Palliative Care in Advanced Liver Disease

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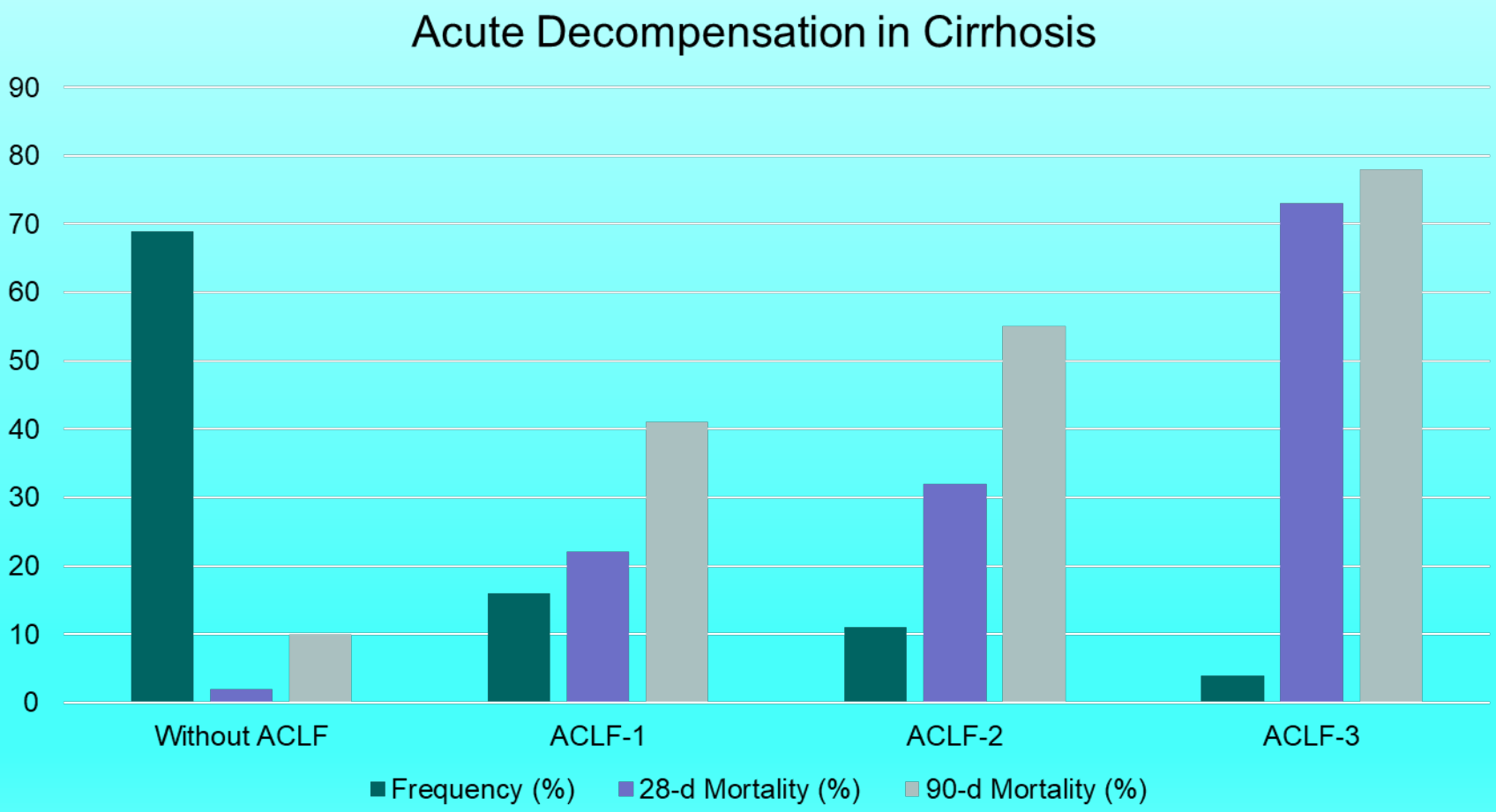
Mortality in Cirrhosis

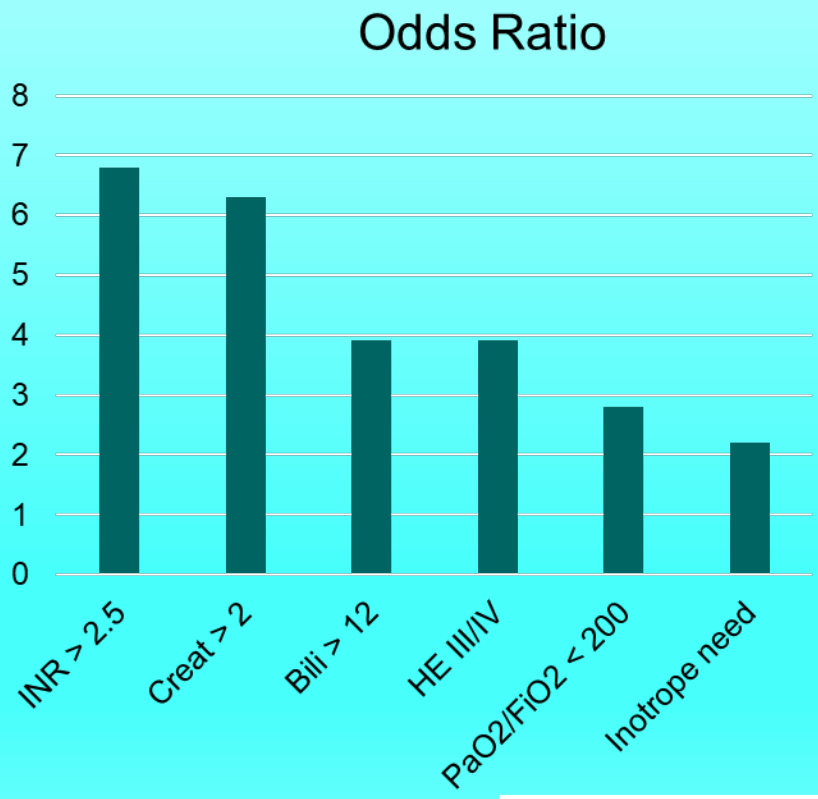
- Stable Cirrhosis:
  - Prognosis determined by MELD-Na score
  - Provides 90 day mortality.
  - http://www.mdcalc.com/meldna-meld-na-score-for-liver-cirrhosis/
- Acute on Chronic Liver Failure (ACLF)
  - Mortality Provided by CLIF-C ACLF Calculator
  - Provides mortality at 1, 3, 6 and 12 months.
  - http://www.clifresearch.com/ToolsCalculators.aspx
- Acute Decompensation (without ACLF):
  - Mortality Provided by CLIF-C Acute decompensation Calculator
  - Provides mortality at 1, 3, 6 and 12 months.
  - http://www.clifresearch.com/ToolsCalculators.aspx
- Survival of Ambulatory Patients with HCC (MESIAH)
  - Provides survival at 1, 3, 6, 12, 24 and 36 months.
  - https://www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/model-estimate-survival-ambulatory-hepatocellular-carcinoma-patients-mesiah

Acute Decompensation
Type and Mortality

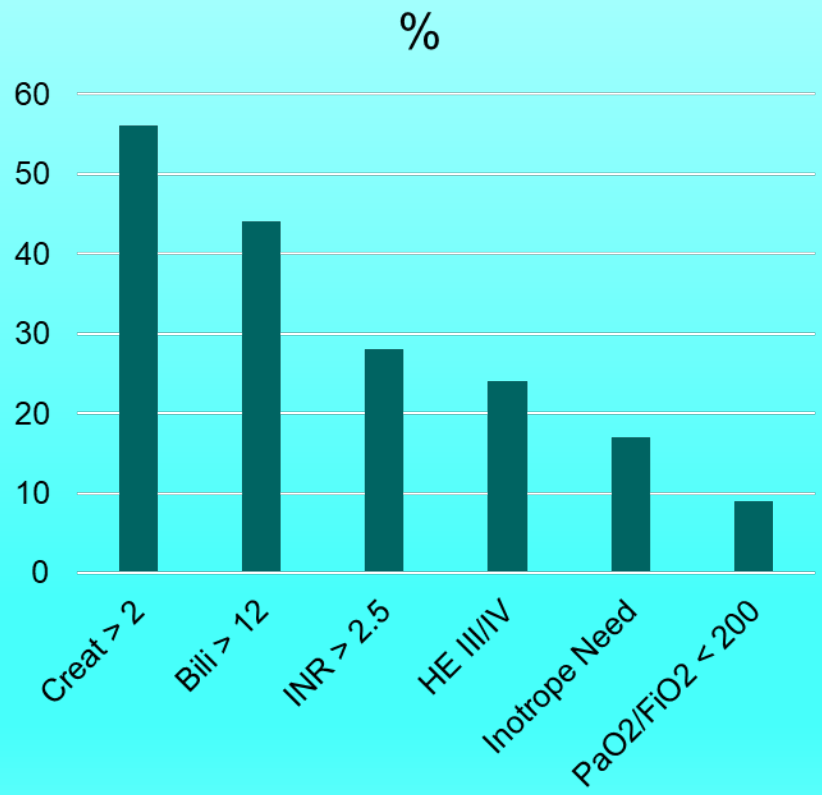


Organ Failure in Acute-on-Chronic Liver Failure

Organ Failure Mortality Impact



Frequency of Organ Failure



48% have >/= 2 Organ Failures

	DATA	SCORES
Bilirubin	____ mg/dl	Liver score ____ Liver failure ○ Yes ○ No
Creatinine	____ mg/dl	Kidney score ____
Renal replacement therapy	○ Yes ○ No	Renal failure ○ Yes ○ No
Use of vasopressors (Hepatorenal syndrome indication)	○ Yes ○ No	
West-Haven grade for HE	○ 0 ○ 1 ○ 2 ○ 3 ○ 4	Brain score ____ Cerebral failure ○ Yes ○ No
INR	____	Coagulation score ____ Coagulation failure ○ Yes ○ No
MAP	____ mm/Hg	Circulation score ____
Use of vasopressors (Circulatory failure indication)	○ Yes ○ No	Circulation failure ○ Yes ○ No
Select one ● PaO_2 (preferred) ○ SpO_2	____	Lung score ____ Respiratory failure ○ Yes ○ No
FiO_2	____ %	
Mechanical Ventilation	○ Yes ○ No	
		Total Number Failures ____ CLIF Organ Failure Score ____
		ACLF Grade ____

CLIF-C AD Score and expected mortality rates

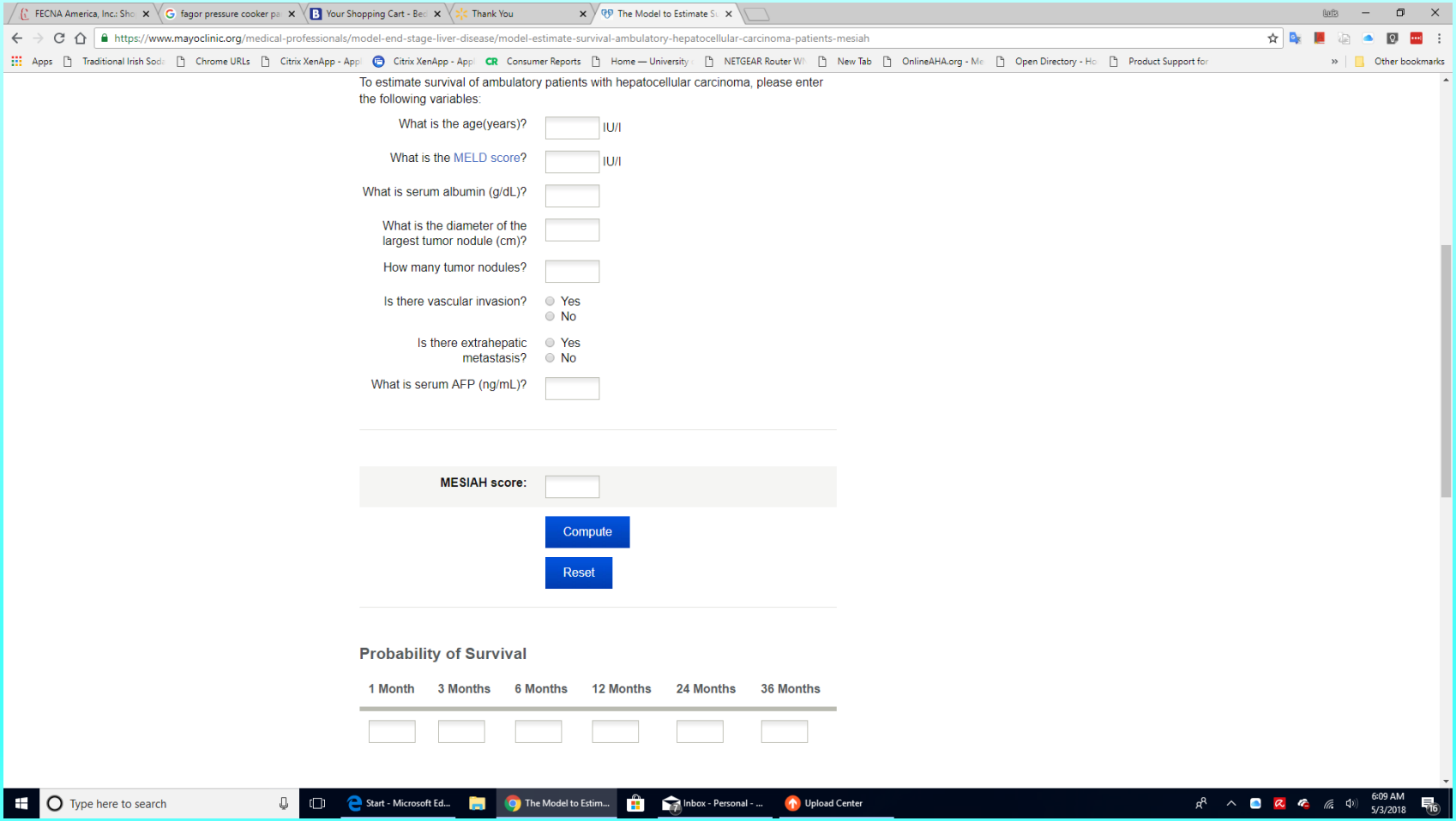
Patients with Acute Decompensation and no ACLF

	DATA	SCORES
Age	years	
White-cell count	10^9cells/L	
Creatinine	mg/dl	
INR		
Sodium (Na)	mmol/L	
		CLIF-C AD Score
		Probability of dying at 1 month %
		Probability of dying at 3 month %
		Probability of dying at 6 month %
		Probability of dying at 12 month %

Reset Compute

The MESIAH Score

Model of **E**stimated **S**urvival **I**n **A**mbulatory patients with **H**CC



Complications of Cirrhosis Affecting Palliative Care

- Ascites and Hepatic Hydrothorax.
- Hyponatremia.
- Hepatorenal syndrome.
- Hepatic Encephalopathy.
- Malnutrition/ Anorexia.
- GI bleeding: Varices, Portal gastropathy & Gastric Antral Vascular Ectasia
- Pruritus
- Hepatopulmonary Syndrome.

Difficult Decisions with Shifting Balance

- Is patient a liver transplant candidate?
- Effect of illness in:
  - patient's survival
  - patient's Quality of Life
    - patient's relation to family
    - family's Quality of Life
- Effect of therapy in:
  - patient's survival
  - patient's Quality of Life
    - patient's relation to family
    - family's Quality of life

Ascites and Palliation

- **PATHOGENESIS**

- Hepatic sinusoidal HTN stimulates hepatic baroreceptors,
  - causing severe peripheral **arterial vasodilation**,
  - leading to functional **intravascular underfilling** despite hypervolemia,
  - inducing **neurally mediated Na retention**, with high aldosterone, renin, vasopressin & norepinephrine
- Decreased intravascular oncotic pressure due to hypoalbuminemia
- Na intake larger than output.

- **CONSEQUENCES**

- Abdominal distention with early satiety.
  - Decreased food intake worsening malnutrition.
- Breathing difficulty.
- Decreased mobility: isolation.
- Renal dysfunction with diuretic use.
- Risk of Infection (SBP).
- Protein depletion by paracentesis.

Ascites and Palliation

- **TREATMENT**
  - Diet:
    - Na restriction below Na excretion (usually 1-2 gm Na per day);
    - 1.2-1.5 gm protein/kg;
    - 3 meals + 4 snacks
  - Diuretics to increase Na excretion.
  - Improve liver function and nutrition.
  - Repeated large volume paracentesis
  - TIPSS (if MELD </= 20)
  - Midodrine
  - D/C betablockers in refractory ascites + Variceal banding.

- **LIMITATIONS**
  - Poor oral intake due to palatability.
  - Quality of life issues due to food preferences.
  - Worsening malnutrition worsens ascites (less oncotic pressure).
  - Renal dysfunction due to diuretics causing encephalopathy.
  - Paracentesis: hospital visit & cost vs. tunneled permanent catheter for bedside drainage (infection risk) + daily Ciprofloxacin
  - TIPSS may worsen encephalopathy & accelerate loss of liver function
  - Increase bleeding risk

Transjugular Intrahepatic Porto-Systemic Shunt

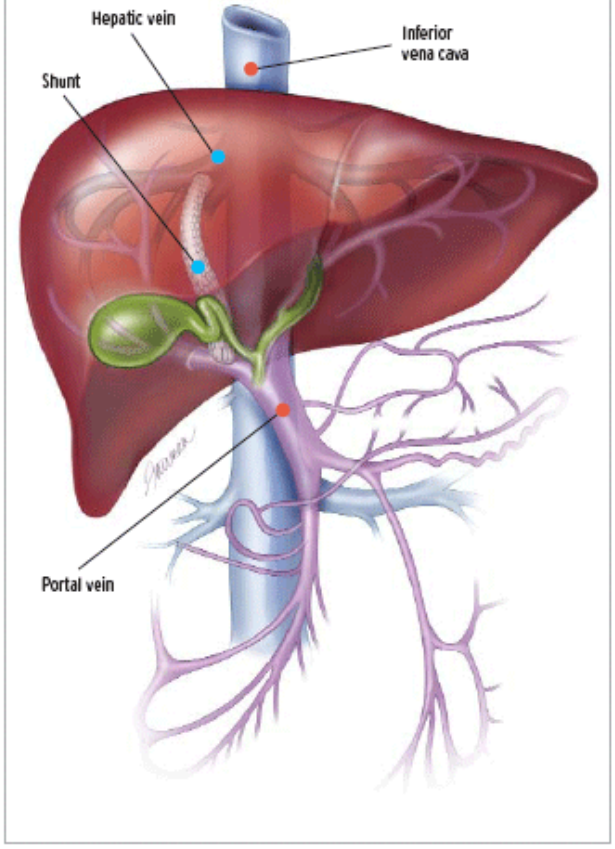


FIGURE 1. Transjugular intrahepatic portosystemic shunt

Mortality (%) at 3 months after Elective TIPSS

Malinchoc et al. Hepatology 2000;31:864-871

- Table of 3 month mortality after TIPS, compared with hospitalized cirrhotics not receiving TIPSS (http://www.soapnote.org/digestive-system/meld/)
- MELD is “UNOS MELD”
  - Creat >/=1 and </= 4 mg/dL;
  - Bili is >/= 1 mg/dL
- Group A: Alcoholic or Cholestatic Liver Disease.
- Group B: Viral, NASH, Cryptogenic, A_1AT deficiency, Wilson, MTX, etc.
- MELD 3-month Mortality from Weisner R S3mo=0.98465exp(MELD score-10)*0.1635 Gastroenterology 2003;124:91-96
- **Guideline:** TIPSS is good alternative for MELD </= 15; could be considered if there is no other choice for MELD </= 18
- In refractory ascites improves survival up to MELD of 20.

MELD	Alcohol/ Cholestasis	Viral/NASH/MTX/ Wilson/A1AT/Crypto	*Hospitalized without TIPS*
10	15	27	***1.6***
12	17	30	***2.2***
14	22	37	***3***
15	23	39	***3.5***
16	25	42	***4***
17	28	46	***5***
18	30	49	***6***
19	32	52	***7***
20	35	57	***8***
21	38	60	***9***
22	43	64	***11***
23	43	71	***12***
24	47	73	***14***
25	50	78	***17***

Hepatic Hydrothorax and Palliation

- **PATHOGENESIS**

- Preferential passage of ascites from abdomen to chest, due to diaphragmatic fenestrae/defect and negative intra-thoracic pressure.
- Many times ascites is not found (complete passage)
- Diagnosis is by Nuclear medicine scan after injection of “tracer” into abdomen with passage to chest after partial thoracentesis.

- **CONSEQUENCES**

- Dyspnea and cough due to hydrothorax.
- Risk of Spontaneous Bacterial Pleuritis (wrongly called Empyema).
- Need for frequent (often daily) thoracentesis to alleviate dyspnea; bleeding risk with each tap.

Hepatic Hydrothorax and Palliation

- **TREATMENT**

- Improve nutrition.
- Na restriction + diuretics.
- TIPSS
- If TIPSS contraindicated
  - Pleuro-venous (Denver) shunt.
  - Tunneled pig-tail catheter for intermittent evacuation + daily Ciprofloxacin
- CHEST TUBE IS CONTRAINDICATED

- **LIMITATIONS**

- Food limitations and palatability.
- Decompensation and death from TIPSS.
- Decompensation and infection with shunt or pig-tail catheter.

Hyponatremia and Palliation

- **PATHOGENESIS**
- Decreased free water clearance due to vasodilation with vascular “under filling” and appropriate ADH secretion
  - Water retention in excess of Na retention, with dilutional hyponatremia, but with total body excess of both, Na and water.

- **CONSEQUENCES**
- Confusion/ slow mental activity
- Fatigue/ weakness
- Seizures
- Hepatorenal syndrome
- Refractory ascites
- Death

Hyponatremia and Palliation

- **<u>TREATMENT</u>**
  - Fluid restriction (give artificial saliva for comfort)
  - Tolvactan
  - Increase Blood pressure
    - d/c beta-blockers
    - midodrine
- **<u>LIMITATIONS</u>**
  - Quality of life
  - Decreased food/ calorie intake
  - Expensive ($300/tab);
    - only approved for short therapy (30 d);
    - not recommended in liver disease (APKLD)

Hepatorenal Syndrome and Palliation

- **PATHOGENESIS**

- Usually preceded by refractory ascites & hyponatremia.
- Extreme vasodilation with renal hypoperfusion
- Relaxation of efferent glomerular arteriole decreases GFR.
- Often triggered by infection, bleeding episode, or NSAIDs.

- **CONSEQUENCES**

- Worsening confusion due to azotemia.
- Hyperkalemia, hyperphosphatemia, anasarca.
- Worsening ascites
- Death in few weeks.

Hepatorenal Syndrome and Palliation

- **TREATMENT**

- Volume expansion with IV albumin + vasopressors:
  - octreotide SQ + midodrine PO,
  - norepinephrine IV,
  - terlipressin IV)
- TIPSS
- Treat infection & control bleeding

- **LIMITATIONS**

- Need of IV access (at least for albumin)
- Expense of albumin
- Need of ICU for norepinephrine or terlipressin
- Poor outcome of TIPSS in high bilirubin (>/= 4) & creatinine (MELD > 18)

Hepatorenal Syndrome and Palliation

- **PREVENTION**

- Low protein ascites (<1.5 g/dL) while hospitalized: Ciprofloxacin 500 mg/day
- SBP: Antibiotics plus Volume expansion with albumin 1.5 g/kg at diagnosis + 1 gm/kg 48 h later.
- Post-SBP after discharge: long term Ciprofloxacin 500 mg/d
- Alcoholic Hepatitis: Trental
- Azotemia (CrCl 41-80) + Ascites: long term Trental.
- Ascites + Child > 9 and Cr > 1.2, Bili > 3, or Na < 130: long term Ciprofloxacin 500 mg/d
- Recurrent or refractory ascites: Midodrine 7.5 mg TID

- **LIMITATIONS**

- Cost.
- Risk of antibiotic resistance.
- Risk of PMC with Ciprofloxacin.
- Nausea from Trental.

Hepatic Encephalopathy and Palliation

- **PATHOGENESIS**

- Inability of liver to clear ammonia, mercaptans, false neurotransmitters, and endogenous benzodiazepines due to shunting of blood and low hepatocyte mass
- Triggers: Narcotics, benzodiazepines, sedatives, electrolyte misbalance, infection, excessive protein intake, GI bleed, azotemia.

- **CONSEQUENCES**

- Prolonged reaction time; should not drive.
- Reversal of sleep
- Personality changes
- Confusion
- Isolation
- Coma
- Death
- Physician's fear to control pain/ anxiety

Patients Have Significantly Decreased Survival After an Overt HE Event

HE = hepatic encephalopathy.

Bustamante et al. *J Hepatol*. 1999;30:890-895. Figure adapted from Bustamante et al. *J Hepatol*. 1999;30(5):890-895. With permission from Elsevier.

Hepatic Encephalopathy and Palliation

- **TREATMENT**
- Keep protein intake about 1.2-1.5 gm/kg
  - Divide protein intake throughout the day.
- Lactulose: 3-4 BM/d
- Antibiotics: rifaximin, neomycin, metronidazole
- Zn
- L-carnitine supplementation
- Probiotic Yogurt BID
- Frequent (7) meals a day

- **LIMITATIONS**
- Diarrhea
- Abdominal bloating
- Pseudomembranous colitis, azotemia, malabsorption, neuropathy, cost
- Seizures
- Pain: acetaminophen up to 2 g/d, tramadol
- Mood: low dose SSRIs

Malnutrition/ Anorexia and Palliation

- **PATHOGENESIS**
- Disgeusia
- Hypermetabolism
- Early satiety
- Diet restrictions
- Confusion
- Depression
- Repetitive paracentesis

- **CONSEQUENCES**
- Weakness
- Worsening ascites
- Immobility
- Death

Malnutrition/ Anorexia and Palliation

- **TREATMENT**

- Frequent small meals/snacks (6/day) + high calorie supplement (Boost Plus 2 cans/hs)
- Flavorings without Na nor K (Ms. Dash)
- Tube feeds
- Ascites control
- TIPSS for truly refractory ascites; less gastric fullness.

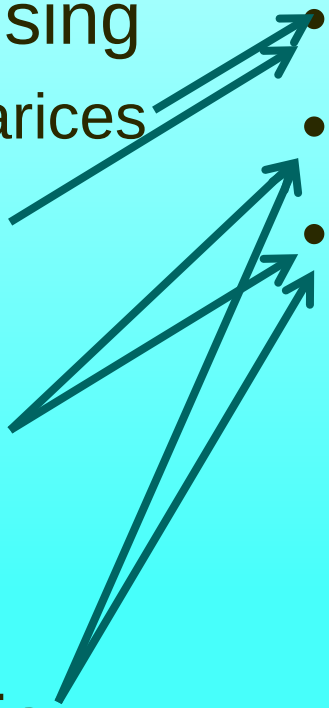
- **LIMITATIONS**

- Cost of low-Na food, fresh fruits & vegetables
- Need to cook special diet
- Taste
- May need assistance to eat (tremor)
- No allowance of nasoenteric tubes in nursing homes (PEG contraindicated in cirrhotic ascites)

GI bleeding and Palliation

- **PATHOGENESIS**
- Portal HTN causing
  - Esophageal Varices
  - Gastric varices
  - Portal HTN gastropathy, enteropathy or colopathy
- Gastric Antral Vascular Ectasia

- **CONSEQUENCES**
- Massive GI bleed
- Low grade GI bleed
- Fe deficiency anemia



GI bleeding and Palliation

- **TREATMENT**
  - Acute:
    - Octreotide IV
    - Cefotaxime IV for infection/rebleeding risk.
    - Therapeutic endoscopy
    - TIPSS
  - Chronic/prevention:
    - Beta-blockers, banding, TIPSS, Surgical shunt
    - Electrocoagulation (APC) for GAVE
    - Fe replacement
    - Octreotide LAR
    - Erythropoyetin

- **LIMITATIONS**
  - Hospitalization.
  - Symptomatic hypotension (rare) from b-blocker
  - Worsening of encephalopathy (TIPSS)
  - Need for repeated endoscopy
  - Fe excess
  - Cost

Pruritus and Palliation

- **PATHOGENESIS**

- Bile acids accumulation with mu-receptor stimulation

- **CONSEQUENCES**

- Quality of life:
  - constant need for scratching,
  - poor sleep,
  - skin infections
- Worsening of depression.
- Fatigue.

Pruritus and Palliation

TREATMENT	**LIMITATIONS**
Bile salt binders (cholestiramine, cholestipol, colesevelam)	Constipation – encephalopathy, poor absorption of other drugs.
Hydroxizine	Sedation
Rifampin	Worsening of jaundice, pseudomembranous colitis, antibiotic resistance
Sertraline	Increased bleeding risk
Naltrexone	Narcotic antagonism
Dronabinol.	

Hepatopulmonary Syndrome and Palliation

- **PATHOGENESIS**

- Vascular shunting (AVM's) in the lungs allowing non-oxygenated blood to go for recirculation

- **CONSEQUENCES**

- Hypoxemia
- Laborious breathing
- Fatigue
- Severe dyspnea with activity.
- Increased mortality

Hepatopulmonary Syndrome and Palliation

- **TREATMENT**

- Oxygen supplementation
- Coil-embolization of large pulmonary AVMs.
- Garlic tablets.
- Trental.

- **LIMITATIONS**

- Sedation worsens hypoxemia.
- Oxygen supplementation may not correct hypoxemia.
- Garlic odor.
- Nausea.

SUMMARY

- There are several useful tools to predict mortality in cirrhosis.
- Advanced liver disease makes choices of palliation interventions more difficult.
- Many drugs that help to alleviate pain and discomfort may aggravate the underlying liver disease associated disorders, affect the ability of the patient to function or to relate to others, and potentially accelerate death.
- There are no easy therapeutic choices in patients with advanced liver disease; careful balance of pros- and cons- should be done.

Questions ?

Trans-jugular Intrahepatic Porto-Systemic Shunt