January 14, 2015

Editor-in-Chief
World Journal of Hepatology

Dear Editor:

Thank you for your kind letter and careful review of "*Primary biliary cirrhosis: pathophysiology, clinical presentation and therapy"* submitted as manuscript #15764 to the World Journal of Hepatology. We have thoroughly revised the manuscript in accord with the reviewers' criticisms as follows.

Reviewed by 02539941
The review presented by authors gives the detailed view on the epidemiology, pathophysiology, clinical presentation, treatment, and prognosis of primary biliary cirrhosis, with a focus on recent advances. It is a comprehensive and updated review, and it provides some reference for clinical practice

1. **Criticism 1: A minor error occurs at : page 6, line 11, is "gp120" or "gp210"?**

Response to criticism:
As per the criticism, gp120 is changed to gp210 on p. 6.

2. Criticism 2: Please delete the part of "complication" of PBC, which had similar diagnosis and treatment in other etiologies of cirrhosis.

Response to criticism: The lengthy text on complications of cirrhosis in the paper has been replaced by a brief table (Table IV), as follows:

CHANGE TO:
<u>Hyperlipidemia</u>

Complications of chronic cholestasis include osteoporosis (described above) and hyperlipidemia. The hyperlipidemia in PBC is, however, apparently not associated with adverse cardiovascular effects[61,198-200]. It is unusual for cholesterol-lowering agents to be needed, but statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are a safe therapy, even when serum liver function tests are abnormal[201]. Fibrates have been used safely in some patients[202], but occasionally cause paradoxical elevations of serum cholesterol[203].

Complications from Cirrhosis from advanced PBC

Patients with cirrhosis from advanced PBC are subject to all the usual complications of cirrhosis, including hepatoma development, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatorenal syndrome, and esophageal variceal bleeding. The diagnosis and treatment of these complications are briefly listed in Table IV, which includes references for further reading on these complications.

Future Trends

The future of PBC promises to be exciting…...

The following is the added new Table IV in the revised version:

Table IV. Complications of cirrhosis or portal hypertension in patients with primary biliary cirrhosis

Complication	Special considerations in PBC	References
Hepatoma	Like other cirrhotics, patients with PBC have increased risk of developing hepatomas.	[190,204-206]
	In patients with PBC who have no0t undergone a liver biopsy to document the diagnosis of cirrhosis, hepatoma screening should be initiated when the Mayo score >4.1.	[127]
	Surveillance for hepatoma in patients with cirrhosis from PBC should be performed every six months by abdominal ultrasound or an alternative modality of abdominal imaging.	[207]
Spontaneous bacterial peritonitis	Diagnosed by abdominal paracentesis revealing >250 polymorphonuclear leukocytes/mm^3 in ascitic fluid.	[208]
	Treated with a short course of multiple antibiotics, generally including either a third-generation cephalosporin or flouroquinolones.	[209]
Hepatic encephalopathy	Diagnosed clinically by confusion, delirium, or stupor on physical examination, depending on degree of hepatic encephalopathy; possible presence of asterixis on physical examination; and elevated serum ammonia level in a cirrhotic patient.	[210]
	Treatment options include rifaximin, lactulose, supportive care, and reversal of underlying precipitating causes, such as dehydration, infection, or gastrointestinal bleeding.	[210-212]
Hepatorenal syndrome	Type 1 HRS defined as doubling of serum creatinine	[213,214]

(HRS)	level, reaching a level >2.5 mg/dl in <2 weeks. Type 2 HRS defined as a less severely elevated serum creatinine level. Must exclude other causes of renal failure, especially hypovolemia in both types of HRS. Treatment includes avoidance of nehprotoxic medications; short-term trial of volume expansion; and administration of vasopressin analogues, such as terlipressin, and α-adrenergic agonists, such as norepinephrine or midodrine. Ultimate treatment for type 1 HRS refractory to therapy is liver transplantation.	[214-216]
Esophageal varices	Usually occur only after Mayo score becomes >4.1. Patients with advanced PBC can develop portal hypertension before developing established cirrhosis from nodular regenerative hyperplasia. Esoohageal varices usually diagnosed and graded by esophagogastroduodenoscopy. Specific therapies for esophageal varices include: endoscopic banding, endoscopic injection therapy, and non-selective beta-blockers. Transjugular intrahepatic shunt (TIPS) is recommended for refractory variceal bleeding, especially when the MELD score<18.	[217-221] [222,223]

CHANGED FROM:

Complications

Hepatoma

Complications of PBC can arise from either cirrhosis or cholestasis. As with other cirrhotics, patients with PBC have an increased risk of hepatoma (190,198,199). Risk factors for hepatoma development include age >70 years, male sex, prior blood transfusions, and evidence of portal hypertension (200). Abdominal ultrasound is recommended every 6 months for hepatoma surveillance in all patients with cirrhosis (201). In patients without a liver biopsy, hepatoma screening should be considered when the Mayo score is >4.1 (27).

Esophageal Varices

The timing for initiating variceal surveillance is controversial, with some

authorities recommending initiating surveillance when the patient's platelet counts are <200,000/mm^3 or when <140,000/mm^3 (202,203). Varices are rarely found with Mayo scores <4.1. A high AST/ALT ratio may predict varices in PBC (204). Patients with PBC may develop portal hypertension before developing cirrhosis from nodular regenerative hyperplasia (205,206). Varices in PBC are managed like varices occurring in other etiologies of cirrhosis. Specific therapies for esophageal varices include endoscopic banding, injection sclerotherapy, and non-selective beta-blockers. Transjugular intrahepatic shunt (TIPS) is recommended for refractory variceal bleeding, especially when the MELD score <18. Therapy for variceal bleeding is reviewed elsewhere (207,208).

Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis, another important complication of cirrhosis, is diagnosed by abdominal paracentesis revealing >250 polymorphonuclear cells/mm^3 in ascitic fluid (209). Treatment regimens generally include a third generation cephalosporin or flouroquinolones, with antibiotic preference depending on the patient's history of prior infections, local patterns of antibiotic resistance, and etc. (210).

Hepatic Encephalopathy

Hepatic encephalopathy poses a significant burden on patients with cirrhosis (211). The diagnosis is primarily clinical. Physical examination may reveal confusion, deliriousness, or stupor depending on the degree of encephalopathy. Asterixis may be elicited on physical exam. Elevated serum ammonia levels support the diagnosis. The West Haven scale is used to grade the severity of the encephalopathy (211). Rifaximin is useful to treat and prophylax for hepatic encephalopathy (211,212). Other treatment

options include lactulose with rifaximin, supportive care, and treatment of underlying precipitating causes, such as dehydration, infection, and gastrointestinal bleeding (213).

Hepatorenal Syndrome

Hepatorenal syndrome (HRS) is another serious complication of end stage liver disease. The renal failure is caused by intrarenal vasoconstriction, associated with end stage liver disease and circulatory dysfunction (214). Type 1 HRS is arbitrarily defined as a doubling of serum creatinine level, reaching a value >2·5 mg/dL in <2 weeks. Patients with less severe serum creatinine elevation are defined as having type 2 HRS (215). Due to a lack of specific diagnostic tests, HRS is diagnosed only after excluding other disorders that can cause renal failure. If renal failure is secondary to volume depletion, renal function rapidly improves after volume expansion, using 1.5 liters of isotonic saline, but negligibly improves after volume expansion in patients with HRS. Liver transplantation is the treatment of choice for patients with cirrhosis and type 1 HRS who are transplant candidates because it can cure both the cirrhosis and the HRS. Medical management of HRS includes use of vasopressin analogues, such as ornipressin or terlipressin, and α-adrenergic agonists, such as norepinephrine or midodrine. Intravenous albumin helps expand intravenous volume and improve arterial underfilling (215). HRS is reviewed elsewhere (215-217).

Hyperlipidemia

Complications of chronic cholestasis include osteoporosis (described above) and hyperlipidemia. The hyperlipidemia in PBC is, however, apparently not associated with adverse cardiovascular effects (61,218-220). It is unusual for cholesterol-lowering agents to be needed, but statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors)

are a safe therapy, even when serum liver function tests are abnormal (221). Fibrates have been used safely in some patients (222), but occasionally cause paradoxical elevations of serum cholesterol (223).

Future Trends

The future of PBC promises to be exciting……

Reviewed by 00926880

This is a very good review article on Primary Biliary Cirrhosis. Although this is not a systematic review, the article gives a balanced view on the pathophysiology clinical presentation and therapy of primary biliary cirrhosis. The approach is scientific and logical. The references are up-to-date. I have only very minor criticisms of this review:

(1). Criticism 1: Page 25, line 5, 'exam' should be 'examination';
Response to criticism:
CHANGE TO: "Physical examination" in Hepatic encephalopathy section of Table IV.
FROM: "physical exam" on p. 25, line 5. (Note the text which included a section on Hepatic encephalopathy is replaced by Table IV).

(2) Page 24, last line, 'etc.', better to avoid using the term 'etc.'
Response to criticism:
Entire section on Spontaneous bacterial peritonitis (containing the last line on page 24 with the term "etc.") is deleted and replaced by section on Spontaneous bacterial peritonitis in Table IV (which does not contain the sentence with the term "etc.").

(3) The references are not in a single format:
(a) pages for reference 2, 303-30, reference 4, 265-276;
Response to criticism:
CHANGE TO: Page range for all references is now corrected to be listed with all numbers: e.g. 303-330 and not 303-30.

(b) reference 10, 3 authors followed by et al, reference 32, 6 authors followed by et al; (c) reference 24 has 13 authors without using et al. Reference 11 has 11 authors.
Response to criticism:
CHANGE TO: All references now uniformly have the first 10 authors listed, and use "et al." if more than 11 authors exist for an article. This has resulted in changes for references: 10, 32, 42, 46, 52, 53, 61, 63, 71, 85, 93, 96, 97, 98, 99, 100, 103, 105, 107, 108, 110, 111, 113, 114, 116, 121, 127, 138, 139, 140, 141, 142, 143, 189, 203, and 218.
The change to all references with >11 authors to "et al." has resulted in use of "et al." only for references 24, 28, 48, 89, 108, 111, 113, 116, 122, 125, 126, 144, 178, and 211.

Reviewed by 02861252

Good work

Response to criticisms: No changes required.

Other changes

1. As per journal policy, the manuscript has been revised to list all PMID numbers for every reference in the references.
2. As per journal policy, the manuscript has been revised to list all the doi numbers for every reference in which a doi number is available.

Thank you for your interest in this manuscript for your prestigious journal. Please note that we will perform any further revisions necessary for publication.

Warm regards,

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