“STUDY ON INFECTIONS PRECIPITATING HEPATIC ENCEPHALOPATHY IN DECOMPENSATED CHRONIC LIVER DISEASE”

Dissertation submitted by

DR.ANIL KUMAR ADLA

In partial fulfillment of the requirements for the degree of

DOCTOR OF MEDICINE

IN

GENERAL MEDICINE

THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY

APRIL 2017

DEPARTMENT OF GENERAL MEDICINE

PSG INSTITUTE OF MEDICAL SCIENCES & RESEARCH

COIMBATORE

DECLARATION BY THE CANDIDATE

"STUDY ON INFECTIONS PRECIPITATING HEPATIC ENCHEPHALOPATHY IN DECOMPENSATED CHRONIC LIVER DISEASE" is a bonafide and genuine Research work carried out by me under the guidance of **DR. K. JAYACHANDRAN** Professor and Head of the Department of general medicine, PSG institute of Medical Sciences &

Research. Coimbatore in partial for the award of M.D. in General medicine to be held in 2017. This dissertation has not been submitted in part of full to any other University or towards any other degree before this below mentioned date.

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Phone : 91 422 - 2598822, 2570170, Fax : 91 422 - 2594400, Email : ihec@psgimsr.ac.in

To
Dr Anil Kumar Adla
Postgraduate
Department of General Medicine
PSG IMS & R
Coimbatore

Ref: Project No. 14/419

Date: April 6, 2015

Dear Dr Anil Kumar Adla,

Institutional Human Ethics Committee, PSG IMS&R reviewed and discussed your application dated 06.12.2014 to conduct the research study "*Infections precipitating hepatic encephalopathy in decompensated chronic liver disease*" during the IHEC meeting held on 12.12.2014.

The following documents were reviewed and approved:

1. Project Submission form
2. Study protocol
3. Informed consent forms
4. Proforma
5. Permission letter from concerned Head of the Department
6. Current CVs of Principal investigator, Co-investigator
7. Budget

The following members of the Institutional Human Ethics Committee (IHEC) were present at the meeting held on 12.12.2014 at IHEC Secretariat, PSG IMS & R between 10.00 am and 11.00 am:

Sl. No.	Name of the Member of IHEC	Qualification	Area of Expertise	Gender	Affiliation to the Institution Yes/No	Present at the meeting Yes/No
1	Dr. P. Sathyan (Chairperson, IHEC)	DO, DNB	Clinician (Ophthalmology)	Male	No	Yes
2	Dr. S. Bhuvaneshwari (Member-Secretary, IHEC)	MD	Clinical Pharmacology	Female	Yes	Yes
3	Dr. S.Shanthakumari	MD	Pathology, Ethicist	Female	Yes	Yes
4	Dr. D. Vijaya	M Sc, Ph D	Basic Medical Sciences (Biochemistry)	Female	Yes	Yes

The study is approved in its presented form. The decision was arrived at through consensus. Neither PI nor any of proposed study team members were present during the decision making of the IHEC. The IHEC functions in accordance with the ICH-GCP/ICMR/Schedule Y guidelines. The approval is valid until one year from the date of sanction. You may make a written request for renewal / extension of the validity, along with the submission of status report as decided by the IHEC.

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Following points must be noted:

1. IHEC should be informed of the date of initiation of the study
2. Status report of the study should be submitted to the IHEC every 12 months
3. PI and other investigators should co-operate fully with IHEC, who will monitor the trial from time to time
4. At the time of PI's retirement/intention to leave the institute, study responsibility should be transferred to a colleague after obtaining clearance from HOD, Status report, including accounts details should be submitted to IHEC and extramural sponsors
5. In case of any new information or any SAE, which could affect any study, must be informed to IHEC and sponsors. The PI should report SAEs occurred for IHEC approved studies within 7 days of the occurrence of the SAE. If the SAE is 'Death', the IHEC Secretariat will receive the SAE reporting form within 24 hours of the occurrence
6. In the event of any protocol amendments, IHEC must be informed and the amendments should be highlighted in clear terms as follows:
   a. The exact alteration/amendment should be specified and indicated where the amendment occurred in the original project. (Page no. Clause no. etc.)
   b. Alteration in the budgetary status should be clearly indicated and the revised budget form should be submitted
   c. If the amendments require a change in the consent form, the copy of revised Consent Form should be submitted to Ethics Committee for approval
   d. If the amendment demands a re-look at the toxicity or side effects to patients, the same should be documented
   e. If there are any amendments in the trial design, these must be incorporated in the protocol, and other study documents. These revised documents should be submitted for approval of the IHEC and only then can they be implemented
   f. Any deviation-Violation/waiver in the protocol must be informed to the IHEC within the stipulated period for review
7. Final report along with summary of findings and presentations/publications if any on closure of the study should be submitted to IHEC

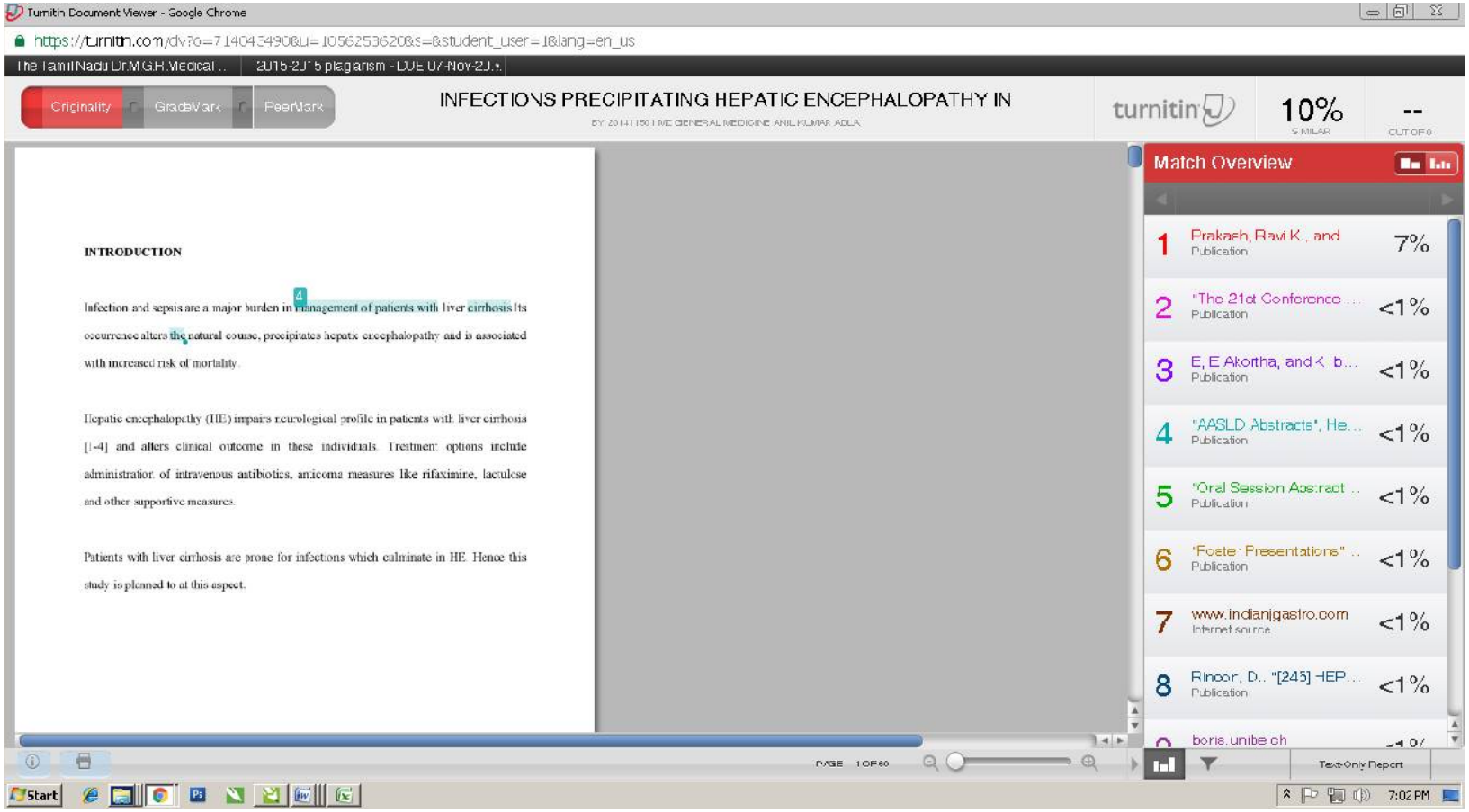
Kindly note this approval is subject to ratification in the forthcoming full board review meeting of the IHEC.

Thanking You,

Yours Sincerely,

SECRETARY
PSG IMS&R
COIMBATORE-641004
INSTITUTIONAL HUMAN ETHICS COMMITTEE

Dr S Bhuvaneshwari
Member-Secretary
Institutional Human Ethics Committee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INTRODUCTION
Infection and sepsis are a major burden in management of patients with liver cirrhosis Its occurrence alters the natural course, precipitates hepatic encephalopathy and is associated with increased risk of mortality.
Hepatic encephalopathy (HE) impairs neurological profile in patients with liver cirrhosis [1-4] and alters clinical outcome in these individuals. Treatment options include administration of intravenous antibiotics, anticoma measures like rifaximine, lactulose and other supportive measures.
Patients with liver cirrhosis are prone for infections which culminate in HE. Hence this study is planned to at this aspect.
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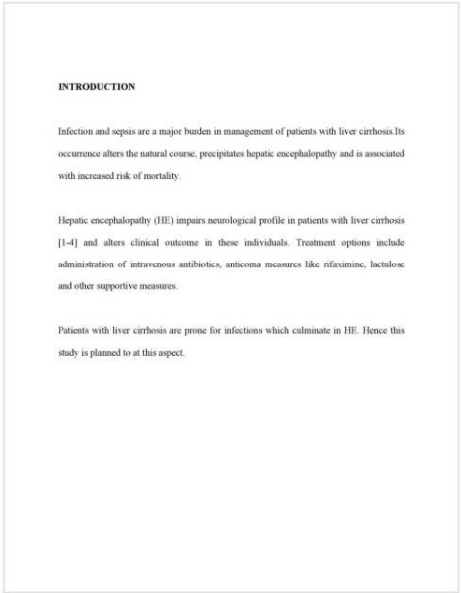

INTRODUCTION

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I hereby declare that PSG Institute of Medical Sciences and Research, Coimbatore, shall have the rights to preserve, use and disseminate this dissertation in print or electronic format for academic/research purpose.

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Signature of Candidate

DR.ANIL KUMAR ADLA

ACKNOWLEDGEMENT

I would like to thank the Head of the Department and my guide for this thesis **DR.K.JAYACHANDRAN** Professor and Head of department, Department of general medicine for his valuable guidance and support throughout the study.

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Most of all I would like to thank the patients who cooperated with me and without whom this study would not have taken place

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AIMS AND OBJECTIVES

- To assess spectrum of infections precipitating hepatic encephalopathy in patients with decompensated chronic liver cirrhosis.

MATERIAL AND METHODS

Source of data:

Patients with cirrhosis admitted to PSG Hospital during the study period fulfilling the inclusion and exclusion criteria.

Ethics Committee Permission:

The study was initiated after obtaining permission from the institutional ethics committee, PSG Institute of Medical Sciences and Research, Coimbatore.

Study center

The study was done in the Department of Internal Medicine and Department of Gastroenterology, PSG IMSR, COIMBATORE.

Type of Study: It is a observational type of study.

Inclusion Criteria:

Patients of with diagnosis of liver cirrhosis and hepatic encephalopathy admitted in PSG hospitals were included.

Exclusion Criteria:

Patients with history of Gastrointestinal bleed, Hepatocellular carcinoma were excluded.

Study Period: The study included prospectively recruited patients since February 2015 to August 2016.

Method of collection of data:

Data was collected through a pretested proforma which included various patients details like age, sex, detailed past history, personal history, treatment history, clinical examination, diagnosis, and

laboratory investigations (Liver function tests, Complete blood counts, prothrombin time, renal functions, serology for hepatotropic viruses, ultrasound abdomen and serum ammonia).

Sepsis screening:

Blood for total counts and pan cultures were done in all cases prior initiation of antibiotics. Pan cultures included blood, urine and ascitic fluid cultures. Ascetic fluid was sent for culture in blood culture bottles during the admission. In few selected individuals serum procalcitonin levels were measured.

Measuring serum ammonia levels:

Stasis free venous blood was collected sodium heparin containing vacutainer and immediately transported in ice bath within 20 minutes of sampling. During sampling clenching of fist or application of tourniquet were avoided. This is done to avoid ammonia levels due to release from skeletal muscle.

Testing for hepatic encephalopathy:

Modified West Haven criteria were used for grading hepatic encephalopathy (HE) in all patients. Clinical findings and data on grades of hepatic encephalopathy were entered into proforma which was used for later analysis.

West Haven Criteria for Altered Mental Status

Grade	Symptoms
0 (minimal)	• No detectable changes in behavior or personality
1	• Euphoria or anxiety • Impaired performance of addition or subtraction • Shortened attention span • Trivial lack of awareness
2	• Minimal disorientation to time or place • Inappropriate behavior • Impaired performance of subtraction • Lethargy or apathy • Subtle personality change
3	• Confusion • Gross disorientation • Somnolence to semistupor (may respond to verbal stimuli)
4	• Coma (no response to verbal or noxious stimuli)

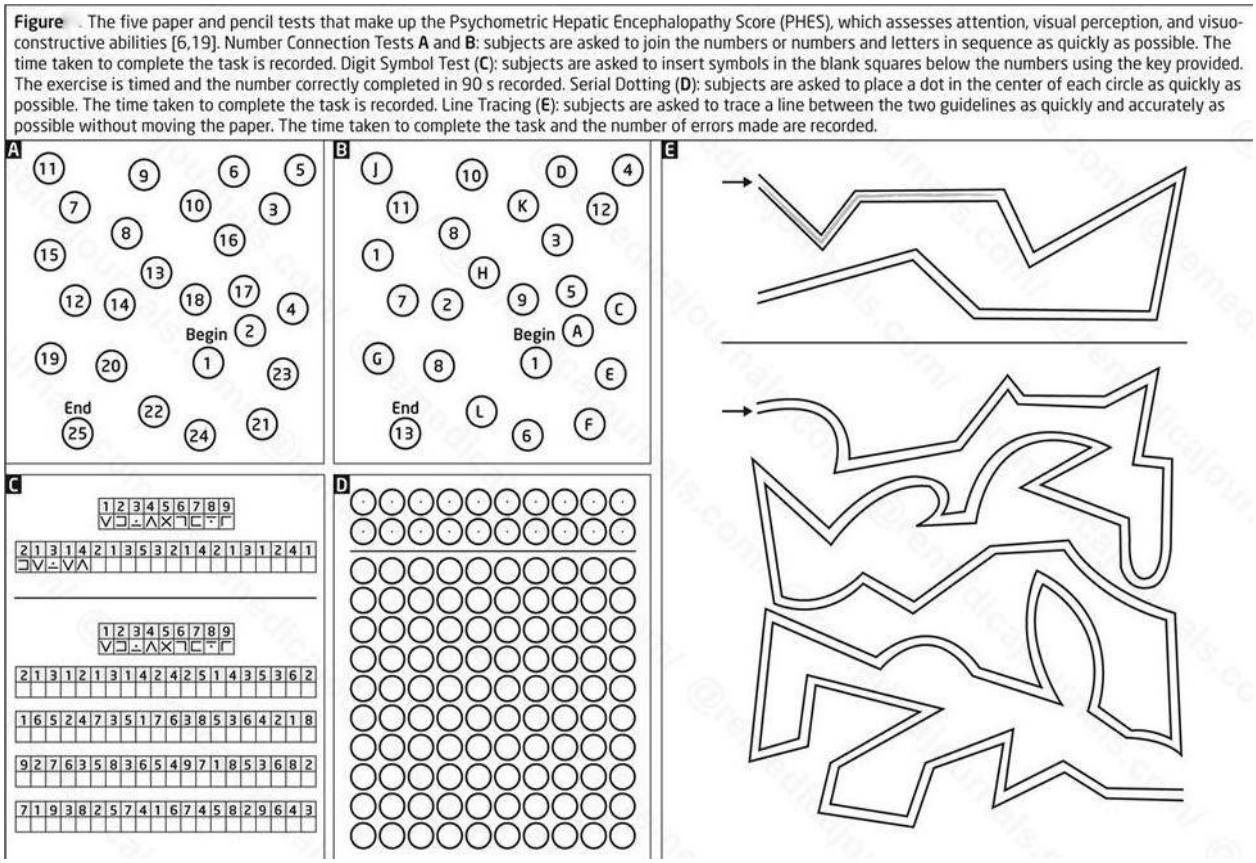


Figure . The five paper and pencil tests that make up the Psychometric Hepatic Encephalopathy Score (PHES), which assesses attention, visual perception, and visuo-constructive abilities [6,19]. Number Connection Tests **A** and **B**: subjects are asked to join the numbers or numbers and letters in sequence as quickly as possible. The time taken to complete the task is recorded. Digit Symbol Test (**C**): subjects are asked to insert symbols in the blank squares below the numbers using the key provided. The exercise is timed and the number correctly completed in 90 s recorded. Serial Dotting (**D**): subjects are asked to place a dot in the center of each circle as quickly as possible. The time taken to complete the task is recorded. Line Tracing (**E**): subjects are asked to trace a line between the two guidelines as quickly and accurately as possible without moving the paper. The time taken to complete the task and the number of errors made are recorded.

Special tests were used for diagnosing minimal hepatic encephalopathy (MHE).

These are shown in image above.

[6]

STATISTICAL METHODS

1. **Clinical data of patients collected**

2. **Several variables have been collected and entered in the Microsoft excel sheet.**

3. **All analyses were done with SPS software**

4. **Value of p< 0.05 is considered as statistically significant.**

5. **Statistical analysis have been done for all variables and they were analyzed accordingly.**

6. **The data are reported as mean +/- SD or the median, depending on their distribution**

REVIEW OF LITERATURE

Hepatic encephalopathy (HE) is a umbrella term which includes range of neurologic and neuropsychiatric impairments in patients with significant liver disease [1–4].

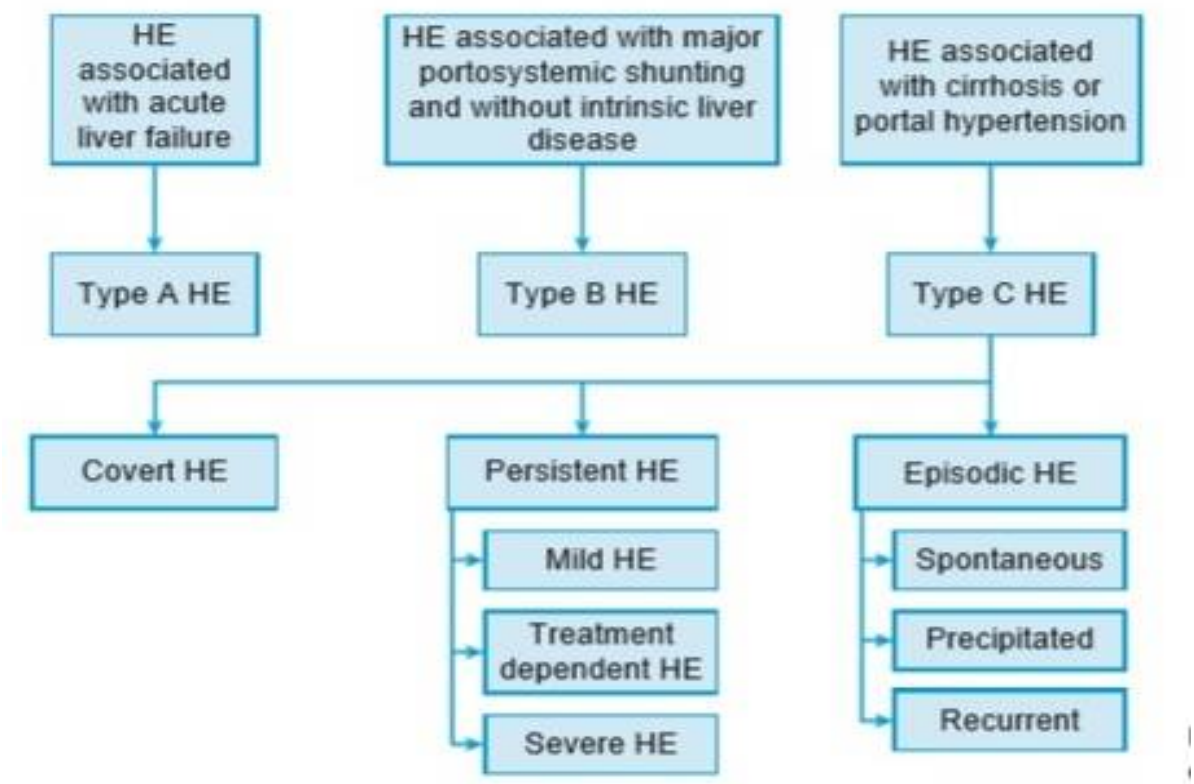
This was initially observed by Gabuzda and colleagues, who came across similar syndromes while treating patients with ascites. This was a landmark study which illustrated role of ammonia in causing HE. The study also used resins for its treatment. [5,6].

Types of hepatic-encephalopathy:

HE can be classified as 3 types as described below.

- 1st type is Type-A that was related to that of ALF.
- 2nd type is Type B that was related to that of porto-systemic shunts san any kind of the liver disease which is intrinsic.
- 3rd type is the Type C that was related to that of CLF or that of the cirrhosis.

Out of this 3 types, 3rd type that is Type C was the frequently occurring and it has been divided as persistent encephalopathy, and episodic encephalopathy, and also the minimal HE. [8]

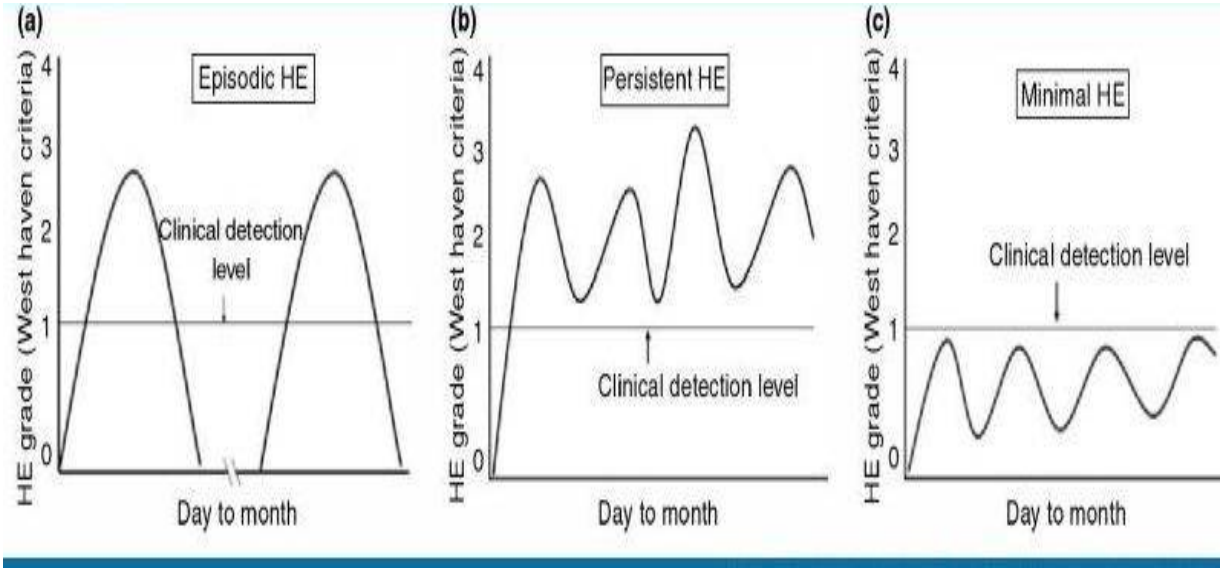


Subtypes of Type C Hepatic encephalopathy:

- Periodic VARIATIONS of mental condition of patients varying with that of severity-extent as well as time taken for the episode characterizes Episodic HE. Such sort of episodic events may be because of the underlying precipitating factors which are the causatives of hypoxic ischemic encephalopathy. or it can also occur even when the obvious precipitating factors are absent, this condition is known as spontaneous-hepatic-encephalopathy.

- Recurrent Hepatic-encephalopathy: In this condition HE occurs two times or greater than 2 times in a period of one year.

- Persistent Hepatic-encephalopathy was defined as the occurrence of the impairment of cognition baseline that lasts for greater than two weeks that is owing to the hepatic dysfunction which causes negative impression on that of social function as well as the function of occupation.



Other Types of Hepatic Encephalopathy:

- Minimal hepatic encephalopathy (MHE) has a definition that hepatic encephalopathy that occurs in the patients who had hepatic disease with completely competent mental condition and that of CNS examination however these individuals will have defects of cognition in an abled neuro-psychometric assessment scales [2].

- Overt-HEPATIC-ENCEPHALOPATHY is defined as a condition of the clinical scenario of the Hepatic encephalopathy, that too in several ranges of neurological as well as mental variations as seen in the patients with that of hepatic disease. did

Classifying of hepatic encephalopathy & semi quantification of the Extent-of-severity of overt Hepatic Encephalopathy.

It was done with the use of West Haven criteria [10].

Hepatic encephalopathy holds 5 levels which were ranged from level zero to level IV. This is shown in next table.

Table 2. WHC and clinical description.

WHC including MHE	ISHEN	Description	Suggested operative criteria	Comment
Unimpaired		No encephalopathy at all, no history of HE	Tested and proved to be normal	
Minimal	**Covert**	Psychometric or neuropsychological alterations of tests exploring psychomotor speed/executive functions or neurophysiological alterations without clinical evidence of mental change.	Abnormal results of established psychometric or neuropsychological tests without clinical manifestations	No universal criteria for diagnosis. Local standards and expertise required
Grade I		• Trivial lack of awareness • Euphoria or anxiety • Shortened attention span • Impairment of addition or subtraction • Altered sleep rhythm	Despite oriented in time and space (see below), the patient appears to have some cognitive/behavioural decay with respect to his/her standard on clinical examination, or to the caregivers	Clinical findings usually not reproducible
Grade II	**Overt**	• Lethargy or apathy • Disorientation for time • Obvious personality change • Inappropriate behavior • Dyspraxia • Asterixis	Disoriented for time (at least three of the followings are wrong: day of the month, day of the week, month, season or year) ± the other mentioned symptoms	Clinical findings variable but reproducible to some extent
Grade III		• Somnolence to semi-stupor • Responsive to stimuli • Confused • Gross disorientation • Bizarre behavior	Disoriented also for space (at least three of the following wrongly reported: country, state [or region], city or place) ± the other mentioned symptoms	Clinical findings reproducible to some extent
Grade IV		Coma	Does not respond even to pain stimuli	Comatose state usually reproducible

All conditions are required to be related to liver insufficiency and/or PSS.

Pathogenesis of Hepatic encephalopathy:

Exact molecular basis responsible for the HE is still unknown. Possible mechanisms include primary gut-derived toxins. In addition along with NH_3, Various numbers of the putative toxins is being considered as that of evidential mediation involved in hepatic encephalopathy [12].

Another interesting issue in the Hepatic-Encephalopathy is that of absence of this particular clinical scenario in the individuals with that of Porto-systemic shunting of the blood nevertheless in the patients who has no hepatic disease. However there are exceptions for that of rule where overt-HE was very less commonly evidenced [13].

Implication of clearance of intestinal toxins in the prevention of HE can be proven by the fact that Overt HE occurs in patients with normal liver architecture but with lack of portal perfusion and further manipulation of splanchnic venous circulation, like splenorenal shunts. However, lack of portal perfusion alone is not significant to cause HE as the hepatic arterial flow increases and compensates for the portal deficit.

Ammonia-NH_3;

It has been evidenced that lot of data is available which shows that NH_3 As a important mediator in the process of hepatic encephalopathy. During the period when many other theories were developed, few if any studies showed a correlation between the ammonia blood level and this verity of HE. As mentioned previously, this particular problem was presumably due to ammonia assay problems prevalent at that time. In the current quoted literatureat least three studies show good

Ammonia has direct neurotoxic effects in very high levels more so in patients with urea cycle defects [14]. Seizures and florid cerebral edema are common in

acute liver failure with urea levels (over 200mol/L) [15]. In chronic liver disease cerebral edema is subtle with no seizure history.

Other postulated mechanisms for HE in patients with chronic liver disease include:

- **GABA/benzodiazepines**
- **Endogenous opiates**
- **Plasma amino acid imbalance/falseneurotransmitter**

Figure : eliciting possible mechanism's for hepatic encephalopathy

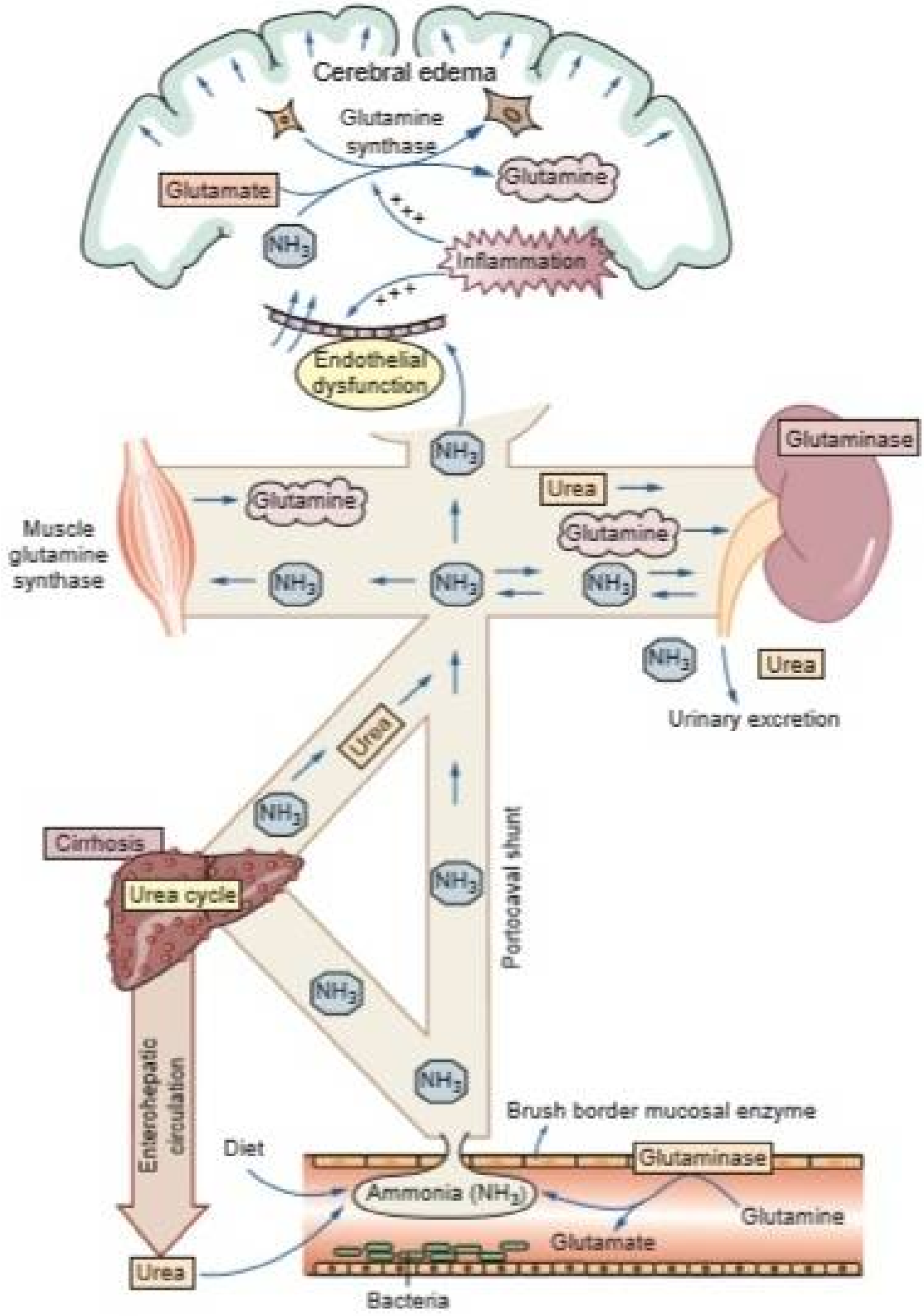
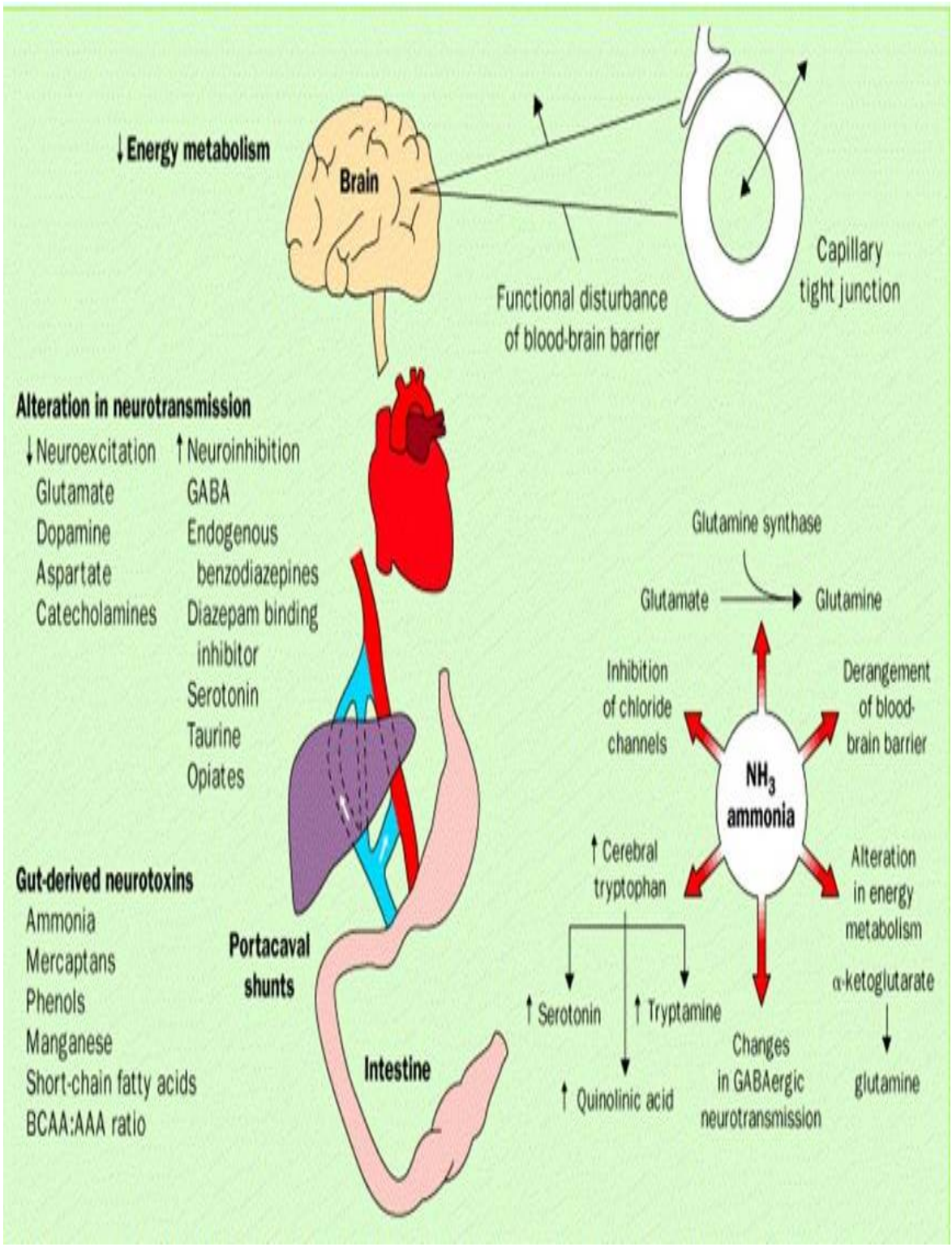


Figure : eliciting possible mechanism's for hepatic encephalopathy

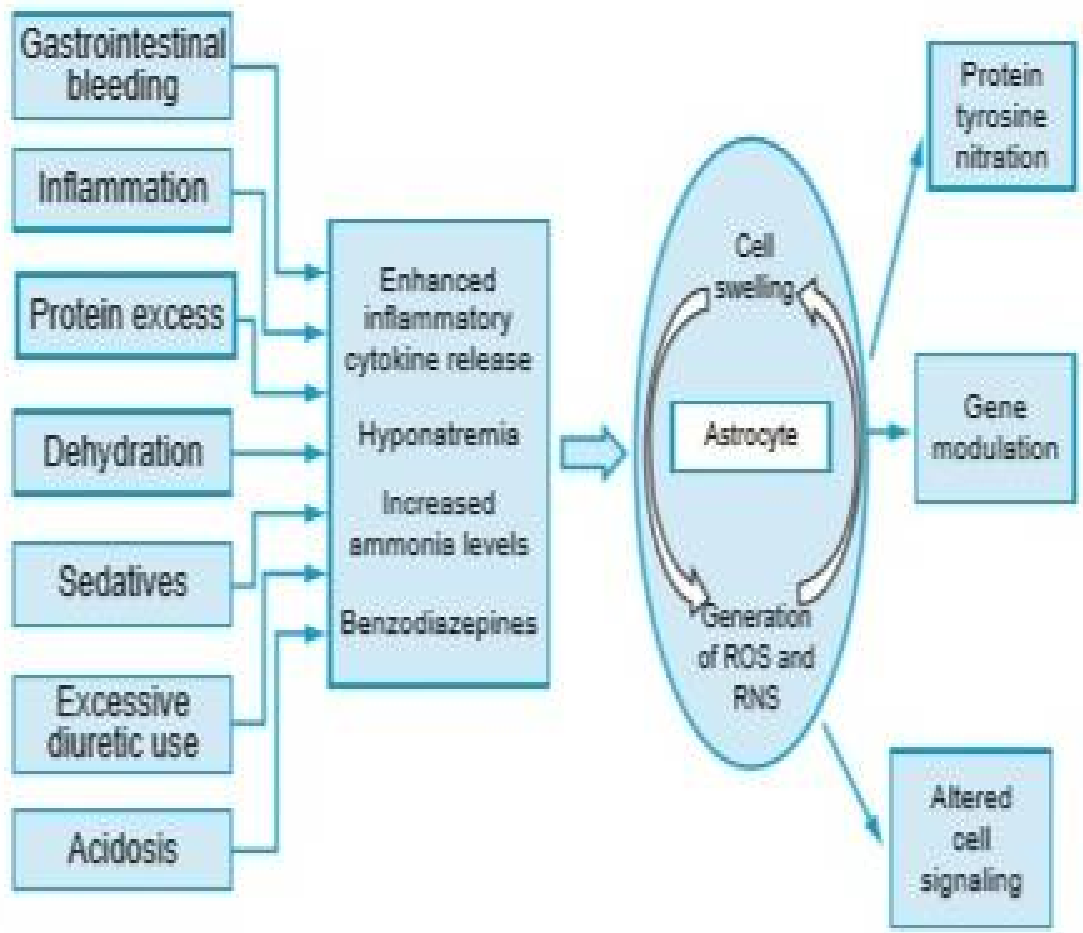


Precipitating factors for hepatic encephalopathy:

Hepatic encephalopathy is of 2 types: spontaneous and precipitated.

The main precipitating factors in the development of HE in those individuals of CLD include:

- Sepsis
- Electrolyte imbalance
- Gastrointestinal bleed
- Renal failure
- Excessive diuretic use


Gastrointestinal bleeding
Inflammation
Protein excess
Dehydration
Sedatives
Excessive diuretic use
Acidosis
Enhanced inflammatory cytokine release
Hyponatremia
Increased ammonia levels
Benzodiazepines
Cell swelling
Astrocyte
Generation of ROS and RNS
Protein tyrosine nitration
Gene modulation
Altered cell signaling

Precipitating factors for OHE by decreasing frequency.

Episodic	Recurrent
Infections*	Electrolyte disorder
GI bleeding	Infections
Diuretic overdose	Unidentified
Electrolyte disorder	Constipation
Constipation	Diuretic overdose
Unidentified	GI bleeding

Modified from Strauss E, da Costa MF The importance of bacterial infections as precipitating factors of chronic hepatic encephalopathy in cirrhosis. Hepato-gastroenterology 1998;45:900–904.

*More recent unpublished case series confirm the dominant role of infections.

Role of systemic sepsis:

Infections in cirrhotic patients have often been known to precipitate bouts of overt HE. Encephalopathy develops in severe infections in patients having no underlying liver disease, which gives reasons to think that this syndrome could be mediated by other mechanisms [20]. Covert HE is seen to first appear after the elevation of acute inflammatory markers in blood.

The best illustration of the role of inflammatory markers in covert HE was that of precipitation of hyperammonemic condition with the help of per-oral glutamine challenge [21]. Fast degradation of the glutamine with the help of intestine glutaminases activity causes two to three fold increase in blood ammonia. An oral glutamine challenge assay with the help of specific tests of psychometry leads to the revelation of an important phenomenon. This test in general do not change psychometry- performance in many number of patients until systemic markers of inflammation were elevated. The reason behind it has to be determined [22], the most probable being the attachment of inflammatory cells/cytokines to that of endothelial cells of cerebrum so that normal exclusion effect can be enabled [22,23,24]. Early identification and treatment of infections is hence crucial in the management of HE regardless.

Bacterial infections represents one of most common and important reason for that of hepatic failure as well occurrence of hepatic complications and death in these patients owing to cirrhotic process.

And hepatic encephalopathy was one of the most important cause of repeated hospitalizations, increased costs of healthcare in cirrhosis and impaired health-related quality of cirrhosis patient.

Bacterial infections makes a series of altered function events of immune which develops Subsequently during the development of cirrhotic event .

In majority of cases, infections in general were resulted from the gram –ve bacteria originated from the intestines, and also gram +ve bacterial causes are the

most commonly encountered causes of the infection most commonly in the patients who were hospitalized.

Negative impact by infections in cirrhosis patients were attained by various indices of prophylaxis which includes antibiotic usage, early detection in high-risk group and management of infections once it developed.

The method of prevention of infections with the help of diagnostic tools related to the processes involved in changed gut microbes as well translated bacterial mechanism and altered function of immunity by investigation on the mechanisms of altered gut microflora, translocation of bacteria, and immune dysfunction which will lead to development of most effective prevention as well as safer method to compare which are currently available. Investigation which are specific for initial clinical scenario of infection helps in appropriate diagnostic as well as for management of infection. [74]

Severity and incidence of infections higher in cirrhosis patients compared to that of patients without cirrhosis. [75]

Mortality rate is higher in infection with multiresistant organisms in

Cirrhosis then in non-cirrhosis patients. [75]

Incidence of end organ damage is more in the cirrhosis patients then in Non-cirrhosis patients. [75]

Delay in diagnosis and starting treatment results in higher mortality in Patients with unstable hemodynamical status. [75]

Patients with SBP, addition of supplementary albumin to antibiotic treatment reduces mortality. [75]

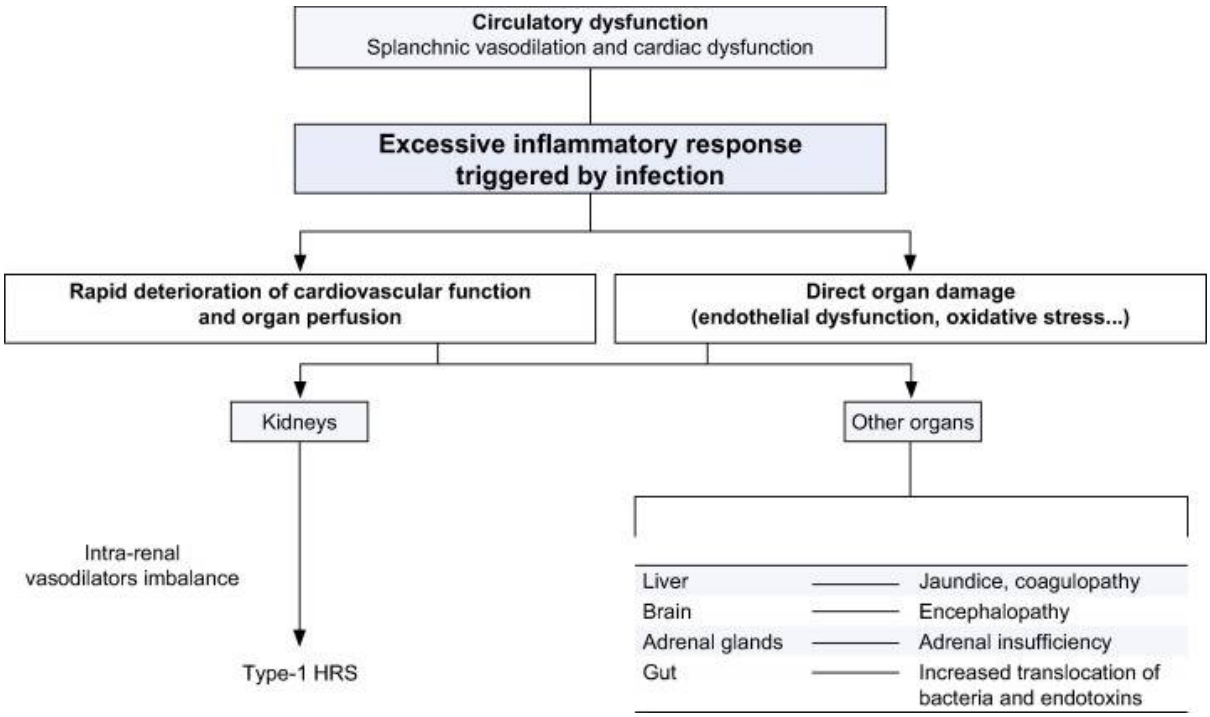
SBP and UTI are more commonly occurs past skin infections, pneumonia , soft -tissue pathologies in cirrhosis patients. [75]

Various factors related to increase in chances of infections were varied liver malfunction, reduced ascetic proteins concentration, variceal bleeding, previous spontaneous bacterial peritonitis as well as hospital stay/admission. [75]

CONSEQUENCES OF BACTERIAL INFECTION:

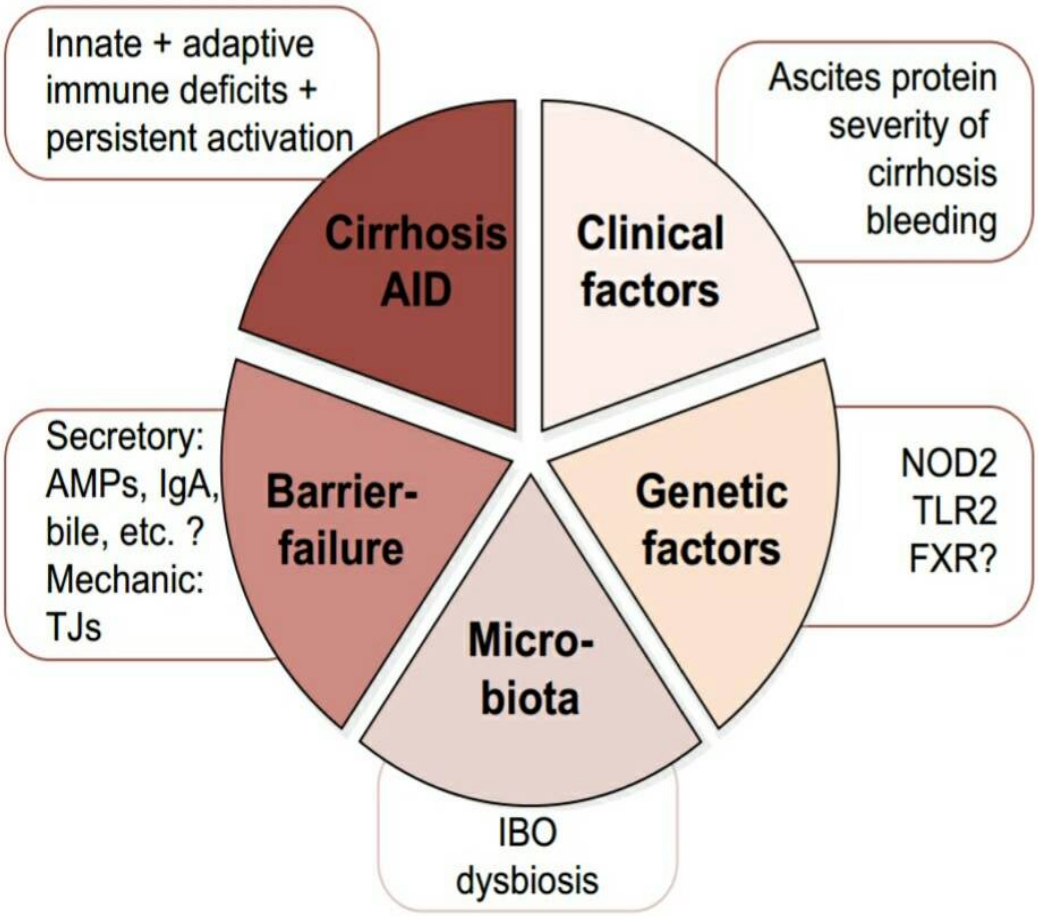
Septicemia caused by the bacteria were the causes of decompensation of liver cirrhotic process in an acute phase. [76]

Acute bacterial infection will show cirrhosis which can be compensated and related to new-onset hepatic as well as other organs failure.



ABOVE FLOW CHART SHOWING PATHOPHYSIOLOGICAL BASIS INVOLVED IN OF ACUTE ON CLF AND END ORGAN DYSFUNTION OF CIRRHOSIS CAUSED VIA INFECTION.

PATHOGENESIS OF BACTERIAL INFECTIONS IN CIRRHOSIS:



occurrence of bacterial infections in cirrhotic individuals owing to various causes which consists altered functions of liver, portal vein-systemic-shunt, more severe translocated bacteria, cirrhotic process related altered function of immunity as well as genetics.

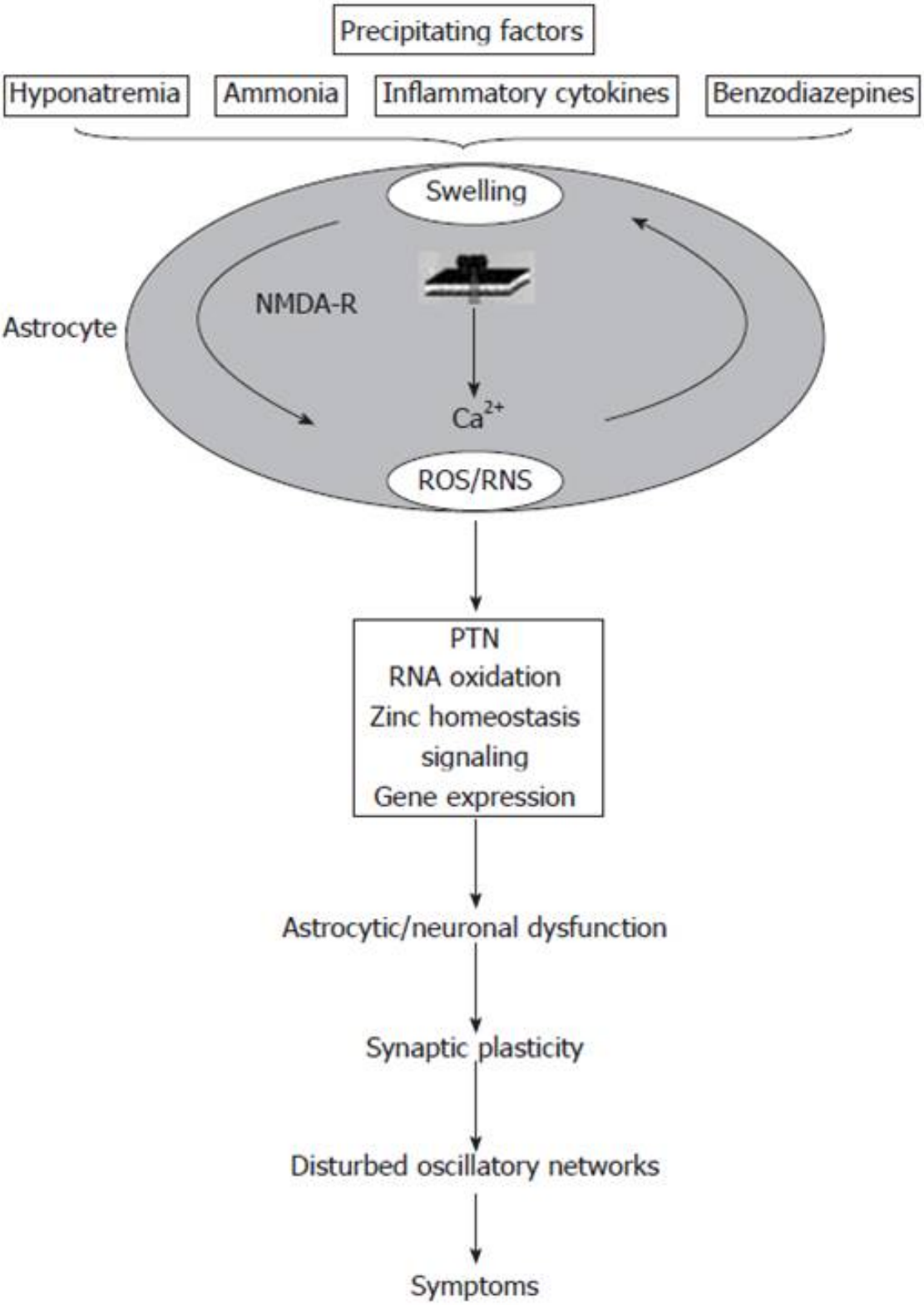
Gut microbiota

Intestinal barrier dysfunction

Immune dysfunction

Genetic predisposition to the bacterial infections

Mechanisms of Hepatic encephalopathy:



Diagnosis of hepatic encephalopathy:

Variation in patient mental condition / before to performing of psychometric test of the individuals of suspected / known cirrhotic patients to be regarded due to HE that is until proven nevertheless. Individuals suffering from cirrhosis which cannot be compensated were more inclined to develop overt Hepatic encephalopathy. HIGHER STAGE liver diseases associated with other events which could make variations of mental condition, which has to-be identified as well as to be treated. Practically, HE as well as other causes along with the encephalopathy which have been treated concomitantly in most of the chronic liver disease patients. Hypothyroidism has often also been encountered with HE [27].

Underlying cirrhosis or portosystemic shunts without cirrhosis, very rarely, which is primary to the diagnosis or rather suspicion for HE. When encountered with overt HE with a well-preserved function of liver seek for greater collaterals of portosystemic circulation, which is a major focus of septic and occult intake of drug activity on central nervous system active.

In patients with Diabetes have been proposed that they were related with overt hepatic encephalopathy reported to be associated with overt HE even while it is being comparatively was being preserved. This was linked to motility-movement disorders in diabetic individuals related to bacterial overgrowth in small-intestine [28,29]. The clinical signs of asterixis, loss of motor activity and confusion are

found with biochemical evidence, with this neurological deterioration is attributable to HE.

Asterixis

Tremor of the wrist when it is kept in dorsiflexion is called as Asterixis, it resembles like a bird flapping its wings. The term “Asterixis” word came from Greek *a* (not) and the *sterixis* (fixed-position). Which denotes failure to maintain actively position or posture and in 1949 it was 1st said by Adams and Foley [1]. This is elicited classically by dorsiflexion of hand when fingers and forearm are extended and series of involuntary and rapid movements, extension-flexion type of wrist movements, this is also known as “hepatic flap” [4]. This can elicited with protrusion tongue, foot dorsiflexion, clenching of fist, and forced closure of eyes. This is due to supra-spinal motor centers and abnormal function in its pathophysiology. This can be seen classically in grade 2 hepatic encephalopathy in West-Haven-scale. However, this type of encephalopathy symptoms also seen in some other system failures and imbalance in electrolytes.

Other neurologic findings

Hyperreflexia, hypertonia, transient decerebrate posturing and extensor plantar reflexia may occur. This signs are classified into three categories: coordination and motor abnormalities, dementia, and progressive signs of cerebral-dysfunction, and signs which are also occur in metabolic-encephalopathy. The most common abnormality in these patients is the disruption of smooth-pursuit eye movement (S P E M) [30]. When patient had this sign in one episode of hepatic encephalopathy

while stay in all its remission [31]. Signs like asterixis, hyperreflexia, nystagmus, ataxic to finger-nose, ataxic to heel-shin, and dysdiadakokinesia.

Table 4. Differential diagnosis of HE.

Overt HE or acute confusional state	
Diabetic	(hypoglycemia, ketoacidosis, hyperosmolar, lactate acidosis)
Alcohol	(intoxication, withdrawal, Wernicke)
Drugs	(benzodiazepines, neuroleptics, opioids)
Neuroinfections	
Electrolyte disorders	(hyponatremia and hypercalcemia)
Nonconvulsive epilepsy	
Psychiatric disorders	
Intracranial bleeding and stroke	
Severe medical stress	(organ failure and inflammation)
Other presentations	
Dementia	(primary and secondary)
Brain lesions	(traumatic, neoplasms, normal pressure hydrocephalus)
Obstructive sleep apnea	

Hyponatremia and sepsis can both produce encephalopathy per *se* and precipitate HE by interactions with the pathophysiological mechanisms. In end-stage liver disease, uremic encephalopathy and HE may overlap.

Scales to assessment of overt-HE in Clinicals:

These include the following:

- **West Haven criteria**
- **HESA (hepatic encephalopathy scoring algorithm)**
- **CHESS (clinical hepatic encephalopathystaging scale)**

Table 2. WHC and clinical description.

WHC including MHE	ISHEN	Description	Suggested operative criteria	Comment
Unimpaired		No encephalopathy at all, no history of HE	Tested and proved to be normal	
Minimal	**Covert**	Psychometric or neuropsychological alterations of tests exploring psychomotor speed/executive functions or neurophysiological alterations without clinical evidence of mental change.	Abnormal results of established psychometric or neuropsychological tests without clinical manifestations	No universal criteria for diagnosis. Local standards and expertise required
Grade I		• Trivial lack of awareness • Euphoria or anxiety • Shortened attention span • Impairment of addition or subtraction • Altered sleep rhythm	Despite oriented in time and space (see below), the patient appears to have some cognitive/behavioural decay with respect to his/her standard on clinical examination, or to the caregivers	Clinical findings usually not reproducible
Grade II	**Overt**	• Lethargy or apathy • Disorientation for time • Obvious personality change • Inappropriate behavior • Dyspraxia • Asterixis	Disoriented for time (at least three of the followings are wrong: day of the month, day of the week, month, season or year) ± the other mentioned symptoms	Clinical findings variable but reproducible to some extent
Grade III		• Somnolence to semi-stupor • Responsive to stimuli • Confused • Gross disorientation • Bizarre behavior	Disoriented also for space (at least three of the following wrongly reported: country, state [or region], city or place) ± the other mentioned symptoms	Clinical findings reproducible to some extent
Grade IV		Coma	Does not respond even to pain stimuli	Comatose state usually reproducible

All conditions are required to be related to liver insufficiency and/or PSS.

Laboratory diagnosis

Laboratory investigations which gives an limited value for diagnosing HE, specially for a hepatic cirrhosis patient with previous episodes of overt HE who are presenting to hospital in altered mental-status. These investigations will helps ruling out the causes of hepatic-encephalopathy, other precipitating causes of HE.

Box 18.5 Laboratory testing for hepatic encephalopathy (HE).

Evidence for chronic liver disease

- Increased prothrombin time/INR
- Decreased serum albumin
- Pancytopenia/leucopenia/thrombocytopenia
- Hypergammaglobulinemia
- Hepatitis serology
- Autoimmune serology

Metabolic encephalopathies

- Hypoxia/hypercapnia:
  - Arterial blood gas
  - Clinical chemistry
  - Pulmonary evaluation
- Hypoglycemia:
  - Clinical chemistry
- Renal failure/azotemia:
  - Blood chemistry
  - Urine analysis
  - Renal imaging
- Hyponatremia
  - Blood chemistry
  - Urine analysis
  - Evaluate for chronic cardiac/renal/liver disease
- Diabetic coma (ketoacidosis/hyperosmolar):
  - Arterial blood gas
  - Clinical chemistry
  - Urine analysis

Toxic encephalopathy

- Alcohol:
  - Serum alcohol level
  - Serum tylenol/salicyate level
  - Blood/urine toxic screen
- Drugs (hypnotics, analgesics, heavy metals (lead/mercury/manganese)):
  - Serum alcohol level
  - Serum tylenol/salicyate level
  - Blood/urine toxic screen

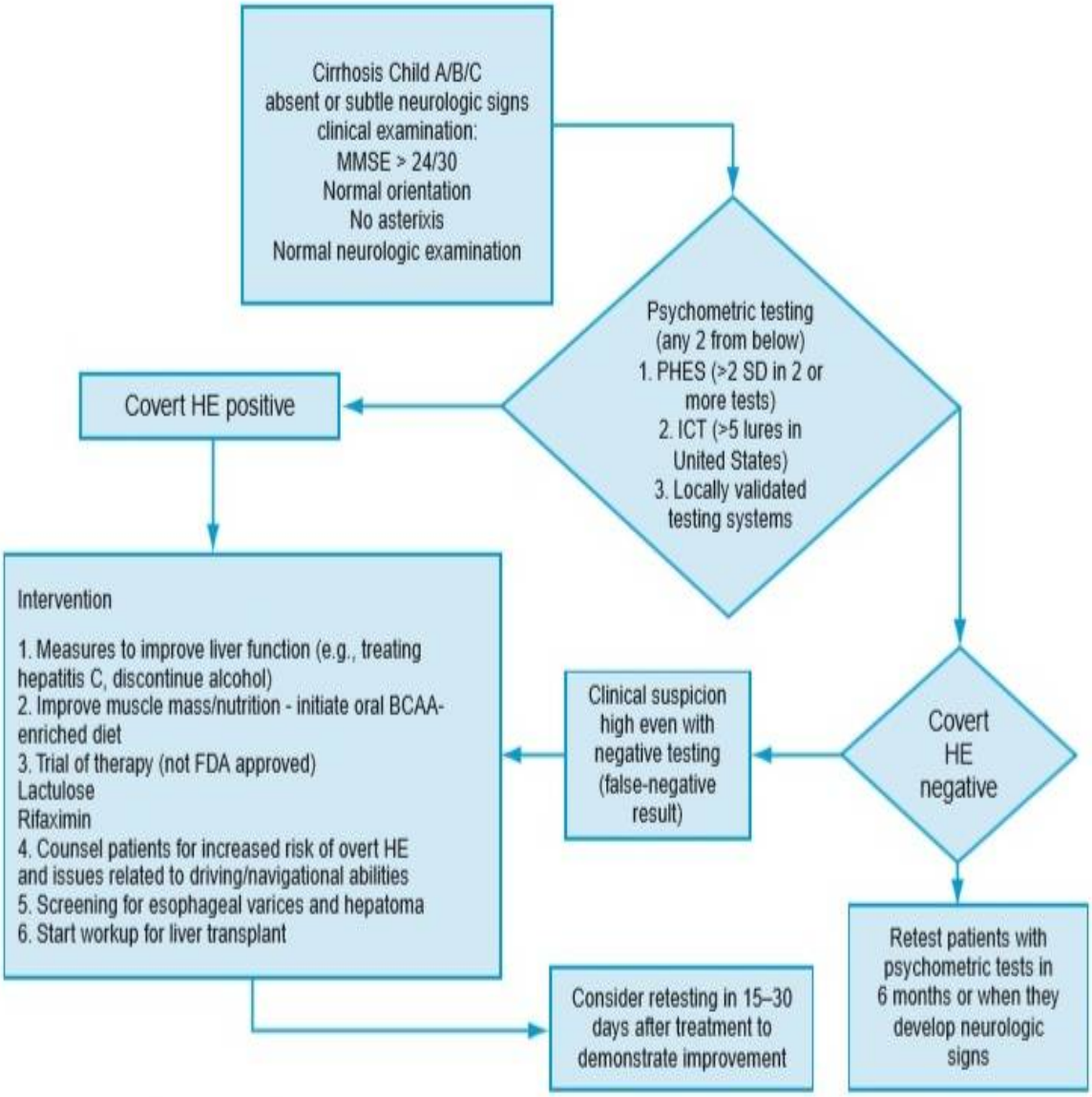
Diagnosing HE

- Serum ammonia (arterial/venous)
- CSF glutamine
- Plasma branched chain amino acid/aromatic amino acid ratio

Precipitation of HE

- Gastrointestinal bleeding:
  - Complete blood count
  - Coagulation profile
  - Clinical chemistry
- Infection:
  - Complete blood count with differential count
  - Ascitic fluid studies
  - CSF studies
  - Microbiology studies: culture/Gram stain:
- Hypokalemia/alkalosis:
  - Clinical chemistry
- Acute hepatic injury:
  - Liver function tests
  - Coagulation profile
  - Toxic/metabolic/infectious/ischemic etiology workup
- Azotemia/diabetic coma:
  - Clinical chemistry
  - Arterial blood gas

CSF, cerebrospinal fluid; INR, international normalized ratio.


Cirrhosis Child A/B/C
absent or subtle neurologic signs
clinical examination:
MMSE > 24/30
Normal orientation
No asterixis
Normal neurologic examination
Psychometric testing
(any 2 from below)
1. PHES (>2 SD in 2 or more tests)
2. ICT (>5 lures in United States)
3. Locally validated testing systems
Covert HE positive
Intervention
1. Measures to improve liver function (e.g., treating hepatitis C, discontinue alcohol)
2. Improve muscle mass/nutrition - initiate oral BCAA-enriched diet
3. Trial of therapy (not FDA approved)
Lactulose
Rifaximin
4. Counsel patients for increased risk of overt HE and issues related to driving/navigational abilities
5. Screening for esophageal varices and hepatoma
6. Start workup for liver transplant
Clinical suspicion high even with negative testing (false-negative result)
Covert HE negative
Consider retesting in 15–30 days after treatment to demonstrate improvement
Retest patients with psychometric tests in 6 months or when they develop neurologic signs

Blood serum ammonia:

Impaired mental-status in liver failure patients should be considered and start treating like hepatic encephalopathy which is unless proven as other. So blood serum-ammonia is not routinely recommended in diagnosing of hepatic-encephalopathy. It will help in some rare circumstances but now it limited predominantly to using in a research settings. Some studies showed a strong correlation between arterial and venous ammonia levels [7].

Cerebrospinal fluid amino acids

When the concentration of ammonia increases in brain, which releases glutamate from cellular stores which is converted into glutamine, in astrocyte cells. Aminoacid is released in large quantities into cerebro-spinal fluid (CSF) which causes increase in its concentrations. So many postmortem human and experimental studies reports showed minimum of 2-fold increase in the glutamine levels in CSF of the hepatic encephalopathy patient with HE [33]. Phenylalanine and tyrosine are the other amino acids which increase in great amounts in HE[34]. This biogenic-amines act as agents to nor epinephrine and dopamine, which can alter the mono-aminergic acion in the brain. The significant rise in levels of amino acid will also cause same level of neurologic deterioration which is demonstrated by levels of CSF alanine.

This predicted to arise from metabolism of glutamine, this is incorporated into Krebs-cycle. These investigations are presently involved in studies and research which will take long time before it is clinically applicable. Individuals with

hepatic-encephalopathy will most commonly have coagulopathies, hence lumbar-puncture performed only if it is absolutely indicated.

Psychometric-tests:

Minimal hepatic-encephalopathy was the neurocognition disorder where individual has an mal-performance in various psychometric tests. This usually occurs in cirrhotic individuals how ever it can be observed in initial stages of fibrotic process as well as portosystemic shunting. This entity, recognized during 1970s, were originally called as sub-clinical HE which was relied on the performance of individuals in trail-making as well as various cognitive test [32,35]. A study was conducted by Hamster et al to understand the several neuro-cognitive domains altered in this condition. [36]. He conducted greater than three hindered various test of psychometry to estimate cognition domain which is varying from premorbid-intelligence levels and verbal-abilities to visuomotor-function and its coordinatents.

With the help of statistic analysis of discrimination it has been found that line-tracing test, peg-board, aiming-steadiness motor performance-scale, and digit symbol test can potentially helpful in differentiation of cirrhosis and non-cirrhosis individuals. These were initial efforts that resulted in standardization in testing methods that is currently known as minimal HE.

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Paper & pencil tests

PHES-Psychometric Hepatic-Encephalopathy-Score)

Test battery has been devised byWeissenborn and Schomerus et al. which depends upon the results of Hamster study [15]. PHES constitutes these tests: number-connection-test-A (NCT-A), number-connection-test-B (NCT-B), digit-symbol-test (DST), line-tracing-test i.e,LTT, and serial dotting test i.e,SDT. Test-battery has been advocated on higher number of volunteer individuals in germany who are in good health that is to collect normal data which is according to aged wise & has been further assessed by testing on that of individuals with non-alcoholic cirrhosis. Such testing domains are motor speed, d accuracy as well as visual-perception, visuo-spatial-orientation, visual-construction, concentration, & to a smaller amount of extent memory. Many articles has proven that age & education has an influence seen-on tests such as NCT-A as well as NCT-B [37]. Test-battery primarily had utmost attention in Italy, Spain, and Mexico, and Great Britain has been attained local normative information. Scarce info availability as well as copyrighted issues, that too with problems evidenced in applying as well as giving score to the test, has its attention in US [38].

RBANS (Repeatable-Battery-for-Assessment-of –Neuropsychological-Status)

It was the established-battery for that of assessment of dementia as well as for various neurocognitive disorders [39]. This was a paper and pencil test which has 4 alternative forms (A, and, andC, and D) and it lasts for almost twenty to thirty minutes for administrating. This have extensive normative databases throughout

that of ages twenty to eighty nine years in US [37]. Initial reports which were applied on individuals who have been on wait for hepatic transplantation has shown a close correlation b/w model for end stage liver-disease (MELD) score and its-performance in that of RBANS [40]. The main drawback associated with it was that of appreciable learning effect showed in the individuals who were tested at close timings, which will limit its usage with assessment of response for therapy.

Computerized-psychometric-tests

In the past some years several computerized test-batteries has been advocated for diagnosis of minimal Hepatic-Encephalopathy [38]. Such testing systems aimed at intervening in few problems which were important that were observed with that of paper & pencil test which consists available-issues, concerned principles about administration of the test, as well as-scoring.

Many computerized testing's were able to generate aged matching result at the termination of the test period. Such tests were seen in internet and it could be in usage-free-of-charge or for a basic fee. It also offers convenient of abled for administration in the op settings. Most popular testing-systems were inhibitory-control-test (ICT) as well as cognitive-drug-research (CDR) -test.

Inhibitory-control-test

It was an organized test used in main purpose in determination of deficits in attentiveness as well as responsive inhibitedness in that of individuals of ADHD attention-deficit-disorder, schizophreniaC as well as traumatic-brain-injury. In Bajaj et al study, it was found that test as well as the subject has been showed in various letters at five hundred ms sessions on the screen of laptop. The individual has been enquired to put attention at the X and Ys which were interlayed in-between those words. These people were asked for response that is by typing space bar that is at the time X was followed by Y /or Y was followed by X, which was the "target," and for refraining from that of response when X was followed by X or Y was followed by that of Y, which was the "lure." The individual have to go via 6 runs of two minutes for every time that too with addition for trained run in the beginning. These were graded basing upon lureresponse, as well as greater than 5 lures diagnosed as that of minimal hepatic encephalopathy with eighty eight percent sensitivity. In US, such tests were being in investigation chiefly and has been applied by a 1 investigator.Dr.Bajaj, in 2 centers Wisconsin & Virginia [43]. Neverthless, this was not being performed appropriately in countries like Europe, which makes it least popular in different part of Atlantic [44].

Cognitive-drug-research-test

CDRT testing system is validated in diagnosing of the minimal-HE with the help of investigators from Newcastle, [45]. The CDR-test was presented on the computer-screen that too as patients responded to the “Yes/no” response-box. This battery was consisted with 7 various tests. These scores were demonstrated on the scale-of-performance in 5 various-domains, that consists power-of-attraction, and continuity of attention, and quality of episodic memory, and quality of-working-memory, and speed-of-memory. Nevertheless , 1 limitation in this testing is the patients has to be undergone practicing sessions of one to seven days that is before the date of testing that is for familiarity.

Critical-flicker-fusion-frequency-test

It was designed by Kerchiefs etal. In year-2002 that is helpful in the diagnosing of minimal-HE, it was currently a well-organized neuro-physiologic-test basing with the principle of hepatic-retinopathy [46]. Muller-cells of the retina (which are glial cells) we been proposed to have the same changes as that of the brain-astrocytes . This has been considered to cause variation in the perception in light frequency as received by the retina. This test has shown a patient light-pulses, beginning with greater frequencies of 60 Hertz, which will reduce in a progressive manner by 0.1 Hertz/second. With this higher frequencies the individual perceived these as a solo stream of light, however the critical-frequency was when individuals initially receive it as the discrete light-pulses. Critical-frequency of less than 39Hertz diagnosed as minimal-HE that too of higher sensitivity as well as that of

specificity, and it usually coorganised with paper-and-pencil psychometric tests. These tests could been administer in ip as well as op setting and it lasts for about fifteen minutes as a whole.

Binocular-vision was a preimportant tool in case of optimal performing in the test. This was not affected by education/occupation and it was just merely related to age. This was majorily applied in that of therapy trials in individuals with HEi.e,hepatic-encephalopathy due to the capability of demonstration of improving that too with no learning-effect [47,48,49]. There is very scarce information available in US , it was the major reason which makes it low popular

Electro-encephalo-gram

Electroencephalograms (EEG) is useful in studying neuro-physiologic state of individuals who had cirrhosis [50,51,52]. This was in general applied in that of research as well as that of clinical setting. In the Earlier one , it has been in use for following: To assess effects of therapy (dietary /pharmacologic), porto-systemic shunt insertion,or surgery or hepatic transplantation. For quantifying the status of the physiological variations in brain and also to assess its association with that of several tests which were applied in diagnosing minimal-Hepatic-encepahlopathy.It was the common used diagnosis tool with diagnosis of cirrhosis patients those with bad consciousness.

Various findings on EEG in general were:

_ Generalized slowness of background ElectroEncephaloGram activity, that was objectively quantifiable but could be observed in that of various metabolic-encephalopathies.

_ Reduced amplitude waves.

_ Occurrence of triphasic waves as well as the bursts of slow-activity of theta as well as delta range.

Brain-imaging:

Increasing in the past decades, cerebral edema was characterised by several types of magnetic-resonance-imaging I,e MRI techniques of brain [16]. This was majorily observed in white matter-brain and all grades of HE. A computerized tomographic- CT scan of the brain was performed routinely with the patients with changed mental condition, that too to find the absence of concomitant etiologies such as intracranial-hemorrhage as well as space-occupying-lesions.

Treatment:

*The present standard of treatment of overt hepatic encephalopathy comprises 4 important plans :

(i) Supporting care for the individual who had altered mentation;

(ii) Concurrent etiological factor of hepatic encephalopathy are searched and managed when possible;

(iii) Stimulating causes were identified and are corrected promptly; and

(iv) Empirical therapy in Hepatic encephalopathy till current times, lactulose has been approved management tool for HE in the US. Currently lactulose, along with rifaxmin, which is been used long time only being accepted treatment in the US, is available for managing some types of individuals with recurrent episodes of HE [53].

Supportive care

*NG tube which can deliver large quantities of lactulose is commonly used as treatment modality for HE [11]. Aspiration is hence a consequential risk in patients of intensive care units. Elective intubation is preferred individuals of high grade HE (e.g., stage 3 or 4, by WestHaven-scale), is well justified only if severe upper GI bleeding has been a factor. Supplementation of nutrients for patients who are not conscioust. Generally nutrition supplement is limited for initial days in inpatient care owing to frequency of investigations as well as the necessity of lavage measures of intestine to remove blood.

Some more etiological factors - encephalopathy

*The 2nd strategy is to find out the what are other factors causing encephalopathy in unconscious patients with overt HE as the diagnosis of HE is made only in the absence of other causes of encephalopathy. In case of co-existence of the other causes, they have to be diagnosed and treated. Care should be taken to avoid induction of complications due to lactulose dosing like dehydration and hypomagnesemia.

Precipitating factors

The 3rd strategies which are employed in management in recurrent episodes of significant HE which is very important. In patients with advanced hepatic cirrhosis (Child–Pugh=class C) recurrent episodes of minimal or significant HE are precipitated are defined factors. Identification and the correction of the prompt factors is very effective therapy in treatment of HE. The recovery rates of HE is with correction of factors which precipitate alone has been reported as 80–90%[54]. Because of the overlap (e.g., lactulose is also used in to clear GI bleed) sometimes it is so difficult in find out what is actually reversed the episode of HE. Further matters which are complicating and many cirrhosis patients who have 2 are more than 2 simultaneous precipitating factors for hepatic encephalopathy. When studies like randomized controlled trials conducted this type of issues made it very difficult in treating of minimal or significant HE. Multiple precipitating factors and added concomitant causes of hepatic encephalopathy together will cause difficulty in conducting the "controlled trial". The events, seeking for factors and treatment of precipitating factors is very important and effective treatment of minimal and significant hepatic encephalopathy. Especially in patients with large spontaneous/surgically created portosystemic shunt which tend to have more episodes of spontaneous encephalopathy [55].

Some of the additional comments which are warranted on precipitating factors of hepatic encephalopathy. Sepsis is to be the most likely dominant factor of HE. In many cases identifying and treating of major focus of the infection is not successfully in many cases, recovery from episodes of the HE can be very

much protracted or patient who may have tendency of recurrent episodes of significant hepatic encephalopathy[56]. Patients with cirrhosis may have tendency to develop HE in severe forms, then sepsis will be the first suspecting factor. The basic and important issue with sepsis is that in can induce or capable of causing encephalopathy by its own [20]. In difficulties of managing of HE this is one more example, upper GI bleeding is also a frequent cause and precipitating factor of recurrent episodes of hepatic encephalopathy. Large undue amounts of ammonia is produced by digested blood in gut which precipitates the HE. In addition to this absence of essential aminoacid isoleucine fromed in hemoglobin make it still more ammoniogenic than other types of protein [19, 57]. Periodic catharsis and gut lavage is insisted to clear blood in gut and empirically one will see patient recovering from symptoms of significant HE with this type of therapys. Because the laxative effect of lactulose it is very difficult in knowing whether its unique action or purgative effect is resulting is responsible in the recovery of bouts of HE. Regardless, gut cleansing has been the definitive treatment. In conditions when the constipation/ or ileus is noted, removing blood out of gut could not be attained unless motility of intestine is being better.

It has been suggested GI motility has been decreased by HE itself, neverthles producing the self continuing mechanism in episode of hepatic encephalopathy. In conditions of constipating patients , intestinal obstruction, ileus, per-rectal lactulose is proved to be effective for in management of overt hepatic encephalopathy [58]. Low sodium levels as per number of studies have been reported that it has potential to clearly increase the chance of occurrence of

hepatic encephalopathy [59]. Hyponatremic condition also results in aggravation of cerebral edema which exists previously in individuals of high grade cirrhosis [26].

Drug therapy

LACTULOSE

Lactulose is a non-absorbed disaccharide which used in treatment of HE [10,60]. In 1977 United States Food and drug administration made use of Lactulose used exclusively for treatment in hepatic encephalopathy. Data shows, lactulose use is superior to the use of placebo in treatment of minimal or covert HE [61,62,63].

Lack of data in support on lactulose in treatment of significant HE which is related to mechanism of actions of this type of drugs. The data which is generated on based on lactulose in treating minimal HE it has efficacy in treatment of HE [63].

Lactulose is used widely in treatment of decompensated chronic liver disease patients with minimal and significant hepatic encephalopathy.

Rifaximin

Rifaximin is a broad spectrum antibiotic which is minimally absorbed. Rifaximin is used in many trials in Europe previously[64,65,66,67]. There was no control-placebo study trial was performed. When compared with veriety of similar agents Rifaximin (lactitol, lactulose, and some other types of antibiotics) which displayed consistently the same type of efficacy [66,67]. The recent study trial in united states of America on rifaxmin in which data provided clearly

indicates rifaximin decreases episodes of HE in patients who at high risk with these hepatic encephalopathy events (reduction upto 58%)[53]. Rifaximin is thought to reduce the duration of HE. There is no indication for its use except in prolonged overt HE.

Other types of treatment

Since 1950 Neomycin which is been used for treatment of hepatic encephalopathy [68]. Same as other types of treatment for hepatic encephalopathy there is no evidence of abundance in supporting the efficacy of neomycin

*A the study trial conducted in Brazil by colleagues and strauss which essentially proved neomycin which is no more effective [54]. Another mechanism of action of Neomycin has another type of mechanism of action which inhibits the glutaminase enzyme which is important in formation of ammonia in blood in large amount results in improvement in the condition of hepatic encephalopathy patients.

Other type of Antibiotics which reverse hepatic encephalopathy:

*Metronidazole [69], vancomycin [70], paramomycin[71], and few other antibiotics have been reported to reverse HE [65]. The probable mechanism of action is in the suppression of bacterial overgrowth. Redution of intestinal motility might be helpful. The advantage of Rifximin in cirrhotic patients for bacterial overgrowth is the sparing of bacterial flora. As the drug is solubilized by bile salts,it becomes less active once bile salts are absorbed into the small bowel resulting in the lack of effect over the bacterial flora.

The use of prokinetics and selected delivery antibiotics might be considered in future for the therapy of HE.

Other therapies

Immunization by urease [71], resection of colon or bypassing [72], portal vein stump arterialization [73] are some treatment methods under study. Using of Endogenous benzodiazepines in patients with no prior exposure to the drug resulted in awakening from coma by about 30 % with Flumazenil.

Liver transplantation:

When medical treatment fails, then organ transplantation may require. This organ transplantation which is not performed usually due to many causes such as infection, organ availability, cost. It may also due changes hepatic encephalopathy grades in frequent admissions. The preference and priority for earlier organ transplantation for cirrhosis patients before episodes of hepatic encephalopathy which may occur can improve in patients neurological status and outcomes [17,18,40].

RESULTS

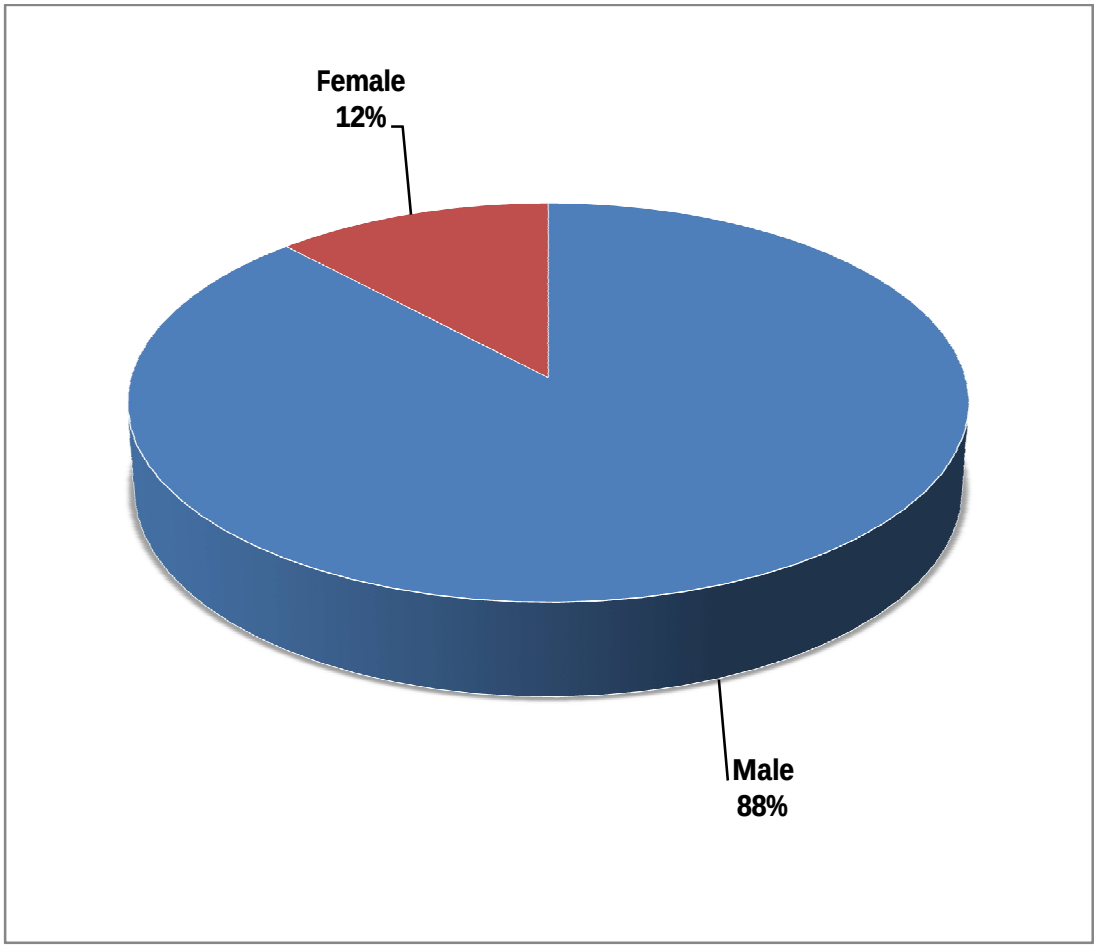
In this study, out of 50 patients, males were 44 (88%) and females were 6 (12 %)

Table 1: Sex wise distribution

Sex	Number	Percentage
Male	44	88%
Female	06	12%
Total	50	100%

In this study, Males are more in number compared to females.

Figure: Sex wise distribution



Females were 12 % and males were 88 %.

Table 2: Age wise distribution

Age groups (years)	Number	Percentage
<50	22	44%
50-60	19	38%
61-70	07	14%
>70	02	4%
Total	50	100%

Mean age = 52.54±10.03 years

In this study, 22 patients (44 %) were in the age group less than 50 years.

19 patients (38 %) were in the age group of 50 – 60 years.

7 patients (14%) were in the age group of 61 -70 years.

2 patients (4%) were in the age group of greater than 70 years.

Mean age of this study is 52.54±10.03 years

Figure: Age wise distribution

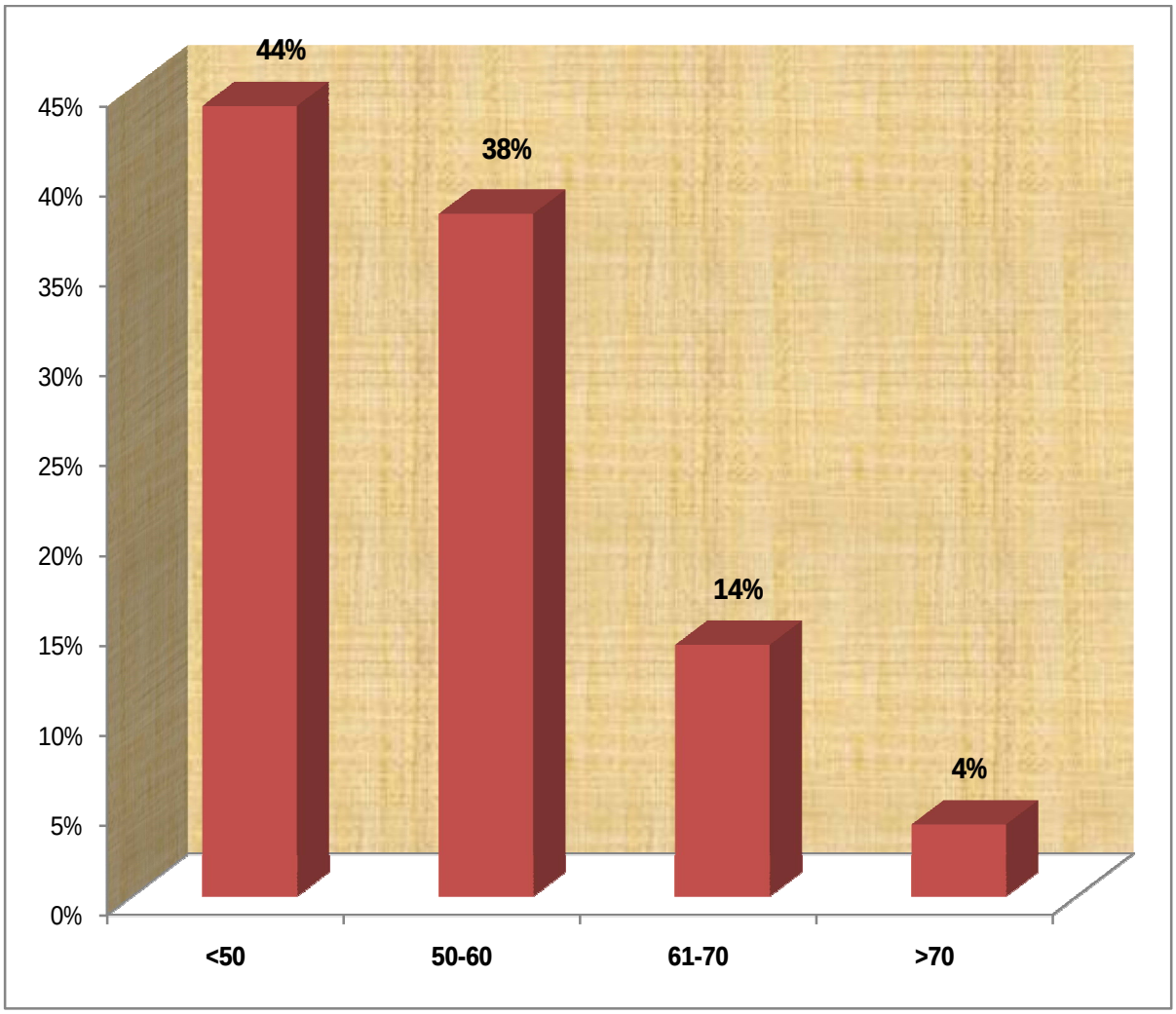
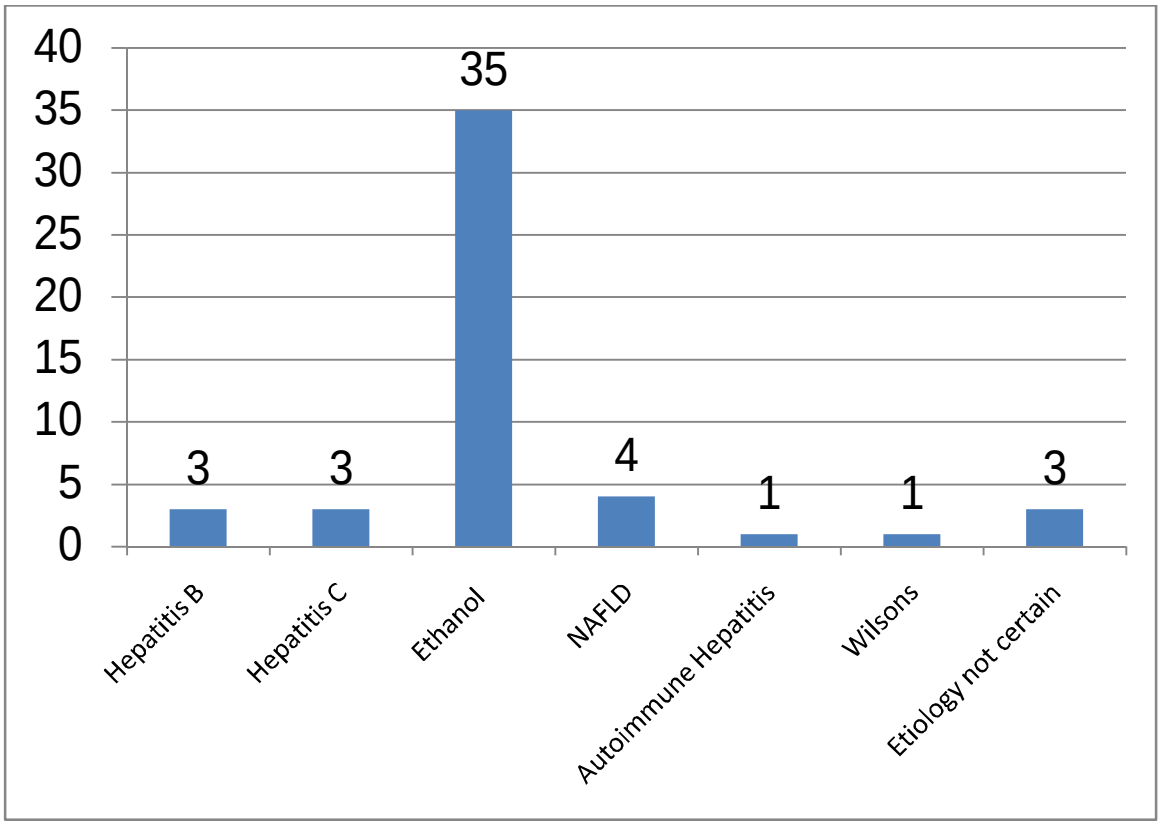


Table 3 : Etiology of Liver cirrhosis:

Etiological Disease	No of Patients
Hepatitis B	3
Hepatitis C	3
Etthanol	35
NAFLD	4
Autoimmune Hepatitis	1
Wilsons	1
Etiology not certain n	3
Total	50



Out of 50 subjects in the study, alcohol was the etiological factor in 35 patients (70%) 4 patients (8%) have NAFLD as the cause , 3 patients each has Hepatitis B. Hepatitis C as the etiological cause 1 each has etiological cause of Autoimmune hepatitis (2%), Wilsons disease (2%), and cause was not known in 3 cases (6%).

The most common etiology for liver cirrhosis in the present study was alcohol followed by NAFLD , Hepatitis C and Hepatitis B infection. 1 had autoimmune mediated liver disease and 1 had wilsons disease.

Figure showing etiology of liver cirrhosis in the present study.

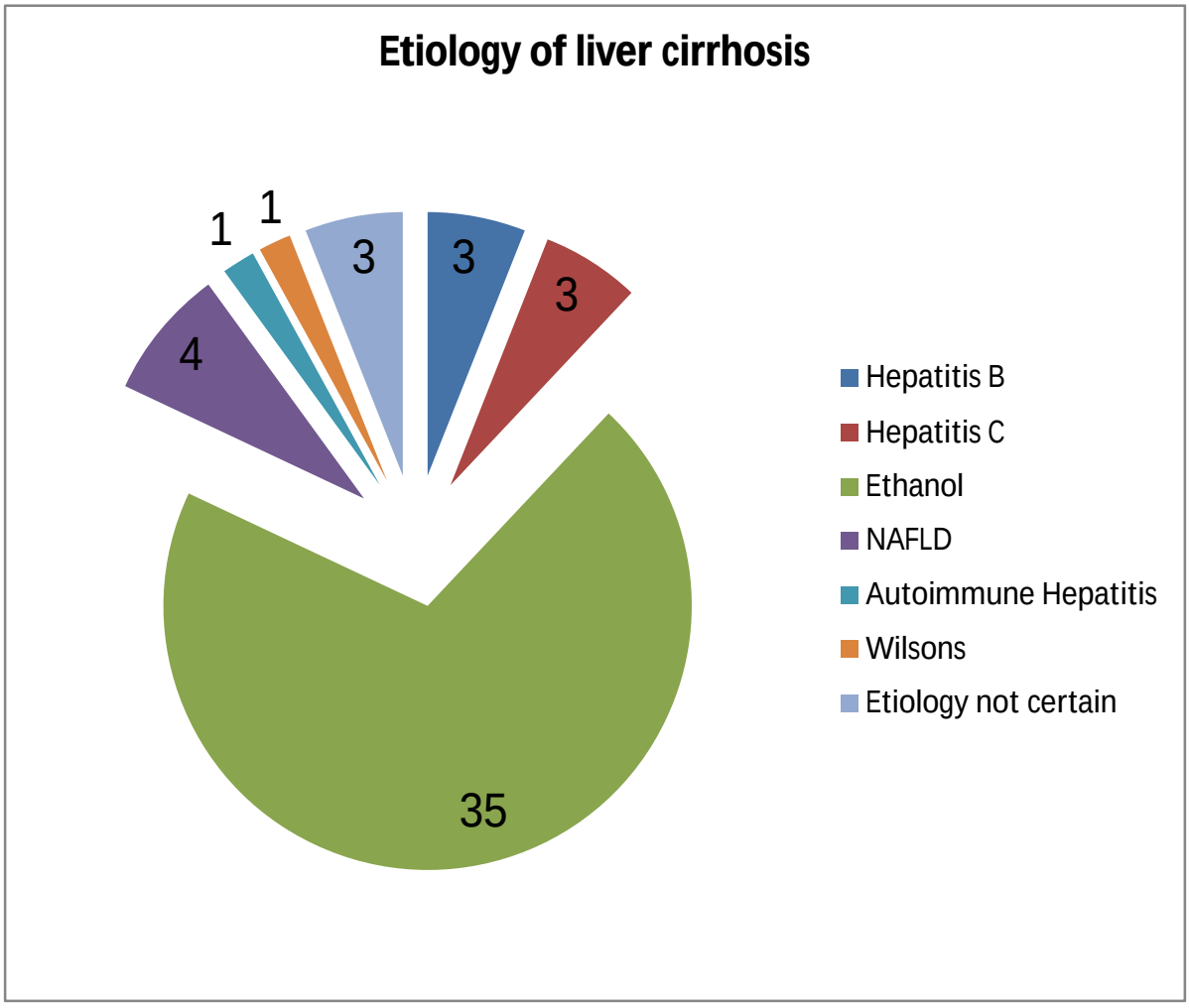


Table 4 : Infections precipitating Hepatic encephalopathy in DCLD

Infections precipitating Hepatic encephalopathy	**Frequency***	**Percentage***
Septicemia	15	30%
Urinary Tract Infection	20	40%
Spontaneous Bacterial Peritonitis (SBP)	05	10%
Respiratory Tract Infection	07	14%
Cellulites	03	06%
Total	50	100%

Out of 50 patients in the study, Septicemia is the infection precipitating Hepatic encephalopathy in DCLD in 15 patients (30 %). 20 patients (40%) had Urinary tract infection as the precipitating factor. 5 patients (10 %) had spontaneous bacterial peritonitis as the precipitating factor 7 patients (14%) had respiratory tract infection as the precipitating factor 3 patients (6%) found to have cellulites as the precipitating factor.

Figure: Infections precipitating Hepatic encephalopathy in DCLD

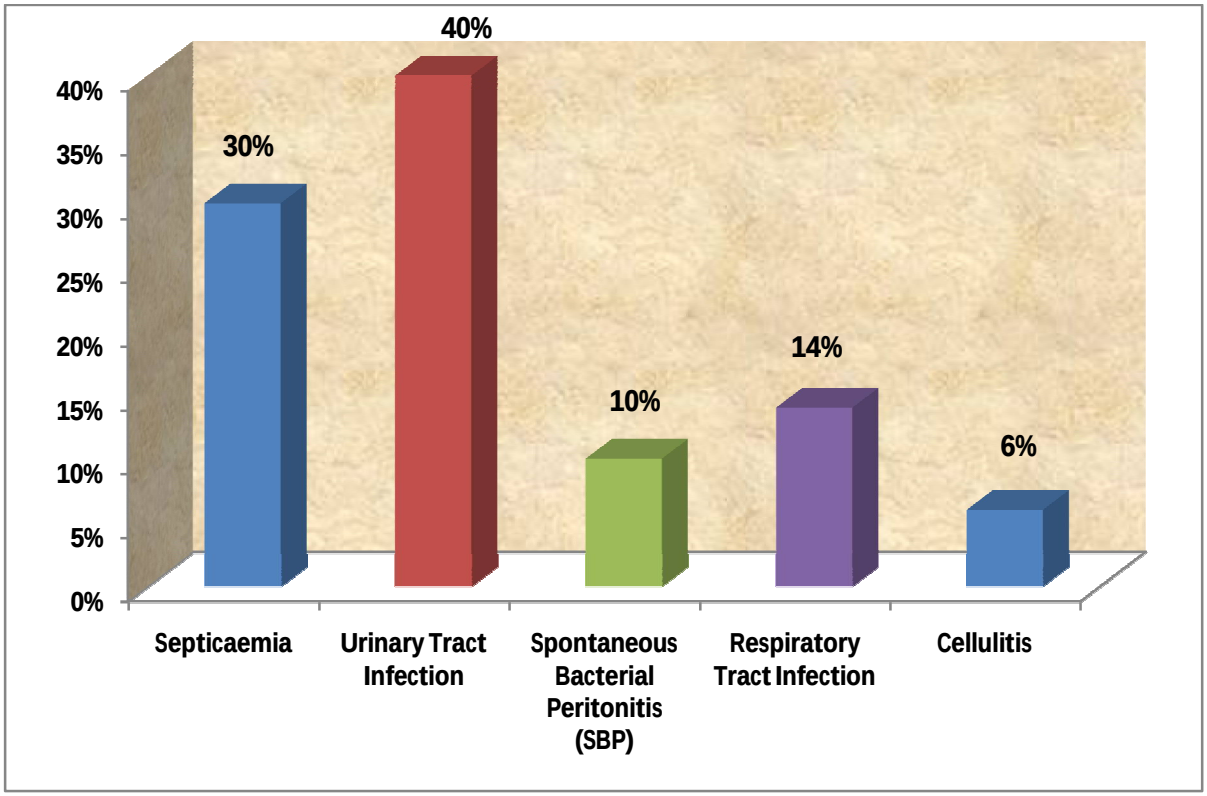


Table 5

	Mean	**Standard Deviation (SD)**
Patient age	52.54	10.03
Total count	13676	8581.103
Platelet count	109000	103576.7
Bilirubin	10.246	8.13
PT/INR	10.68	1.70
MELD score	26.22	8.77

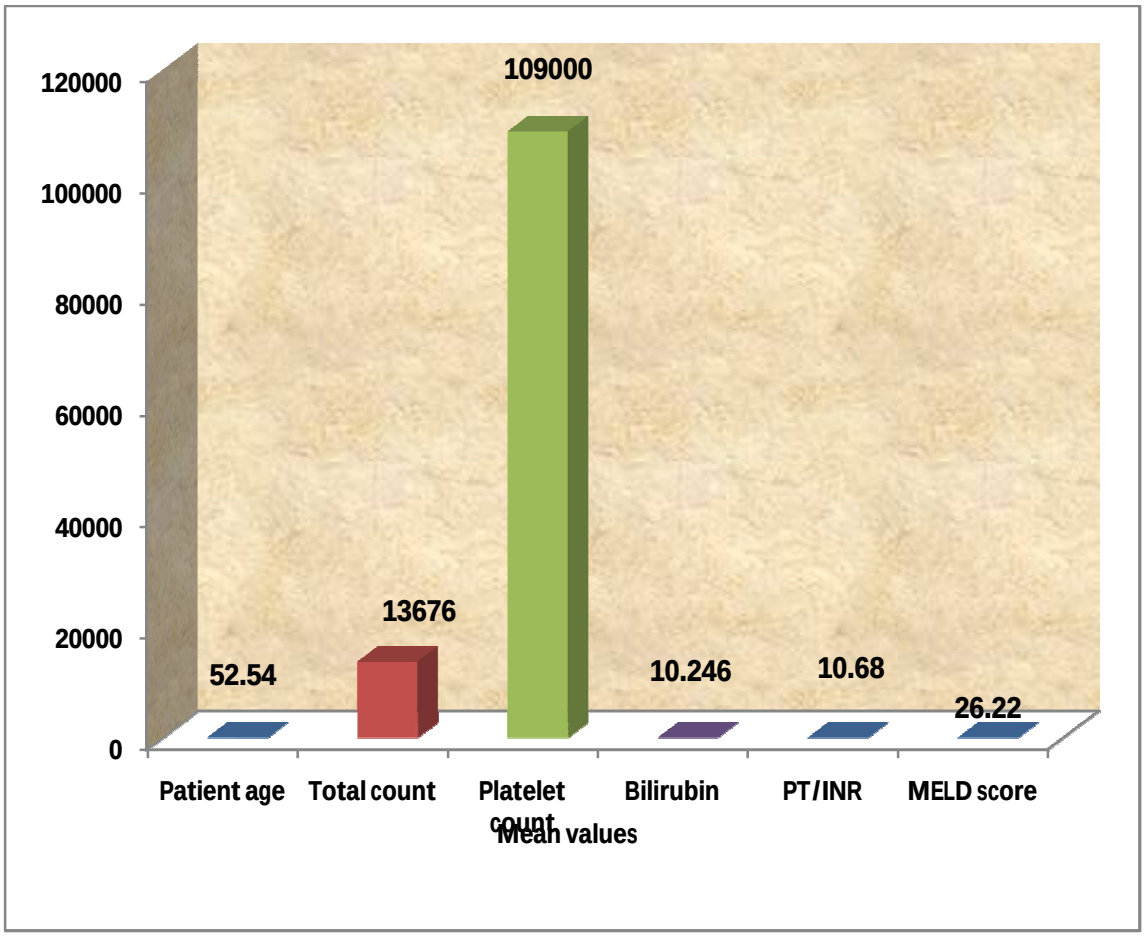
In this study among 50 patients, in terms of investigations:

Mean platelet count found to be 13676,

Mean bilirubin value noted in these patients found to be 10.25.

Mean MELD score found to be 26.22 among these patients.

Figure


120000
100000
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0
109000
13676
52.54
10.246
10.68
26.22
Patient age
Total count
Platelet count
Bilirubin
PT/INR
MELD score
Mean values

Table 6: Septicemia precipitating Hepatic encephalopathy in DCLD

Infection	Frequency	Percentage
Septicemia	15	30%

Out of 50 patients in the study, Septicemia found in 15 patients (30%).

Table 6: Causative agents for Septicemia

Causative agents for Septicemia	Frequency	Percentage
E.coli	07	46.7%
Klebsiella	03	20.3%
Enterococcus	01	6.6%
Staphylococcus	01	6.6%
Streptococcus agalactiae	01	6.6%
Pseudomonas aeruginosa	01	6.6%
Myroides	01	6.6%

Out of 30 patients with septicaemia in the study, E.coli found in In terms of causative agents of septicemia, out of 15 patients who showed blood culture proven sepsis,

7 patients (46.6%) had E.coli sepsis, 3 patients (20 %) had klebsiella sepsis, 1 (6.6 %) patient had enterococcus sepsis, 1 patient each had staphylococcal (6.6 %), pseudomonas sespsis (6.6 %) , myroides sepsis (6.6 %).

In terms of urosepsis, out of the causative agents for urinary tract infection are E.coli 09 (45%),klebsiella 05(25%),enterococcus 03(15%),staphylococcus 02(10%) and candida albicans 02 (10%).

Figure: Causative agents for Septicaemia

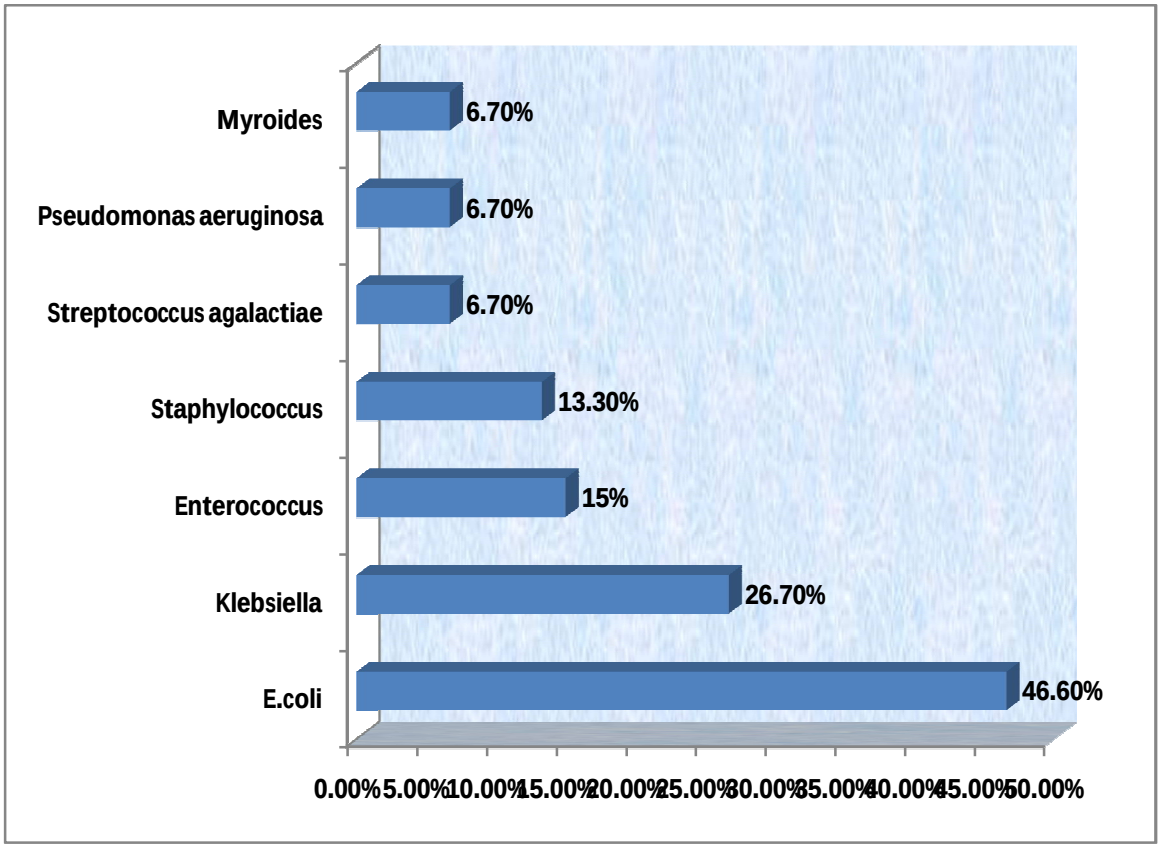


Table 7 : UTI precipitating Hepatic encephalopathy in DCLD

Infection	Frequency	Percentage
Urinary Tract Infection	20	40%

Out of 50 patients, 20 (40 %) had Urinary tract infection as precipitating factor.

Table 8: Causative agents for Urinary Tract Infection

Causative agents for UTI	Frequency	Percentage
E.coli	09	45%
Klebsiella	04	20%
Enterococcus	03	15%
Staphylococcus	02	10%
Candida albicans	02	10%

In terms of urosepsis, out of the causative agents for urinary tract infection 9 are E.coli (45%),

Klebsiella in 05(25%), enterococcus in03(15%), staphylococcus in 02(10%) and candida albicans in 02 (10%).

Figure: Causative agents for Urinary Tract Infection

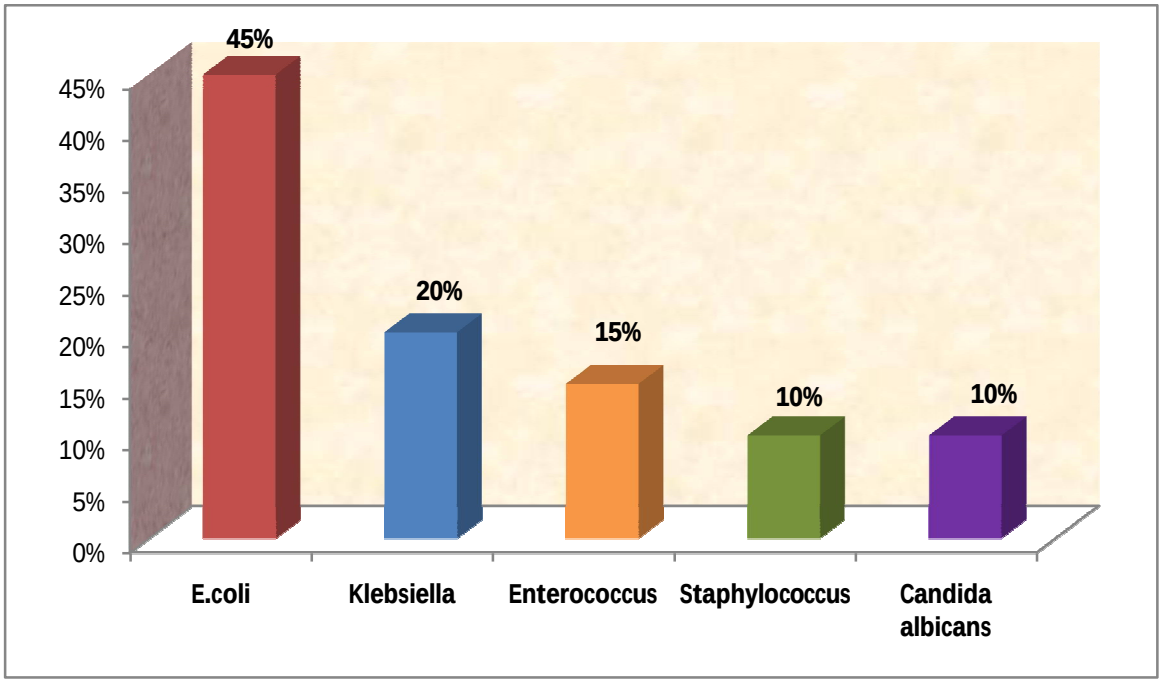


Table 9 : Spontaneous Bacterial Peritonitis (SBP) precipitating Hepatic encephalopathy in DCLD

Infection	Frequency	Percentage
Spontaneous Bacterial Peritonitis (SBP)	05	10%

Out of 50 patients, 5 had spontaneous bacterial peritonitis as precipitating factor of HE in DCLD.

Table 10: Causative agents for Spontaneous Bacterial Peritonitis (SBP)

Causative agents for Spontaneous Bacterial Peritonitis (SBP)	Frequency	Percentage
E.coli	03	60%
Klebsiella	01	20%
Sphingomonas paucimobillis	01	20%

Out of 5 cases with spontaneous bacterial peritonitis, 3 (60%) had E.coli sepsis. 1 patient (20 %) had Klesiella sepsis, 1 patient had sphingomonas paucimobilis (20%).

Figure: Causative agents for Spontaneous Bacterial Peritonitis (SBP)

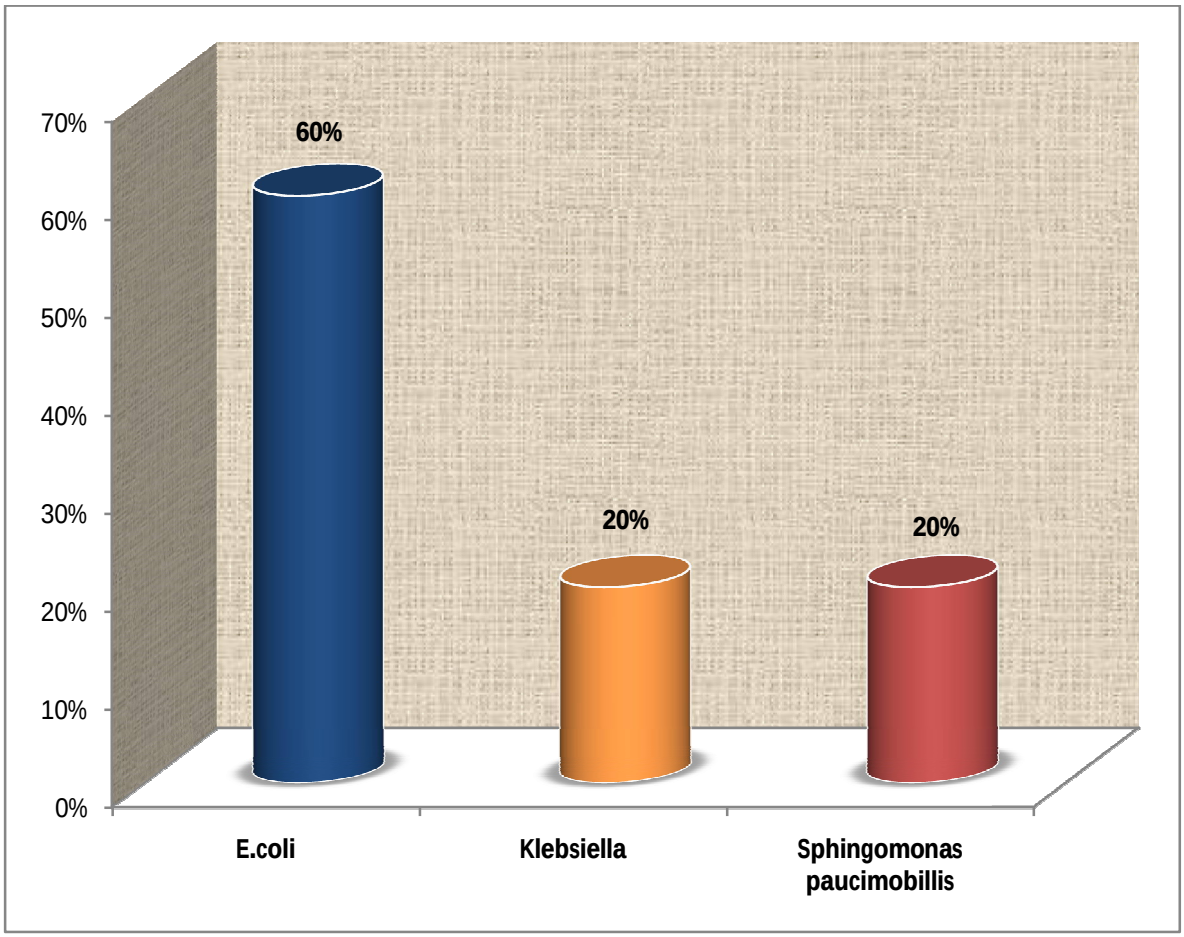


Table 11: Respiratory Tract Infection (RTI) precipitating Hepatic encephalopathy in DCLD

Infection	Frequency	Percentage
Respiratory Tract Infection	07	14%

Out of 50 patients, 7 had respiratory tract infection as precipitating factor of hepatic encephalopathy.

Table 12: Causative agents for Respiratory Tract Infection

Causative agents for RTI	Frequency	Percentage
Klebsiella	04	57.1%
Candida species	01	14.3%
E.coli	01	14.3%
Staphylococcus	01	14.3%

The causative agents for respitarory tract infection are klebsiella 04 (57 %), candida species seen in 01 (14.3 %) , ,E.coli seen in 01 (14.3%) and staphylococcus seen in 01 (14.3%).

Figure: Causative agents for Respiratory Tract Infection

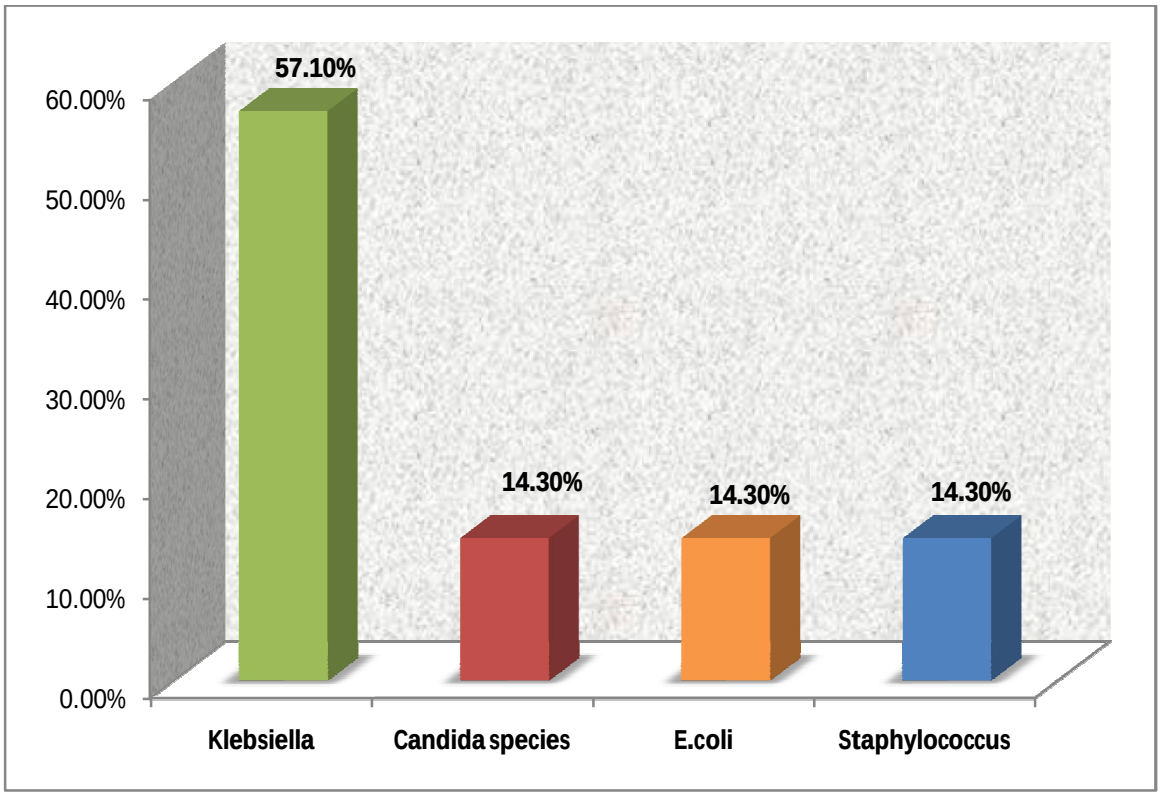


Table 13 :Cellulitis precipitating hepatic encephalopathy:

3 of 50 individuals had skin infections – cellulites as a precipitating factor for hepatic encephalopathy.

Table below illustrates frequency of patients with cellulites in the present study.

Infection	Frequency	Percentage
Cellulites	03	6%

Table 14 showing causative agents for cellulites:

Causative agents for cellulites	Frequency	Percentage
Streptococcus pyogenes	01	33.33%
Staphylococcus aureus	01	33.33%
Pseudomonas aeruginosa	01	33.33%

Out of 3 individuals, the causative agents for cellulites were streptococcus pyogenes in 01(33.33%), staphylococcus aureus seen in 01(33.33%), pseudomonas aeruginosa seen in 01(33.33%) .

Figure: Causative agents for Cellulitis

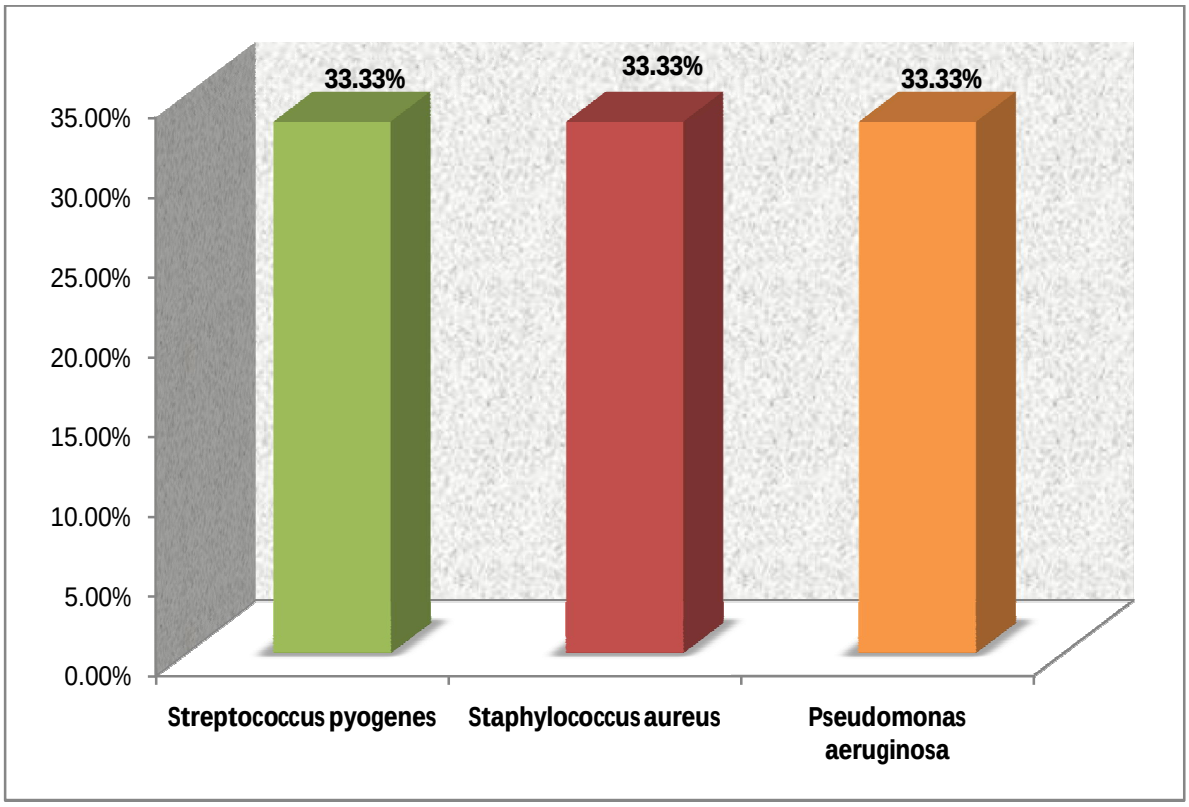


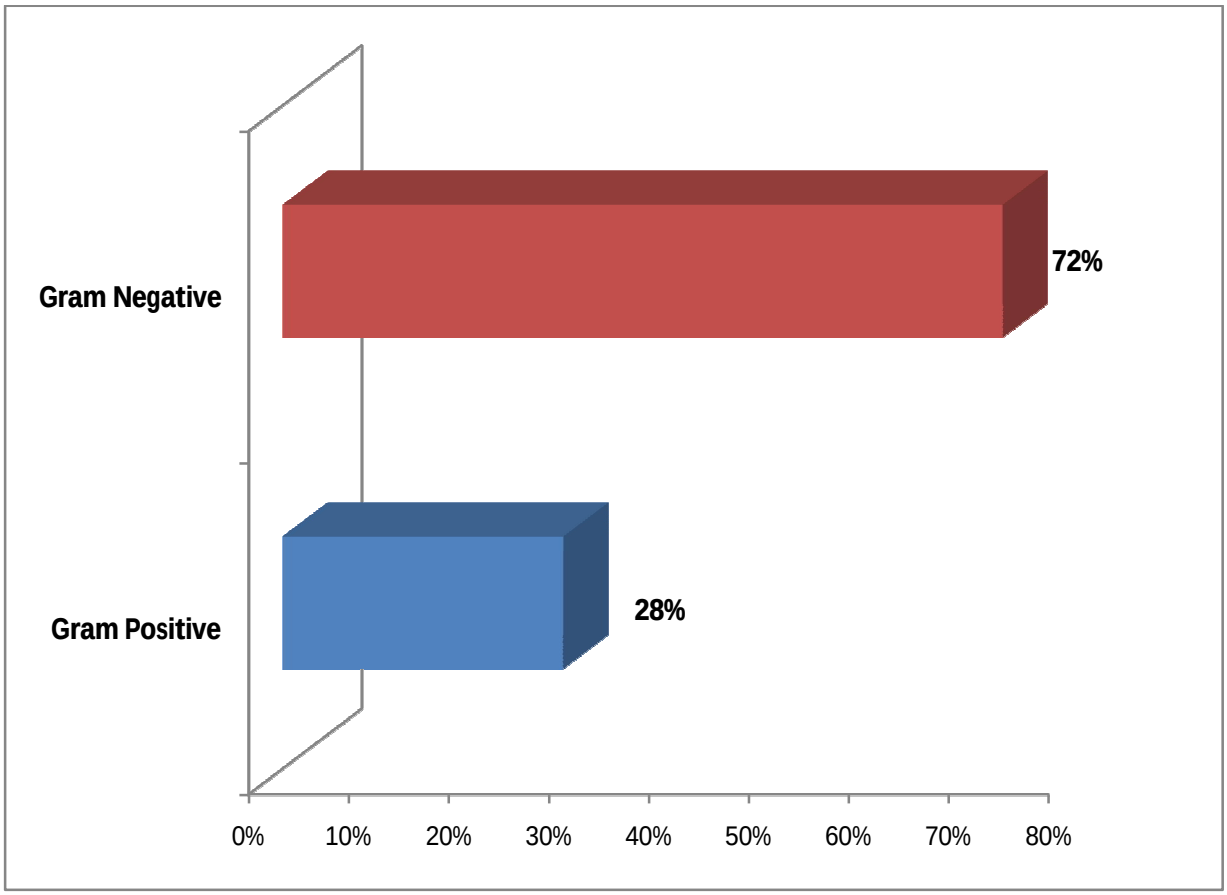
Table 15: Distribution according to Gram positivity

Gram stain	Number	Percentage
Gram Positive	14	28%
Gram Negative	36	72%

Out of 50 patients, 14 patients (28 %) had gram positive infections,

36 patients (72%) had gram negative infections.

Figure: Distribution according to Gram positivity



DISCUSSION

In our study , out of total 128 patients with decompensated chronic liver disease with hepatic encephalopathy studied, 50 patients who met criteria of culture proven sepsis were enrolled .

In our study 44(88%) were males , 06 (12%) were females. This finding of male preponderance is consistent with other studies .

Study done by Franca A etal. showed male : female ratio 69:31.Study done by Mattos etal. finds 71.2 % males. Study done by Wyke RJ ETAL. showed male : female ratio of 70:30.

Out of 50 patients in our study, 22 patients (44%) were less than 50 years , 19 (38%) were in the age group of 50 to 60 years , 7 patients (14%) were in the age group of 60 to 70 years, 02 patients (4%) were in the age group of 70 to 80 years. Mean age of the patients is 52.54±10.03 years

Among 50 patients studied , More number of patients were in the age group of less than 50 years (44%) followed by patients in age group of 50 to 60 years .This finding is consistent with studies done by Wyke R.J etal, Mattos etal.

T.S. Ferreira etal. study showed mean age of 52.89 years. FrancaA etal. study showed mean age of 45 years.

In terms of etiological factors of cirrhosis of liver, out of 50 patients, 35 (70 %) were found to have ethanol consumption, 4 patients (8%) were found to have NAFLD, 3 (6%) were found to have Hepatitis B, 3 (6%) were found to have Hepatitis C , 1 (2%) had were autoimmune hepatitis, 1 (2%) were Wilson's, and 3 (6%) were found to have no obvious cause. In our study ,Ethanol consumption is found to be most common etiological factor of cirrhosis followed by non alcoholic fatty liver disease (NAFLD) and others.

This study finding is consistent with Mattos etal. study which showed alcohol consumption is most common etiological factor of about 35.4 %. Study by Franca A etal. showed alcohol consumption as most frequent cause in about 42 % of patients.

In terms of culture proven sepsis, out of 50 patients in the study, 20 patients (40 %) had urosepsis, 15 patients (30 %) had blood culture proven sepsis, 5 patients (10%) had ascitic fluid culture proven sepsis i.e spontaneous bacterial peritonitis , 7 patients (14%) with endo-tracheal aspirate culture proven sepsis ie respiratory tract infection, 3 patients (6 %) with cellulitis .

This study showed highest number of patients with urinary tract infection followed by septicemia, respiratory tract infection and spontaneous bacterial peritonitis.

In our study , out of 50 patients, With the pan culture of blood, urine and ascitic fluid cultures , it was found that the most frequent infection was urosepsis in 40% followed by blood culture proven sepsis, endotracheal aspirate culture sepsis and ascitic fluid culture sepsis.

In terms of causative agents of septicemia, out of 15 patients who showed blood culture proven sepsis, 7 patients (46.6%) had E.coli sepsis, 3 patients (20 %) had klebsiella sepsis, , 1 (6.6 %) patients had enterococcus sepsis, 1 patient each had staphylococcal sepsis (6.6 %), pseudomonas sespsis (6.6 %) , myroides sepsis (6.6 %).

In terms of urosepsis, out of the causative agents for urinary tract infection are E.coli 09 (45%),klebsiella 05(25%),enterococcus 03(15%),staphylococcus 02(10%) and candida albicans 02 (10%).

The causative agents for respitarory tract infection are klebsiella 04 (57 %), candida species 01 (14.3 %),E.coli 01 (14.3%) and staphylococcus 01 (14.3%).

The causative agents for spontaneous bacterial peritonitis are E.coli 03 (60%), klebsiella 01(20%), and sphingomonas paucimobilis 01 (20%).

The causative agents for cellulitis streptococcus pyogens 01(33.33%), staphylococcus aureus 01(33.33%),pseudomonas aeruginosa 01(33.33%) .

Out of 50 patients in our study, 20 patients (40%) were found to have E.coli sepsis , 13 patients (26%) had Klebsiella sepsis, 5 patients (10 %) had

Staphylococcal sepsis , 4 patients had Enterococcus sepsis, 3 patients (6%) had candida albicans sepsis.

In our study, E.coli found to be most frequent organism causing infection followed by Klebsiella .

Study done by Franca A etal. reported E.coli as the frequent organism causing infection in about 60 % cases

Study done by Qiu- ming wang etal. showed pneumococcal and E.coli were the common bacterial causes , Where as study done by Wyke RJ etal. reported 66.36 % cases were Streptococcal,Staphylococcus aureus, E.fecalis , S.epidermidis as the causes. E.coli found in 19.63 % cases. Klebsiella pneumonia in 12.15 % cases.

In this study, Out of 50 patients, gram negative infections were found in 38 patients (76%) and gram positive infections in 12 patients (24%) .

In this study , it is found that gram negative infections were more common . This finding is more consistent with other studies. Study done by WR caly etal. reported gram negative infection reported in 72.34 % patients.

Study done by Intekhab Ala metal. showed gram negative infection is most common .

In our study , out of 50 patients on follow up, 6 patients died. Mortality rate found to be 12 % of study population.

In our study, mortality rate is in consistent with studies done by Mattos etal, FrancaA etal where mortality found to be 8.9 % and 12%.

Where as mortality is high other studies such as done by Edna strauss etal, WR caly etal, Qiu-ming wang etal.. Mortalirty was 46.47% in study done by Edna strauss etal. Mortality was 30% in the study done by WR caly etal. In the study done T.S.Ferreira etal, mortality was reported as 29%.

CONCLUSION

1. In this study ,It is found that patients with hepatic encephalopathy associated with infections as the precipitating factor .
2. In this study, it is found that urinary tract infection is the most common among several infections associated with hepatic encephalopathy.
3. It is found that E.coli is the major etiological organism precipitating infection in this study.

RECOMMENDATIONS

Hepatic encephalopathy is a major cause of morbidity and mortality. They are associated with many infections which will worsen the clinical condition of patient. These infections also play a major role in mortality, length of hospital stay and financial burden to the family. Thus patients with hepatic encephalopathy require special care and management facilities as they are more commonly associated with Infections.

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74. The current manuscript reports an in-depth review and a position statement on bacterial infections in cirrhosis. 2014 European Association for the Study of the Liver. Published by Elsevier B.V. Journal of Hepatology 2014 vol. 60 j 1310–1324 Keywords: Cirrhosis; Bacterial infection; Multiresistant bacteria; Diagnosis. Received 26 September 2013; received in revised form 30 December 2013; accepted 26 January 2014 ⇑ Corresponding author. Address: Liver Unit, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERehd, Instituto de Salud Carlos III, Madrid, Spain. E-mail address: pgines@clinic.ub.es (P. Ginès). Position Paper Open access under CC BY-NC-ND license.

75. Bacterial infections in cirrhosis: A position statement based on the EASL Special Conference 2013

CASE SHEET PROFORMA

Age :

Sex:

Ip no:

Total count:

Platelet count:

Diagnosis:

Cultures:

CHILD and MELD score:

Organism:

ABBREVIATIONS

HE hepatic encephalopathy

SBP Spontaneous bacterial peritonitis

CFF critical flicker frequency

CHESS clinical hepatic encephalopathy staging scale

GABA g-aminobutyric acid HE hepatic encephalopathy

HESA hepatic encephalopathy scaling algorithm

MARS molecular adsorbents recirculating system

MELD model for end-stage liver disease

MMSE mini-mental state examination

PHES psychometric hepatic encephalopathy score

ALF Acute Liver Failure

CLF – Chronic Liver Failure

S.No	sex	Sl.No	age	meld	child	PT	INR	BILLIRUBIN	PALTELET	TC	HE GRADE	IP NO	DCLD &	INFECTION	ORGANISM
1	F	1	60	16	C	22.5	2.06	11.6	96000	3700	1	I15000085	AUTO IMMUNE STATUS	SEPTICEMIA,SBP	ECOLI
2	M	2	62	31	C	41.5	4.63	19.4	31000	6400	2	I15000805	HCV/CKD	ESOPHAGIAL CANDIDIASIS,URINE CANDIDURIA	CANDIDA ALBICANS
3	M	3	43	27	C	23	2.23	18.3	52000	11600	2	I15001666	OH RELATED	UROSEPSIS,SEPTICIMIA	E COLI+ENTROCOCCUS FECALIS,STAPH
4	F	4	56	22	C	14.5	1.16	1.1	140000	8200	3	I15001998	DCLD,CRYPTOGENIC	SEPTICEMIA	KLEBSIELLA
5	M	5	55	30	C	23.3	2.17	25.4	31000	4700	3	I15002673	OH,HBV	SEPTICEMIA,LRTI	KLEBSIELLA
6	M	6	54	21	C	31.5	3.21	14.5	130000	21000	2	I15005891	OH	SBP	KLEBSIELLA
7	M	7	52	23	C	19.1	1.64	2.3	148000	9000	1	I15006141	BA-ARDS	SBP	E COLI
8	M	8	57	24	C	20.7	1.84	2.3	171000	14700	2	I15006828	OH	ASCITIC FLUID,WOUND	E COLI,STREP PYOGENS
9	M	9	48	32	C	24.6	2.31	6.9	76000	16500	2	I15007780	OH,LRTI	SEPTICEMIA	MYROIDES SPECIES
10	F	10	69	19	C	29.7	2.98	5.6	92000	10100	1	I15003164	CRYPTOGENIC,SBP	LRTI/URINE	KLEBSIELLA/ECOLI
11	M	11	55	30	C	20.2	1.7	26.2	33000	14000	3	I15003880	OH,HBV	SBP/LRTI/SEPTICEMIA	KLEBSIELLA PNEUMONIA
12	M	12	49	21	C	21	1.88	2.5	85000	6600	2	I15004237	OH RELATED	SBP	SPHINGOMONAS PAUCIMOBILLIS,ECOLI
13	M	13	46	32	C	37.1	3.98	12.1	72000	7400	2	I15010540	OH RELATED	URINE	E COLI
14	M	14	65	16	C	20	1.3	11	407000	10700	2	I15010549	OH	UROSEPSIS	ENTROCOCCUS
15	M	15	43	20	C	32	3.22	14.3	51000	10900	1	I15011287	OH	SBP/SEPTICEMIA	ECOLI
16	M	16	45	32	C	33	3.29	17.1	151000	15200	3	I15012886	WILLSONS	THROAT/URINE	KLEBSIELLA PNEUMONIA /STREPTOCOCUS SALIVARIOUS
17	M	17	52	48	C	31.9	3.13	26.3	121000	28200	3	I15014210	SBP,SEPTIC SHOCK	URINE	CANDIDA ALBICANS
18	M	18	57		C	28.34	2.69	7.4	72000	9300	2	I15014824	DCLD,DM,CVA	SEPTICEMIA/HAP	STREPTOCOCCUS AGALACTIAE/KLEBSILLA PNEUMONIA
19	M	19	55	24	C	29.6	2.84	21	73000	12500	2	I15014613	DM	SEPTICEMIA	STAPHYLOCOCCUS SPECIES
20	F	20	60	26	C	19.7	1.77	3.3	99000	17300	2	I15016097	NAFLD/AKI	URINE	STAPHYLOCOCCUS AUREUS
21	M	21	66	52	C	54	6.23	22.2	8000	25000	1	I15017439	CRYPTOGENIC,SBP	URINE/SEPTICEMIA	ECOLI/KLEBSIELLA
22	M	22	43	19	C	16.1	1.31	4	117000	10800	2	I15017587	OH/AKI	URINE	ENTROCOCCUS FAECELIUM
23	M	23	66	29	C	21	1.88	3.9	44000	10100	2	I15017979	NAFLD/DM	URINE/LRTI	CANDIDA ALBICANS/KLEBSIELLA PNEUMONIA
24	M	24	38	43	C	26.5	2.67	14.2	29000	24900	2	I15018031	OH/SBP	SEPTICEMIA	STAPHYLOCOCCUS SPECIES
25	M	25	60	27	C	27.6	2.6	4.6	32000	10400	3	I15018122	DLCD/HCV	SPUTUM/BLOOD	KLEBSILLA PNEUMONIA/STREPTOCOOCCUS PYOGENS

S.No	sex	Sl.No	age	meld	child	PT	INR	BILLIRUBIN	PALTELET	TC	HE GRADE	IP NO	DCLD &	INFECTION	ORGANISM
26	M	26	69	26	C	22.7	2.03	5.6	20000	4200	2	I15019367	NAFLD/AKI	UROSEPSIS	ECOLI
27	M	27	36	24	C	21	1.79	11.3	56000	13000	2	I15021451	OH SBP	ASCITIC FLUID	ECOLI
28	F	28	75	16	C	20.4	1.77	2.8	80000	1500	1	I15022342	HCV	UROSEPSIS	ECOLI
29	M	29	54	28	C	24	2.28	6.1	46000	11000	1	I15025147	OH SBP	ASCITIC FLUID	ECOLI
30	M	30	59	20	C	19.2	1.65	4.6	87000	10200	2	I15025446	OH SBP	ASCITIC FLUID/URINE	STAPHYLOCOCCUS (CONS)
31	F	31	42	13	B	13.2	1.02	2.9	156000	25100	1	I15025561	CRYPTOGENIC/LRTI	LRTI	KLEBSIELLA PNEUMONIA
32	M	32	42	23	C	23.5	2.15	20.7	40000	10100	2	i15026657	DCLD/UGI BLEED	UTI,SEPTICEMIA	ENTEROCOCCUS FECALIS/STAPHYLOCOOCUS AERUGINOSA
33	M	33	43	41	C	21.2	2.88	37.3	96000	22000	2	I15025913	DCLD/SBP	ASCITIC FLUID	E.COLI
34	M	34	54	40	C	28.4	2.74	18.2	69000	17800	3	I15027449	DCLD/SBP	UTI,BLOOD	E.COLI,ENTEROCOCCUS FECALIS, STAPHYLOCOCCUS AUREUS
35	M	35	44	27	C	150	23	2.8	109000	52000	3	I15028204	DCLD/AKI	BLOOD	STAPHYLOCOCCUS AUREUS(MSSA)
36	M	36	76	27	B	17.3	1.45	1.4	25000	3800	1	I15029529	DCLD/RUGHT LOWER LIMB CELLULITIS/AKI	ASCITIC FLUID,WOUND,BLOOD	S.PYOGENES/S.AUREUS/E.FECALIS
37	M	37	57	11	C	15.9	1.3	5.5	515000	22000	2	I15028856	DCLD,RIGHT LOWER LIMB DIABETIC FOOT, SEPSI	SPUTUM/BLOOD/WOUND	CANDIDA SPECIES/E.COLI
38	M	38	51	9	B	15.1	1.21	7.6	484000	19500	1	I15029156	DCLD/PERIANAL ABSCESS	BLOOD	PSEUDOMONAS AERUGINOSA
39	M	39	42	28	C	22	2.05	13.8	59000	28200	3	I15029625	DCLA/CULTURE+ SBP	ASCITIC FLUID/URINE	KLEBSIELLA PNEUMONIA
40	M	40	46	29	C	19.6	1.69	3.7	124000	9100	2	I15029480	DCLD/AKI	SEPTICIMIA/URINE	E.COLI/ENTEROCOCCUS FAECIUM/CANDIDA SPECIES
41	M	41	47	24	C	25.1	2.3	2.3	69000	12600	2	I15031397	DCLD/SBP	BLOOD/URINE	K.PNEUMONIAE
42	M	42	55	28	C	32.3	3.35	11	126000	12500	2	I15031670	DCLD/SBP	ASCITIC FLUID/UTI	MYROIDES SPECIES/E.COLI
43	M	43	46	37	C	46.6	13	12.4	43000	5600	2	I15031551	DCLD/LRTI/RIGHT LOWER LIMB CELLULITIS	URINE/LRTI	KLEBSIELLA/CANDIDA SPECIES
44	M	44	67	11	C	19.8	1.72	3.1	86000	6200	3	I15034156	DCLD/RIGHT LOWER LIMB CELLULITIS/ UTI	URINE /WOUND	K.PNEUMONIAE/E.COLI/E.FAECIUM
45	M	45	35	25	C	22.1	1.97	6.7	107000	18600	2	I15036405	DCLD	UROSEPSIS/SEPTICEMIA/WOUND	E.COLI/PSUDOMONAS AERUGINOSA
46	M	46	42	27	C	22.6	2.04	10.2	185000	15500	2	I15033297	DCLD-OH/AKI	UROSEPSIS	E.COLI/E.FAECIUM/CANDIDA
47	M	47	58	27	C	22.23	2.24	8.7	120000	9300	1	I15036122	DCLD-HBV/SBP	ASCITIC FLUID	KLEBSIELLA SPECIES
48	M	48	40	24	C	23.4	2.13	6.4	111000	7200	2	I15035008	DCLD-OH/SBP	ASCITIC FLUID	E.COLI
49	M	49	46	25	C	18.2	1.54	2.9	228000	15100	2	I15038115	DCLD-OH	SEPTICEMIA	E.COLI
50	M	50	45	31	C	26.8	2.54	6.8	48000	12500	3	I15035972	DCLD-OH/LRTI	TRACHEAL ASPIRATE	STAPH. AUREUS