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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 dramatically. Limited data exists 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 levels 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 levels 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 non-existent, while an appreciable number of patients have low/intermediate vitamin B12 levels. Significant savings could be achieved by eliminating folate testing on inpatients.
Introduction

Folate is a water soluble B-vitamin found in leafy green vegetables, fruits, grains and cereals\textsuperscript{1,2}. As a coenzyme in one-carbon metabolism, it plays a critical role in the biosynthesis of DNA\textsuperscript{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\textsuperscript{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)\textsuperscript{7}.

Red blood cell folate levels reflect tissue stores and can remain normal for 3-4 months in the absence of dietary folate\textsuperscript{3,8}. While both folate and vitamin B12 deficiency can cause a megaloblastic anemia, only B12 deficiency is associated with neurologic sequelae\textsuperscript{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\textsuperscript{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\textsuperscript{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)\textsuperscript{8}. Similar results have been seen in other studies, in both Canada and the United States (where fortification with folate was instituted in January 1998)\textsuperscript{10-15}. 
In the post-fortification 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.

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 pre-fortification study in Denver, Colorado made up of 83% inpatients found that 2.3% of folate levels were below normal. 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. To our knowledge, only one study, published in 2013 by Theisen-Toupal et al., 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 regarding 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 three major Canadian academic hospitals (including a major cancer centre), correlate it with the indications for testing and other laboratory abnormalities (i.e. 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 three 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 (biochemistry, hematology, radiology, etc.) 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 (CBC), ferritin, vitamin B12,
reticulocyte count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), international normalized ratio (INR), albumin, bilirubin, thyroid stimulating hormone (TSH) and beta-human chorionic gonadotropin (b-hcg).

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 University Health Network. The mean red blood cell folate level was 1436 ± 20 nmol/L. There were four 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 four 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 electronic patient record. All of the patients with low red blood cell folate levels were anemic, but only two of the three patients had an elevated mean corpuscular volume. The
third patient’s mean corpuscular volume was near the upper limit of normal. None of the blood films performed suggested a megaloblastic anemia. Based on a cost per test of $12.54, the cost per low red blood cell folate was $10,713 with $32,140 being spent per year on inpatient red blood cell folate testing.

The mean vitamin B12 level was 467 ± 10 pmol/L. There were 98 vitamin B12 levels (3.1%) that fell below the lower limit of normal (<138 pmol/L) and 426 (13.5%) that were in the intermediate range (138-221 pmol/L). Thus, 16.6% of the vitamin B12 levels performed were in the low or intermediate range. None of the patients with low red blood cell folate levels had low or intermediate vitamin B12 levels.

Discussion

This study found that at the University Health Network (UHN) in 2010, only 4/2563 (0.16%) of red blood cell folate levels performed were in the deficient range, compared with 98/3154 (3.1%) low and 426/3154 (13.5%) intermediate vitamin B12 levels. Of the four low red blood cell folate levels, one was thought to be spurious, while the other three were likely related to alcohol abuse, a malabsorption syndrome and decreased oral intake due to schizophrenia. Only two of the three patients with folate deficiency had an elevated mean corpuscular volume and none of these patients were vitamin B12 deficient. None of the blood films performed demonstrated a megaloblastic anemia.

Our results confirm the study findings of Theisen-Toupal et al. from 2013 in which 2/2093 (0.1%) serum folate levels were deficient at a large academic medical center in Boston in the year 2011. In their study, the comorbidities related to deficiency were phenytoin use, depression
and alcohol abuse. In the cases of folate deficiency, the indications for testing were stroke in one case and elevated mean corpuscular volume in a patient with alcohol abuse in the second. The authors noted that no change in management occurred in either case based on the folate results\textsuperscript{18}. The results of our study are also similar to those seen in the Canadian Health Measures Survey in which less than 1\% of outpatients were folate deficient\textsuperscript{8}. Similar results were seen in a 2001 Canadian study of inpatients and outpatients where the prevalence of red blood cell folate deficiency was 0.7\% at one hospital and 1.9\% at another\textsuperscript{5}. In that study, the most common indications for testing yielding a low folate level were anemia (not macrocytic or megaloblastic), vitamin B12 deficiency, alcohol abuse and celiac disease. The authors argued that without megaloblastic blood film changes, the anemias were unlikely the result of folate deficiency and that folate testing should no longer be performed as part of the work-up for anemia and should only be performed based on clinical risk factors (malnourished pregnant women, alcoholics or patients with malabsorption syndromes)\textsuperscript{5,6}.

The low prevalence of folate deficiency that we found in inpatients is almost certainly the result of grain fortification. In Australia, where mandatory grain fortification was instituted in 2009, the rate of red blood cell folate deficiency in a mix of inpatients and outpatients fell from 3.4\% in April 2009 to 0.5\% by April 2010\textsuperscript{19}. Conversely, in Poland, where grain products are not fortified, the prevalence of serum folate deficiency in a group of inpatients was found to be 32\%\textsuperscript{20}. While folic acid supplementation has been well documented to result in a significant decrease in neural tube defects, these results suggest that it has also essentially eliminated folate deficiency related anemia\textsuperscript{5,21}.
To our knowledge this is the first study to assess the prevalence of folate deficiency in a clearly defined and diverse group of Canadian inpatients following grain fortification with folic acid. In an era of pressures to reduce health care costs, our results have several implications. First, red blood cell folate testing as an orderable investigation should be restricted to only the most unique scenarios. Assuming a cost of $12.54 per test (which does not include ancillary costs), $32,140 could be saved per year at the UHN by eliminating red blood cell folate testing. Additional savings could be achieved if folate testing was abolished in outpatient and emergency department settings where the rate of folate deficiency has already been shown to be vanishingly low. Interestingly, in the Boston study, the authors reported the cost per folate test to be less than two dollars, yet the cost passed on to patients/insurers for 2093 serum folate tests was $316,043 ($151/test) with a cost per deficient result of $158,022. Second, folate deficiency as an etiology of elevated mean corpuscular volume should be de-emphasized in medical education. Anecdotally, both of us have seen folate deficiency and vitamin B12 deficiency taught with equal weight as etiologies of a macrocytic anemia. More emphasis should be placed on vitamin B12 deficiency given the one in six rate low/intermediate levels in our study, coupled with the implications of a missed diagnosis.

The strengths of our study include the completeness of red blood cell folate sampling. All laboratory results performed on inpatients at the UHN are reported in the electronic patient record. Therefore, we are confident that no red blood cell folate levels were missed. The electronic patient record also allowed us to reliably exclude outpatient and emergency department patients. Our study was performed at an institution with a wide variety of inpatients including medical, surgical, psychiatric, oncology, transplant and critical care patients. No major
inpatient groups were missed making our results generalizable to other urban institutions.

The weaknesses of our study include the limits of information that could be garnered from the electronic patient record. Unfortunately, the rationale for folate testing and the etiology of deficiency were subject to bias as they had to be inferred from clinical notes and the patient’s medical history. Given the limited number of low red blood cell folate levels, correlations between folate levels and indications for testing and other lab values should be considered hypothesis generating. Additionally, our results represent the experience at a major downtown teaching hospital and may not be applicable to smaller or more rural centers.

In conclusion, our study found that red blood cell folate deficiency in inpatients is exceedingly rare while vitamin B12 deficiency remains quite common. Given a cost of $12.54 per red blood cell folate test, were folate testing to be removed as an orderable investigation, $32,140 per year could be saved on inpatients alone. Further savings could be achieved by limiting folate testing in outpatients. Folate deficiency as an etiology of anemia should be de-emphasized in Canadian medical training given the rarity of deficiency in both inpatients and outpatients.
References


Clinical and laboratory variables for patients found to have low RBC folate levels at the UHN in 2010. N/D = Not Determined

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>38</td>
<td>77</td>
<td>63</td>
<td>57</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>M</td>
<td>F</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td><strong>RBC Folate Level (nmol/L)</strong></td>
<td>234 (Aug 4)</td>
<td>1459 (May 8)</td>
<td>241 (Nov 20)</td>
<td>242 (Feb 27)</td>
</tr>
<tr>
<td>Normal: 254-1151</td>
<td></td>
<td>240 (June 3)</td>
<td>&gt;2500 (Sept 13)</td>
<td>657 (March 9)</td>
</tr>
<tr>
<td><strong>Vitamin B12 Level (pmol/L)</strong></td>
<td>234 (Aug 4)</td>
<td>447 (May 8)</td>
<td>335 (Nov 20)</td>
<td>&gt;1476 (Feb 27)</td>
</tr>
<tr>
<td>Low: &lt;138 Intermediate: 138-221 Normal: 222-652</td>
<td></td>
<td>430 (June 3)</td>
<td>370 (Sept 13)</td>
<td>775 (March 9)</td>
</tr>
<tr>
<td><strong>Blood Film</strong></td>
<td>Slight polychromasia Slight target cells Occasional spherocytes</td>
<td>Polychromasia</td>
<td>N/D</td>
<td>N/D</td>
</tr>
<tr>
<td><strong>Hemoglobin (g/L)</strong></td>
<td>108</td>
<td>82</td>
<td>119</td>
<td>107</td>
</tr>
<tr>
<td>Normal: 140-180</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mean Corpuscular Volume (fL)</strong></td>
<td>105</td>
<td>81</td>
<td>97.9</td>
<td>90.4</td>
</tr>
<tr>
<td>Normal: 80-95</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Presumed Etiology of Folate Deficiency</strong></td>
<td>Alcohol Abuse</td>
<td>Palatal Squamous Cancer</td>
<td>Malabsorption Syndrome NYD</td>
<td>Decreased Oral Intake due to Schizophrenia</td>
</tr>
</tbody>
</table>
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
- RBC folate should no longer be ordered except in very specific circumstances (malabsorption, starvation, etc.)
- At our institution alone, eliminating RBC folate testing could save $32,000 per year