Assessment and Management of Hypertension in Transplant Patients

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ABSTRACT
Hypertension in renal transplant recipients is common and ranges from 50% to 80% in adult recipients and from 47% to 82% in pediatric recipients. Cardiovascular morbidity and mortality and shortened allograft survival are important consequences of inadequate control of hypertension. In this review, we examine the epidemiology, pathophysiology, and management considerations of post-transplant hypertension. Donor and recipient factors, acute and chronic allograft injury, and immunosuppressive medications may each explain some of the pathophysiology of post-transplant hypertension. As observed in other patient cohorts, renal artery stenosis and adrenal causes of hypertension may be important contributing factors. Notably, BP treatment goals for renal transplant recipients remain an enigma because there are no adequate randomized controlled trials to support a benefit from targeting lower BP levels on graft and patient survival. The potential for drug-drug interactions and altered pharmacokinetics and pharmacodynamics of the different antihypertensive medications need to be carefully considered. To date, no specific antihypertensive medications have been shown to be more effective than others at improving either patient or graft survival. Identifying the underlying pathophysiology and subsequent individualization of treatment goals are important for improving long-term patient and graft outcomes in these patients.


EPIDEMIOLOGY AND OUTCOMES
Hypertension after kidney transplantation is common, but the prevalence varies depending on the population studied and definition used. The overall prevalence, defined as the use of antihypertensive agents with or without an elevated BP, has been reported to be as high as 85%. Demographic

Hypertension is one of the most common clinical problems seen in kidney transplant recipients and is associated with shortened allograft survival and increased cardiovascular (CV) morbidity and mortality. Recently published evidence-based guidelines suggest that a goal BP of <140/90 mmHg be adopted for the general population, regardless of risk factors. This review is warranted to examine the many aspects of the epidemiology, pathophysiology, and management considerations of post-transplant hypertension and evaluate whether the BP goals for the general population are justified for the kidney transplant recipient. In addition, this review will focus on pharmacotherapy, drug-drug interactions, and alterations in pharmacokinetics and pharmacodynamics of antihypertensive medications, which are not often considered and therefore may lead to adverse patient events.
risk factors for post-transplant hypertension include pretransplant hypertension, elevated body mass index, male sex, African-American race, and older donor age. Transplant-specific risk factors include delayed graft function, calcineurin inhibitor (CNI) and glucocorticoid use, recurrent disease, acute rejection, and post-transplant proteinuria.\(^{3,4,9,10}\)

Although it is generally accepted that hypertension negatively influences kidney transplant outcomes,\(^{11,12}\) the precise effect of post-transplant hypertension on renal allograft outcomes is difficult to gauge because hypertension both accelerates renal failure and is, itself, worsened by declining allograft function. Nevertheless, studies have attempted to examine the relationship between BP and graft survival independent of allograft function. In a single-center observational study of deceased-donor transplant recipients, the odds ratio of allograft failure per 10 mmHg increase in BP measured at 1 year after transplantation (after adjustment for renal function) was 1.15 (95% confidence interval [95% CI], 1.02 to 1.30) for systolic pressure, 1.27 (95% CI, 1.01 to 1.60) for diastolic pressure, and 1.30 (95% CI, 1.05 to 1.61) for mean arterial pressure.\(^{13}\) Similarly, in a study of living donor transplant recipients at the same center, BP during the first post-transplant year was found to be associated with renal allograft survival, independent of renal function.\(^{14}\) These results are paralleled by results from multicenter studies examining the relationship between hypertension and graft loss. The Collaborative Transplant Study, a large cohort study of nearly 30,000 kidney transplant recipients, showed a graded association between systolic and diastolic BP and allograft failure.\(^{15}\) Although the results of these observational studies suggest that lower BP is favorable, whether aggressive BP management improves allograft survival remains to be evaluated in rigorous, controlled clinical trials.

In addition to decreased allograft survival, post-transplantation hypertension is associated with decreased patient survival. Each 10-mmHg increment of systolic BP >140 is associated with a hazard ratio of death of 1.18 (95% CI, 1.12 to 1.23), and this risk persists after adjusting for allograft function.\(^{4}\) Perhaps the association between hypertension and death in kidney transplant recipients is mediated by the increased risk of CV disease because uncontrolled hypertension post-transplant is associated with an increased risk of de novo congestive heart failure and ischemic heart disease.\(^{16,17}\) However, as with allograft failure, it has not been demonstrated in prospective studies that tight BP control mitigates the risks of CV disease and death in these patients. Nonetheless, strong observational data showing a relationship between higher BPs and worse outcomes warrant the treatment of post-transplant hypertension and the pursuit of prospective clinical trials to establish optimal BP targets.

**DIAGNOSIS OF HYPERTENSION**

Major epidemiologic and interventional trials in the general population have used BP measurements taken in the clinic to determine the presence or absence of hypertension. However, these readings may not accurately reflect the BP outside the clinic. BP variability is common and is superimposed on the diurnal variation. Patients may also exhibit white-coat or masked hypertension.\(^{18}\) Therefore, BP readings obtained during transplant clinic visits could be potentially misleading. The negative effect of masked hypertension on the progression of native kidney disease is of substantial concern; however, this has never been evaluated in the renal transplant population.

Recent studies have assessed the correlation between ambulatory BP monitoring (ABPM), home BP monitoring (HBPM), and office clinic BP monitoring (CBP) in the post-transplant setting. An important aspect in the conduct of these research studies is the care that should be taken to avoid bias, such as the use of standardized techniques, as used in clinical trials of hypertension with >1 measurement of BP, can provide improved concordance rates between CBP and ABPM as seen in a study by Haydar et al.\(^{19}\) Other researchers have demonstrated that HBPM determinations had a significantly better agreement with ABPM than CBP (72% versus 54%) even though both the CBP and the HBPM correlated with ABPM.\(^{20}\) The use of ABPM is being recommended more broadly in the general population to better assess the clinical importance of nocturnal hypertension, masked hypertension, and white-coat hypertension on the risk for vascular events. Patients with high-normal or normal CBP with asymptomatic target organ damage or high CV risk should undergo ABPM for possible masked hypertension.\(^{21}\) A consensus paper on BP in the general population published in 2013 provides important insights and new definitions for these conditions.\(^{21}\) The diagnostic utility of ABPM should be considered in the kidney transplant recipient because it may prove helpful in guiding management decisions.

**PATHOPHYSIOLOGY**

There are several putative factors that contribute to post-transplant hypertension in the renal transplant recipient.

**DONOR FACTORS**

Several donor factors have been independently associated with post-transplant hypertension. These include pre-existing donor hypertension, older donor age, and poor allograft quality. Recently, several genetic variants, including polymorphisms within genes that encode for ABC2, ABC1, CYP 3A5, and APOL-1 have been associated with early graft dysfunction and subsequent post-transplant hypertension.\(^{22–27}\) The size of the donor kidney relative to the recipient also plays a role in the development of post-transplant hypertension. A disparity between donor and recipient size can lead to a relative underdosing of nephrons and subsequent maladaptive hyperfiltration, glomerular hypertrophy, and intraglomerular hypertension.\(^{28,29}\) Donor quality has been known for a long time to be an important contributor to post-transplant hypertension. Recipients of poor-quality donor...
kidneys (extended criteria donors) are well known to have a higher incidence of hypertension post-transplant.30

Acute Rejection and Chronic Allograft Injury

Any cause of injury to the transplanted kidney can lead to de novo or worsening of post-transplant hypertension. Among the most common causes are acute rejection (cellular and antibody-mediated acute rejection) and chronic allograft injury (including chronic antibody-mediated rejection and interstitial fibrosis/tubular atrophy), thrombotic microangiopathy, and recurrent glomerular disease. Acute rejection is often associated with hypertension. This may be associated with stimulation of the renin-angiotensin system, depending on the volume status of the patient. As such, the renal transplant recipient with new onset hypertension should be investigated for acute rejection. A recent report of patients with antibody-mediated rejection because of non-DSA antibodies that bind to angiotensin II type I receptors has also been reported and suggests that AT1 receptor blockers might prevent this newly described type of hypertension.31–33 Hypertension associated with acute rejection responds quite well to treatment of rejection, whereas hypertension not associated with acute rejection often is worsened with the addition of or a dose increase in corticosteroids.

Hypertension associated with chronic allograft injury is similar to that associated with CKD. Recurrent disease that results in injury to the allograft also leads to hypertension, and interestingly, focal glomerulosclerosis is the type of recurrent disease most often reported to be associated with worsening of BP control.34

Other correctable, although rare, causes of early graft dysfunction that are associated with severe hypertension include a kink in the transplant renal artery and a Page kidney. A renal artery kink can be confirmed by the finding of a parvus tardus wave form on Doppler ultrasound.35 A Page kidney is caused by external compression of the kidney and can occur because of a hematoma caused by transplant biopsy, lymphocele, or urinoma in the acute setting.36

Immunosuppressive Medications and Post-Transplant Hypertension

Immunosuppressive medications are associated with post-transplant hypertension, however, with lower-severity using agents, such as the mTOR inhibitors or mycophenolate mofetil. Corticosteroids, in particular, have been considered to be an important cause of hypertension in renal transplant patients. Transplant centers have either lowered the steroid dose or withdrawn steroids to decrease the risk of post-transplant hypertension.37 There has been a continued debate as to whether modification of steroid use improves BP control.38,39 Some centers report that immunosuppressive protocols with alternate day steroids or complete steroid withdrawal result in improved BP control,40 but others counter that the risk of acute rejection is higher with steroid withdrawal,37,41 which could then adversely affect BP.

An increase in the prevalence of post-transplant hypertension has been seen since the widespread use of CNI-based immunosuppressive regimens, particularly with cyclosporine. CNIs are well established as a cause of post-transplant hypertension, as first demonstrated in studies of cardiac transplant recipients,42 and have recently been shown to worsen hypertension in patients with HLA-identical kidney transplants.43 The pathophysiology of cyclosporine-induced hypertension may be related to direct vascular effects. The renal sodium retention stimulated by cyclosporine is likely related to afferent glomerular arteriole vasoconstriction.44,45 Tacrolimus activates the renal sodium chloride cotransporter and likely also causes a sodium sensitive form of hypertension.46 Registry data and observations from clinical trials have suggested lower rates of post-transplant hypertension with a tacrolimus-based regimen compared with a cyclosporine-based regimen.3,47,48 Some studies have reported a benefit of switching patients from a cyclosporine-based to tacrolimus-based regimen with regard to BP control.48 Given the importance of adequate immunosuppression to avoid rejection, decisions about adjusting immunosuppressive medications to facilitate BP control need to be carefully considered. It may be easier and safer to use lifestyle modifications or antihypertensive medication rather than modify immunosuppression.

Recipient Factors

Many patients have longstanding hypertension by the time they receive a kidney transplant, either associated with their native kidney disease or with endocrine factors, which may lead to vascular stiffening and loss of compliance. These vascular changes may contribute to the hypertensive process, especially if there is volume excess.

Other recipient factors which contribute to post-transplant hypertension include the genetic profile of the recipient, recipient age, recipient body mass index, presence of obstructive sleep apnea, presence of endocrine tumors (e.g., pheochromocytoma, adrenal adenomas),49–53 Secondary hypertension may develop before kidney transplantation but remain unrecognized, or it may present as a new condition post-transplant. After transplantation, the most common etiology of secondary hypertension is transplant renal artery stenosis (TRAS), causing a form of renovascular hypertension. However, other causes must also be considered (Table 1). In this setting, failure to diagnose and initiate specific therapy may compromise transplant kidney outcomes, in particular, longevity of renal function. Clues include resistant hypertension, any degree of hypokalemia, absence of expected hyperkalemia, accelerated presentation of target organ events, or declining allograft function. Even when suspected, secondary causes may be difficult to detect, the diagnosis may be difficult to confirm, the effect on the full clinical

Table 1. Causes of secondary hypertension after kidney transplantation

| Primary aldosteronism |
| Kidney-related causes |
| Acute rejection |
| TRAS |
| Ischemic nephropathy |
| Hydronephrosis |
| Nonkidney-related causes |
| Primary aldosteronism |
| Obstructive sleep apnea |
picture may be difficult to quantify, and the intervention may be challenging.

TRAS is reported to occur in 1%–23% of kidney transplant recipients, most commonly because of stenosis at the renal artery anastomosis, but it may also occur at more proximal sites, such as the renal artery anastomosis. Presentation may include worsened hypertension, hypokalemia because of secondary aldosteronism, or a decline in renal function. However, some patients may present with a more subtle form of TRAS. The diagnosis of TRAS is often made after renal biopsy, particularly if the renal transplant recipient has a bruit over the renal allograft because of the use of different and less familiar views of arterial connections compared with in situ imaging of the native kidneys. Dorsalis pedis Doppler should be used in patients with a classic bruit, but it may also be present in 23% of patients with TRAS.

Primary hyperaldosteronism is a common cause of secondary hypertension and is an important cause of resistant hypertension. With this degree of penetrance and the common association of hypertension with CKD, prevalence rates are likely to be at least as high in the kidney transplant population. Even with diuretic therapy, it is unlikely for a transplant patient to require potassium supplementation.

Therefore, the presence of hypokalemia to any degree in association with severe hypertension should raise diagnostic suspicion to specifically search for primary hyperaldosteronism, especially if the patient is receiving an ACE inhibitor or ARBs.

Detection of primary hyperaldosteronism in a renal transplant recipient was first reported in 1985 as a result of an aldosterone-producing adrenal adenoma. Since then, several additional cases have been reported, primarily caused by aldosterone. The association of primary hyperaldosteronism and obstructive sleep apnea, especially if they have a disturbed sleep pattern and daytime somnolence. It may be an important contributor to the development of pulmonary hypertension if not diagnosed and treated.

The diagnosis hyperaldosteronism depends on an elevated aldosterone to renin ratio, confirmed by evidence for autonomous aldosterone production (Table 2). Treatment is directed at suppressing the effect of aldosterone because of its potential vascular toxicity. A trial of spironolactone or eplerenone is reasonable and may even be helpful for facilitating BP control in patients on higher doses of corticosteroids.

**Agents and strategies for BP treatment**

There are no randomized controlled trials (RCTs) to examine optimal levels of BP in kidney transplant recipients to prolong graft survival or limit the risk of CV events. There are also no data to define optimal treatment strategies.

The lack of evidence supporting treatment goals or use of specific medications should not amount to therapeutic nihilism. Recent evidence-based guidelines in the general population suggest that goal BP be liberalized to less than 140/90 mmHg, regardless of CKD disease or CKD CKD presence, and less than 150/90 mmHg for people >65 years.

Kidney Disease Improving Global Outcomes and National Kidney Foundation.

**Table 2. Evaluation for primary aldosteronism after renal transplantation**

<table>
<thead>
<tr>
<th>Clinical clues</th>
<th>Resistant hypertension</th>
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</thead>
<tbody>
<tr>
<td>Biochemical clues</td>
<td>Hypokalemia or normokalemia when hyperkalemia would be expected, hypematrema (usually mild), hypomagnesemia, glucose intolerance, diabetes mellitus</td>
</tr>
<tr>
<td>Screening</td>
<td>Aldosterone to renin ratio</td>
</tr>
<tr>
<td>Confirmatory testing</td>
<td>Aldosterone not suppressed by sodium or volume load, adrenal CT scan</td>
</tr>
<tr>
<td>Surgical consideration</td>
<td>Adrenal vein sampling, assess patient comorbidities</td>
</tr>
<tr>
<td>Treatment</td>
<td>Aldosterone antagonist for short trial or long term, consideration for adrenalectomy</td>
</tr>
</tbody>
</table>
have developed guidelines for the diagnosis and treatment of hypertension in patients with CKD or with renal transplants. However, these guidelines are all on the basis of expert opinions, rather than data from RCTs. Table 3 includes recommended BP thresholds at which antihypertensive treatment should be started and maintained while on treatment. Although the BP thresholds for treatment and BP treatment targets have been revised upward for patients with CKD to be the same as those for patients with hypertension in the absence of complications or comorbidities, the BP threshold for treatment of kidney transplant recipients remains at 130/80 mmHg, regardless of proteinuria.

The goal BP for renal transplant patients should be carefully individualized on the basis of all CV and renal disease progression risk factors, especially in the absence of conclusive data. Our opinions are that lower BP goals (<140/90 mmHg) may be beneficial given the epidemiologic data linking prolonged graft survival with lower levels of BP in kidney transplant recipients.

The first important consideration in hypertensive patients is the timing of the development of hypertension with respect to kidney transplantation. In the first several weeks to months post-transplantation, hypertension may be influenced by volume overload, higher doses of corticosteroids, and CNI levels and poor or delayed allograft function. Ideally, the management of these patients would focus on the achievement of ideal volume status and the employment of lower doses of both corticosteroids and CNIs while avoiding acute rejection episodes. Thiazide or loop diuretics should be considered. β-Blockers and calcium channel blockers (CCBs) can also be used as needed or indicated for medical comorbidity. ACE inhibitors and ARBs should be avoided early post-transplantation because of their hemodynamic effect on GFR and potassium homeostasis.

Nonpharmacologic management with lifestyle modifications should always be considered, including exercise, weight control, cessation of smoking, and dietary salt modification. There are some data supporting the salutary effect of dietary sodium restriction in this population. In a relatively small number of kidney transplant recipients, a 3-month trial of an 80–100 mmol/d sodium-restricted diet resulted in a statistically significant drop in systolic and diastolic BP compared with a control group on a nonrestricted diet. Curtis et al. demonstrated that sodium restriction significantly lowered BP in a group of renal transplant patients taking CNI, but this effect was not seen in an azathioprine-treated group. These data suggest that CNI-treated patients may derive some benefit from dietary sodium reduction. The utility of nonpharmacologic methods for reducing BP is largely based on the hypertensive general population.

The choice of antihypertensive medication should be on the basis of efficacy, tolerability, lack of known drug-drug interactions, and medical comorbidity. CCB, diuretics, β-blockers, α1 blockers, ACE inhibitors, and ARBs have all been used singly or in combination to reduce BP in the transplant population. CCBs are considered a therapeutic standard in renal transplant patients because of their demonstrated efficacy in the general population regardless of age, sex, and salt intake and their potential ability to counteract the vasoconstrictive effects of CNIs.

**USE OF RENIN-ANGIOTENSIN SYSTEM BLOCKADE IN THE TRANSPLANT RECIPIENT**

The clinical benefit of renin-angiotensin system blockade has been clearly demonstrated in nontransplant populations with elevated CV risk, including patients with proteinuric CKD. In contrast, studies of long-term CV or renal outcomes in kidney transplant recipients treated with ACE inhibition or ARBs have been less conclusive.

A number of prospective randomized trials comparing ACE inhibitor/ARB therapy to either a different class of antihypertensive agents or placebo have been reported. However, the trials included small sample sizes and limited follow-up periods. A study by Suwelack et al. of 96 nondiabetic hypertensive patients randomized to receive either quinapril or atenolol within 3 months of transplant offers the longest reported follow-up, showing similar effects on BP and graft function between groups at 5 years and a significant increase in proteinuria in atenolol-treated patients compared with those receiving quinapril. Analyses of graft and patient survival were not performed. The largest trial to report patient and graft survival included 502 transplant recipients (10% diabetic) within 10 years of transplant randomized to receive either candesartan or placebo. Compared with placebo, candesartan therapy was associated with lower BP, less proteinuria, and higher serum creatinine and potassium concentrations. The primary end point of all-cause mortality, CV mortality, and graft survival was similar between groups at 23 months. Enrollment into this study was halted prematurely because of a lower than expected primary event rate.

A study by Ibrahim et al. randomized 154 patients (37% diabetic) within

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**Table 3. Recommended BP levels (mmHg) at which drug treatment should be started and BP targets on treatment**

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Uncomplicated Hypertension</th>
<th>CKD</th>
<th>Diabetes</th>
<th>Renal Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>JNC 8, 2014&lt;sup&gt;a&lt;/sup&gt;</td>
<td>≥140/90</td>
<td>≥140/90</td>
<td>&gt;140/90</td>
<td>n/d</td>
</tr>
<tr>
<td>ESH/ESC, 2013&lt;sup&gt;b&lt;/sup&gt;</td>
<td>≥140/90</td>
<td>≥140/90</td>
<td>&gt;140/90</td>
<td>n/d</td>
</tr>
<tr>
<td>KDIGO, 2009, 2012&lt;sup&gt;d&lt;/sup&gt;</td>
<td>n/d</td>
<td>≥140/90</td>
<td>&gt;130/80&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&gt;130/80</td>
</tr>
</tbody>
</table>

<sup>n/d</sup>, not defined.
<sup>a</sup>Reference 116.
<sup>b</sup>If urine albumin excretion >30 mg/24 h.
<sup>c</sup>Reference 117.
<sup>d</sup>Reference 118.
<sup>e</sup>Reference 63.
3 months of transplant to receive either losartan or placebo. At 5 years, the composite primary end point of graft loss because of biopsy-proven interstitial fibrosis/tubular atrophy or a doubling of the fraction of renal cortical volume occupied by interstitium occurred in 6 of 47 losartan-treated patients versus 12 of 44 receiving placebo (P = 0.08). There was no difference in time to ESRD or death between groups.

In addition to limited sample sizes and clinical follow-up time, the ability to draw firm conclusions from prospective randomized studies of ACE inhibition/ARBs in transplant recipients is limited by a considerable variation in methods and reported outcomes between studies. Two systematic meta-analyses have attempted to consolidate these data and are worth noting. Hiremath et al. identified 21 randomized trials of ACE inhibition/ARBs in three databases spanning 1966–2007 involving 1549 patients. With a 27-month median follow-up time, the use of ACE inhibition/ARBs was associated with significant reductions in GFR (–5.8 cc/min), hematocrit (–3.5%), and (–0.47 g/d) without a significant effect on serum potassium. Effects on patient and graft survival were not assessed because of insufficient data. Cross et al. published a Cochrane Database systematic review 2 years later, which included 10 studies comparing ACE inhibitor with placebo with 445 patients and 7 studies comparing ACE inhibitor with CCBs with 405 patients. Compared with CCBs, the use of ACE inhibitors was associated with a significant reduction in GFR (–11.49 cc/min), proteinuria (–0.28 gm/d), and hemoglobin (–1.3 gm/dl), with a 2.74-fold elevated relative risk of hyperkalemia. Data for graft loss were inconclusive when comparing ACE inhibitors to either placebo or CCBs, and effects on patient survival were not reported.

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Although results from prospective trials have not provided sufficient data regarding hard outcomes, such as effect on graft and patient survival, several large retrospective database analyses have offered some insight, albeit with opposing conclusions. Using the Austrian Dialysis and Transplant Registry and Eurotransplant databases, Heinze et al. identified 2031 patients receiving kidney transplant at a single center between 1990 and 2003. Compared with no ACE inhibitor/ARB therapy, any documented ACE inhibitor/ARB use was associated with improved 10-year patient (74% versus 53%, P < 0.001) and graft (59% versus 41%, P = 0.002) survival. However, another retrospective analysis of 17,209 patients transplanted between 1995 and 2004 from the Collaborative Transplant Study was unable to show a difference graft survival at 6 years in those either on or off ACE inhibitor/ARB therapy at 1 year post-transplant, including subpopulations of diabetic patients and patients at higher pretransplant CV risk.

Therefore, definitive evidence for benefit of ACE inhibitor/ARB therapy in transplant recipients is lacking. Although ACE inhibitor/ARB therapy is associated with anemia, hyperkalemia, and reduced GFR, these drugs are effective in reducing BP and proteinuria. An ongoing prospective, blinded, RCT of >500 at-risk transplant recipients involving 11 Canadian transplant centers will evaluate the effectiveness of ramipril versus placebo on a composite end point of doubling of serum creatinine, ESRD, or death and will hopefully add crucial insight into this controversial and unresolved clinical dilemma.

### PHARMACOLOGIC PRINCIPLES IN POST-TRANSPLANT HYPERTENSION THERAPEUTICS

The benefit to risk ratio of antihypertensive medication in the kidney transplant recipient needs to be carefully considered to minimize adverse events. For most drugs and most of the general population, pharmacokinetic considerations are of less importance than they are in the kidney transplant population given the variability of renal function, medical comorbidity, and large medication burden. Pharmacokinetic differences are most readily apparent in the use of certain drugs in subpopulations with impaired systemic clearance. For example, in the renal transplant patient with CKD and diabetes mellitus, the presence of gastroparesis can influence the time course of drug absorption and therefore the onset of action. From a practical point of view, however, it is the pharmacodynamic properties of a drug (i.e., characteristics that describe its biologic effects) that are of the greatest importance in most transplant patients.

Drug-drug interactions can be pharmacokinetic and/or pharmacodynamic in the renal transplant patient with treated hypertension. One such pharmacodynamic interaction is evident with the addition of a diuretic to a pre-existing drug regimen. Therein, the enhanced antihypertensive response is typically reflected by 1) a leftward shift of the curve (less drug required to effect the same reduction in BP), 2) a greater peak (sometimes called plateau) response, or 3) a steepening of the response slope at its midpoint. Pulse-rate lowering compounds typically can be expected to improve the dose response to an antihypertensive medication whose administration engenders a tachycardic response. A similar sequence of events unfolds with compounds that diminish sympathetic nervous system and renin-angiotensin system activity if these systems have been activated by other therapies. Complete dose-response curves are rarely generated for antihypertensive drugs in the kidney transplant patient. Therefore, it is particularly important in this patient population to understand additivity of response with combinations of antihypertensive agents rather than relying on multiple titration steps of monotherapies. True tachyphylaxis, in which enzyme induction steps up drug metabolism, is generally not observed with antihypertensive drugs in the hypertensive kidney transplant patient.

Whereas drug-drug interactions are commonly recognized occurrences in the hypertensive population, drug-nutrient interactions are less well appreciated. The grapefruit juice–CCB interaction is one that has been known since 1989 and is one that is most pertinent to cyclosporine-treated patients. The basis for this interaction appears to relate to both flavonoid and nonflavonoid components of grapefruit juice interfering with enterocyte CYP3A4 activity. This increases the bioavailability of CYP3A4–metabolized drugs...
with a limited absorption. Although a number of the CCBs are susceptible to this interaction, it appears most prominently with felodipine with a doubling of the bioavailability. Amlodipine and nifedipine and nondihydropyridine CCBs have better inherent bioavailability and hence are less affected by grapefruit juice with only a 20%-30% increase in blood levels.

Two major pathways exist for cytochrome P450-mediated drug interactions: enzyme induction and inhibition. Induction refers to increased synthesis or decreased degradation of cytochrome P450 isozymes, events that step up conversion to inactive metabolites, decrease plasma levels of the substrate, and thereby reduce the pharmacodynamic effect. Examples of inducing substances include rifampin and phenobarbital. The converse applies to substances that are inhibitors of cytochrome P450–metabolized compounds. A number of cytochrome P450-related interactions can occur with antihypertensive agents, which with the exception of suppression of CYP3A4 activity by drugs, such as verapamil and diltiazem, are typically of little consequence (Table 4). The cytochrome P450 interaction with verapamil and diltiazem can be put to clinical use. For example, CNI cost can be decreased if coadministered with diltiazem or verapamil in that its slowed metabolism would require lowering its dose to keep blood levels in a therapeutic range. This dose manipulation, although economically prudent, complicates dosing of this immunosuppressant agent. A diltiazem dose of 120 mg/d is sufficient to reduce CNI dose in the order of 60%; however, use of this interaction still requires careful therapeutic monitoring.

The ability to metabolize a drug through a specific cytochrome P450 pathway is also modulated by genetic polymorphisms with some individuals being poor (slow) and others being extensive (rapid) metabolizers. Although these polymorphisms have major effects on the pharmacokinetic profiles of commonly used antihypertensive drugs (e.g., metoprolol) and lesser used drugs (e.g., hydralazine, α-methyldopa, minoxidil), they have not been shown to influence variation in the antihypertensive effect of these drugs at conventional doses; however, slow metabolizers of β-blockers can have exaggerated β-blocker effects that occur at low doses.

Medication dose adjustment in the setting of CKD may involve one (or both) of two approaches. To maintain a therapeutic drug level and at the same time avoid drug accumulation and possible concentration-dependent toxicity in a patient with CKD, the maintenance dose of a medication is reduced and/or the time interval between doses is extended. In practice, dose adjustment should match the degree to which renal function is reduced; however, in the case of antihypertensive medications this is seldom the case (Table 5). Antihypertensive medications are typically dosed until the desired effect is achieved, and dosage reduction is only considered when goal BP has been reached and/or drug concentration–dependent side-effects appear.

The blueprint for success in any antihypertensive regimen requires there be an ongoing careful assessment of the pharmacokinetic and pharmacodynamic interplay of the various medications. A number of host factors influence the dose response to an antihypertensive medication, and these should be carefully sorted through, particularly when the

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Cytochrome P450 Interaction Potential</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>No significant interactions; most ACE inhibitors are prodrugs that undergo hepatic and/or enterocyte metabolism.</td>
<td>Prodrug conversion to active diacid ACE inhibitors is minimally affected by hepatic disease as occurs in heart failure.</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Hydrochlorothiazide and chemically related diuretics are not metabolized. Furosemide and spironolactone are metabolized to glucuronide and sulfated metabolites, respectively.</td>
<td>Neither has a significant effect on the cytochrome P450 system. Coadministration of verapamil with eplerenone results in an approximately 2-fold increase in the area-under-the curve for eplerenone.</td>
</tr>
<tr>
<td>Angiotensin-receptor blockers</td>
<td>Losartan and irbesartan are primarily metabolized by CYP2C9. Losartan undergoes metabolism to an active metabolite E-3174 via CYP2C9, which creates the potential for interaction with inhibitors or stimulators of this P450 isozyme.</td>
<td>Coadministration of losartan with enzyme inducers, such as rifampin and phenobarbital, decrease losartan and E-3174 levels, whereas enzyme inhibitors, such as fluconazole, decrease the levels of E-3174. These changes are inconsequential and seem not to affect the BP lowering effect of losartan.</td>
</tr>
<tr>
<td>β-Adrenergic blocking agents</td>
<td>Pharmacokinetics of a number of β-adrenergic blocking agents are strongly affected by cytochrome P450 inducers and inhibitors as relates to CYP2D6.</td>
<td>Rifampin increases propranolol clearance by 2–3-fold; quinidine and diphenhydramine increase blood levels of β-blockers, such as timolol or metoprolol.</td>
</tr>
<tr>
<td>CCBs</td>
<td>These drugs serve as substrates for and inhibitors of CYP3A4. Verapamil and diltiazem are known inhibitors of CYP3A4. Symptomatic hypotension can occur when CYP3A4 inhibitors are given with dihydropyridine CCBs.</td>
<td>Concomitant use of azole antifungals with dihydropyridine CCBs should be done with caution; most CCBs inhibit the metabolism of cyclosporine; diltiazem inhibits the metabolism of triazolam and methylprednisolone.</td>
</tr>
</tbody>
</table>
Hypertension has long been known to be a well-recognized problem, there has been little improvement in the prevalence of pediatric hypertension over the last three decades. The most recent annual report from the North American Pediatric Renal Trials and Collaborative Studies registry indicates that immediately post-transplant, >80% of children require antihypertensive medications; 70% of deceased and 60% of living donors still require antihypertensive medications 5 years after transplantation. A study from the Midwest Pediatric Nephrology Consortium using data from six centers determined that 68% of children with healthy weight and 80% of overweight/obese children had uncontrolled BP (≥95th percentile for age, sex, and height) 1 year after transplantation. Similarly, recent data from the ESPN/ERA-EDTA registry on BP control among pediatric ESRD patients in Europe confirmed a high rate of hypertension in pediatric transplant recipients: hypertension was diagnosed in 66.9% with more than one-third having elevated BP despite being on antihypertensive therapy. Sinha et al. conducted a retrospective analysis of all current pediatric kidney transplant patients in the United Kingdom, with data collected at 6 months and 1, 2, and 5 years after transplantation: the rate of uncontrolled hypertension has been unchanged (25%–27%) during follow-up. As in other studies, >50% of patients were taking antihypertensive medications of whom 32%–37% remained hypertensive. These authors also determined that among children who initially were nonhypertensive, 49% progressed to hypertension over 2-year follow-up period.

The prevalence of hypertension is even higher with ABPM, approaching 70%–80%. Studies show the prevalence of masked hypertension (normal office BP and elevated ABPM) was 50% greater than that identified using casual BP and an increased prevalence of nondippers among children with kidney transplants. A study by Polónia et al. concurs with other studies showing significant rates of nocturnal hypertension in pediatric transplant recipients and that a significant proportion of patients thought to be adequately controlled by medications still had masked hypertension.

As in adults, hypertension is associated with worst allograft function. In one study, higher systolic BP at 3 months post-transplant was independently associated with lower measured GFRs at 1 year post-transplant. Sorof et al. analyzed data from 5251 pediatric kidney transplant recipients using the North American Pediatric Renal Trials and Collaborative Studies database to determine whether the use of antihypertensive medications is associated with higher rates of graft failure. Using annual follow-up data, the authors showed that the requirement for antihypertensive agents was associated with significantly higher rates of subsequent graft failure. Another study evaluated the effect of early hypertension on allograft survival in children according to actual BP measurements. In this study, for each 10% increase in systolic BP at 1 year after transplantation there was a doubled risk for subsequent graft failure. These associations were independent of donor type, cause of kidney failure, age at transplant, use of CNI, and presence or absence of acute rejection within the first year of transplant. Even after adjustment for baseline GFR, systolic BP remained a significant and independent predictor of graft failure.

Children and young adults with kidney transplants are at a high risk for morbidity and mortality because of CV disease, which is one of the leading causes of death in this population. It is not yet clear how much of this increased morbidity is from traditional CV risk factors,
such as hypertension. However, hypertension has been shown to be associated with early markers of CV disease, including cardiac and vascular remodeling. Children post-transplant have a high prevalence of left ventricular hypertrophy (LVH), the most common cardiac abnormality in this population. The previously mentioned Midwest Pediatric Nephrology Consortium study demonstrated the prevalence of LVH to be 40% in children 1-year post-transplant, with hypertension associated with an increased LVM index. Most of the studies have demonstrated the persistence of cardiac hypertrophy years after transplantation, but some showed improvement.

Several pediatric cross-sectional studies showed increased carotid artery intima media thickness (cIMT), an early marker of atherosclerosis, compared with healthy controls. In most of these studies, elevated casual or ABPM was associated with increased cIMT. A recent study assessed changes in cIMT and LVM index during a follow-up of 9.1 ± 0.9 years. In this study, carotid artery ultrasound and echocardiography were performed at baseline and twice more during follow-up. BP management was classified according to the recipient’s ABPM results, performed at yearly intervals. The baseline cIMT was significantly higher in transplant recipients than in healthy controls. Importantly, at the last examination, 82% had optimal BP control, the overall prevalence of LVH was only 4.5%, and there was no evidence of progression of cIMT over time. The authors suggested that the lack of progression of cIMT and the low prevalence of LVH might reflect the effect of longstanding BP control.

Strategies to control BP post-transplant in children are similar to those in adults and are discussed elsewhere in this article. Specific to children, the most recent Kidney Disease: Improving Global Outcomes guidelines suggest maintaining BP at <90th percentile for sex, age, and height if <18 years old (2C level of evidence). In cases of significant proteinuria (>600 mg/m² per 24 hours), ACE inhibitor or an ARB as first-line therapy should be considered (level of evidence was not graded). Guidelines also suggest that ABPM be considered to assess for nocturnal hypertension and resistant hypertension but stopped short of making recommendations for routine use. However, work published since the development of these guidelines suggests that use of annual ABPM leads to improved rates of achievement of goal BP compared with standard therapy in children with kidney transplants. One of the important considerations with specific benefit to children is steroid-avoidance protocols, which in addition to improvement of BP control, have shown significant improvement of growth in children post-transplant.

In conclusion, both adult and pediatric transplant recipients commonly have hypertension post-transplantation. Despite evidence from the general population that hypertension control is associated with improved CV morbidity and mortality, many kidney transplant recipients have poorly controlled BP. What is surprising is that many of these patients continue to follow-up with their organ transplant programs or nephrologists who are well-versed on the treatment of hypertension and are knowledgeable of the adverse consequences of elevated BP for both patient and graft survival. Much of the challenge in the management of these patients may relate to the complexity of medical care that they require. Despite the more liberal BP goals in the current evidence-based guidelines for the general population, we feel that there is sufficient epidemiologic evidence to suggest that some kidney transplant patients may benefit from lower BP goals. These goals need to be carefully individualized. ABPM may be a helpful tool to determine the adequacy of BP treatment in adults, as has been demonstrated in pediatric kidney transplant recipients.

Secondary causes of hypertension, such as hyperaldosteronism TRAS and obstructive sleep apnea, needs to be considered in patients with resistant hypertension. Future clinical trials are needed to define optimal BP treatment goals and therapies and how they influence graft and patient survival.

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DISCLOSURES

None.

REFERENCES


43. Krämer BK, Del Castillo D, Margreiter R, Sperschneider H, Olbricht CJ, Ortuño J,


BRIEF REVIEW


90. Opelz G, Zeier M, Laux G, Morath C, Döhler


