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Diagnosis of Iron Deficiency Anemia in Renal Failure Patients During the Post-erythropoietin Era

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● The purpose of this study was to evaluate the sensitivity and specificity of laboratory methods in the diagnosis of posterythropoietin-era, iron-deficient, chronic renal failure patients. The patient population comprised 25 anemic (hemoglobin <11 g/dL) patients with creatinine greater than 3 mg/dL; 20 were dialysis patients, two were transplant patients, and three patients had renal failure from other causes. Criteria for study inclusion were as follows: bone marrow iron was the reference standard and was graded 0 to +4, ranging from absent to diffuse homogeneous iron staining; serum ferritin concentration and serum transferrin saturation were tested in terms of sensitivity and specificity. The reference standard indicated that iron deficiency existed in 40% of patients. Neither serum ferritin nor transferrin saturation were completely adequate diagnostic tools. Serum ferritin levels less than 200 ng/dL were 100% specific for the diagnosis but only 41% sensitive. Transferrin saturation of less than 20% was 88% sensitive, but only 63% specific. By excluding patients with hypoproteinemia (transferrin values of <150 mg/dL), the sensitivity of the test increased to 100% and the specificity to 80%. We conclude that transferrin saturation is an adequate screening tool in anemic chronic renal failure patients, provided that hypoproteinemia is not present. By determining both the serum ferritin concentration and the transferrin saturation, a high sensitivity and specificity can be achieved, even in patients with hypoproteinemia. Furthermore, we believe that on this basis, iron therapy in patients with renal insufficiency can be improved.

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INDEX WORDS: Renal failure; anemia; iron deficiency; transferrin; transferrin saturation; ferritin; erythropoietin.

ANEMIA is common in patients with chronic renal insufficiency. The causes include acquired deficiency of erythropoietin (EPO) production, occult blood loss, blood loss during hemodialysis, an increased tendency to bleed, frequent blood sampling, and increased iron consumption with therapeutically administered EPO.¹⁻⁴ Iron deficiency is not always easy to diagnose in patients with renal insufficiency, with or without EPO therapy. Both serum ferritin concentration and the transferrin saturation have been commonly used; however, both are subject to error.⁵⁻⁷ Other tests, such as erythrocyte ferritin, erythrocyte zinc protoporphyrin, the percentage of hypochromic erythrocytes, and red blood cell indices, have been discussed as valuable adjuncts.^{8,9} However, serum ferritin and transferrin saturation remain the most commonly used

laboratory tests to diagnose iron deficiency in patients with chronic renal failure receiving EPO. Availability of an accurate and simple test is indispensable in these patients, particularly since the administration of recombinant EPO commonly leads to unrecognized iron insufficiency.¹⁰⁻¹⁴ We tested the hypothesis that serum ferritin and transferrin saturation differ in sensitivity and selectivity in terms of diagnosing and evaluating anemia in patients with chronic renal failure. We selected bone marrow biopsy with iron staining as our reference standard for iron stores. All patients in our study were anemic; however, not all had iron deficiency as the etiology of their anemia. The purpose of our study was to demonstrate the value of ferritin and transferrin saturation in predicting stainable bone marrow iron content of chronic renal failure patients in the post-EPO era.

MATERIALS AND METHODS

Patients and Their Characteristics

From January to August 1993, 25 patients with chronic renal failure and anemia were evaluated at the Fourth Medical Clinic, University of Erlangen-Nürnberg. The patients, 13 men and 12 women, ranged from 44 to 84 years in age. All patients had a creatinine concentration greater than 3.0 mg/dL for at least 3 months and all had a normochromic normocytic anemia with a hemoglobin value less than 11.0 g/dL and a mean corpuscular volume between 73 and 98 μm^3 . Each patient underwent a bone marrow examination to clarify the

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anemia after history, physical examination, hematologic values, folate, and B12 concentrations left doubt as to the cause of the anemia. Nevertheless, the patients were informed as to the nature of the study and consent was obtained after receiving approval from the Institutional Review Committee.

Twenty patients had end-stage renal disease. Sixteen were being managed by hemodialysis and four by continuous ambulatory peritoneal dialysis. Five patients had chronic renal insufficiency with creatinine values ranging from 3 to 9 mg/dL. Two patients had poorly functioning renal allografts and three had renal failure from other causes. The transplant patients were receiving cyclosporine and methylprednisolone. No patient had active bacterial infection and none had undergone a recent major operation. Twenty-three patients received EPO for 2 to 26 months, while two were not being treated with EPO because their hemoglobin values were higher than 10 g/dL. Iron therapy had been withdrawn in the patients receiving it from 13 to 30 days before the study, and no blood had been transfused in any patient for at least 2 months prior to evaluation.

Laboratory Evaluation

Red blood cell indices and hemoglobin, as well as the serum iron value (colorimetric method), were obtained by automated methods. The hematocrit was measured by centrifugation. The serum ferritin value was measured by an immunoradiometric assay with polyclonal reagents. The serum transferrin levels were measured as described elsewhere using an immunologic method.^{7,15} The measurements of transferrin correlate closely with indirect transferrin concentrations determined from measurements of total iron binding capacity, with a correlation coefficient of 0.96.¹⁶ Thus, the more accurate immunochemical assays of transferrin concentrations were used to calculate the total iron binding capacity according to a formula described elsewhere¹⁶: serum transferrin (mg/dL) $\times$ 1.25 = total iron binding capacity (mg/dL). The transferrin saturation index was calculated according the following formula: saturation (%) = serum iron/total iron binding capacity.

Bone Marrow Studies and Assessment of Iron Status

Iron status was evaluated by bone marrow examination. Posterior iliac crest bone marrow aspirations and/or bone marrow biopsies were performed in all 25 patients within 72 hours of the hematologic investigations. The bone marrow was fixed in phosphate-buffered saline, 4% formaldehyde, and then embedded in paraffin. Serial sections were stained for iron with Perl's Prussian blue stain as described elsewhere.¹⁷ The slides were interpreted by a pathologist at a single session using methods that are described in detail elsewhere.¹⁸⁻²⁰ The pathologist had no knowledge of the patients or of their hematologic values. The slides were graded as follows^{19,20}: 0, no iron; +1, slight amount of iron; +2, patchy iron stores present; +3, patchy to diffuse staining; +4, diffuse iron staining; and +5, extensive iron staining (iron overload). Normal values for bone marrow iron content for iron staining ranged from +3 to +4 according to this scale.

Statistical Analysis

"Sensitivity" was defined as the number of patients with a positive test who actually had the disease, "specificity" was defined as the number of patients with a negative test who did not have the disease, "positive predictor value" was defined as the number of positive tests in the patients who had the disease within the total population, and "negative predictor value" was defined as the number of negative tests in patients who did not have the disease within the total population. In our study, iron deficiency is the disease, with the bone marrow iron score as the final criterion.

The Student's *t* test and chi-squared test were used for data fitting a normal distribution. We used the nonparametric Mann-Whitney U test for the analysis of discrete variables. Parametric and nonparametric (Spearman rank) regression analyses were used. Fiducial limits are given as mean $\pm$ SD. *P* < 0.05 was considered to be statistically significant.

RESULTS

The clinical characteristics of our patients are shown in Table 1. Nine patients had type II diabetes mellitus, six had interstitial nephritis with suspected analgesic nephropathy, one had polycystic disease, one had multiple myeloma, five had glomerulonephritis, and three had hypertensive nephrosclerosis. Vitamin B12 and folic acid deficiency were excluded on laboratory and clinical grounds. None of the patients had severe hyperparathyroidism based on regular measurements of parathyroid hormone, none had aluminum intoxication (bone biopsies were performed regularly in the dialysis patients), and none had been exposed to heavy metals. Fourteen patients had been treated with dialysis for 24 months or less, while six were dialyzed for more than 2 years. Nine patients had serum albumin levels less than 3 g/dL. The remaining patients had higher albumin concentrations. Only two of our patients did not receive EPO. Their physicians had withheld the drug because their hemoglobin concentrations were greater than 10 g/dL. Erythropoietin doses ranged between 1,000 and 2,000 U given subcutaneously three times a week in the patients receiving the drug.

The patients were all tested for hemolysis, stool blood loss, menstrual blood loss, and blood loss related to ingestion of medication. Furthermore, their stool was regularly tested as a site of blood loss, generally during their monthly outpatient evaluation. None of the patients had solid tumors; we have no reason to believe that other nondiagnosed chronic diseases contributed to anemia in these patients. The bone marrow exam-

Table 1. Clinical Characteristics of the Patients

Patient No.	Status	Serum Albumin (g/dL)	ESRD Time (mo)	Renal Disease*
1†	TR	3.8	NA	DM
2	HD	2.5	36	IN
3†	TR	2.9	NA	DM
4‡	HD	4.1	20	PCKD
5	HD	2.4	11	IN
6	HD	2.0	48	HNS
7	HD	1.9	84	DM
8	CAPD	3.0	18	DM
9	HD	3.3	3	HNS
10	CAPD	3.2	26	IN
11	HD	3.4	48	IN
12	CAPD	3.3	4	CGN
13	HD	3.7	10	CGN
14	CAPD	3.5	11	DM
15	HD	2.2	12	DM
16†	CRF	2.9	NA	IN
17	HD	2.0	60	CGN
18†	CRF	3.3	NA	DM
19†	CRF	3.4	NA	DM
20	HD	1.7	3	IN
21	HD	2.6	5	MM
22‡	HD	2.2	19	CGN
23	HD	2.3	4	CGN
24	HD	3.1	9	DM
25	HD	2.3	10	HNS

Abbreviations: HD, hemodialysis; CAPD, chronic ambulatory peritoneal dialysis; TR, transplanted; CRF, chronic renal failure (serum creatinine, 3 to 8 mg/dL); NA, not applicable; DM, diabetes; IN, interstitial nephritis; PCKD, polycystic disease; HNS, hypertensive nephrosclerosis; CGN, chronic glomerulonephritis; MM, multiple myeloma.

* The renal disease diagnoses were for the most part clinical and not documented with biopsy.

† The transplant patients had plasma creatinine values of 3.0 and 3.2 mg/dL, while the CRF patients had values of 8.4, 6.1, and 4.2 mg/dL, respectively.

‡ Hemodialysis patients who did not receive EPO therapy. Their hemoglobin values were >10 g/dL but <12 g/dL.

inations performed in patients receiving EPO were generally performed 3 months after the drug was started. Our hemodialysis patients were regularly monitored for adequacy of dialysis and all had a KT/V value greater than 1. The dialysis patients were routinely prescribed a multivitamin preparation and folic acid.

Hematologic variables are given in Table 2. The mean hemoglobin value was 8.37 ± 1.3 g/dL (range, 6.5 to 11 g/dL), the mean corpuscular volume was 91 ± 5.6 μm^3 , the mean ferritin concentration was 657 ± 559 $\mu\text{g/dL}$ (range,

19 to 1,840 ng/mL), and the mean transferrin saturation was $19\% \pm 10\%$ (range, 8% to 50%).

The bone marrow iron scores are given in Table 3. The patients are grouped in terms of their bone marrow scores ranging from 0 to +4. The mean hemoglobin values across the groups was not significantly different. The serum ferritin concentrations were lower in the group receiving score 0 than in those receiving scores of +2 or greater ($P < 0.05$). The marrow contained essentially no iron in three patients (score 0), had only minimal amounts in seven patients (score +1), had slight to patchy staining in seven other patients (score +2), and was patchy to diffuse in 13 others (scores +3 and +4). No patient received an iron overload (score +5) value. Scores 0 and +1 (10 patients) were considered absolute iron deficiency. Score +2 were considered as relative iron deficiency on the basis of the concomitant low hemoglobin value. Higher scores were clearly not iron deficient. Thus, according to bone marrow iron staining as the reference standard for body iron stores, 40% of patients in our study had iron deficiency anemia (bone marrow scores 0 and +1) and an additional 28% had "relative" iron deficiency (score +2 included). An additional 32% had anemia from other, non-iron-related causes. Serum ferritin concentrations were significantly lower in patients with bone marrow iron scores of 0 or +1 compared with patients with scores of +2, +3, or +4. Transferrin saturation values were significantly lower in patients with bone marrow iron scores of 0, +1, or +2 compared with patients with scores of +3 or +4.

A plot of logarithmically displayed ferritin values on the ordinate and bone marrow iron scores (0 to +4) on the abscissa is shown in Fig 1A. A significant correlation (Spearman rank) between ferritin and bone marrow scores was identified. In Fig 1B the relationship between transferrin saturation (%) and the bone marrow scores is given. The variability in the data is readily apparent. No significant relationship between transferrin saturation and bone marrow scores (Spearman rank) could be identified.

In Table 4, we show the serum ferritin and transferrin saturation values in terms of iron deficiency defined as "absolute" (combination A; an iron score of 0 to +1), "relative" (combination B; an iron score of 0 to +2), or "relative

Table 2. Hematologic Characteristics of the Patients

Patient No.	MCV (μm^3)	Iron Score	Hemoglobin (g/dL)	Serum Ferritin (ng/mL)	Serum Iron ($\mu\text{g/dL}$)	Serum Transferrin (mg/dL)	Transferrin Saturation (%)
1	86.7	0	6.5	91	18	212	7
2	91.1	0	7.5	70	54	226	17
3	93.5	0	8.7	88	40	216	13
4*	88.1	1	11.0	220	32	216	12
5	102.0	1	8.5	572	39	168	16
6†	98.5	1	8.8	436	45	98	32
7	100.9	1	7.3	1,250	30	153	16
8	85.0	1	8.6	71	24	253	7
9	93.0	1	9.2	225	76	276	20
10	87.5	1	6.4	19	21	413	4
11	92.5	2	6.3	212	49	231	15
12	93.4	2	6.0	1,291	46	194	17
13	83.7	2	8.4	199	27	243	8
14	86.9	2	7.8	120	41	197	15
15	87.0	2	9.0	1,200	42	152	20
16	88.6	2	8.2	1,420	45	253	13
17†	97.3	2	9.7	1,840	51	130	28
18	89.9	3	9.3	892	129	185	50
19	88.0	3	7.0	472	73	235	22
20†	100.1	3	8.9	1,510	37	72	36
21	81.6	3	10.4	426	71	209	24
22*†	90.2	3	10.2	654	18	149	18
23†	87.9	4	9.7	1,240	35	125	20
24	86.8	4	8.7	433	19	207	19
25	97.7	4	7.1	1,470	53	150	25
Normal ranges	86-98		12-16	120-200	50-150	200-400	20-50

Abbreviation: MCV, mean corpuscular volume.

* Hemodialysis patients who did not receive EPO therapy (see Table 1).

† Patients with serum transferrin concentration <150 mg/dL.

with deletion of patients with low (<150 ng/dL) transferrin values'' (combination B'). Serum ferritin again showed substantial variability, with SD values approaching or exceeding the mean

value. Iron deficiency and non-iron deficiency anemia were only significantly different in terms of this test when the most rigorous (absolute) definition of iron deficiency was used. On the

Table 3. Hemoglobin Concentration, Serum Ferritin Concentration, and Transferrin Saturation for Each Bone Marrow Iron Score for 25 Patients

Bone Marrow Iron Score	No. of Patients	Hemoglobin Concentration (g/dL)	Ferritin Concentration (ng/mL)	Transferrin Saturation (%)
0	3	7.6 $\pm$ 0.9	83 $\pm$ 9*	12.3 $\pm$ 4.1†
+1	7	8.5 $\pm$ 1.3	399 $\pm$ 391*	15.3 $\pm$ 8.5†
+2	7	7.9 $\pm$ 1.3	897 $\pm$ 651	16.6 $\pm$ 5.8†
+3	5	9.2 $\pm$ 1.2	791 $\pm$ 395	30.0 $\pm$ 11.6
+4	3	8.5 $\pm$ 1.1	1,047 $\pm$ 445	21.3 $\pm$ 2.6

NOTE. Data are given as mean values $\pm$ SD.* Lower than values with bone marrow iron scores +2 or greater ($P < 0.05$).† Lower than values with bone marrow iron scores +3 or greater ($P < 0.05$).

Fig 1. (A) Significant correlation (Spearman rank) between serum ferritin concentrations (logarithmic scale) and the semiquantitative bone marrow iron deposit scores in 25 patients. (B) Nonsignificant relationship between serum transferrin saturation and semiquantitative bone marrow iron deposit scores in the same patients.

other hand, when the definition “relative” iron deficiency was used, serum ferritin was no longer of value in establishing the diagnosis of iron deficiency. Rather, a transferrin saturation value of less than 20% was significant, and increased in significance when the transferrin value itself (in terms of hypoproteinemia) was considered.

In Table 5, we also applied the rigorous and more flexible definitions, namely, patients with scores of 0 or +1 were considered to be “absolutely” iron deficient (combination A) and those with scores of 0 to +2 were considered to be “relatively” iron deficient (combination B). We also examined “relative” iron deficiency, when those patients with a transferrin concentration of less than 150 ng/dl (combination B') were ex-

cluded. Again, this approach was applied to account for the confounding variable of hypoproteinemia, which necessarily interferes with interpretation of the transferrin saturation. We calculated sensitivity, specificity, and positive predictor values for serum ferritin less than 200 ng/mL and transferrin saturation less than 20% against the two bone marrow reference standards. In terms of absolute iron deficiency, the serum ferritin test was not sensitive but relatively specific (87%, with 71% positive predictor value), while the transferrin saturation was relatively sensitive (90%) but not specific (40%). In terms of relative iron deficiency, the serum ferritin became even less sensitive, but more specific, while the transferrin saturation remained sensitive. If

Table 4. Iron Deficiency

Combination	Bone Marrow Iron Score (0 to +4)		Serum Ferritin		Transferrin Saturation	
	Iron Deficient	Iron Replete	Iron Deficient	Iron Replete	Iron Deficient	Iron Replete
A (n = 25)	0, +1	+2, +3, +4	304 ± 358	892 ± 546*	14.4 ± 7.6	22.0 ± 9.9†
B (n = 25)	0, +1, +2	+3, +4	548 ± 579	887 ± 432†	15.3 ± 6.9	26.8 ± 9.3*
B' (n = 20)	0, +1, +2	+3, +4	—	—‡	13.3 ± 4.7	28.0 ± 9.2*

NOTE. Iron deficiency according to bone marrow score may be most rigorously defined as “absolute” (0 or +1) or it may include +2 (“relative”). Furthermore, hypoproteinemia can result in low serum transferrin values. In combination A, an iron score of ≤ +1 was considered to represent iron deficiency, while in combinations B and B', an iron score of ≤ +2 was considered to represent iron deficiency. The designation B' represents the criteria of combination B with the omission of five patients with a serum transferrin concentration <150 ng/dL. Serum ferritin and transferrin saturation data are given as mean values ± SD.

* $P < 0.05$ comparing iron deficient to iron replete.

† $P = \text{NS}$ comparing iron deficient to iron replete.

‡ Ferritin calculations for the B' group not indicated.

Table 5. Comparison of Sensitivity, Selectivity, and Positive Predictor Value of Combinations

Combination*	Bone Marrow Score		Serum Ferritin <200 ng/mL				Transferrin Saturation <20%			
	Low	Normal	Sens	Sel	Pred Val	P	Sens	Sel	Pred Val	P
A (n = 25)	0, +1	+2, +3, +4	50%	87%	71%	<0.05	90%	40%	50%	NS
B (n = 25)	0, +1, +2	+3, +4	41%	100%	100%	<0.05	88%	63%	83%	<0.05
B' (n = 20)	0, +1, +2	+3, +4	—	—	—	—†	100%	80%	94%	<0.05

NOTE. Iron deficiency according to bone marrow score may be defined as “absolute” (0 or +1) or it may include +2 (“relative”). Furthermore, hypoproteinemia can result in low serum transferrin values.

Abbreviations: Sens, sensitivity; Sel, selectivity; Pred Val, positive predictor value.

* Combination A bone marrow iron score +2 considered *not* iron deficient; combination B, bone marrow iron score +2 considered iron deficient; and combination B', same as B with five patients having serum transferrin concentrations <150 ng/dL omitted to correct for hypoproteinemia.

† Ferritin calculation not indicated for B'.

hypoproteinemia in terms of low transferrin concentrations was included in the consideration, the sensitivity and specificity of the transferrin saturation (<20%) increased still further, to a sensitivity of 100% and a specificity of 80% with a positive predictor value (in our patients) of 94%. If both tests were considered, a maximum precision was obtained.

DISCUSSION

We have evaluated common laboratory parameters in terms of diagnosing iron deficiency anemia according to bone marrow criteria in a group of patients with renal insufficiency, almost all of whom were receiving EPO. We applied either an extremely rigorous bone marrow criterion (absolute iron deficiency) or a less exclusive definition (relative iron deficiency). Our data place the commonly used ferritin concentrations and the transferrin saturation values in perspective. We believe our most important observation is that hypoproteinemia (ie, patients with reduced transferrin values [<150 ng/dL]) may result in a falsely low appraisal of iron deficiency anemia. Hypoproteinemia is common in the chronically ill, the poorly nourished, and the elderly. The clinician's index of suspicion for iron deficiency should be increased in such patients with anemia.

The introduction of EPO greatly increased the incidence of iron deficiency anemia in patients with chronic renal failure because of increased iron utilization and turnover.^{10,11,21} Iron deficiency occurs in most patients receiving EPO and is the most common cause of treatment failure with the hormone.^{3,5,21} Although numerous diag-

nostic avenues are open,²² the most definitive is examination of the bone marrow iron stores.²³ Red blood cell protoporphyrin, red blood cell volume distribution, and red blood cell ferritin have been suggested as superior alternatives.⁸ Nevertheless, mean cell volume, serum ferritin by radioimmunoassay, and transferrin saturation testing are most commonly used. A correlation between serum ferritin values and bone marrow iron stores has been presumed, but not substantiated, in patients with chronic renal failure given EPO.^{3,5,21}

Guyatt et al¹⁶ conducted a meta-analysis and suggested that radioimmunoassay-determined serum ferritin is the most powerful test for the diagnosis of iron deficiency anemia regardless of renal function. However, frequently, serum ferritin values are normal or increased in chronic renal failure patients despite their receiving EPO.^{5,24,25} A defect in iron mobilization in the face of abundant iron stores has been suggested as an explanation for these findings.^{4,11} Furthermore, ferritin is an acute phase reactant, and thus the serum concentrations may increase for reasons independent of iron metabolism. In our study, the patients with bone marrow iron scores of 0 and +1 would be considered “absolute iron deficiency”; the group with a bone marrow iron score of +2 would be considered “iron deficiency hematopoiesis” or “relative iron deficiency” by other investigators.²⁶ Although serum ferritin concentrations increased with increasing iron stores in our patients, the scatter in the data shown in the figure was such that for any given patient, the predictive value of the diagnosis was minimal.

A more accurate, albeit older method of determining iron status in patients with chronic renal insufficiency is the ratio of the serum iron concentration divided by the iron binding capacity or "transferrin saturation."^{7,27,28} The normal value ranges between 20% and 40%. A transferrin saturation of less than 20% in patients with chronic renal insufficiency has been associated with resistance to EPO therapy.^{3,28} Some investigators have suggested that transferrin saturation is actually superior to serum ferritin concentrations as a marker for iron deficiency.^{7,27,28}

We found that a serum ferritin value of less than 200 ng/mL was not sufficiently sensitive in identifying patients with iron deficiency anemia. However, in terms of specificity, a serum ferritin value of less than 200 ng/mL was highly predictive. All patients with such values had either relative or absolute iron deficiency according to the reference standard. On the other hand, the transferrin saturation had a sensitivity of almost 90%, which makes that test a much more reliable marker in terms of identifying candidates for iron deficiency anemia. The specificity of 63% is not ideal; nonetheless, the test meets the criterion of an adequate screening test for the diagnosis.

Serum transferrin values can be sharply reduced in several chronic illnesses associated with hypoproteinemia, primarily due to protein losses.¹⁵ These include protein losing enteropathy and the nephrotic syndrome. When patients with transferrin values of less than 150 mg/dL were excluded from the analysis, the calculated transferrin saturation value of less than 20% had a sensitivity of 100% and a specificity of 80%, a statistically significant improvement. Exclusion of such hypoproteinemic patients is justified, particularly when hypoproteinemia and its source can be identified.

The diagnosis of iron deficiency anemia and iron status monitoring remain imperative in patients with chronic renal insufficiency, even though the task is not easy,^{29,30} and novel approaches continue to be suggested.³¹⁻³³ Studies including the use of bone marrow examinations are few³⁴; ours is the first to include bone marrow examination as a "gold" reference standard, coupled with conventional tests to examine the sensitivity and selectivity of the latter. On the basis of our findings we recommend both measurements of serum ferritin and determination of

the transferrin saturation. The former test offers excellent specificity, while the latter offers acceptable sensitivity. Patients with transferrin values of less than 150 mg/dL should be considered separately. Those patients deserve an increased index of suspicion with respect to iron deficiency. We believe that in this fashion, iron therapy in patients with chronic renal insufficiency can be improved.

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