Lecture 3[2hrs]

Treatment of Chronic Hepatitis B

Antiviral treatment is indicated for patients with

*HBV DNA levels >2,000 IU/mL in association with a sign of ongoing hepatitis (elevated ALT levels or liver fibrosis demonstrated by liver histology greater than A1/F1 or by non-invasive tools such as liver Fibroscan or Fibrotest).

*All chronic hepatitis B patients with cirrhosis regardless of HBV DNA and serum ALT levels

*Chronic HBV infected patients with a family history of HCC or cirrhosis and extrahepatic manifestations.

If a patient does not meet the criteria for treatment at the time of assessment (normal ALT or HBV DNA negative), their liver enzymes should be checked every six to 12 months.

1-Antiviral Therapy. **include**.

***Pegylated interferon**

*More effective in patients with high serum transaminases and active hepatitis on liver biopsy.

*PEG –IFN gave weekly SC for 1 year.

*Side effects include: - flu-like symptoms, Thyroid abnormality, Bone marrow suppression, depression.

Pegylated interferon contraindicated in decompensated cirrhosis.

***Nucleoside analog include**

*(lamivudine, telbivudine, emtricitabine, entecavir, adefovir, and tenofovir disoproxil fumarate (TDF), Tenofovir Alafenamide)

*These drugs act by inhibiting reverse transcriptase of HBV DNA. It is administered orally and has fewer adverse effects than interferon.0000000000

*These drugs can be used in patients with decompensated cirrhosis.

lamivudine and entecavir can be used for children age 2 years and older and tenofovir is approved for children 12 years and older.

2-Liver Transplantation. Indicated for end-stage liver disease.

Risk factors for the development of HCC with chronic HBV. include

*Presence of Cirrhosis, *Male gender, *Family history of HCC, * Age > 45 years, *Persistently high HBV DNA level, * Concomitant HDV or HCV infection

*Alcohol consumption.

Prevention of HBV include.

*Screening measures of blood products. *Needle exchange programs.

The hepatitis B vaccine

*Synthesized by recombinant DNA technology.

*These vaccines are safe and effective.

*After 3 injections [0-1-6 m] 95–99% of individuals develop protective antibody [anti-HBs] that can prevent infection.

HBV vaccine is given to high-risk groups which include

• Neonates of pregnant mother with HBV (“vertical transmission”).
• Partners of acutely and chronically infected individuals.
• IV drug users.
• Hospital employees.
• Patients from an endemic country.

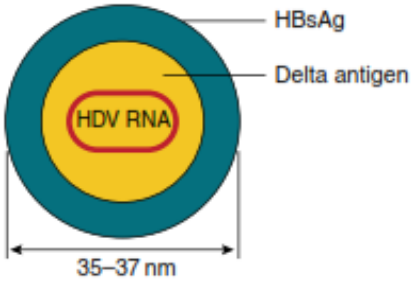
*Family contacts of chronic carriers.

*Chronic transfusion recipients and dialysis patients.

***Hepatitis B Immune Globulin (HBIG) [0.06 ml/kg]**

*****Can offer protection against hepatitis B infection after exposure to the virus.
*It should be given within 12 hours after exposure to the virus in combination with the vaccine.
*The immune globulin with hepatitis B vaccine should be given to the neonates of mothers with acute or chronic hepatitis B to prevent the transmission of the virus from mother to newborn.

4-Hepatitis D Virus (HDV)
*Hepatitis D (HDV) is a defective RNA virus
*Requires the presence of the hepatitis B surface antigen (HBsAg) for its production.
*HDV utilizes the HBsAg to enter hepatocytes
*HDV infection can affect all risk groups for HBV infection.



*Hepatitis D (HDV or delta) infection occurs either as a co-infection with hepatitis B or as a super-infection in a patient with chronic HBV.
*Co-infection produces a more severe acute hepatitis than that caused by hepatitis B alone.
*Super-infection results in severe chronic hepatitis that leads to hepatic cirrhosis and liver failure.
Diagnosis- All patients with HBV should be screened with anti-HDV.
*anti-HDV IgM indicate (acute infection), *anti-HDV IgG indicate (chronic infection)
*Viral load by PCR for HDV RNA.
Treatment
*PEG-IFN for 48 weeks.
*Liver transplantation- for end-stage liver disease.
*Patients require surveillance for HCC
Prevention
*Hepatitis B vaccination is protective against both hepatitis B and HDV infection.

5-Hepatitis C Virus[HCV].

*Hepatitis C was discovered in 1989.
*It is a single-stranded RNA virus.
*It exists as different genotypes [1-6].
*HCV RNA does not integrate into the host's genome.
*The prevalence of HCV infection variable.
*Human is the sole source of infection.
*The principal mode of HCV transmission is parenteral by blood and blood products, Intravenous drug use, and Contaminated medical instruments.
*Vertical transmission of HCV occurs in 2% to 10% for infants born of HCV-RNA positive mothers.
Ways HCV is not Transmitted

*Breastfeeding unless nipples are cracked or bleeding. *Kissing, sneezing, hugging, coughing *Food or water *Casual contact, including sharing eating utensils or drinking glasses.

HCV can cause both acute and chronic liver disease.

Clinical course

The incubation period is 15-150 days.

*The infection is self-limited in 15-30% and the remaining 70–85% Chronic infection develops.

*The acute phase is usually mild and the majority of patients are anicteric.

*Because the acute illness can be very mild detection of acute infection is difficult.

*Patients with symptomatic acute hepatitis are more likely to clear the virus.

*Many cases are identified after an investigation of raised liver enzymes in asymptomatic individuals or after a screening of blood donors.

*Other patients presented with fatigue, malaise, or with stigmata of chronic liver disease with or without signs of decompensation.

*20% of patients with chronic hepatitis will develop cirrhosis by 25 years. Accelerated progression is seen in patients with heavy alcohol use, obesity, and co-infection with HIV or HBV.

*Chronic hepatitis C is a risk factor for the development of hepatocellular carcinoma.

Extrahepatic Manifestations of Chronic hepatitis C include.

lymphoma, porphyria cutanea tarda, lichen planus, keratoconjunctivitis sicca, thyroiditis, and Membranoproliferative glomerulonephritis.

Investigations

1-Serologic tests for detection of *Antibody to HCV (ELISA) and *HCV core antigen

2-Molecular tests by PCR for detection, viral load of HCV RNA and genotype

*HCV-RNA becomes detectable in serum after 7-14 days of exposure, followed by aminotransferase elevation.

*HCV antibodies occur after 4-10 weeks of exposure.

*The core antigen can be detected 1-2 days later than HCV-RNA.

*Anti HCV IgM determination has not proved useful for diagnosing acute HCV infection because these antibodies can be present in similar concentrations both acute and chronic infection.

*False-negative anti-HCV antibody testing may occur in severely immunosuppressed patients, patients with agammaglobulinemia and patients on hemodialysis so diagnosis is confirmed by HCV RNA testing

interpretation of laboratory tests for hepatitis C virus infection

Antibody to HCV	HCV RNA	Interpretation
Negative	Negative	No infection
Positive	Positive	HCV infection
Positive	Negative	Resolved infection
Negative	Positive	Infection [immunocompromised]

Treatment of Acute hepatitis C

*Acute HCV infection usually self-limited disease and in most cases requires supportive care.

*There is a role for treatment of acute hepatitis C if spontaneous viral clearance has not occurred by 12 weeks.

*Treatment

The same regimen that is recommended for chronic HCV infection is recommended for acute HCV infection.

*Liver transplantation for patients who develop fulminant liver failure.

Treatment of chronic hepatitis C.

*The goal of therapy is to cure HCV infection to *prevent hepatic cirrhosis, *decompensation of cirrhosis and *HCC.

*All patients with chronic HCV must be considered for therapy.

Treatment should be considered without delay in patients with

*Significant fibrosis or cirrhosis (METAVIR score F2, F3 or F4), including decompensated (Child-Pugh B or C) cirrhosis,

*Patients with extrahepatic manifestations of hepatitis C infection should be considered for antiviral treatment regardless of the severity of the liver disease.

1-Combination therapy **[Pegylated interferon** a2a or a2b +Ribavirin] this combination therapy, given for 6 to 12 months pegylated IFN-a2a, 180 iu/week

- Pegylated IFN-a2b, 1.5 iu/kg/week
- Ribavirin 1000- 1200 mg / day
- *Side-effects of ribavirin induces hemolytic anemia and is teratogenic
  Contraindication to Ribavirin:-Pregnancy, Anemia, Renal insufficiency, Severe heart disease
  2-Treatment With Direct-Acting Antiviral agents (DAAs).The infection is cured by more than 99%. There are four main classes of DAA which are defined according to their mechanism of action and therapeutic target.

1-Protease inhibitors (PIs)=Telaprevir Boceprevir Simeprevir Paritaprevir Grazoprevir

2-Nucleoside polymerase inhibitors (NPIs)=Sofosbuvir

3-Non-nucleoside polymerase inhibitors (NNPIs)= Dasabuvir

4-NS5A replication complex inhibitors=Daclatasvir, Velpatasvir Ledipasvir Ombitasvir, Elbasvir.

*DAAs are orally administered, efficacious and well-tolerated

*Selection of DAA depend on genotype

*Duration of therapy Sofosbuvir plus ledipasvir for 3 m in compensated cirrhosis and 6 m with ribavirin inpatient with decompensated cirrhosis for genotype 1 and 4

*Sofosbuvir plus Velpatasvir achieves similar results and is pan-genotypic.

2*Liver Transplantation for decompensated cirrhosis

Prevention

*There is no vaccine or specific immune globulin available for hepatitis C prevention.

*Screening measures of blood products. *Needle exchange programs

*Following a needle stick injury from a known case of hepatitis C, liver enzymes and HCV-RNA should be closely followed to determine whether the acute infection has occurred. If the acute infection is present, treatment should be given to eliminating the risk of chronic infection**.**

Autoimmune Liver Diseases

1-AutoImmune Hepatitis [AIH]

*Autoimmune hepatitis is an immunologically mediated chronic, progressive, inflammatory liver disease that predominantly affects females with a personal or family history of autoimmune disease.

*The etiology of AIH is unknown.

*AIH characterized by the presence of

1-interface hepatitis on histological examination,

2-Hypergammaglobulinemia and autoantibodies in serum.

*The onset may be insidious or acute.

*The hepatic presentation can be that of hepatic failure, chronic hepatitis, or cirrhosis.
Clinical features include
*Fatigue, amenorrhea, arthritis, pruritis, fever.
*Physical findings in severe cases include jaundice, spider nevi, palmar erythema, and hepatosplenomegaly, ascites. cushingoid features [hirsutism, pink Cutaneous striae, bruises].
investigations:
liver function tests depend on disease activity.
* Elevated ALT,AST,Low albumin ,elevation of ALP ,GGT reflect intrahepatic cholestasis
*Hypergamaglobulinemia with the elevation of IgG levels.
*ANF, ASMA, anti-SLA, anti LKM1
*Abdominal US
*Liver biopsy is essential for the diagnosis and severity of both types of autoimmune hepatitis and to exclude other causes of liver disease
Types of AIH include
Type 1 autoimmune hepatitis -
*Characterized by the presence of antinuclear factor (ANA), smooth-muscle antibody, or both.
*The peak incidence between ages 16-30 years but patients age may be older.
*Antibodies to Soluble liver antigen [SLA]. may identify patients with severe AIH.

Type 2 autoimmune hepatitis
*Most patients are children aged range 2-14 years.
*Negative smooth muscle antibody and positive antibodies to liver/kidney microsomal (anti- LKM1 hepatitis).
Conditions Associated with AIH include.
*Migratory polyarthritis, combs positive hemolytic anemia, urticarial skin rash, pleurisy, lymphadenopathy, transient pulmonary infiltrates, Hashimoto's thyroiditis, UC, Thyrotoxicosis, Glomerulonephritis nephritis., Myxedema, Nephrotic syndrome.
Treatment includes;
Prednisolone=
*40 mg/day and the dose reduced gradually as the patient and liver function tests improve. Then maintenance dose 5-10mg therapy is continued for at least 2 years after liver function tests become normal and withdrawal of treatment when liver biopsy becomes normal.
Corticosteroids can prevent exacerbation rather than prevent cirrhosis and are less important in asymptomatic AIH.
*Side effects-acne, moon face,wt gain,striae,,hirsutism,osteopenia,DM.HT
*Side effects from prednisolone are uncommon at a maintenance dose of 5-10mg/day.
Azathioprine=
*1-1.5 mg/kg /day orally may be added to the therapy to allow the dose of prednisolone to be reduced to the 5-10mg/day.
Side effects include -nausea, vomiting, pancreatitis, infection, bone morrow suppression, malignancy
Remission of AIH is characterized by the following
-absence of symptoms.
-AST $\leq$ 2 x Normal
-GGT Normal
-liver biopsy show Normal or minimal activity.

Prognosis.
*Most patients develop cirrhosis and its complication.
*HCC is uncommon.
*50% of patients with symptoms die within 5 years if no treatment is given but this falls to 10% with therapy.

2-Primary Biliary Cirrhosis [PBC]
[primary biliary cholangitis]

*Is an autoimmune disease of the small intrahepatic bile ducts resulting in chronic progressive cholestasis that progresses over decades to end-stage liver disease.
*PBC Characterized by positive anti-mitochondrial antibody (AMA) and granulomatous destruction of small intra-hepatic bile ducts.
*Predominantly affects women in middle age and is frequently associated with an autoimmune disease like (Renal tubular acidosis, vitiligo, thyroiditis, sicca syndrome, CREST syndrome, celiac disease, rheumatoid arthritis, glomerulonephritis, and vasculitis).
Clinical features:
*up to 25 % of patients are asymptomatic
*Fatigue in 2/3 of patients.
*RUQ pain, anorexia.
*Pruritus is the most common initial complaint**.**
*Bone pain (related to fat-soluble vitamin deficiency).
*Diarrhea from Malabsorption of fat.
*Jaundice occurs later in the course of the disease and indicate poor prognosis
Physical Examination include
* hyperpigmentation *Scratch marking *hepatosplenomegaly
*Xanthelasma * jaundice and signs of PHT (in advanced disease).
Investigation:
The biochemical pattern is typically cholestatic:
*Elevated alkaline phosphatase, GGT, and 5_nucleotidase (5_NT), with modest elevations of the aminotransferases].
*Elevated serum IgM. *Positive mitochondrial antibody test.
*Elevated serum cholesterol
*US, CT, MR, MRCP, useful to exclude biliary obstruction.
Management:
Ursodeoxycholic acid in a dose of 13-15 mg/kg/day [improve liver function test may slow down histological progression].
Drugs used for Pruritus
*Cholestyramine- [4- 16 gr / day orally taken with breakfast].
Reduce the concentration of bile acid in the body by binding them in the intestine and increasing their excretion in the stool. cholestyramine is ineffective incomplete biliary obstruction.
* Rifampin 150 mg bid. or tid. *Ultraviolet light also helps.
Management of Malabsorption include:
1- Limit fat intake to 40 gr/day **2-**Monthly injection of – vit, k (10 mg).
3- Calcium (calcium gluconate 2- 4 gr / day) and vitamin D.Alfa calcidiol 1 mg /day and bisphosphonates for osteoporosis.
The Associated coeliac disease showed to be excluded.
***Liver Transplantation**-for end-stage liver disease

Secondary Biliary Cirrhosis

*Any disease that permanently and progressively damages bile ducts that not caused by PBC.

Causes include- biliary atresia, hypoplastic duct syndromes, Caroli's disease, choledochal cysts, sclerosing cholangitis, and cystic fibrosis,

*In adults the commonest cause of secondary biliary cirrhosis is primary sclerosing cholangitis (PSC)and bile duct strictures.

Overlap Syndromes

***AMA-negative PBC ('autoimmune cholangitis').**

* Patients with clinical, biochemical, and histological features of PBC but with negative AMA.

The clinical course is similar to PBC and these patients should be considered to have a variant of PBC.

***PBC/Autoimmune Hepatitis Overlap**

Characterized by *AMA Positive and cholestatic LFTs have elevated transaminases, high serum immunoglobulins and interface hepatitis on liver histology,

Treatment -corticosteroid therapy may be beneficial.

3-Primary Sclerosing Cholangitis [PSC].

*PSC is a chronic idiopathic inflammatory disorder of the intra- and extra-hepatic bile ducts that results in biliary strictures, chronic cholestasis and cirrhosis.

*PSC affects about 10% of patients with ulcerative colitis or Crohn's colitis.

*about 30% of patients with PSC have no background of inflammatory bowel disease at the time of presentation.

*Males are twice affected as females usually between the age of 25 – 45 years.

Presentations:

*Jaundice which may fluctuate, weight loss, fatigue, RUQ pain, Pruritus,

*Fever unusual unless there is cholangitis.

*Features of hepatic cirrhosis

Investigations:

*The biochemical pattern is typically cholestatic: [elevated alkaline phosphatase, GGT, and 5_nucleotidase (5_NT), with modest elevations of the aminotransferases]. these abnormalities may fluctuate

*PT may be prolonged *US may be Normal.

*ERCP is diagnostic which shows narrowed irregular obstruction and beading of the extra and intrahepatic ducts. *PTC shows the same finding.

*Liver Biopsy is not helpful diagnostically it is performed only to see if the patient is cirrhotic.

differential diagnosis of PSC is cholangiocarcinoma.

Management:

*Antibiotic used during episodes of cholangitis.

*Ursodeoxycholic acid*Biliary drainage.

*Liver transplantation for decompensated disease

***lgG4-Associated Cholangitis**

Presentation - obstructive jaundice.

Diagnosis*Cholangiography appearances suggest PSC with or without hilar cholangiocarcinoma.

*High serum IgG4 and liver biopsy show a lymphoplasmacytic infiltrate, with IgG4-positive plasma cells. Treatment- steroid therapy.

Inherited Liver Disease

1-Wilsons Disease (hepatolenticular degeneration)

*Normally, dietary copper is absorbed from the stomach and proximal small intestine and is rapidly taken into the liver where it is stored and incorporated into Caeruloplasmin. The accumulation of excessive copper in the body is prevented by its excretion into bile. In Wilson disease daily copper excretion into bile is decreased by 80-90% due to failure of the synthesis of caeruloplasmin.
* Wilson's disease is an autosomal recessive disorder of copper metabolism caused by mutation of the copper transport protein ATP7B on chromosome 13.
*in Wilson disease copper overload develops and excessive copper released in the systemic circulation and deposited in the brain, kidney, eyes and skeleton. These organs are responsible for the extrahepatic manifestation of Wilson disease.
*Prevalence of Wilson is about 1:30,000.

Clinical features. –

Symptoms usually arise between the ages of 5 and 45 years.
*Patients may be presented with Recurrent acute hepatitis with hemolysis [coombs negative] or chronic liver disease of unknown cause in a patient under 40 years old should raise the possibility of Wilson disease.

1-The Hepatic Manifestations

*Can present with asymptomatic elevation of liver enzymes, acute hepatitis
Or* Fulminant hepatic failure (with intravascular hemolysis and renal failure)
Or more insidious onset leading to cirrhosis and portal hypertension.

2-Neurologic Manifestations are

*Copper deposition in the central nervous system results in extrapyramidal symptoms of rigidity, choreoathetoed movements and ataxia.

3-Ocular Manifestations are

1-The Kayser-Fleischer ring (copper deposition in Desçemet's membrane of the cornea) is characteristic of Wilson's disease. The ring may be seen on direct inspection characterized by greenish-brown discoloration of the corneal margin, sometimes seen only by slit-lamp examination.
KF ring disappear with treatment
2.Sunflower cataract which does not interfere with vision.

4-Renal Manifestations are.

*Proximal renal tubular acidosis or Fanconi's syndrome [aminoaciduria, glycosuria, hyperphosphaturia, hypercalciuria]

5-Skeletal Manifestations are.

*Osteomalacia or Osteoporosis or Both

Investigations:

*Acute fulminant Wilson disease is associated with elevation of AST, ALT and bilirubin, Coombs negative hemolytic anemia
*Low Caeruloplasmin is the best single laboratory clue to the diagnosis of Wilson disease.
*High urinary copper [measuring 24-hour urinary copper excretion more than 25 µmol/24 hrs whilst giving D-penicillamine]is a useful confirmatory test
*High serum copper in fulminant liver failure.

*High hepatic copper content > 200microgram/gr dry wt .
*Failure of incorporation of radioactive copper into Caeruloplasmin and decrease in biliary excretion of copper.
*Serum uric acid and phosphates may be low reflecting renal tubular dysfunction
*Urinalysis revealed-hematuria, aminoaciduria, phosphaturia and proteinuria
*Genetic testing is useful in screening families with Wilson's disease**.**

Treatment:

*Avoid foods with copper content [meat, chocolate, nuts and mushrooms]
1-Penicillamine [dose 1- 4 gr/day or 20 mg/kg] **+[pyridoxine** 25 mg / day].
Mode of Action- by increasing urinary excretion of copper.
side effects of penicillamine include - rashes, pemphigus, loss of taste, gastrointestinal upset, arthralgia, proteinuria, leucopenia, thrombocytopenia, aplastic anemia, Nephrotic syndrome, good pasture syndrome, and SLE like**.**
2)Trientine dihydrochloride (1.2–2.4 g/day).
Second-line treatment for the patient who is intolerant to Penicillamine. acts by increasing urinary copper excretion and decrease intestinal absorption of copper.
side effects include – gastritis, Iron deficiency anemia, and Bone marrow suppression.
3) Zinc acetate [50 mg 3 times daily] .acts by inhibiting the absorption of copper from G.I.T and increase exertion of copper in the stools.
***Liver Transplantation** for Patients with advanced liver disease, unresponsive to medical treatment

Prognosis

*Excellent if treatment is started before irreversible damage.
*Long term complication of hepatocellular carcinoma does not occur.

2-Alpha$_1$-AntiTrypsin (α_1-AT) Deficiency**.**

Alpha one antitrypsin (α1-AT) is a serine protease inhibitor produced primarily in the liver. The function of Alpha$_1$-antitrypsin (α_1-AT) is to inhibit multiple proteases including neutrophil elastase, which degrades elastin and other connective tissue.
***α_1-AT** production is controlled by a gene on chromosome 14
*** α_1-AT** deficiency inherited disorder characterized by the development of liver disease or lung disease (or both) in children and adults.
*Incidence is 1/1500.
***α_1-AT** deficiency is transmitted in an autosomal recessive fashion the normal protein is labeled M and abnormal phenotypes include S, Z, and null.
*Normal individuals are PiMM.
*PiZZ and PiSZ phenotypes are associated with severe deficiency and liver disease while PiMZ leads to an intermediate deficiency.
*Pathophysiology of lung disease: increased destruction of elastin in the lungs by the uninhibited action of neutrophil elastase, leading to emphysema.
*Pathophysiology of liver disease: accumulation of the mutant protein in the endoplasmic reticulum of hepatocytes leading to hepatocyte damage.

Liver Manifestations of (α_1-AT) deficiency in children with PiZZ phenotype.

*Cholestatic jaundice in the neonatal period (neonatal hepatitis) with coagulopathy and ascites.
*Poor growth.

Liver Manifestations of (α_1-AT) deficiency in adults with PiZZ phenotype.

*Cirrhosis develops in 2% -19%. *Cirrhosis increases the risk of HCC.

Diagnosis

*Homozygous individuals (PiZZ) have

*Low **α** 1-globulin concentration on serum protein electrophoresis.

*Decreased serum **α_1-AT** levels and it is confirmed by phenotyping.

*Serum aminotransferase, alkaline phosphatase, and GGT may all be elevated.

* Liver biopsy -The characteristic finding includes the presence of periodic acid Schiff (PAS)-positive, diastase-resistant globules in hepatocytes.

Treatment

*Fat-soluble vitamin supplements

* Ursodeoxycholic acid.

*Avoidance of smoking and alcohol**.**

*Infusion of recombinant **α_1**antitrypsin by inhalation or infusion may be beneficial for preventing lung disease associated with **α_1**-antitrypsin deficiency but is ineffective for treating **α_1**- antitrypsin deficiency liver disease.

*Gene therapy may become a possibility in the future.

*Liver transplantation **is curative** for patients with advanced liver disease.

*Screening is recommended for all relatives of patients with α_1-AT deficiency.