**Supplement 1:**

**Case 1:**

A 66 year-old female patient with a past medical history significant for nonalcoholic fatty liver disease, cirrhosis (Child-Pugh class B),  hypertension, stage 3 chronic kidney disease, and osteoporosis presents to her primary care physician with worsening bilateral knee pain. The patient reports that her knee pain is impairing her ability to comfortably ambulate.  She self treats her knee pain with as needed OTC naproxen approximately three times a week. The patient has not been hospitalized in over a year. She does not drink alcohol. Her home medications include torsemide, spironolactone, and lisinopril.  The patient’s most recent labs are significant for international normalized ratio (INR): 1.6 (0.9-1.1), total bilirubin: 2.4 mg/dL (0.3-1.0 mg/dL), serum albumin: 3.1 g/dL (3.5-5 g/dL), serum creatinine: 1.45 mg/dL (0.7-1.5 mg/dL), AST: 38 units/L (8-42 units/L), ALT: 29 units/L (0-35 units/L).  It was determined that she is not a liver transplant candidate. She decided to place a few limitations on her care after the transplant evaluation including do not resuscitate, do not intubate, and no artificial nutrition orders. Her advance directive choices indicate that she is trending towards a more palliative approach to her medical care.

This patient has compensated cirrhosis as evidenced by her lack of recent hospitalizations. She is a candidate for chronic acetaminophen 1 g by mouth three times a day to treat her OA knee pain Acetaminophen is a preferred analgesia for knee OA (57).  The suggested dose regimen is consistent with recent expert opinion recommendations. However it is unclear if the patient would experience a clinically significant difference in analgesia or be at a higher risk for decompensation if a 2 g/day or 4 g/day regimen was chosen.  The patient would be at increased risk of hepatorenal syndrome and acute kidney injury with continued NSAID use given her Child-Pugh class B cirrhosis, stage 3 CKD, and diuretic use. The patient is at increased risk of hepatotoxicity due to increased CYP2E1 activity in NASH patients (47). She should be counseled to stop acetaminophen and immediately contact her physician if she develops any signs and symptoms suggestive of decompensated cirrhosis as defined by EASL (e.g. ascites, bleeding, encephalopathy, or jaundice) (2).  It would be reasonable to obtain an INR, total bilirubin, albumin, electrolytes, and serum creatinine if this patient is develops decompensated cirrhosis and/or is hospitalized.

**Case 2:**

A 45 year old male with cirrhosis secondary to alcohol use disorder is admitted to the hospital for shortness of breath secondary to tense ascites. Other than the complaints listed above, the only other significant history is chronic back pain which has kept the patient out of work for the last several years.  The patient had been admitted approximately twice a month for the past year for episodes of tense ascites. The patient's home medications are lactulose, rifaximin, spironolactone, furosemide, nadalol, ciprofloxacin, and acetaminophen 1000 mg PO TID; all have been restarted in the hospital. The patient's compliance to his home medication regimen is uncertain and the patient endorses continuing to drink a pint or more of vodka daily.  The patient has a Child-Pugh score of 13 (Class C) and while not considered a transplant candidate, has a MELD score of 38.

Due to the severity of liver disease, uncertainty of the adequacy of all metabolic pathways, and the possibility of reduced glutathione stores and CYP2E1 induction secondary to continued alcohol use acetaminophen should be discontinued. NSAIDs would not be an appropriate analgesic option for this patient due to concerns with hepatorenal syndrome and potential additional fluid retention. The patient should be referred to physical therapy or  could be considered for an opioid if an appropriate patient safety agreement could be developed.