for patients with elevated MCHC and anemia or compensated hemolysis, will evaluate the utility of PIEZO1 and KCNN4 genetic screening in defining eligibility for treatment with senicapoc or other drugs. These studies may define patient subsets who may most benefit from genetic testing.

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CONFLICT OF INTEREST DISCLOSURE

Drs. Alper, Brugnara, and Snyder are co-investigators in a clinical project for the treatment of HX (dehydrated stomatocytosis) with Springworks Therapeutics. Dr. Brugnara and Boston Children's Hospital hold patents potentially related to senicapoc. Dr. Alper has received research funding from Quest Diagnostics. Dr. Kaufman, Mr. Niles, Mr. Gallagher, and Dr. Snyder are employees of Quest Diagnostics.

ORCID

Harvey W. Kaufman http://orcid.org/0000-0003-2850-9047
Seth L. Alper http://orcid.org/0000-0002-6228-2512
Carlo Brugnara http://orcid.org/0000-0001-8192-8713

Harvey W. Kaufman[1], Justin K. Niles[1], Denis R. Gallagher[1], Alicia Rivera[2], Seth L. Alper[2], Carlo Brugnara[3], L. Michael Snyder[1]

[1]*Quest Diagnostics, Marlborough, Massachusetts, 01752*
[2]*Division of Nephrology and Vascular Biology Research Center, Beth Israel Deaconess Medical Center, and Department of Medicine, Harvard Medical School, Boston, Massachusetts, 02215*
[3]*Department of Laboratory Medicine, Boston Children's Hospital and Department of Pathology, Harvard Medical School, Boston, Massachusetts, 02115*

Correspondence
Harvey W. Kaufman, Quest Diagnostics, Marlborough, Massachusetts 01752.
Email: Harvey.W.Kaufman@QuestDiagnostics.com

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Correcting the cut-off point of hemoglobin at high altitude favors misclassification of anemia, erythrocytosis and excessive erythrocytosis

To the Editor:

The World Health Organization (WHO) defines anemia according age, gender, and altitude based on statistical distribution considerations and by cut-off points. Anemia in pregnancy and in children aged 6–59 months is defined as hemoglobin (Hb) concentration $<$11 g/dL.[1] Since Hb contains almost 70% of iron in the organism, WHO recommends its measurement to determining prevalence of anemia as screening for iron deficiency (ID) despite that they recognize that anemia is not a specific indication of ID.[1]

Moreover, WHO recommends correcting the cut-off point of hemoglobin to define anemia in high-altitude (HA) populations. The correction ranges from adding up 0.2 g/dL to the cutoff for people living at 1000 m to 4.5 g/dL for those living at $\geq$4500 m.[1] This correction is based on the assumption that populations living at HA increase Hb as altitude increases. Under hemoglobin correction the prevalence of anemia increases as HA increases[2] suggesting these inhabitants are iron deficient when they have normal iron levels.

However, in Tibetans there is a threshold effect for altitude on hemoglobin concentration rather than a continuous relationship. It is only at an altitude of $>$3800–4000 m that the hemoglobin concentration is elevated.[3]

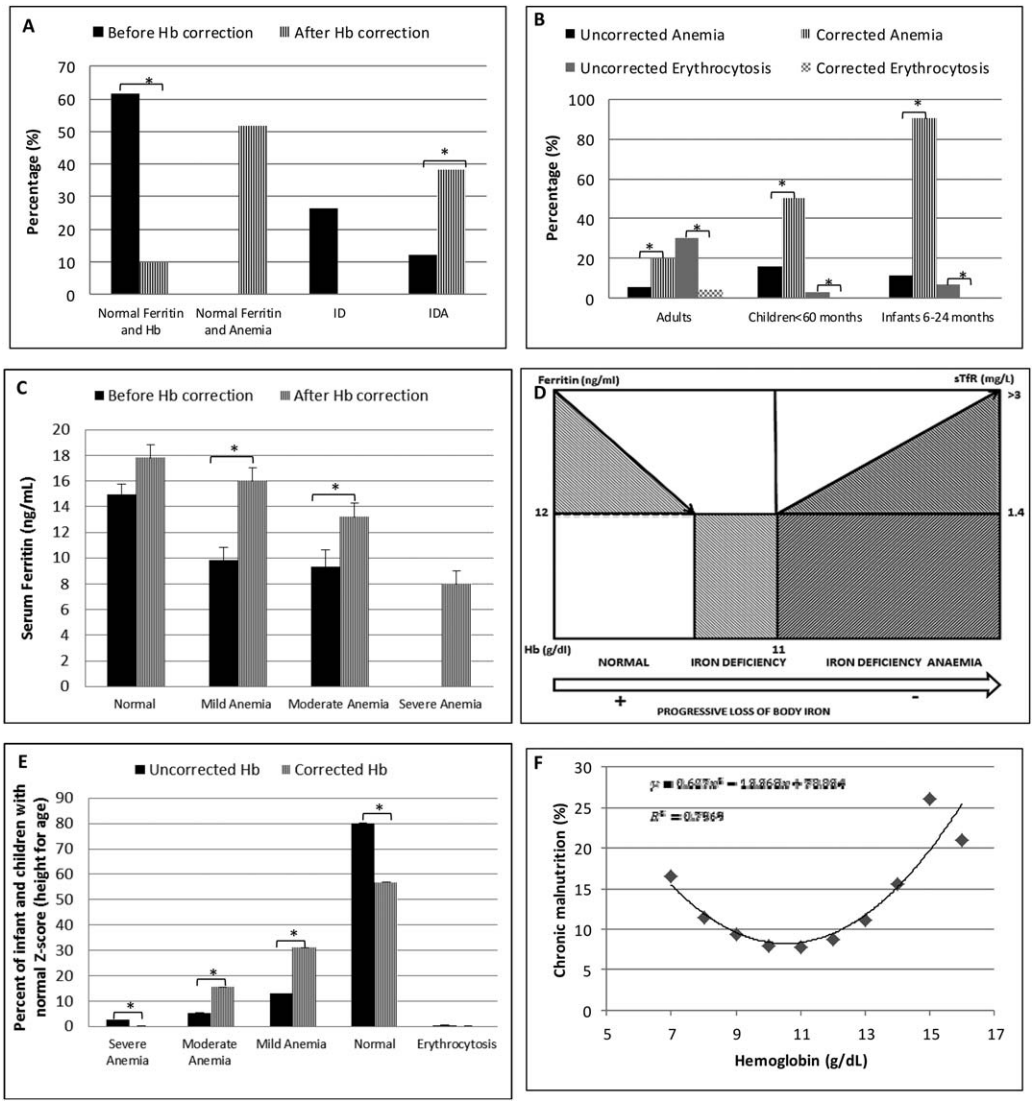

FIGURE 1 (**A**) Prevalence of infants with normal ferritin and normal hemoglobin levels; normal ferritin and anemia ($P < .01$ between groups; Z-score test); iron deficiency; and iron deficiency anemia ($P < .01$ between groups; Z-score test). Black columns: Groups diagnosed according uncorrected hemoglobin. Striped columns: Groups diagnosed according corrected hemoglobin. (**B**) Prevalence of anemia and erythrocytosis in adults from Lima (150 m), Huancayo (3280 m), Puno (3800 m), and Cerro de Pasco (4340 m)(Left Column), Children less than 60 months of age from the Arequipa Region (0–4500 m) (Middle Column), and infants aged 6–24 months from Puno (3800 m). $P < .01$ between groups without and with hemoglobin correction (Chi square test). (**C**) Serum ferritin levels in infants (6–24 months) of Puno, Peru (3800 m) classified according hemoglobin status. Hb is presented with and without correction for altitude. Sample size = 133 infants. $P < .01$ between groups without and with hemoglobin correction (Student *t* test). (**D**) Progressive loss of body iron content. Normal children <60 months and pregnant women are defined as serum ferritin >12 ng/mL and hemoglobin (Hb)> 11 g/dL. Iron Deficiency (ID) was defined as serum ferritin levels <12 ng/mL and hemoglobin >11 g/dL). Iron deficiency anemia was defined as serum ferritin lower 12 ng/mL and hemoglobin <11 g/dL. Reduction in serum ferritin and hemoglobin is aggravated associated with increase in serum soluble transferrin receptor (mg/L). (**E**) Infants and children of Arequipa Region, Peru with normal Z-score of height to age (Percentage) according WHO guidelines ($n = 16\,303$ infants and children). Altitude of residence varies between 0 and 4500 m. $P < .01$ between groups of corrected and uncorrected hemoglobin (*Z*-score test). Hemoglobin correction was performed according WHO recommendations.[1] (**F**) Association between hemoglobin levels (g/dL) and prevalence of chronic malnutrition in infants and children <60 months from Arequipa Region (0–4500 m)(Quadratic regression analysis). *$P < .01$ between groups before and after hemoglobin correction

Hepcidin is a hormone produced in the liver and considered the main regulator of iron homeostasis.[4] After adulthood levels have been attained, hepcidin values will change according iron requirement, which in turn will depend on the availability of iron storage. Serum hepcidin fails when iron demand is high as it would be if highlanders were iron deficient. In Ethiopians highlanders, steady state hepcidin was not lower than at low-altitude (LA) revealing that they were not iron insufficient.[5] It is unknown if the same pattern is observed in other high-altitude settlings as in the Peruvian Andes.

Hb > 14.5g/dL during pregnancy is a risk factor for adverse outcomes in mothers and neonates.[6,7] Excessive erythrocytosis (EE) is diagnosed when men have Hb > 21 g/dL and women >19 g/dL.[8] WHO has not considered that in correcting the Hb distribution curve for altitude, the proportion of subjects with newly defined anemia

TABLE 1 Iron status in adult men and women of Lima (150 m), Huancayo (3280 m), Puno (3800 m) and Cerro de Pasco (4340 m) with diagnosis of anemia or normal hemoglobin levels defined without or with hemoglobin correction by altitude

Variable	Uncorrected Anemia (25)	Corrected Anemia (93)	Uncorrected normal hemoglobin (306)	Corrected normal hemoglobin (364)
Hepcidin (ng/mL)	14.2 ± 2.5	14.0 ± 1.7	14.2 ± 0.2	13.1 ± 0.7
Ferritin (ng/mL)	31.9 ± 8.6*	56.4 ± 6.6[b]	69.2 ± 5.1	74.3 ± 5.4
sTfR (mg/L)	1.86 ± 0.27	2.10 ± 0.19	2.02 ± 0.08	2.22 ± 0.11
sTfR/Log ferritin	1.88 ± 0.61	1.75 ± 0.27	1.44 ± 0.09	1.53 ± 0.09
Body Iron Content (mg/Kg)	7.8 ± 0.8[a]	9.3 ± 0.5	9.9 ± 0.3	9.8 ± 0.3
Hemoglobin (g/dL)	11.6 ± 0.2*	13.97 ± 0.2[a]	15.5 ± 0.1	16.98 ± 0.1[c]
Corrected Hemoglobin (g/dL)	11.6 ± 0.2[a]	11.3 ± 0.1[a]	13.3 ± 0.1	14.5 ± 0.1[c]
CMS score	2.11 ± 0.43[d]	3.11 ± 0.31	2.61 ± 0.17	3.18 ± 0.18[c]

Data are mean ± standard error. Anaemia is defined as Hb < 13 g/dL in men and <12 g/dL in women. Normal Hb values are defines as Hb 13–19 g/dL in men and 12–17 g/dL in women. Erythrocytosis was defined as Hb <19–21 g/dL in men and >17–19 g/dL in women. Correction was performed as WHO recommendations.[1] Chronic mountain sickness score was defined as consensus statement.[11] sTfR= soluble transferrin receptor. Total sample included 475 adults (133 from LA and 342 from HA). From these 98 and 45 were diagnosed as erythrocytosis and EE with uncorrected Hb and 10 and 6 as erythrocytosis and EE with corrected Hb (data do not included). After Hb correction increases the cases of anemia and of normal Hb but cases of erythrocytosis and EE were reduced.

*$P < .01$ respect to the group with corrected anemia, uncorrected normal Hb, and corrected normal Hb.

[a]$P < .01$ respect to the group with uncorrected normal Hb, and corrected normal Hb.

[b]$P < .05$ respect to the group with corrected normal Hb.

[c]$P < .01$ between uncorrected and corrected normal Hb groups.

[d]$P < .05$ respect to the groups with corrected anemia and corrected normal Hb. Number of subjects per group are between parentheses.

increases, but the proportion of subjects with Hb > 14.5g/dL and EE reduces.

To clarify these issues, we have assessed prevalence of anemia and erythrocytosis before and after hemoglobin correction; and based on iron status markers to determine if hemoglobin at HA should be corrected; and to determine clinical outcomes associated with low and high hemoglobin levels.

We have studied adults, infants and children <5 years at different altitudes in Peru. These studies were approved by the Institutional Review Board at the Universidad Peruana Cayetano Heredia, Lima and by a Committee at the Universidad Nacional del Altiplano, Puno. Informed consent was obtained according to Declaration of Helsinki in the studies with adults ($n = 475$) from LA (150 m) and high-altitude (3280, 3800, and 4340 m) and infants from Puno (3800 m) aged 6–24 months ($n = 133$). In population level analysis in 17 703 children <60 months of age from eight provinces of the Arequipa region ranging from 0 to 4500 m was used a secondary analysis of data-base provided by the Regional Direction of Health, Arequipa. Data-base included age, sex, height, weight, and hemoglobin without and with correction by altitude.

Serum hepcidin concentrations were determined using a Hepcidin 25 bioactive ELISA kit (DRG Instruments GmBH. Marburg, Germany). Serum ferritin levels (ng/mL) were determined using a ELISA kit (DRG International, INC., USA). Serum soluble transferrin receptor (sTfR) (mg/L) was detected using sensitive ELISA (DRG Instruments GmBH, Frauenbergstr.18, D-35039, Germany). The index sTfR/log ferritin was calculated. Body Iron Content (BIC) was calculated from sTfR and Ferritin.[9]

In infants 6–24 months in Puno, the prevalence of anemia was 11.3%, but it increased to 94.7% after Hb correction ($P < .01$). Overall, 26.3% had ID (Ferritin ≤ 12 ng/mL) and 12% IDA (Ferritin ≤ 12 ng/mL). After Hb correction, 51.9% had normal ferritin associated to anemia (Figure 1A). In children <60 months in Arequipa Region, the prevalence of anemia was 16.1%, but increased to 50% after Hb correction ($P < .01$), whereas prevalence of erythrocytosis reduced from 3% to 0.7% after correction ($P < .01$; Figure 1B). In adults, the proportion of subjects with newly defined anemia increased from 5.5% to 19.8% ($P < .01$) but the proportion of subjects with EE reduced from 4.8% to 0.2% ($P < .01$), after correction (Table 1).

Infants aged 6–24 months from Puno (3800 m) having normal uncorrected hemoglobin levels (Hb:11–14.5 g/dL) showed higher serum ferritin levels than those with mild anemia (Hb:10.9–10 g/dL). If Hb was corrected, serum ferritin levels were higher in the group newly diagnosed as mild anemia suggesting that infants with normal ferritin levels were included as anemic after Hb correction. The same pattern was observed in the group with moderate anemia (Hb:9.9-7.0 g/dL; Figure 1C).

Serum ferritin and BIC in anemic defined without hemoglobin correction are lower than values in anemic after correction. Serum hepcidin levels were similar between LA and HA adult women (10.51 ± 1.04 and 12.71 ± 1.47 ng/mL, respectively; $P > .05$) and adult men (15.06 ± 1.18 and 15.28 ± 8.82 ng/mL, respectively; $P > .05$). Similarly, hepcidin values were similar between normal and anemic ($P > .05$). Chronic Mountain Sickness (CMS) score score was also increased after Hb correction as subjects with high CMS score are moved to the left of the distribution curve after Hb correction (Table 1).

In summary, adjusting Hb increase the cases of anemia that otherwise have normal BIC. Iron Deficiency Anemia (IDA) is a terminal stage of Iron

Deficiency (ID) (Figure 1D). Therefore, when iron store was reduced we expect cases with low ferritin but normal Hb levels (prelatent ID), however, anemia develops when after depletion of iron store, iron availability to bone marrow decrease leading to iron deficiency erythropoiesis.

The best way to validate Hb correction is the clinical outcome. At HA, correction of maternal hemoglobin reduces the risks for preterm birth and stillbirth in those women newly considered anemic, suggesting that women with normal Hb were erroneously diagnosed as anemic after correction.[2] The prevalence of children with normal nutrition (Z-score height-for-Age) was significantly reduced from 82% to 53% ($P < .01$) in the group with normal hemoglobin after correction (Figure 1E). Surprisingly, low prevalence of chronic malnutrition was in the range of mild anemia, whereas prevalence increase with moderate/severe anemia and with Hb > 14.5 g/dL (Figure 1F). Findings in highlands of Nepal confirm than Tibetan women with low Hb concentrations have better reproductive outcomes than those with high Hb.[10] In Peru, women from Puno (3800 m) have lower Hb concentration and newborns with higher birth-weight than in Huancavelica (3600 m).[6]

In countries with populations living at high-altitude, corrected hemoglobin values are used to make care decisions. In addition, the guidelines of the Ministry of Health in Peru as well as in other countries mandate the obligatory intervention for prevention or treatment with iron supplements in pregnant women and children.[11] Particularly in populations living at HA this may expose to iron overload. Recently, a systematic review provided preclinical evidence of adverse effect of high iron intake in neonates on brain-health-related outcomes in adults.[12]

In conclusion, the new understanding of iron regulation reveals that hemoglobin concentration alone can be very misleading in high-altitude populations. Therefore, the WHO recommendations for correcting hemoglobin for altitude lead to an over-correction in Peru. In Andean population, hemoglobin correction by altitude favors misclassification of anemia, erythrocytosis and EE. Then, it is needed to use appropriate measures to identify ID at altitude.

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AUTHORSHIP CONTRIBUTION

The manuscript was principally authored by G.F.G and A.Z-C and reviewed by all authors; the study was designed by G.F.G, A.Z-C, VRdeC and VT; and data collection and analysis were performed by all authors. VT Contributed data base and performed statistical analysis and interpretation. SY contributed data base from infants and children of Arequipa and participated in the discussion about data. JB and MdelRH contributed with data collection from infants of Puno and participated in the discussion about data

CONFLICT OF INTERESTS

All authors declare no competing financial interests.

Gustavo F. Gonzales[1,2,3], Verónica Rubín de Celis[4], José Begazo[5], María del Rosario Hinojosa[6,7], Sandra Yucra[2], Alisson Zevallos-Concha[1,2,3,8], Vilma Tapia[1,2]

[1]*High Altitude Research Institute*

[2]*Faculty of Sciences and Philosophy*

[3]*Research Circle in Plants with Effects in Health, Universidad Peruana Cayetano Heredia, Lima, Peru*

[4]*Instituto de Ciencia y Tecnología, Genomic and Molecular Biology Laboratory, Universidad Ricardo Palma*

[5]*School of Nutrition, Universidad Nacional del Altiplano, Puno*

[6]*EsSalud, Puno*

[7]*Universidad Nacional del Altiplano, Puno*

[8]*Universidad de Chile*

Correspondence

Gustavo F. Gonzales, Endocrine and Reproductive Laboratory, High Altitude Research Institute and Department of Biological and Physiological Sciences, Universidad Peruana Cayetano Heredia, 430 Honorio Delgado Ave, Lima, Peru.

Email: gustavo.gonzales@upch.pe

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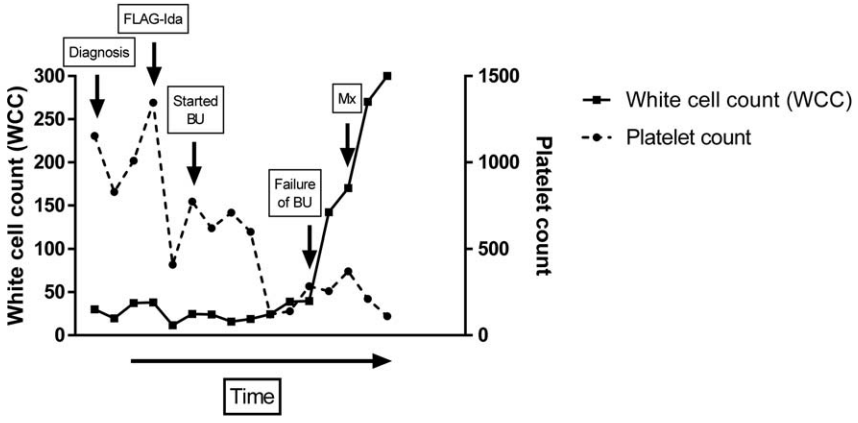
Transformation of MDS/MPN-RS-T to AML: Trisomy 13, resistant thrombocytosis and transient disease control with oral busulfan therapy

To the Editor:

We read with great interest the paper published by Patnaik et al. —"Refractory anemia with ring sideroblasts (RARS) and RARS with thrombocytosis (RARS-T): 2017 update on diagnosis, risk-stratification, and management[1]"—and report on a case of what is now known as myelodysplastic syndrome (MDS)/myeloproliferative neoplasm (MPN) with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) which involved the rare complication of transformation to acute myeloid leukemia.

A 68-year-old gentleman presented in 2014 with fatigue on a background of radical retropubic prostatectomy (RRP) for prostate cancer seven years prior. His hemoglobin (Hb) on presentation was 10 g/dL with a platelet count of 592 $\times$ 10^9/L. Bone marrow aspirate revealed hypercellularity with dysplastic megakaryocytes, dyserythropoiesis and increased numbers of ring sideroblasts (>15%) in keeping with a diagnosis of MDS/MPN-RS-T. Molecular analysis confirmed the presence of the SF3B1 mutation, known to be present in approximately 90% of MDS-RS cases and the majority of MDS/MPN-RS-T cases.[2] Baseline karyotype was normal and the JAK2 mutation was not present. He was managed with erythropoietin (EPO) injections prior to representation in July of 2016 with worsening fatigue; he was found to have a white cell count (WCC) of 30 $\times$ 10^9/L and a platelet count of 1153 $\times$ 10^9/L with bone marrow sampling showing transformation to acute myeloid leukemia (AML) with 35% blasts. Karyotype confirmed the acquisition of trisomy 13 but there was no FLT3-ITD mutation identified by molecular analysis. There was no response to hydroxyurea and he received two cycles of azacytidine but failed to respond, with a rising white cell count, and then was treated with daunorubicin and cytarabine (DA). Bone marrow aspirate following this cycle of chemotherapy revealed 60% blasts and, at this point, the options of palliative management or further chemotherapy were discussed. Intravenous fludarabine, cytarabine and idarubicin (FLAG-Ida) chemotherapy was then commenced; however again there was no response with a rapidly rising WCC and platelet count. At this point, the patient was started on oral busulfan 4–6 mg daily which had led to a swift reduction in the WCC and platelet count and a stable period of four months of maintenance as an outpatient, as demonstrated in Figure 1. Subsequent deterioration required intermittent doses of mitoxantrone to control the WCC before the patient died from progressive disease.

The hybrid nature of MDS/MPN-RS-T has been reflected in the 2016 World Health Organization (WHO) revision of the classification of myeloid neoplasms and acute leukemia, where it is now classified as an MDS/MPN overlap disorder.[3] It is a rare crossover disorder comprising 2–3% of MDS diagnoses. Diagnosis involves the following criteria: thrombocytosis >450 $\times$ 10^9/L, refractory anemia, bone marrow dyserythropoiesis, ring sideroblasts accounting for greater than 15% of bone marrow progenitors and abnormal megakaryocytes. MDS/MPN-RS-T has a number of recognized genetic associations, most commonly the *SF3B1* mutation which is seen in 90% of cases; other less commonly associated gene mutations, which are associated with the



Key: FLAG-Ida, fludarabine, cytarabine, idarubicin; BU, busulphan; Mx, mitoxantrone.

FIGURE 1 Change in WCC and platelet count over time