

ASH Position Paper

Management of hypertension in the transplant patient

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Manuscript Accepted July 7, 2011

Statement of the Problem

The development of hypertension after kidney transplantation is common.^{1,2} Hypertension, defined as a blood pressure greater than 140/90 mm Hg, is associated with an increased risk for both acute rejection and lower graft and patient survival.³ The pathogenesis is multifactorial, and optimal therapy has yet to be clearly defined.

Despite the restoration of kidney function and improvement of intravascular volume control with kidney transplantation, the problems of posttransplant hypertension remain substantial. The incidence of posttransplant hypertension is variable, but considerable. Most studies report incidence rates between 60% and 80%.^{4,5} In one cross-sectional study of 409 stable kidney allograft recipients, the incidence of hypertension was 77.3%, with hypertension defined as a blood pressure greater than 150/90 mm Hg.⁴ In this analysis, the majority of patients (68.9%) required multiple antihypertensive drugs. Similarly, in pediatric kidney transplant recipients, a recent database analysis described the incidence of posttransplant hypertension at 74%.⁵ National guidelines⁶ define hypertension as greater than 140/90 mm Hg, which is also the typical definition used in most studies of patients with kidney transplants. However, national guidelines also recommend treatment goals lower than 130/80 mm Hg for the general population with diabetes or estimated glomerular filtration rate (GFR) below 60 mL/min/1.73 m².⁶ Thus, the true prevalence of posttransplant hypertension using this reference range is likely in excess of 95%.

Given the fact that transplant centers rarely report their data on achieved levels of blood pressure control, coupled with the fact that there is decreased exposure time to their transplant center physicians (as their patients return to their primary nephrologist or primary care physicians), the current status of control rates of hypertension is unknown. This lack of data is concerning, as a major cause of

posttransplant hypertension is related to calcineurin inhibitor (i.e., cyclosporine and tacrolimus) and corticosteroid use. The calcineurin inhibitors are known to be directly nephrotoxic. They decrease renal blood flow and elevate blood pressure through multiple mechanisms including stimulation of endothelin production, or the sympathetic and renin angiotensin systems (RAS). Corticosteroids enhance sodium and water retention.

Treatment is often a challenge. The majority of kidney transplant patients are on complex multidrug regimens, which can be associated with reduced medication adherence. Thus, the likelihood of transplant patients achieving a blood pressure at a recommended goal of less than 130/80 mm Hg, for the general population with diabetes or reduced GFR, is problematic.

Complicating this attempt to achieve “adequate” blood pressure control are significant gaps in our knowledge typified by the following questions: What are optimal antihypertensive treatment strategies with diabetes or chronic kidney disease? Specifically, do kidney transplant recipients derive the same cardiovascular and kidney disease risk reduction benefit with drugs that block the renin-angiotensin system, such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB), as that seen in the general population? And what is the optimal level of blood pressure for protecting against cardiovascular disease and progressive allograft dysfunction? Is it 140/90 mm Hg? Is it 130/80 mm Hg? Or, should the goal be modified based on comorbid diseases? Many, if not most, transplant patients have either diabetes and/or an estimated GFR below 60 mL/min/1.73 m², and probably would benefit from lower blood pressure goals. As will be discussed later in this article, many of these questions remain unanswered. It is the opinion of these authors that until more is known, we should consider the data derived from studies in the general population as being relevant to treatment choices and goals in kidney transplant recipients.

Pathophysiology of Hypertension

The pathogenesis of posttransplant hypertension is poorly characterized. Multiple factors are likely involved

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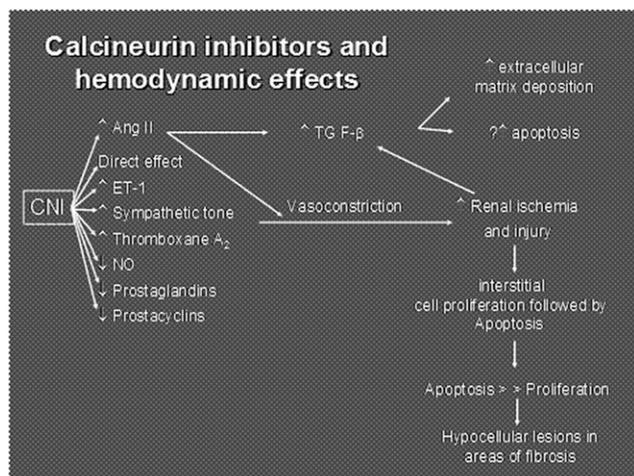


Figure 1. Calcineurin inhibitors and hemodynamic effects.

in the genesis of hypertension,^{7–11} the most important of which may reside in the native diseased kidneys. In addition, the chronic use of calcineurin inhibitors (i.e., tacrolimus and cyclosporine), with or without corticosteroids, induces preglomerular vasoconstriction, which activates sodium conserving mechanisms within the kidney. The intrarenal vasoconstriction is likely mediated by angiotensin II, endothelin, and possibly other mediators. Of these, angiotensin II and endothelin are likely the most important (Figure 1).^{12–21} Additionally, there may be other factors, such as the development of arteriopathy, or interstitial fibrosis and tubular atrophy, which may be related to the chronic administration of calcineurin inhibitors, which result in an increase in blood pressure.²² However, it is clear that with both cyclosporine and tacrolimus, that they increase both systemic and renal vascular resistance. Other important risk factors include: (1) preexisting recipient factors such as pretransplant hypertension, (2) donor-specific factors such as hypertension in the donor, (3) subsequent development of transplant renal artery stenosis, (4) development of chronic allograft dysfunction, and (5) external behavioral factors such as recipient weight gain. Progressive dysfunction in the transplanted kidney may also contribute to blood pressure elevation via impairment of sodium and water retention. Some of the processes that may lead to worsening of graft function include calcineurin inhibitor nephrotoxicity, thrombotic microangiopathy, chronic antibody-mediated rejection, recurrent primary kidney disease, or de novo glomerulonephritis.^{8,10,11}

In large part, posttransplant hypertension is characterized by sodium and water retention with associated volume expansion along with increased sympathetic nervous system activity, intrarenal¹⁸ (afferent glomerular arteriole) vasoconstriction, and lower levels of plasma renin. Lower levels of plasma renin could also be indicative of higher intrarenal levels of angiotensin II and endothelin with subsequent sodium and water retention.

Retention of sodium, and consequent volume expansion, explain a distinctive characteristic of posttransplant hypertension, specifically, the loss of nocturnal reduction of blood pressure.²³ In the general population, loss of nocturnal reduction of blood pressure is associated with left ventricular hypertrophy, lacunar stroke, and microalbuminuria.²⁴ Interestingly, some studies have associated chronic cyclosporine therapy with lack of nocturnal blood pressure reduction when measured with ambulatory blood pressure monitoring devices.²³

Transplant Renal Artery Stenosis

Transplant renal artery stenosis may occur in 10% or more in renal transplant recipients (range, 1%–23%), and the incidence of reported cases is increasing with the prevalent use of Doppler ultrasound and magnetic resonance imaging.^{12,25} Whether this increase is clinically relevant is unknown. Usually transplant RAS is detected between 3 months to 2 years posttransplant, but cases have occurred even years later. Kidneys with multiple renal arteries implanted on a common aortic patch have a higher prevalence of late renal artery stenosis 6 months to 3 years posttransplant.²⁶ Other risk factors associated with RAS include infection with cytomegalovirus and delayed graft function. Unless patients have resistant hypertension, or develop renal dysfunction with progressive blood pressure elevation (with or without RAS blockers), a transplant renal artery duplex is not routinely performed in most centers. Thus, the incidence of renal artery stenosis is likely underreported.

A renal artery duplex can be a useful screening tool.^{27,28} A renal duplex can be accurate, but depends on the experience of the sonographer and the orientation of the kidney and the body habitus of the patient. If one defines stenosis as more than a 50% reduction in lumen diameter, a peak systolic velocity of ≥ 2.5 m/sec was associated with a sensitivity and specificity of 100% and 95% in a study of 109 transplant patients when compared with digital subtraction angiography.²⁷ In general, most reports indicate the benefits of screening with a renal duplex.²⁸ Magnetic resonance angiography or computed tomography angiography can be used for definitive evaluation. As the true incidence of transplant renal artery stenosis is unknown, the clinical benefit of correction is not clear, and the subject of center case series. In our experience, angioplasty and stenting is often preferred, depending on the location of the stenotic area. However, there are a limited number of small reports on angioplasty and/or stenting on long-term outcome.^{29,30}

Outcomes

The precise role of hypertension on patient and allograft outcome posttransplantation has been difficult to define because hypertension is both the cause of, and a consequence of, kidney disease. What is well described in the

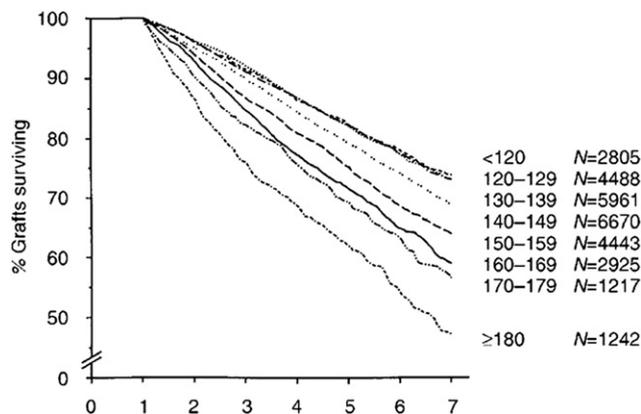


Figure 2. Association of allograft survival and systolic blood pressure at 1-year posttransplant ($P < .0001$). (Adapted from Opelz G, Wujciak T, Ritz E. Association of chronic kidney graft failure with recipient blood pressure. Collaborative Transplant Study. *Kidney Int.* 1998 Jan;53(1):217–22 PMID 9453022.)

literature is that posttransplant hypertension is associated with an increased risk for acute rejection, in particular with African Americans, shorter duration of graft survival, and the development of left ventricular hypertrophy.^{31–33} The Collaborative Transplant Study was a multicenter observational study involving 262 centers and 29,751 subjects whose data were collected between 1987 and 1995.³² Using a multivariate regression model, they demonstrated a striking association between increased systolic blood pressure and decreased allograft survival, regardless of diastolic blood pressure (Figure 2). There was a continuous inverse relationship between systolic blood pressure above 120 mm Hg and duration of graft function. Systolic blood pressures below 140 mm Hg were also associated with better patient survival.

In a historical cohort study of adult allograft recipients, Mange and colleagues³⁴ noted that for each 10 mm Hg increase in systolic, diastolic, and mean blood pressure, there was a 15%, 27%, and 30% reduction, respectively, in the renal allograft survival. Because higher levels of blood pressure are associated with greater degrees of graft dysfunction (in addition to decreased survival and higher proteinuria), it suggests that lower levels of blood pressure may be advantageous for both patient and graft survival. However, there are no prospective studies to evaluate the cardiovascular benefits of planned reduction of blood pressure to any goal in kidney transplant patients, let alone lower goals such as 120 or 130 mm Hg.

Treatment of Hypertension

Given that posttransplant hypertension is often characterized by a lower renin, volume-expanded state, it would make sense that some form of diuretic therapy would be

appropriate. Whether to use thiazide or loop type diuretic depends on the estimated GFR and whether the treating physician feels the volume expansion process is a significant contributing factor to the hypertension. Although not well studied, it is our opinion that some type of diuretic therapy is often required to facilitate achievement of adequate blood pressure control. Because thiazide diuretics may lose some of their volume reducing benefits with estimated GFR below 50 mL/min/1.73 m², more powerful diuretics, such as chlorthalidone or metolazone, or loop diuretics, may be a more appropriate. However, thiazide diuretics may have blood pressure lowering effects outside of their ability to reduce intravascular volume, such as acting as direct vasodilatory agents, which may remain effective with estimated GFR below 50 mL/min/1.73 m². Unfortunately, there are no clinical studies that have examined this important question. Of note, many patients can achieve blood pressure control in the absence of diuretic support.

Calcium channel blockers are an effective class of medications to lower blood pressure in kidney transplant recipients. In the general population, they provide effective reduction of blood pressure regardless of age, gender, ethnicity, and salt intake, which may explain why they are also effective in the kidney transplant patient.³⁵ In addition, they also appear to reverse some of the intrarenal vasoconstriction caused by calcineurin inhibitors.^{35–37} Some clinicians prefer to use calcium channel blockers as, opposed to diuretics, to facilitate achievement of blood pressure control in kidney transplant patients, in conjunction with other drugs. We specifically prefer to use the class of dihydropyridine calcium channel blockers for two reasons: First, as will be discussed later, many patients will derive cardiovascular benefits from beta-blockers. Beta-blockers are safer when used with dihydropyridine as opposed to nondihydropyridine calcium channel blockers to avoid additive effects of reducing atrioventricular node conduction. Second, nondihydropyridine calcium channel blockers interact with cyclosporine, and to a lesser extent tacrolimus, to raise the serum levels of these drugs. Some physicians have purposefully used diltiazem and verapamil to cut the dose of calcineurin inhibitors by 60%–70% as a cost saving strategy. However, one must be extra vigilant in monitoring drug levels of calcineurin inhibitors when using nondihydropyridine calcium channel blockers. Of note, nifedipine, a dihydropyridine calcium channel blocker, also interacts and raises cyclosporine and tacrolimus levels.

Beta-blockers are another important class of antihypertensive agents which should be considered in the treatment for hypertension in the kidney transplant patient. Transplant patients, whether diabetic or not, are at much greater risk for cardiovascular events as compared with the general population.³⁸ Thus, beta-blockade may have a role during the perioperative period to protect against myocardial ischemia, and for long-term management of hypertension.

The heart rate–lowering effects and ability to reduce myocardial oxygen demand may be the key beneficial effects for the transplant patient. Theoretically, they target the increase in the sympathetic nervous activity, which is often seen in transplant recipients. Beta-blockers have been used effectively in transplant patients to control blood pressure.³⁹ However, traditional vasoconstricting beta-blockers (e.g., metoprolol, atenolol) may cause fatigue and may be associated with metabolic consequences such as hyperkalemia, weight gain, and worsening of insulin resistance and increased serum triglycerides. The vasodilating beta-blockers with selective alpha 1 blocking effects, such as carvedilol, labetalol, or nebivolol may be better tolerated, and perhaps may have fewer associated metabolic issues compared with traditional beta-blockers. However, there are no data on the differential effects of beta-blockers on symptoms and metabolism in the transplant patient receiving corticosteroids and calcineurin inhibitors.

Alpha-blockers also represent an important class of antihypertensive agents for transplant patients. Prostatic hypertrophy and bladder detrusor dysfunction secondary to diabetic autonomic neuropathy are not uncommon problems in transplant recipients. Thus, in the hypertensive patient with voiding difficulty, alpha-blockers may be useful. However, these agents can cause orthostatic symptoms and have no proven benefit in reducing mortality in the general population.³¹

Drugs that block the RAS, such as ACE inhibitors and ARBs, are attractive considerations, considering their known benefits in the general population for reducing cardiovascular events and kidney disease progression. However, there are some concerns associated with use of these drugs in transplant patients. First, monotherapy with an ACE inhibitor or ARB is rarely successful in controlling blood pressure in the transplant patient, likely because of volume expansion. They also can induce anemia (a 5%–15% reduction from erythropoietin resistance), hyperkalemia, and a functional decrease in GFR.^{40,41} The latter may raise concerns for acute rejection. Additionally, in the setting of transplant renal artery stenosis, these agents may precipitate acute kidney injury.⁴²

There are multiple theoretical reasons for the use of RAS blockers in the treatment of hypertensive kidney transplant recipients. These include reductions in systemic blood pressure, intraglomerular capillary pressure, and proteinuria.^{39,43} In addition, calcineurin inhibitor nephrotoxicity, may, in part be related to excess effect of angiotensin II (Figure 1).^{44,45} RAS blockers may block angiotensin type 1 receptor antibodies, which may be associated with vascular rejection.⁴⁶ Finally, RAS blockers, as part of an effective blood pressure–lowering regimen, may reduce primary and secondary cardiovascular events, as seen in the general population.⁴⁷ Unfortunately, there are no completed prospective studies demonstrating the advantage of RAS blockers in protection against graft loss, progression of kidney disease, or reduction

in cardiovascular events in kidney transplant recipients. The only prospective, randomized controlled trial involving transplant patients comparing RAS blockers versus placebo was stopped prematurely because of a lack of primary events (composite of all-cause mortality, cardiovascular morbidity, and graft failure).⁴⁸ However, this study did demonstrate better blood pressure control in the RAS blocker (candesartan) arm, and urinary protein excretion decreased during the study by 28.6% in the candesartan arm and increased by 15.4% in the control arm. Serum creatinine and potassium increased in the candesartan-treated patients, but these changes were small and rarely of clinical consequence.⁴⁸

Despite the lack of prospective clinical trials, there are a number of retrospective studies that illustrate the potential benefit of RAS blocking drugs on clinical outcomes in kidney transplant recipients. In a recent retrospective review of more than 2000 recipients of kidney transplants at the University of Vienna, investigators noted that the 10-year survival rates were 74% in patients receiving either an ACE inhibitor or an ARB as part of their antihypertensive regimen, and only 53% in patients not receiving these agents.⁴⁹ Their results were even more remarkable when one considers that the group receiving the RAS blockers were older and required a larger number of antihypertensive medications, as compared with the group not receiving these agents. They were also more likely to have type 2 diabetes and evident cardiovascular disease. Although selection bias limits the interpretation of the results, the data are intriguing, and suggest that there may be an important opportunity to employ RAS blocking drugs as part of an antihypertensive regimen in an effort to reduce cardiovascular events in transplant patients.

Premasathian and colleagues constructed a proportional hazards model to assess the interactive effects of the degree of blood pressure control and type of antihypertensive medications on graft loss in more than 1600 kidney transplant recipients.³⁸ Although their study was retrospective, their Cox regression model illustrated the advantage of calcium channel blockers for reduced risk of graft loss. When they stratified the subjects into blood pressure levels and compared the rates of graft survival between those patients receiving calcium channel blockers and those receiving RAS blocking drugs, there was a favorable effect on graft survival specific to those subjects receiving either an ACE inhibitor or ARB in the cohort of subjects with the highest systolic blood pressure. However, to establish true causality between these drugs and the previous outcomes, one must necessarily integrate results of retrospective studies with results from future randomized clinical trials.

Heinze and colleagues⁴⁹ studied 436 kidney transplant recipients who had delayed graft function. Approximately half of those patients (n = 181) were given either an ACE inhibitor or ARB at the time of transplantation. Those patients who received the RAS blocker had an improvement in 10-year graft survival compared with those who

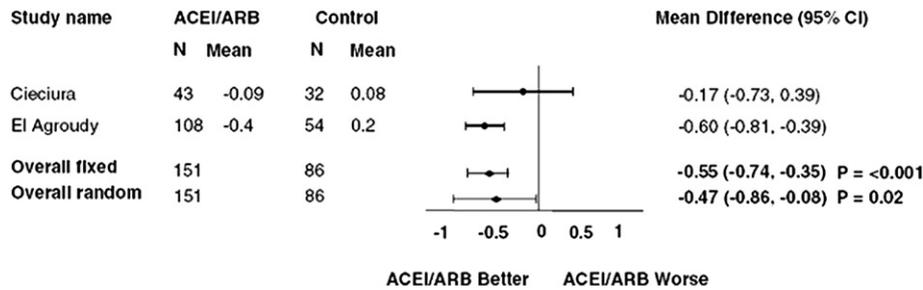


Figure 3. Decrease in proteinuria with use of either angiotensin-converting enzyme inhibitor or angiotensin receptor blockers with at least 12 months of follow-up. (Adapted from: Hiremath S, Fergusson D, Doucette S, Mulay AV, Knoll GA. Renin angiotensin system blockade in kidney transplantation: a systematic review of the evidence. *Am J Transplant.* 2007 Oct;7(10):2350–60). ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval.

did not (44% vs. 32%, respectively). Hiremath and colleagues⁴⁰ performed a systematic review of 21 randomized trials of 1549 patients to determine the effect of ACE inhibition or ARB therapy on graft function and patient survival after kidney transplantation. In this analysis, they observed that drugs that block the RAS were associated with a significant decrease in GFR (-5.8 mL/min), proteinuria (-470 mg/day) (Figure 3), and hematocrit (-3.5%).^{44,50} However, there was insufficient power to determine whether there was an effect on patient or graft survival. The authors suggest that there is a tradeoff between the beneficial effects of proteinuria reduction and potential cardiac protection, with the development of anemia and lowered GFR.

In addition to specific antihypertensive therapy, modification of the immunosuppression regimen may also help to achieve adequate blood pressure control. Corticosteroid minimization, or avoidance, is helpful, because these drugs, particularly in higher doses, have mineralocorticoid effects. Calcineurin inhibitor minimization or withdrawal⁵¹ may also be important to help reduce blood pressure. Within the class of calcineurin inhibitors, when using has less hypertensive effect than cyclosporine²² so conversion from one calcineurin inhibitor to the other, may be a consideration in some patients.

Our algorithm for treatment of posttransplant hypertension is to use either a diuretic (either thiazide or loop diuretics) or a calcium channel blocker, or both, supplemented this with a RAS blocker. If there is evidence of azotemia with this approach, we reduce the diuretic dose or switch to a calcium channel blocker. We also recommend using beta-blockers in patients at risk for, or who have evidence of cardiovascular disease. We also recommend the use of alpha-blockers in patients with voiding difficulty. Fixed-dose combinations may improve medication adherence in subjects who have complex multidrug regimens. As in the general population, tolerability is an important consideration with all choices and doses of antihypertensive agents. Drug–drug interactions and adjustment of dosing also need to be carefully considered. More

studies are needed to define optimal levels of blood pressure and types of therapies to facilitate better long-term patient and graft survival in kidney transplant recipients. Taken together, clinical trials of antihypertensive therapeutics in kidney transplant recipients illustrates that, with diligence, hypertension can be adequately controlled.

Measuring Blood Pressure

As in the general population, blood pressure in the transplant recipient is dynamic. Often, blood pressure dipping at night is less evident. It is likely that “white coat” and “masked” hypertension are as common in the transplant population as they are in the general population. Ambulatory blood pressure monitoring and home blood pressure monitoring may help in deciding about the adequacy of treatment. Unfortunately, there is little published information on the utility of these measures in guiding treatment.

Bulleted Practical Recommendations

1. Kidney transplant patients are at increased risk for cardiovascular disease because of the constellation of reduced GFR, diabetes mellitus, and cardiovascular risk factors (both traditional and nontraditional).
2. Patient survival is likely improved with a blood pressure goal below 130/80 mm Hg, given the information from data registries. A blood pressure goal below 130/80 mm Hg (or perhaps below 120/70 mm Hg) may be optimal for prolonging graft function.
3. Choice of antihypertensive medications posttransplantation depends on the subject’s comorbid conditions and clinical examination. Often patients will require some type of diuretic support based on their volume status and level of kidney function. Dihydropyridine calcium channel blockers may substitute for diuretics in some patients and may be particularly helpful in attenuating some of the intrarenal vasoconstriction associated with calcineurin inhibitor use.

4. The data concerning the use of beta-blockers in post-transplant recipients is limited. Because of the increased risk for cardiovascular disease or evident cardiovascular disease in this population, beta-blockers may be helpful. Prospective studies are needed to examine their potential benefits in the perioperative and immediate postoperative periods.
5. Drugs that block the RAS should be considered for use in most kidney transplant subjects after stable graft function is obtained. Their use may offer both kidney and cardiovascular disease protection. In transplant patients, these agents are effective in reducing proteinuria. It is possible that, as in the general population with native kidney disease, that time-varying albuminuria may be predictive of both kidney and cardiovascular events. Consequently, therapeutic strategies that reduce proteinuria may be an important biomeasure of appropriate treatment. However, there are no prospective clinical studies to support these hypotheses.
6. The treatment of hypertension in kidney transplant subjects is complicated by polypharmacy with subsequent increased risk for drug–drug interactions. Transplant patients need to be educated on the importance of blood pressure control and lifestyle modification, and that often multiple antihypertensive drugs will be required.
7. Minimization or avoidance of corticosteroids or calcineurin inhibitors may be helpful in controlling blood pressure in kidney transplant recipients.
8. Transplant renal artery stenosis, as a cause of graft dysfunction and resistant hypertension, needs to be considered in all patients. Renal artery duplex can be a useful screening tool.

Acknowledgments

We thank Tia A. Paul, University of Maryland School of Medicine, Baltimore, MD, for expert secretarial assistance.

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