The Guerilla Tactics of Hepatitis B Virus in Hemodialysis: Fighting a Stubborn Foe

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The fundamental principles of guerilla warfare allow an irregular, numerically inferior force to fight successfully against a larger, better equipped, and more technologically advanced army.[1] Rather than engaging superior forces directly, guerilla tactics involve unconventional combat using stealth, deception, fear, mobility, and unpredictability. These tactics permit small and scattered guerilla bands to engage a large occupying army over a vast extent of territory, creating chaos, disrupting normal activities, and forcing extensive commitment of energies to counterinsurgency efforts. Front-line troops attempting to locate elusive guerilla forces often engage in long and futile searches for the enemy and are vulnerable to ambush, thus draining morale and diverting resources away from other areas. This approach led infamously to the defeat of the French in Indochina, and later the United States in Vietnam.

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The conventional war against hepatitis B virus (HBV) in hemodialysis has been largely successful following adoption of widespread vaccination policies and infection control procedures including mandatory HBV screening and surveillance and contact isolation of HBV-positive patients.[2] These efforts have led to a 95% decline in HBV infections over time and a stable seroprevalence of 1% in dialysis facilities since 1995.[2] However, the case series of HBV mutant infections reported by Apata et al[3] in this issue of *Kidney Medicine* is an uneasy reminder that the war against HBV is still ongoing. Specifically, guerilla-like tactics employed by rare but emerging mutant virus strains could create new dangers in hemodialysis facilities. This report highlights 4 cases of HBV infections that were associated with an undetectable hepatitis B surface antigen (HBsAg) test result. As a consequence, patient safety was jeopardized owing to a delay in identification of HBV mutant infections and failure to promptly institute HBV isolation procedures to protect patients and dialysis staff. Of considerable worry was the lack of a consistent clinical picture to help dialysis facilities suspect the presence of a mutant HBV infection.

HBV infection remains a world health problem, particularly outside the United States, and is associated with considerable morbidity and mortality related to cirrhosis and hepatocellular carcinoma.[4] With increasing globalization of hemodialysis, the problem of chronic HBV infections in patients from endemic regions is problematic.[4,5] Poor response to HBV vaccination has increased concerns of the ongoing risk for dialysis-related transmission in the immunocompromised end-stage kidney disease population.[6-8] Concern about the threat of HBV mutant infections has increased with the appearance of strains containing variants in the preS1, preS2, and S regions of the HBsAg gene.[9] These mutations create conformational changes in surface antigen structure or reduce expression of HBV surface proteins that lead to undetectable HBsAg by enzyme-linked immunosorbent assay. The presence of these mutant strains has been linked to occult HBV infection in dialysis facilities, and they present with highly variable clinical manifestations, making detection difficult without measuring HBV DNA using quantitative polymerase chain reaction (PCR).[9-11] Although low-level occult HBV viremia or exposure to mutant HBV does not always result in clinically significant hepatic disease in chronic kidney failure, it remains a real safety concern, particularly with the risk for HBV reactivation after kidney transplantation.[9]

Numerically, the ratio of HBV mutant to wild-type strains is likely to be exceeding low. Across the vast expanse of dialysis facilities in the United States, the magnitude of the threat of mutant HBV relative to the entire dialysis population is small. However, silent nosocomial spread of occult HBV represents a public health dilemma. Decision makers will struggle to devise a resource-efficient means to counter the unlikely but potentially disastrous consequences of a mutant HBV outbreak. Combating a hidden foe that can appear anywhere, anytime, and without warning makes the guerilla-like characteristics of mutant HBV strains apparent. Though an uncommon threat, mutant HBV infections have the potential to create disruption, confusion, and chaos to a much higher degree than their frequency implies. This situation is strongly akin to the dilemma faced by military commanders trying to deploy forces against an enemy who prefers to strike where defenses are weakest and attacks least expected.[1]

Vigilance against occult HBV mutant infections appears warranted, but indiscriminate use of HBV DNA PCR for screening and detection would be costly and inefficient. A systems-level strategy of infection prevention should include multiple layers of defense against HBV (Fig 1). Conventional screening using HBsAg will detect some HBV mutants, but, as noted by Apata et al, is highly dependent on the assay used. Because the majority of outpatient hemodialysis in the United States is provided by a limited number of dialysis organizations, there is an opportunity

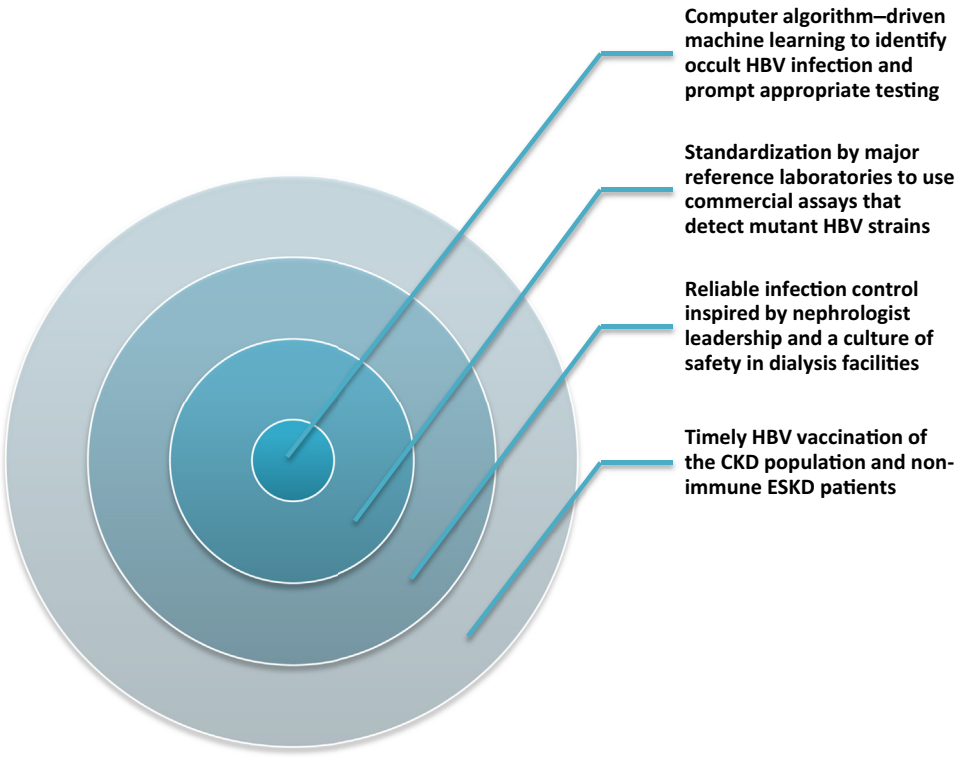

Figure 1. Defense in layers against mutant hepatitis B virus (HBV) strains. A systems-level strategy for protecting patients in dialysis facilities from occult HBV infection. Abbreviations: CKD, chronic kidney disease; ESKD, end-stage kidney disease.

to standardize testing practices to ensure that the more sensitive assays are used.[12]

Although it is beyond the scope of this editorial to make recommendations about industry laboratory standards, it would seem wise for dialysis organizations and their affiliated laboratories to weigh the pros and cons of adopting one of the currently available commercial platforms that can detect the most common HBV mutant surface antigens.[3] This may be economically attractive in the long run, especially in light of the potential downsides of a public health investigation and its associated costs. Furthermore, this would provide additional safeguards against variability in HBsAg assays and infection control practices in the community because dialysis patients may be exposed to HBV in hospital and other settings.[13]

A second consideration is the heterogeneity of serologic profiles for occult HBV infections, whether related to mutant strains or low levels of viremia for wild-type virus.[9-11,13,14] About 20% of occult HBV sera are negative for all serologic markers of HBV infection.[13] Fifty percent are positive for hepatitis B core antibody (HBcAb) and 35% are positive for hepatitis B surface antibody (HBsAb) with or without HBcAb.[13] HBV DNA levels are highest in patients who are positive for HBcAb without HBsAb, and these patients have a potentially higher rate of infectivity.[13] However, the presence of HBcAb is inconsistent, and added to the specter of false-negative HBsAg results makes it challenging for clinicians to reliably identify patients who warrant further testing with HBV DNA PCR. Development of a diagnostic algorithm for patients with discordant serologic profiles over time might help identify at-risk patients because the presence of different HBV markers may vary on an individual basis at different time points and potential exposures.[3,11,13] However, this seems an unrealistic approach in the real world for practicing clinicians, who are not virologists and may not recognize the patterns of possible occult HBV infection without access to complete medical records and the benefit of seeing the entire picture of testing over time.

A computer algorithmic approach using automated analysis of electronic health records may be a better method to identify possible occult HBV infection and discriminate between scenarios that do or do not require more specific HBV DNA PCR testing. One group of researchers used a combination of current biochemical tests, results of prior HBV testing, and *International Classification of Diseases, Ninth Revision* diagnosis codes to develop an algorithm that distinguished acute HBV infection from chronic HBV infection with sensitivity of 99% and specificity of 94%.[15] Major reference laboratories affiliated with dialysis organizations have a large repository of electronic results that could be analyzed algorithmically to prompt clinicians to suspect mutant HBV strains and test for occult HBV infection. Highly dimensional, imbalanced, and nonlinear data sets with vast numbers of interrelated variables can be analyzed using artificial neural networks.[16] The advent of artificial intelligence and machine learning makes this proposed technological solution less fanciful and has been

investigated as a means to overcome the limitations of human interpretation in the diagnosis and classification of HBV infection.[16,17]

Although these systemic process and technological advances hold promise in helping counter the threat of mutant HBV strains and occult HBV infections, basic infection control principles and timely vaccination remain the mainstay of protection against nosocomial transmission of infections in dialysis facilities.[2,13] Ironically, a rational strategic approach is to adopt the first fundamental step of guerilla warfare and use it against HBV: arousing and organizing the people toward a larger goal.[1] Nephrologists Transforming Dialysis Safety is a national initiative to end preventable infections in dialysis by engaging nephrologists to lead and promote infection control.[18] A guerilla campaign will have difficulty succeeding if the local population, in this case nephrologists, dialysis staff, and patients, oppose it as a unified people with a common purpose.[1] Reliable infection control, timely vaccination, and commitment to a culture of safety are the best antiguerrilla countermeasures we can use in the protracted war against HBV.

ARTICLE INFORMATION

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