End-Stage Cirrhosis:

Complications, Diagnosis and Management

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Cirrhosis is defined by pathologic criteria as bridging fibrosis of the liver with regenerative nodules. It is the end stage of a variety of chronic liver diseases including:

- chronic Hepatitis B or C,
- autoimmune Hepatitis,
- alcoholic and non-alcoholic fatty liver disease,
- hemochromatosis,
- Wilson's disease,
- primary biliary cirrhosis and
- primary sclerosing cholangitis.

Most of the scar tissue is produced by stellate cells, which are activated by cytokines produced during chronic inflammation to secrete collagen. Death of liver cells and activation of matrix proteases leads to collapse of the normal "scaffolding" of the liver. The remaining liver cells are stimulated by hepatocyte growth factors to regenerate functioning liver cell mass, but due to the scarring and destruction of the normal liver architecture, nodules of varying size rather than normally-aligned liver cells are formed.

Do patients with cirrhosis always appear ill?

In early stages, cirrhosis may not cause any symptoms and may be associated with few, if any, physical findings. Also, levels of bilirubin

Dan's case

Dan, 54, presents to a walk-in clinic because of abdominal distention. He indicates that he was diagnosed with Hepatitis C about 7 years ago, after investigation for mildly abnormal liver enzymes. His main risk factor was IV drug use during ages 17 to 19. Until 10 months ago, Dan worked in a sawmill but since then has felt too fatigued to continue and is now on income assistance.

Dan takes no medication, but admits to drinking 2-3 beers daily. On examination, he has muscle wasting, spider hemangiomas, scleral icterus and a distended abdomen with shifting dullness. The spleen tip is palpable 2 cm below the costal margin.

He is sent for blood tests and an abdominal ultrasound.

Laboratory results

Laboratory results show:

- Hemoglobin: 134 g/L
- White blood cell count: 4.1 x 10^9/L
- Platelets: 72 x 10^9/L
- Serum sodium: 132 meq/L
- Serum potassium: 4.1 meq/L
- Serum creatinine: 94 µmol/L
- Bilirubin: 52 umol/L
- Alanine aminotransferase: 110 IU/L
- Albumin: 30 g/L
- INR: 1.3
- Hepatitis C virus ribonucleic acid positive
- Ultrasound: nodular echogenic liver, spleen size 15 cm, large amount of ascites

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Table 1
Child-Pugh score

	1 point	2 points	3 points
Bilirubin (total)	< 34 µmol/L	34 µmol/L-50 µmol/L	> 50 µmol/L
Serum albumin	> 35 g/L	28 g/L-35 g/L	< 28 g/L
INR	< 1.7	1.7-2.2	> 2.2
Ascites	None	Mild-moderate or controlled with drugs	Severe
Hepatic encephalopathy	None	Grade I-II or suppressed with drugs	Grade III-IV

and liver enzymes may be normal. If the underlying disease process remains active, there is usually progression to a stage where one or more complications, such as jaundice, ascites, variceal bleed and/or hepatic encephalopathy. If one or more of these occurs, the patient is deemed to have "decompensated" cirrhosis.

How can the severity of liver failure due to cirrhosis be estimated?

There are two scoring systems that are widely used to estimate the severity of liver failure: the Child-Pugh score and the Model of Endstage Liver Disease (MELD) score. The Child-Pugh score (Table 1) is based on three lab parameters and two clinical parameters. If the parameter is normal or nearly normal, one point is given. Moderate abnormalities get two points and severe abnormalities get three points. The sum of the points for the five parameters is the Child-Pugh score. A score of six to seven indicates mild decompensation, eight to nine indicates moderate decompensation and > 10 indicates severe decompensation.

The MELD score is an objective system based only on three laboratory values: creatinine, bilirubin and INR. The MELD score can be obtained by entering patient values into an online MELD computation program at http://www.mdcalc.com/meld. The MELD score has been validated as a good predictor of short-term mortality in decompensated liver disease and it is used by the United Network for Organ Sharing in the US as the basis for ranking patients listed for liver transplantation.

What are the complications of cirrhosis?

The main complications of cirrhosis include:

- GI bleeding
- Ascites
- Hepatic encephalopathy
- Hepatocellular carcinoma

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- Renal failure (hepatorenal syndrome)
- Cirrhotic cardiomyopathy
- Intrapulmonary shunting of blood hepatopulmonary syndrome

There are many possible causes of GI bleeding in patients with cirrhosis. Bleeding from ruptured esophageal varices is the most dramatic, but endoscopy shows that many cirrhotics who present with hematemesis or melena actually have peptic ulcer disease, gastric erosions, or erosive esophagitis as the cause of their GI bleeding. Hence, accurate diagnosis (usually by endoscopy) is essential as soon as feasible in cirrhotic patients with an acute GI bleed.

Esophageal varices rupture because the esophageal wall tension exceeds a critical point. The wall tension is a function of the portal pressure and the diameter of the varix (for a given portal pressure, the larger the diameter, the higher the wall tension and the risk of rupture). Varices rarely bleed if portal pressure is < 12 mmHg.

What can be done to reduce the risk of variceal bleeding?

Bleeding from ruptured esophageal varices is associated with a 30-day mortality of 30% to 50%. Hence, prevention of variceal rupture is the mainstay of management. Table 3 outlines the options for prevention of variceal bleeding.

Cirrhotic patients who have never had a GI bleed but who have clinical evidence of portal hypertension (*i.e.*, splenomegaly, ascites, varices on ultrasound or CT scan) should be assessed periodically with endoscopy to determine the location and size of varices. Large varices should normally be treated with banding. Smaller varices can also be treated with ß-blockers alone. These are effective at lowering portal pressure in about 70% of cases.

Table 2
Prevention of variceal bleeding

Primary prevention
- ß-blockers (reduce mesenteric blood flow)
- Variceal banding with or without a ß-blocker

Secondary prevention
- Variceal banding with or without a ß-blocker
- Angiography
- Embolization
- Transvenous intrahepatic portocaval stent shunt (TIPSS) or surgical shunt

Although less common than esophageal varices, gastric varices can also cause bleeding in cirrhotics. ß-blocker therapy is recommended as the first line of preventative therapy. Band ligation is not effective for gastric varices and the only endoscopic treatment is injection of methacrylate glue. Gastric varices can also be treated by balloon-occluded transvenous obliteration in specialized centers. If bleeding from gastric varices recurs despite ß-blockers and/or endoscopic or radiologic measures, transvenous intrahepatic portocaval stent shunt (TIPPS) should be considered.

Portal hypertensive gastropathy is a third cause of upper GI bleeding due to portal hypertension. In this condition, there are dilated vascular channels in the lining of the stomach. These can present with slow chronic blood loss, or with more brisk intermittent bleeding although rarely as dramatic as variceal hemorrhage. ß-blockers are recommended as the first line of therapy.

How can we deal with other common causes?

Apart from GI bleed, other common causes of cirrhosis include ascites, hepatic encephalopathy and hepatocellular carcinoma. The following details the management of these causes.

Ascites

Ascites is another common complication of cirrhosis. Factors involved in ascites formation include portal hypertension, sodium retention, and hypoalbuminemia. The first step in management is dietary salt restriction, to the equivalent of 60 meq to 80 meq of sodium q.d. If this is not sufficient, spironolactone is added at doses up to 200 mg q.d., with furosemide if necessary at doses up to 80 mg q.d. Treatment options for ascites that remains refractory to salt restriction and diuretics are repeated large-volume paracentesis or TIPSS.

The TIPPS procedure leads to reasonable control of ascites in 58% of patients vs. 19% with paracentesis but encephalopathy worsens in 34% of patients after TIPSS vs. 19% with paracentesis.

Hepatic encephalopathy

Hepatic encephalopathy is a third major complication of cirrhosis. In its mildest (subclinical) stage, it manifests only with subtle psychomotor defects. In Stage 1 encephalopathy there is impaired attention and irritability. Patients with Stage 2 encephalopathy may also have drowsiness, sleep disorder, poor memory and behavioural changes. Patients with Stage 3 display overt confusion and somnolence and Stage 4 encephalopathy is defined as stupor or coma.

The cause of hepatic encephalopathy is the failure of the liver to metabolize protein-derived toxins from the blood. These toxins include ammonia, mercaptans and "false neurotransmitter" amino acids that stimulate γ-amino butyric acid (GABA)-responsive neurons in the brain. Some precipitating factors for hepatic encephalopathy are:

- renal failure,
- GI bleed,
- infection,
- alkalosis,
- constipation,
- excess protein intake and
- benzodiazepines (which stimulate the same GABA-ergic neurons as the false neurotransmitters).

Management involves identification and elimination of precipitating factors, restriction of dietary protein intake and addition of lactulose or a non-absorbable antibiotic. Lactulose is a non-absorbable disaccharide. Its fermentation products increase stool frequency and lower stool pH, which traps ammonia. The usual starting dose for symptomatic patients is 30 ml p.o. t.i.d. and then is adjusted to give three soft stools per day.

Hepatocellular carcinoma

Hepatocellular carcinoma is a common problem in patients with cirrhosis. The risk of hepatoma is greatest in patients with cirrhosis due to Hepatitis B, Hepatitis C, or hemochromatosis and can be more than 100-fold increased over the general population. Hepatocellular carcinomas may arise from malignant transformation of dysplastic regenerative nodules. The management strategy is to detect these tumours while they are small so

Dan's follow-up

Dan returns to the clinic 2 weeks after his first visit. The test results are discussed with him. He is told that he has advanced cirrhosis and that his abdomen is distended with fluid caused by the scarring in his liver.

Dan is advised that alcohol is clearly shown to accelerate liver scarring in patients with Hepatitis C and that he must stop drinking alcohol completely. Referral to an alcohol and drug rehabilitation program is recommended. He is instructed regarding a low-salt diet and is started on 100 mg of spironolactone p.o. q.d.

Three months later

On follow-up 3 months later, Dan's ascites has improved. He has had an assessment from a counsellor and has been completely abstinent from alcohol for the past 3 months. He asks if he should receive treatment for his Hepatitis C but is told that his liver disease has advanced and that treatment may not be possible.

He is referred to a liver unit for a transplant assessment and a decision regarding antiviral therapy.

that intervention is possible. This requires a surveillance program of abdominal ultrasound every six to 12 months and determination of serum α-fetoprotein levels every six months. Suspicious nodules are evaluated further with CT scanning or MRI scan.

The most definitive treatment of hepatocellular carcinoma is surgical excision. However, patients with advanced cirrhosis may not tolerate a liver resection. If the tumour is < 3 cm to 5 cm in diameter, it can sometimes be ablated with percutaneous ethanol injection or with radiofrequency ablation. Larger tumours are sometimes amenable to transarterial chemoembolization.

Liver transplantation is the only long-term solution for patients with decompensated cirrhosis. It is indicated for patients who have moderate to severe decompensation of liver function. It is also used as treatment for hepatocellular carcinoma provided the tumour is small enough that the risk of recurrence after transplant is acceptable. The usual eligibility criteria are a single tumour no larger than 5 cm in diameter or up to three tumours, none of which are > 3 cm in diameter. Patients must have no obvious contraindications such as ongoing alcohol or drug abuse, should have a "physiologic" age < 65 years, be able to comply with complex treatment and follow-up regimen and have adequate social support. The number of donors is substantially less than the number of patients listed for liver transplantation and so the mortality rate on the wait list is around 25%. Outcomes after liver transplantation are an overall one-year survival of about 85% and a five-year survival of 65%. Quality of life is generally good for liver transplant recipients and patients that were working until a few months before the date of their transplant are usually able to return to work.

Q&A *What are some conclusions?*

Cirrhosis and its complications is a problem that is increasing in prevalence due in part to the consequences of chronic Hepatitis C. Managing patients with decompensated cirrhosis is challenging and requires collaboration between the FP, gastroenterologist/liver specialist, liver surgeons, radiologists and transplant team, as well as nurses and paramedical staff. Dx