**Box 2: Initial laboratory tests for patients with prolonged or chronic fatigue**

- Complete blood count
- Erythrocyte sedimentation rate
- Serum urea, electrolyte and creatine levels
- Serum calcium and phosphate levels
- Liver transaminase levels
- Thyroid-stimulating hormone level
- Fasting blood glucose level
- Creatine kinase level
- Urinalysis for protein, blood and glucose
- Ferritin level
- Urine pregnancy test in women of childbearing age

tigue. We use a small battery of routine tests (Box 2). However, in the absence of a positive history or physical examination, laboratory tests are rarely helpful. Minor abnormalities in test results will be common, and most are unrelated to fatigue even in patients complaining of fatigue. Iron deficiency, even in the absence of anemia, can cause fatigue, and treatment of the deficiency with iron appears to help in many such cases. Additional directed tests (e.g., HIV antibody testing) should be considered based on the patient's history and the physical findings.

In the case of our patient with fatigue and elevated transaminase levels but without other typical features of celiac disease (steatorrhea, weight loss), the clinical index of suspicion (pretest probability) of celiac disease was estimated to be between 20% and 30%. Since the test for IgA antiendomysial antibody has a high sensitivity and specificity (about 90% and 95% respectively), the positive likelihood ratio is about 30. By using the Fagan nomogram, we found that the positive predictive value (post-test probability) for this patient increased to about 90%.

The differential diagnosis of fatigue in primary care is very broad, but an organized approach to the patient as we have described can identify key conditions of concern efficiently and reduce the expensive workups for obscure conditions that this undifferentiated complaint can sometimes generate.

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This article has been peer reviewed.

**Competing interests:** None declared.

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HEALTH AND DRUG ALERT

## WinRho and disseminated intravascular coagulopathy

**Reason for posting:** WinRho is a human blood product, $Rh_0$(D) immune globulin, widely used to treat immune thrombocytopenic purpura (ITP) and to prevent Rh alloimmunization in pregnant women who are Rh-negative. Recently, however, a case series[1] described 6 patients with ITP who were given WinRho who subsequently experienced severe hemolysis and disseminated intravascular coagulation (DIC); 5 of them died. The manufacturer, Cangene, has since issued "Dear Health Care Professional" letters in both Canada and the United States that warn of 9 international reports of this serious adverse effect.[2]

**The drug:** WinRho is a gamma globulin fraction of plasma containing antibodies to $Rh_0$(D) derived from blood donors. Donated plasma is stringently screened for known pathogens and then filtered to further reduce the risk of transmission of viruses such as hepatitis B and C, HIV and parvovirus.

WinRho is routinely given to Rh-negative women in their third trimester of pregnancy (28 weeks), postpartum (within 72 h) and after possible exposure to Rh-positive blood after pregnancy termination, amniocentesis or abdominal trauma, to prevent maternal Rh-antibody formation and hemolytic disease of the newborn in future pregnancies. WinRho is also used to treat ITP, an autoimmune disorder of increased splenic platelet destruction.

Pregnant women are treated with 120–300 μg of WinRho, administered intravenously or intramuscularly. Patients with ITP are given a much higher dose, generally 25–50 μg/kg intravenously. Common adverse effects, which often occur within minutes to days after the infusion, include headache, chills and fever, back pain and shaking. Serious but rare adverse effects have included acute respiratory distress syndrome, acute renal insufficiency, acute anemia and hemoglobinuria.[3] The recent postmarketing case reports add DIC as another rare but potentially serious adverse effect, which likely starts as hemoglobinemia and hemoglobinuria.

The 6 cases[1] reported in the fall of 2005 were all submitted to the US Food and Drug Administration between 1999 and 2004. They involved 4 males and 2 females 12–85 years of age with ITP; all received doses of 48–75 μg/kg. Although most patients were discharged

DOI:10.1503/cmaj.060201

**Box 1: Early indications of intravascular hemolysis**

**Symptoms**

- Generalized weakness
- Lightheadedness
- Fever or chills
- Shortness of breath
- Chest pain
- Back pain
- Sudden weight gain
- Fluid retention
- Decreased urine output
- Discoloured urine
- Jaundice

**Signs**

- Dyspnea
- Edema
- Hemoglobinuria
- Hypotension
- Oliguria or anuria
- Pallor or jaundice
- Tachycardia
- Increased bruising
- Prolonged bleeding and clotting times*

*May be difficult to detect in cases of pre-existing immune thrombocytopenic purpura.

feeling well, 4 experienced acute symptoms of hemoglobinemia or hemoglobinuria within 4 hours of receiving the drug (in the other 2 cases, the exact timing was not clear). All 5 patients were adults who died 3–10 days after being treated; their clinical and laboratory findings were consistent with DIC (e.g., increased prothrombin [PT] and partial thromboplastin times [PTT], fibrin degradation [FDP] or split products [FSP] and D-dimer; decreased fibrinogen level), but with no evident cause of DIC other than the drug treatment.

Cangene reports that a total of 9 cases of DIC have been reported internationally (one in Canada). For ITP patients, Cangene estimates the risk of intravascular hemolysis to be less than 1 in 1000; that of DIC, about 1 in 10 000. Patient age, sex and comorbid conditions do not appear to predict the adverse effect; neither do pretreatment renal function or hemoglobin levels, nor concomitant administration of other blood products. Some of the patients in whom DIC manifested had tolerated previous doses of the drug.

There are no known reports of intravascular hemolysis in pregnant women given WinRho.

**What to do:** Patients who receive WinRho should be warned of the risk of this rare but potentially fatal adverse event and advised to immediately report any "red flag" symptoms or signs (Box 1). Consideration should be given to close monitoring of patients with symptoms of acute hemoglobinemia or hemoglobinuria, anemia and renal insufficiency for signs of DIC. Appropriate laboratory tests include complete blood counts; PT and PTT; direct and indirect bilirubin; measurement of serum creatinine, urea, haptoglobin, lactate dehydrogenase, D-dimer and FDP/FSP; and urine dipstick and microscopic urinalysis.

It seems wise to advise pregnant patients of the theoretical risks of receiving a blood product.

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All Health and Drug Alerts are posted online ahead of print and are available at www.cmaj.ca. This article was posted on Feb. 22, 2006.