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British Society of Gastroenterology Best Practice Guidance: outpatient management of cirrhosis – part 3: special circumstances

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ABSTRACT

The prevalence of cirrhosis has risen significantly over recent decades and is predicted to rise further. Widespread use of non-invasive testing means cirrhosis is increasingly diagnosed at an earlier stage. Despite this, there are significant variations in outcomes in patients with cirrhosis across the UK, and patients in areas with higher levels of deprivation are more likely to die from their liver disease. This three-part best practice guidance aims to address outpatient management of cirrhosis, in order to standardise care and to reduce the risk of progression, decompensation and mortality from liver disease. Part 1 addresses outpatient management of compensated cirrhosis: screening for hepatocellular cancer, varices and osteoporosis, vaccination and lifestyle measures. Part 2 concentrates on outpatient management of decompensated disease including management of ascites, encephalopathy, varices, nutrition as well as liver transplantation and palliative care. In this, the third part of the guidance, we focus on special circumstances encountered in managing people with cirrhosis, namely surgery, pregnancy, travel, managing bleeding risk for invasive procedures and portal vein thrombosis.

INTRODUCTION

The prevalence of cirrhosis continues to rise, and cirrhosis is increasingly diagnosed at an earlier stage. As a result, potentially challenging clinical scenarios, such as surgery, pregnancy, invasive procedures, anticoagulation and travel in patients with cirrhosis, are encountered more frequently in practice. The third part of these guidelines on outpatient management of cirrhosis focuses on these scenarios.

SURGERY

Surgery in compensated cirrhosis

It is becoming increasingly common to encounter cirrhosis in patients under consideration for surgery—this may occur in those with an established diagnosis or those where it is found incidentally during workup. The underlying liver disease may be a risk factor for the surgical condition.

Patients with cirrhosis who require surgery are at a greater risk of complications and death compared with patients with healthy livers,[1 2] particularly from hepatic decompensation, worsening liver synthetic function and sepsis following surgery.[3] The degree of risk is dependent on the severity of their liver disease, including the presence of clinically significant portal hypertension (PHTN) (defined as hepatic venous pressure gradient, HVPG≥10 mm Hg), the nature of the planned surgery and its urgency. Therefore, risk stratification is essential for effective preoperative counselling and shared decision-making.[1 2] Detailed guidance on risk assessment for patients with cirrhosis undergoing non-hepatic surgery has recently been published.[4]

There is no single validated test to stratify risk of surgery in patients with cirrhosis and therefore referral to a multidisciplinary team (MDT) including surgeons, anaesthetists and hepatologists

Table 1 Predictive models used in patients with cirrhosis undergoing surgery[1 8]

Surgical procedure	Predictive model Continuous risk score	Higher risk category
All/general	MELD; ASA; age	MELD>14; HVPG>16 mm Hg (particularly HVPG>20 mm Hg)
Cholecystectomy	Child-Pugh score (CP)	CP B/C; CP C; MELD>15
Liver cancer resection		HVPG>10 mm Hg; MELD>9; transient elastography>22 kPa
Abdominal wall hernia repair	CP	MELD>13
CABG		CP>8; MELD>13
Bariatric surgery		CP B/C
Colonic resection		MELD>9
Lung cancer resection		CP B/C
Orthopaedic procedures	CP	
Lumbar spine surgery		CP B/C
Head and neck surgery		CP B/C; MELD>10
Neurosurgery	CP	

ASA, American Society of Anaesthesiologists classification; CABG, coronary artery bypass graft; HVPG, hepatic venous pressure gradient; MELD, Model for End-Stage Liver Disease.

with experience in managing this patient group is recommended prior to surgery. Assessment should include Child-Pugh score Model for End-Stage Liver Disease (MELD, range 6–40)[5] Mayo Postoperative Mortality Risk Scores (https://www.mayoclinic.org/medical-)[1 2] and/or bespoke prognostic scoring systems such as VOCAL-Penn[6] and ADOPT-LC,[6 7] as well as specific anatomical assessment of the feasibility of surgery, to aid MDT decisions. Additional tests, including HVPG where available, may also be undertaken,[8] particularly for specific indications, for example, hepatic resection or gastrointestinal surgery.[9] Interpreting data on clinical risk scores and outcomes for surgery in patients with cirrhosis remains difficult as much data is historic, from small studies and may not reflect developments in perioperative and surgical management.[3] Further research in this area is needed. Table 1 summarises predictive models used in patients undergoing various surgical procedures. These models should be used within the context and expertise of the wider MDT.

In patients with cirrhosis, non-urgent surgery should be deferred until an adequate assessment has been undertaken and their liver disease optimised. The clinical team should consider referral to a unit with experience in managing patients with cirrhosis, where appropriate.[1] Consideration should also be given to non-surgical options if available/appropriate.[3] Care should be taken to optimise nutrition. For patients with compensated cirrhosis, after appropriate perioperative risk stratification and counselling, surgery may then be indicated.

Emergency surgery in patients with cirrhosis carries an increased mortality risk, and cirrhosis is an independent predictor of death. In the emergency setting, where deferring surgery may not be feasible, the patient and surgical, anaesthetic and medical teams must weigh the potential benefits and risks collaboratively.[1]

Table 2 summarises the anaesthetic considerations when planning surgery in patients with cirrhosis.

Surgery in decompensated cirrhosis

Surgery in patients with decompensated cirrhosis carries a significantly higher mortality risk than compensated cirrhosis. Eligibility for liver transplantation, if the patient was to decompensate following surgery, should be determined prior to surgery. In patients with Child-Pugh C or MELD>20, surgery should be avoided or delayed until after liver transplantation, if possible, for all but the most urgent and lifesaving procedures.[1] Good palliation of symptoms is crucial in patients unsuitable for transplant where surgery is considered too high risk, as well as in all patients waiting for surgery post-transplant.

Abdominal wall hernias are common in patients with cirrhosis and ascites, and mortality is high in those undergoing surgery. The clinical team should consider discussion with an experienced centre to guide management of recurrent ascites with transjugular intrahepatic portosystemic shunt (TIPSS) and other sequelae of decompensation in the perioperative/postoperative period.[1] The decision to offer hernia repair and its timing will be influenced by the patient's eligibility for liver transplantation and the nature of their presentation. Where patients have undergone assessment and are awaiting liver transplantation, hernia repair may be deferred until the time of transplantation (when it can be undertaken during or following liver transplantation). In patients who are not candidates for liver transplantation elective repair of symptomatic umbilical hernia (if feasible) can be undertaken and may avoid the added risk of emergency surgery. In patients who develop life-threatening complications of an abdominal wall hernia (skin breakdown with leaking ascites, incarceration, obstruction or strangulation) emergency

Table 2 Anaesthetic considerations in the cirrhotic patient

Preoperative considerations	► Liver-specific risk assessment+evaluation of additional comorbidities and nutrition is required. ► Regional techniques convey less risk of morbidity and mortality than general anaesthesia and should be considered where appropriate. ► Optimisation of ascites with medication/drainage to reduce aspiration risk and respiratory morbidity postoperatively.
Perioperative management	► Invasive monitoring should be considered. ► Medication-related complications due to altered metabolism/elimination should be avoided as much as possible; reduction in opiate dose, prolonged dosing interval and avoidance of constipation. ► Consider reduced paracetamol dosing (2 g/day divided doses). ► Avoid non-steroidal anti-inflammatory drugs (can reduce renal blood flow).
Coagulation (see section on procedures and clotting for more information)	► Complex alterations in coagulation are not adequately assessed in standard laboratory coagulation tests ► Prophylactic transfusion strategies based on platelets and INR are ineffective at reducing perioperative bleeding. ► Platelet counts >50×10^9/L adequately allow clot formation—transfusion above this level can lead to increased risk of thrombus and is unlikely to be beneficial. ► Cryoprecipitate to replace fibrinogen <1 g/L. ► Viscoelastic testing reduces red cell and plasma transfusion in cirrhotic patients.[47]
Postoperative management	► Level 2 care and invasive cardiovascular monitoring should be considered in the early postoperative phase. ► Careful attention to fluid balance is imperative to avoid exacerbation of portal hypertension. ► At least daily monitoring of renal and hepatic function recommended. ► If decompensation occurs seek early hepatology/gastroenterology review.

INR, international normalised ratio; NSAIDs, non-steroidal anti-inflammatry drugs.

repair may still be undertaken but the morbidity and mortality increases significantly.[9]

PREGNANCY

Pregnancy in compensated disease

All women of childbearing age with cirrhosis should undergo prepregnancy counselling (PPC). Details on suitable contraceptive options in cirrhosis can be found elsewhere.[10 11] PPC can occur in a hepatology clinic, or in a formal multidisciplinary setting with obstetricians and hepatologists. The latter may not be available in all centres, so complex cases should be referred to a specialist centre.

Primarily, PPC allows risk stratification of women with cirrhosis and individualised care planning during pregnancy (figure 1). Up to 50% of women with cirrhosis experience amenorrhoea/subfertility, therefore, assisted conception (eg, in vitro fertilisation) may be a topic of discussion.[12 13] PPC also allows the opportunity to review preconception disease control and medications. It gives an opportunity to address any anxieties that the patient and partner may have, and to emphasise the importance of abstinence from alcohol. Finally, it is important that women are well informed about any complications that may occur during pregnancy.

Pregnancies in cirrhosis are associated with an increased risk of maternal complications: mortality, decompensation (compensated cirrhosis 1.2%, previous hepatic decompensation 13%), intrahepatic cholestasis of pregnancy (relative risk 10.6), pregnancy-induced hypertension (5%–22%), pre-eclampsia (4%–14%) and postpartum haemorrhage (PPH) (5%–45%).[14–20] Splenic artery aneurysm rupture can rarely present during pregnancy.[21] Maternal mortality was previously reported to be as high as 14%, however, recent studies

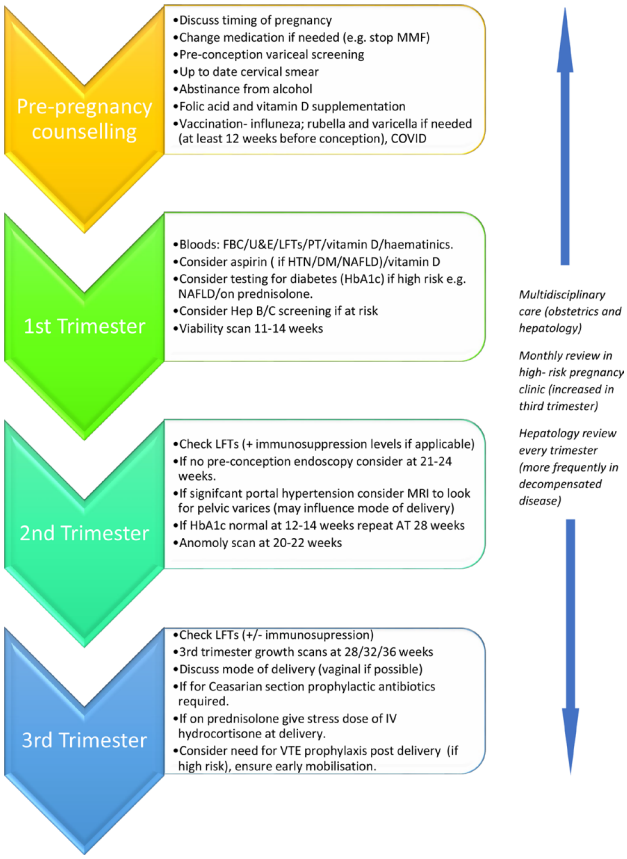

Figure 1 Pregnancy care in cirrhosis. DM, diabetes mellitus; FBC, full bloods count; HbA1c, glycated haemoglobin; HTN, hypertension; IV, intravenous; LFTs, liver function tests; MMF, mycophenolate mofetil; NAFLD, non-alcoholic fatty liver disease/ metabolic dysfunction associated steatotic liver disease (MASLD); PT, prothrombin time, U&E, urea and electrolytes; VTE, venous thromboembolism.

report rates <2%.[14 17 19–23] Preconception MELD scores ≤6 predict positive pregnancy outcomes, while MELD scores ≥10 predict hepatic decompensation during pregnancy (sensitivity/specificity 83%).[22]

Fetal complications include neonatal mortality (<8%), prematurity (19%–67%) and low birth weight (15%–63%).[15–18 20 22 23] Rates of stillbirth and congenital malformations are comparable to the general population.[16 20 22] Preconception Albumin-Bilirubin scores <−2.7 have been demonstrated to predict live birth, and a preconception aspartate aminotransferase (AST)-to-platelet ratio index <0.84 has been shown to predict term pregnancy (≥37 weeks).[24]

Aspirin, folic acid and vitamin D prophylaxis should be considered in those at risk of pre-eclampsia.[25–27] Risk factors include pre-existent hypertension, diabetes, chronic kidney disease and autoimmunity.[28–30] Aspirin prophylaxis should start before complete placental formation (≤16 weeks gestation). The decision to start low-dose (75 mg) versus high-dose (150 mg) aspirin is controversial.[27 29 31]

We recommend that most immunosuppressant and antiviral therapies are continued during pregnancy. Exceptions include mycophenolate mofetil (MMF) (teratogenicity/spontaneous abortion), ribavirin (teratogenicity) and sirolimus (lack of safety data).[10 32] MMF and ribavirin require a wash-out period (6 weeks and 6 months respectively) prior to conception.[10] Patients on entecavir should be converted to tenofovir before pregnancy.[10 33] Copper chelators require dose reduction during pregnancy to limit their teratogenic effects.[34]

PHTN increases during pregnancy, peaking in the second trimester. Varices can, therefore, present or enlarge during pregnancy. Endoscopy is safe provided pregnant women are not oversedated.[10 35 36] The American College of Gastroenterology (AGA) guidelines (2016) recommended variceal screening during the second trimester in women with suspected PHTN.[35] Based on expert opinion, the latest American Association for the Study of Liver diseases (AASLD) guidelines recommend screening endoscopy in the year prior to conception. If there are no varices, it does not need to be repeated in the second trimester. However, if the endoscopy did not occur in the preconception phase, AASLD recommends performing one in the second trimester.[10] We recommend timing this at 21–24 weeks gestation. Non-selective β-blockers can be started/continued in patients with grade 1 oesophageal varices (OV). Risks include fetal hypoglycaemia, bradycardia and intrauterine growth restriction. Endoscopic band ligation can be considered for larger OV, although an individualised approach is recommended based on patient choice/intolerances and high-risk endoscopic stigmata.[10] Although platelets $<110\times10^9$ cells/L can be associated with the presence of varices in the second trimester, other non-invasive surrogate markers for PHTN have not been validated in pregnancy.[20]

Pregnancy in decompensated disease

Pregnancies in women with decompensated liver disease are rare, due to the hormonal imbalances caused by end-stage liver disease. These pregnancies are usually more difficult to manage and should be discussed in a multidisciplinary setting with regular review in outpatients and a low threshold for admission if complications develop.

Prepregnancy MELD scores ≥10 predict the risk of hepatic decompensation during pregnancy, as does a history of previous hepatic decompensation.[14 20] In older studies, the rates of decompensation during pregnancy were reported to be between 12% and 36%.[18 37] A recent US population-based study has demonstrated that rates of hepatic decompensation in pregnancy are lower than expected; 1.2% in compensated cirrhosis and 13% in previous decompensated disease. Variceal haemorrhage is the most common manifestation of decompensation (3%–36%), although ascites (3%–11%), hepatic encephalopathy (<2%) and hepatorenal syndrome can also present during pregnancy.[14–16 18–20 22 23 37]

β-blockers and lactulose can be continued during pregnancy. However, diuretics, rifaximin and most prophylactic antibiotics should be discontinued due to fetal risks and lack of human safety data. Paracentesis should also be avoided where possible. Terlipressin should not be used due to risks of utero-placental ischaemia. In acute variceal haemorrhage refractory to endoscopic therapy, TIPSS insertion can be considered.[38–40] In the context of liver failure, transplantation can be performed successfully in pregnant women.[41 42]

The decision to deliver will be dependent on the presence of materno–fetal complications. Excessive straining and repeated Valsalva manoeuvres during labour, which temporarily increase intra-abdominal pressures, were previously believed to promote variceal rupture. For this reason, C-section rates have been reported to be high (12%–81%) in women with cirrhosis.[15–20 23 37] Pregnancies in these women are also independently associated with induction of labour.[14] C-sections are associated with poor wound healing and infection, which can be problematic in women with cirrhosis who have an increased risk of puerperal infections.[14] Vaginal deliveries are thus a suitable mode of delivery in these pregnancies, while C-sections should be reserved for obstetric indications or based on individualised risk profile.

Pelvic varices, thrombocytopaenia and coagulopathy can increase the risk of PPH in women with decompensated cirrhosis. Management of PPH includes blood/coagulation factors, uterine contractile agents, ligation of bleeding vessels and, if all fails, hysterectomy.

TRAVEL IN PEOPLE WITH CIRRHOSIS

Increasing prevalence, earlier recognition and better management of liver disease mean more people with cirrhosis enjoy a good quality of life and wish to travel.

Patients increasingly seek advice around travel during outpatient appointments.

Some considerations are common across all chronic diseases: advise patients to carry a list of medications, a summary of conditions, complications and therapies in an accessible format. Within the UK, electronic prescribing allows prescriptions to be collected from pharmacies near to the place of stay. If travelling abroad then it is important patients take an adequate supply of their prescribed medications with them. It is advisable to carry a limited supply of medication in hand in case luggage is lost. Additional vaccinations (such as hepatitis A/B) may be required prior to travel if not already taken up. Patients on immunosuppression may be advised against live vaccines such as yellow fever[43] (see part 1).

Adequate travel insurance is crucial—many companies will cover compensated liver disease, but some insurance companies specialise in insuring people with liver disease. Patients should be advised to shop around and consider seeking advice from patient support groups to get the best cover.

People with cirrhosis are often anxious about air travel or visiting destinations at high altitude. However, there is no documented increase in variceal bleeding associated with altitude. Nevertheless, anecdotally, variceal bleeding while on a flight can occur, and it is prudent to ensure appropriate primary prophylaxis for variceal bleeding is initiated prior to travel.

Travel with decompensated liver disease is higher risk and should be considered on an individual basis, considering the destination, the degree of decompensation, suitability for transplant, and mode and duration of travel. Patients on the transplant list should inform their transplant co-ordinator.

Reasons for travel differ—some may have had their decompensation episode away from home and need to get back to their base; others may feel recovered and wish to contemplate holidays; for some it may be important for their quality of life and palliative care.

Once decompensation is declared, insurance premiums increase significantly and for some individuals or destinations may not even be available. It may be advisable to delay travel following an acute decompensation, for example, to complete a banding programme following variceal haemorrhage, and to ensure liver disease is optimised. It is important patients understand the potential risks of travel in order to make an informed decision.

MANAGEMENT OF BLEEDING RISK FOR INVASIVE PROCEDURES

Complex changes occur to haemostatic systems in patients with cirrhosis, with both prothrombotic and anticoagulant arms of the clotting pathways affected. Prothrombin time (PT), activated partial thromboplastin time (APPT) and platelet count do not predict bleeding outcomes in most patients with cirrhosis, including those undergoing invasive procedures. People with cirrhosis are at increased risk of thrombosis, and bleeding risk tends to be related to other factors, primarily PHTN and vessel injury.

Table 3 Procedural bleeding risk in patients with cirrhosis[44 53]

Low risk procedures (bleeding risk <1.5%)	High-risk procedures (bleeding risk ≥1.5%)
Diagnostic endoscopy±biopsy	Polypectomy/EMR/ESD
Paracentesis	ERCP with sphincterotomy
Thoracocentesis	Variceal band ligation
Transoesophageal echocardiography	Therapeutic endoscopic ultrasound
Percutaneous liver biopsy	Dental extraction
Transjugular liver biopsy	
HVPG measurement	
Percutaneous ablation of liver cancer	

EMR, endoscopic mucosal resection; ERCP, endoscopic retrograde cholangiopancreatography; ESD, endoscopic submucosal dissection; HVPG, hepatic venous pressure gradient.

Both the American Gastroenterological Association and the European Association for the Study of the Liver have guidelines on managing clotting in people with cirrhosis undergoing invasive procedures.[44 45] There are also recent British Society of Gastroenterology guidelines on liver biopsy which include management of coagulation.[46] There is broad consensus on the basic principles as follows.

There is no indication for blood products in order to prevent spontaneous bleeding, and no indication for vitamin K to correct PT, although it may be used in the context of cholestatic liver disease (eg, before endoscopic retrograde cholangiopancreatography (ERCP)), to reverse warfarin, or where vitamin K deficiency in suspected (eg, severe malnourishment).

In patients with stable cirrhosis undergoing common, lower-risk procedures (bleeding risk <1.5%) there is no indication to check or correct clotting or platelet count prior to the procedure. See table 3 for procedures with low/high bleeding risk.

In patients undergoing procedures with a higher bleeding risk (>1.5%), laboratory assessment of haemostasis may be useful as a baseline to guide treatment if postprocedural bleeding occurs. Vasoelastic tests may be used to identify subgroups of patients with significantly increased bleeding risk and guide blood product use.[47]

Correction of prolonged international normalised ratio (INR) with fresh frozen plasma (FFP) is not recommended, even for high-risk procedures—in some cases plasma expansion can exacerbate PHTN and increase bleeding risk. Platelet infusion/thrombopoietin receptor (TPO-R) agonists are not recommended if platelets are $>50\times10^9$ or if bleeding can be treated by local haemostasis.[45] For people with

a platelet count $<50\times10^9$ undergoing high-risk procedures platelet transfusion/TPO-R agonists should not be required routinely but should be considered on a case-by-case basis, particularly if platelet count $<20\times10^9$.[44 45] TPO-R agonist should be used with caution in patients with decompensated cirrhosis, and dose adjustments may be required.[48] Consider discussing with haematology and refer to local protocols. If possible, haemoglobin, iron, folic acid and B_{12} should be optimised prior to high-risk procedures.

PORTAL VEIN THROMBOSIS

Increased levels of factor VIII (procoagulant driver) and decreased levels of protein C (anticoagulant driver), combined with reduced portal vein flow velocity and endothelial injury, increase the risk of portal vein thrombosis (PVT).

Many patients are asymptomatic; the diagnosis is often made on routine hepatocellular carcinoma (HCC) surveillance, or coincidentally during liver decompensation. However, PVT is independently associated with worsening decompensation, including

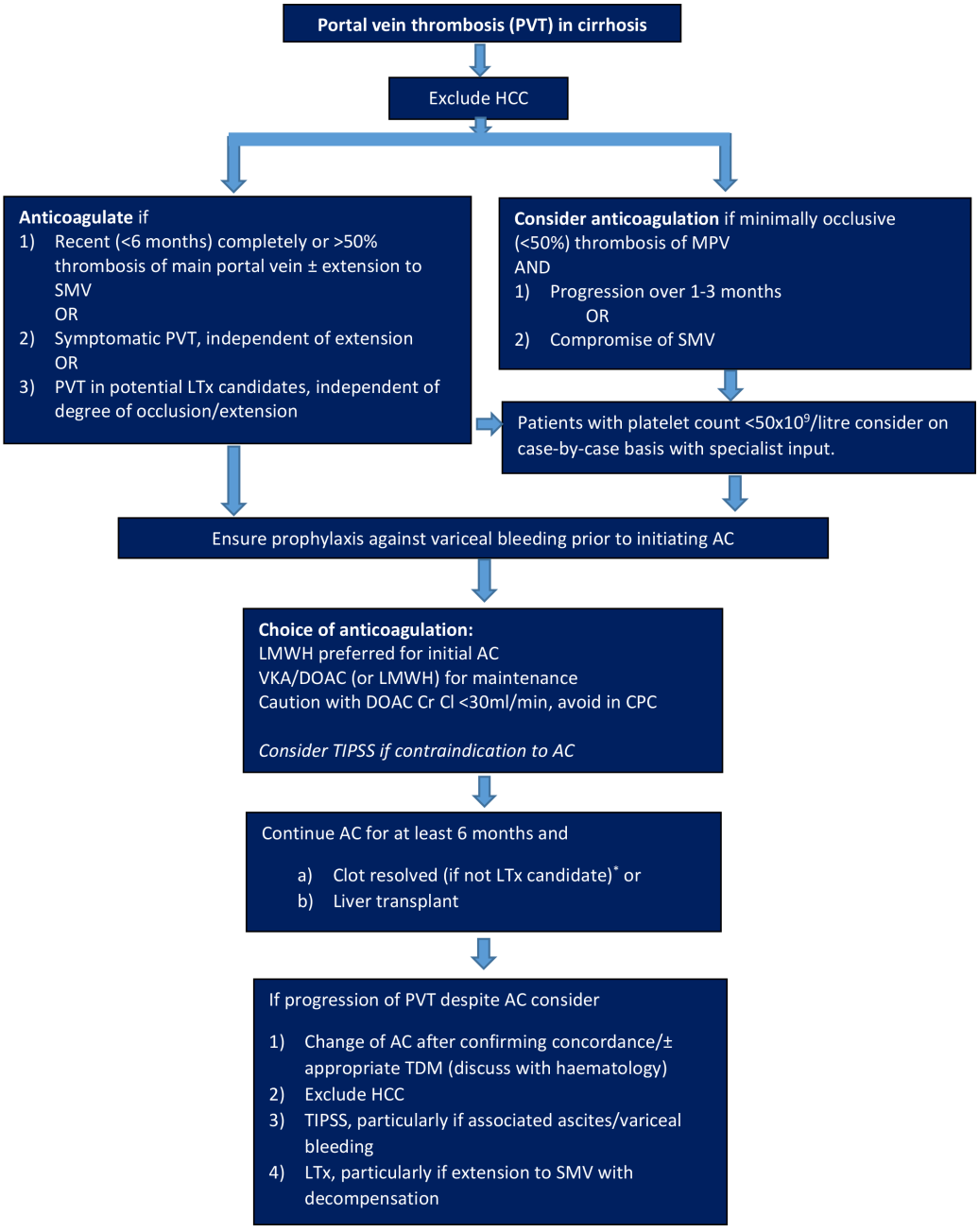

Figure 2 Management of portal vein thrombosis in cirrhosis. *Consider long-term anticoagulation if risk of recurrence outweighs bleeding risk. AC, anticoagulation; CPC, Child-Pugh C; DOAC, direct-acting oral anticoagulants; HCC, hepatocellular carcinoma; LMWH, low-molecular-weight heparin;; LTx, liver transplant; MPV, main portal vein; SMV, superior mesenteric vein; TDM, therapeutic drug monitoring; TIPSS, transjugular intrahepatic porto-systemic shunt; VKA, vitamin K antagonist (ie, warfarin).

variceal bleeding and with increased mortality in liver transplant candidates.[49]

Initial diagnosis is made on Doppler US or CT imaging. MR/CT imaging should be performed to evaluate the extent of the thrombus and rule out neoplastic PVT/HCC. Consider screening for underlying thrombophilic conditions if there are extensive clots or other thromboses.

The management of PVT in cirrhosis is summarised in figure 2. Initial treatment is with anticoagulation, although treatment is not required in all cases. Chances of responding to anticoagulation are higher if treatment is started within 6 months of diagnosis. The recent Baveno VII guidelines recommend treatment in patients with cirrhosis and recent (<6 months) PVT involving >50% of the portal vein trunk lumen, any symptomatic PVT or PVT in potential liver transplant candidates.[50] Treatment can also be considered if there is progression of thrombosis on early follow-up (1–3 months), or compromise of the superior mesenteric vein (SMV).[50]

Anticoagulation has been found to be safe and effective. The risk of bleeding is highest in patients with platelet count <50, so anticoagulation in these patients should be considered on a case-by-case basis.[50] In patients with GOV, beta blockers or variceal band ligation should be initiated prior to starting anticoagulation.

Treatment is initiated with low-molecular-weight heparin (LMWH), dosed by weight. Caution is required in renal impairment and dose adjustments may be required. LMWH or warfarin with a target INR of 2–3 can be used for maintenance, although INR is difficult to interpret in patients with cirrhosis. While data are limited for direct oral anticoagulants, evidence suggests they are safe in Child-Pugh A cirrhosis, and they have the advantage of being much easier to use. Due to the risk of accumulation, they should be used with caution in Child-Pugh B cirrhosis, and they are currently not recommended in patients with Child-Pugh C disease outside clinical trials.[51]

Anticoagulation should be given for at least 6 months, and until the clot has resolved, or until transplant. Long-term anticoagulation can be considered in patients where risk of recurrence outweighs bleeding risk, including patients with underlying thrombophilic conditions, recurrent thromboses, and those with extension into the SMV.

In the case of progressive PVT despite anticoagulation, concordance and therapeutic drug monitoring should optimised in the first instance. A change in dose/therapeutic range (eg, aiming for higher INR) or alternative anticoagulants can be considered with specialist input from haematology. Interventional radiology/TIPSS[52] and surgery can also be considered, particularly in transplant candidates or in patients with acute symptomatic PVT or ischaemia.

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