Hepatocellular carcinoma (HCC) is a complex and heterogeneous disease, often associated with underlying conditions, like cirrhosis or other relevant co-morbidities that worsen the prognosis and make the clinical management more challenging. Current recommendations emphasize the importance of a multidisciplinary approach for the management of HCC patients and stress the crucial role of careful prevention and the management of cirrhosis-associated complications. This article discusses the importance of a multidisciplinary approach in the treatment of HCC patients. Current recommendations for the treatment of cirrhotic patients with HCC are also reviewed.

**Key words:** cirrhosis, hepatocellular carcinoma, multidisciplinary approach

### introduction

Hepatocellular carcinoma (HCC) is currently the sixth most common solid malignancy and the third leading cause of cancer-related death worldwide [1–3]. The incidence of this condition has been steadily increasing over the past decade in Western countries, and the overall incidence of HCC worldwide is expected to continue increasing [1,2]. In Europe, the age-standardized incidence of HCC is higher in Southern regions than in Northern countries [4].

A close correlation between chronic liver disease and HCC exists; therefore, both conditions must be considered when making treatment decisions. In more than 80% of patients, HCC develops in a cirrhotic liver; it has been estimated that once cirrhosis is established, the annual risk of developing HCC ranges between 3 and 4% [2].

An early diagnosis of HCC is crucial to allow potentially curative treatment, with 5-year survival rates of up to 70% in patients who have one asymptomatic HCC and well-preserved liver function [5]. However, HCC is mostly diagnosed at a more advanced stage in the majority (~60–70%) of patients: in this case, prognosis is generally poor and until recently no systemic therapy was effective in prolonging survival [2].

The development of selective targeted drugs represented a major progress in the treatment of advanced HCC. In particular, Sorafenib (Nexavar®, Bayer), a multi-targeted tyrosine kinase inhibitor, was the first systemic agent to demonstrate a small, but significant, improvement in overall survival in patients with advanced HCC and well-preserved liver function [6,7]. Sorafenib is now recommended for patients with advanced HCC as first-line therapy and for patients not eligible to locoregional treatment [8] and is now considered, according to the recently published guidelines issued by the European Association for the Study of the Liver (EASL), as the treatment of HCC with the highest level of evidence and grade of recommendations [1].

Multiple variables affect the course of HCC and the response to treatment: they include liver function, performance status (PS) and tumour stage [9]. Patients with hepatitis B or hepatitis C virus infection carry also a higher risk of developing HCC: 85.5% of patients with HCC present with serologic evidence of infection due to one of these two viruses [9].

The presence of these confounding factors means that no single treatment strategy can be applied to all patients, and therefore therapy should be tailored to each patient’s needs [1,2,9–12]. Of note, specialists in gastroenterology, hepatology, hepatobiliary surgery, transplant surgery, interventional and diagnostic radiology, medical oncology, radiation oncology and nuclear medicine are involved in the management of HCC patients: therefore, it has been proposed that an integrated multidisciplinary approach can help optimize the management of patients [1,9–12]. In particular, since no specific guidelines exist to ensure the best care for HCC patients with cirrhosis, it is crucial to establish a close cooperation between hepatologists and oncologists, together with a cautious approach to decision-making for these patients [1,2].

This review aims to provide an overview of the current treatment strategies for the therapy of HCC and to discuss the importance of a multidisciplinary approach in this clinical setting. Current recommendations for the treatment of cirrhotic patients with HCC will be discussed as well.
defining and updating a treatment strategy for HCC patients according to their natural history

Staging classification systems are important for predicting prognosis in patients with HCC and guiding the therapeutic approach; however, a globally applicable staging system is still lacking. Given the complexity and heterogeneity of the disease, unidimensional systems such as the Child-Pugh, tumour–node–metastasis or PS classification do not allow prognostic accuracy and have limited usefulness in guiding therapy when used alone [9]. Therefore, multidimensional systems, which combine liver function parameters and cancer staging, have been proposed. The comparisons of a number of these systems indicate different prognostic stratification and prediction abilities, depending on the country and patient population studied [13–17].

Among these staging systems, the Barcelona Clinic Liver Cancer (BCLC), devised from the results of cohort studies and randomized clinical trials, is widely accepted and endorsed [9,18–20]. Differing from many of the proposed staging systems, the BCLC system has been externally validated [9,15,17] and is currently endorsed by both the American Association for the Study of Liver Diseases (AASLD) and the EASL [1,2,9].

This system includes different variables linked to tumour stage and extension, liver function, physical status and cancer-related symptoms to stage patients; in addition, it combines each stage with a survival rate and a treatment algorithm, as recently defined in the EASL guidelines (Figure 1) [1,2,9]. Patients classified as having early-stage HCC (BCLC-A), defined as a single nodule or three nodules <3 cm in diameter and a PS score of zero, are eligible to potentially curative therapies such as resection or transplantation. Patients with intermediate-stage HCC (BCLC-B) are asymptomatic (PS score, 0) with multinodular tumours but without vascular invasion or extrahepatic spread and are eligible for locoregional therapy, such as transarterial chemoembolization (TACE). Those with advanced-stage HCC (BCLC-C) are either symptomatic (PS score, 1–2) or have evidence of vascular invasion or extrahepatic spread and are eligible for Sorafenib. Finally, patients with terminal-stage HCC (BCLC-D) have either severe cancer symptoms (PS score, 3–4) or severely decompensated cirrhosis (Child-Pugh class C) and may receive symptomatic treatment only.

the importance of a multidisciplinary approach

Symptoms experienced by HCC patients are diverse and challenging to manage due to the complex interaction of tumour and underlying disease, both negatively affecting the patient outcome. To optimize care and to improve clinical outcomes, patients with advanced HCC should be managed by a multidisciplinary team (MDT), which includes specialists with different roles, expertise and functions [10–12]. The typical MDT comprises a medical oncologist, a hepatologist, a hepatobiliary and/or transplant surgeon, a diagnostic radiologist and/or an interventional radiologist (IR), nurses (either specialized or practitioner) and a pathologist [10]. In addition, we believe that general practitioners (GPs) and supportive care specialist could also be crucial for the MDT. These specialists form an ‘integrated network of care’, with the patient at the centre of the follow-up process (Figure 2).

It has been shown that a multidisciplinary approach helps communication among team members with specific skills, thereby improving patient outcomes [23,24]. The MDT allows for a standardized screening procedure and agreed-upon treatment protocols and helps to coordinate patient management. It also promotes the rapid transfer of clinical information among the members of the MDT, enhancing strong interpersonal working relationships [10].

The team functions best with frequent joint conferences, during which all aspects of the treatment plan are discussed [25]. The results of an observational study carried out in the United States indicated that the use of the MDT paradigm determined statistically significant benefits in the treatment of patients with advanced HCC [26]. In particular, the number of patients referred for treatment doubled; more patients were seen at an earlier stage of disease and the proportions of patients receiving curative treatment and palliative care increased substantially, from 6 to 19% and from 31 to 45%, respectively. The management by an MDT was also associated with a prolonged survival. Thus, the MDT provided marked improvements in clinical outcomes, showing that improved communication within the network of health care professionals with specialized skills optimizes the management of HCC patients.

The MDT members need to agree upon the diagnosis and staging and then proceed to define a treatment plan [10,26]. The specific contribution of each member of the MDT will depend upon the institution, the levels of expertise within the various departments and the disease stage of each patient. Therefore, it has been suggested that responsibilities should be traced and associated with every member contributing to the decision and providing a constant feedback on whether the end points were accomplished or not [26]. In addition, every therapeutic strategy made of many steps could present some features similar to other cases, and this could lead to worthwhile comparisons among different strategies. By acquiring new experience, arbitrary decisions will likely be reduced and the evidence will be gained to guide future cases [26].

We briefly discuss the specific roles and responsibilities of each specialist involved in the management and follow-up of the HCC patient, largely based on a recent excellent article published on this topic [10]. However, these descriptions are general and should be adapted to the specific local regulations and management approaches used in each country.

hepatologist

Hepatologists (or gastroenterologists/internal medicine specialists in some institutions) represent the first contact with the MDT. This specialist is responsible for the identification of patients at highest risk for HCC, for the treatment of the underlying liver disease (including antiviral treatments, which
may have a role in the modulation of HCC progression), for advising patients on lifestyle, for monitoring disease progression, for arranging surveillance plans and for diagnosing HCC. In addition, the hepatologist should assess underlying liver function, monitor treatment complications and has a role in referring patients for potential liver transplantation.

**oncologist**

The medical oncologist has usually the responsibility to initiate systemic or targeted therapy (also in the adjuvant setting) in eligible patients. However, a close interaction between the hepatologist and the oncologist is necessary to maintain a strict monitoring of the underlying liver disease and optimize the clinical outcomes. Oncologist’s responsibilities also include the management of side-effects induced by systemic drugs.

**radiologist/IR/specialist in nuclear medicine**

The radiologist, either diagnostic or interventional, is a key figure in the MDT given the crucial importance of imaging techniques in the diagnosis and treatment of HCC. A careful radiological evaluation plays in fact a key role in the decision process performed by the MDT for the selection of the more appropriate treatment of each individual patient. In Figure 3, two cases of MDT decision following radiological evaluation are reported.

The main responsibility of the diagnostic radiologist is to evaluate imaging techniques (CT, MRI, PET) in order to establish a definitive diagnosis; according to EASL Guidelines, imaging has a central role in patients with very high levels of serum α-fetoprotein. In addition, radiologists help the staging and management of disease and assist in the evaluation of the effectiveness of different treatments.

The IR has a central role in the management of patients with intermediate-stage (BCLC-B) HCC. The IR may also work to downstage patients and make them eligible for surgical interventions. Moreover, the IR could be occasionally involved in the diagnosis of HCC by obtaining tumour tissue samples, as well as by handling and interpreting imaging protocols.
Once a definitive diagnosis of HCC is established, the IR interacts with the other members of the MDT in selecting and performing other ablative treatments. In some centres, hepatologists or hepatobiliary surgeons perform these interventional procedures.

**Hepatobiliary and/or transplant surgeons**

The main role of the hepatobiliary/transplant surgeon is to evaluate whether a tumour is resectable and to remove any primary tumour, in line with current guidelines [27].

**Nurses**

Nurses play a role in arranging diagnostic procedures and appointments with several specialists and have an important role in the management of any adverse event potentially associated with the use of systemic treatments. Moreover, they inform and guide patients and their families.

**Pathologists**

The pathologist retains the responsibility of assessing the stage of progression of HCC. Of note, it has been recently suggested
markers. A pathologist might expand to include the evaluation of tissue expression. It is important to note that in the future the role of pathologist might expand to include the evaluation of tissue markers.

**general practitioners**

In line of principle, the GP does not act strictly within the MDT. The main role of this specialist is the identification of both risk factors and symptoms or signs suggestive of liver disease to get an early detection of chronic liver disease. This favours the referral of patients to a liver specialist for a more complete clinical assessment. The close interaction between the GPs and the different specialists has also a central role in the direct surveillance of patients at greatest risk for HCC.

In addition, GPs are likely to see patients following hospital discharge. Therefore, GPs are ideally positioned to monitor the treatment outcomes and any potential side-effect. GPs should also be involved in diagnosis and treatment of unrelated co-morbidity in HCC patients and to manage any adverse reaction associated with treatments of these conditions.

**supportive care specialists**

The palliative care physician manages pain and therefore has a central role in increasing patients’ quality of life. In patients with HCC, pain is generally determined by metastases to different sites (bone, brain, lymph nodes and other) and may be alleviated by radiation therapy or pharmacotherapy [10].

**hepatology for the oncologists: the management of cirrhotic patients with HCC**

The concomitant presence of HCC and cirrhosis symptoms require interventions involving different competences from liver surgery to supportive care: by globally facing the complex expressions both of HCC and cirrhosis, a multidisciplinary approach assures the best choices and the proper management in each phase of the disease. We briefly discuss in this paragraph the management of cirrhosis in HCC patients, mainly on the basis of our clinical experience and of an excellent review on this topic [30].

Cirrhosis represents a common and relevant risk factor for HCC, which results from several conditions affecting the liver [5]. In clinical practice, cirrhosis is assessed through a complex evaluation: the Child–Pugh score, also known as Child–Turcotte–Pugh (CTP) [30], and the model for end-stage liver disease (MELD) score [31] represent useful tools and are widely used by hepatologists. In particular, the Child-Pugh score has a crucial importance in the assessment and staging of cirrhosis (Table 1) [30].

Eventually, cirrhosis may lead to the development of signs of decompensation and/or several complications such as oesophageal or gastric varices, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome (HRS) and hepatic encephalopathy: their onset may result in a marked worsening of prognosis of HCC patients (Figure 4).

**varices**

Gastro-oesophageal varices can be found in ~50% of cirrhotic patients. Their frequency increases with the severity of liver disease; although only 40% of CTP class A patients have varices, they are present in 85% of CTP class C subjects [32]. Patients with gastro-oesophageal varices can develop haemorrhage, at the rate of 12–15% per year: of note, the mortality rate for each episode of variceal haemorrhage is ~15–20%. Therefore, the primary prevention of variceal haemorrhage is one of the main preventive measures for the HCC patient with compensated cirrhosis.

Three factors identify patients at a high risk of variceal haemorrhage: large variceal size, red wale marks on the varices and advanced liver disease (CTP class B or C) [33]. This event can presently be managed by two different therapies: non-selective beta-blockers (NSBBs) and endoscopic variceal ligation (EVL). NSBBs (e.g. propranolol) decrease portal pressure by reducing the cardiac output and, more importantly, the portal blood inflow through splanchnic vasoconstriction. Results collected in a randomized trial show that, in patients with varices, NSBBs significantly reduce by 10% the incidence of first variceal haemorrhage (from 25 to 15%) over a 24-month follow-up [33]. The efficacy of NSBBs in the prevention of the first variceal haemorrhage is more evident in patients with medium-/large-sized varices (incidence of 14 versus 30% reported in controls). Mortality was shown to

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**Table 1. Child–Turcotte–Pugh (CTP) classification of the severity of cirrhosis (reproduced from [30], with permission)**

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<tr>
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<td>&lt;4</td>
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</tr>
<tr>
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PT, prothrombin time; INR, international normalized ratio.

*5–6 points, CTP class A; 7–9 points, CTP class B; 10–15 points, CTP class C.

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that the histopathological definition of the tumour is imperative both for an appropriate therapy and for an accurate prognostic evaluation, even if the actual importance of histopathological definition has been debated [28,29]. It may be anticipated, however, that in the future the role of pathologist might expand to include the evaluation of tissue markers.

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be significantly lower in patients receiving this therapy versus controls [34].

EVL consists of placing rubber bands around varices until obliteration. Several randomized trials have compared EVL with the NSBB for the treatment of patients with large varices. The results of two meta-analyses indicate that EVL is associated with a small, although significant, advantage in terms of incidence of first variceal haemorrhage, without any difference in mortality [35,36]. However, a more recent meta-analysis showed that the estimated effect of EVL reported in some trials may have been biased and was dependent upon the duration of follow-up, with a shorter follow-up associated with a more positive effect [37]; the same meta-analysis suggested that NSBB and EVL are equally effective. On these bases, a consensus panel concluded that both NSBB and EVL are effective in the prevention of the first variceal haemorrhage in patients with medium/large varices: therefore, the choice among these treatments should be based on patient characteristics and on preferences, local resources and expertise of each centre [38]. In patients with medium-/large-sized varices at high risk of bleeding (e.g. CTP class C, red wale marks), either NSBB or EVL can be used, whereas in patients with medium/large varices not at high risk of haemorrhage, NSBBs are preferred; in these subjects, EVL should be considered in the case of contraindications, intolerance or non-compliance to NSBB. Lastly, in patients with small varices that are at a high risk of bleeding (red wale marks and/or CTP class C), NSBBs should be recommended, given the technical difficulties in performing EVL.

Due to the high mortality rate, acute variceal haemorrhage should be promptly managed, with the aim to provide effective resuscitation, early diagnosis, control of bleeding and prevention of complications (Table 2) [30].

### ascites

Ascites represents one of the most frequent complications of cirrhosis. The 5-year cumulative rate of ascites in compensated cirrhotic patients is ~30% [39]. Once ascites develops, the 1-year survival rate is ~50% versus the 1-year survival rate of

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**Table 2.** Diagnosis and management strategy of patients with acute variceal haemorrhage (reproduced from [30], with permission)

<table>
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<tr>
<th>Diagnosis</th>
<th>Any of the following findings on upper endoscopy carried out within 12 h of admission: active bleeding from a varix or Stigmata of variceal haemorrhage (white nipple sign) or Presence of gastro-oesophageal varices without another source of haemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>General management</td>
<td>Cautious transfusion of fluids and blood products, aiming to maintain a haemoglobin of ~8 g/dl. Antibiotic prophylaxis (3–7 days) with: ciprofloxacin 500 mg b.i.d. (p.o) or 400 mg b.i.d. (i.v.) or ceftriaxone 1 g/day (i.v.) particularly in facilities with known quinolone resistance and in patients with two or more of the following: malnutrition, ascites, encephalopathy, serum bilirubin &gt;3 mg/dl</td>
</tr>
<tr>
<td>Specific initial management</td>
<td>Pharmacological therapy initiated as soon as diagnosis is suspected: octreotide 50 µg i.v. bolus followed by continuous infusion 50 µg/h (3–5 days) and endoscopic therapy (ligation preferable) carried out at time of diagnostic endoscopy (carried out within 12 h of admission)</td>
</tr>
<tr>
<td>Rescue management</td>
<td>Considered in patients with bleeding oesophageal varices who have failed pharmacological + endoscopic therapy or in patients with bleeding gastric fundal varices who have failed one endoscopic therapy: TIPS or shunt therapy (CTP A patients where available)</td>
</tr>
</tbody>
</table>

b.i.d., twice a day; CTP, Child–Turcotte–Pugh; i.v., intravenous; p.o., orally; TIPS, transjugular intrahepatic portosystemic shunt.
The most common infections in cirrhosis are particularly poor in patients who develop refractory ascites. >90% in patients with compensated cirrhosis. The prognosis is.

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should be performed in any patient with cirrhosis and ascites who: (i) is admitted to the hospital; (ii) develops symptoms or signs suggesting SBP (abdominal pain or tenderness on palpation, fever or chills) and (iii) presents a worsening of renal or liver function [43]. The diagnosis of SBP is established with an ascites polymorphonuclear (PMN) cell count of >250/mm³. However, antibiotic treatment should be started even before the results of microbiological cultures become available.

The most widely used antibiotic is i.v. cefotaxime, which leads to SBP resolution in ~90% of the patients; however, the efficacy of this molecule has been recently questioned, especially in the treatment of nosocomial SBP [44], due to the presence of multidrug-resistant organisms in this setting. Other third-generation cephalosporins, such as ceftriaxone, or the combination of i.v. amoxicillin and clavulanic acid may be used. A control paracentesis carried out 48 h after the initiation of antibiotic therapy is recommended to assess the response to therapy, unless a clinical improvement is obvious. If the PMN count has not decreased by at least 25%, antibiotic coverage should be broadened and investigations to rule out secondary peritonitis may be initiated. Antibiotic treatment can be safely discontinued if the ascites PMN count decreases to <250/mm³: this goal is reached in a mean period of 5 days [45].

Intravenous albumin is an important adjuvant to antibiotic therapy in patients with SBP. This therapy improves the decreased arterial blood volume due to SBP, which leads to renal dysfunction. In addition, albumin may also act by binding endotoxin and reducing cytokine and nitric oxide levels. The efficacy of albumin as an adjuvant to antibiotic therapy is supported by the results of a randomized, controlled trial comparing cefotaxime–albumin with cefotaxime alone: patients who received albumin had significantly lower rates of renal dysfunction (10 versus 33%), in-hospital mortality (10 versus 29%) and 3-month mortality (22 versus 41%) [46].

**hepatorenal syndrome**

HRS is a type of renal failure which occurs in patients with cirrhosis and severe liver dysfunction who have serum creatinine >1.5 mg/dl; this condition is more frequent in patients with refractory ascites. HRS has been divided into two types; HRS-1, a rapidly progressive type of acute renal failure usually occurring in hospitalized patients, and HRS-2, a slower type of renal failure usually found in outpatients with refractory ascites. The prognosis of HRS-1 is very poor (median survival 2 weeks) [47], whereas HRS-2 is associated with a relatively prolonged survival (~6 months) [48]. Presently, therapy is recommended only for patients with HRS-1. Liver transplantation is the only therapy able to provide a long-term survival. Several vasoconstrictors, including octreotide, terlipressin, noradrenaline, the combination of octreotide and midodrine or vasopressin have been used as a bridge to transplantation. In patients with HRS-1, diuretics should be discontinued and intravascular volume should be expanded with fluids, such as saline solutions and albumin.

**hepatic encephalopathy**

Hepatic encephalopathy (HE) is a reversible neuropsychiatric syndrome which can accompany decompensated liver disease.

**bacterial peritonitis**

The most common infections in cirrhosis are ‘spontaneous’ peritoneal infections, also known as SBP. These infections occur in 10–20% of hospitalized patients with cirrhosis and ascites and are more frequent in those with severe liver disease. Provided an early recognition of the disease and a prompt antibiotic therapy, in-hospital mortality from an episode of SBP is ~10–20% [42]. Early diagnosis is crucial to effectively manage SBP. It is recommended that a diagnostic paracentesis

>90% in patients with compensated cirrhosis. The prognosis is particularly poor in patients who develop refractory ascites.

Until now, treatment of ascites has not demonstrated to improve survival. However, treating ascites is helpful, in order to improve the quality of life and reduce the incidence of spontaneous bacterial peritonitis.

The diagnosis of ascites is based on physical examination and should be confirmed by abdominal ultrasound (US) and/or paracentesis. Despite the marked worsening of prognosis in patients with this condition, ascites should not be regarded as an emergency—unless the fluid becomes infected—and therefore treatment of patients with cirrhosis and ascites should be based on the administration of oral diuretics in a stepwise manner. In addition, treatment with diuretics should only be initiated in a ‘stable’ cirrhotic patient, i.e. in a patient who does not show any complication like GI haemorrhage, bacterial infection and renal dysfunction, or in whom these complications have been resolved.

Sodium restriction is recommended for all cirrhotic patients who develop ascites. Although in line of principle dietary sodium should be restricted to levels lower than urinary sodium excretion, sodium restriction to 88 mEq/day (i.e. 2 g of sodium per day or 5.2 g of dietary salt per day) can be considered a realistic goal, particularly in an outpatient setting. Most patients will require the addition of diuretics to sodium restriction: spironolactone is currently considered the diuretic of choice. Even though loop diuretics, such as furosemide, are more potent natriuretic agents, the results of randomized, controlled trials have demonstrated that spironolactone is more effective than furosemide alone in the treatment of cirrhotic ascites [40,41]. Therapy with spironolactone should be initiated with a single daily dose of 50–100 mg, and then dosage should be increased in a stepwise manner up to a maximum of 400 mg/day. Since the effect of spironolactone can be observed only after some days of treatment, this molecule can be administered in a single daily dose, and the dose should be adjusted only every 3–4 days.

Clinicians should be aware about the nutritional status of patients on sodium restriction, as the poor taste of a salt-restricted diet may lead to an inadequate food intake. In these cases, the liberalization from sodium restriction and the addition of diuretics can be preferred to a further impairment of the already compromised nutrition of the cirrhotic patient with ascites.

In patients who develop refractory ascites, i.e. ascites resistant to diuretic therapy, large-volume paracentesis should be considered; in this case, albumin must be added if >5 L of fluid are removed.

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Intravenous albumin is an important adjuvant to antibiotic therapy in patients with SBP. This therapy improves the decreased arterial blood volume due to SBP, which leads to renal dysfunction. In addition, albumin may also act by binding endotoxin and reducing cytokine and nitric oxide levels. The efficacy of albumin as an adjuvant to antibiotic therapy is supported by the results of a randomized, controlled trial comparing cefotaxime–albumin with cefotaxime alone: patients who received albumin had significantly lower rates of renal dysfunction (10 versus 33%), in-hospital mortality (10 versus 29%) and 3-month mortality (22 versus 41%) [46].

**hepatorenal syndrome**

HRS is a type of renal failure which occurs in patients with cirrhosis and severe liver dysfunction who have serum creatinine >1.5 mg/dl; this condition is more frequent in patients with refractory ascites. HRS has been divided into two types; HRS-1, a rapidly progressive type of acute renal failure usually occurring in hospitalized patients, and HRS-2, a slower type of renal failure usually found in outpatients with refractory ascites. The prognosis of HRS-1 is very poor (median survival 2 weeks) [47], whereas HRS-2 is associated with a relatively prolonged survival (~6 months) [48].

Presently, therapy is recommended only for patients with HRS-1. Liver transplantation is the only therapy able to provide a long-term survival. Several vasoconstrictors, including octreotide, terlipressin, noradrenaline, the combination of octreotide and midodrine or vasopressin have been used as a bridge to transplantation. In patients with HRS-1, diuretics should be discontinued and intravascular volume should be expanded with fluids, such as saline solutions and albumin.

**hepatic encephalopathy**

Hepatic encephalopathy (HE) is a reversible neuropsychiatric syndrome which can accompany decompensated liver disease.
Neuropsychiatric and psychometric tests in patients with significant liver dysfunction and no other neuropsychiatric diseases may reveal performance abnormalities despite normality of conventional neurologic examination. HE has varying degrees of severity, which range from subclinical to overt HE [49]. Patients with HE display a characteristic spectrum of mental and motor changes, which are frequently divided into stages. They range from mild confusion, agitation, sleep disorders, fine tremor, asterixis to marked confusion, incomprehensible speech and lack of muscular tone and coma.

As the development of HE is not lethal by itself, the management of this condition is focused on the treatment of overt HE rather than on its prophylaxis, although HE can be prevented by limiting the exposure to common precipitants (e.g. sedatives). Commonly used interventions for HE include the correction of primary causes like bleeding, ascites, infection, a reduction in the production and absorption of proteins and medical therapy (Table 3).

Table 3. Treatment recommendations for HE

<table>
<thead>
<tr>
<th>Correction of causes</th>
<th>Intestinal haemorrhages</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Misuse of diuretics/ sedatives</td>
</tr>
<tr>
<td></td>
<td>Ipokaliemia/alkalosis/ hypoxia</td>
</tr>
<tr>
<td></td>
<td>High protein intake</td>
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<tr>
<td></td>
<td>Stipiosis/infections</td>
</tr>
<tr>
<td></td>
<td>Portosystemic anastomosis</td>
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<tr>
<td></td>
<td>Worsening of liver dysfunction</td>
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<tr>
<td></td>
<td>Kidney dysfunction</td>
</tr>
<tr>
<td>Reduced production and absorption of proteins</td>
<td></td>
</tr>
<tr>
<td>Medical therapy</td>
<td></td>
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<tr>
<td>Lactulose</td>
<td></td>
</tr>
<tr>
<td>Intestinal poorly adsorbable antibiotics</td>
<td></td>
</tr>
<tr>
<td>i.v. glucose associated with: l-ornitine, l-aspartate</td>
<td></td>
</tr>
<tr>
<td>The association with branched-chain amino acids has also been explored, but the efficacy of these molecules needs further investigation</td>
<td></td>
</tr>
</tbody>
</table>

conclusions and open issues

HCC is a complex disease, often associated with several underlying conditions that worsen the prognosis and make the clinical management more challenging. Therefore, current recommendations emphasize the importance of a multidisciplinary approach for the management of HCC patients. In particular, the MDT should include several different specialists, with different expertise (oncologists, hepatologists, radiologists/IRs, liver and transplant surgeons, nurses, pathologists, GPs, supportive care specialists). We believe that multidisciplinary discussions among specialists provide the best setting to perform treatment decisions, even if each single specialist should take the full responsibility for the clinical decision in his/her own area of expertise. The importance of a multidisciplinary approach is particularly evident in the prevention and management of the complex cirrhosis-associated complications, which may significantly worsen the prognosis in HCC patients. The MDT plays also a crucial role in tailoring the therapy to the specific needs of each single patient, taking into account international guidelines, specific local regulations, in order to increase the clinical benefits of therapy and improve patient’s quality of life.

Remarkable advances have been reached in the treatment of HCC and associated diseases in latest years. However, further evidence is required to optimize the outcomes in some classes of patients, such as those without underlying cirrhosis and those who failed medical treatment.

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references
