Utility, Charge, and Cost of Inpatient and Emergency Department Serum Folate Testing

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BACKGROUND: Serum folate levels are commonly ordered for multiple indications in the inpatient and emergency department settings. Since mandatory folic acid fortification in 1998, there has been a decreasing prevalence of folate deficiency in the United States.

OBJECTIVE: Our objective was to determine the indications, rate of deficiency, charge and cost per deficient result, and change in management per deficient result in serum folate testing in inpatients and emergency department patients.

DESIGN: Retrospective analysis of all inpatient and emergency department serum folate tests.

METHODS: We analyzed all inpatient and emergency department serum folate tests performed over a 12-month period. We reviewed the charts of 250 patients and all low-normal or deficient serum folate levels to determine indications, comorbidities, and change in management based on result. Charge and cost analyses were performed.

SETTING/PATIENTS: All inpatient and emergency department patients with a serum folate test performed at a major medical center in Boston, Massachusetts.

RESULTS: A total of 2093 serum folate tests were performed in 1944 patients with 2 deficient levels. The most common indications were anemia without macrocytosis and anemia with macrocytosis. The amount charged per deficient result was $158,022. The cost to the hospital per deficient result was less than $2093.

CONCLUSIONS: In folic acid fortified countries, serum folate testing has low utility and poor cost effectiveness for all indications in inpatients and emergency department patients. *Journal of Hospital Medicine* 2013;8:91–95.

Folate deficiency has been associated with a number of medical conditions. It is well established that folate deficiency leads to macrocytic anemia,[1,2] and that supplementation of folic acid during pregnancy leads to decreased rates of neural tube defects.[3] Folate deficiency has also been hypothesized to affect other conditions including dementia, delirium, peripheral neuropathy, depression, cancer, and cardiovascular disease.[4–18] Most of these latter assertions are based on case reports or observational studies, with randomized controlled trials failing to demonstrate benefit of folic acid supplementation.[19–21]

Prior to mandatory folic acid fortification in the United States, the prevalence of folate deficiency was estimated to be between 3% and 16%.[16,22,23] In a study conducted prior to fortification, serum folate levels were evaluated in patients presenting with macrocytosis and anemia.[24] The study found that 2.3% of patients were serum folate deficient, with a change in management occurring in 24% of the deficient patients. The study also found that patients were charged $9979 per result that changed physician management.

In 1998, mandatory folic acid fortification began in the United States, and the prevalence of folate deficiency in the general population decreased to an estimated 0.5%.[23,25] In a postfortification study, serum folate levels were evaluated in patients with anemia, dementia, or altered mental status.[26] The overall rate of serum folate deficiency was 0.4%, with the authors concluding that there was a lack of utility in serum folate testing. Despite this, algorithms addressing the evaluation of anemia continue to include serum folate levels.[2,27,28]

To our knowledge, the use of serum folate testing in the inpatient and emergency department population has never been independently evaluated. In our study, we aimed to characterize the indications, rate of deficiency, charge and cost per deficient result, and change in management per deficient result in inpatient and emergency department serum folate testing. We hypothesized that serum folate testing in these populations would have poor utility and would not be cost-effective for any indication.

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TABLE 1. Demographics, Indications, and Comorbidities

Age, median, y	66.0
Male sex, %	50.8
Race or ethnicity, %	
White	76.0
Black or African American	12.0
Asian	4.4
Hispanic	4.0
Unknown or declined	2.0
Other	1.6
Indications, %*	
Anemia without macrocytosis	43.2
Anemia with macrocytosis	13.2
Delirium	12.0
Malnutrition	6.4
Peripheral neuropathy	6.0
Depression	3.6
Dementia	3.2
Pancytopenia	2.4
Other	10.4
Unknown	6.4
Comorbidities, %	
Depression	23.2
Alcohol abuse	18.4
Chronic anemia	11.2
Malnutrition	9.6
Prior intestinal surgery	8.8
Peripheral neuropathy	6.0
Dementia	5.6
Gastric bypass surgery	4.4
End-stage renal disease	4.0
End-stage liver disease	3.6
Use of phenytoin	3.2
Inflammatory bowel disease	2.4
Use of valproic acid	2.0
Celiac disease	1.2

NOTE: * Indications total more than 100% as patients may have more than 1 indication.

METHODS

We conducted a retrospective review of all serum folate tests ordered in inpatient units and the emergency department at a large academic medical center in Boston, Massachusetts from January 1, 2011 through December 31, 2011. The test was considered to be an inpatient or emergency department test based on the location of the blood draw on which the test was performed. Serum folate values were determined using a chemiluminescent competitive binding protein assay on an E170 analyzer as prescribed by the manufacturer (Roche Diagnostics, Indianapolis, IN). We defined serum folate levels as deficient ($\leq$3.0 ng/mL), low-normal (3.0 ng/mL–3.9 ng/mL),[26] normal (4.0 ng/mL–20.0 ng/mL), and high (>20.0 ng/mL). Erythrocyte folate levels are not routinely ordered at our institution and were not measured in our study.[29] Macrocytosis was defined as mean corpuscular volume of >99 fL. Vitamin B12 deficiency was defined as vitamin B12 level of under 200 pg/mL or vitamin B12 level of 200 to 300 pg/mL, with a methylmalonic acid >270 nmol/L and a normal homocysteine level (5–14 μmol/L).[30,31]

We evaluated 250 randomly selected serum folate levels and all deficient or low-normal serum folate levels and recorded indication, comorbidities, age, sex, race or ethnicity, hemoglobin, hematocrit, mean corpuscular volume, vitamin B12 level, folic acid supplement on presentation, and folic acid supplement on discharge. Indications were determined by chart review. If serum folate was checked at the same time as iron studies, it was assumed that the indication was anemia without macrocytosis or anemia with macrocytosis unless otherwise documented. Comorbidities were selected based on historical risk factors and included depression, peripheral neuropathy, intestinal surgery, gastric bypass, cirrhosis, inflammatory bowel disease, celiac disease, delirium, dementia, alcohol abuse, malnutrition, anemia, end-stage renal disease, vitamin B12 deficiency, or current use of phenytoin, valproic acid, or methotrexate.[32]

A charge analysis was performed using the same methodology as Robinson and Mladenovic.[24] We defined the charge of serum folate testing as our institution's charge to the patient or payer, which was $151.00 per test. Because hospital charges are variable, we also made a second calculation based on the charge per patient or payer from the Robinson and Mladenovic study,[24] which was $71.00. The analytical cost to our hospital of performing each serum folate test was <$2.00. We determined the total charge and cost for all serum folate tests and the charge and cost per deficient result.

The study was reviewed by the institutional review board and determined to be exempt.

RESULTS

In 2011, a total of 2093 serum folate levels were obtained on 1944 inpatients and emergency department patients. Of the total patients, 79.9% were inpatients and 20.1% were emergency department patients. Of the patients with tests performed in the emergency department, 98.1% were admitted to an inpatient unit.

Of the 250 random chart reviews, all had normal or high serum folate levels. The demographics, indications, and comorbidities are listed in Table 1. The most common indications were anemia without macrocytosis (43.2%), anemia with macrocytosis (13.2%; mean corpuscular volume [MCV], 106.8 fL), delirium (12.0%), malnutrition (6.4%), and peripheral neuropathy (6.0%). The other indications included thrombocytopenia, macrocytosis (without anemia), methotrexate use, alcohol abuse, frequent falls, syncope, headache, lethargy, optic nerve neuropathy, paranoia, psychosis, leukopenia, anxiety, and suicidal ideation. All of these individual indications were $\leq$2% of total reviewed indications. There were 16 cases (6.4%) without a documented indication.

Of the 2093 serum folate levels, there were 2 deficient (0.1%), 7 low-normal (0.3%), 1487 normal

TABLE 2. Serum Folate Results

Total tests	2093
Total patients	1944
Low (%)	2 (0.1)
Low-normal (%)	7 (0.3)
Normal (%)	1487 (71.0)
High (%)	597 (28.5)
MCV (StDev)	92.1 (9.2)

NOTE: **Abbreviations**: MCV, mean corpuscular volume; StDev, standard deviation.

(71.1%), and 597 high (28.5%) levels (Table 2). There were 128 patients (6.6%) who had more than 1 serum folate level checked within the prior 12 months, with 1 patient having 5 levels obtained during that time period. All of the deficient and low-normal serum folate results are listed in Table 3. Of the 9 deficient or low-normal serum folate levels, 8 had comorbid risk factors for folate deficiency. One of the deficient cases was on folic acid and multivitamin supplementation on presentation, although nonadherence with these supplements was documented in the medical record. The other deficient case was not on folic acid supplementation and did not receive folic acid supplementation for the deficient result. Vitamin B12 levels were checked simultaneously to serum folate levels in 85.2% of cases and within 6 months in 99.2% of cases. Of these patients, 2.0% were found to have vitamin B12 deficiency.

Based on our institution's charge for serum folate, a total of $316,043 was charged for the 2093 serum folate tests. The amount charged per deficient result was $158,022. Substituting the charge from the Robinson and Mladenovic study,[24] we calculated the corresponding total charge and charge per deficient result as $149,545 and $74,772, respectively. The actual total cost to our hospital was <$4186, with a cost per deficient test of <$2093.

DISCUSSION

Serum folate levels are often obtained when evaluating anemia without macrocytosis and anemia with macrocytosis.[2] They are also frequently obtained in the evaluation of delirium and dementia. A prior study evaluated both inpatient and outpatient serum folate levels in anemia, dementia, and altered mental status and found only 0.4% of serum folate results to be deficient.[26] In their study, the indications for serum folate tests were anemia or macrocytic anemia (60%) and dementia or altered mental status (30%).

We found the indications for serum folate testing in inpatients and emergency department patients to be different than prior studies. The majority of tests were done to evaluate anemia without macrocytosis (43.2%) or anemia with macrocytosis (13.2%). Lower percentages were done for the evaluation of delirium (12.0%) or dementia (3.2%). In addition, there were multiple indications that have not been noted in previous studies, including depression, peripheral neuropathy, malnutrition, pancytopenia, and others. These accounted for 28.0% of all indications. The reason for the difference in indications compared to prior studies is unknown but may be related to our cohort of exclusively inpatients and emergency department patients. Also, we observed a high concurrence of serum folate and vitamin B12 testing, with 85.2% of serum folate levels ordered at the same time as vitamin B12 levels. It appears that the tests are often ordered together even when the indication suggests that vitamin B12 alone may be more appropriate, such as peripheral neuropathy.

TABLE 3. Deficient and Low-Normal Serum Folate Results

	Age, y	Sex	Folate (ng/mL)	Indication	Comorbidities	Hgb (g/dL)	MCV (fL)
Deficient results							
Case 1	35	Male	2.6	Stroke workup	Phenytoin, depression	16.0	91
Case 2	63	Male	2.9	Macrocytic anemia	Alcohol abuse, acute GI bleed	7.7	119
Low-normal results							
Case 3	64	Male	3.3	Macrocytic anemia	Cirrhosis, alcohol abuse	12.3	109
Case 4	42	Male	3.4	Pancytopenia	HIV, B12 deficiency	7.5	93
Case 5	58	Male	3.4	Depression	Depression, alcohol abuse	13.8	98
Case 6	56	Female	3.5	Depression	Alcohol abuse		
Case 7	85	Male	3.6	Delirium	Depression	10.5	91
Case 8	81	Female	3.6	Anemia	Chronic anemia	9.1	95
Case 9	63	Male	3.9	Anemia	Chronic anemia, malnutrition	7.6	88

NOTE: **Abbreviations**: GI, gastrointestinal; Hgb, hemoglobin; HIV, human immunodeficiency virus; MCV, mean corpuscular volume.

We found that serum folate deficiency was rare, occurring in only 2 of 2093 results. Furthermore, the deficient serum folate results may have been checked for inappropriate indications. The first deficient result was noted as part of a stroke workup in a patient not taking folic acid supplementation. Current guidelines do not recommend serum folate testing in patients with new stroke.[33] In the second deficient case, serum folate testing was performed for evaluation of macrocytic anemia with an MCV of 119 fL. Although reasonable, this was an alcoholic patient presenting with acute gastrointestinal bleeding already on folic acid and multivitamin supplementation and known nonadherence with these supplements. In neither case was there a change in management based on the deficient result.

Given the low rate of serum folate deficiency and the lack of change in management based on deficient results, we conclude that there is a low utility of serum folate testing for any indication in inpatients and emergency department patients in folic acid-fortified countries. Based on prior studies, and supported by our results, there is no evidence for checking serum folate levels in delirium, dementia, peripheral neuropathy, malnutrition, or any of the other indications. In addition, our results demonstrate a low utility even in patients with anemia or macrocytic anemia.

The rate of serum folate deficiency in our study was significantly lower than prior studies.[24,26] There may have been geographical factors that led to a lower prevalence of folate deficiency in our study population. Our cohort included inpatients and emergency department patients, whereas previous studies had a majority of outpatients. It is known that serum folate levels can rapidly fluctuate with proper nutrition.[34] It may be that our patients received nutrition in the hospital that corrected serum folate levels prior to laboratory testing.

In addition to the low utility of serum folate testing, the charge per deficient result in our study ($158,022) was more than 100-fold higher than that in the Robinson and Mladenovic study ($1321).[24] Even when correcting for variability in hospital charges by using the charge from the latter study, the charge per deficient serum folate test remained 50-fold higher ($74,772). This implies that the increase in charge per deficient result was driven in part by a decreased rate of deficient tests. Folic acid fortification is likely responsible for some of the decrease. However, we believe another source is the excessive ordering of serum folate tests in patients without previously accepted indications. Because no change in management was made for the deficient patients in our study, the charge per serum folate deficient result that changed management approached infinity. This compares to $9979 in the Robinson and Mladenovic analysis.[24]

The cost to the hospital of a serum folate test was much lower than the charge, and estimated to be <$2093 per deficient result. Because serum folate tests are performed on a highly automated, random access analyzer that performs thousands of other measurements daily, the capital and labor costs for each test was well below $0.50 combined. With the addition of reagent costs, our total cost for each serum folate measurement was <$2.00. It is somewhat difficult to extrapolate these values to other hospitals, as exact costs and charges are variable. Nonetheless, the exceptionally low utility of serum folate testing makes the costs associated with these tests excessive.

Our study has several limitations. We conducted our study at a single institution in a country with mandatory folic acid fortification. Our results may not be generalizable to other institutions or patient populations, such as those in countries without mandatory folic acid fortification. Only 259 (12.4%) charts were reviewed, and indications were determined in 93.6% of charts, which may have caused our frequency to vary from the true frequency. Additionally, the low rate of deficient serum folate results limited our ability to identify associations with deficiency. Further evaluation for geographic variations of serum folate deficiency may reveal variable rates.

We conclude that in folic acid fortified countries, the rate of serum folate deficiency is increasingly rare, and the charge to patients and payers per deficient result is exceptionally high. In addition, testing in our study did not change clinical management, which makes the costs associated with these test wasteful. Further evaluation of serum folate testing of inpatients and emergency department patients in folic acid fortified countries is warranted; however, based on our results the utility appears poor for all indications.

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