End-Stage Liver Disease and Indications for Liver Transplantation

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Aparna Goel, Osama Siddique, and Aijaz Ahmed

Epidemiology of Cirrhosis

End-stage liver disease or cirrhosis is the twelfth leading cause of death in the United States (USA), accounting for over 38,000, or 1.5%, of all deaths in 2014 [1]. Cirrhosis represents an irreversible outcome of progressive hepatic fibrosis, characterized by diffuse nodular regeneration surrounded by dense fibrotic septa with architectural distortion [2]. The marked distortion of the intrahepatic vasculature and hepatic parenchymal extinction result in increased portal pressures and hepatic synthetic dysfunction. In the early stages of fibrosis, treatment aimed at the underlying cause of liver disease may prevent progression of or even reverse hepatic fibrosis. However, without treatment, cirrhosis may result.

The most common etiologies of cirrhosis in the United States are chronic viral hepatitis, alcoholic liver disease (ALD), and nonalcoholic steatohepatitis (NASH).

The viral hepatitis infections that lead to chronic liver disease are hepatitis B and C. While the overall prevalence of chronic hepatitis B infection in the United States is low, there remains a disproportionately high rate of infection in persons emigrating from regions of high or intermediate endemicity. As these persons usually acquire hepatitis B via perinatal transmission, the rates of chronic infection are quite high. Treatment of hepatitis B virus certainly reduces the risk of hepatocellular cancer and cirrhosis, but these significant complications remain an important cause for liver transplantation. Exposure to hepatitis C virus results in chronic infection in 75–85% of persons [3]. The most significant risk factor for acquiring hepatitis C infection is a history of injection drug use. Unfortunately, nearly 75% of hepatitis C infections are undiagnosed in the United States, which is a significant public health concern [4]. There are large-scale screening efforts to diagnose hepatitis C in the community as the virus is readily treatable with new direct-acting antivirals [5, 6].

Alcohol use disorder is a major cause of morbidity and mortality in the United States and accounts for over 88,000 deaths annually [7]. Alcoholic liver disease encompasses a clinical and histologic spectrum of steatosis (fatty change in the liver), alcoholic hepatitis (inflammation, hepatocyte necrosis), and cirrhosis. There is a direct dose-dependent relationship between the amount of alcohol consumed and risk of liver disease; however, genetic factors likely contribute as well.

Nonalcoholic fatty liver disease (NAFLD) is rapidly rising in the United States and is prevalent in approximately 30% of the overall population [8]. It is considered the hepatic manifestation of metabolic syndrome and is seen most frequently in obese patients with diabetes, hypertriglyceridemia, and hypertension. Similar to ALD, NAFLD includes a spectrum of disease from simple steatosis to NASH to cirrhosis. It is unclear what percentage of patients with NAFLD will progress to NASH, but we believe that approximately 15% of patients with NASH will develop cirrhosis.

While chronic hepatitis C virus (HCV) infection is the leading indication for liver transplantation and accounts for approximately 25% of all transplants currently, this is expected to decrease with highly effective and curative treatment of HCV with direct-acting antivirals [9]. Recent trends on the liver transplant waiting list reveal that NASH will likely emerge as the leading indication for liver transplantation in the near future, as the rate of transplants for NASH has increased to over 20% in the past decade [10–12]. ALD remains an important cause of end-stage liver disease, accounting for nearly 20% of all liver transplants in the United States [13]. Of concern is the recent data from National Epidemiologic Survey on Alcohol indicating that the 12-month prevalence of alcohol use, high-risk drinking,

A. Goel · A. Ahmed (✉)
Division of Gastroenterology and Hepatology, Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA
e-mail: aijazahmed@stanford.edu

O. Siddique
Department of Medicine, Memorial Hospital of Rhode Island/ Alpert Medical School of Brown University, Providence, RI, USA

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and alcohol use disorder is on the rise across all sociodemographic groups in the United States [14]. Other causes of cirrhosis include, but are not limited to, cholestatic liver disease such as primary sclerosing cholangitis and primary biliary cholangitis, autoimmune hepatitis, alpha-1 antitrypsin deficiency, hemochromatosis, Wilson's disease, veno-occlusive disease such as Budd-Chiari, and drug-induced liver injury.

Natural History of Cirrhosis

The natural history of cirrhosis is characterized by an initial asymptomatic and often undiagnosed phase, termed compensated cirrhosis. Patients with compensated cirrhosis have normal liver synthetic function and a median survival greater than 12 years [15]. Regardless of the etiology, patients with cirrhosis are susceptible to developing a variety of complications of portal hypertension and liver dysfunction, classified as decompensated cirrhosis. The risk of developing complications of cirrhosis, and hence transitioning from compensated to decompensated cirrhosis, is approximately 5–7% per year [15]. Often, these complications are rapidly progressive, leading to a markedly reduced life expectancy, with a median survival of 1.6 years.

Complications of End-Stage Liver Disease

Portal Hypertension Complications

Many complications from end-stage liver disease are a result of portal hypertension, or increased pressures within the portal venous system. The structural distortion of hepatic parenchyma inherent to cirrhosis and increase in vasodilator production result in elevated resistance to portal blood flow and formation of collaterals [16]. Portal hypertension can lead to the development of ascites, varices, hepatic encephalopathy, hepatorenal syndrome, hepatopulmonary syndrome, and portopulmonary hypertension.

Ascites

Ascites is the pathologic accumulation of fluid within the peritoneal cavity and the most common complication of cirrhosis. Ascites develops as a consequence of sinusoidal fibrosis and systemic vasodilation. The dense fibrotic tissue and "capillarization" of hepatic sinusoids increase splanchnic capillary pressure and result in excess lymph formation that leaks into the peritoneal cavity from the hepatic surface [17]. Additionally, the profound systemic arterial vasodilation due to increased nitric oxide levels activates the renin-angiotensin-aldosterone system, resulting in water and sodium retention, expansion of plasma volume, and hence ascites [18].

All patients with new-onset ascites should have a diagnostic paracentesis performed to determine the serum-ascites albumin gradient (SAAG) and total cell count [19]. A SAAG >1.1 g/dL is consistent with ascites due to portal hypertension. A SAAG <1.1 g/dL warrants further investigation of the etiology of ascites, which may be from malignancy, tuberculosis, nephrotic syndrome, or another inflammatory condition. Ascites due to cirrhosis is initially treated with a combination of diuretics and salt restriction of 2000 mg per day. More stringent restriction in sodium intake is not recommended as it is poorly tolerated and likely to lead to malnutrition. Diuretic regimens usually include a combination of an aldosterone receptor antagonist, such as spironolactone, and a loop diuretic, such as furosemide [20]. Importantly, in patients with alcohol-induced liver injury, cessation of alcohol use is paramount in treating ascites [21]. In some patients with refractory ascites or significant hyponatremia limiting diuretic use, repeated therapeutic paracentesis or transjugular intrahepatic portosystemic shunt (TIPS) placement may be necessary. Hepatic encephalopathy is an unfortunate frequent complication of TIPS, occurring in 30–60% of patients within 1 year after the TIPS procedure [22]. A patent TIPS allows portal blood flow to bypass the liver, where toxic ammonia is converted to urea via the urea cycle. The accumulation of ammonia contributes to hepatic encephalopathy.

Cirrhotic patients with ascites are at risk of developing an infection in the peritoneal fluid, called spontaneous bacterial peritonitis (SBP). This infection occurs without evidence of an intra-abdominal secondary source and is characterized by an elevated ascites fluid absolute polymorphonuclear leukocyte count $\geq$250 cells/mm^3 or a positive bacterial culture [23]. In-hospital mortality after the first episode of SBP ranges from 10% to 50%, and among those who survive, 70% will have a recurrent episode within 1 year [24, 25]. Given the significant mortality associated with SBP, antimicrobial prophylaxis is recommended in patients at high risk of developing SBP or those with a prior episode of SBP [19, 26].

Hepatorenal Syndrome

Hepatorenal syndrome is the development of kidney failure in patients with advanced cirrhosis and marked portal hypertension. It is perhaps the most deleterious complication of refractory ascites and is associated with rapid deterioration and high mortality [27]. In hepatorenal syndrome, the kidneys are structurally normal, but the marked circulatory dysfunction in advanced cirrhosis results in renal failure. As liver disease progresses, increased nitric oxide production results in splanchnic arterial vasodilation and reduced systemic vascular resistance. When increases in cardiac output are unable to compensate for the reduced vascular resistance, arterial underfilling occurs. The underfilling of the renal arterioles results in sodium and water retention, leading to ascites and edema, and further activation of vasoconstrictor

systems. These compensatory mechanisms help maintain effective arterial blood volume but can ultimately lead to intrarenal vasoconstriction, hypoperfusion, and hence renal failure [27–29].

There are two types of hepatorenal syndrome, differing in the rapidity of decline in renal function. Type 1 is associated with a worse prognosis and is defined as a doubling of serum creatinine to greater than 2.5 mg/dL in less than 2 weeks. Type 2 hepatorenal syndrome is a slower, more progressive disease associated with a creatinine greater than 1.5 mg/dL or creatinine clearance less than 40 cc/min. Both are associated with refractory ascites. The median survival with type 1 hepatorenal syndrome is 1 month compared to 6 months with type 2 hepatorenal syndrome [30].

The diagnosis of hepatorenal syndrome is based upon clinical criteria including lack of improvement in renal function after withdrawal of diuretics and expansion of plasma volume, absence of shock, and lack of renal parenchymal disease. Treatment of hepatorenal syndrome includes volume expansion, midodrine for vasoconstriction to increase mean arterial pressure, and octreotide to decrease splanchnic vasodilation. The definitive cure for hepatorenal syndrome is liver transplantation. If liver transplant is not performed within 1 month of developing hepatorenal syndrome, the kidneys usually do not recover, and a combined liver and kidney transplantation may be necessary [30].

Variceal Bleeding

Varices develop due to the increased portal blood flow into a fibrotic liver with high intrahepatic resistance. This leads to the formation of portal-systemic collaterals, including the dilation of the coronary and gastric veins that then constitute gastroesophageal varices [31].

In patients with compensated cirrhosis, gastroesophageal varices are present in 30–40% of patients compared to 85% of patients with decompensated cirrhosis. Varices develop at a rate of approximately 7–8% per year in patients with compensated cirrhosis and progress from small to large varices at a rate of 10–20% per year [32]. Hence, screening for varices with esophagogastroduodenoscopy is recommended in all patients with cirrhosis to identify if varices are present and to stratify risk of bleeding. In patients with small varices at low risk of bleeding, nonselective beta-blockers, such as propranolol, nadolol, or carvedilol, may delay growth or prevent variceal hemorrhage. In patients with small varices with high risk of hemorrhage (stigmata of recent bleeding with red wale marks or varices in patients with decompensated cirrhosis), nonselective beta-blockers are recommended. Lastly, in patients with medium or large varices, either nonselective beta-blockers or serial endoscopic variceal ligation may be used to prevent bleeding [33].

Over 90% of variceal bleeding occurs from esophageal varices and only 10% due to gastric varices. Patients with variceal hemorrhage present with hematemesis and/or melena. Treatment of variceal hemorrhage requires a combination of vasoconstrictor (terlipressin, somatostatin, or analogues such as octreotide) and endoscopic therapy with possible band ligation or sclerotherapy [34]. In patients with bleeding due to gastric varices, the use of tissue adhesives such as *N*-butyl-2-cyanoacrylate is more effective than banding. Antibiotic prophylaxis with either norfloxacin or ceftriaxone is also important as infections, such as SBP, often precipitate variceal hemorrhage [35]. In approximately 10–20% of patients, this standard therapy fails and placement of a TIPS should be considered. The mortality after an episode of variceal hemorrhage ranges from 15 to 25% within 6 weeks. In the past two decades, this mortality has decreased, likely due to improved endoscopic and vasoactive therapies as well as management with antibiotics [31, 34].

Hepatic Encephalopathy

Hepatic encephalopathy describes the wide spectrum of neuropsychiatric complications seen in patients with cirrhosis. The pathogenesis of hepatic encephalopathy is incompletely understood but generally involves ammonia shunting into the systemic circulation. Hyperammonemia results in neuronal dysfunction and decreased excitatory neurotransmission [36]. The degree of serum ammonia elevation does not correlate with the severity of hepatic encephalopathy. The clinical features of hepatic encephalopathy can vary from reduced awareness and irritability to coma as noted in the West Haven Criteria (Table 11.1) [37].

The initial treatment for hepatic encephalopathy is to reduce ammonia absorption from the intestinal lumen with the use of lactulose. Lactulose alters the microbiome in the gut to favor non-urease-producing bacteria, thereby reducing intestinal ammonia production [36]. Rifaximin reduces serum ammonia levels in a similar manner [38, 39]. The nonabsorbable nature of lactulose also results in the production of ammonium from ammonia in the colon and creates a cathartic effect. In addition to these medications, L-ornithine-L-aspartate (LOLA) and probiotics may improve hepatic encephalopathy for some patients. Ornithine and aspartate

Table 11.1 West Haven criteria for hepatic encephalopathy

Stage	Consciousness	Intellect and behavior	Neurologic findings
0	Normal	Normal	Normal exam
1	Mild lack of awareness	Shortened attention span, impaired addition or subtraction	Mild asterixis or tremor
2	Lethargic	Disoriented, inappropriate behavior	Obvious asterixis, slurred speech
3	Somnolent but arousable	Gross disorientation, bizarre behavior	Muscular rigidity and clonus, hyperreflexia
4	Coma	Coma	Decerebrate posturing

are important substrates in the metabolic conversion of ammonia to urea and glutamine, respectively. LOLA thus provides substrates for both of these ammonia detoxification pathways. It is important to identify and address the triggers for hepatic encephalopathy, as infection, gastrointestinal bleeding, dehydration or electrolyte disturbances, and renal insufficiency may be contributing to encephalopathy as well.

Pulmonary Vascular Complications

Hepatopulmonary syndrome is characterized by arterial hypoxemia with a PaO2 of less than 70 mmHg and an arterial-alveolar gradient greater than 20 mmHg in patients with advanced liver disease. It affects anywhere from 10% to 30% of patients with cirrhosis. Hepatopulmonary syndrome develops due to excess nitric oxide and capillary vasodilation, which result in arteriovenous shunting or diffusion-perfusion defects [40]. Patients may have platypnea or orthodeoxia and may describe dyspnea. A transthoracic contrast echocardiogram may detect an intrapulmonary right-to-left shunt indicating intrapulmonary vascular dilations [41]. Rarely, a macroaggregated albumin scan is performed to confirm and quantify such a shunt.

Portopulmonary hypertension is the presence of pulmonary hypertension in patients with portal hypertension from chronic liver disease and occurs in approximately 2% of patients. The severity of liver disease does not correlate with the severity of portopulmonary hypertension. It is classified as group 1 in the current classification of pulmonary hypertension. Vasoactive substances that are usually metabolized by the liver reach the pulmonary circulation via portosystemic collaterals. The chronic exposure of the pulmonary vascular endothelium to these substances leads to smooth muscle endothelial proliferation, vasoconstriction, and obliteration of the vascular lumen. The diagnosis of pulmonary hypertension is by a right heart catheterization. For the diagnosis of pulmonary hypertension, the mean pulmonary pressure must be greater than 25 mmHg with a pulmonary capillary wedge pressure less than 15 mmHg [42].

Hepatocellular Carcinoma

In addition to the portal hypertensive complications noted above, patients with cirrhosis are at risk of developing hepatocellular carcinoma (HCC). Patients with chronic hepatitis B virus infection are also at risk of developing HCC in the absence of cirrhosis. The risk of developing HCC varies with the etiology of liver disease but, in general, ranges from 1% to 5% per year [43]. The incidence of HCC has been rapidly rising in the United States over the last 20 years and is expected to continue its upward trajectory until 2030, largely due to the hepatitis C virus epidemic [44]. Because HCC is asymptomatic in its early course, the diagnosis is often delayed. Hence, screening at-risk patients for HCC with ultrasonography or cross-sectional imaging is recommended for early detection [45]. The diagnosis of HCC is suggested by elevated serum alpha-fetoprotein (AFP) or radiographic findings. The development of decompensation in a patient with previously compensated cirrhosis, abdominal pain, jaundice, and early satiety should all raise suspicion for HCC [46].

The only potentially curative treatment options for HCC are resection or liver transplantation. Treatment modality is dependent upon underlying liver function, degree of portal hypertension, and stage of the tumor. For patients unable to tolerate resection or awaiting liver transplantation, multiple therapeutic options exist including radiofrequency ablation, chemoembolization, radioembolization, and cryoablation [47]. These therapies are often not curative, but may control tumor growth for an interval of time. It is important to remember that a cirrhotic liver remains at risk of developing recurrent and de novo tumors.

Indications for Liver Transplantation and Evaluation

In general, the major indications for liver transplantation are irreversible hepatic failure or liver cancer as noted in Table 11.2. These indications are similar regardless of the etiology of liver disease. In the United States, there are approximately 14,000 candidates awaiting liver transplantation; yet only 7000 transplantations are performed annually [48]. Hence, the process of selecting appropriate candidates for liver transplantation is complicated by the realities of ration-

Table 11.2 Indications for liver transplantation

Fulminant hepatic failure
Complications of cirrhosis
Ascites
Hepatorenal syndrome
Spontaneous bacterial peritonitis
Hepatic encephalopathy
Variceal hemorrhage
Hepatopulmonary syndrome
Portopulmonary hypertension
Liver neoplasms
Hepatocellular carcinoma
Epithelioid hemangioendothelioma
Large hepatic adenomas
Liver-based metabolic conditions
Primary hyperoxaluria
Familial amyloidosis
Alpha-1 antitrypsin deficiency
Wilson's disease
Hemochromatosis
Acute intermittent porphyria
Glycogen storage diseases type I and IV
Tyrosinemia
Cystic fibrosis

ing a limited societal resource. To reduce the gap in available organs, transplant centers are now using organs previously considered unsuitable for transplantation, called extended criteria donor organs or living donors. The average 5-year survival following liver transplantation is more than 70%, owing to improved pre-transplant management, surgical techniques, organ preservation, and immunosuppression.

Timing of Liver Transplantation Referral

There are several predictive models to determine a patient's prognosis from end-stage liver disease. The two most common models are the Child-Pugh classification and Model for End-Stage Liver Disease (MELD) score. The Child-Pugh classification was originally developed to stratify the risk of portacaval shunt surgery in patients with cirrhosis but has since been shown to correlate with survival in patients not undergoing surgery. The variables included in this classification include serum albumin, bilirubin, prothrombin time, ascites, and encephalopathy, and scores range from 5 to 15. A score of 5 or 6 is indicative of Child-Pugh class A or well-compensated cirrhosis; a score of 7 to 9 is Child-Pugh class B cirrhosis or moderate hepatic impairment; and a score of 10–15 classifies as Child-Pugh class C or decompensated cirrhosis. The 1-year survival rates for patients with Child-Pugh class A, B, and C cirrhosis are approximately 100%, 80%, and 45%, respectively [49]. Due to subjectivity in categorizing ascites and encephalopathy in the Child-Pugh classification, the MELD score became more favorable. The MELD score is based entirely on laboratory data including serum bilirubin, creatinine, and international normalized ratio (INR). The MELD score was recently modified to incorporate serum sodium given its correlation with survival [50, 51]. As the MELD system offers objective data that is free of bias and directs donor organs to the sickest irrespective of waiting time, it is the current method of donor organ allocation.

A referral for liver transplantation is recommended in any patient that develops decompensated cirrhosis or has major complications of cirrhosis including cancer. The timely recognition of the need for transplant and referral to a transplant center are very important in this process. Patients with a MELD score ≥ 10 should be referred to a transplant center for evaluation. While transplantation is generally not considered beneficial until the MELD score is above 15, it is important to begin the evaluation process early and before a patient becomes significantly more ill [52].

Liver Transplant Evaluation Process

The evaluation to determine if a patient is a candidate for liver transplantation is relatively uniform across transplant centers and necessarily rigorous. The goal of the evaluation process is to determine (1) if transplantation is the best option for long-term survival, (2) if there are comorbid medical or psychosocial conditions that would outweigh the benefit of transplantation, and (3) the urgency of proceeding with transplantation.

The transplant evaluation process involves several sequential and simultaneous steps as outlined in Fig. 11.1. Ideally, this process can be completed within a few days, but it may be prolonged if additional subspecialty consultations are required. For example, patients with a substance use disorder or significant mental illness may require a referral to transplant and/or addiction psychiatry. Once a thorough medical and psychosocial evaluation of the transplant candidate has been performed, they are presented at a transplant selection meeting with attendees of disciplines from each step of the process above. Based on the discussion at this meeting, the candidate may be listed for transplant, deferred until additional evaluation is completed and/or suggested/required recommendations implemented or declined.

Each transplant center has its unique policies regarding absolute contraindications to transplant. These are listed in Table 11.3. In the past, most transplant centers adhered to a strict policy of requiring 6 months of sobriety prior to wait-listing patients with ALD for transplantation. However, more recent data suggest that the "6-month rule" may not be validated. Some patients with severe ALD

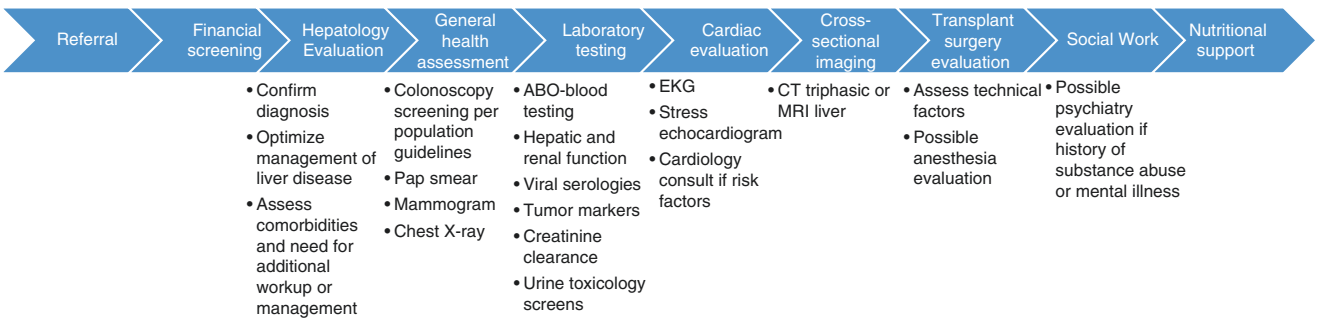

Fig. 11.1 Step-by-step process of evaluating candidacy for liver transplantation

Table 11.3 Contraindications to liver transplantation

Malignancy outside the liver (except non-melanoma skin cancer)
Hepatocellular cancer that has not been downsized to within UNOS criteria-tumor size guidelines, or with portal/hepatic vein invasion or extrahepatic spread
Extrahepatic cholangiocarcinoma > stage 2
Uncontrolled active bacterial infection outside the hepatobiliary system
Active or recent (less than 6 months) abuse of drugs including prescribed substances, failure to go for toxicology screen when requested
Active nicotine use
Advanced cardiopulmonary or other systemic disease
Inadequate social support system
Active opportunistic infection (including invasive fungal, mycobacterial or viral infection)
Active, uncontrolled psychiatric illness

might require longer time for sobriety and rehabilitation. On the other hand, patients with severe alcoholic hepatitis with 6-month survival of only 30% who fail to respond to medical therapy and are carefully selected might do well post-transplantation with less than 6-month sobriety [53]. Several transplant centers in the United States and Europe have developed protocols to consider liver transplantation in this group of patients [54, 55]. Importantly, the involvement of addiction psychiatrists is paramount in the adequate selection of candidates that have the highest predicted risk of relapse. Please see Chap. 45 on substance use disorders for further discussion.

Once a patient is deemed to be an acceptable transplant candidate, they are placed on the waiting list based on their MELD score and blood type. Donor organs are allocated first locally and then regionally. There are several possible exceptions or extra MELD points that candidates can receive for specific clinical conditions, including hepatocellular carcinoma, primary sclerosing cholangitis with biliary sepsis, and hepatopulmonary syndrome.

Conclusions

In summary, end-stage liver disease is a significant cause of morbidity and mortality in the United States. Once complications from cirrhosis arise, including hepatic encephalopathy, ascites, and esophageal variceal bleeding, a liver transplantation should be considered. Additionally, patients with fulminant hepatic failure, liver-based metabolic defect, hepatocellular carcinoma, or a systemic complication of liver disease should be referred for a transplant evaluation. The ensuing workup and decision regarding transplant candidacy is a process involving a multidisciplinary team at the transplant center.

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