

synthesis) and causes an immunologic response. Because alcohol increases AST release and inhibits ALT production, in alcoholic hepatitis, AST remains higher than ALT. A summary of the typical changes in different causes of acute hepatitis is shown in Table 1.

Because viral hepatitis remains an important cause of acute hepatitis, laboratory detection of viral markers and antibodies is critical to diagnose acute viral hepatitis. Hepatitis A virus (HAV), spread by the fecal-oral route, has a very short incubation period of two to four weeks and (in adults) commonly causes jaundice. Because many adults have previously been exposed to HAV, detection of total antibody to HAV cannot be used to diagnose acute infection; IgM anti-HAV is present for only three to six months after exposure and is considered diagnostic for acute HAV infection.

Acute HCV infection is usually clinically silent; at most, 10% to 30% of adults develop jaundice. After an incubation period of two to four weeks, HCV RNA becomes detectable in plasma, and rapidly increases to very high levels (10^7 to 10^8 IU/mL). After another two to six weeks, ALT begins to increase; in about 50% to 70% of cases, anti-HCV is present at the time clinical hepatitis is diagnosed, but it remains negative for several weeks to a few months in the remaining 30% to 50% of cases.⁶ In up to 50% of cases, HCV RNA is cleared during this acute infectious phase;⁷ in some, anti-HCV never develops, while in another 30% antibody declines gradually over time and eventually becomes negative.⁸ In 50% to 80% of cases, however, chronic infection with HCV develops. Once this chronic phase is established, HCV infection does not spontaneously resolve (although anti-viral treatment may be effective, as discussed later).

HBV remains the most common cause of acute viral hepatitis in the United States.

HBV is spread sexually, by injection exposure, and sometimes from close contact with persons with HBV; a mother with HBV can infect newborn infants easily. Jaundice occurs in about one-third to one-half of adults with HBV, but almost never in children less than five. After an incubation period of one to two months, hepatitis B surface antigen (HBsAg) becomes detectable; acute hepatitis generally does not occur until one to two months later, accompanied by development of IgM antibodies to the hepatitis B core antigen (anti-HBc). As the infection wanes, HBsAg becomes undetectable in most cases, and anti-HBs develops over an average of four to six months. Individuals with negative HBsAg and positive anti-HBs have traditionally been classified as having "resolved" HBV infection, and are said to have "cleared" the virus. With more sensitive HBV DNA assays, however, it is clear that small amounts of virus remain in the liver and in the blood;⁹ while posing no apparent risk to the person infected, HBV

can be transmitted to others, especially if organ transplantation occurs. In some individuals, if HBsAg remains positive more than six months, it is termed chronic HBV infection.

Alcoholic hepatitis is less commonly seen than in the past. Laboratory findings differ from those of other forms of hepatitis. AST and ALT are only minimally increased, with peak AST usually <300 IU/L. In contrast to most other forms of hepatitis, AST typically is increased more than ALT, and the ratio of AST/ALT is often >2:1.¹⁰ Increases in bilirubin and prothrombin time are often out of proportion to the change in the enzymes. Alcoholic hepatitis often looks, clinically, like an infectious disease: fever and increased neutrophil count are often present.

Acute hepatitis is now most commonly due to factors other than viral infection. Shock commonly damages the liver; regardless of the cause (bleeding, infection, cardiac problems). The laboratory picture is similar with all causes of shock: rapid, often marked rises in AST and ALT with rapid decrease, marked prolongation of prothrombin time, and no to minimal increase in bilirubin. If the patient survives the underlying shock, recovery of liver function is usually complete.

Toxins, such as overdoses of acetaminophen, are a less common cause of acute hepatitis but the most common cause of fulminant hepatic failure. The laboratory picture is similar to that seen in ischemic hepatitis. Drug reactions are an increasingly common cause of acute hepatitis. In many cases, a rash accompanies the liver injury, sometimes by joint or renal problems, and increased eosinophil count. The laboratory picture

is similar to that of viral hepatitis, although increases in alkaline phosphatase are more commonly found with drug reactions;¹¹ viral markers are absent. Drug reactions most commonly occur shortly after starting a new drug, but some-

times occur after a person has been on a medication for several weeks to a few months. Discontinuation of the medication often leads to resolution of all abnormalities.

We usually start evaluation of a person with acute hepatitis by reviewing the routine laboratory tests, comparing the patterns to those seen in Table 1. If the pattern suggests ischemic or toxic hepatitis and the clinical picture is consistent, no further testing is needed. Although viral hepatitis has become less common, an acute hepatitis panel (approved by CMS) is typically done. The acute hepatitis panel consists of IgM anti-HAV, IgM anti-HBc, HBsAg, and anti-HCV. Because antibody may be negative in up to half of cases of acute HCV at the time of presentation, we also do HCV RNA if the person has risk factors for HCV. If the AST:ALT ratio is >1 and the peak AST is below 10 times the upper reference limit, alcoholic hepatitis is likely. If the diagnosis has not yet been established, less common causes (especially drugs) should be considered.

Table 1 - Laboratory features in acute hepatitis

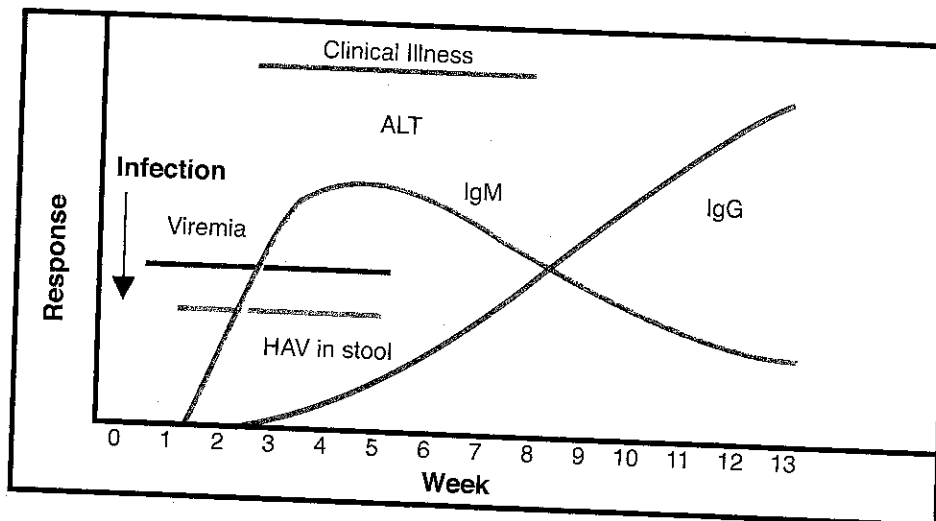
CAUSE	VIRAL	DRUG-INDUCED	TOXIC/ISCHEMIC	ALCOHOLIC
Peak ALT (x upper reference limit)	8 to 40	3 to 40	10 to 100 or more	3 to 5
AST:ALT ratio	<1	<1	Transiently >1 for first 1 to 2 days	>2
Duration of increase (weeks)	5	<2 if drug stopped	1 to 2	3 to 5
Alkaline phosphatase (x upper reference limit)	<3 in 90% to 95%	>3 in 50%	<2	>3 in 25%
Prothrombin time (sec above upper reference limit)	<3	<3	>4	<3
Frequency of jaundice (%)	10 to 70	20 to 30	<10	50 to 70
Viral serologies	Positive	Negative	Negative	Negative

Clinical Course

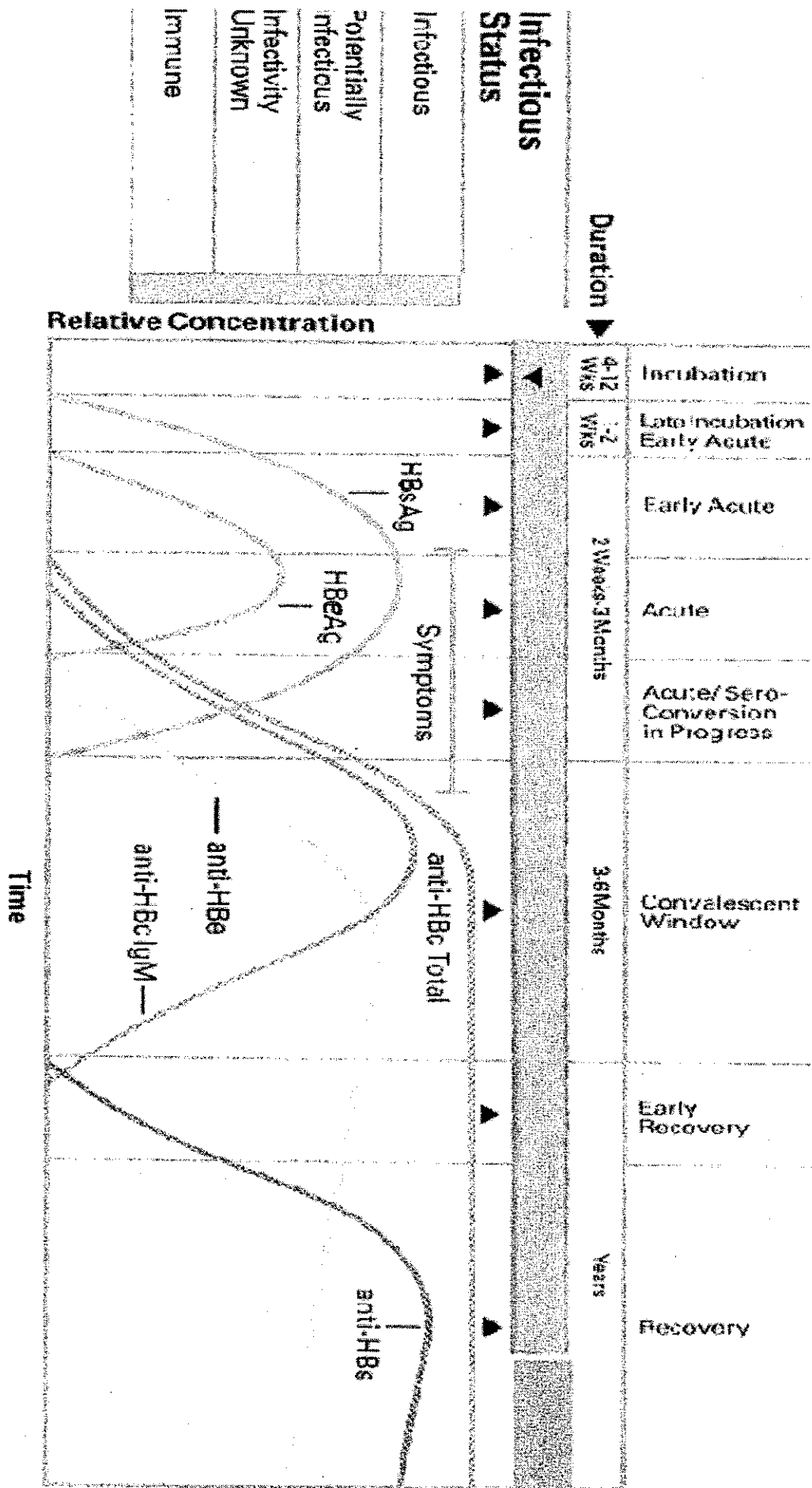
90-95% clearance

- Onset of symptoms is usually abrupt with symptoms lasting approximately 1 – 8 weeks
- Jaundice develops in 70 – 80 percent of adults and in less than 10 percent of children under the age of 6^{3A, slide 5}
- Among children under age 6, 70 percent of infections are asymptomatic^{1, p2}
- HAV replicates in the liver and is shed in the stool^{1, p2}
- Peak infectivity occurs during the 2-week period before onset of jaundice or elevation of liver enzymes when the concentration of virus in stool is highest^{1, p2}
- The concentration of virus in stool declines after jaundice appears^{1, p2}
- Children and infants can shed HAV up to several months after onset of clinical illness^{1, p3}
- A true indication of immunity to HAV is the presence of total anti-HAV and absence of IgM anti-HAV in serum

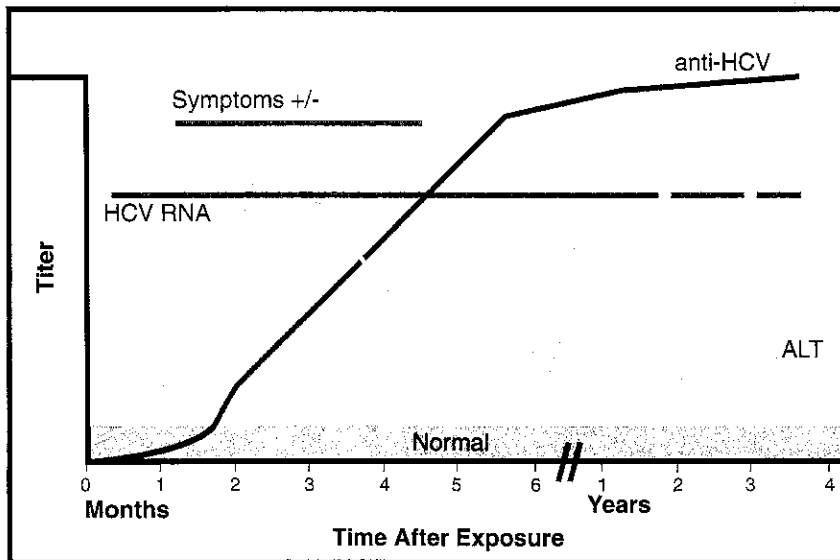
Hepatitis A Virus Infection^{3A, slide 6}



Within three weeks Janet's symptoms had disappeared. She can now be considered immune to the hepatitis A virus. There is no chronic carrier state for hepatitis A.



Serologic Pattern of Acute HCV Infection With Progression to Chronic Infection^{3C, slide 5}



25% HBV → chronic
790% chronic in vertical transmission

quant = down to 50 copies!

75% → chronic

Diagnostic Testing for Hepatitis C

HCV is diagnosed serologically by detecting antibodies specific to the hepatitis C virus (anti-HCV), and by ruling out other viruses such as HAV or HBV. There are limitations on using any anti-HCV assay alone to diagnose or monitor a case of hepatitis. Retesting for anti-HCV may be necessary if the initial result is negative, but clinical signs and symptoms suggest a HCV infection. Furthermore, anti-HCV does not distinguish between an acute, chronic or resolved infection. A supplemental test, RIBA (recombinant immunoblot assay), can also be used to confirm a positive anti-HCV result.¹⁰

Nevertheless, as a screening assay for the blood supply, current anti-HCV assays have been very effective in the U.S. at reducing post-transfusion hepatitis to a very low level.

Hep C Genotype (1 - through 6)
+ most common (60-70%) in U.S. & Europe.

2 & 3. are less common. 4, 5, 6 rare

80-90% response to ifn.
3, 6 → India, far east, Australia
4, 5 → Africa, middle east.

Δ - only 2 HBV.

E - similar to HAV, 0 chronic. Endemic to India, Asia, Africa, C. Ama.

F/G - still in research

Test for viral hepatitis available at CCRMC Lab

1. Acute Hepatitis Panel

HBs AG

Anti-HBc IgM (cover early window p HBsAg clearance)

Hep A IgM

Hep C Ab

2° EBV, CMV, HSV,

2. Chronic Hepatitis Panel = ↑LFTs > 6 mo

HBs Ag

Anti-HBc, Total IgM + IgG

Hep A, Total → for vaccine

Hep C Ab

3. Individual Test

Iz → HBs Ab

A) Hep B

(1) Hepatitis B Surface Ag (HBsAg)

(2) Hepatitis B Surface Ab (HBsAb)

(3) Hepatitis B Core IgM Ab (HEPBCIGM)

(4) Hepatitis B Core total (HEPBCABT) natural infxn. If only ⊕, ✓ HBV

(5) Hepatitis B e Ag (HEPBEAG)

(6) Hepatitis B e Ab (HEPBEAB)

(7) Hepatitis B DNA, Quantitative (HEPBDNAQUANT)

B) Hepatitis C

(1) Hepatitis C Ab (HEPC) immune Ab.

(2) Hepatitis C RNA, Quantitative (HEPCPCR)

(3) Hepatitis C Ab by RIBA (HEPCRIBA) if ⊕, cleared

(4) Hepatitis C Genotype (HEPCGEN) if ⊖, false ⊕ HCV Ab.

Bx- staging - fibrosis
grading - inflam.

* Fibro cept = ✓ level fibrosis

chronic HBV =
↑LFTs

HBV carrier =
nl. LFTs, ⊕ SA,
⊕ core, ⊕ SA,
may be still
infections!

replication? may be ⊖ if
precore mutant: eAg ⊖. ✓ DNA. 10-15% in
Americans. In Asia 50%!
- LFTs ↑
DNA by PCR.