Review

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Management of the major complications of cirrhosis: Beyond guidelines

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Summary

Along with a growing understanding of the pathophysiology of cirrhosis and its complications, new therapies and management strategies have emerged in recent years. Many of these advances have helped inform the current EASL clinical practice guidelines[1] on the management of some of the key complications of cirrhosis, such as ascites, variceal bleeding and infection. However, there are still some aspects of management where the evidence base is less clear, and/or where opinions amongst practitioners remain divided. Some of these more controversial areas are explored in this section, wherein we present evidence culminating in a suggested management approach based on expert opinion and extending beyond the current guidelines.

Keywords: Cirrhosis; Decompensation; Management; Guidelines; Controversies.

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Introduction

Improvements in our understanding of the pathophysiology of cirrhosis and the identification of new therapeutic targets have created new treatment opportunities.

However, growing pressure on healthcare budgets and a trend by healthcare managers to recourse to clinical guidelines to justify which therapeutic options may or may not be adopted in practice, create barriers to the incorporation of innovative therapies, despite often compelling scientific evidence. Thus, whilst guidelines are clearly important to ensure uniformity of care standards, sometimes one must also use expert opinion to justify a management strategy, which is particularly the case for some aspects of the management of cirrhosis and its complications, for which the evidence is often less definitive. Whilst some management strategies lie beyond the current clinical practice guidelines,[1] they are nonetheless commonly encountered and could be adopted into practice, whilst we await more definitive data. Such topics include the management of refractory ascites, minimal encephalopathy, diabetic care in advanced liver disease, and optimal management of patients discharged from hospital with decompensated cirrhosis.

How to improve current care pathways to prevent readmission to the hospital with further decompensation and morbidity?

An estimated 1.5 billion people worldwide have chronic liver disease, with a marked 13% increase in cirrhosis cases noted in the last decade.[2] This translates into increased cirrhosis-associated morbidity, especially from acute decompensation events, and mortality. Whilst our understanding of the pathophysiological drivers of acute decompensation of cirrhosis has improved considerably over the last decade, the management still remains largely reactive, often necessitating intensive therapies and protracted hospital admissions in response to late presentations.[3] Moreover, even after resolution of an acute decompensation event, re-admission to hospital with further complications is common, with 90-day readmission rates estimated at between 21–53%, based on the population and number of cirrhosis complications.[4,5] Those with more advanced disease, prior encephalopathy and/or those who have previously received prophylactic antibiotics, have higher readmission rates, generating a substantial health and societal care cost.

In addition to optimal management of cirrhosis complications per the recent EASL guidelines,[1] patients with advanced liver disease also require support and management for substance/alcohol abuse, nutrition and frailty.[6] This in turn requires a programme of education for patients and carers alike, following discharge from hospital back into the community. In this regard, the delivery of current management protocols is often wanton in ensuring adequate and equitable access to specialist advice, timely follow-up, and sufficient community support, following hospital discharge. This in an era when many other chronic disease management protocols, such as for heart failure, have turned to technology to help improve outcomes and patient engagement. This begs the question, what could aide early recognition of new cirrhosis complications and be used to provide

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effective community cirrhosis monitoring and management for patients at risk of decompensation? The urgent need to address this question has intensified in light of the COVID-19 pandemic, and the consequent need to streamline healthcare resources and reduce patient footfall, both for emergency admissions and routine out-patient assessments.

The role of remote monitoring of cirrhosis

Telemedicine is a terminology encompassing several different practices including teleconsultation (imparting specialist knowledge to another practitioner through case presentation); telemonitoring (adopting technology such as wearables to remotely monitor signs and symptoms), and televisits (where patients can be assessed by a healthcare provider in a remote location). COVID-19 has certainly seen a growth in televisits and telephone consultations, but it is difficult to obtain key metrics of changing clinical status in the absence of hospital tests and assessment. In this regard, the ability to adopt smartphone technology and low-cost sensing equipment to acquire key physiological data remotely, could potentially help differentiate acute decompensation from chronic stable cirrhosis, as shown by a study of continuous heart rate variability (HRV) monitoring; a loss of HRV was associated with decompensation and inflammation, whilst an HRV threshold could identify patients at a high risk of mortality.[7] Indeed, the potential of remote monitoring in cirrhosis has been shown by several studies, including a study of 25 patients with cirrhosis and ascites, where Bluetooth-linked weighing scales and an App, enabled providers to feedback responses over 30 days of monitoring.[8] The authors reported good compliance with remote weight measurement on >70% of the study days, whilst demonstrating the feasibility of monitoring changes in weight (increase or decrease) where interventions were recommended for more than 50% of alerts. In another example, a "Patient Buddy App" was used to provide education on cirrhosis complications and evaluate the risk of hepatic encephalopathy (HE). This study in 40 patients showed that some HE-related admissions (a potentially reversible cause of hospital admissions) were avoided, albeit the study had no control group.[9] The study findings did reveal an expected 40% readmission rate but this was from non-HE causes, raising the question of whether some complications of cirrhosis, such as infection or bleeding, can be prevented or their impact reduced with technological interventions. Such interventions are generally associated with good compliance, going against the dogma that patients always gain most from traditional doctor-patient direct consultations. Further evaluation of such technology is needed and the potential for 'digital therapies' to be applied remotely in cirrhosis certainly warrants evaluation.

Key points

Hepatologists need to embrace technology and broader care networks, to deliver high-quality care for patients with decompensated cirrhosis in the community.

Machine learning algorithms to define patients at risk of cirrhosis complications

The use of machine learning algorithms and potential artificial intelligence are also gaining momentum, although their application in decompensated cirrhosis is limited. However, in 1 study, applying feature selection criteria and several machine learning models to the CANONIC study dataset,[10] demonstrated improved sensitivity and specificity for mortality prediction.[11] This preliminary data does show that agnostic evaluation of variables in patients with cirrhosis may help define a population at risk of new complications and progression, and in the future, generate a risk algorithm that may complement remote monitoring, and guide early intervention when integrated into community-care pathways. However, such methods clearly require rigorous testing and validation, especially in prospective datasets.

Specialist cirrhosis-care nursing support

Whilst other chronic conditions such as heart failure have a well-established framework for specialist and community nursing supported by data,[12] this is still significantly lacking in liver disease. A study in 47 patients who received dedicated specialist nurse led follow-up, where the nurses had received prior training (including in palliative care), showed significant buy-in from participants and carers, and improved coordination of care and quality-of-life feedback.[13,14] Whilst controlled studies are limited in this area, such studies encourage further investment for the delivery of specialist nursing care to patients with cirrhosis, as recently summarised in a Position paper on this subject, as part of the European Horizon 2020 programme, LiverHope.[15] The role of specialist nursing for cirrhosis extends to counselling for nutrition, education of patients and carers on potential complications, awareness of risk of falls, and care of skin fragility. This is in addition to providing support for alcohol use disorders when applicable. Alongside regular follow-up assessment and review of diet and medication compliance, this specialised support would help ensure continuity of high-quality care once patients are discharged from hospital.

Expert opinion

- The need for close follow-up of decompensated cirrhosis after hospital discharge is clear, and remote monitoring should be seen as a viable option, supported by technological infrastructure.
- The use of machine learning and data science to help improve prognostic indicators will help guide triaging of patients to personalised interventions and treatment algorithms.
- Technology should be supported by increased investment in specialist cirrhosis nursing, to assist with early intervention and thereby reduce need for hospitalisation.

How to diagnose and manage chronic kidney disease in decompensated cirrhosis?

Chronic kidney disease (CKD) has become a major global public health problem. The prevalence of CKD in the general population is around 10% in high-income countries, where diabetes mellitus, obesity and hypertension represent the main causes.[16] Specific conditions such as IgA nephropathies or virus-induced glomerulopathies are well described in cirrhosis.[17] However, non-specific causes, associated with ageing and metabolic syndrome, especially diabetes mellitus, may account for the majority of CKD in the population with cirrhosis, especially in patients with NASH (non-alcoholic steatohepatitis). Recent studies have shown that CKD may affect nearly half of such patients.[18,19] The diagnosis and staging of CKD in decompensated cirrhosis remains challenging. Indeed, non-invasive tools used to estimate renal function including serum creatinine or estimates of glomerular filtration rate (GFR), such as creatinine or cystatine-based equations, have poor accuracy in decompensated cirrhosis.[20–22] The present reference standard remains measurement of GFR through clearance of an exogenous marker, which is expensive, time-consuming and only available in select centres.[23] In non-liver transplant (LT) candidates, the measure of GFR may be useful to adapt the dosage of drugs which are metabolised by the kidney and for prognostication. In LT candidates, the assessment of GFR is particularly important. Indeed, if measured GFR is below 30 ml/min, combined liver and kidney transplantation rather than LT alone may be proposed.[24]

Of note, whilst the current EASL CPG guidelines[1] highlight in detail the new classifications of acute kidney injury (AKI) and the limitations of using tubular damage markers and rarely acquired biopsy information, to distinguish this from hepatorenal syndrome (HRS)-induced AKI, the overlay of HRS on CKD is much more challenging. By definition, if CKD is suspected, a further drop in GFR thought to be related to HRS and systemic inflammation would be hard to attribute as being causal to further kidney injury, beyond the contributions of chronic progression of structural damage and/or comorbidities like diabetes. However, If HRS is suspected, the management should follow the current EASL CPG algorithm for HRS whilst we await better markers of tubular damage.

There is no specific treatment for CKD. First, risk factors should be screened and treated. Second, the management involves renoprotective strategies to slow kidney deterioration,[16] based on control of blood pressure (below 130/80 mmHg) and reduction of proteinuria.[16] Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are the drugs of choice.[25] In contrast, beta-blockers (selective) are not first-line drugs and their renoprotective effects are unclear.[25] In decompensated cirrhosis, the use of ACEIs and ARBs is contraindicated given their poor tolerance. Indeed, they increase the risk of developing AKI by inducing arterial hypotension and reducing the GFR.[26,27] Recent EASL guidelines recommend stopping non-selective beta-blockers (NSBBs) in patients with cirrhosis and AKI.[1] Whether they should be continued once AKI has resolved has never been investigated.

At the later stage of end-stage renal disease, patients should theoretically be considered for renal replacement therapy (RRT) and, eventually, transplant evaluation. Several techniques of RRT could be proposed including in-centre haemodialysis or home haemodialysis, requiring arteriovenous fistula placement, or peritoneal dialysis. No large study has evaluated RRT for CKD in decompensated cirrhosis. It may be assumed that initiating RRT in a patient with end-stage cirrhosis and multi-organ failure, who is not a candidate for transplantation, is unreasonable. Conversely, initiation of RRT to treat ascites in a patient without severe liver insufficiency, or starting RRT in the context of AKI superimposed on CKD, should be discussed, especially in patients listed for LT. Arteriovenous fistulas should be avoided because of a high associated risk of complications (bleeding, infection); central venous dialysis catheters are preferred. Continuous RRT may be the safest option.

Expert opinion

- Patients with cirrhosis should be screened for CKD given its high prevalence in this population, especially in those with metabolic syndrome.
- GFR should be measured using clearance of exogenous markers in LT candidates since current estimates of GFR have poor accuracy in decompensated cirrhosis, and these patients may be candidates for combined liver and kidney transplantation.
- To date, no specific treatment for CKD is available in decompensated cirrhosis, as nephroprotective strategies are contraindicated.
- When end-stage kidney disease occurs, RRT may be proposed to bridge to transplantation.

Key points

There is a high prevalence of CKD in patients with cirrhosis, and despite limitations in measurement of GFR, this should be determined early for those being considered for transplantation, with renal replacement therapy used as a bridge to transplantation.

Should we screen for type 2 diabetes mellitus in patients with decompensated cirrhosis? And how to manage it?

Abnormalities in glucose metabolism are frequent in patients with cirrhosis, with glucose intolerance affecting 30–50% of patients, and type 2 diabetes mellitus (T2DM) affecting 30%.[28–31] Diabetes and cirrhosis are closely interconnected, cirrhosis inducing insulin-resistance and, conversely, diabetes worsening liver disease and increasing the risk for complications of cirrhosis as well as mortality.[29,32]

Key points

Diabetes mellitus should be screened for in decompensated cirrhosis and insulin therapy used as the first-line option, albeit, under careful supervision and cautiously to avoid precipitating hypoglycaemia and metabolic encephalopathy.

Management of patients with T2DM is based on lifestyle changes and pharmacological therapies.[33] Such strategies may be challenging in patients with decompensated cirrhosis. Firstly, poor nutritional status is frequently associated with end-stage cirrhosis and contraindicates hypocaloric diets. Secondly, ascites, oedema and fatigue frequently hamper physical exercise programmes.

Most pharmacological treatments of diabetes are difficult to manage in patients with impaired liver function and/or altered kidney function, a common state in decompensated cirrhosis. For instance, metformin increases the risk of lactic acidosis and should not be used in this population. Other drugs (thiazolidindiones, insulin secretagogues, alpha-glucosidase inhibitors or dipeptyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists) have yet to be studied in depth in decompensated cirrhosis. However, given most are eliminated either by the liver or the kidney, their use is not recommended in patients with decompensated cirrhosis.[33,34]

Insulin remains the only drug that can be recommended in decompensated cirrhosis. However, one must be mindful that its hepatic metabolism is reduced in decompensated cirrhosis, thus decreasing the need for it. Because of patients' highly variable insulin requirements and the risk of hypoglycaemia, treatment should be initiated during hospitalisation, with close monitoring of blood glucose levels.

The main objective of T2DM treatment is tight glucose control, which has been shown to decrease both micro- and macrovascular complications of diabetes, and to increase survival.[33] Self-monitoring of blood glucose and/or continuous glucose monitoring facilitate optimal glycaemic control. Glycated haemoglobin (HbA1c) enables long-term glycaemic status to be assessed. A level below 7% is usually considered as the optimal target.[33] In decompensated cirrhosis, monitoring HbA1c is not accurate as its levels may be decreased by several mechanisms, including anaemia, portal hypertension, poor nutritional status and shortened erythrocyte life span.[35] Therefore, self-monitoring of blood glucose is the only means to evaluate glucose control. In patients with encephalopathy, continuous glucose monitoring may represent the best option.

The benefit of tight glycaemic control in cirrhosis, especially in decompensated patients, has never been demonstrated. Detrimental effects of diabetes on survival could be more pronounced in patients with model for end-stage liver disease (MELD) scores below 10 than in patients with MELD scores over 10,[36] as the latter are more likely to die from complications of cirrhosis than from complications of T2DM. If glycaemic control is too tight, patients may be exposed to hypoglycaemia, which can precipitate metabolic encephalopathy. Conversely, blood glucose levels over 10 mmol/L may increase the risks of diabetic ketoacidosis and hyperosmolar hyperglycaemic complications.

Expert opinion

- Patients with decompensated cirrhosis should be screened for diabetes given its high prevalence in this population.
- HbA1c should not be used, neither for the diagnosis, nor for assessing glycaemic control over the preceding 3 months.
- Insulin therapy is the only evidence-based option for treating T2DM. It should be initiated in hospital due to high variations in glucose levels and risks of hypoglycaemia, which may alter mental function and be confused with HE, thereby complicating management. Optimal fasting blood glucose levels should not exceed 10 mmol/L to avoid hyperglycaemic complications.

How best to classify and manage hepatic encephalopathy in decompensated cirrhosis?

HE has been traditionally split into *overt* (with neurological and/or psychiatric abnormalities that can be detected clinically) and *minimal* (with abnormalities that are detected on neuropsychological or neurophysiological tests).[37] As the clinical diagnosis of mild forms of overt HE is operator-dependent, it has been suggested that HE is called overt when at least temporal disorientation (for example, 3 mistakes out of 5 questions exploring orientation to time, according to Italian guidelines[38]) and/or flapping tremor are present (≥grade II according to the West Haven criteria). By contrast, grade I HE changes, which are usually detected by caregivers or physicians who are well acquainted with the patient's normal personality and behaviour, are grouped with abnormalities on tests (minimal HE) and collectively named covert HE.[39] Whichever their denomination or exact classification, mild forms of HE are common, they can affect quality of life, social and family relations, earning capacity, and the ability to drive. In addition, they are associated with a higher likelihood of developing overt HE over time.[40] Over recent years, screening for mild HE has become easier, with bedside tools becoming available and their use more widespread. For example, the animal naming test is universally and rapidly applicable (requiring no equipment and only 60 seconds of time), can be performed by physicians, nurses and caregivers, and has limited spontaneous variability, making it useful for follow-up/monitoring.[41] By contrast, attributing neuropsychiatric abnormalities to liver

Key points

Recognition and screening for mild HE using easily accessible tests, such as animal naming, is important and may help identify those at risk of progression to overt HE. Moreover, ammonia-lowering strategies may treat progression and help clinch a diagnosis in those with high functional capacity.

failure and defining neuropsychiatric status within a transplant work-up process remains challenging, with adequate differential diagnosis requiring experience, equipment/personnel that are not routinely available to standard gastroenterology/hepatology wards, and time, including that needed to evaluate response to treatment.

Controversies in management

Current management guidelines indicate that non-absorbable disaccharides should be used as secondary prophylaxis after an episode of overt HE, and rifaximin should be added if a second episode occurs within 6 months (recurrent overt HE).[39] Indications for the treatment of milder forms of HE are less stringent.[39] While treatment has been shown to revert neuropsychological abnormalities, it remains to be established if it also affects the likelihood of developing overt HE over time. The expert opinion here would be to consider treatment of minimal HE also as prophylaxis to prevent more severe overt HE. It should also be added that in situations where experience in the diagnosis of minimal HE is scarce, a response to a course of ammonia-lowering treatment solves the problem while also confirming the diagnosis at the same time. This is of particular relevance to high-functioning individuals with jobs of responsibility, in whom the diagnosis may be more difficult because they place themselves at the top end of neuropsychological performance, thus producing "normal" performances (with reference to healthy population norms) even when they are functissoning considerably below their baseline .[42] Shunt-related minimal HE poses even more diagnostic challenges, as its persistence may make it more difficult to distinguish from other forms of neuropsychiatric impairment, especially dementias and extrapyramidal syndromes.

As the pathophysiology of minimal HE is identical to that of more severe forms, treatment is the same. Virtually all agents shown to be effective for overt HE have also been shown to be effective for milder forms. Of interest, one randomised controlled trial (RCT) also showed that a 6-month nutritional intervention (30–35 kcal/kg of body weight/day, 1.0–1.5 g vegetable protein/kg of body weight/day) improved neuropsychiatric performance and also decreased the risk of developing overt HE over time compared to no intervention.[43] Within the context of milder forms of HE, "ecological" solutions such as nutritional interventions, vegetable/dairy diets (with extreme attention being paid not to compromise overall protein-energy intake), prebiotic fibre, probiotics and symbiotics (taking into account the great heterogeneity in the content of probiotic species and their vitality in various products and brands) may play a relevant role, despite formal evidence in their favour being less stringent than that available for non-absorbable disaccharides and non-absorbable antibiotics. Finally, ammonia-lowering strategies can obviously be associated with simple, direct vigilance modulation, for example with timed coffee administration.[44] Of interest, trials with psychoactive drugs modulating vigilance are underway, together with several others targeting inflammation, general and specific nutritional deficits, the microbiota, the intestinal barrier, and the urea cycle.

Expert opinion

- Minimal forms of HE are common, and may affect quality of life and independence, and over time, are associated with a higher likelihood of developing overt HE.
- Screening tools for minimal HE are readily available, do not require specialist equipment and may help with follow-up and disease monitoring.
- Minimal HE should be treated as 'prophylaxis' to prevent more severe overt HE, and treatment challenge may help confirm the diagnosis.

What is the role for "acute" hepatic venous pressure gradient response to NSBBs in the management of clinically significant portal hypertension?

Patients with clinically significant portal hypertension (CSPH) on primary prophylaxis are protected from acute variceal bleeding (AVB) if HVPG decreases to values ≤12 mmHg,[45] or if HVPG decreases by >10%,[46] and HVPG-guided therapy has been shown to reduce portal hypertension-related decompensations and mortality.[47] Whilst HVPG response to therapy clearly differentiate patients' future risk, the 'gold standard' is to measure HVPG at baseline, and then to repeat the measurement after chronic NSBB administration. HVPG responses appear to be maintained over a long period of time.[48]

To date, 6 studies evaluating the role of *acute* HVPG responses have been published, as outlined in Table 1. A reduction of HVPG between 10% to 12% with intravenous propranolol (followed by 0.2 mg/hour) protected against AVB at 2 years. Interestingly, studies demonstrating a prognostic value for acute HVPG response in primary bleeding prophylaxis, also demonstrated a reduction in the occurrence of ascites and cirrhosis complications in HVPG responders.[46,49,50] However, there was only a moderate correlation between acute and chronic HVPG response, with the prognostic value of the chronic response having a greater correlation with the development of ascites.[46] In 1 study evaluating acute response after oral carvedilol administration, 92% of patients had maintained a haemodynamic response at 6 months.[49]

Observational studies suggest that HVPG monitoring might be useful to stratify risk and to guide choice of therapy. In the PREDESCI trial and

Key points

Measurement of acute HVPG can guide management of primary and secondary variceal bleeding risk and may have prognostic value for other complications including ascites.

Table 1. The role of acute HVPG responses.

Study	Number of patients	Interventions	Patient characteristics	Findings
Villanueva *et al.* Gastroenterology 2009[95]	n = 105	"Acute" HVPG response to i.v. propranolol (0.15 mg/kg followed by 0.2 mg/h); Nadolol (titrated according to HR)	Primary prophylaxis (all high-risk varices); HVPG ≥12 mmHg; Definition of HVPG response: ≤12 mmHg/≥20%	AVB: HVPG response: 4% *vs.* non-response: 46% at 2 years (independently predictive); Ascites: decreased; Mortality: trend towards decrease, moderate correlation between "acute" and "chronic" HVPG response
La Mura *et al.* J Hepatol 2009[96]	n = 166	"Acute" HVPG response to i.v. propranolol (0.15 mg/kg); Propranolol or nadolol (titrated according to HR/SAP)	Primary (n = 78; small: 22%; large: 78% varices, red wale marks: 29%) and secondary prophylaxis (n = 88); HVPG ≥12 mmHg; Definition of HVPG response: ≥12%	AVB: HVPG response: 7%/16% *vs.* non-response: 21%/40% at 1/2 years (independently predictive); AVB (primary prophylaxis): trend towards decrease; AVB (secondary prophylaxis): decreased (independently predictive); Mortality: HVPG response: 5%/5% *vs.* non-response: 13%/35% at 1/2 years (independently predictive);
Hernández-Gea *et al.* Am J Gastroenterol 2012[46]	n = 83; n = 78 with information on HVPG response	"Acute" HVPG response to i.v. propranolol (0.15 mg/kg); Nadolol (titrated according to HR); "Chronic" HVPG response (1–3 months)	Primary prophylaxis (all large varices); HVPG ≥12 mmHg; Definition of HVPG response: ≥10%	Bleeding: "chronic" HVPG response: 5% *vs.* non-response: 17% at 2 years (independently predictive); AVB: "chronic" HVPG response: 5% *vs.* non-response: 14% at 2 years; Ascites: "chronic" HVPG response: 27% *vs.* non-response: 89% (independently predictive); "acute" HVPG response: 17% *vs.* non-response: 49% at 2 years; Refractory ascites: decreased if "chronic" haemodynamic response; "acute" HVPG response: 5% *vs.* non-response: 18% at 2 years; SBP: comparable; HRS: decreased if "chronic" HVPG response; trend towards decrease if "acute" HVPG response; HE: trend towards decrease if 'chronic' hemodynamic response; Mortality: decreased if "chronic" HVPG response
Kirmake *et al.* J clinical and Experimental Hepatology 2016 [97]	n = 69	"Acute" HVPG response to oral carvedilol (25 mg). Carvedilol 12.5 mg/day	Primary or secondary prophylaxis (large varices or history of variceal bleeding). Response defined as a decrease ≥10% or <12 mmHg.	AVB: "acute" HVPG response: 6% *vs.* non-response: 26% at 6 months; Worsening ascites: "acute" HVPG response: 26% *vs.* non-response: 74% at 6 months
Fortea *et al.* WJCC 2018[51]	n = 76	Acute" HVPG response to i.v. propranolol (0.15 mg/kg); nadolol or propranolol (titrated according to HR). Non responders were treated with carvedilol (titrated according to HR)	Primary prophylaxis Response defined as a decrease ≥10% or <12 mmHg.	Acute decompensation in compensated cirrhosis. "acute" HVPG response 12.7% *vs.* non-response receiving carvedilol 20% at 1 year (NS) Acute decompensation in decompensated cirrhosis: "acute" HVPG response: 21% *vs.* non-response receiving carvedilol 21% (NS)
Villanueva *et al.* Lancet 2019[50]	n = 201	Acute" HVPG response to i.v. propranolol (0.15 mg/kg) Responders were randomly assigned to propranolol (up to 160 mg twice a day) *vs.* placebo and non-responders to carvedilol (≤25 mg/day) *vs.* placebo	Compensated cirrhosis and CSPH without high-risk varices.	Cirrhosis decompensation (ascites, bleeding, or HE) or death: 16 (16%) in the β blockers group *vs.* 27 (27%) in the placebo group. Ascites: 9 (9%) in the β blockers group *vs.* 20 (20%) in the placebo group AVB: 4 (4%) in the β blockers group *vs.* 3 (3%) in the placebo group Mortality did not differ according to randomisation

AVB, acute variceal bleeding; CSPH, clinically significant portal hypertension; HE, hepatic encephalopathy; HR, heart rate; HRS, hepatorenal syndrome; HVPG, hepatic venous pressure gradient; SBP, spontaneous bacterial peritonitis.

in a retrospective study, carvedilol was used in HVPG acute non-responders to intravenous propranolol.[50,51] In these patients, carvedilol facilitated further HVPG reduction and improved clinical outcomes long term, even in this high-risk group.

Whilst some may consider HVPG assessment a specialist investigation, the practicality is well within the means of any interventional radiology unit, and if following standard procedures for evaluating pressure measurements, is a highly reproducible and safe test. Indeed, its risks (and costs) are significantly lower than transjugular biopsy alone, which is routinely performed. As such, acute HVPG response after AVB in those who are not deemed candidates for pre-emptive transjugular intrahepatic portosystemic shunt (TIPS), may best guide the medical strategy for secondary prophylaxis, albeit, further evidence is required to strongly recommend this approach.[52]

Expert opinion

- Assessment of "acute" HVPG response is feasible and safe in patients with cirrhosis and CSPH and it has an acceptable correlation with chronic response.
- Acute HVPG response has a good correlation with all clinical outcomes, not only bleeding risk but also the occurrence of ascites and its complications.
- HVPG-guided therapy could improve the management of patients with CSPH, both for primary and secondary prophylaxis of AVB, reducing costs and adverse effects by identifying ineffective therapy.

What are the limitations of NSBB therapy in decompensated cirrhosis?

Current guidelines recommend NSBBs for primary and secondary prophylaxis of AVB[1,53] based on high-quality RCTs that usually exclude patients with decompensated liver disease, particularly those with refractory ascites. Some studies investigating the issue of safety in this group of patients suggested that NSBBs were associated with increased mortality,[54] and higher post paracentesis circulatory dysfunction.[55] These observations led to the hypothesis that worsening cardiac function in some patients with cirrhosis exposes them to the detrimental effects of NSBBs.[56,57] Further studies[58,59] and a recent *post hoc* analysis of 3 RCTs where vaptans and NSBBs were co-administered in patients with ascites, did not show an increase in mortality.[60] Moreover, NSBBs have been shown to decrease the risk of spontaneous bacterial peritonitis (SBP),[61] despite a prior study suggesting an increased risk of AKI,[62] albeit this was refuted on subgroup analysis.[58,60,63] Additionally, lower dose NSBBs (≤80 mg) are associated with reduced mortality after SBP.[64]

In patients with sepsis and septic shock, the prior use of NSBBs does not seem to be associated with worse outcome,[65] and this is similarly the case for acute-on-chronic liver failure (ACLF).[66] Recently, Tergast *et al.* observed a significant increase in 28-day transplant-free survival with NSBB use on multivariate analysis in an ACLF subgroup. However, this advantage was completely lost in patients with mean arterial pressure <65 mmHg.[63]

Patients with refractory ascites have a more pronounced hyperdynamic state, and reduced cardiac output compared to those without refractory ascites,[67] which is further exacerbated in patients with azotemia and HRS.[68] Indeed, it has been shown that patients treated with NSBBs have significantly lower left ventricular performance[67] and that this is correlated with impairment of autoregulation of renal flow and the occurrence of AKI.[69] However, not all patients develop impairment of cardiac autoregulation with NSBBs, as shown by a prospective study in patients with refractory ascites undergoing large volume paracentesis (LVP).[70] Furthermore, dosing and type of NSBB are also important considerations. Clinical studies showing a detrimental effect with NSBBs used higher doses of propranolol (160 mg).[54] By contrast, lower doses between 40 mg and 80 mg seem to confer an advantage. Current EASL guidelines recommend propranolol at a daily dose of ≤80 mg.[1] However, carvedilol was not recommended in the guidelines for patients with refractory ascites because of concerns related to its potential hypotensive effects. Recent studies have suggested carvedilol is safe at low doses (6.25–12.5 mg), provided that patients maintain systolic pressures ≥90 mmHg.[71] Moreover, carvedilol has a role in reducing inflammation and mitochondrial dysfunction.[72] These are common events in decompensated cirrhosis, and importantly, carvedilol has since been demonstrated to improve survival in patients with ascites.[73]

Expert opinion

- NSBBs are not absolutely contraindicated in decompensated cirrhosis. However, high doses of NSBBs should be avoided.
- NSBBs should be temporarily discontinued or titrated in patients with progressive hypotension (systolic pressure <90 mmHg), during acute conditions such as sepsis, SBP or AKI, which can further impair cardiovascular function.
- Carvedilol should be considered as a beta-blocker option in decompensated cirrhosis at low doses.

TIPS in patients with decompensated cirrhosis and an elevated MELD: Is there a 'safe' threshold to improve management of refractory ascites in non-transplant candidates?

Refractory ascites is a severe complication of cirrhosis that is associated with poor survival.[74]

Therefore, patients without contraindications should be promptly evaluated for LT. If there is a short waiting period or a high MELD score which can lead to a LT in less than 3–6 months, LVP with albumin infusion (LVP+A) is a safe and effective treatment and the best bridge to LT.[75] The scenario changes when a longer waiting time is expected or the patient has absolute contraindications for LT. In this situation, it is extremely important to tease apart refractory ascites (either diuretic-resistant or diuretic-intolerant) from recurrent/recidivant ascites (defined as ascites that recurs at least on 3 occasions within 12 months, despite adequate diuretic treatment). In those with recurrent/recidivant ascites, an RCT showed that TIPS using polytetrafluoroethylene (PTFE)-covered stents improved 1-year transplant free-survival without increasing the incidence of HE compared to LVP+A, and it is in our expert opinion, the best treatment approach provided patients do not have absolute contraindications for TIPS (Box 1).[76]

Key points

TIPS should be considered in patients with refractory ascites, especially in those being considered for liver transplantation, using smaller size stents, and with due consideration of prophylactics for HE. MELD, whilst an indicator of risk, should be used in conjunction with a holistic review of the patient including age, frailty and comorbidities.

Box 1. Contraindications for TIPS placement.

Absolute

- Overt Recurrent/Chronic Hepatic encephalopathy
- Severe Pulmonary artery hypertension: meanPAP>35mmHg and PVR >240 dyn.cm^{-5}
- Heart failure

Relative

- Age >70 years
- MELD >18

MELD, model for end-stage liver disease; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; TIPS, transjugular intrahepatic portosystemic shunt.

Guidance regarding the best treatment option for patients with refractory ascites is more controversial. Several meta-analyses based on aggregate data of RCTs comparing TIPS using bare stents *vs.* LVP+A, showed that TIPS was more effective than LVP+A in controlling ascites but patients had a higher incidence of HE, without an improvement in survival.[77] In contrast, 1 specific meta-analysis using the individual data of previous RCTs, which allowed the authors to analyse survival as a time-dependent event, demonstrated a survival benefit for patients receiving TIPS in comparison to those treated with LVP+A.[78] Interestingly, the benefit of TIPS was observed for all MELD risk categories and no relationship between MELD and the treatment received (TIPS or LVP+A) was observed. So, does this mean that regardless of the MELD value, TIPS is a better option than LVP+A? The answer is no; it is clear that there is a degree of liver insufficiency beyond which TIPS is likely to be harmful. Unfortunately, the available information about what is the "safe" MELD threshold value for TIPS is scarce and outdated.

Although different studies attempted to find predictors of poor outcome in patients with refractory ascites treated with TIPS, most of these have several weaknesses that likely explain why the variables and defined cut-offs are difficult to reproduce. These studies only included patients in whom initially strict exclusion criteria for TIPS were applied and, therefore, this induces bias with a highly preselected population. For instance, excluding patients from studies with a MELD, bilirubin, creatinine or age above a given value (not always the same in the different studies) may underestimate the potentially poor outcome of TIPS in patients with higher MELD, bilirubin, creatinine or age. In addition, most prognostic studies are based on old cohorts of patients treated with TIPS for variceal bleeding or for refractory ascites. Although the MELD score was initially shown to predict prognosis after elective TIPS for either prevention of variceal rebleeding or for treatment of refractory ascites,[79] at the same MELD value, prognosis is worse in patients with refractory ascites.[80] Therefore, MELD cut-off values are different for patients with variceal bleeding or with refractory ascites.[81] In addition, a remarkable number of studies assessing prognosis in patients treated with TIPS used bare stents, while current evidence shows that prognosis is better with covered stents, a fact that may also influence the applicability of prognostic markers.[82–84] In addition, a better general management of patients with refractory ascites, which includes prophylaxis and treatment of HE,[85] and the use of smaller stent sizes,[86] likely improves the overall prognosis of patients with refractory ascites treated with TIPS. The implementation of these therapeutic strategies could modify the prognosis of patients with refractory ascites currently treated with covered TIPS. Thus, it is plausible that a certain MELD value, platelet count, or bilirubin level, among other prognostic factors evaluated that were previously associated with a poor prognosis, may no longer be so.

Despite all these considerations, and until new evidence is available, MELD is still the most used prognostic factor when considering a TIPS in patients with refractory ascites. In most centres an MELD value ≥18–20[80,87] is considered a contraindication. There is no question that TIPS in such patients is associated with a poorer outcome than in patients with a lower MELD value. However, the prognosis of these patients with poor liver function who undergo other therapies such as LVP+A or AlfaPump™ instead of TIPS, remains unanswered.[88] Therefore, when evaluating patients for TIPS with refractory ascites, the expert opinion is to use scores such as MELD as a guide but not as a definitive rule. The decision should also include a holistic and evidence-based approach taking into consideration, among other factors, age, frailty

measures,[89] bilirubin, platelet count[90] and comorbidities of the patient, as well as the expertise of the centre, as mortality is lower in centres that perform ≥20 TIPS per year.[91] Patients with refractory ascites and severe liver dysfunction in whom TIPS is contraindicated are usually treated with LVP+A. In these patients, the use of AlfaPump has been shown to reduce the number and volume of paracentesis.[92,93] That said, AlfaPump does not improve survival and is associated with frequent and potentially serious adverse effects.[92,93]

Although only tested in a non-randomised observational study, patients with refractory ascites treated with covered TIPS dilated to only 6–7 mm, had the same efficacy controlling ascites but with significantly less HE than those patients in whom the stent was dilated to 8–10 mm.[86] Therefore, it could well be that using smaller stents may expand the indication of TIPS in patients with refractory ascites and compromised liver function.[94] This should obviously be evaluated in adequate clinical studies.

Expert opinion

- In patients with recurrent ascites, and no contraindications to TIPS, PTFE-covered stents are the best treatment option to improve 1-year transplant free-survival without increasing the incidence of HE.
- When evaluating patients for TIPS with refractory ascites, scores such as MELD <18 can be used as a guide but not as a definitive rule, and should be considered alongside other factors such as age, frailty and patient comorbidities.
- Smaller stents may expand the indication for TIPS in patients with refractory ascites and compromised liver function.

Conclusions

Whilst the above sections are by no means an exhaustive list of controversial areas in cirrhosis management, they do address many commonly encountered areas of practice and provide a suggested management approach based on current evidence, even if this is limited. Many of these areas are topics of considerable research interest, particularly those where new biomarkers are being tested (*e.g.* surrogates of portal hypertension or kidney injury), or where modelling of large data sets will potentially inform new prognostic stratification. This research will undoubtedly help address such controversies and lead to updates of the current practice guidelines.

Abbreviations

ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; AVB, acute variceal bleeding; CKD, chronic kidney disease; CO, cardiac output; CSPH, clinically significant portal hypertension; GFR, glomerular filtration rate; HbA1c, glycated haemoglobin; HE, hepatic encephalopathy; HRV, heart rate variability; HVPG, hepatic venous pressure gradient; LT, liver transplantation; LVP, large volume paracentesis; NSBBs, non-selective beta blockers; RCT, randomized controlled trials; RRT, renal replacement therapy; T2DM, type 2 diabetes mellitus; TIPS, transjugular intrahepatic portosystemic shunt.

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