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Eradicating the Viral Triad in Hemodialysis Units

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EDITORIAL

Eradicating the Viral Triad in Hemodialysis Units

In this issue of *Advances in Chronic Kidney Diseases*, Dr James Novak as Guest Editor has curated a collection of manuscripts from a cadre of nephrologists whose curiosity includes the viral nephropathies. The authors present a well-researched group of articles that comprehensively review the vast majority of contemporary viral disorders with which most nephrologists will engage at some point in their careers. However, the bulk of nephrologists will be concerned with 3 viruses more than others, hepatitis C virus (HCV), hepatitis B virus (HBV), and the human immunodeficiency virus-1 (HIV).

Adenovirus,[1] cytomegalovirus,[2] Epstein-Barr virus,[3] Hantavirus,[4] hepatitis A virus,[5,6] HIV,[7] influenza,[8] polyoma virus (eg, BK virus),[9] and parvovirus B19 virus (Fifth disease)[10] among others reproduce in renal parenchyma. These vectors rarely cause acute and/or chronic tubulointerstitial nephritis, considering their prevalences. These infections are frequently indolent, escaping detection until significant kidney tissue has been lost.

This group of viral nephropathies will generally not come under the purview of primary care physicians. However, primary care physicians may chance on these patients as first responders. Therefore, education regarding the potential signs and symptoms of viral nephropathies should be disseminated. The presence of new onset hematuria, leukocyturia, and dipstick albuminuria is widely variable, but even 1 sign is enough to warrant referral to a nephrologist, particularly if there is an increase in the serum creatinine concentration. When these viral nephropathies are engaged by nephrologists, the clinical scenario is often one of intentional immunosuppressions as might occur in a kidney transplant recipient. Essentially, a dormant infection, affianced to its host, is granted license to reawaken and does. Rapid recognition of reactivated virus and reduction of immunosuppression is renal-sparing.

Viral nephropathies that produce glomerulonephritis are confronted by primary care physicians and nephrologists, with cardinal features of hematuria and proteinuria. However, the non-nephrologist more often encounters the viral triad of HCV, HBV, and HIV as a nonrenal disorder. When kidney disease is recognized, infection has usually been long established. For practicing nephrologists, this virologic triad has produced vexation, requiring exasperating effort just to maintain prevalence levels at status quo. Ebola won the prize for intensity of effort, but that intensity was short-lived compared with the eradication efforts devoted to HCV, HBV, and HIV.

One-third of the triad, HIV, can now be contained by highly active antiretroviral therapy (HAART), which saves lives and precludes kidney disease. Patient adherence to HAART is now the most important aspect of therapy, not the agents. To this point, in 2 longitudinal, prospective, observational HIV studies of men and women, Multicenter Acquired Immunodeficiency Syndrome (AIDS) Cohort Study and Women's Interagency HIV Study, only one-third of 198 participants were on an HAART regimen that did not include nephrotoxic tenofovir disoproxil fumarate.[11] Currently, because of the success of HAART, HIV treatment is mostly out of nephrologists' hands now. Likely, the most crucial knowledge for the nephrologists may be recognition of agents that require renal-dosing adjustments. An excellent source for this expertly compiled information may be found at the University of California, San Francisco Web site.[12]

Although the prevalence of HIV in hemodialysis (HD) in-centers may be relatively increased in some urban areas, viral transmissibility is not an overwhelming concern as it is for HBV and HCV. These 2 viruses may induce indirectly glomerular and tubulointerstitial compartmental damage via circulating immune complexes, cryoglobulins, and cytokines. Hepatitis B, the second member of the viral triad, is now rare in HD units, and its prevalence could be reduced to nearly zero in nonendemic areas if hepatitis B surface antigen-positive patients received treatment with lamivudine[13] or the more potent entecavir,[14] if surveillance for surface antigen

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positivity is conducted on an ongoing basis unit-wide. Treatment of HBV-infected ESRD patients treated with HD offers results equivalent to HBV-infected persons not on HD.[13] The probability of success may be increased if treatment plans are conducted in parallel with a dedicated immunization program. However, the true rates of immunization of patients with CKD against HBV are unknown. CKD clinics are rarely equipped to vaccinate patients across the entire vaccine palette proposed for them. The foci of greatest immunization intent have been influenza viruses and the pneumococcus, and justifiably so.

Influenza vaccination rates in patients on dialysis remain suboptimal at just 60%.[15] Immune responsiveness is impaired, although this "truism" has been challenged recently.[16] Recently, a small trial demonstrated that booster immunization may provide vaccine efficacy equal to control subjects.[17] Validation of this study would be a game-changer, if the correct influenza strain could be reliably predicted. In fact, reports of vaccine efficacy are sullied by the imprecision of attributing vaccine failure to the use of the "wrong" vaccine, which is akin to tackling the wrong man in a game of football. The overall incidence rate for pneumonia was reported at 27.9 per 100 patient-years (29.0 in patients on HD vs 18.2 in patients on peritoneal dialysis, $P < .0001$) and was nearly constant from 1996 to 2001.[18] Interestingly, in a more recent Taiwanese study, the incidence density rate of pneumonia was 65.6 per 1000 person-years in patients with CKD and 28.4 per 1000 person-years in individuals without CKD. Pneumonias in patients with ESRD persist and portend cardiovascular disease and death.[19]

Despite that CKD is prevalent in the United States, the Advisory Committee for Immunization Practice (Centers for Disease Control, Atlanta) has not issued a special call for immunization of patients with CKD Stage 4 when the immune response to recombinant HBV is far better than when individuals are immunized after initiation of renal replacement therapy. When the switch from a more vigorous immune response to one suboptimal is not known precisely, consequently, it might prove better to immunize all patients with CKD Stage 4 at a predetermined estimated glomerular filtration rate. And, would that be cost-effective? Only a well-designed study could prove this hypothesis. If proven, implementation would be difficult as knowing when a patient crosses the threshold for immunization requires repetitive serum creatinine–based testing to determine the glomerular filtration rate. Perhaps the recently available toll-like receptor 9-adjuvanted 2-dose injection series for HBV (Heplisav-B; Dynavax, Düsseldorf)[20] will be more greatly adhered to than the currently prescribed 3-dose 40-μg injection series (Recombivax HB Dialysis Formulation; Merck & Co, White House Station).[21]

No matter which vaccine is stocked in one's CKD clinic and intends to administer, my advice is to employ motivational interviewing in early CKD Stage 4 for immunization of all recommended vaccines. Such practice would additionally ensure that vulnerable patients receive an HBV vaccine, the 13- and 23-valent pneumococcal polysaccharide immunizations, and annual influenza vaccinations. If stockage of these vaccines is not possible in one's practice, then urgency of discussion with and education of primary care providers is required because these health care providers must embrace the responsibility of protecting the patients against these pathogens. Irrespective of the aforementioned, patients who are at risk for progression to CKD Stage 5 must be vaccinated against HBV, influenza, and pneumococcus.

HCV, the third member of the triad, is now the greatest nonbacterial threat for in-center HD units. HCV represents a risk for patient and provider. Now, HCV is eminently treatable. Unlike before, there is high tolerability of direct-acting antiviral (DAA) therapy-based regimens, per a recent meta-analysis[22]: <10% of patients in the 42 clinical trials analyzed withdrew from therapy. Efficacy as delineated by 8-week sustained virologic response rates against genotype 1 HCV was >95% for the 6 major DAA studies analyzed for this result. Response rates were 78% to 85% in patients with hepatic decompensation. Many patients enter the dialysis population with known HCV seropositivity and some degree of chronic liver disease. As per the international Dialysis Outcomes and Practice Pattern Study, the prevalence of HCV among patients on maintenance dialysis in the United States is 8.6%,[23] 5-fold greater than the general population. Part of the reason is that 62% of HD units do not screen for HCV.[24] Urban HD units may have a significantly greater prevalence of HCV seropositivity. Seroconversion of a patient from HCV-negative to HCV-positive status is usually attributed to breaks in universal precautions or sterilization procedures. Furthermore, infection with HCV is a known risk factor for developing advanced CKD and glucose intolerance through impaired expression of insulin substrate-1. Worse yet, HCV infection with coincident HIV infection may be encountered.

Unfortunately, until recently, nephrologists have rarely treated HCV. The management and treatment of HCV was minimal attributable to 2 major factors, drug toxicity and altered pharmacokinetics.[25,26] Pegylated interferon-related drug toxicity of HCV-afflicted HD patients in the era preceding DAA therapy manifested as flu-like syndrome, weight loss, and myelosuppression in patients on dialysis. However, patients with ESRD actually and somewhat paradoxically fared better than normal kidney function patients, likely because of higher drug levels of an antiviral agent during monotherapy with pegylated interferon. Early treatment models using interferon monotherapy yielded sustained viral 48-week remission rates of approximately 40% of cases. Combination therapy with ribavirin was associated with a 50% sustained viral response, only 10% less than seen in normal kidney function patients.[26] These studies were small and underscored the widespread fear of ribavirin-mediated hemolysis, a fear that likely led to undertreatment of many HCV-positive patients. Hepatologists essentially did not refer patients with HCV-induced kidney disease to nephrologists, presuming that kidney doctors would forgo therapy for fear of hemolysis. Even had 30% of treated patients withdrawn from therapy because of side effects, 30% to

35% of patients overall were denied the chance for cure from HCV. With the success of DAA therapies, patient-centered approaches to treating both HCV and CKD may be beneficial, so patients and clinicians can consider how to manage both diseases. Patient education and decision support tools may improve disease management and adherence.[27]

Despite the resounding success of contemporary HAART for HIV infections, patients coinfected with HCV and HIV fare worse than monoinfected counterparts in terms of advanced liver fibrosis and cirrhosis.[28-31] Coinfected patients also incur greater degrees of liver-related morbidity and mortality, extrahepatic organ dysfunction, and demonstrate an overall greater mortality rate than HCV-monoinfected individuals.[32] Therefore, nephrologists should collaboratively treat such patients with either an infectious diseases' subspecialist or internist trained in HIV medicine and a hepatologist. Medication reconciliation in this patient population is extremely important because of differences in and interactions of metabolic pathways used by drugs for HIV and HCV. Notably, HBV reactivation may occur in individuals treated with DAA therapy for HCV infection.[1]

Given the rarity of HBV infections in HD units and the ability to successfully treat HIV with HAART, HCV remains the last of the viral triad to overcome. After the success of the multicenter, open-label C-Surfer trial in which 98% of CKD stages 4 and 5 with HCV, genotypes 1 to 6, with compensated liver disease (with or without cirrhosis) experienced a 12-week sustained viral response to therapy comprising the combination of the NS3/4A protease inhibitor glecaprevir and the NS5A inhibitor pibrentasvir, nephrologists were empowered to "easily" treat their HCV cohorts.[33] The rush to treat never transpired, and HCV remains more prevalent in HD units that it rightfully should. Nephrologists are reluctant to treat for possibly several reasons: financial, inadequate education on how to effect therapy, or disinclination because of lack of mandate. None of these reasons/excuses are acceptable.

Placing HCV-coinfected patients aside for the moment, how can HCV be effectively eradicated from HD units, now that DAA therapy has matured to the point of pangenotypicity, with combination therapies as outlined by the World Health Organization?[34] Although multiple regimens for patients with CKD have been trialed successfully, only the combination of glecaprevir and pibrentasvir (Mayveret; Abbvie, North Chicago) is officially endorsed for individuals with CKD: "Data are insufficient on the safety and efficacy of sofosbuvir-based regimens in persons with severe renal impairment. Glecaprevir/pibrentasvir is effective against infection with all 6 major genotypes in persons with chronic kidney disease."[34]

The elimination of HCV from in-center dialysis units is an interdisciplinary process that is gauged toward identification of patients with HCV and determination of the optimal treatment pathway. Initial screening for antibody directed against HCV is recommended by the Centers for Disease Control and prevention on an annual basis. However, the Centers for Medicare and Medicaid Services has not accepted this recommendation, thereby permitting a "no HCV screening" environment. Patients positive for anti-HCV antibody should undergo subsequent identification of "live" RNA virus by "reflex" polymerase chain reaction testing to produce a "viral load" result. This testing is expensive, as is the next recommended step of genotyping. In the capitated and bundled environment in which nephrologists working in dialysis units live, achieving this laudable goal suddenly becomes a penurious procedure. To obviate this financial obstacle, the partnering of nephrology with hepatology is essential.

Ideally, the hepatologist who would ultimately review the patient's care and prescription of a DAA-based drug combination would collaboratively order all necessary laboratory tests and procedures, outside the dialysis "bundle," after the presence of anti-HCV antibody is confirmed and the viral load has been quantified. Genotyping can be coupled with resistance testing. Afterward, a hepatic fibrosis scan, based on transient elastography, is a painless and rapid maneuver that can be used to quantify liver stiffness vis-à-vis cirrhosis. Alternatively, because of the nonuniversal availability and expense of an elastography machine, the noninvasive biomarker-derived FibroSURE test (LabCorp, Burlington) may be substituted to produce a numerical score (<0.21 to >0.74) that well correlates with the extent of liver damage in persons with several non-HCV liver disorders, including HBV, alcoholic cirrhosis, and nonalcoholic fatty liver disease, that is, steatohepatitis.[35] FibroSURE algorithmically generates its score, which correlates with liver biopsy, from serum levels of α2-macroglobulin, haptoglobin, apolipoprotein A1, bilirubin, and gamma glutamyl transpeptidase, age, and gender. Should DAA treatment be advised after collation and interpretation of these data, the patient is treated outside the dialysis unit after sufficient patient education and informed consent.

In the circumstance that an HCV-positive ESRD patient is eligible for heterotopic kidney transplantation, DAA treatment may be delayed until after surgery. This strategy is predicated on the probability that the recipient will live longer with an HCV-infected and treated organ than remaining on dialysis and only undergoing DAA treatment. A recent United States analysis via a Markov state-transition decision model examined the question of whether it was more cost-effective to transplant HCV-infected or HCV-uninfected kidneys into HCV-infected patients.[36] The investigators concluded: "Transplant of an HCV-infected kidney followed by HCV treatment was more effective and less costly than transplant of an HCV-uninfected kidney preceded by HCV treatment, largely because of longer wait times for uninfected kidneys. A typical 57.8-year-old patient receiving HD would gain an average of 0.50 quality-adjusted life-years (QALY, a generic measure of disease burden), including both the quality and the quantity of life lived at a lifetime cost savings of $41,591." The efficacy of this strategy has been long opined by likely all of us,[37] especially given the unpalatably excessive discard rate of HCV-positive kidneys.[38] However, this study does lend some credence to the

practice of delaying DAA therapy in patients with ESRD in lieu of potentially successful orthotopic liver transplantation.

In conclusion, the viral triad of hepatitides B and C and HIV that has produced much heartache for nephrologists and greater sorrow for patients can be overcome with dedicated, evidence-based, and judicious care. It is improbable that the influx of HCV, HBV, and HIV into HD centers will stop, given the nature of their entries in vulnerable and high-risk patients. Nonetheless, the strategies proposed offer overall reductions for these respective virions. Implementation is as important as strategy. The processes of care to achieve these ends require collaboration among nurses, advance practice providers, primary care physicians, nephrologists, infectious disease and/or hepatologists, and patients. We will have to change the mien to change the mean.

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