

Palliative Care in Chronic Liver Disease

Dr. Moe Yeung
MD, BSc, CCFP

Palliative Care and Family Medicine
Clinical Instructor

Disclosures

- None

Objectives

- Describe factors which contribute to prognosis in patients with liver disease
- Identify key transitions points in the course of liver failure
- Overview of the management of common complications of liver disease

Bonus slides:

- Consider pharmacovigilance in patients with impaired liver function

Why do we care

- Canadian statistics
 - 5th leading cause of death in age groups 35-44, 45-54, 55-64 years¹
 - Death rate from liver disease risen by 30% over last 8 years²
 - Obesity and liver cancer on the rise

Epidemiology of chronic liver disease/cirrhosis

- 95% of deaths from liver disease are due to chronic hep B and hep C, non-alcoholic fatty liver disease, liver cancer and alcoholic liver disease
- Other causes include:
 - Cholestatic liver diseases (Primary biliary cirrhosis, Primary sclerosing cholangitis, cystic fibrosis)
 - Metabolic disorders (alpha-1-antitrypsin deficiency, Wilson disease, hereditary hemochromatosis, NASH, amyloidosis)
 - Autoimmune hepatitis

Mr. Homer Jay

- 38 year old Caucasian male with a 38 year old drinking history (6-10 Duff beers/day), and obesity
- No primary care. Presents to ED with hematemesis. Found to have bleeding 6 mm esophageal varices. Controlled with pharmacologic therapies and endoscopic variceal ligation
- Found to have extensive cirrhosis on subsequent imaging. Child Pugh Score C/decompensated cirrhosis

Mr. Homer Jay

- Admitted, referred to hepatologist/liver transplant team. Not a candidate for liver transplantation as continues to drink heavily
- Referred to Palliative care. Family meeting determined goals of care were quality over life prolongation which entailed continuing to drink, spending time with family, as little time as possible in the hospital/avoidance of aggressive interventions

Mr. Homer Jay

- Discharged home, started on beta blockers with home care nursing and wife as caregiver. Decreased appetite, significant weight loss and new encephalopathy requiring lactulose and regular antipsychotics making it difficult at home.
- 2 months after discharge, agreed to transfer to hospice. Nausea, pain and delirium are managed. Terminal bleed 2 weeks after admission, passed away surrounded by family.

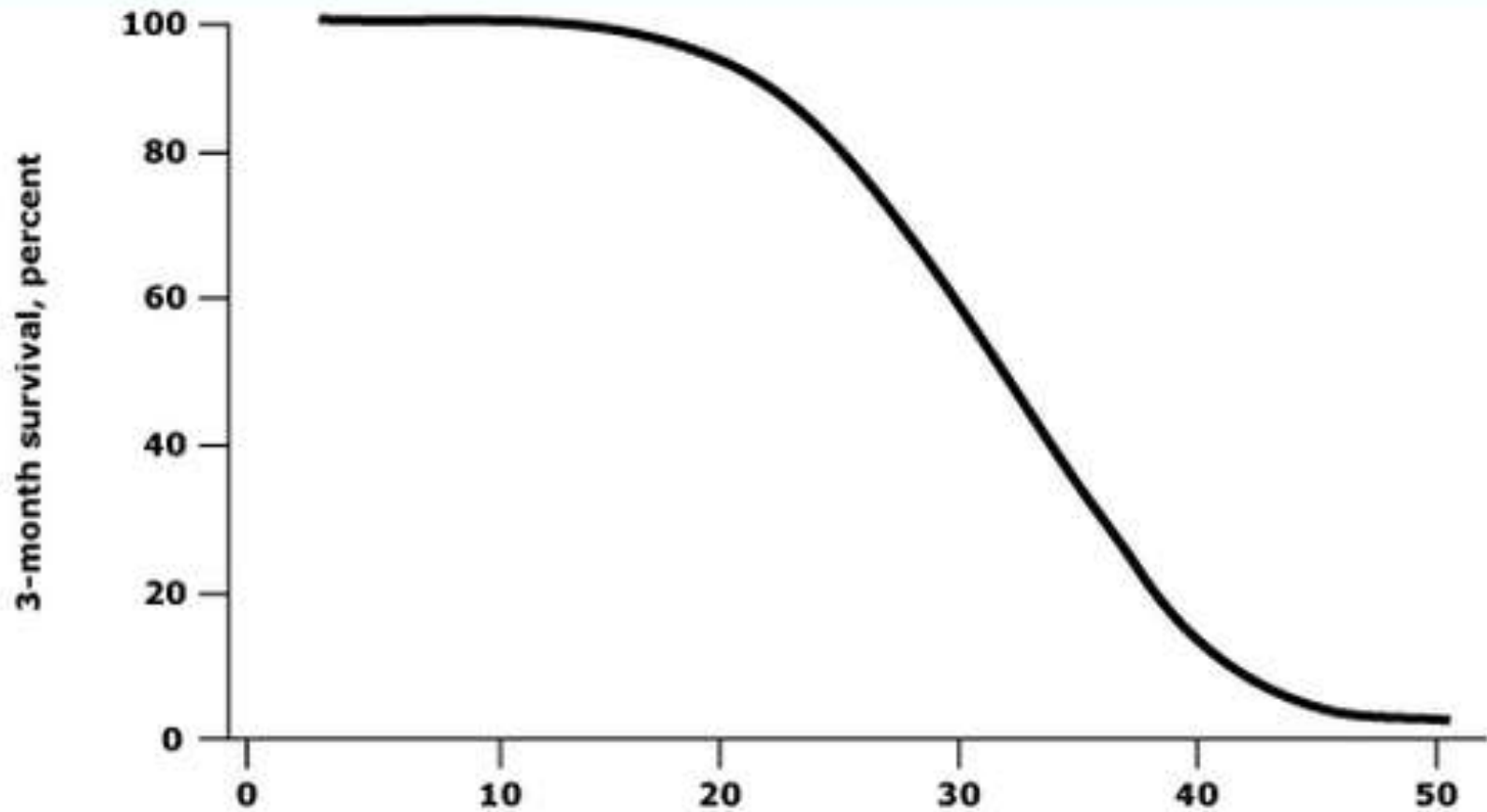
Prognosis

- Highly variable depending on etiology
- Once decompensation occurs, mortality rates are high
- Compensated cirrhosis
 - Median survival is >12 years ³
 - Varices without variceal bleeding considered as compensation
- Decompensated cirrhosis
 - Definition:
 - Ascites, spontaneous bacterial peritonitis
 - Hepatocellular carcinoma
 - Hepatorenal or hepatopulmonary syndrome
 - Hepatic encephalopathy
 - Variceal hemorrhage
 - Systematic review found median survival <6 months with decompensated cirrhosis and Child Pugh score >12 (class C), or a MELD score >21 ⁴

Prognosticating (cont'd)

- Predictive models
 - Child-Pugh ⁵
 - 5 variables: Encephalopathy, ascites, bilirubin, albumin, and prothrombin time
 - Score 5-6 – Child-Pugh Class A
 - Score 7-9 – Child-Pugh Class B
 - Score 10-15 – Child-Pugh Class C
 - One-year survival rates for patients with Child-Pugh class A, B, and C cirrhosis are approximately 100, 80, and 45 percent, respectively ⁶
 - MELD ⁷
 - 4 variables: Bilirubin, creatinine, INR, and etiology
 - Certain conditions impair survival that are not accounted for in the MELD score designated as “standard MELD exceptions” (eg stage II HCC = MELD score of 22)

Estimated 3-month survival as a function of the MELD score in patients with cirrhosis



Prognosticating (cont'd)

- Applicable to all life limiting diseases
 - 3 triggers that suggest a patient is nearing their end of life⁸
 - 1) Asking the surprise question
 - 2) General indicators of decline
 - 3) Specific clinical indicators related to certain conditions

- “...For many conditions it may be difficult, if not impossible and potentially unhelpful, to estimate prognosis accurately...” “...discussions about the end of life should be initiated, if this has not already happened”. – DH End of Life care Strategy 2008 England

Complications of chronic liver disease

- Complications
 - Ascites
 - Hepatic Encephalopathy
 - Esophageal Varices

Ascites

- Intro
 - Most common complication of cirrhosis that leads to hospitalization
 - In patients with compensated cirrhosis, 50% will develop ascites during 10 years of observation⁹
 - Key transition point in disease trajectory of chronic liver disease¹⁰
 - 44% 5-year mortality
 - 15% 1-year mortality
- Diagnosis
 - Diagnostic paracentesis/imaging to confirm etiology

Ascites

- Treatment ¹¹
 - First line
 - Cessation of alcohol (if present)
 - Sodium restricted diet and diet education
 - Dual diuretic therapy (spironolactone and furosemide)
 - Discontinue NSAID, beta blockers, ACE inhibitors and ARBs
 - Evaluation for liver transplantation
 - Second line (Refractory ascites)
 - Consider midodrine
 - Serial therapeutic paracenteses
 - Transjugular intrahepatic portasystemic stent-shunt (TIPS)

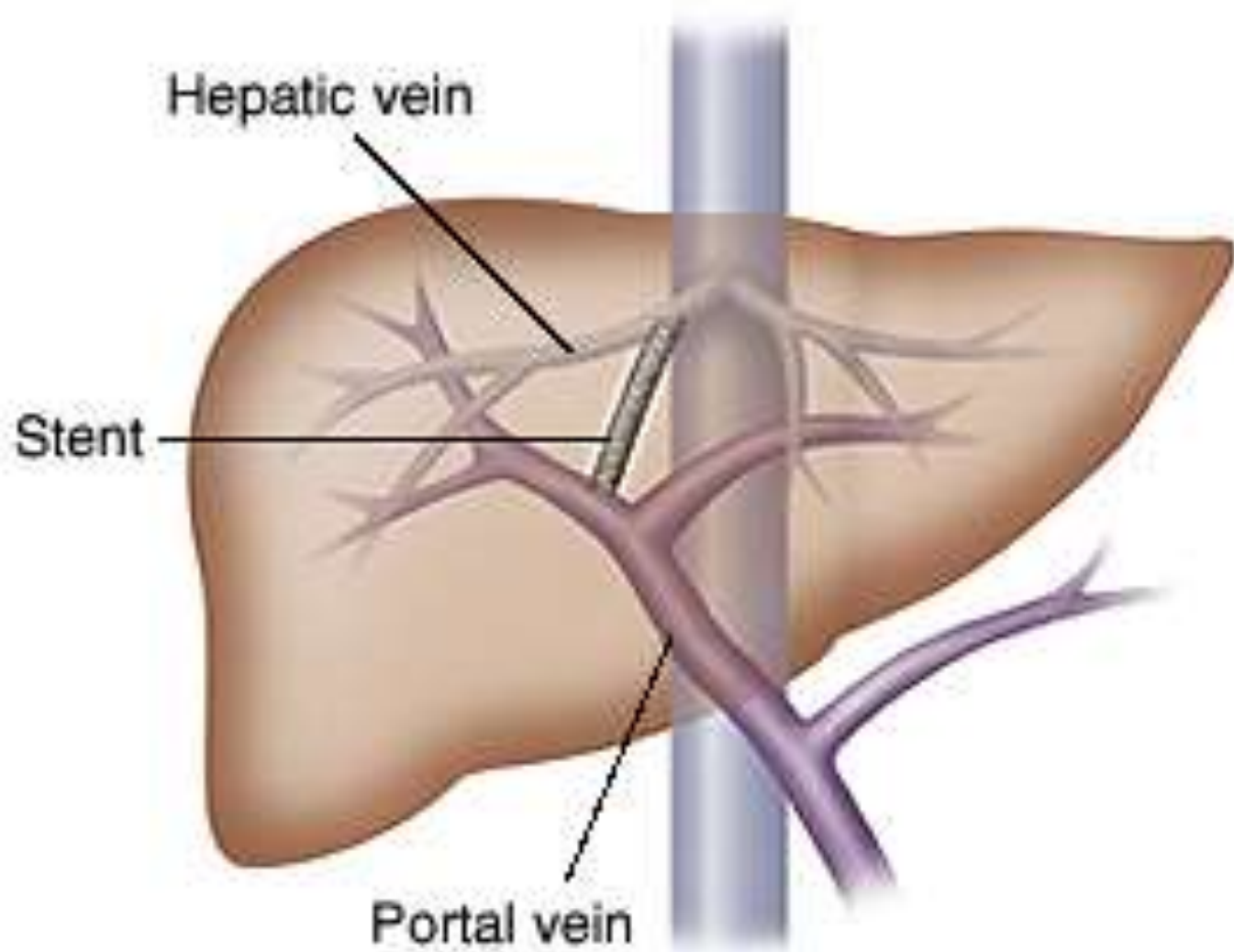
Ascites

- Alcohol-induced liver injury is one of the most reversible causes of liver disease
 - Abstinence can result in dramatic improvement in the period of months
- Sodium restriction (not fluid restriction)
 - <2000 mg/day
- Diuretics
 - Largest RCT (3860 pts) was with combination therapy from the beginning¹²
 - Starting doses of oral diuretics, once a day morning regimen
 - Spironolactone 100 mg (start lower if small/frail, max 400mg/d)
 - Furosemide 40 mg (start lower if small/frail, max 160 mg/d)
 - Increase doses every 3-5 days.

Ascites

- Drugs to avoid¹¹
 - ACEi and ARBs
 - Lowering MAP linked to increase mortality
 - Beta blockers
 - Shown to shorten survival
 - Need to weigh risk versus benefit (eg CHF vs variceal bleed)
 - NSAIDs
- Management of tense ascites¹¹
 - Initial large volume paracentesis (5 L without post drainage colloid infusion, more with 8g/L albumin infusion)
- Management of refractory ascites¹⁴
 - Midodrine 7.5 mg TID
 - Serial paracentesis/indwelling catheters
 - Transjugular intrahepatic portosystemic stent-shunt (TIPS)

TIPS



Hepatic Encephalopathy (HE)

- Intro
 - Brain dysfunction caused by liver insufficiency and/or portosystemic shunting. Can manifest with a wide spectrum from subclinical to coma
 - One of the more debilitating complications
 - Over the course of cirrhosis, 30-40% will have at least one episode of overt hepatic encephalopathy
 - Often repeated episodes in the survivors (40% in 1 year)
 - Difficult to diagnosis (often by exclusion)

Table 2. WHC and clinical description.

WHC including MHE	ISHEN	Description	Suggested operative criteria
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
Grade I		<ul style="list-style-type: none"> • 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
Grade II	Overt	<ul style="list-style-type: none"> • 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
Grade III		<ul style="list-style-type: none"> • 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
Grade IV		Coma	Does not respond even to pain stimuli

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

Encephalopathy

- Treatment
 - 1) Establish goals of care via patient, previous documentation and substitute decision maker
 - 2) Rule out alternative causes of altered mental status
 - 3) Identification/correction of precipitation factors
 - 4) Commencement of empirical HE treatment

Encephalopathy

- Specific drug treatment for episodes of OHE
 - Nonabsorbable disaccharides
 - First line treatment
 - Prebiotic effects, acidifying nature, laxative effect
 - Lactulose 25 mL q12h
 - Dosing titrated to maintain 2-3 soft BMs/day
 - Watch for symptoms overuse (dehydration, cramping, perianal skin irritation)
 - Large meta-analysis did not completely support lactulose but excluded largest trials¹⁷
 - Rifaximin
 - Metanalysis showed equivalent or superior to other agents with good tolerability¹⁸
 - Rifaximin 550 mg po BID or 400 mg po TID
 - Due to cost/accessibility – should be used second line if not able to tolerate lactulose or if lactulose is ineffective

Encephalopathy

- Symptomatic treatment with regular antipsychotics for refractory cases
- For prevention after an episode of overt HE
 - If control of precipitating factor obtained can consider stopping prophylactic treatments
 - Frequent follow up
 - Education
 - Goals of care/prevention
 - Socioeconomic implications
 - Nutrition

Esophageal Variceal Bleeding

- Intro
 - Incidence of varices: Child A – 40%, Child C – 85%
 - Mortality of 20% at 6 weeks post bleed ¹⁹

Variceal Bleeding

- Management
 - Pharmacologic therapies
 - Splanchnic vasoconstrictors
 - Vasopressin and analogues, somatostatin and analogues, nonselective B-blockers
 - Endoscopic therapies
 - Sclerotherapy or endoscopic variceal ligation
 - Shunting therapy
 - TIPS or surgical

Variceal Bleeding

- Management¹⁹
 - Cirrhosis and medium/large varices (no bleed)
 - Treatment with nonselective B-blockers or EVL for prevention (1A)
 - Should adjust B-blocker to maximal tolerated dose (1C)
 - Propranolol 20 mg BID to start. Nadolol 40 mg daily.

Variceal Bleeding

- Management¹⁹
 - Acute episode of variceal hemorrhage
 - Managed best in an ICU with general measures of intravascular volume support, transfusions, airway support (1B)
 - Pharmacologic treatment with somatostatin/analogues initiated as soon as suspected and continued for 3-5 days post confirmation (1A)
 - Combination EGD/pharmacologic treatment. EGD within 12 hours with EVL or sclerotherapy treatment (1A)
 - TIPS for salvage treatment (1C)
 - Balloon tamponade as a temporizing treatment with plans of a more definitive treatment (TIPS or endoscopic therapy) (1B)

Variceal Bleeding

- Patients who have recovered from acute variceal hemorrhage
 - Combination of B-blocker plus EVL is best option for secondary prophylaxis of variceal hemorrhage (1A). Should be initiated once no bleed x 24 hours
 - Median rebleeding rate is 60% within 1-2 years. Decreased to around 40% with B-blocker. 30% with EVL alone. 14% with combination.
 - TIPS in Child A/B patients who experience recurrent variceal hemorrhage despite combination therapy (1A)
 - Refer to transplant center if otherwise candidates (1C)

Terminal Bleed

- If goals of care focused on symptom alleviation without life-prolongation²⁰
 - Ready availability of dark colored linens/towels
 - Universal precautions (gown, gloves, face/eye protection)
 - Suctioning equipment
 - Drugs and explicit instruction on how to use them
 - Midazolam 5-10 mg SC q5 minutes PRN
 - Opioid for pain and dyspnea (Double the PRN dose SC q5-10 minutes)

Bonus slides!

Pain

- Quite common in patients with chronic liver disease
 - Etiology:
 - Inflammatory adhesions
 - Liver capsular distension
 - Edema
 - Gastro-esophageal reflux
 - Musculoskeletal pain (immobility, joints, myalgias)

Pharmacovigilance in liver disease

- Need to have a heightened awareness and monitoring of potentially adverse pharmacologic events in liver failure
- Altered liver metabolism leads to: accumulation of drugs or toxic metabolites, higher bioavailability (as drugs are metabolized slowly), altered volume of distribution given lower serum albumin and changes in body water²¹
- Notable lack of reliable information on the use of medications that are commonly required in the palliative care of patients with liver disease

Pharmacovigilance in liver disease

- Opioids²²
 - Fentanyl pharmacokinetics/dynamics largely unaltered
 - Otherwise generally longer half lives due to decreased elimination, higher bioavailability. Recommend starting at 50% dose and prolonged dosing intervals (q6h)
 - Avoid tramadol/codeine which require liver to be converted to active form in liver
- Nonopioid analgesics
 - Acetaminophen/Ibuprofen can be used with no change. Reduce dose of naproxen/celecoxib by 50%
- Antiemetics
 - Little or no data on half life for many commonly used antiemetics
 - Metaclopramide reported as being safe
 - Limit daily ondansetron to 8 mg due to reduced clearance
- Diuretics
 - Spironolactone and Furosemide both have no major change in pharmacokinetics
- Sedatives
 - Lorazepam - no changes in the clearance/half life
 - Midazolam – dose reduce on an individual basis
 - Diazepam – half-life almost doubled. Use with caution
 - Clonazepam – contraindicated in CLD
 - Oxazepam – No change in Child A/B but caution in severe liver failure

END!



References

- 1. Statistics Canada – 2009 **Ranking and number of deaths for the 10 leading causes of death by age group, Canada, 2009.** <http://www.statcan.gc.ca/pub/84-215-x/2012001/table-tableau/tbl003-eng.htm>
- 2. Morris Sherman, Marc Bilodeau, Curtis Cooper, David, Mackie, William Depew, Jean-Pierre Villeneuve, Vincent Bain. *Liver Disease in Canada: A Crisis in the Making*. March 2013. Canadian Liver Foundation.
- 3. D'Amico G, Garcia-Tsao G, Pagliaro L, Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol*. 2006;44(1):217.
- 4. Salpeter SR, Luo EJ, Malter DS, Stuart B. Systematic review of noncancer presentations with a median survival of 6 months or less. *Am J Med*. 2012 May;125(5):512.e1-6. Epub 2011 Oct 24.
- 5. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg*. 1973;60(8):646.
- 6. Infante-Rivard C, Esnaola S, Villeneuve JP. Clinical and statistical validity of conventional prognostic factors in predicting short-term survival among cirrhotics. *Hepatology*. 1987;7(4):660.
- 7. Freeman RB Jr, Wiesner RH, Harper A, McDiarmid SV, Lake J, Edwards E, Merion R, Wolfe R, Turcotte J, Teperman L, UNOS/OPTN Liver Disease Severity Score, UNOS/OPTN Liver and Intestine, and UNOS/OPTN Pediatric Transplantation Committees. The new liver allocation system: moving toward evidence-based transplantation policy. *Liver Transpl*. 2002;8(9):851.

References

- 8. Thomas.K et al. Prognostic Indicator Guidance (PIG) 4th Edition Oct 2011. The Gold Standards Framework Centre In End of Life Care CIC
- 9. Gines P, Qintero E, Arroyo V, Teres J, Bruguera M, Rimola A, Caballeria J, et al. Compensated cirrhosis: natural history and prognostic factors. *Hepatology* 1987;7:12-18
- 10. Planas R, Montoliu S, Balleste B, Rivera M, Migeuel M, Masnou H, Galeras JA, et al. Natural history of patients hospitalized for management of cirrhotic ascites. *Clin Gastroenterol Hepatol* 2006;4:1385-1394
- 11. Runyon B. Management of Adult patients with ascites due to cirrhosis: Update 2012. AASLD Practice Guideline.
- 12. Stanley MM, Ochi S, Lee KK, Nemchausky BA, Greenlee HB, Alen JI, Allen MJ, et al. Peritoneovenous shunting as compared with medical treatment in pateints with alcoholic cirrhosis and massive ascites. *N Engl J Med* 1989; 321:1632-1638
- 13. Angeli P, Fasolato S, Mazza E, Okolicsanyi L, Maresio G, Velo E, Galimoto A et al. Combined versus sequential diuretic treatment of ascites in non-azotaemic patients with cirrhosis: results of an open randomized clinical trial. *Gut* 2010;59:98-104
- 14. Singh V, Dhungana SP, Singh B, Vijayverghia R, Nain CK, Sharma N, Vhalla A, et al. Midodrine in patients with cirrhosis and refractory ascites: a randomized pilot study. *J Hepatol* 2012; 56:348-354
- 15. Boyer TD, Haskal ZJ. AASLD Practice Guidelines: The role of Transjugular intrahepatic portosystemic shunt (TIPS) in the management of portal hypertension. 2009.

References

- 16. American Association for the study of liver diseases. European association for the study of the liver. Hepatic Encephalopathy in Chronic Liver Disease: 2014 Practice Guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver diseases. *Journal of Hepatology*
- 17. Als-Nielsen B, Gluud LL, Gluud C. Non-absorbable disaccharides for hepatic encephalopathy: systemic review of randomised trials. *BMJ* 2004;328:1046
- 18. Jiang Q, Jiang XH, Zheng MH, Jiang LM, Chen YP, Wang L. Rifaximin versus nonabsorbable disaccharides in the management of hepatic encephalopathy: a meta-analysis. *Eur J Gastroenterol Hepatol.* 2008;20(11):1064.
- 19. Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W, and the Practice Guidelines Committee of The American Association for the Study of Liver Diseases, the Practice Parameters Committee of the American College of Gastroenterology. Prevention and Management of Gastroesophageal Varices and Variceal Hemorrhage in Cirrhosis. 2007
- 20. Harris DG, Noble SI. Management of terminal hemorrhage in patients with advanced cancer: a systematic literature review. *J Pain Sympt Manage.* 2009; 38:913-27.
- 21. Rhee C, Broadbent AM. Palliation and Liver Failure: Palliative Medications Dosage Guidelines. *Journal of Palliative Medicine,* 2007; 10:3 677-685
- 22. Tegeder I, Lotsch J, Geisslinger G. Pharmacokinetics of Opioids in Liver Disease. *Clin Pharmacokinet* 1999 Jul;37(1) 17-40