The Many Faces of Infection in CKD: Evolving Paradigms, Insights, and Novel Therapies

In 1961, Schreiner was the first to note unique susceptibility to infection among patients with kidney failure.[1] It was assumed that general debility from chronic uremia increased the risk of infection; thus, it was postulated that reversal of the uremic state would reduce the risk of infection.[2] Unfortunately, kidney replacement therapy has not reduced the problem of infection; it has only changed the paradigm.[3] Dialysis superimposes myriad new problems onto patients already suffering relentless deterioration from underlying multisystem disease and poor wound healing. ESRD may be considered a state of acquired immunodeficiency.[4] The risk and outcomes of infections in maintenance dialysis patients have been widely reported. Infections constitute the second leading cause of mortality in this population, accounting for 8% of deaths.[5] Half of hemodialysis patients die or are rehospitalized within 30 days of an infection-related admission.[5] However, high rates of infection in patients who undergo dialysis can, at least in part, be attributed to the loss of barriers to infection due to dialysis access, white blood cell and complement dysfunction from contact with dialysis membranes, iron overload, and exposure to bacteria and pyrogens from contaminated dialysis water systems or inadequately cleaned dialysis machines. Risk factors for infection not related to kidney replacement therapy that could apply at all stages of predialysis CKD include the causes and treatment of kidney disease, comorbidities, reduced vaccine effectiveness, and high levels of exposure to health-care facilities.[6] The US Renal Data System reports a doubling of infection-related hospitalizations in patients with ESRD, whereas those for cardiovascular and other causes are in decline.[7]

Despite infectious complications being well recognized in ESRD, this major source of morbidity occurs 3 to 5 times more commonly in patients in earlier stages of CKD than in non-CKD patients. Furthermore, in the United States, individuals with CKD are hospitalized for infection 8 to 20 times more frequently and with longer lengths of stay than the general population older than 65 years.[8,9] Kidney disease is a continuum, and alterations in immune cellular function may develop well before ESRD, similar to other metabolic abnormalities associated with kidney disease. Dalrymple and colleagues[10] in a cohort study demonstrated temporality as well as a biological gradient of increasing risk of infection with lower estimated glomerular filtration rate, providing further evidence in support of causality.

Some investigators have indicated that there may be a link between infectious events, which increase inflammatory mediators, and subsequent cardiovascular events, including myocardial infarction and congestive heart failure. As demonstrated in a recent pan-Canadian cohort, a single infection is associated with a 1.8-, 3.2-, 1.6-, and 3.4-fold higher risk of cardiovascular ischemia, congestive heart failure, ESRD, and mortality, respectively.[11]

Infectious complications may occupy a far more important place in the chain of morbidity and mortality than previously appreciated, which suggests that prevention and intervention approaches should be considered more actively. In this themed issue of *Advances in Chronic Kidney Disease*, experts in the field provide focused reviews on several timely and pertinent topics in the area of infectious complications in patients with CKD/ESRD.

In the opening review of the issue, Drs. Ahmed and Narayanan tackle the mechanisms of immune dysfunction in CKD. Immune dysregulation in CKD and immunosenescence in the elderly may have much in common as accelerated aging; risk for cardiovascular disease; increased susceptibility to infection; and the frequent occurrence of frailty, cognitive decline, and sarcopenia are manifestations seen in both populations.[12]

The use of tunneled central venous dialysis catheters remains at a staggeringly high rate of 80% at dialysis initiation, resulting in many sepsis complications. This is a major problem in the United States. Drs. Kumbar and Yee in their narrative summarize the epidemiology, diagnosis, and optimal management of catheter-related blood stream infections as well as the interventions aimed at decreasing their incidence, which could improve clinical outcomes in these hemodialysis patients.

Despite the progress in newer technologies and antimicrobial therapy, peritoneal dialysis (PD)–related infections remain common and serious complications of PD. Rapid changes in the epidemiology and outcomes of peritonitis in patients on PD have been reflected by the large number of revisions or updates of the International Society for Peritoneal Dialysis guidelines over the past 2 decades.[13] Drs. Bieber and Mehrotra concisely elucidate in their treatise the latest information in the prevention, diagnosis, and treatment of PD-related infections.

Patients with CKD are at higher risk of *Clostridioides difficile* infection, which is the most common cause of transmissible nosocomial infection in health-care facilities. It is associated with significant morbidity (ie, lower treatment response, higher recurrence, higher rate of colectomy) and mortality. Drs. Mayur and Yee elaborate on the prevention and current management of this scourge of hospitalization.

Although antimicrobial treatment for *Mycobacterium tuberculosis* infection was developed more than 50 years ago, the numbers of *M tuberculosis* cases and deaths continue to increase. Effective cell-mediated immunity, that is hampered with impaired kidney function, is critical to the control of these pathogens. Drs. Cahuayme and Brust provide a comprehensive review of the diagnosis and management of *M tuberculosis* and non-*M tuberculosis*

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infections in the prekidney and postkidney transplant patient. The optimal duration and dosage of therapy are critical to successful cure.

Hepatitis C virus (HCV) infection continues to be the most common hepatotropic viral infection in patients on hemodialysis, whereas hepatitis B virus (HBV) appears to be on the decline. In 1974, the nationwide incidence of HBV infection among chronic hemodialysis patients was 6.2%. By 1999, the incidence had decreased to 0.06% as a result of implementation of infection control precautions: vaccinating against HBV, avoiding dialyzer reuse in patients positive for hepatitis B surface antigen, and screening donor blood for HBV markers.[14] The HCV seroconversion rate in hemodialysis units ranges from 0.011 to 0.036 per patient-year on hemodialysis.[15] Given the absence of a vaccine, strict universal precautions remain the cornerstone to prevent HCV transmission in dialysis units. While explaining the changing epidemiology of these viral infections in dialysis facilities, Dr. Soi and colleagues summarize various therapeutic options and clinical trials that highlight the newer direct-acting antiviral drugs that have revolutionized the treatment of HCV, offering the potential glimpse of a cure for this entity in pretransplant and posttransplant settings.

Dialysis patients have been particularly affected by the deluge of multidrug-resistant organisms that have emerged as important causes of healthcare-associated infections. They are associated with significant morbidity and mortality, with colonization and infection rates often exceeding those seen in persons with other types of health-care exposure.[16] Drs. Midturi and Ranganath illustrate the need to bridle these pathogens through collaborative preventive efforts, best practices, improvements in antimicrobial prescribing practices, and rigorous implementation of standard infection control measures for hygiene and aseptic handling of central venous catheters.

Dr. Vilay expounds on the pharmacokinetics and nuances of antibacterial agent dosing in decreased kidney function. Newer and traditional methods of extracorporeal therapies and the resultant changes in antibacterial agent pharmacodynamics are discussed. General concepts of volume of distribution, rate of elimination, loading and maintenance doses, and therapeutic drug monitoring are delineated.

One strategy to prevent infectious complications is effective vaccination. Despite the evidence of decreased efficacy, current recommendations are to vaccinate patients with CKD and ESRD. Dr. Reddy and colleagues succinctly outline the recommended vaccine schedule and the barriers to vaccination. The relatively low seroconversion appears to correlate with the degree of kidney dysfunction but not with the specific mode of dialysis.[17] Indirect evidence suggests that increasing dialysis adequacy may be associated with an enhanced response.[18] Novel vaccine adjuvants may help achieve improved vaccination results.[19]

In short, infectious complications need more attention, including preventive measures as well as early diagnosis and treatment. Given the risks and associated complications of infections in patients with CKD and ESRD, strategies to prevent infections effectively are of paramount importance. All ESRD and transplant programs require input from an individual with specialized knowledge of laboratory diagnosis, pharmacokinetics of antibiotics, antibiotic choice, antimicrobial resistance, infection control, and infection prevention. Lately, improving quality of care for dialysis patients has been acknowledged as a national priority in the United States. This acknowledgment is evidenced by the US Department of Health and Human Services' National Action Plan to Prevent Health Care-Associated Infections, which establishes national goals for implementing processes to reduce the risk of infections among dialysis patients.[20] Awareness and quantification of this risk could have benefits for patient management, more effective vaccination strategies, and health-care planning. In addition, data that are required to be reported to the National Healthcare Safety Network of the Centers for Disease Control and Prevention will be incorporated in the Centers for Medicare & Medicaid Services' End Stage Renal Disease Quality Incentive Program, which is designed to provide financial incentives for quality improvement.[21]

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