J Gastroenterol (2016) 51:629–650
DOI 10.1007/s00535-016-1216-y

The Japanese Society of Gastroenterology

SPECIAL ARTICLE

Evidence-based clinical practice guidelines for liver cirrhosis 2015

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Received: 12 April 2016 / Accepted: 12 April 2016 / Published online: 31 May 2016

Abstract The Japanese Society of Gastroenterology revised the evidence-based clinical practice guidelines for liver cirrhosis in 2015. Eighty-three clinical questions were selected, and a literature search was performed for the clinical questions with use of the MEDLINE, Cochrane, and Igaku Chuo Zasshi databases for the period between 1983 and June 2012. Manual searching of the latest important literature was added until August 2015. The guidelines were developed with use of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. This digest version in English introduces selected clinical questions and statements related to the management of liver cirrhosis and its complications. Branched-chain amino acids relieve hypoalbuminemia and hepatic encephalopathy and improve quality of life. Nucleoside analogues and peginterferon plus ribavirin combination therapy improve the prognosis of patients with hepatitis B virus related liver cirrhosis and hepatitis C related compensated liver cirrhosis, respectively, although the latter therapy may be replaced by direct-acting antivirals. For liver cirrhosis caused by primary biliary cirrhosis and active autoimmune hepatitis, urosodeoxycholic acid and steroid are recommended, respectively. The most adequate modalities for the management of variceal bleeding are the endoscopic injection sclerotherapy for esophageal varices and the balloon-occluded retrograde transvenous obliteration following endoscopic obturation with cyanoacrylate for gastric varices. Beta-blockers are useful for primary prophylaxis of esophageal variceal bleeding. The V_2 receptor antagonist tolvaptan is a useful add-on therapy in careful diuretic therapy for ascites. Albumin infusion is useful for the prevention of paracentesis-induced circulatory disturbance and renal failure. In addition to disaccharides, the nonabsorbable antibiotic rifaximin is useful for the management of encephalopathy. Anticoagulation therapy is proposed for patients with acute-onset or progressive portal vein thrombosis.

Keywords Liver cirrhosis · Diagnosis · Nutritional therapy · Antiviral therapy · Nonviral cirrhosis · Gastroesophageal varices · Ascites · Hepatorenal syndrome · Hepatic encephalopathy · Liver transplant

Introduction

Liver cirrhosis is a serious cause of death not only in Japan but also in all developed countries. It is a diffuse hepatic process characterized by fibrosis and structurally abnormal nodules, representing the final histological change for a variety of chronic liver diseases. A decrease in the frequency of hepatitis C virus (HCV) infection as a major

The original version of this article appeared in Japanese as "Kankouhen Shinryo Guidelines 2015" from the Japanese Society of Gastroenterology (JSGE), published by Nankodo, Tokyo, 2015. Please see the article on the standards, methods, and process of developing the guidelines (doi:10.1007/s00535-014-1016-1).

The members of the Guidelines Committee are listed in the "Appendix" in the text.

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cause of cirrhosis and an increase in the number of non-B, non-C cirrhosis cases have recently been noted in Japan. Cirrhosis is not a single disease entity, but has serious complications, which exacerbate the disease prognosis. With continuous hepatocyte destruction and collagen deposition, the liver is shrunken in size and distorted in shape, forming multiple nodules of liver cells separated by broad fibrotic bands, which disturbs intrahepatic blood circulation and induces portal hypertension with extensive portocarval shunts. The major complications of cirrhosis, such as gastroesophageal varices, ascites, hepatic encephalopathy, and renal and cardiac disturbances, occur mainly as a consequence of portal hypertension and hyperdynamic circulation and their hemodynamic and metabolic effects.

In 2010, the Japanese Society of Gastroenterology developed evidence-based clinical practice guidelines for liver cirrhosis, and these guidelines were revised in 2015. These were world premiere comprehensive guidelines for liver cirrhosis, because the former American or European clinical practice guidelines for cirrhosis were divided into several themes—that is, hepatitis B, hepatitis C, alcoholic liver diseases, portal hypertension, ascites/hepatorenal syndrome (HRS), and hepatic encephalopathy—and not directed at liver cirrhosis as a whole.

A working committee (Chair, H. Fukui; Vice-Chair, H. Saito; Y. Ueno; H. Uto H; I. Sakaida; A. Shibuya; M. Seike; M. Segawa; and S. Nagoshi) and an evaluation committee (Chair, H. Tsubouchi; Vice-Chair, H. Moriwaki; A. Kato; E. Hashimoto; K. Michitaka; and Y. Murawaki) collaborated to create the guidelines. The revised guideline consists of six sections: conception, diagnosis, treatment, complications, prognosis, and liver transplant. The sections on treatment and complications are subdivided into several items as described below. Eighty-three clinical questions (CQs) were selected, and a literature search was performed for the CQs with use of the MEDLINE, Cochrane, and Igaku Chuo Zasshi databases for the period between 1983 and June 2012. In the theme containing marked recent progress or change, each working committee member added manual searching to get the latest literature until August 2015. The guidelines were developed with use of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system [1]. The quality of evidence was graded as A (high), B (moderate), C (low), or D (very low). The strength of a recommendation was indicated as either ''1'' (strong recommendation) or ''2'' (weak recommendation) [1]. Consensus was previously defined as 70 % or more votes in agreement.

In this article, we summarize the main CQs and statements and our consensuses on the management of liver cirrhosis and its complications.

Diagnosis of liver cirrhosis

Basic information on the cause of liver cirrhosis, on the characteristics of the patients, and from physical examination first gives a clue to the suspected diagnosis. Liver biopsy has been the gold standard for the diagnosis of liver cirrhosis. However, it is an invasive procedure and has some limitations, including sampling error and interobserver variation. Although several noninvasive diagnostic methods have appeared, the combination of selected methods such as the determination of fibrosis scores based on several blood tests, evaluation of tissue stiffness by transient elastography, and a morphological assessment with other imaging tools or liver biopsy is useful for the diagnosis of liver cirrhosis in practice. A diagnostic algorithms is shown in Fig. 1. An ideal simple noninvasive method should be further sought in the combination of numerous blood markers and imaging modalities.

Nutritional therapy

CQ: Does a late-evening snack improve the prognosis of cirrhotic patients?

- Although its effect on prognosis is not clear, it is proposed for cirrhotic patients on the basis of its effect on energy metabolism and quality of life (QOL). (Evidence level C, strength 2)

Comment: A late-evening snack (LES) of 200 kcal such as a rice ball, liquid nutrient, and branched-chain amino acid (BCAA)-enriched supplementation improves nocturnal fasting, improves nutritional status, increasing body protein content [2], and diminishes fat and protein oxidation [3]. It suppresses serum free fatty acid levels [4] and recovers energy metabolism (i.e., respiratory quotient: RQ) [5] at 1 week and serum albumin levels and nitrogen balance at 3 months [6]. Although its effect on survival has not been reported, it improves health-related QOL [7]. Its nutritional effects help cirrhotic patients with refractory ascites undergoing repeated paracentesis [8] and those with hepatocellular carcinoma (HCC) receiving chemoembolization [9].

CQ: Is oral BCAA administration effective for management of liver cirrhosis?

- It is recommended for cirrhotic patients because it relieves hypoalbuminemia and hepatic encephalopathy and improves QOL. (Evidence level B, strength 2)

Comment: Long-term oral BCAA supplementation improves event-free survival, increases serum albumin levels, and improves QOL in patients with decompensated cirrhosis with hypoalbuminemia (serum albumin level of

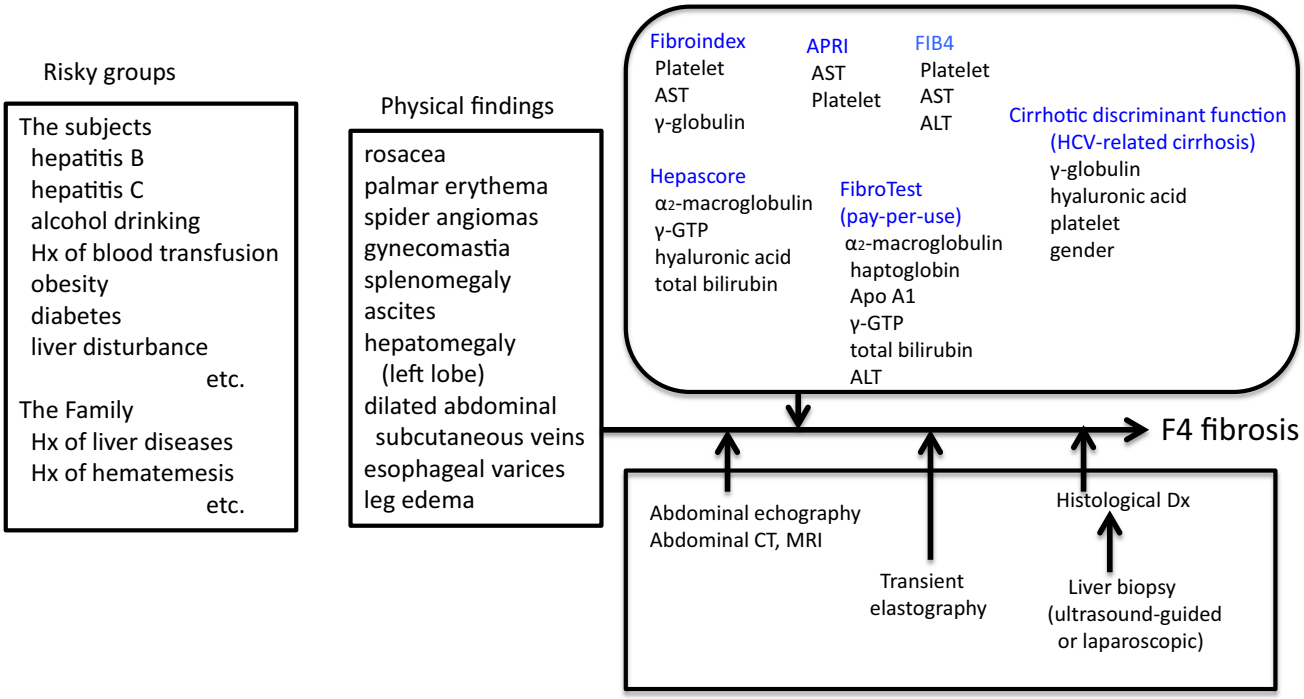

Fig. 1 Diagnostic algorithm for liver cirrhosis. After obtaining basic information on the cause of liver cirrhosis, on the characteristics of the patients, and from physical examination, we should combine several diagnostic tools such as numerous serum biomarkers and imaging modalities as noninvasive alternatives to liver biopsy. This algorithm diagnoses cirrhotic F4 fibrosis. A special blood test or histological characteristics are often needed to determine the cause of cirrhosis. *ALT* alanine aminotransferase, *Apo* apolipoprotein, *APRI* aspartate aminotransferase to platelet ratio index, *AST* aspartate aminotransferase, *Dx* diagnosis, *FIB4* fibrosis 4, *HCV* hepatitis C virus, *Hx* history

3.5 g/dL or lower) [10], whereas BCAA granules show no effect on serum albumin levels in patients with compensated cirrhosis (serum albumin level between 3.6 and 4.5 g/dL) [11]. Perioperative supplementation with a BCAA-enriched nutrient mixture reduces the morbidity associated with postoperative complications, preserves serum albumin levels, and shortens the duration of hospitalization of patients undergoing liver resection for HCC [12]. The annual changes in the Model for End-Stage Liver Disease (MELD) score, Child–Pugh score, and asialoscintigraphic clearance index were smaller and the incidence of ascites was lower in cirrhotic patients taking BCAA granules, which suggests that early interventional oral BCAA administration may prolong the liver transplant waiting period [13]. Although oral BCAA supplementation after an episode of hepatic encephalopathy does not decrease recurrence of hepatic encephalopathy, it relieves minimal hepatic encephalopathy and increases muscle mass. [14]. It is also associated with reduced incidence of HCC in patients with Child–Pugh A cirrhosis [15] and in patients with a BMI of 25 kg/m^2 or higher [16].

Figure 2 shows an algorithm for nutritional therapy in patients with liver cirrhosis.

Antiviral therapy for hepatitis B virus related cirrhosis

CQ: Do nucleoside analogues enhance sustained virological response (SVR) or hepatitis B e antigen (HBeAg) seroconversion in patients with hepatitis B virus (HBV)-related cirrhosis?

- Nucleoside analogues (lamivudine, adefovir, entecavir, and tenofovir) are recommended for such patients because they enhance SVR and HBeAg seroconversion. (Evidence level A, strength 1)

CQ: Do nucleoside analogues relieve liver fibrosis and improve prognosis? Do they suppress the development of HCC?

- Administration of nucleoside analogues is recommended for HBV-related cirrhosis because they relieve liver

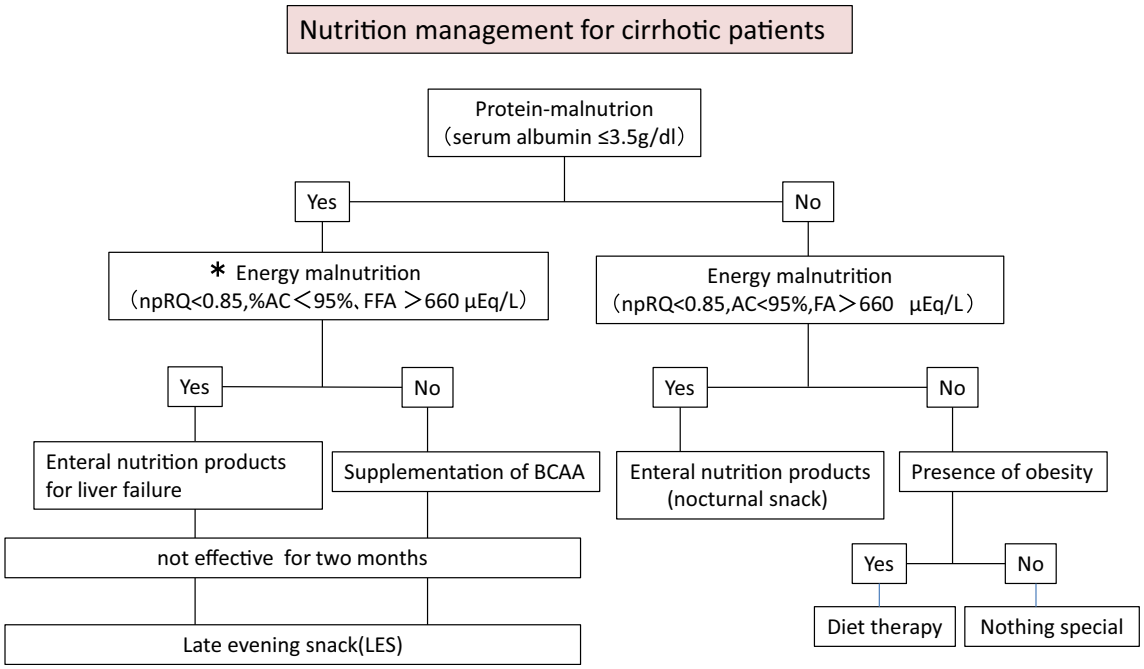

Fig. 2 Algorithm for nutritional therapy in patients with liver cirrhosis. The nonprotein respiratory quotient (*npRQ*) measured by indirect calorimetry is considered to be a good marker to estimate energy malnutrition. A decrease in npRQ (less than 0.85) in cirrhotic patients predicts lower survival rate. However, measurement of npRQ is limited in daily clinical practice. Subjective global assessment (SGA), dual-energy X-ray absorptiometry (DEXA), bioelectrical impedance (BIA), handgrip strength (HG), and L3 skeletal muscle index are used to determine nutrition disorders in patients with liver cirrhosis as nutrition assessments alternative to npRQ. Percent arm circumference (*AC*) and free fatty acid (*FFA*) level are correlated with npRQ. The cut-off values of percent AC and FFA level to predict npRQ = 0.85 are equivalent to 95 % and 660 μEq/L respectively by receiver operating characteristic (ROC) analysis. *BCAA* branched-chain amino acids

fibrosis and improve patient prognosis and prevent the development of HCC. (Evidence level A, strength 1)

CQ: Are adefovir and tenofovir effective for management of lamivudine-resistant HBV-related liver cirrhosis?

- Adefovir add-on therapy or a switch to tenofovir therapy is recommended in this case. (Evidence level A, strength 1)

CQ: Does interferon relieve liver fibrosis and suppress the development of HCC in HBV-related liver cirrhosis?

- Interferon therapy is not recommended for patients with HBV-related liver cirrhosis because there is not enough evidence of its effects on fibrosis and HCC in liver cirrhosis. (Evidence level C, strength 2)

Comment: Continuous lamivudine (LDV) treatment results in HBeAg seroconversion and undetectable HBV DNA levels [17], and delays clinical progression of HBV-related cirrhosis by reducing hepatic decompensation and HCC development [18]. Administration of adefovir dipivoxil (ADV) for 12.6 months (median) offered a clinical benefit [undetectable HBV DNA 41.2 %, alanine aminotransferase (ALT) level normalization 55.2 %] in cirrhotic patients in whom LDV therapy failed [19]. One-year initial entecavir (ETV) therapy was similarly effective in both patients with compensated cirrhosis and patients with decompensated cirrhosis and it improved underlying liver function in decompensated cirrhotic patients [20]. ALT level normalization and HBeAg loss/seroconversion were similarly expected with tenofovir disoproxil fumarate (TDF) and ETV in patients with decompensated cirrhosis [21]. TDF and ETV are superior to LDV in reducing HBV DNA levels, normalizing ALT levels, and suppressing the increase of Child–Pugh scores [22]. Viral resistance to long-term ADV therapy and ETV therapy is rarer (ADV 29 % for 5 years [23] and ETV 0 % for 699 days (median) [24]) than that to LDV (49 % for 699 days (median) [18]). A meta-analysis concluded that TDF and ETV are the most potent antiviral agents for HBeAg-positive patients in the first year of treatment, whereas TDF is recommended for HBeAg-negative patients [25].

Long-term treatment with LDV [26], ETV [27], ADV [23], or TDF [28] was reported to reverse HBV-related cirrhosis to milder fibrosis. ETV was more effective than LDV in reducing fibrosis in advanced hepatic fibrosis or cirrhosis [29]. Long-term LDV or ETV therapy decreased

Child–Pugh scores and MELD scores [20, 30]. Continuous LDV therapy reduces the risk of HCC in HBV-related chronic hepatitis and cirrhosis (Ishak fibrosis score 4–6) [18]. The cumulative incidence of HCC was 6.9 % at 24 months in patients with HBV-related decompensated cirrhosis receiving ETV treatment [20].

ADV as add-on therapy to LDV therapy was effective for management of LDV-resistant HBV-related cirrhosis (undetected HBV DNA 41.2–100 %, ALT level normalization 31–82 %, 2-point decreased Child–Pugh score 64–92 %) [19, 31–34]. Virological breakthrough was rarer in the LDV plus ADV therapy group than in the ADV monotherapy group [35]. TDF retains efficacy against highly LDV/ADV-resistant HBV in heavily pretreated patients [36]. Patients with decompensated cirrhosis receiving LDV plus ADV therapy are at risk of early death and HCC development despite the antiviral effects [37]. Renal disturbance (creatinine clearance less than 50 mL/min) and hypophosphatemia (phosphate level less than 2 mg/dL) were very rare (less than 1 %) in group receiving TDF therapy for 96 weeks [38], whereas the incidences of serum creatinine level elevation and hypophosphatemia (phosphate level less than 2.5 mg/dL) in the group receiving LDV plus ADV add-on therapy for 15–68 weeks were 38 and 16 %, respectively [39].

No study has ever confirmed the beneficial effect of interferon on liver fibrosis in HBV-related cirrhosis. With regard to an HCC-preventing effect, contradictory results were reported both in randomized controlled trials (RCTs) [40, 41] and in meta-analyses [42, 43]. Serious adverse effects, such as bacterial infections and hepatic failure, should not be ignored in interferon therapy for advanced cirrhosis.

Antiviral therapy for HCV-related cirrhosis

CQ: Does interferon therapy suppress the development of HCC and improve the prognosis of patients with HCV-related liver cirrhosis?

- Interferon therapy is proposed for patients with compensated HCV-related cirrhosis because it suppresses HCC development and there is a possibility of an improvement in the prognosis of such patients. (Evidence level B, strength 2)

CQ: Is liver fibrosis relieved when SVR is attained by interferon therapy in HCV-related liver cirrhosis?

- Liver fibrosis is gradually relieved when SVR is attained in HCV-related cirrhosis.

Comment: Although early studies did not show this clearly [44, 45], recent studies reported that achieving SVR with interferon plus ribavirin therapy markedly reduces the risk of HCC [46–49] and improves survival [47, 49] in compensated HCV-related cirrhosis. However, long-term peginterferon therapy did not reduce the incidence of HCC among patients who did not achieve SVRs [50].

Second biopsy after peginterferon α_2a and peginterferon -α_2b therapy revealed a 33–49 % reversal of cirrhosis [51, 52]. The incidence of this reversal was 61–68 % in cirrhotic patients with SVR [52, 53]. Decrease of fibrosis scores was noted in patients with SVR or virological relapse with this therapy [54]. Multiple regression analyses proved that SVR is one significant predictive factor for the relief of severe fibrosis and cirrhosis [54].

CQ: Is interferon equally effective for management of chronic hepatitis and cirrhosis type C?

- The SVR rate of genotype 1 to peginterferon plus ribavirin therapy is lower in patients with compensated cirrhosis than that in those with chronic hepatitis. The rate of SVR of genotype 2 to the therapy is the same between patients with compensated cirrhosis and patients with chronic hepatitis. Peginterferon plus ribavirin therapy is not recommended for patients with decompensated cirrhosis because of their low adherence and SVR rates and the high incidence of adverse events. (Evidence level A, strength 1)

CQ: Is peginterferon plus ribavirin therapy effective for HCV-related cirrhosis which did not respond to first interferon therapy?

- Peginterferon plus ribavirin therapy is not proposed for cirrhotic patients who did not respond to first interferon therapy because the therapy results in a low SVR rate and has little effect on survival and little beneficial effect with regard to HCC development and disease progression. (Evidence level C, strength 2)

CQ: Does interferon therapy not induce adverse events and worsen the prognosis of patients?

- Although interferon therapy in compensated HCV-related cirrhosis is more frequently associated with adverse effects and treatment interruption than in chronic hepatitis, careful dose adjustment allows safe and effective therapy. Interferon therapy is thus proposed as a treatment option for patients with compensated HCV-related cirrhosis. Direct-acting antivirals are also proposed if indicated. (Evidence level B, strength 2)

Comment: The rate of SVR with peginterferon plus ribavirin therapy was reported to range from 10 to 44 % for genotypes 1 and 4 and from 33 to 72 % for genotypes 2 and 3 in compensated cirrhosis [55]. Although HCV clearance by the therapy is associated with a reduced risk of liver decompensation, HCC development, and liver-related death [55], these benefits have to be counterbalanced by the increased risk of side effects, such as severe infections in patients with advanced cirrhosis [56].

Di Marco et al. [57] reported that previous nonresponse to interferon monotherapy did not significantly affect the SVR rate on retreatment with peginterferon alone or peginterferon plus ribavirin therapy. In contrast, Giannini et al. [58] reported that nonresponse to a previous antiviral therapy is an important determinant of reduced response to full-dose therapy with peginterferon and ribavirin in cirrhosis and portal hypertension. Di Bisceglie et al. [59] noted that long-term half-dose peginterferon therapy did not suppress disease progression and HCC development in cirrhotic patients who did not respond to initial peginterferon plus ribavirin therapy and concluded that this therapy is not indicated for these patients.

Peginterferon-α_{2a} plus ribavirin therapy is effective and well tolerated in patients with bridging fibrosis or cirrhosis, although a decrease in platelet counts (less than $50 \times 10^3/\mu L$) during the treatment was significantly more frequent in these patients than in patients with milder fibrosis [60]. In long-term maintenance therapy, most cirrhotic patients are unable to tolerate prolonged treatment with full doses of peginterferon and ribavirin [61]. However, if an SVR is attained by a carefully scheduled therapy, it has a positive impact on decompensated patients as well, improving overall survival and reducing the risk of further events of hepatic decompensation [62]. An additional long-term, low-dose peginterferon therapy for non-SVR patients was proven to add no clinical benefit and was associated with an excess overall mortality [63, 64]. Although this mortality was primarily due to non-liver-related causes [64], long-term interferon therapy should be avoided. Interferon therapy may soon be replaced by therapy with rapidly progressing direct-acting antivirals (i.e., asunaprevir, daclatasvir, and sofosvir) in patients with liver cirrhosis.

Antifibrotic therapy

CQ: Is there any antifibrotic therapy for viral cirrhosis except antiviral therapy?

- No therapy has confirmed efficacy. (Evidence level C.)

Comment: Ursodeoxycholic acid (UDCA) stabilizes serum ALT levels in HCV-related liver cirrhosis [65], and glycyrrhizin injection is useful for the prevention of disease progression [66]. However, their effects on liver fibrosis have not been confirmed. Administration of UDCA for 1 year [67] or angiotensin-blocking agents for 1.5–3.5 years [68] failed to relieve fibrosis in chronic hepatitis and cirrhosis. Colchicine suppressed the serum N-terminal peptide of type III procollagen level in chronic liver diseases, including cirrhosis [69], whereas histological improvement was not observed after 1 year [70], and a meta-analysis failed to reveal its beneficial effects on liver-related mortality and complications [71]. Phlebotomy was reported to prevent the progression of liver fibrosis of chronic hepatitis C [72].

Therapy for nonviral liver cirrhosis

CQ: Does abstinence from drinking alcohol suppress the progression of fibrosis and improve the prognosis of patients with alcoholic liver cirrhosis?

- Abstinence is recommended for such patients because long-lasting abstinence improves their prognosis. (Evidence level A, strength 1)

Comment: Despite large-scale prospective studies in 1960–1980, the effect of abstinence from drinking alcohol on alcoholic fibrosis remains to be clarified. Continued heavy drinking was associated with poor survival of cirrhotic patients [73]. The mortality in patients with advanced alcoholic cirrhosis was extremely high (5 years 71 %, 15 years 90 %) [74]. High age and continuous alcohol consumption of more than 10 g ethanol per day were independent predictors of a poor prognosis [74]. The prognostic importance of abstinence was demonstrated in both Child-Pugh A/B and Child-Pugh C patients [75].

CQ: Does corticosteroid therapy relieve liver fibrosis and improve the prognosis of patients with autoimmune hepatitis and liver cirrhosis?

- Corticosteroid therapy is proposed for patients with active autoimmune-hepatitis-related cirrhosis because relief of fibrosis and improvement of prognosis are expected for responders. (Evidence level A, strength 1.)
- Corticosteroid therapy is not proposed for patients with inactive autoimmune-hepatitis-related cirrhosis because its effect is uncertain. (Evidence level A, strength 1.)

Comment: Fibrosis was relieved in 53 % of patients and progressed in 25 % of patients with long-term corticosteroid therapy [76]. Nodular fibrosis/cirrhosis was relieved in 9 of 14 patients [77]. Cirrhotic change returned to normal by the repeated wedge liver biopsy 14 years later in a female patient [78]. Although cirrhosis was associated with a poorer outlook in some studies [79], the rates of

remission (78 % vs 76 %), treatment failure (14 % vs 13 %), and 10-year survival (89 % vs 90 %) were comparable in patients with and without cirrhosis [80]. As the response is excellent even in those with variceal bleeding or ascites, the treatment should not be withheld in patients with decompensated cirrhosis and active disease [81]. In contrast, corticosteroid therapy is not indicated for patients with inactive cirrhosis, who receive no benefit from the therapy [82].

CQ: Do UDCA and corticosteroid therapy relieve liver fibrosis and improve the prognosis of patients with the cirrhotic stage of primary biliary cirrhosis?

- UDCA therapy is recommended for such patients because it can improve their prognosis. (Evidence level A, strength 1)
- Corticosteroid therapy is not recommended for such patients because it is related to many adverse effects. (Evidence level A, strength 2)

Comment: In contrast to the previous negative data [83, 84], UDCA was reported to delay the progression of liver fibrosis [85, 86] and even relieve fibrosis of cirrhotic patients [87]. Some studies supported its beneficial effect on prognosis [86, 88–90], whereas others, including a Cochrane database systemic review, did not support it [91–94]. Good biochemical response to UDCA is related to good prognosis [95] and poor response is related to disease progression [96] and HCC development [97]. Although the histological stage was considered as a major determinant of the therapeutic effect [98], recent logistic regression analysis showed that not the primary biliary cirrhosis stage but esophageal varices and poor UDCA response were related to high mortality risk [90]. As for the use of corticosteroid therapy, the extrahepatic adverse effects such as infection, diabetes, or peptic ulcer are considered to outweigh the slight improvement of liver function in advanced cirrhosis.

CQ: Do UDCA and corticosteroid therapy improve the prognosis of patients with liver cirrhosis due to primary sclerosing cholangitis?

- Corticosteroid therapy does not improve their survival and is not recommended for them. (Evidence level A, strength 1)
- UDCA therapy is proposed as a treatment option for them, although its effect is uncertain. (Evidence level A, strength 2)

Comment: A Cochrane database systemic review reported that corticosteroid therapy tended to increase the incidence of adverse events and resulted in no cholangiographic improvement [99]. An RCT revealed that high-dose UDCA therapy (28–30 mg/kg/day) did not improve survival, although it suppressed serum ALT and alkaline phosphatase levels [100]. The therapy was associated with increased risk of esophagogastric varices and mortality, suggesting a risk of high-dose UDCA therapy for patients with primary sclerosing cholangitis [100]. On the basis of variable data on its effects on liver tests and survival [100–103], UDCA therapy is not recommended in the American Association for the Study of Liver Diseases (AASLD) [104] and European Association for the Study of the Liver (EASL) [105] guidelines. We propose its careful use as a treatment option after assessment of the benefit–risk balance.

Gastrointestinal bleeding and portal hypertension

CQ: Which is more useful endoscopic variceal ligation (EVL) or endoscopic injection sclerotherapy (EIS) in preventing recurrence of esophageal varices?

- EIS is recommended for preventing recurrence because both the recurrence and the bleeding rates after EIS are lower than the corresponding rates after EVL. (Evidence level A, strength 1)

Comment: Although the eradication rate of esophageal varices was not significantly different between the two groups, the rate of recurrence of esophageal varices was higher in the EVL group than in the EIS group [106]. Gotoh et al. [107] concluded that EVL was ineffective as a prophylactic therapy, because both recurrence of and bleeding from oesophageal varices during a 18-month follow-up period were observed more frequently in the EVL group than in the EIS group (recurrence 56 % vs 16 %, bleeding 20 % vs 0 %). EVL was proved to be no more effective than no treatment in preventing initial variceal bleeding [108]. Repeated EIS was preferable to combined therapy with EVL as a means of preventing the recurrence of esophageal varices [109].

CQ: Are β-blockers useful in preventing bleeding from esophageal varices?

- β-Blockers are useful for primary prophylaxis of esophageal variceal bleeding. The combination of endoscopic therapy and β-blockers is proposed for secondary prophylaxis of esophageal variceal bleeding as it decreases rebleeding and mortality. (Evidence level A, strength 2)

CQ: Is combined therapy with a β-blocker and isosorbide 5-mononitrate (ISMN) useful in preventing bleeding from esophageal varices?

- Combined therapy with a β-blocker and ISMN is proposed for the prevention of variceal bleeding

because it is effective in suppressing both the initial and recurrent bleeding from esophageal varices. (Evidence level A, strength 2)

CQ: Are β-blockers effective for management of portal hypertensive gastropathy?

- Propranolol is proposed for management of portal hypertensive gastropathy because it is effective in relieving portal hypertensive gastropathy. (Evidence level A, strength 2)

Comment: Several RCTs proved that nonselective β-blockers are effective in preventing initial [110] or recurrent [111] hemorrhage from esophageal varices. Several RCTs have reported that β-blockers were as effective as EVL in preventing initial variceal bleeding [112, 113] or as effective as EIS in preventing recurrent variceal bleeding [114], whereas other RCTs have reported that EVL was more effective than propranolol for the primary prevention of high-risk variceal bleeding [115, 116]. Pérez-Ayuso et al. [117] concluded in their RCT that propranolol should be considered the first choice for primary prophylaxis in the case of variceal bleeding, offering similar effects as and fewer severe adverse events than EVL. Funakoshi et al. [118] summarized their meta-analysis as indicating that current evidence is insufficient to recommend EVL over β-blockers as first-line therapy. They further found that the combination of a β-blocker and endoscopic treatment significantly reduced rebleeding and mortality compared with endoscopic treatment alone.

Villanueva et al. [119, 120] reported that combined therapy with nadolol and ISMN was more effective than EIS or EVL alone for the prevention of recurrent variceal bleeding, but Lo et al. [121] reported that EVL was more effective than the combination of nadolol and ISMN. Wang et al. [122] reported that the combination of nadolol plus ISMN was similar to EVL with regard to effectiveness and safety in the prevention of initial variceal bleeding. Another RCT reported that the rebleeding rate of esophageal varices over 6 months was 38 % in the propranolol group, 31 % in the EVL group, 26 % in the proplanorol plus ISMN group, and 22 % in the EVL plus proplanorol plus ISMN group. In a meta-analysis, the rebleeding rate was not significantly different between the β-blocker plus ISMN group and the EVL-alone group, but the combination treatment exhibited a survival advantage over EVL alone when all-cause mortality was evaluated [123]. They concluded that a β-blocker plus ISMN was the best choice for the prevention of rebleeding [123].

Propranolol, in addition to lowering portal pressure, reduces gastric blood perfusion in cirrhotic patients with portal hypertensive gastropathy, which may contribute to prevention of bleeding from these lesions [124]. Long-term propranolol treatment (12 and 30 months) was proven to reduce the frequency of rebleeding from severe portal hypertensive gastropathy [125]. Multivariate analysis showed that the absence of propranolol treatment was the only predictive variable for rebleeding [125]. The occurrence of portal hypertensive gastropathy after EVL for treatment of esophageal varices was significantly reduced by propranolol therapy [126].

CQ: Are vasoactive agents effective for management of esophageal variceal bleeding?

- Vasoactive agents (vasopressin, terlipressin, somatostatin, or octreotide) are effective in controlling esophageal variceal bleeding. The administration of these agents is proposed after EVL. (Evidence level A, strength 2)

Comment: In a meta-analysis, the use of vasoactive agents (vasopressin, somatostatin, and their analogues terlipressin, vapreotide, and octreotide) was associated with a significantly lower risk of acute all-cause death and transfusion requirements, and improved control of bleeding and shortened hospital stay [127]. Studies comparing various vasoactive medications showed no significant differences in efficacy among them [127]. D'Amico et al. [128] reviewed 17 RCTs comparing emergency sclerotherapy with vasopressin (with or without nitroglycerin), terlipressin, somatostatin, or octreotide in their meta-analysis and reported that sclerotherapy did not appear to be superior to the vasoactive drugs in terms of control of initial bleeding, number of transfusions, 42-day rebleeding, or mortality. However, emergency EVL plus octreotide therapy is superior to octreotide therapy alone at a lower cost while combining higher efficacy with a sufficient degree of safety [129].

CQ: Is injection of cyanoacrylate effective for management of gastric varices (GV)?

- Injection of cyanoacrylate is recommended for the management of bleeding GV because it is more effective than β-blocker medication or EVL alone. (Evidence level A, strength 1)

Comment: Endoscopic obliteration using cyanoacrylate is more effective and facilitates the obliteration of GV faster than EIS with alcohol [130]. Endoscopic obturation using cyanoacrylate proved more effective and safer with a lower rebleeding rate than EVL in the management of GV bleeding [131, 132]. It is also more effective than β-blocker medication for the prevention of initial and recurrent GV rebleeding and improving survival [133, 134], and it has proven to be highly effective in the management of fundal GV bleeding [135].

CQ: Is balloon-occluded retrograde transvenous obliteration (B-RTO) effective for management of GV?

- B-RTO is proposed as an elective therapy after hemostasis of initial GV bleeding using cyanoacrylate and as a prophylactic therapy in the management of high-risk GV. (Evidence level C, strength 2.)

Comment: Kanagawa et al. [136] inserted a balloon catheter into an outflow shunt (gastrorenal or gastric–inferior vena cava) via the femoral or internal jugular vein. After blocking the blood flow by inflating the balloon, they injected 5 % ethanolamine oleate iopamidol in a retrograde manner and embolized the GV. They concluded that B-RTO was a safe and effective procedure for the treatment of fundal GV, as eradication of the varices was confirmed in 31 of 32 patients without serious side effects [136]. Hong et al. [137] reported that EIS with cyanoacrylate was associated with a higher rebleeding rate than B-RTO, although the immediate efficacies of these two treatments for bleeding GV and high-risk GV were similar. Akahoshi et al. [138] reported that B-RTO was superior to EIS with cyanoacrylate and ethanolamine oleate in preventing rebleeding from isolated fundal GV with a major shunt. The 8-year cumulative bleeding rates for bleeding GV and nonbleeding high-risk GV after B-RTO were 14 % and 0 % respectively [139]. The cumulative occurrence rate for high-risk esophageal varices was 22 %, and no patients died of variceal bleeding [139]. These results led to a consensus in Japan that B-RTO can serve as a first-choice radical treatment after hemostasis for GV bleeding and prophylactic treatment for high-risk GV.

Ascites

The proper management of ascites begins with an optimal testing strategy for differential diagnosis. Diagnostic paracentesis should include cell count, differential cell count, and measurement of total protein and albumin concentration to rule out asymptomatic spontaneous bacterial peritonitis (SBP). Bacterial culture is also necessary if ascitic fluid infection is suspected. Figure 3 shows the diagnostic algorithm for cirrhotic ascites.

CQ: Is a salt-restricted diet effective for treatment of cirrhotic patients with ascites?

- A salt-restricted diet is considered effective for mild to moderate ascites. A mild salt-restricted diet to maintain appetite is proposed for such patients. (Evidence level C, strength 2)

Comment: Although dietary salt has been restricted in European countries, this may cause protein malnutrition [140]. Contradictory results have been presented on the effect of salt restriction on the disappearance of ascites in patients taking diuretics [141, 142]. The importance of an evening protein snack was stressed over salt restriction in survival of cirrhotic patients with refractory ascites [8]. In

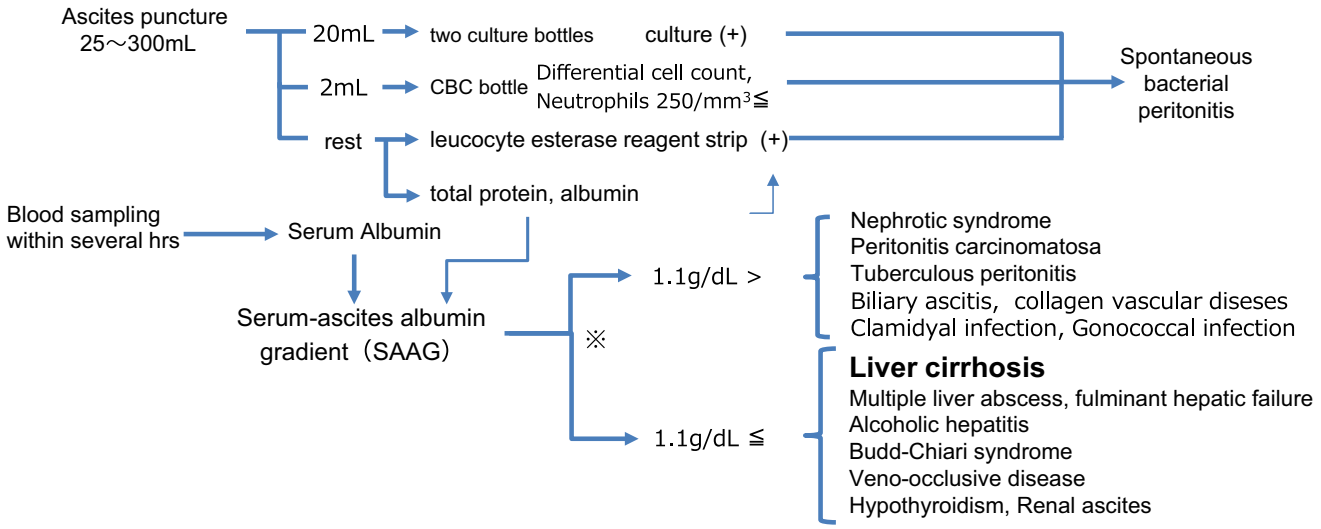

Fig. 3 Diagnostic algorithm for cirrhotic ascites. Ascitic fluid obtained by diagnostic paracentesis should be examined for total protein, albumin, and LDH levels, cell count, and differential cell count. If necessary, Gram and acid-fast staining and culture are performed. If the serum–ascites albumin gradient (*SAAG*) is greater than or equal to 1.1 g/dL, the patient is considered to have portal hypertension. If the SAAG is less than 1.1 g/dL, portal hypertension can be excluded. Although the SAAG is useful for the diagnosis of cirrhotic ascites, we need to determine the cause of ascites as a whole, because there are exceptions. A diagnosis of spontaneous bacterial peritonitis (*SBP*) is made when there is a positive ascitic fluid bacterial culture and an elevated ascitic fluid absolute polymorphonuclear leukocyte count (i.e., at least 250 cells per microliter) without an evident intra-abdominal, surgically treatable source of infection. ※ Of note, SAAG is less than 1.1g/dl in patients with SBP. *CBC* complete blood cell count

Japan, mild salt restriction (85–120 mmol/day) may be proposed to avoid appetite loss.

CQ: Is albumin infusion effective for treatment of cirrhotic patients with ascites?

- It is effective. Albumin infusion is proposed for such patients because it increases the effect of diuretics and prevents paracentesis-induced circulatory disturbance. It also relieves circulatory disturbances and prevents the development of HRS. (Evidence level A, strength 2)

Comment: Albumin binds and transports loop diuretics to the proximal convoluted tubule in the kidney. Albumin infusion improves the response of diuretics and shortens the hospital stay of ascitic patients [143]. A meta-analysis showed that it reduces morbidity (incidence of paracentesis-induced circulatory disturbance and hyponatremia) and mortality of patients with tense ascites undergoing large-volume paracentesis (LVP) as compared with alternative treatments (saline or other plasma expanders) [144]. SBP is a most important precipitating event for the development of type 1 HRS characterized by rapid progressive renal failure with poor prognosis [145]. An RCT proved the preventive effect of albumin infusion on the development of type 1 HRS in patients with SBP receiving antibiotics [146].

CQ: Are loop diuretics more effective than the aldosterone antagonist spironolactone for treatment of cirrhotic patients with ascites?

- No. Spironolactone is recommended as a single drug. (Evidence level A, strength 1)

CQ: Is spironolactone alone or in combination with loop diuretics better for treatment of cirrhotic patients with ascites?

- Although outpatients can be first treated with spironolactone alone, the combination therapy is rather proposed for inpatients receiving intensive therapy to prevent side effects. (Evidence level C, strength 2)

Comment: Controlled studies showed that spironolactone achieves better natriuresis and diuresis than a loop diuretic such as furosemide [140]. In European countries, first-line treatment of ascites is with spironolactone, increasing from 100 to 400 mg/day [140]. If this fails, furosemide is added at a dosage of up to 160 mg/day [140]. However, this sequential therapy more frequently led to adverse effects (in particular, hyperkalemia) than the combined diuretic treatment [147]. The EASL guidelines recommend the combination therapy as a step-up regimen for recurrent ascites [148]. The usual diuretic regimen recommended by the AASLD guidelines consists of single morning doses of orally administered spironolactone (100 mg) and furosemide (40 mg) [149].

CQ: Are vasopressin V_2 receptor antagonists effective for management of ascites or water retention in cirrhotic patients?

- A vasopressin V_2 receptor antagonist combined with loop diuretics and aldosterone antagonists is recommended for such patients on the basis of its effectiveness on hyponatremia and ascites. (Evidence level A, strength 1)

Comment: Given the central role of vasopressin in limiting renal water excretion in cirrhotic patients, use of vasopressin V_2 receptor antagonists is a rational approach for ascetic patients. Among them, tolvaptan (7.5–30 mg/day for 7 days) showed add-on effects to conventional diuretics on ascites in multicenter RCTs for poor responders to the standard diuretic therapy (furosemide at 40 mg/day or greater and spironolactone at 25 mg/day or greater; or furosemide at 20 mg/day or greater and spironolactone at 50 mg/day or greater) [150, 151]. As a dosage of 7.5 mg/day showed the maximum effects with preferable tolerability [151] and a dosage of 3.75 mg/day also exerted significant effects [152], the proper dosage was determined as 3.75–7.5 mg/day. The effects were unrelated to serum albumin levels [150]. Minor increases in serum creatinine levels defined as acute kidney injury by the International Club of Ascites adversely affect survival of cirrhotic patients [153, 154]. To avoid acute kidney injury and electrolyte disturbances caused by high-dose diuretics, we propose the combined use of tolvaptan and diuretics for ascitic patients (Fig. 4).

CQ: Is large volume paracenthesis (LVP) useful for patients with refractory ascites?

- Yes. Paracentesis with albumin infusion is recommended for such patients as the first-line therapy. (Evidence level A, strength 1)

CQ: Is cell-free and concentrated ascites reinfusion therapy (CART) useful for patients with refractory ascites?

- It is useful just like paracentesis with albumin infusion and is proposed for such patients. (Evidence level B, strength 2)

Comment: Paracentesis with albumin infusion is a fast, effective, and safe therapy for ascites in cirrhosis [155]. It achieves a marked reduction of intra-abdominal, intrathoracic, and pulmonary pressures [156] and a rapid fall of portal pressure [157] without any renal and hepatic dysfunction [155]. LVP is considered as the first-line therapy for tense ascites in the EASL guidelines [148] and AASLD guidelines [149]. Although plasma expanders and saline could replace albumin when less than 5 L of ascitic

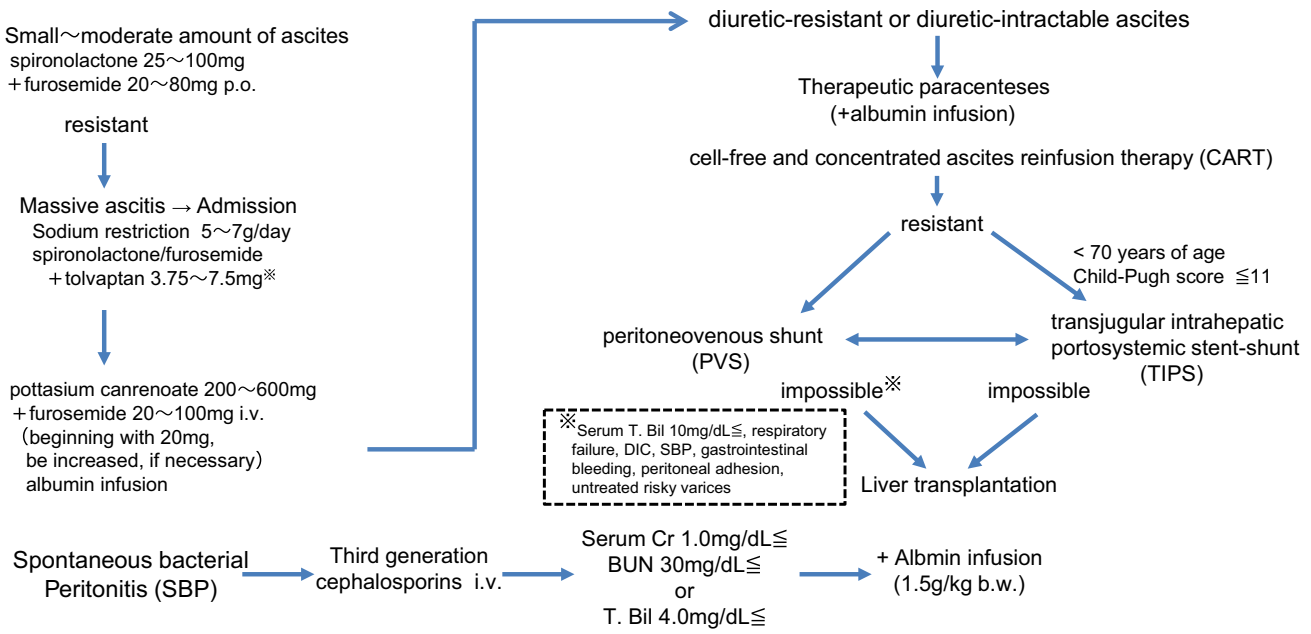

Fig. 4 Therapeutic algorithm for cirrhotic ascites. The first-choice diuretic for a small to moderate amount of ascites is spironolactone (25–100 mg/day). If it is not effective, furosemide (20–80 mg/day orally) is added. Patients with massive or nonresponsive ascites should be admitted. Under sodium restriction (5–7 g/day), either an add-on therapy with the V_2 receptor antagonist tolvaptan (3.75–7.5 mg/day orally) or an intravenous infusion of potassium canrenoate/furosemide is recommended. For those with severe hypoalbuminemia (albumin level below 2.5g/dL), albumin infusion (20–25 % albumin at 50 mL/day, up to 6 times per month) can be considered. (strictly controlled by the public medical insurance systems in Japan). We should be careful of the underfilling state of patients to prevent adverse effects of diuretics. For patients resistant to these medications, therapeutic paracentesis or cell-free and concentrated ascites reinfusion therapy is indicated. Albumin infusion after large-volume paracentesis has been proved to be useful for the prevention of paracentesis-induced circulatory disturbance, although this is restricted in the public medical insurance systems in Japan. Patients with spontaneous bacterial peritonitis (*SBP*) should receive empiric antibiotic therapy, (e.g., an intravenously administered third-generation cephalosporin). The American Association for the Study of Liver Diseases guidelines recommended an add-on albumin infusion when the serum creatinine (*Cr*) level is greater than 1 mg/dL, the blood urea nitrogen (*BUN*) level is greater than 30 mg/dL, or the total bilirubin (*T. Bil.*) level is greater than 4 mg/dL for the prevention of hepatorenal syndrome. (This therapy is not approved by the public medical insurance systems in Japan). *b.w.* body weight, *DIC* disseminated intravascular coagulation, *i.v.* intravenously, *p.o.* per os

fluid is evacuated in Europe [158, 159], we should be more cautious about LVP for small Asian patients to prevent a risky underfilling state which may lead to hepatic encephalopathy or renal failure. The prognosis of patients does not improve with the procedure [160]. The reinfusion of concentrated ascitic fluid by means of CART is safe and effective just like LVP with albumin infusion [161], although the costs of the instruments and staff and the allergic reactions may be considered as drawbacks [162]. In Japan its benefit to reduce albumin use is emphasized.

CQ: Is peritoneovenous shunt (PVS) useful for treatment of patients with refractory ascites?

- Despite many serious complications and no survival advantage compared with diuretic therapy, it can relieve symptoms and shorten the hospital stay. It may be proposed for patients when other treatments are impossible. (Evidence level A, strength 2)

CQ: Is transjugular intrahepatic portosystemic stent–shunt (TIPS) useful for treatment of patients with refractory ascites?

- Compared with LVP with albumin infusion, TIPS is more effective in controlling ascites, preventing its recurrence, and improving mental QOL and survival. Although it frequently causes hepatic encephalopathy and needs technical skills, it can be proposed for appropriately selected patients. (Evidence level A, strength 2)

Comment: PVS was specifically designed to palliate ascites by reintroducing ascitic fluid into the systemic circulation (LeVeen or Denver shunt). PVS was reported to increase the glomerular filtration rate and provide palliation in 83 % of patients with intractable ascites waiting for liver transplant [163]. Control of ascites was achieved sooner after PVS than after TIPS, but long-term efficacy favored TIPS [164]. PVS significantly prolonged the time to the

recurrence of ascites compared with diuretic treatment [165] and LVP with albumin infusion [166]. However, the poor long-term patency, excessive complications (disseminated intravascular coagulation, cardiac failure, sepsis, etc.), and no survival advantage compared with medical therapy in controlled trials have restricted the use of PVS to when other treatments are impossible [149]. Several meta-analyses based on RCTs revealed that TIPS is superior in controlling ascites than LVP, although it causes hepatic encephalopathy more frequently [167–170]. The use of narrow-diameter dilation by TIPS decreased the incidence of severe hepatic encephalopathy [171]. The introduction of a covered stent offers better symptomatic control and overall survival, especially in patients with a MELD score of less than 16 at the baseline [172, 173].

Although previous meta-analyses [167, 169, 170, 174] concluded that TIPS does not improve survival compared with LVP, recent meta-analyses [145, 173] involving newer RCTs reported that TIPS significantly improves transplant-free survival. Improvement in mental QOL assessed by the mental component score of SF-36 was associated with TIPS [175].

A therapeutic algorithm for cirrhotic ascites is shown in Fig. 4.

CQ: Are prophylactic antibiotics for cirrhotic patients with gastrointestinal (GI) bleeding or severe liver disease useful in preventing SBP or improving survival?

- They are useful. Prophylactic use of antibiotics is proposed for cirrhotic patients with GI bleeding because it significantly suppresses the development of SBP, bacterial infection, and sepsis and significantly reduces infection mortality and overall mortality. (Evidence level A, strength 2)
- It is also proposed as an optional treatment for those with an ascites protein concentration lower than 1.5 g/dL and advanced liver failure because it significantly suppresses the development of SBP and severe infection and significantly reduces mortality. (Evidence level A, strength 2)

CQ: Are prophylactic antibiotics for cirrhotic patients with an episode of SBP useful in preventing the recurrence of SBP or improving survival?

- Prophylactic use of antibiotics is proposed for such patients because it is useful in preventing the recurrence of SBP. (Evidence level A, strength 2)

Comment: The mortality rates of cirrhotic patients with SBP at 1 and 12 months were reported to be 32.5 % and 66.2 %, respectively [176]. A meta-analysis of 1241 cirrhotic patients with upper GI bleeding revealed that prophylactic use of antibiotics significantly suppressed not only the development of SBP but also bacterial infection and sepsis and significantly reduced infection mortality and overall mortality [177]. Recurrence of upper GI bleeding was further proved to be suppressed by the therapy [178]. Norfloxacin prophylaxis reduced the incidence of SBP, delayed the development of HRS, and improved survival in cirrhotic patients with low ascites protein levels (less than 1.5 g/dL) and advanced liver failure (Child-Pugh score of 9 points or greater with a serum bilirubin level of 3 mg/dL or greater) or impaired renal function [179]. Fluoroquinolone prophylaxis also reduced the risk of the development of a first episode of SBP and mortality in cirrhotic patients with low ascites protein levels [180].

Hepatorenal syndrome

CQ: Is terlipressin with albumin infusion effective for treatment of cirrhotic patients with HRS?

- Terlipressin with albumin infusion is proposed for patients with type 1 HRS because 46 % of them improve with this therapy. (Evidence level A, strength 2)

CQ: Are sympathomimetic drugs or octreotide effective for treatment of cirrhotic patients with HRS?

- Combination treatment with octreotide, midodrine, and albumin infusion improves the survival of patients with type 1 and type 2 HRS. Norepinephrine infusion and albumin infusion is proposed for patients with HRS because they are as effective as octreotide, midodrine, and albumin infusion. (Evidence level C, strength 2)

Comment: Two types of HRS have been described. Type 1 is a rapidly progressive acute renal failure defined by a doubling of the initial serum creatinine level to greater than 2.5 mg/dL in less than 2 weeks [181]. It often develops after a precipitating event, particularly SBP. Type 2 HRS is characterized by moderate renal failure (initial serum creatinine level increase from 1.5 to 2.5 mg/dl) in patients with refractory ascites, showing a steady or slowly progressive course [181]. Several meta-analyses concluded that terlipressin showed higher efficacy in reversing renal function than placebo in type 1 HRS patients receiving albumin infusion [182–184]. Two of them also reported survival improvement with terlipressin therapy [183, 184]. A case–control study revealed that the regimen of octreotide, midodrine, and albumin significantly improved short-term survival and renal function in both type 1 and type 2 HRS [185]. In addition, RCTs showed that norepinephrine is as safe and

effective as terlipressin, but is less expensive in the treatment of type 1 and type 2 HRS [186–188]. Norepinephrine and albumin are proposed because norepinephrine is the only drug approved by the National Health Insurance in Japan.

The International Club of Ascites recently proposed a revised consensus recommendation where an increase in initial serum creatinine level greater than twofold from the baseline without a response to withdrawal of diuretics and volume expansion with albumin (1 g/kg) for 2 days is considered as type 1 HRS [154]. This revision was in the expectation of a better therapeutic effect by early diagnosis.

CQ: Is PVS effective for management of HRS?

- PVS is not recommended in patients with HRS because it has no survival benefit. (Evidence level A, strength 1)

CQ: Is TIPS effective for management of HRS?

- Improvement of renal function, relief of ascites, and improvement of prognosis are expected by TIPS in appropriately selected patients. (Evidence level C)

CQ: Does liver transplant improve the prognosis of patients with HRS?

- Yes. Liver transplant is recommended for both type 1 and type 2 HRS if indicated. (Evidence level B, strength 1)

Comment: PVS occasionally improves renal function in patients with HRS, but does not prolong survival and has a high risk of severe complications [189]. It has currently very little role in the management of refractory ascites and is not recommended for patients with HRS [148, 190]. Several noncontrolled studies suggest the effects of TIPS on HRS. It improved renal function in type 1 HRS [191, 192] and provided probable survival benefits in most of the nontransplantable cases [192]. TIPS further improved renal function and sodium excretion in type 1 HRS patients who responded to combination therapy of midodrine, octreotide, and albumin, leading to normalization of renal function at 12 months [193]. It was concluded that TIPS is an effective treatment for type 1 HRS in suitable patients. A cohort study concluded that liver transplant offered a clear survival benefit to type 1 HRS patients regardless of the therapy they received [194]. More than 50 % of type 1 HRS patients die within 1 month without liver transplant, and the median survival time of patients with type 2 HRS is approximately 6 months [195]. In contrast, patient survival rates after liver transplant at 1 and 5 year were 77 % and 69 %, respectively, in type 1 HRS and 74 % and 61 %, respectively, in type 2 HRS.

Hepatic encephalopathy

CQ: Do protein-restricted diets improve the prognosis of cirrhotic patients with hepatic encephalopathy?

- Protein-restricted diets are not proposed for long-term management of cirrhotic patients because they may enhance protein breakdown and worsen the prognosis of cirrhotic patients. (Evidence level C, strength 2)

Comment: A low-protein diet was proved to cause higher protein breakdown compared with diets with a normal protein content. The latter is metabolically more adequate and tolerable for cirrhotic patients with episodic hepatic encephalopathy [196]. Restriction of the protein content in the diet does not confer any benefit to patients during an episode of encephalopathy [197].

CQ: Are disaccharides effective for management of hepatic encephalopathy?

- Disaccharides are recommended for patients with hepatic encephalopathy because they improve the parameters and relieve the symptoms of hepatic encephalopathy. (Evidence level A, strength 1)

Comment: RCTs showed nonabsorbable disaccharides such as lactulose improve the parameters of hepatic encephalopathy (psychometric test scores and venous ammonia levels) [198, 199]. Nonabsorbable disaccharides seemed to reduce the risk of no improvement in patients with hepatic encephalopathy but they showed no significant effect on mortality compared with placebo or no intervention [200]. Lactulose appears to have the most beneficial effect on minimal hepatic encephalopathy, followed closely by probiotics and synbiotics [201].

CQ: Do nonabsorbable antibiotics relieve hepatic encephalopathy?

- Nonabsorbable antibiotics are proposed for patients with hepatic encephalopathy because they improve the parameters and relieve symptoms of hepatic encephalopathy. (Evidence level A, strength 2)

Comment: Over a 6-month period, treatment with rifaximin maintained remission from hepatic encephalopathy more effectively than did placebo [202]. Driving simulator performance improves significantly in patients with minimal hepatic encephalopathy after treatment with rifaximin compared with placebo [203]. A meta-analysis revealed that rifaximin appears to be at least as effective as disaccharides or other oral antibiotics for the treatment of hepatic encephalopathy, with a better safety profile [204]. Sharma et al. [205] demonstarated by their RCT that the combination of lactulose plus rifaximin is more

effective (i.e., higher recovery from hepatic encephalopathy and lower mortality) than lactulose alone in the treatment of overt hepatic encephalopathy. Another recent meta-analysis further showed that rifaximin had a beneficial effect on secondary prevention of hepatic encephalopathy, increased the proportion of patients who recovered from hepatic encephalopathy, and reduced mortality [206].

CQ: Is a BCAA-enriched amino acid solution effective in management of overt hepatic encephalopathy?

- It is recommended for management of overt hepatic encephalopathy because it is effective for management of disturbance of consciousness due to hepatic encephalopathy, including coma. (Evidence level A, strength 1)

CQ: Are a BCAA enriched oral mixture and BCAA granules effective for treatment of patients with hepatic encephalopathy?

- Long-term oral BCAA supplementation is recommended for such patients because it relives hepatic encephalopathy and improves the nutritional state. (Evidence level A, strength 1)

Comment: A meta-analysis of seven RCTs showed an improvement in mental state caused by an BCAA-enriched amino acid solution, and the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines on parental nutrition recommended this solution for grade III to grade IV hepatic encephalopathy [207]. In contrast, another meta-analysis could not present convincing evidence for the benefit of this solution in patients with hepatic encephalopathy because of the low methodological reliability of the old RCTs [208].

Long-term oral BCAA supplementation raises plasma albumin levels and improves QOL [209]. It prevents progressive hepatic failure, improves surrogate markers, improves perceived health status [210], and improves event-free survival in patients with decompensated cirrhosis with an adequate daily food intake [10]. It relieves minimal hepatic encephalopathy, improves neuropsychological test scores, and increases the muscle mass [14]. It may inhibit hepatic carcinogenesis in patients with compensated cirrhosis with a serum albumin level of less than 4.0 g/dL [11]. A recent meta-analysis [211] involving eight trials of orally administered BCAA supplements and seven trials of intravenously administered BCAAs concluded that BCAAs had a beneficial effect on hepatic encephalopathy, although we need additional randomized clinical trials to determine the effect of BCAAs compared with interventions such as nonabsorbable disaccharides, rifaximin, or other antibiotics.

CQ: Is B-RTO effective for management of hepatic encephalopathy?

- It is proposed for adequately evaluated and selected patients with portosystemic hepatic encephalopathy because it is effective for these patients. (Evidence level C, strength 2)

Comment: Several noncontrolled case series reported that the occlusion of the large portosystemic shunt by B-RTO relieves hepatic encephalopathy [212–215]. B-RTO is also reported to augment portal venous blood flow and improve liver function test findings [214, 215]. An elevated hepatic venous pressure gradient after B-RTO is one aspect of the effect of liver function [215]. Careful evaluation of portal hemodynamics is necessary to select patients for the efficacy and safety of B-RTO.

Portal vein thrombosis

CQ: Are anticoagulants useful for treatment of cirrhotic patients with portal vein thrombosis (PVT)?

- Yes. Anticoagulation therapy is proposed for patients with acute-onset or progressive PVT and for candidates for liver transplant. (Evidence level C, strength 2)

Comment: The prevalence of PVT in cirrhotic patients on evaluation or at liver transplant ranges from 5 to 26 % [216]. Survival after liver transplant was worse in recipients with complete PVT [217]. Moreover, the mortality was related to its extension (5.9 % for partial PVT vs 17.5 % for complete PVT) [218]. Partial or complete recanalization after anticoagulation mostly by low molecular weight heparins was achieved in 60 % of patients, where early initiation of anticoagulation was the only factor associated with recanalization [219]. Rethrombosis after complete recanalization occurred in 38.5 % of patients after the stopping of anticoagulation [219]. Benefits of continuous anticoagulation are expected in patients awaiting liver transplant with a MELD score greater than 15 and PVT with extension to the superior mesenteric vein [220].

Splenectomy and partial splenic embolization

CQ: Are splenectomy and partial splenic embolization (PSE) effective in relieving pathological states of cirrhosis such as ascites, hypoalbuminemia, hepatic encephalopathy, and esophagogastric varices?

- Although splenectomy and PSE occasionally relieve these states, we should be aware of procedural complications. (Evidence level C)

Comment: Although PSE and splenectomy increase platelet and leukocyte counts, PSE allows preservation of adequate splenic tissue to safeguard against overwhelming infection [221]. Beneficial effects of PSE on refractory ascites after liver transplant were reported [222, 223]. PSE reduced prothrombin time and increased serum albumin levels at 12 months [224]. PSE also lowered the hepatic encephalopathy grade and serum ammonia levels in cirrhotic patients after B-RTO [225]. Although splenectomy reduced the indocyanine green retention rate and increased the technetium-99m-labeled galactosyl human serum albumin value (markers of hepatic functional reserve), it had no effect on serum albumin levels [226]. Laparoscopic splenectomy with EVL was superior to TIPS in the prevention of gastroesophageal variceal rebleeding in cirrhotic patients in a controlled study [227]. PSE combined with EVL was reported to be effective for the control of esophageal varices and hypersplenism, reducing the flow rate and velocity of the main portal vein [228]. Portal thrombosis, ascites, and sepsis are common major complications for PSE and splenectomy.

Liver transplant

CQ: Does liver transplant increase the survival of patients with decompensated cirrhosis?

- Although liver transplant increases survival rates, its indication should be carefully evaluated in each patient. (Evidence level B, strength 2)

Comment: There is no study to answer this question directly. Merion et al. [229] analyzed 12,966 patients on the waiting list for liver tranplant and reported that significant and progressively increasing survival benefit was demonstrated in candidates with a MELD score of 18–20. The same group further extended the analysis to 38,899 patients and reported that a survival benefit from liver transplant is seen for candidates with a MELD score of 12 or greater, whereas there is no survival benefit from liver transplant for those with a MELD score of 9–11 and there is even harm to those with a MELD score of 6–8 [230]. A significant survival benefit of living donor liver transplant was observed in Japanese patients with a MELD score of 15 or greater [231].

CQ: Are antiviral therapies useful for management of recurrent HBV and HCV hepatitis after liver transplant?

- Antiviral therapies are recommended for viral cirrhosis patients receiving a liver transplant because they are useful for management of recurrent HBV and HCV hepatitis. (Evidence level A, strength 1)

Comment: Before the introduction of antiviral therapy for liver transplant, 67 % of patients had hepatitis B recurrence at 3 years, and their survival rate was 68 % at 1 year and 44 % at 3 years [232]. After liver transplant for HCV cirrhosis, 20–40 % of patients progressed to allograft cirrhosis within 5 years [233]. The rate of their decompensation was more than 40 % at 1 year and more than 60 % at 3 years [233]. Although nucleoside analogues are useful for preventing hepatitis B recurrence, the recurrence rate was lowest in patients who received combined hepatitis B immunoglobulin plus nucleoside analogue prophylaxis (6.6 %) compared with those receiving nucleoside analogue prophylaxis alone (19.0 %) or hepatitis B immunoglobulin prophylaxis alone (26.2 %) [234]. The combination of hepatitis B immunoglobulin and ADV was more effective than hepatitis B immunoglobulin plus LDV prophylaxis [234].

In recurrent hepatitis C, antiviral therapy slows disease progression (particularly in sustained virological responders) [235]. Peginterferon-α_{2b} plus ribavirin therapy for 48 weeks led to SVR in 48 % of F0–F2 fibrosis patients and 18.5 % of F3–F4 fibrosis patients [235]. Fibrosis progression by one or more stages was noted in 26 % of treated F0–F2 fibrosis patients, 54 % of treated F3–F4 fibrosis patients and 70 % of untreated F0–F2 fibrosis patients [235].

Acknowledgments This article was supported by a Grant-in-Aid from the Japanese Society of Gastroenterology. The authors thank the investigators and supporters for participating in the studies. The authors express special appreciation to Dr. Akihiko Oshige, Dr. Kouhei Oda, and Dr. Seiichi Mawatari (Kagoshima University).

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Appendix

The members of the Guidelines Committee who created and evaluated the Japanese Society of Gastroenterology ''Evidence-based clinical practice guidelines for liver cirrhosis'' are listed below.

Creating Committee

Chair: Hiroshi Fukui (Nara Medical University)

Vice-Chair: Hidetsugu Saito (Department of Gastroenterology, Keio University)

Members: Yoshiyuki Ueno (Department of Gastroenterology, Yamagata University Faculty of Medicine), Hirofumi Uto (Center for Digestive and Liver Diseases, Miyazaki Medical Center Hospital), Katsutoshi Obara (Department of Advanced Gastrointestinal Endoscopy, Fukushima Medical University), Isao Sakaida (Department of Gastroenterology and Hepatology, Yamaguchi University Graduate School of Medicine), Akitaka Shibuya (Department of Gastroenterology, Kitasato University School of Medicine), Masataka Seike (Central Clinical Facilities/Liver Disease Consultation Unit, Oita University Hospital), Sumiko Nagoshi (Department of Gastroenterology and Hepatology, Saitama Medical Center, Saitama Medical University), and Makoto Segawa (Department of Gastroenterology and Hepatology, Yamaguchi University School of Medicine)

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Chair: Hirohito Tsubouchi (Kagoshima City Hospital)

Vice-Chair: Hisataka Moriwaki (Gifu University)

Members: Akinobu Kato (Morioka Municipal Hospital), Etsuko Hashimoto (Institute of Gastroenterology, Tokyo Women's Medical University), Kojiro Michitaka (Gastroenterology Center, Ehime Prefectural Central Hospita), and Yoshikazu Murawaki (Tottori Saiseikai Sakaiminato General Hospital)

The Japanese Society of Gastroenterology

President: Tooru Shimosegawa (Division of Gastroenterology, Tohoku University Graduate School of Medicine)

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