

Hot Topics in....

Viral Hepatitis

SEDICO Letter

Hereby, we proceed in issuing a new edition of News Letters, as we promised; we will be committed to enrich health knowledge of our medical staff, especially the youth generation.

And here, we introduce the main topics, discussed during our panel discussion, held on June 5th 2008, with title Hepatic Disorders.

The panel was honored by the participation of:

Prof. Dr. Omar Heikal, Prof. Dr. Hesham El-Khaiat, Prof. Dr. Mohammed Marei Makhlouf, Prof. Dr. Mohammed Helmy Abu-Zeid and Prof. Dr. Nouaman El Garem

Until another issue, we will remain committed to achieving our goal of establishing an interactive culture of health knowledge.



Prof. OMAR HEIKAL MD
"Pregnancy and Liver
Disease"



**Dr Mohamed Aly Marei
Makhlouf**
"Fatty Liver"



**Prof. Dr. Nouaman El
Garem**
"Management of Ascites"



Prof. MOH. H. Abou Zeid MD
"Extra hepatic Manifestations of
Hepatitis C Virus (HCV) Infection "



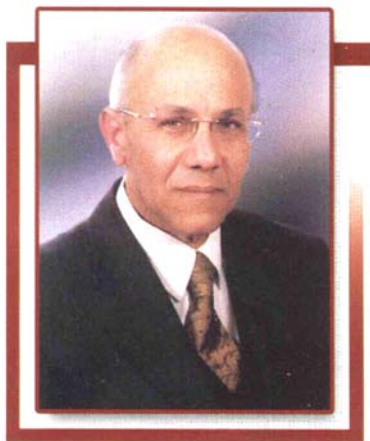
Prof. Hisham Raafat Elkhayat
"Preventing drug resistance in
long-term HBV TTT "



www.sedico.net

SEDICO Newsletter
Volume 2

Prof Dr. Omar Heikal MD



Prof. Omar Heikal MD
Prof Medicine, GIT, Hepatology
Director Military Medical
Academy
EASLMEMBER
Clinic phone: 02 3748 00 83
17 Tahrir st. Eldoki
omar-heikal@hotmail.com

Pregnancy and Liver Disease

Liver dysfunction in Pregnancy maybe:

- * Liver D unique to pregnancy
- * Unrelated to pregnancy
- * Chronic condition existed before pregnancy

Physiologic changes during Pregnancy

Increased;

Blood volume, cardiac output by 35-50%, ALPh, Clotting Factor → hypercoagulable state

Decreased;

Gallbladder contractility, Hemoglobin
Uric acid, Albumin, Total protein
Antithrombin III

NO changes;

- ALTs, ASTs, gamma GT
- Bilirubin
- Prothrombin time

Benign, Physiologic changes in liver during Pregnancy

- Palmer erythema
- Spider angiomas
- Low serum albumin
- High s alkaline ph 3-4 fold due to placental production

Acute viral hepatitis most common cause of jaundice in Pregnancy

- Screening all pregnant women for HBsAg since risk of transmitting virus to baby is high, transmission is preventable
- Liver affected 10%-20% in Preeclampsia, eclampsia, in need for urgent delivery

Spectrum of liver diseases in Pregnancy

- Preexistent liver diseases; Liver cirrhosis, Portal hypertension, Primary biliary cirrhosis, Autoimmune hepatitis, Wilson disease, Alcoholic hepatitis, Chronic HBV, HCV
- Liver D coincidental with but not induced by Pregnancy;
- Acute viral hepatitis, other viral, (Herpes S, CMV) Gallstone D, Budd-Chiari syndrome

Liver D induced by Pregnancy;

Frist trimester; Hyperemesis gravidarum
Second, third trimesters;

- * Acute fatty liver of Pregnancy AFLP
- * Intrahepatic cholestasis of Pregnancy IHCP
- * Preeclampsia, eclampsia, HELLP syndrome (hemolysis, elevated liver enzymes, low platelet counts)

Diagnosis

- * Abdominal Ultrasound is safety image for fetus, mather
- * CAT, ERCP, involve radiation, maternal& Fetal complication, may be done if mandatory (second, third trimester)
- * MRI ; is Safe ,may be used in pregnancy if other non-ionizing imaging are inadequate

Preexisting Liver D, Pregnancy

- * Outcome of preg depends on early diagnosis, severity of liver D
- * Liver Cirrhosis, BPC, P++;
- * Preg uncommon, infertile, tend to be past childbearing age
- * Life threatening complication of LC, bleeding OV
- * SBP → treat
- * Ursodeoxycholic acid in BPC → safe Preg, Breast feeding

Autoimmune hepatitis, Wilson D

- * Affect young women of childbearing age
- * AIR; carry successful preg , course of D

Unpredictable; spontaneous remission, / exacerbation, maternal death

- * Corticosteroids proper treat AIH, safe in preg
- * Azathioprine category D (positive risk to fetus)

Liver D during but not induced by Pregnancy

- * Hepatitis A; is self limited D not affect outcome of preg
- * Hepatitis A Vaccine; given to children >2y in high risk country safe in preg, fetus
- * Urgent Prophylaxis; vaccine & hepatitis A immunoglobulin

Hepatitis E

- * Responsible large epidemic in Asia, Africa
- * Self-limited in pregnant women
- * Caused high death rate (25%) in pregnant women.
- * Premature delivery, still-birth, miscarriage
- * Pregnant women avoid traveling to highly endemic areas
- * Proper control of faeco-oral contamination

Herpes simples virus

- * Can Cause fulminate liver failure, death
- * Rate of transmission to fetus 30%-50%
- * Abnormal LFTs, PT; in 90% of infected pregnant women

- * Acyclovir is very effective, safe, 400mg tds/d for 5-7days
Cesarean delivery preferable

Hepatitis B

- * Acute infection HBV during preg no effects but in;
- * HBeAg +rate fetal transmission is high(90% vs. 10% if negative)
- * High viral load, infection during third trimester
- * Fetal transm. (90% vs. 10%)
- * Pregnant W must be vaccinated in risk exposure
- * Screening all preg W for HBsAg & vaccination of all new born,

HBV

- * IF mother + for HBsAg, newborn receive HBvaci & HB Igs within 12H of birth
- * (Breastfeeding is not contraindicated in vaccine)
- * Lamivudine safe in preg W, lower rate transmission of virus mother to newborn

HCV

- * Vertical transm. of HCV <5% very low risk
- * Higher risk in;
- Co-infected HIV ,high viremia at delivery >6h rupture of membranes → delivery

- * Mode of delivery not influence rate transmission
 - * Breast feeding not risk of transmission
 - * HCV not transmitted by (normal, legal, ethic) sex relation
- Transmission:** in abnormal relation
- * INF& Ribavirin; contraindicated in pregnancy.
 - * Due to High risk of teratogenicity
 - * Chronic HCV male, female under therapy not advanced for conception nor pregnancy

Liver diseases Unique to pregnancy

- * Hyperemesis gravidarum;
- Presentation:** during first trimester resolves after 20 weeks, leaves no ill effect on mother or baby
- Prevalence < 1 %
- Symptoms:** severe nausea, vomiting, ketosis
- Lab feature:** elevated (levels ALT, AST >200U/L)
- Treatment :** supportive, intravenous (Iv) fluids
- Outcome:** being for mother and fetus

Acute fatty liver of pregnancy

- * **Presentation:** during third trimester; 50% of patients have eclampsia, rare but potentially fatal
- * **Prevalence:** 1/10,000 higher prevalence in multiple gestation, primiparous woman, male fetus
- * **Symptoms:** nausea, vomiting, abdominal pain, jaundice; can progress rapidly to hepatic failure, hypoglycemia
- * **Lab. Features:** platelets * <100,000 , AST and ALT 300-1 ,000U/L; decreased antithrombin 111; elevated PT ; low fibrinogen; elevated bilirubin; DIC
- * **Treatment:** prompt delivery; liver transplant
- * **Outcome:** maternal death rate::: 10%; fetal death rate up to 45%

Intrahepatic cholestasis of pregnancy -IHCP

- * **Presentation:** third trimester; rare before week 26 , benign cholestasis
- * **Prevalence:** < 10%; higher in multiple gestation, multiparous woman
- * **Symptoms:** sever pruritus, which resolves postpartum; jaundice
- * Prognosis, excellent to mother

Intrahepatic cholestasis of pregnancy

- * **Lab. Features:** AST and ALT < 1,000U/L; Ngamma GT, elevated ALph and bile acids; normal PT, total bilirubin
- * **Treatment:** ursodeoxycholic acid; delivery at fetal maturity if no fetal distress
- * **Outcome:** increased incidence of gallstones; may recur with subsequent pregnancies; monitoring for fetal distress, fetal death rate 10%- prematurity

Preeclampsia and eclampsia

- * **Presentation:** after week 22
- * **Prevalence:** 5-7%; with HELLP syndrome
- * **Symptoms:** high blood pressure,
- * Proteinuria; edema; seizure; renal failure; pulmonary edema
- * **Lab. features:** platelets> 70,000; signs RF,ALT, AST in 30%
- * **Treatment:** BP control- B blockers; methyldopa, Mg sulfate, early delivery Outcome: maternal death rate 1%

HELLP syndrome

HELLP (hemolysis, elevated liver E, low plat count)

- * **Presentation:** second or third trimester or after delivery; 20% also have eclampsia
- * **Prevalence:** 0.1 % of all pregnancies-→ **Symptoms:** abdominal pain, Mild renal dysfunction → seizure or renal failure.
- * Rare, DIC → maternal morbidity, pulm.
- * Edema, ARF growth retardation,

Prof. Dr. Hisham Raafat Elkhayat



**Prof. Hisham Raafat Elkhayat,
M.D, FAGC, FASGE
Prof of Hepatology , Theodor
Bilharz Research Institute
Fellow of Harvard Medical School
Member of EASL, AASLD, ASGE,
ACG,AGA**

[hrelkhayat@yahoo.com.](mailto:hrelkhayat@yahoo.com)

Preventing drug resistance in long-term HBV TTT

Introduction to HBV replication and How Nucleotid(s)es analogue work?

* The hosts' immune attack against HBV is a critical component of liver injury. This is mediated by cellular responses against HBV peptides (mainly hepatitis B 'e' antigen [HBeAg] derived) that are expressed on the surface of the infected hepatocyte in association with HLA class I molecules. Cytotoxic CD8+ lymphocytes recognize these peptides. This recognition reaction can lead to either direct lysis of the infected hepatocyte or the release of interferon alpha and 1NF -alpha, which can down-regulate viral replication in surrounding hepatocytes without direct cell killing.

* Viral particles can also be taken up by antigen presenting cells (macrophages), which degrade the viral proteins to peptides that are then presented on the cell surface bound to HLA class II molecules. These are recognized by CD4+ cells leading to stimulation of T-cell proliferation and cytokine synthesis, causing inflammation and providing help for B-cell responses.

* During chronic HBV infection, equilibrium is established at which the rate of clearance of HBV-infected hepatocytes approximately equals the rate of infection of non-infected hepatocytes. The rate of emergence of resistant virus may depend upon the availability of non-infected hepatocytes and hence upon the rate of clearance of hepatocytes infected by the previously dominant drug-susceptible variants.

* Hepatocytes are the major target for HBV and the primary site of viral DNA replication.

After an infectious HBV virion has bound to a hepatocyte, its genome, free of the envelope and nucleocapsid, is transported to the nucleus where it is converted from partially double-stranded DNA to covalently closed circular DNA (cccDNA), shown in yellow. The cccDNA serves as a template for the transcription of viral RNA (shown in green) by host cell enzymes.

Viral messenger RNA (mRNA) is transported to the cytoplasm and translated into viral proteins.

Viral pregenomic RNA (pgRNA, shown in green in the nucleocapsid in the cytoplasm) serves as a template/or the production of viral DNA.

Viral pregenomic RNA (pgRNA, shown in green in the nucleocapsid in the cytoplasm) serves as a template for the production of viral DNA.

The conversion of pgRNA (within the nucleocapsid) to new partially double-stranded DNA is mediated by the HBV polymerase .

Nucleocapsids containing new viral DNA acquire an outer envelope complete with surface proteins in the endoplasmic reticulum, and are secreted from the cell via the Golgi complex. Viral proteins (surface antigen and 'e' antigen) are also secreted from the infected cell, forming subviral particles that do not contain a viral core.

Nucleoside and nucleotide analogues licensed as antiviral for the treatment of chronic hepatitis B target HBV polymerase and thereby inhibit the formation of new HBV DNA and reduce the number of infectious virus particles secreted from the cell.

- The natural substrates of HBV polymerase are deoxynucleoside triphosphates (dNTPs). These are the natural building blocks of DNA. Nucleoside and nucleotide inhibitors mimic these natural dNTPs. Nucleos(t)ide analogues compete with natural dNTPs substrates for binding to the HBV polymerase and incorporation into the growing DNA strand , leading to DNA chain termination and failure of HBV replication.

How antiviral drug resistance occurs?

- Antiviral drug resistance arises from genotypic changes that occur in HBV polymerase and are selected by drug treatment because they confer the phenotype of reduced susceptibility to that drug. Potential clinical manifestations of this so-called genotypic resistance are virological rebound and biochemical rebound which lead to progression of the disease to cirrhosis and HCC.

- Incomplete suppression of virus replication by an antiviral drug provides an opportunity for pre-existing drug-resistant variants to be selected and outgrow the wild-type virus.

Clinical consequence of viral resistance:

- Resistance is a serious problem as seen by its adverse effects not only on markers of treatment efficacy but in patient morbidity and mortality. As well as impairing response to current therapy, the emergence of resistance to one drug may compromise the treatment response to subsequent HBV antiviral.

- In a pivotal study by Liaw et Al, it was shown that whilst Lamivudine treatment reduces disease progression in patients with chronic hepatitis B, the emergence of lamivudine resistance substitutions attenuates these benefits. Over time patients with lamivudine-resistance mutations may lose the initial clinical benefit of treatment. In this study of long-term lamivudine therapy of HBeAg (+) patient's duration of lamivudine resistance was an independent predictor of hepatitis flares. Rates of hepatic decomposition and liver disease-related serious adverse events were significantly higher in patients who had lamivudine-resistance mutations for more than 4 years.

- Lamivudine resistance creates a difficult-to-treat 'patient population.

How we can detect early antiviral resistance before virological & biochemical rebound?

- The two most common methods used for detecting genotypic changes associated with antiviral resistance in HBV from clinical samples is the INNO LiPA and Direct sequencing technique.

- The INNO line probe assay (LiPA) HBV DR2 is a commercially available kit that is able to detect the ADV resistance-associated mutations (A181T and N236T) in addition to LVD resistance-associated mutations (L80V/I, V/G173L, L180M, and M204V/II).

- The advantages of this method include its ease of use and its high sensitivity for detecting mutations present in a minority of the viral population.

- The disadvantage of the LiPA test is that it only detects the

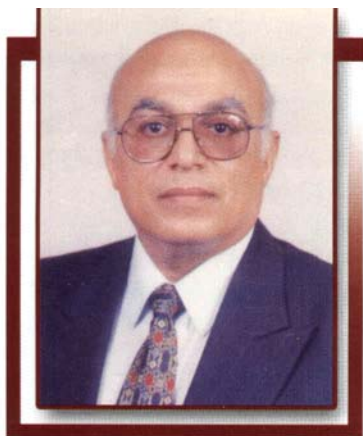
known substitutions that have been included in the kit and thus may miss novel or recently described substitutions .

- Direct sequencing is a more time consuming, specialized technique that is less sensitive for the detection of mutations present in a minority of viruses, but is able to detect all mutations in the HBV polymerase.

How can we reduce the risk of Drug Resistance?

- Physician must have a clear indication for starting therapy, following the latest guidelines.
- Encourage patient compliance.
- Maximize antiviral activity.
- Suppress HBV DNA to lowest possible level; by using the most potent drug from the start (The least potent agent is Adefovir & lamivudine, where as the most potent agents are Tenofovir, Telbivudine, and Entecavir).
- Maximize genetic barriers (the genetic barrier to resistance depends, in part, on the number of substitutions required for virologic breakthrough). Resistance to LVD and Adefovir (ADY) requires one substitution. Resistance to Entecavir (ETV) requires three substitutions (two LVDr substitutions and at least one ETVr substitution).
- Avoid sequential treatment.

Prof. Dr. Mohamed Helmy Abou Zeid



Prof. MOH. H. Abou Zeid MD
Prof of Int, Medicine Consultant
Nephrologist
Cairo University

rnabouzeid@yahoo.com

Extra hepatic Manifestations of Hepatitis C Virus (RCV) Infection

Does Hepatitis C Present By Manifestations Other than Liver Disease?

In Addition to Hepatic Involvement (Acute and Chronic Hepatitis), HCV Infection Have Been Reported to Cause Several Extra hepatic Manifestations Which Include:

A. Hematologic Diseases

1. Cryoglobulinemic Syndrome
2. Lymphoma

B. Autoimmune Disorders

1. Thyroiditis
2. Sjogren's Syndrome

C. Renal Diseases

1. Glomerulonephritis

D. Dermatological Diseases

1. Porphyria Cutanea Tarda

2. Lichen Pianos

3. Leukocytoclastic vasculitis

E. Diabetes Mellitus

F. Ocular Diseases

1. Corneal Ulcer
2. Uveitis
3. Scleritis
4. Sicca Syndrome

G. Neurological

1. Neuropathy

Extra hepatic Manifestations Of HCV Infections May Be The Presenting Symptoms In 15 % Of Cases , So Patients With HCV May Present To Hematologist; Nephrologists; Dermatologist; Endocrinologist; etc .. And They In Addition To GP Should Be Aware Of These Manifestations Because These Manifestations Respond Will To HCV Treatment.

Here I Will Discuss Collectively the Main Presenting Symptoms of These Extra hepatic Manifestations.

The Most Common Extra hepatic Manifestations Of HCV Is Skin Involvement Patients Usually Present To Dermatologist By purpura; Reynaud's Phenomena; Cutaneous Vasculitis; Pruritis ; Psoriasis; Porphyria Cutanea Tarda; Lichen Plans Some Patients May Seek Medical Advice From Rheumatologist For Arthralgia; Arthritis; Myalgia. Or Patient May See Neurologist For Sensory Or Motor Neuropathy Or May Be Referred To Nephrologists Because Of Manifestations Of Nephrotic Syndrome ; Acute Nephritis ; Proteinuria ; Hernaturia Or High Renal Chemistry ; Occasionally Patients Present To Ophthalmologist For Corneal Ulcer; Uveitis; Or Sicca Syndrome

Prof. Dr. Mohamed Aly Marie Makhlouf



Dr Mohamed Aly Marie Makhlouf.
Professor of Internal Medicine.
Faculty of Medicine.
Ain Shams University.
Consultant Gastroenterology,
Hepatology and Endoscopy.
Member of the National Specialized
Councils,
Committees' for Higher Education,
Health and Population.
32 Falaky Street, Cairo, Egypt. 11111.
Tel: 0227949795,0233359393,
010 1259393.

makhlouf54@hotmail.com

Fatty Liver

Introduction:

Fatty liver disease is becoming one of the most common conditions affecting the liver worldwide. The incidence of viral liver disease may be declining, mostly because of improved health conditions and better infection control. On the other hand, the incidence of fatty liver is probably on the increase, especially in modernized societies.

Definition:

ALFLD: alcoholic fatty liver disease, as the name implies, is related to alcohol intake, and is more prevalent in Europe and North America.

NAFL: non alcoholic fatty liver is a benign condition in which the fat content of the liver is more than 5-10% by weight. It is more a "condition" rather than a "disease", and usually seen as a "bright liver" on ultrasound examination. It may be called type 1, or simple steatosis.

NAFLD: this is non alcoholic fatty liver disease, and is the same except there may be symptoms, like dyspepsia, or right upper quadrant abdominal pain. Also there may be slight elevation of liver transaminases (ALT & AST).

NASH: this is non alcoholic steato-hepatitis, it is a rather serious disease, and may proceed to fibrosis, cirrhosis, with all its' complications including even hepato-cellular carcinoma (HCC). Serum AST & ALT are usually raised, histologically there is macro & micro vesicular fatty changes and lobular inflammation.

Prevalence:

Males and females are equally affected, but studies have shown that females may show a more advanced form. i.e. the condition is more progressive in females.

Risk Factors for fatty liver disease:

Obesity.

Diabetes Mellitus.

Lipid abnormality: the most important is hyper triglyceridemia.

Pathogenesis:

First hit-second hit theory: it is generally said that the disease starts with a state of insulin resistance with or without other minor metabolic defects, this will lead to fat accumulation in the liver, steatosis or NAFL. This is the first hit.

Next, the accumulated fat, if increases, will cause cell injury. The progress of this injury to inflammation and necrosis is probably dependant on some genetic, environmental, and/or dietary factors. The hepato-cellular injury in the fatty liver is the second hit.

Diagnosis:

No definite blood test can diagnose fatty liver; however, a group of findings may point to the diagnosis.

Symptoms: Fatigue, weakness and malaise. RUQ abdominal pain and fullness. Dyspepsia.

Abdominal Ultrasound will show a bright, hypochoic liver.

hepatic steatosis

Routine liver function test may be normal or show elevated ALT.

The following conditions should be excluded:

*Alcohol consumption.

chronic viral hepatitis B & C: HBsAg, HBcAb, HCV Ab.

Autoimmune liver disease: AMA, ANA, Anti L-KM Ab.

*Drugs such as: Chloroquine, diltiazem., nifedipine, amiodarone and estrogens.

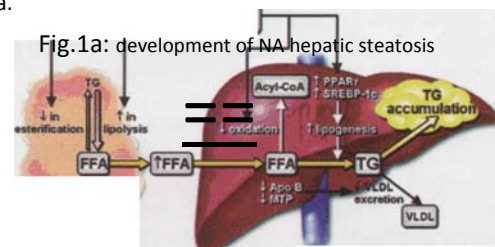
*In young non obese, non diabetic: Ceruloplasmin, S-Ferritin and alpha 1 antitrypsin.

Treatment:

In most instances, treatment of fatty liver and steato-hepatitis requires control of the underlying conditions. This may include reduction of high blood triglycerides, good control of diabetes, or not drinking alcohol. In some cases, surgical reversal of intestinal bypass for obesity is required.

Losing weight can be difficult....

However, it must be done because the alternative may be eventual cirrhosis and the need for a liver transplant.



Adipose tissue

Liver



Prof. Dr. Nouaman El Garem
Ass.prof.of Internal Medicine
Ain Shams University
ngarem2@yahoo.com

Management of Ascites

Ascites is the presence of fluid within the peritoneal cavity and is a common complication of cirrhosis of the liver.

The pathogenesis of the development of Ascites in liver disease is controversial, but is probably secondary to renal sodium and water retention. Several factors are involved.

Sodium and water retention

* Occur as a result of peripheral arterial vasodilatation and consequent reduction in the effective blood volume.

* Nitric oxide has been postulated as the putative vaso-dilatator, although other substances (e.g. atrial natriuretic peptide and prostaglandins) may be involved.

* The reduction in effective blood volume activates various neurohumoral pressure systems such as the sympathetic nervous system and renin-angiotensin system, thus promoting salt and water retention

Portal hypertension

Exerts a local hydrostatic pressure and leads to increased hepatic and splanchnic production of lymph and transudation of fluid into the peritoneal cavity

Low serum albumin

(a consequence of poor synthetic liver function) may further contribute by a reduction in plasma oncotic pressure

Management

In patients with ascites, urine sodium excretion rarely exceeds 5 mmol in 24 hours. Loss of sodium from extra renal sites accounts for approximately 30 mmol in 24 hours.

The normal daily dietary sodium intake may vary between 120 and 200 mmol, resulting in a positive sodium balance of approximately 90 -170 mmol in 24 hours (equivalent to 600-1300 ml of fluid retained).

The aim is to both reduce sodium intake and increase renal excretion of sodium -and by doing so produce a net reabsorption of fluid from the ascites back into the circulating volume.

The maximum rate at which ascites can be mobilized is 40 ml/hour

Management:

- Check serum electrolytes and creatinine at the start and every other day
- Weigh patient and measure urinary output daily.
- Bed rest alone will lead to a diuresis in a small proportion of people by improving renal perfusion, but in practice is not helpful.
- By dietary sodium restriction it is possible to reduce sodium intake to 40 mmol in 24 hours and still maintain an adequate protein and calorie intake with a palatable diet.
- Fluid restriction is probably not necessary unless the serum sodium is under 128 mmol /L
- The diuretic of first choice is the aldosterone antagonist spironolactone, starting at

• Chronic administration produces gynaecomastia; amiloride, 5-15 mg daily, is then substituted.

* The aim of diuretic therapy should be to produce a net loss of fluid approaching 700 ml in 24 hours (0.7 kg weight loss or 1.0 kg if peripheral edema is present).

* Although 60% of patients respond with this regimen, diuresis is often poor and the spironolactone can be increased gradually to 500 mg daily providing there is no hyperkalaemia

* A loop diuretic, such as furosemide (furosemide) 20-40 mg or bumetanide

1 mg daily may be added if response is poor. These loop diuretics have several potential disadvantages, including hyponatraemia, hypokalaemia and volume depletion

* Ascetic fluid is mobilized more slowly than interstitial fluid and diuretics should be given with great care in those without peripheral edema.

* Diuretics should be temporarily discontinued if arise in serum creatinine level occurs, representing overdiuresis and hypovolaemia.

* Hyponatraemia occurring during therapy almost always represents haemo-dilution secondary to a failure to clear free water (usually a marker of reduced renal perfusion) and should be treated by stopping the diuretics the sodium level falls below approximately 128 mmol/L as well as introducing water restriction.

* Hyponatraemia occurring during therapy almost always represents haemo-dilution secondary to a failure to clear free water (usually a marker of reduced renal perfusion) and should be treated by stopping the diuretics the sodium level falls below approximately 128 mmol/L as well as introducing water restriction.

* Diuretics should also be stopped if there is hyperkalaemia or development of precoma paracetsis

* This used to relieve symptomatic tense ascites

* It is also used as a means of rapid therapy in patients with ascites and peripheral edema, thus avoiding prolonged hospital stay

* The main danger of this approach is the production of hypovolaemia as the ascites re-accumulates at the expense of the circulating volume,

* In patients with normal renal function and in the absence of hyponatraemia, this has largely been overcome by the administration of albumin (8g per liter of ascetic fluid removed) or plasma expanders.

* In practice, up to 20 L can be removed over 4-6 hours. This procedure has more complications in end-stage cirrhosis if the patient has renal failure