Viral Hepatitis: The *Dert-de-Dert* Edition

HEPATITIS A

DISTILLATION: HAV causes a self-limited acute hepatitis. Transmission is F/O, occurring sporadically and as point-source epidemics. It does not convert to chronic infection, but may rarely degenerate into AHF. Extrahepatic disease includes arthritis, optic neuritis, and rash. Diagnosis is via IgM and IgG serology. Treatment is supportive. Both live-attenuated vaccine and HAV immune globulin are available.

DISTRIBUTION: Southern Asia, Sub-Saharan Africa, Americas
TMX: F/O
EPI: 50% sporadic in the U.S; travel to endemic region; point source epidemic
Declining incidence in U.S due to routine vaccination
VIRAL BIOLOGY: Naked SS + RNA; Picronaviridae; Enterovirus
PATH: Hepatocellular injury via CD8+, NK, innate immunity
NATURAL Hx
Self-limited acute hepatitis syndrome
Acute Hepatic Failure (AHF) in < 1 % of cases
RF: concurrent HCV
Peds: usually asymptomatic
Adults: symptomatic illness is more probable
HAV + HCV predisposes to AHF and FHF (second leading cause)
Fecal shedding occurs 1 – 2 wks prior to symptoms, and ceases after resolution of symptoms
PRESENTATION
Prodome: fatigue, myalgia, RUQ pain
Syndrome: jaundice, bilirubinuria, acholic stool
Atypical: prolonged cholestasis, relapsing hepatitis
Extrahepatic: leukocytoclastic vasculitis, arthritis, optic neuritis
DX: viral serology
Anti-HAV IgM rises at symptom onset and is detectable for 6 mos.
Anti-HAV IgG rises at symptom resolution and is detectable indefinitely
Thus, we use 'standard IgM/IgG' serology to diagnose HAV
TX: Supportive, Transplant; no antivirals
PREV: vaccine and immune globulin
HAV vaccine
All PEDS, Chronic liver disease, immunocompromised, nursing homes, IV drug abuse, travel
Post-Exposure Prophylaxis (PEP)
Pt is not immunized to HAV
HAV vaccine (**+ HAVIG** if > 40 yrs + chronic liver disease OR other medical illness)

HEPATITIS E

DISTILLATION: HEV is very similar, in clinical presentation and disease progression, to HAV infection. There is no vaccine, and HEV immune globulin is generally ineffective. AHF occurs in pregnant women during the third trimester.

DISTRIBUTION: endemic to Asia, Africa, Central America (similar to HAV)
EPI: highest risk of AHF in pregnant women during last trimester
TMX: F/O. Most cases are due to exposure to contaminated food and water.
DX: Anti-HEV Ab; HEV RT-PCR on serum or stool
TX: supportive
PREV: no vaccine; HEVIG not effective; avoid water, shellfish

CLINICALLY, the disease is very similar to acute HAV

HEPATITIS C

DISTILLATION: HCV is a persistent infection. It is the leading cause of chronic liver disease and transplantation. Acute HCV converts to chronic infection in 70& of cases; of these, 20% convert to cirrhosis, with subsequent risk elevation for HCC. The icteric illness occurs during the replicative phase. Most acute infection is asymptomatic. Extrahepatic disease includes cryoglobulinemia, glomerulonephritis, and Sjogren's. It is an RNA virus, and thus subject to a high rate of mutation, with generation of quasi-species and immune evasion. Histology demonstrates the classic changes of viral hepatitis (periportal and interface inflammation) with steatosis. Diagnosis is via IgM (acute) and viral RNA, but *not* IgG. Treatment is combined IFN + Ribavirin, and is associated with a plethora of adverse reactions. The duration of therapy is determined by viral genotype. There is no vaccine. However, patients with HCV should be vaccinated against HBV and HAV.

DISTRIBUTION: Wordwide. Highest prevalence in China, Sub-Saharan Africa, Egypt, Brazil
TMX: IV drugs, sexual, transfusion (prior to screening), household fomites (toothbrush, razor), hemodialysis, vertical (perinatal; at delivery only since the placenta is impermeable)
EPI

Leading cause of chronic liver disease
Leading indication for transplantation
60% infection by IV drugs, 15% via sexual contact

NATURAL Hx

Acute HCV → Chronic HCV : 70% in adults (relatively age-invariant)
Chronic HCV → Cirrhosis : 20% of cases
RF: male gender, EtOH, age > 40 yrs at initial infection, co-infection with HIV
Latency is 30 yrs
Cirrhosis → HCC : 1 – 6% per yr (this is similar to the rate in other conditions)
Risk increases ONLY when cirrhosis occurs
Latency is 20 yrs

VIRAL BIOLOGY: Enveloped SS + RNA; 6 genotypes; 70% infected with GENOTYPE 1
PATH: Invasion of hepatocyte via LDL/VLDL receptor
Lifecycle is entirely cytoplasmic
No genomic integration
Hepatocellular injury via CD8+ response
PRESENTATION
Most infection is **asymptomatic**
A self-limited hepatitis
Prodrome: nausea, fever, abdominal pain
Syndrome: jaundice
Occurs during the highest viral RNA copy titre (replicating phase)
Extrahepatic Disease: Cryoglobulinema (mixed essential type), Glomerulonephritis, Sjogren's, increased risk of Lymphoma
DX: viral serology
Acute: anti-HCV IgM, +ve HCV RNA
The IgM maybe undetectable until > 10 wks after infection
Chronic: HCV RNA in serum > 6 mos.
IgG is not informative due to quasi-species variation; IgM declines to undetectable titres
Expect moderate elevations of AST and ALT in 70% of cases
HISTOLOGY: portal and interface inflammation, lymphoid aggregates, occasional steatosis
TX: combination therapy with IFNα-2a/b + Ribavirin
ARs of IFN: pancytopenia, flu-like syndrome, depression, thyroid disease
ARs for Ribavirin: hemolytic anemia, teratogenicity
IFN during the acute phase prevents conversion to chronic HCV; combined therapy reduces the risk of cirrhosis and HCC
With HCV GENOTYPE 1: requires longer therapy
Vaccinate for HAV and HBV ; avoid EtOH
PREV: No vaccine

HEPATITIS B

DISTILLATION: HBV is a viral infection with a variegated natural history. Conversion to chronic infection becomes less likely with age. Nearly 1/3 of all chronic infection is associated with cirrhosis or HCC; cirrhosis is *not* necessary for development of HCC. Rarely, acute HBV progresses to FHF. It is a dsDNA virus, and may be classified as a chronic cancer virus due to its ability to integrate into the host genome and initiate cellular transformation. Diagnosis is a nuanced topic. Anti-Hbs Ab is considered neutralizing, and indicative of cleared infection or immunization. Circulating HBs Ag indicates early acute or persistent infection. HBc does not generate neutralizing antibodies, but *does* elicit IgM. Treatment for chronic HBV is IFN + oral antiviral therapy.

DISTRIBUTION: Eastern Asia, Sub-Saharan Africa (similar to other viruses, but uncommon in the Americas)

TMX: percutanous or parenteral blood contact, sexual activity, vertical, IV drugs

Vertical TMX occurs at birth, since the placenta is impermeable to HBV

Sexual TMX from asymptomatic carriers

EPI

1/3 of cases are associated with cirrhosis OR HCC

> 100 –fold increase in risk of HCC

NATURAL Hx

Conversion of ACUTE HBV → CHRONIC HBV depends on **age at initial infection**

90% : if infected in infancy

10% : if infected in adulthood

Conversion of ACUTE HBV → FHF : < 1%

Conversion of CHRONIC HBV → HCC : mean latency of 35 yrs

RF: higher DNA copy titre, early age at initial infection, male gender, tobacco, cirrhosis, exposure to Aflatoxin

DOES NOT require pre-existing cirrhosis (as in HCV)

PATH: Heptocellular injury is due to CD8+ response against cells expressing HBcAg and HBeAg

HBV may also integrate as a provirus into the host genome → chronic cancer virus → HCC

VIRAL BIOLOGY: Enveloped dsDNA

Replicates via an RNA intermediate

Genome includes a reading frame encoding both c and e antigens

HBe antigen is secreted into the serum during active replication

HBc antigen accumulates in the cytoplasm (and may form inclusion bodies)

Integrates into the host genome

PRESENTATION

In infants and peds: asymptomatic

Prodrome: NVD, anorexia, headache, low-grade fever

This occurs during the incubation period (6 – 24 wks)

Syndrome: icteric illness in 30 – 50% of adults

Extrahepatic: glomerulonephritis, cryoglobulinemia, polyarteritis nodosa

DX: viral serology

Early Acute	: HBsAg + , Anti-HBsAb - , AntiHBcAb –
Acute	: HBsAg + , Anti-HBsAb - , AntiHBcAb IgM +
Chronic	: HBsAg + , Anti-HBsAb - , AntiHBcAb IgG +
Previous Cleared Infection	: HBsAg - , Anti-HBsAb + , AntiHBcAb IgG +
Vaccination	: HBsAg - , Anti-HBsAb - , AntiHBcAb IgG –

HBs is the earliest indicator of acute infection
Anti- HBs is neutralizing
    Requires 1 – 4 mos. for seroconversion
Anti-HBc is non-neutralizing, but may distinguish acute from chronic and cleared infection
HBc is not detectable in serum
HBe correlates with replication index and infectivity

Screening for HCC: AFP and U/S
    Do this in HBV carriers (HBsAG +ve) with signs of cirrhosis
TX
    Acute (Uncomplicated) Hepatitis: supportive + oral antiviral therapy
    AHF: transplantation
    Chronic: IFN-α + oral antiviral therapy
PREV: vaccination (surface antigen)
    All neonates, adults with RFs (chronic liver disease, HIV, immunosuppression)
    Use for PEP
    Prevents vertical TMX if given with HBIG to neonate

HEPATITIS D

DISTRIBUTION: Worldwide.
EPI: RFs for infection are same as those for HBV
TMX: similar to HBV
VIRAL BIOLOGY: partial virus-like particle with closed plasmid RNA (1.7 kbp)
        Requires concurrent infection with HBV to complete lifecycle
        The HDAg is complexed with HBsAg particles in serum
        Site of infection is limited to hepatocytes
NATURAL Hx:
    The outcome depends on superinfection or co-infection
    CO-INFECTION with HBV: typically resolves
    SUPERINFECTION with HBV: results in chronic active HBV + HDV
    Chronic infection may convert to CIRRHOSIS
    AHF occurs in both patterns of infection
PATH: unknown mechanism of cellular injury
DX: serum anti-HDAb IgM and IgG
TX: high-dose IFN
    The oral antivirals are INEFFECTIVE; but they do treat HBV
PREV: HBV vaccination will prevent infection with HDV