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When do children need kidney replacement therapy?

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Abstract

Kidney replacement therapy (KRT) can provide lifesaving support for children with severely impaired kidney function. The decision about who needs KRT and when is often complex. Many acute kidney problems will resolve with conservative management but some children with chronic or acute kidney impairment will find themselves in a position where KRT is required either as a bridge to recovery or kidney transplantation. Less commonly, children with metabolic disorders may find that the ability of their own kidneys is overwhelmed by excessive production of certain metabolites. These children may also benefit from short term KRT. This article aims to help paediatricians in training understand which children need kidney replacement therapy, the various types of treatment available, and when they are used.

Keywords acute kidney injury; children; dialysis; end stage kidney disease; kidney replacement therapy; kidney transplant

What is kidney replacement therapy?

Kidney replacement therapy (KRT) refers to treatments that replace critical functions of a patient's own native kidneys. These include extracorporeal treatments such as dialysis and haemofiltration, and kidney transplantation.

Children need KRT if their kidney function is not sufficient to support health and growth. This can occur acutely. Even temporary disturbance of kidney function can lead to life-threatening accumulation of toxins and electrolytes. In some children with severe AKI, kidney replacement therapy is needed to support their recovery. Children with End Stage Kidney Disease (ESKD) can become symptomatic with impaired growth, bone disease and cardiovascular morbidity. Kidney replacement therapy can improve their symptoms, growth and cardiovascular health.

Children with severe acute kidney injury (AKI)

Children with AKI need supportive therapy to optimize their general recovery, and recovery of their kidney function. In some severe cases, KRT is also required. Patients with very little or no urine output are most at risk of complications such as life-threatening hyperkalaemia or fluid overload; where it is

available, early initiation of KRT should be considered for these patients.

Healthy kidneys maintain the balance of children's fluid status and blood pressure, electrolytes, acid-base balance. Absolute indications for kidney replacement therapy include hyperkalaemia, intravascular volume overload/systemic hypertension, metabolic acidosis and severe symptomatic uraemia which do not improve with medical management. This is most likely to be the case for a child passing little or no urine (see [Box 1](#)).

Infants with severe symptomatic hyperammonaemia

Children with metabolic disorders such as urea cycle defects can present with life threatening encephalopathy secondary to hyperammonaemia. Recent international guidelines recommend kidney replacement therapy in the most severely affected patients.¹ (see [Box 2](#)). Hyperammonaemia and certain toxins can also be managed with high clearance dialysis to ameliorate initial toxicity before maintenance therapies are established.

When should acute kidney replacement therapy be started?

Aside from the immediate life-threatening consequences of metabolic disturbance (e.g. hyperkalaemia resulting in cardiac arrhythmia and non-resolving acidosis), there are other considerations when deciding if a child should receive acute KRT.

In adult patients requiring intensive care, early proactive initiation of KRT is associated with lower patient mortality and better recovery of kidney function. Evidence is also emerging to support proactive kidney replacement therapy in children with severe AKI, in particular those with significant fluid overload. Retrospective studies support early initiation of kidney replacement therapy to aid recovery of both the child, and their kidney function. Any child for whom kidney replacement therapy may be required warrants early discussion with a paediatric nephrology team.

Which modalities of kidney replacement therapy are used to manage AKI?

Continuous kidney replacement therapy for AKI

Continuous kidney replacement therapy is generally used in paediatric intensive care (see [Box 3](#) for another example). Because treatment runs continuously, it mimics continuous kidney function and is therefore more physiological than intermittent dialysis. Various continuous kidney replacement modalities are used; the most common in UK PICUs is continuous veno-venous haemofiltration (CVVH). [Figure 1](#) shows a typical continuous kidney replacement therapy machine.

CVVH uses convection to clear solutes such as urea from the circulation. Aqueous fluid with low molecular weight solutes is filtered from plasma through the dialyser membrane, with larger molecular weight molecules such as albumin retained in the circuit. Filtered fluid is discarded and substituted with crystalloid replacement fluid. The composition of replacement fluid can be tailored according to the patient's electrolyte levels. The rate of replacement fluid is adjusted to achieve a desired net fluid balance for the patient. To remove fluid from the patient, the rate of replacement is lower than the filtration rate.

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KRT in acute kidney injury

A 4 year old girl presents to the emergency department with a 2 day history of bloody diarrhoea and worsening lethargy following a school trip to a petting farm. She is pale and lethargic, but warm peripherally and well perfused with systolic blood pressure 118 mmHg measured manually. Initial blood results show Hb 46 g/L, platelets 14, WBC 21, Na 134 mmol/L, K 7.3 mmol/L, urea 46 mmol/L, bicarbonate 12 mmol/L, creatinine 456 μ mol/L. She is unable to pass urine for urinalysis. You suspect Shiga toxin associated haemolytic Uraemic Syndrome.

After medical management of hyperkalaemia with calcium gluconate, sodium bicarbonate, intravenous fluid bolus and furosemide, she does not pass urine over the subsequent 4 hours. Her bladder appears empty on ultrasound.

After discussion with the tertiary paediatric nephrology unit, she is transferred for kidney replacement therapy. A peritoneal dialysis catheter is placed on the emergency theatre list, and acute peritoneal dialysis commenced that night. Within 4 hours, her plasma potassium concentration has reduced to 4.3 mmol/L with urea 37 mmol/L. She receives peritoneal dialysis for 5 days until her urine output returns and kidney function recovers.

Box 1

If high solute clearance rates are needed, for example to establish rapid control of severe hyperammonaemia, diffusive clearance can be used together with convective clearance. The combination of diffusive clearance (dialysis) and convective clearance (filtration) is known as continuous veno-veno-haemodiafiltration (CVVHDF). Vascular access is needed with a large (typically minimum 10 Fr) central venous catheter to allow

KRT in hyperammonaemia

A 5-day-old boy with a history of worsening irritability and vomiting presented with cyanosis, gasping and no spontaneous movement. He was haemodynamically unstable. Initial investigations showed plasma ammonia concentration 857 μ mol/L, and a urea cycle disorder was suspected. He was ventilated. Because of his haemodynamic instability and very high ammonia level causing encephalopathy, a double lumen central venous catheter was inserted and continuous kidney replacement therapy (CVVHDF) was started. After one hour of CVVHDF he began moving spontaneously. After 2 hours, plasma ammonia concentration had decreased to 342 μ mol/L. A diagnosis of OTC deficiency was subsequently made, and he went on to receive a successful liver transplant.

Possible indications for KRT in treatment of hyperammonaemia¹:

- Rapidly deteriorating neurological status, coma, or cerebral oedema
- Persistently high blood ammonia levels >400 μ mol/L (681 μ g/dL) refractory to non-kidney replacement therapy (NKRT) medical measures
- Rapid rise in ammonia levels >300 μ mol/L (511 μ g/dL) within a few hours that cannot be controlled via NKRT medical measures

Box 2

Short-term CVVH as a bridge to recovery in PIMS-TS

A 6 year old boy presents to the emergency department with fever, sore throat, lethargy, erythematous rash, cracked lips, neck pain and diarrhoea. He has not passed urine for 24 hours. He is breathing in air but hypotensive and shocked with systolic blood pressure 68 mmHg. On examination, he has an erythematous rash, bleeding cracked lips, conjunctival injection, and lymphadenopathy. Investigations show pH 7.28, 22.5 HCO₃, Lactate 2.2, WBC 18.2, Hb 94, plt 36, Troponin 109, Ferritin: 6698, potassium 7.4 mmol/L, urea: 42.9 mmol/L, creatinine 321 μ mol/L. Chest X-ray shows bilateral infiltrates.

Following fluid resuscitation with 40 ml/kg isotonic fluid, blood pressure and perfusion improve however he passes no urine. Plasma potassium concentration remains elevated at 7.2 mmol/L. After discussion with the paediatric intensive care and paediatric nephrology units, he is transferred for kidney replacement therapy.

Following transfer to PICU, a temporary central venous catheter (Vascath) is inserted under anaesthetic, and continuous veno-venohaemofiltration started. After 24 hours, plasma electrolyte and acid-base status normalized. After 48 hours of supportive care, he begins to pass urine and CVVH is discontinued.

Nasopharyngeal aspirate for respiratory viral pCR is positive for Covid-19. A diagnosis of Paediatric Inflammatory Multisystem Syndrome Temporally related to SARS-CoV-2 infection (PIMS-TS) is made.

Box 3

sufficient blood flow through the circuit and dialyser (typically 100–500 mL/minute).

Extracorporeal circuits are anticoagulated to reduce clotting, particularly in the filter membrane. Heparin can be used, although the patient will receive some heparin and therefore a degree of systemic anticoagulation. Citrate is an alternative which allows anticoagulation of the extracorporeal circuit, but not the patient. Citrate works by complexing with calcium and thereby inactivating the clotting cascade in the extracorporeal circuit. During treatment, exogenous calcium is then infused back into blood as it re-enters the patient, thereby restoring functional coagulation in the patient. The balance of citrate levels in the extracorporeal circuit, and calcium infusion to the patient must be carefully managed to avoid complications such as symptomatic hypocalcaemia and citrate toxicity, although these are rare in children with normal liver function.

Continuous kidney replacement therapy in neonates

For infants and neonates, extracorporeal therapies carry additional risks because the extracorporeal circuit volume represents a greater proportion of the small child's circulating blood volume than for larger children. Traditionally, peritoneal dialysis was the only option for babies weighing less than approximately 2.5 kg, however in recent years two novel systems have been developed for infants and are currently undergoing evaluation in clinical trials. The Newcastle Infant Dialysis and Ultrafiltration System (NIDUS) uses a simple but novel system to achieve clearance and fluid removal. It uses a similar principle as an exchange blood transfusion: an aliquot of blood is removed from the patient, dialysed, and then returned to the patient. Because the NIDUS

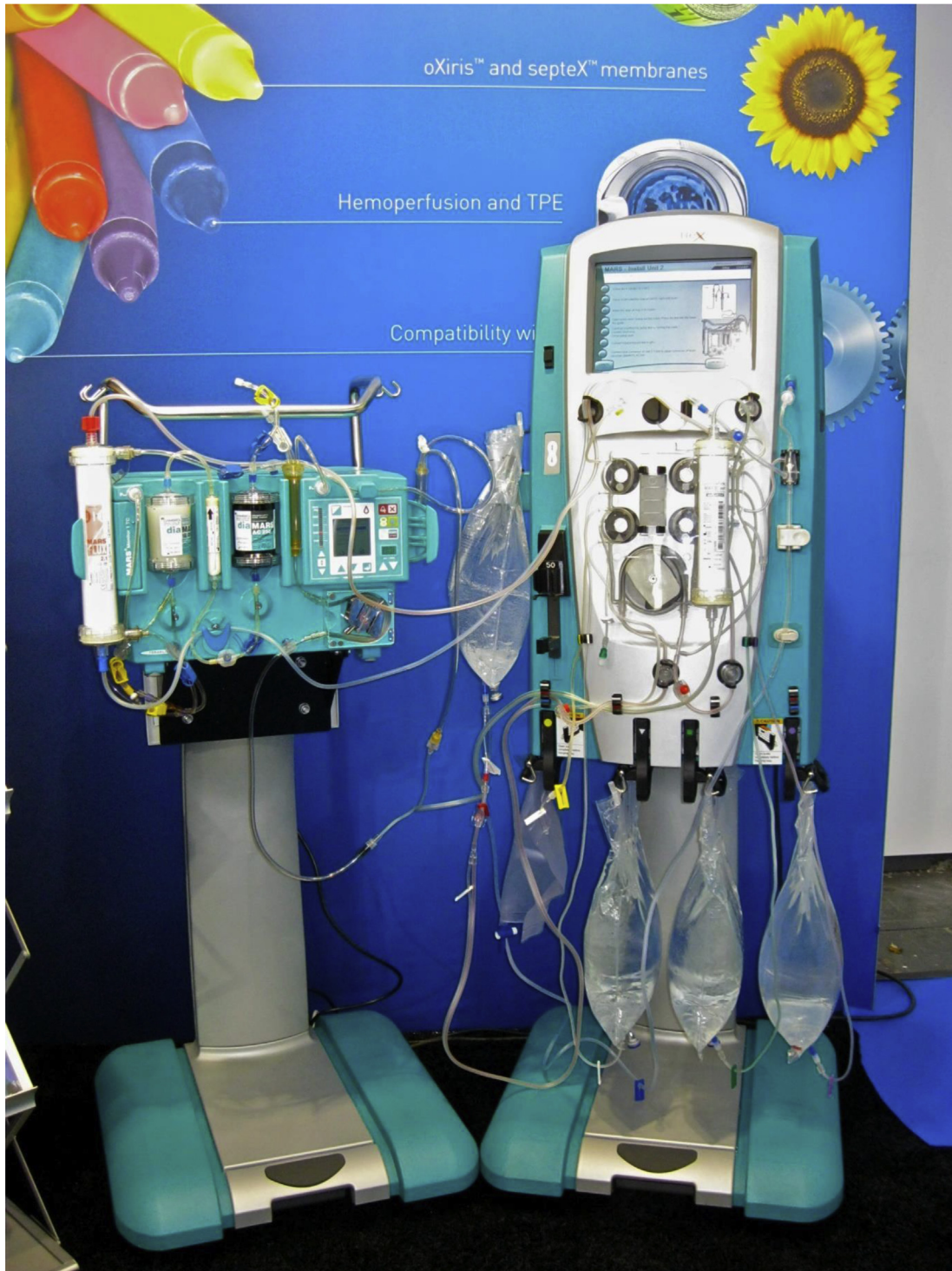


Figure 1 The Prismaflex CVVH system. Reproduced under Creative Commons license.

does not use a continuous circuit, vascular access requirements are less stringent than other therapies, and infants as small as 800 g bodyweight can be dialysed via a 22 gauge cannula.² The CARdiorenal PEDIatric EMERGENCY (CARPEDIEM) machine has also been developed to allow continuous kidney replacement therapy in infants. This is a continuous circuit therapy that requires double lumen vascular access which has been used to dialyse small infants with success.³

Intermittent kidney replacement therapy for AKI

Whilst continuous kidney replacement therapy allows superior physiological control of fluid and solute removal, it is generally only used in intensive care. Some children with AKI require kidney replacement for several days or weeks before sufficient recovery of their kidney function allows kidney support to be discontinued. For children not requiring respiratory or circulatory support on PICU, intermittent dialysis on a paediatric

nephrology ward is used. Options include both acute peritoneal dialysis and haemodialysis; choice of modality depends on the needs of the individual child and paediatric nephrology unit practices.

Children with end-stage kidney disease (ESKD)

Most children with ESKD receive KRT. The choice of KRT modality depends on factors such as size of the child, timing of the child's presentation to nephrology services, family factors that influence suitability for home dialysis therapies, medical comorbidities which may preclude certain modalities for individual patients, and practice patterns of the treating paediatric nephrology unit. For example, haemodialysis is technically challenging in small infants because the volume of blood circulating in the extracorporeal dialysis circuit represents a relatively large proportion of the child's total blood volume. Peritoneal dialysis is generally preferred in infants but may not be feasible for those who have had previous abdominal surgery with a stoma. Pre-emptive transplantation is preferred for children with ESKD; this may not be feasible for children who present at a late stage as workup for kidney transplantation typically takes several months.

For children with ESKD, dialysis is generally used as a bridge to kidney transplantation. Home therapies (peritoneal dialysis or home haemodialysis) are usually preferable however the family situation may not be suitable to safely undertake dialysis at home. Decisions about KRT are made in partnership with the family with support of a kidney multi-professional team including specialist nurses, family support workers, dietitians, social workers, psychologists, play therapists and doctors.

For some children with extensive co-morbidities, the burdens of KRT may be considered greater than its benefits for the individual child. In such situations, the child's family may opt for a conservative pathway with a focus on symptom control.

Pre-emptive kidney transplant

First-choice kidney replacement therapy for children with ESKD is a pre-emptive kidney transplant, i.e. transplant before dialysis is required. A living related donor transplant is preferable to deceased donor transplant and has favourable transplant longevity. For many children with ESKD, pre-emptive living donor transplant is achieved, however it is not always feasible for various reasons including size of the child, availability of a suitable living donor and timing of presentation with ESKD.

Children must be at least 10 kg bodyweight for kidney transplantation. Extensive preparation for both the recipient and donor is essential. Donor and recipient blood group and HLA tissue typing bloods are used to assess compatibility. Vascular imaging is performed to ensure patency of vessels for the transplant operation (iliac vessels or aorta/inferior vena cava in small children). A recent echocardiogram is needed to ensure that the child's heart will support the fluid loading required at the time of transplant operation. Additional vaccinations are needed prior to receiving transplant immunosuppressive medications. Bladder function must be assessed to ensure that urinary drainage from the transplant can be established. A detailed psychosocial assessment with play therapy preparation for the child is needed so that they are fully prepared for the operation and post-

transplant care. This preparation takes several months, and is vital to ensure the safety and optimisation of the transplant for the child.

When successfully transplanted, children's appetite, growth, energy levels and overall wellbeing improve. The duration for which a kidney transplant provides sufficient function varies. The most significant factor influencing this is concordance with immunosuppressive medication. Transplants typically last somewhere in the region of 15 years, although this varies considerably according to quality of the donor organ, concordance with immunosuppressive medication, native kidney disease, bladder drainage and other factors. See [Box 4](#).

Peritoneal dialysis (PD)

In PD, the peritoneal membrane is utilized to exchange solutes and water. Solute such as urea, phosphate, potassium and sodium diffuse out of peritoneal capillaries into dialysate solution which is instilled into the abdomen via a peritoneal dialysis catheter. Excess intravascular fluid is drawn from peritoneal capillaries by the osmotic load of the dialysate fluid. Spent dialysate fluid is then drained to an effluent bag.

PD access comprises an intra-abdominal catheter. During surgical catheter placement, the catheter is tunnelled through the abdominal wall; two cuffs minimise infection risk. The tip of the catheter is usually coiled in the pelvis. Constipation can affect catheter position and function.

For most children on PD, automated peritoneal dialysis (APD) is performed overnight during sleep. An APD machine cycles heated dialysate fluid from sterile bags into the patient's abdomen, leaves it to dwell within the abdomen for a specified time, then drains spent fluid to an effluent bag. This automated cycle is repeated approximately 6–12 times, depending on the dialysis prescription.

Life after kidney transplantation

A 5 year old boy has been under the care of the paediatric nephrology team since birth following antenatal detection of dysplastic kidneys. For the first 5 years of life he had advanced chronic kidney disease with polyuria. With regular input from paediatric renal dietitians, specialist nurses and a paediatric nephrologist he grew along the ninth centile and maintained acceptable blood count (on darbepoietin and iron supplements), bone chemistry (on vitamin D and phosphate binders) and acid-base status (on sodium bicarbonate supplementation). When he reached 3 years of age, his father underwent living kidney donor workup in preparation for transplant when required. At 5 years of age, the child began to experience worsening symptoms of reduced appetite and vomiting and high blood pressure. A decision was taken to proceed with pre-emptive living related donor transplant. Three months following transplant he had normal kidney function, blood count and blood pressure taking regular immunosuppressive medication. His energy levels had markedly improved, as had his appetite and growth. Later that year, he won a silver medal for swimming at the annual national transplant games.

Box 4

Continuous ambulatory peritoneal dialysis (CAPD) can be used as an alternative but is generally preferred for adults. CAPD involves the patient or parents undertaking manual exchanges of dialysate fluid several times in a 24-hour period without the need for a machine.

Peritoneal dialysis is a home therapy which can be successfully undertaken even in very small and young babies (See [Box 5](#)). Prior to embarking on peritoneal dialysis, specialist nurses usually undertake a home visit to ensure suitability of the child's home to accommodate dialysis fluid supplies and the machine. Parents or carers are trained to undertake peritoneal dialysis for the child at home.

Peritonitis is a common complication of peritoneal dialysis. If a child experiences fever, vomiting, abdominal pain or cloudy peritoneal dialysis effluent fluid then urgent medical assessment is needed with advice from the paediatric nephrology team. A sample of peritoneal dialysis fluid should be sent urgently for microscopy, and treatment started with intraperitoneal antibiotics if microscopy is suggestive of infection. Intravenous antibiotics should be given if the child has signs of sepsis in discussion with the paediatric nephrology team.

Haemodialysis

Haemodialysis uses diffusion to clear solutes such as urea and potassium from the patient. In addition, excess fluid is removed from the patient by ultrafiltration generated by a pressure difference across the dialysis membrane between the patient blood side (higher pressure) and the dialysate fluid side of the membrane.

A typical haemodialysis treatment regimen for children dialysed in a paediatric nephrology unit comprises three sessions per week, each session lasting between three and five hours. More frequent dialysis sessions are needed for infants because it is rarely possible to achieve adequate control of fluid status when receiving liquid feeds with three dialysis sessions per week. This is because a limited volume of fluid can be safely removed from the child each session.

Vascular access for haemodialysis must support high blood flows, typically up to 300 mL/minute. Arteriovenous fistulae are

PD in a low-birthweight baby

A boy is found to have bilateral hydronephrosis and small dysplastic kidneys on antenatal ultrasound. He is born at 36 weeks gestation with birthweight 2.1 kg. He passes very little urine and develops metabolic acidosis, electrolyte disturbance with hyperkalaemia (7.6 mmol/L) and progressive uraemia (26 mmol/L) by day 5.

A peritoneal dialysis catheter is inserted, and dialysis commenced on day 5. Plasma potassium concentration improves to 4.3 mmol/L within 3 hours of commencing peritoneal dialysis. The peritoneal dialysis prescription is progressively optimized over the subsequent four weeks. With input from the paediatric renal dietician the nutritional prescription is optimized and he starts to gain nutritional weight. Specialist peritoneal dialysis nurses train parents to undertake dialysis at home, and he is discharged home after 8 weeks. He is initially reviewed weekly in the infant dialysis clinic by a specialist dialysis nurse, dietician and paediatric nephrologist.

Box 5

Shifting between different dialysis modalities

A 4-year-old boy receiving PD for ESKD secondary to kidney dysplasia experiences recurrent Pseudomonas peritonitis. His PD catheter is removed, and a central venous catheter inserted to establish haemodialysis.

His mother finds haemodialysis in the paediatric nephrology unit challenging, because this involves three four-hour sessions for three days every week, which take the entire day including travel. After discussion with the paediatric nephrologist and dialysis specialist nurses, the patient's mother is trained to undertake haemodialysis at home using a NxStage machine. After 1 month of training, the boy is established on a home dialysis regimen of 5 sessions per week. This gives the family more time at home and allows relaxation of some dietary restrictions.

Box 6

the preferred form of access with lower rates of infection and malfunction than central venous dialysis catheters.⁴ With support from specialist dialysis nurses and play therapists, many children can successfully needle their own arteriovenous fistulae.

Attending the paediatric nephrology unit three days per week impacts children's education, social interaction and quality of life. Teachers provide education during dialysis, and play therapists work with children to engage them in activities and games. Home dialysis therapies are preferred when feasible for the family (see [Boxes 5 and 6](#)).

Haemodiafiltration

Haemodiafiltration uses both diffusion and convection to clear solutes from the patient. Convective clearance allows molecules with larger molecular weight known as "middle molecules" to be removed. Beta 2 microglobulin is an example of a middle molecule cleared by haemodiafiltration; by comparison urea is considered a small molecule and albumin a relatively large molecule.

Clinical trials comparing outcomes of adult patients treated with conventional haemodialysis to haemodiafiltration have shown variable results. An international trial in children suggested a potential cardiovascular benefit from haemodiafiltration over conventional haemodialysis treatment.⁵

Home haemodialysis

Some families are capable of training to undertake haemodialysis for their child at home. Parents are trained by specialist paediatric dialysis nurses to deliver dialysis care, with telephone support from a home haemodialysis team.

Various equipment set ups are available for home haemodialysis. In children, the NxStage system is common comprising a simplified dialysis machine and sterile bags of dialysate fluid delivered to the patient's home. For adult patients, home adaptations for water purification with standard dialysis machines can be used.

Summary

Kidney replacement therapy can provide lifesaving support for children with severely impaired kidney function. Children with anuric AKI can be supported until they recover sufficient kidney function; children with ESKD can be stabilized until they can receive a kidney transplant. Acute life threatening

hyperammonaemia can be rapidly controlled. Kidney transplantation is the best long-term kidney replacement therapy to improve the symptoms, growth and wellbeing of children with ESKD. Early discussion with a paediatric nephrology team is advised for any child who may need kidney replacement therapy. ◆

REFERENCES

- 1 Raina R, Bedoyan JK, Lichter-Konecki U, et al. Consensus guidelines for management of hyperammonaemia in paediatric patients receiving continuous kidney replacement therapy. *Nat Rev Nephrol*, 2020; <https://doi.org/10.1038/s41581-020-0267-8> [published online ahead of print, 2020 Apr 8].
- 2 Coulthard MG, Crosier J, Griffiths C, et al. Haemodialysing babies weighing <8 kg with the Newcastle infant dialysis and ultrafiltration system (Nidus): comparison with peritoneal and conventional haemodialysis. *Pediatr Nephrol* 2014; **29**: 1873–81.
- 3 Carney EF. Paediatrics: CARPEDIEM—continuous renal replacement therapy for infants. *Nat Rev Nephrol* 2014; **10**: 422.
- 4 Hayes WN, Watson AR, Callaghan N, Wright E, Stefanidis CJ. European Pediatric Dialysis Working G. Vascular access: choice and complications in European paediatric haemodialysis units. *Pediatr Nephrol* 2012; **27**: 999–1004.
- 5 Shroff R, Smith C, Ranchin B, et al. Effects of hemodiafiltration versus conventional hemodialysis in children with ESKD: the HDF, heart and height study. *J Am Soc Nephrol : JASN (J Am Soc Nephrol)* 2019; **30**: 678–91.

Practice points

- Kidney replacement therapy (KRT) is indicated in children whose renal function cannot adequately eliminate the by-products of metabolism
- Judicious early use of KRT may also improve the outcomes for individuals with AKI
- Common indications in children include acute kidney injury with anuria and end stage kidney disease, where KRT may act as a bridge to the definitive KRT, kidney transplantation
- Less commonly, KRT can be used in the treatment of children with decompensated metabolic conditions including urea cycle disorders which do not improve with medical treatment alone