# Influence of Recent Advances in Medical Management on Clinical Outcomes of Cirrhosis

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**Cirrhosis and its disease-related complications are the 12th leading cause of mortality among US adults and are the 5th leading cause of death for individuals aged 45 to 54 years. Hospitalization costs for disease-related complications are estimated at $18,000 per episode of care, and 10% of admitted patients die. Despite these ominous findings, the survival rate of patients with cirrhosis has improved during the past 2 decades. This observation coincides with the conducting and reporting of high-quality randomized controlled trials and observational studies. Therefore, the improved prognosis in cirrhosis may be related to the effective translation of research findings to clinical practice for this patient population. Although explicit data to support this claim are not available, this article reviews the reported trends in clinical outcomes for patients with cirrhosis and the existence of evidence-based medical information that is available to care for these chronically ill patients.**

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**ES = endoscopic sclerotherapy; EVL = endoscopic variceal ligation; HCC = hepatocellular carcinoma; RCT = randomized controlled trial; SBP = spontaneous bacterial peritonitis**

Cirrhosis and its disease-related complications are the 12th leading cause of mortality among US adults and are responsible for nearly as many fatalities as diabetes mellitus.[1] For individuals aged 45 to 54 years, cirrhosis is the fifth leading cause of death. Hospitalization costs for disease-related complications are estimated at $18,000 per episode of care, and 10% of admitted patients die.[2] Despite the widespread success of liver transplantation, a growing proportion of individuals who are developing end-stage liver disease will not receive this treatment because of advancing age, comorbid illness, and organ availability. However, over the past 2 decades, the median survival rate of patients with compensated and decompensated cirrhosis has increased. Current methods of diagnosis and treatment, resulting from high-quality randomized controlled trials (RCTs) and observational investigations, may be in part responsible for this trend. We discuss the clinical epidemiology of cirrhosis and portal hypertension and review time trends in survival and the influence that advances in medical management may have on clinical outcomes.

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A question-and-answer section appears at the end of this article.

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## NATURAL HISTORY AND PROGNOSIS

### Compensated Cirrhosis

Observational cohort studies of compensated cirrhosis that were reported in the English language included the following: diseased populations evaluated at tertiary referral centers, study periods between the years 1958 and 1990, predominant hepatic disease etiologies including alcohol and chronic viral hepatitis, and patient follow-up rates greater than 80%.[3] From reported investigations of large cohorts,[4-17] the median survival of patients with compensated cirrhosis is estimated at between 7 and 10 years from the time of diagnosis. Nearly 100% of individuals affected by compensated cirrhosis from chronic viral hepatitis can expect to survive at least 2 to 5 years after diagnosis[7,9,13-17] (Figure 1). In the absence of clinical decompensation, the development of splenomegaly,[7,13,14] thrombocytopenia,[7,13,14] and/or quiescent esophageal varices[7,10,11,13,14] is associated with a reduced median survival of 4 to 7 years. A population-based study from a similar time period demonstrated equivalent outcomes.[5]

The long-term risks of selected disease-related complications of compensated cirrhosis also have been reported (Figure 2). Estimates of 4% to 12% for the annual development of esophageal varices have been reported.[14,18,19] Among patients identified with esophageal varices, the risk of hemorrhage was estimated at 25% to 40% within 2 years of diagnosis.[20] Subsequently, the annual risk of bleeding was reduced to 1% to 3%.[21] Ascites[5,7,9,14-16] and hepatic encephalopathy[5,14] occurred at rates of 5% and 6% per year, respectively. Among patients with compensated and decompensated cirrhosis, the annual risk of developing hepatocellular carcinoma (HCC) was between 1% and 6%.[4-17,22-25]

### Decompensated Cirrhosis

Most studies of decompensated cirrhosis have come from tertiary referral centers that evaluate patients with liver disease from alcohol and chronic viral hepatitis.[4,5,7,12,26-33] During the past 4 decades, the transition rate from compensated to decompensated cirrhosis has remained unchanged, between 5% and 10% annually.[7,9,13-16] In turn, 2-year survival rates after onset of complications related to portal hyperten-

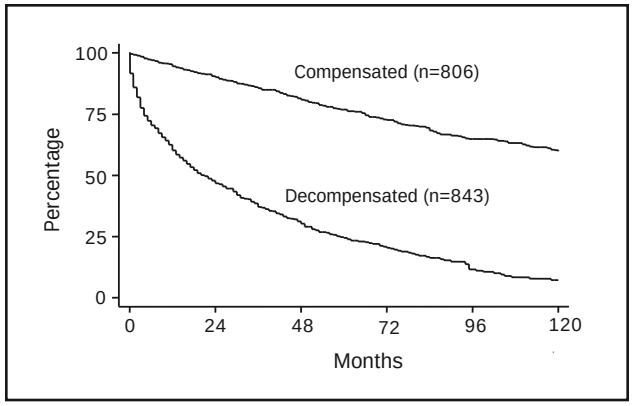


FIGURE 1. Survival of patients with compensated or decompensated cirrhosis from time of diagnosis. Adapted from D'Amico G. Natural history of compensated cirrhosis and varices. In: *Complications of Cirrhosis: Pathogenesis, Consequences, and Therapy* [AASLD postgraduate course syllabus]. Alexandria, Va: American Association for the Study of Liver Diseases; 2001:118-123, with permission.

sion have remained below 50%[4,5,7,12,26-33] (Figure 1). The major causes of death from decompensated cirrhosis without liver transplantation are progressive liver failure, HCC, gastrointestinal bleeding, sepsis, and renal failure.[4-17,26-33]

## RECENT ADVANCES IN THE MEDICAL MANAGEMENT OF SELECTED COMPLICATIONS OF CIRRHOSIS

Several selected therapies examined in clinical investigations have helped individuals with cirrhosis and/or portal hypertension. Although several interventions can reduce morbidity and resource use, the following advances have been associated strongly with improved survival.

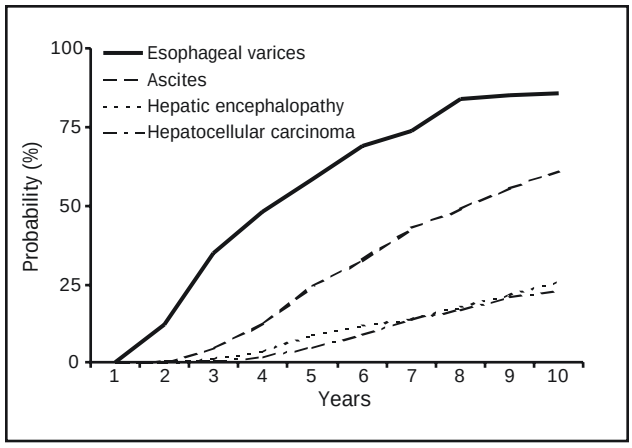


FIGURE 2. Cumulative risk of complications related to cirrhosis. Adapted from *Am J Gastroenterol*,[14] with permission.

### Approaches for Treatment and Prevention of Acute Variceal Hemorrhage

Treatment approaches for acute variceal hemorrhage have evolved on the basis of advances in endoscopic technique and intensive care medicine. Remarkably, no single reported controlled trial has shown a survival benefit when compared with usual care. Proposed reasons for this phenomenon are the inclusion of study patients who have survived prior bleeding episodes, as well as the ongoing improvements in the standard of care that reduce the ability of newer therapies to make a significant difference. Despite this limitation, a recent examination of control groups in acute variceal hemorrhage trials between 1960 and 2000 showed an overall 40% risk reduction in mortality (change in incidence from about 55% to 40%).[34] The introduction of endoscopic sclerotherapy (ES) and endoscopic variceal ligation (EVL) into widespread clinical practice is also responsible for significantly improved 30-day survival rates compared with historical cohorts treated without endoscopic therapy.[35] In terms of pharmacological therapy, a recent meta-analysis showed significant reductions in mortality with use of terlipressin compared with placebo or with inactive therapy.[36] To date, terlipressin is the only drug that has been associated with improved survival in acute variceal bleeding.

A large body of evidence also supports the use of β-blockers for the prevention of esophageal variceal bleeding in cirrhosis. Eleven RCTs have shown a 40% risk reduction with use of β-blockers as primary prophylaxis against index esophageal variceal hemorrhage (change in incidence from 25% to 15% during 2 years). Propranolol (9 RCTs) and nadolol (2 RCTs) appeared equally effective. Patients with medium to large esophageal varices and no evidence of ascites benefited the most. Nonsignificant risk reductions (from 7% to 2%) were observed among patients with small esophageal varices. Similar results were shown in comparisons between β-blockers and ES or combination therapy.[37]

Long-acting oral nitrates have been used for primary prophylaxis. However, an increased frequency of pharmacological adverse events including renal dysfunction and death among patients with advanced liver disease has raised concerns.[38,39] Among patients ineligible for or intolerant of pharmacological therapy, a similar degree of benefit from EVL has been recognized.[40] Although EVL is effective in preventing initial esophageal variceal hemorrhage, direct comparisons between optimal dose β-blocker therapy and/or EVL have not been performed. The addition of a combined therapy arm, considering its use in clinical practice, would further increase an already large sample size needed for such a trial.

Among secondary prophylaxis trials, the use of nonselective β-blockers compared with placebo in 12 RCTs

showed 30% to 40% risk reductions in recurrent bleeding. A meta-analysis revealed significant improvements in bleed-related mortality from β-blockers.[41] Similar findings were observed when β-blockers were compared or combined with ES.[42] Based on complications from ES (including esophageal stricture and perforation), the use of EVL monotherapy as part of secondary prophylaxis strategies has been shown to be effective.[43]

### Antibiotic Prophylaxis for Bacterial Infection in Gastrointestinal Bleeding

Bacterial infection is a well-described complication in patients with cirrhosis.[44-46] The main predisposing factor is related to increased organism translocation from the intestinal lumen into the bloodstream.[47] Reduced serum opsonic activity[48] and impaired reticuloendothelial system phagocytosis[49] also influence the risk of infection. With the development of gastrointestinal hemorrhage, individuals with cirrhosis experience even greater risks of bacterial infection, sepsis, and death.[50]

The prevalence of bacterial infection among prospective hospitalized patients with cirrhosis was 44% (range, 14%-67%).[44-46,50-56] More importantly, an estimated in-hospital mortality rate of 23% (range, 9%-48%) was observed, with higher rates among individuals with gastrointestinal hemorrhage.[50-56] For this subgroup, the presence of bacterial infection also has been associated independently with greater blood transfusion requirements, increased failure rate to control variceal bleeding, and higher risk of short-term mortality.[50,51] Given these compelling observations, 5 prospective RCTs[52-56] were performed to examine the efficacy of prophylactic antibiotic treatment during gastrointestinal hemorrhage. The overall rate of infection in actively treated patients was 13% (34 of 264 patients) compared with a control group rate of 45%. Meta-analysis also confirmed a 37% risk reduction in mortality (incidence, 24% vs 15%) after antibiotic prophylaxis.[57]

### Diagnosis and Treatment of Spontaneous Bacterial Peritonitis

The prevalence of spontaneous bacterial peritonitis (SBP) among hospitalized patients has remained stable during the past 3 decades, ranging between 12% and 21%.[58] However, mortality from SBP has declined from a 15% to 50% range[59-67] to an 8% to 17% range,[68-71] in concert with advances in diagnosis and treatment. Practice guidelines for the management of ascites[72,73] have included standardized methods for the paracentesis technique and for ascitic fluid analysis. Expanded definitions that capture the broad clinical spectrum of SBP now identify more individuals who are eligible for therapy. Clinical trials demonstrating the safety and efficacy of non-nephrotoxic systemic antibiotics[65-67,69] have been incorporated into clinical practice. Observational studies[59-64,68,70] have identified clinical risk factors for index and recurrent SBP with subsequent confirmation of beneficial effects from antibiotic prophylaxis. Recently, the use of intravenous albumin with cefotaxime compared with antibiotic monotherapy was associated with significant improvements in renal impairment and survival among selected patients.[74] Subsequent confirmation among independent populations is awaited to determine whether all patients with SBP may benefit from this therapy.

### Ablative Therapies for HCC

Hepatocellular carcinoma is the fifth leading cause of cancer worldwide; most cases are related to cirrhosis.[25] Despite the use of surveillance methods for detecting early-stage disease, only 30% of individuals are deemed eligible for recognized therapies.[75] Surgical resection often is prohibited in the setting of portal hypertension and/or advanced liver disease. The use of ablative therapies in conjunction with liver transplantation is associated with 5-year survival rates of 50% to 75%. This contrasts with the 2-year survival rates of 20% to 50% in untreated populations with similar degrees of HCC involvement.[76-79] Conducting RCTs to show a survival benefit with use of ablative therapies has been limited by large sample size requirements. However, a recent meta-analysis revealed that arterial chemoembolization extended survival in patients with unresectable multifocal HCC and preserved hepatic function (41% of treated patients vs 27% of controls).[80] Because early-stage unresectable HCC is recognized as a priority indication for liver transplantation in the United States,[81] it is likely that more patients will be identified for ablative therapies. Increased clinical experience with patients ineligible for liver transplantation will determine whether short-term benefits with ablative therapies are compatible with patient preferences.

## TIME TRENDS IN SURVIVAL AND CAUSES OF DEATH

National statistics from various geographic areas note declining cirrhosis-related mortality rates since the mid-1970s.[82-86] Despite an increasing number of hospital discharges for cirrhosis between 1993 and 2000 in the United States, the annual in-hospital mortality rate remains stable.[2] Even among patients awaiting liver transplantation, the 1-year waiting list survival rate has improved from 60% in the early 1980s to greater than 80% in the late 1990s.[87] Coinciding with the improved outcomes of patients with cirrhosis was the publication of high-quality RCTs in hepatology, which began in the early 1980s.

When examined by time period or era, a measurable increase in median survival for patients with compensated

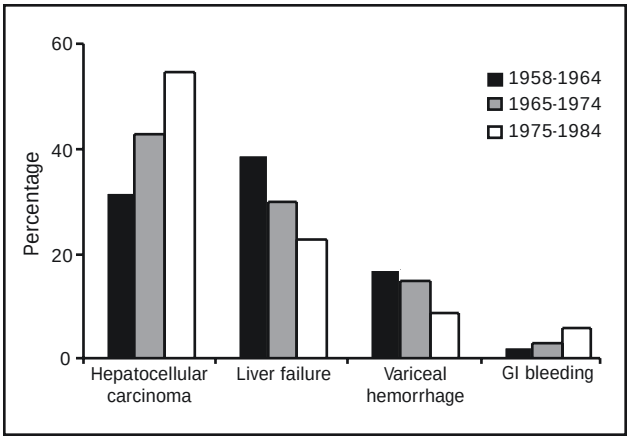


FIGURE 3. Time trend of liver-related causes of death among 582 patients with compensated cirrhosis at the time of diagnosis. GI = gastrointestinal. Adapted from *Liver*,[8] with permission.

and decompensated cirrhosis has been observed during the past 40 years.[4,7-9,12-16] The prevalence of death from progressive liver failure has declined (in the same time period), whereas mortality from HCC has increased.[4,7-9,12-16,25] For example, Tanaka et al[8] reported the natural history and prognosis of 582 patients with compensated cirrhosis. During a 26-year period, median survival increased significantly, from 7 to 10 years, when the periods 1958 through 1964 and 1975 through 1984 were compared. Improved survival at 5 (56% vs 70%) and 10 (37% vs 50%) years, respectively, also was noted. The risk of death from progressive liver failure (39% vs 23%) and variceal hemorrhage (17% vs 9%) also declined during these periods. Notably, a significant increase in the percentage of deaths from HCC was observed (32% vs 55%) (Figure 3).

Several reasons aside from the application of evidence-based medical care may explain these observations. General advances in health care technology are likely responsible in part for improved survival over time in all chronic conditions with increased risk of short-term and long-term mortality.[88] An increase in early detection and treatment of disease-related complications, based on increasing hospitalization rates for cirrhosis beginning in the 1960s, also may be responsible.[89] However, 2 investigations showed that reduced mortality rates between the 1970s and 1980s were not related to the rates of medication use with diuretics, albumin, and lactulose for patients with cirrhosis.[8,12]

Despite these general trends reported from observational studies, it is difficult to overlook the existence of improved survival rates from potentially lethal complications such as variceal hemorrhage[34,35] and SBP.[90,91] These successes reflect the application of evidence-based methods for diagnosis, treatment, and prophylaxis in the clinical arena. In this regard, it has been suggested that the increasing incidence and prevalence of HCC may imply an increased use of surveillance programs and ablative therapies for cirrhosis.[92,93] Therapies such as interferon for chronic hepatitis C[15,16,94,95] and ursodeoxycholic acid for primary biliary cirrhosis[96] have also been associated with improved survival by halting disease progression in precirrhotic individuals. Finally, a better understanding of general nutrition for healthy and diseased populations, including those with cirrhosis, has been linked to improved outcome as well.[97,98]

TABLE 1. **Management Points for Selected Complications of Portal Hypertension***

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| Nonselective β-blockers (propranolol, nadolol) are recommended as primary prophylaxis to prevent esophageal variceal bleeding in patients with medium-large esophageal varices. The goal of β-blocker therapy is a resting heart rate of 55 to 60 beats/min and/or a reduction in resting heart rate of 25% or more |
| EVL may be used for patients who are intolerant to or unable to receive β-blocker therapy. A total of 3 or 4 sessions every 1 to 4 weeks is required for eradication of varices. Surveillance endoscopy is required to detect recurrent varices that require band ligation when present |
| Management of acute variceal hemorrhage should include EVL, vasoactive drug therapy for at least 5 days, and antibiotic prophylaxis (oral norfloxacin, 400 mg twice daily for 7 days, or comparable intravenous preparation if oral intake is contraindicated) |
| Antibiotic prophylaxis used with gastrointestinal bleeding of any etiology should be provided with use of oral norfloxacin, 400 mg twice daily for 7 days |
| Hospitalized patients with spontaneous bacterial peritonitis should be treated with an intravenous broad-spectrum antibiotic (third-generation cephalosporin preferred). Intravenous albumin (1 g/kg at diagnosis, then 1 mg/kg every other day) is reserved for patients with a baseline serum creatinine level ≥1.5 mg/dL |

*EVL = endoscopic variceal ligation.

## EFFECTIVENESS OF TRANSLATING SCIENTIFIC RESULTS INTO CLINICAL PRACTICE

The extent to which scientific results have been translated into clinical hepatology practice has not been widely addressed. Despite the availability of practice guidelines for managing complications of portal hypertension related to cirrhosis,[72,73,98-101] (Tables 1 and 2), the proportion of eligible patients receiving medical therapies supported by evidence-based medicine remains uncertain. To date, only 4 studies have directly examined medical practice patterns involving known disease-related complications. However, their results suggest that further investigation and effort to improve the delivery of evidence-based health care are needed.

### Management of Ascites

Based on 2 published experiences,[102,103] large-volume paracentesis is used appropriately in more than 75% of patients with symptomatic tense ascites. Referral for peritoneo-

venous shunt surgery occurs in less than 10% of patients.[102] The frequency of transjugular intrahepatic portosystemic shunt placement for refractory ascites based on increased experience and availability remains unknown.

Results have been conflicting surrounding the medical management of mild to moderate ascites. A primary goal of volume reduction to comfortable levels was endorsed by only 48% of 295 self-described practitioners in gastroenterology and hepatology.[103] Remarkably, 49% of respondents believed that a primary goal of complete ascites elimination by using high-dose oral diuretics was more important. Despite recommendations for a low-sodium diet with or without spironolactone as initial therapy,[89] only 7% of those surveyed adhered to this stepwise approach. Notably, the use of dietary sodium restriction and oral diuretics in compensated cirrhosis was recommended by 69% of practitioners, despite the absence of data supporting this strategy.[103]

### Dietary Management of Hepatic Encephalopathy

The concept of dietary protein restriction for the treatment of hepatic encephalopathy was based primarily on uncontrolled observations made nearly 50 years previously.[98] Among 1046 cirrhotic patients hospitalized in the United Kingdom,[104] some degree of protein restriction was prescribed by reporting dietetic services for 759 patients (73%). Importantly, more than 50% of departments reported the practice of protein restriction in cirrhotic patients without hepatic encephalopathy. Overall, less than 25% of patients received adequate nutritional support while hospitalized. The patterns of nutrition consultation in ambulatory patients with cirrhosis are unknown.

### Screening and Surveillance for HCC

Only 84% of 473 survey respondents from a single investigation routinely use screening and surveillance methods for HCC.[105] However, the exclusive screening of patients with chronic viral hepatitis and iron overload disease was reported by 50% of respondents. Although 69% of clinicians used serum α-fetoprotein and abdominal ultrasonography for screening and surveillance, more than 50% of individuals repeated testing beyond 6-month intervals. Predictors of screening and surveillance program use included the beliefs that increased survival and cost-effectiveness exist, neither of which has been proved conclusively.

## IMPROVED CLINICAL OUTCOMES FROM SPECIALIST-BASED COLLABORATION IN PATIENTS WITH CIRRHOSIS

Nearly 1 in 5 patients with chronic illness require hospitalization for disease-related complications resulting in excessive lengths of stay and resource use.[106] However, improved clinical and economic outcomes have been associated with specialist consultation vs generalist care for many conditions.[107] Among US veterans hospitalized with decompensated cirrhosis,[108] the use of formal gastroenterology consultation by hepatology-trained physicians significantly reduced length of stay and hospitalization costs compared with nongastroenterology clinicians alone. Hospital readmission rates and long-term mortality (Figure 4) also were reduced after patients received specialist medical advice. However, these data are limited currently by retrospective analysis and the potential lack of generalizability to other populations and health care systems. Additional

TABLE 2. **Important Points From Existing Practice Guidelines in the Management of Cirrhosis and Portal Hypertension***

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|---|
| All patients eligible for the benefits of primary prophylaxis should undergo diagnostic upper endoscopy to exclude the presence of large esophageal varices |
| When no or small esophageal varices are found, endoscopy should be repeated at 1- to 3-year intervals for surveillance |
| All hospitalized patients with ascites (especially those with acute gastrointestinal bleeding) should undergo diagnostic paracentesis to exclude SBP. Repeated diagnostic paracentesis after 48 hours of antibiotic therapy is recommended to document resolving infection |
| Patients with a history of SBP should receive antibiotic prophylaxis (oral norfloxacin, 400 mg twice daily for 7 days, or trimethoprim-sulfamethoxazole DS, 1 tablet daily) to prevent recurrent infection |
| All hospitalized patients with acute gastrointestinal bleeding should be given antibiotic prophylaxis to reduce the incidence of recurrent variceal bleeding (when applicable), bacterial infection, and in-hospital mortality |

*Based on the absence of explicit professional society guidelines regarding the diagnosis and management of hepatocellular carcinoma, no formal recommendations were included in this table. SBP = spontaneous bacterial peritonitis.

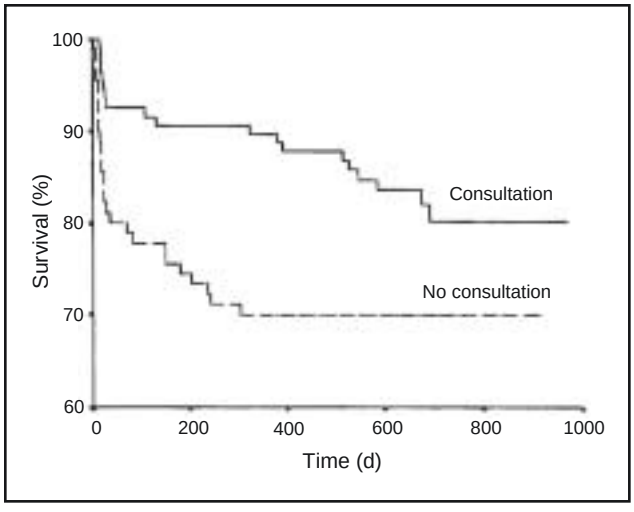


FIGURE 4. Kaplan-Meier estimates of survival among patients who had a gastroenterology consultation compared with those who did not (*P*=.02 by the log-rank test). From *Hepatology*,[108] with permission.

studies to confirm these findings are needed to fully determine the effect of specialist input on clinical outcomes. Although not formally examined, the occurrence of longitudinal ambulatory specialist care also may have contributed to the study results. Higher thresholds for hospitalization and the more frequent use of evidence-based therapies are other possible hypotheses.[109]

## CONCLUSIONS

Cirrhosis and its disease-related complications are major causes of morbidity and mortality among adults worldwide. Whether the incidence of disease is increasing is unclear; however, advances in medical management coupled with improved general population health likely will result in greater prevalence and burden of disease. Efforts to improve prevention of and treatment of disease-related complications must continue because liver transplantation is not possible for those with advancing age and serious comorbidity. Preventing the development of cirrhosis among individuals with known chronic liver disease appears to be the next frontier. Meanwhile, the field of hepatology should continue to strive for best clinical practice in all health care delivery settings for patients with cirrhosis.

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## Questions About Management of Cirrhosis

1. Which <u>one</u> of the following statements about survival in patients with cirrhosis is <u>*false*</u>?
   a. Patients with decompensated cirrhosis have 5-year survival rates exceeding 50%
   b. The development of ascites and hepatic encephalopathy is associated with reduced short-term survival
   c. The risk of death from variceal bleeding has declined over the past 4 decades
   d. HCC is now the most common cause of liver-related death
   e. The annual in-hospital mortality rate for patients with cirrhosis has remained stable in the United States

2. Which <u>one</u> of the following statements about the treatment of hospitalized patients with complications of cirrhosis is <u>*false*</u>?
   a. Mortality rates from SBP have declined over time
   b. Intravenous cefotaxime is recommended for patients without SBP and a serum creatinine level ≥1.5 mg/dL
   c. Antibiotic prophylaxis is recommended for patients with gastrointestinal bleeding from esophageal varices
   d. Patients with ascites and gastrointestinal bleeding require diagnostic paracentesis on admission to exclude SBP
   e. Repeated paracentesis for SBP should be performed 48 hours after diagnosis to document treatment response

3. Which <u>one</u> of the following is associated with a survival <u>*benefit*</u> in patients with HCC and compensated cirrhosis?
   a. Radiofrequency ablation
   b. Alcohol injection
   c. External beam radiation therapy
   d. Arterial chemoembolization
   e. Systemic chemotherapy

4. Which <u>one</u> of the following rates <u>*best describes*</u> the risk reduction with β-blocker therapy as primary prophylaxis against variceal bleeding?
   a. 5%
   b. 10%
   c. 25%
   d. 40%
   e. 75%

5. Which <u>one</u> of the following clinical events is associated with a <u>*lower-than-predicted*</u> survival rate from compensated cirrhosis?
   a. Leukopenia
   b. Increased aspartate aminotransferase/alanine aminotransferase ratio
   c. Esophageal varices
   d. Cutaneous spider angiomata
   e. Hyperkalemia

Correct answers:
1. *a*, 2. *b*, 3. *d*, 4. *d*, 5. *c*