Are medication restrictions before FOBT necessary?
Practical advice based on a systematic review of the literature

Gerald Konrad MD MSc CCFP Alan Katz MB ChB MSc CCFP FCFP

Abstract

Objective To determine whether medication interventions enhance the sensitivity and specificity of guaiac-based fecal occult blood testing (FOBT) when screening for colorectal cancer (CRC).

Data sources We searched PubMed-MEDLINE, CINAHL, and the Cochrane databases using the MeSH headings occult blood, feces/analysis, and guaiac/analysis, linking them to variations of anticoagulants, heparin, warfarin, iron, aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), clopidogrel, cyclooxygenase-2 inhibitors, and ascorbic acid (vitamin C). Study selections were limited to English studies involving humans.

Study selection All resulting titles and abstracts were reviewed for studies that included manipulation of medications associated with guaiac-based FOBT. If the study's relevance was unclear from the abstract, the full article was reviewed. The search resulted in 31 pertinent studies.

Synthesis No studies addressed the effects of medication interventions on the sensitivity or specificity of FOBT screening. Randomized controlled trials, however, showed no increase in the rate of positive results among those taking NSAIDs. The literature is mixed regarding the effect of NSAIDs on the positive predictive value of a positive FOBT result, although no change in positive predictive value has been shown for warfarin. Iron will not affect FOBT results in vivo. Ascorbic acid might inhibit positive FOBT results both in vitro and in vivo, but it has not been studied in screening populations.

Conclusion Studies evaluating the effects of medication intervention on FOBT screening for CRC are limited by their lower quality and because they do not address sensitivity and specificity. Available evidence, however, does not suggest a benefit from withholding NSAIDs, anticoagulant medications, or iron during the screening period. These recommendations should be abandoned in order to maximize adherence to screening. Positive FOBT results obtained among patients taking these medications deserve full evaluation for CRC. Until further studies clarify the effect of ascorbic acid on FOBT screening, withholding this medication before testing seems prudent.

Fecal occult blood testing (FOBT) remains an appropriate screening option for colorectal cancer (CRC). However, FOBT is limited by a lack of patient adherence. A consistently reported barrier is the lack of physician endorsement for screening. Other barriers include embarrassment or unpleasantness (the "yuk" factor), anxiety regarding results, lack of symptoms or health concerns, and practical issues such as inconvenience and cost. Dietary restrictions and medication restrictions have also been implicated as barriers to screening.

The most recently reported survey data, published in 2007, showed that only 30.2% of eligible Canadians were adherent to CRC screening guidelines. Clearly, addressing barriers to screening is a worthy task for physicians who endorse screening for CRC. A recent systematic review suggested that dietary restrictions were unnecessary when performing FOBT, a position endorsed by Cancer Care Ontario. The Ontario panel also advised against restricting medications other than ascorbic acid before FOBT screening. A systematic review of bleeding risks among patients

This article has been peer reviewed. Cet article a fait l’objet d’une révision par des pairs. Can Fam Physician 2012;58:939-48
taking anticoagulant or antiplatelet medications concluded that these medications did not diminish the positive predictive value (PPV) of the FOBT.\textsuperscript{18}

Manufacturers of guaiac-based FOBTs available in Canada continue to recommend medication restrictions before testing. The patient instructions for Hemoccult II and Hemoccult II SENSA recommend avoiding nonsteroidal anti-inflammatory drugs (NSAIDs) for 7 days, but allow up to 1 adult acetylsalicylic acid (ASA) tablet daily. Both recommend avoiding ascorbic acid supplements and citrus juices.\textsuperscript{19,20} The insert for Tri-Slide suggests consideration of avoiding gastric irritants such as NSAIDs and anticoagulant medications after discussion with the physician. Avoidance of ascorbic acid is also recommended.\textsuperscript{21} ColoScreen and Hema-Screen recommend continuing usual medications with the exception of ascorbic acid.\textsuperscript{22,23} Despite a lack of recommendations from manufacturers, 16% of primary care physicians,\textsuperscript{24} 32% of gastroenterologists,\textsuperscript{25} and 10% of internal medicine residents\textsuperscript{26} have reported discontinuing anticoagulant medications before FOBT. Forty-seven percent of gastroenterologists have reported withholding iron supplements.\textsuperscript{25}

This systematic review explores the evidence for medication restrictions before CRC screening with guaiac-based FOBT.

**DATA SOURCES**

PubMed-MEDLINE, the Cochrane databases, and CINAHL were searched using the key words and MeSH terms occult blood, feces/analysis, and guaiac/analysis. These terms were linked to variations of anticoagulants, heparin, warfarin, clopidogrel, iron, aspirin, NSAIDs, cyclooxygenase-2 inhibitors, and ascorbic acid (vitamin C). The search was limited to English studies involving humans. References from relevant articles were also explored for further resources.

**Study selection**

Our PubMed search revealed 417 articles. Cochrane and CINAHL database searches revealed no additional studies. All titles and abstracts were reviewed for studies that included the manipulation of medications before or during guaiac-based FOBT. If the study’s relevance was unclear from the abstract, the full article was reviewed. The resulting 31 pertinent studies are summarized in Tables 1 to 3.\textsuperscript{27–57}

**SYNTHESIS**

Nonsteroidal anti-inflammatory drugs

There is a common assumption that FOBT screening for patients taking NSAIDs or anticoagulant medications is adversely affected by the increased predisposition to upper gastrointestinal (GI) bleeding and by increased false-positive rates among these patients. If so, this reduction in specificity would result in unnecessary follow-up evaluations. There might also be a danger if one assumes that a positive FOBT from a patient taking these medications has a reduced PPV. Attributing a positive result to a medication effect could mistakenly result in neglecting further necessary evaluations.

Unfortunately, there are no studies that evaluate the effects of NSAIDs and anticoagulant medications on the sensitivity and specificity of guaiac-based FOBT screening. Such studies would necessitate evaluating subjects with negative FOBT results for lower GI pathology. Most studies look at either the rate of positive FOBT results or the PPV of a positive result.

Only 2 randomized controlled trials compared rates of positive guaiac-based FOBT results between users of NSAIDs and control subjects, with no significant difference found between groups.\textsuperscript{27,28} Several randomized trials compared rates of positive FOBT results between ASA and ibuprofen,\textsuperscript{29} between various formulations of ibuprofen,\textsuperscript{30} and among ASA, warfarin, or both in combination.\textsuperscript{31} None showed differences between groups, but there were no control groups.

Cross-sectional studies reported low rates of positive Hemoccult results (0% to 5.5%) among patients taking anti-inflammatory agents.\textsuperscript{32,33} The PPV for CRC or large adenomas of a positive FOBT result, however, was 25% in a group of rheumatoid disease clinic patients using NSAIDs,\textsuperscript{32} which compares favourably with the PPV for positive Hemoccult screening of up to 17.9% in the general population reported in a large Minnesota trial.\textsuperscript{34} This substantial PPV makes it clear that a positive result should not be attributed solely to NSAID use.

Two cohort studies looking at the effects of NSAIDs on FOBT showed inconsistent results. A non-randomized prospective crossover study of medical patients taking either no ASA, 81 or 325 mg of ASA daily, or warfarin showed no difference in the rates of positive Hemoccult II results between the control period and different treatments.\textsuperscript{34} Quantified fecal blood in controls increased slightly when they switched to 325 mg of ASA daily ($P=.02$). This difference, however, disappeared when controls were compared with all patients taking ASA in the study ($P=.14$). Conversely, in a cohort study of subjects screened with Hemoccult II, NSAID users had a significantly higher rate of positive results at 27% compared with 4% for those not taking NSAIDs ($P<.01$).\textsuperscript{35} These results, however, might not be valid because they relied on self-reported adherence to the instructions to withhold NSAIDs during the screening period. Only 26 of 1797 subjects admitting to continuing NSAIDs during the testing. Neither study reported follow-up of positive FOBTs, so PPV was undetermined.
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<td>Fries and Britton (1973)</td>
<td>Rheumatoid arthritis (N = 27) (mean age 56.3 y)</td>
<td>Fenoprofen (1.4-2.4 g/d) for 6 wk High-dose ASA (4-6 g/d) for 6 wk Placebo for 3 wk</td>
<td>RCT, double-blind crossover with temporal controls</td>
<td>Placebo: 15.4% positive FOBT results ASA: 17.1% positive results Fenoprofen: 20% positive results No significant difference between groups</td>
<td>Unspecified guaiac-based FOBT; true positives not determined</td>
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<tr>
<td>Greenberg et al (1999)</td>
<td>Healthy house officer volunteers (mean age 29.8 y)</td>
<td>ASA (30, 81, or 325 mg/d) for 30 d (n = 10 in each group) Placebo for 30 d (n = 10)</td>
<td>RCT, double blind</td>
<td>0 positive results using Hemoccult II or Hemoccult SENSA, in all groups</td>
<td>No control group; unspecified guaiac-based FOBT</td>
</tr>
<tr>
<td>Brooks et al (1970a)</td>
<td>Rheumatoid arthritis (mean age 51.5 y)</td>
<td>Ibuprofen (600 mg/d) for 4 wk (n = 41) ASA (3.6 g/d) for 4 wk (n = 45) U-24568 (600 mg/d) for 4 wk (n = 41)</td>
<td>Randomized, double blind</td>
<td>Total positive FOBT results not clarified No significant differences between groups</td>
<td>No control group; unspecified guaiac-based FOBT</td>
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<tr>
<td>Brooks et al (1970b)</td>
<td>Rheumatoid arthritis (mean age 53.1 y)</td>
<td>Ibuprofen (900 mg/d) for 4 wk (n = 60) ASA (3.6 g/d) for 4 wk (n = 62)</td>
<td>Randomized, double blind</td>
<td>Total positive FOBT results not clarified No significant differences between groups</td>
<td>No control group; unspecified guaiac-based FOBT</td>
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<tr>
<td>Zuin et al (2000)</td>
<td>Healthy volunteers (mean age 27.7 y)</td>
<td>Ibuprofen tablet (800 mg/d) for 7 d (n = 18) Ibuprofen fast-melting tablets (800 mg/d) for 7 d (n = 18)</td>
<td>Two-sequence crossover</td>
<td>0 positive FOBT results</td>
<td>No control group; unspecified FOBT</td>
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<tr>
<td>Hurlen et al (2006)</td>
<td>AMI survivors (mean age 60.9 y)</td>
<td>ASA (160 mg/d) for 3 mo (n = 94) Warfarin (INR 2.8-4.2) for 3 mo (n = 84) ASA (75 mg/d) plus warfarin (INR 2.0-2.5) for 3 mo (n = 89)</td>
<td>Randomized</td>
<td>ASA: 8.5% positive hemo FEC results Warfarin: 7.1% positive results ASA with warfarin: 5.6% positive results No significant differences between groups</td>
<td>No control group; 14 of 19 positive results retested (3 remained positive, 2 with diverticulosis and 1 with normal findings on colonoscopy)</td>
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<tr>
<td>Bahrt et al (1984)</td>
<td>Rheumatoid disease clinic patients (age not reported)</td>
<td>Unspecified NSAID, salicylate, or steroid use (n = 145)</td>
<td>Cross-sectional</td>
<td>Anti-inflammatory: 5.5% positive results using Hemoccult</td>
<td>No control group; all positive results evaluated (2 colonic neo-plasms [PPV 25%])</td>
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<tr>
<td>Norfleet (1983)</td>
<td>Healthy volunteers (N = 27)</td>
<td>Control period for 3 d ASA (1300 mg/d) for 7 d</td>
<td>Temporally controlled trial</td>
<td>0 positive Hemoccult II test results during both test periods</td>
<td>Blood loss quantified with HemoQuant; no difference between groups</td>
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<tr>
<td>Greenberg et al (1996)</td>
<td>Medical, cardiac, and anticoagulation clinic patients (mean age approximately 60 y)</td>
<td>Control for 1 wk, then ASA 325 mg/d for 8 wk (n = 25) ASA 325 mg/d for 1 wk, then ASA 81 mg/d for 8 wk (n = 46) ASA 81 mg/d for 1 wk, then ASA 325 mg/d for 8 wk (n = 4) Warfarin (unspecified INR) for 4-6 wk (n = 25)</td>
<td>Cross-sectional with crossover</td>
<td>Control week: 0 positive results using Hemoccult II ASA 81 mg/d: 14% positive results ASA 325 mg/d: 4% positive results Warfarin: 12% positive results No significant differences between groups</td>
<td>Blood loss quantified with HemoQuant; no difference between groups</td>
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<tr>
<td>Niv (1987)</td>
<td>Israeli screening population taking NSAIDs (aged &gt; 40 y)</td>
<td>Self-reported discontinuing NSAIDs during FOBT (n = 1771) Self-reported NSAID use during FOBT (n = 26)</td>
<td>Cohort</td>
<td>NSAID users: 27% positive results using Hemoccult II Nonusers: 4% positive results (P &lt; .01)</td>
<td>Relied on self-reporting of compliance with FOBT instructions</td>
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<td>Pye et al (1987)</td>
<td>Asymptomatic subjects with positive screening results on Hemoccult or Feca-EIA (aged 50–74 y)</td>
<td>NSAID use according to self-report (n = 50) No NSAID use according to self-report (n = 405)</td>
<td>Cross-sectional 4.2% total positive Hemoccult or Feca-EIA results from screening population of 10931 All positive results evaluated with colonoscopy NSAID users: PPV 20% for neoplasia Nonusers: PPV 32% No significant difference (P = .1) Hemoccult and Feca-EIA (immunologic test) results not reported separately</td>
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<tr>
<td>Kahi and Imperiale (2004)</td>
<td>VA patients referred for colonoscopy with positive Hemoccult II FOBT results (N = 193) (mean age 66 y)</td>
<td>ASA or NSAID use according to self-report and record review (n = 135) No ASA or NSAID use according to self-report and record review (n = 58)</td>
<td>Cross-sectional ASA or NSAID users: PPV 21% for &quot;abnormality&quot; Nonusers: PPV 19% No significant differences between groups No correlation between ASA dose and colonoscopic pathology; not a screening population; large polyps and CRC were not reported separately from other colonic pathology</td>
</tr>
<tr>
<td>Clarke et al (2006)</td>
<td>Scottish patients referred for colonoscopy with positive HemaScreen (guaiac) FOBT results (aged 50–69 y)</td>
<td>Self reported ASA, NSAID, or antiocoagulant use (n = 301) No ASA, NSAID, or antiocoagulant use (n = 308)</td>
<td>Cross-sectional ASA, NSAID, or antiocoagulant use: PPV 47.5% for colorectal neoplasia Nonusers: PPV 56.5% (P = .012) PPV for CRC with no significant differences between groups (P = .7); anticoagulants made up only 7.7% of prescriptions</td>
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<td>Sawhney et al (2010)</td>
<td>VA patients referred for colonoscopy with positive Hemoccult II results (mean age approximately 68 y)</td>
<td>No medications according to review of pharmacy profile (n = 518) ASA (n = 264) NSAIDs (n = 218) Warfarin (n = 85) Clopidogrel (n = 41)</td>
<td>Cross-sectional Controls: PPV 30.5% for advanced neoplasia ASA users: PPV 20.5% (P &lt; .01) NSAID users: PPV 19.7% (P &lt; .01) Warfarin users: PPV 20% (P = .05) Clopidogrel users: PPV 7.3% (P &lt; .01) Not a screening population; included positive FOBT results for evaluation of symptoms</td>
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<td>Doran and Hardcastle (1982)</td>
<td>CRC patients and age-matched controls</td>
<td>Temporal control without ASA, then ASA (600 mg/d) for 3 d (n = 50) Age-matched subjects with temporal control, then ASA (600 mg/d) for 3 d (n = 50)</td>
<td>Temporally controlled trial with control cohort component CRC patients during temporal control: 70% positive Hemoccult II results CRC patients taking ASA: 82% positive results (P &lt; .02) Age-matched cohort: single subject with positive Hemoccult II results before and while taking ASA 51Cr-RBC labeling in CRC patients (n = 25) showed no correlation between blood volume and ASA use or tumour location</td>
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<td>Kewenter et al (1984)</td>
<td>Patients taking dicumarol (N = 849) (mean age 67 y)</td>
<td>Dicumarol, unspecified dose</td>
<td>Cross-sectional 15% positive results using Hemoccult II PPV 19% for CRC and adenomas among 79 subjects evaluated further (57 of 67 with ≥3 of 6 positive samples; 22 of 61 with &lt;3 of 6 positive samples) No correlation between positive Hemoccult result and anticoagulation index</td>
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Several cross-sectional studies examined patients with positive FOBT results to determine if the PPV was affected by NSAIDs. Two showed a sizeable PPV of around 20% among NSAID users with no difference from controls. Two others, however, noted lower PPVs among NSAID users than controls. However, as in the previous studies, PPVs among the NSAID users were substantial enough to justify further evaluation.

One study evaluated the effect of ASA on FOBT of patients with known CRC. It found that 600 mg of ASA given daily for 3 days did not increase the rate of positive Hemoccult II results in this group. Chromium-51 red blood cell labeling confirmed no increase in quantified fecal blood loss when taking ASA.

**Anticoagulant medications**

There is little literature exploring the effects of anticoagulant medications on FOBT results. A single cross-sectional study of 849 patients taking dicumarol revealed a rate of positive Hemoccult II results of 15%. Further evaluation of most of these patients showed a PPV of 19% for CRC and adenomas.

Studies comparing the rates of positive FOBT results for subjects taking anticoagulant medications with the
### Table 2. Studies examining FOBT and iron

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<td>Lifton and Kreiser (1982)&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Healthy male hospital employees (aged 20-27 y)</td>
<td>1-wk control period followed by 1 wk taking 300 mg of ferrous sulfate 3 times daily and 1 wk of 300 mg of ferrous gluconate 3 times daily (N = 10)</td>
<td>Temporally controlled trial, in vitro testing</td>
<td>Control periods: 0% positive Hemoccult results Ferrous sulfate: 65% positive Hemoccult results Ferrous gluconate: 50% positive Hemoccult results In vitro testing: positive Hemoccult results with ferrous sulfate 275 mg/L of sterile water and ferrous gluconate 310 mg/L</td>
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<td>Kulbaski et al (1989)&lt;sup&gt;47&lt;/sup&gt;</td>
<td>Medical students</td>
<td>Control period followed by 3 d taking 325 mg of ferrous sulfate 3 times daily (N = 4)</td>
<td>Temporally controlled trial, in vitro testing</td>
<td>0% positive Hemoccult results for control period and test period In vitro testing: positive Hemoccult results with ferrous sulfate 324 mg/10 mL water</td>
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<td>McDonnell et al (1989)&lt;sup&gt;48&lt;/sup&gt;</td>
<td>Healthy volunteers (aged 22-35 y)</td>
<td>Control period for 3 d followed by 7 d taking 300 mg of ferrous sulfate 3 times daily (N = 25)</td>
<td>Temporally controlled trial, in vitro testing</td>
<td>0% positive Hemoccult II results for control period and test period In vitro testing: positive Hemoccult II results with ferrous sulfate 0.3 mg/mL at pH &lt; 6.0; positive Hemoccult II results with ferric chloride 0.1 mg/mL (pH = 2.75) Negative Hemoccult II results for ferrous sulfate 0.3 mg/mL when pH titrated to ≥ 6.0</td>
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<td>Ahlquist et al (1985)&lt;sup&gt;49&lt;/sup&gt;</td>
<td>Healthy, asymptomatic volunteers and patients with GI symptoms or abnormal laboratory test results (aged 15-88 y, mean age 59 y)</td>
<td>Healthy volunteers self-reporting use or nonuse of iron supplements (n = 106) Symptomatic patients self-reporting iron supplementation (n = 86) Symptomatic patients self-reporting no iron supplementation (n = 577)</td>
<td>Cross-sectional</td>
<td>Volunteers: no difference in Hemoccult II results between users and nonusers of iron supplements GI symptoms, taking iron: 17.4% positive Hemoccult II results GI symptoms, not taking iron: 9.8% positive Hemoccult II results (P = .04) Iron use not defined; specific Hemoccult II results for volunteers not reported; true positives not reported differentially for iron use and nonuse; control group not compared with symptomatic group</td>
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<td>Morris et al (1976)&lt;sup&gt;50&lt;/sup&gt;</td>
<td>US veterans with known GI pathology or bleeding</td>
<td>Stool samples from patients taking unreported dose of iron (n = 55 samples) Stool samples from patients not taking iron (n = 185 samples)</td>
<td>Cohort</td>
<td>0% false-positive Hemoccult results in patients taking iron 16% false-positive Hemoccult results in patients not taking iron (P = .02) 28% false-negative Hemoccult results in patients taking iron 47% false-negative Hemoccult results in patients not taking iron (P = .24) False positives determined by 51Cr-RBC labeling, ≤ 2 mg Hb/g stool; false negatives determined by 51Cr-RBC labeling, &gt; 2 mg Hb/g stool</td>
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<tr>
<td>Laine et al (1988)&lt;sup&gt;51&lt;/sup&gt;</td>
<td>Healthy volunteers (aged 23-50 y)</td>
<td>Control testing followed by 325 mg of ferrous sulfate 3 times daily for 14 d (n = 14) Control testing followed by 325 mg of ferrous sulfate 3 times daily for 7 d (n = 13)</td>
<td>Temporally controlled trial × 2</td>
<td>All Hemoccult II results before and after iron supplementation were negative (single equivocal trace result) Stool blood quantified with HemoQuant unchanged with iron; upper GI endoscopy showed increased erythema, subepithelial hemorrhage, and erosions following iron for 14 d in 12 of 14 subjects</td>
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<td>Eliakim et al (1988)⁵²</td>
<td>Cross-sectional</td>
<td>Patients with anemia treated with iron (aged 18-65 y)</td>
<td>Patients treated &gt; 2 wk with 500 mg of ferrous calcium citrate 3 times daily (n = 13), 160 mg of ferrous sulfate daily (n = 6), or 308 mg of ferrous fumarate twice daily (N = 6)</td>
<td>All Hemoccult II results negative</td>
<td></td>
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<td>Coles and Starnes (1991)⁵³</td>
<td>Temporally controlled trial</td>
<td>Healthy volunteers (aged 27-42 y)</td>
<td>7-d control periods followed by 324 mg of ferrous sulfate 3 times daily for 7 d and ferrous gluconate 3 times daily for 7 d (N = 14)</td>
<td>All Hemoccult results during control and treatment weeks were negative</td>
<td>Stool blood quantified with HemoQuant; unchanged with iron supplementation</td>
</tr>
<tr>
<td>Anderson et al (1990)⁵⁴</td>
<td>Randomized, crossover</td>
<td>Healthy volunteers (aged 19-40 y)</td>
<td>Placebo for 2 wk, then 600 mg of ferrous gluconate twice daily, 300 mg every night for 2 wk (n = 25) Ferrous gluconate 600 mg twice daily, 300 mg every night for 2 wk, then placebo for 2 wk (n = 25) Placebo for 2 wk, then 325 mg of ferrous sulfate 3 times daily for 2 wk (n = 25) 325 mg of ferrous sulfate 3 times daily for 2 wk, then placebo for 2 wk (n = 25)</td>
<td>Ferrous gluconate: All Hemoccult II and Hemoccult SENSA results were negative during treatment phase; single positive Hemoccult SENSA result during placebo phase Ferrous gluconate: All Hemoccult II and Hemoccult SENSA results were negative during treatment and placebo phases</td>
<td>78 subjects completed study; 4 subjects completed only treatment phase</td>
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⁵¹Cr-RBC—chromium-51 red blood cell, FOBT—fecal occult blood testing, GI—gastrointestinal, Hb—hemoglobin.

### Table 3. Studies examining FOBT and ascorbic acid

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<td>Jaffe et al (1975)⁵⁵</td>
<td>Case report, in vitro testing</td>
<td>Case report, in vitro stool testing</td>
<td>Iron deficiency anemia patient taking ascorbic acid (500 mg 4 times daily)</td>
<td>Negative Hemoccult results reverted to positive when ascorbic acid was discontinued Ascorbic acid level of 15.4 mg/dL (0.15 mg/g wet-weight stool) completely inhibited Hemoccult reaction for lysed blood in stool</td>
<td>Unreported blood concentration in stool</td>
</tr>
<tr>
<td>Jaffe and Zierdt (1979)⁵⁶</td>
<td>Temporally controlled trial</td>
<td>Volunteer subjects (no further information given)</td>
<td>Swallowed 20 mL of autologous blood followed by increasing doses of ascorbic acid (N = 4)</td>
<td>Hemoccult results initially positive in all subjects Required 1500 mg/d of ascorbic acid for complete inhibition of Hemoccult reaction</td>
<td>Incomplete inhibition at lower doses</td>
</tr>
<tr>
<td>Zierdt and Zierdt (1985)⁵⁷</td>
<td>Cross-sectional</td>
<td>Hospitalized patients requiring FOBT</td>
<td>Patients taking ascorbic acid (1 patient taking 1 g/d, other doses not reported) (N = 4)</td>
<td>All patients had negative Hemoccult and ColoScreen results, but 2 had positive benzidine test results (including patient taking 1 g/d of ascorbic acid)</td>
<td>True and false positives not reported</td>
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FOBT—fecal occult blood testing.
rates for controls showed mixed results. One study showed no difference in the rate of positive FOBT results between warfarin users and controls, nor was there a difference in quantified fecal blood. Two others showed an increased rate of positive FOBT results among those taking warfarin or heparin compared with controls. The PPV for CRC or adenomas among users was 12.5% in the first study, but the PPV for controls was not reported. In the second study the PPV of 19.8% was not significantly different from that for controls.

A single randomized trial compared rates of positive FOBT results among survivors of myocardial infarction who were randomized to receive warfarin, ASA, or a combination. There were no significant differences in the rates of positive results between the group receiving warfarin and those receiving ASA or ASA plus warfarin. Unfortunately, a control group was not included in this study.

Four studies compared the PPV of a positive FOBT result between users and nonusers of anticoagulant medications. Three showed no statistically significant difference in the PPV between users and nonusers. In the fourth, the PPV for large polyps or tumors was higher for warfarin users at 16.1% compared with 11.4% for nonusers (P < .01), but this difference disappeared after adjusting for age and sex.

**Clopidogrel**

Only a single study evaluated the effect of clopidogrel on guaiac-based FOBT results. This cross-sectional study of patients who presented for colonoscopy following a positive screening FOBT result showed a PPV for advanced neoplasia of 7.3% for those taking clopidogrel. Among the control patients the PPV was 30.5% (P < .01).

**Iron**

The literature consistently shows that ferrous forms of iron can produce positive results using standardized guaiac-based test cards such as Hemoccult in vitro. However, it is inconsistent regarding the effect of oral iron on in vivo testing using standardized guaiac-based cards. A single small trial reported an increased rate of positive Hemoccult results in 10 subjects given 300 mg of ferrous sulfate 3 times daily and 300 mg of ferrous gluconate 3 times daily. Similarly, a single cross-sectional study of patients with GI symptoms compared subjects who reported taking and not taking iron. The rate of positive Hemoccult II results was higher among those reporting iron use. However, self-reported iron use did not influence Hemoccult II results in a group of healthy volunteers in this study. No previous or subsequent studies have been able to confirm the ability of oral iron supplementation to cause false-positive results when using standardized guaiac-based cards.

In the only randomized, prospective, double-blind study reported, 78 healthy volunteers were treated with placebo, 1500 mg of ferrous gluconate daily, or 975 mg of ferrous sulfate daily for 2 weeks each in a crossover trial. There was only 1 positive result among 326 samples tested with Hemoccult II and Hemoccult SENSA. The lone positive sample was collected during the placebo phase of the study.

**Ascorbic acid (vitamin C)**

As early as 1936, Barrett noted the ability of ascorbic acid to reverse the colour change of a positive guaiac test. The most consistent recommendation among FOBT manufacturers regarding medication restrictions is to withhold ascorbic acid during testing. The primary reference on which this is based is a case report in which an anemic patient ingesting 2 g of ascorbic acid daily was shown to have repeatedly negative Hemoccult but positive benzidine-based FOBT results. Results of Hemoccult testing became positive when ascorbic acid was withheld. Subsequent in vitro studies showed that complete inhibition of Hemoccult occurred with a fecal ascorbic acid concentration of 15.4 mg/dL, although the concentration of blood present in the stool was not reported. Other in vitro studies have also confirmed the ability of ascorbic acid to inhibit positive guaiac reactions. The 2 lone human studies involving a total of 8 subjects showed an inhibitory effect of ascorbic acid in 6 of the subjects taking 1000 to 1500 mg daily.

**DISCUSSION**

No research has studied the effects of NSAIDs and anticoagulant medications on the sensitivity and specificity of guaiac-based screening FOBTs. However, randomized controlled trials showed no difference in the rate of positive results among subjects taking these medications. Cohort studies revealed mixed findings, although the 1 study showing an increase in positive results depended on self-reported patient compliance with instructions. Most cross-sectional PPV studies (5 of 7) showed no difference in PPV among patients with positive FOBT results taking NSAIDs or anticoagulant medications. Such studies, however, are difficult to interpret because it is unknown whether all patients with positive results agreed to colonoscopy or whether a cohort existed that declined further investigation, a confounder referred to as transfer bias. Neither study that quantified fecal blood showed a difference between users and nonusers of these medications.

If such medications increase the risk of upper GI bleeding, why would this not be reflected in a reduction in specificity of guaiac-based FOBTs? This inconsistency likely occurs because blood originating more proximally...
looses its pseudoperoxidase activity as it transits the gut. It is this pseudoperoxidase activity that allows hemoglobin to oxidize guaiac, inducing the blue colour change. During gut transit hemoglobin is broken down to porphyrins, thereby losing this ability. While the specificity of guaiac-based FOBTs has not been evaluated for patients taking NSAIDs or anticoagulant medications, a study using immunochemical FOBTs demonstrated that the use of NSAIDs or anticoagulant medications among high-risk or minimally symptomatic individuals had no adverse effect on specificity when explicitly studied.

Most important, studies evaluating PPV in patients taking NSAIDs and anticoagulant medications consistently show that the PPV is sufficiently high to justify further evaluation for CRC when a positive guaiac-based FOBT result is encountered.

The effect of iron supplementation on guaiac-based FOBTs has been laid to rest in the literature. While iron can cause a positive guaiac response in vitro, this is not the case in vivo.

While it is clear that as a strong reducing substance, ascorbic acid is able to inhibit a positive guaiac reaction, it is challenging to apply these study results to clinical situations because several unknowns remain. It was shown that in elderly subjects taking 200 mg of ascorbic acid daily, the average stool concentration of ascorbic acid was 2.7 mg/DL. However, the degree of absorption and, subsequently, the stool concentration of ascorbic acid when supplementing with higher doses is unknown. Likewise, the amount of fecal occult blood typically present in patients with early, asymptomatic CRC and the concentration of fecal ascorbic acid required to inhibit a positive guaiac response for that amount remain undetermined. Fortunately, daily dosing of ascorbic acid is rarely required, so abstaining during FOBT to prevent false-negative results seems reasonable.

**Conclusion**

The research evaluating the effects of medications on guaiac-based FOBT screening is varied and of generally poor quality. The preponderance of the literature, however, fails to reveal significant differences in the rates of positive test results or PPV among patients taking NSAIDs, anticoagulant medications, or iron supplements. When positive screening results are encountered, the PPV is sufficiently high to justify further workup in these patients. Ascorbic acid can theoretically inhibit positive guaiac reactions, although this has not been shown in screening populations. However, until further research clarifies its effect on sensitivity, withholding high-dose ascorbic acid supplementation during FOBT screening seems a prudent recommendation.

Dr Konrad is Associate Professor in the Department of Family Medicine and Unit Director for the Family Medical Centre teaching unit at the University of Manitoba in Winnipeg. Dr Katz is Professor in the Department of Family Medicine and the Department of Community Health Sciences at the University of Manitoba, and Research Director for the University of Manitoba Family Medicine Residency Training Program.

**Contributors**

Dr Konrad conducted the literature review and prepared and revised the manuscript. Dr Katz contributed to the concept and design of the review, revised drafts of the manuscript, and read and approved the final manuscript.

**Competing interests**

None declared

**Correspondence**

Dr Gerald Konrad, Family Medical Centre, 500-400 Tache Ave, Winnipeg, MB R2H 3E1, telephone 204 237-2863, fax 204 231-2648, e-mail gkonrad@sbgh.mb.ca

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