B surface antigen (HBsAg) is measured trimonthly until there is a satisfactory antibody response (>10 iu/L 2–3 months after last vaccine). If antibody levels are >10 iu/L, then it can be assumed that immunity is sufficient and antibody levels can be measured annually, with booster doses as necessary. The usual dose of hepatitis B vaccine is doubled for patients on dialysis. If a patient is exposed to hepatitis B or has been to an endemic area, such as the Middle and Far East, and has antibody titers <100 iu/L in the last year, then hepatitis B immunoglobulin and vaccine should be given by intramuscular injection, and the patient should be screened weekly for HbsAg for 3 months. Patients who are or who might become HbsAg positive should be dialyzed in a separate room with their own machine.

Although screening for hepatitis C or HIV is not universally recommended at present, many units do so. Hepatitis C can be spread nosocomially, so a separate room is recommended for the patient who is hepatitis C positive, but a dedicated machine is not necessary. HIV is less infectious, but the same criteria apply. Testing for hepatitis C antibody 3 monthly and for HIV annually is a reasonable compromise [50].

Nutrition in Hemodialysis

Nutrition in the management of CKD is discussed in ▶ Chap. 66, "Management of Chronic Kidney Disease in Children," but there are some nutritional issues that are specific to hemodialysis. Malnutrition is common in children on hemodialysis and is associated with increased mortality [51]. Both UK [52] and US [53] guidelines advise an increase in the recommended protein intake for age in children on hemodialysis, varying from around 20 % in very small children to up to 50 % in older ones. This increase is not as large as that recommended for children on peritoneal dialysis. It is to allow for losses of amino acids into the dialysate, which depend on their plasma concentrations and molecular weights.

Dietary supplementation may be necessary to achieve an adequate intake of protein. Studies of the effect of dietary supplementation on nutritional status and growth have given variable results [54]. Because of this, some centers have explored the use of intradialytic parenteral nutrition (IDPN). There are only four studies of IDPN during hemodialysis in children, and these involve very small numbers so it is difficult to draw conclusions about its effectiveness [52, 54].

There may be specific deficiencies occurring in patients on hemodialysis, one of which is carnitine. Carnitine has a MW of 162 Da and is water soluble and unbound. Carnitine therefore may be cleared by dialysis, and deficiency in dialysis patients has been reported to be common. The biologically active L-carnitine plays an important role in fatty acid metabolism and energy production in cardiac and skeletal muscles, and carnitine deficiency has been associated with poor response to erythropoietin, intradialytic hypotension, cardiomyopathy, and muscle weakness. However, studies of the benefits of carnitine supplementation have been inconsistent [55].

CKD-MBD

Abnormal mineral metabolism and altered bone structure and composition is almost universal in children on dialysis [56], and bone-related problems which adversely affect quality of life, including bone and joint pain and fractures, are the most common complaint in young adult survivors of pediatric renal replacement therapy programs [7]. Morbidity and mortality are affected by abnormal mineral metabolism: there is an association with extra-skeletal and, in particular, vascular calcification, although the pathological mechanisms are yet to be unraveled. In order to reflect the complex issues surrounding these areas, it has been suggested that the term

CKD-mineral and bone disorder (CKD-MBD) should be used as an encompassing definition [57].

Current management of CKD-MBD hinges on the concept of an optimum range for plasma parathyroid hormone (PTH) levels, which is a range that maintains normal bone turnover without increasing the risk for ectopic calcification. The risks of extra-skeletal calcification are thought to be increased with both low and high bone turnover because both types result in high plasma calcium and phosphate levels. Low bone turnover, associated with low PTH levels, may be deleterious because of the inability of bone to buffer changes in plasma calcium and phosphate. On the other hand, high bone turnover, associated with high PTH levels, may also be deleterious because high PTH levels mobilize calcium and phosphate from bone, increase tubular reabsorption of calcium, and promote gut absorption of calcium and phosphate by hydroxylation of 25, OHD3. PTH itself is thought to be an independent risk factor for myocardial fibrosis, arteriolar thickening, and hypertension [58]. There are detailed guidelines from the USA (KDOQI) [59] and Europe [60, 61] on PTH management and all aspects of calcium, phosphate, and vitamin D control in order to achieve these aims. European recommendations for children on dialysis are that the plasma PTH should be kept at up to 3 times the upper limit of normal and KDOQI sets higher levels of 3–5 times the upper limit of normal. However, there is limited evidence for these recommendations [58], and review of the evidence that is available suggests that in children, high PTH levels are associated with abnormalities of vascular structure and function and vascular calcification. Indeed, these vascular abnormalities are less common in children on dialysis with PTH levels $< 2 \times$ the upper limit of normal [62]. What is known is that hyperphosphatemia and a high calcium $\times$ phosphate product are toxic to the vasculature and should be prevented. It is also known that too much and too little intake of calcium are both bad and that high PTH levels, and plasma levels of vitamin D that are either too low or too high, are associated with increased cardiovascular morbidity [63]. This is discussed further in ▶ Chap. 69, "Mineral and Bone Disorders in Children with Chronic Kidney Disease."

Drug Prescribing in Patients on Hemodialysis

Great care needs to be taken when prescribing for children with renal failure and is fully described in ▶ Chap. 67, "Handling of Drugs in Children with Abnormal Renal Function."

Drug handling in hemodialysis is made more complicated by reduced bioavailability due to abnormal gastrointestinal motility, nausea, vomiting, and anorexia. The drug volume of distribution may be altered by the presence of volume overload and reduced if there is volume depletion or muscle wasting. Protein binding is altered by acidosis, malnutrition, and inflammation. This can result in high levels of the free drug despite normal blood levels (e.g., phenytoin).

Many drugs will be cleared by hemodialysis. Their removal depends on the molecular weight of the drug and the degree of protein binding. Drugs with a large volume of distribution are generally lipid soluble and not confined to the circulation or even the total body water, and thus, they are not well cleared by hemodialysis. It is logical to administer drugs known to be cleared by hemodialysis immediately at the end of the dialysis session.

There is a tendency within units to administer drugs intravenously during the hemodialysis process. This is particularly helpful with iron therapy, which is often poorly tolerated orally. However, there is no evidence that other drugs such as erythropoietin or activated vitamin D are more effective when administered intravenously, although this route does overcome concordance issues.

Hemodialysis for Acute Kidney Injury

Hemodialysis is sometimes used as treatment for acute kidney injury (AKI), but unstable patients may be better managed by continuous veno-venous hemofiltration, which does not cause

major fluid shifts and disturbances to BP and cardiac output. Situations in which hemodialysis may be more useful are when there is a need to rapidly remove large volumes of fluid, particularly if there is pulmonary edema, or an urgent need for the fastest possible clearance of toxic metabolites, such as with inborn errors of metabolism, drug poisoning, or tumor lysis syndrome.

Emergency hemodialysis in AKI is usually started with a temporary percutaneous dual-lumen non-tunneled catheter. The principles of management are not different from chronic hemodialysis. A short (e.g., 2 h) session may be the best starting point, followed by daily sessions. Optimum weight assessment may be particularly difficult in the children presenting acutely, and awareness of potential reactions to the procedure are necessary as these are unpredictable in the new patient.

More complete descriptions of the treatment of AKI are given in ▶ Chap. 64, "Evaluation and Management of Acute Kidney Injury in Children."

Long-Term Outcome

Despite all the improvements that have taken place over the years, such as more biocompatible and high-flux dialysis membranes and UF-controlled machines, and better understanding of the management of nutrition, anemia, and CKD-MBD, morbidity and mortality in adults on conventional three times per week dialysis are showing no signs of improvement. Amyloidosis, malnutrition, LVH, and accelerated atherosclerosis remain common. However, hemodiafiltration has been demonstrated to improve mortality rates, and nocturnal daily hemodialysis has improved survival to levels not dissimilar to transplanted patients [12].

Although mortality in children on dialysis remains low, it is still around 30 times greater than that of the age-matched normal population [64] and in young adults on dialysis is equivalent to that of an 85-year-old [65]. Most of this excess mortality is due to CVD. Age at the start of dialysis also affects outcome: dialysis before 1 year of age increases the mortality risk by 2.7 and between 1 and 5 years by 1.8. Comorbidity, which affects a significant proportion of patients, increases mortality risk 7.5 times [66]. Lifespan is reduced by 40–60 years in children on dialysis, with about 50 % of deaths due to CVD [67]. The challenge to pediatric nephrologists is to improve the long-term outcome for these children. Much can be gained by careful attention to fluid overload and LVH and to metabolic abnormalities, particularly CKD-MBD and prevention of anemia, but further research is needed on the benefits of more frequent dialysis, types of dialysis, and the prevention of CVD. Most importantly, minimizing the duration of dialysis by early or even preemptive renal transplantation is currently the best option for our patients.

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