Immunological Aspects of Gastrointestinal and Liver Disease
MUCOSAL IMMUNITY

There are two part of immunity in Gut:

- systemic (peripherally) eradicate foreign antigens.
- mucosal immunity system.
Mucosal Immunity System:

Two ability: (suppression)
- These responses are supported by several phenomena that have been observed in the gut, including oral tolerance and controlled or physiological inflammation.

- Selective process

(dynamic ability):
- to adapt to environmental stimuli in a way that best suit the needs of the host-

- Aberrations in this balance result in inflammatory diseases.
The alternative pathways of immune regulation observed in the mucosal immune system are most likely explained by the distinct organization of the lymphoid structures and lymphocyte populations that are present.
Anatomy of the Gut-Associated Lymphoid Tissue (GALT)

**Definition:**
is composed of a single layer of epithelial cells separating the external environment from the underlying loose connective tissue.

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### Innate and Adaptive Immunity in the Gut

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<th>Adaptive immunity</th>
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<tr>
<td><strong>physicochemical</strong></td>
<td><strong>cellular</strong></td>
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<tr>
<td>Mucus</td>
<td>NK cells (? some IELs)</td>
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<td>Tight junctions</td>
<td>Macrophages</td>
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<td>Epithelial membranes</td>
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<td>Luminal/brush border enzymes</td>
<td>PRRs (Toll-like receptors)</td>
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<td>Epithelial cells</td>
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<td>pH ranges</td>
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<td>somatostatin</td>
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<td>trefoil factors</td>
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<td>Peyer’s patches</td>
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<td>Epithelial cells/antigen presentation</td>
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**COMPONENTS OF THE PEYER'S PATCH**
- Follicle-associated epithelium
- Dome region
- Follicles - B cell zones with germinal centers
- Parafollicular regions - enriched with T cells

**LYMPHOcyTES OF THE GALT**

1. PP lymphocytes
   - MAdCAM-1
   - TGFβ
   - α4β7
   - T_H3 cell
   - IgM+ B cell
   - IgA+ B cell

2. Intraepithelial Lymphocytes
   - E cadherin
   - intestinal epithelial cell
   - CD3
   - CD45RO
   - αEβ7

3. Lamina Propria Lymphocytes
   - CD2 CD8
   - CD45RO
   - α4β7
   - flat endothelial venule in LP
Structure of Secretory IgA

It consists of at least two IgA molecules covalently linked by a J chain and the secretory component, which is added as the antibody crossed the mucosal epithelial cells into the lumen.

1. Plasma cells in the LP secrete IgA which is then linked by J chain to form IgA dimers.
2. IgA dimers bind to polymeric Ig receptors located on the basolateral aspect of the epithelial cell.
3. The IgA-polymeric Ig complex is transcytosed across the epithelial cell. Once the complex reaches the lumen, secretory component (SC) is cleaved from the polymeric Ig receptor and the IgA-SC complex is released.

SECRETORY IgA

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Plasma cells in the LP secrete IgA which is then linked by J chain to form IgA dimers.
Oral Tolerance

There are several phenomena that support the idea that suppression is the general response of the gut. One of these is oral tolerance (OT), which is defined as the active non response to a soluble antigen that is administered through the oral route. Multiple mechanisms are involved in the induction of OT.

**Low-dose tolerance:**
By the CD4+ cells secreting the cytokines TGF-β, IL-10, and IL-4

**Higher doses:**
Of fed antigens can induce allergy or deletion. Antigen-specific CD8+ suppressor T cells may also play a role in this process. Loss of OT may be the mechanism responsible for the immune response to commensal flora and dietary antigens, leading to food allergies and possibly inflammatory bowel disease (IBD). Use in the treatment of autoimmune/inflammatory disorders.
The stomach is divided into three regions: the body and fundus produce acid (through parietal cells) pepsinogen (.. chief cells) antrum (where G cells produce gastrin)
Pernicious Anemia

**Def.** is an organ-specific autoimmune disease characterized by chronic inflammation of the stomach (gastritis) with subsequent loss of parietal cells.

**Pathogenesis and immunity:**

<table>
<thead>
<tr>
<th>Normal</th>
<th>Atrophic</th>
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![Stomach comparison](image)
Pernicious Anemia

Autoimmune Atrophic Gastritis (Type A)

- Vitamin B₁₂
- Autoantibodies
- Intrinsic factor
- Chief cell
- Parietal cells
- Pepsinogen
- Achlorhydria
- Maldigestion/malabsorption
- Intrinsic factor
- Vit. B₁₂ deficiency
- Posterior funiculi
- Pyramidal-tract

Atrophic mucosa
Fundus
Corpus

Pernicious anemia:
- Hyperchromic, macrocytic anemia
- Hypersegmented granulocytes
- Funicular myelosis

Diagram shows the interaction between the stomach components and their roles in the development of Pernicious Anemia.
Chronic Atrophic Gastritis

Autoimmune Atrophic Gastritis

Types of intrinsic factor antibodies:
Chronic Atrophic Gastritis

Autoimmune Atrophic Gastritis

Anti-Parietal Cells (Rat stomach)

Diagnosis of autoimmune gastritis however, it can be ascertained histologically:

(1) Antiparietal and anti-IF antibodies in the serum.

(2) Achlorhydria and hyper gastrinemia

(3) serum v. B12 levels, usually low.
**Chronic Atrophic Gastritis**

**Gastric auto-antibodies**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Parietal Cell Antibody</th>
<th>Intrinsic Factor Antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pernicious Anemia</td>
<td>Serum 90%IgG – 65%IgA – 25% IgG Gastric Juice 70%IgA</td>
<td>Blocking Type 70% , IgG Binding Type 35% IgA</td>
</tr>
<tr>
<td>Relatives of patients with PA</td>
<td>30%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Other autoimmune diseases Thyroid disease Diabetes mellitus Addison's disease</td>
<td>20%</td>
<td>5%</td>
</tr>
<tr>
<td>Iron Deficiency anemia</td>
<td>25%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Healthy Adults &gt;60 years Females &lt;20 years</td>
<td>10%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>
Gluten-Sensitive Enteropathy

- Also known as celiac disease or celiac sprue,
- is characterized by inflammatory injury to the mucosa of the small intestine after ingestion of gluten in genetically predisposed individuals.
- inciting agent is gluten
• More specifically, GSE is caused by T-cell-mediated recognition of gliadin
• Genetics plays a major role in the pathogenesis of GSE.
• The disease is associated with DQ2 in over 90% of cases and with DQ8 in the rest of the cases.
• Some gliadin peptides induce epithelial cells to express IL-15, which in turn triggers activation and proliferation of CD8+ intraepithelial lymphocytes that are induced to express NKG2D, a natural killer cell marker.
• These lymphocytes become cytotoxic and kill enterocytes with surface MIC-A, an HLA class I–like protein expressed in response to stress.
• Thus, unlike the CD4+ T cells, these NKG2D+ CD8+ T cells do not recognize gliadin.
• The resulting epithelial damage may contribute to the process by which other gliadin peptides cross the epithelium to be deamidated by tissue transglutaminase. Deamidated gliadin peptides are then able to interact with HLA-DQ2 or HLA-DQ8 on antigen-presenting cells and be presented to CD4+ T cells. These T cells produce cytokines that contribute to tissue damage and the characteristic mucosal pathology.
Symptoms:

• Malabsorption
• steatorrhea,
• weight loss relating to the flattening of proximal small intestinal villi
• Diarrhea
• Anemia
• osteoporosis
• In addition, there is a strong association between GSE and autoimmune disease.
• The gold standard for the diagnosis of GSE is a small-bowel biopsy.

• Histologically, GSE is characterized by a triad of villous atrophy, hyperplastic crypts, and intraepithelial lymphocytosis.

• Serologic tests are useful for the diagnosis and management of GSE

• IgA antibodies to tTG, and gliadin are typically identified.

• In IgA deficiency, it is acceptable to look at IgG antibodies to endomysium, tTG, and gliadin instead of IgA.
Treatment

• The only disease-controlling action is the removal of all gluten from the diet for life.
• Poor control is thought to be a major factor in the development of IEL lymphomas.
Inflammatory Bowel Disease

• IBD: is group of inflammatory conditions of the colon and small intestine

• The major types of IBD are
  Crohn's disease
  ulcerative colitis
Crohn’s Disease

- Is chronic granulomatous inflammation that can involve entire GIT but in most cases initially present as terminal ileitis
- Complex disorder with immunologic, environmental and genetic components
- Crohn's can affect any part of the gastrointestinal tract, from mouth to anus (skip lesions)
- Crohn's disease is transmural, involving all layers of the bowel
- There is a dense infiltration of lymphocytes and macrophages and the presence of granulomas.
A. Crohn’s disease

Typical sites of manifestation

Typical pattern

- HLA-DR1
- DQw5
- Assoc. with smoking
- Shorter breast feeding period
- Refined carbohydrate

Segmental
Discontinuous
Transmural
Fissural
Bladder fistula
Inflammatory conglomerate tumor
Diarrhea

Transmural inflammation
Ulcerations
Fissures

Skip lesions
Epidemiology

- In the United States, approximately 380,000 to 400,000 individuals are thought to be affected with CD
- can occur at any age,
- a bimodal peak in the third and fifth decades of life
- The incidence appears to be greater in whites than in blacks
Immunopathogenesis

• There is a strong association with a single gene, *NOD2* located on chromosome 16 and referred to as *IBD1*.

• *NOD2* is an intracellular pattern recognition receptor involved in the binding of muramyl dipeptide, the product of peptidoglycan,

• Of the three major mutations in *NOD2* defined in CD, all result in the failure of muramyl dipeptide binding and loss of NFκB activation.
• Much evidence supports that CD is primarily a TH1-mediated immune response.
• Polarization of helper T cells to the TH1 type is well-recognized in Crohn disease, and emerging data suggest that TH17 T cells also contribute to disease pathogenesis.
The lesions in the bowel are characterized by infiltration of mononuclear cells with increased production of inflammatory cytokines including TNF, IL-1, IL-6 and IL-12.
symptoms

• (alternating diarrhea and constipation, bloody stools, abdominal pain )
• fever
• weight loss
• bowel obstruction, abscess formation, fistulization to skin and internal organs,
• **Management**
  
• Management of CD is generally accomplished by medical rather than surgical means,

• Surgery is rarely curative as the disease often recurs after resection.

• Medical management depend on the location, severity of disease, and extraintestinal complications.

• Therapy is targeted to two goals: (1) to treat acute flare-ups and (2) to maintain remission.

• Immunosuppressors such as azathioprine, 6-mercaptopurine, and methotrexate are targeted toward maintaining remission.
D. Pathological mechanisms

Crohn's disease
ulcerative colitis

- Ulcerative colitis is a disease that causes inflammation and sores, called ulcers, in the lining of the rectum and colon.
- extends only into the mucosa and submucosa with infiltration of lymphocytes, granulocytes, and mast cells.
- **Ulcerative proctitis** refers to inflammation that is limited to the rectum.
- Disease of the entire colon is termed **pancolitis**
Epidemiology

• Ulcerative colitis can occur in people of any age, but it usually starts between the ages of 15 and 30, and less frequently between 50 and 70 years of age.

• up to 20 percent of people with ulcerative colitis having a family member or relative with ulcerative colitis

• A higher incidence of ulcerative colitis is seen in Whites
Immunopathogenesis

• Some data suggest that ulcerative colitis is a TH2-mediated disease,

• UC is thought to be mediated by a mixed inflammatory immune response that is generally characterized by the secretion of cytokines IL-5, IL-13, and IFN-γ.
Clinical Features .

• diarrhea
• lower abdominal pain,
• rectal bleeding
• In severe cases, one can see the complications of this toxic megacolon and colorectal carcinoma.
• blood loss from the inflamed intestines can lead to anemia
• Complications of ulcerative colitis can involve other parts of the body, arthritis, erythema nodosum, uveitis
Treatment

- surgery is curative (total colectomy), in contrast to CD.
- Medical therapies include those that are used to treat CD – 5-ASA formulations, steroids, and immunomodulators.
**Figure 14.4** Characteristics of Crohn’s disease and ulcerative colitis (a and b). Courtesy of Jonathan B. Kruskal, MD - Beth Israel Deaconess Medical Center, Boston MA.
OVERVIEW

- Liver is the largest and most metabolically complex organ
- It is about 2% of total body weight
- Functions of liver:
  1. Detoxification of waste products: deamination of acids to produce urea
  2. Destruction of senescent red blood cells
  3. Synthesis and secretion of bile
  4. Synthesis of the plasma protein including the clotting factors and synthesis of plasma lipoproteins
  5. Metabolic functions: glycogen synthesis, gluconeogenesis, storage of glycogen, some vitamins, ..
Anatomy of liver

Hepatic lobule
The hexagonal lobule contains central venule PORTAL TRIAD arteriole bile duct portal vein central venule lymphocytes dendritic cells Kupffer cells

MICROANATOMY OF THE LIVER

LSECs make up the walls of the hepatic sinusoid. They function as a barrier between the sinusoidal contents and the hepatocytes. They are thought to play a role in antigen presentation.

Kupffer cells are mainly situated in the periportal area. This strategic location allows them to efficiently phagocytose antigens and pathogens entering from the portal-venous blood.

Stellate cells of Ito are the fat-storing cells of the liver that become active during liver fibrosis.
Liver immunology

- The Liver is able to mount active responses to eliminate microorganism while avoiding unnecessary immune responses toward innocuous antigen, which could also result in injury to hepatocyte.

- The liver has natural tendency toward immune tolerance rather than the induction of immunity. (dendritic cells and Kupffer cells may contribute to tolerance induction by deletion or apoptosis of T cells).

- Liver sinusoidal endothelial cells (LSECs):
  1. serve as a barrier to prevent leukocytes from reaching hepatocytes
  2. have a role in receptor mediated endocytosis of macromolecules, which are believed to be subsequently transported to hepatocytes for metabolism
  3. are also believed to contribute to the activation of CD4+ and CD8+ cells as they constitutively express all molecules necessary for
Diseases of the liver
Viral hepatitis

• Hepatitis: injury to hepatocytes associated with influx of acute and chronic inflammatory cells in the liver.
• Viral hepatitis is systemic viral infection that is caused by viral agent which has affinity for the liver tissue.
• To date 6 hepatitis viruses have been identified: A, B, C, D, E, and G.
• Acute viral hepatitis is also caused by viral infections such as CMV, EBV, HSV, Yellow Fever Virus, and Rubella virus.
• Jaundice is the hall mark of infection but it develops late.
Hepatitis B

- **Hepatitis B virus**: characteristic:
  - It is a 42nm enveloped virus with incomplete circular double-stranded DNA, known as Dane particles and belong to family of Hepadnavirus.
  - DNA polymerase in virion and HBV-encoded polymerase act as reverse transcriptase.

- **HBV antigens**:
  - **HBsAg**: surface (coat) protein, produced in excess as small spheres and tubules.
  - **HBcAg**: inner core protein, is retained in infected hepatocytes.
  - **HBeAg**: also located in the core, is important indicator of transmissibility, is marker of active viral replication, and is secreted into the blood.

- HBV has one serotype based on the surface antigen.
-HBV can produce:
  - Acute hepatitis
  - Nonprogressive chronic hepatitis
  - Progressive chronic disease ending in cirrhosis
  - Fulminant hepatitis with massive liver necrosis
  - An asymptomatic carrier state (5% is chronic carrier states)
  - It also play important role in the development of hepatocellular carcinoma

-epidemiology and transmission:
  - HBV affect more than 400 millions worldwide
  - HBV is prevalent in South-east Asia, china, Africa, US, and Europe
  - It passed on through vertical and horizontal transmission
  - Virus is present in serum in large quantity and can be transmitted through blood, and body fluid, with the exception of stool
  - Infection from needle stick : 6-30%
Pathogenesis and immunology

- HBV replication is not directly cytotoxic
- Liver injury is a consequence of immune response which is directed at viral clearance
- Immune response is T-cell responses involving both MHC class II restricted CD4+ cells and MHC class I restricted CD8+ cells to HBV antigen
- Strong response in acute and self-limited hepatitis B infection
- Attenuated response seen in chronic carriers of HBV
- More specifically, cytotoxic T-lymphocytes develop acute liver injury
• Interestingly, the extent of hepatocyte injury is the result of antigen non-specific cytotoxic by-products as to TNF, free radicals and proteases

• TNF@ and IFN are cytokines, have antiviral effect

• Antigen-antibody complexes cause arthritis, rash, and glomerulonephritis

• Hepatocellular carcinoma may be related to integration of part of the viral DNA into hepatocyte DNA
For stages of HBV infection:

First stage: characterize by

- $\uparrow$ Of HBV replication
- Normal serum transaminase level
- HBeAg is +ve

Second stage:

- Reflect immune response in which inflammation result in destruction of HBV-infected cells
- $\uparrow$ In transaminase level
- When the patient stay in this stage beyond 6 month chronic HBV infection risk of progression to cirrhosis and HCC

Third stage:

- Indicate the end of viral replication although, low level of HBV DNA may be present
- HBeAg -ve
- HBeAb appears
- Transaminase level normalized
Final stage:
• Clearance of HBsAg
• HBsAb confers protective immunity

Prevention:
1. Vaccine that contains HBsAg as immunogen
2. Hyperimmune serum globulins obtained from donors with high titers of HBsAb
3. Education of chronic carriers regarding precautions

Treatment:
In acute hepatitis infection
• Asymptomatic in 70% of adult and 90% in child
• Symptomatic nausea, anorexia, fatigue, fever, and right upper quadrant pain
• Treatment: supportive
In chronic HBV infection, the ability of liver to respond to endogenous interferon is impaired so,

- IFNa-2b (recombinant IFN) resembles naturally occurring anti viral cytokines
- It up-regulates MHC class I molecules that are not expressed by hepatocytes
- Thereby increase susceptibility to recognition by CD8+ T-lymphocytes
- Result in, at first year, HBeAg is seroconversion in 46% of treated patients

**Lamivudine**

- Used to treat HIV
- Was approved for treatment of HBV
- Inhibit reverse transcriptase terminating viral DNA synthesis
- More tolerable and safe than IFNa-2b
• Uncertainty about the duration of therapy
• Develop lamivudine-resistant strains of HBV

Adefovir dipivoxil
• Recently, has been approved for the treatment of HBV infection
• No adefovir dipivoxil-resistant strains have been developed
• Has tolerability, oral route administration
Hepatitis C

- Enveloped virus with one piece of single-stranded, positive polarity RNA and belong to family of Flavivirus.
- No polymerase in virion and RNA dependent-RNA polymerase lacks a proofreading function, making genomic variation of virus and control of HCV difficult.
- The structural components include the core and two envelope proteins.
- One of the envelope proteins (E2) contains the binding sites for CD81 which is present in hepatocytes and B-lymphocytes.
- Has regulatory proteins as helicase, protease, and polymerase.
- Has 100 subtypes and 6 genotypes.

Genotype 2 and 3 have the best response to antiviral therapy.
Epidemiology and transmission:

- Hepatitis C affects 170 million people worldwide.

- For some time, blood transmission was the primary cause of HCV infection in developed countries.

- Transmission by blood transfusion has decreased considerably, however, by intravenous drug use and percutaneous exposure are continuing to emerge.

- Infection from needle stick injury is 3-5%.

- Sexual transmission and from mother to child possibly occurs as well.
Pathogenesis and immunology

- Hepatitis C infection is milder form than HBV infection
- The pathology which result of both
  - Direct cytopathic effect of virus
  - Immune response caused by cytotoxic T-cells
- Acute HCV infected patients are:
  - Asymptomatic
  - Rarely, symptomatic with jaundice, malaise and nausea
- 75-80% of affected individuals become chronic with prolonged asymptomatic period from 20-30 years
- Non specific symptoms of fatigue
- Sever complication and death occur when the patients progress to cirrhosis and HCC
• **Extra hepatic manifestation of HCV:**
  - Associated with autoimmune and lymphoproliferative states as cryoglobulinemia, vasculitis, and membranoproliferative glomerulonephritis
  - Correlated with lichen planus, sicca syndrome and porphyria cutanea tarda
  - Coinfection with HIV-1 and HBV and tend to accelerate the disease process.

• **Prevention:**
  - There is no vaccine
  - Hyperimmune globulins are not available
  - Anti-HCV IgG does not confer immunity to subsequent HCV infection
Treatment:
(1) Immunomodulatory drugs, pegylated IFNa-2b, and ribavirin
-HCV RNA level and HCV genotype must be obtained before starting medical therapy
-serum HCV RNA level testing to determine the effectiveness of medical therapy
(2) Liver transplantation for patients with decompensated HCV related cirrhosis and with early stage of HCC
-Complications include reinfection of the graft with HCV
-Recurrence of hepatitis and even cirrhosis
(3) New therapies are required
-it may be possible to develop virus-specific inhibitors as HCV protease, helicase, polymerase inhibitors or cell surface receptor CD81 inhibitor
Other hepatitis viruses

Hepatitis A:
• Hepatitis A is small RNA virus that belong to the Picornavirus family
• Prevalence of virus correlated with area of poor hygiene and sanitation
• HAV replicates in liver and is transported by bile in the stool
• Transmission of hepatitis A occur through fecal-oral route
• Infection is acute and resolve spontaneously in the majority of cases but small numbers of cases result in fulminant hepatitis and death
• Tow formalin-inactivated hepatitis A vaccines are currently a viable
• Ig is a viable for individuals who require passive immunoprophylaxis
- given within 2 weeks after exposure to HAV or two weeks before travel to areas where HAV is
Hepatitis D:
- Hepatitis D virus is RNA containing passenger virus
- Can not replicate without helper virus (HBV)
- HDV need:
  - the nucleocapsid assembly function of HBV
  - the HBsAg derived envelop
- The best prevention is vaccination against hepatitis B

Hepatitis E:
- Hepatitis E virus is RNA virus belong to the family of Calicivirus
- Cause endemic and epidemic hepatitis, mostly in Asia, Middle East, North-Africa, Mexico and South-America
- Clinical illness occurs between the age 15-34 with peak incidence from 20-29
- Most epidemic result from fecal contamination of water source
• Person to person transmission is uncommon and exposure to blood products and IV drug use do not seem to increase risk

• The disease is acute and often resolves spontaneously

• Fulminant hepatitis failure is rare with mortality at 0.1-0.6 %

• Infection in pregnancy has mortality of 15-25 %
Primary biliary cirrhosis

- Normal bile ducts
- Inflammation and scar tissue destroy ducts

Gallbladder
Liver
Hepatic duct
Cystic duct
Common bile duct
Primary biliary cirrhosis

- It is an autoimmune disease of the liver that result in chronic injury to the intrahepatic bile duct epithelium.
- Affect middle-age women with ratio 9:1 male to female.
- Symptoms:
  1. pruritis
  2. fatigue
  3. hyperlipidemia
  4. osteoporosis
  5. ascitis
  6. portal hypertension
  7. esophageal varices
Primary biliary cirrhosis

Diagnosis:
1- elevated liver enzyme ...(alkaline phosphate)
2- histological finding
3- presence of antimicrochondrial antibody in the serum

Stages:
Stage I .... cc by portals inflammation and lymphoplasmacytic infiltration
Stage II .... cc by extension of inflammation to the periportal area
Stage III .... cc by formation of fibrous septa between cell and bile duct loss
Stage IV ... cc by frank cirrhosis.
Pathogenesis of the disease

In general a host is infected with microorganism that contain antigen similar to antigen resent in the host.

The microbial antigen will induce immunologic response when presented to the immune system of the host.

The antibody that produce will cross react with the host antigen and lead to injury and disease.

In the disease the autoantibody is the antimicrochonderial AB that is act against the autoantigen E2 subunit of pyruvate dehydrogenase complex.
Cont.

High titers of antibodies against mitochondrial elements are characteristic of the disease. Anti-mitochondrial antibodies (AMA) target the E2 component of the pyrurate dehydrogenase complex (PDC-E2).

The main epitopes have been localised within the inner lipoyl-binding domain of the subunit.

Also, these epitopes are recognised by portal CD4 helper and CD8 cytotoxic T cell, and that explains why we see inflammatory cell in the pathogenesis of the disease.

Also, bile duct destruction secondary to the accumulation of bile acid is thought to play a role in disease progression.

A very important note that the injury of PSC is limited to the intrahepatic duct and the extrahepatic are not affected.
Treatment

1- cholestyramine and rifampin .... Pruritis.
2- Ursodiol .. Is the only treatment of PBC

- It has multifactorial effect:
  - is found to cause a normalization of enzyme and improve histological finding
  - it promote both endogenous bile acid secretion and membrane stabilization.
Primary sclerosing cholangitis

It is a chronic disease which characterise by chronic inflammation and fibrosis of intra and extra hepatic bile duct.

The primary injury in large and median sized bile duct the small one are gradually disappear as a result of obstruction.

It similar PBC ....... That the bile epithelium is the target tissue .

Cause : unknown , but it consider there is autoantibody .

It occur in fourth and fifth decade

Men affected more than women

Symptoms : 1- puritis    2- fatigue
            3- bile stasis and jundice
            4- one of the complication is cholangiocarcinoma
Diagnosis:
1- abnormality of liver enzyme
2- characteristic histological finding.
3- serum autoantibody.
4- found beaded pattern (stricture and dilatation of bile duct) by endoscopy retrograde cholangiopancreatography.
Etiology

Some immunopathogenesis studies suggest that it is an autoimmune disease that is characteristic of presence of hypergammaglobinemia and multiple autoantibody and specific MHC hepatocyte.

The autoantibody in the disease is perinuclear antinutrophil cytoplasmic antibody (pANCA) and the antigen of the it is either a nuclear envelope protein (myeloid-specific tubulin-beta isotype 5) or histone H1.
Pathophysiology

- Inflammation damages bile ducts both inside and outside of the liver.
- The resulting scarring of the bile ducts blocks the flow of bile, causing cholestasis.
- Chronic biliary obstruction causes portal tract fibrosis and ultimately biliary cirrhosis and liver failure.
Treatment

- There is some drug use to improve the liver enzyme but there is no improvement of liver histology.
- Using ERCP with a balloon to dilate the restriction area of the bile duct.
- Also liver transplant survival is excellent.
Autoimmune hepatitis

Autoimmune hepatitis is a disease in which the body’s immune system attacks liver cells.

This immune response causes inflammation of the liver, also called hepatitis.

Autoimmune hepatitis is typically chronic, meaning it can last for years, and can lead to cirrhosis—scarring and hardening—of the liver. Eventually, liver failure can result.
Symptoms and diagnosis

- Autoimmune hepatitis occurs mainly in adolescent or young adult women (about 70% of the time).
- Early symptoms are fatigue, abdominal discomfort, and aching joints.
- When autoimmune hepatitis progresses to severe cirrhosis, there may be jaundice, marked swelling of the abdomen from fluid inside the abdomen, intestinal bleeding, or mental confusion.

**Diagnosis:**

1. Elevated liver enzyme...transaminase
2. Histology
Etiology and type

- Unknown, but some environmental trigger like virus infection “measles, cytomegalovirus” and drug.

Type:

1- type 1: is cc by anti nuclear and anti smooth muscle antibody (anti actin is more specific).

2- type 2: is rare and it is cc by antibody to liver kidney microsome (LKM-1) and anti-liver cytosol (ALC-1).
The autoantigen is liver specific membrane protein asialoglycoprotein receptor.

**HISTOLOGY**

Chronic hepatitis with marked *piecemeal necrosis* and lobular involvement.

Numerous plasma cells.

*Interface hepatitis*: hallmark finding.
There is **CD4+ regulatory T cell** which express the IL-2 receptor (CD25) are known to **suppress** the proliferation and effectors function of the autoreactive **CD4+ and CD8+ T cell**.

The absence of these cell will lead to in **autoimmune disease** like autoimmune **thyroditis and gastritis**.

In the autoimmune hepatitis these cell are **decrease** and that lead to **increase** the con. Of anti-LKM and soluble liver antegen antibodies.
Early diagnosis is essential as medical treatment is successful.

Prednisolone alone or in combination with azathioprine is the mainstay of treatment.

Most patient require lifelong immunosuppression.

Liver transplantation is require for patient that has intolerance to the immunosuppressive agent.
THANK YOU!