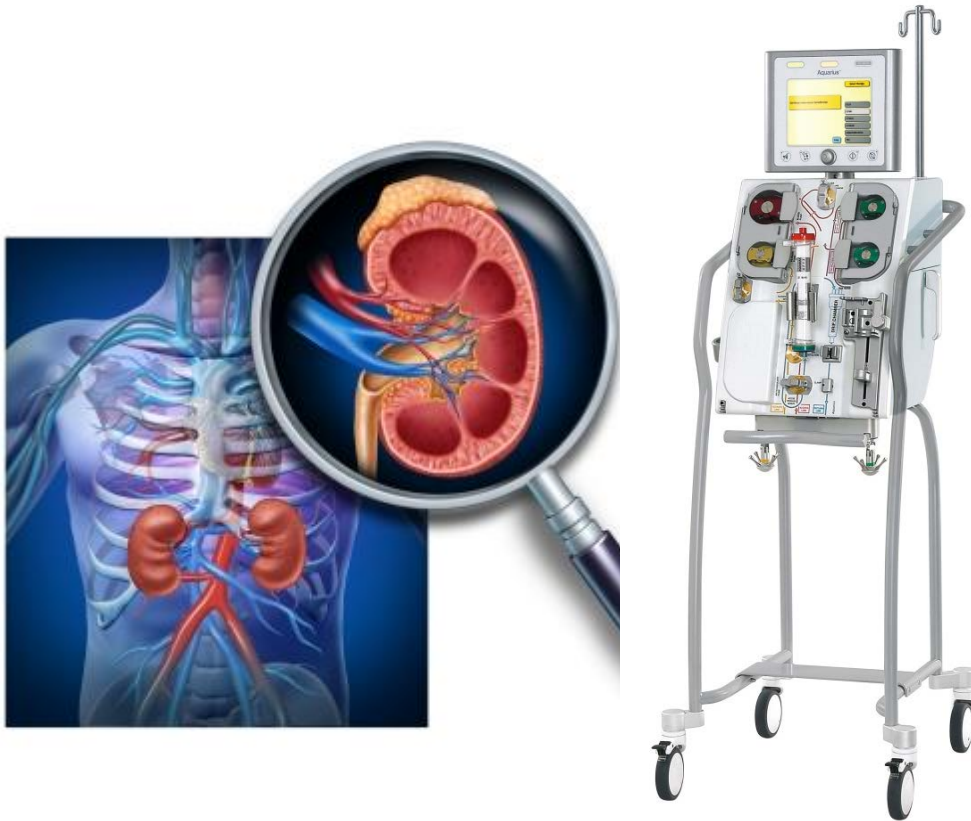




Aquarius Study Day Adult Pre-Reading Study Pack



An Introduction to CRRT (Continuous Renal Replacement Therapy)

Name.....

Date.....

Hospital.....

Please take the opportunity to read this booklet prior to attending the study day.

Anatomy and Physiology of the Kidney

The kidneys are two bean shaped organs, located just below the inferior boundary of the rib cage. Each kidney can function independently of the other and weighs approximately 110 – 170 grams and is about the size of a human fist.

The adult kidneys receive 1200 millilitres of blood (25% of cardiac output) every minute. That is 72 litres per hour or 1728 litres per day.

Normal kidney function is measured in terms of glomerular filtration rate (GFR). Normal GFR is typically 90-120 millilitres per minute. An estimation of Glomerular Filtration Rate (eGFR) can be calculated using the MDRD (Modifications of Diet in Renal Disease) formula developed by Levy et al (1999) that is based on age and serum creatinine.

The kidneys have several functions and Continuous Renal Replacement Therapy (CRRT) can only support some of these. The main functions of the kidneys are to maintain a normal balance of fluids, electrolytes, minerals and acid-base. It uses the following mechanisms continuously to preserve equilibrium and homeostasis.

- **Fluid balance** - Through ultrafiltration and reabsorption of water.
- **Electrolyte balance** - Through reabsorption and excretion of electrolytes.
- **Acid-base balance** - Through reabsorption and excretion of buffering ions.
- **Excretion of drugs and by-products of metabolism** - Nitrogen - Urea – Creatinine.

However, CRRT cannot replace other vital kidney functions:

- **Synthesis of erythropoietin** - Stimulates the bone marrow to produce healthy red blood cells and help them mature.
- **Regulation of blood pressure** - Secretes renin to help regulate blood pressure through the renin-angiotensin system. Renin promotes sodium retention and it also causes vasoconstriction.
- **Maintenance of calcium: phosphorus balance** - A normal ratio is 2:1 - The kidneys produce the active vitamin D and

regulate calcium - The kidneys are also the major excretor of phosphorus.

The Blood Pathways

Blood leaves the heart, enters the abdominal aorta and enters the kidney through the renal artery. The renal artery divides into seven branches of arterioles until it becomes the afferent arteriole. The afferent arteriole carries blood to the glomerulus, where it is filtered. It then leaves the glomerulus through the efferent arteriole, and is returned to the venous system. This system branches into many larger vessels until it becomes the renal vein. Blood leaves the kidney via the renal vein, and is returned to the heart via the inferior vena cava.

The Afferent and Efferent Arterioles

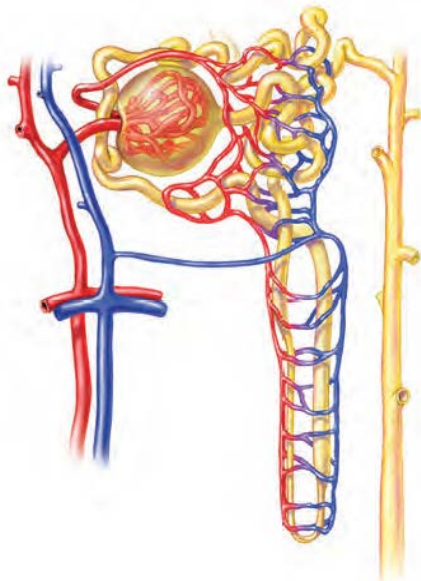
In the diagram of the glomerulus above, the afferent arteriole has a larger lumen than the efferent arteriole. Therefore, blood flows into the glomerulus faster than it flows out, which creates a pooling of blood in the Bowman's capsule. Hydrostatic pressure on the blood will force fluid to cross the glomerular membrane and enter the tubules. This is ultrafiltration. As filtrate flows through the tubular network, special cells will respond to the need for reabsorption and secretion.

Glomerular filtration

Blood flows through the afferent arteriole into the glomerular capsule. It is here that water and most solutes in plasma pass from blood across the wall of the glomerular capillaries into the glomerular capsule. Blood leaves the capsule via the efferent arteriole.

Components of the Kidney

The cortex (outer layer) contains 80% of the nephrons. These nephrons filter the blood continuously to maintain electrolyte balance. The medulla (inner layer) contains 20% of the nephrons. These nephrons also filter the blood, but have the added responsibility to concentrate urine. This becomes an important diagnostic tool in measuring the level of Acute Kidney Injury. The renal pelvis is the start of the collecting system, containing the collecting tubules and the ureter. Additionally, ureters carry urine into the bladder where it is stored until it is eliminated from the body through the urethra.



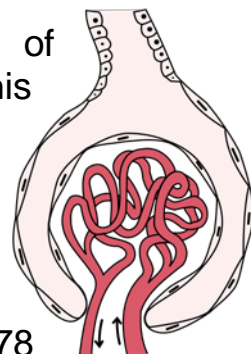
The Nephron

The functional unit of the kidney is called a nephron. Each kidney has about one million nephrons. Each nephron contains a glomerulus, which functions as an individual filtering unit. It also contains tubules for secretion and absorption of substances.

The Glomerulus

The glomerulus consists of a group of cells with selective permeability. This selective permeability means that certain substances will cross the

membrane and others will not be allowed to cross. Through selective permeability, the kidney regulates fluid and electrolyte balance. The kidneys produce approximately 180 litres of filtrate per day. Only 1.5 - 2 litres are excreted as urine. The remaining 178 litres remain in the body. This is simply recycled body water.



The main physiological processes in the nephron are:

Tubular reabsorption - This system returns most of the filtered water and many of the filtered solutes back to the blood. In fact, about 99% of the approximate 180 litres of filtrate is returned to the blood stream. Solute that are reabsorbed, both actively and passively include: sodium, potassium, chloride, calcium, phosphate, urea, bicarbonate, amino acids and glucose.

Tubular Secretion - As fluid moves along the tubule and through the collecting duct, waste products, (such as excess ions and drugs) are added into the fluid.

Try this quick revision! Fill in the missing words to complete the description.

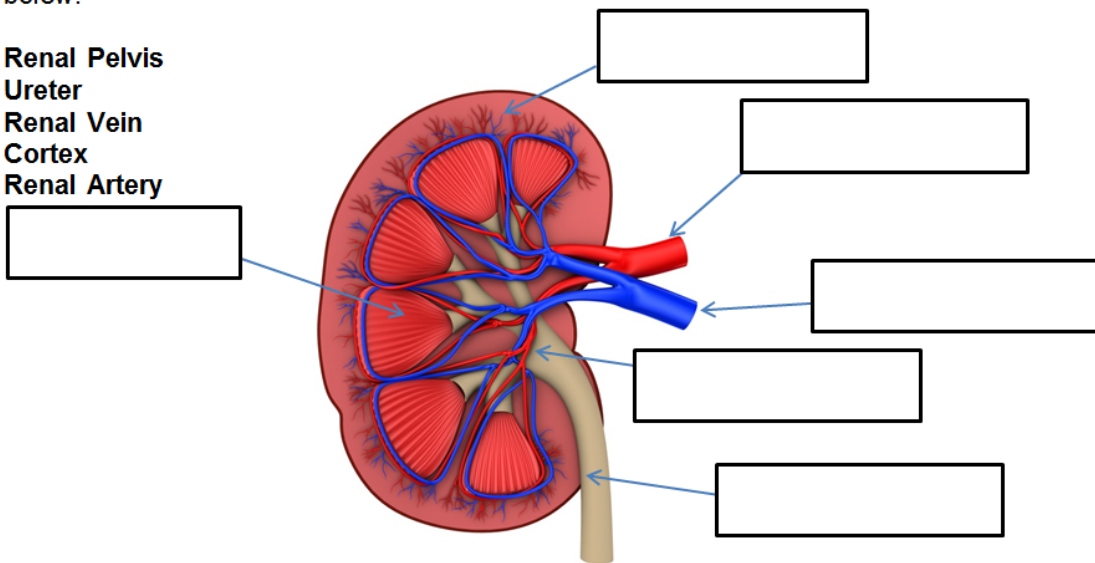
Blood enters the kidney from the _____. Then enters the nephron from afferent arterioles into the _____ (_____). This is a network of fine capillaries and acts like a sieve. Water, amino acids, salts, urea, creatinine and other waste products are forced out into the glomerular capsule using _____ pressure, by a process called _____. Large molecules cannot normally pass through, so remain in the blood system e.g. protein, red and white

blood cells. If these are found in urine it usually indicates a problem e.g. an infection. Blood leaves the capsule via the _____ arteriole. Some substances forced out need to be _____ back into the blood stream. Most of the reabsorption takes place in the _____ of _____.

Based on what you have just read, please complete these two diagrams.

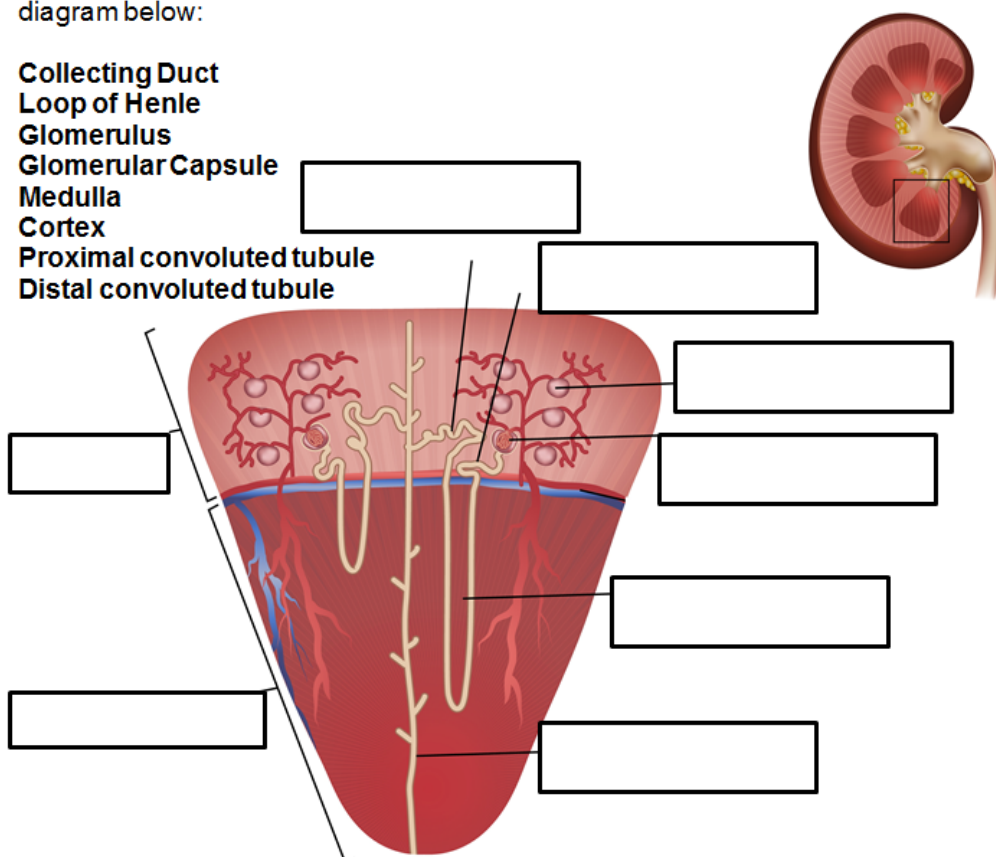
Insert these 6 words into the kidney diagram below:

- Renal Pelvis
- Ureter
- Renal Vein
- Cortex
- Renal Artery



Insert these words into the Nephron diagram below:

- Collecting Duct
- Loop of Henle
- Glomerulus
- Glomerular Capsule
- Medulla
- Cortex
- Proximal convoluted tubule
- Distal convoluted tubule

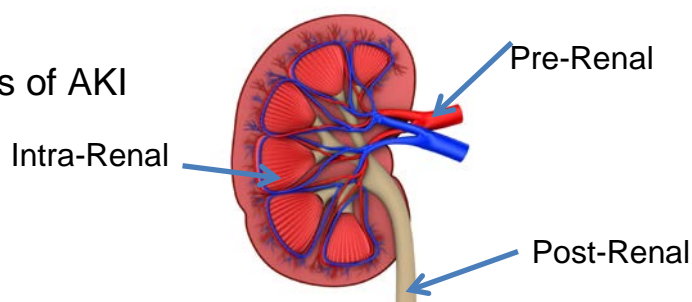


Acute Kidney Injury (AKI)

Acute Kidney Injury (AKI) results from the sudden loss of kidney function. In the setting of critical care patients Jefferson et al (2007) defined it simply as “an abrupt decline in glomerular filtration rate.” There is no universally accepted definition of AKI and definitions continue to evolve, aided by a series of tools which help identify an emerging AKI from **RIFLE (2004)**, through **AKIN (2007)**, to **KDIGO (2012)**

For the most current information, please refer to **NICE Guideline 169 (2013)** <https://www.nice.org.uk/guidance/cg169>

Three classifications of AKI



Pre-renal Failure - The most common form of ARF in an ICU environment, Pre-renal failure typically results from decreased blood flow to the kidneys. The reduction in glomerular filtration enables the solutes in the blood to accumulate but does not cause any structural damage to the kidney itself. Examples of situations leading to pre-renal failure may include dehydration, haemorrhage, congestive heart failure, sepsis, and embolism/thrombosis.

Intra-renal Failure - Intra-renal failure typically involves direct injury to the kidney itself. The most common cause is acute tubular necrosis (ATN). Some causes of ATN are ischemia, hypertension, nephrotoxins and some systemic vascular diseases such as lupus. Potential nephrotoxins are amino glycosides, heavy metals, contrast dyes. Prolonged ischemia in the kidney will cause intra-renal failure as well.

Post-renal Failure - In post-renal failure, the underlying cause is typically a bilateral obstruction below the level of the renal pelvis and may be due to tumour development, thrombi, urinary tract obstruction, or hypertrophic prostate. The kidney is capable of maintaining the body's equilibrium until about 50% of the nephrons are damaged. After 50% loss of kidney function, the body begins to make trade-offs to maintain homeostasis. After 90% loss of kidney function, some form of CRRT or intermittent haemodialysis is necessary to preserve life.

Indications for CRRT

An AKI combined with:

- Haemodynamic instability (cardiovascular)
- Severe fluid overload unresponsive to diuretics
- Hypercatabolic states/trauma - rhabdomyolysis
- High fluid requirements (nutrition, blood products)

Non-renal indications:

- Sepsis Lactic acidosis and acid-base disturbances
- Acute respiratory distress syndrome (ARDS)
- Multiple organ dysfunction score (MODS)
- Chronic congestive heart failure (CHF), or decompensated CHF Pre- and post-cardiovascular surgery / coronary artery bypass graft (CABG)
- During extracorporeal membrane oxygenation (ECMO) for fluid management.

CRRT can be modified at any time of the day and night to allow adaptation to the rapidly changing hemodynamic situation of critically ill patients. CRRT therapy indications may be renal, non-renal, or a combination of both. It is the treatment of choice for the critically ill patient needing renal support and/or fluid management.

CRRT therapy goals!

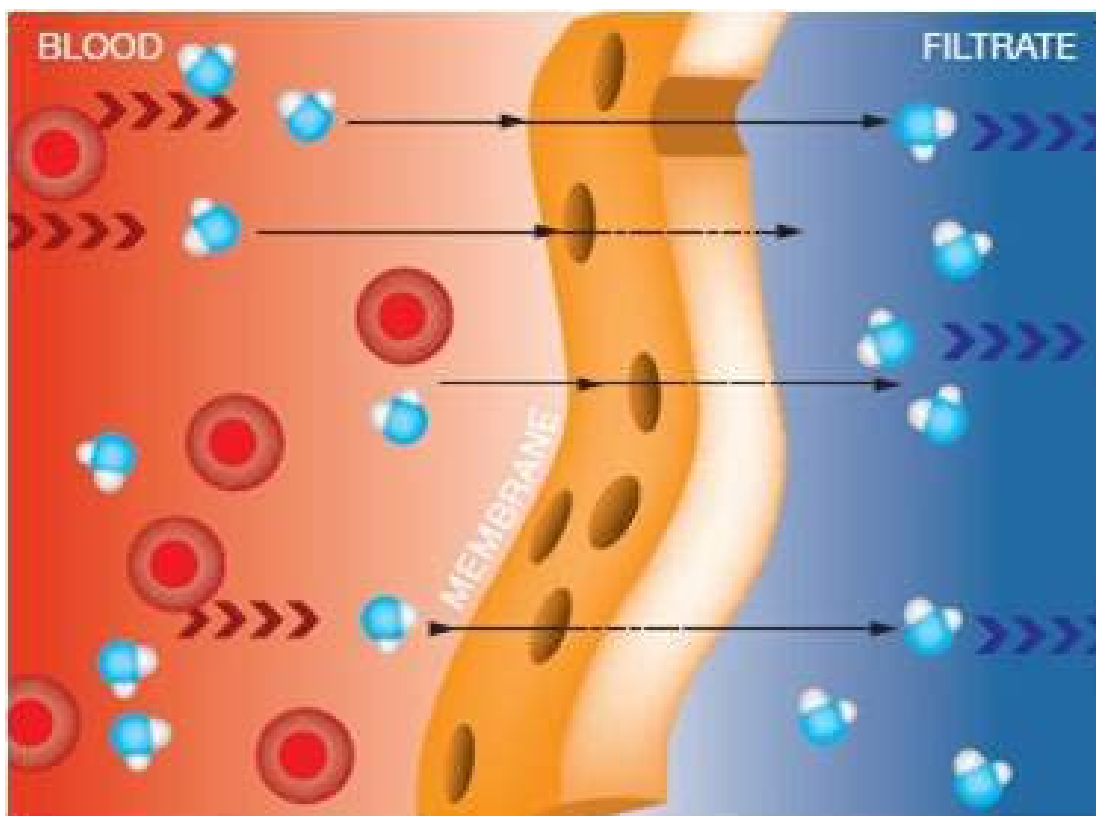
All CRRT therapies have as their goal the removal of additional water and cleaning of the blood...but ...How do we actually do this? The Aquarius uses the transfer mechanisms of **ultrafiltration**, **diffusion**, **convection** described in the following section; Plasma water only is removed by **ultrafiltration**, wastes are removed from the blood by **diffusion** and **convection** through the filter membrane.

Notes:

Ultrafiltration

Ultrafiltration can be defined as: 'the movement of fluid across a semi-permeable membrane with a hydrostatic pressure'. Positive pressure is generated on the blood side of the membrane and negative pressure is generated on the fluid side. Compare this with the process within the glomerulus...

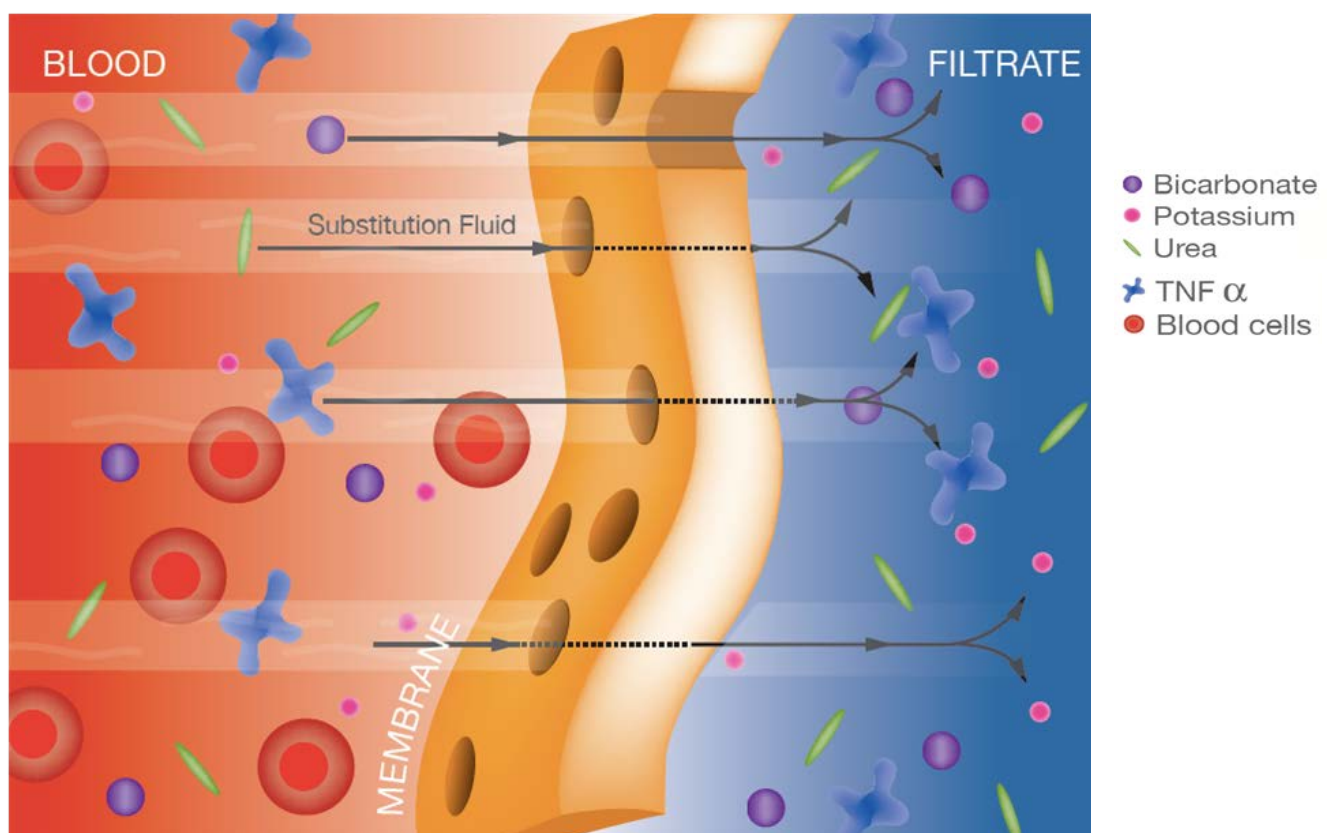
This gradient, positive to negative, influences the movement of fluid from the blood side to the fluid side; this can then be removed by the filtrate pump and placed in the waste bag. Minimal solute clearance happens by convection during ultrafiltration. Ultrafiltration is found in **SCUF** and **CVVH**.



Notes:

Convection

Convection can be defined as; 'the movement of fluid across a semi-permeable membrane creating a solute drag'. Pressure difference between the blood and ultrafiltrate causes plasma water to be filtered across. This causes solvent drag for small and large molecules across the membrane leading to their removal from the blood. The ultrafiltrate containing the solute should be replaced by substitution solutions. Convection is an **active** transport mechanism, its solute clearance being predictable for a given amount of therapy. Simply put, the faster the substitution fluid flow rate, the better the solute clearance. Convection is found in **CVVH** and **CVVHDF**.

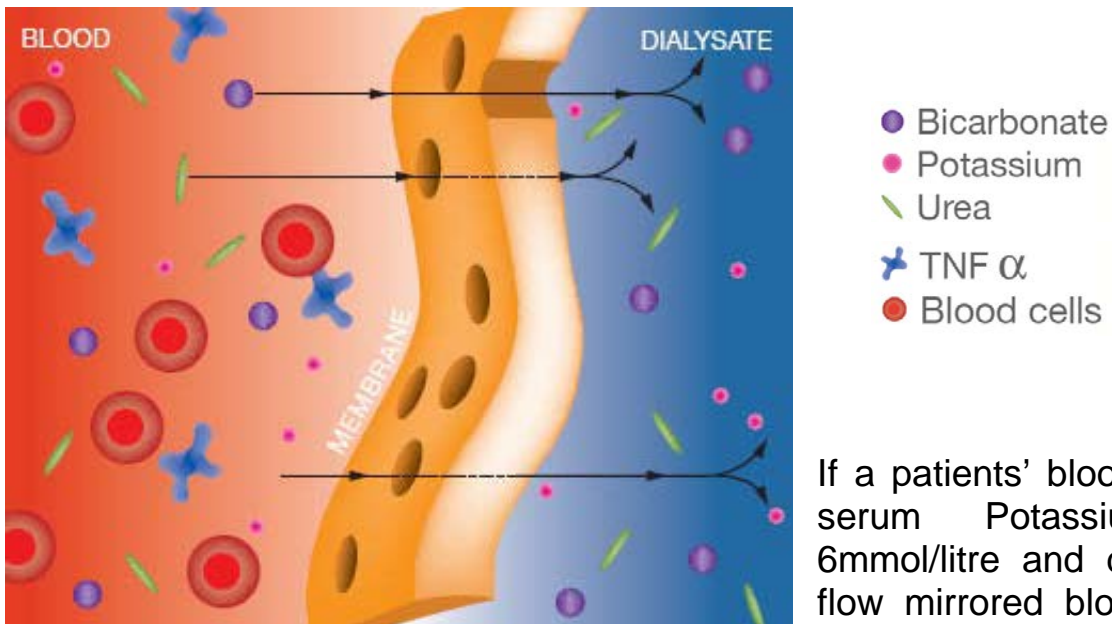


The solute (waste) transport is directly proportional to the solvent (plasma water) transport (the solvent transport in turn, depends on the pressure gradient) and permeability (pore size) of the membrane. Solute clearance overall with convection is affected by amount of ultrafiltration, solute concentration in plasma, and sieving characteristics of the membrane for the solute.

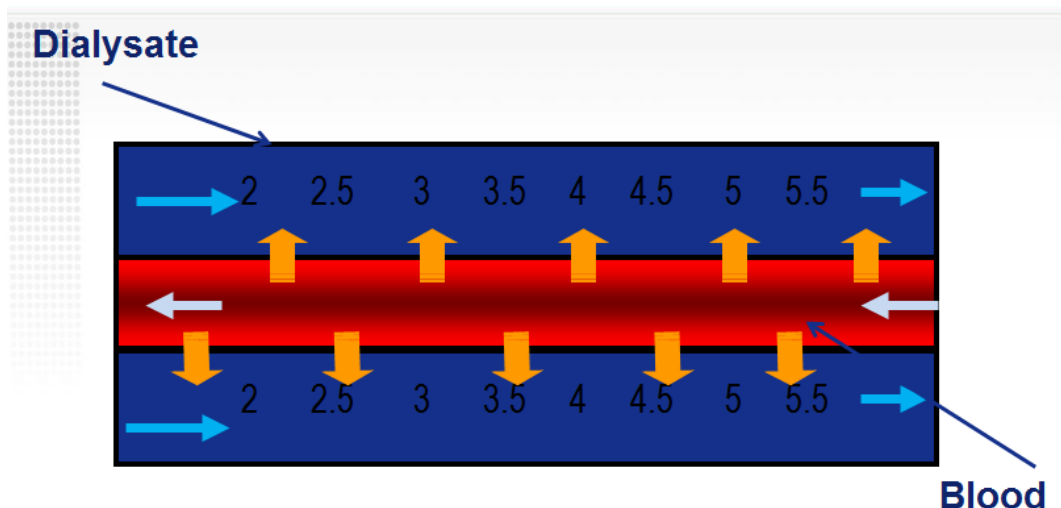
Diffusion

Diffusion can be defined as; 'the movement of solutes across a semi-permeable membrane through a concentration gradient'.

Diffusion occurs when blood flows on one side of the filter membrane, and dialysate solution flows counter-current on the other side, the dialysate does not mix with the blood. Diffusion is a passive transport mechanism, less predictable than convection in its solute clearances and limited in its larger molecule clearance, but still remains useful for moving smaller sized molecules. Diffusion is found in **CVVHD** and **CVVHDF**.



If a patients' blood had a serum Potassium of 6mmol/litre and dialysate flow mirrored blood flow, Urea would move from the blood to dialysate until the concentration gradient equalises, 3mmol/litre on either side of the membrane. All dialysers therefore use the counter-current (dialysate flowing in the opposite direction to blood flow, see below) the principle being to extend that concentration gradient and allow diffusion to occur along the full length of the filter membrane.

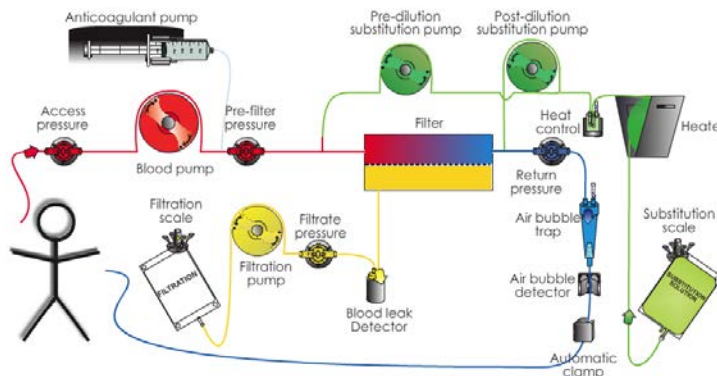


Continuous Veno-Venous Haemofiltration (CVVH)

Hemofiltration employs both **convection** and **ultrafiltration**.

Plasma water (filtrate) is removed from the patient's blood by convection, 'dragging' with it small and middle sized solutes. This 'water' is then replaced with clean fluid, either before the filter (pre dilution) or after the filter (post dilution).

The ultrafiltrate containing the solute should be replaced by substitution solutions which must be sterile, and have near physiological levels of electrolytes and buffer.



Primary therapeutic goal: Solute removal and management of fluid volume

Primary clinical indications: Uraemia, severe acid/base or electrolyte imbalance

Removal of larger molecular weight substances required

Principle used: convection

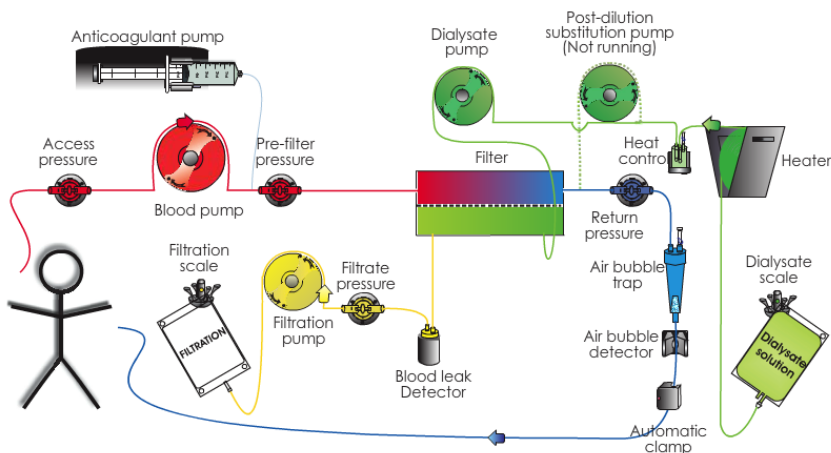
Therapy characteristics: Requires substitution solution to drive convection

Effective at removing small, medium, and large molecules.

Continuous Veno-Venous Haemodialysis (CVVHD)

Haemodialysis employs **diffusion**. Dialysate fluid is circulated through the haemofilter to create a concentration gradient between the patients' blood and the dialysate. Small solutes can diffuse from the blood to the dialysate solution or from the solution to the blood.

Primary therapeutic goal: Solute removal and management of fluid volume



Primary indications: Uraemia, severe acid/base or electrolyte imbalance

Principle used: diffusion

Therapy characteristics: Requires dialysate solution to drive diffusion

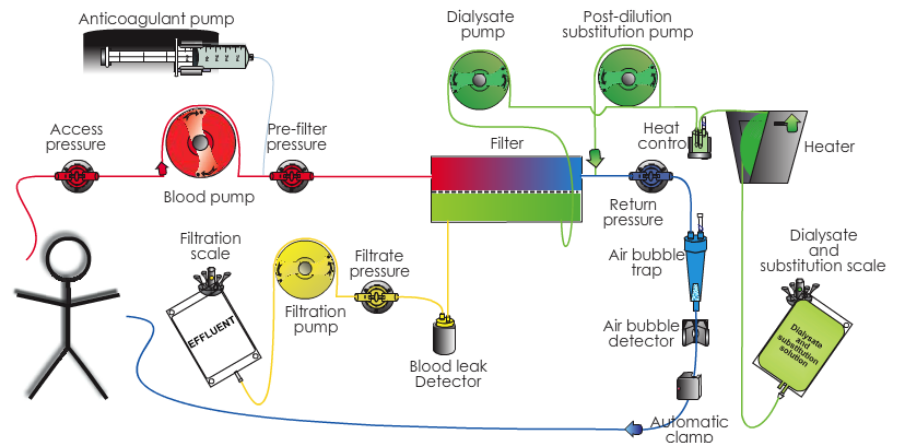
No substitution solution

Effective at removing small to medium molecules.

Continuous Veno – Venous Haemodiafiltration

Haemodiafiltration employs both **diffusion** and **convection**.

Therefore, some fluid and solutes are removed by convection and then replaced as post dilution. Fluid is also passed through the filter to create a concentration gradient for diffusion of solutes.



Primary therapeutic

goal: Solute removal and management of fluid volume

Primary indications: Uraemia, severe acid/base or electrolyte imbalance, Removal of large molecular weight substances required

Principle used: diffusion and convection

Therapy characteristics: Requires dialysate fluid and substitution solution to drive diffusion and convection

Effective at removing small, medium and large molecules.

Notes:

Dose Related CRRT

“How much treatment is appropriate to prescribe for each patient?”

In other words; **How do we calculate a correct programme for each person?**

Like many other treatments, CRRT dose is weight related, adjusted to patient body weight. The evidence base for dosing of CRRT began with a publication in the *Lancet*, a landmark study was carried out by **Ronco and Bellomo (2000)**. Their study looked at measuring improvements in **survival** rate and **recovery of renal function** after different doses of CRRT therapy. The outcome of this particular research was initially widely used to support therapy prescribing. In recent years **Palevsky et al (2008)** and **Bellomo et al (2009)** found during further research that there was no difference in survival between a prescription of 25 and 40 ml/kg/hr therapy dose as initially suggested. Even in a subgroup of sepsis patients, higher therapy doses (40 ml/kg/hr) appeared to have little impact on mortality.

Vesconi et al (2009) first produced research currently underpinning prescribing practice. The conclusions drawn from a large multi-centre observational study were that it is not the **prescription** dose; but the **delivery** to that patient that is key to understanding the therapy effect. They identified a significant difference between the prescribed dose and the delivered dose. Typically, therapy dose would be **prescribed** at **35 ml/kg/hr**, in practice the **delivered** therapy dose was on average **8ml/kg/hr less**.

It is now accepted and recommended that the **Prescription dose** should **exceed** that calculated to be **adequate** because of this. **Delivered dose** of therapy should be assessed to ensure the adequacy of the prescription. **Prescribed dose** of therapy should be assessed **daily** to account for any measured shortfalls in delivered dose

The **Acute Kidney Injury Network (2011)** recommends that patients with Acute Kidney Injury and/or multi-organ failure treated by continuous renal replacement therapy should receive a minimum:

A delivered therapy dose equivalent to ≥ 25 ml/kg/hr.

35ml/kg/hr programming for CVVH

Patient Weight	Total Exchange ml/Hr	Post-Dilution ml/Hr	Pre-Dilution ml/Hr	Min. Blood Pump (ml/min)	Filtration Ratio
< 50kg	1800	1100	700	180	10%
60kg	2100	1400	700	200	12%
70kg	2500	1800	700	220	13%
80kg	2800	1900	900	220	14%
90kg	3200	2100	1100	250	14%
100kg	3500	2400	1100	280	14%
120kg	4200	2800	1400	300	16%

‘Where do we give the substitution fluid into the filter circuit? Before (Pre) or after (Post) filter membrane? Does it make any difference?’

Pre-Dilution: Is where all the replacement fluid (treatment) is mixed with blood **before** the filter.

Advantages

- Prevents increases in haematocrit by diluting the blood.
- Reduced chance of clotting.
- Increasing membrane efficiency.

Disadvantages

- Decreased concentration of solutes being removed.
- Decreased clearances.

Post-Dilution: Is where all the replacement fluid (treatment) is mixed with the blood **after** the filter.

Advantages

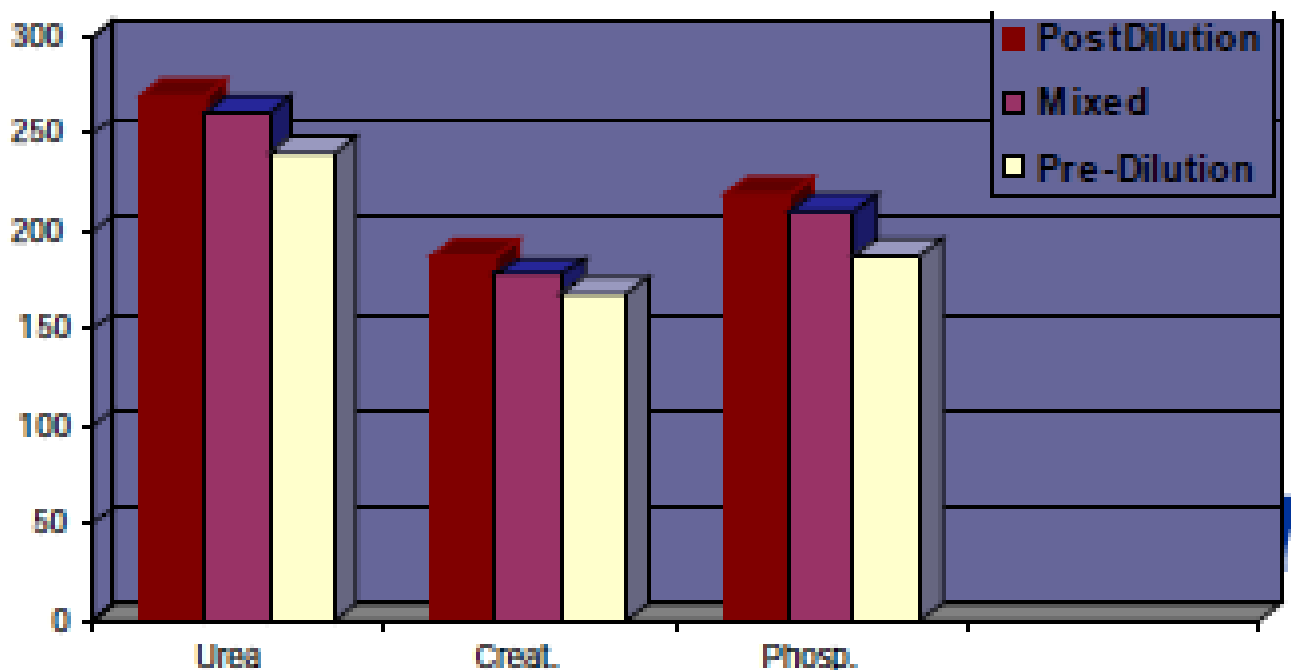
- Increased concentration of solutes being removed.
- Increased clearances.

Disadvantages

- Increases in haematocrit.
- Increased chance of clotting.
- Decreasing membrane efficiency.

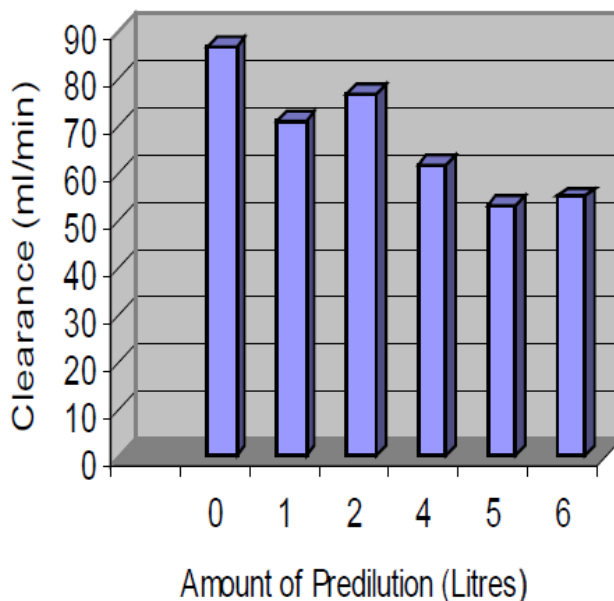
Exclusive Pre and Post dilution programmes have advantages and disadvantages. The Aquarius has the ability to do both at the same time.

How do we choose the proportions of Pre and Post dilution? Some of the evidence is as follows. Pedrini published research in 2000 looking at small molecule (Urea, Creatinin, Phosphorus) removal in a 6 litre exchange. The graph below shows clearances of small molecules using all pre, all post, and a 50:50 mix of both as a mixed therapy. Using both does indeed give a clearance between all pre and all post, but read on...



Bellomo (2008) looked at a controlled dose of Vancomycin clearance in a 6l exchange. Knowing how much Vancomycin was administered was a useful benchmark to measure clearance of middle molecules. Where Pedrini had used a 50:50 mix, Bellomo studied other combinations; 1litre pre/5 litres post, 2 litres pre/4 litres post and so on.

The increased clearance at a mix of 2 litres pre/4 litres post dilution achieved the best compromise of **both** clearance **and** extended filter life. Currently, a **one third** pre-dilution with **two thirds** post-dilution split may be used as a starting point.



Individual patient circumstances may guide ICU clinicians to choose **all predilution** where premature clotting of circuits is to be avoided (paediatrics), and **all post dilution** where aggressive clearance is paramount (poisonings).

As part of the more advanced training available on the study day, your clinical specialist will discuss ways in which pre and post dilution mix can be manipulated to achieve clinical outcomes.

Can you name three situations where pre and post dilution mix could be appropriately altered?

Notes:

Filtration Ratio

“What is filtration ratio?” a measure of haemoconcentration in the filter or **filtrate** removed as a **percentage of blood flow**.

Why is it important?...managing it well influences how long the filter lasts. As examples:

The **lower** the filtration ratio, the **longer** the filter may last. A blood pump speed targeted to a lower filtration ratio may also make the best of good access.

Consider how low blood pump speeds may adversely affect the filter.

Best practice aims for a Filtration Ratio between 10 and 25%

Notes:

References

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