Introduction

The first successful renal transplant in a companion animal was performed on a cat in 1984 at the University of California-Davis, School of Veterinary Medicine by Dr. Clare Gregory and Dr. Ira Gorley. Since that time, it is estimated that over 500 cases of feline renal transplantation have been performed at various centers around the country. The ability to perform renal transplantation as a treatment of renal failure for cats was attributable to a number of factors including the development of microsurgical techniques in the cat, the ability to use an allograft from an unrelated donor and the application of the drug cyclosporine for immunosuppressive therapy in the cat. In a study comparing long term survival of cats that had undergone renal transplantation to a control population of medically treated cats, transplantation appeared to prolong survival time and quality of life compared with the medical management of the disease. Although cats have historically been the most predominant species to have undergone the procedure and thus will be the focus of this lecture, information will be presented on our current experience with canine transplantation.

Indication for transplantation

The most common histopathological diagnosis identified from native kidney biopsy samples of cats that have had a renal transplant performed is chronic interstitial nephritis. Other underlying conditions for which transplantation has been performed include oxalate nephrosis, polycystic kidney disease, membranous glomerulonephropathy, Lily and ethylene glycol toxicity, amyloidosis, pyelonephritis, and renal dysplasia. Although limited information currently exists in dogs, successfully transplantation has been performed for cases of both membranous glomerulonephropathy and renal dysplasia.

Case selection

Thorough screening is essential for a potential renal transplant recipient to decrease the incidence of morbidity and mortality that can occur following the procedure. Although the best time to intervene with surgery is not completely known, clinicians with experience in the field suggest that the best candidate for renal transplantation is a patient in very early decompensated renal failure. Indications of decompensation include continued weight loss and worsening of the anemia and azotemia in the face of medical therapy. It is important to note that the degree of azotemia, anemia, urine specific gravity and age, do not determine, in themselves, a suitable patient for transplantation. Feline candidates should be free of other disease conditions including diffuse hypertrophic cardiomyopathy, recurrent urinary tract infections, uncontrolled hyperthyroidism and underlying neoplasia. Cats with a fractious temperament are also often declined as candidates. Not enough information currently exists to determine if cats with diabetes should be declined as potential candidates. Renal transplantation is considered a treatment option for cats whose underlying cause of renal failure was associated with Calcium Oxalate urolithiasis. Additionally, cats with a history of upper respiratory tract infections, underlying inflammatory bowel disease as well as those with certain echocardiographic abnormalities, have also been transplanted successfully. Current evaluation at our facility involves various laboratory tests (complete blood count/chemistry/blood type and
cross-match/thyroid evaluation), evaluation of the urinary tract (urinalysis, urine culture, urine protein:Cr ratio, abdominal radiographs, abdominal ultrasound), evaluation for cardiovascular disease (thoracic radiography, electrocardiography, echocardiography, blood pressure), and screening for infectious disease (FeLV/FIV, Toxoplasma titer, IgG and IgM). Once determined to be a suitable candidate, the recipient must also be blood crossmatched to 2 or 3 blood donor.

**Donor selection**

The kidney donors are cats from an animal shelter that would otherwise be euthanized. An owner may elect to use one of the family’s other cats as a kidney donor. The renal donor should be a healthy, young adult that is crossmatch compatible to the recipient. The donor should have no evidence of renal insufficiency based on a complete blood count, serum chemistry profile and urinalysis. The cat must be FeLV/FIV negative. A contrast enhanced CT is performed to assure that the donor has two normally shaped, well vascularized kidneys. The client is required to adopt the donor cat since no cat is ever euthanized for the program.

**Preoperative care**

Upon admission to the hospital, the recipient is placed on intravenous fluid therapy of a balanced electrolyte solution at 1.5-2 times the daily maintenance requirements. This rate may vary in cases of severe dehydration or in patients with underlying cardiac disease. For some patients in acute renal failure or those unable to handle fluid therapy, stabilization with hemodialysis is often required before transplantation can be considered. Additionally, if the cat is hypertensive, the calcium channel blocker amlodipine (Norvasc, 0.625mg/cat PO q24h) may be indicated before surgery. Blood products need to be available for surgery. Some cats in chronic renal failure are not transfusible because of incompatabilities despite the fact that the cats are of the same blood type. Blood crossmatching is an important consideration particularly if the patient is traveling a great distance to the transplant clinic. If a delay in the transplant procedure is expected, erythropoietin (Epogen, 100IU/kg three times per week for the first 1-2 weeks and then tapered accordingly) or preferably, Darbopoietin (Aranesp, 6.25 units/cat once weekly for the first month then taper accordingly) can be administered and may greatly reduce the need for blood products at the time of surgery. Phosphate binders and gastrointestinal protectants are given if deemed necessary. If the cat is anorectic, a nasogastric, esophagostomy or PEG tube may be placed to administer nutritional support prior to surgery.

**Immunosuppression for the feline renal transplant recipient**

The immunosuppressive protocol currently used at our facility consists of a combination of the calcineurin inhibitor Cyclosporine and the glucocorticoid, prednisolone. These medications are used in combination for their synergistic effects. Cyclosporine administration is begun 72-96h prior to transplantation at a dose of 1-4mg/kg PO q12h depending on the cat’s appetite. Currently, the 12-hour trough level is measured, just prior to the next oral dose. Because of interpatient and intrapatient variability in the absorption of oral cyclosporine and its metabolism, blood levels should be monitored regularly to maintain therapeutic concentrations and minimize toxic side effects. Currently a trough level of 300-500 ng/ml is maintained for the first 30-90 days following surgery, and is then reduced to approximately 200-300 ng/ml for long term therapy. Prednisolone is administered beginning the morning of surgery. At our facility, prednisolone is started at a dose range of 0.5-1mg/kg q24h orally for the first 3 months and then tapered to q48h. If renal function starts to deteriorate in the first weeks to months following transplantation, Azathioprine (0.3mg/kg/72 hours) may be added to the immunosuppressive protocol. Cats receiving Azathioprine should have their white blood cell count monitored regularly.
Another option for immunosuppression is the addition of ketoconazole (10 mg/kg PO q24h) to the cyclosporine and prednisolone. With this protocol, cyclosporine and prednisolone are administered once a day instead of twice a day. This protocol can reduce the cost of immunosuppression and may be more appealing for owners whose work schedules do not permit twice-daily a day dosing or whose cats are difficult to medicate. Hepatotoxicity, secondary to ketoconazole administration, is the main concern when using this protocol. The administration of ketoconazole is commonly performed for canine recipients.

**Surgery**

Renal transplantation should be performed by veterinarians familiar with vascular surgery. The donor is brought into the surgical suite approximately 30-45 minutes prior to the recipient. At the time of the original incision, the donor is given a dose of mannitol (0.25g/kg IV). During this time, the donor kidney will be prepared for the nephrectomy. The left and right kidneys are examined for a vascular pedicle that consists of a single artery. The left kidney is preferred because it provides a longer vein than the right kidney. The renal artery and vein are cleared of as much fat and adventitia as possible. The ureter is dissected free to the point where it joins the bladder. At some facilities, hypothermic storage is used to preserve the donor kidney until the recipient surgery is performed. This technique is preferred by some surgeons because it reduces personnel and resources needed for the transplantation procedure. Cold preservation also minimizes ischemic injury that can occur to the kidney. Currently at our facility, the nephrectomy will be performed when the recipient is prepared to receive the kidney. Fifteen minutes prior to nephrectomy, an additional dose of mannitol (1g/kg IV) is given to the donor cat. Mannitol is used to reduce the incidence and duration of acute tubular necrosis that can occur during warm ischemia.

The majority of the recipient surgery is performed using an operating microscope. The renal artery is anastomosed end-to-side to the caudal aorta (proximal to the caudal mesenteric artery), and the renal vein is anastomosed end-to-side to the caudal vena cava. Partial occlusion clamps are used to obstruct blood flow in both the aorta and the caudal vena cava. Holes are created in both the aorta and vena cava to match the size of the renal artery and vein. Both aorta and vena cava as well as the allograft are flushed preferably with a preservation solution. The renal artery is anastomosed to the aorta using 8-0 nylon in a simple continuous pattern and the renal vein is anastomosed to the vena cava using 7-0 silk in a simple continuous pattern.

Once the vascular anastomosis is complete, a ureteroneocystotomy is performed using an intravesicular mucosal apposition technique. A ventral midline cystotomy is performed and then the end of the ureter brought directly into the bladder lumen through a hole created at the bladder apex. The bladder is everted, the distal end of the ureter is excised, periureteral fat removed and the end of the ureter is spatulated. The ureteral mucosa is sutured to the bladder mucosa using either 8-0 nylon or 8-0 vicryl in a simple interrupted pattern. Following completion of the anastomosis, the bladder is inverted and closed routinely. An extravesicular technique or an anastomosis of the ureteral papilla can also be performed for ureteroneocystotomy. Prior to closure, a biopsy of one of the native kidneys is performed if applicable and the allograft pexied to the abdominal wall using 6 interrupted sutures of 4-0 polypropelene. The recipients’ native kidneys are usually left in place to act as a reserve in case graft function is delayed.
Postoperative care and perioperative complications

Minimal stress and handling of the patient and keeping the patient warm is extremely important during the postoperative period. The recipient is administered balanced electrolyte solutions until water and food are accepted. Packed cell volume, total protein, a renal panel and blood cyclosporine levels are checked every 2-4 days. While a catheter is in place, the cat is maintained on IV antibiotic therapy (cefazolin, 22 mg/kg IV q8h). Once all catheters are removed, the cat is then maintained on oral antibiotic therapy (Clavamox, 62.5mg PO q12h) for another 2-3 weeks or until the feeding tube is removed and cyclosporine levels regulated. Voided urine is collected daily to assess urine specific gravity. Because of an association that has been identified between postoperative hypertension and postoperative CNS disorders, indirect blood pressure is monitored every 1-2 hours during the first 48-72h to monitor for the development of hypertension. If the systolic blood pressure is equal to or greater that 180mmHg, hydralazine (2.5mg SQ for a 4kg cat) is administered. The hydralazine dose can be repeated if the systolic pressure has not decreased within 15-30 minutes. If the cat is refractory to hydralazine, acepromazine (0.005-0.01mg/kg IV) has been used. It is important to note that the incidence of hypertension and CNS disorders is not seen with equal frequency between transplant centers and thus the cause of CNS disorders in cats following renal transplantation still remains a challenge for some clinicians.

Patients are discharged from the hospital when graft function is determined to be satisfactory and trough whole blood levels of cyclosporine are stable. Delayed graft function may occasionally occur due to the shock of ischemia and reperfusion injury. If ultrasonographic examination of the kidney reveals good cortical blood flow, the kidney will probably function. If the transplanted kidney fails to function, the kidney should be biopsied prior to re-transplantation.

Long-term management and complications

Initially, the patient is examined once a week until the cyclosporine blood levels are stable. During each exam, clinical pathological assays are performed including packed cell volume, total protein, plasma creatinine, blood urea nitrogen and phosphorus, a cyclosporine level and a urinalysis if a urine sample is available. The intervals between veterinary visits are increased once the cat stabilizes. It is recommended that a complete blood count and serum chemistry panel be performed every 3-4 months and an echocardiography performed every 12 months. If a feeding tube has been placed, it should be removed once oral intake of food and water is deemed appropriate.

Renal complications following transplantation have included renal rejection, retroperitoneal fibrosis, oxalate nephrosis, renal torsion, hemolytic uremic syndrome and renal failure. Both acute and chronic rejection are seen in the feline transplant recipient. With acute rejection, loss of function of the affected organ can be seen within the first few weeks following surgery. Histopathological examination of the organ shows mononuclear leukocyte infiltration of the tissue, with loss of normal structure. Sonographic examination of allograft rejection in the cat often reveals a significant increase in cross sectional area to the allograft, a subjective increase in echogenicity and a decrease in corticomedullary demarcation. Although normal allograft enlargement is expected during the first week postoperatively, a gradual decline should then occur. Rejection should be suspected if the renal enlargement persists or progresses beyond this period. Suspected acute rejection episodes are treated with intravenous administration of cyclosporine (6.6mg/kg q24h given over 4-6h) and prednisolone sodium succinate (Solu Delta
Cortef, 10mg/kg IV q12h). Chronic rejection is characterized by gradual loss of organ function over months to years, often without evidence of a rejection episode.

Complications have also occurred possibly secondary to immunosuppressive therapy. These have included hemolytic uremic syndrome, gingival hyperplasia, infection (bacterial, viral, fungal, protozoal) diabetes and neoplasia. Infections in the transplant patient cause direct morbidity and mortality due to the infection itself, and may also activate the rejection process.

**Conclusion**

Renal transplantation offers a unique method of treatment for renal failure in cats. In a review of the first 136 cases performed at our facility, 92% of the cats recovered sufficiently and went home following surgery. In this group of patients, the 6mo and 3yr survival were 79% and 32%, and the mean and median survival times were 1000 and 616 days. The longest survivor from our facility lived 13 years following his transplant. The most common complications that we have identified in our patients include infection, neoplasia, retroperitoneal fibrosis and allograft rejection. Survival times are steadily improving as more patients have been treated, problems recognized, and complications avoided. Clients who are interested in renal transplantation for their pet need to understand the risks and that it is a commitment for the lifetime of the animal.