Norovirus Infections in Kidney Transplant Recipients

By Sanjeev Nair

Diarrhea post-kidney transplantation is a common complication. It is often attributed to immunosuppressive regimens. Norovirus (NoV) infections are the most common causes of acute gastroenteritis worldwide (1). In the transplant population, NoV infections can result in chronic diarrhea, which has long-standing after-effects on nutrition, quality of life, elevated tacrolimus levels, and resultant toxicity and graft dysfunction. Even though the first cases were reported in 2009 (2), awareness about this infection and approaches to its management leave space for improvement.

The knowledge gap is accentuated because the illness is not uniformly defined. It has been suggested that in the absence of an agreed-upon definition, nephrologists use the World Health Organization definition to diagnose patients with diarrhea, i.e., three or more loose or liquid stools per day. Acute diarrhea would last fewer than 14 days, whereas patients with symptoms lasting more than 14 days or for 1 month would be classified as having persistent or chronic diarrhea, respectively (3). As recently as 2020, an observational study published in India researched posttransplant diarrhea and identified 51.5% of participants as having infectious causes of diarrhea but concluded that 75% of these infectious diarrheas could not have an identified causative organism (4).

Published in December 2021, a study by Gäckler et al. (5) sought to address the gaps in our understanding about the clinical characteristics of NoV infections post-kidney transplantation. The study enrolled 60 patients with kidney transplants diagnosed with NoV infection by a positive stool polymerase chain reaction (PCR) test and aimed to identify the characteristics of chronic NoV infections in kidney transplant recipients and their effect on allograft function. The study also evaluated the safety and efficacy of using intravenous immunoglobulin (IVIg) as a therapeutic measure in patients with chronic diarrhea. NoV gastroenteritis occurred a median of 52 months after transplant and resulted in a cumulative median hospital length of stay of 8 days for patients admitted with acute gastroenteritis. Thirty-one of the 60 patients were found to have chronic infection. Patients with chronic infections compared with those with acute infection stayed longer in the hospital (10 vs. 7 days) and were hospitalized more frequently for their illness (17 patients vs. 1 patient). Multivariate analysis showed that both diabetes mellitus and the administration of lymphocyte-depleting induction therapy were independent prognostic factors for the development of chronic NoV infection among kidney transplant recipients (diabetes mellitus: $p = 0.042$; hazard ratio [HR], 4.9; 95% confidence interval [CI], 1.1–22.9 and lymphocyte-depleting induction therapy: $p = 0.035$; HR, 13.6; 95% CI, 1.2–153.2).

Of the total patients, 45% developed acute kidney injury at the time of initial admission, which normalized in those patients with acute NoV infection. However, long-term allograft outcome was affected among patients for whom chronic NoV infection developed. These patients continued to exhibit impaired kidney function 6 and 12 months after initial admission ($p = 0.001$). In addition, 18 kidney transplant recipients with chronic NoV infection were treated with IVIg based on severity perceived by treating clinicians. Thirteen of these patients had no further clinical signs of NoV infection and did not require further hospitalizations. However, 10 of the 13 patients demonstrated NoV in stool samples even following therapy (see visual abstract for details).

This study goes a long way in demonstrating the clinical significance of chronic NoV infection with regard to allograft function. With the availability of multiplex PCR panels to aid in the accurate identification of pathogens in community-acquired gastroenteritis (6), including NoV infections, kidney transplant recipients with acute or chronic diarrhea should ideally benefit from targeted pharmacologic therapy to treat infective causes. Currently, therapy is restricted to decreasing immunosuppression.

Nitazoxanide, a thiazolide antimicrobial agent that exerts its effect against parasitic worms, protozoa, bacteria, and viruses, has been used in patients with NoV infections. But unpublished data from a placebo-controlled randomized controlled trial showed that nitazoxanide, although safe for use, did not show any difference in symptomatic resolution or time to clinical resolution (7). Although immunoglobulins have been shown to play a central role in the clearance of NoV infections in animal studies (8), oral immunoglobulins have not proven to be consistently beneficial (9). The study by Gäckler et al. (5) provides evidence that patients improve symptomatically with IVIg even though this was not simultaneously associated with a clearance of the virus. Further clinical trials that stratify patients by pre- and post-treatment immunoglobulin levels along with severity of clinical symptoms may provide clearer insight into the benefits of IVIg as a therapeutic strategy in NoV infections.

Other strategies that have been tried include ribavirin and a vaccine against NoV, which require trials in the pretransplant population to demonstrate effectiveness in controlling the disease. It is also relevant to this discussion to note that sapovirus, another virus in the *Caliciviridae* family, can also present with similar symptoms and has been reported to cause infections in the posttransplant setting (10, 11) and in one reported instance following a treated case of NoV infection with persistent symptomatic infection, ultimately resulting in graft loss and a return to dialysis (12). ■

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The author reports no conflicts of interest.

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