Determining Optimum Hemoglobin Sampling for Anemia Management from Every-Treatment Data

Adam E. Gaweda,* Brian H. Nathanson,† Alfred A. Jacobs,* George R. Aronoff,* Michael J. Germain,‡ and Michael E. Brier*§

*Department of Medicine, University of Louisville, Louisville, Kentucky; †OptiStatim, LLC, Longmeadow, Massachusetts; ‡Baystate Medical Center, Tufts University School of Medicine, Springfield, Massachusetts; and §Robley Rex Medical Center, Department of Veterans Affairs, Louisville, Kentucky

Background and objectives: Anemia Management Protocols in ESRD call for hemoglobin (Hb) monitoring every 2 to 4 weeks. Short-term Hb variability affects the reliability of Hb measurement and may lead to incorrect dosing of erythropoiesis stimulating agents. We prospectively analyzed short-term Hb variability and quantified the relationship between frequency of Hb monitoring and error in Hb estimation.

Design, setting, participants, & measurements: Using the Crit-Line III TQA device, we prospectively observed Hb during each dialysis treatment in 49 ESRD patients and quantified long- and short-term Hb variability. We estimated Hb from data sampled at regular intervals; 8×, 4×, 2×, or 1× per month to establish how well we account for short-term variability at different monitoring intervals. We calculated the Hb estimation error (Hb_{err}) as a root mean-squared difference between the observed and estimated Hb and compared it with the measurement error.

Results: The most accurate Hb estimation is achieved when monitoring 8× per month (Hb_{err} = 0.23 ± 0.05 g/dl), but it exceeds the accuracy of the measurement device. The estimation error increases to 0.34 ± 0.07 g/dl when monitoring 4× per month, 0.39 ± 0.08 g/dl when monitoring 2× a month, and 0.45 ± 0.09 g/dl when monitoring 1× per month. Estimation error comparable to instrument error information is as follows: 8× per month, 15 patients; 4× per month, 22 patients; 2× per month, 6 patients; 1× per a month, 6 patients.

Conclusions: Four times a month is the clinically optimal Hb monitoring frequency for anemia management.

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Anemia management in ESRD patients is a matter of intense interest for patients, providers, and payors. Clinical trials have suggested adverse consequences if the hemoglobin (Hb) is too high (1–4) or too low (5). Additionally, erythropoiesis-stimulating agents (ESAs) are expensive drugs, warranting judicious use. As a result, a number of protocols are used at dialysis facilities in an attempt to maintain Hb concentration within a range much narrower than that seen by the general population (6). In all these protocols, decisions to start, stop, or change the ESA dose are made at specific threshold values or on the basis of the change from the previous Hb measure. What is often not appreciated when using such clinical protocols is the inherent error or variability in an Hb value, which may lead to inappropriate, premature, or delayed ESA dosing changes.

ESAs stimulate production of new erythrocytes. However, the measured Hb does not inform about the total mass of circulating erythrocytes because of hemodilution from body water gain between dialysis sessions (7). Besides the interdialytic weight gain, the measured Hb is also affected by "short-term" factors such as assay error, storage, handling, acute blood loss, or other conditions (8–10). "Long-term" Hb behavior is primarily related to the dosing of ESA and iron through an anemia management protocol and changes within the patient that can alter the response over time such as slow blood losses, inflammation, and changes in iron metabolism. Because of the inaccuracy of a single Hb value, some facilities attempt to determine the Hb trend in addition to a point estimate. However, these trends and point estimates may be obscured or misleading because of the short-term variability of the Hb. From this perspective, an Hb estimate merely represents a probability range wherein lies the true Hb, value and how to best incorporate this knowledge into an anemia management protocol is unknown.

Typically, the measured Hb value is not questioned, and there is no clinically accepted standard on how often Hb should be measured in hemodialysis patients. The National Kidney Foundation Kidney Dialysis Outcomes Quality Initiative (NKF KDOQI™) guidelines (11) recommend weekly Hb monitoring after every ESA dose adjustment. The current Food and Drug Administration label for ESA (12) recommends twice a week monitoring after dose adjustment until Hb has stabilized, with subsequent monitoring performed at regular but unspecified intervals. As a result, Hb monitoring varies from once a week to

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Correspondence: Dr. Adam E. Gaweda, University of Louisville, Department of Medicine, Division of Nephrology, 615 S Preston Street, Louisville, KY 40202. Phone: 502-852-5757; Fax: 502-852-7643; E-mail: adam.gaweda@louisville.edu

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monthly between the dialysis facilities across the United States (8,13).

The change in Hb over time represents a synthesis of unique processes that individually may have divergent influences on Hb trends. We reasoned that it may be possible to tease out individual processes to provide a clearer picture of long-term ESA effect as opposed to short-term influences such as interdialytic weight gain. We used Fourier series, a mathematical methodology, originally used in engineering sciences to process complex signals, to deconstruct changes in Hb to help define optimal Hb sampling with the goal of minimizing the impact of short-term Hb variability on ESA dosing.

Materials and Methods

Study Design and Participants

The data used in this study were obtained from a prospective interventional case controlled trial. The primary hypothesis of that trial was that frequent Hb monitoring (3×/wk) used in conjunction with the AMIE computer algorithm (14) would reduce undesirable long-term Hb variability compared with 1× per month monitoring (15). Institutional Review Board approval for the trial was obtained from Baystate Medical Center. The study adhered to the Helsinki Declaration of 1975, and all participating patients gave signed informed consent. From March 19, 2007 to July 5, 2008, 49 unselected patients, comprising one dialysis facility, had Hb levels assessed each dialysis treatment over the course of 15 months.

The trial was a case-controlled study where the subjects served as their own controls. Phase 1 was the baseline data collection period, with standard monthly Hb monitoring and ESA dose changes. Phase 2 used the Crit-Line III TQA (Hema Metrics, Ogden, UT) device to control blood. There were no changes in the ESA protocol or use of the Crit-Line Hb values during this phase. Phase 3 was the active use of the AMIE algorithm based on Hb monitoring with Crit-Line.

Hemoglobin Assay

Crit-Line is an optical monitor that noninvasively and continuously monitors the hematocrit (Hct) and oxygen saturation of the blood in the blood lines on dialysis. Hct is converted to Hb using the formula

$$\text{Hb} = 0.3112\ \text{Hct} + 0.71$$

The measurement error of this device is ±1% Hct (±0.31 g/dl Hb) (16).

Statistical Analyses

For each subject, we performed a frequency analysis of their Hb data over time to determine the number and magnitude of distinct cyclic components in the longitudinal Hb data. Frequency analysis is based on the idea of the Fourier series, which breaks down any longitudinal data into a pattern of independent sine waves (cycles) with different amplitude and frequency. Such a pattern is called a frequency spectrum (17).

As mentioned before, measurements of Hb concentration represent an estimate of the true Hb or its trend. The reliability of this estimate is a function of the short-term Hb variability. Our ability to account for this short-term variability largely depends on how often the Hb is observed. We used the frequency analysis to quantify long- and short-term Hb variability and to analyze the reliability of Hb estimation at regular monitoring frequencies of 8×, 4×, 2×, or 1× per month. We defined the long-term variability (Hb Var_{LT}) as the mean amplitude of Hb cycles observable up through the frequency of once a month and the short-term variability (Hb Var_{ST}) as the mean amplitude of Hb cycles observable at frequencies more than once a month. We examined the relationship between Hb Var_{LT} and Hb Var_{ST} using regression analysis. We analyzed the estimation reliability by computing the estimation error (Hb_{err}) using root mean squared difference between the observed and the estimated Hb:

$$Hb_{err} = \sqrt{\sum_{i=1}^{N} (Hb_{obs}[i] - Hb_{est}[i])^2 / N}$$

where Hb_{obs} is the observed Hb level, Hb_{est} is the estimated Hb, and N is the number of Hb observations. This estimation error can be viewed as a quantitative measure of the effect that the short-term Hb variability has on the reliability of Hb estimation.

For every monitoring frequency, we compared the estimation error to the reported Crit-Line measurement error and selected the optimal frequency for each subject individually. We defined the optimal monitoring frequency as one that results in the minimum absolute difference between the estimation error and the measurement error of the Crit-Line device. The estimation errors at different sampling frequencies were compared using an ANOVA analysis with Bonferroni correction for multiple comparisons. All computations were performed in MATLAB® 2010a (The Mathworks, Natick, MA).

Results

Table 1 shows the demographic and laboratory data of the study participants. The mean Hb level across the study population was 11.9 ± 0.6 g/dl. The mean and SD of Hb per individual was 1.03 ± 0.29 g/dl. The median Epoetin alfa dose administered per individual was 2400 (interquartile range = [950, 5075]) U/Tx.

Table 2 lists the Hb statistics per study participant. On average, two Hb measurements per week result in a mean estimation error of 0.23 ± 0.05 g/dl. Monitoring Hb once a week

Table 1. Patient demographics

Variable	Value
Age	
Median	70
IQR	(52, 76)
Range	(25, 90)
Gender	
Percent male	46.9% (23/49)
Percent female (*N*)	53.1% (26/49)
Ethnicity	
Percent white	93.9% (46/49)
Percent African American	2.0% (1/49)
Percent other	4.1% (2/49)
Comorbidities	
Percent with diabetes	59.2% (29/49)
Percent with hypertension	81.6% (40/49)
Percent with polycystic kidney disease	8.2% (4/49)
Percent died ($n = 3$), change in treatment modality before the study terminated ($n = 1$), or transferred from the clinic ($n = 1$)	10.2% (5/49)

Table 2. Hemoglobin statistics per study participant

ID	*N*	Hemoglobin				Hb Var_{LT}		Hb Var_{ST}		Hb_{err}			
		Mean	SD	Minimum	Maximum	Mean	SD	Mean	SD	8×	4×	2×	1×
1	474	12.5	0.72	10.1	14.3	0.102	0.103	0.018	0.015	0.28	0.42	0.47	0.50
2	474	12.1	0.92	10.1	14.3	0.166	0.135	0.017	0.013	0.30	0.38	0.42	0.46
3	474	12.0	1.16	9.2	14.6	0.236	0.140	0.020	0.018	0.29	0.40	0.46	0.56
4	174	12.7	1.14	10.1	14.9	0.189	0.209	0.032	0.022	0.33	0.45	0.50	0.51
5	474	11.5	0.58	10.2	13.3	0.098	0.051	0.014	0.013	0.21	0.29	0.34	0.40
6	239	11.0	0.62	9.6	12.1	0.093	0.107	0.018	0.015	0.17	0.27	0.31	0.35
7	472	11.5	1.20	8.6	14.6	0.262	0.115	0.018	0.018	0.22	0.33	0.39	0.50
8	473	12.2	0.80	10.1	14.3	0.133	0.129	0.015	0.014	0.21	0.31	0.38	0.41
9	466	11.0	0.89	9.1	13.4	0.171	0.077	0.018	0.020	0.26	0.36	0.42	0.50
10	474	11.9	0.63	10.7	13.8	0.117	0.075	0.014	0.012	0.23	0.33	0.36	0.41
11	474	11.4	1.21	8.8	14.0	0.280	0.155	0.013	0.013	0.16	0.26	0.31	0.38
12	474	12.5	0.79	11.1	14.3	0.130	0.151	0.011	0.010	0.17	0.24	0.30	0.32
13	474	12.0	1.01	9.6	15.6	0.200	0.079	0.019	0.018	0.29	0.41	0.48	0.56
14	474	11.4	1.49	7.9	15.4	0.301	0.255	0.017	0.017	0.24	0.35	0.41	0.47
15	474	11.8	0.71	9.4	13.8	0.129	0.062	0.016	0.014	0.24	0.36	0.40	0.43
16	474	11.7	1.09	9.0	14.8	0.242	0.118	0.017	0.016	0.26	0.39	0.42	0.48
17	473	12.6	0.76	11.1	14.4	0.127	0.114	0.015	0.013	0.24	0.33	0.38	0.41
18	474	11.1	1.26	8.6	14.0	0.274	0.174	0.015	0.013	0.24	0.32	0.37	0.43
19	474	11.9	1.04	9.6	14.3	0.214	0.152	0.015	0.014	0.23	0.33	0.37	0.42
20	474	11.8	1.11	8.8	14.1	0.221	0.174	0.016	0.018	0.16	0.25	0.33	0.46
21	474	11.2	1.40	8.6	14.6	0.253	0.250	0.015	0.016	0.20	0.29	0.39	0.44
22	474	11.9	1.00	9.9	15.0	0.192	0.147	0.015	0.014	0.21	0.34	0.39	0.43
23	316	12.2	0.96	10.1	14.0	0.163	0.197	0.013	0.012	0.15	0.20	0.24	0.31
24	474	11.6	0.97	8.7	14.6	0.196	0.116	0.019	0.017	0.27	0.39	0.46	0.52
25	467	13.4	1.30	10.1	17.4	0.241	0.184	0.023	0.024	0.30	0.44	0.54	0.66
26	474	11.9	1.44	8.6	16.2	0.328	0.193	0.020	0.021	0.21	0.34	0.44	0.51
27	474	12.1	1.47	8.0	14.5	0.291	0.280	0.011	0.012	0.13	0.21	0.26	0.33
28	474	11.3	1.28	8.4	13.6	0.238	0.216	0.017	0.016	0.26	0.36	0.42	0.48
29	474	12.2	1.13	8.1	14.9	0.250	0.169	0.019	0.017	0.32	0.42	0.47	0.52
30	474	11.5	1.01	9.4	14.4	0.180	0.165	0.016	0.014	0.25	0.35	0.42	0.46
31	474	12.1	1.34	9.3	16.2	0.269	0.185	0.021	0.020	0.31	0.44	0.49	0.57
32	474	11.8	1.19	8.3	13.8	0.212	0.222	0.014	0.015	0.18	0.26	0.33	0.40
33	467	11.9	1.76	7.4	15.6	0.338	0.308	0.015	0.014	0.24	0.31	0.38	0.44
34	474	12.5	1.14	10.0	15.3	0.224	0.154	0.019	0.017	0.31	0.41	0.47	0.50
35	474	13.3	0.49	11.6	15.1	0.081	0.059	0.011	0.011	0.15	0.22	0.26	0.30
36	474	12.4	0.78	10.3	14.4	0.120	0.093	0.018	0.017	0.27	0.38	0.45	0.50
37	474	11.7	0.72	10.2	13.3	0.132	0.092	0.015	0.013	0.22	0.32	0.37	0.41
38	474	10.8	1.15	8.8	14.0	0.245	0.138	0.019	0.020	0.23	0.35	0.42	0.50
39	474	12.1	0.70	10.4	14.6	0.134	0.086	0.013	0.012	0.19	0.28	0.33	0.37
40	267	10.8	1.13	7.4	13.4	0.262	0.130	0.025	0.023	0.32	0.41	0.47	0.66
41	474	11.3	1.40	8.1	14.3	0.293	0.139	0.023	0.024	0.31	0.45	0.57	0.69
42	474	11.6	0.63	9.8	13.4	0.113	0.046	0.016	0.014	0.23	0.38	0.41	0.44
43	472	12.1	1.50	8.9	16.8	0.312	0.240	0.016	0.017	0.22	0.32	0.38	0.45
44	208	12.0	0.71	10.3	13.5	0.139	0.133	0.012	0.009	0.13	0.18	0.20	0.23
45	474	11.6	0.98	8.7	13.8	0.207	0.130	0.014	0.014	0.18	0.28	0.34	0.42
46	474	12.7	1.11	10.3	15.5	0.186	0.196	0.019	0.016	0.30	0.41	0.46	0.49
47	474	12.1	0.69	10.7	13.8	0.133	0.108	0.011	0.009	0.15	0.24	0.28	0.30
48	474	12.4	1.40	9.2	16.5	0.278	0.175	0.021	0.024	0.22	0.40	0.49	0.60
49	459	10.9	0.98	8.7	13.7	0.184	0.136	0.017	0.017	0.24	0.35	0.41	0.46

Underlined estimation error values show the optimal monitoring frequencies.

Table 3a. Estimation errors by sampling period

Sampling	Mean	SD
8× per month	0.23	0.05
4× per month	0.34	0.07
2× per month	0.39	0.08
1× per month	0.45	0.09
Total	0.35	0.11

increases this error to 0.34 ± 0.07 g/dl, every 2 weeks increases this error to 0.39 ± 0.08 g/dl, and every 4 weeks increases this error to 0.45 ± 0.09 g/dl. Table 3 shows that the obtained estimation error values are statistically different from one another. Figure 1 shows a box-and-whisker plot of the estimation error distribution for the monitoring frequencies. The dashed line at 0.31 g/dl represents the reported measurement error of the Crit-Line device. Comparison of the estimation error to the theoretical minimum defined by the Crit-Line device accuracy shows that 4× per month measurement is the optimal Hb measurement frequency. Linear regression analysis shows that long-term variability increases as short-term variability increases (slope = 7.3, $P = 0.008$). Because Fourier series decomposes the data into independent cyclic components, this relationship is not a mathematical consequence of the method.

The results of the frequency analysis are shown in Table 2, and specific examples can be seen in Figures 2 and 3 for two subjects at the extremes of short-term variability. The top panel of both plots shows the longitudinal Hb data, whereas the bottom panel show the corresponding frequency spectra (cycles) of the data in the top panel. The variability around the Hb trend (treatment to treatment variability) increases as the value of short-term variability increases. The periodic, global movement of Hb from a trough to a peak is described by long-term variability. As this value increases, Hb "cycling" increases.

Comparison of the individual estimation errors reported in Table 2 shows that optimal sampling frequency is patient dependent with the following summary: twice weekly Hb monitoring was optimal for 15 (31%) study participants, weekly Hb monitoring was optimal for 22 (45%) study participants, every 2 weeks was optimal for 6 (12%) study participants, and every 4 weeks was optimal for 6 (12%) study participants.

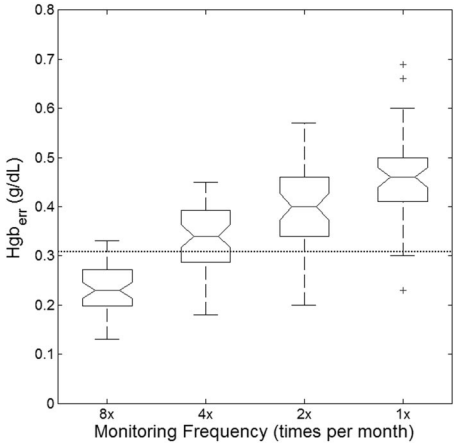

Figure 1. Box-and-whisker plot of the Hb estimation error for different monitoring frequencies. The central mark of the box represents the median and the edges represent 25th and 75th percentiles. The dashed line at 0.31 g/dl corresponds to the reported measurement error of the Crit-Line instrument.

Discussion

Monitoring Hb response over time is a critical step in anemia management. An estimation of true Hb from insufficient data without accounting for short-term variability may lead to inappropriate or unnecessary dose adjustments, leading to Hb cycling and exposing patients to harmful side effects (18–21). At this time, no clinically accepted standard exists for the frequency of Hb monitoring, and dialysis facilities use a variety of schedules, ranging from weekly to once every 5 weeks (monthly). The NKF KDOQI™ guidelines published in 2006 (11) recommended weekly Hb monitoring after ESA initiation or dose adjustment, but recognized that "... there are no reported studies that have systematically compared different protocols (*i.e.,* different frequencies of Hb/Hct measurements) for monitoring the Hb/Hct response to Epoetin therapy ..." Several researchers have attempted to systematically study Hb observation frequency. Khan and Krishnan (13) retrospectively analyzed the relationship between Hb monitoring frequency and Hb variability from 3212 U.S. dialysis facilities. They reported that more frequent Hb monitoring was associated with less Hb variability.

One goal of our study was to quantify the relationship between the frequency of Hb sampling and the reliability of the Hb estimation to establish the optimal observation frequency. We applied a signal processing technique called Fourier analysis to prospectively collected Hb data, measured at every dialysis treatment in a cohort of 49 ESRD patients. We performed Fourier analysis on the original data sampled at four different rates within the ranges recommended by the NKF KDOQI™ and Food and Drug Administration. Our results are based on a noninvasive technique that does not impact the observed Hb concentration by the removal of blood from the

Table 3b. Comparison of mean estimation errors by sampling period

Difference	8× per month	4× per month	2× per month
4× per month	0.10 ($P < 0.001$)		
2× per month	0.16 ($P < 0.001$)	0.06 ($P = 0.001$)	
1× per month	0.23 ($P < 0.001$)	0.12 ($P < 0.001$)	0.06 ($P = 0.001$)

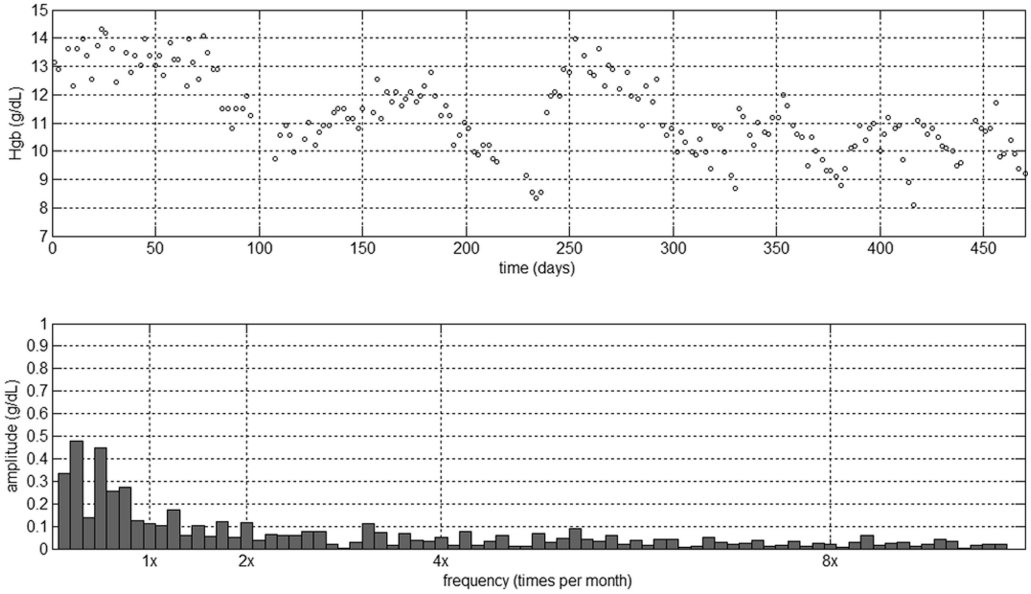

Figure 2. Hemoglobin over time (top) and the corresponding frequency spectrum (bottom) for subject 41.

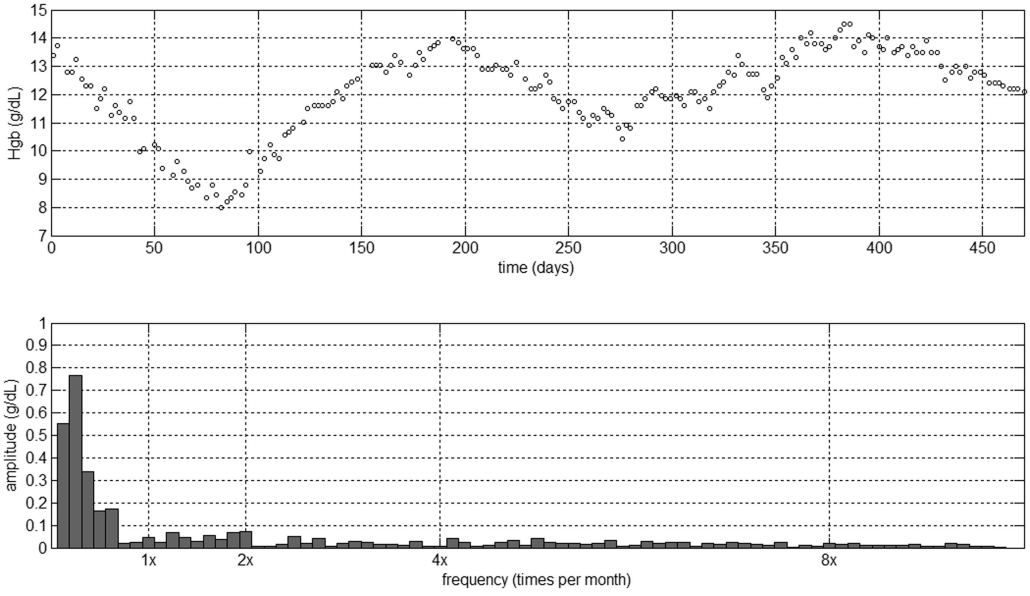

Figure 3. Hemoglobin over time (top) and the corresponding frequency spectrum (bottom) for subject 27.

patient that would traditionally be required and therefore does not contribute to Hb variability. The accuracy of the Crit-Line device is also within those specified by Clinical Laboratory Improvement Amendments for the measurement of Hb (22), and as the results show, the device is adequately sensitive to distinguish between all but the most intensive sampling of 2× per week.

Our results show that for most patients (34 of 49), weekly Hb determinations provide the best estimate of true Hb and Hb trend. In some patients with less short-term variability, bi-weekly or monthly sampling is sufficient, but more frequent monitoring is not detrimental. Short-term Hb variability is a natural phenomenon caused by a number of factors that have a limited capacity for intervention, such as interdialytic weight gains (7). On the other hand, the long-term Hb variability is primarily affected by the ESA- and iron-dosing patterns. Our results show that long-term Hb variability increases together with its short-term counterpart. This finding confirms our hypothesis that short-term Hb variability may have a detrimental effect on the selection of an appropriate ESA or iron dose by compromising the reliability of Hb estimation.

We can illustrate this point with the following example. Assume that subject 41 is due for a monthly dose adjustment and the Hb is observed every 4 weeks. The Hb measurement is corrupted by an error of ~0.7 g/dl (Table 2), which we assume approximates the SE. For a stable true Hb of 10 g/dl, the

measured value would, with 95% certainty, be in a range of 8.6 to 11.4 g/dl. Measuring Hb once weekly would decrease this range to 9.1 to 10.9 g/dl (a 35% decrease) and measuring twice weekly to 9.4 to 10.6 g/dl (a 55% decrease). Because anemia management protocols call for either an increase or decrease in ESA depending on the current Hb, a too wide range of possible values increases the probability of incorrect dose adjustment, which may lead to an undesirable long-term effect on Hb.

The ultimate goal of our study was to determine the optimal Hb monitoring strategy for an individual and a dialysis population. We showed that frequent Hb observation could allow for the reduction of the potentially harmful effects of short-term Hb variability. Obviously, because of interindividual differences in the short-term variability, some patients can have their Hb monitored less frequently than others. Noninvasive Hb monitoring is not the standard of care in most dialysis facilities. Frequent Hb determination would increase the number of blood draws, leading to more blood loss. One way to address this problem would be to quantify the effect of other, more easily measurable factors, such as the predialysis weight or the interdialytic weight gain, on the short-term Hb variability. This topic is beyond of the scope of this study but warrants additional research.

To date, the published literature has focused on describing Hb variability. Several statistical measures have been proposed for this purpose (21,23,24). These measures focus on the data dispersion around a mean or a linear trend and are sensitive to the amount of data used for analysis. Therefore, they provide only a partial description of the Hb variability. In our view, the use of data dispersion measures alone is insufficient to address this issue. An individual with substantial long-term variability may exhibit comparable or larger data dispersion than an individual with significant short-term variability, because very frequent Hb fluctuations produce more values close to the mean. On the other hand, frequent fluctuations may also be associated with undesirable rapid Hb changes. This point is best shown by subjects 27 and 41 discussed earlier. We think that the frequency analysis provides a more comprehensive view of Hb variability by taking into account both long- and short-term fluctuations. Frequency analysis also helps us address the question of how to monitor patients in the face of short-term Hb variability.

This study has the same limitations as its parent study (15). The most important ones are the relatively small sample size and homogeneous study population that may not be representative of the ESRD population across the United States. Particularly notable is the fact that ESA doses here are lower than the national mean. A larger study with a more heterogenous population would improve the external validity and generalizability of the reported results.

In this study, we did not address the frequency of ESA dose adjustments. The frequency of Hb observations and the frequency of ESA dose adjustments are two separate concepts, and care must be taken not to confuse one with the other. Frequent Hb observation allows one to accurately determine the outcomes of the ESA dose adjustments, whereas manipulating the ESA dose too frequently using unreliable Hb data would lead to overly aggressive adjustments and a subsequent increase in long-term Hb variability. In other words, frequent Hb monitoring should be considered a necessary (but not sufficient) step for optimal ESA dose adjustment. However, the question of optimal frequency for ESA adjustment is beyond the scope of this study.

Conclusions

We applied a rigorous mathematical principle to determine optimal Hb sampling frequency. Our study showed an advantage of frequent Hb sampling that should be considered when implementing an anemia management protocol in ESRD patients. We showed that frequent Hb monitoring reduces the effect of uncontrolled short-term Hb variability that can have a substantial effect on dosing decisions. Clinically, monitoring Hb once a week seems to be the optimal frequency because it allows one to estimate Hb with a reliability comparable to that of the measurement instrument.

Future studies on larger, heterogeneous patient populations are needed to confirm these findings. A cost-effectiveness analysis is also necessary to establish financial viability of frequent Hb observations. Even if the increased frequency may be cost prohibitive, understanding the impact of short-term Hb variability on the reliability of Hb measurement may be valuable in developing better ESA dose adjustment algorithms.

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Disclosures

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