

Folate Testing in Hospital Inpatients



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ABSTRACT

INTRODUCTION: Since Canada began fortifying grain products with folic acid in 1998, the rate of folate deficiency in outpatients has decreased substantially. Limited data exist on the prevalence of folate deficiency in Canadian hospital inpatients.

METHODS: The electronic patient record at a large urban academic institution was reviewed for all red blood cell folate and vitamin B12 level tests performed on inpatients between January 1 and December 31, 2010. Chart reviews were performed on patients found to have folate deficiency to determine the indication for folate testing and the etiology of deficiency.

RESULTS: There were 2563 red blood cell folate and 3154 vitamin B12 level tests performed in 2010. Of these, only 4 (0.16%) red blood cell folate levels were in the deficient range (<254 nmol/L), compared with 98 (3.1%) and 426 (13.5%) vitamin B12 levels that were in the deficient (<138 pmol/L) and intermediate (138–221 pmol/L) range, respectively. Of the 4 patients with folate deficiency, the etiology appeared to be alcohol abuse in one, a malabsorption syndrome in the second, decreased oral intake due to schizophrenia in the third, with the final low folate level appearing to be spurious. At a cost of \$12.54 per test, \$32,140 could be saved each year at this institution if red blood cell folate testing on inpatients was restricted.

CONCLUSION: Folate deficiency in inpatients is nearly nonexistent, while an appreciable number of patients have low/intermediate vitamin B12 levels. Significant savings could be achieved by eliminating folate testing on inpatients.

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Folate is a water-soluble B vitamin found in leafy green vegetables, fruits, grains, and cereals.^{1,2} As a coenzyme in one-carbon metabolism, it plays a critical role in the biosynthesis of DNA.^{3,4} Folate deficiency has been associated with pregnancy complications (neural tube defects, oral clefts, congenital heart disease), increased homocysteine concentrations, malignancy, atherosclerotic disease, and megaloblastic anemia.^{5,6} Risk factors for deficiency include: alcohol abuse, poor dietary intake, malabsorption syndromes (celiac, inflammatory bowel disease), medications

(methotrexate, phenytoin), and states of increased requirements (pregnancy, hemolysis, dermatitis).⁷

Red blood cell folate levels reflect tissue stores and can remain normal for 3–4 months in the absence of dietary folate.^{3,8} While both folate and vitamin B12 deficiency can cause a megaloblastic anemia, only B12 deficiency is associated with neurologic sequelae.⁹

In an effort to reduce the incidence of neural tube defects by increasing the dietary folate intake of reproductive age women, Canada began mandatory fortification of all flour and certain grain products with folic acid (the synthetic form of folate) in November 1998.¹⁰ Following this change, the prevalence of folate deficiency fell from 1.78% in 1997/1998 to 0.41% in 1999/2000, while the rate of B12 deficiency remained unchanged.¹¹ In a recent analysis of the Canadian Health Measure Survey, nearly 100% of unselected Canadian outpatients met or exceeded the accepted cut-off for red blood cell folate (>305 nmol/L).⁸ Similar results have been seen in other studies,

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in both Canada and the United States (where fortification with folate was instituted in January 1998).¹⁰⁻¹⁵

In the postfortification era, it is unclear which patients remain at risk for folate deficiency. In one predominantly outpatient study, the most common indications for folate testing were anemia and dementia/altered level of consciousness. The authors found that only 4/1007 serum folic acid levels were low (0.4%), 75% of which were in patients with a macrocytic anemia and none in those with confusion.⁶

While much work has been done looking at outpatients using laboratory databases, little research has focused on inpatients, a group at presumably higher risk of conditions contributing to folate deficiency. One prefortification study in Denver, Colo. made up of 83% inpatients found that 2.3% of folate levels were below normal.¹⁶ Two more recent studies from hospitals in the United States and Canada found the incidence of folate deficiency to be <1%, although the proportion of inpatients making up these samples was not defined.^{5,17} To our knowledge, only one study, published in 2013 by Theisen-Toupal et al,¹⁸ has examined folate deficiency exclusively in inpatients. This single-center study at an American academic institution found 0.1% (2/2093) of serum folate levels to be in the deficient range. The authors noted that the rate of folate deficiency in their study was significantly lower than in prior studies, and that the low rate of deficient folate levels limited the ability to identify associations with deficiency. The possibility of geographic variation in folate deficiency was also raised. Their results, while consistent with previous work, require confirmation at other institutions before definitive conclusions about the role of folate testing in hospitalized inpatients can be made. Additionally, no recent analysis focusing solely on Canadian inpatients has been performed.

Each year in Canada and the United States, thousands of inpatient red blood cell folates are ordered. Our study sought to determine the rate of red blood cell folate deficiency in inpatients at 3 major Canadian academic hospitals (including a major cancer centre), correlate it with the indications for testing and other laboratory abnormalities (ie, vitamin B12 deficiency), determine the most common etiologies of folate deficiency, and calculate the cost per positive test.

We hypothesized that the rate of folate deficiency would be extremely low (<1%) and that significant cost savings could result from restricting folate testing. The most common indication for folate testing was anticipated to be a macrocytic anemia, and the most responsible etiologies were expected to be a mix of alcohol abuse, medications, and malabsorption syndromes.

METHODS

The University Health Network (UHN) is a partnership of 3 major downtown academic hospitals (Toronto General Hospital, Toronto Western Hospital, and Princess Margaret Hospital) in Toronto, Canada. The UHN's electronic patient record includes all investigations (eg, biochemistry, hematology, radiology) and clinical documentation for rendered outpatient and inpatient services.

The UHN electronic patient record was retrospectively reviewed for all red blood cell folate (only red blood cell folate is available at the UHN) and vitamin B12 levels performed in the 2010 calendar year. Using patient encounter numbers, inpatients were identified and included in our analysis, while outpatients and emergency patients were excluded. Additional variables obtained from these patients included: complete blood count, ferritin, vitamin B12, reticulocyte count, aspartate aminotransferase, alanine aminotransferase, gamma-

glutamyl transpeptidase, alkaline phosphatase, international normalized ratio, albumin, bilirubin, thyroid-stimulating hormone, and beta-human chorionic gonadotropin.

In patients found to have a low red blood cell folate (<254 nmol/L), chart reviews were performed by one of the authors. The indications for testing and the most likely etiology of folate deficiency were determined by consensus between the authors. The cost per red blood cell folate assay (\$12.54) was obtained from the UHN's Laboratory Medicine Program, and the cost per folate deficient result was calculated. Other ancillary costs were not included.

Ethics approval was obtained from the UHN's Research Ethics Board.

RESULTS

In the year 2010, there were 2563 red blood cell folate and 3154 vitamin B12 levels performed at the UHN. The mean red blood cell folate level was 1436 ± 20 nmol/L. There were 4 red blood cell folate levels (0.16%) that fell below the normal range (<254 nmol/L). The characteristics of these patients are shown in the [Table](#). Of the 4 low values, one appeared to be an error, as levels within the normal range were reported in the preceding and following months of this value. Based on chart reviews, the presumed etiologies of folate deficiency in the other patients were alcohol abuse in the first, a malabsorption syndrome in the second, and decreased oral intake secondary to schizophrenia in the third. The reasons for testing may have been anemia or related to the etiology of deficiency, however, this was not clearly outlined in the

CLINICAL SIGNIFICANCE

- Folate deficiency is extremely uncommon in Canadian inpatients, with only 4 of 2563 (0.16%) red blood cell folate levels in the deficient range.
- A significant number of inpatients have deficient (3.1%) or intermediate (13.5%) vitamin B12 levels.
- Red blood cell folate should no longer be ordered except in very specific circumstances (eg, malabsorption, starvation).
- At our institution alone, eliminating red blood cell folate testing could save \$32,000 per year.

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