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DISCLOSURES

None.

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See related article, "Transmembrane TNF-α Facilitates HIV-1 Infection of Podocytes Cultured from Children with HIV-Associated Nephropathy," on pages 862–875.

Should Transplant Referral Be a Clinical Performance Measure?

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ESRD providers and policymakers have long been at the forefront of efforts to improve health care quality. The Medicare program currently monitors dialysis facility performance related to vascular access, dialysis dose, mineral metabolism, anemia management, bloodstream infections, patient satisfaction, hospitalization, and mortality.[1] By contrast, access to kidney transplantation is not a routine part of Medicare quality improvement efforts. This may be because transplantation is viewed as beyond the purview of dialysis facilities. In addition, the severe shortage of organs for transplantation may raise questions about the ultimate effect of any quality improvement initiatives.

However, many of the barriers to receiving a kidney transplant occur while patients with ESRD are being cared for by dialysis facilities. Obtaining a transplant requires patients to successfully complete a series of six sequential steps: (*1*) medical suitability (*i.e.,* no absolute contraindications to transplantation); (*2*) interest in considering a deceased or living donor transplant; (*3*) referral to transplant center initiated by the patient, nephrologist, or other dialysis facility staff; (*4*) transplant center workup, including medical history, physical examination, psychosocial assessment, evaluation and treatment of medical conditions, and laboratory studies; (*5*) placement on deceased donor waiting list or identification of potential living donor; and (*6*) transplant from deceased or living donor. Most patients on dialysis are unable to complete the first three steps, which occur before transplant providers are involved.[2]

In this issue of the *Journal of the American Society of Nephrology*, Patzer *et al.*[3] show that interventions directed at dialysis facility practices can improve transplant referral, a task that reflects successful completion of the first three steps in the kidney transplant process. The authors randomly assigned 134 Georgia facilities to a control group that received usual care or an intervention group that received transplant education and engagement activities that targeted dialysis facility leadership, staff, and patients. After 1 year, intervention facilities referred 7.3% more patients to transplant centers. The benefit of the

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intervention was especially striking among black patients on dialysis, a group that has long been disadvantaged in receiving kidney transplants.

Strengths of the study include a randomized design, inclusion of large numbers of patients and facilities, and a reasonably high level of intervention fidelity. The main limitations relate to the potency and ultimate effect of the authors' approach. Despite a successful intervention, over 80% of patients on dialysis at intervention facilities were not referred to transplant centers. Of course, not all patients should be referred to a transplant center. Absolute medical contraindications to kidney transplantation include systemic infections, extreme obesity, and an active or recent malignancy. In addition, some patients may be uninterested in transplantation, even after they have been adequately informed about its benefits and risks. Although the appropriate proportion of patients who should be referred is unclear and likely to vary across facilities, the high proportion of unreferred patients in the study suggests that additional work is needed to enhance the potency of the intervention. Moreover, the primary study outcome of faxed referral form or patient self-referral is insufficient to guarantee further progress in the transplant process. In our group's work, we found that many patients fail to make an initial visit to the transplant center, even after a referral is placed. We also found that many patients who make an initial visit subsequently fail to fully complete the transplant center workup, which typically requires multiple visits over several months.[2]

The findings by Patzer *et al.*[3] raise the question of whether transplant referral should be a clinical performance measure for dialysis facilities. Good performance measures are those that address an important process or outcome, are positively influenced by practices undertaken by health care providers, and are based on transparent, minimally burdensome, and accurate data reporting.[4] We know that access to transplantation is important, and this Georgia quality improvement study shows that dialysis facility practices can improve the process. As a condition of Medicare coverage, dialysis facilities are already required to discuss treatment options with patients on a regular basis and note the results of these discussions in patient medical records. Thus, obtaining information relevant to transplant referral should be readily available from such records. It is also necessary to carefully define numerators and denominators for clinical performance measures. In the case of transplant referral, an appropriate denominator would be all patients under age 70 years old (because few transplants are performed at older ages) without any absolute contraindications to transplantation. The numerator may be all patients with a documented referral to a transplant center or even better, all patients who make at least an initial visit to a transplant center.

There are several challenges in implementing this proposed clinical performance measure. Absolute medical contraindications to transplantation may vary across transplant centers, and it would be desirable to develop uniform definitions of absolute contraindications. It is not clear how to count patients who have relative contraindications, lack health insurance, or are uninterested in transplantation. I recommend that dialysis nephrologists discuss relative contraindications (*e.g.,* heart failure or noncompliance) with transplant center physicians to determine whether a transplant referral is warranted (in which case the patient is included in the denominator) or not (in which case the patient is excluded from the denominator). Because lack of health insurance can be an absolute barrier to transplantation, such patients may also need to be excluded from the denominator. However, dialysis providers should work diligently to treat relative contraindications when possible and assist patients in obtaining insurance. I recommend including uninterested patients in the denominator, because our group's work indicates that many patients categorized as uninterested reported being interested after they were fully informed about transplantation.[2] It is worth noting that the standardized transplantation ratio, an indicator of actual to expected numbers of transplants, is not an ideal dialysis facility clinical performance measure, because it reflects not just tasks performed by dialysis facilities but also tasks performed by transplant centers as well as regional variations in organ donation.[5]

Because of the severe shortage of deceased donor kidneys, it may be argued that increasing referrals to transplant centers will only add to an already long waiting list. However, the fact that there are relatively few deceased donor kidneys makes it especially important that this scarce resource be allocated in an equitable manner. In addition, transplant centers may be able to help some patients identify potential living donors, which would increase the supply of kidneys available for transplantation. There are also other things that transplant centers can do to improve their part of the transplant process. They should communicate regularly with dialysis facilities on issues related to medical suitability, referral patterns, and completion of the transplant workup. They should ensure that referred patients are able to get appointments quickly. They should track referred patients to determine reasons why patients may not complete the transplant workup in a timely manner. They should streamline the workup to require fewer visits to the transplant center. They should determine if certain subgroups of patients are especially unlikely to complete the workup and develop methods to better address their needs.

I urge ESRD providers and policymakers to include kidney transplantation in their efforts to improve health care quality. A transplant referral clinical performance measure would be an important step in enhancing the efficiency and equity of access to what is currently the best treatment for ESRD.

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DISCLOSURES

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See related article, "A Randomized Trial to Reduce Disparities in Referral for Transplant Evaluation," on pages 935–942.

Inflammation as a Therapeutic Target To Improve Vascular Function in Kidney Disease

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Cardiovascular disease is a leading cause of morbidity and mortality in patients with CKD. Chronic inflammation and oxidative stress are postulated to link cardiovascular disease and CKD and may be part of a vicious cycle, with CKD leading to increased inflammation and subsequently more rapid loss of renal function.[1] Several mechanisms have been posited to connect CKD with chronic inflammation. These include impaired cytokine clearance, with higher levels of circulating cytokines and inflammatory markers in those with CKD. Inadequate dietary antioxidant intake and excessive free-radical production contribute to oxidative stress, causing further renal and systemic injury, and driving an amplifying loop among oxidative damage, inflammation, and CKD. Chronic inflammation in CKD likely damages the vascular endothelium over time, resulting in dysfunction and ultimately atherogenesis. This inflammation-mediated endothelial damage may be the crux of the CKD–inflammation–cardiovascular disease diathesis, and disrupting this malign axis is a crucial goal.

The IL-1 cytokine system plays an important role in systemic inflammation, vascular injury, and kidney disease. Integral to the IL-1 system are inflammasomes, wheel-like cytosolic protein complexes that respond to various danger signals by facilitating release of IL-1α and IL-1β.[2] These cytokines subsequently bind ubiquitous IL-1 receptors, thereby activating neutrophils and endothelial cells, augmenting reactive oxygen species production, and inducing acute-phase response protein release.[2] Agents targeting the IL-1 system (either IL-1 inhibitors or IL-1 receptor antagonists) have proven to be effective in some systemic inflammatory diseases, such as gout, rheumatoid arthritis, and adult-onset Still disease. Rilonacept is a soluble decoy receptor protein that acts by binding to IL-1α and Il-1β, thereby preventing activation of IL-1 receptors,[3] and has regulatory approval for treatment of a rare group of genetic inflammatory syndromes.

In this issue of the *Journal of the American Society of Nephrology*, Nowak *et al.* report a pilot trial of IL-1 inhibition and its effect on vascular function in persons with nondialysis-dependent CKD.[4] This study enrolled 42 adults with stage 3 or 4 CKD (mean eGFR, 38±13 ml/min per 1.73 m^2), mostly attributed to diabetic or hypertensive nephropathy, with chronic inflammation (high-sensitivity C-reactive protein [hsCRP], 2–30 mg/L). Participants were on stable antihypertensive, diabetic, and statin therapy before enrollment. Equal numbers were randomized to the IL-1 inhibitor rilonacept or placebo for 12 weeks. Participants in the treatment arm received an initial subcutaneous injection of 320 mg rilonacept, followed by weekly 160 mg injections for the remainder of the study; those in the placebo arm underwent the same regimen with inert injections. The primary end points were changes in a measure of endothelial function (brachial artery flow-mediated dilation [FMD_{BA}]) and large artery stiffness (aortic pulse-wave velocity [aPWV]), assessed at 4-week intervals. FMD_{BA} in the treatment arm showed an absolute 1.1% increase from baseline to 12 weeks, compared with an absolute 0.9% decrease in the placebo arm ($P<0.01$). There was no significant change in aPWV in the treatment or placebo group. Several secondary end points were assessed. Systemic inflammation, as reflected by hsCRP level, decreased by >50% in the rilonacept group ($P<0.01$) but other markers (IL-6, IL-1Ra, IL-18, and IL-18 binding protein) were not lowered with the treatment. A supraphysiologic dose of the superoxide scavenger ascorbic acid was given in a subgroup of participants to test whether it differentially affected FMD_{BA} on the basis of treatment status. The point estimate showed greater effect in

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