Paediatric Intensive Care Unit

Guidelines for Continuous Veno-Venous Haemofiltration (CVVH) and Continuous Veno-Venous Haemodiafiltration (CVVHDF) within the Cardiac Paediatric Intensive Care Unit at Leicester Royal Infirmary.

Staff relevant to:	PICU nursing staff trained in extended role, Consultants and ANP's within PICU.
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1. Introduction and who this guideline applies to

The purpose of this guideline is to provide support and direction when caring for a child requiring haemofiltration and haemodiafiltration. The following guideline refers only to the use of the Baxter Prismaflex or PrisMax machine for children on the Cardiac Paediatric Intensive Care Unit (CPICU) at Leicester Royal Infirmary who are receiving Continuous Veno-Venous Haemofiltration (CVVH) or Continuous Veno-Venous Haemodiafiltration (CVVHDF). This guideline is intended to be used by all PICU nursing staff trained in extended role, Consultants and ANPs within CPICU.

Clinical guidelines are 'guidelines' only. The interpretation and application of clinical guidelines will remain the responsibility of the individual. If in doubt consult a senior colleague or expert. Caution is advised when using the guidelines after the review date. Deviation from this guideline must be documented in the nursing notes with an explanation of the circumstances.

Please use this guideline in conjunction with the following:

- Continuous Renal Replacement Therapy UHL Paediatric Intensive Care Guideline C15/2018
- ECMO Levitronix CentriMag - Neonatal and Infant UHL Childrens Intensive Care Guideline C110/2016

2. Description of Therapies

Continuous renal replacement therapy (CRRT) is a supportive therapy used for the management of fluid balance and metabolic derangement, with or without evidence of acute injury kidney injury (AKI), in critically ill patients.

Aims of the therapy include:

- Relieving hypervolaemia and maintaining fluid balance
- Removing excess urea & creatinine
- Correcting and maintaining metabolic and electrolyte balance
- Removing toxins

Indications for commencing treatment:

- Fluid overload
- Electrolyte imbalance
- Acute Kidney Injury (AKI)
- Inborn errors of metabolism
- Sepsis*
- Rhabdomyolysis
- Tumour lysis*
- Drug intoxications
- Optimising nutrition*

(* other indication(s) needed to support decision, not enough on its own)

In the East England, East Midlands and South Yorkshire (EMEESY) Children's Kidney Network, CRRT is utilised in the following forms; Peritoneal Dialysis (PD), Continuous Veno Venous Haemofiltration (CVVH) and Continuous Veno Venous Haemodiafiltration (CVVHDF). This guideline focuses on the use of CVVH and CVVHDF; these are both delivered using the Baxter Prismaflex/ PrisMax machine.

Using a dedicated double lumen vascath and an extracorporeal circuit, blood is continuously removed and returned to the patient. This continuous technique allows fluid and waste products to be removed gradually over a 24hr period, providing more haemodynamic stability for critically ill children who are often cardiovascularly unstable. This treatment can also be incorporated into a patient's Extra Corporeal Membrane Oxygenation (ECMO) circuit and run simultaneously.

The extracorporeal circuit incorporates a blood pump and a filter containing a semi-permeable membrane. A pressure gradient within the circuit forces fluid and solutes across the membrane to form effluent fluid. Dialysis fluid can also be added to the other side of the filter, this causes molecules to move across with a concentration gradient. The processes utilised are *ultrafiltration*, *convection* and *diffusion*.

2.1 Ultrafiltration

This is the movement of fluid through a semi-permeable membrane driven by a hydrostatic pressure gradient. On the Prismaflex/ PrisMax, a positive pressure is generated by the blood pump on the blood side of the semi-permeable membrane and a negative pressure by the effluent pump on the other side. This results in the movement of fluid from the positive pressure side (blood side) to the negative pressure side (effluent side).

2.2 Convection

This occurs when large volumes of fluid crossing the semi-permeable membrane down the hydrostatic pressure gradient results in solvent drag across the membrane. Large molecules can be moved efficiently if the flow is fast enough. Pre blood pump and replacement fluid is added to the circuit to increase the flow across the semi-permeable membrane.

2.3 Diffusion

This is the movement of solutes across a semi-permeable membrane caused by a concentration gradient. Solutes move from an area of higher concentration to an area of lower concentration. On the Prismaflex/ PrisMax this is achieved by the addition of dialysate fluid which is run counter-currently to the blood flow on the other side of the semi-permeable membrane, to ensure the concentration gradient is maintained the whole length of the filter.

The movement of molecules in CRRT are driven by the above processes but are limited by the size of the solute particles. The Prismaflex/ PrisMax filters have pores that allow passage of molecules up to 35,000 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 myoglobin (17,200 Daltons), insulin (active) and interleukins (varies). Small molecules are more efficiently removed by diffusion and larger molecules by convection.

Please note that diffusion is a two way process, so particles will move into the blood from the dialysate fluid if the concentration in the blood is lower than the fluid. After some time, the concentration within the blood should match that within the fluid.

2.4 Adsorption

Some molecules are removed in CRRT by adherence to the artificial semi-permeable membrane; this is the process by which inflammatory markers are thought to be removed. High levels of these molecules can cause the filter to clog and become less effective.

On CPICU the Baxter Prismaflex or PrisMax machine is used and have several different modes. The two main modes utilised for CRRT are Continuous Veno Venous Haemofiltration (CVVH) and Continuous Veno Venous Haemodiafiltration (CVVHDF).

2.5 Continuous Veno-Venous Haemofiltration (CVVH)

This mode of CRRT utilises the principles of ultrafiltration and convection and is ideal for removing middle and large molecules.

- Biochemistry is controlled by removing large volumes of filtrate and replacing it with electrolyte containing fluid (replacement fluid). The more filtrate you remove and replace the more efficient haemofiltration is in controlling biochemical disturbance.

- As most solutes are distributed within the extracellular and intracellular fluid compartments (total body water), the volume of filtration (replacement) necessary to control biochemistry relates to total body water. Clinical experience has shown that a replacement of approximately 50% of bodyweight (1kg = 1litre) is usually adequate for solute and electrolyte removal.

- Low blood flow rate, high haematocrit and high plasma protein concentration will limit the rate at which filtration can occur and solutes (particularly of higher molecular weight) can be removed.

2.6 Continuous Veno-Venous Haemodiafiltration (CVVHDF)

This mode of CRRT utilises the principles of ultrafiltration, convection and diffusion; using both convective and diffusive transport systems will optimise the clearance of molecules of varying sizes.

- The addition of dialysate flow with CVVHDF will improve the efficiency of acid base, waste and control of electrolyte balance. Waste and electrolytes diffuse from the patient's blood into the dialysate fluid surrounding the fibres. The "saturated" dialysate fluid (effluent) is removed from the filter and discarded.

- Diffusion is a two way process, molecules that are at a low concentration in the blood and high in the dialysate fluid will diffuse into the blood and vice versa (e.g. bicarbonate).

- Convective transport systems utilised in CVVH are limited by the blood flow achieved. If higher replacement rates are indicated, but not achievable, adding in dialysate flow will optimise clearance. Reasons for not achieving desired replacement rates could be due to patient stability or issues with access limiting the blood flow rates.

- This is practically important when treating children with inborn errors of metabolism, for overdose of drug or therapeutic agents and for patients with a high lactate.

- Increasing dialysate flow will at least theoretically improve clearance; however this is limited by the relatively low dialysate flow rates generated by CRRT equipment.

CVVHDF should always be selected when setting up the PrisMax, no matter the intended therapy for use.

3. Prescribing Guidance and Flow Rates

All fluid handling rates on the Prismaflex and PrisMax are set in millilitres

3.1 Calculating treatment parameters

The CVVH/CVVHDF prescription is based on a 24hr period. Shorter sessions of CVVH/CVVHDF will require adjustment of the flow rates and filters to achieve the same **daily** amount of filtration. The prescription needs to account for the patient's current situation and the desired management over the next 24 hours. In general it is difficult to achieve a negative balance of more than 5-10% of patient's body weight over 24 hours.

3.2 Blood Flow Rate

This is the volume of blood passing through the filter in a given time relative to body weight. These are affected and determined by the patient stability and the vascular access. Clotting in the lines or filter is most likely to occur when blood is travelling slowly therefore blood flow rates should be run at the higher end of the range if possible. There is no such thing as too much blood flow, other than maximum pre-programmed limits determined by the circuit size/machine. Blood flow rates should be adjusted in high flow CRRT to compensate for excessive haemoconcentration of the filter.

Standard blood flow rates are 6-9ml/kg/min (up to 12-15ml/kg/min in lower weight babies), with a minimum rate of 30ml/min once initiated on treatment.
In patients >30kgs aim for a blood pump speed of 180-240ml/min. The machine will allow speeds up to maximum of 400ml/min but this is not often achievable or necessary.

3.3 Replacement rate

Replacement rates = ultrafiltration + convection
Medium size molecule clearance (e.g. products of inflammation/cytokines)

Total replacement rate is the volume of fluid taken out of the patient and replaced with replacement fluid every hour in ml/hr. It is also known as the volume of exchange.

Total replacement is calculated on 30ml/kg/hr, this is the starting point to provide effective solute waste control. This is calculated based on normal creatinine clearance of 25ml/kg/min, allowing for interruptions to treatment, however replacement can be increased for enhanced clearance. For example septic/metabolic patients may have higher replacement rates, up to 80ml/kg/hr have been used. If a higher replacement is used a proportional higher blood pump speed is needed to stop the filter clotting. This is only possible if the patient's cardiovascular status and vascular access will tolerate it.

The Prismaflex/ PrisMax allow for a mix of pre and post dilution replacement rates. As a usual starting rate 10mls/kg/hr pre dilution and 20mls/kg/hr post dilution is recommended. This may be altered dependent on the patient's clinical status and the condition of the circuit e.g if circuit pressures are rising indicating that the filter is clotting then increasing the amount of pre-dilution may prolong the life of the filter. Maximum pre dilution would be 90%, as 10% post dilution minimum is required to prevent clots forming in the bubble trap.

3.4 Dialysate flow rate

Dialysate rates = diffusion
Small molecule clearance (e.g urea/ammonia)

Initial dialysate flow rate should be 20ml/kg/hr. As with replacement, increasing the rate will increase efficiency of therapy. Dialysate will rapidly change electrolyte and waste balance. Dialysate flow

should **not** start at high volume rates because of the potential to change patient's osmotic pressure. Higher rates of dialysate are used in patients with Hyperammonaemia (up to 50ml/kg/hr) to clear ammonia quickly, but in other cases dialysate flow should only be increased if treatment is not effective.

Dialysate flow is not affected by blood flow and increasing it does not cause haemo-concentration in the filter.

In AKI no evidence exists to support one mode over another. Some proponents of CRRT recommend a combination of convection and diffusion to optimise removal of small and medium sized molecules (assuming that SIRS/Sepsis plays a part in most AKI models)

A typical starting prescription for fluid overload, oliguria would be 30ml/kg/hr convection, with the addition in SIRS/Sepsis of 20ml/kg/hr diffusion

3.5 High Volume Treatment

In patients with metabolic diseases ideally total body water should be exchanged in 8 hours, however this is usually not possible to achieve as enough blood flow cannot be achieved to avoid the filter clotting. In the case of metabolic patients the highest practical replacement rate should be used and dialysate flow used from the start. The normalisation of ammonia and metabolic acidosis being the point at which to consider a reduction in flow rates.

High volume replacement or dialysate flow rates have a dramatic effect on electrolyte balance, regular review of potassium, phosphate, calcium, sodium and pH balance are essential. All flow rates should be reviewed every 24 hours and reduced when patient improves or when desired outcome has been achieved. **Medical staff must prescribe any changes in flow rates.** The danger of haemoconcentration of blood in filter can be a problem with high volume replacement.

3.6 Flow Rates: Special Considerations

Hyperkalaemia

High potassium levels can cause arrhythmias and lead to cardiac arrest if not treated. Do not delay commencing therapy in these patients and consider increasing flow rates if clearance is needed quickly.

Hyperammonia

The higher the ammonia level and the longer it stays at that level, the higher the risk of brain damage to the patient. It is essential that ammonia is cleared as quickly as possible to reduce this risk. When starting CVVHDF on a patient with hyperammonia consider increasing flow rates, depending on ammonia level and patient stability.

Hypernatraemia and Hyperuraemia

If sodium and urea are cleared too quickly, disequilibrium syndrome can occur and the osmotic gradient in the brain will change causing cerebral oedema. When starting CVVH/CVVHDF in these patients, start slowly by using lower flow rates, depending on sodium and urea levels. You can also consider using a smaller filter size to decrease clearance.

3.7 'Unintended Pt Fluid Loss or Gain Limit'

This is the difference between the fluid removal measured on the machine and the set fluid removal rate over the last 3 hours. Once this limit has been reached the machine will stop and treatment will not be able to be continued. Therefore if a clamp has been left on a bag the alarm cannot be continuously over ridden. The default limit is 60-400mls, but should be set based on patient's weight (usually at 10ml/kg/3hrs) but this is dependent on clinical condition and haemodynamic stability. This should be assessed and prescribed on the prescription chart.

3.8 Patient fluid removal rate

This is calculated on an hourly basis depending on actual patient fluid balance, desired fluid balance and condition and stability of the patient. Individual prescription depends on input (i.e. nutrition, IV fluids, drugs) and output (i.e. urine, gastric, drain losses). The Prismaflex/ PrisMax will continue to run at the set hourly rate until changed by staff. The rate **must** be reviewed every hour. Beware of removing fluid too quickly.

If a negative balance is required it needs to be prescribed on the prescription chart. This may be calculated on a 12 hourly basis or over a specified period of time (i.e. ml/hr).

Net fluid removal rate refers to desired net removal (e.g. 0ml/hr would mean a neutral balance to the patient, 10ml/hr would mean -10ml/hr to the patient). Desired removal rate and hourly actual fluid balance both need to be added together to work out patient fluid removal rate to be programmed (e.g. if total hourly input amount of IV fluids and infusions is 45ml/hr and 10ml/hr net removal is prescribed = 55mls/hr needs to be programmed into the machine).

Do not remove fluid bolus given to support blood pressure or intravascular loss. Blood products which have **not** been administered for volume should be added to the fluid loss to be programmed.

If the machine shows a minus number that means that it has gained that amount of fluid. This may occur when you first commence treatment, but will readjust itself after a few minutes.

Deciding exactly how much fluid to remove from the patient is complex as it depends on many clinical factors including urine output, insensible loss, hypervolaemia/hypovolaemia and clinical observations. Once fluid removal is started, close observation of the patient's cardiovascular and fluid balance status needs to be undertaken.

EXTREME CAUTION should be used when setting the patient fluid loss rate, as the Prismaflex/ PrisMax will try to remove that amount of fluid and it has no way of assessing the effect on the patient. It will continue to remove fluid even when the patient is **HYPOVOLAEMIC.** In low body weight children extra caution is advised in assessing and programming fluid removal rates. No Paediatric CRRT equipment is accurate ml for ml and there may be some discrepancies in what the machine actually achieves.

4. Replacement fluids and adding electrolytes

4.1 Fluids: Prismasol 4 & Hemosol BO

Prismasol 4									
Sodium	Potassium	Calcium	Magnesium	Chloride	Phosphate	Lactate	Bicarbonate	Glucose	Citrate
140	4	1.75	0.5	113.5	0	3	35	6	0

Hemosol BO									
Sodium	Potassium	Calcium	Magnesium	Chloride	Phosphate	Lactate	Bicarbonate	Glucose	Citrate
140	0	1.75	0.5	109.5	0	3	35	0	0

Prismasol 4 should be used as the standard replacement fluid unless the patient's serum potassium is over 6.0mmol/L. If the patient is receiving a potassium infusion, has potassium chloride in the intravenous maintenance or as a supplement this should be reviewed and is usually stopped at the commencement of therapy.

Prismasol 4 and Hemosol BO are bicarbonate based replacement/dialysate fluids and must be mixed before use. If the patients U&E's/ blood sugars drop after starting treatment ensure fluid has been mixed properly.

Prismasol 4 has added potassium at a dose of 4mmol/L and glucose of 6.1mmol/L. Hemosol BO and Prismasol 4 also contain a low magnesium concentration (0.5mmol/l). When considering electrolyte balance remember the patients electrolyte levels will became similar to the concentration in the replacement/dialysate fluid and the higher the replacement/dialysate flow rate the faster this will happen.

If the patient has serum potassium **over** 6.0.mmol/L the potassium free Hemosol BO solution should be used as the initial replacement/dialysate fluid. Caution should be taken when using Hemosol BO as this fluid does not contain any glucose therefore very close monitoring of patient's blood glucose is essential. As the serum potassium falls below 6.0mmol/L, the replacement/dialysate fluid should be exchanged for the Prismasol 4 solution.

If the patient has serum potassium **less than** 6.0mmol/L at the commencement of therapy Prismasol 4 solution should be used at the outset. The use of Prismasol 4 solution negates the use of extra potassium infusions. The patient's serum potassium will settle out at about 4.0mmol/L (the same as the concentration within the fluid) if Prismasol 4 is used.

4.2 Adding electrolytes to replacement and dialysate fluid

With the exception of sodium and glucose if the patient requires other electrolytes the first line would be to administer this directly to the patient. If access is a major problem you may need to consider adding electrolytes to the replacement/dialysis solution and where possible advice should be sought from pharmacy to ensure there are no compatibility problems.

- Prior to additions being made to bags discussion must take place with pharmacy.
- Additives are always prescribed to be added per litre of fluid and as a total dose. Care needs to be taken when making up the fluid as a result.
- When additives are required more frequent blood sampling will be required.

4.3 Management of Hypernatraemia on CRRT

In cases of hypernatraemia in patients requiring CRRT it may be necessary to add sodium to replacement/dialysis fluids to ensure sodium correction does not occur too rapidly. The sodium content of both Prismasol 4 and Hemosol BO is 140mmol/L, so without the addition there is a significant risk the patient's serum sodium could drop too quickly.

If the patient's plasma sodium is greater than 160mmol/L it will be necessary to add 30% sodium chloride to bags of Prismasol 4 or Hemosol BO to prevent a rapid fall in plasma sodium. It should never fall >10mmol/L in 24 hours. Sodium chloride 30% contains 5mmol/ml of sodium.

Target Na^+ (mmol/L)	**Addition to 5 litre bag (either Prismasol 4/Hemosol BO)**	
150	10mls of sodium chloride 30%	Remove same volume from replacement/dialysate bag before addition (i.e. for target 150mmol/L remove 10mls from Prismasol 4/Hemosol BO, then add 10mls sodium chloride 30%)
160	20mls of sodium chloride 30%	
170	30mls of sodium chloride 30%	
180	40mls of sodium chloride 30%	
190	50mls of sodium chloride 30%	

If an addition is required this must be clearly documented on the patients CVVH/CVVHDF Daily Prescription and Record Chart and the patient's serum sodium must be closely monitored.

5. Anticoagulation: Heparin

As with any extracorporeal circuit, the circuits used for CRRT require the administration of anticoagulation to prevent the development of clots and keep the blood flowing in the circuit.
On CPICU unfractionated heparin should be used as the first line anticoagulant. Heparin inhibits coagulation by preventing the conversion of prothrombin to thrombin and fibrinogen to fibrin. Heparin displays almost immediate action following intravenous administration.

The clotting time then returns to normal within 2-6 hours after the infusion is discontinued. It binds extensively to plasma proteins and is activated in the liver and excreted in the urine.

The action of heparin can be reversed with Protamine Sulphate. The dose is dependent on the heparin rate - see the BNFC for more information. The protamine dose should be based on the cumulative heparin dose given over the previous 2 hours.

5.1 Contraindications:

- Active bleeding
- Imminent or recent surgery
- Coagulopathies such as thrombocytopenia, especially in septic and oncology patients
- Heparin Induced Thrombocytopenia (H.I.T)
- Disseminated Intravascular Coagulation (D.I.C)
- Liver disease
- Haemophilia
- Diabetes
- Pericarditis

CVVH/CVVHDF may be carried out in the above circumstances with minimal or no heparin or with an alternative agent such as Epoprostenol/Prostacyclin (please see section 5 and the table in section 6 for more information).

NB. It is possible to use less heparin if a faster blood flow is obtained, if the pre-dilution rate is increased, or if the patient is on warfarin, aspirin or another anti platelet agent.

5.2 Administration & dosage:

If running CVVH/CVVHDF as a stand-alone therapy heparin should be drawn up as per the IV Monograph, set up on an external syringe pump and administered into the heparin line on the circuit. The heparin bolus and infusion should be prescribed on the patient's prescription chart. Heparin for line locks is prescribed on the CVVH/CVVHDF prescription chart.

The initial bolus (if appropriate) should be given as blood reaches the pre filter port; this is then followed by a continuous infusion. The aim is to raise the patients clotting time sufficiently to prevent clotting in the filter and lines, while not increasing the risk of bleeding to the patient.

HEPARIN

Care: there are different strengths available – check!

Use 1,000units/ml for these infusions

Dose: for treatment or prevention of thrombotic episodes, after complex cardiac surgery procedures and for patients on CVVH

Loading dose:

Neonate <35weeks post-conceptional age:	50units/kg
Neonate >35weeks post-conceptional age:	75units/kg
Paediatric:	75units/kg

Initial maintenance dose:

Neonates and children <1year of age:	25units/kg/hour
Paediatric (>1 year of age):	20units/kg/hour

Usual range 10-40 units/kg adjusted according to APTT - Higher doses may be required

Method of administration:

Loading dose: IV bolus over 10 minutes (check if required with medical team)
Maintenance dose: Continuous IV infusion

Draw up 500 units/kg into a syringe and make up to 50ml with sodium chloride 0.9% or glucose 5%.

1ml/hour = 10 units/kg/hour 4ml/hour = 40 units/kg/hour

Dilution:

Sodium chloride 0.9% or glucose 5%

Change infusion every 24 hours

Adverse effects:

Haemorrhage and thrombocytopaenia
Very rarely: hyperkalaemia (via hyperaldosteronism), hypersensitivity reactions, local skin irritation or skin necrosis

Notes:

Check clotting screen (baseline FBC, INR & APTT) prior to commencing heparin
Check APTT regularly, advise 4 hours post loading dose and 4 hours after each alteration in dose
Check APTT and FBC daily and potassium levels on alternate days
Consult the pharmacist before use in renal or hepatic impairment
Heparin has short half-life but if antidote required give protamine

Above taken from IV Monograph (Sept 2021), please also refer to Medusa for any recent updates

5.3 Anticoagulation whilst on ECMO

If patient is also on ECMO there is no need to separately anticoagulated the CVVH/CVVHDF circuit, anticoagulation will be provided from the heparin used for the ECMO circuit. Refer to guidance in ECMO protocol for more information.

5.4 Monitoring

The level of anticoagulation is monitored by measuring the Activated Clotting Time (ACT). This is measured using the Hemochron machine regardless if patient is on ECMO or receiving CVVH/CVVHDF as a stand-alone therapy.

A clotting time that is taken pre-filtration and is not heparinised, such as at initial insertion of haemofiltration catheter must always be taken. This is essential because each individual will respond differently to the same dose of heparin; therefore, their response to it (i.e. the increase in the clotting time following heparin) will be different. The initial ACT should be 100-130 seconds. If already on ECMO, there is no need for pre-treatment ACT.

Once commenced on treatment you will need to check an ACT within 30 minutes. Further ACT's should be taken 1-2 hourly until ACTs are within range for 2 consecutive measurements, at which time they can be monitored 4 hourly. ACTs should be checked a minimum of 4-6 hourly whilst receiving CVVH/ CVVHDF.

The aim is to maintain the patients clotting time within the pre-determined limits on the prescription chart, usually 190-210 seconds. However this may change depending on patient situation.

If the patient is already on ECMO, take an ACT when first commencing therapy, if stable further monitoring can then be done at the same time the ACT's are taken for ECMO circuit. Continue with ECMO parameters for heparinisation.

If the ACT is low, thrombosis and clotting may occur **in the circuit and patient**
If the ACT is too high, bleeding may occur **in the patient**

The patients clotting must also be monitored closely via laboratory bloods. Should the patients clotting become deranged the ACT target range may need to be reviewed and reduced.

6. Anticoagulation: Epoprostenol

If patient has contraindications to heparin then Epoprostenol can be used as an anticoagulant, or it can also be used in combination with heparin if heparin alone is proving inadequate. Epoprostenol is used to anticoagulate the patient and therefore the blood that is traveling through the circuit.

Epoprostenol is a prostaglandin and a potent inhibitor of platelet aggregation, which means it stops platelets being able to adhere to one another and create a clot. This inhibition is dose related. It also has vasodilating properties and can be used in patients with pulmonary hypertension.

6.1 Administration and dosage – see next page

EPOPROSTENOL
(Prostacyclin)

Dose:

Persistent pulmonary hypertension:

All ages: 2 - 40 nanograms/kg/minute = 0.12 - 2.4 micrograms/kg/hour

(Remember that 1 microgram = 1000 nanograms)

Platelet aggregation inhibitor / digital ischaemia:

The dose for these indications in children are unclear

Suggested dose for all ages: 2.5 – 10 nanograms/kg/minute

However higher doses may be used, likely upper dose of 20 nanograms/kg/min, but can go up to 40 nanograms/kg/min

Method of administration:

Continuous IV infusion

Dilution: DO NOT MIX WITH GLUCOSE 5%

Epoprostenol is complicated to prepare, please follow instructions carefully:

1. Reconstitute a 500 microgram powder vial with 10ml of the glycine buffer provided in with the 50ml solvent vial.
2. Return this solution to the 50ml solvent vial and mix well. *SAVE THE 50ML VIAL*

   The concentration of this solution is 10 micrograms/ml (10,000 nanograms/ml).

3. **This solution needs filtering using the 0.22 micron filter provided before further dilution or administration**

For older children and higher doses this 10 microgram/ml solution can be given without further dilution via a central line.

Rates: 0.012ml/kg/hour = 2 nanograms/kg/minute
0.24ml/kg/hour = 40 nanograms/kg/minute

However for younger children and at lower doses the solution will need further dilution with sodium chloride 0.9%.

The most the solution can be diluted is by a 1 to 6 dilution with sodium chloride 0.9% (minimum final concentration 1.43micrograms/ml)

Suggested dilutions:

Option 1:

Dilute **10ml** (10micrograms/ml) of the filtered solution up to 50ml with sodium chloride 0.9%. **This gives a concentration of 2 microgram/ml (2000 nanograms/ml)**

At this concentration,	0.06ml/kg/hour	= 2 nanograms/kg/min
	1.2ml/kg/hour	= 40 nanograms/kg/min

Option 2:

Dilute **20ml** (10micrograms/ml) of the filtered solution up to 50ml with sodium chloride 0.9%. **This gives a concentration of 4 microgram/ml (4000 nanograms/ml)**

At this concentration,	0.03ml/kg/hour	= 2 nanograms/kg/min
	0.6ml/kg/hour	= 40 nanograms/kg/min

The manufacturer recommends changing infusions every 12 hours. However, the loss of potency is very small and not clinically significant
Therefore, it is recommended the infusion is changed every 24 hours

Adverse effects:

Epoprostenol is a powerful inhibitor of platelet aggregation and there is a possible risk of haemorrhage
If withdrawn suddenly can cause pulmonary hypertensive crisis
Bradycardia, tachycardia or profound hypotension
Facial flushing and reddening over infusion site. Headache, gastrointestinal problems including nausea and colic pain. Jaw pain, chest pain and tightness, sweating and dry mouth

Storage: Freeze dried powder: Store below 25°C and protect from light
The concentrated 50ml vial should be stored in the fridge (2-8°C) for subsequent infusions up to 24 hours after reconstitution.

Notes: Epoprostenol should not be administered with any other drugs or solutions
Platelet aggregation inhibition can result in unwanted bleeding therefore anticoagulant monitoring is required especially if concomitant heparin is infused
The extension set and the in-line filter must be changed at least every 48 hours

Above taken from IV Monograph (Sept 2021), please also refer to Medusa for any recent updates

Due to its vasodilating effects, Epoprostenol should not be stopped suddenly to avoid rebound pulmonary hypertension. If planning to discontinue CVVH, wean Epoprostenol gradually by reducing by 2 nanograms/kg/minute every 15 minutes prior to stopping therapy. If CVVH stops unexpectedly (i.e if it clots or the patient's access stops working), continue Epoprostenol and wean by 2 nanogram/kg/minute every 15 minutes until off. Observe for signs of rebound pulmonary hypertension.

When administering Epoprostenol it must be delivered directly to the patient using a syringe driver, not through the Prismaflex/ PrisMax machine. Use a dedicated central line for administration, if struggling with access you may consider adding a 3-way tap on to return line of circuit.

6.2 Monitoring

Epoprostenol will not affect the ACT so there is no bed side monitoring required, it may however be of use to check the overall coagulation status regularly. Clotting should therefore be sent 12 hourly as a minimum, but more often if clinically indicated. The results should not be used to titrate the Epoprostenol rate, but if clotting is abnormal discuss anticoagulation with the consultant or paediatric renal critical care nurse.

When titrating Epoprostenol, consider the patient's blood pressure in conjunction with the filter pressures. If filter pressures are rising then the Epoprostenol rate can be increased, but monitor closely for signs of hypotension. If the patient becomes hypotensive, the rate will need to be decreased to reduce vasodilator effects.

6.3 Side Effects

- Hypotension due to vasodilation
- Patients can develop raised intracranial pressure
- Inhibition of platelet aggregation can cause unwanted bleeding, therefore monitor coagulation status carefully, particularly if on other anticoagulants
- Nausea, vomiting, headache, hypotension, flushing, chest pain, anxiety, dizziness, bradycardia, dyspnoea, abdominal pain and tachycardia - although these are mainly described in adults who are not on CRRT.

6.4 Contraindications

- Treat any hypovolaemia before commencing infusion
- Avoid sudden withdrawal due to the potential for rebound pulmonary hypertension
- Contraindicated in severe left ventricular dysfunction and pulmonary veno-occlusive disease
- Contraindicated in patients with oesophageal varices due to the inhibition of platelets and increased blood flow in the portal venous system
- Inhibition of platelet aggregration can cause unwanted bleeding, therefore monitor coagulation status carefully, particularly if on other anticoagulants
- Vasodilator effect may augment or be augmented by other vasodilators
- Caution if patient has abnormal coagulation

7. Anticoagulation treatment table

	Heparin	Epoprostenol	Heparin/ Epoprostenol combination
Indication	Standard first line therapy	HIT Allergy to heparin Bleeding (particularly intracranial) Risk factors for bleeding	Heparin alone is inadequate (i.e. if filter life < 24hrs excluding elective changes or access problems) High risk of filter clotting (e.g. HUS, hypercoagulopathic state including DIC, septicaemia)
Dosage range	10-40 unit/kg/hr	4-8nanogram/kg/min **MAX** **10nanogram/kg/min**	Heparin: 10-40unit/kg/hr Epoprostenol: 4-8nanogram/kg/min
Starting dose	20 units/kg/hr	4nanogram/kg/min	Heparin: 10units/kg/hr Epoprostenol: 4nanogram/kg/min
Titration point	0 190-210 seconds	If circuit life < 48hrs: Increase by 2nanogram/kg/min increments Monitor patient and decrease if there are signs of hypotension	ACT 160-200 seconds If ACT >200 seconds: ↓heparin by 10% If ACT<160 seconds: ↑ heparin by 10% If circuit life < 36hrs: Increase epoprostenol by 2nanogram/kg/min increments
Delivery method	Via heparin port on CVVH/CVVHDF circuit using an external syringe pump	To patient via a central line. If no spare access add a 3-way tap onto return line of CVVH/CVVHDF circuit	Heparin to CVVH/CVVHDF circuit via Heparin port Epoprostenol to patient

8. Considerations prior to commencing therapy

8.1 Access

Temporary central venous lines (CVL) are used for CRRT within PCCU. Follow the guideline for insertion of CVL in CPICU. The use of ultrasound guidance when inserting CVL should strictly be adhered to during insertion.

- Once the CVVH/CVVHDF catheter is inserted obtain baseline bloods and a non-heparinised Activated Clotting Time (ACT).
- Obtain most recent haematocrit (Hct), ensure this is programmed into Prismaflex/PrisMax.
- Each lumen should then be locked with the exact volume as stated on the catheter with heparin 100 units/ml and labelled stating 'Heparin 100 units/ml insitu'.

<table>
<tr><th>Weight</th><th>Type</th><th>Size</th><th colspan="2">Line lock</th></tr>
<tr><td rowspan="2"><10kg</td><td>Braun or similar</td><td>2 x 18G (green) peripheral cannula</td><td>0.2ml or 1.3ml with connection Heparin 100units/ml</td><td rowspan="6">Prescribe on front of CVVHDF chart</td></tr>
<tr><td rowspan="2">Gam Cath</td><td>6.5Fr x 7.5cm</td><td rowspan="5">Lock using volume of line Heparin 100units/ml</td></tr>
<tr><td>6.5Fr x12.5cm</td></tr>
<tr><td rowspan="2">10-20kg</td><td rowspan="2">Gam Cath</td><td>8Fr x 10cm</td></tr>
<tr><td>8Fr x12.5cm</td></tr>
<tr><td rowspan="2">>20kg</td><td rowspan="2">Gam Cath</td><td>11Fr x15cm</td></tr>
<tr><td>11Fr x 20cm</td></tr>
</table>

Heparin line lock MUST be aspirated and discarded before connection to patient.

8.2 Prior to connecting

Obtain baseline bloods: to include ABG, FBC, U+E, LFT, magnesium, phosphate, total calcium and clotting.

Check patient's electrolytes are within normal range. If any are low, consider replacing these prior to starting on CVVH/CVVHDF.

9. Setting up

9.1 Equipment required

- 50mL luer lock syringe for anticoagulation
- Giving set for administration of anticoagulant
- Syringe driver
- Anticoagulation: Heparin or Epoprostenol
- 3x 5 litre bag of Prismasol 4 or Hemosol BO (one for each scale)
- 1 litre bag 0.9% Saline with 2000 units of Heparin for 1st prime (if using an ST circuit)
- 1 litre bag Plasmalyte 148 for 2nd prime
- Ensure at least one adult unit of packed cells available
- Prismaflex/ PrisMax circuit - HF20/ST60/ST100/Oxiris
  - If patient requires less efficient treatment then a smaller circuit can be used, for more efficient treatment next size up filter can be used. Discuss with Paediatric Renal Critical Care Nurse prior to commencing.
  - If patient is on ECMO only use the ST circuits as blood flow from ECMO circuit is too fast for the HF20 circuits.

Circuit	Patient Weight (kg)	Extracorporeal Blood Volume (ml)	Machine Maximum Replacement Rate (ml/hr)	Machine Maximum Blood Pump Speed (ml/min)
HF20	<11kg	58	780	100
ST60	12-30kg	93	2250	180
ST100	>30kg	152	9000	400
Oxiris	>30kg	193	8000	450

Aseptic non-touch technique should be utilised when setting up and connecting the patient

9.2 Priming

Plasmalyte 148 is now the priming fluid of choice; this will be suitable for the majority of patients. If the patient has a high potassium level, 0.9% sodium chloride can be used instead. ST Circuits will initially be primed with Plasmalyte 148 and Heparin (2000 units of Heparin added to a 1 litre bag of Plasmalyte 148), then primed with a plain bag of Plasmalyte 148. The HF20 circuit will just need one prime without Heparin.

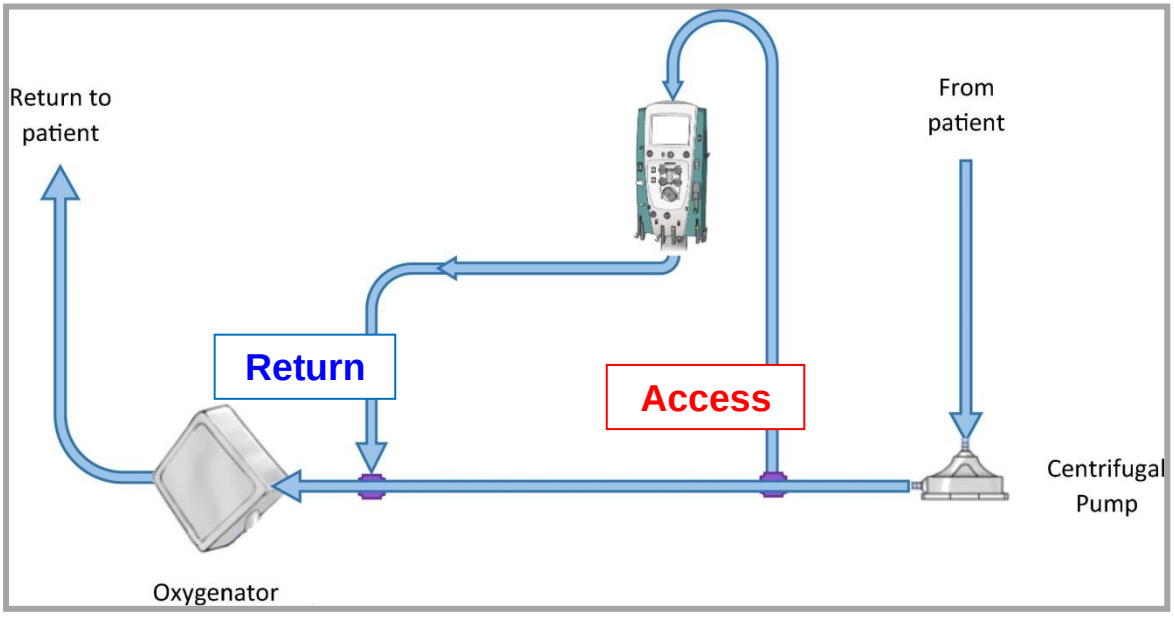
Circuit	If serum potassium <6mmol/l		If serum potassium >6mmol/l	
	1st prime	2nd prime	1st prime	2nd prime
HF20	1 litre Plasmalyte 148	N/A	1 litre sodium chloride 0.9%	N/A
ST60 & ST100	1 litre 0.9% Sodium Chloride with 2000 units heparin	1 litre Plasmalyte 148	1 litre Sodium Chloride 0.9% with 2000 units heparin	1 litre Sodium Chloride 0.9%

Blood priming should no longer be undertaken; if patient needs blood, give as transfusion prior to or alongside commencing treatment.

A 4.5% HAS prime can be considered if required, please discuss with consultant.

9.3 Connecting CVVH/CVVHDF circuit to ECMO circuit

Below diagram shows where to connect Access and Return lines, these should be connected using the pigtails on the ECMO circuit. This can only be done by ECMO trained staff.



10. Considerations during Therapy

10.1 Care and clinical monitoring of patient

- Continuous monitoring of cardiovascular and respiratory parameters should be undertaken.
- Ensure cardiovascular observations are recorded hourly on PCCU chart or half hourly depending on stability of patient.
- All patients who are receiving CVVH/CVVHDF should have central/peripheral temperature*, heart rate and arterial blood pressure and preferably CVP monitoring (*****central temperature does not have to be a rectal temperature).
- Fluid balance needs careful monitoring because of the large volumes of fluid being removed/infused. Weigh patient on daily basis if possible.
- There are inherent errors in all the measures of fluid balance therefore it is wise to assess the following factors before deciding upon the hydration status of the patient in relation to CRRT:
    - Fluid balance
    - Clinical examination (HR, ABP, CVP, CRT etc.)
    - Biochemistry
    - Haematocrit
    - Weight (if possible)

Always treat the patient NOT the machine

10.2 Temperature control

As the patient's blood is removed from their body and pumped through the circuit it significantly cools down so it is essential that a blood warming device is used during treatment.

- If patient is also on ECMO no further heating of the circuit is required
- The Prismacomfort sleeve heater (Barkey) should be set 1-2^{o}C above the desired patient temperature and attached to the Return line.
- As the heater sleeve covers the Return line it is essential that a portion of the line is left exposed next to the patient's catheter so any air will be visible.
- Consider using heater wires on both the Return and Access lines if the patient is a low weight baby and not on ECMO
- If using the PrisMax, the Prismacomfort should be used for HF20 circuits and the TherMax used for ST circuits. The TherMax should be set at 37 ^{o}C.
- Additional warming devices may be required (e.g. overhead heater, Bair hugger).
- Close monitoring of the patient's temperature is paramount.
- Beware of the heater masking pyrexia.

10.3 Pharmacokinetics

Drug removal by haemofiltration/haemodiafiltration depends on molecular weight, albumin binding, water solubility and volume of distribution, therefore some drugs handling properties are changed by the therapy. Filtration will remove non-protein bound, water soluble drugs, which are available in the circulation. Adding dialysate flow will cause more efficient drug removal by diffusion. Drug dose changes should be checked with literature (in drug information folder) and a pharmacist.
*Contrast is efficiently removed by filtration
*IVIG does not pass through the haemofilter most commonly used on PCCU

10.4 Blood sampling frequency

This specifies the minimum frequency, but will be dictated by patient's clinical condition.

Test	Frequency	Special notes
Arterial blood gas	4 hourly	Carry out initial gas 1 hr after treatment commenced. Particular attention to; pH, lactate, bicarbonate, sodium, potassium & blood sugar.
FBC	Daily	Consider wash back if Hb is low.
U&E's	4 hourly on ABG 12 hourly in labs	If using Prismasol 4 fluid remember to gradually discontinue potassium in maintenance, infusions & supplements.
Clotting	Every 12hrs	Increase frequency if on Protein C or Antithrombin III.
Other electrolytes	Calcium, Magnesium & Phosphate 12 hourly	These are slowly filtered out.

11. Septic Patients

11.1 Transmembrane Pressure (TMP)

TMP is the hydrostatic pressure gradient across the filter membrane i.e. the difference in pressure between the blood compartment and the dialysate compartment. This is the driving force that causes ultrafiltration. A rise in TMP suggests that there is clogging occurring in the filter. This is a natural occurrence during treatment and can occur more frequently in septic patients, thought to be due to the adsorption of inflammatory markers to the filter membrane. Unfortunately once the TMP starts to rise there isn't much that can be done to resolve the issue. Making the Prismaflex/PrisMax work less by reducing the patient fluid removal or replacement rate may stop TMP rising too quickly but this will mean treatment is less effective. So ultimately the only solution is to electively stop treatment and set up a new circuit.

11.2 Oxiris Circuit

In septic patients who require fluid and uremic toxin removal, an Oxiris set should be used. This set is intended for patients with excessive endotoxin, cytokine and inflammatory mediators and can be used in both CVVH and CVVHDF. Due to the adsorption properties of the set, it should only be in use for up to 72 hours, at which point it should be changed electively. This can either be for another Oxiris set if further blood purification is required, or for a standard ST set if inflammatory mediators have been reduced but further uremic toxin removal or fluid/electrolyte management is required.

12. Potential problems whilst undergoing treatment

12.1 Cardiovascular instability

This normally occurs as patient is being commenced on treatment. It can be more common in patients who are already unstable e.g. septicaemia, however patients who are 'stable' may also develop instability when commencing treatment.

Action: Ensure emergency drugs and fluid boluses are drawn up prior to connection.
Consider the use of inotropes.

12.2 Hypernatraemia

Often occurs as a result of fluid restriction and excessive sodium intake e.g. in fluids and drugs. Haemofiltration replacement fluid itself contains approximately 140mmol/l, but sodium chloride 30% may be added to fluid bags if needed. See section 7.3 for more information.
Action: Minimise sodium intake in drugs, infusions and TPN.
Increase free water intake (water which does not contain electrolytes).

12.3 Hyponatraemia

May be present as part of fluid overload. When haemofiltration removes large amounts of fluid, the hyponatraemia may be worsened, as the fluid removed is plasma water (therefore has a high sodium content).
Action: Increase sodium intake and decrease free water intake.

12.4 Coagulation of circuit in a patient with Haemolytic Uraemic Syndrome. (H.U.S)

Despite a low platelet count and high dose heparin it may be very difficult to keep continuous therapies running.
Action: A combination of heparin and Epoprostenol may be a more effective form of anticoagulation. **NB** Epoprostenol will not affect ACT.

12.5 Emergency Disconnection

In some circumstances emergency disconnection is required such as lines have clotted, technical failure or evacuation of the unit. In these circumstances wash back of the patient's blood should be considered if possible. If time allows lines should be disconnected and CVVH/CVVHDF catheter flushed with sodium chloride 0.9% and locked with heparin (or at least flushed with sodium chloride 0.9% if time does not allow preparation and administration of heparin).

12.6 Cardiac Arrest

In the event of cardiac arrest while the patient is undergoing CVVH/CVVHDF treatment should be stopped and the line aspirated, flushed and locked as time allows. It may be an option to wash back the blood in the circuit to the patient, if deemed necessary. In some circumstances continuing filtration may be appropriate (e.g. if being used for life threatening electrolyte disturbance like **Hyperkalaemia**). Haemofiltration catheters are central venous access and can be used instead of standard central lines in an emergency.

13. Supporting References

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14. Education and Training

All PICU nursing staff caring for patients receiving CVVH & CVVHDF are required to be trained in line with this extended role. Initial training session and ongoing training will be provided.

15. Monitoring Compliance

None

16. Key Words

Acute Kidney Injury (AKI), Anticoagulation, Dialysate, Fluid balance, Electrolyte, Extra Corporeal Membrane Oxygenation (ECMO), Prismaflex, PrisMax, Prismasol, Hemosol

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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.

17. Contact and review details

Guideline Lead (Name and Title)	**Executive Lead**
Nicole Justice – Paediatric Renal Critical Care Nurse Claire Westrope – Consultant PICU/ECMO Fiona Taylor – Senior Sister	**Chief Nurse**

Details of Changes made during review:
Major review and update undertaken 2024 – main changes as follows:
Contents moved to beginning of document
Addition of 'PrisMax' throughout document as new machine will hopefully be in use soon
Addition of 'Flow Rates: Special Considerations' section
Addition of time frame for ACTs – within 15 minutes of starting and 4 hourly thereafter
Contraindications and monitoring guidance added for Epoprostenol
Guidance added for considerations prior to commencing – Access
Equipment list added for set up
Addition of considerations for septic patients
Format updated

REQUIREMENT	ACTION
Where is the Policy available:	Within PICU in the CVVH/CVVHDF resource folder. UHL Intranet.
Copy to be sent to personnel with a request for inclusion in induction documents	No
Process for monitoring the effectiveness of this document	Will be audited internally.
Patient version.	No
Groups/persons consulted.	PICU Clinical Nurse Manager, PICU Educators, PICU Consultants, PICU Pharmacists, Nephrology Consultants
This Policy is subject to the Freedom of Information Act	