VOLUME - V
ISSUE - XXXIV
JUL / AUG 2009

The Crux

BIMONTHLY FORUM FOR THE LABORATARIANS

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Editorial

Helicobacter pylori was rediscovered in 1982 by two Australian scientists, J. Robin Warren and Barry J. Marshall as a causative factor for ulcers. In their original paper, Warren and Marshall contended that most stomach ulcers and gastritis were caused by colonization with this bacterium, not by stress or spicy food as had been assumed before.

The *H. pylori* hypothesis was poorly received, so in an act of self-experimentation Marshall drank a Petri dish containing a culture of organisms extracted from a patient and soon developed gastritis. His symptoms disappeared after two weeks, but he took antibiotics to kill the remaining bacteria at the urging of his wife, since halitosis is one of the symptoms of infection. This experiment was published in 1984 in the Australian Medical Journal and is among the most cited articles from the journal.

In 1997, the Centers for Disease Control and Prevention, with other government agencies, academic institutions, and industry, launched a national education campaign to inform health care providers and consumers about the link between *H. pylori* and ulcers. This campaign reinforced the news that ulcers are a curable infection, and that health can be greatly improved and money saved by disseminating information about *H. pylori*.

In 2005, the Karolinska Institute in Stockholm awarded the Nobel Prize in Physiology or Medicine to Dr. Marshall and his long-time collaborator Dr. Warren "for their discovery of the bacterium *Helicobacter pylori* and its role in gastritis and peptic ulcer disease".

It was a previously widely accepted misunderstanding that the use of chewing gum resulted in gastric ulcers. The medical profession believed that this was because the action of masticating on gum caused the over-stimulation of the production of hydrochloric acid in the stomach. The low (acidic) pH (pH 2), or hyperchlorhydria was then believed to cause erosion of the stomach lining in the absence of food, thus causing the development of the gastric ulers.

On the other hand, in the recent past, some believed that natural tree resin extract, mastic gum, actively eliminates the *H. pylori* bacteria. However, multiple subsequent studies have found no effect of using mastic gum on reducing *H. pylori* levels.

The DISEASE DIAGNOSIS section of this issue considers Peptic Ulcer at length.

INTERPRETATION simply unravels all markers of Hepatitis B for you.

The overflow of Phlebotomy from the previous issue is carried on in this issue too in the TROUBLESHOOTING segment.

BOUQUET, this time too has haematology photomicrographs for you to consider and diagnose. They are spot diagnostic quizzes. Jokes and proverbs form the rest of the component of this enchanting portion of the communique.

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DISEASE DIAGNOSIS

PEPTIC ULCER

INTRODUCTION

A peptic ulcer, also known as ulcus pepticum, PUD or peptic ulcer disease, is an ulcer (defined as mucosal erosions equal to or greater than 0.5 cm) of an area of the gastrointestinal tract that is usually acidic and thus extremely painful. As much as 80% of ulcers are associated with Helicobacter pylori, a spiral-shaped bacterium that lives in the acidic environment of the stomach, however only 20% of those cases go to a doctor. Ulcers can also be caused or worsened by drugs such as aspirin and other NSAIDs. Contrary to general belief, more peptic ulcers arise in the duodenum (first part of the small intestine, just after the stomach) than in the stomach. About 4% of stomach ulcers are caused by a malignant tumor, so multiple biopsies are needed to make sure. Duodenal ulcers are generally benign.

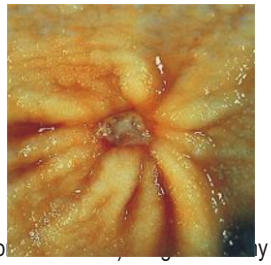
HISTORY

John Lykoudis, a general practitioner in Greece, treated patients for peptic ulcer disease with antibiotics, beginning in 1958, long before it was commonly recognized that bacteria were a dominant cause for the disease. *Helicobacter pylori* was rediscovered in 1982 by two Australian scientists, J. Robin Warren and Barry J. Marshall as a causative factor for ulcers. In their original paper, Warren and Marshall contended that most stomach ulcers and gastritis were caused by colonization with this bacterium, not by stress or spicy food as had been assumed before. The *H. pylori* hypothesis was poorly received, so in an act of self-experimentation Marshall drank a Petri dish containing a culture of organisms extracted from a patient and soon developed gastritis. His symptoms disappeared after two weeks, but he took antibiotics to kill the remaining bacteria at the urging of his wife, since halitosis is one of the symptoms of infection. This experiment was published in 1984 in the Australian Medical Journal and is among the most cited articles from the journal. In 1997, the Centers for Disease Control and Prevention, with other government agencies, academic institutions, and industry, launched a national education campaign to inform health care providers and consumers about the link between *H. pylori* and ulcers. This campaign reinforced the news that ulcers are a curable infection, and that health can be greatly improved and money saved by disseminating information about *H. pylori*. In 2005, the Karolinska Institute in Stockholm awarded the Nobel Prize in Physiology or Medicine to Dr. Marshall and his long-time collaborator Dr. Warren "for their discovery of the bacterium *Helicobacter pylori* and its role in gastritis and peptic ulcer disease". Professor Marshall continues research related to *H. pylori* and runs a molecular biology lab at UWA in Perth, Western Australia. It was a previously widely accepted misunderstanding that the use of chewing gum resulted in gastric ulcers. The medical profession believed that this was because the action of masticating on gum caused the over-stimulation of the production of hydrochloric acid in the stomach. The low (acidic) pH (pH 2), or hyperchlorhydria was then believed to cause erosion of the stomach lining in the absence of food, thus causing the development of the gastric ulcers. On the other hand, in the recent past, some believed that natural tree resin extract, mastic gum, actively eliminates the *H. pylori* bacteria. However, multiple subsequent studies have found no effect of using mastic gum on reducing *H. pylori* levels.

CLASSIFICATION

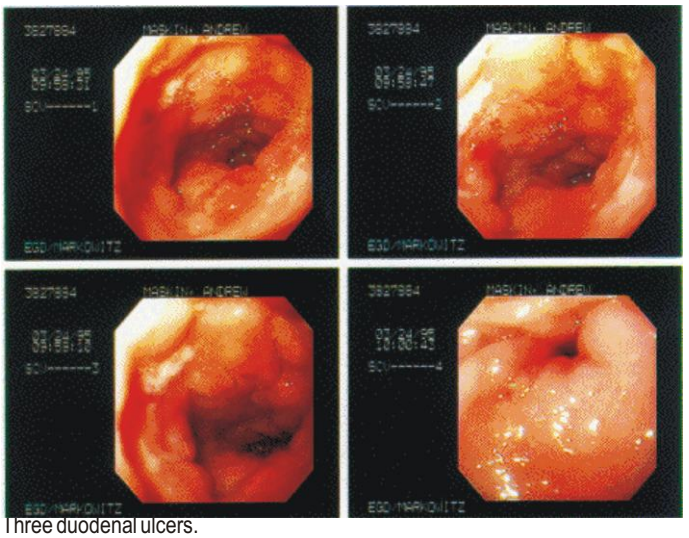
A peptic ulcer may arise at various locations:

Stomach (gastric ulcer)



A benign gastric ulcer (fro y specimen

Duodenum (duodenal ulcer)



Three duodenal ulcers.

Esophagus (called esophageal ulcer)

Meckel's Diverticulum (called Meckel's Diverticulum ulcer)

Types of peptic ulcers:

Type I: Ulcer along the lesser curve of stomach, Type II: Two ulcers present - one gastric, one duodenal, Type III: Prepyloric ulcer, Type IV: Proximal gastresophageal ulcer, Type V: Anywhere along gastric body, NSAID induced.

EPIDEMIOLOGY

In Western countries the prevalence of *Helicobacter pylori* infections roughly matches age (i.e., 20% at age 20, 30% at age 30, 80% at age 80 etc). Prevalence is higher in third world countries. Transmission is by food, contaminated groundwater, and through human saliva (such as from kissing or sharing food utensils.) According to Mayo Clinic, however, there is evidence that the infection can be transmitted by kissing. A minority of cases of Helicobacter infection will eventually lead to an ulcer and a larger proportion of people will get non-specific discomfort, abdominal pain or gastritis.

Sex: In the United States, the prevalence of gastric ulcer has shifted in the past 2 decades, from a disease predominantly affecting males to one that is equally present in both sexes. The male-to-female ratio is 1:1 in the United States and 18:1 in India.

Age: The incidence of gastric ulcer increases with age because of a combination of increasing NSAID use and a high prevalence of *H pylori* infection in persons older than 50 years. The prevalence of *H pylori* in elderly individuals is the result of a cohort effect of the generally poorer socioeconomic condition in past decades compared to today.

Mortality/Morbidity: The mortality rate is approximately 1 case per 100,000 persons, based on the 1979 estimates from the advanced nations. The mortality rate is higher in patients older than 75 years, which can be attributable to a high rate of NSAID use in this age group. The other high-risk groups include people with chronic renal insufficiency and diabetes. Gastric ulcers are also associated with considerable morbidity related to chronic epigastric pain, nausea, vomiting, and anemia.

CLINICAL PRESENTATION

History: Patients may present with a wide variety of symptoms, or they may remain completely asymptomatic. Gastric and duodenal ulcers usually cannot be differentiated based on history alone. Classic gastric ulcer pain is described as pain occurring shortly after meals, for which antacids provide minimal relief. The pain from gastric ulcer is typically located in the epigastrium; however, it can also be perceived in the right upper quadrant and elsewhere. Duodenal ulcer pain often occurs hours after meals and at night. Pain is characteristically relieved with food or antacids. Pain with radiation to the back is suggestive of a posterior penetrating gastric ulcer complicated by pancreatitis. Patients with bleeding gastric ulcers may give a history of hematemesis, melena, or episodes of presyncope. Melena can be intermittent over several days or multiple episodes in a single day. Rarely, a briskly bleeding ulcer can present as gross

hematochezia.

Physical:

Physical examination usually is not helpful. Epigastric tenderness may or may not be present. Right upper quadrant tenderness may suggest a biliary etiology or, less frequently, PUD. In the presence of gastric outlet obstruction, abdominal distension and succussion splash may be found. A palpable mass should raise the suggestion of a gastric malignancy. Involuntary guarding is indicative of peritonitis secondary to gastric perforation. Patients should be checked for melena, which is indicative of bleeding from a gastroduodenal ulcer. Digital rectal examination can be easily performed in the office to check for melena.

Symptoms of a peptic ulcer can be:

Abdominal pain, classically epigastric with severity relating to mealtimes, after around 3 hours of taking a meal (duodenal ulcers are classically relieved by food, while gastric ulcers are exacerbated by it); bloating and abdominal fullness; waterbrash (rush of saliva after an episode of regurgitation to dilute the acid in esophagus); nausea, and lots of vomiting; loss of appetite and weight loss; hematemesis (vomiting of blood); this can occur due to bleeding directly from a gastric ulcer, or from damage to the esophagus from severe/continuing vomiting. melena (tarry, foul-smelling feces due to oxidized iron from hemoglobin); rarely, an ulcer can lead to a gastric or duodenal perforation. This is extremely painful and requires immediate surgery.

A history of heartburn, gastroesophageal reflux disease (GERD) and use of certain forms of medication can raise the suspicion for peptic ulcer. Medicines associated with peptic ulcer include NSAID (non-steroid anti-inflammatory drugs) that inhibit cyclooxygenase, and most glucocorticoids (e.g. dexamethasone and prednisolone). In patients over 45 with more than two weeks of the above symptoms, the odds for peptic ulceration are high enough to warrant rapid investigation by EGD. The timing of the symptoms in relation to the meal may differentiate between gastric and duodenal ulcers: A gastric ulcer would give epigastric pain during the meal, as gastric acid is secreted, or after the meal, as the alkaline duodenal contents reflux into the stomach. Symptoms of duodenal ulcers would manifest mostly before the meal—when acid (production stimulated by hunger) is passed into the duodenum. However, this is not a reliable sign in clinical practice.

Complications:

Gastrointestinal bleeding is the most common complication. Sudden large bleeding can be life-threatening. It occurs when the ulcer erodes one of the blood vessels. **Perforation** (a hole in the wall) often leads to catastrophic consequences. Erosion of the gastro-intestinal wall by the ulcer leads to spillage of stomach or intestinal content into the abdominal cavity. Perforation at the anterior surface of the stomach leads to acute peritonitis, initially chemical and later bacterial peritonitis. The first sign is often sudden intense abdominal pain. Posterior wall perforation leads to pancreatitis; pain in this situation often radiates to the back. **Penetration** is when the ulcer continues into adjacent organs such as the liver and pancreas. Scarring and swelling due to ulcers causes narrowing in the duodenum and **gastric outlet obstruction**. Patient often presents with severe vomiting. **Pyloric stenosis.**

PATHOPHYSIOLOGY

Tobacco smoking, not eating properly, blood group, spices and other factors that were suspected to cause ulcers until late in the 20th century, are actually of relatively minor importance in the development of peptic ulcers. A major causative factor (60% of gastric and up to 90% of duodenal ulcers) is chronic inflammation due to *Helicobacter pylori* that colonizes (i.e. settles there after entering the body) the antral mucosa. The immune system is unable to clear the infection, despite the appearance of antibodies. Thus, the bacterium can cause a chronic active gastritis (type B gastritis), resulting in a defect in the regulation of gastrin production by that part of the stomach, and gastrin secretion can either be decreased (most cases) resulting in hypo- or achlorhydria or increased. Gastrin stimulates the production of gastric acid by parietal cells and, in *H. pylori* colonization responses that increase gastrin, the increase in acid can contribute to the erosion of the mucosa and therefore ulcer formation. Studies have shown eating cabbage or cabbage juice can increase the mucosa lining in the stomach. In addition to an increase in acid secretion, *H pylori* infection also predisposes patients to ulcer disease by disrupting mucosal integrity. The bacterium's spiral shape and flagella facilitate its penetration into the mucous layer and its attachment to the epithelial layer. Subsequently, it releases phospholipase and proteases, which cause further mucosal damage. A cytotoxin-associated gene (cag A) has been isolated in approximately 65% of the bacteria. The products of this gene are associated with more severe gastritis, gastric ulcer, gastric cancer, and lymphoma. Another major cause is the use of NSAIDs. The gastric mucosa protects itself from gastric acid with a layer of mucus, the secretion of which is stimulated by certain prostaglandins. NSAIDs block the function of cyclooxygenase 1 (cox-1), which is essential for the production of these prostaglandins. Newer NSAIDs (celecoxib, rofecoxib) only inhibit cox-2, which is less essential in the gastric mucosa, and roughly halve the risk of NSAID-related gastric ulceration. As the prevalence of *H. pylori*-caused ulceration declines in the Western world due to increased medical treatment, a greater proportion of ulcers will be due to increasing NSAID use among individuals with pain syndromes as well as the growth of aging populations that develop arthritis. The incidence of duodenal ulcers has dropped significantly during the last 30 years, while the incidence of gastric ulcers has shown a small increase, mainly caused by the widespread use of NSAIDs. The drop in incidence is considered to be a cohort-phenomena independent of the progress in treatment of the disease. The cohort-phenomena is probably explained by improved standards of living which has lowered the incidence of Hp-infections. Glucocorticoids lead to atrophy of all epithelial tissues. Their role in ulcerogenesis is relatively small. There is debate as to whether Stress in the psychological sense can influence the development of peptic ulcers. Burns and head trauma, however, can lead to "stress ulcers", and it is reported in many patients who are on mechanical ventilation. Smoking leads to atherosclerosis and vascular spasms, causing vascular insufficiency and promoting the development of ulcers through ischemia. Nicotine contained in cigarettes can increase parasympathetic nerve activity to the GI tract by acting on the nicotinic receptors at synapses - increased stimulation to the enterochromaffin-like cells and G cells increases the amount of histamine and gastrin secreted and therefore increases the acidity of the gastric juice. A family history is often present in duodenal ulcers, especially when blood group O is also present. Inheritance appears to be unimportant in gastric ulcers. Gastrinomas (Zollinger Ellison syndrome), rare gastrin-secreting tumors, cause multiple and difficult to heal ulcers.

Stress and ulcers

Despite the finding that a bacterial infection is the cause of ulcers in 80% of cases, bacterial infection does not appear to explain all ulcers and researchers continue to look at stress as a possible cause, or at least a complication in the development of ulcers. An expert panel convened by the Academy of Behavioral Medicine Research concluded that ulcers are not purely an infectious disease and that psychological factors do play a significant role. Researchers are examining how stress might promote *H. pylori* infection. For example, *Helicobacter pylori* thrives in an acidic environment, and stress has been demonstrated to cause the production of excess stomach acid. A study of peptic ulcer patients in a Thai hospital showed that chronic stress was strongly associated with an increased risk of peptic ulcer, and a combination of chronic stress and irregular meal times was a significant risk factor. A study on mice showed that both long-term water-immersion-restraint stress and *H. pylori* infection were independently associated with the development of peptic ulcers.

Differential diagnosis of epigastric pain

Peptic ulcer, Gastritis, Gastric carcinoma, GERD, Pancreatitis, Hepatic congestion, Cholecystitis, Biliary colic, Inferior myocardial infarction, Referred pain (pleurisy, pericarditis, MI).

DIAGNOSIS

Laboratory Studies

The diagnosis of gastric ulcer can be made based on a characteristic clinical history; however, a high index of suspicion for gastric ulcer is needed in patients without risk factors for PUD. Routine laboratory tests, such as complete blood cell count and iron studies, can help detect anemia. Anemia and weight loss are alarm signals and mandate early endoscopy to rule out other sources of chronic GI blood loss.

Imaging Studies

Upper GI radiography: A double-contrast barium study performed by an expert GI radiologist has equivalent accuracy in diagnosing a typical gastric ulcer. However, diagnostic biopsies cannot be performed with radiological studies, and

radiographic evidence of a healing ulcer is not adequate to rule out gastric cancer. Benign gastric ulcers are normally found on the lesser curvature, although they can occur anywhere in the stomach. These ulcers tend to project beyond the contour of the stomach, with radiating folds extending to the ulcer margin. In contrast, malignant ulcers usually have irregular heaped-up margins that protrude into the lumen of the stomach.

Other Tests

***H pylori* testing:** A strong relationship exists between PUD and *H pylori* infection. Therefore, to prevent recurrence of ulcer disease, diagnosing and eradicating *H pylori* infection is important. *H pylori* infection can be diagnosed using various invasive or noninvasive methods.

Invasive tests: Biopsy: Identification of the organism in an endoscopically obtained biopsy specimen remains the criterion standard for diagnosis of *H pylori* infection. Routinely, 2 biopsy samples are obtained from the antrum and the body of the stomach. Gastritis is apparent on routine histological slides stained with hematoxylin and eosin; however, special staining with Giemsa or Warthin-Starry silver stain provides almost 100% accurate results. False-negative results can occur in patients with active gastrointestinal bleeding and in patients taking antisecretory agents. Culture: This is the most specific method; however, it is not routinely performed in clinical practice because of the fastidious nature of the organism. Rapid urease test: This test contains urea-impregnated agar and a pH indicator that changes color if urease is present in the biopsy sample. This test is quick and accurate, with a sensitivity and specificity of higher than 90%.

Noninvasive tests: Antibody testing: Serological testing is simple, inexpensive, and widely available. Serology can be used to test and treat people with recurrent epigastric pain and symptoms suggestive of PUD and without any alarming signs for malignancy. Urea breath testing (UBT): This test is useful for documenting the eradication of *H pylori* after treatment. *H pylori* produces a large amount of urease. Patients ingest carbon-labeled urea (ie, carbon 13 or carbon 14) that is broken down by urease with release of the labeled carbon. A failure to detect exhaled labeled carbon dioxide confirms the eradication of the bacteria. UBT should be performed 4 weeks after *H pylori* eradication to prevent false-negative results. Stool antigen: This test, helps identify bacterial antigens in stool. The test has been shown to be extremely accurate with a sensitivity of 89-98% and with a specificity of greater than 90% in helping to diagnose infection or to document eradication. To assess for eradication of *H pylori*, stool antigen should be checked only after 8 weeks of completion of therapy.

Procedures

Esophagogastroduodenoscopy (EGD): Diagnostic EGD is the modality of choice in establishing a diagnosis of gastric ulcers. EGD provides the opportunity to perform multiple mucosal biopsies to check for *H pylori* and to rule out malignancy. Endoscopy is a relatively safe procedure in experienced hands. This allows direct visualization to obtain biopsy specimens and also to perform endoscopic therapy for bleeding ulcers. The ability to directly visualize the mucosa makes endoscopy the preferred modality for the diagnosis of gastric ulcer and gastric cancer. A repeat endoscopy after 6 weeks of therapy is recommended to confirm healing of a gastric ulcer and to help definitively rule out gastric malignancy. Upper endoscopy with biopsy is the most sensitive and specific method for diagnosing gastric and esophageal cancer. A single biopsy offers 70% accuracy in diagnosing gastric cancer, but 7 biopsy samples obtained from the base and ulcer margins increase the sensitivity to 99%. Brush cytology has been shown to increase the biopsy yield, and this method may be useful particularly when bleeding is a concern in a patient with coagulopathy.

Gross appearance

Gastric ulcer is a discrete mucosal lesion with a punched-out smooth ulcer base, which often is filled with whitish fibrinoid exudates. Ulcers tend to be solitary and well circumscribed and usually are 0.5-2.5 cm in diameter. Most gastric ulcers tend to occur at the junction of the fundus and antrum, along the lesser curvature. Benign ulcers tend to have a smooth, regular, rounded edge with a flat smooth base and surrounding mucosa that shows radiating folds. Malignant ulcers usually have irregular heaped-up or overhanging margin). The ulcerated mass often protrudes into the lumen, and the folds surrounding the ulcer crater are often nodular and irregular.

The possibility of other causes of ulcers, notably malignancy (gastric cancer) needs to be kept in mind. This is especially true in ulcers of the greater (large) curvature of the stomach; most are also a consequence of chronic H. pylori infection. If a peptic ulcer perforates, air will leak from the inside of the gastrointestinal tract (which always contains some air) to the peritoneal cavity (which normally never contains air). This leads to "free gas" within the peritoneal cavity. If the patient stands erect, as when having a chest X-ray, the gas will float to a position underneath the diaphragm. Therefore, gas in the peritoneal cavity, shown on an erect chest X-ray or supine lateral abdominal X-ray, is an omen of perforated peptic ulcer disease.

Microscopic appearance

A gastric peptic ulcer is a mucosal defect which penetrates the muscularis mucosae and muscularis propria, produced by acid-pepsin aggression. Ulcer margins are perpendicular and present chronic gastritis. During the active phase, the base of the ulcer shows 4 zones: inflammatory exudate, fibrinoid necrosis, granulation tissue and fibrous tissue. The fibrous base of the ulcer may contain vessels with thickened wall or with thrombosis.

***H. pylori* diagnosis is now rendered easy by the evolution of rapid immunochromatography based platforms.**

TREATMENT

Medical Care

The medical treatment of gastric ulcers is aimed at restoring the balance between aggressive factors (acid secretion) and mucosal protective factors. In patients infected with *H pylori,* the most effective treatment is therapy to eradicate the organism and to suppress acid secretion. In patients with bleeding PUD, volume resuscitation with IV fluid and blood products is the most important initial therapy. An intravenous proton pump inhibitor (PPI) is started. This is followed by checking for acute anemia, thrombocytopenia, or coagulopathy, which needs correction with vitamin K or fresh frozen plasma.

Histamine 2 blockers (H2 blockers): Therapy can be directed toward histamine release, that is, H2 blockers, such as cimetidine, ranitidine, famotidine, and nizatidine. These agents selectively block the H2 receptors in the parietal cells. All H2 blockers are comparable in efficacy and, when used in twice-daily doses for a period of 8 weeks, have a healing rate of higher than 70%.

Hydrogen pump antagonists or PPIs: PPIs are drugs that covalently bind and irreversibly inhibit the H+/K+ adenosine triphosphatase (ATPase) pump, effectively inhibiting acid release. Omeprazole, lansoprazole, rabeprazole, pantoprazole, and esomeprazole given in daily or twice-daily doses for 4 weeks heal 80-100% of gastric ulcers if *H pylori* infection is not present or has been eradicated. All PPIs are comparable in efficacy. The PPI should preferentially be taken on an empty stomach to allow maximum inhibition of H+/K+ pumps. Omeprazole binds irreversibly with the H+/K+ pumps and suppresses acid secretion. This inhibition is at its maximum in 24-48 hours, and when Omeprazole is stopped, the secretory activity gradually returns to normal in the next 2-3 days. Newer forms of the PPI delivery system include Omeprazole SoluTab, which is a chewable version of Omeprazole with more rapid action. Oral suspension of esomeprazole, which appears to be rapid acting with prolonged efficacy is also available. Studies have shown that continuous intravenous infusion of omeprazole in patients with active bleeding from gastric ulcer decreases the following: need for transfusion, mortality, and hospital stay

Mucosal protectants

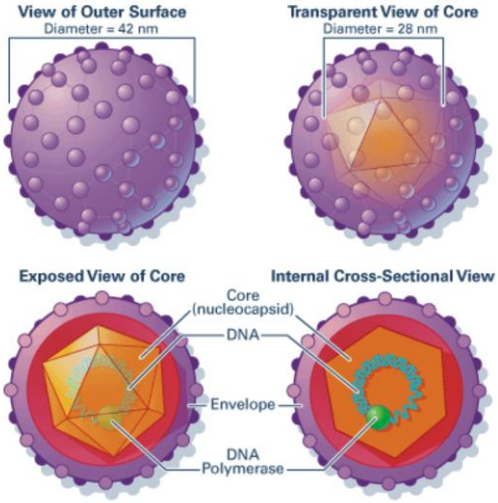
Mucosal protectants, such as bismuth and sucralfate, can also be effective in healing gastric ulcers; however, they are not as effective as H2 blockers. Patients taking NSAIDs should discontinue them if possible. If discontinuing NSAIDs is not possible, omeprazole at 40 mg/dl (or another PPI) should be given concurrently. However, only misoprostol has been shown to be cytoprotective when taken with NSAIDs. However, the use of misoprostol is limited because of its adverse effects, including diarrhea and abdominal pain observed in 14-40% of patients, and because it needs to be taken 4 times a day. A 2005 study showed that in patients with aspirin-induced ulcer, contrary to popular belief, aspirin plus esomeprazole was superior to clopidogrel in preventing recurrent gastric ulcer bleeding.

INTERPRETATION

HEPATITIS B MARKERS

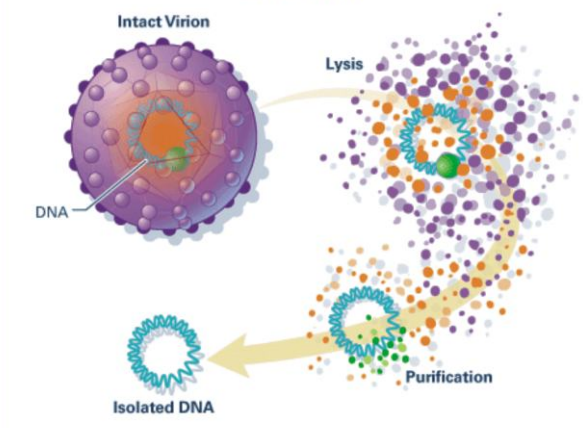
Serologic testing for the diagnosis of hepatitis B virus (HBV) infection involves measurement of a panel of distinct HBV-specific antigens and host antibodies that react to these antigens. The interpretation of these tests can be complicated, and multiple possibilities exist based on the overall panel of responses. In general, the panel of responses can determine whether a patient is susceptible to infection, immune as a result of resolved infection, immune as a result of vaccination, acutely infected, or chronically infected.

1 Intact Hepatitis B Virion (Dane Particle)



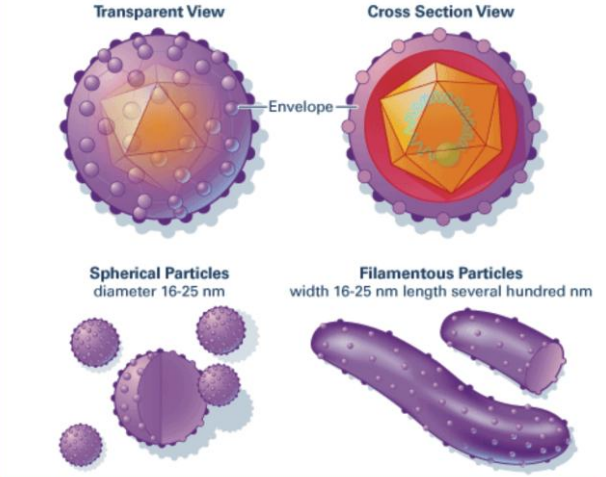
The intact hepatitis B virion, also known as the Dane Particle, is a sphere that is approximately 42 nm in diameter. The intact HBV virion consists of an outer envelope and an inner 28 nm icosahedral core, also known as the nucelocapsid. The HBV core contains a single molecule of partially double stranded HBV DNA and viral DNA polymerase.

2 HBV DNA



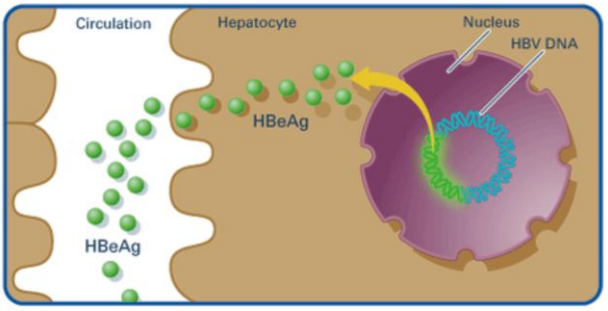
The intact hepatitis B virion present in blood contains partially double-stranded DNA. The presence of HBV DNA in serum appears very early with acute infection and generally indicates active viral replication. Following lysis of the intact virion and purification of the DNA, hybridization methods or PCR techniques are used to detect and quantify the HBV DNA. Measurement of HBV DNA is not generally used to diagnose acute or chronic HBV infection. Instead, the HBV DNA test most often is used as a quantitative test to determine the response to therapy for HBV infection.

3 Hepatitis B Surface Antigen (HBsAg)



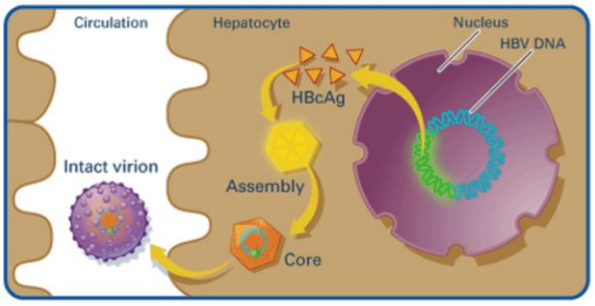
Early in acute infection, HBsAg is the first viral antigen to become detectable. The HBsAg exists as the major component of the surface (envelope) of the intact hepatitis B virion and as excess viral envelope in the form of subviral lipoprotein particles (spheres and filaments). The presence of HBsAg for longer than 6 months generally indicates chronic infection. Patients with resolved HBV infection will not have detectable HBsAg.

4 Hepatitis B e Antigen (HBeAg)



Circulating HBeAg typically appears in acute infection soon after HBsAg appears. The HBeAg is secreted from cells actively infected with HBV, but it is not part of the intact hepatitis B virion. The HBeAg will become undetectable in patients who have resolution of their HBV infection. In patients with chronic HBV infection, most, but not all, have detectable HBeAg. The presence of HBeAg generally correlates with a higher degree of infectivity. The function of HBeAg remains incompletely understood, but it may play a role in modifying the host immune response.

5 Hepatitis B Core Antigen (HBcAg)



The HBcAg is an intracellular antigen synthesized within infected hepatocytes; once formed, much of it is assembled into the viral core (nucleocapsid). Free HBcAg does not circulate in significant quantity in the blood (it circulates only as part of the viral core). Accordingly, HBcAg is not detected on serum tests.

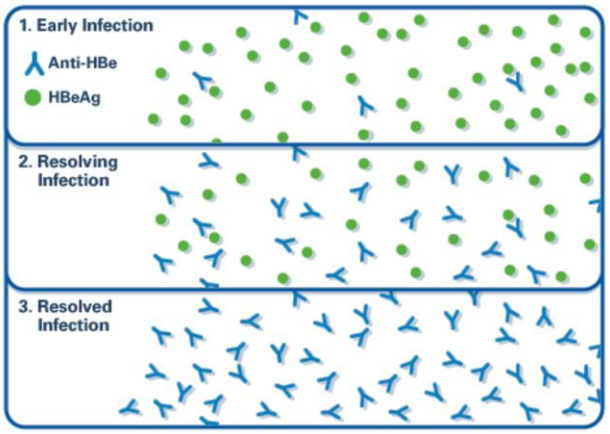
6 Total Hepatitis B Core Antibody (Total anti-HBc)

The anti-HBc antibodies are produced as a response to HBcAg peptides (smaller fragments of the HBcAg). Total anti-HBc is the first host antibody response to develop in response to acute HBV infection. During acute infection, anti-HBc predominantly consists of IgM antibodies. The anti-HBc persist with resolved infection and with chronic infection. Six months or longer after infection, the total anti-HBc predominantly consists of IgG anti-HBc.

7 IgM Hepatitis B Core Antibody (IgM anti-HBc)

The IgM anti-HBc antibodies are produced as a response to HBcAg peptides (smaller fragments of the HBcAg). These antibodies are the first to appear as part of the host response to HBV infection. The presence of IgM anti-HBc is considered diagnostic of infection with HBV within the prior 6 months.

8 Antibody to Hepatitis B e Antigen (Anti-HBe)



The anti-HBe antibodies are produced in response to circulating HBeAg and the appearance of these antibodies typically coincides with declining HBeAg. Detectable serum titers of anti-HBe generally do not develop until the immune system has cleared most of the HBeAg from blood. The presence of anti-HBe generally indicates a favorable immune response to HBV infection. Patients with resolved HBV infection will have anti-HBe; most patients with chronic HBV infection do not have anti-HBe, but some with HBeAg-negative chronic infection will have anti-HBe.

(to be continued...)

BOUQUET

In Lighter Vein

Two physicians board a flight out of Seattle. One sits in the window seat, the other in the middle seat. Just before take-off, an attorney sits in the seat by the aisle. The lawyer kicks off his shoes, wiggle his toes, and starts to settle in, when the physician in the window seat says, "I think I'll get up and get a coke."
"No problem," says the attorney, "I'm by the aisle. I'll get it for you."
While he's gone, one of the physicians picks up the attorney's shoe and spits in it. When he returns with the coke, the other physician says, "That looks good, I think I'll have one too."
Again, the attorney obligingly fetches the drink. While he's gone, the other physician picks up the other shoe and spits in it.
The lawyer comes back and they all sit back and enjoy the flight. As the plane is landing, however, the attorney slips his feet into his shoes and realizes immediately what has happened.
"How long must this go on?" he asks the physicians. "This fighting between our professions? This hatred? This animosity? This spitting in shoes and pissing in cokes?"

A lawyer defending a man accused of burglary tried this creative defense: "My client merely inserted his arm into the window and removed a few trifling articles. His arm is not himself, and I fail to see how you can punish the whole individual for an offense committed by his limb." "Well put," the judge replied. "Using your logic, I sentence the defendant's arm to one year's imprisonment. He can accompany it or not, as he chooses."
The defendant smiled, with his lawyer's assistance he detached his artificial limb, laid it on the bench, and walked out.

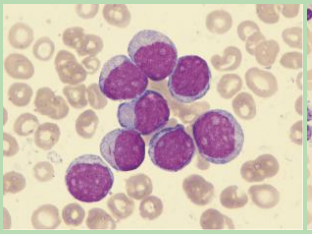
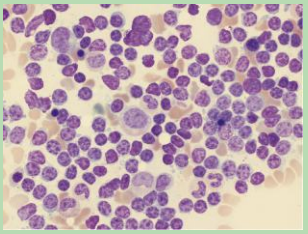
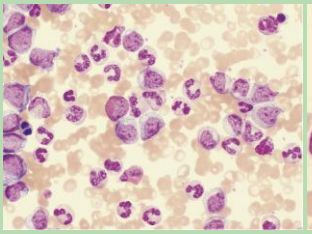
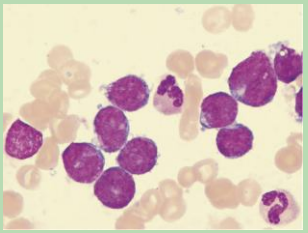
Two 80 year old men sat talking over the weather and the latest in medical science, and such, when one brings up the latest male medical miracle, Viagra.
The other wasn't familiar with Viagra and asked the first man what it was for. The first man said, "It's the greatest thing I've ever known. The Fountain of Youth!! Makes you feel like a man of 30."
The second then asked, "Can you get it over the counter?"
"You probably could, if you took 2 pills", said the first man.

Wisdom Whispers

- "To have no enemies is equivalent to wealth."
- "What costs nothing is worth nothing."
- "Trust not your gossip to a priest who has been a friar."
- "A bit of fragrance clings to the hand that gives flowers."
- "The common soldier's blood makes the general great."
- "That is good wisdom which is wisdom in the end."
- "An ounce of practice is worth a pound of precept."
- "It is difficult to soothe the proud."
- "You cannot have peace longer than your neighbour chooses."
- "He who saves in little things, can be liberal in great ones."
- "Better one good thing that is than two good things that were."

Brain Teasers

Try and diagnose the given haematological pathologies from the pictures provided

1. 
2. 
3. 
4. 

Answers: 1-AML, 2-CLL, 3-CML, 4-ALL.

TROUBLESHOOTING

PHLEBOTOMY

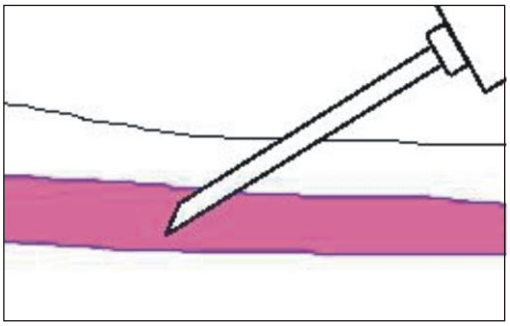
BLOOD COLLECTION: (Continued from last issue)

PATIENT'S RIGHTS: The patient has the right to: Impartial access to treatment or accommodations that are available or medically indicated, regardless of race, creed, sex, national origin, or sources of payment for care. Considerate, respectful care. Confidentiality of all communications and other records pertaining to the patient's care. Expect that any discussion or consultation involving the patient's case will be conducted discretely and that individuals not directly involved in the case will not be present without patient permission. Expect reasonable safety congruent with the hospital practices and environment. Know the identity and professional status of individuals providing service and to know which physician or other practitioner is primarily responsible for his or her care. Obtain from the practitioner complete and current information about diagnosis, treatment, and any known prognosis, in terms the patient can reasonably be expected to understand. Reasonable informed participation in decisions involving the patient's health care. The patient shall be informed if the hospital proposes to engage in or perform human experimentation or other research/educational profits affecting his or her care or treatment. The patient has the right to refuse participation in such activity. Consult a specialist at the patient's own request and expense. Refuse treatment to the extent permitted by law. Regardless of the source of payment, request and receive an itemized and detailed explanation of the total bill for services rendered in the hospital. Be informed of the hospital rules and regulations regarding patient conduct.

VENIPUNCTURE SITE SELECTION: Although the larger and fuller median cubital and cephalic veins of the arm are used most frequently, the basilic vein on the dorsum of the arm or dorsal hand veins are also acceptable for venipuncture. Foot veins are a last resort because of the higher probability of complications. Certain areas are to be avoided when choosing a site: Extensive scars from burns and surgery - it is difficult to puncture the scar tissue and obtain a specimen. The upper extremity on the side of a previous mastectomy - test results may be affected because of lymphedema. Hematoma - may cause erroneous test results. If another site is not available, collect the specimen distal to the hematoma. Intravenous therapy (IV) / blood transfusions - fluid may dilute the specimen, so collect from the opposite arm if possible. Otherwise, satisfactory samples may be drawn below the IV by following these procedures: Turn off the IV for at least 2 minutes before venipuncture. Apply the tourniquet below the IV site. Select a vein other than the one with the IV. Perform the venipuncture. Draw 5 ml of blood and discard before drawing the specimen tubes for testing. Cannula/fistula/heparin lock - hospitals have special policies regarding these devices. In general, blood should not be drawn from an arm with a fistula or cannula without consulting the attending physician. Edematous extremities - tissue fluid accumulation alters test results.

PROCEDURE FOR VEIN SELECTION: Palpate and trace the path of veins with the index finger. Arteries pulsate, are most elastic, and have a thick wall. Thrombosed veins lack resilience, feel cord-like, and roll easily. If superficial veins are not readily apparent, you can force blood into the vein by massaging the arm from wrist to elbow, tap the site with index and second finger, apply a warm, damp washcloth to the site for 5 minutes, or lower the extremity over the bedside to allow the veins to fill.

PERFORMANCE OF A VENIPUNCTURE: Approach the patient in a friendly, calm manner. Provide for their comfort as much as possible, and gain the patient's cooperation. Identify the patient correctly. Properly fill out appropriate requisition forms, indicating the test(s) ordered. Verify the patient's condition. Fasting, dietary restrictions, medications, timing, and medical treatment are all of concern and should be noted on the lab requisition. Check for any allergies to antiseptics, adhesives, or latex by observing for armbands and/or by asking the patient. Position the patient. The patient should either sit in a chair, lie down or sit up in bed. Hyperextend the patient's arm. Apply the tourniquet 3-4 inches above the selected puncture site. Do not place too tightly or leave on more than 2 minutes. The patient should make a fist without pumping the hand. Select the venipuncture site. Prepare the patient's arm using an alcohol prep. Cleanse in a circular fashion, beginning at the site and working outward. Allow to air dry. Grasp the patient's arm firmly using your thumb to draw the skin taut and anchor the vein. The needle should form a 15 to 30 degree angle with the surface of the arm. Swiftly insert the needle through the skin and into the lumen of the vein. Avoid trauma and excessive probing. When the last tube to be drawn is filling, remove the tourniquet. Remove the needle from the patient's arm using a swift backward motion. Press down on the gauze once the needle is out of the arm, applying adequate pressure to avoid formation of a hematoma. Dispose of contaminated materials/supplies in designated containers. Mix and label all appropriate tubes at the patient bedside. Deliver specimens promptly to the laboratory.



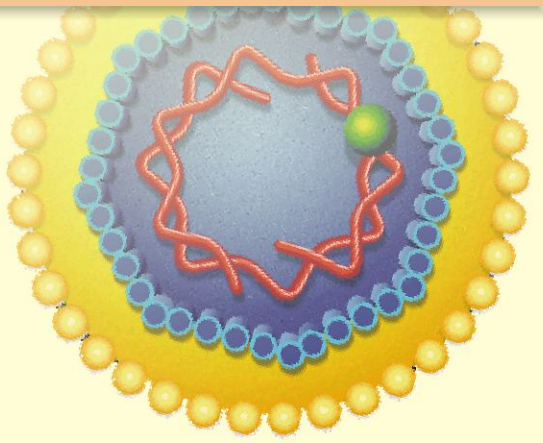
PERFORMANCE OF A FINGERSTICK: Follow the procedure as outlined above for greeting and identifying the patient. As always, properly fill out appropriate requisition forms, indicating the test(s) ordered. Verify the patient's condition. Fasting, dietary restrictions, medications, timing, and medical treatment are all of concern and should be noted on the lab requisition. Position the patient. The patient should either sit in a chair, lie down or sit up in bed. Hyperextend the patient's arm. The best locations for fingersticks are the 3rd (middle) and 4th (ring) fingers of the non-dominant hand. Do not use the tip of the finger or the center of the finger. Avoid the side of the finger where there is less soft tissue, where vessels and nerves are located, and where the bone is closer to the surface. The 2nd (index) finger tends to have thicker, callused skin. The fifth finger tends to have less soft tissue overlying the bone. Avoid puncturing a finger that is cold or cyanotic, swollen, scarred, or covered with a rash. Using a sterile lancet, make a skin puncture just off the center of the finger pad. The puncture should be made perpendicular to the ridges of the fingerprint so that the drop of blood does not run down the ridges. Wipe away the first drop of blood, which tends to contain excess tissue fluid. Collect drops of blood into the collection device by gently massaging the finger. Avoid excessive pressure that may squeeze tissue fluid into the drop of blood. Cap, rotate and invert the collection device to mix the blood collected. Have the patient hold a small gauze pad over the puncture site for a couple of minutes to stop the bleeding. Dispose of contaminated materials/supplies in designated containers. Label all appropriate tubes at the patient bedside. Deliver specimens promptly to the laboratory.

ADDITIONAL CONSIDERATIONS: To prevent a hematoma: Puncture only the uppermost wall of the vein. Remove the tourniquet before removing the needle. Use the major superficial veins. Make sure the needle fully penetrates the upper most wall of the vein. (Partial penetration may allow blood to leak into the soft tissue surrounding the vein by way of the needle bevel). Apply pressure to the venipuncture site. **To prevent hemolysis (which can interfere with many tests):** Mix tubes with anticoagulant additives gently 5-10 times. Avoid drawing blood from a hematoma. Avoid drawing the plunger back too forcefully, if using a needle and syringe, and avoid frothing of the sample. Make sure the venipuncture site is dry. Avoid a probing, traumatic venipuncture. **Indwelling Lines or Catheters:** Potential source of test error. Most lines are flushed with a solution of heparin to reduce the risk of thrombosis. Discard a sample at least three times the volume of the line before a specimen is obtained for analysis. **Hemoconcentration:** An increased concentration of larger molecules and formed elements in the blood may be due to several factors: Prolonged tourniquet application (no more than 2 minutes). Massaging, squeezing, or probing a site. Long-term IV therapy. Sclerosed or occluded veins. **Prolonged Tourniquet Application:** Primary effect is hemoconcentration of non-filterable elements (i.e. proteins). The hydrostatic pressure causes some water and filterable elements to leave the extracellular space. Significant increases can be found in total protein, aspartate aminotransferase (AST), total lipids, cholesterol, iron. Affects packed cell volume and other cellular elements.

(to be continued...)

Tulip Group

Hepatitis B Infection



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Printed and published by D.G. Tripathi, Edited by Dr. R.J. Sood M.D. (path.) for and on behalf of Tulip Diagnostics Private Ltd, Gitanjali, Tulip Block, Dr. Antonio Do Rego Bagh Alto Santacruz, Bambolim Complex Post Office, Goa - 403202, INDIA.
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