Chapter 9

Occult Blood

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INTRODUCTION

This document summarizes our review of the literature on fecal occult blood and gastric occult blood. Occult blood is the unexpected presence of nonvisible blood in the stool or other body fluids. A daily loss of 2–3 mL of blood is generally considered the lower limit for abnormal bleeding that may be indicative of gastrointestinal pathology. Increased sensitivity of fecal occult blood tests (FOBT) beyond this limit is associated with higher rates of false positives and decreased test specificity. Fecal occult blood testing is commonly used in outpatient settings to screen for colorectal neoplasia in asymptomatic individuals. FOBT has also been used to monitor gastrointestinal bleeding in high-risk hospitalized patients and to detect upper gastrointestinal bleeding. In emergency department settings, FOBT can indicate bleeding caused by trauma or other conditions. Three methodologies are currently used for FOBT, including chemical or peroxidase-based methods, heme-porphyrin assays, and immunological methods. FOBT is not reliable for detecting occult blood in gastric fluid, so other methods such as Gastroccult (Beckman Coulter, Fullerton, CA, USA) have been developed for this purpose. These guidelines will focus on the use of FOBT for detecting colorectal neoplasia and other gastrointestinal lesions. We will also review data concerning the preferred methodology for FOBT in these settings. The utility of Gastroccult testing in an inpatient setting will be addressed. The literature search performed for occult blood testing is seen in Literature Search 60.

Does annual or biennial guaiac-based FOBT, in the average-risk asymptomatic outpatient population older than 50 years (no family history or other risk factors for colorectal cancer [CRC]), reduce mortality from colorectal cancer compared to no FOBT screening?

Guideline 134. We strongly recommend that clinicians routinely provide guaiac-based FOBT for asymptomatic individuals older than 50 years at least biennially to reduce mortality from colorectal cancer. Three large randomized controlled trials have illustrated a 15%–33% reduction in mortality from annual or biennial FOBT. FOBT is easy and inexpensive and poses no risk to the patient.

Strength/consensus of recommendation: A

Level of evidence: I and II (randomized controlled trials and case-control studies)

CRC is the second leading cause of cancer death in the United States, with more than 570,000 new cases per year. The lifetime incidence in the US population is ~6%, a rate that justifies mass screening. Colorectal carcinoma has a well-defined natural progression, and survival correlates strongly with the stage of the tumor. Screening can change the overall prognosis and outcome in patients with early disease. FOBT detects blood loss in the stool arising from colorectal neoplasms and has become a standard practice to screen for CRC. However, the optimal approach for the prevention of CRC remains uncertain (1–4).

Three randomized controlled trials, Minnesota Colon Cancer Control Study, Nottingham, United Kingdom (UK), and Funen, Denmark, enrolled more than 250,000 participants and demonstrated a 15%–33% reduction in mortality from annual or biennial FOBT (5–14). The Minnesota Colon Cancer Control Study enrolled 46,551 volunteers aged 50–80 years, randomized to annual FOBT, biennial FOBT, or control (no intervention) (5). Participants were asked to submit 6 guaiac-impregnated paper slides (slides contained 2 smears from each of 3 consecutive stools). Dietary restrictions, such as avoidance of aspirin, red meat, and vitamin C, were in place but were not verified. The Hemoccult II (HO) method (Beckman Coulter), with rehydration for most samples, was used in the hospital laboratory. All volunteers with positive results were encouraged to obtain a full examination and colonoscopy. After a 13-year follow-up, the volunteers receiving annual FOBT had a 33% reduction in mortality compared to controls. This remained unchanged after 18 years. The volunteers receiving biennial FOBT for 13 years had a 6% reduction in mortality compared to controls. The results in the biennial group were not significant after 13 years; however, after an 18-year follow-up, the mortality reduction in the biennial group was statistically significant, at 21% (6).

The European studies were similar in design to the Minnesota study, with a few exceptions. The Nottingham, UK, trial recruited 152,850 people aged 45–74 years who lived in Nottingham between 1981 and 1991 (7). The participants were
randomly assigned to biennial FOBT or no screening. No dietary restrictions were used, except in cases of borderline results. Participants received the original Hemoccult home test kit (single slide rather than triple slides), with instructions from their primary care physician. The specimens were shipped to the medical center and results analyzed without rehydration by 1 of 3 investigators. A 15% reduction in cumulative CRC mortality was found in participants who received biennial screening, with a median follow-up of 7.8 years. This mortality reduction was still apparent after an 11-year follow-up (8). In Funen, Denmark, 140,000 people aged 45–75 years who lived in Funen were allocated to biennial FOBT or no screening (9). The HO assay was used with dietary restrictions but without rehydration. Biennial screening for 10 years decreased CRC mortality by 18%. Further delineation in this study illustrated that the mortality reduction was most pronounced in patients with lesions above the sigmoid colon (10). The Denmark study is still in progress.

The conclusions in the 3 randomized trials were similar, although the magnitude of mortality reduction differed. These differences have been attributed to multiple factors, including variations in compliance rates, study population, test sensitivity, and length of follow-up. Compliance is a major impediment to FOBT, and it has been estimated that <25% of the population undergoes FOBT despite aggressive publicity (15). The European trials may have better external validity because they enrolled all eligible members of the population as opposed to volunteers. The Minnesota study has also been criticized for rehydrating test samples, which increases test sensitivity (16, 17). In the Minnesota study, 28%–38% of the volunteers in the test group received colonoscopy, whereas only 4% of the participants in the European trials underwent colonoscopy for a positive fecal occult blood result. Both annual and biennial screening techniques were used. Although annual testing in the Minnesota trial further decreased mortality compared with biennial testing, it occurred at the expense of additional testing (1). The follow-up periods were also not consistent between trials.

The randomized studies have also shown that patients who receive annual or biennial FOBT have both a longer survival time than patients who are not screened or are at an earlier stage of CRC on detection (5–10, 13, 14). However, these conclusions are made with caution because of lead-time bias. The increased survival may be due to the detection of cancer at an earlier stage.

Other studies corroborate the results of the 3 randomized controlled trials. A recent large controlled trial including 91,999 individuals aged 45–74 years was performed in Burgundy, France (18). Individuals received either biennial FOBT using a guaiac-based method (without dietary restriction or rehydration) or no screening. The population was followed up for 11 years. CRC mortality was 33% lower in the population that had at least 1 FOBT screening than in the control group. O’Leary et al. (19) examined the efficacy, as well as the cost-effectiveness, of FOBT compared to more invasive methods. Colonoscopy averted the greatest number of deaths from CRC (31%), followed by annual FOBT (29%), flexible sigmoidoscopy (21%), and biennial FOBT (19%). However, flexible sigmoidoscopy was the most cost-effective. Several case-control studies have confirmed the ability of annual or biennial FOBT to lower mortality from CRC by 25%–80% (20–25). These studies typically compared patients who died from CRC to age- and sex-matched controls and retrospectively determined whether they had received FOBT. Case-control studies provide direct estimates of efficacy of screening uninfluenced by non-compliance; however, screened patients may differ from non-screened patients in terms of CRC risks. A recent abstract at the Digestive Disease of the Week (DDW) by Bampton et al. (26) illustrated that screening patients with an immunoassay for hemoglobin (InSure, Enterix, NJ), after an initial colonoscopy, detected additional pathology.

The utility of FOBT in combination with sigmoidoscopy for the detection of CRC has been examined by several studies, including 2 randomized controlled trials (11, 27, 28). One study randomized 24,465 volunteers to either 16 years of biennial Hemoccult II testing or a single flexible sigmoidoscopy and HO test (11). Screening with HO biennially for 16 years detected more CRCs than single screening, but the difference in length of follow-up makes mortality rates difficult to compare. At 13 Veterans Administration centers, 2885 asymptomatic individuals aged 50–75 years received a colonoscopy to detect neoplasmia, in addition to flexible sigmoidoscopy and FOBT (27). In those patients with CRC, a combination of flexible sigmoidoscopy and FOBT identified 75.8% of the cancers. FOBT detected 5% of cancers that were not seen on flexible sigmoidoscopy. In the Colon Project, Winawer et al. (28) enrolled 21,756 patients aged 40 years or older to either a study group (annual rigid sigmoidoscopy and FOBT) or control group (annual sigmoidoscopy alone). They found an increased survival in the study group but no significant effect on mortality. More studies with similar designs will be necessary to determine whether the addition of flexible sigmoidoscopy to FOBT is warranted. Although the evidence is not clear, based on currently available studies, the American Gastroenterological Association (AGA) recommends combining the tests and performing FOBT every year and sigmoidoscopy every 5 years (29). FOBT should be performed first because a positive test warrants a colonoscopy and sigmoidoscopy can be avoided.

Two randomized control studies showed no reduction in mortality from CRC screening. Kewenter et al. (12) reported a study of 68,308 participants in Goteborg, Sweden, randomized into screening or control groups. More CRCs were detected in the screened group, but no significant differences in mortality rate were found. These participants were only followed up for 2–7 years, which may not have been long enough to detect a statistical difference in mortality rates. In another study, all residents of Jiashan County, China, aged 30 years or older were enrolled in a randomized controlled trial to screen for CRC (30). The screening method was immunological FOBT. The study showed a reduction in mortality from rectal cancer but no reduction in mortality from colon cancer. These results may differ from other randomized controlled trials because of the study population, screening method, or other disparities in the study design.

Most studies illustrate that FOBT reduces CRC mortality at minimal risk to the patient (1–14). Studies performed in the UK, using the knowledge gained from the Nottingham trial, also
illustrated that screening for CRC with FOBT can be successfully implemented in a population between 50 and 69 years old (31, 32). The 2003 AGA guidelines recommend yearly FOBT of 2 samples from each of 3 consecutive stools in all average-risk men and women starting at age 50. Currently, the AGA recommends against rehydration because it substantially increases the false-positive rate. Either an immunochemical test without dietary restrictions or guaiac-based tests with dietary restriction are advocated (29). In contrast to the AGA, there is 1 meta-analysis showing that dietary restriction does not significantly affect the positivity rate for nonrehydrated guaiac-based FOBT and advises against dietary restriction (33).

Although there is strong evidence to support FOBT for colorectal screening, studies have not addressed several key points. No trials have shown the preferred methodology for FOBT screening in CRC, including whether the guaiac-based assays should be rehydrated or nonrehydrated. Other issues include the need for dietary restrictions, the recommended length of follow-up, the most beneficial frequency of screening, and the strategy for follow-up of positive fecal occult blood results.

**Does annual or biennial guaiac-based FOBT, in the asymptomatic population older than 50 years, significantly decrease the incidence of CRC?**

**Guideline 135. We cannot currently recommend for or against the use of guaiac-based FOBT to reduce the incidence of CRC. Randomized control studies addressing this question are conflicting; however, the differences in length of follow-up make it difficult to draw direct comparisons. More studies need to be performed to resolve this question.**

**Strength/consensus of recommendation: I**

**Level of evidence: I and II (randomized controlled trials and case-control studies)**

The concept that FOBT may lower the incidence of CRC has been debated. Some experts have postulated that screening for CRC with FOBT will decrease the incidence of cancer. Patients with positive fecal occult blood results may receive colonoscopy, and in a percentage of cases precursor lesions (i.e., adenomatous polyps and villous adenomas) will be detected and removed, preventing cancer from developing. On the other hand, small benign adenomatous polyps are less likely to bleed than carcinomas, and they may not be efficiently detected by mass screening. In many cases, FOBT will discover early-stage cancers without necessarily decreasing the incidence of disease but rather only the rate of mortality (1, 2, 4).

The 3 randomized controlled trials addressing the use of FOBT made different conclusions concerning the effect of FOBT on the incidence of CRC (5, 7, 9). The Minnesota Colon Cancer Control Study involved 46,551 volunteers tested annually or biennially for fecal occult blood. This study found a decreased incidence of CRC in both screened groups at 13 and 18 years of follow-up (34). After 18 years, the number of cases of CRC was 417, 435 and 507 in the annual, biennial, and control groups, respectively. In the Nottingham, UK, study 4.3% more cancers were detected in the biennially screened population after 7.8 years of follow-up (7). In the Funen, Denmark trial an equal number of cancers were seen in the screened and control populations, which included a 10-year follow-up period (9). The different conclusions in the 3 studies have been attributed to the variation in length of follow-up (7.8 years in the UK, 10 years in Denmark, and 18 years in Minnesota). The Denmark trial, which is ongoing, may answer this question. In addition, hydrated fecal occult blood samples were used in the Minnesota trial, which increases test sensitivity and may help detect more precursor lesions. The design of the Minnesota study may actually have underestimated the true effect on the incidence of CRC in each group (34). The subjects in the control group were not prevented from undergoing screening through their personal physicians. Compliance with the protocol was also not optimal and may have attenuated the true effect. Finally, a hiatus occurred in the screening program (4.5 years for the annual group and 3.6 years for the biennial group), which may have masked the true incidence.

Other studies investigating the effect of FOBT on the incidence of CRC are also conflicting. A randomized controlled trial was performed on 27,000 inhabitants of Goteborg, Sweden, aged 60–64 years (35). After the original randomized controlled trial was completed (12), a subsequent study determined the incidence of CRC in the test and control group during a 7-year follow-up. The control group had more colorectal neoplasms than the test group, with the greatest effect during the first 2 years. However, if the entire length of screening and follow-up was included, the incidence of CRC in the 2 groups was similar. The increased incidence of cancer in the control group during rescreening may have been due to a lead-time effect. Niv et al. (36) did not find any difference in the incidence of CRC in screened vs nonscreened volunteers during a 3-year screening and 8-year follow-up period. A similar incidence of CRC in the screened and control group was also found in a study done in Burgundy, France (18). In contrast, a case-control study done on 357 patients with advanced CRC and age- and sex-matched controls strongly suggested that screening reduced the incidence of advanced CRC (37).

In conclusion, although randomized controlled trials have been performed to determine whether FOBT decreases the incidence of CRC, the results to date are unclear. Ongoing studies with longer lengths of follow-up may clarify this issue.

**Should FOBT be performed in the central laboratory or at the point of care for asymptomatic patients who require screening for CRC?**

**Guideline 136. We cannot recommend for or against FOBT performed in the central laboratory or at the point of care to screen for CRC in asymptomatic patients. Experts suggest that home collection of specimens with analysis either in the physician office or laboratory is**

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The validity of testing for occult blood at the point of care vs the central laboratory has not been adequately addressed. Specimens for FOBT may be obtained at home, by the patient, or in association with a DRE. Specimens can then be mailed to a central laboratory for testing, delivered to an outpatient clinic for analysis, or collected at the bedside during examination for immediate FOBT. Home collection of samples with physician office analysis is neither traditional POCT (i.e., immediate collection, with prompt results at the bedside) nor central laboratory testing. Categorization of nontraditional POCT techniques is controversial.

The AGA and other experts imply that traditional FOBT at point of care is not recommended, because of lack of sensitivity (29, 38). The significance of a single positive FOBT obtained during DRE compared to the recommended home collection of 6 specimens has also not been evaluated. In addition, specimens received by DRE may be affected by the lack of dietary and medication restrictions in these patients. In a study by Fisher et al. (39), published as an abstract in the DDW, only 5% of patients with significant pathology by colonoscopy had a positive FOBT result by DRE. Some clinicians believe that induced rectal trauma at the time of digital examination leads to a high false-positive rate. However, Eisner and Lewis (40) performed a retrospective study on 270 patients who underwent colonoscopy for any positive FOBT. The frequency of colonic abnormalities was similar with both collection methods, which argues against a high false-positive rate with DRE. Many clinicians perform DRE as part of a routine physical or hospital admission, in part because it may be the only opportunity to screen for CRC in certain patients. However, no large prospective trials have compared the accuracy of central laboratory testing to nontraditional or traditional POCT.

Three main categories of FOBT are available in the United States, guaiac-based/chemical methods, immunological assays, and heme-porphyrin methods (38). Guaiac-based methods such as the HO detect pseudoperoxidase activity in hemoglobin. The pseudoperoxidase present in hemoglobin interacts with guaiac, impregnated in a card, producing a blue color. False-positive results can occur in patients taking certain medication or in patients who consume rare red meat, turnips, and horseradish, which contain peroxidase. High doses of vitamin C can produce false-negative results. The sample used for guaiac-based methods can be rehydrated to increase sensitivity at the expense of specificity and PPV (17). The Hemoccult SENSA (HOS) (Beckman Coulter) is also a guaiac-based method with acceptable sensitivity and specificity and fewer false positives than the rehydrated HO. Guaiac-based methods are inexpensive and easy to perform and can be interpreted in the physician’s office (POCT). However, dietary and drug restrictions are required, and there will still be a delay in processing the test if rehydration is performed (1, 3, 15).

The immunological and heme-porphyrin methods were developed to improve sensitivity. Immunological methods include the HemeSelect (HSel; Beckman Coulter), which uses reverse passive hemagglutination and detects intact hemoglobin and globin. It was designed to specifically detect colonic lesions (but not upper gastrointestinal bleeding). These methods are more expensive than guaiac-based methods and require more involved interpretation. The HemoQuant (HQ; SmithKline Diagnostics; no longer available) is a heme-porphyrin test, which detects porphyrin. Patients with CRC generally have fecal hemoglobin concentrations >2 mg/g feces. The test has a high sensitivity for bleeding both from upper and lower gastrointestinal sources, but this compromises its specificity for CRC (1, 3, 15). (Sensitivity and specificity are dependent on the study and population examined; analytically, this test has better sensitivity because it is touted to be able to detect 1.5 mg hemoglobin per gram of stool, whereas the guaiac cards do not begin to turn positive until levels of 5 mg/g of stool are reached. In studies, Hemoccult using rehydrated stool has sensitivities of 30–50%, with specificities around 95%, whereas HQ has sensitivity of 40%–60%, but much lower specificities accordingly.)

A large study was done on 8104 asymptomatic patients scheduled for routine physicals at Kaiser Permanent Medical

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recommended over traditional point-of-care testing (POCT) for occult blood by digital rectal examination (DRE). In addition, the randomized controlled trials illustrating CRC mortality reduction used the central laboratory to perform FOBT. However, no trials have compared these methodologies and addressed the benefits of POCT, which include convenience and an increase in compliance.

Strength/consensus of recommendation: I
Level of evidence: III (retrospective trial, expert opinion)

Which FOBT method, guaiac-based, heme-porphyrin assay, or immunological, is the most accurate (sensitivity, specificity, positive predictive value [PPV]) in an outpatient setting for the detection of CRC in asymptomatic individuals older than 50 years?

Guideline 137. We cannot currently recommend an ideal fecal occult blood method for the detection of CRC according to the current literature and available methodology. Although guaiac-based testing is not extremely sensitive, it is reasonably specific, cheap, and easy to use and poses no risk to the patient. In addition, 3 large randomized controlled trials used guaiac-based methods to illustrate a reduction in CRC mortality. Although guaiac-based methods are widely used in the United States, there is insufficient evidence to recommend guaiac-based methods over other types of assays.

Strength/consensus of recommendation: I
Level of evidence: II and III (prospective comparative trials, descriptive studies, and opinion)
Center to compare the ability of HO, HSeL, HOS, and a combination of HOS and HSeL to detect CRC (41). Each patient received all 3 testing methods. Dietary restrictions were in place but not confirmed, and no rehydration of samples was performed. Patients with positive results by any testing method received a colonoscopy, and all patients were followed up for 2 years. The HOS had the highest sensitivity for the detection of CRC, at 79.4%, but the lowest specificity, at 86.7%. HO had the highest specificity (97.7%) but a poor sensitivity (37.1%). The HSeL was neither the most sensitive nor the most specific. All had PPV < 9.0%. Combination testing was also performed. If a positive HOS result was obtained by screening, it was confirmed with the HSeL method. This resulted in a sensitivity of 65.6%, a specificity of 97.3%, and a PPV of 9.0%. The value of combination testing in an outpatient setting beyond this study is uncertain.

Several other studies have been performed to determine the accuracy of FOBT methods in asymptomatic individuals eligible for CRC screening (16, 41–50). A wide range for sensitivities, specificities, and PPVs is obtained when the results of different studies are compiled. The variations could be the result of differences in study population, age of participants, dietary requirements, preparation of specimens (i.e., rehydration), endpoints measured, screening intervals, and years of follow-up. The large discrepancies in the ranges for sensitivity, specificity, and PPV make the data in the literature difficult to interpret. Immunological methods (i.e., HSeL) are generally more sensitive and less specific, but interpretation of the available literature suggests that the differences are not striking. Guaiac-based methods such as HO are more specific and for their convenience tend to be the method of choice. All methods have poor PPVs because of the relatively low prevalence of CRC in the asymptomatic screened population.

A few articles have examined the accuracy of FOBT in symptomatic or high-risk patients with family histories of CRC (51–54). Similar to the studies done with asymptomatic patients, these studies are also not consistent. Four studies on symptomatic patients compared HO to the heme porphyrin method, HQ (51–54). Barber et al. (52) compared the HQ and HO methods in 184 patients with bleeding as a result of iron deficiency and concluded that the HQ had an overall better performance for detecting gastrointestinal lesions. On the other hand, St. John et al. (54) reported that HO was more sensitive than HQ for the detection of CRC in a cross-sectional study. The range of sensitivities for the detection of CRC or gastrointestinal lesions was between 26% and 89.5% for HO and 26% and 74.2% for HQ. Specificities ranged from 32.4% to 99.3% for HO and 81%–94.7% for HQ. Most of the authors questioned the added benefit of quantitative HQ, especially because of the increased cost and inconvenience (51, 52, 54). Ahlquist et al. (51) suggested that neither HO nor HQ is optimal for screening high-risk patients.

Patient and physician compliance is a major obstacle in FOBT. Averages from the literature estimate that only 50% of the eligible population undergoes FOBT for CRC screening, but in reality the numbers may be <25% (15). Cole et al. (55) performed a study on 1818 residents aged between 50 and 69 years to determine compliance rates with different FOBT methodologies. Participation was higher with immunological methods that involve more convenient sampling and remove the need for dietary and drug restrictions. By contrast, a meta-analysis found that moderate dietary restrictions did not affect completion rates (33). In addition to providing optimal sensitivity and specificity, the preferred methodology for FOBT should maximize patient participation.

The literature does not demonstrate that any 1 FOBT method is superior for the detection of CRC. After a review of the literature, Young et al. (56) also concluded that no FOBT method fulfills the needs of all target populations. This study recommends using the patient population and colonoscopy resources to determine the most reliable method. No studies incorporated a cost analysis into their study design to aid in the differentiation of methodologies. In general, guaiac-based methods are used clinically because they are easy to use and inexpensive and have been shown to decrease mortality from CRC in at least 3 randomized controlled trials. The AGA recommends either guaiac-based testing with dietary restriction or an immunochemical method (29).

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**Is FOBT useful in symptomatic patients to differentiate bleeding caused by upper gastrointestinal lesions (including gastroesophageal cancer) from bleeding caused by lower gastrointestinal lesions?**

**Guideline 138.** We cannot currently recommend FOBT to differentiate upper from lower sources of gastrointestinal bleeding. A limited number of cohort and case-control studies have demonstrated that FOBT can detect bleeding caused by upper gastrointestinal lesions, but there is no evidence to support that guaiac-based FOBT can determine the origin of bleeding.

**Strength/consensus of recommendation:** I

**Level of evidence:** II (case-control and cohort studies)

Both upper and lower gastrointestinal lesions can result in positive FOBTs. Traditionally, guaiac-based FOBT was designed to detect lower gastrointestinal sources of bleeding by monitoring intact hemoglobin. In the case of upper gastrointestinal bleeding, hemoglobin undergoes degradation by intestinal enzymes as it passes through the gastrointestinal tract, which frequently causes a false-negative result with guaiac-based tests. However, in patients with significant bleeding (5–10 mL per day) from an upper gastrointestinal source, intact hemoglobin can still be detected in the stool. The ability of guaiac-based tests to detect bleeding is variable and depends on anatomic, physiologic, and dietary factors. Immunochemical tests are very sensitive for colonic bleeding but do not detect blood from the upper gastrointestinal tract. In contrast, the heme-porphyrin test, which measures porphyrin, the breakdown product of hemoglobin, can quantify bleeding from any gastrointestinal source. However, most
immunological and porphyrin methods require laboratory processing (38).

Studies have shown that guaiac-based FOBT can detect upper GI sources of bleeding (57, 58). However, these studies do not suggest that FOBT can differentiate the source of bleeding and have questioned the utility of FOBT for detecting bleeding caused by gastric or esophageal lesions. A prospective study was published using 248 patients with positive guaiac-based FOBTs (HO) (58). All of the patients were referred for further evaluation (colonoscopy or upper endoscopy). Of all patients, 48% had gastrointestinal lesions identified; 21.8% were colonic and 28.6% were upper gastrointestinal, illustrating that guaiac-based FOBT can detect bleeding throughout the gastrointestinal tract, but without discrimination. A study done in high-risk inpatient pediatric patients with known upper and lower gastrointestinal sources of bleeding suggested the use of highly sensitive guaiac-based methods for suspected upper gastrointestinal bleeding in children. However, the authors did not suggest that this method may be used to differentiate the source of bleeding (59). In 178 patients starting dialysis, guaiac-based FOBT detected more CRCs than upper gastrointestinal tumors (57).

Heme-porphyrin methods have also been shown to detect bleeding from upper gastrointestinal sources. Harewood et al. (60) tested 56 patients with known upper gastrointestinal lesions and found that heme-porphyrin methods detected upper gastrointestinal blood loss more frequently than guaiac-based or immunological-based assays. Another study compared guaiac-based methods with heme-porphyrin methods in 106 healthy volunteers, 170 patients with gastrointestinal symptoms, 44 patients with gastrointestinal cancer, 75 patients with benign polyps, and 374 patients with other benign gastrointestinal lesions (61). The heme-porphyrin-based method was more sensitive for gastrointestinal bleeding and was better in detecting bleeding from proximal lesions.

Immunological FOBT are insensitive for upper gastrointestinal sources of bleeding (62, 63). Nakama et al. (62, 63) performed 2 studies using patients with documented upper and lower digestive tract diseases and healthy controls. In 1 study, immunological FOBT was performed on 226 subjects (124 with upper gastrointestinal disease, 34 with CRC, and 68 healthy controls) (63). The sensitivity for upper digestive tract disease was only 19%. In the other study, immunological FOBT was performed on 150 patients with gastric cancer, 150 patients with CRC, and 300 healthy volunteers (62). FOBT was positive in 8% of patients with gastric cancer and 7% of patients without gastric cancer. In these studies, immunochromatographic occult blood tests could detect only a low percentage of patients with upper gastrointestinal bleeding. These studies recommended against the use of immunological FOBT to screen for suspected upper gastrointestinal lesions.

In an article by Rockey et al. (64), groups of 10 healthy volunteers drank blood mixed with tomato juice for 3 consecutive days and were tested for fecal occult blood by a variety of methodologies. The highly sensitive guaiac-based method (HOS) detected blood in all subjects after ingestion of 20 mL of blood and in 50% of subjects after ingestion of 10 mL and was more sensitive than the HO for detecting upper gastrointestinal bleeding. Immunochemical assays did not detect occult blood in any of the subjects. These data raised “the possibility that a combination of a highly sensitive guaiac-based FOBT test plus an immunochemical method could aid in differentiating occult upper from lower GI bleeding.”

Evidence supports the fact that upper gastrointestinal bleeding can be detected by FOBT, but no in vivo human studies have addressed the ability of FOBT to differentiate the source of bleeding. Although clinicians would find a rapid, easy-to-use, sensitive method to differentiate upper from lower sources of gastrointestinal bleeding useful, there is no evidence to suggest that the guaiac-based FOBT can make this distinction.

Can guaiac-based FOBT be used in patients receiving therapeutic anticoagulation to predict whether a patient is at high risk for gastrointestinal bleeding?

**Guideline 139.** _We cannot currently recommend for or against the use of guaiac-based FOBT to predict gastrointestinal bleeding in patients receiving anticoagulation. Although the current literature is sparse, it suggests that positive fecal occult blood results do not correlate with the level of anticoagulation. From these data, it can be extrapolated that FOBT would not be predictive of bleeding risk. More studies need to be done to directly address this issue._

**Level of evidence:** II and III (prospective trials and expert opinion)

Evidence-Based Practice for Point-of-Care Testing

Many inpatients and outpatients receive anticoagulation for cardiovascular-related events. Bleeding is a significant risk for patients receiving anticoagulation. A few studies have investigated the effects of anticoagulants on FOBT results. A prospective crossover study of 100 patients older than 40 years was done (65). Patients were assigned to groups taking no aspirin or warfarin, daily aspirin (81 mg or 325 mg), or warfarin but no aspirin. Each patient collected stool at home, and occult blood testing was done in the central laboratory by the HQ or HO methods. No increase in the rate of positive FOBT was seen in the patients taking warfarin. In addition, the international normalized ratio (INR) level, which is used to monitor anticoagulation therapy, was not associated with occult blood by HQ. A small dose-dependent increase in gastrointestinal blood loss was seen in patients taking aspirin; however, the quantity detected was still within the normal limits of 2 mg hemoglobin per gram of stool.

A study by Blackshear et al. (66) investigated 117 patients receiving anticoagulation for atrial fibrillation. The patients received either standard warfarin (INR 2–3), warfarin (INR < 1.5) and 325 mg of aspirin, or aspirin alone. After 1 month of therapy, the patients mailed specimens to the laboratory for HQ FOBT. The patients taking warfarin and aspirin had slightly more fecal hemoglobin than those taking standard...
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warfarin. None of the results were significantly different from the reference population without atrial fibrillation. In a prospective study, 256 patients receiving anticoagulation were screened with HO with no rehydration (67). The positive rate was higher in the patients receiving anticoagulation (12% vs 3%), but the patients with positive results had previously undiagnosed lesions of the gastrointestinal tract. This study postulated that anticoagulants might unmask bleeding from preexisting lesions.

The few trials examining FOBT on anticoagulated patients are consistent. Fecal blood level in patients treated with anticoagulation or low-dose aspirin are normal or minimally increased compared to controls (38, 65–68). Some recommendations suggest stopping aspirin before FOBT is performed, but Greenberg et al. (65) suggested that aspirin and warfarin do not compromise the accuracy of FOBT and that the cardiovascular disadvantages of discontinuing anticoagulation outweigh the minimal FOBT benefits. In addition, the INR does not correlate with positive FOBT results (65–67). These studies conclude that a positive FOBT should not be attributed solely to anticoagulation therapy and should lead to a formal evaluation.

Whether qualitative or quantitative hemoglobin monitoring in the stool may predict bleeding events is not known, but the studies described imply otherwise. FOBT can be done at the point of care (i.e., DRE at inpatient bedside) or by home collection (i.e., presumably in outpatients). No study has described the effect of anticoagulation on guaiac-based FOBT results done on inpatients after DRE. Although clinicians use FOBT at the point of care to predict gastrointestinal (GI) bleeding in inpatients or outpatients receiving anticoagulation, this practice cannot be substantiated by the literature.

Can Gastroccult testing of gastric fluid from a nasogastric tube be used to detect gastrointestinal bleeding in high-risk intensive care unit (ICU) patients receiving antacid prophylaxis?

**Guideline 140.** We cannot currently recommend for or against the use of Gastroccult to detect gastric bleeding in ICU patients receiving antacid prophylaxis. Only 1 study to our knowledge has indirectly addressed this issue. No randomized controlled trials have been performed.

**Strength/consensus of recommendation:** I

**Level of evidence:** III (small study and clinical evidence)

FOBT should not be used to measure occult blood in gastric fluid, because of interferences from low pH, certain medications (antacids and vitamin C lead to false-negative results), and metal ions (iron and copper salts lead to false-positive results). The presence or absence of occult blood in gastric fluid is useful in emergency department or ICU settings for the detection of bleeding caused by trauma or a deteriorating gastric condition (stress ulcer syndrome). Gastroccult tests are used for this purpose. The pseudoperoxidase in hemoglobin reacts with guaiac and a buffered, stabilized hydrogen peroxide solution, producing a blue color in the presence of blood. Two in vitro studies have illustrated that Gastroccult is a simple, rapid, and convenient method for the evaluation of patients with suspected occult blood in gastric fluid. Gastroccult, unlike Hemoccult, is not influenced by pH or sucralfate (69, 70).

Derrida et al. (71) used Gastroccult every 4 h to identify blood in gastric juice of 41 ICU patients at risk for gastrointestinal bleeding (patients with overt gastrointestinal bleeding were excluded) and receiving antacid prophylaxis; 27% (14/41) had at least 1 positive Gastroccult reading and received an upper endoscopy. No endoscopy was performed in patients with negative Gastroccult findings. In 13/14 patients, a source of gastric bleeding was detected. This study suggests that Gastroccult testing may aid in detecting occult bleeding in critically ill patients. However, this small study did not perform upper endoscopy on negative-testing patients, which would have documented the false-negative results obtained with the Gastroccult test.

Current data are insufficient to recommend the use of Gastroccult for ICU patients to detect upper gastrointestinal bleeding. Although this practice is widespread, more studies will be necessary to document the utility of Gastroccult testing for this application.

In summary, FOBT is rapid, inexpensive, easy to use, and useful in a variety of practice settings to assist clinicians in detecting gastrointestinal bleeding and to guide the selection of appropriate follow-up testing. Annual or biennial FOBT on 2 samples from each of 3 consecutive stools is recommended for all average-risk men and women beginning at age 50 to reduce mortality from CRC. Most experts agree that FOBT, although reducing CRC mortality, does not affect the incidence of CRC. This issue remains controversial because the literature conclusions are not consistent. Although FOBT is inexpensive and poses minimal risk to the patient, many patients with no pathology will incure the discomfort, cost, and risk of colonoscopy if a positive result is obtained. Despite consensus among expert groups that FOBT reduces mortality from CRC, the screening rates remain low and the follow-up of positive FOBT is inadequate. The medical community should not only optimize the clinical utility of FOBT but also improve patient and physician compliance and enforce regular FOBT to maximize the benefit for patients. No studies have investigated the role of FOBT if any, in the treatment of patients with CRC.

The use of FOBT at the point of care cannot be advocated, because of lack of medical evidence, although its convenience and the opportunity for greater compliance are appealing. The randomized controlled trials performed FOBT in the central laboratory, and no clinical trials have investigated the role of POCT vs the central laboratory.

Currently, no specific FOBT methodology can be recommended. However, the most recent AGA recommendation suggests either yearly guaiac-based tests with dietary restriction or an immunochemical test without dietary restriction. The AGA also recommended against rehydrating FOBT because it leads
to substantially higher false-positive rates. Guidelines on the preferred methodology in specific settings, including a cost analysis, need to be published.

The use of FOBT in hospitalized patients has not been thoroughly explored. Studies suggest that FOBT results do not correlate with the level of anticoagulation; however, the utility of FOBT to monitor anticoagulation has not been addressed. According to current evidence, the use of FOBT to differentiate upper and lower gastrointestinal lesions also cannot be advocated. Furthermore, the role of occult blood testing on nongastrointestinal specimens such as nipple discharge and sputum is unknown. The small numbers of studies that have examined the role of occult blood in nipple discharge or sputum for the diagnosis of breast or lung cancer have shown that occult blood testing is neither a sensitive nor a specific method (72–75).

Gastrocrott is frequently used in the inpatient setting to detect blood in gastric fluid or vomitus. Studies on Gastrocrott testing are sparse, and no definitive guidelines on the clinical utility of Gastrocrott at the point of care can be determined from the literature.

Finally, new methodology has recently been developed to detect DNA mutations in the stool that are associated with CRC. Studies are currently in progress that compare FOBT to DNA-based methods.

REFERENCES


PUBLIC COMMENTS

1. Received during the AACC presentation: Can you address the utility of digital rectal examination for point of care fecal occult blood? We added a recommendation addressing the use of FOBT in the central laboratory or at the point of care. This recommendation states that although most experts advise against testing for occult blood by DRE, the evidence to support this is insufficient.
2. Dr. Callum G. Fraser wrote a letter suggesting that several points and references be added to the discussion. We added discussions pertaining to the following references (31–33, 38, 55, 56) that can be found throughout the guidelines.
3. Dr. Gary Lee Utz wrote: “The POC issue in FOBT does not appear to be adequately addressed in the draft guidelines.” In response to his comment, we added a separate recommendation discussing the utility of FOBT at the point of care vs the central laboratory. Evidence to recommend FOBT at the point of care is insufficient.
4. Brenda L. M. Franks asked, “Do you have any plans to address FOB testing for patients on intensive anticoagulant therapy?” We added a recommendation on the use of FOBT in patients receiving therapeutic anticoagulation. The evidence was insufficient to recommend for or against the use of FOBT to predict gastrointestinal bleeding in patients receiving anticoagulation.