Received: 8 April 2019 | Revised: 8 May 2019 | Accepted: 13 May 2019

DOI: 10.1002/ajh.25509

AJH WILEY

SOLVING CLINICAL PROBLEMS IN BLOOD DISEASES

A physician or group of physicians considers presentation and evolution of a real clinical case, reacting to clinical information and data (boldface type). This is followed by a discussion/commentary

Hemoglobin Southampton complicated by cerebral ischemia, moyamoya, and hydroxyurea-induced methemoglobinemia

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1 | CASE PRESENTATION

An 11-year-old female known to be heterozygous for hemoglobin (Hb) Southampton (Casper) presented with painless loss of vision in her left eye. She reported no light perception in her left eye upon waking that morning. Within 2 hours, she was able to perceive motion and had relative sparing of the inferior and nasal visual fields. Ophthalmologic examination 3 hours after waking showed a normal fundus with patent vasculature, her extraocular movements were full and without pain, and her pupils constricted equally to direct and indirect light (no afferent pupillary defect). The remainder of her neurologic examination was normal. She denied any current headache but reported headaches in the past associated with left eye visual changes. Given her transient monocular vision loss, neuroimaging was obtained to evaluate for stroke. Computed tomography angiography (CTA) demonstrated internal carotid arteriopathy with bilateral cavernous and ophthalmic segmental stenosis. She was hospitalized for monitoring and further diagnostics and prescribed aspirin 81 mg daily.

Her hemoglobinopathy, Hb Southampton (Figure 1), was diagnosed at 2 years of age by genetic testing after an acute episode of severe hemolysis during a mild respiratory illness. This was a de novo mutation; no other family members were affected. Molecular genetic testing also demonstrated several additional Hb abnormalities, including an α-globin gene triplication ($\alpha\alpha\alpha^{anti\ 3.2}$), Hb A_2-Yialousa [HBD:c.82G>T(p.A28S)], and the *XmnI* polymorphism at −158 in the $^{G}\gamma$ promoter region (HBG2:c.-211C>T). Capillary zone electrophoresis (CZE) is shown in Figure 1. After this initial presenting hemolytic episode, she continued to have intermittent acute hemolytic episodes, especially when ill, and was soon transitioned to chronic transfusions for 4 years. Despite this, she continued to have chronic symptomatic anemia, and at 5 years of age she underwent total splenectomy. This significantly decreased her hemolytic episode frequency and improved her baseline (pre-transfusion) Hb concentration from about 8 to 11 g/dL (Table 1), allowing her to discontinue regular transfusions. Off transfusions, her P_{50} was 20.3 mm Hg (normal 23.5-27.5). She took daily folic acid and penicillin prophylaxis and had no major hemolytic episodes for 5 years.

Reported in at least seven individuals, most commonly as a de novo mutation, Hb Southampton is a rare, unstable β-globin variant [HBB:c.320T>C(p.Leu107Pro)].[1-8] This substitution disrupts the α-helix of the β-chain and significantly distorts the tertiary structure of the Hb molecule, predisposing to spontaneous loss of the heme group. Denaturation of the globin chains subsequently occurs, along with the generation methemoglobin (metHb), hemichromes, and Heinz bodies, resulting in premature erythrocyte destruction. The clinical phenotype consists of a chronic hemolytic anemia, hepatosplenomegaly, methemoglobinemia, and easily-triggered hemolytic episodes, particularly with infections. Hb Southampton is a high O_2 affinity variant, consistent with this patient's low P_{50}.[9] Similar to other unstable Hb variants, splenectomy has been reported to decrease chronic hemolysis and transfusion requirements.

Two months before her current presentation with amaurosis fugax, she was evaluated for a transient ischemic attack (TIA) when

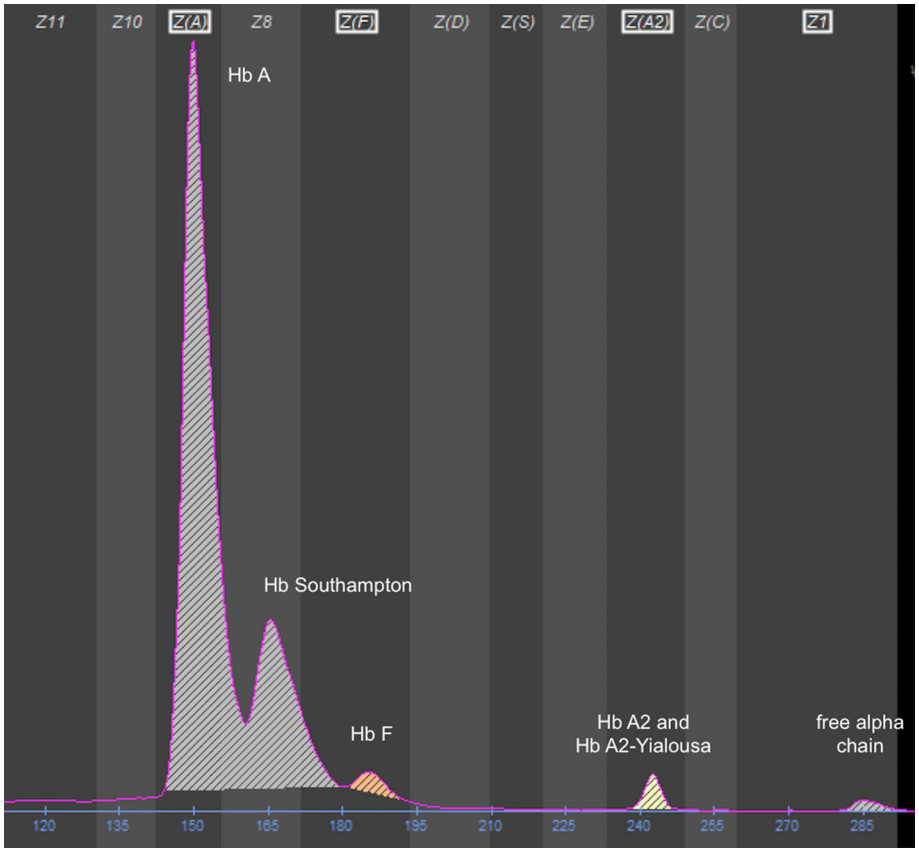

FIGURE 1 Capillary zone electrophoresis (CZE) showing the close migration of Hb A and Hb Southampton. Hb F is mildly increased. Total Hb A_2 is mildly decreased (with co-migrating Hb A_2 and A_2-Yialousa). The smallest, rightmost peak likely represents free α-globin chains which are present due to combination of the unstable β-hemoglobinopathy and coinherited α-globin triplication [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Clinical laboratory measurements by splenectomy status and exposure to hydroxyurea

	Typical range of values		Single values	
Measurement	Pre-splenectomy[a]	Post-splenectomy[b]	Pre-hydroxyurea[c]	Post-hydroxyurea[d]
Hb (g/dL)	6-9	10-12	10.0	9.1
Hematocrit (%)	20-27	32-38	34.1	29.9
ARC (K/μL)[e]	500-1000	250-500	N/A	N/A
NRBC (#/100 WBCs)	1-10	15-65	10	25
Platelets (K/μL)	150-300	750-1250	873	909
Unconjugated bilirubin (mg/dL)	4-8	4-8	4.8	5.0
LDH (units/L)	1500-3500	250-350	915	849

Abbreviations: ARC, absolute reticulocyte count; Hb, hemoglobin; LDH, lactate dehydrogenase; NRBC, nucleated red blood cells; TIA, transient ischemic attack.
[a]Approximately 4-year interval.
[b]Approximately 6-year interval.
[c]Values upon admission for TIA.
[d]Nadir or maximum values within 1 week of administration of hydroxyurea.
[e]Many values not able to be calculated due to numerous red blood cell inclusions.

she had brief, left-sided sensory loss during a febrile illness. This was complicated by an exacerbation of hemolysis (nadir Hb concentration of 7.5 g/dL). Her current admission labs included a complete blood count (CBC) showing WBC 18.3 K/μL, Hb 12.3 g/dL, MCV 112 fL, and platelets 599 K/μL. There was marked polychromasia. Reticulocytes were unable to be quantified due to numerous erythrocyte inclusions. Magnetic resonance imaging (MRI) and angiography (MRA) of the brain demonstrated severe steno-occlusive vascular disease consistent with the CTA findings and also showed bilateral white matter T2 hyperintensities consistent with remote infarction (Figure 2). Collateral vessel proliferation was also noted, suggesting chronic vascular remodeling. She had no recurrent visual changes and her neurologic examination remained normal. She was discharged from the hospital on 81 mg aspirin daily with ongoing outpatient follow-up in a multidisciplinary cerebrovascular disease clinic.

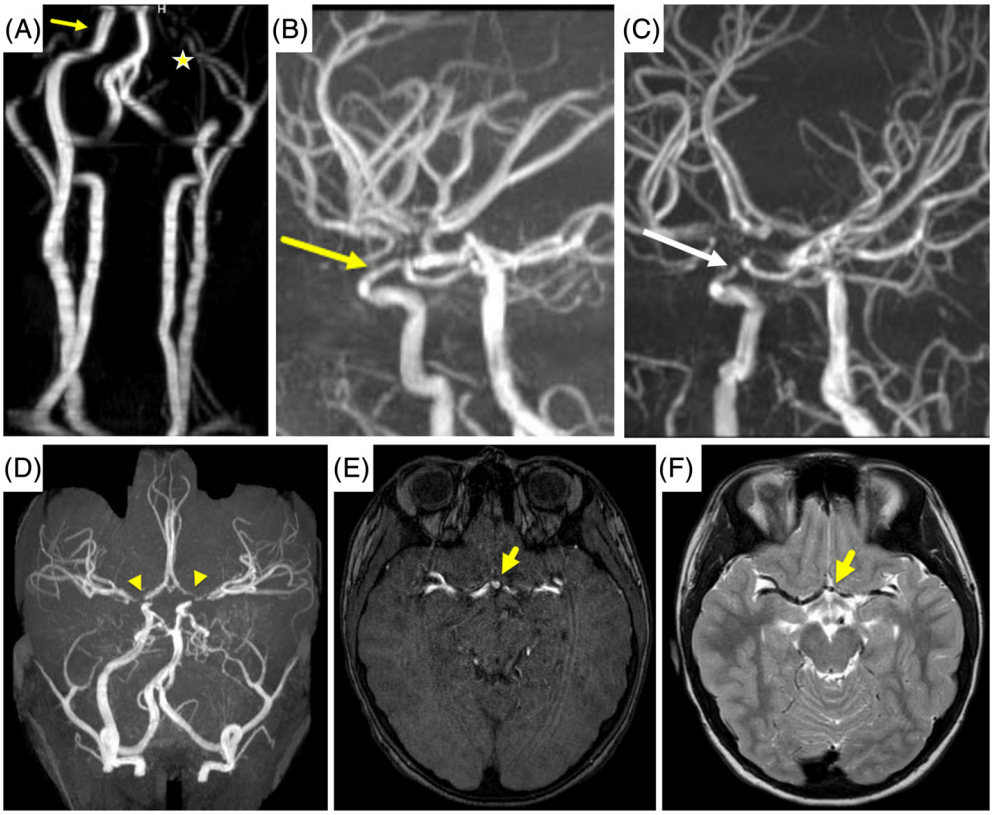

FIGURE 2 Representative magnetic resonance (MR)-based angiographic projections illustrating steno-occlusive disease in the described patient. A, Anteroposterior-projected MRA of the neck with absent left internal carotid artery (ICA, star) in comparison to the present right ICA. B, MRA time-of-flight-reconstructed oblique view at the right ICA distal stenotic narrowing. C, This MRA from 2 years after B demonstrates progressive stenotic occlusion at the distal right ICA (arrow) at the level of the Circle of Willis. D, Bilateral occlusive disease of the bilateral ICA termini on axial view of the Circle of Willis from the MRA after her initial presentation. E, Bulbous appearance (arrow) of the left A1/A2 junction suggestive of possible cerebral aneurysmal dilatation on MR time-of-flight imaging with F, adjacent distal A1 segment stenosis as illustrated on T2-weighted MRI; both images were from her initial MR imaging 2 years before documented progression [Color figure can be viewed at wileyonlinelibrary.com]

The findings in this case are suggestive of chronic intracranial ischemia. Moyamoya syndrome is a well-recognized sequela of sickle cell disease (SCD) but has also been reported in unstable hemoglobinopathies including Hb Southampton,[1,2] Hb Alesha,[10] and Hb Fairfax (in association with beta thalassemia).[11] Moyamoya, meaning "puff of smoke" in Japanese, describes the angiographic appearance of intracranial collateral vasculature. Cerebral arteriopathy, such as moyamoya, is an important cause of recurrent stroke in children.[12] Moyamoya has a biphasic cerebrovascular phenotype, where ischemic stroke predominates in the first decade of life while brain parenchymal hemorrhage occurs more often in adulthood (peaking in the fifth decade of life). Other features of moyamoya include headache, seizure, focal acute neurologic deficits, and cognitive decline.

One month later, she again presented with headache and new focal neurologic findings, including right facial droop and hemiparesthesia. These signs and symptoms resolved shortly after arrival to the emergency department, and imaging was deferred due to the patient's severe anxiety. Her CBC showed a WBC of 21.3 K/μL, Hb 10.0 g/dL, MCV 117 fL, and platelets 873 K/μL (Table 1**). She was admitted again to the hospital for monitoring and further management. The result of VerifyNow Aspirin testing (Accriva Diagnostics, San Diego, California) was 429 aspirin resistance units (therapeutic level < 550), suggesting adequate platelet inactivation. Nevertheless, her aspirin dose was increased to 162 mg daily as this second TIA episode was considered evidence of treatment failure. During this admission, hydroxyurea 1000 mg daily (~20 mg/kg) was initiated in an attempt to decrease her Hb Southampton fraction by inducing fetal Hb (HbF) production as well as minimize her chronic, post-splenectomy thrombocytosis.**

Within 2 hours of her first oral dose of hydroxyurea, her Hb O_2 saturation measured by pulse oximetry (SpO_2) decreased from >95% to 80%-84% and did not improve with 15 L oxygen supplementation by a nonrebreathing facemask. She was transferred to the intensive care unit (ICU) for concerns of persistent hypoxemia although, notably, she did not have respiratory distress, cyanosis, or neurologic or mental status changes. Venous blood gas showed the following: pH 7.43, PO_2 31 mm Hg, PCO_2 37 mm Hg, and O_2 saturation of 62%. Co-oximetry showed a carboxyhemoglobin level slightly elevated to 2.7% (normal < 1.5) and a methemoglobin (metHb) level of 12.4% (normal < 1.5). She had not had metHb tested prior to this episode. Her Hb was mildly lower at 9.6 g/dL and her total bilirubin was 5.0 mg/dL (Table 1**). Given the moderate methemoglobinemia, a**

slightly increased serum lactate level, and a concern about her abnormal pulse oximetry readings, she was given methylene blue by the ICU staff. This was stopped prematurely due to severe myalgias during the infusion and ultimately did not affect her SpO_2 readings. At this time, her mother recalled that she has a known history of unreliable pulse oximetry readings during anesthesia for her splenectomy.[13]

Despite low SpO_2 readings, she remained clinically well and was discharged on aspirin only. Hydroxyurea was not given again because it was temporally associated with exacerbation of the unstable Hb phenotype yielding increased metHb production. Her Hb decreased modestly to 9.1 g/dL during the admission, accompanied by a marked increase in nucleated red blood cell count, as shown in Table 1**. At outpatient follow up 48 hours later, the SpO_2 had spontaneously improved to >90% and her Hb had increased to 10.7 g/dL. Transcranial Doppler ultrasonography (TCD) performed 4 days after the single dose of hydroxyurea showed an abnormally increased mean maximal velocity of 159 cm/s in the left posterior cerebral artery (PCA) with peak systolic velocities of 216 cm/s in the right and left PCAs. PCA velocities were higher than middle cerebral artery (MCA) velocities bilaterally. Turbulent flow was also identified in both MCAs. She had not had any prior TCD performed for comparison.**

Unstable Hbs are caused by mutations that result in globin-chain auto-oxidation or excessive oxidation from even minor oxidative challenges and are one cause of congenital Heinz body hemolytic anemia. Oxidative hemolysis often leads to some degree of methemoglobinemia in which the normal reductive processes in red blood cells are saturated by increased metHb production. Pulse oximetry estimates Hb oxygen saturation by determining the light absorption of Hb at only two wavelengths (to estimate the relative abundance of oxyHb and deoxyHb). Because metHb cannot be distinguished by these two wavelengths alone, individuals with methemoglobinemia may have spuriously low SpO_2 measurements, between 80% and 85%, despite a normal partial pressure of O_2 in arterial blood, making pulse oximetry unreliable in this circumstance.[14] Of note, SpO_2 may also be falsely reduced after methylene blue itself due to colorimetric interference, so metHb co-oximetry levels rather than pulse oximetry must be used to evaluate O_2 saturation after its administration.

Because of the patient's second stroke-like episode and moyamoya, chronic monthly transfusions were resumed to arrest the progression of her cerebrovascular disease. With a goal of minimizing transfusions and uncertainty about whether the single dose of hydroxyurea was causally associated with the increased metHb production, a repeat trial of hydroxyurea at a lower dose (500 mg daily, ~10 mg/kg) was attempted 5 months later as an outpatient. One week later, her SpO_2 was again lower than baseline (83%-91%), consistent with an exacerbation of the unstable Hb phenotype with increased metHb production.

Although hydroxyurea clearly decreases hemolysis (and vaso-occlusion) in SCD by increasing HbF, attempts to use it in patients with unstable hemoglobinopathies have had mixed results. Hydroxyurea increased Hb concentration and/or decreased the instability of the hemoglobinopathy in patients with Hb Templeuve,[15] Perth,[15] and Volga,[16] but it increased hemolysis in a patient with Hb Köln.[16] None of the previous Hb Southampton reports describe hydroxyurea use. In this case, hydroxyurea, even at low doses, appears to precipitate mild-to-moderate methemoglobinemia, likely by exacerbation of the unstable Hb phenotype, which results in spurious SpO_2 readings.

Due to concerns for precipitating acute and chronic methemoglobinemia, even without overtly increased hemolysis (Table 1**), hydroxyurea was discontinued permanently. She continues on aspirin 162 mg daily and monthly simple transfusions (pre-transfusion Hb of 11.5 g/dL). She receives pre-transfusion phlebotomy and deferasirox in order to limit iron loading (current serum ferritin: 356 ng/mL; hepatic iron content: 4.0 mg/g dry weight). However, her MRI/MRA 2 years after the previously described events demonstrates progressive distal right internal carotid artery (ICA) steno-occlusive disease without evidence of acute ischemic injury (**Figure 2C**). She is now being considered for surgical revascularization and also for bone marrow transplantation.**

2 | DISCUSSION

This case illustrates several challenges associated with Hb Southampton which provide valuable insight into the management of patients with this and other unstable hemoglobinopathies. This child experienced serial stroke-like episodes and had covert ("silent") cerebral infarction as a consequence of her chronic cerebrovascular ischemia with vascular remodeling. These are known complications of SCD, but there is increasing case-based evidence that unstable hemoglobinopathies may also be under-recognized risk factors for cerebral vasculopathy. Therefore, providers need to be aware of the pre-stroke symptoms of cerebral vasculopathy, including headaches, weakness, visual or speech disturbances, developmental delay, or seizures. A high index of suspicion and early neuroimaging may allow earlier risk stratification, intervention, and prevention of irreversible neurologic injury.

All reported patients with Hb Southampton and moyamoya had neurologic signs and symptoms between ages 9 and 12 years of age. Moyamoya is a progressive condition in which the initial vascular remodeling phase is asymptomatic and lasts months to years. Although earlier detection may be possible, the natural course of moyamoya in unstable hemoglobinopathies remains unclear. Experience with SCD suggests several explanations for endothelial activation in hemolytic anemias,[17] although the pathobiology of smooth muscle proliferation in moyamoya and the cause of moyamoya in unstable hemoglobinopathies are unknown. Complicating the understanding of etiologic factors is that all Hb Southampton patients with moyamoya had also undergone splenectomy to improve chronic hemolysis by the time of symptom onset. Splenectomy also appears to increase the risk of arterial and venous thrombosis in chronic hemolytic conditions,[18,19] thought to be a result of rentention of abnormal RBCs, alterations of lipid profiles, and platelet and endothelial activation. Thus, delineating the exact cause and relative pathologic contributions of chronic hemolysis vs post-splenectomy vascular alterations is extremely difficult.

This patient had moderately elevated cerebral arterial blood flow velocities, a risk factor for stroke in SCD, but her TCD velocities were

higher in the posterior circulation than the anterior circulation, which is uncommon in SCD.[20] However, this likely represents altered blood flow due to her documented bilateral ICA stenosis rather than PCA stenosis. TCD screening can identify children with SCD at high risk of stroke,[21] and the Stroke Prevention Trial in Sickle Cell Anemia (STOP) showed that chronic transfusions can substantially decrease the risk of stroke in these patients.[22] The role of screening TCD programs in patients with unstable hemoglobinopathies is unknown. Likewise, the role of chronic transfusions to prevent neurologic complications in patients with Hb Southampton has not been established by high-quality evidence given the infrequency of unstable hemoglobinopathies. In this case, the rationale for chronic transfusions for neuroprevention is inferred from literature supporting the practice in SCD and acute anemic events of any cause.[23,24] A multicenter registry collecting data as well as standardized monitoring (eg, TCD and/or MRI/MRA at important intervals in vascular biology, such as at diagnosis, prepuberty, and adulthood) for patients with unstable hemoglobinopathies could inform future practice and improve outcomes.

The current scientific statement from American Heart Association/American Stroke Association indicates that surgical revascularization is the primary treatment for moyamoya in children. Aspirin therapy is given for thromboprophylaxis prior to surgery and to promote patency of the graft vessels.[25] There has been a historical reluctance to use aspirin in SCD patients with moyamoya due to a concern that its use may precipitate intracranial hemorrhage. However, this increased risk generally occurs well into adulthood and is not exclusive to SCD-associated moyamoya, so clinical practice trends are starting to change. Aspirin has been used in other individuals with congenital hemolytic anemias post-splenectomy due to increased platelet activation and thrombotic risk. In this patient, the risk-to-benefit ratio after two stroke-like events warranted antiplatelet therapy despite her unstable hemoglobinopathy, but no clear guidelines exist for this scenario.

This patient's several coinherited Hb abnormalities could modify her phenotype. In particular, the α-globin gene triplication (ααα/αα) might favor $\alpha\beta^{Southampton}$ dimer assembly and increase the fraction of the unstable Hb Southampton; however, the close migration of Hb Southampton and Hb A by CZE (Figure 1) and co-migration with Hb A by high performance liquid chromatography (not shown) prevents a simple quantitative determination. Her Hb Southampton fraction is at least 15% to 20%, consistent with prior reports. The α-triplication might also cause α:β imbalance, resulting in increased hemolysis. Indeed, CZE shows evidence of a small amount of free α-globin chains (Figure 1). Hb A_2-Yialousa (a δ^+ thalassemic variant) explains her mildly decreased total Hb A_2 fraction (Hb A_2 and Hb A_2-Yialousa co-migrate by CZE). Unfortunately, the HBG2:c.-211C>T polymorphism has not significantly increased her Hb F fraction (2%-3%).

Finally, this case demonstrates the limitations of pulse oximetry in patients with some unstable hemoglobinopathies. The resultant spurious SpO_2 readings due to easily-triggered methemoglobinemia may lead to management errors in the acute setting. Indeed, persistent, unexplained low SpO_2 measurements, especially in asymptomatic individuals, should prompt the consideration of a variant Hb, a clinical scenario comprehensively reviewed by Verhovsek et al.[26] Additionally, the fact that hydroxyurea exacerbates the unstable Hb phenotype with increased metHb production in Hb Southampton reflects the broader reality that optimal management approaches in unstable hemoglobinopathies may vary, and evidence to guide therapy in these situations is sparse. Increased awareness and study of the underappreciated clinical manifestations of unstable hemoglobinopathies is needed to better guide future management strategies.

ACKNOWLEDGMENTS

The original, diagnostic molecular genetic testing was performed at the Hemoglobin Diagnostic Reference Laboratory, Boston Medical Center (Dr David H.K. Chui).

CONFLICT OF INTEREST

The authors have no conflicts of interest relevant to this article to disclose.

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How to cite this article: Boucher AA, Gurunathan A, Taylor JM, Ricci KW, Vadivelu S, Quinn CT. Hemoglobin Southampton complicated by cerebral ischemia, moyamoya, and hydroxyurea-induced methemoglobinemia. *Am J Hematol*. 2019;94:949–954. https://doi.org/10.1002/ajh.25509