

Genitourinary Interventions in Autosomal Dominant Polycystic Kidney Disease: Clinical Recommendations for Urologic and Transplant Surgeons

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Abstract

Autosomal dominant polycystic kidney disease is the fourth most common single cause of end-stage renal disease worldwide with both renal and extrarenal manifestations, resulting in significant morbidity. Approaches to the management of this disease vary widely, with no broadly accepted practice guidelines. Herein, we reviewed the various surgical and interventional management options that are targeted toward treating the symptoms or addressing the resulting kidney failure. Novel treatment modalities such as celiac plexus blockade and renal denervation appear to be promising in pain relief; however, further studies are lacking. Renal cyst decortication seems to have a higher success rate in targeting cyst-related pain compared with aspiration only. In terms of requiring major surgical intervention, such as need and timing of native nephrectomy, there are several considerations when deciding on transplantation with or without a pretransplant native nephrectomy. Patients who are not candidates for native nephrectomy may consider transcatheter arterial embolization. Based on our review of the contemporary indications for genitourinary interventions in the management of autosomal dominant polycystic kidney disease, we

propose an algorithm that depicts the decision-making process on assessing the indications and timing of native nephrectomy in patients with end-stage renal disease awaiting transplant.

Key words: End-stage renal disease, Native nephrectomy, Renal transplant complications, Renal transplantation

Introduction

Polycystic kidney disease is an inherited systemic disease characterized by numerous fluid-filled cysts in the kidneys.¹ It is one of the most common genetic renal diseases, accounting for up to 10% of patients who develop end-stage renal disease (ESRD).^{2,3} Polycystic kidney disease can be inherited as either an autosomal dominant trait, known as autosomal dominant polycystic kidney disease (ADPKD), or as an autosomal recessive one.⁴ Almost 90% of patients with polycystic kidney disease have ADPKD.⁵ A main feature of ADPKD is significantly enlarged kidneys caused by cystogenesis and cell proliferation, resulting in huge cysts that are responsible for many of the disease manifestations.⁶ Kidneys in ADPKD patients can reach up to 40 cm in length (approximately 3 to 4 times the normal length), and up to 8 kg in weight, resulting in significant renal dysfunction.⁷ Patients with ADPKD may experience abdominal pain, hematuria, and infected cysts, in addition to many nonrenal complications.⁶ Fifty percent of these patients will reach ESRD by the time they are 60 years old.⁸

Approaches to the management of ADPKD vary widely, with no broadly accepted practice guidelines. There are several medical and surgical treatment modalities that target the symptoms and address the resultant chronic kidney disease.

In this study, our objective was to explore the role of minimally invasive and open surgical interventions utilized in the management of ADPKD, when initial

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medical treatment fails. Another rare indication would be intervention in an attempt to stabilize kidney function and control hypertension by cyst decortication.

Herein, we review the current indications for intervention in ADPKD, including the role of native nephrectomy (NN). We also propose an algorithm describing the timing and necessity of nephrectomy in candidates, whether pre- or posttransplant.

Interventions for Intractable Pain

Around 60% of ADPKD patients report pain that could be multifactorial.⁸ It can be related to ruptured cysts, passage of stones (stone incidence is up to 30% in ADPKD patients), urinary tract infections (cyst infections or pyelonephritis), and /or to compression of enlarged cysts on surrounding renal parenchyma with distension of renal capsule or compression on adjacent organs.^{8,9} Regardless of the etiology, pain is managed in a sequential multidisciplinary approach.^{3,10}

When pharmacological and conservative measures for pain are no longer successful, other interventions become necessary. These include nerve blocks, renal denervation (surgically or by percutaneous transluminal catheter-based radio-ablation), kidney cyst aspiration and sclerotherapy, and surgical interventions aimed at cyst decortication or deroofing.^{3,11}

Celiac plexus and splanchnic blockade

Celiac or splanchnic blockade has been recently introduced in patients with noncancer-related pain, including those with ADPKD or large pancreatic cysts.^{9,12,13} Local anesthetics are initially used in such blocks. If these agents are effective, neurolytic agents with longer half-life are introduced for extended efficacy.¹⁴ However, studies reporting efficacy of such blockade in ADPKD patients are scarce. A cohort study by Casteleijn and associates from the Netherlands reported the results of 44 ADPKD patients who underwent sequential nerve block.¹⁵ After 12 months of follow-up, substantial improvement in pain was noted in 36 patients, leading to cessation of daily opioid use, with minimal adverse events related only to the procedure itself.¹⁵ Their data indicated that a multidisciplinary stepwise treatment protocol, with the application of sequential nerve blocks, is effective in obtaining substantial relief from chronic refractory pain.¹⁵ Caution should

be taken to exclude other causes of ADPKD-related pain, such as infection, stone, or ruptured cyst, before applying blockade.

Renal denervation

A relatively new treatment to help relieve renal capsule-related pain is renal denervation. Those nerves are in proximity to the renal artery. Denervation can be performed laparoscopically, or even percutaneously through a catheter-based transluminal approach, to ablate both efferent and afferent renal sympathetic nerve fibers.¹⁶ Valente and associates were the pioneers of this procedure.¹⁷ These authors performed a successful laparoscopic bilateral renal denervation on a 41-year-old ADPKD patient with disabling pain.¹⁷ Three other publications reported the use of renal denervation, with almost total pain relief.^{16,18,19} Furthermore, sympathetic nerve ablation is currently under trial for refractory hypertension.²⁰ In summary, the role of renal denervation and its efficacy in relieving pain and controlling hypertension in patients with ADPKD are not well established, and further investigations are needed.

Minimally invasive kidney cyst aspiration with or without sclerotherapy

Although it was initially described in a series of 11 patients by Bennett and colleagues in 1987, percutaneous ultrasonographic-guided renal cyst aspiration has been an early intervention to relieve ADPKD-related pain.²¹ Others investigations have followed¹⁵; however, most cases have reported transient pain relief, with around one-third of patients exhibiting pain relief for up to 18 months.²¹ This has mainly been attributed to fluid secretion and reaccumulation, due to active chloride transport process, causing cyst regeneration.⁹ Aspiration alone is useful when few dominant cysts are responsible for the symptoms, which is rarely noted in ADPKD.¹¹

As an adjunct to aspiration, sclerotherapy has been incorporated by injecting sclerotic agents such as absolute ethanol, N-butyl cyanoacrylate, minocycline hydrochloride, and iodized oil.²² This can somewhat increase the success rate, as it prohibits early cyst reformation. Kim and associates reported an 80% relief of patients after 54 months of follow-up after using both N-butyl cyanoacrylate and iodized oil.²³

Cyst decortication, fenestration, or deroofting

A practical and relatively simple approach to relieve renal pain is decortication or fenestration of large cysts, as this will alleviate pressure on the kidney capsule and surrounding compressed parenchyma.¹¹ Decortication can either be performed by an open or laparoscopic/robotic approach, through access of the intra- or retroperitoneal space.²² The retroperitoneal approach avoids spillage into the abdominal cavity, which can result in ileus and peritonitis, particularly in cases of cyst infection. This technique exhibits a higher success rate, of 85% to 90%, compared with aspiration only.²⁴⁻²⁶

A substantial pain relief was noted in a series of 37 ADPKD patients who underwent laparoscopic decortication for refractory pain. Almost two-thirds of those patients witnessed more than 50% improvement in pain at follow-up of 11 years.²⁶ After failure of all previously mentioned methods, NN was an option to manage intractable pain.²⁷

Attempts at Stabilizing Renal Function

The success of any surgical intervention in preserving kidney function from deteriorating is a matter of debate. The role of decortication in preserving renal function has been entertained in several publications, but results were anecdotal. Surgical cyst decortication was associated with reduced kidney function in those with initially compromised glomerular filtration rate but overall did not exhibit a significant impact on renal function in most studies. The role of this surgical procedure in altering the natural course of renal function is yet to be determined.^{26,28} We strongly believe that at present and in the absence of level I evidence supporting percutaneous or surgical intervention for preserving renal function. In addition, we emphasize that the only scenario for intervention to preserve kidney function is in cases of cyst impingement on the collecting system, causing significant obstruction.

Preparation for Transplantation

In symptomatic ADPKD patients who develop ESRD and are transplant candidates, it is prudent to carry out the customary clearances performed in the general ESRD populations to allow a safe transplant. Nevertheless, these patients, who have massively enlarged kidneys secondary to the huge cysts, are eligible for pretransplant nephrectomy. We herein highlight NN indications with a detailed view on the

surgical complications and the timing in relation to transplant.

Patients who are deemed nonsurgical candidates can also be offered an alternative option to NN, which is transcatheter arterial embolization (TAE) of the renal arteries. The concept of embolization emerges from the fact that it reduces kidney volume in ADPKD patients.²⁹ Embolic agents are placed in the main renal arteries, thus obstructing blood flow to the kidneys, causing renal ischemia and subsequent shrinkage of the native kidneys. Several agents have been utilized, including polyvinyl alcohol, ethanol, and microcoils.³⁰

Postembolization syndrome is a common consequence of TAE, but it is transient and usually does not last more than 72 hours. Prophylactic antipyretics, antiemetics, proton pump inhibitors, antibiotics, and corticosteroids are recommended.^{30,31} The failure rate of TAE is noted to be around 4% and mostly due to missed accessory renal arteries and initially large basal renal volume.³¹

Native Nephrectomy in Autosomal Dominant Polycystic Kidney Disease

As mentioned before, a radical solution for intractable pain, uncontrolled hypertension, and persistent infection, not responsive to medical treatment, is NN. Other indications for NN include symptomatic nephrolithiasis, recurrent and/or severe bleeding/hematuria, suspicion of renal malignancies, and space restrictions prior to transplant.³² Nonetheless, the decision to proceed with NN and its timing are not without caveats and should be planned after careful assessment and in the context of a variety of considerations. In a unique study aimed at identifying patients who may require NN, Cristea and associates used the pretransplant maximal kidney length (MKL) to predict ultimate kidney fate.³³ Pretransplant MKL in 84 ADPKD patients was measured from computed tomography scans and ultrasonographic images. Their study revealed that a pretransplant MKL of more than 21.5 cm is a strong predictor of subsequent nephrectomy.³²

Surgical approaches and complications

A variety of surgical approaches exist for NN, including an open approach and a minimally invasive laparoscopic approach, with or without hand assistance. The latter can either be performed in a transperitoneal or a retroperitoneal fashion.³⁴

Although working space is greatly limited and the large cysts distort anatomy, laparoscopic NN has proven to be technically feasible and is gaining popularity. Extensive experience is necessary to optimize patient outcomes, and there must be a low threshold for conversion if needed. Unilateral laparoscopic nephrectomy for ADPKD was first reported in 1996,³⁵ following which there have been multiple reports on unilateral, simultaneous bilateral, and simultaneous bilateral laparoscopic NN in association with kidney transplant.^{36,37}

The largest kidneys can be removed laparoscopically through an extended hand-port infraumbilical incision, which is still significantly smaller than the open nephrectomy incision.³⁸ This translates into a lesser need for analgesics, diminished ileus, faster recovery, and shorter hospital stay.³⁹ The renal allograft can be transplanted intraperitoneally, through the same lower abdominal midline incision used for kidney extraction. Others, however, have utilized a second Gibson incision, placing the allograft extraperitoneally, thus obviating the risk for rotation and securing access in case of future complications, without reentering the peritoneum.

Martin and colleagues reported the Mayo clinic series of laparoscopic bilateral NN in 37 patients, of whom 15 patients underwent simultaneous NN and kidney transplant, whereas the other 22 patients underwent staged laparoscopic NN followed by elective transplant at a later date.³⁷ Similar operative time and blood loss were noted in the 2 cohorts, with simultaneous group having a significantly shorter hospitalization (5 vs 7 days in the simultaneous and staged groups, respectively). The authors concluded that the recovery was faster, with patients having 1 anesthetic, 1 operation, and 1 hospitalization. Furthermore, simultaneous cases were completed successfully without any intraoperative complications or conversions to open approach, and all patients had immediate graft function. A closer look into the patients and their postoperative course revealed that 7 of 15 patients (45%) underwent a second Gibson incision for transplant, with 1 patient needing reoperation on postoperative day 1 for diminished arterial flow and requiring intraperitoneal repositioning (no additional details provided). Another patient in this series with preoperative anemia and history of Osler-Weber-Rendu syndrome required reoperation due to reduced flow on Doppler ultrasonography and was transfused with 6 units of

blood. A third patient with an estimated blood loss of 550 mL developed postoperative hypotension and required 2 units of blood transfusion. Three patients had to be readmitted in the first month: one for subacute pulmonary embolism, the second for dehydration due to acute pancreatitis/diarrhea, and the third for hypotension. The authors also reported that all patients had good graft function at last follow-up but mentioned that 2 patients were being treated for recurrent antibody-mediated rejection. The overall surgical complication rate was 46% (53% vs 41% for the simultaneous and staged groups, respectively), and major complications (Clavien group 3 to 5) were noted in 20% and 23% of the simultaneous and staged groups, respectively. Nevertheless, authors continue to favor the simultaneous approach.

Kramer and colleagues reported the University of Maryland experience in 20 patients who underwent open bilateral NN with simultaneous transplant.⁴⁰ Patients had significant blood loss, on average 723 mL (50-2000 mL), necessitating blood transfusions in 90% of the patients, averaging 3.3 units per patient.

Patel and associates reported a series of ADPKD patients who underwent transplant at Guy's Hospital in London.⁴¹ Of 157 patients transplanted, only 31 (20%) needed NN (pretransplant NN in 10 patients, simultaneous in 1 patient, and post-transplant NN in 20 patients). The vast majority of patients in this series did not require NN, and the authors concluded that indications for NN should be strict, with timing individualized relative to transplant.⁴¹

Skauby and associates compared the outcomes of 159 patients, half who underwent kidney transplant alone (group A) and half who underwent simultaneous NN and transplant (group B).⁴² Group B experienced more intraoperative events and required more blood transfusion (1.6 vs 0.1 units for group A). There was a significantly higher number of patients requiring blood transfusions in group B versus group A (37 vs 3 patients). The average blood requirement per patient in group B versus group A was 1.6 versus 0.1 units. Several other postoperative complications were noted in this study, including lymphoceles, hematomas, arterial thrombosis, splenic rupture necessitating splenectomy, hydrothorax, and intestinal perforation. There was no difference in graft and patient survival between the 2 groups, with the author concluding that the simultaneous

procedure did not seem to negatively impact patient outcomes.⁴²

Transplantation in Autosomal Dominant Polycystic Kidney Disease

As per the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, transplantation is an ideal choice of renal replacement therapy.³ Nonetheless, transplant in ADPKD patients has some special considerations. The transplanted kidney is best placed in the iliac fossa, via a lower Gibson incision, allowing adequate exposure, direct identification of the iliac vessels, and proper retroperitoneal placement of the graft. This warrants ample space for implantation, which could be restricted in case of enormous polycystic kidneys that extend beyond the iliac crest.³⁸

Outcomes of kidney transplant in patients with ADPKD are similar to those of non-ADPKD patients, based on the reported experience of several transplant centers. Illesy and colleagues followed 80 patients with ADPKD who had undergone kidney transplant for 25 years.⁴³ They had similar graft survival and overall survival rates compared with non-ADPKD patients. This was in accordance with other studies reporting similar rates.^{44,45} A retrospective study by Goncalves and colleagues from Portugal evaluated 48 transplant patients with ADPKD in terms of graft survival and posttransplant complications.⁴⁶ Data were compared with data in 397 non-ADPKD transplant patients. There was a significantly higher incidence of posttransplant diabetes mellitus in the ADPKD group (33.3% vs 17.1%, but no difference was noted in terms of posttransplant hypertension and erythrocytosis). Immediate graft function, immunological graft losses, and patient survival between the ADPKD group and the non-ADPKD group were also not significant.⁴⁶ Roozbeh and associates conducted a retrospective evaluation of 1200 transplant patients, 51 of whom had ADPKD.⁴⁷ After 67 months of follow-up, patient outcome was slightly better in the ADPKD group, without any increased complication rate attributed specifically to ADPKD.

Justification and Timing of Native Nephrectomy in Context of Renal Transplant

Patients with ADPKD can undergo nephrectomy at various time intervals, in context of their transplant. There is persistent controversy regarding the optimal

timing and need for nephrectomy. Several studies have addressed this issue.

Pretransplantation nephrectomy

Anselmo and colleagues analyzed 53 patients who underwent both open NN and transplant to evaluate the indications, timing, and complications of NN.⁴⁸ Of 53 patients, 46 underwent pretransplant, 6 underwent posttransplant, and 1 underwent simultaneous NN and transplant. The major indication for NN in the pretransplant group was spatial restriction, whereas the major indication in the posttransplant group was infection. Complications were bleeding in 3 cases (less than 6% of patients) and incisional hernia in 5 cases. Although these authors did not perform subgroup analyses to address the risk of morbidity relative to the timing of native nephrectomy, they concluded that NN should be performed only when clearly indicated; in addition, in their experience, pretransplant NN is preferred.⁴⁸ Nevertheless, pretransplant NN is not well supported by the transplant community and is usually performed with stringent indications.⁴² One possible explanation is the potential risk for blood transfusions and consequent allosensitization.

Maxeiner and associates conducted another retrospective study to evaluate data of ADPKD patients undergoing NN, either before or after transplant, and to identify advantages of optimal surgical timing with postoperative outcomes in the 2 groups.⁴⁹ Group 1 consisted of patients who underwent NN before transplant and group 2 consisted of patients undergoing NN posttransplant. Patients in group 2 had a significantly shorter hospital stay and no postoperative kidney failure, whereas more severe complications were observed in group 1, albeit being statistically insignificant. Based on that, the time of NN, before or after transplant, does not seem to affect short- and long-term outcomes.⁴⁹ Therefore, NN can be safely performed either before or after kidney transplant, depending on the intricacies of indications and the patient's status.

We believe that unilateral nephrectomy, compared with bilateral nephrectomy, is a less morbid procedure and should be reserved for patients with recurrent pyelonephritis and cyst infection and those with recurrent hemorrhage and need for blood transfusion. The index kidney, causing the bleeding, is usually confirmed by cystoscopy at time of

nephrectomy. Alternatively, the larger kidney should be removed for spatial consideration on the ipsilateral side of future transplant.

Posttransplant nephrectomy

Advocates of this approach support the fact that preemptive transplant done in the course of mild to moderate renal insufficiency is superior to when performed during ESRD, since a longer period of dialysis negatively influences transplant.^{50,51} The presence of non anuric native kidneys may still improve quality of life and avoid fluid shift that may occur during transplant. As such, a small series published by Kaplan and associates revealed a better perioperative outcome in the posttransplant nephrectomy group compared with the pretransplant nephrectomy group, in terms of shorter hospital stay and fewer complications.⁵²

Chebib and associates at the Mayo Clinic reported their experience with indications, timing, and complications of NN in ADPKD patients.⁵³ Their study included 35 ADPKD patients who underwent pretransplant NN versus 79 who underwent posttransplant NN. Patients were followed up until graft loss, death, or closure of study (June 2014). Patients with posttransplant NN had significantly fewer overall complications.⁵³ Patient and graft survival rates were similar in the pretransplant NN group compared with other transplant recipients. It was also noted that posttransplant NN did not affect survival rates. The authors concluded that posttransplant NN does not negatively affect patient and graft survival and actually has fewer complications than pretransplant NN. Other advantages of posttransplant NN is that the procedure is performed in the setting of improved kidney function.

Kirkman and associates from Manchester University Hospitals reported on 35 patients who underwent pretransplant nephrectomy.⁵⁴ Patients with pretransplant nephrectomy had more critical care unit admissions, more complications, and higher mortality than the posttransplant group. Therefore, nephrectomy after transplant appears to be the preferred and safer approach. They supported pretransplant NN only when there are strict and clear indications.⁵⁴

Simultaneous nephrectomy with transplant

As mentioned above, simultaneous NN with kidney transplant has its own risks and complications, such as blood loss and resultant need for blood

transfusion, graft hypoperfusion, visceral organ lacerations and injury, risk of sepsis from cyst rupture, fluid shift, risk of postoperative acute tubular necrosis, and intraperitoneal graft torsion.⁴⁰ As such, bilateral nephrectomies are not embraced among surgeons.

At first glance, it seems that most authors that reported on the feasibility of simultaneous NN and transplant in one setting have concluded that this procedure offers unique advantages in terms of a single hospitalization, with long-term results similar to staged or transplant-only procedure. A critical look into the postoperative course of these patients, in the majority of these reports, has shown a substantially higher risk of hemorrhage, with transfusions reaching up to 90%, reexploration for compromised blood flow to the allograft, and readmissions for major complications. The simultaneous approach has historically been criticized as it increases perioperative risks for recipients, which could be attributed to a more extensive surgery, compared with an elective transplant, resulting in higher fluid shifts, blood loss, and profound hypotension. The consequent adverse effects on the allograft perfusion are to be expected. Alternatively, graft hypoperfusion could be a sequela of intraperitoneal torsion when a single lower midline incision is used, compromising graft stability and fixation, compared with the retroperitoneal approach. Our group feels that putting these patients at major risk that can potentially affect the recipient or allograft are a big price to pay simply to decrease the number of incisions or hospitalizations. Furthermore, these risks can be readily obviated by staging the NN procedure, thus eliminating the homeostatic and clotting deficiencies observed in ESRD patients undergoing surgeries, and ensuring that kidney transplant is performed in the most optimized and elective setting. In an era of individualized medicine and shared decision-making, there will be the anecdotal patient who will request simultaneous bilateral NN and transplant. We advise that NN be performed after thorough discussion with the patient (and family), explaining all risks involved, and following stringent perioperative criteria.

Decision Making as to Indications and Timing of Nephrectomy and Transplantation

As demonstrated above in the various studies, there is a need for a consensus on the timing and

indications of NN in ADPKD patients undergoing transplant. When we consider the contemporary literature review and our own experiences, we herein propose an algorithm to determine the need and timing of nephrectomy in transplant patients with ADPKD (Figure 1). This algorithm serves as a guide to decision making in managing ADPKD transplant candidates.

Conclusions

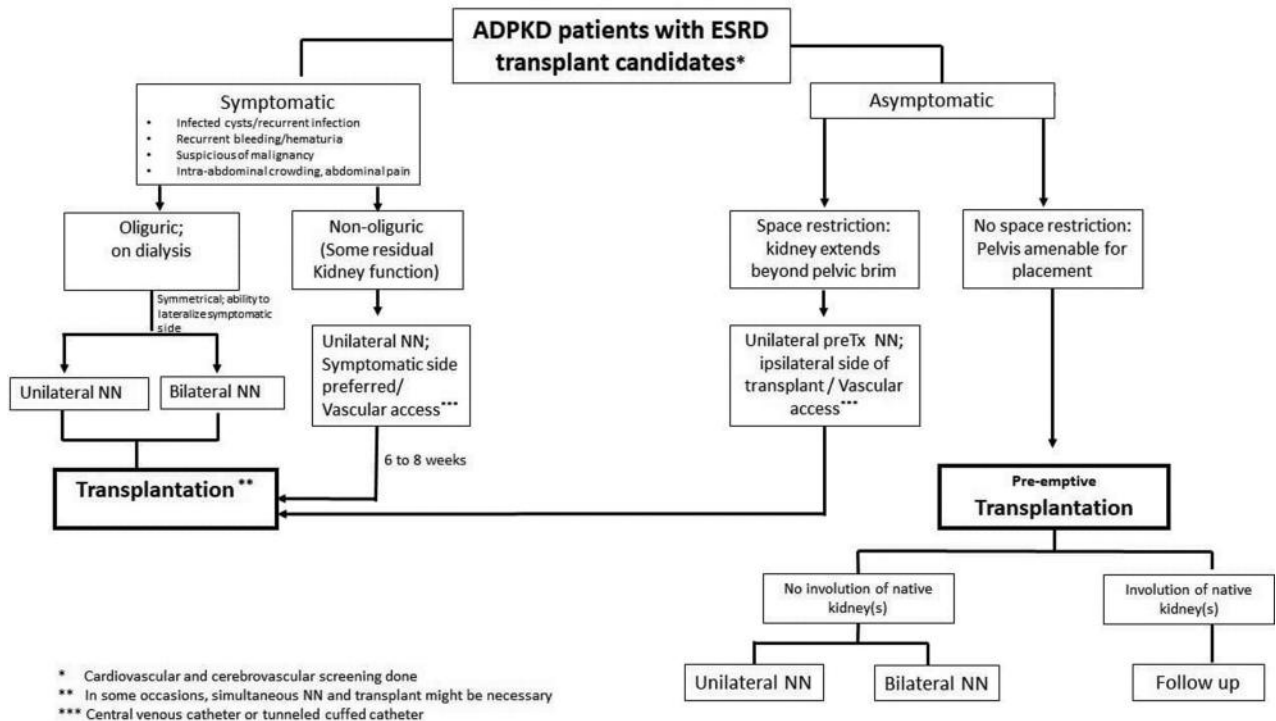
Autosomal dominant polycystic kidney disease is the fourth most common single cause of ESRD worldwide with renal and extrarenal manifestations. We reviewed various surgical management options targeted toward treating associated symptoms, such as cyst aspiration and renal denervation, or that address the resulting kidney failure (nephrectomy or transplant). Newer treatment modalities such as celiac plexus blockade and renal denervation appear to be promising in pain relief; however, studies with large numbers of patients are lacking to support their use. In terms of more invasive surgical procedures, there are several considerations when deciding on transplant with or without NN. We reserve NN solely for symptomatic patients or those with space

restrictions and insist on having clear indications before its performance. We propose a structured algorithm to better assess the need and timing of NN in transplant patients with ADPKD.

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Figure 1. Algorithm to Help Define the Need and Timing of Native Nephrectomy in Patients With End-Stage Renal Disease Secondary to Autosomal Dominant Polycystic Kidney Disease Who Are Considered for Renal Transplant



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