CHAPTER 2

Monitoring the Patient Awaiting Transplantation

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INTRODUCTION

Liver transplantation is the only treatment for patients with end-stage liver disease (ESLD). The success of liver transplantation led in most countries to a marked increase of patients on the waiting list, whereas the number of liver transplantations during the same time period increased only slightly. With the growing discrepancy between the numbers of donors and recipients, the median waiting time for liver transplantation has increased dramatically, exceeding in some countries 1–2 years. As a result, the number of patients who die while waiting is increasing and many others die after removal from the list because their clinical deterioration precludes successful transplantation. Accordingly, the management of patients on the waiting list is getting more important with the aim to maintain clinical stability so that liver transplantation can eventually be successfully performed. This is achieved by (1) prophylactic measures to prevent complications of ESLD and (2) early recognition and treatment of complications of advanced liver disease. Most stable patients can be managed as outpatients, with regular controls at the transplant center and in close collaboration with the referring physicians. The frequency of controls is determined by the clinical condition and the current treatment regimen (e.g. treatment for hepatitis C) and by the requirements of the national transplant and allocation organization. In the USA, for example, the frequency of blood controls is determined by the actual model for end-stage liver disease (MELD) score. Since the MELD score is a good predictor of 3 months' mortality on the waiting list, it is useful to see the patients at the intervals outlined in Table 2.1.

The most common complications of advanced liver disease, encountered in patients on the waiting list include refractory ascites, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome (HRS), fluid and electrolyte disturb-

Table 2.1 *Adult Patient Reassessment and Recertification Schedule*

MELD Score	*Status Recertification*	*Laboratory Values no Older Than*
≥25	every 7 days	48 h
≤24 but >18	every 1 month	7 days
≤18 but ≥11	every 3 months	14 days
≤10 but >0	every 12 months	30 days

http://www.optn.org/PoliciesandBylaws/policies/docs/policy_8.doc

ances, portal hypertensive bleedings, hepatic encephalopathy (HE), hepatocellular carcinoma (HCC), malnutrition and progress of other medical diseases. In addition, there are disease-specific aspects such as control of viral hepatitis and prevention of alcohol relapse. In this chapter the different aspects in the care of patients on the waiting list will be reviewed.

Refractory Ascites

The management of ascites and its complication is extensively covered in Chapter 3. Ascites is the most common complication in patients with ESLD. Approximately 50% of patients with compensated cirrhosis will develop ascites over a 10-year period [1]. Development of ascites is associated with 50% mortality after 2 years. The International Ascites Club recently recommended a new grading system for patients with ascites:

Grade 1: ascites can only be detected by ultrasound;
Grade 2: moderate ascites with symmetrical distention of the abdomen;
Grade 3: large or tense ascites with marked abdominal distension [2].

At the onset, ascites (Grade 2) usually can be easily controlled with diuretics and salt restriction (see Chapter 3), but with worsening portal hypertension the development of treatment-refractory or treatment-resistant ascites (Grade 3) is increasing. In this situation aggressive diuretic therapy places the patient at risk of developing renal failure, electrolyte disturbances, volume depletion and HE. Therefore, renal function and electrolytes have to be monitored carefully and any deterioration of renal function should be fully investigated. If ascites can no longer be controlled with diuretics or the use of diuretics is associated with renal insufficiency and electrolyte disturbances, patients can either be treated with large-volume paracentesis and plasma expanders or transjugular intrahepatic portosystemic shunt (TIPS).

In recent years five large randomized controlled trials have compared TIPS to repeated large-volume paracentesis [3–7]. In all studies ascites was better controlled with TIPS compared to large-volume paracentesis. In contrast to

large-volume paracentesis, which has no effect on the mechanisms leading to ascites, TIPS is associated with a reduction in portal hypertension that decreases the activity of sodium-retaining mechanisms and improves the renal response to diuretics. Whether TIPS also improves survival is still controversial. In two studies the survival was improved in the TIPS group; however, this could not be confirmed in the other studies. There is also no evidence that TIPS improves the outcome after transplantation. Whether TIPS increases the technical difficulties of transplantation in some patients is controversial but such difficulties are usually uncommon in experienced centers [8,9].

Until recently the major disadvantages of TIPS were (1) the high rate of shunt stenosis (up to 75%), which led to the reappearance of ascites and (2) the development of HE (up to 77%) [10]. However, the recent introduction of polytetrafluoroethylene (PTFE)-covered prostheses improves TIPS patency and decreases the number of clinical relapses and reinterventions without increasing the risk of encephalopathy [11].

Paracentesis with albumin replacement remains the first treatment option for patients with refractory ascites on the waiting list [2]. Paracentesis with plasma volume expansion is safe, less costly and more widely available. Plasma volume expansion with albumin is superior to other plasma expanders (saline, polygeline, dextran-70) for large-volume paracentesis greater than 5 L [12,13]. To reduce the frequency of repeated paracentesis, patients should continue to receive diuretics as tolerated. If the frequency of paracentesis is greater than three times per month, the International Ascites Club recently recommended considering TIPS insertion [2]. In addition, TIPS should be considered for patients who do not tolerate large-volume paracentesis or where large-volume paracentesis is ineffective due to multiple adhesions or loculated ascites (Fig. 2.1).

Although randomized studies are lacking, TIPS should also be considered for patients with treatment-refractory hepatic hydrothorax. This results in resolution of the hepatic hydrothorax in approximately 70% of patients [14].

The peritoneovenous shunt (Le Veen shunt) is rarely used today due to the higher complication rate compared to TIPS or large-volume paracentesis [15]. In addition shunt-related adhesions can make subsequent liver transplantation more difficult. Therefore, the Le Veen shunt should not be considered in patients on the waiting list.

Spontaneous Bacterial Peritonitis

SBP is characterized by infection of the ascitic fluid in the absence of any known intra-abdominal source of infection. The diagnosis is established when there is a positive ascites culture and/or a polymorphonuclear cell

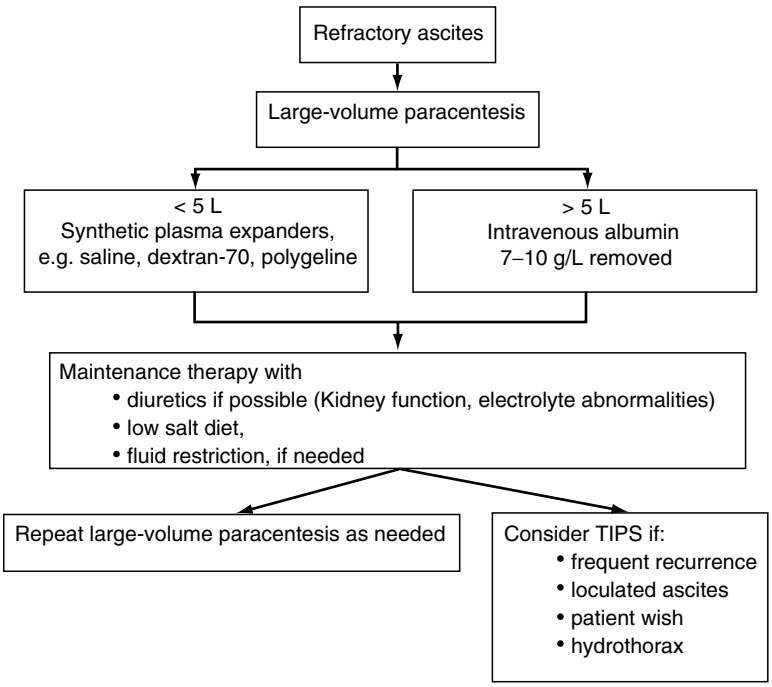

Fig. 2.1 *Treatment options for patients with refractory ascites.*

count (PMC) $\geq 250\,\text{cells/mm}^3$. The prevalence of SBP ranges between 10% and 30% in patients with ascites and is sufficiently common to justify a diagnostic paracentesis in every cirrhotic patient with ascites admitted to the hospital [16]. In addition, a paracentesis should be performed whenever there is clinical evidence for peritonitis (abdominal pain, rebound tenderness), clinical signs of infections (fever, leucocytosis, elevated C-reactive protein (CRP)), development of renal insufficiency, or HE.

In patients with a previous episode of SBP, the 1-year probability for a recurrent SBP ranges between 40% and 70% [17]. In addition, patients who never had SBP but have an increased bilirubin ($>40\,\mu\text{mol/L}$) and/or a low total ascitic fluid protein count ($>10\,\text{g/dl}$), as well as patients with variceal bleeding, have an increased risk for SBP. In patients with a previous history of SBP, the continuous administration of norfloxacin (400 mg/day) significantly reduced the 1-year probability of SBP from 68% in the placebo group to 20% in the norfloxacin group [18]. Secondary long-term prophylaxis is therefore recommended for all patients with a history of SBP (Table 2.2).

Patients without a history of SBP who have high ascitic fluid protein content ($>10\,\text{g/dl}$) have a low risk of infection (0% at 1 year, 3% at 3 years); primary prophylaxis is probably not justified in this patient population. It is unclear whether primary prophylaxis is justified in patients at high risk for SBP such as patients with an ascitic fluid protein content $<10\,\text{g/L}$ or an

Table 2.2 *Diagnostic Criteria of Hepatorenal Syndrome*

Major criteria

1. Chronic or acute liver disease with advanced hepatic failure and portal hypertension.
2. Low glomerular filtration rate, as indicated by serum creatinine >133 μmol/L (1.5 mg/dl) or 24-h creatinine clearance <40 ml/min.
3. Absence of shock, ongoing bacterial infection, volume depletion, and current or recent treatment with nephrotoxic drugs.
4. No sustained improvement in renal function (decrease in serum creatinine to 1.5 mg/dl or less, or increase in creatinine clearance to 40 ml/min or more) following diuretic withdrawal and expansion of plasma volume with 1.5 L of isotonic saline.
5. No proteinuria (<500 mg/dl) and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease.

Additional criteria

1. Urine volume <500 ml/day in patients with cirrhosis.
2. Urine sodium <10 mEq/L.
3. Urine osmolality greater than plasma osmolality.
4. Serum sodium concentration <130 mEq/L.

Type of hepatorenal syndrome

Type 1: progressive impairment in renal function as defined by a doubling of initial serum creatinine above 220 μmol/L (2.5 mg/dl) in less than 2 weeks.

Type 2: stable or slowly progressive impairment in renal function not meeting the above criteria.

From [28].

elevated serum bilirubin (>40 μmol/L). In one study, the long-term antibiotic prophylaxis for primary prevention was superior compared to short-term prophylaxis, which was administered only if patients were hospitalized [19]. However, the emergence of infections caused by norfloxacin-resistant bacteria was significantly higher in the continuous long-term prophylaxis group. The benefits of primary prophylaxis in this patient group must therefore be carefully weighed against the selection of norfloxacin-resistant bacteria, but might be justified in selected cases on the waiting list (Table 2.3).

Patients with an upper gastrointestinal bleeding in the presence or absence of ascites are at high risk for severe bacterial infection including SBP. Several studies of gastrointestinal (GI) bleeders with oral or intravenous antibiotics showed a significant reduction of infections including SBP in the antibiotic group [20–25]. No difference was found whether the antibiotic was adminis-

Table 2.3 *Prevention of Complications in Patients on the Waiting List*

Aim	*Intervention*
I. Prevention of infections	
A. Acute variceal bleeding	First choice: oral norfloxacin 2 × 400 mg for 7 days Alternative: oral ciprofloxacin 2 × 500 mg for 7 days
B. Primary prevention of SBP	
1. Ascitic fluid protein high (>10 g/L)	Prophylaxis unnecessary
2. Ascitic fluid protein low (<10 g/L)	Prophylaxis controversial Short-term (during hospitalizations) or long-term prophylaxis with daily nor floxacin or trimetoprim-sulfamethoxazole can be considered
C. Secondary prevention of SBP	First choice: norfloxacin 400 mg daily Alternative: trimetoprim-sulfamethoxazole daily
II. Prevention of HRS in patients with SBP	Intravenous albumin (1.5 g/kg day 0 and 1 g/kg after 2 days)
III. Prevention of variceal bleeding	
A. Primary prevention of variceal bleeding	First choice: propranolol or nadolol (stepwise increase in dose until 25% reduction in heart rate) Alternative: band ligation
B. Secondary prevention of variceal bleeding	First choice: band ligation alone or in combination with propranolol or nadolol Alternative especially as bridge to OLT: TIPS

SBP: spontaneous bacterial peritonitis; HRS: hepatorenal syndrome.

tered orally or intravenously. Antibiotic prophylaxis is recommended in all cirrhotic patients with an upper GI bleed irrespective of the presence or absence of ascites. Although several antibiotic regimes are effective, the oral administration of norfloxacin (2 × 400 mg for 7 days) or ciprofloxacin (2 × 500 mg for 7 days) appear to be the first choice (Table 2.3) [25].

Empiric antibiotic treatment should be started when the neutrophil count is $>250/mm^3$ and SBP is suspected. Currently intravenous treatment with a third-generation cephalosporin (e.g. cefotaxime 2 g every 8–12 h, ceftriaxone 1 g/24 h for 5–7 days) is recommended [16]. Therapy needs to be modified according to the culture results. SBP resolves in approximately 90% of patients. The most important negative predictor of survival is the development of renal insufficiency. The administration of albumin (1.5 g/kg at diagnosis and 1 g/kg at day 3) is able to prevent the development of renal insufficiency and reduces the mortality from 30% to 10% (Table 2.3) [26].

Renal Failure, Fluid, and Electrolyte Disturbances

Patients with ESLD are at increased risk to develop renal failure, either spontaneously (HRS) or due to iatrogenic interventions (diuretics, nephrotoxic drugs). Patients with advanced cirrhosis and ascites are at highest risk. Renal vasoconstriction associated with advanced liver disease leads to severe renal vasoconstriction and functional renal insufficiency [27]. Renal failure occurs in up to 10% of patients with advanced liver disease and even more frequently in patients on the waiting list.

HRS can only be diagnosed after other causes of renal failure have been excluded, including obstruction, volume depletion, glomerulonephritis, acute tubular necrosis, and drug-induced nephrotoxicity [28]. All diuretics should be stopped and a fluid challenge with 1.5 L of isotonic saline should be administered to exclude volume depletion (Table 2.2). From the clinical presentation, two types of HRS can be distinguished:

1. Type I HRS is characterized by rapidly progressive renal failure with an increase in the serum creatinine to more than 220 μmol/L within 14 days and marked oliguria. Type I HRS occurs mostly in patients with type II HRS with a recent precipitating event (severe infection, e.g. SBP, large-volume paracentesis without plasma volume expansion).
2. Patients with type II HRS have refractory ascites with stable or slowly progressive impairment in renal function (Table 2.2).

The prognosis of patients with HRS is poor with a median survival of only 15 days in patients with type I and 150 days in patients with type II [29]. Until recently there was no effective therapy apart from liver transplantation, but fortunately this has changed in recent years. The combination of vasoconstrictor drugs, such as vasopressin analogues, noradrenaline, and the combination of midodrine and octreotide together with plasma volume expansion with albumin (1 g/kg intravenously on day 1, 20–40 daily thereafter) is effective in approximately two-thirds of patients (Fig. 2.2) [10]. It has been shown

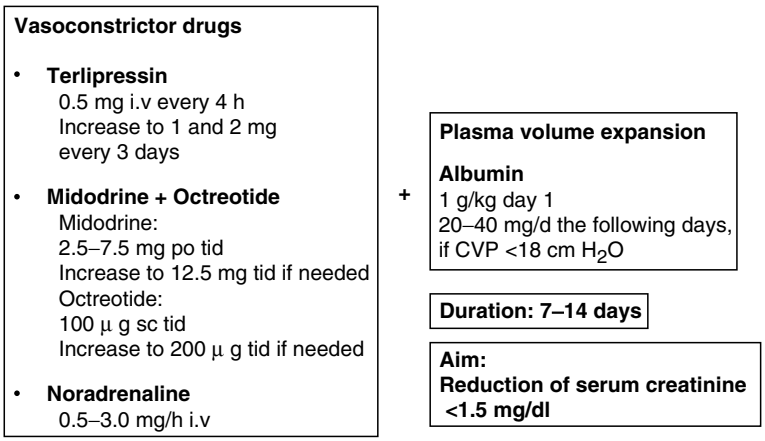

Fig. 2.2 *Therapeutic options for patients with hepatorenal syndrome.*

that the combination of terlipressin and albumin is clearly more effective than terlipressin alone [30]. Surprisingly the recurrence rate is low and responders have a higher rate of survival than nonresponders [30,31]. The response to treatment increases the probability that the patients with HRS survive long enough to undergo transplantation. There is some preliminary evidence that the improvement of renal function reduces post-transplantation morbidity and mortality [32]. There is also evidence that TIPS is effective in patients with HRS [33,34]. For both treatment options the available information is still insufficient; results from randomized controlled trials are lacking.

Hemodialysis has no effect on survival and should not be used routinely. However, as a bridge to transplantation, it might be useful in patients who fail to respond to medical treatment.

Patients with advanced liver disease and portal hypertension have a decreased effective arterial blood volume with activation of the renin–angiotensin–aldosterone system, the sympathetic nervous system, and increased secretion of antidiuretic hormones (ADHs). The activation of these counteracting regulatory mechanisms leads to renal vasoconstriction. In this situation renal perfusion is dependent upon prostaglandin-mediated vasodilatation. Nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit prostaglandin synthesis, may lead to a further decrease in renal blood flow and may precipitate acute renal failure [35]. Therefore, NSAIDs should be avoided in patients with ESLD. In addition, all potentially nephrotoxic drugs should be used with caution and overtreatment with diuretics should be avoided. It is generally recommended to stop diuretics if serum creatinine is greater than 1.7 mg/dl (150 μmol/L) and serum urea is greater than 22 mg/dl (8 μmol/L). Several studies have clearly shown that pretransplant renal function significantly impacts on post-transplant survival [36,37].

The most common electrolyte abnormality in patients with advanced liver cirrhosis is dilutional hyponatremia defined as a serum sodium <130 mmol/L. This occurs as a consequence of an impaired free water clearance by the kidney due to a nonosmotic hypersecretion of ADH. Impaired free water clearance occurs several months after the onset of sodium retention and ascites formation and therefore represents a late event in the course of decompensated liver disease. Hyponatremia indicates a poor prognosis and for some authors is an important predictor of survival. It has been proposed to incorporate serum sodium concentration in the MELD score; however, this remains controversial [38]. As long as the serum sodium remains above 125 mmol/L, no specific prophylactic measures are required.

If the serum sodium concentration falls below 125 mmol/L, diuretics should be withheld and an attempt made to expand the effective circulating blood volume by infusion of albumin (100 g/24 h) or red blood cells. This will usually result in a transient drop in the serum sodium concentration, following which the sodium will rise as ADH secretion is turned off by the increased blood volume. Once the serum sodium starts to rise, the colloid infusion can be tapered. Free water restriction should be instituted although there is no data-supported specific threshold for initiating fluid restriction [39].

It is important to remember that attempts to rapidly correct hyponatremia with hypertonic saline can lead to more complications [40]. Transplantation is contraindicated if the serum sodium is below 120 mmol/L due to the risk of developing central pontine myelinolysis.

Portal Hypertensive Bleeding

The management of portal hypertensive bleeding is extensively covered in Chapter 3. In this section only the prophylactic measures will be reviewed. Several studies have been published regarding the result of upper GI endoscopy in patients being evaluated for liver transplantation. Overall 66–85% of these patients had varices and 16–46% presented with large (Grade III to IV) varices [41–43]. Therefore, it is generally accepted that at the time of listing all patients should undergo an upper GI endoscopy. In the rare patients, where no varices are found, endoscopy should be repeated in 2–3 years, and in patients with small varices, who do not undergo some kind of primary prophylaxis, endoscopy should be repeated yearly [44].

Prevention of a First Variceal Bleed (Primary Prophylaxis)

The high mortality rate of a first variceal bleeding episode justifies the development of prophylactic regimes to prevent the development of, and bleeding from, varices. Noncardioselective beta-blockers such as propranolol and nado-

lol have been the mainstay of primary prevention. In cirrhotics with esophageal varices, both propranolol and nadolol have been shown to reduce the risk of an initial bleeding episode by 40–50%; there was a trend toward reducing mortality [45,46]. It is customary to adjust the dose of beta-blockers until a 25% fall of the heart rate is achieved. About 30% of patients will not respond to beta-blockers with a reduction in hepatic venous pressure gradient (HVPG), despite adequate dosing. These nonresponders can only be detected by invasive measurements of HVPG. Beta-blockers may cause side-effects such as fatigue and impotence that may lead to noncompliance, especially in younger males.

While the side-effects of endoscopic sclerotherapy outweigh its benefit in primary prophylaxes of esophageal variceal hemorrhage [47], endoscopic band ligation has recently been shown to be effective and well tolerated [48]. Thus, in summary, the following scheme is recommended for primary prophylaxis of variceal hemorrhage:

1. Selection of patients with at least medium-sized esophageal varices and/or red color or ''red wale signs.''
2. Noncardioselective beta-blocker (propranolol or nadolol) dose titrated to reach a reduction of resting heart rate of at least 25%, but not to lower than 50–55/min.
3. In patients with esophageal varices who do not tolerate or have contraindications to beta-blockers, endoscopic band ligation is indicated (Table 2.3).

Secondary Prevention of Variceal Bleeding

About 60% of patients surviving an acute variceal hemorrhage will develop recurrent bleeding within the first year [9,50]. Clinical predictors of early recurrence include severity of the initial hemorrhage, the extent of the underlying liver disease, impaired renal function, and encephalopathy. Endoscopic features include active bleeding at the time of endoscopy, large varices, and stigmata of a recent hemorrhage [51]. There is a strong correlation between the severity of portal hypertension, the survival rate, and the rebleeding risk. The high rebleeding rate with its associated morbidity and mortality justifies the implementation of a secondary prevention program. Different pharmacologic agents have been used for secondary prevention of variceal bleeding, but there is sufficient evidence of efficacy only for noncardioselective beta-blockers [52].

In a meta-analysis of 10 randomized trials comparing propranolol to endoscopic sclerotherapy for secondary prevention, both treatment options were similarly effective [46]. However, sclerotherapy was associated with significantly higher rates of side-effects. Sclerotherapy has also been compared to band ligation in several trials, which were summarized in a

recent meta-analysis [53]. Ligation is associated with a lower rebleeding rate (25% versus 30%), fewer complications, lower overall costs and higher rates of survival. In a recent randomized trial the combination of nadolol plus endoscopic banding was more effective for the prevention of variceal rebleeding than endoscopic banding alone [54].

Therefore, endoscopic treatment should be considered in the context of a combined pharmacologic and endoscopic strategy (Table 2.3) [55]. TIPS is currently considered an effective bridge to transplantation by most clinicians. Meta-analysis comparing TIPS with endoscopic treatment found a lower rebleeding rate in patients with TIPS placement [56,57]. However, TIPS was associated with a higher incidence of encephalopathy, and no difference was found regarding the overall survival.

Additionally, the long-term use of TIPS is limited by the frequent shunt occlusion. During the first year, 50–70% of TIPS occlude and as a consequence 20% of the patients develop rebleeding [58]. Regular investigation, usually with Doppler ultrasound and intervention, is often required to avoid shunt occlusion. Misplaced TIPS in the portal vein or vena cava may complicate later liver transplantation [8]. For this reason TIPS placement should be restricted to experienced interventional radiologists.

Hepatic Encephalopathy

Clinically detectable encephalopathy (HE) is found in one-third of patients with ESLD [59]. Usually it presents with changes in mental status as a result of a precipitating event (see below). An important precipitating event is the use of benzodiazepines, prescribed for sleep disturbances. Rarely, patients present with recurrent episodes of HE without an obvious precipitating event. This can either be due to the presence of new spontaneous portosystemic shunts or as the result of severe parenchymal liver disease. Several recent studies describe the presence of subtle changes in mental function in 30–70% of patients that can only be detected by neuropsychological testing in patients who appear otherwise neurologically intact (minimal HE) [60,61].

It is important to remember that the diagnosis of HE is a diagnosis of exclusion. Other etiologies such as intracranial space-occupying lesions, vascular events, other metabolic disorders, and infectious diseases should be excluded. Ammonia levels are widely scattered in patients with liver disease; individual values are a poor predictor of the degree of encephalopathy. In spite of these limitations, ammonia levels are frequently useful when there is uncertainty if mental changes are the result of HE. Changes in ammonia levels should not be considered an indicator of therapeutic benefit; improvement in mental status is the sole therapeutic end point. The severity of HE is most commonly graded according to the West Haven criteria (Table 2.4) [62].

Table 2.4 *West Haven Criteria for Semiquantitavie Grading of Mental State*

Grade 1

1. Lack of awareness
2. Euphoria or anxiety
3. Shortened attention span

Grade 2

1. Lethargy or apathy
2. Minimal disorientation for time or place
3. Subtle personality change
4. Inappropriate behaviors
5. Impaired performance of subtraction

Grade 3

1. Somnolence to semistupor but responsive to verbal stimuli
2. Confusion
3. Gross disorientation

Grade 4

1. Coma (unresponsive to verbal or noxious stimuli)

As soon as deterioration in the mental status is recognized, a search for a precipitating event should be immediately started. Among the factors are:

1. Renal and electrolyte abnormalities, especially uremia and hypokalemia and dehydration.
2. Gastrointestinal bleeding (increases the nitrogen load in the gut).
3. Infection – cultures, especially from ascites to exclude spontaneous bacterial peritonitis are important.
4. Constipation.
5. Use of benzodiazepines, narcotics, or other sedatives (sometimes urinary screening is necessary to exclude their presence).
6. Excessive dietary protein intake.
7. Worsening liver function, e.g. portal vein thrombosis.
8. Noncompliance with medications, especially lactulose or lactilol.

Development of acute HE is associated with a poor prognosis. In a recent study 1- and 3-year survival was only 42% and 23%, respectively [63].

The mainstay of therapy centers on correcting the precipitating event. Depending on the level of consciousness, intubation has to be considered to

prevent aspiration. In these patients a nasogastric tube should be placed and treatment with nonabsorbable disaccharides such as lactulose or lactilol should be started. In cooperative patients this can be given by mouth. The usual starting dose is 20 ml, 3–4 times daily with the aim of achieving 2–4 soft bowel movements per day. Although recent reviews have pointed out the weaknesses of the clinical trials that support the use of the nonabsorbable disaccharides, they are still first-line treatment [64,65].

If patients are not improving after correcting the precipitating cause and administration of lactulose, neomycin 3–6 g/day in divided doses might be added. Alternatively, metronidazole can be used [66]. Classically, low protein diet (minimum 30 g/day) is recommended for patients with encephalopathy. During an acute episode of HE, enteral nutrition is frequently interupted for a few days due to coma or delirium. During this period the patient relies on gluconeogenesis from protein to maintain glucose metabolism in the brain. Gluconeogenesis is one of the most significant sources of endogenous ammonia production and can lead to worsening of the encephalopathy. Therefore, stuporous or comatose patients should be provided with a minimum of 400 calories per day in the form of intravenous glucose to minimize gluconeogenesis.

Once the patient recovers from an intercurrent episode of clinical encephalopathy, a moderate dose of protein (40 g/day) is instituted and is increased up to the maximum tolerated dose within the next few days. It is important to avoid long-term protein restriction to prevent further worsening of the nutritional status. Changes in the diet might help to increase the tolerance for proteins; there is some evidence that vegetable and milk proteins are less encephalogenic in than equal quantities of meat protein [67]. Other therapeutic interventions such as ornithine-aspartate, sodium benzoate, and branched-chain amino acids are less well established [59,68].

■ PORTOPULMONARY HYPERTENSION AND HEPATOPULMONARY SYNDROME

Portopulmonary Hypertension

Portopulmonary hypertension (PPHTN) is defined by:

1. Increased pulmonary arterial pressure (PAP; mean pressure determined by right heart catherization of >25 mmHg at rest and >30 mmHg during exercise)
2. Increased pulmonary vascular resistance (PVR; >240 dyne/s/cm^5).
3. Pulmonary wedge pressure of less than 15 mmHg in patients with portal hypertension [69].

Reports on the incidence of PPHTN vary greatly. In a recent study in patients with cirrhosis and refractory ascites, 16% of the patients fulfilled the criteria for PPHTN [70]; whereas in other studies the incidence was significantly lower [71]. So far no clear relationship between the severity of hepatic dysfunction or the degree of portal hypertension and the severity of pulmonary hypertension has been conclusively established [71]. In addition, little is known about the risk of developing PPHTN while waiting for liver transplantation.

The detection of PPHTN before liver transplantation, however, is crucial because the presence of pulmonary hypertension of any severity increases the perioperative and long-term risk of liver transplantation [72,73]. The most common presenting symptom is progressive dyspnea on excertion; however, patients with even severe PPHTN can be completely asymptomatic.

Echocardiography is the screening method of choice [74,75]. Using a systolic right ventricular pressure (RVsys) of more than 50 mmHg as a cutoff, the sensitivity and specificity to detect moderate to severe PPHNT is 97% and 77%, respectively. Only these patients need to undergo right heart catheterization to fully characterize pulmonary hemodynamics. If moderate to severe PPHNT is confirmed, treatment with pulmonary vasodilators should be instituted with the aim of decreasing PAP to <35–40 mmHg and PVR to <400 dyne/s/cm^5 [76]. Although rare, PPHTN can develop after the initial evaluation for liver transplantation [76,77]. In another study PPHNT was diagnosed in 65% of patients only in the operating room prior to transplantation [73].

These data clearly suggest that regular echocardiographic examinations of liver transplant candidates on the waiting list are mandatory, although the optimal screening frequency remains to be determined. In patients with normal echocardiographic findings at initial evaluation, the echocardiography should be repeated annually and in patients with an RVsys between 35 and 50 mmHg, every 6 months (Table 2.5) [76].

Hepatopulmonary Syndrome

Hepatopulmonary syndrome (HPS) is defined as a triad consisting of:

1. Chronic liver disease.
2. Hypoxemia (PaO_2 <70 mmHg or alveolar to arterial oxygen gradient >20 mmHg).
3. Intrapulmonary arteriovenous dilatation or shunts as detected by contrast echocardiography, lung perfusion scanning, or pulmonary angiography [69].

Table 2.5 *Recommended Follow-up Examinations for Patients on the Waiting List*

Complication	*Examination*	*Time Interval*
Portopulmonary hypertension	Echocardiography	12 months, if baseline examination normal; 6 months, if RVsys at baseline between 35 and 50 mmHg
Hepatopulmonary syndrome	Pulse oxymetry in standing position	6–12 months: arterial blood gas analysis if $SpO_2 < 97\%$; if $PaO_2 < 70$ mmHg, perform echocardiography
	Alternative: arterial blood gas standing	6–12 months: if $PaO_2 < 70$ mmHg, perform echocardiography
Known hepatocellular carcinoma	Abdominal CT or MRI	3 months
	Chest CT	3 months
	Bone scan	3–6 months
Cancer screening:		
Hepatocellular carcinoma	Abdominal ultrasound	3 months
	Alternative: abdominal CT or MRI	6 months
Cholangiocarcinoma	Abdominal ultrasound and CA 19-9	6 months
Colon cancer in primary sclerosing cholangitis patients	Colonoscopy	12 months
Breast cancer in women >40 years	Mammography	12 months
Cervical cancer in women >40 years	Cervical smear	12 months
Prostate cancer in men >45 years	Prostate-specific antigen	12 months

HPS is a serious complication that should be diagnosed before liver transplantation. The reported incidence of HPS in patients with chronic liver diseases is variable (4–32%) and depends on the diagnostic criteria and the tests used to detect intrapulmonary shunts [78,79]. A recent prospective study demonstrated that the survival of patients with HPS is significantly shorter (median

survival 11 months) compared to patients without HPS (median survival 41 months) [78].

Medical management has so far been disappointing. Increasingly, liver transplantation has been advocated as the treatment of choice for patients with HPS; normalization of hypoxemia can be expected in approximately 82% within 15 months after liver transplantation. After liver transplantation up to 30% of patients with HPS will die; this is almost twice the death rate experienced by all other transplant recipients [80]. Although the optimal screening methods and interval have not been defined so far, it is probably useful to screen patients every 6–12 months for signs of hypoxemia (Table 2.5). Hypoxemia is the prerequisite for the diagnosis of HPS; therefore, every diagnostic approach should begin with the documentation of hypoxemia at rest. The routine measurement of arterial blood gases has been advocated in all liver transplant candidates [81]. Considering the prevalence of HPS this would lead to a large number of unnecessary arterial blood gas analyses. Therefore, a recent study evaluated the usefulness of pulse oxymetry for the detection of arterial hypoxemia in liver transplant candidates [82]. If arterial blood gas analysis is restricted to patients with an O_2-saturation below 97% only 32% of all patients would need an arterial blood gas analysis. This would still maintain a high sensitivity (96%) and acceptable specificity to identify hypoxemic patients (75%). If hypoxemia is established, the diagnosis of HPS should be confirmed by echocardiography or lung perfusion scanning. For patients with HPS an increase in the MELD score equivalent to a 15% risk of mortality (MELD score = 24) might be requested in the USA (see Chapter 6).

Hepatobiliary Cancer

Hepatocellular carcinoma can complicate all common forms of liver cirrhosis, but occurs most commonly in hepatitis B- or C-induced liver cirrhosis. HCC may be the indication for liver transplantation or may develop on the waiting list. Follow-up of transplant candidates will differ. The management of patients with hepatoma is considered in detail in Chapter 8.

Cholangiocarcinoma (CCA) is a well-recognized complication of primary sclerosing cholangitis (PSC). The reported frequency is as high as 7–36% in patients undergoing liver transplantation. The occurrence of CCA is unpredictable and is often difficult to diagnose. Liver transplantation is only for a selected group of patients with early-stage CCA who undergo preoperative radiation and chemotherapy in the absence of metastases. The issue of how patients with PSC should be screened on the waiting list is still unresolved. However, screening is important, because if the tumor is detected at early stages, where it is still confined in the biliary tree, transplantation still offers

the best chances for cure. Currently the best approach probably consists of an ultrasound or magnetic resonance cholangiography and CA 19-9 level every 6 months (Table 2.5). Management of patients with PSC prior to transplantation is discussed in Chapter 10.

Other Cancers

The most common extrahepatic cancer in PSC patients with ulcerative colitis is colon cancer. Patients with ulcerative colitis should undergo yearly colonoscopy while awaiting liver transplantation.

Annual mammography and cervical smear should be obtained yearly in women over 40 years and an annual prostate-specific antigen (PSA) level should be measured in men over 45 years awaiting liver transplantation (Table 2.5).

■ MANAGEMENT OF OTHER MEDICAL DISEASES

Diabetes Mellitus

Patients with established diabetes mellitus will need careful monitoring to ensure that blood sugar is maintained within acceptable limits. There should be a low threshold for instituting insulin-based control since diabetic transplant recipients almost always require insulin in the initial post-transplantation period.

Hypertension

Patients with arterial hypertension will need monitoring to ensure that blood pressure is optimally controlled. If there are any cardiac abnormalities on screening, electrocardiogram (ECG) and echocardiography should be repeated at 6-monthly intervals.

Preventing Further Liver Damage

Patients with ESLD are at increased risk of developing fatal hepatic failure if they develop superimposed acute hepatitis A [83]. Vaccination against hepatitis A and B is much more effective in patients with compensated liver cirrhosis compared to patients with decompensated disease [84]. Therefore, all patients with chronic liver disease should be vaccinated against hepatitis A and B as early as possible in the course of their disease (see Chapter 7).

If possible, potentially hepatotoxic drugs should be avoided, especially medications that increase the risk of GI bleeding or renal insufficiency.

Malnutrition

Malnutrition is common in patients with chronic liver disease awaiting transplantation, and is a risk factor for mortality following liver transplantation [85,86]. Unfortunately, nutritional supplementation has not been proven to affect outcome [87]. However, most of the studies done to date were either poorly controlled or not adequately powered to detect small differences in survival.

In general, the total amount of calories provided should be at least 30–35 kcal/kg/day [88]. Protein restriction should not be considered routine. Adults can receive daily 1–2 g of protein/kg of dry body weight. Patients with ESLD awaiting liver transplant should take daily multivitamin and other supplements as needed. Specific fat-soluble vitamin supplementation should be provided if a deficiency is present.

Temporary Suspension from the Waiting List

Patients may temporarily be inactivated on the waiting list for several reasons and reactivated as soon as the temporary problem is resolved. The most common reasons for temporary suspension are intercurrent infections and variceal bleeding. Such infections should be vigorously treated; management of bleeding and portal hypertension is discussed in Chapter 3.

Disease-specific aspects of the pretransplantation management of patients with viral hepatitis (Chapter 7), hepatoma (Chapter 8), alcoholic liver disease (Chapter 9), autoimmune diseases (Chapter 10), metabolic diseases (Chapter 11), and fulminant hepatic failure (Chapter 13) are covered elsewhere.

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