Variability of Hepatitis B Testing in British Columbian ESRD Patients: The Case to Focus on Implementation of Guidelines

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Background: Hepatitis B virus (HBV) immunization protocols are routinely followed in dialysis units. Recommendations for retesting and booster dose administration are variable and less well known.

Design: Quality improvement report.

Setting & Participants: Provincial dialysis cohort in all 5 regional centers in British Columbia (n = 1,055).

Quality Improvement Plan: (1) Describe the variations in HBV testing practice patterns between centers and modalities of dialysis, (2) propose an evidence-based protocol for HBV follow-up testing, and (3) compare the current practice for HBV follow-up testing with the protocol.

Measures: (1) Number of HBV tests performed based on geographic center and dialysis modality; (2) tabulation of local, national, and international guidelines to determine concordance and develop British Columbian protocol, and (3) percentage of patients who received recommended HBV testing based on protocol.

Results: (1) Significant variation noted in HBV testing frequency among the 5 regional centers and between hemodialysis and peritoneal dialysis patients ($P < 0.001$); (2) current available guidelines generally are concordant, but vary in regard to frequency of follow-up testing; and (3) comparing recommended testing frequency with actual testing, 50% of patients were tested as recommended; 13%, less than recommended; and 37%, more than recommended. Hemodialysis patients often were tested more than recommended (hemodialysis, 47% versus peritoneal dialysis, 16%; $P < 0.01$). Patients with current or past HBV infection were tested more than recommended ($P < 0.01$). All variability remained significant when adjusted for age, sex, and dialysis therapy duration in a multivariate model.

Limitations: The cohort was ascertained from laboratory data; therefore, information for vaccination and booster dose administration was not available.

Conclusion: In a cohort of dialysis patients initially screened for hepatitis B, 50% of patients are being appropriately monitored with retesting compared with an evidence-based protocol. Patients with known HBV infection and hemodialysis patients are being tested more than recommended. Adherence to a protocol for retesting would ensure appropriate follow-up and reduce unnecessary retesting, potentially leading to significant cost savings.

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INDEX WORDS: Quality improvement report; hepatitis B; hemodialysis; peritoneal dialysis; immunization; clinical practice guidelines.

Patients with end-stage renal disease are at greater risk of hepatitis B virus (HBV) infection and therefore are routinely tested and vaccinated if not previously infected or immune. Antibody to hepatitis B surface antigen ([HBsAg] anti-HBs) titers often decrease after vaccination in dialysis patients, requiring revaccination.[1,2] Studies also have shown evidence of decreasing antibody titers in long-term dialysis patients who are naturally immune against HBV.[3] Although clear protocols for HBV immunization of patients with end-stage renal disease exist in renal programs in British Columbia, no such overt protocols exist for follow-up testing after initial screening. Continued HBV screening after initial vaccination is critical to ensure appropriate response to the vaccine, document sustained immunologic response, and monitor for potential seroconversion.

An initial survey of HBV testing protocols in hemodialysis (HD) and peritoneal dialysis (PD) patients in British Columbia showed a variety of testing recommendations among renal units. Al-

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though most programs recommended yearly retesting, some recommended more frequent evaluation. The recommendations for giving HBV vaccine "booster" doses were variable. In addition, no information was readily available about actual testing practice versus recommended testing frequency.

Therefore, the objectives of this study are to: (1) describe the variations in HBV testing practice patterns among geographic centers and between modalities of dialysis (HD and PD), (2) propose an evidence-based provincial protocol for HBV follow-up testing for dialysis patients, and (3) compare the current practice for HBV follow-up testing with the proposed protocol.

METHODS

Study Cohort

Patients were identified from the Patient Registration Record and Outcome Management System (PROMIS) database, an electronic database capturing longitudinal data for all dialysis patients in British Columbia, Canada, a province with a population of approximately 4.3 million. This database captures all laboratory testing performed on all long-term dialysis patients in British Columbia regardless of dialysis unit or ordering practitioner.

The study cohort was formed using all active HD and PD patients in British Columbia on January 1, 2005, with baseline HBV tests (including HBsAg, anti-HBs, and antibody to hepatitis B core antigen) available before January 1, 2005, and 1 year of complete laboratory data follow-up. Thus, the cohort follow-up was ascertained based on laboratory data availability of the aforementioned 3 baseline HBV tests. All patients in the PROMIS database sign a consent form allowing access to their information for statistical and quality improvement purposes.

Development of Testing Protocol

An evidence-based protocol for HBV follow-up testing was developed in consultation with the British Columbia Centre for Disease Control based on current HBV testing recommendations for dialysis patients.[4-11] The protocol was created to provide a uniform recommended practice on which to evaluate current testing patterns. It was designed to assist users in both interpreting HBV serological test results, which can often be confusing, and determining testing recommendations.

The protocol was then compared with the actual testing of the study cohort. The number of HBV tests performed was determined by the number of unique laboratory dates identified in 1 calendar year (January 1, 2005, to December 31, 2005). Patients were classified as having a testing frequency the same as or more or less than recommended based on the number of tests they underwent in the calendar year.

Statistical Methods

Descriptive statistics for the cohort's baseline demographic characteristics are presented as mean ± SD or median with interquartile range, and percentages, when appropriate. One-way analysis of variance, Kruskal-Wallis, and χ^2 tests were used to compare baseline characteristics among HBV infection scenarios. Comparison of the proportion of appropriate testing among centers, dialysis modalities, and baseline HBV infection scenarios were performed using χ^2 test. We further adjusted for age, sex, and duration of disease in the multivariate analysis by using multinomial logistic regression modeling, in which appropriate testing categories as the outcome of interest (treating the appropriately tested group as the reference) and centers, dialysis modality, and baseline HBV infection scenario as predictors. Two-sided P less than 0.05 is considered significant. All analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC).

RESULTS

Study Cohort

Of 1,919 dialysis patients recorded in British Columbia on January 1, 2005, a total of 1,055 patients had all 3 HBV tests registered before January 1, 2005, and 1 year of complete follow-up (January 1, 2005, to December 31, 2005). Of 864 patients without complete data, the reasons included 317 patients with no HBV tests done before January 1, 2005; a total of 374 patients with some, but not all, of the 3 HBV tests; and 173 patients without a year of complete follow-up (Fig 1). Excluded patients were older (mean age, 64 ± 16 versus 61 ± 16 years; $P <$ 0.001), but did not differ with respect to dialysis modality, sex, dialysis duration, or previous transplant. Figure 2 shows definitions of HBV status based on baseline serological test results. Note

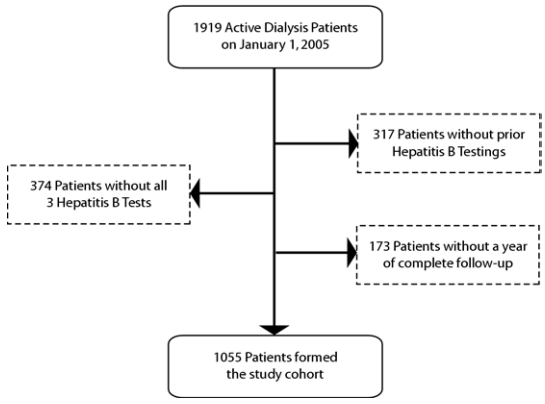

Figure 1. Formation of study cohort.

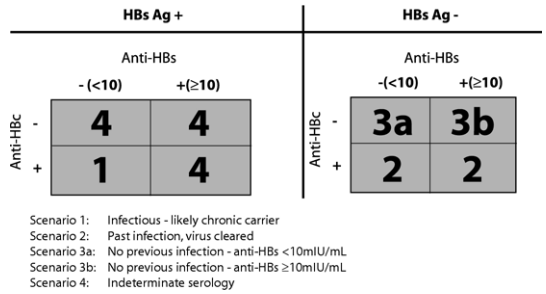

Figure 2. Definition of hepatitis B status. Abbreviations: HBsAg, hepatitis B surface antigen; anti-HBs, antibody to hepatitis B surface antigen; anti-HBc, antibody to hepatitis B core antigen.

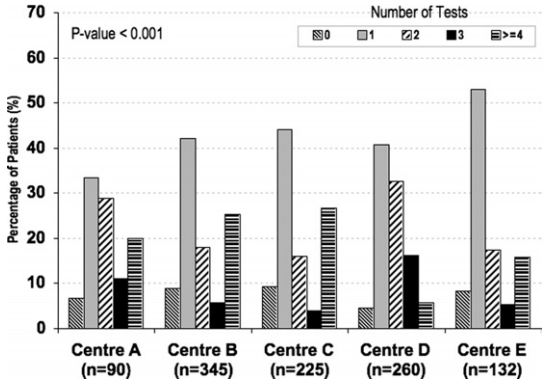

Figure 3. Variability in testing frequency by geographic center.

the 4 categories: current infection, past infection, no previous infection, and indeterminate serological results.

As listed in Table 1, the cohort had a mean age of 61 years and 60% were men. Median duration of dialysis therapy was 2.2 years. Median time from baseline HBV testing to January 1, 2005, was 6.9 months (interquartile range, 1.0 to 12.9). Two percent of patients had serological test results indicating current infection, 17% had past infection, and 81% had no evidence of previous infection. There was no difference in HBV status between HD and PD patients. More HD patients had received a previous kidney transplant (9.5% versus 3.2%).

Variations in HBV Testing Practice Patterns by Center, Dialysis Modality, and HBV Status

There was significant variation in the frequency of retesting independent of protocol recommendations. Figure 3 shows the significant variations in testing frequency among the 5 geographically distinct centers ($P < 0.001$). Figure 4 shows the variation between HD and PD patients. Note that 24.8% of HD patients had more than 4 tests performed per year compared with 5.5% of PD patients ($P < 0.001$). Sixteen percent of PD patients had no tests in the calendar year compared with only 4% of HD patients. As shown in Fig 5, testing also varied by HBV status. Note that 14.3% of patients with known HBV infection had more than 4 tests performed in the year.

Development of Testing Protocol

In consultation with the British Columbia Center for Disease Control, an evidence-based protocol for HBV follow-up testing was proposed, as shown in Fig 6. This protocol was developed after a review of current national recommendations and an updated review of the literature.[5-11] Table 2 lists similarities and differences in the British Columbian "consensus" protocol compared with the other currently published recommendations in the literature. Of note, testing

Table 1. Baseline Characteristics According to Hepatitis B Status

Variable	Total	Infectious	Past Infection	No Previous Infection		*P*
				Anti-HBs < 10 mIU/mL	Anti-HBs ≥ 10 mIU/mL	
No. of patients	1,052	21 (2)	175 (17)	510 (48)	346 (33)	—
Age (y)	61 ± 16	58 ± 16	65 ± 14	63 ± 15	57 ± 15	<0.001
Men (%)	60	76	59	61	57	0.3
Dialysis duration (y)	2.2 (1.0-4.4)	2.8 (0.7-5.7)	2.4 (1.0-4.1)	1.8 (0.8-3.9)	3.0 (1.3-4.7)	<0.001
Previous transplant (%)	8	5	6	8	8	0.7

Note: Values expressed as number (percent), mean ± SD, or median (interquartile range) unless noted otherwise. Patients with indeterminate serological test results (n = 3, scenario 4 in Fig 2) were omitted from this analysis.

Abbreviation: anti-HBs, antibody to hepatitis B surface antigen.

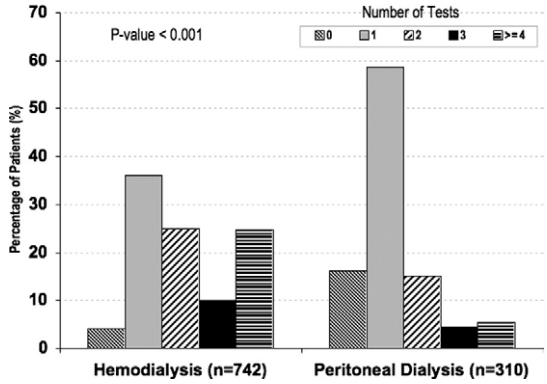

Figure 4. Variability in testing frequency by dialysis modality.

frequencies listed in this table reflect the minimum acceptable frequency and do not account for the need for repeated testing if exposed to such high-risk situations as potential infection control breaches or travel to high-risk areas.

Comparison of Current Practice for HBV Testing With the Proposed Protocol

Table 3 lists how appropriate testing was defined. If no tests were ordered in 1 year of follow-up, this was considered testing less than recommended for all groups. If more than 4 tests were ordered in 1 year of follow-up, this was considered testing more than recommended for all groups. Note that for patients in the "no-infection" group with anti-HBs titers less than 10 mIU/mL, up to 3 tests per year were considered appropriate to take into account repeated evaluation of antibody status. Patients with indeterminate serological test results (scenario 4; n = 3) were excluded from the analysis of appropriate testing frequency because the protocol requires patient-specific assessment, including clinical evaluation and generally retesting.

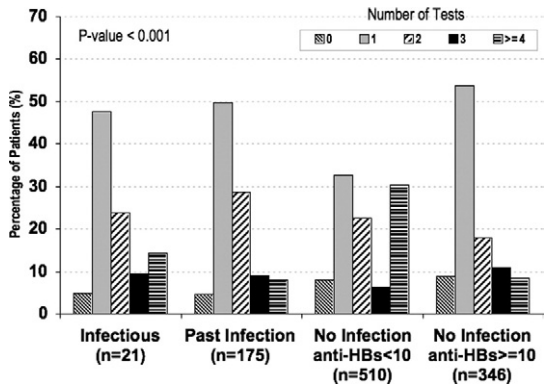

Figure 5. Variability in testing frequency by hepatitis B status. Abbreviation: anti-HBs, antibody to hepatitis B surface antigen.

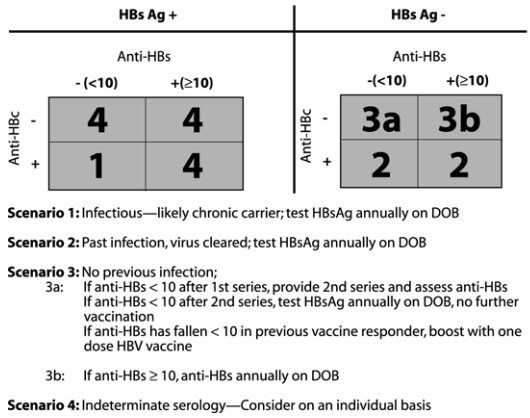

Figure 6. Proposed hepatitis B testing protocol. Abbreviations: HBsAg, hepatitis B surface antigen; anti-HBs, antibody to hepatitis B surface antigen; anti-HBc, antibody to hepatitis B core antigen; DOB, date of birth.

As listed in Table 4, when the protocol developed was compared with actual testing practices in the study cohort, 50% of patients were tested at the same frequency as recommended; 13%, less than recommended; and 37%, more than recommended. Of note, appropriateness of testing varied by dialysis modality ($P < 0.01$), with HD patients more likely to be tested more than recommended (HD, 47% versus PD, 16%) and less likely to be tested less than recommended (HD, 6% versus PD, 30%).

To evaluate whether undertesting in PD patients was related to fewer clinic visits, we linked the number of PD clinic visits during the 1-year follow-up to HBV testing category. PD patients were classified as having 0 to 3 visits (n = 278) or 4 visits or more (n = 32) in the year. Using logistic regression with clinic visit as the outcome and appropriate testing as the predictor, there was no difference among the 3 testing categories (testing frequency same as or more or less than recommended) in terms of the likelihood of having 4 or more clinic visits per year ($P = 0.5$).

Appropriateness of testing also varied in relation to HBV serological status ($P < 0.01$). As listed in Table 4, patients classified as infectious (scenario 1) or past infection (scenario 2) were

Table 2. Comparison of British Columbian Consensus Protocol With Others

	US Centers for Disease Control and Prevention[5]	European Renal Association-European Dialysis and Transplant Association[8]	Canadian[9]	British Columbian Consensus
Universal screening & immunization of susceptible patients	✓	✓	✓	✓
Postvaccination testing for anti-HBs 1-2 mo after first series	✓	✓	✓	✓
1 Attempt at revaccination of nonresponders (failure to achieve anti-HBs ≥ 10 mIU/mL) with 3 doses	✓	✓	✓	✓
Booster dose for vaccine responders if anti-HBs < 10 mIU/mL	✓	✓	✓	✓
Frequency of surveillance of HBsAg in susceptible patients*	Monthly	Every 3-6 mo	Every 3-6 mo	Yearly
Frequency of anti-HBs testing in vaccine responders/immune patients	Yearly	Every 6 mo	Yearly	Yearly
Frequency of repeated testing for patients immune from past infection (anti-HBc$^+$, anti-HBs$^+$, HBsAg$^-$)	Not necessary	Not specified	Not specified	Yearly†

Abbreviations: anti-HBs, antibody to hepatitis B surface antigen; anti-HBc, antibody to hepatitis B core antigen; HBsAg, hepatitis B surface antigen.

*Susceptible patients defined as unvaccinated, partially vaccinated, or nonresponders.

†A case of hepatitis B reactivation in an HBsAg-negative anti-HBc-positive patient highlights the possibility of reactivation in the immunocompromised host.[11]

most likely to be overtested (48% and 46%, respectively), whereas patients with no previous infection and anti-HBs titers less than 10 mIU/mL (scenario 3a) were most likely to be undertested (19%). There was also significant variation in proportions of appropriate testing among the 5 geographically distinct centers (30% to 66%; $P < 0.01$; data not shown). As shown in Fig 7, on multivariate modeling adjusted for age, sex, and duration of dialysis therapy, HD (versus PD) remained a strong predictor of testing more than recommended (odds ratio, 5.98; 95% confidence interval, 3.93 to 9.1). Note again that patients with scenario 3a serological test results (no previous HBV infection and anti-HBs titer < 10 mIU/mL) were much more likely to be tested less than recommended (odds ratio, 2.89; 95% confidence interval, 1.79 to 4.67) compared with scenario 3b serological test results (no previous HBV infection and anti-HBs > 10 mIU/mL).

The impact of a previous kidney transplant or transplantation during the follow-up period was evaluated. Kidney transplantation did not lead to increased testing, with the same proportion of testing more than recommended (39% versus 37%) in patients with a previous kidney transplant than those without.

Table 3. Comparison of Hepatitis B Testing to Recommendations

	No. of Tests/y				
Serological Status	0	1	2	3	≥4
1. Infectious	L	S		M	
2. Previous infection	L	S		M	
3. No infection					
3a	L	L	S	S	M
3b	L	S		M	
4. Indeterminate serological results	To be considered on individual basis				

Abbreviations: L, testing frequency less than recommended; S, testing frequency the same as recommended; M, testing frequency more than recommended.

Table 4. Actual Versus Recommended Hepatitis B Testing

Variable	Total	Less Than Recommended	Same as Recommended	More Than Recommended	*P*
Overall	1,052	137 (13)	521 (50)	394 (37)	—
By dialysis modality					
Hemodialysis	742	45 (6)	352 (46)	345 (47)	
Peritoneal dialysis	310	92 (30)	169 (54)	49 (16)	<0.001
By hepatitis B status					
Infectious (scenario 1)	21	1 (5)	10 (47.5)	10 (47.5)	
Past infection (scenario 2)	175	8 (4)	87 (50)	80 (46)	
No previous infection (anti-HBs < 10 mIU/mL) (scenario 3a)	510	97 (19)	238 (47)	175 (34)	
No previous infection (anti-HBs ≥ 10 mIU/mL) (scenario 3b)	346	31 (9)	186 (54)	129 (37)	<0.001

Note: Values expressed as number (percent). Patients with indeterminate serological test results (n = 3; scenario 4 in Fig 2) were omitted from this analysis.

Abbreviation: anti-HBs, antibody to hepatitis B surface antigen.

DISCUSSION

This study shows in a provincial cohort of dialysis patients initially screened for HBV that 50% of patients are being appropriately monitored with retesting, as determined by best evidence. However, significant variability exists in testing practices, with resource and other implications discussed next.

HBV vaccination is an important first step in reducing the risk of infection and transmission in dialysis patients. However, patients with end-stage renal disease face additional challenges after vaccination, making careful surveillance mandatory. Response rates to vaccination are suboptimal (50% to 60% response) compared with the general population (95% response).[12,13] In addition, it is known that anti-HBs titers often decrease postvaccination in dialysis patients, requiring revaccination.[1,2] Even natural immunity is not completely protective because decreasing antibody titers in long-term dialysis patients who are naturally immune against HBV have been reported.[3]

Our data show that patients on HD therapy are more likely to be tested more than recommended than patients on PD therapy. This may be the

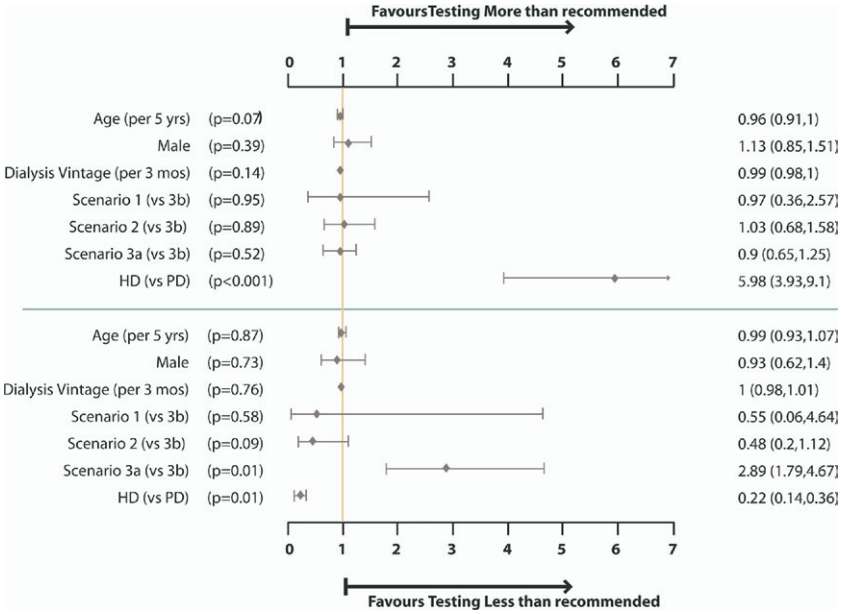

Figure 7. Multivariate model of predictors of testing. Abbreviations: HD, hemodialysis; PD, peritoneal dialysis.

result of availability of the patient for testing and ease of obtaining blood samples. Although patients on HD therapy are at greater risk of exposure because of the potential for exposure to blood during their treatment,[14] there is no justification for more frequent testing given the characteristics of the patients and no acute outbreaks of HBV infection during the year of follow-up. Interestingly, patients with known HBV infection or past infection were also more likely to be tested more than recommended. These patients should have their HBsAg tested yearly, but approximately 50% have more than 1 test performed per year and 8% of patients had more than 8 repeated tests performed in 1 year. Whether this is caused by practitioner knowledge factors (unfamiliarity with the recommended testing recommendations) or system factors (test result not immediately available and therefore redrawn) is unknown.

We also note that 30% of PD patients were tested less than recommended. With an average of only 4 clinic visits per year in stable PD patients, we hypothesized that patients with more clinic visits would have an increased chance of appropriate testing frequency. However, we found that this was not the case. This finding provides an opportunity to focus on PD unit practices in terms of how HBV vaccination and serological monitoring is conducted and tracked and how the medical staff is educated regarding this important intervention.

Another important finding is that patients with no previous evidence of infection and anti-HBs titers less than 10 mIU/mL (scenario 3a in the testing protocol) are being tested less than recommended. This group of patients generally requires either a booster dose of HBV vaccine or a second HBV vaccination series to develop or maintain seroprotection. A repeated anti-HBs test is required after the second series of immunization. However, we found that 20% of patients in this category had 1 or fewer tests performed in a year, indicating that either they were not being offered repeated vaccination or their anti-HBs titer was not being rechecked.

Of note, the protocol used in this study differed slightly from the current US Centers for Disease Control and Prevention recommendations, specifically with yearly HBsAg determination in patients with past infection (versus no repeated HBsAg testing) and with the omission of monthly HBsAg testing in susceptible patients. However, given that we found patients with past infection were already overtested and susceptible patients were already undertested, these results would be accentuated if compared with the US-based guidelines.

Geographic variability was also evident in this study, with appropriate testing frequencies varying from 30% to 66% in the different units. Because no provincial document exists about follow-up testing, it may be that each local group has developed their own strategy. It was beyond the scope of this study to examine specific ordering practices for these tests, but certainly one explanation for differential testing is that individual physician (general practitioners and specialist physicians) or nursing practice patterns lead to differential test ordering practices independent of recommendations that are in place. In this study, center size and number of nephrologists did not correlate with percentage of appropriate testing; ie, more physicians did not lead to more testing variation.

Several limitations of this study must be noted. First, the cohort included only patients with all 3 HBV laboratory tests recorded at baseline. This excluded almost 700 patients with incomplete baseline data. These patients may represent a cohort of undertested patients not captured in this study. In addition, the cohort was ascertained based on laboratory data alone. Therefore, we were unable to report information about past vaccination and booster doses required to maintain an acceptable anti-HBs titer. Data for hospitalization and travel during the 1-year period, which may be an additional valid reason for repeated testing, also were not available.

Because testing frequency is only one component of a comprehensive HBV infection control program, an important next step will be to prospectively evaluate testing recommendations in concert with vaccination rates, appropriate booster dose use, and appropriate infection control precautions (including isolation of HBsAg-positive patients).

This study reinforces the idea that although it is important to have evidence-based protocols to ensure effective and consistent practice, it is equally important to evaluate adherence and understanding of protocol recommendations. This

study identifies a large variation in HBV test and retest frequency, which has resource implications for laboratories and clinical units. The laboratory costs to perform standard HBV tests (HBsAg, anti-HBs, and antibody to hepatitis B core antigen) average Can $50.00, which does not include nursing and physician time to order, interpret, and disseminate the results to patients. Therefore, the reduction in inappropriate testing would significantly reduce costs. For example, if the 37% of patients who were overtested had just 1 less set of HBV laboratory tests per year, this would save more than $20,000 per year in direct laboratory costs alone. In addition, a standardized protocol would improve appropriate follow-up.

There do not appear to be specific formal tracking mechanisms or educational programs for HBV testing in dialysis units. Studies have shown that education and formal feedback lead to more appropriate clinical behaviors by medical professionals.[15,16] A useful next step would be to determine why variations are occurring, target educational strategies toward reinforcing the protocol in these groups, ensure "buy-in" from clinicians, and make changes to the protocol if the reasons for protocol violation reveal opportunities to refine the protocol.

In conclusion, in a cohort of dialysis patients initially screened for HBV in British Columbia, approximately 50% of patients are being appropriately monitored with retesting compared with an evidence-based protocol. Significant testing variation exists among geographic centers, HBV serological status, and dialysis modalities. Patients with known HBV infection and HD patients are being tested more than recommended. Following the recommendations of an evidence-based protocol would ensure appropriate and adequate follow-up, as well as reduce unnecessary retesting and potentially lead to significant cost savings.

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