

## Occult Gastro-intestinal Bleeding : Detection, Interpretation, and Evaluation

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Occult gastrointestinal bleeding refers to the bleeding otherwise not apparent to the patient. It is usually identified only by tests that detect faecal blood or, if bleeding is sufficient, it manifests as iron deficiency. Occult gastrointestinal bleeding can also refer to the bleeding that is clinically evident but from an obscure source. Obscure gastro-intestinal bleeding is the least common form of occult gastrointestinal bleeding. There is evidence that screening persons who have no symptoms, with the use of faecal occult blood testing or sigmoidoscopy can reduce mortality from colorectal cancer<sup>1-3</sup>. This article reviews various tests to detect the occult gastrointestinal bleeding, their interpretation, and brief outline of evaluation of positive faecal occult blood test results.

Normally 0.5 – 1.5 ml blood per day is lost in stools amounting to ~ 2 mg haemoglobin per gram of stool<sup>4-6</sup>, an amount that is typically not detected by occult blood tests. Nonetheless, occult blood is commonly detected in the stool using a variety of faecal occult blood tests that detect blood from various lesions in the gastrointestinal tract, primarily including the colonic cancers<sup>7,8</sup>. Various causes of occult gastrointestinal bleeding are listed in table I.

### Faecal occult blood tests

Broadly speaking, three types of tests are used to detect faecal occult blood. These include:

1. Guaiac based tests:
  - (a) HemeOccult
  - (b) HemeOccult II
  - (c) HemeOccult II Sensa

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2. Heme-porphyrin tests:
  - (a) HemoQuant test
3. Immunochemical tests:
  - (a) HemeSelect test
  - (b) FlexSure OBT

Table I : Causes of occult gastro-intestinal bleeding.

- A. Mass lesions
  1. Carcinoma (any site)
  2. Large (>1.0cm) adenoma (any site)
- B. Inflammation
  1. Erosive oesophagitis
  2. Ulcer (any site)
  3. Erosive gastritis
  4. Ulcerative colitis
  5. Crohn's disease
- C. Vascular disorders
  1. Vascular ectasia (any site)
  2. Portal hypertensive gastropathy or colonopathy
  3. Varices (any site)
  4. Haemangioma
  5. Dieulafoy's vascular malformations
- D. Infectious diseases
  1. Worm infestations
  2. Tuberculous enterocolitis
  3. Amoebiasis
- E. Surreptitious bleeding
  1. Haemoptysis
  2. Oropharyngeal bleeding
- F. Other causes
  1. Haemosuccus pancreaticus
  2. Haemobilia
  3. Long-distance running

## Guaiac based tests

Guaiac-based tests for faecal occult blood detect the pseudo-peroxidase activity of heme, either as intact haemoglobin or as heme. Such activity converts colourless guaiac to a blue colour in the presence of an oxygen donor like hydrogen peroxide in the developing reagent. Several different guaiac-based tests are available and of them two most commonly used are: HemeOccult II and HemeOccult II Sensa (SmithKline Diagnostics, San Jose, California). HemeOccult II has a low sensitivity for detecting colorectal neoplasms in asymptomatic patients at average risk<sup>9,10</sup>, while HemeOccult II Sensa is more sensitive to peroxidase like materials and, thus, in detecting faecal heme<sup>11,12</sup>.

The likelihood that a guaiac-based test will be positive is generally proportional to the quantity of faecal heme, which in turn is related to the size and location of bleeding lesion<sup>13,14</sup>. Guaiac-based tests are generally best at detecting large and more distal lesions. The inconsistency of faecal occult blood tests in detecting faecal blood is emphasised by the finding that faecal haemoglobin levels must exceed 10 mg/gram of stool (10 ml of daily blood loss) for HemeOccult II tests to be positive 50% of the time<sup>15</sup>, although stools containing haemoglobin levels of < 1 mg/gram of stool can result in positive test<sup>16</sup>.

The advantage of these tests is that they are very simple and rapid tests that can be performed in the physician's office itself, so considered as the waived tests according to Clinical Laboratory Improvement Amendments of 1988. Many factors influence the results of guaiac-based tests; some of the important ones are summarised in table II and the recommendations for performing guaiac-based tests are mentioned in table III.

## Heme-Porphyrin test

The heme-porphyrin test, HemoQuant (Mayo Medical Laboratories, Rochester, Minnesota) measures haemoglobin derived porphyrin spectrofluorometrically and allows exact measurement of

total haemoglobin in stool. The advantage of this test is that the factors that may interfere with or cause false-positive guaiac-based tests like presence of vegetable peroxidases and rehydration do not affect the results. However, like guaiac-based tests it gives false-positive results with non-human haemoglobins which limits its clinical utility. Moreover, it is a laboratory test and takes around 90 minutes to get the result. The amount of haemoglobin present in stools as determined by HemoQuant test can be graded as: Normal < 2 mg/gram of stool; borderline 2-4 mg/gram of stool; increased > 4 mg/gram of stool<sup>17</sup>.

Table II : Factors affecting the results of guaiac-based tests.

### (A) False-positive results.

1. Intake of foods that contain peroxidase activity (uncooked fruits and vegetables).
2. Drugs: Topical iodine, aspirin, NSAIDs.
3. Non-human haemoglobins: red meat.
4. Rehydration

### (B) False-negative results.

1. Vitamin C (Ascorbic acid) intake.
2. Storage of slides.
3. Improper sampling or developing.
4. Lesion not bleeding at time of stool collection.
5. Haemoglobin degradation by colonic bacteria.

## Immunochemical tests

They include HemeSelect test (SmithKline Diagnostics) and FlexSure OBT (SmithKline Diagnostics). These tests detect intact or nearly intact haeme haemoglobin by various immunological techniques; at least theoretically, the technique is more specific for detecting loss of blood from the lower intestine because blood from lower sites is less degraded during transit<sup>8</sup>.

Immunochemical tests use antibodies directed against human globin epitopes and can detect

colonic blood at a level of as little as 0.3 ml of blood added to stool and do not detect small quantities of blood from upper gastrointestinal tract<sup>12</sup>. Unfortunately, these tests are limited by loss of globin antigenicity at room temperature and require processing in laboratory.

The HemeSelect test is similar to enzyme linked immunosorbant assay and needs to be done in the laboratory, while FlexSure OBT (Smithkline Diagnostics) is a simpler immunoassay which can be done in the physician's office. A product that is identical to HemeSelect is used in mass screening in Japan: this test is performed using automated instrumentation<sup>18</sup>.

Table III : Recommendations for testing occult blood in stool using guaiac-based tests<sup>29</sup>.

1. Test two areas from each of 3 consecutive stools to sample.
2. Test all samples within 4 days of collection.
3. Do not rehydrate slide prior to development.
4. For 3 days prior to test, avoid large doses of vitamin C, oral iron, aspirin, and other non-steroidal anti-inflammatory drugs, red meat and certain fruits and vegetables that contain catalases and peroxidases (like cucumber, horseradish, cauliflower, etc.) especially if the slides are rehydrated.
5. Even one positive should be considered a positive test even without dietary restriction.

### Intra-luminal haemoglobin degradation and faecal occult blood tests

In the upper gastro-intestinal tract, haemoglobin is cleaved to form haeme and globin by gastric pepsin, proteases, pancreatic proteases, or both types of proteases in the proximal small intestine. Some intra-luminal haeme (generally < 15%) is reabsorbed in the small intestine. A portion of haeme that is not absorbed and is converted to porphyrin and iron through poorly understood mechanisms has been termed the "intestinal converted fraction" of haeme. This fraction is not

detected by guaiac-based tests but is detected by haeme-porphyrin assay (HemoQuant test), which measures both haeme and porphyrins and is therefore a highly accurate indicator of bleeding, regardless of the level. Globin in the upper gastrointestinal tract is digested by pepsin and pancreatic and intestinal proteases and is, thus, not detected by the immunochemical faecal occult blood tests. The biology of intra-luminal haemoglobin degradation suggests that a guaiac-based test combined with an immunochemical test could help differentiate occult bleeding in upper gastrointestinal tract from that in the lower gastrointestinal tract<sup>17</sup>.

### Interpretation of occult blood test results

A positive test for occult blood is not necessarily indicative of disease. There are inherent errors in collection and storage of specimens and in interpretation of reactions<sup>16</sup>. Various factors affecting the detection of occult blood in stool are summarised in table IV.

Table IV : Factors affecting the detection of faecal occult blood<sup>17</sup>.

1. Anatomical level of lesion.
2. Stool transit time.
3. Stool mixing.
4. Intraluminal haemoglobin degradation.
5. Intrinsic features of bleeding of gastrointestinal lesion (like intermittent bleeding).

In screening studies, 2-16% of patients tested had positive results, although many tests may have been falsely positive<sup>1,20</sup>. The sensitivity of HemeOccult test is only 20% in persons with normal faecal blood loss, i.e., < 2 mg haemoglobin/gram of stool. It increases to 90% at haemoglobin concentration > 25 mg/gram of stool. Moreover, HemeOccult will give 1-3% false-positives even with strict protocol for stool collection. Sensitivity of HemeOccult and HemoQuant is only ~20-30% for colorectal cancer and ~13% for polyps<sup>10</sup>.

In one study, replicate stool samples with known lesions were tested with HemeOccult, HemeOccultSensa, HemoQuant, and HemeSelect. HemeSelect, the immunological test, was found to be the most sensitive test for detecting adenomas and carcinomas, while maintaining specificity<sup>21</sup>. The performance of HemeOccult, HemeOccultSensa, HemoQuant, and HemeSelect recently were tested prospectively in patients aged 50 years or older in a large managed care setting<sup>11</sup>. Results of this study suggest that HemeSelect and a combination test in which HemeSelect is used to confirm positive HemeOccult Sensa provide more accurate results than HemeOccult in screening for colorectal cancer. In a recent cost-effectiveness analysis of colorectal cancer screening in Japan, strategies that used an immunochemical test rather than a guaiac-based test were also found to be most cost-effective<sup>22</sup>. The advantages and disadvantages of various faecal occult blood tests are shown in table V.

## Evaluation of positive faecal occult blood test

### (a) Colonoscopy vs barium enema

In virtually all other patients with positive faecal occult blood test, the colon should be evaluated first with either colonoscopy or a combination of air-contrast barium enema and sigmoidoscopy<sup>23</sup>. Colonoscopy allows diagnosis and treatment (for example adenoma excision) in one step but incurs a risk, although small, of perforation (~0.8% for polypectomy during the procedure); perforation can also occur during simple diagnostic colonoscopy<sup>23</sup>.

The combination of barium enema and flexible sigmoidoscopy offers lower risk and lower cost, but one disadvantage of barium enema is that abnormal examination results requiring subsequent colonoscopy occur in ~15% or more of patients<sup>24-26</sup>. Moreover, a barium enema may not detect even large

Table V : Advantages and disadvantages of various tests for detecting faecal blood.

S. No.	Test	Advantages	Disadvantages
1.	Guaiac-based test	<ol style="list-style-type: none"> <li>1. Readily available.</li> <li>2. Convenient.</li> <li>3. Inexpensive.</li> <li>4. Good patient-compliance in motivated patients.</li> <li>5. Can be performed in physician's office.</li> </ol>	<ol style="list-style-type: none"> <li>1. Dependent upon degree of hydration.</li> <li>2. Affected by storage (haemoglobin degradation).</li> <li>3. Affected by site of bleeding.</li> <li>4. Dietary restrictions required.</li> </ol>
2.	Heme-porphyrin test	<ol style="list-style-type: none"> <li>1. No interference with dietary peroxidases or rehydration.</li> <li>2. Highly accurate indicator of bleeding, regardless of level.</li> </ol>	<ol style="list-style-type: none"> <li>1. Needs laboratory setup.</li> <li>2. Time consuming (~90 minutes required).</li> <li>3. False positive results with non-human haemoglobins.</li> </ol>
3.	Immunochemical test	<ol style="list-style-type: none"> <li>1. Highly specific, as it detects only human haemoglobin.</li> <li>2. FlexSure OBT can be performed in physician's office.</li> <li>3. Dietary restrictions are not required.</li> <li>4. Stable upon 30 days.</li> <li>5. Detects as little as ~0.3 mg/gram of Stool.</li> </ol>	<ol style="list-style-type: none"> <li>1. Needs laboratory setup.</li> <li>2. Affected by storage (haemoglobin degradation).</li> <li>3. Affected by site of bleeding.</li> </ol>

( $\geq 1$  cm) adenomas in ~40% of cases<sup>27</sup>. The false-negative rate is presumably much higher for smaller adenomas, but smaller adenomas are common and have less clinical significance than larger adenomas. Thus, although colonoscopy is more expensive than barium enema, the overall cost of these two diagnostic strategies is approximately the same. The optimal approach depends upon the local expertise and costs.

A recently published study demonstrated that if faecal occult-blood test is performed first, fewer total endoscopic examinations are performed than if sigmoidoscopy is performed first. Clearly, performing a faecal occult-blood test before sigmoidoscopy is a cost-effective practice<sup>28</sup>.

Four large scale, randomised trials have shown that annual or biennial screening of people without symptoms by means of faecal occult blood testing significantly reduces the mortality from colorectal cancers<sup>1-3,30</sup>. The reduction in mortality is evidently a consequence of the earlier detection and surgical resection of colorectal tumours.

#### (b) Upper GI endoscopy

In patients less than 45 years of age with obvious symptoms referable to upper gastro-intestinal tract (like heart-burn, dyspepsia, nausea, vomiting, weight loss, etc.), it is reasonable to proceed first with upper gastro-intestinal endoscopy to look for a source of bleeding. In asymptomatic patients with positive faecal occult blood test whose colonic evaluations are negative, the cost effectiveness of evaluation of upper gastro-intestinal tract is uncertain, and this procedure is not recommended<sup>31</sup>.

#### (c) Small intestinal evaluation

Evaluation of the small intestine is unnecessary in most patients with positive faecal occult blood test or iron deficiency anaemia who have

negative evaluation of the colon and upper gastro-intestinal tract. However, with persistent chronic blood loss that responds poorly to iron supplementation or requires transfusion, further evaluation is needed to find the source of bleeding. A small intestinal enteroclysis study may be useful in such cases.

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