Kidney International, Vol. 64, Supplement 87 (2003), pp. S78–S86

Erythropoeitin dose variation in different facilities in different countries and its relationship to drug resistance

Roger N. Greenwood, Claudio Ronco, Fiorella Gastaldon, Alessandra Brendolan, Peter Homel, Len Usvyat, Lenore Bruno, Mary Carter, and Nathan W. Levin

Lister Renal Unit, Stevenage, United Kingdom; Department of Nephrology, St. Bortolo Hospital, Vicenza, Italy; Beth Israel Medical Center, Manhattan, New York; and Renal Research Institute, New York, New York

Erythropoeitin dose variation in different facilities in different countries and its relationship to drug resistance.

Background. The correction of anemia using erythropoeitin (EPO) is accorded high priority in the management of patients undergoing hemodialysis (HD). Target hemoglobin (Hb) levels have been established in many countries. Following an observation that the mean facility EPO dose in a chain of facilities in the United States varied by more than two-fold, an examination of the practice of anemia correction in other settings was carried out.

Methods. We reviewed demographic and laboratory parameters in prevalent HD patients in 50 United States facilities and in a single HD facility in Vicenza, Italy. The mean EPO dose profile of the United States facilities was compared with the profiles in 10 facilities in the eastern United Kingdom (UKER) and in 20 facilities reporting to the United Kingdom Renal Registry (UKRR). Analysis of the factors that correlate with EPO resistance was carried out using the United States and Italian data.

Results. The average EPO doses, by facility, in the 51 United States, the 10 UKER, and the 19 UKRR facilities were 19,569, 8,416, and 7,992 international units per week (IU/wk), respectively. While examination of the UKRR revealed a similar degree of inter-facility variation (2.6-fold), much larger doses of EPO were being administered in the United States patients, particularly in the low Hb group. Multivariate analysis of the United States data suggested that factors related to inflammation, including low albumin, the use of tunneled catheters for vascular access, and low protein catabolic rate (enPCR) correlated with low Hb and relative EPO resistance.

Conclusion. Despite similar guidelines for anemia management, significant differences in practice are observed. While there seems to be a reluctance to administer large EPO doses to individual patients in Europe, this does not seem to apply in the United States, where more EPO is given. EPO resistance seems relative rather than absolute in many patients, allowing some to respond to the higher doses.

The anemia of chronic kidney disease (CKD) has been well characterized and the intricacies of treatment, primarily with erythropoietin (EPO) and iron, are familiar to those caring for patients in the various stages of this illness. Evidence-based guidelines for the management of anemia have been developed in many countries. The United States National Kidney Foundation DOQI guidelines were published in 1997 [1]. Several European countries also established their own guidelines in the mid 1990s. Recently, the European Renal Association published the European Best Practice Guidelines (EBPG), which addressed standards in a number of areas, including anemia management [2]. These initiatives have been generally successful in increasing hemoglobin (Hb) levels in patients with CKD and particularly in end-stage renal disease (ESRD) patients receiving dialysis. In the United States, clinical performance measures on anemia management, among other quality issues, have been instituted nationwide, with clear demonstrations of improvement in standards of care. Several European countries have renal registries in place that effectively monitor outcomes according to the agreed standards.

It is well known that in order to respond to EPO or EPO analogs the patient must be replete with iron, which, due to poor absorption and tolerance by the oral route, is most often administered intravenously. Also, EPO/analogs themselves can be administered by the intravenous route or by the subcutaneous route, the latter often providing the opportunity for self-administration, sometimes at home, and being slightly more economic from the dose response aspect. As a result, practice patterns can be highly variable, despite the aim toward a common goal. It is also recognized that individual patients respond very differently, with a minority appearing to be drug resistant. Intercurrent infection is probably the most common reason why patients become temporarily (and reversibly) resistant, but some more chronic conditions can have a more insidious effect. These are well documented and include iron deficiency, real or functional, myelofibrosis, malignancy, vitamin deficiency, thalassaemia, sickle cell disease, and, very rarely, anti-

Key words: end-stage renal disease, chronic kidney disease, erythropoetin, EPO, albumin, catheters.

bodies directed against EPO. Since patient demographic profiles in countries with mature renal replacement services tend not to be too dissimilar, and despite some of the above issues, it could reasonably be presumed that similar experiences would be reported in anemia management.

During a routine quality assurance meeting it was noted that the mean dose of EPO per patient receiving the drug varied widely between facilities in a chain of 53 renal centers managed by the same service provider, The Renal Research Institute, New York (RRI). Despite shared protocols covering a wide range of technical, psychosocial, pharmaceutical, and medical care areas, the review revealed a 2.5-fold variation in the EPO usage, despite this being one of the most expensive components of total therapy. Our group was aware that interfacility comparisons had been carried out elsewhere. We felt it would be instructive to review the comparative data that was readily available and to explore why there were these large interfacility differences.

METHODS

RRI (United States) sample

All patients who had been receiving HD for at least six months prior to April 2003 and had received at least one HD treatment and received EPO in that month in 53 Renal Research Institute–owned or managed facilities were selected for study (N = 4381). The majority of the facilities were in New York, but some also were in Connecticut, North Carolina, Michigan, Illinois, and California. Demographic, disease, and therapy parameters recorded included age, gender, race, years on dialysis, weight in kg, body mass index (BMI) (computed as the ratio of the post-dialysis body weight to the square of the patient's height in meters), the presence of a tunneled permanent catheter for vascular access, and the presence of diabetes. The EPO doses per week (IU and IU/kg) were recorded for the months of March 2003. Dialysis dose was reflected in the two-pool equilibrated Kt/V (eKt/V), where K is the clearance of urea by the dialyzer (mL/min), t is dialysis duration, and V is the volume of body water. Computation of the eKt/V from pre- and post-dialysis urea measurements allowed the derivation of the equilibrated protein catabolic rate, which was normalized to the patient's body weight (enPCR) and expressed in g/kg/day. Laboratory parameters included Hb expressed in g/dL, albumin in g/dL, parathyroid hormone (PTH) in pg/mL, calcium in mg/dL, phosphorus in mg/dL, transferrin saturation (%), ferritin, total white blood cell count (WBC), lymphocyte count, and neutrophil count in 10^9/L.

Since all patients had been receiving HD for at least six months, management of anemia should have been past the initiation phase and ongoing in all patients. In order to gain insight into the relative resistance to EPO, three Hb levels were chosen for the analysis of responsiveness to the drug. These were Hb <10, 10 to 12, and >12 g/dL.

United Kingdom samples

A survey of EPO usage in 10 nephrology/dialysis facilities in the Eastern Region of the UK National Health Service was carried out in June 2002. Coordination of data collection was done by Ortho-Biotech. While EPO use was recorded in all dialysis patients, the mean dosage of EPO in only those HD patients who had been receiving the drug for more than three months was used in this study (N = 1035). At the time of the data collection, the United Kingdom Renal Association Standard required that 85% of all HD patients should have an Hb >10 g/dL. The European Best Practice Guidelines recommended that 85% of dialysis patients should have an Hb >11 g/dL. Patient demographic data (including weight) was not part of the survey, and dosage was expressed as the total number of units administered per week (IU/wk). Although not recorded, the most common route of administration of EPO in the United Kingdom at that time was subcutaneous, including the majority of HD patients.

The United Kingdom Renal Registry, which receives automated electronic download of patient data from renal centers, had participation from 38 of the 63 adult nephrology/dialysis units in England and Wales in 2002. The December 2002 report contained data on EPO provision in 19 of these centers. The mean and median weekly dose for those patients receiving the drug is reported and expressed in IU/wk.

Italian sample

In May 2003, 105 patients undergoing regular HD in the renal center in St. Bortolo Hospital in Vicenza, in northeastern Italy, were receiving EPO. Demographic and laboratory data was available which allowed some comparative analysis with the much larger group from the RRI in the United States. The dose of EPO could be expressed as IU/wk or IU/kg/wk.

Analysis

Normally distributed continuous variables were characterized by mean ± standard deviation; skewed continuous variables were characterized by the median, minimum, and maximum, and categorical variables were characterized by frequency/total and expressed as a percent. Severity of EPO resistance was defined as either EPO dose/Hb or by EPO dose /(weight × Hb). A natural log transformation was applied to normalize skewed variables in order to use them in parametric analyses. Univariate analyses to determine possible predictors of EPO resistance were done using either Pearson correlations

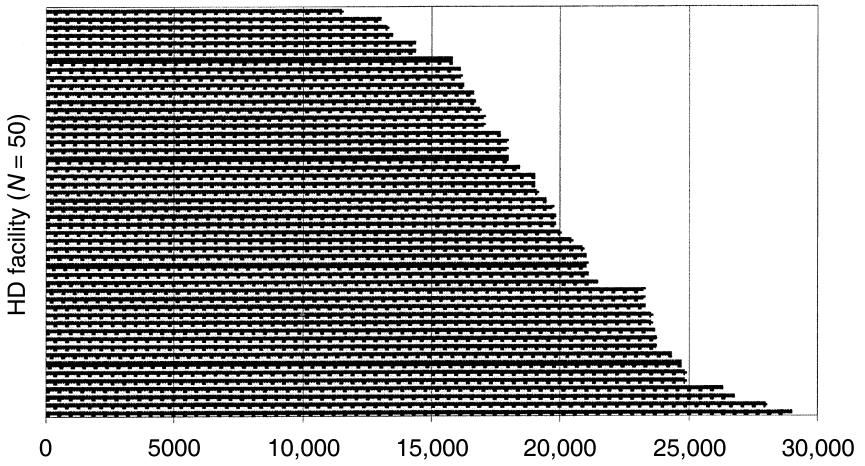

Fig. 1. Distribution of the mean erythropoeitin (EPO) doses (IU/wk) in 50 Renal Research Institute facilities.

in the case of continuous covariables (e.g., age, log ferritin), or the Student *t* test in the case of categorical predictors (e.g., gender). Multiple regression with fixed entry was used to test for the strength of correlation between each predictor controlling for all other predictors. In addition, patients with severe anemia were defined as patients with Hb <10 g/dL and receiver operator characteristics (ROC) analysis was used to determine the optimal cut-off for predicting severe anemia based on EPO dose. EPO-resistant patients were then defined as patients with severe anemia who were also above the threshold established by the ROC analysis. The *t* test and the chi-square test were used to identify significant univariate predictors of EPO resistance in the case of continuous and categorical predictors, respectively. Logistic regression with fixed entry was used to test for the strength of association between each predictor and EPO resistance, controlling for all other predictors. All statistical tests were done using a 0.05 level of significance. All analyses were done using SPSS 10.1 (SPSS, Inc., Chicago, IL, USA).

RESULTS

Inter-facility EPO dose variation

The distribution of the mean EPO doses in 50 of the 53 RRI facilities is shown in Figure 1. The mean facility dose, using the total number of HD patients receiving the drug as the denominator, ranged from 11,475 to 28,932 IU/wk. There was a 2.5-fold variation around a mean facility dose of 19,569 IU/wk. The distribution of mean EPO doses in the 10 UKER facilities and in the 19 facilities reporting to the United Kingdom Renal Registry are shown in Figure 2. The mean facility dose in the UKER facilities ranged from 7210 to 9294 IU/wk, which shows a 1.3-fold variation around a mean facility dose of 8,416 IU/wk. The mean facility dose in the UKRR facilities ranged from 4929 to 12,667 IU/wk, a 2.6-fold variation around a mean facility dose of 7992 IU/wk. While a larger variation of mean dose is seen in the UKRR data compared to the UKER data, the amount of EPO is of a similar order in the eastern region of the United Kingdom as in England and Wales as a whole.

The distributions of facility doses in the 50 RRI and UKRR centers are compared in Figure 3. While both show an approximate 2.5-fold variation in dose, much more EPO is being administered in the United States centers.

Scatter plots of Hb and weekly EPO dose for the RRI and UKER patients are shown in Figure 4. The left upper quadrant illustrates the most satisfactory outcome, with Hb in the target range at the cost of modest doses of EPO. The poorest outcome is represented by the lower right quadrant, which represents failure to achieve target Hb at the expense of large doses of EPO. While it appears that more RRI patients are achieving target, it is clear that proportionally more patients are receiving large doses of the drug to achieve this outcome. Clearly, it is not common practice to give large doses of EPO to correct low Hb in the UKER. One interpretation of this figure is that more effort (i.e., higher EPO dosing) is put into patients who are failing to respond to moderate doses in the United States, whereas some of these patients, who are presumably relatively EPO-resistant, remain below target in the United Kingdom.

Demographic and clinical characteristics related to EPO resistance

Table 1 shows the demographic and clinical characteristics and selected laboratory parameters in the 4381 patients in the RRI sample. Table 2 shows the univariate associates of clinical and laboratory parameters with EPO to Hb ratios, with and without adjustment for weight. Almost all factors are significant, and there is a similar pattern of results for the ratios with and without adjustment for weight. Albumin (low), low transferrin

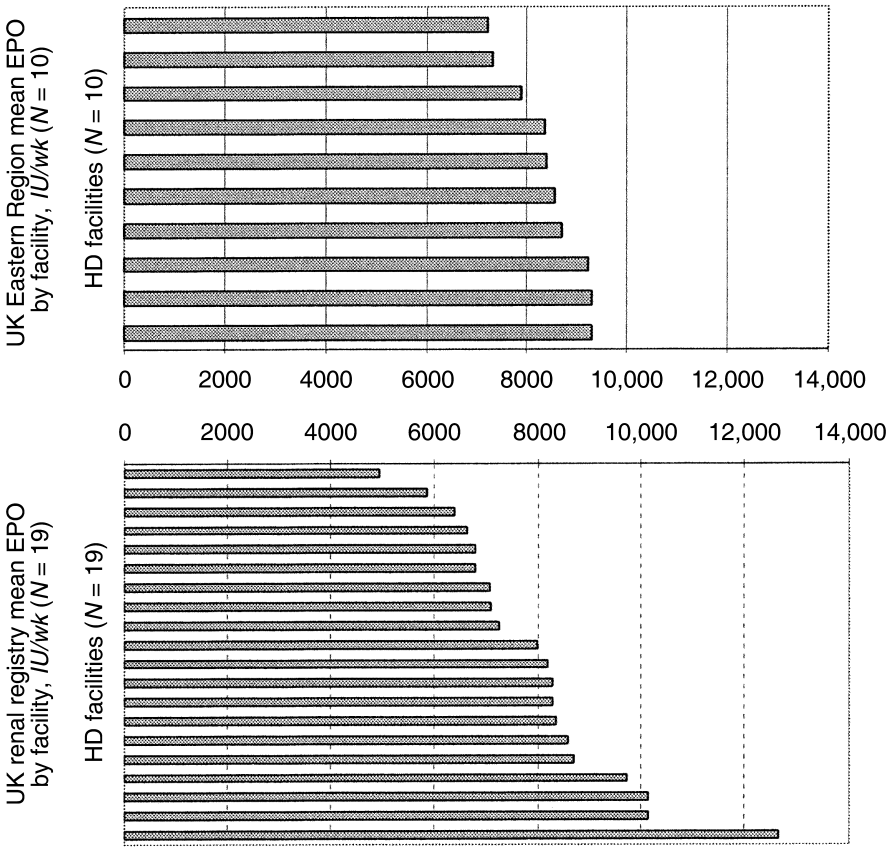

Fig. 2. Distribution of the mean erythropoeitin (EPO) doses (IU/wk) in 10 UK Eastern Region (UKER) facilities and in 19 facilities reporting to the UK Renal Registry.

saturation, low ferritin, and low lymphocyte count appear to have the strongest influences. Table 3 shows a multiple regression analysis illustrating the effect of regressing each of the measures of EPO resistance onto their respective univariate predictors. There appear to be three main factors among the significant multivariate predictors. Based on inspection of the beta coefficients, parameters that suggest the presence of inflammation appear to be the most important, namely low albumin and low lymphocyte count. Another class of predictors includes a low enPCR and low phosphate, both markers of malnutrition. Finally, there are also markers of iron depletion, transferrin saturation, and ferritin. Catheter use is also important. Multiple regression of the Italian data yielded similar results. EPO resistance adjusted for weight was significantly related to albumin (beta = −.31, $P = 0.002$), transferrin saturation (beta = −.29, $P = 0.002$), and Kt/v (beta = −.25, $P = 0.009$). The beta coefficients for EPO resistance not adjusted for weight were –0.25 for albumin ($P = 0.009$), −0.30 for transferrin saturation ($P = 0.002$), and –0.32 for Kt/v ($P = 0.001$).

In order to establish a possible empirical definition of EPO resistance, we defined severe anemia as having an Hb <10g/dL. An ROC analysis was done to determine how well EPO dose could identify patients with Hb <10/g/dL. This yielded an area under the curve of 0.81 ($P < 0.001$), which indicated that EPO dose was a fairly good predictor of severe anemia. An EPO dose of 7543 IU/treatment (22,629 IU/wk) was found to optimize sensitivity and specificity at about 0.74.

A total of 216 patients, or 5%, were identified as EPO-resistant by this definition. Table 4 shows the univariate associations with resistance to EPO as defined by severe anemia and EPO dose equal to or greater than 7543 IU/treatment. Many of these parameters had also been significant predictors of the continuous measurement of EPO resistance. Resistant individuals are younger, heavier, have lower albumin, lower Ca × P product, lower mean corpuscular volume (MCV), lower phosphorus, low transferrin saturation, lower enPCR, lower lymphocyte count, higher neutrophil count, and higher catheter use. Table 5 shows the results of a multivariate logistic regression of resistance, as defined above, showing the odds ratios of the significant factors. The three significant factors were age, albumin, and enPCR. Similar results were found when the weight-controlled measure of EPO resistance was used to determine a cut-off for EPO dose and severe anemia. The small size of the Italian group precluded doing a similar set of analyses to look at predictors of EPO resistance in patients with Hb <10 g/dL and high levels of EPO.

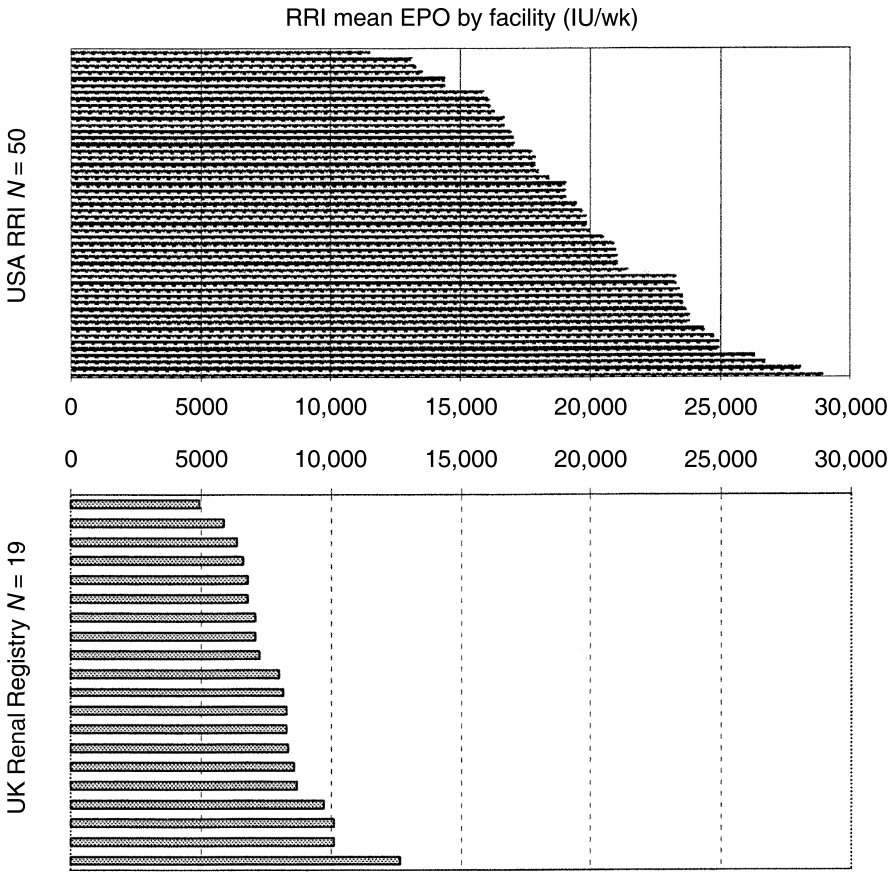

Fig. 3. Comparison of facility mean erythropoeitin (EPO) doses (IU/wk) in 50 Renal Research Institute (RRI) and 19 UK Renal Registry (UKRR) facilities. Percent patients with Hb >10 g/dL was 90 and 81, respectively.

DISCUSSION

The starting point for this study was the observation of large (2.5-fold) inter-facility differences in the consumption of EPO, one of the most expensive components of renal replacement therapy. The observation was particularly interesting in that the 53 facilities involved were managed by a single provider, and routine quality assurance along agreed guidelines and targets was accorded high priority. Indeed, standards for the correction of anemia have been in place for a number of years and these are thoroughly ingrained into the clinical management culture in these centers. Also, the intricacies of anemia management with iron and EPO have become better understood since EPO was first introduced into routine clinical practice over 13 years ago. A cursory review of facility data suggested that the observed variations could not be explained by any obvious differences in clinical or demographic profiles. Our group thought it would be instructive to look further to see if similar differences existed in dialysis patients in other health care environments. In doing this, we were aware that most countries with mature renal replacement programs have developed anemia management guidelines and the European Renal Association have published Best Practice Guidelines including anemia management.

Our starting point was the United Kingdom, where we were aware that data on anemia correction in HD patients was available both on a regional level and through the national renal registry (UKRR) [3]. The comparison of parameters between different databases is fraught with difficulties, many of which would apply to dosages of drugs. First, the dose profile in any individual facility is likely to be skewed and mean values have to be interpreted with caution. Median values are likely to be more representative. Also, taking a mean or median among different facilities may not provide data sufficiently robust to draw scientific conclusions. Furthermore, it is known that the route of administration of EPO can affect outcome. Because of perceived economic advantages the main route of administration in the United Kingdom at the time of this study was subcutaneous; the practice in the United States was generally intravenous. Nonetheless, we felt that our study might be instructive if differences were large, in which case we might be able to draw broad conclusions. Interestingly, the variation in dosage among 19 centers currently reporting to the UKRR was of a similar order to that

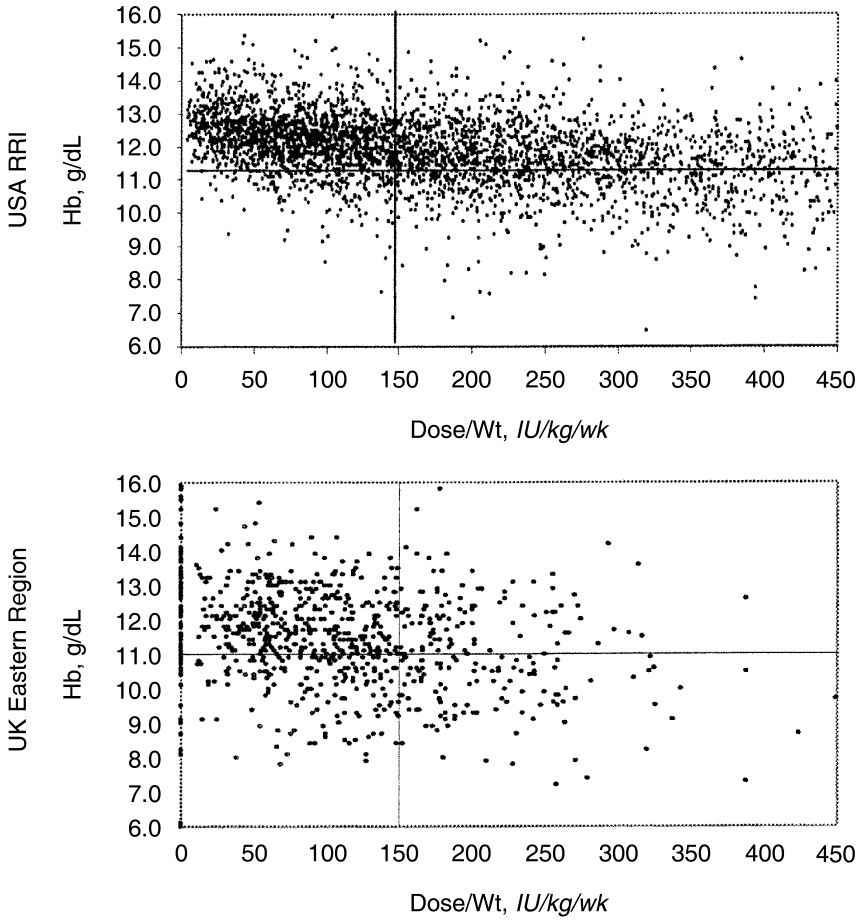

Fig. 4. Scatter plot of Hb vs. weekly erythropoeitin (EPO) dose for the Renal Research Institute (RRI) and UK Eastern Region patients.

Table 1. Demographic and clinical characteristics and selected laboratory parameters of the 4381 patients in the Renal Research Institute (United States) sample

Parameter	Summary
Age	60.6 ± 15.3
Male	54%
White	36.5%
Time since start of dialysis *years*	3 (0, 33)
Weight *kg*	75.1 ± 29.9
BMI	27.1 ± 7.4
Catheter	29%
Diabetic	43%
Albumin	3.9 ± 0.4
Bio PTH	159.4 (4, 2787)
Phosphorus	5.4 ± 1.6
Ca × P	50.4 ± 15.3
eKt/V	1.4 ± 0.3
enPCR	0.89 ± 0.24
MCV	93.9 ± 7.5
Transferrin saturation	32.3 ± 14
Ferritin	606
WBC	6665 (1300, 65100)
Lymphocytes	22.7 ± 9.0
Neutrophils	63.7 ± 10.8
EPO	5000.0 (1000, 50909)
EPO/Hb ratio	420.0 (61.8, 6376.9)
EPO/(weight × Hb)	5.8 (0.48, 115.3)

Abbreviations are: BMI, body mass index; PTH, parathyroid hormone; enPCR, equilibrated protein catabolic rate; MCV, mean corpuscular volume; WBC, white blood cells; EPO, erythropoeitin; Hb, hemoglobin.

Table 2. Univariate associates of clinical and laboratory parameters with EPO/Hb and EPO/(weight × Hb) ratios

Parameter		Log EPO/Hb (*P* value)	Log EPO (weight × Hb) (*P* value)
Age		−0.06 (<0.001)[a]	−0.02 (0.23)
Weight *kg*		0.06 (<0.001)	NA
Albumin		−0.24 (<0.001)	−0.27 (<0.001)
Phosphorous		0.06 (<0.001)	0.03 (0.04)
Ca × P		0.04 (0.006)	0.01 (0.45)
eKT/V		−0.10 (<0.001)	−0.01 (0.69)
enPCR		−0.13 (<0.001)	−0.11 (<0.001)
Transferrin saturation		−0.19 (<0.001)	−0.16 (<0.001)
Log WBC		−0.05 (<0.001)	−0.07 (<0.001)
Lymphocytes		−0.14 (<0.001)	−0.14 (<0.001)
Neutrophil		0.10 (<0.001)	0.10 (<0.001)
Log ferritin		−0.19 (<0.001)	−0.17 (<0.001)
Sex	Female	6.07 ± 0.80 (0.09)[b]	1.86 ± 0.83 (<0.001)
	Male	6.03 ± 0.81	1.69 ± 0.83
White	Non-white	6.03 ± 0.80 (0.05)	1.75 ± 0.85 (0.03)
	White	6.08 ± 0.79	1.80 ± 0.80
Catheter	No	5.99 ± 0.80 (<0.001)	1.70 ± 0.82 (<0.001)
	Yes	6.20 ± 0.79	1.93 ± 0.83

For abbreviations, see Table 1.
[a] Results for continuous predictors reported as Pearson correlation *r* (*P* value)
[b] Results for categorical predictors reported as mean ± SD (*P* value)

Table 3. Multiple regression analysis showing the effect of regressing each of the measures of EPO resistance onto their respective univariate predictors

Parameter	Log EPO/Hb Beta coefficient (*P* value)	Log EPO/Weight × Hb Beta coefficient (*P* value)
Age	−0.14 (<0.001)	NA
Weight	0.05 (0.006)	NA
Albumin	−0.23 (<0.001)	−0.21 (<0.001)
Ca × P	0.07 (0.19)	NA
eKT/V	0.008 (0.69)	NA
Phosphorous	−0.03 (0.58)	0.05 (0.01)
Transferrin saturation	−0.09 (<0.001)	−0.06 (0.001)
enPCR	−0.07 (<0.001)	−0.05 (0.01)
Log WBC	−0.12 (<0.001)	−0.14 (<0.001)
Lymphocytes	−0.20 (<0.001)	−0.21 (<0.001)
Neutrophil	−0.04 (0.19)	−0.06 (0.10)
Log ferritin	−0.13 (<0.001)	−0.12 (<0.001)
Sex	−0.02 (0.29)	−0.07 (<0.001)
White	0.02 (0.32)	−0.04 (0.05)
Catheter	0.03 (0.11)	0.03 (0.07)

For abbreviations, see Table 1.

Table 4. Univariate associations with resistance to EPO defined by anemia (Hb <10 g/dL) and an EPO dose equal to or greater than 7543 IU/Tx or 22,629 IU/wk

Parameter	Nonresistant	Resistant	*P* value
Age	60.7 ± 15.3	56.9 ± 15.4	<0.001
Weight	74.9 ± 20.6	78.4 ± 26.0	0.016
Albumin	3.9 ± 0.4	3.5 ± 0.6	<0.001
Ca × P	50.6 ± 15.3	45.3 ± 15.0	<0.001
eKT/V	1.4 ± 0.3	1.3 ± 0.3	<0.001
MCV	94.1 ± 7.3	91.8 ± 10.0	<0.001
Phosphorous	5.4 ± 1.6	5.0 ± 1.6	<0.001
Transferrin saturation	32.8 ± 14.7	27.6 ± 16.4	<0.001
enPCR	0.9 ± 0.2	0.8 ± 0.2	<0.001
Lymphocytes	22.9 ± 8.9	20.6 ± 10.0	0.001
Neutrophils	63.48 ± 10.7	66.7 ± 12.0	<0.001
Catheter	129/3172 (4%)	89/1322 (6%)	0.002

For abbreviations, see Table 1.

observed in the 53 RRI–United States centers. There was a 2.5-fold variation in the reported mean facility dose and a 3-fold variation in the median values. Less variation was observed among the 10 facilities in the eastern part of the United Kingdom. However, the mean values were closely comparable, suggesting a uniform approach to the management of anemia correction. Also, it is known from the Dialysis Outcomes and Practice Patterns Study (DOPPS) [4] that the mean and median EPO dose for a point-prevalent sample of HD patients in Euro-Dopps who had been on dialysis for more than 90 days and who were receiving EPO therapy in the years 1998 to 1999 was 88 IU/kg/wk. Dividing the UKRR (2002) median EPO dose by the average weight from one of the reporting centers (Stevenage), a comparative figure of 86 IU/kg/wk is obtained. Although this is only a rough assessment, it suggests that the practice of anemia

Table 5. Multivariate analysis of resistance (Hb <10 g/dL and an EPO requirement equal to or exceeding 7543 IU/Tx or 22,629 IU/wk) showing the odds ratios of the significant factors

Parameter	Odds ratio	*P* value
Age	0.97	<0.001
Albumin	0.23	<0.001
enPCR	0.16	<0.001

For abbreviations, see Table 1.

management in the United Kingdom does not differ substantially from that in other European countries.

The most striking comparison to emerge was the very large difference in EPO usage between the United Kingdom and the RRI-United States facilities. Over twice as much EPO seemed to be administered in the United States to achieve roughly the same objective. The scatter plots of Hb against EPO dose for individual patients in the UKER and RRI-United States were revealing. They showed a stark difference in practice, whereby EPO doses in the United Kingdom patients are rarely above the 250 to 300 IU/kg/wk mark. This contrasts with the United States patients, who commonly received doses above this, some receiving as much as 450 IU/kg/wk, which would equate to 34,000 IU/wk. Such doses would be rarely administered in the United Kingdom (RG, personal communication, 2000). Doses above 30,000 IU/wk would rarely be administered in the St. Bortolo Hospital in Vicenza, Italy. The scatter plots suggest the higher doses are effective in correcting anemia, and a higher percentage of RRI-United States patients had a Hb above 10 gm/dL than the UKER patients (90% vs. 81%). Given this observation, we embarked upon a second phase to this study, which investigated the factors that lead to high EPO dose requirements.

Parameters that suggested the presence of inflammation appeared to be the most important determinants of high EPO dose requirement. Most important were low albumin and low lymphocyte count. Another class of predictors included a low enPCR and low phosphate, both markers of poor nutrition. Also, as might be expected markers of iron depletion, low transferrin saturation and low ferritin levels came out in the analysis. Catheter use was also important. Analysis of the Italian data yielded similar results, EPO resistance being related to albumin, low transferrin saturation, and low Kt/V, a marker of under-dialysis. Relatively few catheters were used in the Italian patients. Focusing further on EPO resistance using ROC analysis, a dose of 7500 IU/treatment or 22,500 IU/wk identified 216 patients (5%) with low Hb as EPO resistant by this definition. Resistant individuals were younger, had lower albumin and phosphorus, lower enPCR, lower lymphocyte and higher neutrophil counts, and higher catheter use. The three most

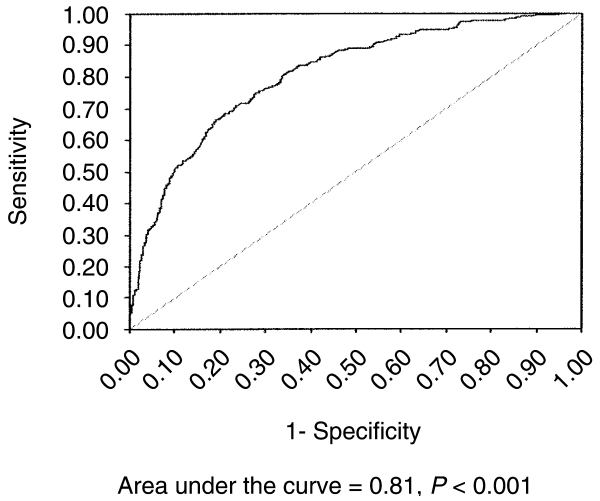

Fig. 5. Receiver operator characteristics (ROC) analysis to determine the optimal cutoff for predicting severe anemia (Hb <10 g/dL) based on erythropoeitin (EPO) dose.

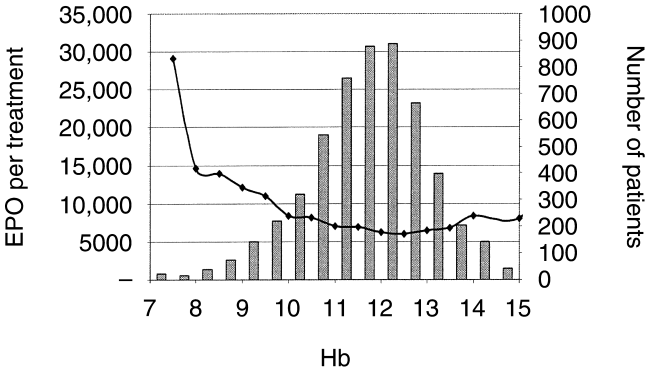

Fig. 6. Distribution of erythropoeitin (EPO) dose across the whole Hb range for U.S. Renal Research Institute patients.

significant factors to emerge from multivariate logistic regression were age, albumin, and enPCR.

The distribution of EPO dose across the whole Hb range for the RRI-United States patients is plotted in Figure 6. In this group of facilities, and consistent with the above, very high doses of EPO are being given to patients with Hb levels lower than 10 g/dL. What is somewhat surprising is the stability of dose for used in patients who have achieved Hb levels between 11 to 13.0 g/dL. Should the RRI data be representative of the United States dialysis population, it could be argued that there is little to support the current policy to restrict Hb level to less then 12.5 g/dL. In support of a relaxation is the evidence from a large observational study that patients show no deleterious effect of having Hb >12.5 g/dL. It seems likely that more attention to the patients with low Hb and high EPO requirement would impact more on the economics of the whole dialysis program. While patients with low albumin and low PCR will be present in any RRT program, the high catheter use in the United States is amenable to some correction through the creation of more natural arteriovenous fistulas for vascular access, as is seen in most European countries.

Inflammation from whatever source is of topical interest as regards the holistic management of patients on dialysis. The origin of inflammation in dialysis patients is clearly multifactorial. The use of ultrapure water, with minimal endotoxin content, has been associated with lower C-reactive protein (CRP) concentrations and decreased EPO requirements [5]. In this study, all patients in the RRI group were exposed to water containing less than 0.06 EU/mL, which would not have affected EPO resistance to any known extent. By contrast, infections are common, particularly with use of chronic tunneled jugular vein catheters, which were used in 29% of the RRI patients. Catheter usage was significantly greater in the low Hb groups.

The mechanism of impaired EPO response is likely to be through pro-inflammatory cytokines. CRP and cytokines were not measured routinely in this study but there was a correlation between lower lymphocyte counts and higher neutrophil counts in those patients who were EPO resistant. The value of their measurement as an indication of inflammation been recently reported by Reddan et al [6]. This group highlighted the close association of adverse cardiovascular outcomes and all-cause mortality with increases in neutrophils, and to a lesser extent reduction in lymphocytes. Gunnel et al [7] defined EPO resistance by the ratio of the weekly EPO dose to hematocrit (EPO/Hct). The best predictors of resistance to EPO were levels of CRP, but low transferrin levels were also predictive when albumin and CRP were excluded from analysis. As shown also in this study is the inhibitory effect of inflammation on erythopoeisis in a number of diseases, including AIDS; the anemia of rheumatoid arthritis can be overcome by large dose of EPO [8]. Both iron deficiency and lack of reutilization of iron from reticuloendothelid macrophages are reasons for EPO resistance. An increase in lactoferrin receptors, enabling them to internalize more iron, makes the latter less available. Recently, Ganz [9] has suggested that hepcidin, a 25-amino acid peptide made by hepatocytes, may be a major factor in regulating iron. Evidence from transgenic mice expressing mRNA for hepcidin suggests that it reduces iron absorption and iron release from macrophages. In inflammation, hepcidin production may increase substantially, so that it is possible that this substance plays an important role in EPO resistance.

REFERENCES

1. NKF-DOQI Work Group: NKF-DOQI clinical practice guidelines for the treatment of anemia of chronic renal failure. *Am J Kidney Dis* 30(Suppl 3):S192–S240, 1997

2. EBPG Expert Group on Renal Anemia: European best practice guidelines for the management of anemia in patients with chronic renal failure: *Nephrol Dial Transplant* 14(Suppl 5):1–50, 1999
3. Ansell D, Feest T (editors): *UK Renal Registry*, Bristol, UK, 2002
4. Young EW, Goodkin DA, Mapes DL, *et al*: The Dialysis Outcomes and Practice Patterns Study (DOPPS): An international hemodialysis study. *Kidney Int* 57(Suppl):S74–S81, 2000
5. Sitter T, Bergner A, Schiffl H: Dialysate related cytokine induced and response to recombinant human erythropoietin in haemodialysis patients. *Nephrol Dial Transplant* 15:1207–1211, 2000
6. Reddan DN, Klassen PS, Szczech LA, *et al*: White blood cells as a novel mortality predictor in hemodialysis patients. *Nephrol Dial Transplant* 18:1167–1173, 2003
7. Gunnell J, Yeun JY, Depner TA, Kaysen GA: Acute phase response predicts erthropoietin resistance in hemodialysis and peritoneal dialysis patients. *Am J Kidney Dis* 33(1):63–72, 1999
8. Trey JE, Kushner I: The acute phase response and the hematopoietic system: The role of cytokines. *Crit Rev Oncol Hematol* 21:1–18, 1995
9. Ganz T: Hepcidin, a key regulation of iron metabolism and mediator of anemia of inflammation. *Blood* March:27, 2003