Update on the Current Status of Kidney Transplantation for Chronic Kidney Disease in Animals

Lillian R. Aronson, VMD

KEYWORDS
- Transplantation • Immunosuppressive therapy • Cyclosporine • Allograft rejection • Retroperitoneal fibrosis • Lymphoma

KEY POINTS
- Renal transplantation is a viable treatment option for cats in chronic renal failure or those that have suffered irreversible acute kidney injury.
- Extensive screening of a potential recipient is critical to prevent both short- and long-term complications.
- Renal donation was not found to affect normal life expectancy in cats.
- Lifelong immunosuppression, consisting of a combination of cyclosporine and prednisolone are necessary to prevent allograft rejection.
- Treatment of complications directly related to the allograft or those secondary to chronic immunosuppressive therapy still remain a significant challenge for the clinician.

INTRODUCTION

Chronic kidney disease (CKD) is a progressive and debilitating disease in cats and dogs with no known cure. Although medical management may be effective initially in stabilizing a patient and improving his or her quality of life, it is not sufficient to maintain a patient with end-stage renal failure. Kidney transplantation was first introduced in 1984 as a novel therapy for cats suffering from CKD and continues to remain an accepted treatment option for this population of patients. Although some question the justification for the technique, in a report comparing survival time of cats that had undergone transplantation to a population of cats treated medically, renal transplantation improved patient quality of life and prolonged survival times compared with the medical management of the disease. The majority of this article focuses on cats, because historically they have been the most predominant species to undergo renal transplantation in veterinary therapeutics.

The author has nothing to disclose.

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CANDIDATE PRESENTATION

Transplantation is often performed in patients when evidence of kidney decompensation is identified in the face of appropriate medical therapy or in patients with acute irreversible kidney injury. Clinical signs indicative of decompensation include worsening of the anemia and azotemia and continued weight loss. Although objective data are lacking with regard to the optimal time for intervention, based on studies investigating prognostic factors and survival in cats with naturally occurring CKD, conversation with owners regarding transplantation should occur proactively when a cat is in International Renal Insufficiency Society CKD stage 3. At 1 facility, a serum creatinine of greater than 4.0 mg/dL or significant aberrations in calcium and phosphorus levels are indications for transplantation. In a review of 156 cases performed at the author’s facility from 1998 to 2015, 15% of the cats were in International Renal Insufficiency Society CKD stage 3 and 85% were in International Renal Insufficiency Society CKD stage 4 at presentation. Limited information regarding the degree of azotemia as a risk factor for postoperative morbidity and mortality exists. In 1 study, cats with a serum creatinine greater than 10 mg/dL and increased blood urea nitrogen (specific value not given) were more likely to die before discharge. In a second study, the severity of azotemia significantly increased the risk of neurologic complications in the perioperative period, but was not related to long-term survival.

Both congenital and acquired disorders have been treated successfully with renal transplantation (Box 1). It is unclear whether patients in chronic renal failure secondary to amyloidosis are appropriate candidates because of the potential effects on the transplanted kidney. Patients with a history of pyelonephritis or recent infection have been treated successfully with transplantation if the infection is confined to one kidney and that kidney is removed before immunosuppression and transplantation. Cats with renal failure secondary to ethylene glycol toxicity should only be considered for transplantation after the elimination of the ethylene glycol and its metabolites from the body.

RECIPIENT EVALUATION

Extensive screening (Box 2) is performed before transplantation to identify any contraindications to moving forward with the procedure. At our facility, findings that preclude transplantation include severe cardiac disease, underlying neoplastic disease,

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**Box 1**

**Conditions successfully treated with transplantation**

**Acquired conditions**
- Chronic interstitial nephritis (cat, dog); most common
- Oxalate nephrosis (cat)
- Membranous glomerulonephropathy (cat, dog)
- Toxic nephropathy; ethylene glycol, Lily (cat)
- Pyelonephritis (cat)

**Congenital disorders**
- Polycystic kidney disease (cat)
- Renal dysplasia (cat, dog)
positive feline leukemia or feline immunodeficiency virus status, heartworm-positive status, recurrent or existing urinary tract infections that fail medical therapy or a cyclosporine challenge, uncontrolled hyperthyroidism, and a fractious temperament. Although cats with inflammatory bowel disease historically were not considered candidates because of the assumption that they may be at increased risk for allograft rejection, 6 cats with confirmed inflammatory bowel disease and 8 cats with suspected inflammatory bowel disease based on biopsy or ultrasonographic findings have been transplanted successfully at our facility with no episodes of allograft rejection reported (LR Aronson, personal communication, 2014). Recipient age has been identified as a factor associated with survival after discharge in both cats and dogs. In 1 feline study, median survival times decreased with advancing age, and in a second study, cats older than 10 years of age had higher mortality rates, particularly during the first 6 months after surgery. However, if no complications developed during the first 6 months, these patients did similarly to the younger population in the long term.1,7 A third study found cats older than 12 years of age had a lower overall survival rate than younger cats.8 In a study of 26 dogs that had undergone renal transplantation, for every 1-year increase in age, the odds of death by 6 months after surgery increased by 42%.9 In cats, preoperative blood pressure and weight have also been shown to influence overall survival.1

Thoracic radiography performed preoperatively has identified significant soft tissue mineralization in 9 of 156 cats that have undergone renal transplantation at the author’s facility (Fig. 1). All 9 cats had an elevated calcium × phosphate product that was significantly greater than cats that did not have evidence of soft tissue mineralization at the time of presentation. This finding was not associated with any complications preoperatively, during the surgical procedure, or in the long term.

### Typing and Cross-Matching Incompatibilities

Because an owner may live a significant distance from a transplant facility, blood typing as well as determination of red blood cell crossmatch compatibility between
the recipient and potential feline kidney donors and blood donors should be performed
before travel to the transplantation facility. Although uncommon, incompatible cross-
match tests between AB-compatible donor and recipient pairs have been identified.
Absence of a novel red blood cell antigen, identified as Mik, has resulted in naturally
occurring anti-Mik alloantibodies after an AB-matched blood transfusion. Addition-
ally in dogs, dog erythrocyte antigen matching as well as mixed lymphocyte response
testing is performed between recipients and potential donors.

Cardiovascular Disease and Hypertension

Systolic murmurs are common on presentation and most are thought to be physio-
logic and associated with anemia of chronic renal failure. Structural cardiac abnor-
malities are also common in patients presenting for transplantation and most changes
are no longer seen as a contraindication to surgery. In 1 study evaluating 84 potential
recipients, 78% of patients had abnormalities including papillary muscle and septal
muscle hypertrophy. It was suggested that these changes may be related to age, hy-
pertension, chronic uremia, or early changes of hypertrophic cardiomyopathy. No
preoperative echocardiographic changes in that study were significant predictors
of 1-month survival. In a second study evaluating 127 feline renal transplant recipi-
ents, preoperative echocardiographic changes including the presence of an
arrhythmia, mitral and tricuspid regurgitation, systolic anterior motion of the mitral
valve, septal muscle and left ventricular free wall hypertrophy, and increased aortic
peak flow velocity, as well as radiographic evidence of heart failure at presentation
were not associated with survival to discharge or long-term survival. One study,
however, did find increased left ventricular wall thickness as a risk factor for periop-
erative mortality.

Preoperative hypertension is common in human transplant recipients and hyperten-
sion persisting in the postoperative period has been associated with graft damage and
suboptimal outcomes. The effect of preoperative and postoperative hypertension
in cats is unclear. In 1 study, preoperative hypertension negatively influenced overall
survival; however, in our experience evaluating 127 transplant recipients, 38%
were diagnosed with preoperative hypertension yet this factor was not associated
with survival to discharge or decreased survival time. In another study, preoperative
hypertension did not predict episodes of postoperative hypertension and treatment
with antihypertensive medication preoperatively did not decrease significantly the
postoperative incidence of the condition. Antihypertensive therapy should be initiated
before transplantation if indicated. Intraoperative hypotension was a risk factor for
perioperative mortality and decreased long-term survival in 1 report. Cats with severe hypertrophic cardiomyopathy and atrial dilatation are rejected as candidates for renal transplantation. For cats with less severe disease, a decision regarding candidacy is made on a case-by-case basis.

**Urinary Tract Evaluation**

A thorough evaluation of the urinary tract is essential to identify underlying infection, obstruction, or neoplastic disease. A cyclosporine (Neoral, Sandoz Pharmaceuticals) challenge is required for patients with a history of urinary tract infections. Cyclosporine is administered for approximately 2 weeks at a recommended dose necessary to obtain therapeutic blood levels. Once appropriate levels are obtained, urine is subsequently evaluated at that time and at the end of the 2-week trial for the presence of an infection. Although negative urine culture results will not guarantee a patient will remain free from infection after transplantation, positive urine culture results will eliminate cats and dogs with occult infections as candidates for transplantation. It has been the author’s experience that patients harboring an infection will often show clinical signs (lethargy, depression, anorexia) and have a positive urine culture within 48 to 72 hours after initiation of the cyclosporine trial.

Renal transplantation is a treatment option for cats whose underlying cause of renal failure is associated with calcium oxalate urolithiasis in conjunction with chronic interstitial nephritis. For patients presenting with hydronephrosis secondary to obstructive calcium oxalate urolithiasis or another cause, pyelocentesis and culture are recommended. Immunosuppression in a patient harboring an infection can not only potentiate the rejection process but also lead to increased morbidity and mortality. If neoplasia or feline infectious peritonitis is suspected, a fine-needle aspirate or biopsy should be performed.

**Evaluation for Infectious Disease**

Significant morbidity and mortality has occurred secondary to the reactivation of latent *Toxoplasma gondii* infections, and for this reason serologic testing (IgG and IgM) for toxoplasmosis is now performed on all potential transplant recipients. Sero-positive recipients are placed on lifelong prophylactic clindamycin (25 mg orally [PO] every 12 hours) in conjunction with their immunosuppressive therapy. Trimethoprim-sulfa (15 mg/kg PO every 12 hours) has also been used in cats that did not tolerate clindamycin therapy. Although seropositive donors are no longer used for seronegative recipients, successful transplantation has been performed between a seropositive donor and a seropositive recipient. Three patients at the author’s facility that tested negative for *T gondii* before immunosuppression and transplantation, subsequently tested positive for the parasite within 3 months after surgery, and the infection was fatal in 2 of the 3 patients. For this reason, the author now recommends serologic testing (IgG and IgM) during the first 3 months after transplantation in patients that were seronegative before transplantation, and depending on the findings, subsequent evaluation should be performed regularly in the future.

Successful transplantation has been performed in cats with a history of upper respiratory tract infection. Cats with a history of an upper respiratory tract infection or those that have developed clinical signs of an upper respiratory tract infection during the perioperative period have been treated successfully with L-lysine, oral antibiotics, topical antibiotics, antiviral medication, and an appetite stimulant used alone or in combination (LR Aronson, personal communication, 2014).
KIDNEY DONORS

Standard screening of kidney donors includes a serum chemistry profile, complete blood count, blood typing, urinalysis and culture, and serologic testing for toxoplasmosis (IgG and IgM). Feline leukemia and feline immunodeficiency virus testing is performed additionally in cats and heartworm testing is performed in dogs. Computed tomographic angiography is performed to characterize the renal vasculature and to evaluate the renal parenchyma for any abnormalities such as infarcts that might exclude an animal from being a donor (Fig. 2). In a study of 114 potential feline donors, 45 had multiplicity of the right renal vein, and 8 had multiple left renal arteries. A suitable home is found for any donor candidate that fails the screening process. Perioperative morbidity and long-term outcome of unilateral nephrectomy has been evaluated recently in 99 feline kidney donors with a median interval between nephrectomy and follow-up of 10 years. Three cats developed stable, chronic renal insufficiency a median of 6.2 years after nephrectomy; 2 cats had episodes of acute kidney injury 4 and 6 years after kidney donation which resolved with medical therapy, and 1 cat was diagnosed with idiopathic cystitis, which resolved spontaneously. Renal-related deaths were identified in 6 cats; 4 died of acute ureteral obstruction secondary to calcium oxalate urolithiasis a median of 7 years after surgery, and 2 cats died of chronic renal failure, 12 and 13 years after kidney donation. Although renal donation was not found to affect normal life expectancy in cats, because of the morbidity and mortality associated with stone formation in cats with 1 functioning kidney, abdominal radiographs are now recommended at yearly wellness visits to identify...
any early evidence of new stone formation. In a study of 14 canine donors, renal and hematologic variables were normal in dogs evaluated up to 2.5 years after unilateral nephrectomy for kidney donation.22

PREOPERATIVE TREATMENT

Hemodialysis is performed before transplantation in anuric patients and those that are severely azotemic and develop pulmonary edema and/or pleural effusion when intravenous (IV) fluid therapy is initiated. After successful transplantation, IV fluid therapy can often be administered without complication in this population of patients. For hypertensive cats, the calcium channel blocker amlodipine (Norvasc) is often indicated before surgery. If a delay in the transplant procedure is expected and the patient is anemic, darbepoetin (6.25 mg/kg once a week for 2–4 weeks until the packed cell volume is approximately 25% and then every other week) can be administered and can reduce greatly the need for blood products during the perioperative period. At the time of surgery, depending on the stability of the patient, anemia is corrected with either packed red blood cells or whole blood transfusions. The first unit administered is preferably one that was collected previously from the crossmatch-compatible donor cat. If the patient is anorectic, an esophagostomy tube may be placed to administer nutritional support before and after surgery. Gastrointestinal protectants and phosphate binders are given if deemed necessary.

Immunosuppressive Therapy

The immunosuppressive protocol currently used for cats at our facility consists of the calcineurin inhibitor cyclosporine in combination with the glucocorticoid prednisolone. This combination also has been an essential component for immunosuppression in canine transplantation between related dogs. The mechanism of action of cyclosporine and glucocorticoids has more recently been elucidated in the cat. In 1 report, cyclosporine inhibited expression of messenger RNA for IL-2, IL-4, interferon-γ, and tumor necrosis factor-α in a dose-dependent manner.23 In a second report, the use of cyclosporine significantly decreased production of interferon-γ, IL-2, and granulocyte macrophage colony stimulating factor.24 Dexamethasone alone suppressed production of only granulocyte macrophage colony stimulating factor; when combined with cyclosporine, however, a significant decrease in production of interferon-γ, IL-2, and granulocyte macrophage colony stimulating factor occurred.24 Inhibition of these cytokines is thought to be critical to graft survival, because they are known to play a role in human graft rejection.25–27

In cats, an oral liquid microemulsified formulation of cyclosporine (Neoral, 100 mg/mL) is recommended, so the dose can be titrated for each individual cat. Neoral is preferred because of its better gastrointestinal absorption and more predictable and sustained blood concentrations.11 Currently, cyclosporine therapy is initiated 72 hours before transplantation at a dose of 1 to 4 mg/kg PO every 12 hours depending on the patient’s appetite. It has been the author’s experience cats that are anorectic or hyporexic have a much lower drug requirement to obtain appropriate preoperative drug levels. Because of its bitter taste, cyclosporine is placed into a gelatin capsule before dosing. A 12-hour, whole-blood, trough concentration is obtained the day before surgery to allow adjustment of the preoperative oral dose into a therapeutic range. The ideal 12-hour trough concentration is 300 to 500 ng/mL measured by high-pressure liquid chromatography.28 This level is maintained for approximately 3 months after surgery and then tapered to approximately 250 ng/mL for maintenance therapy.
Prednisolone therapy is begun the morning of surgery at 0.5 to 1.0 mg/kg every 12 hours PO and continued at that dosage for the first 3 months. The dosage is then tapered to once daily.

Antifungal medications delay the metabolic clearance of cyclosporine and have been used in conjunction with cyclosporine particularly in related dogs to help reduce the cost of posttransplant immunosuppression as well as improve the convenience of dosing for owners. In 1 protocol, after the administration of ketoconazole (10 mg/kg PO every 24 hours), cyclosporine and prednisolone are administered once a day, and cyclosporine doses are adjusted into the therapeutic range by measuring 24-hour whole blood trough levels. Ketoconazole inhibits hepatic and intestinal cytochrome P450 oxidase activity, resulting in increased blood cyclosporine concentrations. If signs of hepatotoxicity are identified, ketoconazole administration should be discontinued. Additionally, in dogs, cataract formation has been identified with use of ketoconazole. Itraconazole has been shown to exhibit less toxicity in human renal transplant patients and has recently been investigated in cats. In a separate pharmacokinetic study and case report, the coadministration of the antibiotic clarithromycin with cyclosporine resulted in a significant increase in the bioavailability of cyclosporine in 4 research cats and was used successfully in conjunction with cyclosporine in a once a day protocol for a feline kidney transplant recipient.

**Mesenchymal Stem Cell Therapy**

An area of growing interest is human transplantation is the use of autogenous mesenchymal stem cells (MSC) to lower the incidence of acute rejection, decrease the risk of opportunistic infections, and improve long-term outcomes. In preclinical models, MSC therapy has been shown to influence renal function and graft survival positively. In a randomized controlled study in living-related kidney transplants in humans, the use of autogenous MSCs given at the time of reperfusion improved outcomes at 1 year, including better allograft function and a reduction in adverse events. Recent in vitro work in cats found that feline MSCs and their supernatant reduced the formation of neutrophil reactive oxygen species in a dose-dependent manner when cocultured with feline neutrophils. Although the use of stem cell therapy has the potential to offer great benefits to the feline renal transplant recipient, harvesting autogenous MSC's would require that the recipient undergo an additional surgical procedure performed 7 to 10 days before the transplant procedure. Performing an additional surgery will add to the overall cost of the transplant procedure and, in a debilitated patient, may result in significant morbidity.

**ANESTHETIC MANAGEMENT**

The anesthetic management for the feline renal transplant recipient has been described previously. A sample anesthetic protocol for both recipient and donor is listed in Box 3. There are some practical points to consider with regard to the anesthetic management of these patients. Because both donor and recipient may be under anesthesia for an extended period of time, esophageal temperatures are monitored continuously, and a forced air warmer is used throughout the procedure to prevent hypothermia. A double-lumen indwelling jugular catheter is placed, preferably into the recipient’s right jugular vein preserving the left side of the neck in the event esophagostomy tube placement is required. Electrolytes, packed cell volume/total protein, and venous blood gases as well as systemic arterial blood pressure via a noninvasive Doppler technique are monitored throughout the operation. Mannitol is administered to the donor cat at the time of the abdominal incision (0.25 g/kg of...
mannitol IV) and 20 minutes before nephrectomy to minimize renal arterial spasms, improve perfusion, and to prevent tubular necrosis that can occur during the warm ischemia period. Mannitol (0.5–0.1 g/kg IV) is occasionally administered to the recipient if there is concern regarding perfusion of the allograft. Recently, the influence of anesthetic variables on both short- and long-term survival in the feline renal transplant recipient has been reported.\(^8\) Prolonged anesthesia (>6 hours), intraoperative hypoxemia, and cats older than 12 years of age were all associated with reduced overall survival.\(^8\) If severe hypertension occurs in the immediate postoperative period, it is treated with the subcutaneous administration of hydralazine (2.5 mg subcutaneously [SC] for a 4-kg cat).

For canine patients, enoxaparin (0.5–1.0 mg/kg SC every 24 hours) is administered the day before surgery and continued for 7 days after transplantation to prevent complications associated with thromboembolic disease. Additionally, because of the potential for an intussusception to occur after surgery, morphine is used as a

### Box 3

**Sample anesthetic protocol for a renal donor and recipient**

<table>
<thead>
<tr>
<th><strong>Donor</strong></th>
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<tbody>
<tr>
<td><strong>Preoperative</strong></td>
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<tr>
<td>Butorphanol: 0.5 mg/kg IM</td>
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<tr>
<td>Telazol: 3-4 mg/kg IM</td>
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<tr>
<td><strong>Epidural</strong></td>
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<tr>
<td>Bupivacaine: 0.1 mg/kg</td>
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<tr>
<td>Morphine: 0.15 mg/kg</td>
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<tr>
<td><strong>Induction</strong></td>
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<tr>
<td>Oxymorphone: 0.1 mg/kg</td>
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<tr>
<td>Midazolam: 0.5 mg/kg</td>
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<tr>
<td>Lidocaine: 1 mg/kg</td>
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</tr>
<tr>
<td>Etomidate: 0.2 mg/kg ± glycopyrrolate or atropine</td>
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<tr>
<td><strong>Intraoperative</strong></td>
<td></td>
</tr>
<tr>
<td>Mannitol: 0.25 g/kg at the time of incision and 1 g/kg before nephrectomy</td>
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<tr>
<td><strong>Postoperative</strong></td>
<td></td>
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<tr>
<td>Buprenorphine: 0.02 mg/kg 8 hr postinduction</td>
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<table>
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<tr>
<th><strong>Recipient</strong></th>
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<tbody>
<tr>
<td><strong>Epidural</strong></td>
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<tr>
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</tr>
<tr>
<td>Etomidate: 0.2 mg/kg ± glycopyrrolate or atropine</td>
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</tr>
<tr>
<td><strong>Intraoperative</strong></td>
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<tr>
<td>Fentanyl infusion</td>
<td></td>
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<tr>
<td><strong>Postoperative</strong></td>
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<tr>
<td>Buprenorphine: 0.02 mg/kg 8 hr postinduction</td>
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<tr>
<td>Hydralazine if needed for hypertension: 2.5 mg/4 kg cat SC</td>
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**Abbreviations:** IM, intramuscularly; SC, subcutaneously.
premedicant to induce ileus, at the time of the initial incision and for pain management after surgery.

**SURGERY**

Allograft preparation and the surgical technique for feline and canine transplantation have been described previously. Briefly, 3 surgeons participate in each procedure: 2 surgeons work on both the donor and recipient, and a third surgeon closes the donor after nephrectomy. At the time of the abdominal incision and just before nephrectomy, mannitol is administered to the donor. Some surgeons also recommend the alpha-adrenergic agonist, acepromazine (0.1 mg/kg IV).

Preoperative computed tomographic angiography of the donor provides information about the renal vasculature, identifying cats that would be suitable for the surgical procedure. A single renal artery and vein with a minimal length of 0.5 cm are preferable. The left kidney is preferred because it provides a longer vein than the right kidney. If multiple renal veins are present, the smaller vein can be sacrificed. The vasculature is cleared of as much fat and adventitia as possible, and the ureter is isolated for its entire length. Templates are made to accurately measure the width of the artery and vein to determine the sizes of aortotomy and venotomy to be performed in the recipient. At the authors’ facility, vascular ligation and nephrectomy are performed when the recipient is prepared to receive the kidney. Alternatively, hypothermic storage to preserve the donor kidney can be performed until the recipient is prepared for surgery. This technique minimizes ischemic injury that can occur to the kidney and can reduce personnel and resources needed for the procedure. If multiple arteries are identified in the donor, with the use of hypothermic storage, removing a segment of aorta that includes all arteries (Carrel patch), can be used to harvest the kidney.

An operating microscope with 5× to 22× magnification capabilities is used for the majority of the recipient’s surgery. In the current technique, after the placement of vascular occlusion clamps, windows are created in the aorta and vena cava using the previously made templates. The aorta and vena cava are flushed with heparinized saline solution, and sutures of 8-0 nylon are preplaced at the cranial and caudal aspects of the window created in the aorta. The graft is harvested after the second mannitol infusion and then flushed with an ice cold phosphate-buffered sucrose organ preservation solution. The renal artery is anastomosed end-to-side to the caudal aorta using 8-0 nylon, and the renal vein is anastomosed end-to-side to the caudal vena cava using 7-0 silk. The vascular clamps are removed and any hemorrhage

![Fig. 3. Vascular dissection of the renal vein (A) and renal artery (B) in the kidney donor. The vasculature is cleared of as much fat and adventitia as possible down to the vena cava and aorta. The left kidney is preferred because it has a longer vein.](image-url)
Fig. 4. After the placement of vascular occlusion clamps, windows are created in the aorta and vena cava and the aorta and vena cava are flushed with a heparinized saline solution. The renal artery is anastomosed end-to-side to the caudal aorta using 8-0 nylon and the renal vein is anastomosed end-to-side to the caudal vena cava using 7-0 silk.
along the suture lines are controlled with light pressure (Fig. 5). Any significant leaks may need to be repaired with additional sutures. If renal arterial spasm occurs after the release of the vascular clamps the application of topical lidocaine, chlorpromazine, or acepromazine has been effective in some cases to eliminate this problem.29

After the vascular anastomosis, a ureteroneocystostomy is performed to appose the ureteral and bladder mucosa. Both intravesicular and extravesicular techniques have been described.11,40,41 At the authors’ facility, an intravesicular mucosal apposition technique is used. After a ventral midline cystotomy, a mosquito hemostat is placed through the apex of the bladder and the end of the ureter grasped and brought into the bladder lumen. The bladder is everted, and the distal end of the ureter removed. The end of the ureter is spatulated, and the mucosa is sutured to the bladder mucosa using 8-0 nylon or Vicryl in a simple interrupted pattern (Fig. 6). After completion of the anastomosis, the bladder is inverted and closed routinely.

Two extravesicular techniques have also been described. In the first technique, the entire ureter and ureteral papilla with a 2-mm cuff of bladder are harvested from the donor and anastomosed to a 4-mm defect made at the apex of the recipient’s bladder. The ureteral papilla is sutured in a 2-layer pattern—mucosa to mucosa and seromuscular layer to seromuscular layer.41 (Fig. 7) In a second technique, a 1-cm seromuscular incision is made on the ventral surface of the bladder, allowing the bladder mucosa to bulge through the incision. A smaller incision (3–4 mm) is made through the bladder mucosa and the ureteral mucosa is sutured to bladder mucosa using 8-0 nylon (Fig. 8A). Once complete, the seromuscular layer is apposed in a simple interrupted pattern over the ureter with 4-0 absorbable suture (Fig. 8B).11,42

After cystotomy closure, the allograft is pexied to the abdominal wall to prevent torsion (Fig. 9). The recipient’s native kidneys are typically left in place unless there is an indication for removal. Patients with polycystic kidney disease may require a unilateral nephrectomy to create space in the abdomen for the allograft. Before closure, a biopsy of one of the native kidneys is performed.

The surgical techniques for canine renal transplantation are similar to those described previously for cats, with a few minor differences. Magnification may or may not be necessary in dogs depending on patient size. For the vascular

Fig. 5. Allograft after release of vascular clamps (A). Any hemorrhage along the suture lines are controlled with light pressure. Significant leaks may need to be repaired with additional sutures. Note a biopsy has been taken of the native kidney. Close up view of the vascular anastomosis (B).
anastomosis, the renal vessels can be anastomosed end to side to either the iliac vessels or to the caudal aorta and vena cava. Intestinal intussusception after renal transplantation and immunosuppression is common. For this reason, enteroplication is performed in all recipients.\textsuperscript{43,44}

**Fig. 6.** (A–E) A mosquito hemostat is placed through the apex of the bladder, and the end of the ureter grasped and brought into the bladder lumen (A, B). The bladder is everted, and the distal end of the ureter removed. The end of the ureter is spatulated (C, D), and the mucosa is sutured to the bladder mucosa using 8-0 nylon or Vicryl in a simple interrupted pattern. It is important that no periureteral fat is exposed. ([A–D] From Aronson LR, Philips H. Renal transplant. In: Tobias KM, Johnston SA, editors. Veterinary surgery: small animal. Philadelphia: Saunders, 2012; with permission; and [E] Courtesy of Dr Daniel Degner, Animal Surgical Center of Michigan, Burton, MI).
Fig. 7. Extravesicular technique for ureteroneocystostomy. The entire ureter and ureteral papilla are harvested from the donor (A, B) and anastomosed to a defect made at the apex of the recipient’s bladder (C). The ureteral papilla is sutured in a 2-layer pattern—mucosa to mucosa and seromuscular layer to seromuscular layer (C, D). (From Renal transplant, in Tobias and Johnston. Veterinary Surgery Small Animal. Saunders; 2012. p. 2019-e407, Figure 119-6; with permission.)

Fig. 8. (A, B) Extravesicular technique for ureteroneocystostomy. A 1-cm seromuscular incision is made on the ventral surface of the bladder, allowing the bladder mucosa to bulge through the incision. A smaller incision is made through the bladder mucosa, and the ureteral mucosa is sutured to bladder mucosa using 8-0 nylon. The seromuscular layer is apposed in a simple interrupted pattern over the ureter with 4-0 absorbable suture (B).
POSTOPERATIVE MONITORING AND TROUBLESHOOTING PERIOPERATIVE COMPLICATIONS

There are a number of aspects that need to be considered with regard to postoperative management that are critical to the success of each case (Box 4). Fine suture material is used for the vascular anastomosis and pexy of the allograft, and inappropriate patient handling can lead to catastrophic results and any patient struggling should be avoided. The placement of a double lumen catheter before the surgical procedure allows for minimal stress and handling during blood sampling. Many patients are under anesthesia for approximately 4 to 6 hours and hypothermia is a concern during the recovery period. Prevention or correction of hypothermia if needed in conjunction with prevention of hypotension will help to ensure appropriate allograft perfusion. If hypotension occurs (mean arterial pressure of <100), it needs to be treated aggressively with IV fluid boluses and then adjustments in maintenance fluid therapy and/or the

<table>
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<th>Box 4</th>
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<tbody>
<tr>
<td>Critical aspects to postoperative care</td>
</tr>
<tr>
<td>• Minimizing stress and handling</td>
</tr>
<tr>
<td>• Prevent hypothermia</td>
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<tr>
<td>• Fluid therapy and treating electrolyte imbalances</td>
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<tr>
<td>• Antibiotic therapy</td>
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<tr>
<td>• Pain management</td>
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<td>• Monitor for seizure</td>
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<td>• Treatment of hypertension</td>
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<tr>
<td>• Prevent hypotension</td>
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<td>• Management of anorexia</td>
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<td>• Regulate cyclosporine levels</td>
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administration of blood products to prevent acute tubular necrosis and delayed graft function.

Perioperative antibiotic therapy is continued until removal of the double lumen catheter and the patient is then switched to oral antibiotic therapy until the feeding tube is removed. If the cat is positive for *T gondii*, clindamycin (25 mg PO every 12 hours) administration is continued for the lifetime of the cat. Postoperative pain has been controlled successfully at our facility with methadone (0.15–0.3 mg/kg IV every 4–6 hours), buprenorphine (0.005–0.02 mg/kg IV every 4–6 hours), or a constant rate infusion of butorphanol (0.1–0.5 mg/kg/h).

Depending on the stability of the cat, packed cell volume, total protein, electrolytes, blood glucose, and acid–base status are evaluated initially 2 or 3 times daily and then as needed. A renal panel is evaluated every 24 to 48 hours, and voided urine is collected daily for assessment. Resolution of azotemia should occur within 24 to 72 hours after surgery. If improvement is not identified or if clinical status and renal function decline after initial improvement, an ultrasonographic examination of the allograft is recommended. The allograft is examined for appropriate renal blood flow and any signs of hydronephrosis or hydroureter. Emergency surgery may be warranted if evidence of obstruction exists. If graft perfusion is adequate and no evidence of obstruction exists, graft function may be delayed. If the transplanted kidney fails to function, the kidney should be biopsied before a second transplant is undertaken.

Hypophosphatemia in the early postoperative period has been reported to occur in 37% of cats after successful transplantation and may require treatment. The development of hypophosphatemia after transplantation in cats does not affect survival. Blood cyclosporine concentrations are measured every 3 to 4 days, and the oral cyclosporine dose is adjusted as needed into the therapeutic range.

The occurrence of severe hypertension (>200 mm Hg) in the postoperative period has been associated with postoperative seizure activity in the feline renal transplant recipient. The incidence of hypertension and its association with seizures has varied among veterinary transplant centers, and so the exact cause of neurologic complications in cats may be difficult to determine. In cats, the occurrence of seizures was not correlated with intraoperative blood pressure, cholesterol or magnesium concentrations, serum electrolyte or blood glucose concentrations, osmolality, erythropoietin or cyclosporine administration, or the degree of azotemia. In 1 study, an increase of 10 mg/dL in blood urea nitrogen or 1 mg/dL in serum creatinine would increase the likelihood of postoperative neurologic complications by 1.6- and 1.8-fold, respectively.

Indirect blood pressure should be monitored every 1 to 2 hours during the first 48 to 72 hours for evidence of hypertension. If systolic blood pressure is equal to or greater that 180 mm Hg and the cat is not painful or anxious, the vascular smooth muscle relaxant hydralazine (Sidmack Laboratories; 2.5 mg/4 kg cat SC) should be administered. The dose can be repeated if systolic blood pressure does not decrease within 15 minutes. If hypertension is refractory to hydralazine, acepromazine (0.005–0.01 mg/kg IV) can be administered. The cause of postoperative hypertension is unclear in the feline renal transplant recipient, but it does not seem to be induced by ischemia–reperfusion injury or elevated plasma renin concentration after reperfusion of the graft.

With resolution of azotemia and appropriate pain control, most cats will start eating within 24 to 48 hours after surgery. If continued anorexia is thought to be associated with alterations in gastric motility, the administration of metoclopramide (0.2–0.4 mg/kg SC every 6–8 hours) may improve the cat’s appetite. If the cat remains anorexic, esophagostomy tube feeding is initiated.
LONG-TERM MANAGEMENT AND COMPLICATIONS

After discharge, patients are evaluated weekly for the first 6 to 8 weeks, and if stable the frequency of visits is gradually decreased. Eventually, the visits can be decreased to every 3 to 4 months for long-term maintenance. A thorough physical examination is essential in these patients; however, firm abdominal palpation should be avoided. Body temperature and weight are monitored carefully, and steady weight gain often begins within the first month after discharge. If the patient is doing well clinically, a renal panel, packed cell volume, total protein, cyclosporine level as well as evaluation of a free catch urine should be adequate at each visit. Typically, anemia secondary to chronic renal failure resolves within 1 month after surgery.\(^{51}\) If anemia persists, but graft function remains adequate, iron supplementation should be considered. If concerns exist, a full complete blood count and serum chemistry panel as well as a urine culture should be performed. Regardless, a full complete blood count and chemistry profile should also be performed every 6 to 12 months, even in the stable patient. Toxoplasmosis titers should be performed regularly even in patients that tested negative before transplantation and immunosuppression. Echocardiography should be performed every 6 to 12 months in patients diagnosed with underlying cardiac disease before transplantation and treated accordingly if complications exits. If there are any concerns regarding allograft function, an abdominal ultrasound examination should be performed as an initial investigative step to identify any evidence for a urinary obstruction or thrombosis. The feeding tube is removed once oral intake of food and water is deemed appropriate.

LONG-TERM COMPLICATIONS

Complications can be divided into those causing allograft dysfunction and those secondary to immunosuppressive therapy (Box 5). Some of the more common complications are acute rejection, retroperitoneal fibrosis, and calcium oxalate urolithiasis.

**Acute Rejection**

The incidence of acute allograft rejection in the cat ranges from 13% to 26% and occurs most commonly within the first few months after surgery (Fig. 10).\(^{1,52}\) Common

<table>
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<tr>
<th>Box 5 Long term complications</th>
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<tr>
<td><strong>Causes of allograft dysfunction</strong></td>
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<tr>
<td>• Acute rejection</td>
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<tr>
<td>• Retroperitoneal fibrosis</td>
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<tr>
<td>• Calcium oxalate nephrosis</td>
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<tr>
<td>• Delayed graft function</td>
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<tr>
<td>• Hemolytic uremic syndrome</td>
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<tr>
<td>• Vascular pedicle complications</td>
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<tr>
<td><strong>Complications associated with immunosuppressive therapy</strong></td>
</tr>
<tr>
<td>• Infection (bacterial, viral, fungal, parasitic)</td>
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causes of rejection include low cyclosporine concentrations, poor owner compliance, and presence of another disease process that potentiates the rejection episode. Clinical signs may include depression, decreased appetite, and polyuria/polydipsia; however, clinical signs in some affected animals may be minimal. For this reason, frequent evaluation of cyclosporine levels is particularly critical during the early postoperative period to maintain the cyclosporine level in a therapeutic range and hopefully prevent changes in serum creatinine. Additionally, temperature should be monitored, because hyperthermia may be associated with allograft rejection. Histopathologic, sonographic, and scintigraphic evidence of allograft rejection in cats has been described previously.

The protocol for treatment of acute allograft rejection is listed in Box 6. If abdominal ultrasound examination capabilities are available at the clinic, the allograft should be evaluated to rule out a ureteral obstruction, and a urine sediment and culture should be evaluated to rule out an obvious infection. Treatment should not be delayed; therefore, these tests should only be performed before initiating therapy if these diagnostic capabilities are available in-house.

A rare complication of acute allograft rejection that has been identified in 2 cats is allograft rupture. The pathogenesis is thought to be related to an increase in intragraft

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**Box 6**

**Treatment for acute allograft rejection**

**Do not delay treatment**

1. Place intravenous catheter and submit complete blood count, chemistry panel, packed cell volume, total solids, and cyclosporine level

2. Intravenous cyclosporine (50 mg/mL). Give 6.6 mg/kg of the solution slowly over 6 hours. Each milliliter of the IV solution should be diluted in to 20 to 100 mL 0.9% NaCl or D5W and administered as a constant rate infusion

3. Fluid bag and line should be covered so that the medication is not exposed to light

4. Solu-delta cortef: Give 10 mg/kg IV every 12 hours

5. If azotemia has not resolved, dosing can be repeated the following day

6. After resolution of azotemia, patient is placed back on oral medication
pressure and cortical and capsular ischemia secondary to interstitial/medullary edema and cellular infiltration. A partial ureteral obstruction in conjunction with an infection potentiating a rejection episode was likely the cause of allograft rupture in a 5-year-old domestic shorthair cat.

Retroperitoneal Fibrosis

Although partial and complete ureteral obstructions have occurred secondary to stricture or granuloma formation, the most common cause of ureteral obstruction is retroperitoneal fibrosis. Twenty-nine of 138 recipients (21%) developed clinically important retroperitoneal fibrosis a median of 62 days (range, 4–730 days) after renal transplantation. Similar to human patients, males were overrepresented (66%). In human transplant patients, the condition has been associated with infection, operative trauma, presence of foreign material such as talc, insufficient immunosuppression, urine leakage, or hemorrhage during the transplant procedure. In human surgical patients who have not undergone a transplant, the condition has been identified secondary to a local inflammatory response to atherosclerotic disease and has occurred concurrently in patients with a systemic autoimmune disease. Hydronephrosis often without hydroureter is noted on abdominal ultrasound examination, and occasionally a capsule can be identified surrounding the allograft. Surgical ureterolysis has been successful in relieving the extraluminal compression and restoring normal renal function. Recurrence of the condition can occur and has been treated successfully with repeating surgical ureterolysis.

Calcium Oxalate Urolithiasis

Previous work in cats has found that renal transplantation is a treatment option for cats whose underlying cause of renal failure is associated with calcium oxalate urolithiasis. No difference in long-term outcome was found in a control group of 49 cats whose underlying cause of renal failure was not related to stone disease and a group of 13 stone formers. Development of calculi within the allograft occurred in 5 of the 13 cats and in 4 of these 5 cats calculi were found attached to the 8-0 nylon suture at the ureteroneocystostomy site. Two cats that formed calculi after surgery were diagnosed with a concurrent urinary tract infection. A change in suture material to the use of absorbable suture material for the ureteroneocystostomy has eliminated the nidus for stone formation. Patients that are known stone formers should be screened more thoroughly for infection.

Fig. 11. Retroperitoneal fibrosis in a cat. Note the thick grey-white fibrous tissue surrounding the allograft kidney and ureter (A). Surgical ureterolysis. The ureter has been dissected free from the encasing fibrous tissue (elevated by Q-tip) and the mechanical obstruction of the ureter has been eliminated (B).
Infection

Infectious complications, both acquired and opportunistic, are common in the feline renal transplant recipient and can result in morbidity and mortality and also may activate the rejection process (Fig. 13). In a retrospective study of 169 feline recipients, 47 infections developed in 43 cats. Bacterial infections were most common followed by viral, fungal, and protozoal. One-half of the infectious complications occurred within the first 3 months after surgery, when higher levels of immunosuppression were maintained. Risk of infection was increased in patients that developed diabetes mellitus. The prevalence of certain types of infections vary depending on

Fig. 12. A 10-year-old female spayed (FS) domestic short hair that developed an acute onset of azotemia 2 years after renal transplantation. Abdominal radiographs and ultrasound examination identified multiple calculi within the renal pelvis causing an obstruction. The owner elected euthanasia. Stone analysis revealed that the stones were 100% calcium oxalate (A). Abdominal ultrasound image of a different cat identified a ureteral obstruction secondary to calculi attached to the 8-0 nylon suture at the ureteroneocystostomy site (arrow) (B). Both cats were diagnosed with calcium oxalate urolithiasis in conjunction with chronic interstitial nephritis at the time of presentation for transplantation.

Immunosuppressive Therapy

Fig. 13. Pyogranulomatous cystitis associated with T gondii in an 8-yr-old FS domestic short hair. A mass was identified on abdominal ultrasound 6 weeks after transplantation, resulting in a ureteral obstruction. Surgery was performed to remove the mass (A). Histologic examination of the mass revealed severe necrotizing pyogranulomatous cystitis with numerous intralesional tachyzoites and bradyzoite cysts (arrow) (B).
the location of the transplant facility. Infection was second only to rejection as the leading cause of death or euthanasia in the feline renal transplant recipient. Treatment protocols and treatment success can vary greatly depending on the pathogen involved.

NEOPLASIA

In 3 separate veterinary studies, lymphoma was the predominant neoplasia identified (Fig. 14). Similar to posttransplant lymphoproliferative disorders in humans, all lymphomas were mid- to high-grade, diffuse, large B-cell lymphomas. The most likely mechanism for development of neoplasia in humans is the activation of latent oncogenic viruses such as the Epstein-Barr virus. Other potential mechanisms include promotion of DNA mutations from cyclosporine therapy, decreased immune surveillance and neoplastic cell clearance, and chronic antigenic stimulation from the allograft. In 2 recent studies, posttransplant malignant neoplasia occurred in 24% and 22.5% of the cases and cats that underwent transplantation and immunosuppression had a 6.1 and 6.6 times higher odds of developing a malignancy than a group of age-matched controls. Additionally, cats undergoing renal transplantation and cyclosporine-based therapy had a 6.7 times higher odds of developing lymphoma compared with controls. The development of neoplasia did not significantly affect overall survival.

DIABETES MELLITUS

The feline renal transplant recipient is 5.45 times as likely to develop diabetes mellitus compared with cats in chronic renal failure that have not undergone transplantation. In a large multicenter study of 187 patients, 13.9% of cats developed posttransplant diabetes at a median of 132 days from the time of surgery. The mortality rate for cats with diabetes mellitus was 2.38 times higher than that of the feline renal transplant recipients that did not develop diabetes and the median time from diagnosis until death was 275 days. Glycemic control can be successfully maintained with a number of management techniques, including dietary management, dose reduction of immunosuppressive therapy, and the use of glipizide or insulin therapy. In some cases, a combination of therapies is necessary.

Fig. 14. An 11-year-old FS domestic short hair with a 1-week history of lethargy and vomiting approximately 22 months after renal transplantation. Abdominal ultrasound examination revealed a 10-cm mass involving segments of the small and large intestine. A biopsy of the mass confirmed lymphoma.
COMPLICATIONS IN DOGS

Information regarding the canine renal transplant recipient is limited. Commonly reported complications include thromboembolic disease, allograft rejection, infection (bacterial, fungal, or protozoal) of the respiratory tract, central nervous system, nasal cavity, skin, and upper and lower urinary tracts. Two canine patients from the author’s facility developed skin infections 16 weeks (Nocardia spp. and Staphylococcus aureus) and 17 weeks (Mycobacterium spp.) after transplantation; both responded to appropriate antibiotic therapy. Successful management of pneumonia secondary to a multidrug-resistant Pseudomonas has been described.

Multiple types of neoplasia, including transitional cell carcinoma, ceruminous gland adenocarcinoma, and pheochromocytoma, were identified in 1 canine patient that survived 60 months after transplantation surgery.

OUTCOME

Renal transplantation in cats offers a unique method of treatment, improving a patient’s quality of life and prolonging life expectancy compared with the medical management of renal failure. Based on published and unpublished reports, 70% to 93% of cats have been discharged after surgery, and median survival times have ranged from 360 to 653 days (LR Aronson, personal communication, 2015). Currently at the authors’ facility, the 6-month and 3-year survivals are 79% and 32%, respectively, and the longest survivor lived for approximately 13 years after his surgery. Continued experience with the management of both short- and long-term complications, as well as the ability to identify specific risk factors during the perioperative and postoperative period, will hopefully continue to improve long-term outcomes in these patients. Median survival was only 24 days (range, 0.5–4014) in a retrospective case series of 26 dogs. One-half of the dogs in this study received a kidney from a related donor and one-half received a kidney from an unrelated donor. The lack of an effective protocol for immunosuppression in unrelated dogs suggests that, at this time, renal transplantation should be reserved only for dogs in which a compatible relative is available as a potential donor.

REFERENCES


