Caring for the Hospice Patient with Liver Disease

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Objectives

• Common Causes of Liver Disease
• Hospice Criteria for Terminal Diagnosis of Liver Disease
• Treatment of Symptoms of Liver Disease

Common Causes of Liver Disease

• Cirrhosis of Liver without Alcohol 571.5
• Alcoholic Cirrhosis 571.2
• Chronic Hepatitis (HBV, HCV) 571.4
• Hepatocellular Carcinoma 155.0
• Primary Biliary Cirrhosis 571.6
• Autoimmune hepatitis 571.42
• Hepatic Encephalopathy 572.2

Common Causes of Liver Disease

• Hepatorenal Syndrome 572.4
• Hepatopulmonary Syndrome 573.5
• Hemochromatosis 275.03
• Primary Sclerosing Cholangitis 576.1
• Alpha-1-antitrypsin Deficiency 273.4
• Nonalcoholic Fatty Liver Disease 571.8

Cirrhosis

• 4.5-9.5% of global population
• Histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury that leads to portal hypertension and end stage liver disease
• Usually indolent, asymptomatic and unsuspected until complications of liver disease
• Biopsy is gold standard for diagnosis
Classification of Cirrhosis

• Child-Pugh-Turcotte (CPT): based on encephalopathy, ascites, bilirubin, albumin, and PT/INR

• One year survival for class A (100%), B (80%), C (45%); also predicts complications

Classification of Cirrhosis

• Model for End Stage Liver Disease (MELD): predicts 3 month survival based on creatinine, bilirubin, and INR and gives transplant priority to those more likely to die without

• Further refinement by giving extra points for hyponatremia and HCC

Cirrhosis

• Signs/Symptoms:
  jaundice
  nodular liver
  ascites
  palmar erythema
  Dupuytren’s contracture
  gynecomastia
  hypogonadism
  fatigued hepatic
  muscle atrophy
  variceal bleeding
  bacterial infections
  hypertrophic osteoarthropathy
  spontaneous bacterial peritonitis

Cirrhosis

• Increased: AST/ALT, ALP, GGT, bilirubin, immunoglobulins
• Decreased: albumin, prothrombin time, sodium, hemoglobin, platelets, WBCs.
• Consequences: impaired hepatocyte function, increased intrahepatic resistance, and hepatocellular carcinoma
• Prognosis and Treatment depend on etiology
Transplant

- Indications: CPT>7 or appropriate MELD score, unresectable liver malignancy, inherited metabolic disorder, no alternative therapy, medical compliance and funding

- Contraindications: HIV, methadone dependence, stage 3 HCC, extrahepatic malignancy, AIDS, cholangiocarcinoma, severe systemic infection, multiorgan failure, advanced cardiopulmonary disease, active substance abuse

Alcoholic Liver Disease

- Signs/Symptoms:
  - fever
  - jaundice
  - liver bruit
  - bleeding
  - gynecomastia
  - clubbing
  - neuropathy
  - ascites
  - hepatosplenomegaly
  - anorexia
  - encephalopathy
  - palmar erythema
  - caput medusa
  - Dupuytren’s contractures
  - testicular atrophy
  - spider angiomata

- Biopsy indicated if enzyme elevations persist for >6 months, other lab evidence of liver failure, uncertain diagnosis, in patients with more than 1 liver disease, prognostication

- Patients with alcoholic cirrhosis without alcohol consumption without transplant have 5 year survival of 60% versus 30% for those who continue to drink alcohol

Alcoholic Liver Disease

- Disproportionate elevation of AST:ALT usually >2:1, AST and ALT usually <300 IU/L
- Macrocytosis
- Folate and B12 deficiency
- Thrombocytopenia
- Leukocytosis
- Elevated alcohol
- Elevated GGT
- Elevated bilirubin
**Hepatitis B Infection**

- **Signs/Symptoms:**
  - fatigue, jaundice
  - ascites, encephalopathy
  - edema, splenomegaly

- **Extrahepatic manifestations:**
  - polyarteritis nodosa
  - glomerular nephropathy and nephritis
  - aplastic anemia

- **Treatments:** antivirals such as entecavir, tenofovir, and lamivudine, interferon alpha

- **5 year survival:**
  - decompensated liver disease is 14-35%
  - compensated liver disease is 85-90%

- **5 year rate of progression to cirrhosis:** 12-20%

- **HBV may lead to hepatocellular carcinoma without evidence of cirrhosis**

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**Hepatitis C Infection**

- **Acquired through IV drug use (68%) and STD (15-20%) and needle sticks (4%)**

- **Cases acquired through blood transfusion in 1960-1980 now increasing morbidity and mortality and cost of HCV**

- **60-80% develop long term HCV infection and 20-30% of those develop cirrhosis**

- **HCV accounts for 1/3 of HCC**

- **Factors that increase risk of cirrhosis:**
  - age
  - male
  - Caucasian
  - HIV
  - HBV
  - schistosomal infection
  - NASH
  - alcohol
  - iron overload

- **Signs/Symptoms:**
  - fatigue, RUQ pain
  - nausea, anorexia
  - weakness, musculoskeletal pain
  - weight loss, abdominal swelling
  - dark urine, fluid retention
  - itching

- **Extra-hepatic manifestations of chronic HCV:**
  - mixed cryoglobulinemia
  - B-cell non-Hodgkin’s lymphoma
  - glomerulonephritis
  - seronegative arthritis
  - keratoconjunctivitis sicca
  - lichen planus
  - neuropathy
  - cognitive disorders
  - porphyria cutanea tarda
  - thyroiditis
  - autoantibodies
  - diabetes mellitus
Hepatitis C Infection

- Most common cause of chronic liver disease and indication for transplant in U.S.
- 6 genotypes: type 1 most common in U.S. (70-75%) and most resistant to interferon therapy
- Treatment: Interferon alpha
- Decompensated cirrhosis 5 year survival is 50%
- CDC estimates 8000-13000 deaths per year from chronic HCV

Hepatocellular Carcinoma

- 5th most common neoplasm in the world and 2nd most common cause of cancer-related death
- Affects mainly patients with cirrhosis mostly from HCV, HBV, and/or alcohol abuse
- Signs/Symptoms: pain, early satiety, jaundice, palpable mass

Hepatocellular Carcinoma

- Risk factors: cirrhosis, HBV, NASH, aflatoxin, male, alcohol, diabetes, Betel nuts, tobacco, red meat, coffee
- Complications: decompensated cirrhosis, HCV, hemochromatosis, co-infection with HCV/HBV/HIV, increasing age, positive family history, contaminated drinking water, abnormal epidermal growth factor, alpha1antitrysin deficiency, saturated fat, statins

Hepatocellular Carcinoma

- Paraneoplastic manifestations: erythrocytosis, hypercalcemia, hypoglycemia, diarrhea
- Treatments: surgical resection, liver transplant, percutaneous ablation with ethanol, radiofrequency ablation, arterial embolization, chemotherapy, palliation
Hepatocellular Carcinoma
- Yearly screening of cirrhosis patients with imaging is recommended
- Patient with HCV/HCC has 1% 2 year survival
- Mortality is expected to double or triple over next decade.
- Even though new HCV infection is declining, cirrhosis and HCC is increasing.
- With transplant, 1 year survival is 83% and 5 year survival is 70% (UNOS)

Hemochromatosis
- Autosomal recessive iron overload disease
- Inappropriate increase in iron absorption in the duodenum and upper small intestine
- Deposition of iron in liver, pancreas, heart, joints, skin, pituitary gland

Hemochromatosis
- Leads to cirrhosis, restrictive cardiomyopathy, diabetes, arthropathy, hyperpigmentation, gonadal failure
- Increased risk of cirrhosis and hepatocellular carcinoma
- Treatment: phlebotomy (goal: ferritin <50ng/ml), chelation therapy, transplant

Primary Biliary Cirrhosis
- Autoimmune, chronic, cholestatic, granulomatous, progressive destruction of small intrahepatic bile ducts with portal inflammation and fibrosis
- Predominantly affects middle-aged women
- Leads to impaired bile secretion
- Diagnosis 2 out 3: elevated ALP, AMA, and histology showing destruction
Primary Biliary Cirrhosis

- Signs/Symptoms/Extramanifestations:
  - hepatosplenomegaly
  - hyperpigmentation
  - osteoporosis
  - cirrhosis stigmata
  - cutaneous scleroderma
  - vitamin D deficiency
  - hyperbilirubinemia
  - Sjogren’s syndrome
  - cognitive impairment
  - xanthelasmas
  - itching
  - osteomalacia
  - hemorrhage
  - CREST syndrome
  - steatorrhea,
  - cytopenias
  - arthritis
  - RUQ pain

- Labs: Elevated alkaline phosphatase, GGT, anti-mitochondrial antibodies and IgM, ANA, lipids, later elevated bilirubin

- Treatment:
  - Ursodeoxycholic acid (bile acid replacement) turns off cycle, 30% respond
  - Budesonide
  - plasmapheresis with FFP
  - ion-exchange resins (questran)
  - S-adenosyl-L-methionine
  - transplant

Primary Sclerosing Cholangitis

- Chronic cholestatic liver disease with inflammation, fibrosis, and strictures of bile ducts leading to end stage liver disease
- Primarily affects young-middle aged men
- Elevated ALP and nonspecific antibodies
- Cholangiography is gold standard for diagnosis

- Signs/Symptoms:
  - pruritus
  - vitamin deficiencies
  - abdominal pain
  - hyperpigmentation
  - weight loss
  - steatorrhea
  - fever/chills
  - night sweats
  - fatigue
  - metabolic bone disease
  - jaundice
  - peristomal varices
  - gallstones
  - bacterial cholangitis
  - polyps
  - biliary strictures
  - IBD
  - cholangiocarcinoma

- Treatment: ursodeoxycholic acid (most studied, but not proven), endoscopic dilatation, sphincterotomy, stent, surgical resection, and transplant
- Survival rate without transplant 10-18 years
- Cholangiocarcinoma occurs in 7-15%
Alpha-1-Antitrypsin Deficiency

- Protein made in liver and transported in blood to lungs where it protects fragile alveoli
- Common genetic disorder with pulmonary emphysema and liver cirrhosis and panniculitis
- 1 in 5000 in U.S. newborns, Scandinavian
- Accelerated by smoking and dust exposure and increased prevalence of HCC

Signs: Prolonged jaundice after birth, bleeding, and abnormal liver enzymes
Cirrhosis/liver failure around age 50
Emphysema in 30-40s with smoking and 50-60s if no smoking
Panniculitis manifests as spontaneous necrosis
Treatment: IV alpha-1-antitrypsin augmentation therapy, vaccines, bronchodilators, inhaled corticosteroids, transplant

Nonalcoholic Fatty Liver Disease

- Most common form of chronic liver disease in Western world (20-35% adults and 5-17% children)
- Dysregulation of lipid metabolism and immune system, genes, environment
- Independent risk factor for CV disease
- Nonalcoholic steatohepatitis 3-5% and cirrhosis 3-5%
- Risk factors: metabolic syndrome, obesity, diabetes II, dyslipidemia

NASH also associated with TPN, rapid weight loss, hypothyroidism, abdominal surgery, drugs
Signs/Symptoms: fatigue, malaise, RUQ pain, elevated enzymes
Biopsy is gold standard for diagnosis
Treatment: no proven effective therapy, lifestyle modification including diet and exercise, bariatric surgery, insulin sensitizing drugs
Autoimmune Hepatitis

- Chronic, with circulating autoantibodies and high serum globulin
- Type 1: ANA and/or ASMA and/or AAA
- Type 2: ALKM-1 and or ALC-1
- Diagnosis: serologic and histologic findings and exclusion of other liver disease and scoring system

Autoimmune Hepatitis

- Signs/Symptoms:
  - hepatosplenomegaly
  - jaundice
  - stigmata of liver disease
  - fatigue
  - elevated transaminases
  - malaise
  - anorexia
  - nausea
  - abdominal pain
  - itching

Autoimmune Hepatitis

- Glucocorticoids, Azathioprine, Cyclosporine, Tacrolimus, Methotrexate, Mycophenolate mofetil, Transplant
- Immunosuppressive treatment should be instituted in patients with serum aminotransferases greater than 10-fold the upper limit of normal, at least five-fold the upper limit of normal in conjunction with serum gamma-globulin levels at least two-fold the upper limit of normal, and/or histologic features of bridging necrosis or multilobular necrosis.

Hospice Criteria for Terminal Diagnosis of Liver Disease

Local Coverage Determination (LCD) for Hospice – Liver Disease

1. Patient must have both:
   - Prothrombin time prolonged more than 5 seconds over control or INR >1.5 (biosynthetic capacity of clotting factors I, II, V, VII, IX, X, XII, XIII), vitamin K does not correct
   - Serum albumin <2.5gm/dl (protein biosynthesis), more common in chronic vs. acute

LDC for Hospice – Liver Disease

2. Patient must have at least one of the following:
   - Ascites, refractory or non-compliant
   - Spontaneous bacterial peritonitis
   - Hepatorenal syndrome, elevated creatinine and BUN with oliguria (<400ml/day), and urine sodium <10mEq/L
   - Hepatic encephalopathy, refractory or non-compliant
   - Recurrent variceal bleeding, despite intensive therapy
LCD for Hospice – Liver Disease

3. Documentation of these factors supports eligibility:
- Progressive malnutrition
- Muscle wasting with reduced strength and endurance
- Continued active alcoholism (>80gm ethanol/day)
- Hepatocellular carcinoma
- HBsAg positive
- Hepatitis C refractory to interferon treatment

LCD for Hospice - Liver Disease

- Patients awaiting liver transplant who otherwise fit criteria may be certified for the Medicare hospice benefit, but if a donor organ is procured, the patient must be discharged from hospice.
- Notice: No mention of elevated aminotransferases (hepatocellular injury), alkaline phosphatase (cholestasis), or bilirubin (toxin clearance) because these do not accurately reflect liver function

Symptoms and Complications

- Encephalopathy
- Variceal bleeding
- Ascites
- Spontaneous bacterial peritonitis
- Pruritus

Symptoms and Complications

- Hepatorenal syndrome
- Hepatopulmonary syndrome, portopulmonary hypertension, and hepatic hydrothorax
- Cardiovascular effects of liver disease
- Pain

Encephalopathy

- Damaged liver is unable to remove toxins such as ammonia and manganese from the blood which then cross the blood-brain barrier and damage brain cells
- May be exacerbated by TIPS procedure which redirects blood around the liver
Encephalopathy

- Precipitants:
  - benzodiazepines
  - narcotics
  - alcohol
  - increased ammonia
  - excess protein intake
  - infection
  - metabolic alkalosis
  - vomiting
  - diarrhea
  - hemorrhage
  - diuretics
  - paracentesis
  - shunt placement
  - spontaneous shunt
  - portal vein thrombosis
  - hepatic vein thrombosis
  - hepatocellular carcinoma

- Signs/Symptoms:
  - sleep disturbances
  - mood changes
  - cognitive deficits
  - psychiatric disorders
  - coma
  - asterixis
  - hyperactive DTRs
  - motor disturbances
  - decerebrate posture

- Treatment:
  - Treat precipitating factors
  - Sugar molecules (lactulose) and antibiotics (neomycin) to reduce GI tract ammonia production
  - L-ornithine L-aspartate converts ammonia into glutamine in muscle
  - Experimental use of neuropharmacologic drugs
  - Transplant and artificial livers

Variceal Bleeding

- Devastating complication, prior to current therapies, mortality was 30%
- Treatment: resuscitation, vasoconstrictors, sclerotherapy, band ligation, TIPS, variceal obliteration, surgical shunt
- Beta blockers as primary prophylaxis in compensated cirrhosis with varices
- Dark towels and education

Ascites

- Portal hypertension leads to fluid retention
- Sodium retention leads to volume expansion plus hypoalbuminemia which leads to low oncotic pressure
- 2 year survival of cirrhosis with ascites is 50% and decreases with diuretic resistant ascites
- Treatment:
  - Low sodium diet
  - Diuretics
Ascites

- Treatment if diuretic resistant (10%):
  - Transplant
  - Large volume paracentesis (8.4L/2 weeks + albumin 6-8g/L if following 2000mg sodium diet with no urine sodium)
  - TIPS
  - Peritoneovenous shunt (rare)
  - Midodrine (increases renal perfusion)

TIPS

- Transjugular Intrahepatic Portosystemic Shunt
- Hepatic encephalopathy occurs in ~ 30%
- Thrombosis and stenosis rates have decreased with coated stents
- Contraindications: encephalopathy, alcoholic hepatitis, MELD >18, advanced age, renal disease

Spontaneous Bacterial Peritonitis

- Infection of preexisting ascitic fluid without evidence of intra-abdominal source
- Signs/Symptoms: fever, abdominal pain, tenderness, AMS, positive fluid culture and/or elevated PMN leukocyte count >250 cells/mm3
- High mortality
- Treatment: prophylaxis in high risk, early diagnostic paracentesis, IV antibiotics

Pruritus

- Interferes with quality of life including sleep deprivation and depression
- Intrahepatic itch is associated with HBV, HCV, cholestasis of pregnancy, PBC
- Extrahepatic itch is associated with obstructive tumor and PSC
- Itch seems to be much higher in PBC
### Pruritus

- Usually generalized, intermittent, starts in palms/soles, and worse at night
- May lead to secondary lesions such as excoriations, hyper/hypopigmentation, lichenification, prurigo nodules, and scars
- Likely non-histaminergic pathway since most chronic itch does not respond to antihistamines

### Hepatorenal Syndrome

- **Type I**: more serious, creatinine clearance <20ml/min in 2 weeks or twofold increase in creatinine to >2.5mg/dL, oliguria
- **Type II**: less severe, ascites resistant to diuretics
- May occur in acute or chronic liver failure, may be precipitated by acute insult, and is least common in PBC

### Pruritus

- May be related to hormones in females
- Consider endogenous opioids as source for itching, because they cause degranulation of cutaneous mast cells and activate mu receptors
- No direct correlation between level of bile salts etc. and itching

### Hepatorenal Syndrome

- Development of acute renal failure in setting of advanced liver disease
- Arterial splanchnic vasodilation leads decreased renal perfusion leads to decreased GFR
- Signs/Symptoms: oliguria, benign urine sediment, very low urine sodium, rising creatinine

### Pruritus

- Treatments:
  - SSRIs (sertraline)
  - SNRIs (mirtazapine)
  - neuroleptics (gabapentin)
  - sedating antihistamines (hydroxyzine)
  - opioid antagonist (naltrexone)
  - UV light
  - behavioral therapy
  - bile acid resin (cholestyramine)
  - bile acid (ursodeoxycholic acid)
  - rifampicin
  - molecular adsorbent recirculating system

### Hepatorenal Syndrome

- Criteria:
  - Chronic or acute liver failure and portal hypertension
  - Creatinine >1.5mg/dL that progresses over days to weeks
  - Absence of other apparent cause
  - Urine red cell excretion <50 and protein excretion <500mg/day
  - Lack of improvement with volume expansion with albumin for at least 2 days and withdrawal of diuretics
Hepatorenal Syndrome

- Treatment:
  - Vasopressin analogues + albumin can correct by causing constriction
  - Clonidine can raise GFR 25% by lowering renal sympathetic tone and vascular resistance, but benefit is not sustained
  - Midodrine + Somatostatin = vasoconstrictor + vasodilator inhibitor
  - Norepinephrine + Albumin = vasoconstrictor + protein replacement
  - TIPS and Dialysis and Transplant

Pulmonary

1. Hepatopulmonary Syndrome (20%):
   - hepatic dysfunction + hypoxemia + intrapulmonary vascular dilations
   - Type 1 (improves with oxygen) and Type 2 (true shunt)
   - Etiology unknown, worsens cirrhosis prognosis
   - Signs/Symptoms: cyanosis, clubbing, nail bed telangiectasias, orthodeoxia, platypnea, dyspnea, hypoxemia
   - Treatment: transplant, medications give no benefit, TIPS (?), 5 year mortality is 20%

2. Portopulmonary Hypertension (2-10%):
   - cirrhosis leads to pulmonary artery hypertension
   - Etiology unknown
   - Signs/Symptoms: fatigue, edema, dyspnea, syncope, chest pain, JVD, increased P2 of the S2, TR, right heart failure
   - Treatment: vasodilators (prostacyclin and sildenafil)
   - Transplant contraindicated in most and only helps in very mild disease along with long term vasodilator therapy; 5 year mortality is 50-90%

3. Hepatic Hydrothorax (10%):
   - pleural effusion in cirrhosis without underlying cardiopulmonary disease resulting from ascites moving into pleural space (usually right side)
   - Symptoms: dyspnea, cough, hypoxemia, chest discomfort
   - Treatment: serial thoracenteses, fluid/sodium restriction, diuretics, draining catheters

Cardiovascular

“Cirrhotic Cardiomyopathy”:
   - Increased cardiac output
   - Increased contractility at rest
   - Decreased systemic vascular resistance
   - Systemic hypotension
   - Blunted response to stress
Pain in Liver Disease

Pain

- Most pain medications are metabolized by the liver
- Try to avoid complications including encephalopathy, hepatorenal syndrome, and bleeding
- Liver dysfunction = metabolism impairment
- Drug removal affected by hepatic blood flow, enzyme capacity, and plasma protein binding

Low serum protein or albumin can cause increased levels of free drug if it is usually protein bound
- Severe cholestasis can affect some drug clearance
- Cirrhotic patients often have renal impairment, which may require dose adjustment of renal eliminated drugs

Acetaminophen:
- Doubled half-life
- In cirrhosis and no alcohol: maximum dose 2-3g/day for long term use
- In cirrhosis + alcohol: no long term studies, but consensus is <2g/day
- 3-4g/day short term use still safe despite FDA changes

NSAIDs:
- Increased serum levels due to liver metabolism and highly protein bound
- Renal impairment in cirrhosis due inhibition of prostaglandins leading to decreased renal perfusion, reduced GFR, and sodium retention
- Also cause increased bleeding in cirrhosis
- No studies for COX-2 inhibitors in cirrhosis

Opioids:
- No evidence based guidelines exist
- Mayo Clinic says opioids should be avoided due to increased encephalopathy
- In cirrhosis, decreased clearance, increased bioavailability, and prolonged half-life lead to drug accumulation
- Careful monitoring for side effects required
Pain

Opioids:
• Opioids should be adjusted for GFR
• Morphine is poorly excreted in renal insufficiency
• Hydromorphone and fentanyl seem to be the least affected by renal dysfunction
• Fentanyl has less hemodynamic disturbance due to lack of histamine release

Pain

Opioids:
• High hepatic extraction (first pass metabolism): morphine and fentanyl have higher bioavailability in cirrhotic patients
• Liver dysfunction = decreased clearance
• Liver disease does not impact methadone bioavailability due to low hepatic extraction

Pain

Opioids:
• Metabolism of methadone, fentanyl, and hydromorphone does not yield toxic metabolites and may be better tolerated
• Methadone should be avoided with active alcohol use because alcohol inhibits metabolism of methadone

Pain

Others:
• Less potent TCAs should be used and started at very low doses and beware of side effects
• Anticonvulsants should also be started at low and less frequent doses
• Gabapentin is preferred because it is not metabolized by the liver or protein bound, but it is renally excreted (pregabalin is similar)

What Have We Learned?

• Common Causes of Liver Disease
• Hospice Criteria for Terminal Diagnosis of Liver Disease
• Treatment of Symptoms of Liver Disease
References

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