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ORIGINAL RESEARCH

Hemoglobin Concentration Variations Over Time in General Medical Inpatients

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BACKGROUND: A decrease in hemoglobin concentration [Hb] with no apparent cause is frequently observed in critically ill patients. Scarce information is available about this situation in general ward-admitted patients (GWAP).

OBJECTIVES: To describe [Hb] variation with no obvious cause in GWAP, and to estimate the prevalence and predictors of patients with [Hb] decreases $\geq$1.5 g/dL.

DESIGN, SETTING AND PATIENTS: Prospective, observational study in internal medicine GWAP, carried out at two teaching hospitals in Buenos Aires, Argentina. Patients with a history of, or admitted for diseases associated with decreases in [Hb], as well as those with length of stay less than three days, were excluded.

MEASUREMENTS: Upon hospitalization, complete personal and clinical data were recorded. Furthermore, Katz index, APACHE II acute physiology score (APS) and Charlson score were calculated. [Hb] and hematocrit (HCT) were also assessed during hospitalization.

RESULTS: A total of 338 patients were evaluated, 131 were included. A mean [Hb] decrease of 0.71 g/dL was observed between admission and discharge ($P < 0.001$; 95% CI, 0.47-0.97). Forty-five percent of the included patients had decreases in [Hb] $\geq$ 1.5 g/dL. This was associated with a higher APS, a higher [Hb] at admission, and a discharge diagnosis of infectious or gastrointestinal disease. No bleeding episodes were observed.

CONCLUSIONS: An [Hb] decrease was frequently observed during GWAP hospitalization with no evident blood loss. Even though this decrease has multiple causes, the severity of the acute illness seems to play a major role. ***Journal of Hospital Medicine*** **2010;5:283–288.** © *2010 Society of Hospital Medicine.*

KEYWORDS: anemia, critical illness, hemoglobin, iatrogenic anemia, internal medicine inpatients.

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Studies of the red blood cell mass performed in hospitalized patients were first done in the early 1970s.[1] Thereafter, a decrease in the hemoglobin concentration ([Hb]) and its potential causes have been further reported, especially in critically ill patients.[2–5] The decrease in [Hb] can occur as a result of blood draws for diagnostic testing; blood loss associated with invasive procedures and bleeding; occult gastrointestinal bleeding; hemolysis; shortening of red cell survival; iron, folic acid or cobalamine deficiencies; renal, liver or endocrine failure; hemodilution associated with fluid therapy; and the so-called anemia of inflammation (AI).[6–8] The latter would be a consequence of a blunted response of the bone marrow due to several factors such as inadequate secretion of erythropoietin, inhibition of the proliferation and differentiation of the erythroid precursors of the bone marrow and an hepcidin-mediated functional iron deficiency.[8–10]

As mentioned, most studies were done in critically ill patients and scarce information is available about general ward admitted patients (GWAP) with less severe illnesses. In this scenario, some of the proposed mechanisms may have a less clear role. It is widely accepted that [Hb] may decrease without overt bleeding in GWAP. However, given the lack of information on this matter, laboratory controls and invasive procedures are undertaken to determine its potential causes.

The purpose of the present study is to describe [Hb] variation over time in nonbleeding GWAP, to estimate the proportion of patients with [Hb] decreases $\geq$1.5 g/dL, and to evaluate possible related variables.

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TABLE 1. Demographic Data of 131 Patients

	n	%	Mean ± (SD)	Median	Min/Max
Age, years			71.9 (17.4)	77	18/97
18-40	11	8.4			
41-60	16	12.2			
61-80	52	39.7			
>80	52	39.7			
Gender					
Female	75	57.2			
Lenght of stay (days)			7 (4.8)	6	3/28
APS			4.9 (4.2)	4	0/22
0-4	71	54.2			
5-8	36	27.5			
>8	24	18.3			
ADL			4.5 (2.3)	6	0/6
0-2	33	25.2			
3-5	11	8.4			
6	87	66.4			
CHARLSON			2.2 (2.3)	2	0/11
0	32	24.4			
1	32	24.4			
2	22	16.8			
3	18	13.7			
>3	27	20.6			
Readmissions	28	21.4			
PWSBL	14	10.7			
Anemia at admission	63	48.1			
[Hb] at admission			12.5 (1.7)	12.5	8.6/17
[Hb] at admission males			12.8 (1.9)	12.6	8.7/17
[Hb] at admission females			12.3(1.5)	12.3	8.6/15.5

Abbreviations: ADL, Katz daily activity index; APS, APACHE II acute physiology score; CHARLSON, Charlson comorbidity score; [Hb], Hemoglobin concentration; PWSBL, procedure without significant blood loss; SD, Standard deviation.

Materials and Methods

A 16-week (September 2004-January 2005) prospective observational study was conducted in Internal Medicine GWAP at 2 Buenos Aires teaching hospitals.

All consecutive patients older than 16 years were evaluated. Patients admitted for the following reasons were excluded: bleeding, trauma, surgery, invasive procedures associated with blood loss (biopsies, biliary drainage, endovascular therapeutic procedures, and chest tubes), blood transfusions, anemia, chemotherapy, and acute renal failure.

Patients with a bleeding history, chemotherapy or radiation therapy within two months prior to admission, patients on dialysis and patients with current oncologic or hematologic disease were excluded, as well as those with length of stay less than 3 days, or with less than 2 [Hb] or hematocrit (HCT) measurements.

Patients were followed until discharge, death or transfer to a critical care unit. Patients were withdrawn from the study if they presented with bleeding or hemolysis, underwent red blood cell transfusion or therapy affecting hemoglobin levels (iron, chemotherapy or erythropoietin) or if either a surgical or invasive procedure associated with blood loss was performed.

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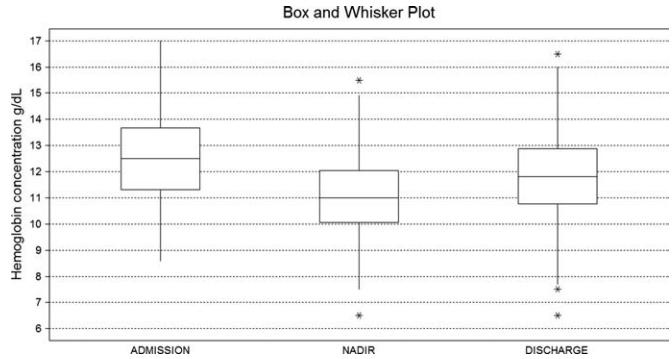

FIGURE 1. Box and whisker plot of changes in hemoglobin concentration during hospital stay. The line within the box denotes the median and the box spans the interquartile range. Whiskers extend from the 10th to 90th percentiles.

Data were collected from patients' medical records and additional information was obtained from treating physicians and patients by the authors (AL, NC, SM, AN, MH). Standardized case report forms were completed during the hospitalization including: age, sex, admissions in the previous 3 months (readmissions) and whether or not the patient lived in a nursing home. Patients were categorized according to discharge diagnosis as reported by Nguyen et al.[4] with modifications related to our general ward population. Upon admission Katz daily activity index (ADL),[11,12] APACHE II acute physiology score (APS),[13,14] and Charlson comorbidity score (Charlson)[15,16] were assessed. In all cases the [Hb] and HCT values were registered on admission and on days 3, 6, 10 and prior to discharge as well as any other determination required by the treating physician. Anemia was defined as [Hb] $\leq$ 13 g/dL for men and $\leq$ 12 g/dL for women.[17] Based on previous reports a $\geq$1.5 g/dL decrease in [Hb] and of $\geq$4.5 points in HCT compared to admission values were considered a "significant fall".[1,4] Acute renal failure was defined as an increase in creatinine level $\geq$0.5 mg/dL or a 50% increase from baseline.[18,19]

Every procedure without significant blood loss (PWSBL) such as venous catheter placement, thoracentesis, lumbar punction, paracentesis, skin biopsy, arthrocentesis, and diagnostic angiogram was also recorded. The study was approved by the Hospital's ethical committee.

Data analysis and processing were performed with Excel 2000 and Stata version 8.0 (Stata Corp; USA). For continuous variables, results were expressed by the mean value ± its standard deviation (SD), and compared with Student's *t*-test. The chi-square test was used to compare categorical variables. A survival curve was developed with the Kaplan-Meier method to analyze the time to a "significant fall" in [Hb]. Finally, Cox proportional hazard modeling was performed to assess the association between a "significant fall" in [Hb] and other variables. We accepted $P < 0{,}05$ as significant.

Results

A total of 338 patients were admitted to the Internal Medicine Inpatient Services in the study period. Thirty-nine

TABLE 2. Proportion of Patients With a Nadir Fall in the [Hb] for Different Cutoff Points

[Hb] fall (g/dL)	≥0.5	≥1	≥1.5	≥2	≥2.5	≥3	≥3.5	≥4	≥4.5
% of patients	80.9	60.3	45.0	28.2	17.6	9.9	5.3	3.8	2.3

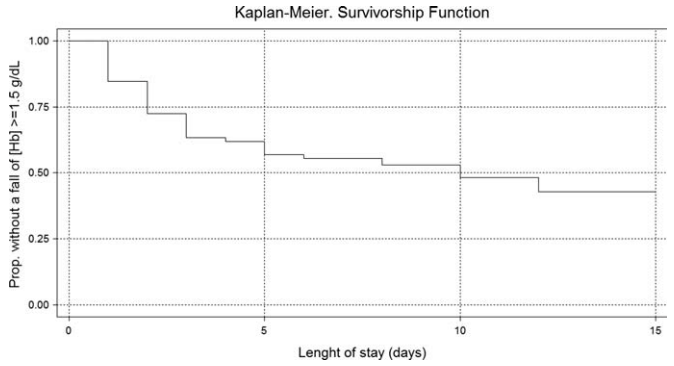

FIGURE 2. Kaplan Meier plot showing the proportion of patient without a fall in the hemoglobin concentration ≥1.5 g/dL.

percent (131) of these patients were included. Exclusion criteria were: diagnosis at admission (n = 95, 45.9%), past medical history (n = 56, 27%) and length of stay less than 3 days, or less than 2 determinations of [Hb] or HCT (n = 56, 27%). Data collection was discontinued for the following reasons: discharge (81.7%), death (6.9%), surgery or procedures associated with blood loss (5.3%), transfer to a critical care unit (3%), transfusions (2.3%), and chemotherapy (0.8%). The baseline characteristics of the study patients are shown in Table 1.

Diagnoses at discharge were divided into the following categories: infections (25.2%), electrolyte disturbances (7.6%), cardiac diseases (9.9%), neurologic (19.1%), respiratory (16.8%), gastrointestinal (10.7%), and other diagnosis (10.7%).

No evidence of bleeding was found in the included patients. Bleeding was only observed in 4 of the initially evaluated patients who were excluded since they failed to meet the required number of [Hb] determinations before bleeding.

A mean decrease in [Hb] of 0.71 g/dL was found between admission and discharge day ($P < 0.001$; 95% CI, 0.47-0.97). Mean nadir [Hb] was 1.45 g/dL lower than admission [Hb] ($P < 0.001$; 95% CI, 1.24-1.67). Mean nadir day occurred between hospitalization days 3 and 4. Mean [Hb] at discharge was 11.8 ± 1.8 g/dL. This value is higher than the mean concentration at nadir (0.74 g/dL $P < 0.001$; 95% CI, 0.60-0.97) (Figure 1).

Table 2 shows the rate of patients with a decrease in the [Hb] for different cutoff levels. Forty-five percent of the study population (59 patients) had a "significant fall" in [Hb] during hospitalization. This was observed on day 2 in 50% of the patients. Likewise, a "significant fall" in HCT value was found in 42.7% of patients. If [Hb] decrease during hospitalization is analyzed as a proportion of [Hb] at admission, 52.7% of patients had a 10% or greater [Hb] decrease during their hospital stay.

TABLE 3. Univariate Analysis

	Patients with a "significant fall"	Patients without a "significant fall"	*P* Value
n	59 (45%)	72 (55%)	
Age, years	73.15 (18.7)	70.83 (16.2)	0.448
Gender, female	32 (54.2%)	43 (59.7%)	0.527
Length of stay (days)	8.30 (5.6)	5.91 (3.7)	<0.007
APS	6.13 (4.5)	3.97 (3.7)	<0.004
ADL	4.33 (2.5)	4.68 (2.1)	0.410
CHARLSON	2.03 (1.8)	2.37 (2.5)	0.382
Nurse home residents	4 (6.8%)	3 (4.2%)	0.700
Readmissions	11 (18.6%)	17 (23.6%)	0.490
PWSBL	6 (10.2%)	8 (11.1%)	0.862
Anemia at admission	20 (33.9%)	43 (59.7%)	<0.004
[Hb] at admission	13.09 (1.7)	12.01 (1.5)	<0.001
Diagnosis at discharge			
Infectious	20 (33.9%)	13 (18.1%)	<0.05
Respiratory	8 (13.6%)	14 (19.4%)	0.370
Neurologic	9 (15.2%)	16 (22.2%)	0.312
Gastrointestinal	11 (18.6%)	3 (4.2%)	<0.01
Cardiac	2 (3.4%)	11(15.3%)	<0.05
Electrolyte disturbances	6 (10.2%)	4 (5.6%)	0.512
Others	3 (5.1%)	11 (15.3%)	0.087

NOTE: Continuous variables are expressed by the mean value and its standard deviation (SD). Categorical variables are expressed by the number of cases and the percentage within its category.
Abbreviations: ADL, Katz daily activity index; APS, APACHE II acute physiology score; CHARLSON, Charlson comorbidity score; [Hb], Hemoglobin concentration; PWSBL, procedure without significant blood loss.

Using Kaplan-Meier analysis, the estimated proportion showing no "significant fall" of [Hb] was 0.63 (95% CI, 0.55-0.71) on day 3 and 0.48 (95% CI, 0.29-0.67) on day 10. By day 15, only 3.8% of the initially included patients were still hospitalized and showed no decrease in [Hb] ≥ 1.5 g/dl. These patients maintained their [Hb] stable for the rest of the follow up period (Figure 2).

In the univariate analysis, comparing patients that experienced a decrease in [Hb] ≥ 1.5 g/dL with those who did not, significant differences were only found in the following variables: length of stay, APS, anemia at admission, [Hb] at admission, and infectious, gastrointestinal or cardiac diseases at discharge diagnosis (Table 3).

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TABLE 4. Cox Proportional Hazard Model

Variable	HRR	*P* Value	95% CI
APS	1.07	0.007	1.02-1.12
ADL	1.11	0.132	0.97-1.27
Charlson	0.88	0.121	0.75-1.03
Nurse home resident	1.52	0.361	0.62-3.72
PWSBL	0.67	0.390	0.27-1.66
Readmission	1.14	0.710	0.57-2.29
Female sex	0.98	0.944	0.57-1.69
Age	1.39	0.098	0.94-2.07
[Hb] at admission	1.27	0.005	1.07-1.51
Diagnosis at discharge			
Infectious	2.70	0.015	1.21-6.05
Neurologic	1.42	0.457	0.57-3.55
Gastrointestinal	3.74	0.002	1.62-8.64
Cardiac	0.41	0.289	0.08-2.12
Electrolyte dist.	2.08	0.176	0.72-6.05
Others	0.95	0.946	0.24-3.81

Abbreviations: ADL, Katz daily activity index; APS, APACHE II acute physiology score; CHARLSON, Charlson comorbidity score; CI, confidence interval; electrolyte dist, electrolyte disturbances; [Hb], hemoglobin concentration; HRR, hazards relative ratio; PWSBL, procedure without significant blood loss.

In the Cox proportional hazard model adjusting for the variables shown in Table 4, a significant independent direct association was found between a "significant fall" in [Hb] during hospital stay and APS, [Hb] at admission, and either diagnosis of infectious or gastrointestinal disease at discharge. Similar results were found if a "significant fall" was redefined as a 12% decrease in [Hb] or as a 4.5 point decrease in HCT from baseline.

Discussion

This study describes the variation of [Hb] and HCT values in GWAP without bleeding or other obvious medical conditions associated with a decrease in the red blood cell mass. As previously described,[4,20,21] we found that [Hb] decreases during hospital stay are frequently observed. The mean [Hb] fall from admission was 1.45 g/dL, and was mainly recorded between hospitalization days 3 and 4. In approximately half of the study population, a $\geq$1.5 g/dL decrease in [Hb] was observed. In the survival analysis, 40% and 55% of patients are expected to present such a fall on day 4 and 12 respectively. In accordance with prior reports[4,21] a greater decrease in [Hb] occurred in the first days of hospitalization, and a high proportion of patients were already anemic at the time of admission.

The following variables were associated with a decrease in the [Hb] during hospitalization: higher APS score, higher [Hb] at admission, and diagnosis of infectious or gastrointestinal disease at discharge. Even though several mechanisms seem to contribute to the decrease in [Hb] during hospitalization our data suggest that 1 of these factors seems to be the severity of the disease, as previously proposed by Nguyen et al.[4] This observation is supported by the association found in our study between [Hb] decrease and APS. No association was found with Charlson, ADL, and being a nursing home resident. These variables, which have not been previously analyzed, seem to indicate that patients with chronic illnesses are not more likely to have decreases in [Hb] during hospitalization.

Patients with higher [Hb] at admission had a greater [Hb] decrease during their hospital stay. This finding could suggest that the mechanism related to this decrease had less effect on patients with lower [Hb]. This is similar to that observed in the anemia of chronic diseases where [Hb] does not usually fall to extreme values. Our analysis reveals a greater decrease during the first days of hospitalization. Given the high rate of patients anemic at admission, it is possible that the decrease in [Hb] had begun prior to admission.

Previous papers describe a low prevalence of cyanocobalamine (2%), folic acid (2%), and iron (9%) deficiency in patients admitted to critical care units.[3] In these patients an inadequate bone marrow response has been proposed as a mechanism for [Hb] decrease, a phenomenon that has been called AI or anemia of critical illness.[8,22–28] Inflammatory response associated with acute disease causes this hypoproliferative anemia through 3 different pathways: relative erythropoietin deficit, a direct inhibition of the erythropoiesis in the bone marrow through different mediators (ie, interleukin [IL]-1, IL-6, tumor necrosis factor [TNF]α) and a functional iron deficit. This relative iron deficiency is produced mainly by the IL-6 induced overexpression of the hepcidin gene in hepatocytes. Hepcidin causes impaired intestinal iron absorption and an inadequate delivery of iron from the iron-recycling macrophages to the erythroid precursors in the bone marrow.[8,9]

AI could explain some of our findings, such as the greater decrease observed in the first hospital days when inflamatory mediators levels are expected to be higher. The association between APS and infectious disease diagnosis and a greater [Hb] decrease may also be explained by this mechanism. Nonetheless, the daily bone marrow production of red blood cells is small compared with the circulating red mass cell and therefore it is necessary to have a better explanation on how AI could be associated with this rapid decrease in the [Hb]. Rice et al.[30,31] have explored some mechanisms leading to a rapid decrease in the red mass cell related to acute variations in erytropoietin level. A role of this mechanism and other could be hypothesized.[29]

Overt bleeding was not found in our study population and procedures without significant blood loss (PWSBL) were infrequent, therefore it is unlikely that they could have had an impact on the decrease of [Hb]. The influence of other variables, such as blood volume drawn for diagnostic testing and occult blood losses (especially from the gastrointestinal tract) was not investigated. Parenteral hydration and hemodilution neither were evaluated in our study nor were extensively described in the literature. We think this last

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mentioned mechanism plays a role in the large [Hb] decrease during the first days of hospitalization. However a lack of association was mentioned in the only study that evaluated this issue in critically ill patients. Intravascular hemolysis has been cited as an infrequent event in these patients.[2,4]

Only patients without a clear explanation for their [Hb] decrease were included because they represent a matter of concern for hospitalists and other treating physicians. Therefore 60% of the initially evaluated patients were excluded, since they were admitted for conditions likely to cause a decrease in [Hb]. Nevertheless, it seems likely that the mechanisms involved in the included patients may play a role in those with an obvious cause for [Hb] variation as well. Accordingly, the decrease of [Hb] expected in patients admitted with disorders known to cause a decrease in the red blood cell mass would be greater than the 1 observed in our study population.

This [Hb] drop during hospitalization may be clinically relevant in a number of ways: it could cause the attending physicians to order costly and invasive studies, it could have prognostic value as it occurs in patients admitted with myocardial infarction, and it could trigger an acute coronary syndrome.[20] We observed an association between [Hb] drop and a higher APS in our patients. This score has been validated as a prognostic factor in previous studies. However, it is not possible to conclude that this [Hb] drop is associated with a worse prognosis.

Our study had several limitations. The sample's heterogeneity inherent to our general ward population could have altered our results and their generalization. To overcome this bias we used a categorization system based on discharge diagnosis. However, this particular system has several limitations. The small sample size and the absence of follow up data after discharge limited our capacity to detect any prognostic significance of [Hb] decrease. In the present study, the total decrease of [Hb] may have been underestimated because the onset of the acute illness precedes hospital admission by a variable time. Finally, a relatively small sample size limited our ability to detect other possible significant predictors of [Hb] decrease. However, this study was not designed to assess the mechanisms associated with the decrease of [Hb], but rather to establish its occurrence, measure it and explore related variables.

These results may be useful for further studies to evaluate [Hb] variation in admitted patients and its relation to other variables, such as bone marrow production, oxygen use, erythrocyte survival, nutritional deficiencies, and erythropoietin and inflammatory mediators levels.

In conclusion, our general medical inpatients had a mean 1.45 g/dL [Hb] decrease during hospitalization, which was greater in the first days of hospitalization, even though an evident cause was not present. These findings would help attending physicians in general wards make a rational and efficient approach when dealing with patients' decrease in [Hb].

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