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The following authors/planners have no financial relationships to disclose:

Angela N. Bartley, MD; Jay L. Bock, MD, PhD, FCAP; Frederick A. Browne, MD, MBA; Jane C. Dale, MD, FCAP

Eileen M. Esposito, RN, MPA, DNP, CPHQ; Cynthia Foss Bowman, MD, FCAP; Tim R. Hamill, MD, FCAP

Bradley S. Karon, MD, PhD, FCAP; David J. Ledden, PhD; James H. Nichols, PhD; David A. Novis, MD, FCAP

Deborah A. Perry, MD, FCAP; Barb Flamich, MT (ASCP)

The following authors/planners have financial relationships to disclose:

Barbara M. Goldsmith, PhD, FACB

- *Nova Biomedical, One-time Consulting Fee, Trainer*
- *T2 Biosystems, One-time Consulting Fee, Consultant*

Barbara L. Haller, MD, PhD, FCAP

- *Ortho Diagnostics, Consulting Fee and Travel Expenses, Advisory Board Member*

Dawn M. Taylor, MT(ASCP)

- *St. Johns Health Laboratory, Salary, Employee*

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Learning Objectives

Upon completing the reading and answering the learning assessment questions, you should be able to:

1. Define the most common causes of gastrointestinal (GI) bleeding.
2. Distinguish the different presentations of GI bleeding.
3. Identify the most common screening and diagnostic tests for GI bleeding.
4. Discuss the sources for specimen and testing errors in fecal occult blood testing (FOBT).
5. Describe a multidisciplinary approach to diagnosing and treating GI bleeding.

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Case Study

Susan Chen is the daytime supervisor of the Large City Hospital Emergency Department stat lab. She and her staff perform rapid testing for the thousands of patients who are seen each year. They have noticed an increase in patients evaluated for intestinal bleeding, especially the elderly. They note that some patients present for "acute gastrointestinal (GI) bleeding" while others are suspected of "chronic intestinal bleeding". Testing varies for these patients and the lab staff wants to learn more. They ask their pathologist, Dr. Enrique Vasquez, to help them understand the origin, diagnosis, and treatment of this category of patients. Dr. Vasquez works with his pathology resident, Dr. Christine Adams, to present the following report.

INTRODUCTION

In the course of a day, the normal wear and tear within the adult alimentary lumen produces less than 1/3 of a teaspoon (1-2 mL) of blood. More than that is never normal. Pathologic bleeding may occur anywhere along the GI tract, from the mouth to the anus, and may result from lesions ranging in severity from bleeding gums and nosebleeds to inflammatory bowel disease or cancer.

The manner in which GI bleeding makes itself known to patients and what doctors do to treat it depend upon their ability to determine the:

- Presence of bleeding
- Location of the bleeding
- Cause of the bleeding

These determinations require that physicians employ both laboratory tests and radiology studies.

THE PRESENCE OF BLEEDING

The rate and severity with which bleeding occurs generally sets the level of anxiety it provokes, both in patients who experience it and in physicians who treat it. A torrent of bright red blood gushing from an artery that has suddenly burst is likely to set off an explosion of alarm and activity. The ebb of dark blood—dark because it has already released its oxygen to tissues—that oozes from a slowly leaking vein tends to encourage a slower, more deliberative response.

Small amounts of intermittent bleeding are frequently occult and may not be detected clinically until a patient presents with signs of anemia, as discussed below.

Acute Gastrointestinal Bleeding

Actively bleeding lesions located in the lower gastrointestinal tract (LGI) tract-- the portion of the gut that is distal to the duodenum—release blood per rectum, the term for which is "hematochezia." Blood that passes immediately appears bright red or maroon. Blood that leaks more slowly has time to saturate fecal material,

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altering its color and consistency to material resembling fresh tar. Briskly bleeding lesions located in the upper gastrointestinal tract (UGI) proximal to the duodenum commonly (but not always) discharge blood orally, the term for which is hematemesis. Blood, which passes slowly congeals with gastric contents to be regurgitated in slurry resembling wet coffee grounds. What is not regurgitated passes through to the colon and produces black, tarry melanotic stools. Hematemesis and melena are the most common presenting signs of acute upper gastrointestinal hemorrhage.

It is usually not necessary to use laboratory tests to diagnose the presence of acute GI bleeding--vision will do.

It is usually not necessary to use laboratory tests to diagnose the presence of voluminous, brisk acute GI bleeding—vision will do. The task is to determine the source of bleeding so it can be stopped. However, bleeding may be so profuse that the search has to be put on hold, at least briefly while physicians institute measures to prevent shock and death. Several scoring systems have been devised to stratify the risk of death from GI bleeding, and in so doing, direct more progressively assertive medical action. One such system, the Blatchford scoring system (Table 1 in the Appendix), assigns a clinical risk number (zero to 23), depending on the results of laboratory tests and clinical findings; the higher the number, the more aggressive the therapy.

The common denominator of all shock, regardless of its cause is the inability of the body to oxygenate tissues. Oxygen delivery requires, among other things, enough hemoglobin to carry oxygen and a sufficient heart pump to deliver it. As with severe hemorrhage resulting from any cause in any location, the first round of testing assesses patients' abilities to maintain competency of their cardiovascular and oxygen delivery systems. In the earliest moments, the extreme nature of this catastrophic event requires that these tests be simple and rapid.

The most accessible measurements of impending vascular collapse are blood pressure and pulse. They are related inversely. With persistent loss of blood, pressure falls. To maintain delivery of enough oxygen, the heart compensates by increasing its rate, measurable as a hastening pulse. The tipping point is about 100 for both the heart rate and systolic pressure. The United States Navy General Medical Officer manual informs its doctors that one in five bleeding patients whose systolic pressure falls below 100 mmHg and whose pulse simultaneously rises above 100 beats per minute will not survive.[1] Put another way, patients cannot survive losing more than about 1/3 of their circulating blood volume acutely. The kidneys, sensing disaster attempt to prevent vascular depletion by ceasing to create urine. Measurements of blood urea nitrogen (BUN), creatinine, and electrolytes record the degree of dehydration and later with therapy, the efficiency or rehydration. To keep the heart pumping, intravascular volume must be first expanded with isotonic fluids. If persistent bleeding renders the situation more desperate, sensitive intravascular probes must be inserted to continuously record the effectiveness with which these fluids maintain vascular pressures.

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Restoration of oxygen carrying capacity requires administration of red blood cells. Tests to determine patients' blood types and anti-red blood cell antibodies are embedded in the initial battery of tests that physicians order on bleeding patients. Percutaneous oximeters at the bedside measure the success of blood transfusions to oxygenate tissue. These clothespin-shaped instruments are clipped to fingers or ears. One arm of the pin emits light beams of several wavelengths that pass through the tissue and strike a photodiode located on the other light emitting diodes (LEDs). The absorption of light on the photodiode is proportional to the amount of blood that is oxygenated (oxyhemoglobin) and the instrument converts the reading to a percentage of tissue oxygenation. Arterial blood gas determinations can also measure the success of oxygenation and tissue perfusion with oxygenation saturation and pH.

For the 97% of patients who survive this acute episode of bleeding, doctors will initiate the search for the origin of bleeding.

Case Study, cont'd

Susan and her staff can relate to this scenario. They frequently are performing stat CBCs, blood gas testing, and sending specimens for blood typing and crossmatching as well as dispensing the blood units they receive from the Blood Bank for emergency transfusion. More comprehensive metabolic testing such as tests for liver and renal function is sent to the central laboratory.

Chronic Gastrointestinal Bleeding

Chronic bleeding from the gastrointestinal tract is more often of capillary rather than of venous or arterial origin. Unlike arterial bleeding, venous bleeding is generally protracted and inconspicuous. By the time bleeding becomes obvious to the patient, the responsible lesion has matured. Mature lesions may announce their presence with disturbing intestinal signs and symptoms such as abdominal pain, nausea, and darkening stools.

More commonly, symptoms are vague and confusing, related only to the dwindling capacity of blood to supply tissues with oxygen. Patients see their doctors because they feel tired and weak. They may become dizzy and short of breath when they climb stairs. Measurement of hemoglobin and hematocrit confirms the presence of anemia, and determination of red blood cell indices usually characterizes the anemia as hypochromic and microcytic. Hypochromic microcytic anemia, a sign of iron deficiency, is most often caused by chronic blood loss and without another obvious source of hemorrhage— recent surgery, trauma, gynecological hemorrhage—blood loss is invariably the result of bleeding from the GI tract.

Patients with chronic UGI bleed often present with confusing and vague symptoms. They often feel tired and weak and usually have hypochromic and microcytic anemia.

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Frequently, bleeding intestinal lesions offer *no* clues as to their presence, vague or otherwise. Because patients are so often unaware of their *occult* bleeding, testing for the presence of gastrointestinal bleeding is a basic component of routine physical examinations. Indeed, patients are often surprised with this information on the occasion of what they thought was to be an uneventful routine yearly examination. Because the presence of GI bleeding is often not obvious, doctors need laboratory tests to detect it. These tests are usually thought of as screening tests for colon cancers or precancerous lesions such as polyps. However, not all chronic GI bleeding is caused by those conditions. See the discussion below.

Case Study, cont'd

The stat lab staff can relate to this. They are surprised by how many older patients they see with very low hemoglobin and hematocrit values and who have only recently appreciated how tired they are. Dr. Vasquez discusses how people gradually accommodate to slow blood loss, while rapid blood loss causes symptoms much sooner.

TESTING FOR THE PRESENCE OF GASTROINTESTINAL BLEEDING

Blood lost anywhere along the course of the GI tract, from the mouth onward, passes distally to the large intestine where it mixes with fecal material. The amount of blood lost may be quantified in several ways. A classic method involves tagging the patient's own red blood cells with radioactive chromium ^{51}Cr, injecting those RBCs back into the patient, and then measuring stool samples for the ^{51}Cr by a radioimmunoassay. This is an expensive, laborious procedure and is not used for routine detection of GI bleeding. Other tests quantify the amount of hemoglobin in feces by fluorescent techniques, which are sensitive methods to establish that iron deficiency anemia is caused by GI bleeding. However, these too are laborious methods which must be performed in reference laboratories, and are also not commonly used.

More basic laboratory tests to detect GI bleeding, collectively referred to as Fecal Occult Blood Tests (FOBTs) or Fecal Immunochemical Tests (FITs or iFOBTs) measure byproducts of blood that may accumulate in the GI tract.

Blood that leaks into the gastrointestinal lumen encounters an osmotically and pH-hostile environment that causes lysis of red blood cells and releases free hemoglobin. The hemoglobin breaks down to hematin and globin. Some of this hematin is absorbed back into the cells lining the gut where enzymes convert the hematin to bilirubin. Most of the hematin, however, remains in the GI lumen where it is converted by colonic bacteria to porphyrin (Figure 1 on the following page).

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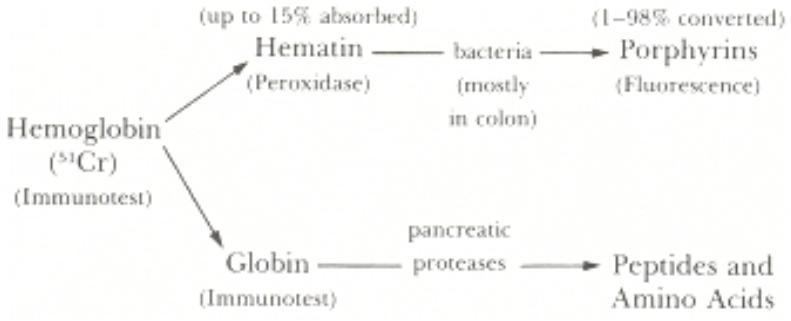
Figure 1. Hemoglobin Break Down



Case Study, cont'd

Susan and her staff ask why the emergency department (ED) doctors ask for FOBTs when they suspect UGI bleeding.

Dr. Vasquez replies that most GI bleeding is from the upper tract, and tells the staff the reason in the next part of his discussion.

Commonly used tests to detect the presence of GI bleeding employ the following methodologies:

1. Colorimetric tests using guaiac to detect peroxidase activity from hematin and hemoglobin.
2. Immunochemical tests to detect human globin in undegraded hemoglobin.

Each test measures different components of hemoglobin and its byproducts. They vary in cost, the sensitivity and specificity with which they detect GI bleeding, and the numbers of specimens that are usually tested. What they all have in common is that in order to detect GI bleeding, the responsible lesions must be bleeding actively and in volumes large enough to exceed the lowest limits to the tests' sensitivities. The more the bleeding the more likely a test is to be positive. Continuously bleeding lesions are more likely to be detected than intermittently bleeding lesions.

For instance, these tests are used mostly to screen for colon cancer and precancerous polyps. Cancers bleed more frequently than polyps and larger lesions bleed more than smaller ones, so cancers will more likely be detected than polyps and large cancers and polyps will more likely be detected than small lesions.

Guaiac Tests

The most commonly used, simplest, cheapest and quickest method for determining whether or not blood is leaking into the gastrointestinal track employs the use of the naturally-occurring chemical guaiac. Guaiac detects the presence of intralumenal hematin and hemoglobin. Guaiac is a phenolic wood resin obtained from the Guaiacum tree (Image 1. on the following page).

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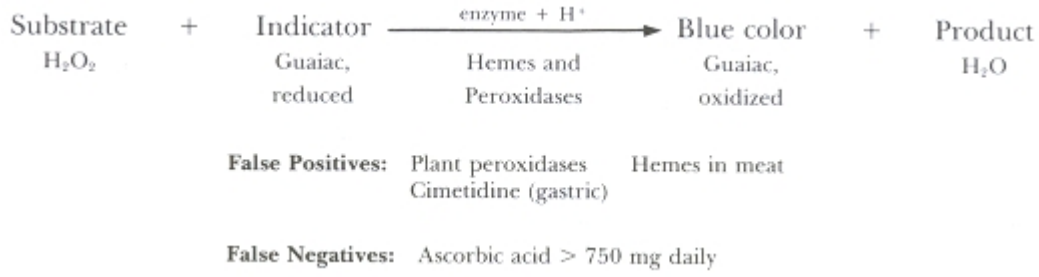
Image 1. Guaiacum Sanctum

Common Name: Guayacan

The word guaiac comes from the Taino people who occupied what is now the Bahamas long before Columbus dropped in. The people are gone, but the tree is still there. In fact, it's the national tree of the Bahamas. The English latched onto this word in the first half of the 16th century, making it perhaps the truly first word of American origin adopted into the English language. The Europeans imported the guaiacum back to their homelands, believing the plant was a remedy for syphilis. It wasn't. Guaifenesin, however, a derivative of guaiacum, is the expectorant employed in cough medicines. In the early 19th century the biochemist Planche stumbled upon the color producing combination of guaiac and horseradish peroxidase. A Dutch chemist, Van Deen, discovered that guaiac was helpful for determining the presence of occult blood. It wasn't until 1967 that Greegor suggested using guaiac in a home test to pick up intestinal bleeding.

When guaiac is mixed with peroxide and fecal material containing blood, peroxidase activity present in the blood oxidizes the guaiac, turning it from a neutral to a blue color (Figure 2). The iron in blood does not enter into this chemical reaction, which is why iron ingested orally in dietary supplements or iron replacement therapy does not influence the test results. Blood in the stool is usually not visible until it reaches a concentration of about 50 mg of hemoglobin per gram of stool. The guaiac-based FOBT can detect a blood loss as low as 10mL/day (about two teaspoonfuls), which is about 6-20 times the normal daily blood loss.

Figure 2. Principle of Peroxidase-Based Tests



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Guaiac testing is waived under the CLIA complexity model. A number of waived kits are available commercially. They generally contain cards with spaces on which fecal matter is smeared. A small amount of fecal matter is placed on the space, the flap is closed, and a hydrogen peroxide developer is added to the opposite side of the window. If hemoglobin is present in a quantity that exceeds the lowest level of test sensitivity, a blue color appears.

The test performs well in identifying GI bleeding that originates in the colon, but does not do as well in identifying GI bleeding that originates proximal to the colon. Intestinal bacteria are so efficient in breaking hemoglobin down to porphyrin that by the time blood reaches the colon, the hemoglobin and its peroxidase-like activity is almost gone. However, UGI bleeding may be large enough or the passage of blood so rapid that not all the hemoglobin is degraded and the guaiac test will be positive.

Case Study, cont'd
OK, so now the lab staff understands the importance of FOBT screening even when the source is suspected to be the UGI tract. But, they ask, won't UGI bleeding always be obvious? Not always says Dr. Vasquez, especially before an endoscopy or other procedure.

Colonic bleeding, especially bleeding from small cancers and polyps, tends to be intermittent, so a negative guaiac test does not rule out its presence. To increase the likelihood of discovering bleeding, it is necessary to test three separate stool samples on three different days. With some tests, the clinical sensitivity of a single FOBT in detecting blood is about 30%. If three tests are performed, the sensitivity increases to 92%.

Guaiac tests for occult GI bleeding are influenced by the number of tests performed. To increase the likelihood of discovering bleeding, it is necessary to test three separate stool samples on three different days.

As with all testing, manufacturer's directions MUST be followed. General directions include that those performing these tests must:

- Store test cards at specified environmental conditions. Improperly stored cards may have discolored backgrounds, making distinction between positive and negative results difficult.
- Use test cards and developer solutions prior to their expiration dates.
- Collect several stool samples—one per day over several days.
- Do not collect samples from patients who are menstruating, have vaginal bleeding, or have actively bleeding hemorrhoids.
- Do not allow fecal samples to come in contact with toilet bowl water or chemicals.
- Perform tests no later than 14 days after collecting the specimen.
- Read the color reaction within the time specified in test directions.
- Use positive and negative controls.

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- Confirm that the tester can distinguish a blue positive color from other colors and is not color blind.
- Follow dietary and medication instructions.
- Label patient samples and developer solutions.
- Use only reagents and cards from the same kit—do not mix and match components from different kits.

The guaiac oxidation reaction may be blocked by reducing agents such as ascorbic acid (Vitamin C), which is present in citrus fruits and juices. When dietary intake of ascorbates--rich juice exceeds 750mg/mL/day, the equivalent of drinking ½ to 4 gallons of juice (depending on whether the juice is pasteurized or fresh), or of pure Vitamin C supplements exceed 250mg/day, the test may become falsely negative.

When dietary intake of ascorbates exceeds 750mg/mL/day, the guaiac test for occult GI bleeding may become falsely negative.

Foods containing blood such as red meat, and foods with peroxidase or peroxidase-like properties such as radishes, turnips, cabbage, cauliflower, horseradish, uncooked broccoli, cucumbers, mushrooms, green beans, artichokes and melons can generate color reactions that may be interpreted falsely as positive test results (Table 2 below). To reduce the possibility of obtaining a falsely positive result, clinicians often advise patients to avoid the above foods for at least three days before guaiac testing. Some kit manufacturers include alcohol in the developer to denature plant peroxidases. Waiting three days before testing a specimen also results in the loss of the plant peroxidase activity. Dietary restrictions may not be necessary if samples are not tested immediately. Some sources suggest that patients eat roughage before collecting stool samples since roughage may cause lesions to bleed and be detected.

Table 2. Strict Low-Peroxidase Diet for Occult Blood

Do *not* ingest		
Rare red meat	Carrot	Mushrooms
Bloodwurst	Cauliflower	Parsnip
Horseradish	Cucumber	Pumpkin
Broccoli	Grapefruit	Turnips
Cabbage	Green beans	Zucchini

Wetting the smeared side of the paper with a few drops of water several minutes before adding the developer, i.e., "rehydration" enhances the guaiac reaction and was a technique used to increase sensitivity. However, water also facilitates falsely positive reactions generated by the presence of plant peroxidase and meat heme. This rehydration technique is no longer recommended nor widely used because it causes too many false positive reactions. Testing wet fecal specimens can also promote false positives. This may be a problem in the ED when providers do not want to wait for a specimen to dry before adding

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developer. In any event, those performing the test must follow manufacturers' recommendations regarding hydration of the specimen.

It is unwise to perform FOBTs on samples taken by digital rectal examination because the rectal exam may cause minor bleeding. If the result is negative, it will be impossible to determine if the negative result reflects a sample that is not truly representative of colonic material. Also, since the digital exam may cause minor bleeding, if the FOBT test is positive, it will be impossible to determine whether the positive test resulted from the exam or from a colonic lesion. A positive FOBT taken on a sample obtained by digital rectal examination must be confirmed by repeating the FOBT according to the manufacturer's specifications, namely on evacuated stool samples.

Positive tests resulting from bleeding caused by drugs such as aspirin and non steroidal anti-inflammatory agents (NSAIDs) that erode the gastric lining will likely be misinterpreted as representing intrinsic lesions. If patients are ingesting those medicines, they must stop doing so at least three days prior to, and during testing. Other agents that might cause bleeding or interfere with the test include:

- Corticosteroids
- Phenylbutazone
- Reserpine
- Anticoagulants
- Antimetabolites
- Chemotherapy agents
- Iodine antiseptics

Case Study, cont'd

The lab staff says they frequently saw problems in testing before they started to do all the stool guaiac testing for the ED. At least now they can control the process and enter the results in the electronic medical record (EMR). They worry about the testing performed on the in and outpatient units and suggest a QA monitor be considered along with education for the healthcare providers doing the testing.

FOBT test kits are designed to be performed on only one specimen source---fecal material for the following reasons:

- The test is standardized only for stool specimens. Various fluids and tissues differ in different pH environments and other conditions, all of which may affect peroxidase reactions.
- The Food and Drug Administration (FDA) approves FOBT tests for use on stool specimens only. The FDA considers use of the test on other specimens to be "off label".
- The process of obtaining other specimens such as inserting nasogastric tubes or endoscopes to retrieve samples from the stomach or small intestine often produce bleeding that will confound interpreting test results.

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The FOBT guaiac test is standardized only for feces and is not appropriate for specimen sources that have other pH or fluid conditions. It is not established or approved for stomach, breast, or other fluid sources.

In aspirates of gastric or duodenal contents, Cimetidine, an H2 blocker drug used for gastric acidity causes falsely positive reactions. Because Cimetidine is absorbed before reaching the colon, it has no effect on the outcome of FOBTs if the test is used only for feces. A separate waived test is approved for gastric secretions, and controls for the pH of gastric fluids. Breast nipple discharges should never be used for guaiac testing to detect blood.

Case Study, cont'd

Susan remembers being asked to test different body fluids. Now she has information to use in declining that testing.

Despite all the limitations of the guaiac-based FOBT, it has been an effective cancer screening test. Colorectal carcinoma is the third most common cancer in the US with 50,000 annual deaths attributed to it. Since 1985, the incidence of this cancer has decreased from 66.3 to 49.5 cases/100,000 population and much of this is attributed to screening programs which include FOBT. Since early detection of colorectal carcinoma in a less advanced stage results in better survival, this relatively simple and cheap test can help to contribute to better outcomes. Long term studies of patients who had annual FOBT screening showed 21 to 33% decreased mortality from colorectal cancer.

Immunochemical Tests

Fecal immunochemical tests (FITs) for GI bleeding are more current options for screening. These tests employ antibodies directed to the globin part of human hemoglobin. Because the antibody is specific for *human* hemoglobin, there are no cross reactions with animal hemoglobin in meat or with plant peroxidase activity so dietary restrictions are not necessary. FITs may be waived strip tests using immuno-chromatographic technology or they may be non waived automated procedures run on fecal samples submitted in collection vials to clinical laboratories. The test employs a sandwich immunoassay using a combination of two antibodies to human globin: the first *capture antibody* fixes free human hemoglobin to a solid surface; a second *detection* or *label* antibody, to which is conjugated a color-producing compound, generates a color when it too fixes to the hemoglobin molecule.

One strip method uses a card to collect the fecal specimen and a test device that allows the liquid extraction of hemoglobin from the fecal sample and puts the extracted sample in contact with a strip. The extracted sample flows down the strip where it can react with the anti-hemoglobin antibodies and conjugate. The background is considered a negative control. External controls are also used.

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As with ALL laboratory testing, anyone performing ***any*** test kit to detect the presence of GI bleeding must meticulously follow manufacturer's instructions:

- Kit components must be maintained under proper storage conditions and only kit components within the same lot number may be used together.
- Expiration dates must be followed.
- Stool must not come in contact with toilet bowel water or chemicals.
- Several stool samples from different days should be tested and each stool should be sampled in several places.
- Strip testing specimens must be allowed to dry.
- Specimens and cards must be labeled.
- Reading must be performed within the time limits specified by the manufacturer.
- For patients who are menstruating or who have bleeding hemorrhoids, testing must not be used until bleeding has stopped.

Studies have shown immunochemical tests are more sensitive than traditional guaiac-based FOBTs in detecting colon cancers and large polyps. Since they are more sensitive, they may result in additional work-ups for lesions that turn out to be inconsequential. Manufacturers can adjust the level of hemoglobin detected so that the test is not overly sensitive. Immunological tests also may not detect UGI bleeding for reasons similar to those stated above, such as intermittent bleeding or bleeding below levels of detection. Although immunological tests are more expensive than guaiac-based FOBTs, third party reimbursement for them is higher. They may be considered more "patient friendly" because some believe fewer stools need to be collected or sampled. However, if a lesion bleeds intermittently, multiple stool samples need to be tested even for FITs.

Large scale studies evaluating whether or not these tests actually decrease mortality from colorectal carcinoma are pending, but preliminary studies are encouraging. The American Cancer Society's most recent Guideline for Screening and Surveillance for the Early Detection of Colorectal Adenoma and Cancer states that for individuals at average risk for developing colorectal cancer, "immunochemical tests are more patient friendly and are likely to be equal or better in sensitivity and specificity." Their use may well increase, but currently most screening lab tests for GI bleeding are guaiac-based tests because they are more well-established and cheaper.

DNA Tests for Colon Cancer Screening

A newer test to detect colorectal cancers and premalignant lesions is the DNA mutation test. While the test does not detect bleeding, it does identify DNA mutations in cells shed by colon cancers or its precursor lesions and can detect changes from other cancers that shed cells through the GI tract. Multiple DNA alterations occur with colonic cancers and the test is set up to identify the most common of those or mutations most effective at picking up significant lesions. The original test required that patients collect entire stool samples in a special container, which was transported quickly to a laboratory or office so that

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the entire specimen could be frozen to avoid DNA degradation and then be transported to the testing laboratory. The procedure is complex, with DNA extraction from a homogenized stool and multiple steps required to get to a point where the mutation markers can be identified by polymerase chain reaction (PCR). Newer versions of the test can prevent DNA degradation by using a stabilizing buffer. Additional improvements include more efficient recovery of DNA, improved sensitivity in detecting DNA markers, and the ability to only submit a sample of a stool. Any mutation detected must then be evaluated with further patient testing, such as colonoscopy. While the testing is expensive, costing hundreds of dollars, newer versions are cheaper and current DNA mutation testing may be more sensitive and specific for colon cancer detection than fecal occult blood testing. It also does not require special patient preparation. Improved DNA mutation testing may be effective in identifying precursor lesions such as polyps. Large scale studies need to be conducted to see if the testing is effective on a population wide basis and decreases mortality from colon cancer. Several commercial laboratories offer this testing.

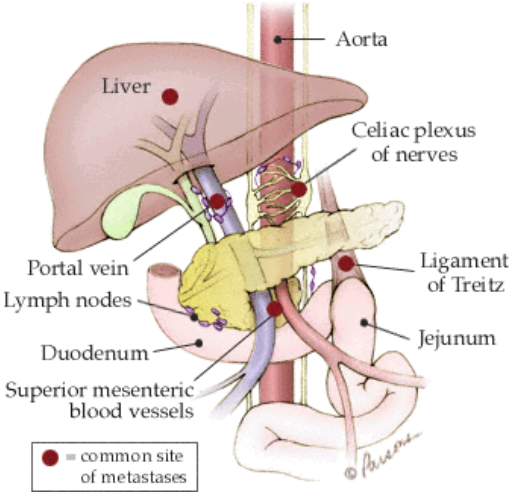
DNA stool testing is used to detect DNA mutations that can be found in colon cancers, precursor lesions, or in other cancers that may shed cells through the GI tract. It does not detect GI bleeding from benign sources.

The Location of Bleeding

Once the presence of gastrointestinal bleeding is established, the venue of diagnostic testing that must be employed to locate its source shifts from the laboratory to endoscopy and radiology.

Clinicians categorize GI bleeding sites as either being upper GI or lower GI. The border that demarcates the two is the Ligament of Treitz, a fibrous band that anchors the duodenum at its junction with the jejunum to the posterior wall of the abdominal cavity (Image 2.).

Image 2. Ligament of Treitz



Václav Treitz (1819-1872)

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The division is not arbitrary. It is the farthest limit that a gastroscope can visualize. To see beyond the Ligament into the lumen of the small intestine requires either an enteroscope, which can only visualize the proximal small bowel, or other tools used by radiologists or gastroenterologists; barium swallow radiograph, angiography, ultrasound, nuclear imaging, CT scan, and MRI.

A new technique termed capsule endoscopy, which employs a pill-shaped camera that patients swallow shows promise in detecting small bowel lesions. Less than 10% of GI bleeding emanates from the small bowel.

Moving south, direct vision of the alimentary lumen again becomes possible at the terminus of the small bowel, specifically the ileocecal valve. A colonoscope inserted per rectum can visualize the entire large bowel including the cecum. Endoscopes of all sorts do a fine job identifying mass lesions such as cancers and polyps. They do a slightly poorer job with vascular lesions, which are sometimes detected only by arteriography or nuclear imaging.

It is not always obvious in a patient passing blood per rectum whether bleeding is originating in the upper or in the lower GI tract. Inserting a nasogastric tube, aspirating the fluid, and observing what returns to the syringe may sort this out: if blood fills the syringe the gastroenterologist will search for the lesion with a gastroscope; if the contents are non-bloody, the gastroenterologist will reach for the colonoscope. If bleeding is so brisk that blood floods the gastrointestinal lumen, obscuring the endoscopist's view, arteriography may be the only way to pinpoint the site of bleeding.

At the other end of the spectrum, bleeding may be too slow for detection by either endoscopy or arteriography. In these instances, it is possible to inject patients with red blood cells tagged with technetium-99m and identify bleeding at rates under 0.4mL/minute.

If all these instruments fail to locate the source of bleeding, it may be necessary to perform an exploratory laparotomy.

THE CAUSE OF BLEEDING

The lesions that cause GI bleeding are identified by their appearances seen through endoscopes, on radiographic and ultrasound images, and under microscopes. The specific techniques chosen to identify the sources of bleeding are dictated largely by the urgency with which clinicians must make the diagnosis. An actively bleeding patient in dire straits requires the endoscopist to arrive at a direct visual diagnosis immediately. A chronically bleeding patient who is barely symptomatic can wait for clinical assessment or the pathologist to complete a microscopic examination of biopsy material completed over the course of several days.

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Acute Gastrointestinal Bleeding

Upper Gastrointestinal Bleeding

Emergency Departments in communities serving 100,000 residents, say the size of Manchester, NH or South Bend, IN, will hospitalize about 80 patients yearly for UGI hemorrhage. Nationwide, this comes to slightly less than a quarter of a million hospital admissions per year.[2] Half the patients are older than 65 years of age, about 1/5 older than 85. The number has been declining steadily over the last decade, inversely related to the increasing use of proton pump inhibitors, antibiotic therapy for ulcer-inducing *H. pylori,* and non-erosive arthritic medications. The leading causes of UGI bleeding include peptic ulcers, inflammation (gastritis and duodenitis) and cancer.

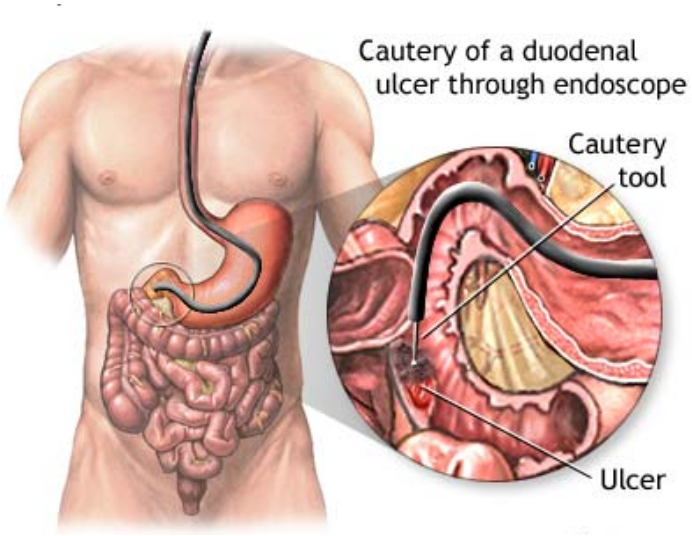
Case Study, cont'd

The ED lab staff wonders why they are seeing so many elderly patients with UGI bleeding. Dr. Vasquez surmises that the numbers of patients taking non steroidal medications for arthritis may be an explanation. Also, the number of elderly patients who are depressed or drink alcohol may account for the incidence. In some populations there is also a higher incidence of *H. pylori,* a bacteria that can cause inflammation and ulcers, see below.

Of these, peptic ulcer--the most common cause of UGI bleeding—is responsible for about half the cases of ED admissions for UGI hemorrhage. Two thirds of these patients are over the age of 60 and one quarter over the age of 80. One in 10 to one in 20 will not survive the bleeding episode. The direct hospital medical costs in caring for these patients exceed 2 billion dollars annually.

Patients who present to EDs with UGI bleeding are endoscoped as soon as they are hemodynamically stable. Endoscopy can locate the site of bleeding, retrieve biopsy tissue by which to identify the nature of the lesion, and in many instances coagulate the lesion to stop the bleeding (Image 3).

Image 3. Electrocautery of a Bleeding Duodenal Ulcer



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Gastric and duodenal ulcerations occur when the protective mucous membrane barrier lining these organs is stripped away and becomes unable to resist the corrosive effects of gastric acid. Eventually, the thinning alimentary wall allows caustic elements to access the underlying blood vessels which open and release their contents. Two agents are most commonly responsible for destroying the gastric and duodenal barriers. The first is *Helicobacter pylori* bacteria. Antibiotics that eradicate *H. pylori* can eliminate 80-90% of these ulcers. The second is non steroidal anti-inflammatory drugs (NSAID). Over half the individuals ingesting NSAID require discontinuing or modifying their dosage to relieve symptoms of inflammation and ulcer. Other irritants, such as alcohol, steroids, and cigarette smoke damage the gastric mucosa in a similar noxious way. Gastric bleeding may occur in patients stressed by burns or trauma. Vascular malformations such as angiodysplasia are prone to precipitous hemorrhage. If bleeding of any etiology occurs in patients receiving anticoagulation medicine, hemorrhage can be fatal.

Esophageal bleeding often presents catastrophically and without warning. Most commonly, the bleeding reflects the end stages of alcohol disease: liver disease with varices, esophageal ulcers, and Mallory-Weiss tears. Esophageal varices are esophageal vessels that become engorged, dilated and then burst as a result of intense back pressure in the portal vein, the normal outflow of which has become impeded by a scarred (cirrhotic) often alcohol-weary liver. One third to one half the patients with variceal bleeding exsanguinate to death unless treated. Tying a band around the bleeding vessel under endoscopic guidance, similar to the non-endoscopic procedure performed on hemorrhoids will stop 80-90% of variceal bleeds. Mallory-Weiss tears result from rending of the esophageal wall, commonly during an episode of alcohol-induced convulsive vomiting and retching.

Tumors occurring anywhere in the GI tract trigger growth of blood vessels, the walls of which are thinner and more fragile than normal vessels, and may also bleed acutely. Large, matured malignant tumors of the esophagus and stomach are usually fatal within a few years of their discovery. Early tumors may be too small to be detected by the radar of radiology. UGI endoscopy, and in particular endoscopic ultrasound is the most effective means by which to determine the nature and extent of early UGI malignancies.

Lower Gastrointestinal Bleeding

EDs treat about half as many patients for acute LGI bleeding than for UGI bleeding. Many of these patients are elderly, incurring all the increased risks of mortality and morbidity that come with advancing age. Common causes of LGI bleeding include hemorrhoids, tumors, and polyps. These are all diagnosable clinically, endoscopically, or radiologically.

Chronic Gastrointestinal Bleeding

Any lesion capable of announcing itself overtly and acutely is also capable of making an appearance slowly and furtively. Added to the culprits listed above are inflammatory bowel disease such as Crohn's disease and ulcerative colitis, and infectious diarrheas. Patients with these disorders often present with diarrhea, abdominal discomfort and fatigue from anemia. Often, they have blood in their stools. A positive test for blood demands further diagnostic testing. This may include endoscopy, radiologic procedures, and tissue biopsy.

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In clinical practice, testing for chronic occult bleeding has become a euphemism for cancer screening, and in particular screening for colorectal cancer as discussed above. This is because malignant gastrointestinal lesions commonly ooze blood into the gut lumen before they produce symptoms in patients. Detecting the presence of malignant lesions in their silent, early stages before they position themselves to metastasize is associated with improved patient survival. The American Cancer Society recommends that patients over 50 years of age, and those with family histories of cancer or who harbor other risk factors for cancer be screened yearly for occult GI bleeding.

Case Study, cont'd

The ED lab staff wants to know why screening for an occult cancer would be started in the ED. Dr. Vasquez says that the test can help the emergency physician sort out other possible conditions, but sometimes the ED is the best chance to reach patients who do not get regular care. A positive test would trigger a referral to a primary care doctor if no other acute cause was found in the ED.

For every 100 asymptomatic patients aged 45 years or older, about five will have a positive stool guaiac test if they are not on a rigid peroxidase-free diet, and about 2 will have a positive test if they are. Approximately 20 to 30% of that latter group will have a benign tumor such as a polyp and about half that many will have colorectal carcinoma. Most of these detected malignancies are in early stages of growth, not yet having invaded tissue beyond the muscular layer of the colonic wall. The chance of surviving such a tumor for at least 5 years is better than 80%, compared to less than 50% if the tumor has pierced the wall. Viewed another way, 65 to 80% of colorectal carcinomas and 20 to 40% of benign colonic adenomas are detected by the three-stool guaiac test.

Approximately 30 to 60% of guaiac positive subjects will harbor gastrointestinal lesions other than cancer or polyps that might be responsible for occult bleeding (e.g., hemorrhoids, diverticulosis, inflammatory bowel disease, peptic ulcer, gastritis, esophagitis, and esophageal varices). In less than 15% of subjects with positive test results, search for a reason comes up empty handed. The results may indicate the presence of lesions that are yet undetectable, or they may be false-positive tests due to dietary ingestion of vegetable peroxidase.

Case Study, Conclusion

After listening to Dr. Vasquez, the lab staff suggests that he should make the presentation to the ED staff so they can better appreciate the use and limitations of the various lab tests when assessing a patient with GI bleeding. They also think the inpatient and outpatient units would benefit from the information. Dr. Vasquez suggests that the lab staff work with Dr. Adams on setting up educational sessions. He would like Dr. Adams to partner with her gastrointestinal and radiology resident peers in presenting the clinical and diagnostic information, but he believes the laboratory staff can best teach the technical requirements for good fecal occult blood testing.

Making the presentation collaborative with clinical colleagues would be a good demonstration of "Transformation in Pathology" by having pathologists collaborate with their clinical peers in promoting best testing approaches for patients.

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SUMMARY

Gastrointestinal bleeding is a common medical and surgical problem and may arise from many causes. Determining its source and intensity requires combined clinical and laboratory testing. While fecal occult blood testing (FOBT) is frequently regarded as colon cancer screening, it may be used to detect bleeding from a number of gastrointestinal sources. FOBT is a commonly used test, but it is subject to a number of influences and requires users to be aware of good specimen procurement and testing technique. DNA mutation testing may replace FOBT for colon cancer screening but it does not detect other causes of intestinal bleeding.

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Additional Resources

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Appendix

Table 1. Blatchford Scoring System

Admission Risk Markers for GI Hemorrhage and Associated Score Component Values

Risk Marker	Score Component Value	Risk Marker	Score Component Value
Blood urea nitrogen--mg per dL (mmol per L)		**Systolic blood pressure--mm Hg**	
≥18.2 and <22.4 (≥6.5 and <8.0) 2	2	100 to 109	1
≥22.4 and <28.0 (≥8.0 and <10.0) 3	3	90 to 99	2
≥28.0 and <70.0 (≥10.0 and <25.0) 4	4	<90	3
≥70.0 (≥25) 6	6	**Other markers**	
Hemoglobin in men--g per dL (g per L)		Pulse ≥100 per minute	1
≥12.0 and <13.0 (≥120 and <130) 1	1	Presentation with melena	1
≥10.0 and <12.0 (≥100 and <120) 3	3	Presentation with syncope	2
<10.0 (<100) 6	6	Hepatic disease	2
Hemoglobin in women--g per dL (g per L)		Cardiac failure	2
≥10.0 and <12.0 (≥100 and <120) 1	1		
<10.0 (<100) 6	6		

GI = gastrointestinal

Adapted from Blatchford O, Murray WR, Blatchford M. A risk score to predict need for treatment for upper gastrointestinal haemorrhage. *Lancet.* 2000;356:1319. American Family Physician Risk Score Identifies Patients with Upper Gastrointestinal Bleeding. Available at: http://www.aafp.org/afp/20010401/tips/3.html. Accessed March 24, 2010.

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Education Activity Authors

David Alan Novis, MD, FCAP: David A. Novis, MD, is Medical Director of Oxford Diagnostic Laboratory in Marlborough, MA and President of Novis Consulting. Dr. Novis is board certified in Anatomic and Clinical Pathology and a member of the College of American Pathologists (CAP) Point of Care Testing (POCT) Committee.

Cynthia Foss Bowman, MD, FCAP: Cynthia Foss Bowman, MD, is the Vice Chair of Laboratory Medicine in the Department of Pathology and Laboratory Medicine for the North Shore Long Island Jewish Health System and Medical Director of the Clinical Laboratories at Long Island Jewish Medical Center (LIJMC). She practices Anatomic and Clinical Pathology and is Chief of Clinical Chemistry, Immunology, and Point of Care Testing at LIJMC. Dr. Bowman is currently Chair of the CAP POCT Committee.

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