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A randomized trial of iron deficiency testing strategies in hemodialysis patients[1]

Steven Fishbane, Warren Shapiro, Paula Dutka, Osvaldo F. Valenzuela, and Jessy Faubert

Winthrop-University Hospital, Mineola, and Brookdale Medical Center, Brooklyn, New York, USA

A randomized trial of iron deficiency testing strategies in hemodialysis patients.

Background. Diagnosis of iron deficiency in hemodialysis patients is limited by the inaccuracy of commonly used tests. Reticulocyte hemoglobin content (CHr) is a test that has shown promise for improved diagnosis in preliminary studies. The purpose of this study was to compare iron management guided by serum ferritin and transferrin saturation to management guided by CHr.

Methods. A total of 157 hemodialysis patients from three centers were randomized to iron management based on (group 1) serum ferritin and transferrin saturation, or (group 2) CHr. Patients were followed for six months. Treatment with intravenous iron dextran, 100 mg for 10 consecutive treatments was initiated if (group 1) serum ferritin <100 ng/mL or transferrin saturation <20%, or (group 2) CHr <29 pg.

Results. There was no significant difference between groups in the final mean hematocrit or epoetin dose. The mean weekly dose of iron dextran was 47.7 ± 35.5 mg in group 1 compared to 22.9 ± 20.5 mg in group 2 ($P = 0.02$). The final mean serum ferritin was 399.5 ± 247.6 ng/mL in group 1 compared to 304.7 ± 290.6 ng/mL in group 2 ($P < 0.05$). There was no significant difference in final TSAT or CHr. Coefficient of variation was significantly lower for CHr than serum ferritin and transferrin saturation (3.4% vs. 43.6% and 39.5%, respectively).

Conclusions. CHr is a markedly more stable analyte than serum ferritin or transferrin saturation, and iron management based on CHr results in similar hematocrit and epoetin dosing while significantly reducing IV iron exposure.

Treatment of iron deficiency is an important component of care for patients on hemodialysis. Failure to recognize and adequately treat iron deficiency leads to suboptimized anemia therapy, with difficulty reaching target hematocrit or hemoglobin levels or the need for excessively high epoetin doses [1–3]. As a result of this, diagnostic tests for iron deficiency are performed on a regular basis, generally every three months [4]. Testing is important not only to detect iron deficiency, but additionally to avoid overtreatment with intravenous iron drugs, agents that may occasionally cause severe adverse reactions [5–8]. Testing must accurately detect iron deficient patients who require intensified iron treatment while excluding patients who are iron replete. Ideally, the results of iron monitoring should allow for consistent maintenance of the target hemoglobin level, while avoiding excessively high epoetin doses and unnecessary intravenous iron use while allowing these goals to be achieved without excessive cost.

Tests assessing the iron status in general use in American dialysis units are serum ferritin and transferrin saturation [4]. Both tests have limited accuracy when used in hemodialysis patients. Previous studies have demonstrated the serum ferritin at levels of 100 to 200 ng/mL to have a sensitivity of only 41 to 48%, and a specificity of 75 to 100% for detecting iron deficiency [9, 10]. Using higher cutoff levels of serum ferritin would improve sensitivity, but at the cost of a significant drop off in specificity. A transferrin saturation of 20 to 21% has sensitivity of 81 to 88%, but with a specificity of only 63% [9, 10]. Decreasing the cutoff value would improve the specificity, but in this case would incur a significant loss of sensitivity.

Reticulocyte hemoglobin content (CHr) is a test of iron status that potentially may be more accurate [11, 12]. Initial studies in hemodialysis patients have suggested excellent utility for this test as a guide to iron management [13–15]. Our group found a sensitivity of 100% and specificity of 80% among a group of 32 hemodialysis patients [13]. These promising results made clear the need for a more rigorous evaluation of CHr. The purpose of the current study was to compare CHr to serum ferritin and transferrin saturation as a guide to iron management in hemodialysis patients.

[1] **See Editorial by Besarab, p. 2412.**

Key words: serum ferritin, transferrin saturation, reticulocyte hemoglobin content, hematocrit, epoetin dose, anemia.

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METHODS

Patients

One hundred fifty-seven hemodialysis patients from three dialysis centers were enrolled. Participating centers were Winthrop-University Hospital Dialysis at Bethpage (B:WUHD), a 12-station suburban unit, WUHD at Mineola (M:WUHD), a 35-station suburban unit, and Brookdale Medical Center Dialysis (B), a 28-station urban unit. Eligibility criteria included age older than 18 years, hemodialysis treatment for three months or more, use of epoetin for three months or greater with no change in dose for four weeks, no blood transfusion in the previous three months, no intravenous iron treatment in the previous month, no hematologic disease other than anemia, and no hospitalization or significant bleeding episodes (requiring hospitalization or blood transfusion) in the previous three months.

Patients were assigned at random to one of two study groups: group 1, iron management based on serum ferritin and transferrin saturation; and group 2, iron management based on CHr.

Each patient was followed for six months. Hemoglobin and hematocrit (Hct) were measured every two weeks, and the dose of epoetin was adjusted to maintain hematocrit between 33 and 36%. The same dosing protocol was used at all centers, and personnel independent of the study and unaware of patients' randomization made all epoetin-dosing changes. The protocol called for 25% dose reductions for Hct >36% and holding doses if Hct >40%, or 50% dose increases for Hct <33%. Epoetin response was characterized using an epoetin response index (ERI) calculated as Hct/weekly epoetin dose*100. Higher values are consistent with greater responsiveness to epoetin treatment. Serum ferritin, transferrin saturation and CHr were measured every four weeks. Intravenous iron dextran, 100 mg for 10 consecutive hemodialysis treatments, was initiated if (in group 1) serum ferritin <100 ng/mL or transferrin saturation <20%; or (in group 2) CHr <29 pg.

Intravenous iron was only administered if the patient met the above criteria. More than one course could be administered during the six months of study. Intravenous iron was not administered if serum ferritin was >800 ng/mL or transferrin saturation >50%.

Iron status tests

Serum ferritin and transferrin saturation were determined every four weeks by standard methods. Reticulocyte hemoglobin content (CHr) was determined using the ADVIA® 120 hematology system (Bayer Corporation, Tarrytown, NY, USA). CHr is derived from the simultaneous measurement of volume and hemoglobin concentration in reticulocytes. The CHr value is an indication of the hemoglobin content of each reticulocyte, reported in picograms.

Statistical analysis

Primary outcome measures were hematocrit, epoetin dose, iron dose requirements, serum ferritin, transferrin saturation and CHr. The Student *t* test was used to analyze differences between baseline and end of study, and differences between groups for continuous variables. Log transformation was used for non-normally distributed data. Fisher's Exact Test was used to compare groups for categorical variables. Variation in test results was expressed as coefficient of variation. Each patient's standard deviation of test results was squared to obtain individual variances. The square root of the pooled variances was divided by the pooled mean of all test results to yield the coefficient of variation for each test. For calculation of positive predictive value, the number of patients with a positive response to intravenous iron treatment was divided by the number predicted by the testing to need iron treatment. A positive response was defined as an increase in 3 basis points in Hct and/or a decrease of 15% in weekly epoetin dose in the eight weeks after treatment with intravenous iron. All results are reported as mean ± standard deviation. P values of < 0.05 were considered statistically significant.

RESULTS

A total of 157 patients were enrolled and randomized, of whom 19 were withdrawn during the study period. Withdrawals were due to prolonged hospitalization ($N = 8$), bleeding requiring blood transfusion (3), transplant (1), withdrawal of consent (1), protocol violation (4), and death (2). Patients completing the study were from WUHD-Mineola ($N = 74$), Brookdale (51), and WUHD-Bethpage (13). Patient characteristics are reported in Table 1. Specifically, factors other than iron that could impact on anemia management, such as dialysis dose (Kt/V), urea reduction ratio (URR), serum aluminum and parathyroid hormone level (PTH) were not significantly different between the groups at baseline.

The mean Hct remained in the targeted range (33 to 36%) throughout the study period in both groups (Table 2). There was no significant difference between the two groups as to mean Hct at any time point. The mean epoetin dose requirement trended lower for both groups, however, the results did not reach statistical significance (Table 2). Epoetin dose adjustments were required at a mean of 2.8 + 2.0 times per patient. The ERI was not significantly different between the two groups at the end of the study (group 1, 0.30 vs. group 2, 0.32; P = NS).

Of 74 patients in group 1, serum ferritin and transferrin saturation were tested 419 times, resulting in 59 (79.7%) subjects receiving 104 courses of intravenous iron. In

Table 1. Patient characteristics

	Group 1 ($N = 74$)	Group 2 ($N = 64$)
Center (B:WUHD-M:WUHD-B)	26:43:5	25:31:8
Age *years*	60.5 ± 14.5	60.0 ± 14.6
Percent men	51	56
Months on dialysis	33.4 ± 32.7	38.1 ± 39.4
Ethnicity:		
Causcasian	36	28
African-American	31	30
Hipanic	5	4
Other	2	2
Cause of ESRD:		
Diabetes	28	23
Hypertension	19	16
CGN	11	8
PCKD	8	4
Other	8	13
Hct *%*	35.4 ± 3.4	35.8 ± 3.5
Epoetin dose *U/weeks*	12232 ± 11029	12237 ± 12001
Serum ferritin *ng/mL*	229.6 ± 178.8	251.7 ± 231.3
TSAT *%*	24.7 ± 12.7	22.3 ± 11.7
CHr *pg*	31.1 ± 1.8	30.8 ± 1.7
Serum aluminum *μg/L*	16.8 ± 11.3	15.2 ± 10.1
Kt/V	1.69 ± 0.31	1.66 ± 0.30
URR *%*	74.2 ± 5.6	75.0 ± 5.5
PTH *pg/mL*	192.7 ± 166.4	183.4 ± 170.1

Abbreviations are: ESRD, end-stage renal disease; CGN, chronic glomerulonephritis; PKD, polycystic kidney disease; TSAT, transferrin saturation; Hct, hematocrit; CHr, reticulolyte hemoglobin content; Kt/V, dialysis dose; URR, urea reduction ratio; PTH, parathyroid hormone.

Table 2. Hematocrit and weekly epoetin dose by treatment group

Week	BL	8	16	24	28
Group 1	35.4	35	34.6	34.7	35
Hct *%*	(3.4)	(3.3)	(3.4)	(3.3)	(3.4)
Group 2	35.8	34.6	35.5	35.4	35.3
Hct *%*	(3.5)	(3.4)	(3.3)	(3.5)	(3.2)
Group 1	12232	12077	12100	11902	11772
EPO *U/week*	(11029)	(11444)	(11029)	(11320)	(11780)
Group 2	12237	12200	11300	10933	10949
EPO *U/week*	(12001)	(12049)	(11785)	(12095)	(12154)

Results in parentheses are standard deviation. Abbreviations are: BL, baseline; Hct, hematocrit; EPO, erythropoietin.

group 2, there were 64 patients in whom CHr was tested 369 times, resulting in 27 (42.1%) patients receiving 42 courses of intravenous iron ($P < 0.05$ compared to group 1). The mean weekly dose of intravenous iron dextran was 47.7 + 35.5 mg in group 1 patients compared to 22.9+20.5 mg in group 2 ($P = 0.02$; Fig. 1 and Table 3). The predictive value of serum ferritin <100 ng/mL or transferrin saturation <20% in group 1 for a positive response to intravenous iron, was 43.8%, compared to 72.7% for CHr <29 pg in group 2. The stimulus for iron treatment in group 1 was transferrin saturation <20% alone in 67.3% of the 104 intravenous iron courses, serum ferritin <100 ng/mL alone in 19.2% and both parameters being low in 13.5% of intravenous iron courses. Of the 104 intravenous iron courses in group 1, CHr was <29 pg prior to the iron course in 22% of cases. In contrast, in group 2, intravenous iron courses by protocol could only be generated by CHr <29 pg. In fact, of the 42 courses of intravenous iron generated by CHr <29 pg in group 2, the serum ferritin was less than 100 ng/mL in 16 (38%), and transferrin saturation was less than 20% in 30 (71.4%) iron courses.

The mean serum ferritin at baseline was not significantly different between the groups (229.6 + 178.8 ng/mL vs. 251.7 + 231.3 ng/mL, groups 1 and 2, respectively; P = NS; Table 4). At study conclusion mean serum ferritin increased significantly in group 1 to 399.5 + 247.6 ng/mL, compared to no significant change in group 2, final 304.7 + 290.6 ng/mL ($P < 0.05$ comparing final group 1 vs. final group 2). The mean transferrin saturation was not significantly different between the groups at baseline (Table 4). At study conclusion, mean transferrin saturation had increased significantly in group 1 to 29.4 ± 17.8% compared to no significant change in group 2, final 25.8 ± 16.6%. Mean CHr was not significantly different between the groups at baseline, and did not change significantly in either group throughout the study, final 31.1 ± 1.8 pg group 1, and 30.8 ± 1.8 group 2 (P = NS).

The mean reticulocyte hemoglobin content (CHr) among all samples tested was 31.0 ± 2.4 pg with values ranging from 20.2 pg to 40.9 pg (Fig. 2). The reticulocyte response to treatment with intravenous iron in a single patient is depicted in Figure 3. In this patient, the mean CHr value at the baseline was 24.6 pg. By two weeks after treatment with intravenous iron, the mean hemoglobin content of the patient's reticulocytes increased from 24.6 pg to 28.4 pg. The distribution width of CHr narrowed significantly, indicating the growth of a more stable, homogeneous population of cells with improving iron carriage. The total reticulocyte count and Hct had not yet increased. By four weeks after iron treatment, the CHr had normalized at 31.8 pg, and both the reticulocyte count, and Hct rose significantly. Additionally, the hemoglobin content of the mature red cell population, as indicated by the CH value, rose significantly at four weeks.

Comparison of test variability was measured longitudinally for the three iron tests and is reported as coefficient of variation (%CV). Reticulocyte hemoglobin content (CHr) was found to have significantly less variation than the other tests, with CV of 3.4% compared to serum ferritin of 43.6% and transferrin saturation of 39.5% (Fig. 4). Recalculation of CV, excluding post-intravenous iron treatment results, yielded 2.6% for CHr, compared to serum ferritin at 24.5% and transferrin saturation at 27.2%.

DISCUSSION

The major findings of the current study are that (*1*) CHr had much less variability than either serum ferritin

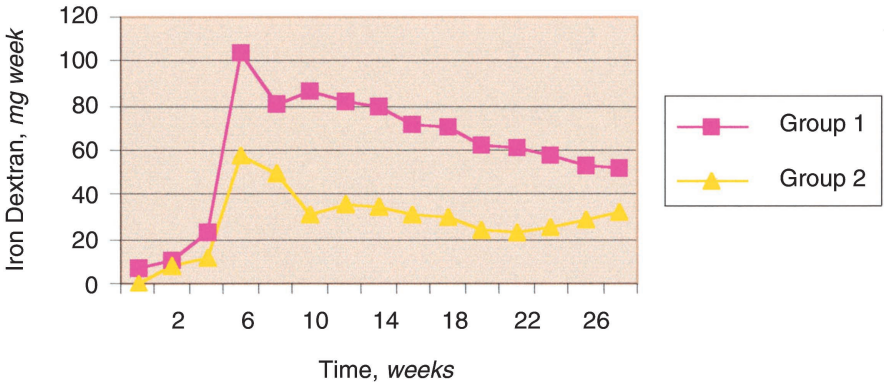

Fig. 1. Intravenous iron dextran weekly dose requirements by study group. (Reproduction of this figure in color was made possible by Bayer Diagnostics, Inc.)

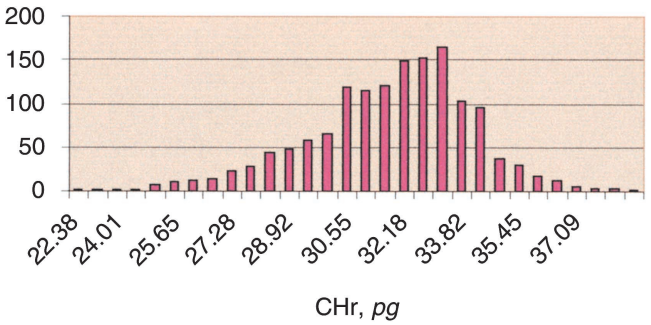

Fig. 2. Distribution of reticulocyte hemoglobin content (CHr) values among all subjects. (Reproduction of this figure in color was made possible by Bayer Diagnostics, Inc.)

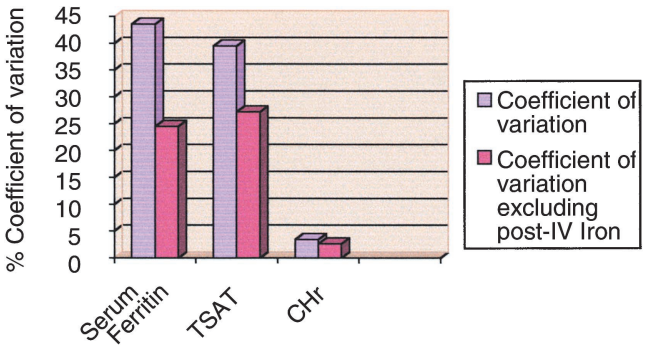

Fig. 4. Coefficient of variation (CV) for the three tests. Blue bars represent all tests, purple bars represent CV excluding tests performed after intravenous iron treatment. (Reproduction of this figure in color was made possible by Bayer Diagnostics, Inc.)

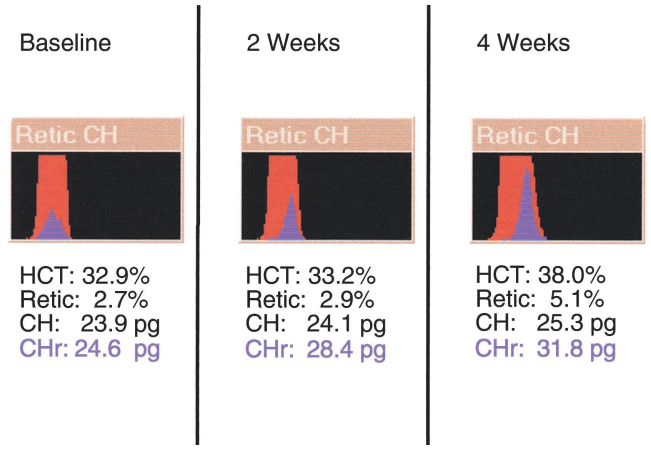

Fig. 3. Histograms of reticulocyte hemoglobin content (CHr). Results are from a single patient at baseline, and then 2 and 4 weeks after intravenous iron treatment. As hematocrit (Hct) and CHr improve, the population of reticulocytes matures and normalizes compared to mature cells. (Reproduction of this figure in color was made possible by Bayer Diagnostics, Inc.)

or transferrin saturation; (*2*) iron management guided by CHr led to less use of intravenous iron compared to management guided by serum ferritin and TSAT but was without any detrimental effect on hematocrit or epoetin requirements; and (*3*) iron testing by either method on a monthly basis facilitated attaining a high-end National Kidney Foundation–Dialysis Outcomes Quality Initiative (NKF/DOQI) target hematocrit values with stable epoetin dose requirements (there was a non-significant trend to lower dose requirements for both groups).

The primary goal of iron supplementation in hemodialysis patients is to support epoetin therapy, enabling the consistent achievement of a hematocrit of 33 to 36%. The NKF/DOQI Guidelines for Anemia Management stress that most hemodialysis patients will require regular treatment with intravenous iron to achieve the target hematocrit [4]. The guidelines recommend that dosing with intravenous iron be based on maintaining serum ferritin >100 ng/mL and transferrin saturation >20%. Both tests, however, are somewhat inaccurate measures of iron status. Sensitivity, the ability to detect iron deficiency, is quite low for serum ferritin: 41 to 48% at a test level of 100 to 200 ng/mL [9, 10]. It is readily apparent why this is so. Serum ferritin is a potent positive acute phase reactant, and a variety of causes independent of iron status may markedly raise its value [16–18]. A high serum ferritin level in a dialysis patient may reflect iron

Table 3. Iron testing and resulting iron treatment by study group

	Group 1 ($N = 74$)	Group 2 ($N = 64$)	P value
Number of tests of primary parameter (Group 1–TSAT, serum ferritin, Group 2–CHr)	419	369	
Number of patients in whom testing triggered a course of IV iron	59 79.7%	27 42.1%	<0.05
Number of courses of IV iron triggered	104	42	<0.05
Mean weekly dose of IV iron	47.7 + 35.5	22.9 + 20.5	0.02
Positive predictive value of testing schema	43.8%	72.7%	

IV is intravenous.

Table 4. Iron parameters by patient group

	Serum ferritin *ng/mL*		Transferrin saturation *%*		CHr *pg*	
	Baseline	Final	Baseline	Final	Baseline	Final
Group 1 (SD)	229.6 (178.8)	399.5[a] (247.6)	24.7 (12.7)	29.4[a] (17.8)	31.1 (1.8)	32.1 (1.8)
Group 2 (SD)	251.7 (231.3)	304.7 (290.6)	22.3 (11.7)	25.8 (16.6)	30.8 (1.7)	30.8 (1.8)
P value	NS	0.05	NS	0.04	NS	NS

[a] $P < 0.05$ final compared to baseline

sufficiency, but it is equally likely to be driven by some other stimulus. Iron deficiency may still be present, and the diagnosis missed. Specificity, the ability to exclude patients without iron deficiency, is adequate for serum ferritin, with values between 75 and 100% [9, 10]. Transferrin saturation is probably a more accurate measure, with sensitivity between 81 and 88% but with a poor specificity of 63% [9, 10]. Calculated as serum iron divided by total iron binding capacity, transferrin saturation reflects the quantity of iron in circulation [19]. In epoetin treated patients, where superphysiologic bursts of red cell production lead to rapid fluxes in serum iron concentration, transferrin saturation may poorly reflect iron sufficiency [9, 10]. A low value may reflect iron deficiency, or may simply be a reflection of intense erythropoiesis with dysequilibrium between iron storage, circulation and the erythron. Taken together, these considerations help explain why nephrologists are often faced with the dilemma of transferrin saturation concentrations that indicate iron deficiency at the same time as the serum ferritin is high, raising concern of iron overload.

Reticulocyte hemoglobin content (CHr) has the potential to be a more accurate test of iron status in hemodialysis patients. Recently, this test was reviewed in depth by Brugnara and colleagues [20]. The CHr test is a direct measure of iron sufficiency at the level of the reticulocyte, the first circulating form of erythrocytes [20, 21]. In epoetin treated patients, a direct measure of iron status has a distinct advantage compared to indirect measures such as serum ferritin or transferrin saturation. Because reticulocytes only remain in circulation for approximately 24 hours [22], CHr is a "snapshot" of iron status, informing about immediate iron sufficiency. The test has been studied in hemodialysis patients, and several reports have been published (13–15). In an initial evaluation of CHr in 32 hemodialysis patients, we found the sensitivity and specificity to detect iron deficiency to be 100% and 80% respectively [13]. Mittman et al [14] studied CHr in 364 hemodialysis patients, and found that changes in CHr over time correlated with changes in hemoglobin and hematocrit levels. Eighty-two percent of iron deficient patients responded with an increase in CHr of 2 pg when treated with intravenous iron [14]. Bhandari et al studied 22 hemodialysis patients with initial serum ferritin <60 ng/mL, and found that CHr rose after intravenous iron treatment. The authors concluded that CHr improved monitoring of response to intravenous iron therapy and helped identify patients with functional iron deficiency [15]. More recently Cullen et al studied CHr in 36 hemodialysis patients, and found it to be superior to percentage hypochromic red blood cells, a test used frequently in Europe [23]. The percentage of hypochromic cells indicates a subpopulation of mature red blood cells that demonstrates evidence of insufficient iron.

We have found CHr to be a far more stable test than transferrin saturation or serum ferritin. The coefficient of variation for CHr was on the order of 90% lower than for the other tests. The high level of variability for serum ferritin and transferrin saturation explains an important problem in the current approach to iron testing in hemodialysis patients. Recommendations for iron treatment by NKF-DOQI call for intensified intravenous iron treatment if either test has a low result. Because of the extreme variability of the tests, however, it is probable that in any given testing cycle one of the two tests will be low. This is likely to lead to unnecessary treatment of patients without iron deficiency, and excessive use of intravenous iron. In fact, that is exactly what we found, that iron management based on these tests led to a 113% greater dosing for intravenous iron compared to CHr, with no benefit in terms of hematocrit or epoetin requirement.

We expect that iron management based on CHr would reduce the overall cost of iron management because of the reduced intravenous iron requirements. Patients managed by CHr (group 2) required 25 mg less per week of intravenous iron compared to patients in whom iron treatment was guided by serum ferritin and transferrin saturation. More important than financial savings is the reduced exposure of patients to the potentially harmful effects of intravenous iron. Risks of treatment such as tissue and vascular oxidation have not been extensively studied [24], but have the potential to be clinically rele-

vant. As such, it is best to avoid unnecessary exposure to excessive iron treatment.

The cutoff level for CHr that we chose to guide treatment was 29 pg. Our previous study using the semi-automated CHr assay on the H*3 hematology analyzer (Bayer Corporation) used a value of 26 pg [13]. The present study used the ADVIA120 system (Bayer Corporation), which utilizes an automated assay for the CHr. Using a CHr cutoff value other than 29 pg to guide treatment would lead to different effects on anemia treatment. For example, if the cutoff value was raised to 30 pg, more patients would be treated with intravenous iron, reducing some of the benefit of lower iron costs and risk exposure. On the other hand, because of the greater accuracy of CHr compared to serum ferritin and transferrin saturation, iron treatment would be more focused on patients with true iron deficiency. As a result, there might be benefit in terms of achieving the target hematocrit with a reduced dosing requirement for epoetin. This would be a useful subject for further study.

In conclusion, we have found that iron management based on CHr is simple and practical to perform. The test may be performed during routine blood testing for hemoglobin and hematocrit, by the same hematology analyzer, at little incremental cost. Compared to management based on serum ferritin and transferrin saturation, CHr led to a significantly reduced need for intravenous iron, without any decrease in hematocrit or increase in epoetin dose requirements. The superior performance of CHr might be explained by a far lower level of test variability compared to serum ferritin and transferrin saturation. Finally, the use of monthly iron testing in both groups led to hematocrit levels well above national averages, without a need for excessively high epoetin doses.

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Reprint requests to Steven Fishbane, M.D., 222 Station Plaza North, Suite 510, Mineola, New York 11501, USA.
E-mail: sfishbane@winthrop.org

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