ORIGINAL RESEARCH

Hospital-Acquired Anemia: Prevalence, Outcomes, and Healthcare Implications

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BACKGROUND: Evidence suggests that patients with normal hemoglobin (Hgb) levels on hospital admission who subsequently develop hospital-acquired anemia (HAA) may be at risk for adverse outcomes. Our objectives were to (1) determine the prevalence of HAA and (2) examine whether HAA is associated with increased mortality, length of stay (LOS), and total hospital charges.

METHODS: The population consisted of 417,301 adult hospitalizations from January 1, 2009 to August 31, 2011, in an academic medical center and 9 community hospitals. Patients with anemia on admission, and hospitals in the health system without available laboratory data were excluded; 188,447 hospitalizations were included in the analysis. Demographics, comorbidities, and outcomes were retrieved from administrative data; Hgb values were taken from the electronic medical record. Regression modeling was used to examine the association between demographics, comorbidity, hospitalization type, and HAA variables (mild: Hgb >11 and <12 g/dL for women, and >11 and <13 g/dL for men; moderate: Hgb 9.1 to \leq 11.0 g/dL;

Anemia is associated with poor quality of life and increased risk for death and hospitalization in population-based and cohort investigations.^{1–7} Evidence suggests that patients with normal hemoglobin (Hgb) values on hospital admission who subsequently develop hospital-acquired anemia (HAA) have increased morbidity and mortality compared with those who do not.^{8,9} HAA is multifaceted and may occur as a result of processes of care during hospitalization, such as hemodilution from intravenous fluid administration, procedural blood loss and phlebotomy, and impaired erythropoiesis associated with critical illness.^{8,9} Moreover, correcting anemia by red blood cell transfusion also carries risk.^{10–13}

Received: March 11, 2013; Revised: May 17, 2013; Accepted: May 21, 2013 2013 Society of Hospital Medicine DOI 10.1002/jhm.2061 Published online in Wiley Online Library (Wileyonlinelibrary.com). severe: Hgb $\leq\!\!9.0$ g/dL) on mortality, LOS, and hospital charges.

RESULTS: Among 188,447 hospitalizations, 139,807 patients (74%) developed HAA: mild, 40,828 (29%); moderate, 57,184 (41%); and severe, 41,795 (30%). Risk-adjusted odds ratios and 95% confidence intervals for in-hospital mortality with HAA were: mild, 1.0 (0.88–1.17; P = 0.8); moderate, 1.51 (1.33–1.71, P < 0.001); and severe, 3.28 (2.90–3.72, P < 0.001). Risk-adjusted relative mean LOS and hospital charges relative to no HAA were higher with HAA: LOS: mild, 1.08 (1.08–1.10, P < 0.001); moderate, 1.28 (1.26–1.29, P < 0.001); severe, 1.88 (1.86–1.89, P < 0.001). Hospital charges: mild, 1.06 (1.06–1.07, P < 0.001); moderate, 1.18 (1.17–1.19, P < 0.001); severe, 1.80 (1.79–1.82, P < 0.001).

CONCLUSIONS: HAA is common and associated with increased mortality and resource utilization. Factors related to its development necessitate further study. *Journal of Hospital Medicine* 2013;8:506–512. © 2013 Society of Hospital Medicine

Our primary objective was to examine the prevalence of HAA in a population of medical and surgical patients admitted to a large quaternary referral health system. Our secondary objectives were to examine whether HAA is associated with increased mortality, length of stay (LOS), and total hospital charges compared to patients without HAA.

METHODS

Patient Population and Data Sources

The patient population consisted of 417,301 hospitalizations in adult patients (\geq 18 years of age) who were admitted to the Cleveland Clinic Health System from January 2009 to September 2011. Data for these hospitalizations came from 2 sources. Patient demographics, baseline comorbidities, and outcomes were extracted from the University HealthSystem Consortium's (UHC) clinical database/resource manager. UHC is an alliance of 116 US academic medical centers and their 272 affiliated hospitals, representing more than 90% of the nation's nonprofit academic medical centers. These data had originally been retrieved from our hospitals' administrative data systems, normalized according to UHC standardized data specifications,

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Additional Supporting Information may be found in the online version of this article.

and submitted for inclusion in the UHC repository. Data quality was assessed using standardized error checking and data completeness algorithms and was required to meet established minimum thresholds to be included in the UHC repository.

The second source of data was measured Hgb values retrieved from the hospitals' electronic medical record from complete blood count testing. Present-onadmission (POA) anemia was defined by an International Classification of Diseases, 9th Revision, Clinical Modification diagnosis code of anemia with a positive POA indicator; these patients were excluded from the analysis (Figure 1). Patients without available Hgb values and those with Hgb data dated 3 days or more after discharge date were also excluded. In addition, 2 hospitals within the health system did not have electronically available laboratory data and therefore were excluded from the analysis as well. The final dataset consisted of 188,447 patient hospitalizations. The institutional review board approved this investigation, with individual patient consent waived.

Anemia

The World Health Organization (WHO) defines anemia as a Hgb value l < 12 g/dL in women and < 13g/dL in men. HAA was defined as a nadir Hgb value during the course of hospitalization meeting WHO criteria. We further grouped Hgb by degree into no anemia, mild anemia (Hgb >11 and < 12 g/dL in women, >11 and < 13 g/dL in men), moderate anemia (Hgb >9 and ≤ 11 g/dL), and severe anemia (Hgb ≤ 9 g/dL).

Outcomes

Outcomes were all-cause in-hospital mortality, total hospital LOS, and total hospital charges.

Data Analysis

For risk adjustment, we used methods developed by Elixhauser and colleagues¹⁴ for use with in-patient administrative databases. These included a comprehensive set of comorbidity indicators, used to control for patients' underlying conditions in models of

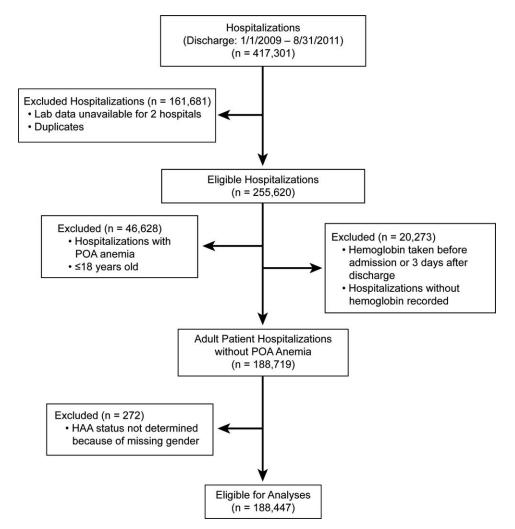


FIG. 1. Consort-style diagram of hospitalizations. Abbreviations: HAA, hospital-acquired anemia; POA, present on admission.

TABLE 1.	Patient	Characteristics and	Comorbidities	Stratified by	y Hospital-	Acquired	Anemia Groups

	Hospital-Acquired Anemia Group							
Characteristic	No Anemia, n = 48,640	Mild, n = 40,828	Moderate, n = 57,184	Severe, n = 41,795	Р			
Age at admission, y	55 ± 18	58 ± 18	58 ± 19	61 ± 17	< 0.000			
Female	25,123 (52)	17,938 (44)	35,858 (63)	23,533 (56)	< 0.000			
Race/ethnicity					< 0.000			
White	39,100 (80)	32,610 (80)	45,977 (80)	33,810 (81)				
Black	7580 (16)	6607 (16)	8946 (16)	6204 (15)				
Other	1960 (4.0)	1611 (3.9)	2261 (4.0)	1781 (4.3)				
Hospitalization type	× 7			· · · ·	< 0.000			
Surgery	9681 (20)	14,076 (34)	26,100 (46)	27,865 (67)				
Medicine	38,958 (80)	26,750 (66)	31,081 (54)	13,922 (33)				
Hypertension	25,591 (53)	22,218 (54)	29,963 (52)	24,257 (58)	< 0.000			
Heart failure	2811 (5.8)	3182 (7.8)	5086 (8.9)	4278 (10)	< 0.000			
Valvular disease	1201 (2.5)	1259 (3.1)	2126 (3.7)	1890 (4.5)	< 0.000			
Pulmonary circulation disease	667 (1.4)	730 (1.8)	1221 (2.1)	1484 (3.6)	< 0.000			
Peripheral arterial disease	2417 (5.0)	2728 (6.7)	4187 (7.3)	4508 (11)	< 0.000			
Paralysis	1216 (2.5)	1175 (2.9)	1568 (2.7)	1305 (3.1)	< 0.000			
Other neurologic disorders	3013 (6.2)	2780 (6.8)	3599 (6.3)	2829 (6.8)	< 0.000			
Chronic obstructive pulmonary disease	9225 (19)	7885 (19)	10,960 (19)	8057 (19)	0.000			
Diabetes without chronic complications	8306 (17)	7733 (19)	10,417 (18)	7911 (19)	< 0.000			
Diabetes with chronic complications	1547 (3.2)	1922 (4.7)	2989 (5.2)	2779 (6.6)	< 0.000			
Hypothyroidism	5008 (10)	4258 (10)	6938 (12)	5567 (13)	< 0.000			
Renal failure	2006 (4.1)	3278 (8.0)	5787 (10)	5954 (14)	< 0.000			
Liver disease	1394 (2.9)	1341 (3.3)	1788 (3.1)	2013 (4.8)	< 0.000			
Peptic ulcer disease, excluding bleeding	5 (0.01)	9 (0.022)	15 (0.026)	30 (0.072)	< 0.000			
Acquired immune deficiency syndrome	49 (0.10)	74 (0.18)	79 (0.14)	56 (0.13)	0.000			
Lymphoma	182 (0.37)	310 (0.76)	624 (1.1)	718 (1.7)	< 0.000			
Metastatic cancer	489 (1.0)	789 (1.9)	1889 (3.3)	1993 (4.8)	< 0.000			
Solid tumor without metastasis	499 (1.0)	760 (1.9)	1297 (2.3)	1123 (2.7)	< 0.000			
Rheumatoid arthritis/collagen vascular disease	1250 (2.6)	1260 (3.1)	2214 (3.9)	1729 (4.1)	< 0.000			
Coagulopathy	1096 (2.3)	1402 (3.4)	2517 (4.4)	6214 (15)	< 0.000			
Obesitv	7404 (15)	5177 (13)	7112 (12)	5279 (13)	< 0.000			
Weight loss	972 (2.0)	1240 (3.0)	2746 (4.8)	5841 (14)	< 0.000			
Fluid and electrolyte disorders	7262 (15)	7501 (18)	12,828 (22)	17,201 (41)	< 0.000			
Alcohol abuse	3312 (6.8)	1977 (4.8)	1699 (3.0)	1319 (3.2)	< 0.000			
Drug abuse	3357 (6.9)	1554 (3.8)	1197 (2.1)	657 (1.6)	< 0.000			
Psychoses	3479 (7.2)	2345 (5.7)	2544 (4.4)	1727 (4.1)	<0.000			
Depression	5999 (12)	4662 (11)	2044 (4.4) 6605 (12)	4895 (12)	< 0.000			

outcomes. Among the 30 variables defined by Elixhauser and colleagues, we excluded the 2 administrative anemia codes because this was our variable of interest (Table 1). For all models, demographics, medical conditions, and hospitalization type (medical vs surgical) were included as covariables in addition to the anemia groupings (no HAA and mild, moderate, and severe HAA).

Logistic regression was used to assess the association of HAA with in-hospital mortality, and linear regression to assess the association of HAA with hospital LOS and total hospital charges. LOS and total charges were logarithmically transformed because of rightskewed distributions. The exponential of the resulting regression coefficients quantifies the relative change in LOS or total charges compared to patients without HAA. Unless otherwise specified, a *P* value of ≤ 0.05 was considered statistically significant. The Bonferroni method was used to adjust for multiple comparisons.

Our primary analysis excluded patients with anemia at the time of hospitalization based on

administratively determined POA anemia positive indicator coding. We also performed a sensitivity analysis to exclude patients with anemia based on the first Hgb values determined by laboratory testing.

All analyses were performed using SAS version 9.2 (SAS Inc., Cary, NC) and R version 2.13 (www. r-project.org).

RESULTS

Prevalence of HAA

Among the 188,447 hospitalizations, 139,807 patients (74%) developed HAA and 48,640 (26%) did not. Of the 74%, 40,828 developed mild, 57,184 moderate, and 41,795 severe HAA (Figure 2). Patients who developed HAA were older than those who did not and had more comorbidities, including hypertension, heart failure, peripheral arterial disease, and renal and liver disease. They were hospitalized more commonly for surgical intervention than were those who did not develop HAA (Table 1). Time-related patterns for developing HAA, however, showed that it developed

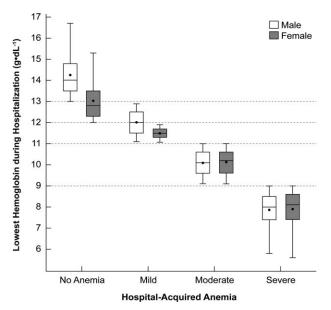


FIG. 2. Lowest hemoglobin during hospitalization stratified by gender and hospital-acquired anemia groups. Lower and upper ends of boxes represent 25th and 75th percentiles, center lines and dots within boxes are median and mean, respectively, and vertical lines extending above and below boxes are minimum and maximum of the data.

earlier in men and more frequently with medical versus surgical hospitalization (Figure 3).

Hospital Mortality and HAA

Unadjusted mortality progressively increased with increasing degree of HAA: no HAA, 0.78% (n = 378); mild HAA, 0.99% (n = 405); moderate HAA, 1.5% (n = 881); and severe HAA, 4.6% (n = 1936) (P < 0.001) (Figure 4A). Patients with mild HAA did not have higher risk-adjusted mortality than those not having HAA (odds ratio: 1.02, 95% confidence interval [CI]: 0.88-1.17). However, as HAA increased to moderate and severe, risk of hospital mortality increased in a dose-dependent manner compared with patients not developing HAA: moderate HAA, 1.51 (95% CI: 1.33-1.71, P < 0.001) and severe HAA, 3.28 (95% CI: 2.90-3.72, P < 0.001) (Figure 5A) (see Supporting Information, Supplement A, in the online version of this article).

Resource Utilization and HAA Length of Hospital Stay

Unadjusted median (25th, 75th percentiles) LOS was progressively higher in patients who developed HAA: no HAA, 3 days (2, 4); mild HAA, 3 days (2, 5); moderate HAA, 4 days (2, 6); and severe HAA, 7 days (4, 12) (P < 0.001) (Figure 4B). Mild HAA was associated with a mean relative increase of 1.09 (95% CI: 1.08-1.10, P < 0.001); moderate HAA, 1.28 (95% CI: 1.26-1.29, P < 0.001); and severe HAA, 1.88 (95% CI: 1.86-1.89, P < 0.001). For example, if expected LOS was 4 days for a patient with no HAA, then for a patient with severe anemia, it would be 7.52 (a 1.88-fold increase) when all comorbidities

were the same (Figure 5B) (see Supporting Information, Supplement A, in the online version of this article).

Total Hospital Charges

Unadjusted hospital charges became progressively higher as degree of HAA increased (P < 0.001) (Figure 4C). The mean relative increase was 1.06 (95% CI: 1.06-1.07, P < 0.001) for mild HAA compared with no HAA, 1.18 (95% CI: 1.17-1.19, P < 0.001) for moderate HAA, and 1.80 (95% CI: 1.79-1.82, P < 0.001) for severe HAA. For example, if the expected total charge was \$30,000 for a patient with no HAA, then for a patient with severe anemia, it would be \$54,000 (a 1.80-fold increase) when all comorbidities were the same (Figure 5C) (see Supporting Information, Supplement A, in the online version of this article).

Sensitivity Analysis

Among patients without anemia based on the first available Hgb value (n = 96,975), 50% of patients developed HAA: mild HAA, 24% (n = 23,063); moderate HAA, 19% (n = 18,134); and severe HAA, 8% (n = 7373). There was a similar relationship between increasing magnitude of HAA and an increase in mortality, LOS, and total charges in the unadjusted and adjusted analyses (see Supporting Information, Supplement C, in the online version of this article).

DISCUSSION

A substantial number of patients entering our health system became anemic during the course of their hospitalization. Among those who developed HAA, in-hospital mortality was higher, LOS longer, and total hospital charges greater in a dose-dependent manner. A recent editorial noted that HAA might be a hazard of hospitalization similar to other complications, such as infections and deep vein thrombosis.¹⁵ Our findings have significance in terms of demonstrating increased mortality and resource utilization associated with a potentially modifiable hospital-acquired condition. Even mild HAA was associated with increased resource utilization, although not increased hospital mortality.

Others have noted negative consequences of HAA in subpopulations of hospital patients. Salisbury and colleagues examined 17,676 patients with acute myocardial infarction who had normal Hgb on admission.¹⁶ They defined HAA as development of new anemia during hospitalization based on nadir Hgb. HAA developed in 57.5% of patients and was associated with increased mortality in a progressive manner. Risk-adjusted odds ratios for in-hospital death were greater in patients with moderate and severe HAA, 1.38 (95% CI: 1.10-1.73) and 3.39 (95% CI: 2.59-4.44), respectively.¹⁶ A separate investigation of 2902 patients from a multicenter registry

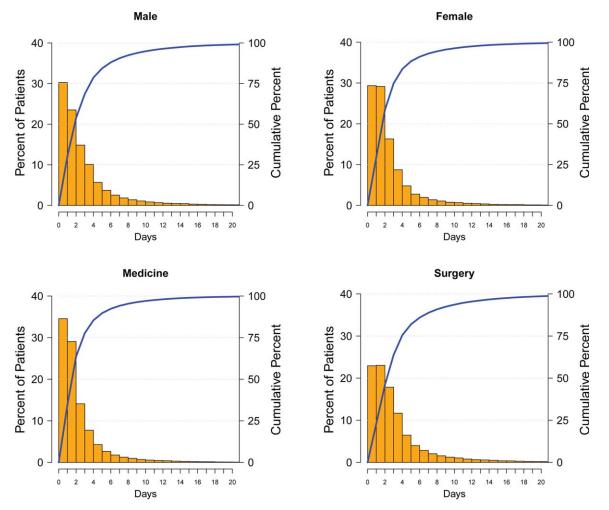
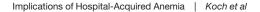


FIG. 3. Distribution of number of days from admission to reaching lowest hemoglobin values, stratified by gender and hospitalization type, and depicted by percentage histograms (orange bars, left axis) and cumulative percentage curves (blue curves, right axis).

of patients admitted to the hospital with acute myocardial infarction reported that nearly half of those with normal Hgb values on admission developed HAA.¹⁷ Most of these patients did not have documented bleeding; therefore, the authors suggested that HAA was not a surrogate for bleeding during hospitalization. Moreover, HAA was associated with higher mortality and worse health status 1 year after myocardial infarction.¹⁷ Others have reported that development of HAA is not uncommon in the setting of acute myocardial infarction and is associated with increased long-term mortality.¹⁸

Development of anemia during hospitalization is multifactorial and may result from procedural bleeding, phlebotomy, occult bleeding, hemodilution from intravenous fluid administration, and blunted erythropoietin production associated with critical illness.^{8,9} An investigation of general internal medicine patients reported phlebotomy was highly associated with changes in Hgb levels and contributed to anemia during hospitalization.¹⁹ The authors reported that for every 1 mL of blood drawn, mean decreases in Hgb and hematocrit were 0.07 ± 0.011 g/L⁻¹ and $0.019 \pm 0.003\%$, respectively. They suggested reporting cumulative phlebotomy volumes to physicians and use of pediatric-sized tubes for collection.¹⁹ Salisbury and colleagues reported that mean phlebotomy volume was higher in patients who developed HAA; for every 50 mL of blood drawn, the risk of moderate to severe HAA increased by 18%.²⁰ In an intensive care population, Chant and colleagues reported small decreases in phlebotomy volume were associated with reduced transfusion requirements in patients with prolonged stay.²¹

Attempts to ameliorate HAA should focus on modifiable processes-of-care factors. Patients with chronic illness have blunted erythropoiesis⁸ and therefore cannot mount an adequate response to blood loss from procedures or phlebotomy. Whether use of erythropoietin, iron, or both would be effective in this population requires further investigation. One of the most studied risk factors for HAA is blood loss from hospital laboratory testing.²⁰ Sanchez-Giron and Alvarez-Mora found that all laboratory tests could be performed with smaller-volume collection tubes without need for additional samples.²² Others have



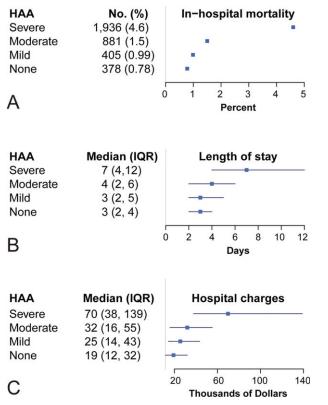


FIG. 4. Forest plots of hospital-acquired anemia (HAA) and outcomes. For in-hospital mortality, squares represent percentages. For length of stay and hospital charge, squares represent median and lines represent interquartile range (IQR).

proposed batching laboratory requests, recording cumulative daily blood loss due to phlebotomy for individual patients,²³ and use of blood conservation devices in intensive care units.

Figure 3 suggests that surgical patients develop anemia slightly later than medical patients. Features specific to surgery, such as perioperative intravenous fluid loading, "third spacing," and subsequent plasma volume expansion when reabsorption occurs days later, likely contribute to differences in trends for development of HAA.^{24–26} In addition, specific surgical cases with highly anticipated red blood cell loss should make use of antifibrinolytic agents to reduce blood loss and red cell salvage devices to reprocess and infuse shed blood.

Limitations

A recent commentary explored the question of benchmarks for anemia diagnosis, and in particular, what defines the lower limit of normal.²⁷ Although we used WHO criteria, others have used criteria establishing lower benchmarks according to race and gender.²⁷ Our results would have been similar if we had used these lower benchmarks, because our moderate and severe anemia Hgb cutoff values were beneath alternative benchmarks for diagnosing anemia. For example, Beutler and Waalen provide a definition of anemia that includes an Hgb cutoff of 12.2 g/dL for white

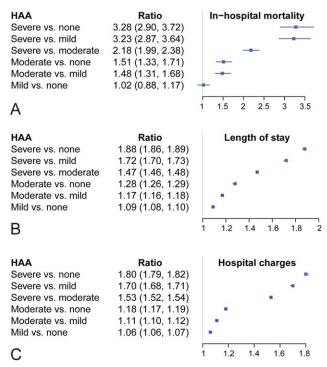


FIG. 5. Forest plots of adjusted outcomes and hospital-acquired anemia (HAA). Squares represent the effect size (ratio), and lines represent confidence intervals.

women aged 20 to 49 years, 11.5 g/dL for black women of similar age, 13.7 g/dL for white men, and 12.9 g/dL for black men.²⁷

Our study is limited by the nature of administrative data. However, use of demographic data, hospitalization type, and use of a large number of comorbidities for risk adjustment improved our findings. Adding nonadministrative clinical laboratory data from the electronic record for patient Hgb values provided us with a more accurate diagnosis of HAA and an ability to further subdivide anemia into mild, moderate, and severe categories that have prognostic implications. We are aware of the inherent limitations associated with use of administrative data. However, coded data are currently readily available and are the source of information on which many healthcare policies are made.^{28,29}

The POA anemia administrative code was used to identify patients with preexisting anemia. We did not use the first Hgb value upon admission because it is often made following interventions (eg, surgical patients have preoperative laboratory testing prior to admission, and the first Hgb value available following hospitalization is commonly obtained following surgical interventions). However, we performed a sensitivity analysis that defined preexisting anemia based on the first available Hgb value. The results from the sensitivity analysis were consistent with our primary findings with the use of administrative data coding. Of note, use of administrative codes for determining POA indicators is consistent with methods employed for all current publically reported quality and patient safety initiatives. Specifically, the Agency for Healthcare Research and Quality Patient Safety Indicators used by the Centers for Medicare and Medicaid Services to assess hospital quality of care and to modify reimbursement for services.

Our focus was on development of HAA; treatment of HAA with red blood cell transfusion and standardized blood draw orders were not investigated. Finally, our results are reflective of a single health system; further work with multicenter data would help clarify our findings.

CONCLUSION

Development of HAA is common and has important healthcare implications, including higher in-hospital mortality and increased resource utilization. Treating HAA by transfusion has attendant morbidity risks and increased costs.^{11,12,30} Hospitals must continue to focus on improving patient safety and raising awareness of HAA and other modifiable hospital-acquired conditions. Closer prospective investigation for both medical and surgical patients of cumulative blood loss from laboratory testing, procedural blood loss, and a risk-benefit analysis of treatment options is necessary.

Disclosure: Nothing to report.

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