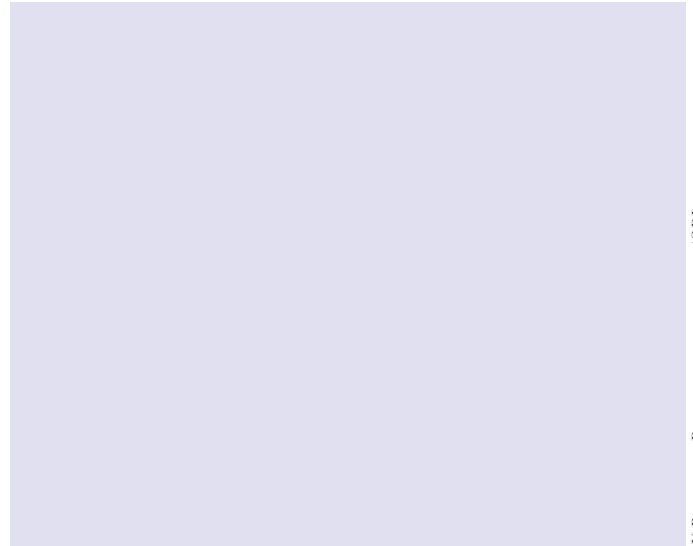


## RENAL FAILURE

## — options for renal replacement therapy

By CAROLINE ASHLEY, MSc, MRPharmS

*The second article in this month's special feature outlines the different types of renal replacement therapy available for patients with renal failure. Drug dosing in these patients is also summarised*



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A patient undergoes haemodialysis

**S**evere renal impairment (glomerular filtration rate <10 ml/min) or end-stage renal failure necessitates the initiation of some form of renal replacement therapy in order to remove the accumulated toxins and ameliorate the fluid overload caused by the lack of functioning kidneys. There are four types of renal replacement in clinical use:

- Haemodialysis
- Peritoneal dialysis
- Haemofiltration
- Haemodiafiltration

All methods of renal replacement therapy work by presenting blood to one side of a semi-permeable membrane and dialysis solution or pressure or both to the other side. The essential features of any treatment are:

- A semi-permeable membrane. This is either a synthetic membrane as used for haemodialysis or haemofiltration, or it is a natural membrane, for example, the patient's peritoneum. Synthetic dialysis membranes are packaged within an artificial kidney, which contains thousands of long, thin-walled tubes of

semi-permeable membrane, resembling a handful of straws, through which the patient's blood flows. Dialysis filtrate is formed in and removed from the spaces between the artificial kidney fibres

- A method of delivering blood to the membrane, ie, a pumped dialysis machine
- A method of delivering dialysis fluid and removing the excess water and waste products, for example, peritoneal dialysis catheter or pumped dialysis machine

Transplantation is considered to be a type of renal replacement therapy, but will not be discussed in this article.

## HAEMODIALYSIS

**H**aemodialysis is the traditional method of renal replacement, using a "kidney machine". It has revolutionised the outlook for patients with end-stage renal failure over the past 40 years. However, dialysis only partially replaces some aspects of renal function. Many of the co-morbidities associated with end-stage renal disease, such as accelerated cardiovascular disease, remain unaffected, and this contributes to the high mortality among these patients.

In the process of haemodialysis, blood is removed from the patient, passed across a semi-permeable membrane within the lumen of an artificial kidney, and returned to

the patient. Buffered dialysis fluid is perfused through the artificial kidney countercurrent to the direction of blood flow.

The dialysis fluid is produced by the dialysis machine mixing a prepared concentrate of electrolytes with deionised water. Contamination of water with chemical impurities carries significant risks. Aluminium is associated with osteodystrophy and encephalopathy, chloramines cause haemolysis, and bacteria and endotoxins cause febrile reactions and septicemia. Solute clearance is achieved principally as a result of diffusion down a concentration gradient between the blood and dialysis fluid compartments. Ultrafiltration, or removal of water, occurs by convection across the dialysis membrane, down a transmembrane hydrostatic pressure gradient. The effluent coming from the filter is a combination of dialysis fluid plus water and waste products removed from the patient. Modern dialysis machines use volumetric methods to regulate dialysis flow rates to and from the dialyser, allowing removal of a predetermined ultrafiltration volume. They also monitor the blood pathway, and if problems arise such as an occluded line or a sudden drop in the patient's blood pressure, the safety system activates a venous clamp and switches off the blood pump, thus minimising risk to the patient. Patients on maintenance haemodialysis therapy usually dialyse for between three and five hours, three times each week.

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**Haemodialysis access** In order to perform haemodialysis on a regular basis, a reliable method of attaching the patient's systemic circulation to the extracorporeal circuit of the dialysis machine must be established. The simplest and most efficient method is through the formation of an arteriovenous (AV) fistula. In this process, an artery and a vein are joined surgically in order to allow blood at arterial pressure into the venous system close to the skin surface. The walls of the "arterialised" vein dilate over a period of six to 12 weeks, and will then allow the repeated insertion of wide-bore needles. AV fistulae are usually created in the forearm of the non-dominant arm, although other sites are possible, for example, upper arm and thigh. A working fistula gives a "buzzing" sensation and care should be taken to avoid restricting blood flow in that limb.

For short-term rapid vascular access, or for those patients whose vasculature does not support the creation of an AV fistula, double lumen catheters are inserted into large central veins, usually the subclavian or internal jugular. However, as with all central venous cannulae, these carry a high risk of infection and require careful aseptic maintenance. Catheters intended for long-term use are usually tunnelled under the skin before entering the central vein. They have cuffs to facilitate anchoring and minimise the risk of infection. Since these catheters are prone to biofilm formation inside the body, they are kept patent between dialysis sessions by locking them with heparin. Urokinase and alteplase have also been used to maintain dialysis catheter patency. Catheter areas are maintained by swabbing with aqueous povidone-iodine or chlorhexidine solutions, and the application of povidone-iodine or mupirocin ointment to the skin exit site.

**Anticoagulation** Passing a patient's blood across a dialysis membrane will activate the clotting cascade, so in most cases patients undergoing haemodialysis will require anticoagulation. The main objective is to stop clots forming in the dialysis circuit while minimising the risks to the patient from abnormal bleeding. The choice of anticoagulant regimen will depend on the patient's own bleeding tendency and other risk factors such as the type of dialysis membrane used. Among the agents which may be used are heparin, epoprostenol, sodium citrate, low molecular weight heparins (LMWHs) and danaparoid.

Unfractionated heparin is the standard first-line agent, mainly due to its low cost and long-term safety record. The usual regimen is a loading dose followed by a continuous infusion for the length of the dialysis. A number of clotting tests may be used to monitor therapy, eg, activated partial thromboplastin time (APTT), kaolin cephalin clotting time (KCCT), and the regimen adjusted according to pre-set parameters.

LMWHs are now routinely used in a number of dialysis units. A single bolus dose at the beginning of dialysis is usually all that is required. They are often used in those patients where unfractionated heparin is causing problems, for example, thrombocytopenia or hair loss. However, efficacy is monitored by measuring Factor Xa levels, rather than APTT, so it can be difficult to optimise dosage. In addition, LMWHs are renally excreted, so will tend to accumulate in severe renal impairment, leading to an increased risk of bleeding. Their effects cannot be reversed by protamine, so the patient should be closely monitored.

Epoprostenol, or prostacyclin PGI<sub>2</sub>, has a number of important properties. It reduces platelet aggregation, acts as a potent vasodilator, is very short acting (<5 minutes) which permits rapid reversal if the patient starts bleeding, and it has no direct effect on the clotting cascade. It is specifically administered to patients at high risk of the complications of anticoagulation, for example, high risk of bleeding post-surgery or in liver failure, thrombocytopenia, and those for whom heparin is contraindicated.

Sodium citrate binds calcium in the blood. This impairs the clotting cascade and leads to an anticoagulant effect. The citrate is metabolised by the liver to reverse this effect, so its use may be a problem in patients with liver failure.

Danaparoid, a heparinoid, has been used on occasions. It is also renally excreted and has an extremely long duration of action in end-stage renal failure, so there are associated risks of haemorrhage which cannot be reversed by protamine.

## — PERITONEAL DIALYSIS

The peritoneum is the membrane that lines the abdominal cavity. It has a relatively large surface area (2–3m<sup>2</sup>) and an excellent capillary blood supply, so it is a natural semi-permeable membrane that can be used to perform peritoneal dialysis. This technique enables the removal of nitrogenous waste products and water from the body. Dialysis fluid containing an osmotic agent (usually glucose) is instilled into the peritoneal cavity via a Silastic catheter that has been surgically inserted through the abdominal wall (commonly used catheters are the Tenckhoff and the Oreopoulos). Fluid is removed from the body by ultrafiltration by means of an osmotic pressure gradient. Solutes cross the peritoneal membrane by diffusion down a concentration gradient, from blood to dialysis fluid. Frequent changes of dialysate result in a high level of removal of both fluids and solutes. The higher the concentration of glucose in the dialysate, the greater the degree of fluid removal. The concentrations of glucose available in commercially produced peritoneal dialysis fluid range from 1.36 per

cent (weak), through 2.27 per cent (medium) to 3.86 per cent or 4.25 per cent (strong). An alternative osmotic agent is the starch derivative icodextrin (7.5 per cent).

There are several different peritoneal dialysis regimens, all of which are based on the essential cycle of fluid inflow, followed by dwell time, and then drainage.

Continuous ambulatory peritoneal dialysis is the simplest system. It consists of between three and five exchanges per day or approximately two litres each time. Most patients use the "disconnect" exchange system. A bag of warmed dialysis fluid and a drainage bag are attached to the peritoneal dialysis catheter each time. The old dialysis fluid and waste products are drained out of the abdomen, then the fresh fluid instilled in its place. Dialysate runs in and out under gravity and by capillary action. It remains in the abdomen between exchanges for between four and six hours. When the exchange is complete, the bags are removed, leaving the patient with just the end of the catheter.

Automated peritoneal dialysis requires a programmable machine to regulate inflow, dwell time and drainage. It is often performed at night over a period of 12 to 14 hours, leaving the patient free of dialysis during the day. Solute exchange can be increased by leaving fluid in the peritoneum during the day.

Tidal peritoneal dialysis is a variation on automated peritoneal dialysis, where the fluid is incompletely drained, and is then followed by a partial volume inflow. It is used in patients with slow drainage, or who experience pain on complete drainage.

Intermittent peritoneal dialysis is a hospital-based regimen in which a cyclor automates multiple short exchanges over 24 hours, twice a week.

Peritoneal dialysis has several advantages over conventional haemodialysis:

- It is technically relatively simple, so it can be performed at home or work by the patient themselves, once they have been suitably trained. Little or no special equipment is required, so peritoneal dialysis can be easily adapted to the patient's lifestyle.
- It provides continuous excretory function with steady-state biochemistry. The constant fluid removal results in less haemodynamic fluctuations which means it is often better tolerated than haemodialysis, especially in those patients with poor cardiac reserve.

However, it does also have some disadvantages:

- It is not as efficient as haemodialysis, and adequate excretory function often depends on the patient's residual renal function. Consequently it is not suitable for certain patients.

- The patient is at risk of developing peritonitis, due to the introduction of bacteria through the indwelling catheter. Recurrent bouts of peritonitis can damage the peritoneum, reducing the dialysis efficiency of the peritoneal membrane, until peritoneal dialysis becomes impracticable.
- The presence of the indwelling catheter may cause body-image or psychosexual problems.

Despite these problems, peritoneal dialysis is a safe, effective and well-tolerated form of renal replacement therapy.

## — CRITICALLY ILL PATIENTS

Traditional methods of renal replacement therapy such as intermittent haemodialysis and peritoneal dialysis are generally considered unsuitable for use in the critically ill patient. Intermittent haemodialysis involves a relatively large volume extracorporeal circuit, and produces rapid water and solute removal, which can aggravate cardiovascular instability in this group of patients. It requires specialised equipment and staff, while peritoneal dialysis is generally not sufficiently effective in correcting the uraemia seen in the hypercatabolic intensive-care patient. Furthermore, peritoneal dialysis requires the introduction of dialysis fluid into the peritoneal cavity, which can lead to other complications such as diaphragmatic splinting in patients who are receiving mechanical ventilatory support, and sepsis. Continuous haemofiltration and continuous haemodiafiltration are now routinely used in the management of cardiovascularly unstable patients with acute renal failure in the intensive care unit setting. As with haemodialysis, patients will need to have suitable vascular access established, and will need to be anticoagulated to maintain the patency of the filter.

## — HAEMOFILTRATION

Haemofiltration is the process of ultrafiltration and convection by which water and solutes (including drugs) are removed from the blood through a highly permeable membrane as pressure is applied. The rate of blood flow past the membrane generates the hydrostatic pressure which forces plasma water across the membrane, dragging various solutes with it. The solution produced is called ultrafiltrate or haemofiltrate. Large volumes of fluid need to be removed if solutes are to be cleared effectively from the plasma. Solute removal occurs largely by convection, as water-soluble molecules pass across the membrane along with the large volumes of ultrafiltrate.

There are two types of haemofiltration. Continuous arterio-venous haemofiltration

is a process of continuous ultrafiltration that removes between 10 and 20 litres of plasma water a day, most of which is replaced by a sterile isotonic physiological solution. The technique employs an arterial access (often the femoral artery) to provide the transmembrane pressure necessary to produce sufficient ultrafiltrate. The blood is returned through venous access. As filtration rates rely on arterial pressure, the patient's blood pressure must be stable and high enough to achieve adequate filtration.

Continuous veno-venous haemofiltration is similar, except that venous access is used both to remove blood from, and return it to the patient. Since venous pressure is lower than arterial pressure, a peristaltic pump is introduced in order to propel blood around the extracorporeal circuit. Ultrafiltration rates removing up to 50 litres of plasma water a day can then be achieved simply by increasing the speed of the blood pump. Additionally, a pump can be attached to the ultrafiltration line, and fluid sucked out of the extracorporeal circuit at a pre-set rate. The veno-venous technique is the most widely used method of continuous haemofiltration.

## — HAEMODIAFILTRATION

Similarly, there are two types of haemodiafiltration. Continuous arterio-venous haemodiafiltration is a process employing both continuous ultrafiltration and diffusion to remove water and solutes. It is a more complex process than haemofiltration, but better solute clearance is achieved. Access is again via an arterial line, with blood being returned to the patient by a venous line. However, in contrast to continuous arterio-venous haemofiltration, here dialysis fluid is introduced through the filter in a countercurrent direction to the blood flow in order to create a concentration gradient (between the blood compartment and the dialysate compartment) across the semi-permeable membrane, in the same way as in haemodialysis. Dialysis fluid is usually pumped through the filter at a rate of one to two litres per hour, depending on the patient's clinical condition. Increasing the rate beyond two litres per hour does not increase the efficiency of the system any further, but does significantly increase costs. Although the ultrafiltration rate achieved by this technique (5 to 10 litres per day) is considerably less than that seen during continuous arterio-venous haemofiltration, the infusion of replacement fluid is still required to maintain the patient's circulating volume.

The replacement fluids are crystalloid solutions, containing plasma electrolytes at levels similar to physiological ones. A buffer is required to replace bicarbonate

losses during filtration. Unfortunately, it is not currently possible to produce a stable solution containing enough bicarbonate, so sodium lactate is commonly used instead. It is assumed that the lactate is converted to bicarbonate in the liver. However, in patients with compromised liver function or liver blood flow, or those with multi-organ failure, the lactate can accumulate, thus aggravating an already existing metabolic acidosis. In this situation, lactate-free haemofiltration solution is employed, and bicarbonate 8.4 per cent is infused centrally, titrated to the patient's blood pH.

Continuous veno-venous haemodialysis (or Haemodiafiltration) is, to all intents and purposes, the same as above except that a venous access is used to remove blood from the patient, and an external pump is used to propel blood around the extracorporeal circuit.

### — DRUG REMOVAL BY DIALYSIS

Many factors are known to influence the removal of a drug by dialysis, but generally the most significant drug characteristics that favour drug removal are:

- Low molecular weight (substances with a molecular weight of <500 daltons are easily removed by dialysis, those with a molecular weight of up to 5,000 daltons have some degree of dialysability, and some of the high flux filters used for haemodiafiltration can clear molecules up to 20,000 daltons)
- Low percentage of drug bound to plasma proteins. Only unbound free drug is available to pass through the semi-permeable membrane.

- Low apparent volume of distribution (Vd). (Drugs with a small Vd may be highly polar and therefore more likely to remain in the circulation and so be available for removal by dialysis. Drugs with a large Vd are more likely to be lipophilic or highly protein or tissue bound, therefore not available for removal. As an approximate guide, if the Vd is <1L/kg there will be significant drug removal, whereas drugs with a Vd >2L/kg will have a low dialysability.)
- High degree of water solubility. (The more hydrophilic a molecule is, the more likely it is to remain in the plasma compartment, and therefore be available for removal by dialysis.)
- High degree of renal clearance in patients with normal renal function

In addition, several dialysis process characteristics also affect drug clearance, for example:

- The duration of the dialysis procedure
- The rate of blood flow through the artificial kidney
- The type of dialyser membrane used
- The flow rate and composition of the dialysis fluid

All these factors combine to determine the overall clearance of a drug by dialysis. It is usually possible to judge whether or not a drug will be significantly cleared by dialysis by examination of its pharmacokinetic parameters.

### — GUIDE TO EMPIRICAL DOSING

Drug clearance is the sum of the contributions made by a number of different routes of elimination, so that alterations to drug dosages need only be considered if

renal clearance exceeds 25 per cent of total body clearance. Many drugs have a fairly broad therapeutic index, so rigorous adjustment of doses in patients undergoing renal replacement therapy is not usually necessary. Only those drugs with a narrow therapeutic index, for example, aminoglycosides, require special attention. Prescribing becomes an empirical judgement based on knowledge of the type of therapy the patient is receiving, and the kinetic parameters of the drug in question. One way of making such a judgement, based on sound principles, is to dose the patient in accordance with the theoretical glomerular filtration rate achieved by that particular mode of renal replacement therapy, as summarised below in Table 1.

Given the estimated glomerular filtration rate for the particular mode of therapy, it is then a matter of searching the literature for relevant dosing studies, or using standard text books and "educated guesses" from pharmacokinetic data. For some drugs, renal patients will require the same loading dose as that given to those patients with normal renal function. Time to steady-state is four to five half-lives, and if the half-life is prolonged due to decreased renal clearance, this time to steady state will be much longer, hence the importance of the loading dose to achieve a therapeutic effect as soon as possible. To compliment this empirical approach to drug dosing, serum drug level monitoring is essential if the drug has a narrow therapeutic index. The patient should also be monitored for drug toxicity, and the dose should be adjusted according to response.

### FURTHER READING

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*Table 1: Dosing guide for renal replacement therapy patients*

Renal replacement therapy	Typical theoretical glomerular filtration rate (achieved during therapy [ml/min])	Dosage guide (based on classification of renal impairment from appendix 3 of BNF)
Haemodialysis	180-200 during dialysis (0-10 between dialysis periods)	Severe renal impairment. Dose routinely after haemodialysis session if it is known or predicted that the drug is significantly removed by dialysis
Continuous ambulatory peritoneal dialysis	5-10	Severe renal impairment
Haemofiltration	10-20	Average ultrafiltration rate <15ml/min — severe renal impairment Average ultrafiltration rate >15ml/min — moderate renal impairment
Haemodiafiltration	15-25	Moderate renal impairment