

Dialysis Facility Ownership and Epoetin Dosing in Hemodialysis Patients: A Dialysis Provider's Perspective

Together with the other articles in this section, the following is a commentary on Thamer M, Zhang Y, Kaufman J, Cotter D, Dong F, Hernan MA: Dialysis facility ownership and epoetin dosing in patients receiving hemodialysis. *JAMA* 297:1667-1674, 2007

THE CHALLENGE OF ANALYZING HEMOGLOBIN LEVELS AND EPOETIN DOSES

“Lies, Damned Lies, and Statistics”

Attributed to Benjamin Disraeli and popularized by Mark Twain

The article by Thamer et al¹ and the accompanying editorial by Coyne² raise the question of whether the profit status of dialysis facilities is a principal factor influencing a higher hemoglobin level or higher erythropoietin dose. For the reasons outlined below, including flaws in the analysis of data and incomplete and biased interpretation of the results, we disagree with this assertion in the Thamer et al article; further, we take issue with the inference made in the Coyne editorial and argue that appropriate anemia treatment protocols in for-profit and not-for-profit dialysis facilities are essential to good patient care.

HOW DOES THIS STUDY COMPARE TO PRIOR STUDIES?

The only other publication addressing profit status, erythropoietin dosage, and hemoglobin outcomes is the 2006 US Renal Data System Annual Data Report,³ which presented similar data to the Thamer et al report. Relative to the target hemoglobin in these studies, there are 5 prospective randomized controlled trials involving hemoglobin outcomes in renal failure patients: 2 in chronic kidney disease patients and 3 in dialysis patients (Table 1).

Note that all these studies targeted hemoglobin values well above 12 g/dL (120 g/L). The

targeted hemoglobin value was achieved and maintained in 3 of the 5 studies. It was not achieved in the other 2 but was well above 12 g/dL (120 g/L). Therefore, there is no scientific evidence that a hemoglobin value of 12 g/dL (120 g/L) is a threshold level above which there is significant health risk in dialysis patients. In particular, there are no studies that demonstrate that the intermittent excursion of a hemoglobin value above 12 g/dL (120 g/L) is the same as maintaining a target of this level. This is relevant since it has been shown⁹ that physicians promptly respond and correct hemoglobin values when they exceed 12 g/dL (120 g/L). There are several observational studies¹⁰⁻¹³ in which patients with a range of hemoglobin values of 12 to 13 g/dL (120 to 130 g/L) have no greater mortality than those with the target range of 11 to 12 g/dL (110 to 120 g/L). The US Food and Drug Administration, Centers for Medicare and Medicaid Services, and the dialysis community should not conclude that facilities, whether for-profit or not-for-profit, are not properly caring for patients because hemoglobin values intermittently exceed 12 g/dL (120 g/L). One should not extrapolate conclusions reached in the chronic kidney disease population to patients on dialysis therapy since such therapy has a profound impact on these outcomes (particularly congestive heart failure). As to comparing anemia treatment outcomes in cancer patients to patients with end-stage renal disease, it should be obvious to experienced clinicians that these are extremely different populations.

The analysis and conclusion of the article by Thamer et al and the accompanying editorial by Coyne are limited by misrepresentation of operations in dialysis facilities and inappropriate statistical analyses. It is physicians, not nurses or managers, who prescribe treatment and determine appropriate outcomes, whether in for-profit or not-for-profit facilities. Physicians prescribe orders in response to a number of clinical factors in each individual patient, and commonly imple-

Address correspondence to J. Michael Lazarus, MD, or Raymond M. Hakim, MD, PhD, Fresenius Medical Care North America, 920 Winter St, Lexington, MA 02451. E-mail: Michael.Lazarus.MD@fmc-na.com, Raymond.HakimMD@fmc-na.com

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Table 1. Randomized Controlled Trials in Renal Patients

Study	N	Experimental Group			Control Group	
		Goal Hemoglobin (mg/dL)	Achieved and Maintained Mean Hemoglobin	Increased Risk of Death	Goal Hemoglobin	Achieved and Maintained Mean Hemoglobin
Predialysis Patients						
Drueke et al ⁴	603	13.5-15.0	13.5*	No	10.5-11.5	11.6
Singh et al ⁵	1432	13.5	12.6-13.0†	Yes	11.3	11.3
Dialysis Patients						
Besarab et al ⁶	1233	~14.0‡	~14.0‡	Yes	~10.0‡	~10.0‡
Foley et al ⁷	146	13.5-14.0	12.2-13.0§	No	9.5-10.0	10.4
Fururland et al ⁸	339	13.5-16.0	13.5 ± 1.5	No	9.0-12.0	11.4 ± 1.3

*Estimated from Figure 2. Actual values not provided.

†Actual value not provided. Mean increase in hemoglobin was 2.5 over baseline (10.1). From Figure 2A, mean hemoglobin maintenance value appears to be ~13 g/dL (130 g/L).

‡Value estimated from hematocrit of 42% (in experimental group) and 30% (in control group).

§Actual value not provided. Mean increase in hemoglobin was 1.8 over baseline (10.4). From Figure 2A, mean hemoglobin maintenance value appears to be ~13 g/dL (130 g/L).

ment these orders through algorithms or protocols. Thamer et al insinuated and Coyne has flatly portrayed dialysis facilities as allowing nursing staff and management staff to practice medicine. Neither seems to understand that in the practice of medicine, particularly in dialysis facilities, physician-derived algorithms or protocols are recognized and effective tools for delivering patient care and improving outcomes. Algorithms *are* physician orders and when properly prescribed, obviate any need for nursing decision-making in the frequency and/or dosing of erythropoietin. Nursing staff and facility management and company-employed physicians have no role in the development of these algorithm orders in Fresenius Medical Care North America (FMCNA) facilities. It is a gross distortion to suggest that dialysis providers (at least this dialysis provider) determine hemoglobin levels or the dose of erythropoietin for any patient.

Except for the very small percentage of dialysis facilities that are joint ventures with physicians, physicians derive no financial benefit from erythropoietin use or dosage. FMCNA Medical Directors are salaried for administrative duties and are motivated only to achieve a percentage of patients with hemoglobin values above 11 g/dL (110 g/L) in their facilities. Medical Directors write orders only for their own patients. Other attending physicians have no financial relationship with providers. Medical leadership of the company share in the bonus plan and stock

option plan for all executives, which are overseen by the Securities and Exchange Commission and are public record.

What then could account for the differences in hemoglobin levels and erythropoietin doses in different providers as reported by Thamer et al?

1. The authors hardly comment on the relationship between the lower end and the upper end of the hemoglobin distribution curve. Understanding that there is a relatively fixed Gaussian distribution curve with a large standard deviation for hemoglobin values in patients treated with erythropoietin,¹⁴ one must examine the percent of patients failing to meet the lower limit (11 g/dL [110 g/L]) as well as exceeding an upper limit (>12 g/dL [120 g/L]). While not-for-profit facilities have fewer patients above hemoglobin of 12 g/dL (120 g/L), they also had a greater percentage of patients (3% more) below 11 g/dL (110 g/L) than the for-profit facilities. In the single not-for-profit chain (chain 5), 6% more patients are below 11 g/dL (110 g/L) than in the for-profit chains. If the Centers for Medicare and Medicaid Services intend to minimize the percent of patients above a hemoglobin concentration of 12 g/dL (120 g/L), they must be prepared to allow a greater percentage of patients to be below 11 g/dL (110 g/L).

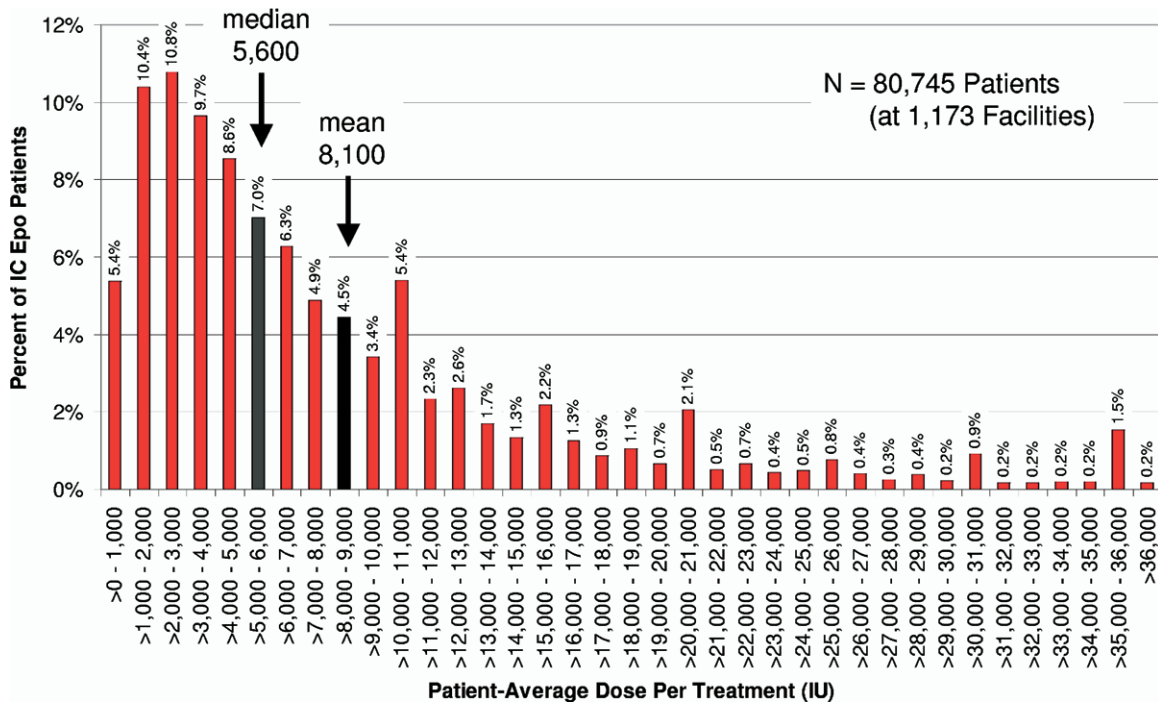


Figure 1. Distribution of epoetin dose per treatment (December 2006 in-center administrations at legacy Fresenius Medical Care facilities).

Multiple observational or retrospective studies indicate that patients who have hemoglobin values less than 11 g/dL (110 g/L) have higher hospitalization rates, higher mortality, and lower quality of life.

2. The analysis by Thamer et al reports the *mean* dose of erythropoietin per week by provider. This is an inappropriate analysis of erythropoietin utilization since the distribution of erythropoietin utilization is highly asymmetric, with a skew to the right (see Fig 1). With this asymmetric distribution, the median dose of erythropoietin is the more appropriate reference point. The median dose for FMCNA is approximately 5,600 units per treatment, whereas the mean dose is approximately 8,100 units per treatment (approximately 30% higher than the median dose). An appropriate statistical approach in such an asymmetric distribution should include more than a simple comparison of the mean. In the circumstance where the mean is not representative of the true central tendency in a population, as in the case of

a small portion of extremely high values, an appropriate statistical method may involve log transformation of the data in order to have a comparison that is less sensitive to extreme values or truncation of the data to exclude outliers that may not be uniformly represented in the populations being compared. We do not have the median erythropoietin dose for not-for-profit facilities, but suggest there will be a much smaller difference in the median values between for-profit and not-for-profit facilities than the means reported by Thamer et al.

3. The mean dose of erythropoietin in for-profit facilities, to the extent that it is a valid measurement, is strongly influenced by one provider (chain 2). Excluding data from chain 2 reveals a smaller difference in the mean, and we suspect little difference in the median dose of erythropoietin between for-profit and not-for-profit facilities.
4. It is important to study and understand the population of patients who require higher

doses of erythropoietin, and determine if there are differences between for-profit and not-for-profit providers. Several studies have consistently shown that, in general, African American patients on dialysis require higher erythropoietin doses to achieve target hemoglobin values. An analysis of the patients with the highest 1% erythropoietin dose requirement in FMCNA facilities indicates that 60% are African American; this is out of proportion with the number of African Americans in the facilities examined. It is noteworthy that there is a 6% lower prevalence of African Americans served by the not-for-profit facilities than by the for-profit facilities, which may account for some of the differences in erythropoietin dosing. This finding is not commented on by Thamer et al.

5. Other possible differences between for-profit and not-for-profit facilities and erythropoietin utilization could relate to differences in treatment of iron deficiency or route of erythropoietin administration: subcutaneous versus intravenous. There is no information about differences in the prescription of iron use and route of erythropoietin administration by physicians in for-profit and not-for-profit facilities, but there are no policies being promoted by this provider which would affect the use of erythropoietin.
6. The hemoglobin distribution curve in not-for-profit facilities is to the left of the hemoglobin distribution curve in for-profit facilities. In addition to the usual internal reporting requirements in their own continuous quality improvement programs and to End-Stage Renal Disease Networks, for-profit chains also report quality outcomes externally on a quarterly basis to financial institutions. Furthermore, large chains endeavor to avoid being identified in the Centers for Medicare and Medicaid Services Dialysis Facility Compare website as having facilities that fail to achieve the goal of 80% of patients with a hemoglobin value above 11 g/dL (110 g/L). For-profit chains are sensitive to these evaluations and have focused more intently on achieving the goal of having 80% of

patients with hemoglobin values of 11 g/dL (110 g/L). Physicians are encouraged to meet the target of 80% of patients achieving a hemoglobin value of 11 g/dL (110 g/L), but are not encouraged or rewarded to seek hemoglobin values higher than the 11 to 12 g/dL (110 to 120 g/L) hemoglobin target range nor higher epoetin dose utilization.

WHAT SHOULD LARGE DIALYSIS CHAINS DO?

We conclude that there appear to be multiple possible reasons for the hemoglobin findings of Thamer et al and the US Renal Data System in different categories of providers. We believe it is our responsibility to continue to advocate for a percentage (currently 80% as advocated by the National Kidney Foundation Kidney Dialysis Outcomes Quality Initiative and the Centers for Medicare and Medicaid Services) of patients to achieve a hemoglobin level of 11 g/dL (110 g/L). Attaining this target will obviously lead to a certain percentage of patients with hemoglobin values transiently greater than 12 g/dL (120 g/L). We must carefully distinguish between a targeted goal which may be occasionally and intermittently exceeded and an achieved and maintained hemoglobin level. In the absence of any evidence that dialysis patients who *transiently* exceed hemoglobin of 12 g/dL (120 g/L) suffer any harm, we believe that it is best for physicians to err on the side of reducing the percent of patients with hemoglobin less than 11 g/dL (110 g/L).

With the realization that, as the percentage of patients with hemoglobin greater than or equal to 11 g/dL (110 g/L) increases, there is inevitably a higher percentage of patients with hemoglobin greater than 12 g/dL (120 g/L), FMCNA developed a "high-end" anemia management program. This program identifies facilities with a high or atypical percentage of patients above 12.5 g/dL (125 g/L) and encourages physicians in those facilities to modify their prescriptions for erythropoietin. Also, FMCNA is the only company we are aware of that has instituted a mandatory (computer-driven) minimum 25% reduction in the erythropoietin dose when the hemoglobin values reaches 13 g/dL (130 g/L), a policy consistent with the Erythropoietin Monitoring Policy of the Centers for Medicare and Medicaid Ser-

vices. We believe that this is a safer approach than accepting a larger percentage of patients below 11 g/dL (110 g/L).

Finally, anemia management is appropriately determined on an individual patient basis by that patient's physician. Treatment algorithms or protocols or standing orders are appropriate tools for the delivery of good medical care in this particular setting. They allow for and set the expectation for a prompt time sensitive response by physicians. Treatment algorithms must be physician derived and should follow rules in which nursing decisions (eg, ranges of outcome) are avoided. We are confident that such algorithms are in place in FMCNA facilities.

**J. Michael Lazarus, MD
Raymond M. Hakim, MD, PhD**

Fresenius Medical Care North America

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ADDENDUM

Since submission of this editorial, the US House of Representatives has passed the Children's Health and Medicare Protection (CHAMP) Act, in which a Performance Standard for providers and facilities in the ESRD Program for 2008 is to achieve an average hematocrit of 33.0% or more in 92% of patients.¹⁵ According to our database, achieving a hematocrit above 33.0% (hemoglobin above 11 g/dL [110 g/L]) in 92% of patients will likely cause 69% of patients to transiently have a hematocrit above 36% (hemoglobin of 12 g/dL [120 g/L]) and 32.5% of patients to transiently exceed a hematocrit of 39% (hemoglobin of 13 g/dL [130 g/L]).

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