Acute viral hepatitis

Objectives:

- Recognise the different type of acute viral hepatitis
- Know the possible complications and outcome of acute viral hepatitis
- Aware of the other cause of acute hepatitis in KSA
- To have fair knowledge about the latest results of epidemiological aspect of viral hepatitis A,B,C IN KSA

[Color index : Important | Notes | Extra]

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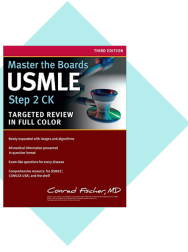
Resources:

- 435 slides



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"Medicine is an art, nobody can deny it."

Epidemiology of Hepatitis in Saudi:

What the doctor mentioned regarding the epidemiology of Hepatitis in Saudi:

- Overall prevalence of HBsAg among saudis in the 80s according to regions was 5-10% which is considered very high
- Good news about HBV: when the prevalence of HBeAg positive saudi pregnant females was calculated 5.4% were positive for its ANTIBODY while only 3.7% were positive for the antigen
- History of HBV infection control in KSA:

-Vaccination of all infants at birth + all children at school entry

-Vaccination of all groups at risk of HBV (including healthcare workers) became mandatory from 1990!

-Screening of all expatriates coming to work in KSA.

- Comparison of prevalence of HBsAg among saudi children in 1989 and 1997-according to age(0-12yrs):This study showed that the prevalence majorly decreased AFTER VACCINE (from 5-10% to 0-2%)
- Prevalence of HBsAg among Saudi population before and after vaccination in over 18 yrs: NO ONE WAS POSITIVE FOR HBsAg AFTER VACCINE
- Note that anti-HBs against surface antigen will not stay positive for life,however repeating the vaccination is not necessary in all groups because the immune system can react to the virus by MEMORY!
- In certain groups monitoring of the antibody levels is favorable because these groups are at higher risk ,thus require monitoring and booster(ex:healthcare workers).
- If a person tested positive for HBV ,he/she will not transmit to spouse nor children if they were vaccinated.
- This person should measure the viral load:if it was less than 2000 IU then he is only a chronic carrier (disease not active)
- Study done to calculate the number of positive cases of HBV and HCV (2009-2014):only 1% have HBV from the age of (18-70) due to the successful vaccination program.
- HCV: overall prevalence in Saudi in the last 18 yrs is very low
- Why is HCV more common in Egypt compared to Saudi?

-because before information was collected on hepatitis ,egyptians tries to cure schistosomiasis(Bilharzia) using a drug called “foadi”.

This drug was given by 20 injections which lead to the wide spread of hepatitis C (because the Egyptians only boiled the injection-poor infection control)

- HAV:13 regions in Saudi children were checked for HAV

-It was noticed the highest prevalence rate was at the borders in areas like Jazan and Tabook (why?due to low socioeconomic status!!!)

- In a comparison of prevalence of anti-HAV amongst Saudi children in 1989 -1997 -according to region:ALL REGIONS SHOWED A DROP IN PREVALENCE EXCEPT JAZAN!
- The changing pattern of hepatitis A prevalence within the Saudi population over 18 yrs:from 53% to 18% due the development in the socioeconomic status.

❖ Acute hepatitis definition:

An infection or inflammation of the liver. **most cases of acute hepatitis are from viral hepatitis A or B**. Hepatitis C for unknown reasons **rarely** presents with an acute infection, and is found as a silent infection on blood tests.

Types of hepatitis	
Infectious	**Noninfectious**
-Hepatitis A -Hepatitis B -Hepatitis C -Hepatitis D -Hepatitis E mostly in INDIA *note that hep **E** is MOST dangerous in PR**E**GNANT WOMEN!!!! -Others include :EBV, CMV and HSV seen in immunocompromised patients.	- Alcoholic hepatitis - Drug induced hepatitis - Autoimmune hepatitis - Numerous hereditary diseases that can cause hepatitis (such as haemochromatosis and wilson's)

❖ Viral Hepatitis is Classified into:

- Acute viral hepatitis: lasts **less than 6 Months**
- Chronic viral hepatitis: lasts **More than 6 Months**

Viral Hepatitis Overview:

	A	E	B	C	D
Source	Feces		Blood/blood-derived body fluids		
Route of transmission	Fecal-oral		Percutaneous – permucosal		
Chronic infection	No		yes		
prevention	pre/post-exposure immunization	Ensure safe drinking water	Pre/post-exposure immunization	-Blood donor screening -Risk behavior modification	-Pre/post-exposure immunization - Risk behavior modification

- Hepatitis A & B are more prevalent in developing countries.
- Hepatitis E is particularly prevalent in india, pakistan, southeast Asia, and parts of Africa.
- Hepatitis D requires the outer envelope of the Hepatitis B surface antigen for replication and therefore can be transmitted only as a coinfection with HBV, or as a superinfection in a chronic HBV carrier.
- H**A**V & H**E**V : f**E**c**A**l

❖ Signs and Symptoms of the 3 phases of acute Hepatitis:

- Acute hepatitis has a wide spectrum of clinical presentations, ranging from virtually asymptomatic to fulminant liver failure.
- Sometimes acute hepatitis may only present with transient flu-like symptoms such as fever, myalgias, and malaise. **"note that icteric means jaundice"** icteric=jaundice

Pre-icteric phase	icteric phase	post-icteric phase
Anorexia Fatigue Nausea Vomiting Arthralgia Myalgia Headache Photophobia Pharyngitis	Enlarged liver Tender upper quadrant Discomfort Splenomegaly (10-20%) General adenopathy	Cessation of symptoms , liver enlargement And continuous fatigue

❖ Basic 4 steps of viral Hepatitis Diagnosis:

1-Take the patient's history

2-Physical examination

3-Liver function test (**ALT ,AST** are elevated **>5-10 times of normal**)

- Elevation of serum transaminases **is not diagnostic**, but they are helpful.
- ALT is typically elevated more than AST for all forms of viral hepatitis (Opposite of alcoholic hepatitis).
- In acute hepatitis, ALT is >1,000. It is generally not as high as in drug-induced hepatitis.
- The plasma bilirubin reflects the degree of liver damage.
- The alkaline phosphatase (ALP) rarely exceeds twice the upper normal limit.
- Prolongation of prothrombin time (PT) indicates the severity of the hepatitis.

4-Serological tests (5 types of markers may be found : A,B ,C ,E ,or autoimmune markers)

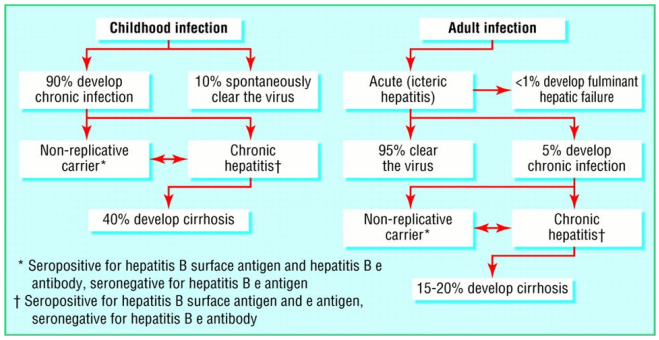
- Most important factor for diagnosing viral hepatitis. (will be discussed)

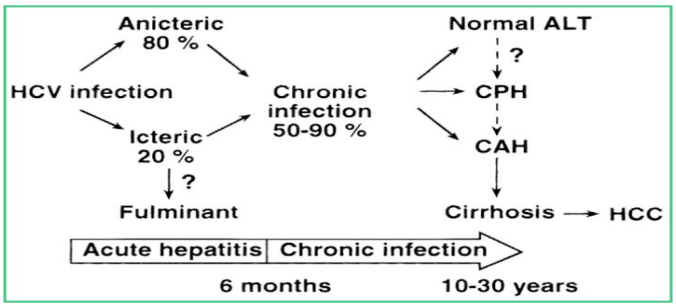
What is the differential diagnosis of Viral Hepatitis ?

1. Infectious Mononucleosis (we almost never see it in saudi)
2. Drug Induced Hepatitis (the most seen), note that it is crucial to ask about the drug history and the use of herbal substances!
3. Chronic Hepatitis.
4. Alcohol Hepatitis
5. Cholecystitis consider it especially in females, Cholelithiasis common in females over 50!
6. Autoimmune hepatitis

Hepatitis A (for Acute)	
Transmission	**- Fecal-oral route (95%):** person to person contact, contaminated food or water. Infection is also more common in areas of overcrowding and poor sanitation. In occasional outbreaks, water and shellfish have been the vehicles of transmission. -Southern part of the globe is more affected by HAV . **- Infected plasma (<5%)** **- Sexual route (<5%)**
Diagnosis	**Anti-HAV:** **IgM** diagnostic of acute infection. fall to low levels within about 3 months of recovery (acute) **IgG** previous infection or immunity. persists for years (chronic)
Prevention	- Hygiene (eg: hand washing) - Sanitation (eg: clean water sources) - **Hepatitis A vaccine** (pre-exposure) "Active vaccine" - **Immunoglobulin** (pre- and post-exposure) "passive" Immunization should be considered for those at particular risk, such as close contacts of HAV-infected patients, elderly, those with other major disease, perhaps pregnant women, and for individuals with chronic hepatitis B or C infections, HAV infection in patients with chronic liver disease may cause serious or life-threatening disease

Hepatitis B	
Transmission	**1-Horizontal transmission** (person to person) is the main transmission route eg: sexual intercouse **2-Perinatal transmission** (positive HBsAg mothers) especially if they are HBeAg positive Vertical transmission from mother to child in the perinatal period is the most common cause of infection worldwide and carries the highest risk of ongoing chronic infection. **3-Illegal injection drug use** **4- Heterosexual transmission** **5- Contaminated equipment** used for therapeutic injections and other health care related procedures **6- Folk medicine practice** **7-Blood and blood products transfusion** without prior screening
Concentration in fluid	**Highest:** in blood ,serum,wound exudate. **Moderate:** semen ,vaginal fluid,saliva **Lowest:** urine, feces, sweat, tears, breastmilk

Natural history	Chronic infection: **children 90%, Adults 5%** We don't see childhood infections a lot now because of vaccination 
Diagnosis (Important)	**Serum serology:** ● **HBsAg:** - Present in acute or chronic infection - Detectable as early as 1-2 weeks after infection - It persists in chronic hepatitis regardless of whether symptoms are present or not. If virus is cleared, then HBsAg is undetectable. In acute liver failure from hepatitis B, the liver damage is mediated by viral clearance and so HBsAg is negative, with evidence of recent infection shown by the presence of hepatitis B core IgM ● **HBeAg:** - Reflects active viral replication, and presence indicates infectivity. - Appear shortly after HBsAg. ● **Anti-HBsAg Antibody:** - Present after vaccination or after clearance of HBsAg, usually detectable 1 to 3 months after infection. - In most cases, it indicates immunity. ● **Hepatitis B core antibody (Anti-HBc):** - Assay of IgM & IgG combined. - Useful because it may be the only serologic marker of HBV infection during the "window peek" in which HBsAg is disappearing, but anti-HBsAg is not yet detectable. ● **Viral load:** HBV **DNA** measured by PCR; if it persists > 6 weeks, patient is likely to develop chronic disease **Serologic Patterns** | | Surface antigen | e-antigen | Core antibody | Surface antibody | | --- | --- | --- | --- | --- | | Acute or chronic infection | Positive | Positive | Positive IgM or IgG | Negative | | Resolved, old, past infection | Negative | Negative | Positive IgG | Positive | | Vaccination | Negative | Negative | Negative | Positive | | "Window period" | Negative | Negative | Positive IgM, then IgG | Negative |
Prevention strategies in KSA	Introducing HBV vaccine in EPI program; and Mandatory screening of blood donors and expatriates. **Vaccination of risk groups.** Health education especially among medical personnel.

<table>
<tr><th colspan="3">Hepatitis C</th></tr>
<tr><td>Transmission</td><td>Routes of Hep C transmission:
1-Percutaneous
–Injecting drug use
–Clotting factors before viral inactivation
–Transfusion, transplant from infected donor
–Occupational (needlestick)
2-Permucosal which includes (Not common)
–Perinatal
–Sexual</td><td>Nosocomial transmission
Recognized primarily in context of outbreaks
Contaminated equipment
1-hemodialysis (reported in the us)
2-endoscopy
Unsafe injection practices
1-plasmapheresis, phlebotomy
2-multiple dose medication vials
3-therapeutic injections</td></tr>
<tr><td>Natural history
-12 weeks of therapy via antivirals will cure more than 90% of cases</td><td colspan="2">Chronic infection is common 90%
 
</td></tr>
<tr><td>Diagnosis</td><td colspan="2">Serum serology:
• Hepatitis C antibody (Anti-HCV) :
Key marker of HCV infection.
Sometimes not detectable until months after infection, so its absence does not rule out infection.
• Viral load:
HCV RNA measured by PCR .
Detectable 1 to 2 weeks after infection- more sensitive than HCV antibody.</td></tr>
<tr><td>Prevention</td><td colspan="2">- Avoiding shared use of Razors or brushes and any item that pierces the skin.
- Strict adherence of the universal precautions in health facilities.
- Educating and training of HCWs to the proper use of standard precautions</td></tr>
</table>

Complications:

1- In severe cases, acute hepatitis may result in **liver failure and its complications.**

This is known as fulminant hepatitis-happens within 8 weeks! (uncommon) and may be life-threatening-must be treated urgently It occurs commonly in Hepatitis B, D, and E than in other types.

Complications of fulminant hepatitis include:

- Hepatic encephalopathy - look for asterixis and palmar erythema
- Hepatorenal syndrome. A life-threatening medical condition that consists of rapid deterioration in kidney function in individuals with cirrhosis or fulminant liver failure.
- Bleeding diathesis (Prolonged prothrombin time)

2- Cirrhosis - Hepatocellular carcinoma "HCC" (with chronic hepatitis = C + B + D)

Management and Treatment:

The goal of chronic hepatitis therapy is:

1) Reduce DNA polymerase to undetectable level
2) Convert those patients with e-antigen to having anti-hepatitis e-antibody

Most individuals do not need hospital care. Acute hepatitis is usually self-limiting that return to normal structure and function.

What should be avoided?

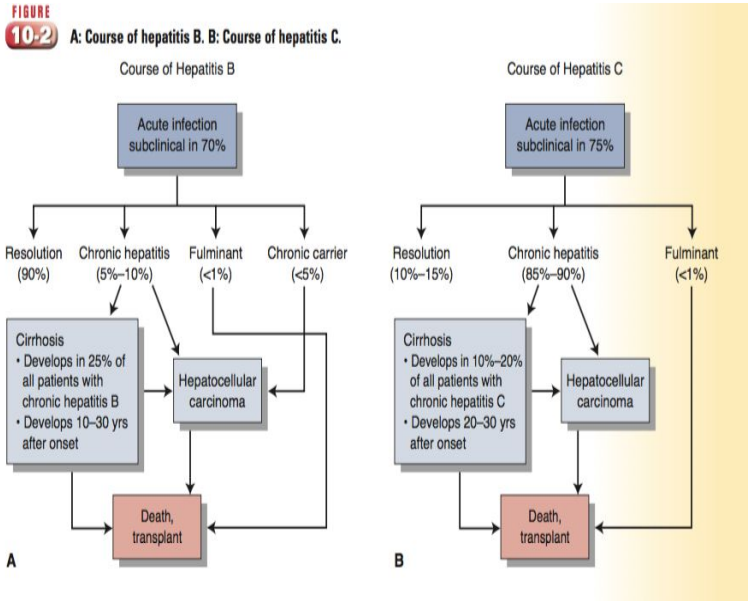
- Drugs such as sedatives and narcotics, which are metabolised in the liver.
- Alcohol should be avoided during the acute illness.
- Elective surgery (a risk of postoperative liver failure.).

Hepatitis A and E	Supportive therapy.
Hepatitis B	**Acute:** supportive. **chronic:** with interferon or lamivudine
Hepatitis C	Dual therapy with pegylated interferon-alpha given as weekly subcutaneous injection, together with oral ribavirin, a synthetic nucleotide analogue.

Only acute hepatitis C gets medical therapy (Interferon+Ribavirin) and in acute hepatitis A (accompanied with HepB) if the patient presents with detectable HBsAg and clinical and epidemiological factors suggestive of chronic infection can be considered for treatment without waiting 6-month period (Interferon **or** lamivudine **or** tenofovir **or** adefovir **or** entecavir)

➔ Liver transplantation is very rarely indicated for acute viral hepatitis complicated by liver failure, but is commonly performed for complications of cirrhosis resulting from chronic hepatitis B and C infection.

Helpful summaries :



CLINICAL PEARL 10-3

Hepatitis Serology

Hepatitis A

- Hepatitis A antibody (anti-HAV)
  - Anti-HAV is detectable during acute infection and persists for life, so its presence does not distinguish between active disease and immunity. IgM-specific antibody denotes acute infection.

Hepatitis B

- Hepatitis B surface antigen (HB_sAg)
  - Present in acute or chronic infection
  - Detectable as early as 1 to 2 weeks after infection
  - It persists in chronic hepatitis regardless of whether symptoms are present. If virus is cleared, then HB_sAg is undetectable.
- Hepatitis B e antigen (HB_eAg)
  - Reflects active viral replication, and presence indicates infectivity
  - Appears shortly after HB_sAg
- Anti-HB_sAg antibody (anti-HBs)
  - Present after vaccination or after clearance of HB_sAg—usually detectable 1 to 3 months after infection
  - In most cases, presence of anti-HBs indicates immunity to HBV
- Hepatitis B core antibody (anti-HBc)
  - Assay of IgM and IgG combined
  - Useful because it may be the only serological marker of HBV infection during the "window period" in which HB_sAg is disappearing, but anti-HB_sAg is not yet detectable
  - Does not distinguish between acute and chronic infection, and presence does not indicate immunity
- Viral load
  - HBV DNA measured by PCR; if it persists for more than 6 weeks, patient is likely to develop chronic disease

Hepatitis C

- Hepatitis C antibody
  - Key marker of HCV infection
  - Sometimes not detectable until months after infection, so its absence does not rule out infection
- Viral load: HCV RNA measured by PCR
  - Detectable 1 to 2 weeks after infection—more sensitive than HCV antibody

Hepatitis D

- Hepatitis D antibody (anti-HDV)
  - Presence indicates HDV superinfection
  - The antibody may not be present in acute illness, so repeat testing may be necessary.

1. A 45-year-old man presents to accident and emergency, having returned from a holiday to India a week ago. He has subsequently been unwell with nausea and reduced appetite. Over the past 2 days he has become jaundiced. He mentions that his two brothers with whom he went on holiday have also become jaundiced in the last 2 days. On examination, he is apyrexial and there is a palpable liver edge. Liver function tests reveal a raised ALT, AST and bilirubin. All other blood tests are normal. What is the most likely diagnosis?

A. Hepatitis A
B. Hepatitis B
C. Hepatitis C
D. Gilbert's syndrome
E. Malaria

2. A 40-year-old man presents to accident and emergency having returned from a holiday to India a week ago. He has subsequently been unwell with nausea and reduced appetite. Over the past 2 days he has become jaundiced. On examination, he is apyrexial and there is a palpable liver edge. Liver function tests reveal a raised ALT, AST and bilirubin. A diagnosis of hepatitis A is suspected. What is the most appropriate treatment?

A. Intravenous hydrocortisone
B. Pegylated interferon alpha plus ribavirin
C. Conservative management
D. Acyclovir
E. Chloroquine

3. You see a 57-year-old man who has been diagnosed with hepatocellular carcinoma (HCC). You are asked about risk factors in HCC by your consultant. Which of the following is not a known predisposing factor for developing hepatocellular carcinoma?

A. Hepatitis B virus
B. Liver cirrhosis
C. Hepatitis C virus
D. Hepatitis A virus
E. Aflatoxin

4. A 40-year-old school teacher develops nausea and vomiting at the beginning of the fall semester. Over the summer she had taught preschool children in a small town in Mexico. She is sexually active, but has not used intravenous drugs and has not received blood products. Physical examination reveals scleral icterus, right upper quadrant tenderness, and a palpable liver. Liver function tests show aspartate aminotransferase of 750 U/L (normal < 40) and alanine aminotransferase of 1020 U/L (normal < 45). The bilirubin is 13 mg/dL (normal < 1.4) and the alkaline phosphatase is normal. What further diagnostic test is most likely to be helpful?

1. Liver biopsy
2. Abdominal ultrasound
3. IgM antibody to hepatitis

4. Antibody to hepatitis B surface antigen
5. Determination of hepatitis C RNA

5. A 60-year-old man with known hepatitis C and a previous liver biopsy showing cirrhosis requests evaluation for possible liver transplantation. He has never received treatment for hepatitis C. Though previously a heavy user of alcohol, he has been abstinent for over 2 years. He has had two episodes of bleeding esophageal varices. He was hospitalized 6 months ago with acute hepatic encephalopathy. He has a 1-year history of ascites that has required repeated paracentesis despite treatment with diuretics. Medications are spironolactone 200 mg daily and lactulose 30 cc three times daily. On examination he appears thin, with obvious scleral icterus, spider angiomas, palmar erythema, gynecomastia, a large amount of ascitic fluid, and small testicles. There is no asterixis. Recent laboratory testing revealed the following:
Hemoglobin = 12.0 mg/dL (normal 13.5-15.0) MCV = 103 fL (normal 80-100)
Creatinine = 2.0 mg/dL (normal 0.7-1.2) Bilirubin = 6.5 mg/dL (normal 0.1-1.2) (normal < 40) (normal < 40) (normal 0.8-1.2)
What is the best next step in the management of this patient's liver failure?

1. Repeat liver biopsy.
2. Start treatment with interferon and ribavirin.
3. Refer the patient for hospice care.
4. Continue to optimize medical treatment for his ascites and hepatic encephalopathy and tell the patient he is not eligible for liver transplantation because of his previous history of alcohol abuse.
5. Refer the patient to a liver transplantation center.

Answers

1. A. Hepatitis A (A) is the most common type of viral hepatitis in the world. The hepatitis A virus is a picornovirus that is transmitted faeco-orally, usually due to the ingestion of contaminated water. The virus replicates in the liver and is excreted in the bile and then the faeces of infected individuals. Following infection, the viraemia causes the prodromal symptoms of fever, malaise, anorexia and nausea. Subsequently, jaundice may develop. As this happens, the spleen or liver may be palpable. The history of travel, the friends being affected and the clinical features should identify hepatitis A as the correct answer in this case. Gilbert's syndrome (D) is an inherited hyperbilirubinaemia that is completely asymptomatic and is normally detected as an incidental finding of a raised bilirubin with other blood results within the normal parameters. While the affected individuals in this question are brothers, the jaundice has been acquired, making Gilbert's syndrome the incorrect answer. Hepatitis B (B) is transmitted intravenously and is also sexually transmitted. In addition, it may also be transmitted vertically from mother to child. Clinical features may be similar to those seen in hepatitis A. In addition, extrahepatic features, such as rashes, arthralgia and glomerulonephritis, are more common. The outbreak of disease among three travellers makes hepatitis A the more likely option in this question. Hepatitis C (C) is transmitted by the intravenous route and is sexually transmitted. Acute infection is usually asymptomatic or mild, making this answer incorrect for this question. The majority of patients develop a chronic infection which predisposes to developing liver cirrhosis. The most common presenting features of malaria (E) are fevers, headache, vomiting or diarrhoea. While patients with malaria may develop jaundice and have a palpable liver, the absence of the other features of malaria, including pyrexia, make this answer incorrect.

2. C. Treatment of hepatitis A infection is with conservative management (C), using supportive measures where required. Hepatitis A usually has a self- limiting course and the majority of patients make a full recovery. A small minority of patients may develop fulminant hepatitis. Intravenous hydrocortisone (A) is not a treatment for hepatitis A. Pegylated interferon alpha plus ribavirin (B) is a treatment for hepatitis C. Acyclovir (D) is a guanosine analogue antiviral drug, but it is not used in the treatment of hepatitis A. Chloroquine (E) is an anti-malarial.

3. D. Chronic hepatitis B (A) and C (C) infections, liver cirrhosis (B) and aflatoxin (E) (a carcinogen from the mould *Aspergillus flavus*) are all known predisposing factors for developing hepatocellular carcinoma. Chronic inflammatory changes results in hepatocyte damage and mutation in the cellular reparation machinery. Hepatitis A (D) does not usually lead to chronic infection and thus is not deemed to be a predisposing factor to hepatocellular carcinoma.

4. C. This patient has evidence for acute hepatitis as is suggested by the history, physical examination, and laboratory data showing hepatocellular injury. The epidemiology favors acute hepatitis A; the patient's history of travel to Mexico and work as a teacher are risk factors for hepatitis A. The incubation period of about 1 month is also typical. Hepatitis B and C are less likely without evidence for drug abuse or blood transfusion. Antibody to hepatitis B surface antigen would not be evidence for acute hepatitis B. HCV RNA is the appropriate test for acute hepatitis C infection, but this disease typically causes mild transaminase elevation and rarely presents with icterus. Liver biopsy is not indicated in acute hepatitis as the diagnosis is usually apparent from the examination, liver enzymes, and serological evidence of recent viral infection. Abdominal ultrasound would not be helpful as liver enzymes suggest hepatocellular damage, not biliary obstruction.

5. E. Cirrhosis caused by hepatitis C is the most common cause for liver transplantation in the United States. A previous history of alcoholism is not a contraindication to transplantation, although most transplant centers require abstinence from alcohol for 6 months before transplantation is considered. Three-year survival rate after transplantation in most centers now exceeds 80%. The model for end-stage liver disease (MELD) scoring system is used in the United States to allocate cadaveric livers to potential donors. Patients with complications of cirrhosis (esophageal variceal bleeding, hepatic encephalopathy, and uncontrolled ascites) or who have significantly elevated bilirubin, INR, and serum creatinine are usually made eligible for transplantation. Repeat liver biopsy would be unnecessary and potentially risky due to the patient's coagulopathy. Patients with end-stage cirrhosis from hepatitis C do not benefit from interferon and ribavirin therapy. Hospice care is inappropriate until the patient is evaluated by a transplant center.