VIRAL HEPATITIS

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PGY-4
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HEPATITIS A

* Non-enveloped, single-stranded RNA virus.
* Only one known serotype.
* The primary route of transmission of HAV is the fecal-oral route, by either person-to-person contact or ingestion of contaminated food or water.
* Epidemiologic risk factors for HAV infection:
  - Unknown 65%
  - International travel 15%
  - Contact with a patient who has hepatitis 12%
  - Men having sex with men 9%
  - Food or waterborne outbreak 7%
  - Child or employee in a daycare center 4%
  - Injection drug use 2%
* Ingested HAV traverses the small intestinal mucosa and reaches the liver via the portal vein.

* The precise mechanism of hepatic uptake in humans is unknown.

* Cytoplasmic replication (seen on electron microscopy as a fine granular pattern).

* Upon maturation, hepatic sinusoidal release into the biliary tree, passed into the small intestine, and eventually excreted in the feces.

* The lack of injury to cells in cell culture systems suggests that HAV is not cytopathic. Immunologically mediated cell damage is more likely.
* Incubation period is commonly 2 to 4 weeks (rarely up to 6 weeks).

* **Five clinical patterns:**
  1. Asymptomatic without jaundice.
  2. Symptomatic with jaundice and self-limited after approximately 8 weeks.
  3. Cholestatic: With jaundice lasting 10 weeks or more.
  4. Relapsing: Two or more bouts of acute HAV infection occurring over a 6-to 10-week period.
  5. FHF: Elderly, chronic liver disease, HIV infection.

* Prodromal symptoms include fatigue, weakness, anorexia, nausea, vomiting, and abdominal pain. Extrahepatic manifestations are less frequent and consist most commonly of an evanescent rash (14%) and arthralgias (11%).
* IgM anti-HAV : Positive from the onset of symptoms, remains positive for approximately 4 months.

* IgG anti-HAV : Detectable at the onset of the disease, remains present usually for life; marker of previous HAV infection.

* Testing for HAV RNA (in serum, stool, and liver tissue) is limited to research laboratories.

* Because the disease is usually self-limited, the treatment is supportive.
Postexposure Prophylaxis

Groups at High Risk of Hepatitis A Virus Infection

Healthy persons who travel to endemic areas, work in occupations for which the likelihood of exposure is high, are family members of infected patients, or adopt infants or children from endemic areas

Men who have sex with men

Persons who have tested positive for human immunodeficiency virus

Persons with chronic liver disease

Persons with clotting factor disorders

Users of injection and noninjection illicit drugs

Single-antigen HAV vaccine or IG (0.02 mL/kg) as soon as possible (within 2 weeks of exposure).
HEPATITIS D

* Initially identified by Rizzetto in 1977 during a major outbreak of hepatitis D in the Mediterranean basin.
* Unique nuclear antigen in hepatocytes of patients with severe chronic hepatitis B infection and fulminant HBV infection.
* Estimated that 5% of HBV carriers worldwide are co-infected (15-20 million cases).
*Genotype 1- Mediterranean, North America, Europe
*Genotype 2- South East Asia
*Genotype 3- South America

*The mode of HDV transmission is linked closely to that of HBV transmission.

*HDV is a satellite virus (obligate relationship to HBV).
*Single-stranded RNA virus, encodes a protein, hepatitis delta antigen (HDAg).
*Virion consists of the HDV genome complexed with HDAg in an envelope protein composed of lipids and HBsAg
*HDV with its HBV envelope protein enters the host
*The HDV RNA-HDAg complex migrates to the nucleus.
*The pathogenic mechanism of HDV-induced liver damage is most likely related to the immunologic response to HDV.
HDV

Superinfection (previously HBsAg+)
- HBsAg+
- HBV DNA+
- IgM anti-HBc –*
- IgM anti-HDV+

Serologic results

Clinical features
- Abrupt increase in ALT from baseline
- Decompensation of previously compensated liver disease

Prognosis
- Progression to cirrhosis

Coinfection (previously HBsAg –)
- HBsAg+
- HBV DNA+
- IgM anti-HBc+*
- IgM anti-HDV+

Acute hepatitis
- Double peak in ALT (as HDV is established after HBV)

Resolution in most cases as HBV resolves
The only therapeutic option currently available is interferon alpha, the efficacy of which is related to the dose and duration of treatment.

Pegylated IFNa as the treatment of choice for chronic hepatitis D. Treatment should be administered for one year.

PREVENTION

Because the ability of HDV to infect a host depends on the preexistence of HBsAg, vaccination against HBV confers protection against HDV.
HEPATITIS E

* Nonenveloped, RNA virus.

* Genotype 1: Asia
* Genotype 2: Mexico, West Africa
* Genotype 3: United States
* Genotype 4: China, Taiwan, Japan, and Vietnam.
* Slight male predominance (male-to-female ratio up to 4:1).

* Particularly high attack and mortality rates among pregnant women (2nd and 3rd trimester).

* HEV infection is transmitted predominantly through the fecal-oral route. Most reported outbreaks have been related to consumption of fecally contaminated drinking water.

* The virus enters the host primarily through the oral route, although the mechanism(s) by which the virus reaches the liver is unknown.

* Incubation period of four to five weeks with HEV being detectable in the stool approximately one week before the onset of illness and for up to two weeks thereafter.
* Asymptomatic infection.
* Anicteric hepatitis.
* Acute icteric hepatitis.
* Severe hepatitis leading to fulminant hepatic failure.

* Enzyme immunoassays (EIAs) for the detection of:
  * IgM anti-HEV appears in the early phase of clinical illness, lasts 4 to 5 months, and can be detected in 80% to 100% of cases during outbreaks of acute hepatitis E.
  
  * IgG anti-HEV appears in serum a few days after IgM anti-HEV, titer increasing during the convalescent phase.

HEV RNA in stool and serum specimens.
* Acute hepatitis E usually is self-limited and requires only supportive care and no specific intervention.

* In pregnant women, no proven benefit to terminating the pregnancy has been documented; postpartum hemorrhage resulting from deranged coagulation requires treatment with fresh-frozen plasma.

**Prevention of hepatitis E**

* Measures to improve the quality of available water and sanitation.
Hepatotropic Viruses

- Hepatitis A
- Hepatitis D
- Hepatitis E

Nominal Viruses

- HSV
- CMV
- EBV
HERPES SIMPLEX VIRUS

* Enveloped, double stranded DNA virus.
* Episomal (non integrated) retention of viral DNA in the infected cell giving rise to the potential for reactivation or recurrence.
* Both HSV- 1 and HSV- 2 have been implicated in the development of viral hepatitis.
* HSV typically causes mucocutaneous vesicular oral or genital lesions.
* **Immunocompetent:**

   Mild, asymptomatic liver enzyme elevations may be seen in 14% of patients with acute genital HSV infection.

* **Immunocompromised (depressed cell mediated immunity/steroids/ transplant):**

   May present with fulminant hepatitis, especially in the first month post transplant.

* **Pregnant Women:**

   HSV hepatitis usually has a fulminant course. Most common in late gestation, typically (in 65% of patients) in the third trimester. Maternal and perinatal mortality rates approach 40%.
* **Anicteric Hepatitis:**
  Fever, leukopenia, and markedly elevated serum aminotransferase levels (1000’s). Coagulopathy (including disseminated intravascular coagulation).

* Mucocutaneous lesions are present in only 50% of cases, so a high index of clinical suspicion is important to ensure timely diagnosis. If present, DFA or skin biopsy may be helpful.

* CT: nonspecific low density non enhancing lesions.
Herpes Simplex Virus Hepatitis: An Analysis of the Published Literature and Institutional Cases

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* Retrospective review A total of 137 cases (132 literature, 5 institutional) of HSV hepatitis
* Main features at clinical presentation were fever (98%), coagulopathy (84%), and encephalopathy (80%).
* Most cases (58%) were first diagnosed at autopsy and the diagnosis was suspected clinically prior to tissue confirmation in only 23%.
* Overall, 74% of cases progressed to death or LT, with 51% in acyclovir treated patients as compared to 88% in the untreated subjects (P 0.03).
* Variables on presentation associated with death or need for LT compared to spontaneous survival: male gender, age 40 yr, immunocompromised state, ALT 5,000 U/L, platelet count 75 103/L, coagulopathy, encephalopathy, and absence of antiviral therapy.
Qualitative HSV DNA by PCR.
*ELISA: IgM - HSV > 1:80.

Liver Biopsy:
*Focal or extensive hemorrhagic or coagulative necrosis with few inflammatory infiltrates.
*Intranuclear (Cowdry A type) inclusions.
*Periportal multinucleated hepatocytes show a ground-glass appearance suggestive of viral inclusions.
**Treatment:**

* Empirical therapy should be instituted pending diagnostic confirmation.

* High-dose intravenous acyclovir (at least 10 mg/kg every eight hours) is effective and safe in pregnancy.

* Prolonged therapy may be required because severe relapse has been reported.

* Successful liver transplantation has also been reported.
CMV HEPATITIS

HCMV Human Cytomegalovirus
**Immunocompetent Individuals:**

Primary CMV infection is usually subclinical but may cause a mononucleosis-like illness. Liver involvement is common and is characterized by mild to moderate aminotransferase (88%) and alkaline phosphatase (64%) elevations with or without hepatosplenomegaly.

**Immunocompromised Individuals:**

- Hepatitis
- Pancreatitis
- Acalculus gangrenous cholecystitis
- AIDS-associated cholangiopathy
Post Transplant Patients:

* CMV D+/R- at greatest risk for CMV disease.
* CMV Hepatitis: “Smoldering” and rarely fulminant; CMV syndrome (fever with myelosuppression).
* CMV is known to be a potent up-regulator of alloantigens, thereby increasing the risk of acute rejection and chronic allograft dysfunction.
* CMV is associated with vanishing bile duct syndrome and ductopenic rejection, leading to chronic cholestasis and eventually allograft failure.
* Higher incidence of vascular and hepatic artery thrombosis in liver transplant recipients with CMV disease.
* Accelerated course of HCV recurrence in patients who develop CMV infection after liver transplantation.
*IgM antibodies to CMV.

*CMV antigenemia assay incorporates antibodies directed at the pp65 matrix protein of the CMV virus.

*Multinucleated giant cells with mononuclear portal and parenchymal inflammatory infiltrates and cholestasis are commonly seen on liver biopsy specimens. Large nuclear inclusions, sometimes referred to as “owl’s eye” inclusions may be seen in hepatocytes or biliary epithelial cells.
Treatment

**Immunocompetent adult:**
* Treatment is unnecessary

**Immunocompromised patients:**
* IV Ganciclovir
* Since viremia correlates with disease outcome, ganciclovir should be continued until CMV antigenemia is undetectable.
* Multiple (at least two) weekly negative CMV PCR results should be obtained before antiviral therapy is discontinued.
* Equally important is the reduction in the degree of pharmacologic immunosuppression.
CMV disease prevention after liver transplantation

Preemptive Therapy:
CMV reactivation is aggressively monitored by sensitive assays and upon detection, antiviral therapy is administered preemptively to prevent its progression to clinical disease.

Antiviral Prophylaxis:
Antiviral drugs are administered to patients at risk of CMV disease after liver transplantation.
Prophylaxis with 3 months of valganciclovir and oral ganciclovir

Antiviral prophylaxis is generally regarded as a more efficient approach and is used by the majority of transplant centers.
EBV
**Immunocompetent Individuals:**

*Up to 90% of patients with acute mononucleosis have serum aminotransferase and lactate dehydrogenase elevations.  

*Enzyme levels typically rise over a one to two week period. 

*Elevated levels of alkaline phosphatase are common, and mild hyperbilirubinemia is observed in as many as 45%. 

*Viral-induced cholestasis, autoimmune hemolytic anemia should be excluded in all hyperbilirubinemic patients.
Immunocompetent Individuals:

Hemophagocytic Syndrome

* Natural killer T cell dysregulation, leading to lymphocyte proliferation and activation with uncontrolled hemophagocytosis and cytokine production.

* Fever, hepatosplenomegaly, hepatic synthetic dysfunction, cytopenias, and marked hyperferritinemia.

* Although rare, the syndrome is usually severe and may be fatal.

* Treatment is with immunosuppressive medication.
Immunocompromised Individuals:

Post-transplantation lymphoproliferative disorder (PTLD)

* Uncontrolled proliferation of B cells after liver transplantation.
* Typically in response to primary Epstein-Barr virus infection.
* Intensive immunosuppression with OKT3
* Features suggestive of PTLD include lymphadenopathy, unexplained fever, and systemic symptoms such as weight loss.
* Involves the gastrointestinal symptoms (27%), pulmonary (15%), CNS symptoms (13%).
* Therapy includes a reduction in the level of immunosuppression and antiviral therapy with ganciclovir directed against Epstein-Barr virus.
*Diagnosis of EBV hepatitis is based on clinical features of mononucleosis and laboratory data suggestive of acute EBV infection.

*Most patients (70%) have a leukocytosis with a predominance of lymphocytes and monocytes, and up to 50% have mild thrombocytopenia.

*The Monospot test is sensitive for the detection of heterophile antibodies but is not a specific test for EBV infection.

*EBV-specific immunoglobulin M (IgM)

*Liver biopsy is rarely necessary for diagnosis but, if done, shows portal and sinusoidal mononuclear cell infiltration with no disruption of hepatic architecture; multinucleated giant cells are not a feature.
Time course of various infectious complications in liver transplant recipients.
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