**Introduction**

Extracorporeal therapies (ECT) are those that occur outside of the body and are commonly used in many fields of human medicine; for example in supporting pulmonary function (e.g. extracorporeal membrane oxygenation), taking over full control of an organ system’s function (cardiopulmonary bypass (CPB)) and altering blood composition or removing toxins from the blood (e.g. dialysis and therapeutic plasma exchange (TPE)). Their use has allowed marked advances in patient care, improving the quality of life and life expectancy for many people. Extracorporeal therapies are a new and emerging field in companion animal veterinary medicine but are often only available in referral or experimental settings. Although there are many types of ECT this article will focus only on those most commonly employed in veterinary clinical medicine; dialysis, TPE and CPB. Dialysis and TPE can be used for various clinical indications which will be discussed later, whereas CPB is solely used at this time in veterinary clinical practice to enable open heart surgery. This short update is designed to provide an introduction to these three therapies, including the indications and benefits.

**General principles of extracorporeal therapies**

Extracorporeal therapies, by their nature, require a patient’s blood supply to flow through a synthetic circuit. Depending on the design of the extracorporeal circuit, blood may be drained from and returned to the venous circulation, drained from the venous circulation and returned via an artery, or it may be drained from an artery and returned via a vein. The sites of attachment to the ECT vary depending on the circuit, and the terminology can be confusing. The most common site used in veterinary haemodialysis and TPE procedures is the jugular vein. To this effect, cervical haematomas or severe localized dermatologic disease may make vascular access prohibitively difficult, making the therapy itself impossible. The most common cannulation sites for CPB include the right atrial appendage for venous drainage and the carotid artery for arterial return. A third cannula may be placed into the aortic root to deliver a solution to stop the heart for procedures that require this. For most ECTs patients require anticoagulation in order that blood flows freely without obstruction of the circuit or vasculature. This anticoagulation can be systemic (i.e. both the animal and the circuit are anticoagulated) or regional (i.e. only the extracorporeal circuit is anticoagulated). While it may increase risks associated with cannula placement, coagulopathy itself is not a contraindication to ECT. Some therapies (such as dialysis and plasma exchange) can be performed with the patient conscious or lightly sedated, whereas cardiopulmonary bypass mandates general anaesthesia (with a surgical approach). All extracorporeal therapies involve risks and many of these are procedure specific. The composition of the extracorporeal circuit itself (with respect to the composite plastic or silicone), and priming fluid used bring their own complications including alteration of plasma composition, and disruption to normal homeostasis of the inflammatory, coagulation, fibrinolytic and endocrine systems. Despite these risks, their routine use in human medicine has proven that with close monitoring and sufficient available resources, patients can undergo ECT with minimal complications.

**Dialysis**

Although classically considered a mechanism to reduce the concentration of renally excreted molecules in the blood, it may be more appropriate to think of dialysis as a mechanism to normalise the composition of blood. This allows the concentration of many substances (not simply urea, creatinine and potassium) to be decreased or increased as clinically indicated. Dialysis also allows the removal of excess fluid from the patient, which is often needed in cases of anuric AKI. Furthermore, some intoxications lend themselves to removal by dialysis, so it can be indicated even in patients with normal renal function.

There are many forms of dialysis (see Box 1), and all but peritoneal dialysis require the use of an extracorporeal circuit, therefore we will limit our discussion to haemodialysis. Dialysis performed using intravascular catheters and an extracorporeal circuit is termed haemodialysis and utilises two main principles of dialytic clearance - convection and diffusion (see Box 2). The main difference between the forms of dialysis using extracorporeal circuits are the length and intensity of the treatments themselves. In the USA, dialysis is performed for patients with both acute and chronic renal disease. This is in contrast to the UK, where dialysis is only currently performed in patients with acute kidney injury (AKI).

**Box 1 – Different types of dialysis**

**Peritoneal dialysis** uses the peritoneum as a dialysis exchange surface. A peritoneal catheter is placed and fluid instilled into the abdomen to equilibrate with the blood over a predetermined ‘dwell time.’ The composition of the instilled fluid, along with the number of times it is changed are part of the prescription, and are determined based on the desired intensity and goals of the treatment.

**Haemodialysis** is any dialysis therapy in which the extracorporeal circuit is utilised to provide an interface between the blood and dialysate, the common forms of haemodialysis are described below.

**Continuous renal replacement therapy** is a low intensity, ‘round the clock’ therapy often used to augment renal function in long term ICU patients.

**Intermittent haemodialysis** is often a shorter, intensive treatment performed several times per week and is most often used for long term management of chronic renal disease in humans, cats and dogs (this is not currently offered for animals in the UK).

**Prolonged intermittent renal replacement therapy (PIRRT)** is a hybrid of the two previous treatments, being a medium intensity therapy that is administered over many hours (6-12) and is often repeated every few days.

**Box 2 – Convective and diffusive clearance**

**Convective clearance of a substance** is achieved by generating pressure across a membrane, forcing fluid through the membrane. This fluid movement “drags” some solutes with it to allow removal from the body. No concentration gradient is required.

**Diffusive clearance** is obtained by pure diffusion between blood and dialysate on opposite sides of the membrane. Efficiency of removal will vary with the concentration gradient of the substance between the blood and the dialysate. The blood and dialysate often flow counter-currently to enhance the efficiency of the diffusive process.

Commonly used patient pre-requisites for performing dialysis are shown in Box 3. In rare circumstances, patients that do not meet these can still undergo dialysis, however this would be decided on a case-by-case basis. As dialysis in the United Kingdom is only currently undertaken for severe AKI, the indications are often quite specific (see Box 4). Toxicologic indications also exist (Box 5) however the timeframe from patient exposure to the instigation of therapy can mean dialysis may not always be suitable.

**Box 3 – Patient prerequisites for haemodialysis/therapeutic plasma exchange at the authors institution**

Patients who may be candidates for dialysis/plasma exchange would ideally have:

A good temperament to permit the intensive care required

Absence of dermatalogical disease over the cervical region

One readily accessible jugular vein (i.e. no haematomas or phlebitis) to permit dialysis catheter placement

Body weight over 5kg (in cats)

**Box 4 – Indications for haemodialysis**

Chronic kidney disease with severe reduction in quality of life (not available in the UK at this time)

Acute kidney injury that is not responsive to appropriate conservative management, eg. with oligoanuria (confirmed absent or rapidly declining urine output) and worsening azotaemia

Severe hyperkalaemia or other electrolyte abnormalities that are refractory to medical management

Life threatening volume overload

Acute toxicity with a life-threatening toxin that can be removed using dialysis (such as ethylene glycol)

**Box 5 – Common toxins that are considered amenable to haemodialysis or therapeutic plasma exchange (Harbord et al. 2019; Madore & Bouchard 2019; Rosenthal & Labato 2019)**

Amanita toxicity (refractory)

Aspirin (refractory)

Barbiturates

Calcium channel blockers (diltiazem, verapamil)

Ethylene glycol (if started within 2-4 hrs of exposure)

Methotrexate

Non-steroidal anti-inflammatory drugs

Vincristine (if started within 2-4 hrs of exposure)

**Case 1 – Rolex, 7mnth old MN English Bulldog (Figure 1)**

Presentation – Rolex was presented with azotaemic, anuric AKI with hyperkalaemia. He had multiple precipitating factors for his AKI including general anaesthesia, non-steroidal anti-inflammatory drug use and iatrogenic prostatic urethral injury during cryptorchid castration.

Treatment – After failing to respond to medical management, Rolex underwent a single cycle of prolonged intermittent renal replacement therapy. Within the twelve-hour period following this therapy, his urine output began to markedly increase (reaching 12ml/kg/hr) and his azotaemia began to improve.

Outcome – Rolex was discharged from the hospital with normal renal parameters, and his owner reports he has continued to do well ever since.

**Therapeutic plasma exchange**

Therapeutic plasma exchange (TPE) is a procedure to separate plasma from the cellular portion of blood, discard the plasma, and then replace it with a substitute fluid (Figure 2). It can be accomplished either using centrifugal or membrane-based separation of the blood components. Centrifugal TPE is performed by withdrawing blood (from a central venous catheter), applying a centrifugal force, and filtering off the plasma; this can be performed continuously by attaching the patient directly to an automated centrifugal system using an extracorporeal circuit, or intermittently by manually removing blood from the patient, placing it into the machine for processing, and re-infusing this to the patient. Intermittent centrifugal TPE (Figure 3) can be performed with a single central venous catheter but depending on the machine used it can be more labour intensive than both continuous centrifugal and membrane TPE. The benefits of intermittent centrifugal TPE are that the extracorporeal circuit is not attached to the patient and there is no risk of severe haemodilution from the amount of fluid needed to prime the machine; as such it can be used in smaller patients. Membrane TPE (Figure 4) uses a circuit similar to dialysis, with the patient continually attached and blood flow occurring at all times. Irrespective of the method used, TPE can often be performed within 2-3 hours and at the authors institution is most often used to non-selectively remove plasma proteins (including albumin and immunoglobulins) which are then replaced using donor frozen plasma.

As both types of TPE remove plasma proteins this can be a very useful treatment for diseases in which plasma proteins play an integral role, such as immune mediated haemolytic anaemia, acquired myasthenia gravis (a longer list is provided in Box 6) and various protein bound toxins (Box 5). The utility of the therapy is determined in part by the distribution of proteins between the vasculature and tissues. Some immunoglobulins (such as IgM) are almost totally retained within the vasculature (only around 20% of IgM is within the tissues) and thus TPE is extremely effective for IgM mediated disease. In contrast, IgG is less localized to the bloodstream (around 40-60% is present in the tissues) which may lead to a rebound period after treatment for IgG mediated diseases as immunoglobulins within the tissues redistribute into the vascular tree. For this reason, some diseases and intoxications may require more than one session of TPE to be effective.

**Box 6 – Select diseases in which therapeutic plasma exchange may be beneficial**

Immune mediated haemolytic anaemia

Immune mediated thrombocytopaenia

Severe myasthenia gravis

Cutaneous and renal glomerular vasculopathy\*

Severe hyperbilirubinaemia with kernicterus

Acute toxicity with a protein-bound toxin

\*There is currently very little evidence for a benefit of TPE in these patients, however unpublished work at the authors institution does indicate a trend towards improved survival if used early in the disease course.

One disease worth discussing is cutaneous and renal glomerular vasculopathy (CRGV). The cause of CRGV is as yet unknown and thus optimal treatment is also unknown. A phenotypically similar set of diseases (thrombotic microangiopathies) are often treated with TPE in humans, and thus the authors offer TPE in select cases of CRGV. There is some evidence for efficacy of this treatment so far (Skulberg et al. 2018) and further unpublished work at the author’s institution also suggests a trend towards a survival benefit from TPE. Although the use of TPE for CRGV is promising, it is not considered a cure. Patients with CRGV had died despite treatment with TPE, and it is unclear if earlier treatment or more frequent therapies would change this outcome. The authors currently offer early treatment as in our experience when severe renal disease is present (such as anuria) the outcome with or without treatment is grave.

**Case 2 – Monty, 5 year old MN Cocker Spaniel (Figure 5)**

Presentation – Monty presented with ulceration on his feet and tongue, a short history of vomiting and diarrhea, marked azotaemia, oliguria and thrombocytopaenia. Based on his clinical signs and progression Monty was diagnosed with CRGV.

Treatment – After a multidisciplinary team discussion, it was decided to perform TPE due to progressive worsening of his renal values. Monty underwent 3 cycles of TPE over the course of one week. Regional citrate anticoagulation was used, meaning the blood within the ECT was unable to clot due to marked hypocalcaemia, but Monty’s systemic ionized calcium was maintained within normal limits by calcium gluconate infusion, to reduce his risk of bleeding. In total, 9 units of fresh frozen plasma were used to replace the plasma proteins removed from his blood. After 9 days in the ICU Monty was discharged home clinically well but with a persistent azotaemia, in the recovery phase of his AKI.

Outcome – Thankfully Monty continued to improve at home and his renal values returned to normal within several months.

**Cardiopulmonary bypass**

Cardiopulmonary bypass (CPB) is the extracorporeal circulation and oxygenation of a patient’s blood, bypassing the patient’s cardiac and pulmonary circulation (Figure 6). Amongst other things, it is used to facilitate open heart surgery. It has been in routine clinical use for decades in human medicine, and there are now several sites throughout the world that offer open heart surgery under CPB in clinical veterinary patients. While there are many different types of cardiac disease that are amenable to CPB and surgical correction, the most common are valvular pathologies (such as mitral and tricuspid dysplasia and degeneration), dogs with pulmonic stenosis who have not had a durable response to balloon valvuloplasty, and congenital defects (including atrial/ventricular septal defects, double chambered right-ventricle, Tetralogy of Fallot and cor triatriatum dexter and sinister). While patients with cardiomyopathy may develop atrioventricular valve incompetence, this subset of patients are not good candidates for surgical correction, and this mandates very careful case selection to avoid poor surgical outcomes. While the exact nature of CPB will vary depending on the cardiac defect being repaired, for a patient undergoing mitral valve repair a brief overview of the procedure is shown in Box 7. Due to differences in the circuit and conduct of CPB, some technical difficulties for haemodialysis and TPE associated with small patient size do not apply to CPB. Patients in pre-operative (ACVIM grading) stages B2 and C undergoing mitral valve repair have a very good prognosis, and the majority of patients will no longer require cardiac medications within 3 months of their surgery. Further discussion of CPB is outside of the scope of this article, those interested should contact one of the open-heart surgical centers for further information on the therapies offered. It is worth noting that there is often a waiting list and a significant financial commitment.

**Box 7 – Brief overview of mitral valve surgery**

Patient is maintained under general anaesthesia with appropriate surgical access.

Systemic heparin is administered and carotid arterial and right atrial venous cannulae are placed.

When the CPB circuit is devoid of air, the patient is attached and blood drains from the right atrium into the extracorporeal circuit, while blood is returned via the right carotid artery.

The CPB machine oxygenates the blood, removes CO2, provides circulatory support and allows controlled protective systemic hypothermia (28oC).

The aorta is cross-clamped between the aortic root and aortic arch and the heart is stopped using a mixture of drugs (termed cardioplegia) delivered into the coronary arteries via a cannula in the aortic root.

The left atrium is opened and the mitral valve repaired during this period of asystole when native cardiac and pulmonary function are arrested.

Active systemic rewarming is performed via the CPB circuit and when air has been appropriately removed from the heart the aortic cross-clamp is removed.

The heart either spontaneously beats, or pacing leads are attached to promote a normal rhythm. In some cases defibrillation is needed to regain a normal heart rhythm.

Heparin is antagonized using protamine sulphate and the patient is recovered from anaesthesia and carefully monitored in the ICU.

**Case 3 – Percy 1yr 8mnth ME Boston Terrier (Figure 7)**

Presentation – Percy presented with a congenital double chambered right ventricle leading to right sided congestive heart failure. Percy was in very poor body condition score despite a ravenous appetite, and also had marked ascites.

Treatment – Fibrous bands within the right ventricle were transected to relieve his double chambered ventricle, and his pulmonary outflow tract was widened using a Gore-Tex patch. All interventions were performed under cardiopulmonary bypass with a beating heart.

Outcome – Percy recovered well from surgery, and one year post-operatively is reported to be clinically normal, with marked improvement in his echocardiographic parameters. Percy is now expected to have a normal lifespan and requires no medications.

**Figure Legends**

Figure 1 – Rolex immediately after his PIRRT cycle (left) and one year after discharge (right). Images are courtesy of Rolex’s owner.

Figure 2 - Schematic of the difference between haemodialysis (A) and plasmapheresis (B). Note the larger pore size in the plasmapheresis circuit. Dialysate is the fluid with which blood will equilibrate during haemodialysis.

Figure 3 - A centrifugal machine that can be used for several applications, including centrifugal TPE and autotransfusion. Image courtesy of Dr. Daisy Norgate.

Figure 4 - A portable dialysis machine that can be used for prolonged intermittent and continuous dialysis therapies, and membranous TPE. Machines for intermittent haemodialysis may be similar in size, but routinely require a reverse osmosis system to generate large volumes of dialysate, making them less mobile.

Figure 5 - Monty immediately before one of his TPE cycles (left) and on the day of discharge (right).

Figure 6 - A cardiopulmonary bypass machine set up with its circuitry before being attached to the patient. The circuit has a large priming volume which leads to haemodilution which is advantageous during CPB due to effects on oxygen delivery and blood viscosity.

Figure 7 – Percy immediately post-operatively (left) and one year after discharge (right). Images are courtesy of Percy’s owner.

**References**Harbord, N., Winchester, J. F., Charen, E., Sheth & N., Bhansali, A. (2019). Extracorporeal therapies in acute intoxication and poisoning. In: Critical care nephrology. 3rd edn. Eds C. Ronco, J. A. Kellum, R. Bellomo, Z. Ricci. Elsevier. pp 588-594

Madore, F. R. & Bouchard, J. (2019). Plasmapheresis in acute intoxication and poisoning. In: Critical care nephrology. 3rd edn. Eds C. Ronco, J. A. Kellum, R. Bellomo, Z. Ricci. Elsevier. pp 595-600

Rosenthal, M. G. & Labato, M. A. (2019) Use of therapeutic plasma exchange to treat nonsteroidal anti‐inflammatory drug overdose in dogs. J Vet Intern Med. 33,596– 602

Skulberg R., Cortellini, S., Chan, D. L., Stanzani, G. & Jepson, R. E., (2018) Description of the Use of Plasma Exchange in Dogs With Cutaneous and Renal Glomerular Vasculopathy. *Front. Vet. Sci*. 5:161. <https://doi.org/10.3389/fvets.2018.00161>