Paediatric Intensive Care Unit

Continuous renal replacement therapy in PICU: explanation/definitions/rationale/background

Staff relevant to:	Medical, nursing and allied health professional staff involved in providing and caring for patients on extracorporeal continuous renal replacement therapy with PICU Leicester Children's Hospital
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Written by:	C Westrope
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1. Introduction and Who Guideline applies to

Explanation of continuous renal replacement therapy (CRRT) for use by all levels of medical, nursing and allied health professional staff involved in providing and caring for patients on extracorporeal continuous renal replacement therapy with PICU Leicester Children's Hospital.

Peritoneal Dialysis (PD) please see separate guidance – UHL ref: C111/2016 Peritoneal Dialysis - Nurses Undertaking UHL Childrens Intensive Care Guideline

Continuous renal replacement therapy use is well established in the paediatric critical care population. It has become accepted practice within the PICU for the management of fluid balance and metabolic derangement (with or without evidence of acute kidney injury). There is evidence for its usefulness in clearance of toxic metabolites such as in patients with Inborn Errors of Metabolism (IEM), liver failure or drug overdose. It is also increasingly used in other less specific situations such as septic shock or post stem cell transplant. In both the adult and paediatric critical care population uncertainty exists over indications, ideal methods of treatment, most appropriate dose, most effective form of anticoagulation and potential effects of renal replacement therapy on long term renal recovery

Contents

Definitions

Renal replacement therapies can be divided in those that are intermittent (performed for a few hours on a regular basis) or continuous (performed continuously (24/7) over a period of days. Continuous renal replacement therapies 'Continuous RRT' have developed in the acute intensive care setting to overcome the problems of haemodynaamic instablilty associated with intermittent renal replacement therapies (haemodynamic instability occurs in approximately 20-30% of adult haemodialysis episodes, even with prior haemodynamic stability (re NEJM 2012)). 'Continuous RRT' describes all the continuous renal replacement therapies (both PD and the extracorporeal therapies) The term 'CRRT' is used in published literature to describe only extracorporeal continuous renal replacement therapies (CVVH/CVVHD/CVVHDF), and hence for clarity in this guideline will be used the same way. This particular guideline describes in detail the use of extracorporeal Continuous Renal Replacement ('CRRT') therapy in the PICU setting, however the principles can be applied to Peritoneal Dialysis and practical guidance for PD can be found in **PD Guideline.**

2. Renal replacement therapy principles

To fully understand RRT modalities (types) it is important to understand the principals involved. To mimic the function of the kidneys water and solutes are passed across a semi permeable membrane (haemofilter); fluid balance is controlled and waste products are discarded. The processes involved to achieve this are ultrafiltration, convection and diffusion

Ultrafiltration
Ultrafiltration is the movement of fluid across a semi permeable membrane driven by a hydrostatic pressure gradient. In CRRT a positive pressure is generated by the blood pump the blood side of the semi permeable membrane and a negative pressure generated on the other side (maintained by the effluent pump) resulting in the movement of fluid from the blood (positive pressure side) to the negative pressure side

Convection
Convection occurs when large volumes of fluid crossing the semi permeable membrane down the hydrostatic pressure gradient (as in ultrafiltration) result in solvent drag across the membrane also. These large fluid volumes are generated by the addition of replacement solution (replacement fluid) to the blood side of the filter (either pre or post filter and described as pre dilution or post dilution

Diffusion

Diffusion results in the removal of solutes across the semi permeable membrane driven by their movement down a concentration gradient, created by the addition of electrolyte solution (dialysate) on the opposite side of the membrane to the blood. As the dialysate flow is counter current to the blood flow, these concentration gradients are maintained for the whole length of the filter.

The movement of molecules in RRT are driven by the above processes but limited by the size of the solute particles. Bigger than most classical intermittent haemodilaysis filters, filters used in CRRT have larger pores, allowing passage of molecules up to 50,000 Daltons. This allows for free movement of small ions and molecules (e.g. urea, creatinine, ammonia) across the membrane, as well as some larger molecules such as myoblobin, insulin and interleukins. Small molecules are more efficiently removed by diffusion and larger molecules by convection.

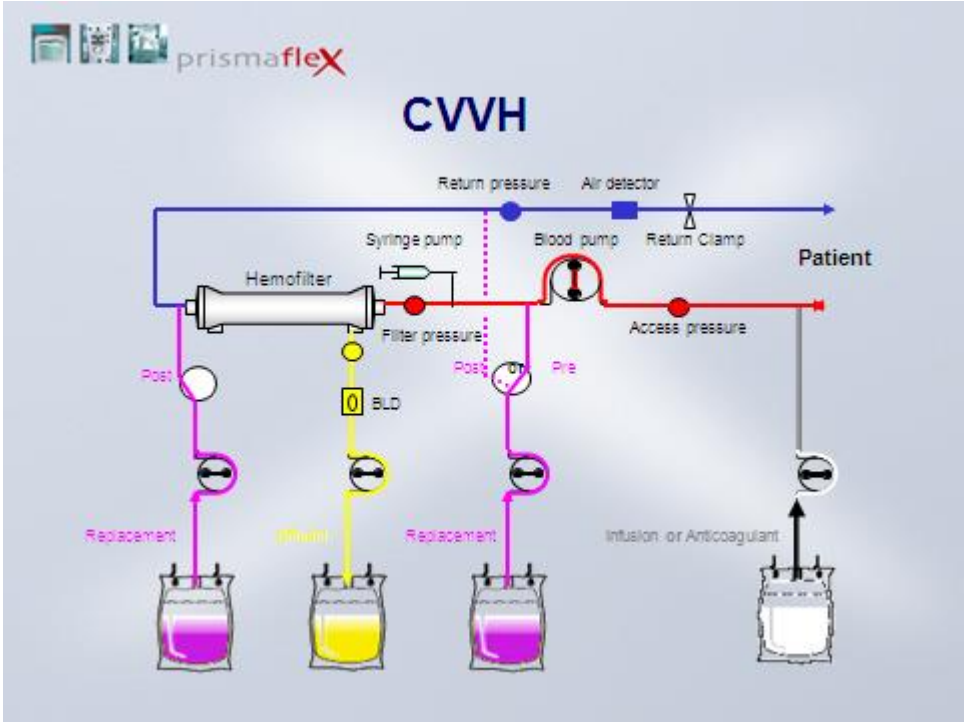
Finally, some molecules are removed in CRRT by direct adherence to the artificial semi permeable membrane. This is the process by which inflammatory markers are thought to be removed during CRRT. However this is not selective and is believed to be responsible for removal of 'good humors' as well as 'bad humors'

2.1 Continuous renal replacement therapies

Continuous renal replacement therapy (CRRT) is used synonymously to describe extracorporeal renal replacement therapies, where blood is pumped out of the venous system of the patient, passed over an artificial semi permeable membrane (artificial kidney/haemofilter) where fluid and solutes are removed (ultrafiltration/convection) or controlled (diffusion) and then the 'cleaned' blood is returned to the patient at the same rate at which it was removed (usually via the same double lumen cannula back into the venous system of the patient). Depending on the processes involved CRRT can be CVVH, CVVHD or CVVHDF

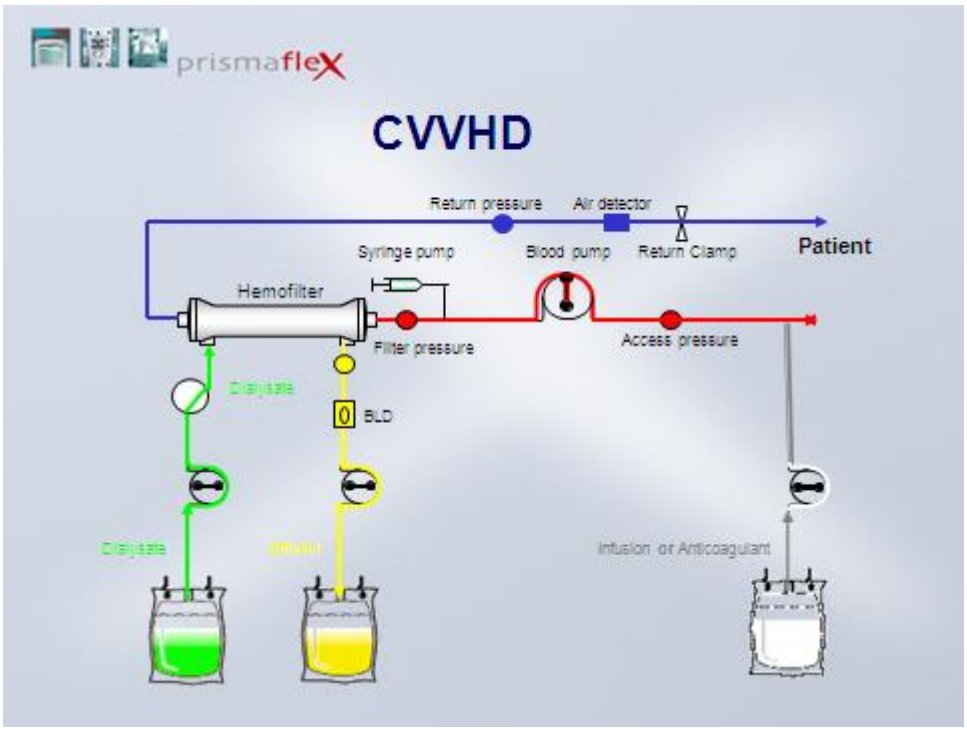
2.2 CVVH

Continuous venovenous haemofiltration results in the removal of solutes and fluids, especially middle and larger size molecules (up to 50,000daltons), by convection, by the addition of a replacement fluid either pre or post filter. This appears to be the most common form of CRRT used in PICU, likely to reflect hardware development; in that the early CRRT machines such as Baxter BM25 only offered this modality



2.3 CVVHD

Continuous venovenous haemodilaysis is simply intermittent haemodialysis performed continuously. In this mode there is clearance of molecules by diffusion across the membrane. Concentration gradients are created through the addition of replacement fluid (diasylate) in a counter current direction, on the opposite side of the filter membrane to the blood.



2.4 CVVHDF

Continuous venovenous haemodialfiltration is the combination of CVVH and CVVHD. In this mode there is clearance by both **con**vection and dif**fusion** (affectionately known as **confusion**), where there is addition of replacement fluid to the blood side of the membrane either pre or post filter to facilitate convection, as well as replacement fluid placed counter current to the blood flow on the opposite side of the membrane creating concentration gradients for diffusion to occur

2.5 PD

In Peritoneal Dialysis (PD), the peritoneum acts as the semi permeable membrane across which ultrafiltration occurs. Solute movement by convection as well as solute movement by diffusion occur across pressure and concentration gradients created by the instillation of dialysate fluid into the peritoneal cavity. Clearance in PD is limited by the availability of the peritoneal membrane, with approximately only one third peritoneal surface being in contact with dialysis solution at any one time

2.6 Indications for CRRT

Common indications include:

- **Fluid Overload**
- **Electrolyte Imbalance**
- **Metabolic Acidosis**
- **Acute Kidney Injury**
- **Clearance of toxins**
- **Septic Shock**
- **SIRS**

Current research focuses are on degree of fluid overload or degree of AKI, and trying to establish triggers at which to consider initiation of therapy. However the diversity in age, size and disease process/response makes a one size fit all model in the PICU setting very challenging.

2.7 CRRT Modality

Choice of modality and dose currently depend not only on the indication for treatment but also the size of the patient, underlying condition and prescribing practitioner, which will either be a Paediatric Intensivist (UK and Europe) or Paediatric nephrologists (North America). No current RCT evidence exists to support choice of modality or dose. As a result there is a wide variation in practice and in some cases a tendency to escalate in a step wise manner from PD to extracorporeal CRRT. In UK PICU's the commonest modalities used are CVVH or PD. This is likely to be a result of practicality and technology development, in that peritoneal access conveys less risk than central vascular access (especially in the neonatal and infant patients) and until the development of more modern CRRT machines (e.g. Primaflex (Baxter) or Aquarius (Nikkiso), CVVH was the only continuous extracorporeal modality available

Small molecule clearance is considered more effective in CVVHD. In the case of hyperammonaemia, the small molecular size of ammonia and the high clearance rates associated with diffusion based therapies led to claims that haemodialysis (intermittent or continuous) was more effective then CVVH for clearance of ammonia. However, published studies [(9)] show it is possible to use CVVH to safely and effectively clear ammonia, even in the neonatal population.

In CVVH, where solute removal is restricted only by the pore sizes in the filter, larger molecules are cleared. This is thought to facilitate removal of inflammatory cytokines and for this reason is the mode of choice in patients with systemic inflammatory response syndrome despite lack of evidence showing measured reduction cytokine levels or any effect of cytokine removal on outcomes in such patients [(2)]

2.8 CRRT Dose

The actual recommended dose of CRRT is also unclear. When prescribing CRRT the 'dose' refers to clearance, which is attributed to ultrafiltrate rate in CVVH and the dialysate rate in CVVHD. This represents GFR (glomerular filtration rate) in the healthy kidney. Normal GFR is 100ml/min/1.73m^2. Adult data suggests ultrafiltrate or dialysate rates of 25ml/kg/hr represent equivalent clearance to normal GFR. Recommended Paediatric dosing regimens stem from this data. To allow for interruptions in treatment the recommended dose in paediatric patients (to represent normal GFR) is 30ml/kg/hr. Higher rates (up to 100ml/kg/hr) are used when increased clearance of molecules (above normal GFR) are considered necessary, such as rapid reduction of ammonia or in septic shock.

As no evidence exists to support the use of one modality over another, this choice remains dependant on unit/clinician preference. Anecdotal data suggests CVVH is the commonest modality chosen. Common sense approach would be to use a combination of diffusion and convection (i.e. CVVHDF) to facilitate clearance of both small and large molecules (and assuming most PICU patients have a degree of SIRS) But in the absence of evidence, best recommendation would be to use the modality with which those delivering the therapy are most comfortable with.

2.9 CRRT Delivery and Nomenclature

Delivery of CRRT requires blood to be pumped out of the venous system of the patient, passed over an artificial semi permeable membrane (artificial kidney/haemofilter) where fluid and solutes are removed (ultrafiltration/convection) or controlled (diffusion) and then the 'cleaned' blood is returned to the patient at the same rate at which it was removed

2.10 CRRT machines

Technological advances over the last 10 years have resulted in the development of specific dialysis machines with high levels of safety and accuracy to deliver continuous renal replacement therapies. However these machines are designed for adult use and these systems are only adapted for use in the smaller paediatric patients by the addition of smaller filters and extra-corporeal circuits to the adult systems. Consequently their safety and accuracy record cannot be applied in the smallest paediatric patient population (<8kg). Examples of adapted paediatric systems available in the UK include Baxter Prismaflex (used in our unit) and Nikkiso Aquarius.

2.11 Vascular Access

Successful deployment of any extracorporeal therapy is dependent on adequate extracorporeal circuit blood flow. This in turn is dependent on adequate flow of blood from the patient via a venous cannula. While there are many patient factors that may influence blood flow from the patient (e.g. volume status, intrathoracic pressures and intra-abdominal pressures) ultimately adequacy of the vascular access is the most important factor.
Specific double lumen venous cannula specifically designed for CRRT (Vascaths) exist with sizes ranging from 5FG (French gauge) for the neonatal population to 14FG for adult sized children (image). As expected in any flow dynamic, shorter larger calibre cannulas are advised for optimum blood flow.

Recommended catheter sizes based on patient weight are shown in table below

Patient weight (kg)	Vascath Size (FG)
<3kg	5
3-5kg	6.5
5-10kg	8
10-20kg	11
20-50kg	12
>50kg	14.5

Constraints on maximal blood flow achievable through small calibre cannulae and reports of poor CRRT circuit survival associated with their use has propagated the opinion that cannulae <7FG should be avoided in the delivery of CRRT in small children (specifically infants and neonates). However there is lack of robust evidence to support these assertion and they are based on small numbers [12]. However a recent report [13] on use of 5F and 6.5FG vascaths for CRRT in neonatal patients showed these cannula can support sufficiently prolonged CRRT to make them a useful means of delivering CRRT in neonates and small infants. The probability of the circuit surviving 40hrs or greater was 50% with 43% expected to survive 60hrs or more (60hrs being the recommended standard). This was in a population where the average duration of therapy was 43hrs.

Vascaths should be inserted into a central vein using semi sedinger technique under USS guidance. Common sites of insertion are femoral, internal jugular and less commonly subclavian veins. There is increasing evidence that cannulation of internal jugular vein is associated with increased CRRT circuit survival when compared to the femoral vein [13] and associated with decreased rate of line related thrombotic events [14] .

2.12 Blood flow rate

Blood flow rate is the speed at which the blood pump is set. It should be sufficient to provide filter blood flow rate that provides adequate flow through the filter (preventing sluggish flow and haemostasis which will cause clotting of the filter) and that yields adequate ultrafiltrate rate without dehydrating the blood (see filtration fraction below)

Blood flow rate is described in millilitres/minute (ml/min). For most paediatric haemofilters minimum blood flow rate is 25ml/min and maximum is 200ml/min
There is no minimum or maximum blood flow rate per kilogram. Blood flow rate is dependent on vascular access, patient status, blood viscosity and filter patency and to optimize maximum filter lifespan the best blood flow you can achieve without causing hemodynamic instability or excessive negative access pressures are recommended

2.13 Filtration fraction

Filtration fraction is the fraction of plasma water removed during CRRT by ultrafiltration, and estimates the degree of blood dehydration at the end of the filter. As blood passes through the filter plasma water is filtered alongside solutes. If too much water is filtered then viscosity of the blood at the end of the filter will increase, making haemostasis more likely. It is recommended the filtration fraction is kept below 30%. Most modern machines calculate filtration fraction for you but it can be calculated
Filtration fraction can be reduced (and filter life increased) by the addition of replacement fluid pre filter in CVVH.

Filtration Fraction example:

In a 3kg baby
Blood flow rate across the filter is 30ml/min
Ultrafiltrate rate is 90ml/hr (30ml/kg/hr)

In one hour 1800ml (30 x 60min) of blood will pass through the filter and 90 ml ultrafiltrate will be removed

Filtration fraction is 100/1800 which is 5%

If in the same baby the ultrafiltrate rate is increased to 100ml/kg/hr
Then in one hour 1800ml of blood will pass through the filter and 300 ml ultrafiltrate will be removed
Filtration fraction is 300/1800 which is 15%

Circuit and filters

Paediatric CRRT circuits are designed to minimize extracorporeal volume hence are available in different sizes depending on the weight of the patient. Some CRRT providers provide the whole circuit including the filter as one, and others provide the components separately so individual components (e.g. the filter) can be changed during therapy.

Examples of this are shown below

Circuit	Patient Weight (kg)	Prime Volume (ml)	Max. Replacement Rate (ml/hr)	Max. Blood Pump Speed (ml/min)
HF20	0-12	60	780	100
ST60	12-25	97	2250	180
ST100	25-100	150	9000	400

2.14 Circuit Priming

As with all extracorporeal circuits, there is potential for reaction between patient's blood and the extracorporeal circuit components on initiation of therapy. To minimize this, circuits are primed with fluid (normal saline/human albumin solution/ plasmalyte/blood) and with heparinised saline. No evidence exists as to which is the best priming fluid. Some feel if the extracorporeal circuit volume exceeds 10% of the patients' blood volume (common in the neonatal and infant population) that blood priming of the circuit prevents haemodilution and haemodynamic instability on initiation of CRRT. Others feel blood priming of the circuit increases the risk of haemodynamic instability of the patient on CRRT initiation (likely related to the high potassium and lactate load of packed red cells which is then delivered at a high rate, in a patient who is already acidotic and hyperkalaemic) and so clear prime the circuit and transfuse the patient as required separately. This decision is largely down to unit/clinician experience and preference and as yet no evidence exists to support or dispute the practice of blood priming

Current manufacturer recommendations are that circuits/filters should be electively changed after 72hrs of therapy to preserve filter function and circuit life.

2.15 Ultrafiltrate rate and dialysate rate

The ultrafiltrate rate is the speed at which the fluid and solutes filtered during CVVH from the blood are removed away from the filter. The speed of this pump setting is determined by the 'dose' of CVVH prescribed (usually 25-30ml/kg/hr to mimic normal GFR)

The dialysate rate is the rate at which fluid is pumped in the counter current direction to blood flow to facilitate diffusive clearance in CVVHD

2.16 Fluid removal

During CRRT plasma water is removed alongside solutes and electrolytes. By measuring the amount of water being removed from the patient, a patients' fluid status can be tightly controlled during CRRT, either by fluid removal in an overloaded patient or by controlling fluid balance to allow for addition of extra fluid to the patient, such as TPN above their normal daily requirements, particularly in those whom fluids have been restricted.

During CRRT all fluid that is given to the patient and removed is measured on weighing scales. Bags containing fluid for replacement fluid (in CVVH) and dialysis are hung on scales. Ultrafiltrate and post filter dialysate fluid are then pumped into empty bags post filter which are also weighed. Patient's fluid input and output can also be programmed into the machine so replacement fluid and fluid removal rates can be controlled to achieve desired overall patient fluid balance. Because fluid changes are made continuously throughout the CRRT course, patients can tolerate significant changes in fluid status without haemodynamic instability.

One caveat however is that current CRRT machines used in PICU are designed for adult patients. This means that the weighing scales, calibrated for adult sized fluid losses, are accurate only to +/- 200mls. I.e. measured fluid losses or gains may have an error margin of +/- 200mls, insignificant in adult patients but could have significant impact on the fluid status of a neonatal or infant patient.

As overall patient fluid balance can be so well controlled by CRRT the patient does not need to be fluid restricted on CRRT which allows for optimization of nutrition in patients in whom fluid restriction may have prohibited this.

2.17 Anticoagulation

As with any extracorporeal circuits, circuits used for CRRT require administration of anticoagulation to prevent development of clots and keep the blood flowing in the circuit. This has to be balanced against consumption of clotting factors and platelets secondary to the activation of Systemic Inflammatory response Syndrome by the contact of blood with the extracorporeal circuit. Anticoagulation can be administered systemically (i.e. to the circuit and the patient) or regionally (circuit only).

The commonest anticoagulant used in CRRT within PICU is still heparin, usually run as an infusion to the patient or the CRRT circuit itself and monitored using bedside tests such as ACT. Heparin infusion is commenced at 10units/kg/hr then titrated to maintain ACT 140-160

Alternatives to Heparin include prostacyclin (2-10ng/kg/min) or no anticoagulation in a patients who have liver impairment, DIC or thrombocytopaenia, or those in who heparin in contraindicated (recent surgery, bleeding). Prostcyclin is associated with shorter circuit survival than heparin, however the risk of patient bleeding is similar.

Citrate anticoagulation, which results in regional anti-coagulation of the circuit, is now recommended as first line anticoagulation treatment in the adult CRRT population [(1)] Citrate prevents coagulation by chelating free ionized calcium to form a citrate-calcium complex. This drops the ionized calcium level within the extra-corporeal circuit preventing clot formation as several steps in the coagulation cascade require the presence of ionized calcium to work. Citrate is not currently used in our unit as we are familiar with heparin owing to our ECMO program.

2.18 Discontinuation of CRRT

There is little or no information in the literature on when or how to discontinue CRRT. If the therapy target based on the indication for CRRT has been achieved, then can consider discontinuing CRRT. This may be restoration of normal fluid status/adequate removal of toxins/ recovery of urine output. In some cases the patient may require a trial period off CRRT to assess if they can manage without therapy.

A trial off CRRT may simply involve disconnection of the patient from the CRRT device, whilst maintaining the patency of the vascular access (usually with a heparin lock) and the CRRT circuit (either by 'wasting the circuit' or using the recirculation technique to maintain flow around the circuit. In the case of AKI where it is unclear if the renal function has recovered enough to maintain fluid and electrolyte homeostasis without CRRT, diuretic medications may be considered to 'kick start' the kidneys during the trial off period. The period of trial off will depend entirely on the patient. Close monitoring of urine output, electrolyte and acid base balance is essential

Long term follow up of renal function should be considered in all patients who have received CRRT.

3. Education and Training

None

4. Monitoring Compliance

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
Treatment algorithm followed and documented	Audit	Consultant Intensivist	As required	Clinical practice meeting

5. Supporting References

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6. Key Words

Continuous renal replacement therapy, Paediatric critical care, Continuous venovenous haemofiltration (CVVH), Continuous venovenous haemodialysis (CVVHD), Continuous venovenous haemodiafiltration (CVVHDF), Ultrafiltration, Convection, Diffusion, Peritoneal Dialysis (PD), Filtration fraction

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The Trust recognises the diversity of the local community it serves. Our aim therefore is to provide a safe environment free from discrimination and treat all individuals fairly with dignity and appropriately according to their needs.
As part of its development, this policy and its impact on equality have been reviewed and no detriment was identified.

CONTACT AND REVIEW DETAILS	
Guideline Lead (Name and Title) C Westrope - Consultant	**Executive Lead** **Chief medical officer**
Details of Changes made during review: **June 2023** **No changes**	