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Surgical Cyst Decortication in Autosomal Dominant Polycystic Kidney Disease

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Abstract

Purpose: To provide a summary of the relevant literature regarding the impact of surgical cyst decortication on hypertension, renal function, and pain management in patients with autosomal dominant polycystic kidney disease (ADPKD).

Methods: Data collection was conducted via a Medline search using the subject headings autosomal dominant polycystic kidney disease, surgery, decortication, and marsupialization. Additional reports were derived from references included within these articles.

Results: Despite a trend for improved blood pressure control after cyst decortication in some studies, this cumulative review of the literature did not provide consistent evidence supporting the role of this procedure in blood pressure management in patients with ADPKD. Surgical cyst decortication was associated with renal deterioration in a subset of patients with compromised baseline renal function but did not otherwise appear to have a significant impact on renal function in the majority of studies reviewed. Improvement in chronic pain after this procedure was ubiquitously reported across all studies examined.

Conclusions: Despite a potential role in blood pressure management in the setting of ADPKD, surgical cyst decortication has not been definitively shown to alleviate hypertension in this clinical setting. Renal function does not appear to improve following this surgery. Patients with compromised baseline renal function appear to be at increased risk for further deterioration in renal function after cyst decortication, although the role of this procedure in altering the natural trajectory of renal failure in this patient subset needs further investigation. Cyst decortication is highly effective in the management of disease-related chronic pain for the majority of patients with ADPKD, providing durable pain relief in this patient population.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenetic disease, affecting 300,000 to 600,000 Americans. It is caused by a genetic mutation in one of the polycystin genes, PKD1 and PKD2, more frequently PKD1 (85%–90% of cases), which is associated with earlier onset and increased severity of disease. These genes encode membrane-spanning proteins that, if mutated, disrupt normal function of the primary cilium on tubule epithelial cells and are associated with a number of functions believed to regulate tubular and vascular development in the kidneys, liver, pancreas, heart, and brain. Cyst formation occurs simultaneously with recruitment of macrophages and fibroblasts. As kidneys progress to end-stage disease, cysts are surrounded by fibrosis and atrophic tubules. The disease presents in adulthood as cysts develop in multiple organ systems.

The pathophysiology believed to result from cyst formation manifests as hypertension, deteriorating renal function, and pain. Enlarging cysts compress renal parenchyma and vasculature to cause an ischemia-induced activation of the renin-angiotensin-aldosterone system (RAAS), as well as pain and trauma to nephrons. Uncontrolled hypertension is associated with accelerated progression to end-stage renal disease (ESRD) and ultimately death.

Treatment of patients with ADPKD is a complex and inexact challenge to the medical community but is traditionally directed at improving or stabilizing renal function, controlling pain, and treating hypertension. Optimal care of these

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patients, however, continues to be the subject of numerous studies. The Consortium for Radiologic Imaging Studies in PKD has recently identified serum high-density lipoprotein-cholesterol, urine sodium excretion, and 24-hour urine osmolality as “potentially modifiable factors” in a search for therapeutic targets. Furthermore, drug therapies targeted to abnormal molecular mechanisms present in ADPKD are in various stages of clinical trials (Clinical Trials ID NCT00428948, NCT00346918, NCT01214421). Additional morbidity associated with ADPKD includes a debatable increased incidence of renal-cell carcinoma (RCC), although evidence suggests that when it does occur, RCC exhibits unique characteristics including earlier onset, multicentricity, and frequent bilaterality. Interestingly, none of the studies cited in this article discuss surgical cyst decortication (CD) as part of the management of the potential increased risk of cancer in this patient subset.

Surgical intervention is a modality for which historic indications have included pain, hypertension, deteriorating renal function, and the presence of malignant cysts but more recently has been considered primarily for patients with ADPKD in whom conservative measures of pain management have failed. Surgical options include renal denervation, cyst aspiration and decortication, and nephrectomy. Surgical intervention by CD in patients with ADPKD has a long history in the medical literature (Table 1). As early as 1911, Rovsing described three cases in which cysts were punctured with consequent pain reduction and renal functional improvement. Nearly 20 years later, Meltzer described the outcomes of 31 cases of surgical cyst decortication as a “…more hopeful prognosis” than usually described with the primary end point of the study being postoperative duration of life, rather than pain reduction or renal functional improvement.

Interest in CD waned after Bricker and Patton reported a rapid postoperative decline in renal function in two ADPKD patients with suboptimal preoperative renal function. Although the small sample size and lack of matched controls in this study present a challenge in drawing definitive conclusions, the authors reported regarding renal function, “the possibility is considered tenable that the procedure was detrimental.” Despite the initial impact of this report, accounts of CD have resurfaced in the literature, beginning in the 1980s and continuing through the past decade with assorted reports of its efficacy in mitigating pain, decreasing hypertension, and altering renal functional deterioration. Variations in length of follow-up, in the primary end points evaluated, and in methodology complicate comparison among these studies. In this article, we explore the therapeutic value of surgical CD by reviewing the first study published on this procedure and relevant contemporary studies.

Methods

A Medline search identifying published reports on CD for ADPKD was performed using Medical subject headings autosomal dominant polycystic kidney disease and subheadings etiology, pathophysiology, prevention and control, surgery, and therapy. We searched within the returned results using AND decortication or AND marsupialization. Selections were made based on studies that described outcomes in patients with ADPKD for whom surgical intervention was considered as part of the disease management. An analysis of the references in returned Medline publications provided additional resources for this article. We did not include studies of laparoscopic CD (LCD) in patients with simple renal cysts. Included in the review is our own report of long-term outcomes after the procedure. Case reports and retrospective series comprised the bulk of the pertinent literature in this review.

Results

Surgical technique

A preoperative abdominal CT image or MRI is obtained to delineate the anatomy of the kidneys and guide treatment. Intraoperative ultrasonography may be used to detect and guide drainage of smaller or subcapsular cysts to maximize the number of cysts decorticated per patient. Specimens of the cysts may be sent for pathologic examination.

Although surgical CD has been reported since the early 19th century, the laparoscopic approach in patients with ADPKD was initially described in 1995 by Teichman and Hulbert in a case report of six patients with ADPKD, all of whom had failed to achieve pain relief by percutaneous cyst aspiration. At the time of their study, LCD had already been used in managing simple renal cysts. At present, LCD, in resemblance to open CD, aims at maximizing the number of cysts treated.

Our technique reflects these goals: As many cysts as possible are decorticated (large cysts), broadly incised (medium-size cysts), or punctured and drained (small cysts). A careful dissection of the renal hilum is performed, and cysts in this area are likewise treated. Hemostasis is obtained by electrocautery and the argon-beam coagulator. At the end of the procedure, the kidney is reexamined with a laparoscopic ultrasonic unit to detect any remaining cysts within a few millimeters of the renal surface; these cysts are also entered and drained. A record of treated cysts is created throughout the procedure. Nephropexy is performed.

The laparoscopic approach is recently the oft-used approach for CD, given the benefits associated with minimally invasive surgery. A study by Dunn and associates that examined 9 years of experience of laparoscopic vs open radical nephrectomy demonstrates a dramatic reduction in estimated blood loss (172 vs 451 mL), hospital stay (3.4 vs 5.2 days), and time to normal activity (3.6 vs 8.1 weeks) using a laparoscopic approach.

Time to ambulation, mean hospital stay, and other parameters pertaining to postoperative recovery, however, will vary, depending on both the degree of surgical invasiveness as well as baseline patient characteristics (eg, age, comorbidities).

Hypertension

Currently, there is no consensus regarding the optimal management of hypertension in ADPKD patients, although increased use of antihypertensive agents has been associated with decreased mortality in this patient population. To this end, research in the Halt Progression of PKD clinical trials is aimed at confirming an appropriate blood pressure target, as well as identifying the proper pharmacologic agents for blood pressure management (Clinical Trials ID NCT00283686). Of note, although hypertension is seen in the
<table>
<thead>
<tr>
<th>Study, year</th>
<th># Cases</th>
<th>Follow-up (mos)</th>
<th>Indication for surgical cyst decortication</th>
<th>Author conclusions</th>
<th>Data or authors suggest association between poor preoperative renal function and postoperative functional decline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rovsing, 1911</td>
<td>3</td>
<td>Not reported</td>
<td>Pain</td>
<td>Improvement in renal function and pain</td>
<td>No</td>
</tr>
<tr>
<td>Meltzer, 1929</td>
<td>31</td>
<td>2 days to many years</td>
<td>Acute hematuria or tumor (duration of survival was end point)</td>
<td>“A more hopeful prognosis than usually given”</td>
<td>No</td>
</tr>
<tr>
<td>Bricker and Patton, 1957</td>
<td>2</td>
<td>13</td>
<td>Improving renal function</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Milam, 1963</td>
<td>2</td>
<td>41</td>
<td>Preservation of renal function</td>
<td>Renal function is not improved by surgical decortication</td>
<td>Yes</td>
</tr>
<tr>
<td>Elzinga, 1992</td>
<td>30</td>
<td>21</td>
<td>Pain and/or renal insufficiency</td>
<td>Improves symptoms of chronic pain; does not slow deterioration of renal function</td>
<td>Yes</td>
</tr>
<tr>
<td>Chehval and Neilsen, 1995</td>
<td>3</td>
<td>16</td>
<td>Pain</td>
<td>“Sustained resolution of symptoms”</td>
<td>No</td>
</tr>
<tr>
<td>Teichman and Hulbert, 1995</td>
<td>6</td>
<td>6-40</td>
<td>Pain</td>
<td>Palliative for chronic pain</td>
<td>No</td>
</tr>
<tr>
<td>Elshry, 1996</td>
<td>2</td>
<td>7</td>
<td>Pain</td>
<td>Reduction in pain is seen with cyst decortication</td>
<td>No</td>
</tr>
<tr>
<td>Brown, 1996</td>
<td>8</td>
<td>12-28</td>
<td>Pain</td>
<td>Cyst decortication is safe and provides pain relief</td>
<td>No</td>
</tr>
<tr>
<td>Ye, 1997</td>
<td>260</td>
<td>60</td>
<td>Pain, hypertension, renal preservation and prolonging duration of life</td>
<td>“Chronic flank pain relieving, ischemia improving, renal failure delaying” results following cyst decortication</td>
<td>No</td>
</tr>
<tr>
<td>Lifson, 1998</td>
<td>7</td>
<td>3-63</td>
<td>Pain</td>
<td>Cyst decortication is “effective for short-to immediate-term pain relief”</td>
<td>No</td>
</tr>
<tr>
<td>Fleming and Barry, 1998</td>
<td>28</td>
<td>Not reported</td>
<td>Pain, abdominal distress</td>
<td>A safe and effective therapy for patients in whom conservative management has failed to control symptoms</td>
<td>No</td>
</tr>
<tr>
<td>Hemal, 1999</td>
<td>2</td>
<td>8-12</td>
<td>Pain</td>
<td>“Prompt and sustained improvement in symptoms”</td>
<td>No</td>
</tr>
<tr>
<td>Dunn, 2000</td>
<td>15</td>
<td>27</td>
<td>Pain</td>
<td>Decreased pain, hypertension unchanged, renal function stable postoperatively</td>
<td>Yes</td>
</tr>
<tr>
<td>McNally, 2001</td>
<td>7</td>
<td>14</td>
<td>Pain, end-stage renal disease secondary to ADPKD</td>
<td>Pain reduced significantly by cyst decortication</td>
<td>No</td>
</tr>
<tr>
<td>Lee, 2003</td>
<td>29</td>
<td>32</td>
<td>Pain</td>
<td>Durable pain relief, hypertension unchanged or improved, renal function unchanged if within normal limits preoperatively</td>
<td>Yes</td>
</tr>
<tr>
<td>Fryczkowski, 2007</td>
<td>15</td>
<td>36</td>
<td>Pain and hypertension</td>
<td>“Laparoscopic cyst decortication...is a safe, effective, and repeatable alternative to non-radical open surgery”</td>
<td>No</td>
</tr>
<tr>
<td>Haseebuddin, 2012</td>
<td>19</td>
<td>130</td>
<td>Pain</td>
<td>Durable pain relief is seen in laparoscopic cyst decortication; related renal progression to end-stage renal disease warrants further study</td>
<td>Yes</td>
</tr>
</tbody>
</table>

ADPKD = autosomal dominant polycystic kidney disease.
The majority of patients with ADPKD, the effect of CD on blood pressure is described in just 9 of 18 studies reviewed. This is a reflection of the differing primary end points of the studies reviewed; we speculate that because pain was the principal impetus for surgical management in the great majority of these studies, the foremost goal of the authors was directed toward defining the role of CD in pain management, with only some groups investigating additional effects of CD.

The effect of CD on hypertension in patients with ADPKD is inconsistent among the studies reviewed; however, CD at the very least does not consistently precipitate worsening hypertension, and either no change or variable improvement may be reasonably expected by the majority of patients after the procedure. Three groups noted that hypertension status and medication did not change. Elzinga and colleagues took three blood pressure measurements on successive days after CD and averaged them; they reported no perioperative improvement in hypertension. Elashry and co-workers reported no change in blood pressure after CD with a mean follow-up of 7 months. Hemal and colleagues reported no change in blood pressure status in either of the patients after 8 or 10 months of follow-up; both remained on an antihypertensive drug regimen after the procedure.

Several of the studies reviewed demonstrated mixed results with regard to blood pressure control. In Dunn and coworkers experience, after a mean follow-up of 27 months, hypertension was worse in 5 of 15 patients but was unchanged or improved in the remaining 10. Lee and associates reported on 21 patients with preoperative hypertension and noted worsening of blood pressure control in 6 patients and improvement in 14. They also noted that hypertension developed in one normotensive patient subsequent to the procedure. Nevertheless, this study revealed an overall improvement in the antihypertensive therapeutic index (ATI) after a mean follow-up of 32 months, indicating that for some of the patients, but not for all, LCD was helpful in decreasing dependence on medical management of hypertension. In our study of 18 patients over a mean follow-up of 130 months, we noted that the ATI showed no statistically significant difference, but there was a trend toward a higher index.

Others have reported an overall improvement in blood pressure control after CD. Fleming and Barry noted that 6 of 22 patients with preoperative hypertension experienced improvement on discharge, while blood pressure was unchanged in the remaining 16 patients. Ye demonstrated a statistically significant decline in mean systolic and diastolic blood pressure in his study of 260 patients, although length of follow-up was not clearly specified in this study. Fryczkowski and coworkers pointed out that preoperative hypertension declined or improved in the remaining 10. Lee and associates reported on 21 patients with preoperative hypertension and noted worsening of blood pressure control in 6 patients and improvement in 14. They also noted that hypertension developed in one normotensive patient subsequent to the procedure. Nevertheless, this study revealed an overall improvement in the antihypertensive therapeutic index (ATI) after a mean follow-up of 32 months, indicating that for some of the patients, but not for all, LCD was helpful in decreasing dependence on medical management of hypertension. In our study of 18 patients over a mean follow-up of 130 months, we noted that the ATI showed no statistically significant difference, but there was a trend toward a higher index.

Theoretically, reducing pressure on surrounding parenchyma—thereby minimizing ischemia-induced activation of the RAAS—could potentially decrease blood pressure in ADPKD patients. Nevertheless, the collective data published on this topic, while suggesting a potential role for CD in helping to control hypertension in patients with ADPKD, does not show this to be consistently reproducible. It should be noted that comparison among studies is complicated by varying definitions of “hypertension control” as well as differences in follow-up duration; in addition, reports often do not include a review of the preoperative and postoperative medications either in number or dose. Furthermore, the per-
Teichman and Hulbert noted that there was no change in any of their six patients when they compared preoperative and postoperative serum creatinine levels, with follow-up varying from 6 to 40 months. Brown and coworkers followed their patients for 12 to 28 months and reported that serum creatinine levels, which were measured in three of eight patients, were unchanged. Elashry and colleagues found that in two ADPKD patients with functioning kidneys, preoperative and postoperative CrCl levels were unchanged at 7 months of follow-up. Similarly, Elzinga and coworkers, after a mean follow-up of 21 months, observed no change in CrCl in patients with ADPKD who had normal preoperative renal function. Ye’s study of 260 patients also showed no statistically significant change in preoperative vs postoperative CrCl values.

In addition, in four reports, there are mixed results with regard to post-CD renal functional outcomes. Hemal and associates reported that in one patient, postoperative CrCl transiently decreased, then returned to preoperative levels; in the other patient, CrCl increased by 50% after the procedure. Dunn and coworkers noted that in their study of 16 patients, 15 of whom had normal renal function initially, renal function declined in one, improved in one, and remained steady in the remaining patients after surgery; mean follow-up was 27 months. Lee and colleagues published a study of 29 patients with a 32-month mean follow-up. They noted that in all five patients with a preoperative CrCl < 30 mL/min, each experienced a decline in CrCl postoperatively. One patient of 21 with normal preoperative renal function had a 22% drop in CrCl at 24 months postoperatively, and another patient’s CrCl levels increased by 49% after 48 months. The remaining 19 patients had stable renal function after surgery.

Our study showed that mean estimated glomerular filtration rate (GFR) decreased significantly postoperatively from preoperative levels at last patient contact. The mean preoperative CrCl level of patients in whom ESRD subsequently developed, however, was 43.4 mL/min vs 75.4 mL/min for those in whom ESRD did not develop (P = 0.01). The decline in mean CrCl of these groups (80% vs 24%, respectively) suggests an association between lower preoperative CrCl and increased vulnerability to renal functional decline.

On the other hand, a study by Fryczkowski and coworkers reported improved renal function after CD. According to this report, patient GFR improved by approximately 10% in a cohort of 15 patients with a mean follow-up of 36 months.

The clinically relevant observation that can be drawn either by direct report or through extrapolation of the data published is that renal function appears to suffer the greatest impairment after surgery if there is poor baseline renal function before surgery. Whether LCD itself alters the natural course of progression to ESRD in patients with compromised preoperative renal function remains an open question. Elzinga and colleagues attempted to answer this question by comparing the slope of reciprocal serum creatinine plots preoperatively and at postoperative follow-up in patients with renal insufficiency (serum creatinine > 1.4 mg/dL). Because they observed no difference in the rate of renal deterioration, they concluded that the progression of renal disease in this subset of patients cannot be attributed to the CD procedure. In our experience, we observed that a decline of renal function appeared to be more pronounced postoperatively if there was initial marked compromised function, which was defined as a CrCl of less than 30 mL/min. The analysis is again limited by the potential effect of renal denervation on renal function by aggressive hilar dissection, as the Symplicity study suggests that denervation may impact renal function. The mechanism posited by the authors is a protective one via blockade of adenosine A1 receptors and subsequent maintenance of renal blood flow and glomerular filtration. It is possible that this may have impacted renal function of patients in varying degrees, depending on the individual surgery.

A further limitation of all the studies reviewed is the absence of an appropriately matched control arm of patients with ADPKD who did not undergo surgical intervention. Either a retrospective 1.2 match with ADPKD patients of similarly staged renal function who did not undergo CD or a prospective study of surgical CD with a large sample size, long-term follow-up, and adequate controls is needed to elucidate the role of this procedure in altering the natural progression to ESRD in patients with ADPKD. Until such insight is gained, we advocate caution in performing LCD in patients with an initial CrCl < 30 mL/min, because several studies suggest that those patients may be at a higher risk for subsequent renal deterioration.

Pain control

Perhaps the most pivotal role that surgical CD has to play for patients with ADPKD lies in its effect on pain. Chronic pain is a common complaint in this patient population, with a negative impact on sleep, activity, mental status, and social relationships. While pain is one of the most common reasons that people seek medical intervention in general, it is one of the most difficult symptoms to treat, and there is no existing standardized protocol for its management in patients with ADPKD. The incidence of pain in these patients is difficult to assess, but according to one study, 60% of patients are afflicted with pain related to their disease. Certainly, treatment of pain should be at the forefront of the physician’s goals in caring for this patient subset.

Current methodology in pain therapy includes noninvasive treatments such as ice, heat, whirlpool, massage, and postural training. Analgesics, progressing from nonsteroidal inflammatory drugs to narcotics, and transcutaneous electrical nerve stimulation are additional options to be explored. While surgery is clearly indicated in the presence of malignant cysts, another potential indication is for reduction of chronic pain in patients with ADPKD in whom conservative measures of pain control have failed. According to the literature, the role of surgical intervention in relieving ADPKD-related pain is unambiguous.

Among the reports we reviewed, pain was an indication for decortication surgery in 15 studies, while the remaining 3 did not address the impact of this procedure on pain. On data review, it is clear that CD has an unmistakable utility in alleviating chronic pain in patients with ADPKD. Indeed, all the studies that evaluate this end point unanimously demonstrate a significant improvement in pain after surgery, which appears to be durable over several years.

The first report of cyst decortication by Rovsing documents postoperative pain relief in his three patients. Elashry and coworkers used a visual pain analog scale in a study of two patients over 7 months and reported a mean 90% resolution in pain. Hemal and associates reported pain relief,
defined as “prompt and sustained improvement of symptoms” in their study of two patients with 8 to 12 month follow-up. McNally and colleagues described pain relief in all three of their patients at a mean follow-up of 16 months.

Brown and coworkers used subjective feedback via interview and documented 40% pain relief in one patient, 50% pain relief in another, and 90% to 100% pain relief in four patients, with follow-up of eight patients ranging from 12 to 28 months. Teichman and Hubert evaluated six patients, five of whom experienced resolution of pain after a follow-up ranging from 6 to 40 months. Elzinga and associates found that the probability of remaining pain free at 1-year follow-up after CD was 80%; after 2 years, it was 62%. Fryczkowski and colleagues used a visual pain analog scale and noted that 73% of his 15 patients were pain-free at 24 months. Dunn and coworkers also used a visual pain analog scale to demonstrate a mean 62% pain improvement in 11/15 patients at a mean follow-up of 27 months.

Lifson and colleagues described five of seven patients as pain free at the conclusion of follow-up, which lasted from 3 to 63 months. In their study of 29 patients, Lee and associates reported >50% pain improvement in 81% of patients at a mean follow-up of 32 months. Ye, who averaged 60 months of follow-up in a study of 260 patients, revealed that 1-year postoperative pain relief was achieved in 92% of cases, while 5-year pain relief was sustained in 81% of cases.

Our group reported on 18 patients with a mean follow-up of 130 months. Of patients last contacted, 67% reported >50% improvement in pain and would readily undergo the procedure again.

Of note, different methods of pain assessment were used by different groups. These included subjective patient reports, the use of pain analog scales, and others. Duration of follow-up also varied substantially among the studies evaluated. Yet despite variability in methodology and follow-up, there is a demonstrable trend that surgical intervention has a positive, reproducible, and durable impact in reducing pain for the majority of patients with ADPKD. Based on these studies, a strong case can be made for the clinical application of CD in treating disease-related pain in this patient population.

While we cautiously conclude that renal function does not improve after the surgery, the impact of CD on the trajectory of renal failure in patients with ADPKD with normal renal function appears to be nil. Of 13 studies that examine this outcome, two suggested worsening renal function, four demonstrated mixed results with function declining in some patients and improving in others; six studies showed no change, and one showed improved function. Some studies reviewed, including our own, demonstrate an association between compromised baseline renal function and accelerated postoperative decline. Despite an exhaustive review of the literature, however, we are unable to find any studies within the last 30 years that used the appropriate patient controls necessary for drawing definitive clinical conclusions regarding the postoperative deterioration of renal function noted in the subset of ADPKD patients with renal insufficiency (CrCl < 30 mL/min). This remains a potential area for additional research.

The literature demonstrates that pain is a frequent indication for surgical intervention and that chronic pain associated with ADPKD is an important factor in quality of life for these patients. We examined 18 studies of which 15 cited pain control as a primary end point. All 15 studies demonstrated that surgical CD was instrumental in relieving pain. A consistent theme among the studies reviewed is that CD is effective in the treatment of disease-related chronic pain for the majority of patients with ADPKD and is durable in the majority of patients out to at least 5 years.

When evaluating the major symptoms of ADPKD—hypertension, renal function, and pain control—it is clear that surgical intervention should be considered predominantly among patients in whom conservative measures of pain relief have failed and who have stage 2 or higher levels of renal function (ie, CrCl > 45 mL/min). These patients can reasonably expect to experience durable relief of their painful symptoms without detriment to renal function.

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Disclosure Statement

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References


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Abbreviations Used
ADPKD = autosomal dominant polycystic kidney disease
ATI = antihypertensive therapeutic index
CD = cyst decortication
CrCl = creatinine clearance
CT = computed tomography
ESRD = end-stage renal disease
GFR = glomerular filtration rate
LCD = laparoscopic cyst decortication
MRI = magnetic resonance imaging
RAAS = renin-angiotensin-aldosterone system
RCC = renal-cell carcinoma