

Mistakes in decompensated liver cirrhosis and how to avoid them

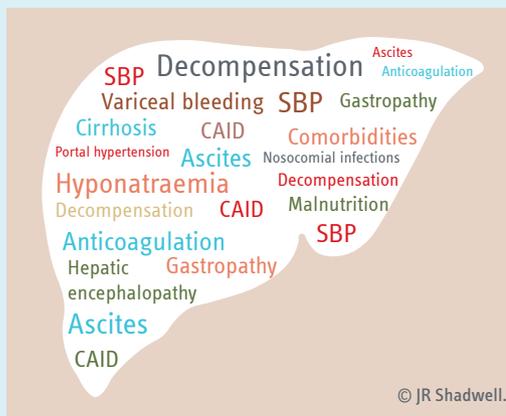
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Patients with early stages of chronic liver disease and even those with compensated cirrhosis can present without any clinical symptoms, which means that liver disease and ongoing liver damage can remain unidentified for many years. However, morbidity and mortality drastically increase once the stage of 'decompensated cirrhosis' has been reached.^{1,2} Decompensated cirrhosis describes the development of clinically overt signs of portal hypertension and/or impairment of hepatic function (e.g. variceal

bleeding, ascites or overt hepatic encephalopathy). The first hepatic decompensation event significantly increases the risk that further complications of liver cirrhosis and decompensation episodes will occur.² Moreover, individuals who have advanced stages of liver cirrhosis are four times more susceptible to infection, which is, in turn, the most frequent trigger of hepatic decompensation.^{3,4}

Optimal management is required to sufficiently treat patients who have decompensated liver cirrhosis, to protect them from future decompensation episodes and prevent further deterioration of hepatic function. However, decompensated liver cirrhosis is a highly complex disease and there are many pitfalls that may occur with regard to comorbidities, management of acute complications and appropriate medication.

In this article, we cover some of the mistakes frequently made when managing decompensated liver cirrhosis and ways to prevent them. The discussion is based on the available evidence and our personal clinical experience.



usually recommended when drugs that markedly increase the risk of peptic ulcers (i.e. high-dose treatment with steroids) are being co-administered. In patients with cirrhosis, PPIs are often used after band ligation of oesophageal varices, which reduces the size of post-ligation ulcers; however, PPIs do not significantly reduce the risk of bleeding in these cases. Many physicians prescribe PPIs to prevent bleeding from gastro-oesophageal varices or portal hypertension gastropathy, while no clear evidence of a beneficial impact is available.²

Even when there is a clear indication for PPI treatment, it is usually only the case for a limited period of time. Despite this, many physicians struggle to withdraw PPI treatment and they often remain a daily medication for years, even if there is no longer a proper indication.

Moreover, PPIs are also often used at an inappropriate dosages. High dosages are warranted mainly for gastric ulcers. For all other indications lower dosages are usually sufficient. In patients who have decompensated cirrhosis high PPI dosages are generally not recommended given the risk of drug metabolite accumulation because of reduced hepatic clearance of the drug.

Mistake 1 Indiscriminate use of proton pump inhibitors

Proton pump inhibitors (PPIs) are some of the most frequently prescribed drugs worldwide.⁵ They are widely considered to be safe and, for the general population, associated with few or no side effects even after long-term use.⁶ By contrast, safety concerns have been raised regarding the usage of PPIs in patients with liver cirrhosis.

An increased incidence of hepatic encephalopathy has been observed in patients with liver cirrhosis who are taking PPIs,^{7,8} with some studies describing the link as dose dependent.^{9,10} Moreover, PPI usage has been associated with a higher risk of bacterial infections (i.e. spontaneous bacterial peritonitis [SBP])^{7,11} and adverse outcomes for patients with SBP.^{9,12} However, the data are conflicting. In our own cohort, we documented an increased short-term risk

of developing acute kidney injury (AKI) and a significantly increased 28-day mortality rate among SBP patients who took a PPI, especially for those taking a high daily dose (e.g. >40 mg/d pantoprazole).⁹ A possible explanation for such adverse effects might be an unfavourable change in a patient's gut microbiota. Alterations of the gastrointestinal microbiota have been linked to PPI use as a result of their ability to lower gastric acid output.¹³

While the debate continues about the extent to which PPIs actually increase the incidence of severe events in patients with advanced cirrhosis, they should be given with care: PPIs are overused in this population despite the frequent lack of a clear treatment indication (e.g. symptomatic reflux disease, peptic ulcers and *Helicobacter pylori* eradication)—up to 85% of patients have a PPI in their regular medication.⁹ In addition, treatment is

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In summary, we highly suggest that both the treatment indication and the dosage of PPI be critically examined. High PPI dosages should be avoided, especially in those at risk of SBP and/or with advanced hepatic impairment.

Mistake 2 Inappropriate use of nonselective β -Blockers

In recent years, there has been intense debate about the therapeutic window for nonselective β -blockers (NSBBs) in patients with liver cirrhosis.^{14,15} Consequently, many physicians are uncertain about the appropriate use of NSBBs, while clear treatment algorithms are often lacking. Issues in this setting include stopping indicated NSBB treatment because of exaggerated safety concerns or giving the wrong dosage and/or type of NSBB.

In general, NSBBs can be considered safe and are associated with improved outcomes in patients with significant portal hypertension.¹⁴ They have been associated with a lower rate of hepatic decompensation, which is suggested to decrease the incidence of SBP, while they have also been shown to reduce the risk of variceal bleeding and to be linked to improved survival.¹⁶⁻¹⁹ At present, their only established

treatment indications remain primary and secondary prophylaxis of variceal bleeding.² However, a prospective randomized trial has demonstrated beneficial effects of NSBBs for patients who have portal hypertension even in the absence of varices.²⁰

Propranolol and carvedilol are the most widely used NSBBs in patients with cirrhosis. Unlike propranolol, carvedilol inhibits α_1 -signaling and is considered to be more effective at lowering portal pressure.^{21,22} The higher efficacy of carvedilol might, however, be accompanied by more pronounced lowering of systemic blood pressure and, theoretically, the potential to impair renal blood supply.²¹

General safety concerns raised regarding the use of any NSBB in patients with advanced stages of cirrhosis, as indicated by refractory ascites and/or SBP,^{23,24} have not been confirmed by other studies and may be related to high NSBB doses and/or a poor haemodynamic status.^{19,25-27} In one study of patients with SBP, only a high dose (180 mg/d) of propranolol decreased survival, whereas a low dose (80 mg/d) improved survival.²⁵ In our own cohort, a low dose of NSBB was associated with improved survival of patients with decompensated liver cirrhosis and ascites,

regardless of the presence of SBP or acute-on-chronic liver failure (ACLF) unless the patient suffered from severe hypotension (mean arterial pressure [MAP] <65 mmHg and/or systolic arterial pressure <90 mmHg).¹⁹

In our opinion, several factors (including the stage of liver disease) should be considered for safe use of NSBBs. Patients who have advanced cirrhosis and ascites and/or are at risk of hepatorenal syndrome might be better treated with propranolol first. In general, low doses of carvedilol and propranolol should be preferred for those with advanced cirrhosis as both drugs are metabolized in the liver—higher doses may lead to accumulation and adverse systemic effects. Using more than 80 mg/d of propranolol is not recommended (i.e. in those with refractory ascites).² In patients at high risk of variceal bleeding but with preserved liver function carvedilol might be the better treatment choice.

Deciding when to discontinue an NSBB might be better based on haemodynamic status and/or signs of adverse effects (e.g. renal impairment and/or hypotension) rather than a clinical status such as ascites or SBP (figure 1). Taking a cautious approach regarding the NSBB dose is supported by other studies. One study with a propensity matched cohort reported increased survival in patients with therapy-refractory ascites who were taking an NSBB. Another study reported increased survival in patients with liver cirrhosis and ACLF who were taking an NSBB. Both studies used relatively low NSBB doses within their cohorts.^{26,27}

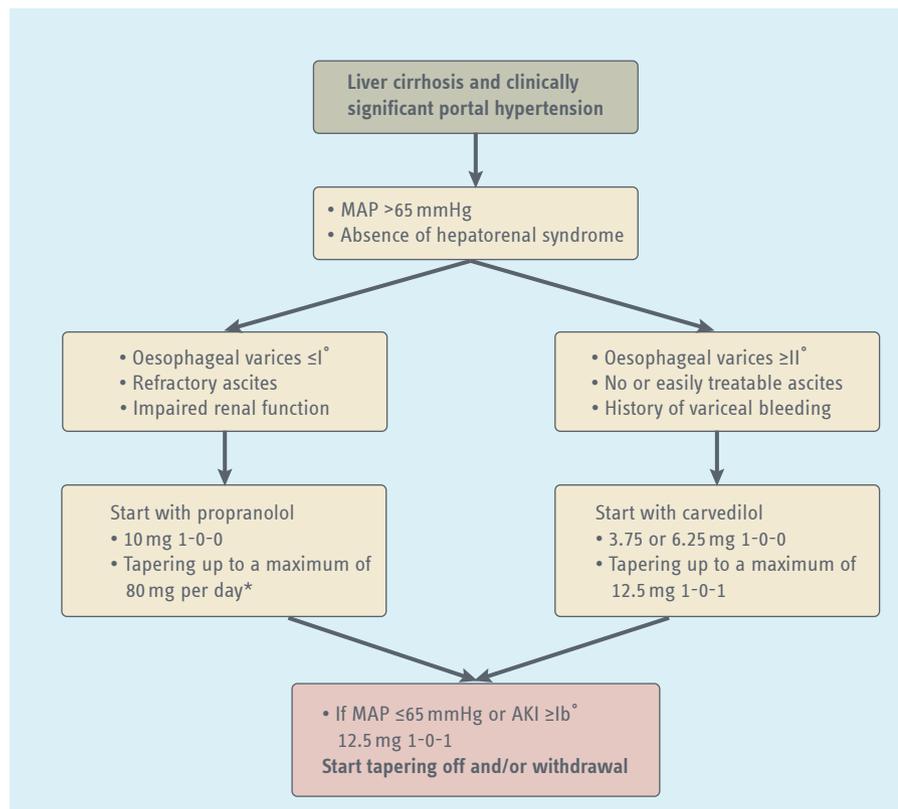


Figure 1 | Discontinuation of nonselective β -blockers. Haemodynamic status and/or signs of adverse effects (e.g. renal impairment and/or hypotension) might be better used to decide when to discontinue nonselective β -blockers, rather than clinical status (e.g. ascites or SBP). AKI, acute kidney injury; MAP, mean arterial pressure.

Mistake 3 Insufficient management of nosocomial infections

Individuals with liver cirrhosis are at a particularly high risk of developing a nosocomial infection. Considerable alterations of various parts of the immune system in patients with advanced cirrhosis (cirrhosis-associated immune dysfunction [CAID]) increase the risk of infection four times.⁴ Infections often act as a trigger for other severe complications of cirrhosis (e.g. renal impairment, gastrointestinal bleeding or ACLF) and are associated with 4–5 times increased mortality.^{2,4,9}

Timely diagnosis of infection is key, but this can be challenging in patients with cirrhosis, since early symptoms can be subtle and the levels of laboratory markers (e.g. CRP) misleading. As such, diagnosis of infection is often delayed, resulting in further clinical deterioration of the patient. Clinical suspicion and experience are of paramount importance—any worsening of a patient's clinical appearance should raise suspicion of an

infection. The presence of bacterial infection should always be ruled out systematically in these cases (e.g. by performing a paracentesis, urine analysis and physical examination).

Nosocomial infections are associated with an even worse prognosis than community-acquired infections. This may at least in part be explained by a higher prevalence of multidrug-resistant bacteria (MDRB), which can decrease the effectiveness of the initial antibiotic regimen and dramatically impact survival.^{28,29} The hazard of MDRB in patients with cirrhosis and nosocomial infections has been widely underestimated in the past. Several centres followed an antibiotic strategy that only considered the site of infection and did not adequately address the risk of MDRB associated with previous exposure to antibiotic substances and nosocomial infections.³⁰

Two multicentre studies have independently documented a high MDRB prevalence among patients with cirrhosis of 31–40%,^{28,29} and the prevalence of MDRB in this population has been increasing over the past 5–10 years.²⁹ Thus, a broad-spectrum antibiotic might be preferable for the treatment of patients with cirrhosis and nosocomial infections. However, uncritical use of broad-spectrum antibiotics may, in turn, lead to an increase in MDRB. Furthermore, MDRB prevalence differs widely between countries, regions and even individual treatment centres within the same area. Close microbiological surveillance at a local level and individual therapeutic strategies, therefore, seem necessary to maximize treatment efficacy while minimizing the further development of MDRB.

In summary, differentiation between nosocomial and community-acquired infections and the overall risk for MDRB must always be considered when selecting the antibiotic treatment.

Mistake 4 Delaying paracentesis in patients with ascites

SBP is the most frequent type of infection in patients with cirrhosis and is associated with a 30-day mortality of up to 20–30%.² While clinical symptoms are frequently rather unspecific, prompt and specific management is required, including adequate empiric antibiotic treatment plus albumin substitution. Analysis of ascitic fluid is, at present, the only valid tool for diagnosing or ruling out SBP. Current EASL guidelines therefore recommend that diagnostic paracentesis is carried out in every patient with cirrhosis and ascites at the time of hospital admission without delay, particularly in cases of gastrointestinal bleeding, encephalopathy and worsening

of liver and/or renal function.² Despite this recommendation, paracentesis is often delayed. Sometimes physicians do not consider SBP in the absence of typical signs of infection. Frequently, concerns about the safety of the invasive procedure delay paracentesis.

Patients with decompensated liver cirrhosis often present with marked alterations of routinely measured coagulation parameters, such as international normalised ratio (INR) and partial thromboplastin time (PTT). In addition, platelet count might be decreased, especially in those with severe portal hypertension. If the platelet count is below $50 \times 10^3/\mu\text{l}$ and/or the INR is above 1.5, it is not unusual to supplement platelets, fresh frozen plasma or coagulation factors before paracentesis is performed. However, it is quite difficult to determine the actual coagulation status based on such routine coagulation tests, which only reflect procoagulant factors. In advanced cirrhosis both procoagulant and anticoagulant factors are significantly reduced.² Thus, routine supplementation of procoagulant factors may even lead to a considerable imbalance of the coagulation system towards a higher risk of thrombosis.

The safety of paracentesis in patients with cirrhosis has been proven in large data sets. Importantly, this includes patients with an increased INR and/or a decreased platelet count. The risk of major bleeding is, in general, very low as long as an ultrasound is performed to rule out the presence of large vessels at the puncture site.³¹

The current EASL guidelines strongly recommend against routine supplementation of platelets or any other procoagulant factors unless the patient suffers from disseminated intravascular coagulation (DIC).² If the platelet count is below $20 \times 10^3/\mu\text{l}$ supplementation can be considered; however, it is of major importance that paracentesis is not further delayed afterwards. In 2014, a study compared early paracentesis (<12 h after hospital admission) with delayed paracentesis (12–72 h after admission) in patients with cirrhosis. Individuals undergoing delayed paracentesis had a longer hospital stay and significantly higher mortality—it was calculated that mortality increased by 3% per hour delay.³²

Mistake 5 Underestimating the impact of comorbidities on the clinical course

Around 40% of patients with liver cirrhosis have other comorbidities that increase overall mortality.³³ Some comorbidities have a considerable impact on prognosis and are associated with severe complications in patients with decompensated cirrhosis.

However, while treating cirrhosis-associated complications, the impact and adequate treatment of relevant comorbidities is often neglected.

Patients with decompensated liver cirrhosis and reduced systolic cardiac function have a higher risk of hepatorenal syndrome and worse survival compared with patients who have sustained cardiac function.³⁴ Although it is tempting to suppose that improving cardiac function would improve survival, treatment can be challenging, as some routine therapeutic options may not be suitable for patients with cirrhosis. Thus, a multidisciplinary approach could be useful.

One of the most prevalent and highly relevant comorbidities in patients with cirrhosis is type 2 diabetes mellitus (T2DM).^{35,36} Indeed, numerous studies have associated T2DM with increased mortality, an increased incidence of hepatic encephalopathy and an overall increase in the likelihood of decompensation.^{37,38} We recently found an association between the degree of glycaemic control and the incidence of SBP in patients with ascites.³⁹ Physicians should, therefore, be aware that patients with T2DM are at an increased risk of developing complications of cirrhosis. However, in the presence of impaired hepatic function, T2DM must be considered as a far more complex disease and specific therapeutic target values may need to be established in the future.

Mistake 6 Neglecting the role of hyponatraemia

Hyponatraemia is frequently present in patients with liver cirrhosis and it is the most common type of electrolyte abnormality to affect patients with decompensated liver disease (up to 50%). In general, two different types of hyponatraemia may occur—hypervolaemic or hypovolaemic. Hypovolaemic hyponatraemia is most frequently caused by excessive use of diuretics. However, in patients with decompensated liver cirrhosis it is far more usual for hyponatraemia to be accompanied by a rather hypervolaemic status, indicated by the presence of ascites and/or peripheral oedema.^{40,41}

The pathological mechanism underlying hypervolaemic hyponatraemia is driven by portal hypertension, which leads to translocation of bacteria and/or bacterial products from the gut (pathogen-associated molecular patterns; PAMPs) and an increased concentration of free nitric oxide, resulting in systemic vasodilation. Systemic vasodilation can be accompanied by insufficient perfusion of the kidneys. Renal hypoperfusion induces activation of the renin-angiotensin-aldosterone system (RAAS),

the sympathetic nervous system and antidiuretic hormone (ADH) distribution, which leads to reabsorption of sodium but excessive retention of free water in the kidneys. The hypervolaemic state might be further worsened by acute kidney injury caused by vasoconstriction of the renal artery, leading to further renal hypoperfusion and/or direct toxic injury related to portal hypertension.²

Physicians often fail to initiate specific treatment and monitoring for hyponatraemia, as its role remains widely underestimated. Hyponatraemia is an indicator of portal hypertension and well known to be associated with a particularly poor prognosis independent of the MELD score.⁴² In addition, hyponatraemia is also directly linked to clinical symptoms that can have a considerable impact on quality of life. Patients with acute, severe hyponatraemia may present with obvious clinical signs, but chronic hyponatraemia, which is typically seen in patients with cirrhosis, may appear asymptomatic at first sight.⁴¹ In patients with cirrhosis, hepatic encephalopathy can be worsened or might even be triggered by hyponatraemia.⁴³

Fluid and sodium restriction are the initial approach to treatment of hypotonic hyponatraemia in patients with liver cirrhosis, being mindful that fluid restriction is a torment for patients, as anadipsia develops due to ADH release. Furthermore, controlling fluid and sodium restriction can be challenging in routine clinical practice for the treating medical staff. Both of these factors result in low therapy adherence. Nonetheless, fluid restriction to 1 L/d remains one of the most effective therapies.² Additional treatment steps include correction of hypokalaemia if present (possibly caused by increased gastrointestinal losses or by diuretic therapy) and use of midodrine to reach a MAP >80 mmHg in patients with persistent hypotension.⁴⁴ Also, treatment with albumin infusions has been suggested in patients with severe hypervolaemic hyponatraemia.⁴⁵

Mistake 7 Paying insufficient attention to malnutrition

Malnutrition is a characteristic symptom of advanced liver cirrhosis. According to the current EASL guidelines it affects 20–50% of patients with liver cirrhosis.² Malnutrition is an important risk factor for several other cirrhosis-associated complications (e.g. bacterial infection, ascites and/or hepatic encephalopathy),^{46,47} significantly increases morbidity (i.e. frailty) and mortality, and has been linked to adverse outcomes after placement of a transjugular intrahepatic

portosystemic shunt (TIPS) and liver transplantation.^{48,49}

Despite its enormous impact, malnutrition often remains untreated or even undiagnosed, especially in patients with a normal or increased body mass index (BMI). Calculation of BMI is often misleading as it does not consider the amount of fluid retention (i.e. due to ascites), so a dry-weight-based BMI should always be used for patients with decompensated cirrhosis. For calculation of the dry-weight-based BMI, it is recommended to subtract 5%, 10% or 15% of body weight depending on the severity of ascites. In addition, peripheral oedema should also be considered (subtract 5%). However, a dry-weight-based BMI within the normal range does not exclude malnutrition in patients with cirrhosis. Indeed, patients with advanced, decompensated liver cirrhosis (Child C) are at a high risk of malnutrition even in case of a dry-weight-based BMI >30 kg/m².

Malnutrition should be considered in the work-up of all patients with cirrhosis and implemented as part of routine clinical assessment at all respective treatment centres. Different approaches have been suggested. The EASL guideline recommends a risk-stratified assessment based on the Child–Pugh stage and dry-weight-based BMI. High-risk groups include those with a BMI <18.5 kg/m² and/or Child C cirrhosis. These patients should directly undergo detailed assessment for sarcopenia and malnutrition.⁵⁰ Non-obese, non-underweight patients with Child A/B cirrhosis should be screened first to classify them into one of three different risk categories. A simple method for initial evaluation is the Royal Free Hospital–Nutritional Prioritizing Tool (RFH–NPT).⁵¹

A detailed nutrition plan for patients with liver cirrhosis does not exist, but it is important that protein restriction be avoided. Consumption of 35 kcal/kg body weight/d and a protein intake of at least 1.2–1.5 g/kg body weight/d is recommended. For patients with hepatic encephalopathy the uptake of vegetables and dairy proteins can be advantageous, but protein intake via meat consumption is not prohibited. For patients who find it difficult to ingest food orally, temporary parenteral nutrition should be considered. Furthermore, supplementation of vitamins, in particular Vitamin D for patients with a level <20 ng/ml, is recommended.⁵⁰

One of the most critical recommendations and the easiest to follow for those with advanced cirrhosis might be regular ingestion of food, as it is the most sustainable way to avoid proteolysis and hypoglycaemia. In our centre, we advise patients with decompensated liver cirrhosis and ascites to have six meals per day, including a

late dinner followed by an early breakfast containing proteins and carbohydrates.

Mistake 8 Withholding anticoagulant therapy in patients with portal vein thrombosis

As synthesis of procoagulant and anticoagulant factors is reduced in patients with liver cirrhosis, bleeding complications and thrombosis can occur.² Portal vein thrombosis (PVT) is a frequent complication that can be difficult to handle. In addition to a prothrombotic status being caused by impaired liver function, the risk of PVT can be increased because of inflammation and decreased portal blood flow, which may both result from portal hypertension.^{52,53} The clinical spectrum of PVT ranges from asymptomatic to acute hepatic decompensation, as indicated by ascites and/or variceal bleeding. PVT is associated with increased mortality and can complicate or even prevent liver transplantation if thrombosis progresses.⁵⁴

Timely and adequate anticoagulant therapy is the initial treatment used to try to prevent further progression of thrombosis and/or even achieve recanalization. However, anticoagulant therapy is often delayed or even completely denied due to fear of increasing the variceal bleeding risk. Of note, a recent meta-analysis did not find any difference in the incidence of major or minor bleedings for patients with cirrhosis and PVT with or without anticoagulant therapy.⁵⁵ The risk of variceal bleeding was even decreased, and the rate of recanalization significantly improved in those receiving anticoagulant therapy.⁵⁵

Screening for oesophageal varices and implementing an adequate prophylactic strategy is recommended prior to initiating anticoagulant treatment. However, this should be performed very soon after PVT diagnosis. If initiation of anticoagulant therapy is delayed to >6 months after PVT diagnosis, the likelihood of recanalization decreases significantly.^{56,57}

Low-molecular-weight heparins are usually considered the most appropriate treatment choice. Vitamin K antagonists are also effective but therapeutic monitoring is required and this can be challenging in patients with an increased INR. Initial studies suggest that therapy with low-dose apixaban and rivaroxaban is also possible in patients with PVT and equivalent to traditional anticoagulation without increased risks such as liver injury.⁵⁸ However, further studies are needed.

In our centre, we usually start with low-molecular-weight heparins at a therapeutic dosage as soon as prophylaxis of variceal

bleeding has been completed. In some patients heparins are replaced by oral anti-coagulants after a couple of weeks. However, treatment should be continued for at least six months. Afterwards, the decision to continue, switch to a prophylactic dosage or withdraw treatment is decided on an individual basis.

The role of prophylactic anticoagulation in patients with decompensated liver cirrhosis still needs to be determined. In a small pivotal trial, fixed-dose enoxaparin (4,000 IU/d) seemed to reduce the occurrence of additional PVTs and even prevented hepatic decompensation: complications such as bleeding or thrombocytopenia were minimal.⁵⁹

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Your decompensated liver cirrhosis briefing

UEG Week

- 'Clinical trials revisited: Redefining the management of patients with decompensated cirrhosis and PBC' session at UEG Week 2018 [<https://www.ueg.eu/education/session-files/?session=2043&conference=153>].
- 'Advances in the management of cirrhosis' session at UEG Week 2018 [<https://www.ueg.eu/education/session-files/?session=2070&conference=153>].
- 'Management of advanced liver cirrhosis' session at 25th UEG Week 2017 [<https://www.ueg.eu/education/session-files/?session=1919&conference=149>].
- 'Complications of liver cirrhosis: Beyond bleeding and ascites' session at UEG Week 2016 [<https://www.ueg.eu/education/session-files/?session=1661&conference=144>].
- 'Complications of cirrhosis: Which prophylaxis should we use?' session at UEG Week 2016 [<https://www.ueg.eu/education/session-files/?session=1590&conference=144>].
- 'From guidelines to clinical practice: Portal hypertensive bleeding' session at UEG Week 2016 [<https://www.ueg.eu/education/session-files/?session=1618&conference=144>].

Standards and Guidelines

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