# The management of varices in acute on chronic liver failure: a systematic review of guidelines and investigation of local practice

## Master of Philosophy

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# Declaration

This thesis is part of a Master of Philosophy degree that I undertook between years four and five of an undergraduate medical degree at Keele University.

The idea for this project was proposed by both Dr Sara Muller, senior lecturer in statistics at Keele University, Dr Rajeev Desai, consultant hepatologist at University Hospital North Midlands NHS Trust (UHNM), and Professor Christian Mallen, honorary senior clinical lecturer and Head of Keele University Medical School. Mrs Joanne Jordan provided valued advice regarding the protocol development for the systematic review as well as the search strategy. Dr Muller and I performed the abstract screening for the systematic review. Dr Muller and Dr Desai performed full text screening and critical appraisals of the guideline as the second reviewers. Dr Dahai Yu screened one of the papers that was written in Chinese, to identify if it should be included or not.

The data for the service evaluation were collected by the Hepatology clinical team at UHNM, including Dr Desai and registrar Dr Abdullah Abbasi, for a previous audit. Dr Muller aided with the statistical analysis that was used for the service evaluation, although I performed all the interpretation myself. Dr Muller, Dr Desai and Professor Mallen have provided valuable comments on my drafted documents, though the ideas behind the thesis are mine. The drawings for the thesis were completed by Saujanya Kesavan.

# Abstract

Varices are a complication of chronic liver disease and are associated with a high mortality if they haemorrhage. Patients need to be managed using the best available evidence to improve their outcomes. This thesis is formed of two parts: a systematic review appraising the quality of international guidelines on the management of varices, and a service evaluation, assessing guideline adherence in managing acute upper gastro-intestinal variceal haemorrhage at the University Hospital North Midlands NHS Trust (UHNM).

Following a systematic search in accordance with the predefined protocol, 49 international guidelines were included in the systematic review and underwent data extraction and quality appraisal against Domain 1 (Scope and Purpose) of the AGREE II checklist. Those that performed moderately or highly in Domain 1 underwent Domain 3 (Rigour of Development) appraisal. Twenty-one guidelines were assessed against Domain 3. The recommendations made by the 28 excluded guidelines and those retained were similar. Some interventions that are used in clinical practice are not supported by high quality evidence, but 19 recommendations were put forward following this review as they are supported by high quality evidence.

Four of the six recommendations put forward from the systematic review specifically for the management of active variceal haemorrhage were used as standards for the service evaluation. These were: terlipressin administration; antibiotic prophylaxis administration; endoscopy within 24 hours; endoscopic band ligation for oesophageal varices. In 149 patients, 37.6% received all recommendation-adherent treatments. Sicker patients (denoted by their Child-Turcotte- Pugh class) were more likely to receive terlipressin and antibiotics; patients presenting out of hours were more likely to receive endoscopy within 24 hours; and patients with grade one varices

were less likely to receive banding. Generally, adherence to terlipressin and antibiotic administration were high. Improvements could be made to improve adherence to the target of endoscopy within 24 hours.

This project highlights potential for improvements in making and applying guidelines in this field.

# Acknowledgements

I would like to thank Keele University Medical School for giving me the opportunity to intercalate.

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I would like to express my appreciation to Mrs Joanna Jordan for providing valuable advice regarding the systematic review, and answering the many questions I had regarding the process.

The service evaluation would have not been possible without the patients admitted at UHNM. I hope that what I have found can improve outcomes for patients like them.

I would like to thank my parents and sister, who have always kept my spirits high throughout the process. My friends, Chandana and Shivang, who have always provided reassurance and kept me sane. A fellow researcher and friend, Amardeep, who helped me understand what a research degree entails and how to be proficient at Stata. Lastly, my fiancé, Harpal, who has been my pillar of support this year. Words cannot express my gratitude for all of them.

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# Abbreviations and Acronyms

| | |
|---|---|
| ACLF | Acute-On-Chronic Liver Failure |
| ALD | Alcohol related Liver Disease |
| ALF | Acute Liver Failure |
| BSG | British Society of Gastroenterology |
| CLD | Chronic Liver Disease |
| CTP | Child-Turcotte-Pugh |
| EASL | European Association for the Study of the Liver |
| EIS | Endoscopic Injection Sclerosis |
| FiO2 | Fraction of inspired Oxygen |
| GOV | Gastro-oesophageal Varices |
| HE | Hepatic Encephalopathy |
| HVPG | Hepatic Venous Pressure Gradient |
| IGV | Isolated Gastric Varices |
| INR | International Normalised Ratio |
| IVC | Inferior Vena Cava |
| LFT | Liver Function test |
| mmHg | Millimetres of mercury |
| MELD | Model of End Stage Liver Disease |
| NAFLD | Non-alcoholic Fatty Liver Disease |
| NASH | Non-Alcoholic Steatohepatitis |
| NICE | National Institute of Clinical Excellence |
| NSBB | Non-Selective beta blocker |
| PaO2 | Partial pressure of Oxygen |
| TIPS | Transjugular intrahepatic portosystemic shunt |
| ug/dL | Micrograms per decilitre |
| VBL | Variceal band ligation |

# 1 Introduction

Liver disease is a common condition that accounts for 2 million deaths per year worldwide (Asrani *et al.*, 2019). It can present a variety of symptoms. Bleeding from varices, which are dilated veins in the upper digestive tract, is one of the important presentations of liver disease as it can be rapidly fatal if not treated. This research project will investigate the management of varices in the upper digestive tract using a systematic review of clinical management guidelines and a service evaluation of patients presenting with bleeding varices at University Hospital North Midlands NHS Trust (UHNM). The first chapter will summarise the basic anatomy of the liver, its functions, the pathophysiology of liver disease, and its complications.

## 1.1 Liver

### 1.1.1 Anatomy

The liver is the largest internal organ in the human body, located in the upper right quadrant of the abdomen. It accounts for 2-3% of the human body weight and weighs around 1.5kg in the average adult male (Abdel-Misih and Bloomston, 2010; Molina and DiMaio, 2012). The liver is closely associated with other organs such as the diaphragm, gall bladder and the right kidney, and is held in position by various ligaments (Abdel-Misih and Bloomston, 2010; Vernon, Wehrle and Kasi, 2021). Anatomically, the liver is split into four lobes: right lobe, left lobe, caudate lobe and quadrate lobe. Functionally, the liver can be split into 8 segments, where each of the segments receive its own blood supply from the branches of the main artery of the liver (Sibulesky, 2013).

#### *1.1.1.1 The vascular supply of the liver*

The vascular supply of the liver is unique and complex, as it has a dual blood supply. The hepatic artery (Figure 1-1) provides 25% of its blood supply (Eipel, Abshagen and Vollmar, 2010). The other 75% of the blood supply comes from the portal vein. The portal vein is created by the confluence of the veins that drain blood from the gastrointestinal system (called mesenteric veins) and the vein that drains the spleen (splenic vein). The portal system collects the nutrients that are absorbed from the gastrointestinal system, so that the liver can process the toxins before the blood reaches the systemic circulation (Carneiro *et al.*, 2019). The portal vein provides most of the blood supply to the liver, which makes the liver unique as other organs receive the majority of their blood supply from an artery.

The veins that drain the blood out of the liver are called the hepatic veins, which are four in number. The hepatic veins drains into the inferior vena cava (IVC) (Carneiro *et al.*, 2019). The IVC pumps blood into the right side of the heart.

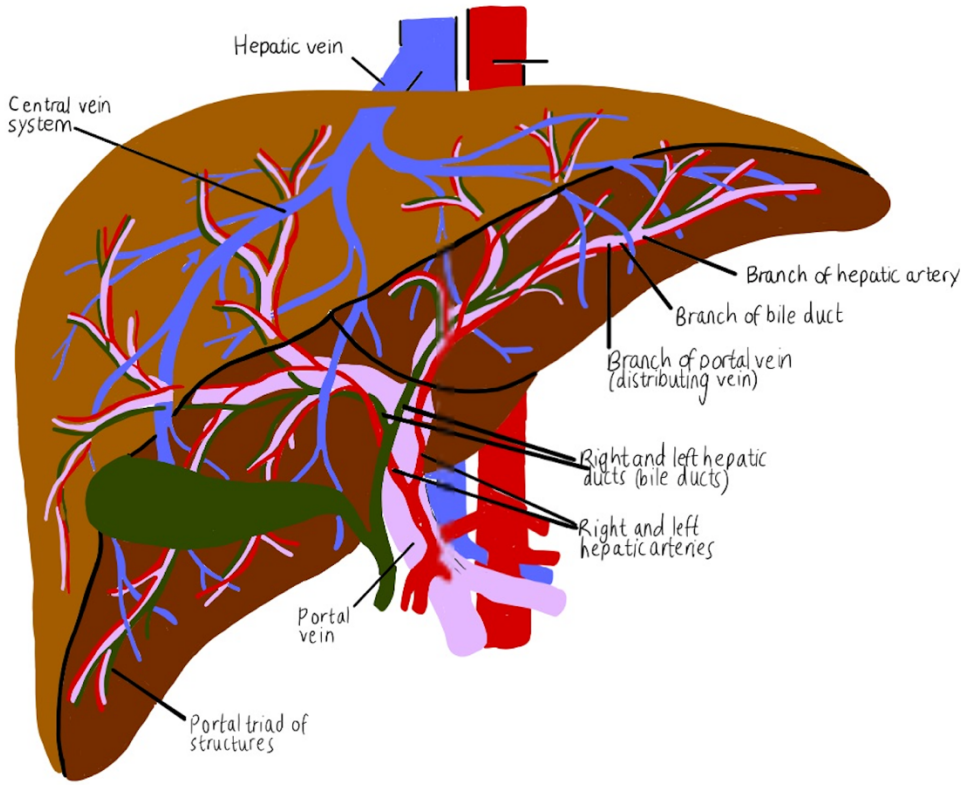

*Figure 1-1: Vascular Supply of the Liver. Re-drawn by Saujanya Kesavan (MediVisuals, 2007).*

#### *1.1.1.2 The histology of the liver*

The liver is arranged in microscopic functional units called sinusoids. They can be described as highly specialised capillaries (Du, Li and Long, 2018). The capillaries are lined by sinusoidal endothelial cells (Brunt *et al.*, 2014). There are other cells types that are also present within the sinusoids including Kupffer cells and stellate cells (Brunt *et al.*, 2014). Kupffer cells are macrophages - they create an immune response to prevent infections (Nguyen-Lefebvre and Horuzsko, 2015). Stellate cells are vitamin A storing cells that can be activated to become myofibroblasts, which promote healing (Tsuchida and Friedman, 2017). They do so by releasing collagen (Du, Li and Long, 2018). However with repeated injury, e.g. in chronic liver disease, this healing mechanism can cause irreversible fibrosis which can lead to complications. This pathological phenomenon leads to liver cirrhosis, which can lead to further complications (see section 1.4).

#### *1.1.1.3 The biliary system*

Within the liver, there are small bile ducts that run adjacent to the branches of the hepatic artery and the portal vein. The branches of the bile duct, hepatic artery and the portal vein together are referred to as the portal triad (Castaing, 2008). The bile ducts are responsible for draining the bile that hepatocytes (liver cells) produce. Bile is a liquid that is essential for the digestion and absorption of the dietary fats. The smaller bile ducts drain into two main tracts which are found within the liver- the right and left hepatic ducts (Babu and Sharma, 2014) (Figure 1-2). They can join together to form the common hepatic duct downstream. The common hepatic duct drains into the cystic duct, which is the main branch that comes off the gallbladder to store the bile. Anatomically, the gallbladder is closely associated to the liver. To release the bile, the gall bladder contracts in response to the arrival of food in the digestive tract and the bile flows out of the cystic duct into the common bile

duct. The common bile duct joins with the pancreatic duct and releases bile directly into the small intestines where bile participates in emulsification and digestion of dietary fats.

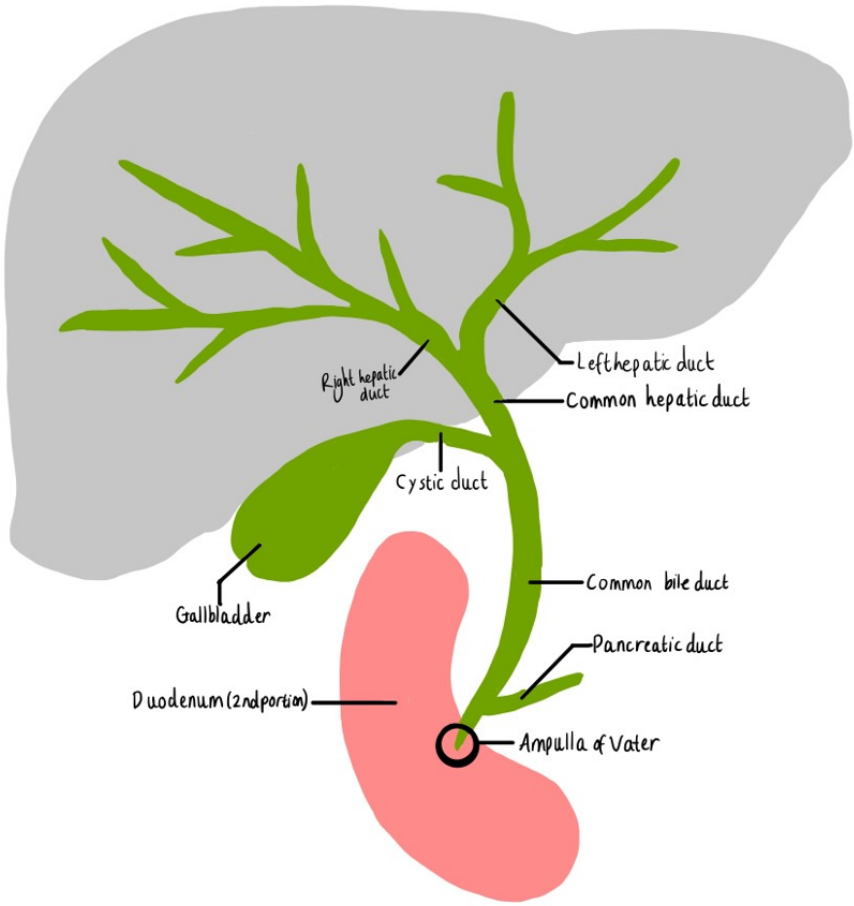


*Figure 1-2: The Biliary System. Re-drawn by Saujanya Kesavan (Themes, 2016).*

### 1.1.2 Function of the liver

The liver performs many functions (Table 1-1) including: bile synthesis, urea metabolism, drug metabolism, and clotting factor synthesis (Kalra *et al.*, 2022). This section will briefly describe the main functions of the liver as relevant to this thesis.

| Functions of the liver | Explanation of those functions |
|---|---|
| Storage | • Storing molecules such as carbohydrates, lipids and vitamins |
| Excretory | • Removal of waste matter that is produced by the body e.g. old red blood cells |
| Metabolic | • There are specialised enzymes that are able to metabolise substances such as glucose and most drugs |
| Endocrine (hormone related) | • Activating and metabolising various hormones that are essential for everyday function including vitamin D, thyroid hormones, and steroids<br>• Secreting hormones such as thrombopoietin and angiotensinogen |
| Synthetic | • Synthesis of many proteins that are used as carrier molecules to transport lipids and insoluble molecules around the body e.g. albumin.<br>• Bile synthesis |
| Immunological | • Specialised immune cells called Kupffer cells reside in the liver which create a response against pathogens that enter the blood stream |

*Table 1-1 An overview of the key functions performed by the liver (Boron and Boulpaep, 2016; Antonelli, Ferri and Fallahi, 2011).*

#### *1.1.2.1 Bile synthesis*

Bile is made up of water, bilirubin, bile salts, cholesterol and some electrolytes (Hundt, Basit and John, 2022).

***Bilirubin formation:***

Red blood cells carry oxygen to tissues. They contain a molecule called haemoglobin, which is made up of haem and globin. After the death of red blood cells, haem is metabolised in the spleen to make a by-product, bilirubin. At this stage, bilirubin is insoluble in the blood, and so it becomes bound to a

carrier protein called albumin (Wolkoff and Berk, 2011). The insoluble form of bilirubin cannot be excreted from the body. For it to be excreted, bilirubin needs to be soluble, and this is achieved by a process called conjugation which occurs in the liver. Unconjugated bilirubin enters the circulation and is transported into the hepatocytes to be conjugated with glucuronic acid (Sticova and Jirsa, 2013). Conjugated bilirubin dissolves in bile and enters the small intestines via the bile ducts to be excreted further down in stool and urine. In liver disease, excessive accumulation of either conjugated or unconjugated bilirubin, leads to clinical manifestation of jaundice (see section 1.4.1) (Joesph and Samant, 2022).

***Bile formation:***

Bile acid is produced through the conversion of cholesterol by hepatocytes (Chiang and Ferrell, 2018). Hepatocytes secrete bile acids, bilirubin, water, cholesterol and electrolytes into the bile canaliculi (Hundt, Basit and John, 2022). This drains through the bile ducts and is eventually stored in the gall bladder. The bile, in combination with pancreatic lipase facilitates digestion of the ingested fats, and then they can be absorbed by the intestines (Trefts, Gannon and Wasserman, 2017).

#### *1.1.2.2 Urea metabolism*

Proteins are in abundance within the human body, and the liver is responsible for synthesising and breaking down most of those proteins into safer constituents (Trefts, Gannon and Wasserman, 2017). Proteins are made up of molecules called amino acids, which have nitrogen chains attached to them. Nitrogenous chains can be harmful to the body if not metabolised properly. To metabolise amino acids, a reaction called the 'Urea cycle' needs to take place, which allows the nitrogen chain to be removed. Ammonia is a waste product of this process, which is toxic, particularly to the brain. Ammonia is converted into urea by the liver, which is a less toxic substance (Elwir and Rahimi, 2017)

and is then excreted by the kidneys. In liver disease, the metabolism of amino acids can become impaired, which causes the build-up of ammonia that can have harmful effects to the functioning of the brain.

#### *1.1.2.3 Drug metabolism*

The liver is one of the main organs that metabolises drugs (Corsini and Bortolini, 2013), alongside kidneys, lungs and skin. Specialised enzymes in the liver such as cytochrome P450 convert drugs into active or inactive metabolites (Almazroo, Miah and Venkataramanan, 2017). Drug metabolism is dependent on two factors: the blood flow to the liver and the availability of the cytochrome enzymes (Rodighiero, 1999). In liver disease, both of these factors can be impaired, which leads to a build-up of different drugs and resultant toxicity.

#### *1.1.2.4 Blood clotting and anticoagulation*

The liver plays an important role in coagulation homeostasis, including blood clotting and anticoagulation. Blood clotting is a complex cascade reaction that is dependent on multiple entities including activation of platelets and clotting factors. The liver produces clotting factors that are essentially precursor enzymes that become activated to cause clot formation to achieve haemostasis (to stop the tissue from bleeding). In liver disease, there may be a deficiency in some clotting factors, and so the time it takes blood to clot may become prolonged (Flores *et al.*, 2017). This can present with excessive bleeding. The liver also produces anticoagulation factors such as protein C and protein S. Impaired production of these factors in patients with liver disease can result in abnormal blood clot formation. As such, patients with liver disease can simultaneously be at high risk of excessive bleeding and abnormal clot formation.

The time it takes for blood to clot is important to measure in patients with liver problems. This can be done through a specialised blood test called prothrombin time (PT). PT is not standardised as different laboratories use different reagents, and this can cause some discrepancy when results from different laboratories are compared. PT can be used to calculate the international normalised ratio (INR), which is a more standardised result to understand the clotting ability of blood that can be used for comparison (Ignjatovic, 2013). In a normal physiological state, the INR should be at or below 1.1. If it is higher, the individual has a coagulopathy – a tendency for prolonged bleeding.

## 1.2 Liver diseases

Liver diseases can broadly be split into acute liver disease and chronic liver disease (CLD).

### 1.2.1 Acute liver disease

Acute liver disease can be described as the acute deterioration in liver function in a patient with no pre-existing liver disease (Dong, Nanchal and Karvellas, 2020). Some people with acute liver disease can develop acute liver failure, which can be defined as the development of altered mental status due to hepatic encephalopathy (see section 1.6.1) within 26 weeks of the onset of jaundice in a patient with no underlying liver disease (Trey *et al.*, 1970).

The majority of patients with acute liver disease do not develop hepatic encephalopathy and so do not meet the diagnostic criteria for ALF. Depending on the cause of acute liver disease, such patients can experience spontaneous recovery (common with viral hepatitis A or E) or go on to develop chronic liver disease (common with auto-immune hepatitis or viral hepatitis B or C).

***Aetiology of Acute Liver Disease:***

The cause of acute liver disease is dependent on the geographical location. In developed countries, the commonest cause of acute liver disease is paracetamol overdose (Bernal, 2003). However, only 2-5% of medication overdoses lead to ALF (O'Grady, 2005). In developing countries the most common causes are viral infections e.g. hepatitis A and E (O'Grady, 2005; Blackmore and Bernal, 2015). They are short-term infections that can present symptomatically in the acute phase but rarely progress to become ALF, and are self-resolving in the vast majority (99%) of patients (Blackmore and Bernal, 2015). Hepatitis A and E are transmitted through the faecal-oral route. Hepatitis B and C can be transmitted through contact with bodily fluids from an infected individual. The common routes can be: vertical transmission (directly passing from mother to baby), sexual intercourse, and the use of contaminated injection needles in the healthcare setting or by intravenous drug users. Hepatitis B initially presents acutely with flu-like symptoms, with rapid spontaneous improvement of symptoms and of the virus from the blood stream within 6 months, in over 90-95% of immune competent patients. If the immune system is unable to clear the virus within 6 months, it can become a chronic infection (Tang *et al.*, 2018) (see section 1.2.2.2.1). It is quoted that 5-10% of those with acute hepatitis B infection go on to develop chronic hepatitis B infection and in due course, CLD (Hyams, 1995).

Other less common causes of acute liver disease include: autoimmune hepatitis, seronegative hepatitis, ischaemic hepatitis (a condition where there is impaired blood flow to the liver), fatty liver disease of pregnancy and Wilson's disease (a pathology where there is impaired copper storage) (Stravitz and Lee, 2019).

### 1.2.2 Chronic liver disease

Chronic liver disease (CLD) can be defined as a progressive decline in the function of the liver for six months or more (Sharma and Nagalli, 2021).

#### *1.2.2.1 Prevalence of liver disease, and associated mortality*

It is important to assess the prevalence and incidence rate of a condition to understand the burden of the problem within a population. Prevalence can be defined as the total number of cases of patients with the pathology over a certain time frame, or at a specific point in time (Spronk *et al.*, 2019). Incidence rate is the number of new cases that arise in a given time period in a population that are at risk of the disease (Spronk *et al.*, 2019). These estimates can be used to make healthcare policy plans for prevention and management for the disease as well as planning health services appropriately.

According to the British Liver Trust, deaths due to liver disease have risen by 400% since the 1970s (British Liver Trust, 2022). Liver disease is also the leading cause of death amongst 35-49 year olds (British Liver Trust, 2022). Despite the advancement in preventative measures and treatment options, the prevalence of the condition has not drastically reduced.

***Prevalence and mortality rates:***

Accurate statistics on the global prevalence of liver disease are limited. Although most countries have national data offices, they do not measure liver disease statistics with rigour, and so, only rough estimates are available. In 2020, cirrhosis ranked 11$^{th}$ on the cause of global mortality, and caused 1.31 million deaths globally (World Health Organization, 2020). It is important to note that this figure is likely to be an underestimate (Asrani *et al.*, 2019). The common causes of CLD

worldwide are: non-alcoholic fatty liver disease (NAFLD), alcohol-related liver disease (ALD) and viral hepatitis (Global burden of disease 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018). However, these figures vary from country to country as the aetiologies vary by geographical location. For example, in developed countries, the common causes are NAFLD and ALD. Whereas in Asian countries and sub-Saharan Africa, the most prevalent cause is viral hepatitis B, C and D (Sharma and Nagalli, 2021).

In the UK, 90% of the causes of CLD are preventable as they are caused by ALD, NAFLD and viral hepatitis(British Liver Trust, 2022). The commonest cause of CLD globally is NAFLD, but in the UK, the commonest cause is ALD (Global burden of disease 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018; Office for Health Improvement and Disparities, 2021).

The cases of ALD have risen, especially since the start of the COVID- 19 pandemic (Office for Health Improvement and Disparities, 2021). In 2020, there were 5,608 recorded cases of ALD, which is a 21% increase from 2019. Easy availability and affordability of alcohol could be why cases are increasing. Currently, the intake of alcohol per adult is estimated to be around 18 units per week, but recommended units are 14 or fewer (Alcohol Change, 2022).

NAFLD is one of the commonest causes of CLD in the UK. This is because NAFLD is closely associated with obesity and is often related to lifestyle behaviours such as diet and exercise. Cases of obesity are on the rise. The Health Survey for England 2019 found that 28% of adults are obese and 36% are overweight in England (NHS Digital, 2020). It has been estimated that 20-30% of the general population in the UK have NAFLD (National Institute of Clinical Excellence, 2016). The rate of childhood obesity is also growing and as a result, cases of CLD have shifted from being more common in an older age group to a younger age group (National Institute of Clinical Excellence,

2016). The majority patients with early-stage NAFLD are asymptomatic, so the estimated prevalence rates are likely an underestimate.

Despite viral hepatitis being a major health problem globally, the prevalence of hepatitis C in the UK is low, where it currently stands between 0.5-1% (Health and Safety Executive, 2022). The prevalence of HBV is even lower than this in the UK (0.1-0.5%). The cases have generally decreased over time with the introduction of both prevention and management interventions e.g. hepatitis B vaccination, anti-viral medications, access to sterile needles for intravenous drug use, and education for safe sex practice (Moon, Singal and Tapper, 2020; Health and Safety Executive, 2022).

***Incidence and mortality:***

The global incidence of CLD in 2017 was 5.2 million (Moon, Singal and Tapper, 2020). CLD is the 11$^{th}$ most common cause of death worldwide (Cheemerla and Balakrishnan, 2021). As shown in Figure 1-3, the age-standardised rate of death per 100,000 attributed to CLD in the UK, has not varied much since 2001 (Office for National Statistics, 2021). In the early 2000s, the rate varied from 3.3 to 3.6 per 100,000 individuals. Since 2014, this rate has remained at or above 3. This suggests that the rate of mortality from CLD has not decreased despite the advances in prevention and treatment strategies.

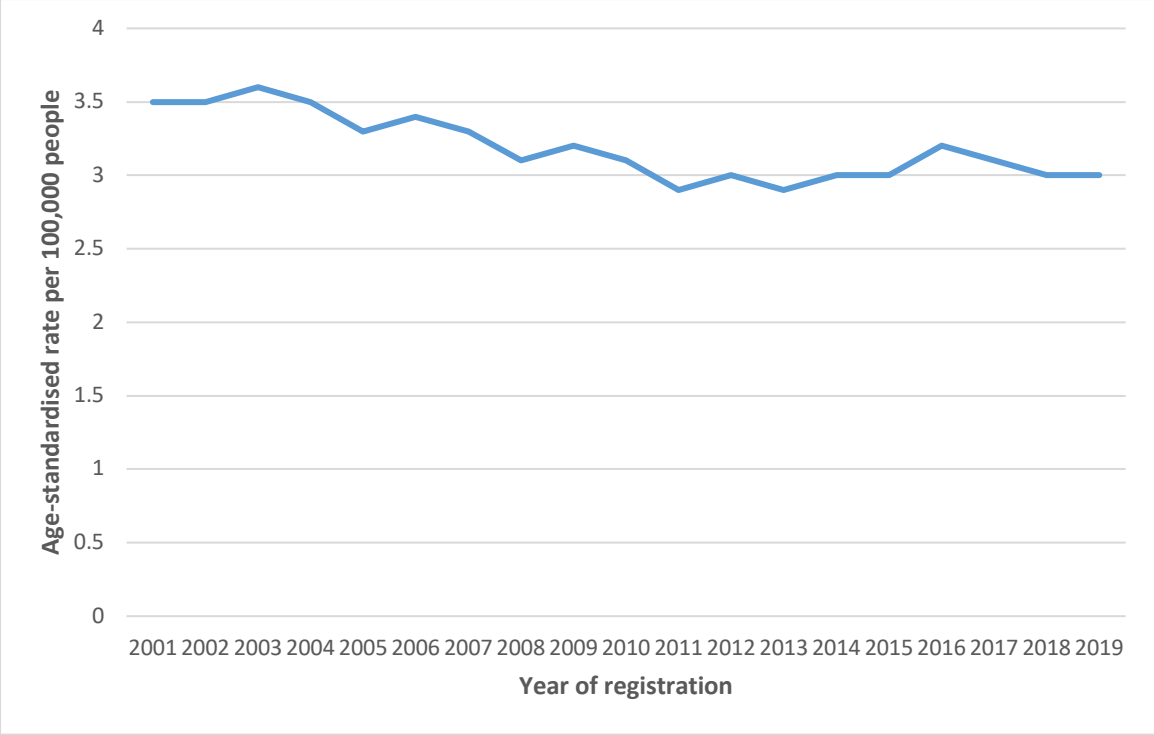


*Figure 1-3: Graph to show age-standardised rates per 100,000 people caused by unspecified chronic liver disease registered between 2001 and 2019 in the UK. This graph has been created using the data that is available freely by the Office for National Statistics (Office for National Statistics, 2021).*

Despite numerous public health measures that have been introduced to prevent liver disease, it is one of the only diseases in the UK where the mortality is still increasing. Mortality from other conditions such as ischaemic heart disease, and lung diseases have decreased over time, whereas in liver disease, there is a certain increase (Figure 1-4) (British Liver Trust, 2022).

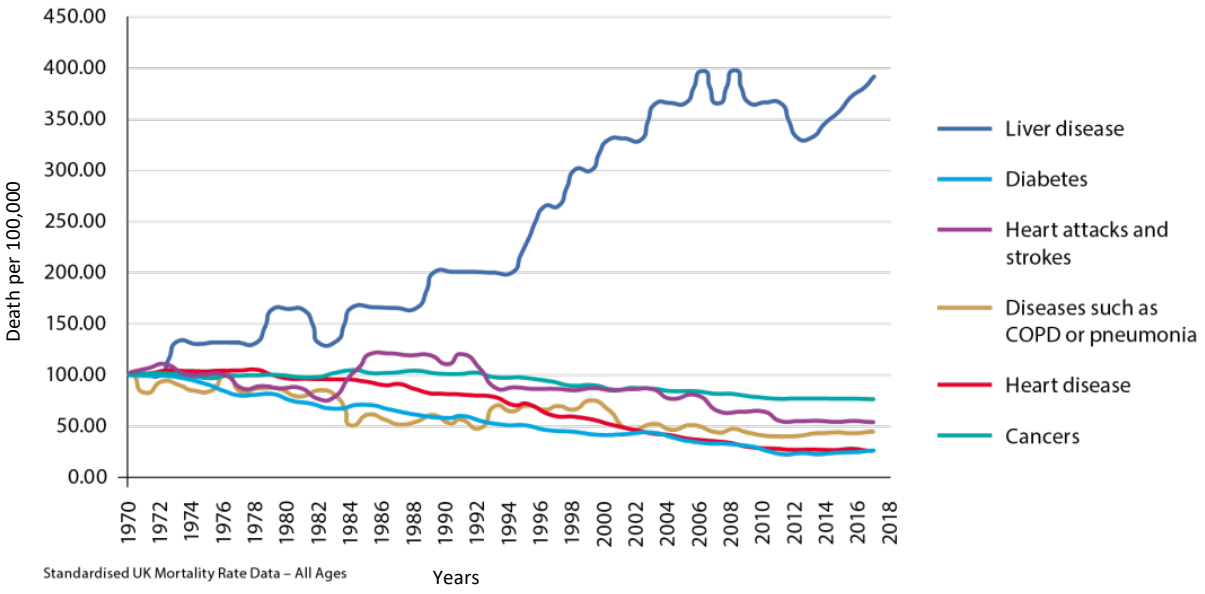


*Figure 1-4: A graph to show the mortality rates of the common diseases in the UK (British Liver Trust, 2022). This graph has been directly taken from the British Liver Trust with permission.*

*Abbreviations: COPD = Chronic obstructive pulmonary disease.*

Liver transplantation data

Patients can be considered for liver transplantation if there is marked progression of CLD (following a comprehensive transplant assessment process). During the period April 2019-2020, 979 liver transplants were performed in England (NHS Blood and Transplant, 2020). The commonest indication for a liver transplant was ALD (25%). The next commonest indication was liver cancer (19%). Metabolic liver disease (which includes NAFLD) accounted for 12% of the liver transplantations. It is also important to note that the cause of liver cancer can be CLD of any cause (see section 1.2.2.2).

### *1.2.2.2 Aetiologies of chronic liver disease*

Depending on the geographical location, the cause of the liver disease may different. In this section, the specific aetiologies will be discussed in detail. In the UK, the commonest aetiologies are

highlighted in Table 1-2, which also highlight the associated hospital admissions rate and mortality rate.

| **The commonest aetiologies of chronic liver disease in the UK** (Public Health England, 2021)**:** | **Associated Hospital Admissions rate in England** (Office for Health Improvement & Disparities 2022): | **Mortality rate in England in under 75 year old** (Office for Health Improvement & Disparities 2022)**:** |
|---|---|---|
| Alcoholic liver disease | 45.5 per 100,000 population. | 10.8 per 100,000 |
| Non-alcoholic fatty liver disease | 3.7 per 100,000 population | 0.47 per 100,000 |
| Viral hepatitis B[1] | / | 0.13 per 100,000 |
| Viral hepatitis C[2] | / | 0.53 per 100,000 |

*Table 1-2: A table to show the commonest aetiologies of chronic liver disease in the UK (Public Health England, 2021).*

#### 1.2.2.2.1 Viral hepatitis

Hepatitis infections B, C and D can lead to CLD. Due to the chronic nature of hepatitis C, patients rarely present with symptoms acutely, and so the disease is commonly identified when it has progressed to later stages (Center for Substance Abuse Treatment, 2011). Around 50-80% of patients with hepatitis C virus will develop a chronic infection (Li and Lo, 2015). There are an estimated 400 million people with chronic hepatitis B virus infection and 170 million people worldwide with hepatitis C virus (Karnsakul and Schwarz, 2017).

#### 1.2.2.2.2 Alcohol-related liver disease

ALD is the most prevalent cause of CLD in the UK (Seitz *et al.*, 2018; Office for Health Improvement and Disparities, 2022). The liver is the primary site of alcohol metabolism and so, it suffers the most damage (Osna, Donohue and Kharbanda, 2017). Alcohol can affect the liver acutely and chronically.

[1] The information on hospital admission rate for hepatitis B was not available.
[2] The information on hospital admission rate for hepatitis C was not available.

Acutely, it can cause alcoholic hepatitis (inflammation of the liver) (Bruha, Dvorak and Petrtyl, 2012). Chronic ALD occurs in stages (Figure 1-5). The first chronic stage is steatosis, where excessive ethanol metabolism leads to fat infiltration within liver cells (Serfaty and Lemoine, 2008). This may not present with clinical signs, but can sometimes be detected in liver function tests (see section 1.4.1.1). The next stage is steato-hepatitis. Alcohol can cause inflammatory changes to the liver, with coinciding fatty changes. Alcoholic hepatitis is by far the most severe presentation of ALD. It can present with jaundice, ascites, bleeding, and encephalopathy (see section 1.4.1 and 1.6). It is associated with a mortality of 40% within six weeks of presentation. However, following recovery from alcoholic hepatitis, if the patient abstains from alcohol, the changes in the liver are reversible and the patient can make a full recovery (Berk and Verna, 2016). If not abstained, irreversible scarring occurs due to progressive liver fibrosis. Fibrosis occurs as a response to inflammation and helps the tissue heal – this is usually a physiological response, but in CLD, the fibrotic changes become exaggerated, which affects the functional ability of the liver. The advanced stage of liver fibrosis is called cirrhosis (Suk and Kim, 2015). Cirrhosis occurs when there is architectural destruction of the liver parenchyma which causes the liver to function poorly. All the causes of CLD have the potential to progress to cirrhosis. The diagnosis of cirrhosis should ideally be made histologically, where a biopsy would show the presence of regenerative nodules, loss of architecture and fibrous bands (Schuppan and Afdhal, 2008). However, the vast majority patients with cirrhosis are diagnosed clinically.

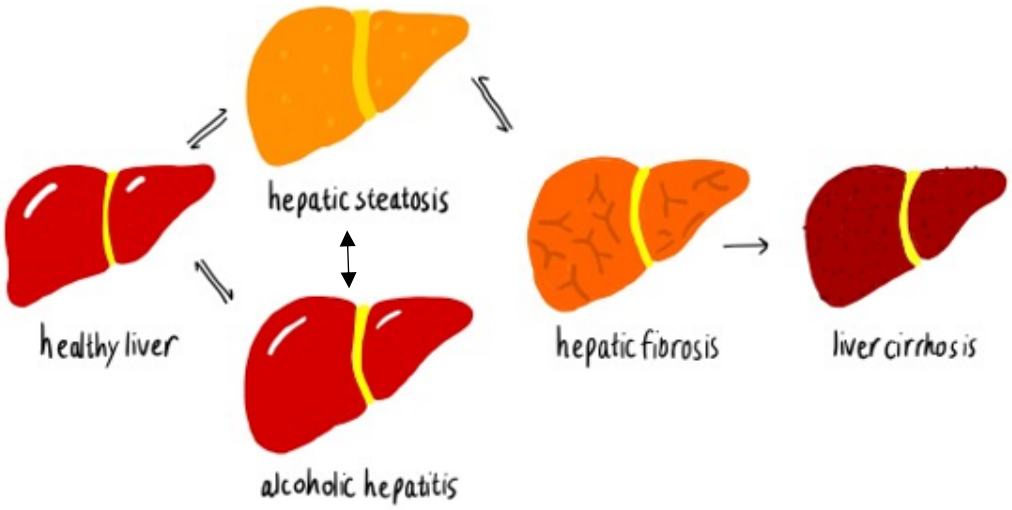


*Figure 1-5: The progression of Alcoholic Liver Disease. Re-drawn by Saujanya Kesavan (Marina, 2019).*

#### 1.2.2.2.3 Non-alcoholic fatty liver disease

As described in section 1.2.2.1, cases of NAFLD are on the rise. NAFLD is a type of CLD, which is associated with fat infiltration to the liver- histologically similar to ALD. Both of the conditions have a similar disease progression and natural history. NAFLD is on the rise due to sedentary lifestyle and high calorific diets (Mitra, De and Chowdhury, 2020). NAFLD is also closely associated with obesity-related metabolic diseases such as type 2 diabetes mellitus, hypertension, dyslipidaemia and cardiovascular disease (Targher *et al.*, 2021).

### *1.2.2.3 Assessing the severity of chronic liver disease*

There are several scoring systems that can be used to assess the severity of liver disease. Two of the most clinically relevant scores were used: Model for End-Stage Liver Disease - Sodium (MELD-Na) and the Child-Turcotte-Pugh (CTP) class. The MELD-Na score was created in 2001 to identify those that would need TIPS (see section 1.7.3.2) or liver transplantation (Kamath *et al.*, 2001). The MELD-Na score can be calculated using blood test results that assess liver function. These include: serum bilirubin, creatinine, sodium levels and the international normalised ratio (INR) (see section 1.4.1.1) (Kamath *et al.*, 2001). Creatinine levels are used to mark the function of the kidneys – the higher the

levels of creatinine, the poorer the function of the kidneys. INR is the measure of how long it takes blood to clot (see section 1.1.2.4).

The MELD- Na score is calculated in two parts (Golla *et al.*, 2022). The MELD score needs to calculated first, and then the sodium levels can be incorporated after that.

The formula to calculate the MELD score:

$$MELD = 9.57\ x\ serum\ creatinine\ \left(\frac{mg^3}{dL}\right) + 3.78\ x\ bilirubin\ \left(\frac{mg}{dL}\right) + 11.2\ x\ INR + 6.43$$

The formula for MELD-Na score:

$$MELD - Na = MELD + 1.32\ x\ (137 - serum\ sodium\ (mmol/l)) - [0.033\ x\ MELD\ x\ (137 - serum\ sodium\ (mmol/l))]$$

The MELD-Na score can easily be calculated by clinicians using online tools. The blood tests results can be inputted, and the score is automatically calculated. The higher the score, the higher the risk of mortality of the patient. The MELD-Na scores typically range for 6 to 40 (Nedea, 2017). MELD-Na scores were calculated by using an online calculator (https://www.mdcalc.com).

The CPT class can be calculated using the CPT score and is also a marker for the severity of liver disease. CPT score was created in 1964 by Charles Child and Jerermiah Turcotte in America to

[3] These are units for measuring serum creatinine and bilirubin

predict the mortality in cirrhotic patients (Child and Turcotte, 1964). This was used to assess the severity of liver disease and predict survival after surgery in such patients (Tsoris and Marlar, 2022). The original scoring system was modified in 1972 by Pugh et al (1973) to incorporate INR into the equation and created specific classes to categorise the patients (Cholongitas *et al.*, 2005). The CPT score uses various factors such as: serum bilirubin levels, albumin levels, prothrombin time, the presence of ascites and changes in neurological status (Child and Turcotte, 1964). Depending on the severity of the factors, different scores are given (Table 1-3).

| | **Numerical scores** | | |
|---|---|---|---|
| **Factors** | **1 point** | **2 points** | **3 points** |
| **Serum bilirubin(mg/dL) (mmol/L)** | <2<br><34.2 | 2-3<br>34.2-51.3 | >3<br>>51.3 |
| **Serum albumin (g/dL)** | >3.5 | 2.8-3.5 | <2.8 |
| **Prothrombin time (seconds)** | 1-3 | 4-6 | >6 |
| **Ascites** | None | Mild | Moderate-severe |
| **Altered mental status (hepatic encephalopathy)** | None | Mild-moderate | Moderate to severe |

*Table 1-3 The Child- Pugh score calculation. Table adapted from Akhtar* et al *(2009).*

The classes are allocated depending on the total score (Akhtar *et al.*, 2009):

- CTP class A: total score between 5-6;
- CTP class B: total score between 7-9;
- CTP class: C 10-15 points.

The higher the class, the higher is the risk of mortality. The survival rate for CTP class B is estimated at 75-95% between 1-5 years, whilst the survival rate for CTP class C is 50-80% (Scott *et al.*, 2011).

## 1.3 Acute-on-chronic liver failure

### 1.3.1 Compensated and decompensated cirrhosis

Cirrhosis is an irreversible state of CLD (see section 1.2.2.2.2). Cirrhosis can present with signs and symptoms associated with portal hypertension e.g. varices, ascites, and hepatic encephalopathy (see section 1.6). If patients are asymptomatic with cirrhosis, this state is called compensated cirrhosis. If patients become symptomatic, this can be termed acute decompensated cirrhosis (see section 1.5 onwards). The rate of decompensation is estimated to be 11% in the UK {Fleming *et al.,* 2011) . Acute decompensation can present as jaundice, variceal haemorrhage, ascites, hepatic encephalopathy, and hepatorenal syndrome (a pathology where there is marked renal disease due to CLD) (Mansour and McPherson, 2018). Decompensation can occur as a result of many causes including excessive alcohol intake, infection, and drug induced liver injury (Mansour and McPherson, 2018). However, in 50% of cases, the cause is often not identifiable (Moreau *et al.*, 2013). Acute decompensation is associated with high mortality (Moreau *et al.*, 2013; Arroyo *et al.*, 2016; Mansour and McPherson, 2018).

### 1.3.2 Acute-on-Chronic Liver Failure

Acute-on-chronic liver failure (ACLF) occurs as a result of worsening acute decompensation. There are several definitions of ACLF that have been proposed by different organisations. They differ slightly in defining the cause of the insult, which can be intrahepatic and/or extrahepatic (Hernaez *et al.*, 2017; Zaccherini, Weiss and Moreau, 2021). In the UK, the most commonly used definition is by the European Association for the Study of the Liver – Chronic Liver Failure Consortium (EASL- CLIF) (Arroyo and Moreau, 2017). ACLF is characterised by three features: acute decompensation, organ failure and a high short term mortality (Arroyo and Moreau, 2017; Arroyo, Moreau and Jalan, 2020).

One of the main marked feature of ACLF is the systemic inflammation, which increases the risk of multiple organ failure and the mortality rate, which stands at 50% (Piano *et al.*, 2017).

#### *1.3.2.1 Precipitants of Acute-on-Chronic Liver Failure*

The trigger for ACLF is similar to that of acute decompensation, and can be intrahepatic or extrahepatic in nature. The cause is often associated with the geographical location of the patient. In Asia, the commonest causes are reactivation of viral hepatitis infections (Zhang *et al.*, 2015). In China, most of the cases (81%) were attributed to reactivation of viral hepatitis (Du *et al.*, 2005). The commoner causes in developed countries tent to be chronic alcoholism. One of the other major precipitants that is seen in both Western and Asian countries is bacterial infection, which can both trigger acute decompensation and further propagate the development of ACLF (Angeli *et al.*, 2018). It is important to prevent and treat the bacterial infections to prevent the development of ACLF.

#### *1.3.2.2 Pathophysiology of Acute-on-Chronic Liver Failure*

The pathophysiology of ACLF is not fully understood. Systemic inflammation is a cardinal feature that leads to the organ failure. Inflammatory mediators called chemokines and cytokines are found in much larger numbers in comparison to patients with cirrhosis without ACLF (Moreau *et al.*, 2013). The excessive levels of these mediators is said to cause a high inflammatory state that can be damaging to healthy tissues, which is the main cause of the organ failure (Arroyo *et al.*, 2016).

Bacterial infection is one the main triggers of ACLF. The immune system responds to the infection by triggering inflammation. Inflammation is mediated by molecules called pathogen-associated molecular patters (PAMPs) and virulence factors (Arroyo *et al.*, 2016; Arroyo and Moreau, 2017). They cause complex cascade reactions which leads to inflammation, and then tissue damage. Sepsis (which is a dysfunctional immune response towards a pathogen) can also be triggered in bacterial

infections, and can cause ACLF (Arroyo *et al.*, 2016). This is predominantly seen in those who develop spontaneous bacterial peritonitis (see section 1.6.2).

Alcohol consumption is also a trigger for ALCF, as it causes changes to the architecture of the small intestines (Arroyo *et al.*, 2016). The gut is a habitat for various types of bacteria, which are beneficial for the body. However, in patients with cirrhosis, excessive alcohol consumption leads to the alteration of the bacteria and intestinal permeability (Kim *et al.*, 2021). This leads to an exaggerated immune response, as damaged cells release danger-associated molecular patterns and other inflammatory cytokines, which are harmful to the normal tissue (Kim *et al.*, 2021). The severity of inflammation in ACLF is correlated to the degree of organ failure- the worse the inflammation, the more the organ damage (Arroyo *et al.*, 2016).

#### *1.3.2.3 Grading Acute-On-Chronic Liver Failure*

The EASL-CLIF consortium have created a scoring based system, called the CLIF consortium organ failure score (CLIF-SOFA), to identify which organs may have been damaged (Moreau *et al.*, 2013) (Table 1-4). By identifying which organs may have had damage, this allows patients with ACLF to be distinguished from those with acute decompensation. The notable organs or systems that are assessed for are the liver, kidneys, brain, circulatory, respiratory and the coagulation system (Moreau *et al.*, 2013). For example, to assess the function of the kidneys, the creatinine levels can be monitored. Creatinine is an excretory product of the kidneys, and if there is kidney failure, it will not be excreted and will build up in the blood. ACLF can also be graded to assess its severity (Angeli *et al.*, 2018) (Table 1-5). The severity of ACLF can potentially be a marker for mortality risk- patients with grade II ACLF have a predicted 28 day mortality risk of 28%, whilst grade III patients have a 28 day mortality risk of 32% (Angeli *et al.*, 2018).

| Organs/system | Measured variable | Score: 1 | Score: 2 | Score: 3 |
|---|---|---|---|---|
| **Liver** | Bilirubin (mg/dL) | <6 | 6-12 | >12 |
| **Kidneys** | Creatinine (mg/dL) | <2 | 2-3.5 | >3.5 |
| **Brains** | Encephalopathy graded according to West Haven | 0 | 1-2 | 3-4 |
| **Coagulation** | INR | <2 | 2 to 2.5 | >2.5 |
| **Circulation** | Mean Arterial pressure (mmHg) | >70 | <70 | The need for vasopressors |
| **Respiration** | PaO2/FiO2 | >300 | <300 and >200 | <200 |

*Table 1-4* The CLIF-SOFA calculator. This is a simplified version of the original *(Moreau* et al.*, 2013)*.

Abbreviations: mg/dL= milligram per decilitre, mmHg= millimetre of mercury, Pa02= partial pressure of oxygen, FiO2= fraction of inspired oxygen.

| Grade of ACLF | Clinical features |
|---|---|
| **No ACLF** | No organ failure, no hepatic encephalopathy or single failure of a non-kidney organ |
| **ACLF Ia** | Single renal failure |
| **ACLF Ib** | Single non-kidney failure, creatinine 1.5–1.9 mg/dl and/or HE grade 1–2 |
| **ACLF II** | Two organ failures |
| **ACLF III** | Three or more organ failures |

*Table 1-5 Grading of ACLF. Table is adapted from EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis (Angeli* et al.*, 2018).*

## 1.4 Manifestations of liver disease

In both acute and chronic liver disease, patients can present with signs and symptoms that occur because of the loss of normal liver function. Some signs are seen in both ALD and CLD, but others can only be seen in CLD due to the progressive nature of the disease. Jaundice is a principal sign that is seen across ALD and CLD. Signs that are associated with a loss of protein synthesis, such as oedema, gynaecomastia and spider naevi, are predominantly seen in CLD. In addition to these changes, fibrosis causes marked changes in pressure of the portal system which leads to portal hypertension (see section 1.5). This then leads to further complications.

### 1.4.1 Jaundice

As explained in section 1.1.2.1, impairment of bilirubin metabolism leads to excessive bilirubin (hyperbilirubinemia) which can manifest with yellow discolouration of skin and sclera (the white part) of the eyes, known as jaundice. A yellow tinge is seen on the skin, which can be accompanied by itching of the skin. This section will focus on the hepatic causes of jaundice for reasons of relevance. Pre-hepatic (such as haemolytic jaundice) and post-hepatic causes of jaundice (biliary obstruction) are not discussed.

Hepatic causes of jaundice lead to an elevation of both unconjugated and conjugated bilirubin (Joesph and Samant, 2022). The loss in function of the hepatocytes leads to disruption in conjugation, which causes a rise in unconjugated bilirubin. This mechanism is seen in both ALD and CLD. However, in CLD there is also marked fibrosis, which can have a compressive effect on the biliary system, and so, there is a raised level of conjugated bilirubin which cannot be excreted.

#### *1.4.1.1 Assessment of jaundice*

The serum bilirubin level can be measured by blood tests – specifically liver function tests (LFTs). As well as identifying the cause of jaundice, serum bilirubin can also be used as one of the first blood tests that can indicate for the presence of liver disease. Liver function tests measure the activity of enzymes found in the liver and the synthetic function of the liver. They are used in both acute and chronic liver disease, and deranged levels of liver enzymes can sometimes signify the cause of the liver disease.

Components of liver function tests include (Lee, Kim and Poterucha, 2012):

- Alkaline phosphatase (ALP)
- Alanine transferase (ALT)
- Aspartate aminotransferase (AST)

- Gama-glutamyl transferase (GGT)
- Bilirubin
- Albumin

## 1.5 Portal hypertension

Chronic liver disease leads to a pathological consequence called portal hypertension. Portal hypertension is defined as the hepatic venous pressure gradient (HVPG) more than 5mmHg (Miñano and Garcia-Tsao, 2010). The hepatic venous pressure gradient is the difference in pressure between the portal vein and the hepatic vein (see section 1.1.1.1). Portal hypertension can occur as a result of other conditions (such as Budd Chiari syndrome or portal vein thrombosis, where it is referred to as non-cirrhotic portal hypertension), but cirrhosis is the commonest cause (Sanyal *et al.*, 2008). Portal hypertension can lead to complications such as varices, ascites and hepatic encephalopathy, which will be explained in the following sections.

### 1.5.1 Pathophysiology of portal hypertension

The flow of blood through any system obeys Ohm's law, which states that pressure (P) is a product of vascular resistance (R) and blood flow (Q), which can be mathematically represented as $P = Q \times R$ (Dib, Oberti and Calès, 2006; Antonov, 2016). In portal hypertension, the pressure within the portal system increases. There are two pathological mechanisms that occur to cause portal hypertension: 1) the rise in vascular resistance; 2) the increased flow through the splanchnic and portal system (Dib, Oberti and Calès, 2006; Turco and Garcia-Tsao, 2019). Both mechanisms will be explained in detail below.

#### *1.5.1.1 Increase in vascular resistance*

The development of cirrhosis is caused by widespread hepatocellular fibrosis. This fibrosis results in distortion of hepatic lobular microanatomy (Nakhleh, 2017). The hepatic sinusoidal epithelial cells and stellate cells undergo phenotypic changes resulting in the production of excessive extracellular matrix, leading to fibrosis (Iwakiri and Trebicka, 2021). This leads to sinusoidal destruction, and a rise in the resistance to blood flow. Additionally, the lack of vasodilatory substances and the overpowering effects of vasoconstrictors leads to severe vasoconstriction, which further increases the vascular resistance (Gana, Serrano and Ling, 2016). Chronic liver disease puts the body at an increased risk of infection, and this can trigger the activation of Kupffer cells. Kupffer cells further propagate the vicious cycle by releasing inflammatory molecules that causes narrowing of the vasculature, as well as scarring (Grønbæk *et al.*, 2012). This perpetuates a cycle of inflammation and healing with fibrosis.

In the early stages of portal hypertension, an increased vascular resistance causes decreased flow through the vasculature which is initially a state of hypodynamic circulation (Bosch, Groszmann and Shah, 2015). In an attempt to bypass the vessels with increased resistance, new blood vessels start to develop through a process called angiogenesis. Collateral vasculature are created between the portal and the systemic system to form portal- systemic collaterals (Iwakiri and Groszmann, 2006; Bosch, Groszmann and Shah, 2015). The systemic circulation is the main circulatory system that supplies oxygenated blood from the heart to the rest of the body and brings deoxygenated blood back to the heart from the organs. This excludes the portal system and the pulmonary system (which is a specific circulation circuit between the heart and lungs). By forming the portal-systemic collaterals, the blood from the portal circulation can be diverted to the systemic circulation bypassing the liver. This is the body's way of adapting to the development of portal hypertension (Iwakiri and Groszmann, 2006).

#### *1.5.1.2 Hyperdynamic circulation*

Increased blood flow through the portal system additionally causes an increase in portal pressure. This occurs as a result of hyperdynamic circulatory dysfunction (which leads to the increased flow). The steps in this process are explained below. It is important to note that most of these pathological mechanisms occur simultaneously.

The increased vascular resistance within the portal system increases the pressure through the portal circulatory system. This increases the flow through the splanchnic system due to circulatory dysfunction (see below) (Ho and Huang, 2015). The splanchnic system is comprised of the portal system and the arterial system that supplies blood to the stomach, spleen, pancreas and the intestines (Harper and Chandler, 2016). Under normal circumstances, the flow within vasculature is tightly controlled with intrinsic vasoconstrictors and vasodilators which allow for adequate perfusion of organs. However, in portal hypertension, the increase in vascular resistance (see section 1.5.1.1) causes circulatory dysfunction within the splanchnic system too.

Circulatory dysfunction occurs because the normal vasoconstrictor/vasodilatory response is impaired. As the pressure within the portal system increases, this triggers a vasodilatory response, which increases flow through the splanchnic system. Vasodilation is the expansion of blood vessels caused by relaxation of smooth muscles in the blood vessels. The main vasodilatory mediator for this is nitric oxide. The splanchnic system has an overwhelming response to the nitric oxide which leads to the overall effect of splanchnic vasodilation (Gana, Serrano and Ling, 2016). Other vasodilators that also mediate this effect include carbon monoxide, prostacyclin, and endocannabinoids (Iwakiri and Groszmann, 2006).

#### *1.5.1.3 Effects of portal hypertension on systemic circulation and how they contribute to hyperdynamic circulation*

It is important to note that portal hypertension affects not only the gastro-intestinal vasculature, but the entire systemic circulatory system. Profound systemic vasodilation results through the effects of nitric oxide released within the portal circulation (Bosch and García-Pagán, 2000). Vasodilation decreases the systemic vascular resistance, leading to a lower mean arterial pressure (Ho and Huang, 2015). As a compensatory mechanism to reduction in mean arterial pressure, the cardiac output (which is the volume of blood pumped out by the heart), increases resulting in hyperdynamic systemic circulation.

As a result of splanchnic vasodilation, the blood pools within the splanchnic system, and so, the returning volume to the heart decreases (Bosch and García-Pagán, 2000). This exacerbates the reduction in systemic mean arterial pressure. In response to this, a complex endocrine cascade reaction called the renin-angiotensin-aldosterone system becomes activated, which increases sodium and water retention from the kidneys to increase circulating plasma volume (Di Pascoli and La Mura, 2019). This further perpetuates an increased blood flow through the splanchnic system, worsening the impact of portal hypertension further (Bloom, Kemp and Lubel, 2015). In summary, hyperdynamic circulatory syndrome is a vicious cycle that is characterised by: splanchnic vasodilation, decreased systemic resistance, increased plasma volume and portal hypertension. Figure 1-6 is a flow chart to show how all the aforementioned concepts, lead to portal hypertension.

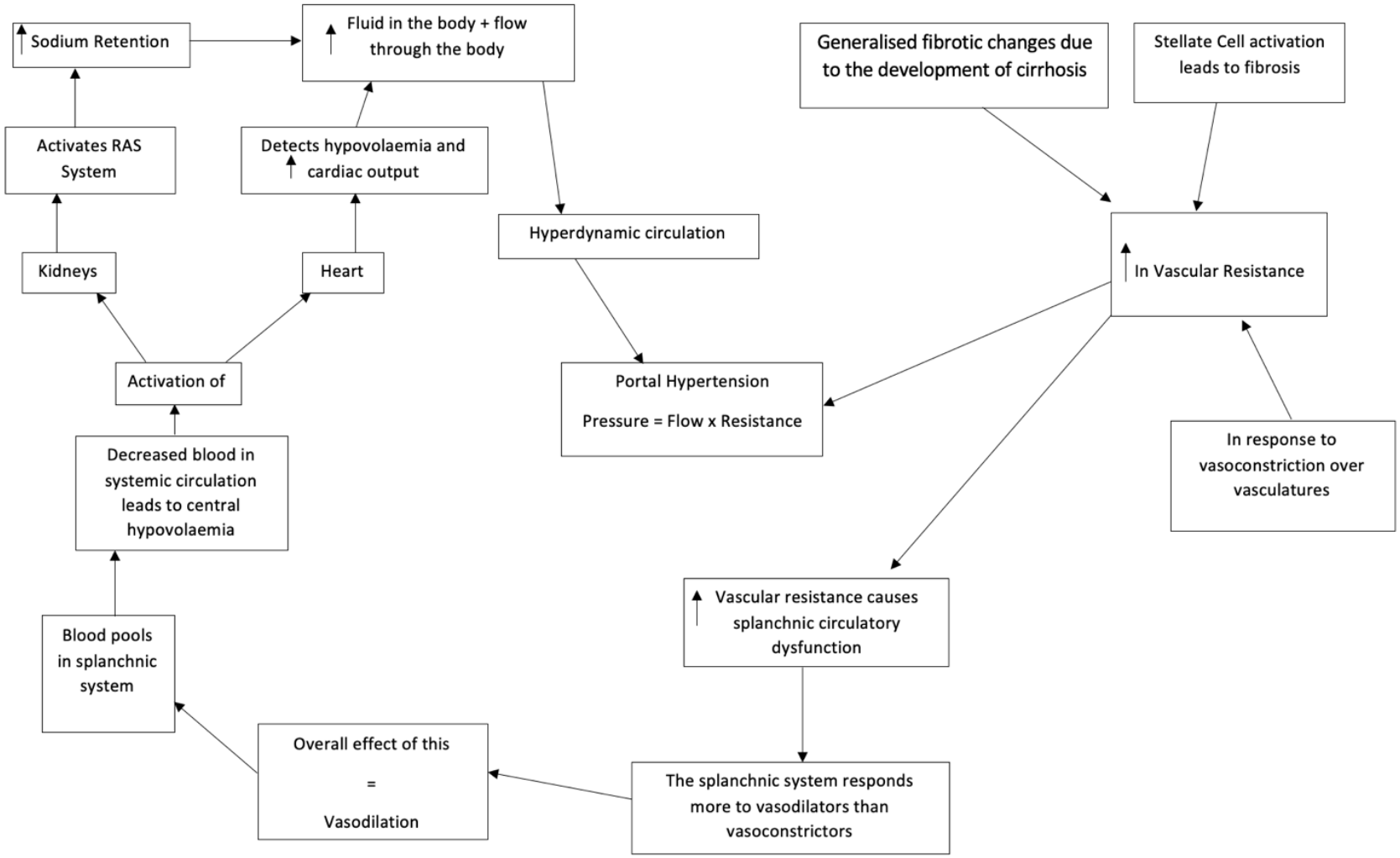


*Figure 1-6: A very simplified flow chart to show the pathophysiology of Portal Hypertension.*

## 1.6 Clinical manifestations of portal hypertension

Clinically significant portal hypertension causes clinical signs and symptoms when the HVPG increases to 10-12 mm Hg (Al-Busafi *et al.*, 2012). HVPG of 16mm Hg or higher is associated with high mortality (Garcia-Tsao, 2017). Portal hypertension can have a profound effect on multiple organ systems, such as the gastrointestinal system (development of varices and ascites), the brain (hepatic encephalopathy), the heart (cirrhotic cardiomyopathy), and the kidneys (hepatorenal syndrome) (Iwakiri and Groszmann, 2006).

The main clinical manifestations that will be discussed are hepatic encephalopathy, ascites, and varices (see section 1.6.1, 1.6.2 and 1.6.3).

### 1.6.1 Hepatic encephalopathy

Hepatic encephalopathy (HE) is a severe but reversible brain condition that occurs as a consequence of advanced CLD and portal hypertension (Ferenci, 2017). In physiological conditions the brain has a selective blood brain barrier (BBB), which is a specialised endothelial lining that prevents the entry of neurotoxins and other metabolites that may be harmful to the brain (Schaefer *et al.*, 2022). However, in cirrhosis, the generalised vascular dysfunction and the increased presence of neurotoxins causes the BBB to become permeable, and so, some neurotoxins enter the cerebral circulation and manifest as HE (Gana, Serrano and Ling, 2016).

HE presents with altered mental status in a patient with severe liver disease. The severity of HE can be graded using the West Haven criteria (Vilstrup *et al.*, 2014) (refer to Table 1-6).

| Grade of hepatic encephalopathy | Presentation |
|---|---|
| **GRADE 0/minimal** | Abnormal neuropsychological tests results if performed, but no clinical manifestations of HE. |
| **GRADE 1** | • Shortened attention span<br>• Changes in emotions e.g. anxiety<br>• Minimal lack of awareness |
| **GRADE 2** | • Disorientation with time<br>• Personality changes<br>• Flapping tremor (when arms and hands extended) |
| **GRADE 3** | • Bizarre behaviour<br>• Confusion<br>• Drowsiness<br>• Reduced consciousness<br>• Flapping tremor |
| **GRADE 4** | Coma |

*Table 1-6*: A modified West Haven criteria for grading hepatic encephalopathy *(Vilstrup* et al*., 2014)*.

Initial management of HE includes the use of lactulose (Vilstrup *et al.*, 2014) with/without enema. Lactulose is an osmotic laxative that also decreases the pH in the intestinal lumen and hence influences the gut microbiome, resulting in reduced toxin production (Jia, 2012). Rifaximin is used for refractory or recurrent HE. This is an non-absorbable antibiotic that targets bacteria in the gut and consequently reduces the production of bacterial toxins acting by a different mechanism to lactulose (Bass *et al.*, 2010).

### 1.6.2 Ascites

The abdominal wall consists of several layers that protect the internal organs. The abdominal organs are covered by a sheath of fibrous membrane called the peritoneum, which has two layers: visceral peritoneum and parietal peritoneum. The potential space between these layers is the peritoneal cavity. The accumulation of fluid in the peritoneal cavity is called ascites (Al-Busafi *et al.*, 2012). Development of ascites in CLD is associated with poor prognosis, with one-year mortality at 40% (European Association for the Study of the Liver, 2010).

Pathogenesis of ascites in CLD:

The pathogenesis of ascites in CLD is multifactorial. The mechanisms of portal hypertension, explained in section 1.5, contribute to the development of ascites. Another key mechanism is hypoalbuminaemia (Moore and Van Thiel, 2013) which leads to imbalance in the osmotic pressures. Serum albumin is a carrier protein that is synthesised by the liver. It also has a high oncotic activity, meaning that it attracts water into the blood vessel, and plays a key role in maintaining the fluid balance between intra and extra vascular spaces (Bernardi, Maggioli and Zaccherini, 2012). However in CLD, the hepatic synthetic function is impaired which leads to a decreased production of albumin. Haemodilution also occurs as a result of the increase in circulating plasma volume (Bernardi, Maggioli and Zaccherini, 2012). The imbalances in oncotic pressures between the intra and extravascular spaces, causes an overall effect of fluid accumulation in the extra cellular space. This results in ascites, subcutaneous oedema, and fluid build-up within the pleural cavity (hepatic hydrothorax).

***Presentation and diagnosis***

Patient presentation can vary depending on the volume of fluid collection within the abdomen (Moore and Van Thiel, 2013). If there is minimal fluid, this can be asymptomatic. But if there is more fluid, symptoms can include abdominal pain and fullness, shortness of breath, and decreased mobility (Runyon, 2009).

Radiological tests such as ultrasound, computerised tomography (CT) or magnetic resonance imaging (MRI) scans of the abdomen can be carried out to establish the presence of ascites (Runyon, 2009). It is also important to identify the cause of the ascites. For this, a diagnostic paracentesis can be performed (Aithal *et al.*, 2021) and the fluid checked for the presence of

white blood cells, protein, pathogens, and specialised enzymes e.g. amylase (McGibbon *et al.*, 2007).

***Management***

Management options for ascites can differ according to the volume of ascites. Ascites can be graded according to its severity, where grade 1) ascites is only visible on ultrasound; grade 2) moderate ascites with the presence of symmetrical distension; grade 3) severe ascites with marked abdominal distension (Moore *et al.*, 2003).

For grade 1 and 2 ascites, patients can be managed as outpatients (European Association for the Study of the Liver, 2010). Dietary salt restriction (<2000 mg/d) is an important therapeutic option (Moore and Van Thiel, 2013). This prevents sodium reabsorption by the kidneys facilitating water excretion. In moderate ascites, diuretics can be used - particularly spironolactone (Moore and Aithal, 2006). Spironolactone is an aldosterone antagonist (see section 1.5.1.3), and so, prevents the reabsorption of sodium from the kidneys (Eggert, 1970). For grade 3 ascites, it is recommended to perform therapeutic paracentesis (Angeli *et al.*, 2018). This is when large volumes of ascites are drained through a needle to give symptomatic relief.

***Spontaneous bacterial peritonitis***

If the ascitic fluid becomes infected due to bacterial translocation from the intestinal lumen, across the intestinal wall into the peritoneal cavity, this can lead to a life-threatening condition called spontaneous bacterial peritonitis (SBP). The risk of death with SBP is around 20% (Piano *et al.*, 2016). Patients can present with abdominal pain and signs of infection e.g. a fever and high

heart rate (Angeli *et al.*, 2018). A diagnostic paracentesis is essential for the diagnosis of SBP, which will show white cell count >250 $mm^3$ (Popoiag and Fierbințeanu-Braticevici, 2021). SBP needs to be treated promptly with antibiotics (Angeli *et al.*, 2018).

### 1.6.3 Varices

Varices are enlarged venous collaterals that develop within the gastro-intestinal system as a result of portal hypertension (see section 1.5). Bleeding varices are a major cause of mortality in patients with CLD (Lebrec, 2001). If gastro-intestinal varices are present, the annual risk of large varices bleeding is 15% (The North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices, 1988). They are the cause of 70% of the upper gastro-intestinal bleeds experienced by patients with portal hypertension (Angeli *et al.*, 2018). It is therefore important to assess those at risk for the development of varices to prevent their development or rupture (Kraja *et al.*, 2017). If they are at risk, they need to be managed accordingly (see section 1.7).

#### *1.6.3.1 Pathophysiology of Varices*

As explained in section 1.5, cirrhosis leads to an increased pressure within the portal system. Blood flow in the portal vein experiences resistance offered by the diseased fibrotic liver whilst flowing towards the inferior vena cave and this resistance results in development of portal-systemic collaterals. The main mechanism by which this occurs is by the opening of pre-existing embryological vessels that had connected the portal system to the systemic circulation (Cárdenas and Ginès, 2009; Bosch, Groszmann and Shah, 2015). By opening the portal-systemic shunts, they act as “release valves” to decompress the high pressure from portal system, and so the blood will now flow to the systemic veins (Roberts and Kamath, 1996; Nardelli *et al.*, 2020). The second mechanism by which portal pressure can be compensated is by the creation of new

blood vessels that bridge the portal and systemic system through the process of angiogenesis (Bosch, Groszmann and Shah, 2015; Gana, Serrano and Ling, 2016). Though both these mechanisms are compensatory, they lead to further problems such as bleeding.

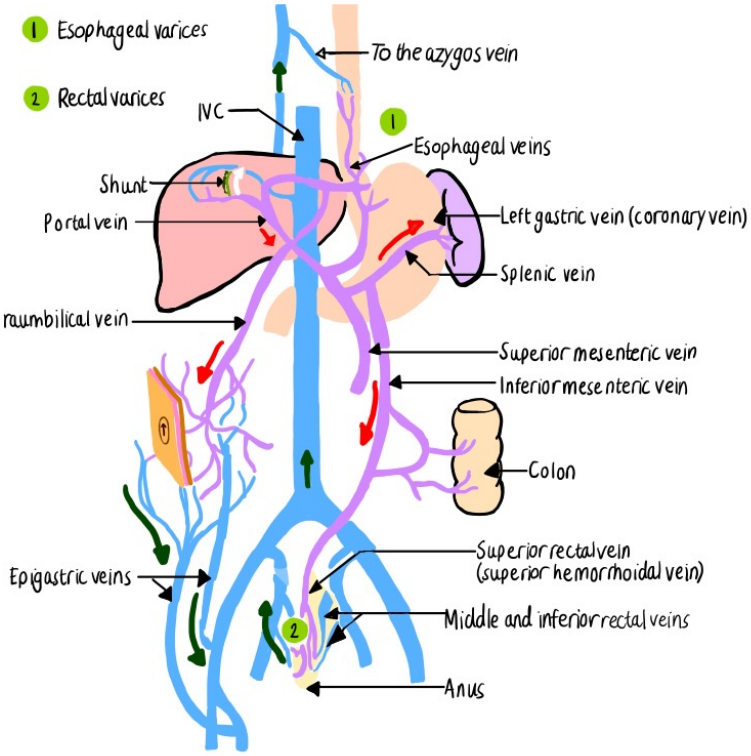


*Figure 1-7: Portal-systemic collaterals. The number 1 and 2 represent where the varices could arise. Re-drawn by Saujanya Kesavan (Moore, Dalley and Agur, 2013).*

The new portal-systemic shunt causes the systemic vein to become dilated, because there is more blood flowing through the systemic blood vessel from the portal system (Roberts and Kamath, 1996). Varices have a correlation with the HVPG - as the HVPG increases, the size of the varicosity also increases (Roberts and Kamath, 1996; Sanyal *et al.*, 2008).

Varices are prone to rupture, causing life threatening bleeding. Varices rupture if the pressure exceeds the elastic limit of the blood vessel (Bosch, Groszmann and Shah, 2015). Bleeding may occur if the HVPG is around 12 mmHg (Hilzenrat and Sherker, 2012). If the pressure of the HVPG

exceeds 20 mmHg, it is associated with life-threatening bleeding that may be resistant to treatment (Sanyal *et al.*, 2008).

#### *1.6.3.2 Location of portal-systemic varices*

Varices are mainly found within the gastrointestinal tract for example the oesophagus, the stomach, the rectum, the spleen, and the intestines (Philips *et al.*, 2016). They are also found less frequently inside the peritoneal cavity and in the retroperitoneum (Akhter and Haskal, 2012).

##### 1.6.3.2.1 Oesophageal varices

Oesophageal varices are found within the oesophagus and occur as a result of shunt development between the left gastric vein (which is part of the portal system) and the azygous veins (which belong to the systemic circulation) (Philips *et al.*, 2016). Oesophageal varices are the commonest type of varices to bleed due to the complex pressure mechanisms that are associated with breathing in and out (Bosch, Groszmann and Shah, 2015). They can be investigated using an oesophago-gastro-duodenoscopy (OGD).

Oesophageal varices can be graded based on their size (Jalan and Hayes, 2000) (Table 1-7). It is important to assess the size of the varices using an endoscope because larger varices at a higher risk of a bleed (Palmer and Brick, 1956). Based on the grade, different management options can be tailored to the patient.

Certain findings can indicate an increased risk of bleeding. On endoscopy, if varices have specs of red, it is called the red wale sign which is an indicator for a high risk bleed. There are severity

scores such as Child-Pugh-Turcotte scores which can be used to identify the risk of mortality of a patient with CLD (see section 1.2.2.3) (Tsoris and Marlar, 2022). The higher the score, the higher the risk of haemorrhaging from varices.

Rupture of oesophageal or gastric varices would present as an upper-gastrointestinal (UGI) bleed. This would cause patients to vomit blood (haematemesis). Different management options are available to control the bleeding from oesophageal varices (see section 1.7.3.2).

| Grade of the oesophageal varices | Features on upper GI endoscopy |
|---|---|
| **Grade 1** | Varices that collapse when the oesophagus is pumped with air through an endoscope |
| **Grade 2** | Varices that may be in between grade 1 and grade 3 |
| **Grade 3** | Varices that are big enough to occlude the lumen of the oesophagus |

*Table 1-7: Grade of varices stated by the British Society of Gastroenterology (Jalan and Hayes, 2000)*

#### 1.6.3.2.2 Gastric varices

Gastric varices develop in the stomach as a result of portal-systemic shunt between the gastric veins (which are from the portal system) and the azygous veins (which arise from the systemic circulation) (Philips *et al.*, 2016). There are different classifications that can be used when assessing gastric varices. A commonly used classification is the Sarin classification which factors in location of the gastric varices in relation to the oesophagus (Sarin *et al.*, 1992) (Figure 1-8, Table 1-8). They can be graded when visualised on an OGD. GOV-1 is the commonest form of gastric varices (Sarin *et al.*, 1992). Though gastric varices bleed less commonly than oesophageal

varices, bleeding from gastric varices is more severe and is associated with a higher rate of mortality (Wani *et al.*, 2015).

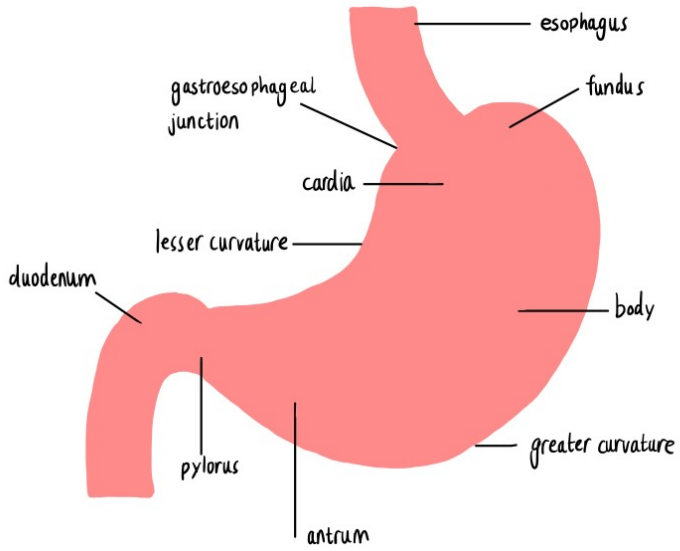


*Figure 1-8: The anatomy of the Stomach. Drawn by Saujanya Kesavan.*

| Sarin classification | Features on upper GI endoscopy |
|---|---|
| **Gastro-oesophageal varices type 1 (GOV 1)** | Oesophageal varices that continue down into the stomach's lesser curvature. |
| **Gastro-oesophageal varices type 2 (GOV 2)** | Oesophageal and gastric varices that are found along the fundus of the stomach. |
| **Isolated gastric varices type 1 (IGV 1)** | Isolates gastric varices that are present in the cardia of the stomach. There are no oesophageal varices present |
| **Isolated gastric varices type 2 (IGV 2)** | Gastric varices that present outside of the cardio-fundal part of the stomach |

*Table 1-8*: The Sarin classification of gastric varices *(Sarin* et al.*, 1992)*.

#### 1.6.3.2.3 Ectopic varices

Porto-systemic varices can occur anywhere along the gastro-intestinal tract. If they occur in parts of GI tract other than oesophagus or stomach, they are called ectopic varices. Ectopic varices account for 1-5% of variceal bleeding (Norton, Andrews and Kamath, 1998). Though

infrequent, they are difficult to treat as their location is hard to access with standard upper GI endoscope (Vangeli *et al.*, 2004).

The common sites of ectopic varices in order of reducing frequency are the rectum, the small intestines (particularly the first part called the duodenum), and the large intestines (Sarin and Kumar, 2012; Sato, 2015).

#### 1.6.3.2.3.1 Rectal varices

Rectal varices form as a result of shunt formation between the superior rectal veins (which arise from the portal system) and the middle/inferior rectal veins, which are part of the systemic circulation (Sato, 2010). The estimated prevalence of rectal varices in cirrhosis can be between 38-65% (Chawla and Dilawari, 1991). Though this figure is high, bleeding from rectal varices is rare (Maslekar *et al.*, 2013; Al Khalloufi and Laiyemo, 2015). They present as a lower gastro-intestinal bleed, which can be life threatening if not treated acutely. They are usually visualised on a lower GI endoscopy (Al Khalloufi and Laiyemo, 2015). Patients with rectal variceal bleeding are initially managed similarly to any other bleed-with prompt resuscitation with fluids and blood products to prevent haemodynamic instability. Specialised endoscopic treatment can be undertaken for the rectal varices once the patient is stabilised (Maslekar *et al.*, 2013).

## 1.7 Gastro-oesophageal varices

Gastro-oesophageal varices are the commonest form of varices. This thesis will focus on gastro-oesophageal varices. The epidemiology, presentation, diagnosis and management options are discussed.

### 1.7.1 Epidemiology gastro-oeseophgeal varices

The presence of clinically significant portal hypertension is the main risk factor for the development of gastro-oesophageal varices. The prevalence of varices is thought to be 30% in patients with compensated cirrhosis and 60% in patients with decompensated cirrhosis (Mantovani and Tsochatzis, 2021). The incidence rate of gastro-intestinal varices is estimated be to around 9% per year in the UK (Mantovani and Tsochatzis, 2021). The severity of liver disease, which can be assessed through the Child-Turcotte-Pugh score (see section 1.2.2.3), can also be an indicator for the presence of varices (Gulamhusein and Kamath, 2017). Forty percent of CPT class A patients are reported to have gastro-oesophageal varices, whereas 85% of CPT class C patients may have varices (Gulamhusein and Kamath, 2017). The rate of progression from small to large varices is estimated to be 10-12% annually .

Gender can also affect the prevalence of gastro-oesophageal varices. Males are more likely have chronic liver disease- they can account for 55-70% of the total cases of chronic liver disease, which can predispose them to varices (Ratib *et al.*, 2014; Lonardo *et al.*, 2015; Scaglione *et al.*, 2015). Numerous studies have also shown that women have a reduced risk of mortality in comparison to men who have been admitted with a variceal haemorrhage (Fabbian *et al.*, 2019; Haukeland *et al.*, 2020; Sohal *et al.*, 2022) and a study involving 166,760 patients with variceal bleeding in the US had found that 32.7% of them were female, underlining the higher risk of varices in males (Fabbian *et al.*, 2019).

Socio-demographic factors have a particular impact on the aetiology of chronic liver disease rather than the development of varices specifically. Alcoholic liver disease in particular can be attributed to social inequalities (Foster *et al.*, 2018). A study in Denmark has found that there is

a higher incidence of ALD in populations with lower education and employment level (Askgaard *et al.*, 2021). Deprived areas within the UK have a higher hospital admission due to chronic liver disease (Collins, 2016). Assuming there is no difference in the clinical presentation of liver disease across different social classes, it could be assumed that hospitals serving more deprived populations will have a higher incidence of varices. However, this has not been studied formally. Obesity is also associated strongly with deprivation in the UK (El-Sayed, Scarborough and Galea, 2012) and is the main cause of non-alcoholic fatty liver disease (NAFLD), which can progress to severe chronic liver disease if lifestyle factors are not modified. This in turn can put the population at higher risk of varices.

### 1.7.2 Presentation

Patients do not have symptoms associated with the presence of varices unless they rupture, which leads to vomiting of fresh red blood. This is referred to as haematemesis. The bleeding associated with gastric varices is more severe, and the patient may be more likely to deteriorate (Kim *et al.*, 2013). Depending on the volume of blood loss, the patient can have different signs. Minor blood loss can be difficult to detect, as vital signs, such as heart rate and blood pressure can be compensated by the body. However, with major blood loss, the blood pressure would be markedly low and the heart rate would be high. These signs are important to monitor for when providing active treatment and progress after treatment.

### 1.7.3 Diagnosis

The presence of varices is normally confirmed by the use of an upper GI endoscopy. This can be undertaken when cirrhosis is diagnosed (Tripathi *et al.*, 2015).Endoscopies can be repeated to

monitor the size of varices (Tripathi *et al.*, 2015). Guidelines exist to aid the clinicians in deciding on how frequently they perform endoscopy (Tripathi *et al.*, 2015).

### 1.7.4 Management

Varices can be managed before they bleed (primary prophylaxis), at the time of bleeding (management of acute bleeding) and after the initial bleeding has been treated (secondary prophylaxis).

The principles of management of oesophageal varices and gastric varices are similar. As gastric varices are less common, research in this area is limited. Specific therapies for gastric varices are limited but will be explained below.

With the appropriate management, it is possible for varices to decrease in size/regress over time. This can be achieved with targeted prophylactic treatment as well as treating the cause of the CLD. For example, those who had varices secondary to alcoholic cirrhosis, might be able to decrease the grade of their varices primarily through alcohol abstinence (Baker, Smith and Lieberman, 1959).

#### *1.7.4.1 Primary prophylaxis*

To prevent the first episode of rupture of gastro-oesophageal varices, primary prophylaxis can be given. Non-cardioselective beta blocker medication (NSBBs) can be used (Tripathi et al., 2015) to reduce the HVPG by causing splanchnic vasoconstriction resulting in an overall effect of decreasing portal pressure (Garcia-Tsao, 2017). If HVPG is below 12mmHg, the risk of a first variceal haemorrhage is considerably reduced (Suk *et al.*, 2007). NSBBs have been used since

1987, and have been rigorously evaluated in clinical trials, and proven to have high efficacy for the treatment of portal hypertension (López-Méndez and Uribe, 2006). Some side effects of certain NSBBs can occur as a result of low blood pressure e.g. dizziness and cold extremities, low blood glucose and spasm of the airways (de Graaf *et al.*, 2011).

Primary prophylaxis can also be given by endoscopic treatment called variceal band ligation (VBL) (Tripathi et al., 2015). An endoscope is used to visualise the varices, and bands can be applied to strangulate the varices (Poza Cordon *et al.*, 2012). Although equal in efficacy to NSBB, VBL is associated with more complications including VBL induced oesophageal ulcers which can also lead to internal bleeding (Angeli *et al.*, 2018).

#### *1.7.4.2 Management of active variceal haemorrhage*

When varices rupture, it can potentially lead to a life-threatening bleed if not controlled properly. The mortality rate is estimated to be around 30% after variceal haemorrhage (Sharara and Rockey, 2001) Patients are resuscitated with intravenous fluids to restore their blood pressure. Blood transfusions can be given if the patient has a major haemorrhage (Tripathi *et al*., 2015) Vasoactive drugs such as terlipressin can be given to stop bleeding (Israelsen *et al.*, 2017). They work by causing vasoconstriction within the splanchnic circulation, and lead to decreased active bleeding from varices (Papaluca and Gow, 2018). In patients with acute variceal haemorrhage, 20% of patients may have an infection when presenting, and 50% of patients develop infection during hospital admission (Lee *et al.*, 2017). So antibiotics are recommended at the time of presentation with acute variceal bleed (Tripathi *et al*., 2015).

Endoscopy is performed after the patient stabilises. Endoscopic treatment in the form of VBL can be performed on oesophageal varices (Haq and Tripathi, 2017). For gastric varices, the

treatment options can differ depending on the grade of the varices e.g. VBL, tissues adhesives or sclerotherapy (de Franchis *et al.*, 2022). Tissue adhesives can be made of different chemical compounds, and they work by acting as a glue when they contact blood (Bryant, Caldwell and Greenwald, 2005). This stops the varices from bleeding. Sclerotherapy can be injected into varices and cause the blood to clot, which prevents it from bleeding (Kojima *et al.*, 2005).

If there is a catastrophic bleed that cannot be controlled with endoscopic therapies, a balloon tamponade tube can be inserted into the oesophagus (Tripathi *et al*., 2015). The common tamponade device used in the UK is Sengstaken-Blakemore tube. It is inserted into the mouth, through the oesophagus and into the stomach. The balloon within the tube is inflated and it will decrease bleeding by compression on the varices. Such compressive therapy can be used until a definitive therapy is attempted e.g. repeat endoscopic treatment or transjugular intrahepatic portosystemic shunt (TIPS) (Tripathi *et al*., 2015).

TIPS is an invasive procedure that is performed by interventional radiologists using imaging techniques (Parvinian and Gaba, 2014). A tube is inserted between the portal vein and the hepatic vein, which decompresses the portal pressure within the portal vein (Patidar, Sydnor and Sanyal, 2014). This will effectively reduce the clinical manifestations of portal hypertension. One of the commonest complications of TIPS is the development of hepatic encephalopathy. This occurs because toxins directly enter the systemic circulation without being processed by the liver (Madoff *et al.*, 2004).

Balloon-occluded retrograde transvenous obliteration (BRTO) can be used in the management of gastric varices (Sabri and Saad, 2011). BRTO is a minimally invasive technique that is performed by interventional radiologists. A balloon is placed between gastric shunts (that develop as a

result of portal hypertension) so that sclerosant (which is additionally given) can close the gastric varices (Sabri and Saad, 2011).

#### *1.7.4.3 Secondary prophylaxis*

After the cessation of the initial bleed, it is important to prevent subsequent episodes of bleeding so that various secondary prophylaxis options can be provided. The treatment of choice is usually NSBB and endoscopic band ligation therapy (Tripathi *et al* 2015; Angeli *et al.*, 2018).

## 1.8 Conclusion

Having described the physiology of the liver, the pathophysiological processes leading to acute variceal bleeding in CLD and potential treatment options, the next chapter will describes the aims of this thesis.

# 2 Thesis rationale

Bleeding varices are a major cause of mortality in patients with CLD (Lebrec, 2001). The mortality rate is estimated to be around 30% after variceal haemorrhage (Sharara and Rockey, 2001). It is important to manage these patients with specific therapies to reduce the mortality rate. As mentioned in section 1.7.3, there are numerous management options for varices. Various organisations and independent groups have written guidelines that propose recommendations for the management of varices. In the next chapter, I will conduct a systematic review to identify and appraise the quality of existing guidelines to understand the rigour of their development and the quality of evidence that has been used to propose various recommendations.

From this systematic review, I will identify recommendations that are supported by high quality evidence and suggested in thoroughly developed guidelines. These recommendations will be used evaluate the service at a local hospital, University Hospitals of the North Midlands NHS Trust (UHNM) in the management of variceal bleeding.

The aim of this thesis is to understand the best evidence for treatment of varices in CLD and use this to evaluate the performance of UHNM in managing this patient group, with the exception that areas for improvement can be suggested. In order to achieve this aim, the following objectives will be met:

- perform a systematic review and narrative synthesis of guidelines that have made recommendations for the management of varices;
- appraise the quality of the guidelines that propose recommendation on varices;
- identify the recommendations that have been proposed for: primary prophylaxis, active haemorrhage and secondary prophylaxis for the management of varices;
- identify the recommendations that are supported by high quality evidence and rigorously developed guidelines;

- perform a service evaluation to assess the performance of UHNM in the management of variceal bleeding against evidence-based recommendations identified from the systematic review;
- assess whether recommendation-adherent management is associated with key patient characteristics and survival.

The next chapter reports in the conduct and findings of the systematic review.

# 3 A Systematic Review of International Guidelines on the management of Gastro-oesophageal Varices in Acute on Chronic Liver Failure.

## 3.1 Introduction

Currently, there are many guidelines that have been published by different organisations and individuals for the management of gastro-oesophageal varices. The Cambridge dictionary defines the word guideline as “information intended to advise people on how something should be done or what something should be” (Cambridge Dictionary., 2022). This definition suggests that a guideline is intended to guide people in order to produce a favourable outcome. In clinical practice, treatment guidelines are published by different organisations for particular diseases in order to aid clinicians in the management of patients. They are often written in conjunction with multiple specialties to provide a broad overview of optimal care. For varices in chronic liver disease, the guidelines are usually developed by e.g. hepatologists, interventional radiologists, and nurses.

Currently there are many guidelines published by different organisational bodies such as the British Society of Gastroenterology (BSG), European Association for the Study of the Liver (EASL), and American Association for the Study of Liver Disease (AASLD). However, there are also guidelines that are not associated with an organisational body and are written independently. As there are many guidelines to choose from, it is important to identify the ones that have been developed rigorously, with evidence-based recommendations that clinicians can use to help them to make informed decisions for the management of their patients.

## 3.2 Aims and objectives

The aim of the systematic review is to identify recommendations that have been proposed by national and international guidelines on varices in patients with ACLF. These guidelines will undergo quality appraisal and data extraction, which will be presented in the form of a narrative synthesis. This will allow the identification of high-quality recommendations that have been rigorously developed.

The objectives of the systematic review are to:

- identify existing recommendations for the management of acute variceal haemorrhage;
- identify existing recommendations for varices primary and secondary prophylaxis;
- critically appraise identified guidelines using the AGREE II checklist (Brouwers *et al.*, 2017);
- compare and contrast the recommendations of different guidelines;
- propose recommendations that are of high quality from guidelines that have been developed rigorously.

## 3.3 Methods

### 3.3.1 Protocol development

I planned the protocol (Appendix 1) prior to the search to be transparent about the specific methods I would use. The protocol followed a standard proforma developed by systematic

review experts at Keele University. Developing the protocol in advance reduces the potential for bias in a systematic review in several ways. First, the need for impromptu decision making can be reduced. This in turn reduces the possibility of making choices about the methods that would lead to 'favourable' or otherwise biased outcomes. Second, protocols allow for reproducibility across the reviewing team, as everyone can use the same method to get the same result. Finally, a written protocol allows others to use the same methods to reproduce the review or as the basis for future reviews.

To identify the key concepts in relation to the research question, I attempted to use the PICO (population, intervention, control, outcomes) method. There were some difficulties with this as this review does not delve into specific interventions or have a control group, as they are not relevant to the research question. However, this approach still gave me a basis from which to start drafting my search strategy and I was able to adapt it by including "guidelines" as an intervention (see Appendix 2). I drafted the protocol and made numerous revisions in an iterative process in conjunction with my supervisors and systematic review experts. For example, in the initial stages, I had not explained in enough depth about the methodological process that I would follow for this review, but with guidance, I was able to modify this and explain the methodology in detail e.g. the process of performing a narrative synthesis.

In order to be transparent about the methodology of the review, I attempted to register the protocol to PROPSERO (https://www.crd.york.ac.uk/prospero/). PROSPERO is a database of planned and published systematic reviews. It also aims to prevent studies being repeated, as a researchers' time could be better spent at looking into subject matters that have not or are not currently being explored. PROSPERO have specific inclusion and exclusion criteria on their website that should be adhered to prior to submitting the protocol. Some of the exclusion

criteria included scoping reviews, systematic reviews that assess sporting outcomes, and systematic critical appraisals. As this systematic review was not explicitly excluded by these criteria, I submitted the protocol. However, after submission, the protocol was rejected on the basis that they do not accept systematic reviews that critically appraise guidelines, which was not updated as part of their exclusion criteria. They had explained that their website has not been updated. It should be noted that it is not mandatory for the protocols of systematic reviews that appraise the quality of guidelines to be uploaded to PROSPERO. I uploaded the protocol to Keele University's repository instead to still maintain credibility and transparency (https://eprints.keele.ac.uk/11080/).

### 3.3.2 Eligibility criteria

For the systematic review, pre-defined inclusion and exclusion criteria were identified. The inclusion criteria were:

- publications detailing acute-on-chronic liver disease with the specific complication of varices;
- guidelines or reviews that propose recommendations.

The exclusion criteria were:

- older guidelines that are superseded by newer versions;
- paediatric-specific guidelines;
- guidelines where the full text was not available online or via the interlibrary loans service;
- guidelines where varices are not mentioned.

### 3.3.3 Systematic search

#### *3.3.3.1 Developing the search strategy*

I developed the search strategy with the aid of Mrs Joanne Jordan, a Research Information Specialist in the School of Medicine at Keele University). I defined all relevant domains separately and combined them to define the overall patient population, the complication of interest and then guidelines. The search was divided into three domains: acute-on-chronic liver disease, varices and guidelines. Each of the domains had alternative terms incorporated into the search (Appendix 2). For each, the necessary truncations, wildcards, and proximity searching were applied, so as not miss any potential papers. Thesaurus headers were also used, which were specific for each database.

#### *3.3.3.2 Databases*

For the search, I used the databases Medline accessed via OVID, Embase via OVID, and Web of Science. Web of Science and Medline were searched from their inception until 12$^{th}$ October 2021. Embase was searched from inception until 15$^{th}$ October 2021.The TRIP database and Epistemonikos were used as checks for guidelines potentially missed from the main search. They are both small medical databases that contain only studies and other forms of evidence suited to clinical use. The search facilities in these databases are less sophisticated and so the search strategies employed were simpler, with only concept terms and no wildcards, truncations, or thesaurus headers. The reference lists of included papers were also searched. Websites of major hepatology organisations such as The European Association for the Study of the Liver (EASL)

were checked for guidelines on their websites. A full list of all of the organisations that were hand-searched is given in the protocol (Appendix 1).

#### *3.3.3.3 Screening process*

All of the citations identified through the search were imported into Zotero, which is a free reference management system (https://www.zotero.org/). This software was also able to identify duplicates, which were then deleted. For the title and abstract screening, Rayyan was used (https://www.rayyan.ai/). Rayyan is a systematic review screening software that allows multiple collaborators to screen citations at the same time. I imported all the articles from Zotero to Rayyan on the 18th October 2021. I screen all the titles were screened on Rayyan. The abstracts were screened by me and the second reviewer, SM. I undertook full text screening of all papers. Second screening of the full text papers was split equally between SM and the third reviewer, RD. Disagreements were resolved through discussion with option for the third reviewer to arbitrate if necessary. Throughout the screening process, a PRISMA flow diagram was used to keep track of the number of studies that were excluded and why.

### 3.3.4 Stakeholder consultation

During the screening process, I had realised that I was identifying far more guidelines than I had anticipated, some of which were several decades old. For practical reasons, I needed to ensure that I did not review more papers than necessary and I was keen to ensure all included papers would be relevant to modern clinical practice. Following a discussion with my supervisors, I contacted five consultant hepatologists that work at UHNM via email, asking them for the dates

at which they believed there had been major changes to clinical practice with the intention to use. The information they provided to ensure that only relevant guidelines were included.

### 3.3.5 Data extraction

A blank data extraction form was created in Microsoft Excel (Appendix 3). A pilot data extraction was conducted at the same time as the development of the protocol. This was to make sure that all of the relevant information can be collected and make sure that the form was usable and in a format that could be used for the narrative synthesis (Higgins *et al.*, 2022). The pilot data extraction was undertaken by SK and SM using the British Society of Gastroenterology guidelines (Tripathi *et al*., 2015).

The headings under which data were extracted were:

- title of the guideline;
- organisational body;
- authors;
- date of publication;
- main recommendation(s);
- condition of recommendation(s).

### 3.3.6 Quality appraisal

In order to appraise the quality of the guideline, there needs to be a tool that can be used to assess whether guidelines are written to an appropriate standard. For this systematic review, I used a quality appraisal tool called Appraisal Of Guidelines Research and Evaluation II (AGREE II) (Brouwers *et al.*, 2017). This tool is designed to aid with identifying the transparency of guidelines and assessing their quality (Table 3-1). There are alternative quality appraisal tools for guidelines, such as The GuideLine Implementability Appraisal (GLIA) and ADAPTE. The different tools have different areas of focus. For example, ADAPTE concentrates on appraising the quality of the clinical content, and GLIA focuses how the guideline can be applied to clinical practice. I chose to use AGREE II as it appraises the quality of the guidelines thoroughly across six different Domains (e.g. Scope and Purpose, Stakeholder Involvement), and so, it is much more comprehensive (Table 3-1). It incorporates aspects of ADAPTE and GLIA e.g. applicability of guidelines, which makes it the best choice for comprehensive of a quality appraisal in this review.

AGREE II is the updated version of the original AGREE tool that was published in 2003. The country of origin for the tool is Canada and it was created by international researchers and guideline developers (Brouwers *et al.*, 2017). It is designed to assess the rigour of guidelines and the quality of their reporting, as there is currently variability between them (Brouwers *et al.*, 2017). It is important to evaluate whether the recommendations are feasible and safe for clinical practice. The updated version of the tool, AGREE II, has been amended to reflect this. For example, an additional question has been added to Domain 3 – "The strengths and the limitations of the body of evidence are clearly described", which was not mentioned in the previous edition (Brouwers *et al.*, 2017).

| Domain | Domain title | Domain concepts |
|---|---|---|
| 1 | Scope and purpose | • The objectives of the guideline<br>• The target population |
| 2 | Stakeholder Involvement | • Has the guideline development group has included all of the relevant professional bodies to write the guideline?<br>• Have the views of the patient been sought? |
| 3 | Rigour of development | • What was the method of coming to recommendations?<br>• Have the benefits and risks of the formulated recommendation been considered?<br>• Is there a link between the evidence used and the recommendations that are made? |
| 4 | Clarity of Presentation | • Are the recommendations specific and unambiguous?<br>• Are the recommendations identifiable? |
| 5 | Applicability | • Has the resource availability has been considered when applying recommendations to clinical practice?<br>• Are facilitators and barriers of applying the recommendations mentioned? |
| 6 | Editorial Independence | • Has the funding body influenced the guideline content?<br>• Have conflicts of interest been addressed and recorded for the guideline development group members? |

*Table 3-1: Summary of AGREE II Domains and concepts. Modified from (Brouwers* et al.*, 2017).*

Developers of the AGREE II tool suggest that users adapt the tool according to what they deem most important in their context (Brouwers *et al.*, 2017). I therefore modified the domain list in the order of priority. I considered Domain 1 (Scope and Purpose) and then Domain 3 (Rigour of Development) to be most important. This is because a guideline should have a thorough aim, mention their target population, and rigorously appraise the quality of evidence that they have used in order to make key recommendations. Table 3-2 and Table 3-3 show the exact items that were considered to assess a guideline against Domain 1 and Domain 3.

| Domain 1: Scope and Purpose Items | Domain concept |
|---|---|
| **i** | The objectives of the guidelines have been outlined. |
| **ii** | The guidelines specify the health questions that it will assess. |
| **iii** | The target population e.g. patients have been specifically mentioned. |

*Table 3-2 Domain 1: Scope and Purpose. Table is adapted from AGREE II checklist (Brouwers* et al*., 2017)*

| Domain 3: Rigour of Development Items | Domain concept |
|---|---|
| **i** | A systematic method been used to identify the evidence available |
| **ii** | The criteria for selecting evidence have been outlined. |
| **iii** | The strengths and weaknesses of the evidence has been outlined. |
| **iv** | The methodology for developing a recommendation has been mentioned. |
| **v** | The benefits and risks of the formulated recommendation been considered. |
| **vi** | There is a clear link between the body of evidence and the proposed recommendation. |
| **vii** | The guideline has been externally reviewed before publication. |
| **vii** | The guideline has mentioned what the procedure is regarding the update of future guidelines. |

*Table 3-3 Domain 3: Rigour of Development. Table is adapted from AGREE II checklist (Brouwers* et al*., 2017).*

Ideally, each guideline would be assessed against all 6 Domains, but this was not realistic in the timeframe of this MPhil project. The AGREE II developers suggest a score of 70% on the most important Domain (Domain 1 in this case) should enable a paper to pass to appraisal with the next Domain (Domain 3 in this case).

Within each Domain, there are specific questions that need to be answered. In Domain 1, there are 3 questions. All of the questions are rated on a 7-point scale, where 1 is least agree and 7 is

strongly agree. So, if the guideline is of a good standard, we can expect them to score higher. To calculate the overall Domain score, this equation is used:

$$\frac{\text{obtained score} - \text{minimum possible score}}{\text{maximum possible score} - \text{minimum possible score}}$$

$$minmum\ possible\ score = no.of\ questions\ in\ the\ domain\ x\ no.of\ reviewers\ x\ 1$$

$$maximum\ possible\ score = no.of\ questions\ in\ the\ domain\ x\ no.of\ reviewers\ x\ 7$$

$$obtained\ score = sum\ of\ all\ of\ the\ scores\ scored\ per\ question\ in\ the\ domain$$

Each reviewer scores each of the questions, and an average score is calculated. This is done to mitigate some of the subjectivity around scoring system as it is user-dependent. This score is converted to a percentage. The developers of AGREE II suggest the use of a score of 70% or more in the user-defined priority Domain before it is taken forward to the next Domain. However, basing whether a guideline moves onto the next stage using the scoring system could be seen as arbitrary, and does not account for guidelines that may have potentially forgotten to answer questions or not know that they were expected to include some of the information. This may especially bias the review against papers written before the advent of checklists for guideline reporting quality. After discussion with Mrs Joanne Jordan, I decided to balance this, by using the raw scores and the insight I had for each guideline to gauge whether it should be allowed to move to the next stage in a traffic light system (see section 3.3.6.1). This categorisation was carried out in consultation with the two other reviewers, SM and RD.

In keeping with guidance on the use of the AGREE II tool, the guidelines retained after full text screening all were appraised against Domain 1, which I considered to be most important. Those that 'passed' Domain 1 were assessed against Domain 3.

#### *3.3.6.1 Traffic light system*

A traffic light system as mentioned in section 3.3.6, will be used to show how well each guideline performed in Domain 1 and 3 (see Table 3-5). By using this system rather than absolute percentage scores, it was much easier to appreciate how well the guidelines were conducted relatively to each other. The error that is associated with giving exact scores can be eliminated through this process, and though colour coding them red, amber and green is essentially subjective, it is still better than giving arbitrary percentage scores that cannot be appreciated relatively to the included guidelines. The traffic light system was used to assess papers in Domains 1 and 3. The papers that did not perform well in Domain 1 were coded red and did not progress to be appraised against Domain 3. The papers that were of moderate quality were coloured amber. These guidelines were appraised against Domain 3. Removing papers rated as red against Domain 1 made the review more manageable, whilst ensuring that those appraised against Domain 3 were addressing clearly defined clinical questions in a defined patient group.

### 3.3.7 Consensus approach

Throughout the process, a consensus approach was taken by myself and the second reviewers in order to thoroughly check that the information was correct as it could be, as well as to improve reliability. I was responsible for extracting the data from the guidelines, which was double checked by one of the second reviewers (RD or SM). The data extraction form was checked to see whether all of the necessary recommendations were extracted and not missed. Where the

second reviewer disagreed with the initial data extraction, they updated the data extraction form. Where there was disagreement over the data to be extracted, this was discussed to reach agreement.

When appraising the quality of the guidelines, the traffic light system was used to categorise the guidelines. This was done by myself and the second reviewer in order to make sure that there was an agreement in the quality of the guideline. This ensures that bias can be kept to a minimum. A similar process to data extraction of written opinions followed by discussion was followed.

### 3.3.8 Translation of Guidelines

Some of the guidelines that were retrieved were not in English. The papers that were available online were translated readily through Google Translate or the translate tool on Microsoft Edge. Some of the papers that were screened on paper copy, due to unavailability of online copies, could not be translated online. Google Lens was used to translate them instead. This is an application that can be downloaded onto most smart phones and can translate text from a paper in real time to a chosen language. The translations were used for full text screening/data extraction and quality appraisal.

### 3.3.9 The strengths of the recommendations

When a guideline makes recommendations, they usually mention the strength of their recommendation i.e. strong or weak, and the quality of evidence they have used to come to that recommendation e.g. systematic reviews, randomised control trials, expert opinion and

etcetera. Some guidelines included in this review did this, whilst others did not. I have laid out the results table in such a way that the main recommendations are quoted alongside of guidelines that support them (Table 3-6). If the guideline had mentioned the strength of the recommendation, that is also included. The commonest tool that is used to make a strength in recommendation is the Grading of Recommendations, Assessment, Development and Evaluation tool (GRADE) (Guyatt *et al.*, 2008). There are different variations of GRADE – e.g. the Oxford system versus the American classification, and so, sometimes it can be difficult to compare the strengths of recommendations if different systems are used to grade them. I have created a table to show the specific grading method that each of the individual papers used (see Table 3-4). Some have used "levels of evidence" where different types of evidence are given different numerical values. For example, level 1 evidence would denote high quality evidence was used such as systematic review and meta-analysis using homogenous randomised control trials (RTCs). The strength of the recommendation will be according to the level of evidence that they have used in the guideline e.g. A would only be given if level 1 studies were used. In general, it is easier to compare guidelines that quote high level evidence and where the strength of the recommendation is also strong e.g. A1. This is because moderate to lower quality evidence can be split into different tiers with some GRADE tools splitting evidence into 5 tiers, whilst others split it into 3, and so the middle and lower tiers are not comparable with the other GRADE tools. The higher quality evidence is comparable though because most of the GRADE tools regard systematic reviews, meta-analyses and RCTs to be of high quality.

Where guidelines made recommendations without describing their strength, or referred to the results of systematic reviews, RCTs or studies that they used to come to their conclusions, but did not formally graded the quality of the evidence, this quality may still be ambiguous. Therefore, those papers that did not use a formal tool were generally rated lower in Domain 3.

## GRADING METHOD USED

**No formal method used**

This was used by: Bosch, Juan G. Abraldes and Groszmann, 2003; Bittencourt et al., 2017; Cales et al., 1991; Chinese Society of Spleen and Portal Hypertension Surgery, 2019; Diaz-Brito, Cardoso and Sarmento, 2018; Dimache et al., 2016; Fejfar, Vanasek, J. Lata, et al., 2017; Fernandez, Aracil, Sola, Soriano, Cardona, et al., 2016; Garcia-Tsao, Lim, and Members of Veterans Affairs Hepatitis C Resource Center Program, 2009; Goshi and Stanley, 2005; Gow and Chapman, 2001; Henry et al., 2021; Lebrec, Vinel and Dupas, 2004; National Agency for Accreditation and Evaluation in Health, 2004; Perumalswami and Schiano, 2011; Reiberger and Mandorfer, 2017; Rodrigues et al., 2020; Rosolowski et al., 2014; Trebicka and Götz, 2018.

**Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) (Guyatt *et al.*, 2008):**

| Quality of evidence | Criteria |
|---|---|
| **High** | Further research is unlikely to change the confidence of the estimated effect |
| **Moderate** | Further research is likely to have an impact on the confidence of effect and could change the estimate |
| **Low** | Further research is very likely to change the confident and is likely to change the estimate. Any change in the estimate is uncertain |

| Strength of the recommendation | Criteria |
|---|---|
| **Strong- 1** | Factors influencing the strength of the recommendation include the quality of the evidence, presumed patient-important outcomes, and cost. |
| **Weak-2** | Variability in preference and values or relatively high uncertainty. Recommendation is made with less certainty or higher cost or resource consumption. |

This was used by: Korean Association for the Study of the Liver (KASL), 2020; Reiberger, Puspok, et al., 2017; Sarin et al., 2019.

**Oxford Centre for Evidence-Based Medicine Levels of Evidence (Oxford Centre for Evidence-Based Medicine, 2009):**

| GRADE | QUALITY OF EVIDENCE |
|---|---|
| **A** | consistent level 1 studies [systematic review of randomized controlled trials (RCT) |
| **B** | consistent level 2 or 3 studies or extrapolations from level 1 studies [systematic review of cohort studies, cohort studies, and low quality RCT] |
| **C** | level 4 studies [systematic review of case–control studies, case–control studies and case series] or extrapolations from level 2 or 3 studies |

| | |
|---|---|
| **D** | level 5 studies [expert opinion] or troublingly inconsistent or inconclusive studies at any level |

| **Level of evidence** | **Type of study** |
|---|---|
| **1a** | Systematic reviews of homogenous RCT |
| **1b** | Individual randomized controlled trials |
| **2a** | Systematic review of (homogeneous) cohort studies of "exposed" and "unexposed" subjects |
| **2b** | Individual cohort study or low-quality randomized control studies |
| **3a** | Systematic review of (homogeneous) case-control studies |
| **3b** | Individual case-control studies |
| **4** | Case series, low-quality cohort or case-control studies |
| **5** | Expert opinions based on non-systematic reviews of results or mechanistic studies |

This was used by: Bosch et al., 2012, Fagiuoli et al., 2017, Farooqi et al., 2007, Farooqi et al., 2016, Mellinger and Volk, 2013, Nevens et al., 2019, Sarin et al., 2008, Sarin et al., 2011, Tripathi et al, 2015, Xu et al., 2020.

**GRADE (Neumann *et al.*, 2016):**

| **Certainty** | **Certainty could be denoted as** | **Interpretation** |
|---|---|---|
| **High** | A | The author has high confidence that the true effect will be similar to the estimated effect |
| **Moderate** | B | The author believes that the true effects is close to the estimated effect |
| **Low** | C | The true effect might be markedly different from the estimated effect |
| **Very low** | D | The true effect is probably different from the estimated effect |

| **Strength of the recommendation** | **Criteria** |
|---|---|
| **Strong- 1** | Factors influencing the strength of the recommendation include the quality of the evidence, presumed patient-important outcomes, and cost. |
| **Weak-2** | Variability in preference and values or relatively high uncertainty. Recommendation is made with less certainty or higher cost or resource consumption. |

This was used by: Bruno et al., 2021, D'Amico, Pagliaro and Bosch, 1999, de Franchis et al., 2022, Hwang et al., 2014, Siau et al., 2022, Spaander et al., 2021, Tripathi et al., 2020, Yoshiji et al., 2021.

**Grading system adopted by the American College of Cardiology and the American Heart Association (Shiffman *et al.*, 2003):**

| Classification | Description |
|---|---|
| **Class I** | The evidence or general agreement that the treatment is useful and effective |
| **Class II** | The evidence and/or the opinions diverge on how useful the treatment is |
| **Class IIa** | The evidence/ opinion favour the treatment |
| **Class IIb** | The evidence/ opinion say that the treatment is less useful/ may have less efficacy |
| **Class III** | The evidence/ opinions say that the treatment is not useful and could potentially be harmful |

| Level of evidence | Description |
|---|---|
| **A** | Data is derived from multiple RTC/ meta-analysis |
| **B** | Data is derives from single RCT/ non-randomised control trials |
| **C** | Based on expert opinion/ case-studies |

This was used by: Boyer and Haskal, 2010, Cheng et al., 2009, Garcia-Tsao, Arun J Sanyal, et al., 2007, Schiavon et al., 2019.

Narváez-Rivera et al., 2013 used the **Modified Delphi method.** The scores were based on 1-9 depending on how much the consensus agreed. If the scores were higher than a six, they were "in agreement" with the statement.

Dworzynski et al., 2012 used **GRADE** to assess the evidence but did not grade the recommendations.

Angeli et al., 2018 have created their own GRADE version for their guideline.

| Classification | Description |
|---|---|
| **Class I** | The evidence or general agreement that the treatment is useful and effective |
| **Class II** | The evidence and/or the opinions diverge on how useful the treatment is |
| **Class IIa** | The evidence/ opinion favour the treatment |
| **Class IIb** | The evidence/ opinion say that the treatment is less useful/ may have less efficacy |
| **Class III** | The evidence/ opinions say that the treatment is not useful and could potentially be harmful |

| Strength of the recommendation | Criteria |
|---|---|
| **Strong- 1** | Factors influencing the strength of the recommendation include the quality of the evidence, presumed patient-important outcomes, and cost. |
| **Weak-2** | Variability in preference and values or relatively high uncertainty. Recommendation is made with less certainty or higher cost or resource consumption. |

The American Collarge of Radiology have created an **appropriateness scale**. The recommendations can be categorised as:

- Usually appropriate
- May be appropriate
- Usually not appropriate

This was used by:

- Kim et al., 2020
- Pinchot et al., 2021

*Table 3-4 Different grading methods that different guidelines have used for their recommendations.*

### 3.3.10 Putting recommendations forward

One of the aims of this review was to identify which recommendations were supported by high quality evidence, which can support their use in clinical practice and the service evaluation in chapter 4. The recommendations that are supported by high quality evidence (A1 or similar) and guidelines that rate green in Domain 3 will be put forward by the review. If there is at least one guideline rating green in Domain 3 that supports the evidence to be of A1 or similar, this recommendation can be taken forward. However, if there are more guidelines that are also green that disagree with each other in regards to the rating, the recommendation cannot be put forward.

## 3.4 Results

### 3.4.1 Guidelines that were retrieved

In total, 7355 citations were identified by the search. Embase yielded 4691, Medline 1405, and Web of Science 1259. All of the articles were imported into Zotero on the 15th October 2021, and the duplicates removed, leaving 5695 citations. I screened all the titles, leaving 548 potential guidelines for abstract review. I screened 548 abstracts, which were further screened by SM, who was the second reviewer. Of those, 190 papers continued to full text screening, and were screened by myself with half of the papers being second screened by SM and half by RD.

### 3.4.2 Stakeholder consultation results

As previously explained in section 3.3.4, the stakeholder consultation was held to potentially reduce the number of included guidelines that may recommend outdated management

strategies at the screening stage. One of the local experts mentioned that the recent management strategies that are used today were implemented when she was training in the 1990s. Some of the outdated methods e.g. shunt surgery were more prominently used in the 1970s rather than recently. I used 1970 as a cut off and attempted to exclude studies that came prior to this, but this cut off did not eliminate any guidelines, as all of the guidelines were published after this time.

Altogether, there were 49 guidelines that were included for data extraction and appraisal against AGREE II Domain 1. The details of these publications are given in Table 3-5. The PRISMA flow chart summarises this process (see Figure 3-1).

### 3.4.3 Data extraction and recommendation results

From the 49 guidelines, all recommendations were extracted to a Microsoft Excel spreadsheet. The recommendations that were proposed by guidelines passing through just Domain 1 can be found in Appendix 4. The recommendations that have been proposed by guidelines passing through to Domain 3 can be found in section 3.4.6 onwards (Table 3-6 to Table 3-13).

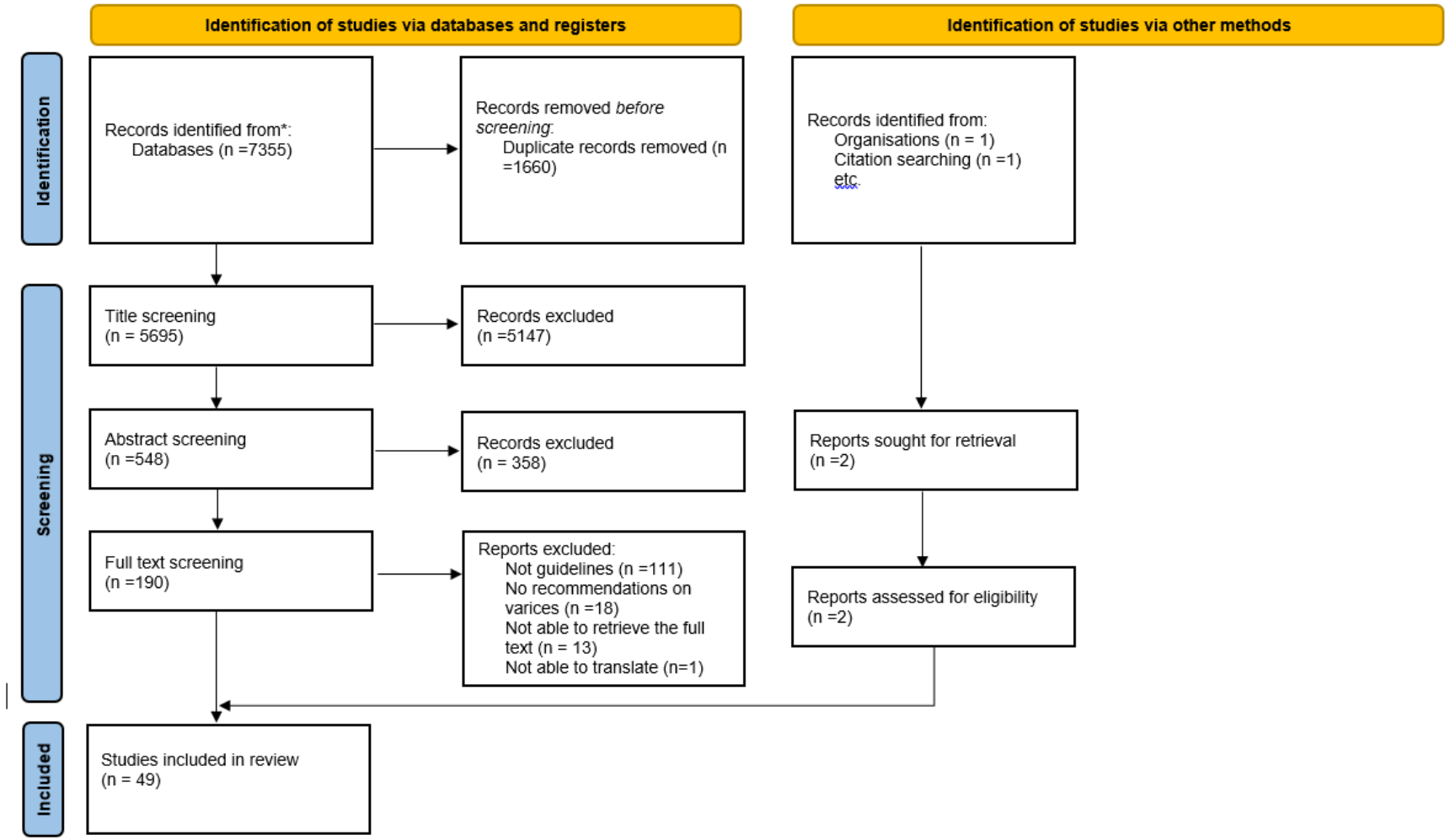


Figure 3-1 The PRISMA flow chart.

### 3.4.4 Traffic light system results

As described in section 3.4.2, 49 guidelines underwent data extraction and were appraised against Domain 1, which assessed for Scope and Purpose. Percentage scores on Domain 1 ranged from 2.78% to 94.44%. Of these, 21 guidelines passed onto Domain 3 (Rigour of Development) appraisal. The percentage scores on assessment of the guidelines against Domain 3 ranged from 3.1% to 70.8%, 7 were rated green, 8 amber and 6 red and only one guideline scoring over 70% (Dworzynski *et al*., 2012). Table 3-5 summarises the traffic light ratings (section 3.3.6.1) of the 49 papers included in the review.

| Author | Title: | Year of development | Country/ Continent | Associated organisations | Domain 1 assessment | Domain 3 assessment |
|---|---|---|---|---|---|---|
| (Angeli *et al.*, 2018) | EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis | 2018 | Europe | European Association for the Study of the Liver | | |
| (Bittencourt *et al.*, 2017) | Sangramento varicoso: atualização das recomendações da Sociedade Brasileira de Hepatologia [Variceal Bleeding: Update Of Recommendations From The Brazilian Association Of Hepatology.] | 2017 | Brazil | The Brazilian Association Of Hepatology | | |
| (Bosch *et al.*, 2012) | Hipertensión portal: recomendaciones para su evaluación y tratamiento [Portal hypertension: recommendations for evaluation and treatment: consensus document sponsored by the Spanish Association for the Study of the Liver (AEEH) and the Biomedical Research Network Center for Liver and Digestive Diseases(CIBERehd)] | 2012 | Spain | Spanish Association for the Study of the Liver | | |
| (Bosch, Juan G. Abraldes and Groszmann, 2003) | Current management of portal hypertension | 2003 | N/A | N/A | | |
| (Boyer and Haskal, 2010) | The role of transjugular intrahepatic portosystemic shunt (TIPS) in the management of portal hypertension: Update 2009 | 2009 | America | American Association for the Study of Liver Diseases | | |
| (Bruno *et al.*, 2021) | Portal Hypertension and Ascites: Patient- and Population-centered Clinical Practice | 2021 | Italy | Italian Association for the Study of the Liver | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Guidelines by the Italian Association for the Study of the Liver (AISF) | | | | | |
| (Cales *et al.*, 1990) | "Les traitements d'urgence des hémorragies digestives hautes de l'hypertension portale de la cirrhose. Réunion de consensus. Paris, 17 novembre 1989. Rapport final" [Emergency treatment of upper digestive hemorrhage in portal hypertension in patients with cirrhosis. Consensus meeting. Paris, 17 November 1989. Final report]. | 1990 | France | N/A | | |
| (Cheng *et al.*, 2009) | Esophagogastric variceal bleeding in cirrhotic portal hypertension: consensus on prevention and management (2008) | 2008 | China | Chinese Society of Gastroenterology, Chinese Society of Hepatology, and Chinese Society of Digestive Endoscopy | | |
| (Chinese Society of Spleen and Portal Hypertension Surgery, 2019) | [Expert consensus on diagnosis and treatment of esophagogastric variceal bleeding in cirrhotic portal hypertension (2019 edition)]. | 2019 | China | Chinese Society of Spleen and Portal Hypertension Surgery, Chinese Society of Surgery, Chinese Medical Association | | |
| (D'Amico, Pagliaro and Bosch, 2008) | Pharmacological Treatment of Portal Hypertension: An Evidence-Based Approach | 2008 | N/A | N/A | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| (de Franchis *et al.*, 2022) | Baveno VII – Renewing consensus in portal hypertension | 2022 | Experts from all over the world | N/A | | |
| (Diaz-Brito, Cardoso and Sarmento, 2018) | Hepatite Vírica Crónica Proposta de um Protocolo para o Tratamento/ Seguimento da Cirrose [Chronic viral hepatitis - Protocol proposal for the management of cirrhosis] | 2018 | Portugal | N/A | | |
| (Dimache *et al.*, 2016) | Nonselective Beta-Blockers In Patients With Cirrhosis: "The Therapeutic Window" | 2016 | Romania | N/A | | |
| (Dworzynski *et al.*, 2012) | Management of acute upper gastrointestinal bleeding: summary of NICE guidance | 2012 | UK | The National Institute for Health and Care Excellence | | |
| (Fagiuoli *et al.*, 2017) | Consensus conference on TIPS management: Techniques, indications, contraindications | 2017 | Italy | Italian Association for the Study of the Liver | | |
| (Farooqi *et al.*, 2007) | Management of variceal bleeding: PSG guidelines 2006 | 2006 | Pakistan | Pakistan Society of Gastroenterology | | |
| (Farooqi *et al.*, 2016) | Clinical practice guidelines on the management of variceal bleeding | 2016 | Pakistan | Pakistan Society of Hepatology and Pakistan Society of Study of Liver Diseases | | |
| (Fejfar, Vanasek, J. Lata, *et al.*, 2017) | Treatment of bleeding caused by liver cirrhosis-associated portal hypertension - Update of Czech Society of Hepatology guidelines | 2017 | Czech | Czech Society of Hepatology | | |
| (Fernandez, Aracil, Sola, Soriano, Cardona, *et al.*, 2016) | Evaluación y tratamiento del paciente cirrótico crítico [Evaluation and treatment of the critically ill cirrhotic patient] | 2016 | Spain | N/A | | |

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|---|---|---|---|---|---|---|
| (Garcia-Tsao, Lim, and Members of the Veterans Affairs Hepatitis C Resource Center Program, 2009) | Management and Treatment of Patients With Cirrhosis and Portal Hypertension: Recommendations From the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program | 2009 | America | Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program | | |
| (Garcia-Tsao, Arun J. Sanyal, *et al.*, 2007) | Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis | 2007 | America | American Association for the Study of Liver Diseases and American college of Gastroenterology | | |
| (Goshi and Stanley, 2005) | Update on the management of variceal bleeding | 2005 | Scotland | N/A | | |
| (Gow and Chapman, 2001) | Modern management of oesophageal varices | 2001 | England | N/A | | |
| (Henry *et al.*, 2021) | AGA Clinical Practice Update on Management of Bleeding Gastric Varices: Expert Review | 2021 | America | American Gastroenterological Association | | |
| (Hwang *et al.*, 2014) | The role of endoscopy in the management of variceal hemorrhage | 2014 | America | American Gastroenterological Association | | |
| (Kim *et al.*, 2020) | ACR Appropriateness Criteria® Radiologic Management of Gastric Varices | 2020 | America | American College of Radiology | | |
| (Korean Association for the Study of the Liver (KASL), 2020) | KASL clinical practice guidelines for liver cirrhosis: Varices, hepatic encephalopathy, and related complications | 2020 | Korea | Korean Association for the Study of the Liver | | |
| (Lebrec, Vinel and Dupas, 2005) | Complications of portal hypertension in adults: a French consensus | 2005 | France | N/A | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| (Mellinger and Volk, 2013) | Multidisciplinary Management of Patients With Cirrhosis: A Need for Care Coordination | 2013 | America | N/A | | |
| (Narváez-Rivera *et al.*, 2013) | Consenso Mexicano de Hipertensión Portal [Mexican consensus on portal hypertension]. | 2013 | Mexico | Mexican Consesus on Portal Hypertension | | |
| (National Agency for Accreditation and Evaluation in Health, 2004) | Complications de l'hypertension portale chez l'adulte: (Paris, 4 et 5 décembre 2003) [Consensus conference: complications of portal hypertension in adults (Paris, December 4-5, 2003). Long text] | 2004 | France | N/A | | |
| (Nevens *et al.*, 2019) | Recommendations on the Diagnosis and Initial Management of Acute Variceal Bleeding and Hepatorenal Syndrome in Patients with Cirrhosis | 2019 | Experts from all over the world | N/A | | |
| (Perumalswami and Schiano, 2011) | The Management of Hospitalized Patients with Cirrhosis: The Mount Sinai Experience and a Guide for Hospitalists | 2011 | Egypt | N/A | | |
| (Pinchot *et al.*, 2021) | ACR Appropriateness Criteria® Radiologic Management of Portal Hypertension | 2021 | America | American College of Radiology | | |
| (Reiberger and Mandorfer, 2017) | Beta adrenergic blockade and decompensated cirrhosis | 2017 | Europe | European Association for the Study of the Liver | | |
| (Reiberger, Puspok, *et al.*, 2017) | Austrian consensus guidelines on the management and treatment of portal hypertension (Billroth III) | 2017 | Austria | Austrian Society of Gastroenterology and Hepatology and the Austrian Society of Interventional Radiology | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| (Rodrigues *et al.*, 2020) | Interventional Algorithm in Gastrointestinal Bleeding—An Expert Consensus Multimodal Approach Based on a Multidisciplinary Team | 2020 | Portugal | N/A | | |
| (Rosolowski *et al.*, 2014) | Therapeutic and prophylactic management of bleeding from oesophageal and gastric varices - recommendations of the Working Group of the National Consultant for Gastroenterology | 2014 | Polish | Working Group of the National Consultant for Gastroenterology | | |
| (Sarin *et al.*, 2019) | Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific association for the study of the liver (APASL): an update | 2019 | Asia | Asian Pacific association for the study of the liver | | |
| (Sarin *et al.*, 2008) | Primary prophylaxis of gastroesophageal variceal bleeding: consensus recommendations of the Asian Pacific Association for the Study of the Liver | 2008 | Asia | Asian Pacific association for the study of the liver | | |
| (Sarin *et al.*, 2011) | Diagnosis and management of acute variceal bleeding: Asian Pacific Association for Study of the Liver recommendations | 2011 | Asia | Asian Pacific association for the study of the liver | | |
| (Schiavon *et al.*, 2019) | Recomendações sobre procedimentos invasivos em pacientes com doenças do fígado e do trato biliar: relatório de reunião conjunta da Sociedade Brasileira de Hepatologia (SBH), Sociedade Brasileira de Endoscopia Digestiva (SOBED) e Sociedade Brasileira de Radiologia Intervencionista e Cirurgia Endovascular (SOBRICE) [29.Recommendations for invasive procedures in patients with diseases of the liver and biliary tract: Report of a joint meeting of the brazilian society of | 2019 | Brazil | Brazilian society of hepatology , Brazilian society of digestive endoscopy and Brazilian society of interventional radiology and endovascular surgery | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | hepatology (SBH), brazilian society of digestive endoscopy (SOBED) and brazilian society of interventional radiology and endovascular surgery (SOBRICE)] | | | | | |
| (Siau *et al.*, 2020) | British Society of Gastroenterology (BSG)-led multisociety consensus care bundle for the early clinical management of acute upper gastrointestinal bleeding | 2020 | UK | British Society of Gastroenterology | | |
| (Spaander *et al.*, 2021) | Esophageal stenting for benign and malignant disease: European Society of Gastrointestinal Endoscopy (ESGE) Guideline – Update 2021 | 2021 | Europe | European Society of Gastrointestinal Endoscopy | | |
| (Trebicka and Götz, 2018) | Vorgehen bei gastrointestinaler Blutung – die neue Leitlinie [Gastrointestinal Bleeding: Update] | 2018 | Germany | N/A | | |
| (Tripathi *et al.*, 2015) | UK guidelines on the management of variceal haemorrhage in cirrhotic patients | 2015 | UK | British Society of Gastroenterology | | |
| (Tripathi *et al.*, 2020) | Transjugular intrahepatic portosystemic stent-shunt in the management of portal hypertension | 2020 | UK | British Society of Gastroenterology | | |
| (Xu *et al.*, 2020) | Chinese guidelines on the management of liver cirrhosis (abbreviated version) | 2020 | China | Chinese Society of Hepatology | | |
| (Yoshiji *et al.*, 2021) | Evidence-based clinical practice guidelines for liver cirrhosis 2020<br><br>(The English version is a digested version) | 2021 | Japan | Japanese Society of Gastroenterology and the Japanese Society of Hepatology | | |

*Table 3-5 Guidelines assessed against AGREE II and quality appraisal ratings on Domains 1 and 3.*

### 3.4.5 Summarising recommendations into broader categories

Similar recommendations were made in multiple guidelines, including those that did and did not pass to the Domain 3 assessment. However, there are some recommendations that have only been made by guidelines excluded after Domain 1 assessment (Appendix 4). The purpose of categorising recommendations that are made by guidelines excluded or retained after Domain 1 assessment is to identify which recommendations are supported by high quality evidence. The guidelines excluded following appraisal against Domain 1 were not clear in their objectives, their target population and/or their research questions.

The recommendations proposed by the 21 guidelines assessed against Domain 3 have been categorised as primary prophylaxis (see Table 3-6 and Table 3-7), active haemorrhage management (Table 3-8- Table 3-12), and secondary prophylaxis (Table 3-13). Most of the recommendations were also made by guidelines that were not assessed against Domain 3. These recommendations that were only made by papers undergoing Domain 3 evaluation are highlighted in the tables.

In each of the following sections, the commonest recommendations are summarised before each of the recommendations are described in more detail, including their Domain 3 score and the strength of the recommendation.

#### *3.4.5.1 Primary prophylaxis*

Recommendations propose that primary prophylaxis (prevention of first variceal haemorrhage, see section 1.7.3.1) can be in the form of pharmacological therapy (Table 3-6) or endoscopic therapy (Table 3-7) in patients that are at risk of bleeding.

##### 3.4.5.1.1 Primary prophylaxis: medical therapy and dosage table

The key management options that have been proposed by guidelines for primary prophylaxis are summarised in Figure 3-2, whilst Table 3-6 details the overall recommendations in the 21 guidelines appraised against Domain 3.

- The pharmacological treatment of choice is non-selective beta blockers (NSBB). These include propranolol and nadolol.
- The endoscopic treatment of choice is variceal band ligation (VBL).
- If patients are intolerant of NSBB, they should have VBL therapy.

*Figure 3-2 Summary of key recommendations across guidelines for primary prophylaxis of varices.*

| Recommendations | Which paper support it | Recommendation strength | Domain 3 assessment |
|---|---|---|---|
| Primary prophylaxis can be either pharmacological treatment or endoscopic treatment (in the form of VBL) for patients that have a risk of bleeding. | (Tripathi *et al*., 2015) | (level 1a, grade A) | |
| | (Sarin *et al.*, 2008) | 1b | |
| | (Schiavon *et al.*, 2019) | Class 1 | |
| | (Farooqi *et al.*, 2016) | 1a;A | |
| The treatment of choice should be NSBB, and if the patient is intolerant to the medication, elastic band ligation can be performed till variceal eradication. | (de Franchis *et al.*, 2022) | (A.1) | |
| | (Tripathi *et al*., 2015) | (level 1a, grade A) | |
| | (Perumalswami and Schiano, 2011) | Not formally assessed | |
| | (National Agency for Accreditation and Evaluation in Health, 2004) | Not formally assessed | |
| | (Diaz-Brito, Cardoso and Sarmento, 2018) | Not formally assessed- referenced a study | |
| | (Lebrec, Vinel and Dupas, 2005) | Not formally assessed | |
| The NSBB of choices can be between propranolol, and nadolol | (Diaz-Brito, Cardoso and Sarmento, 2018) | Not formally assessed | |
| Propranolol is the first choice of NSBB* | (Tripathi *et al*., 2015) | (level 1a, grade A) | |
| Varices can be managed with either NSBB or ISMN or a combination of both* | (Yoshiji *et al.*, 2021) | Recommendation: weak, 100% agreed, evidence level B) B is medium-quality evidence, | |
| If patient is not responding to NSBB, ISMN should be added on* | (Cheng *et al.*, 2009) | Not formally assessed | |
| The alternatives to propranolol is nadolol or carvedilol* | (Tripathi *et al*., 2015) | (level 1b, grade A) | |
| NSBB and carvedilol can be used* | (Bruno *et al.*, 2021) | quality of evidence: moderate strength of recommendation: strong | |
| | (Schiavon *et al.*, 2019) | Class 1 | |
| Propranolol: 40 mg twice daily. Dose | (Tripathi *et al*., 2015) | (level 1a, grade A) | |

| | | | |
|---|---|---|---|
| titrated to maximum tolerated or once heart rate (HR) of 50–55 bpm is reached to a maximum dose of 320 mg* | | | |
| 10 mg/twice daily , titrated to the maximum tolerated dosage; | (Cheng *et al.*, 2009) | Not formally assessed | |
| 80 to 160 mg / day for propranolol* | (National Agency for Accreditation and Evaluation in Health, 2004) | Not formally assessed | |
| The initial dose of propranolol is 10 mg 12/12h orally and of nadolol is 40 mg/day orally. Subsequently, the dose is progressively increased (once a week) until the desired heart rate is reached* | (Diaz-Brito, Cardoso and Sarmento, 2018) | Not formally assessed | |
| 80-160 mg/day for Propranolol* | (Lebrec, Vinel and Dupas, 2005) | Not formally assessed | |
| Carvedilol dosage: oral doses of 3.125 mg twice a day, and titrated to 6.25 mg twice a day. | (Tripathi *et al*., 2015) | (level 1a, grade A) | |
| Nadolol dosage: 40 mg daily dose. Dose titrated to maximum tolerated or once heart rate of 50–55 bpm is reached a maximum dose of 240 mg | (Tripathi *et al*., 2015) | (level 1a, grade A) | |
| Nadolol, the initial dosage is 20 mg/ four times daily, titrated to the maximum tolerated dosage. | (Cheng *et al.*, 2009) | No reference | |
| 80 mg / day for nadolol | (National Agency for Accreditation and Evaluation in Health, 2004) | No reference | |
| | (Lebrec, Vinel and Dupas, 2005) | No reference | |

*These are recommendations that are just made guidelines passing through to Domain 3.

*Table 3-6 Recommendations for primary prophylaxis. Abbreviations : VBL= variceal band ligation, NSBB= non-selective beta blocker, ISMN = isosorbide mononitrate, bpm= beats per minute, mg= milligram .*

Most of the guidelines have recommended the use of pharmacological treatment, whilst some are indifferent about the use of either pharmacological treatment or endoscopic treatment. Pharmacological treatment of varices can differ as different guidelines promote different types of drugs. There are two classes of drugs that have generally been promoted by these guidelines: beta blockers and nitrates (ISMN). The specific type of beta blocker used for varices are non-selective beta blockers (NSBB). They can be propranolol, nadolol or carvedilol. However, guidelines traditionally group propranolol and nadolol as NSBB and write recommendations separately for carvedilol. These recommendations were mostly stand-alone recommendations made by one guideline where the quality of evidence was generally moderate, and so they cannot be put forward (Cheng *et al.*, 2009; Tripathi *et al.*, 2015; Diaz-Brito, Cardoso and Sarmento, 2018; Bruno *et al.*, 2021; Yoshiji *et al.*, 2021). The two recommendations proposed by Tripathi *et al* (2015) state that propranolol should be used first and nadolol/carvedilol can be used as second choice. These can be put forward as Tripathi *et al* (2015) has graded them to be A1 or similar, and has rated green in Domain 3.

Recommendations have been made specifically for the dosages of propranolol, nadolol and carvedilol by different guidelines. Only Tripathi *et al* (2015) has graded the recommendation based on dosages of A1, and has rated green in Domain 3, and so all of these recommendations can be put forward. The remaining guidelines have not stated the strength of the recommendation that they have put forward themselves for the dosages of the medications. They have also rated either amber or red in Domain 3 (National Agency for Accreditation and Evaluation in Health, 2004; Lebrec, Vinel and Dupas, 2005; Diaz-Brito, Cardoso and Sarmento, 2018). As the quality of evidence is not mentioned, it is difficult to understand how these guidelines came to this recommendation.

Six guidelines recommend the use of NSBB first before VBL (an endoscopic therapy), which was only recommended if the patient was intolerant to the medication (National Agency for Accreditation and Evaluation in Health, 2004; Lebrec, Vinel and Dupas, 2005; Perumalswami and Schiano, 2011; Tripathi *et al.*, 2015; Diaz-Brito, Cardoso and Sarmento, 2018; de Franchis *et al.*, 2022). Tripathi *et al* (2015) and de Franchis *et al* (2022) recommend this with a strength of A1 or similar. Both of the papers have rated either amber (de Franchis *et al.*, 2022) or green (Tripathi *et al.*, 2015) in Domain 3. The remaining four guidelines (that also made this recommendation) did not use a formal tool to assess the strength of the recommendation, which may have reduced their Domain 3 rating and received a rating of red (National Agency for Accreditation and Evaluation in Health, 2004; Lebrec, Vinel and Dupas, 2005; Diaz-Brito, Cardoso and Sarmento, 2018). Both National Agency for Accreditation and Evaluation in Health (2004) and Lebrec, Vinel and Dupas (2005) published their guidelines much earlier in comparison to the other guidelines included in Domain 3 and did not update their guidelines, which may explain their Domain 3 rating. As there is a clear difference in the quality of the evidence, and the Domain 3 assessment of the guidelines, the use of NSBB prior to VBL treatment cannot be put forward.

As stated above, some guidelines propose that pharmacological therapy or VBL should be offered as primary prophylaxis (Sarin *et al.*, 2008; Tripathi *et al.*, 2015; Farooqi *et al.*, 2016; Schiavon *et al.*, 2019). These guidelines have been produced in association with relevant organisations, and have been published relatively recently (Sarin *et al.*, 2008; Tripath *et al.*, 2015; Farooqi *et al.*, 2016; Schiavon *et al.*, 2019). They have all used formal methods to grade this recommendation, and have used high quality evidence (ranging from 1a to 1b). However, only Tripathi *et al* (2015) was rated green in Domain 3 of the AGREE II checklist, whilst the others have rated either amber (Sarin *et al.*, 2008; Farooqi *et al.*, 2016) or red (Schiavon *et al.*, 2019). Though Tripathi *et al* (2015) proposed this recommendation as well as potentially using NSBB

first, they are both supported by high quality evidence, and Tripathi *et al* (2015) may have a preference towards NSBB. As all of the guidelines agree that the evidence for the use of pharmacological or VBL treatment is good, despite the quality of the guidelines themselves being variable, this recommendation should be put forward.

#### 3.4.5.1.2 Primary prophylaxis: medical therapy for the specific size of the varice

As the size of a varix is variable (see section 1.6.3.2.1 and 1.6.3.2.2), different medical therapies may be recommended. The management options differ if a varix is deemed to be at risk of bleeding (see section 1.6.3.2.1). The key management options have been highlighted in Figure 3-3, whilst Table 3-7 will show recommendations made by guidelines passing to Domain 3.

Small Varices:

- If at risk of bleeding they should be treated with some form of primary prophylaxis.
- If not at risk of bleeding, they could be considered to be treated only with NSBB.

Medium or Large Varices:

- If at risk of bleeding they should be treated with primary prophylaxis- NSBB or VBL or a combination.
- If not at risk of bleeding, they should still be treated with NSBB or VBL.
- They should be treated with NSBB and if intolerant, they should be started on ISMN.

*Figure 3-3: Summary of common recommendations across guidelines for primary prophylaxis of varices.*

| Recommendation | Guideline | Strength of evidence | Domain 3 assessment: |
|---|---|---|---|
| Small varices: those that are not at risk could be considered to be treated with NSBB | (Korean Association for the Study of the Liver (KASL), 2020) | B2-Quality of evidence: moderate, Strength of recommendation: weak | |
| | (Raffaele Bruno *et al.*, 2021) | quality of evidence: moderate strength of recommendation: conditional | |
| | (Farooqi *et al.*, 2016) | 1b,A | |
| Small varices: those that are at risk should be treated with primary prophylaxis | (Tripathi *et al*., 2015) | (level 1a, grade A) | |
| | (Schiavon *et al.*, 2019) | Not formally assessed | |
| Small varices that are at increased risk of bleeding should be treated with NSBB. E.g. red signs / Child-Pugh class B or C | (Korean Association for the Study of the Liver (KASL), 2020) | B1-Quality of evidence: moderate, Strength of recommendation: strong | |
| | (Cheng *et al.*, 2009) | IIa,C | |
| | (Raffaele Bruno *et al.*, 2021) | quality of evidence: moderate strength of recommendation: conditional | |
| | (Farooqi *et al.*, 2016) | 1b,A | |
| | (Diaz-Brito, Cardoso and Sarmento, 2018) | Not formally assessed | |
| Medium/large varices should be treated with primary prophylaxis, either with NSBB or band ligation | (Korean Association for the Study of the Liver (KASL), 2020) | A1 – Quality of evidence: high, Strength of recommendation: strong | |
| | (Tripathi *et al*., 2015) | (level 1a, grade A) | |
| | (Raffaele Bruno *et al.*, 2021) | quality of evidence: high strength of recommendation: strong | |
| | (Schiavon *et al.*, 2019) | Not formally assessed | |
| | (Reiberger and Mandorfer, 2017) | Not formally assessed | |
| Medium/large varices should be treated with primary prophylaxis, | (Hwang *et al.*, 2014) | Moderate quality | |
| | (Cheng *et al.*, 2009) | IA | |

| | | | |
|---|---|---|---|
| either with NSBB or band ligation **if high risk** of bleeding | | | |
| Medium/large varices should be treated with primary prophylaxis, either with NSBB or band ligation if not high risk of bleeding | (Cheng *et al.*, 2009) | 1C | |
| | (Sarin *et al.*, 2008) | 1a,A | |
| Medium or large varices should be treated initially with NSBB and if intolerant, they should have band ligation | (Hwang *et al.*, 2014) | Moderate quality | |
| | (National Agency for Accreditation and Evaluation in Health, 2004) | Not formally assessed | |
| | (Sarin *et al.*, 2008) | 5D | |

*Table 3-7 Recommendations for primary prophylaxis according to the size of the varices.*

***Treatment options for small varices:***

Altogether, there are three recommendations that have been proposed for the management of small varices. They differ on subtleties regarding bleeding risk (see section 1.7). Three guidelines have recommended that small varices that are not at risk of bleeding could be considered to be treated with NSBB (Farooqi *et al.*, 2016; Korean Association for the Study of the Liver (KASL), 2020; Bruno *et al.*, 2021). The recommendation itself does not seem to be definitive. The quality of evidence ranges from high to moderate, and the strength ranges from strong to weak. The Korean Association for the Study of the Liver (2020) is the only guideline to have rated green, and have acknowledged the evidence to be weak, and so this recommendation cannot be put forward. There may be discrepancies in the strength and quality due to the year of publication as the more recent guidelines have acknowledged that the evidence is still lacking.

If small varices are at risk of bleeding, Tripathi *et al* (2015) and Schiavon *et al* (2019) recommend that they should be treated with some form of primary prophylaxis (without specifying the treatment option). Tripathi *et al* (2015) have rated green in Domain 3 and have graded this recommendation to be A1 or similar, which overrides the lack of formal assessment performed by Schiavon *et al* (2019). Therefore, this recommendation can be put forward.

Five guidelines have specified that NSBB is the chosen primary prophylaxis treatment that should be used (Cheng *et al.*, 2009; Farooqi *et al.*, 2016; Diaz-Brito, Cardoso and Sarmento, 2018; Korean Association for the Study of the Liver (KASL), 2020; Bruno *et al.*, 2021). Despite numerous guidelines making the same recommendation, the evidence quality and the strength of the recommendation is variable (ranging from moderate to high, and strong to conditional respectively). Only Korean Association for the Study of the Liver (2020) has rated green whilst the rest have rated amber (Cheng *et al.*, 2009; Farooqi *et al.*, 2016; Bruno *et al.*, 2021) or red

(Diaz-Brito, Cardoso and Sarmento, 2018). Due to the variability in the evidence, strength and the Domain 3 scores, the use of NSBB as a primary prophylaxis treatment cannot be put forward.

***Treatment options for medium/large varices:***

There are four recommendations that have been proposed for medium/large varices, and they vary because some guidelines have been more specific in the level of detail in comparison to others. Some have specified whether the patient is at risk of bleeding or not, and some have specified what primary prophylaxis treatment should be given.

Five guidelines state that medium/large varices should be treated with either NSBB or VBL for primary prophylaxis (Tripathi *et al.*, 2015; Reiberger and Mandorfer, 2017; Schiavon *et al.*, 2019; Korean Association for the Study of the Liver (KASL), 2020; Bruno *et al.*, 2021). Tripathi *et al* (2015), Korean Association for the Study of the Liver (2020) and Bruno *et al* (2021) were able to recommend this at A1 or similar, whilst Reiberger and Mandorfer (2017) and Schiavon *et al* (2019) did not formally assess the strength and were rated red in Domain 3. This recommendation can be put forward because Tripathi *et al* (2015) and Korean Association for the Study of the Liver (2020) have both rated green in Domain 1 and believe that the strength of the recommendation is A1 or similar.

Cheng *et al* (2009) and Hwang *et al* (2014) have specified that those with medium/large varices that are at risk of bleeding should be treated with NSBB or VBL, but the quality of evidence ranged from high to moderate (Table 3-7). Similarly, the recommendation that states that medium/large varices that are not at risk of bleeding should be treated with NSBB or VBL was supported by evidence quality that ranged from high to low (Sarin *et al.*, 2008; Cheng *et al.*,

2009). As both of these recommendations have also been proposed by guidelines scoring amber in Domain 3, they cannot be put forward.

Three guidelines state that NSBB should be attempted first prior to VBL treatment in patients with medium/large varices (National Agency for Accreditation and Evaluation in Health, 2004; Sarin *et al.*, 2008; Hwang *et al.*, 2014). However, the evidence quality ranges from very low to moderate. The guidelines have either rated amber (Sarin *et al.*, 2008; Hwang *et al.*, 2014) or red (National Agency for Accreditation and Evaluation in Health, 2004), and so, this recommendation cannot be put forward.

### 3.4.6 Management of an acute variceal haemorrhage

The management options for an acute variceal haemorrhage can be multi-faceted and so have been split into five different results tables (Table 3-8 – Table 3-12). They follow the chronological order of treatment that is usually given to the patient which are:

- Vasoactive drugs
- Antibiotic prophylaxis
- Time to endoscopy
- Endoscopic treatment strategies
- Post-endoscopic treatments that can be offered if patients do not respond to pharmaceutical and endoscopic treatments

#### *3.4.6.1 Vasoactive drugs*

Vasoactive drugs are prescribed to vasoconstrict varices, which decreases the rate of bleeding (see section 1.7.3.2). Altogether, there were 17 recommendations proposed on this topic (Table 3-8). The commonest recommendations that have been proposed is in Figure 3-4.

- Combination of vasoactive drugs and endoscopy is the treatment of choice of variceal haemorrhage.
- Vasoactive drugs should be prescribed as soon as variceal haemorrhage is suspected and should be carried on for at least 3-5 days.
- Terlipressin is the vasoactive drug of choice.

*Figure 3-4 Summary of the common recommendations that have been proposed by guidelines in the management of a variceal haemorrhage.*

| Treatment | Which guidelines support it | Strength of guideline | Domain 3 assessment |
|---|---|---|---|
| Endoscopy and vasoactive treatment are the therapy of choice for variceal haemorrhage | (Korean Association for the Study of the Liver (KASL), 2020) | A1 | |
| | (Cheng *et al.*, 2009) | Referenced 2 studies | |
| | (Bruno *et al.*, 2021) | quality of evidence high, strength of recommendation strong | |
| | (Schiavon *et al.*, 2019) | class 1 | |
| | (Farooqi *et al.*, 2016) | 1a;a | |
| Vasoactive drug should be administered as soon as variceal haemorrhage is suspected and should be continued for 3-5 days | (Korean Association for the Study of the Liver (KASL), 2020) | A1 | |
| | (Nevens *et al.*, 2019) | Grade B | |
| | (de Franchis *et al.*, 2022) | A:1 | |
| | (Dworzynski *et al.*, 2012) | Referenced to 6 studies and acknowledges that they are all low quality studies | |
| | (National Agency for Accreditation and Evaluation in Health, 2004) | Consensus meeting- presumably based on expert opinion | |
| | (Bruno *et al.*, 2021) | quality of evidence: high strength of recommendation: strong | |
| | (Rodrigues et al., 2020) | algorithm based with no references | |
| | (Farooqi *et al.*, 2016) | (1b; A)- same for duration | |
| | (Lebrec, Vinel and Dupas, 2005) | Not formally assessed | |
| Drug choice: terlipressin, somatostatin or octreotide | (Yoshiji *et al.*, 2021) | (Recommendation: weak, 100% agreed, evidence level B- B is medium-quality evidence,) | |
| | (de Franchis *et al.*, 2022) | A1 | |
| | (Cheng *et al.*, 2009) | Not formally assessed | |
| | (Rodrigues et al., 2020) | Algorithm based with no references | |
| | (Lebrec, Vinel and Dupas, 2005) | Not formally assessed | |
| Drug choice: terlipressin or octreotide* | (Farooqi *et al.*, 2016) | (1b; A) | |

| | | | |
|---|---|---|---|
| Drug choice: terlipressin or somatostatin | (Tripathi *et al*., 2015) | (level 1a, grade A) | |
| 1st Choice of vasoactive drug: terlipressin | (Nevens *et al.*, 2019) | Grade A (consistent level 1 studies [systematic review of randomized controlled trials (RCT) and RCT]) | |
| | (Dworzynski *et al.*, 2012) | The evidence comparing terlipressin to placebo was predominantly of moderate quality. The available evidence comparing terlipressin to octreotide was of very low quality for most outcomes, and for the outcomes of transfusion requirements and numbers failing initial haemostasis it was of low quality. Data comparing terlipressin to somatostatin was also of very low quality. After some debate they agreed that there was enough data to make a positive recommendation for terlipressin. The group felt it difficult to make a recommendation to not use octreotide or somatostatin, as the available evidence which suggested inferiority of these agents was considered to be of low quality. | |
| | (Siau *et al.*, 2020) | Level of evidence: High<br>Level of recommendation: Strong<br>Agreement: 100% | |
| 1st choice is octreotide: | (Perumalswami and Schiano, 2011) | Not formally assessed -based on author's experience | |

| | | | |
|---|---|---|---|
| | (Hwang *et al.*, 2014) | Moderate quality | |
| Terlipressin: 2mg / 4h IV, reduce to 1mg / 4h 24h after haemostasis | (Cheng *et al.*, 2009) | Not formally assessed | |
| Terlipressin dose: every 4 hours as a slow intravenous injection based on weight: 1 mg if the weight is less than 50 kg, 1.5 mg if the weight is between 50 and 70 kg and 2 mg over 70 kg* | (National Agency for Accreditation and Evaluation in Health, 2004) | Not formally assessed -Meta-analyses referenced | |
| Terlipressin dose: 2mg four times a day* | (Siau *et al.*, 2020) | Level of evidence: High<br>Level of recommendation: Strong (80% agreement) | |
| Terlipressin dose: 1-2mg IV 6/6 h up to 4/4 h * | (Rodrigues et al., 2020) | Not formally assessed | |
| Octreotide is recommended at an initial bolus dose of 50 µg IV followed by a continuous IV infusion of 50 µg/h* | (Cheng *et al.*, 2009) | Not formally assessed | |
| Octreotide is administered as a continuous infusion of 25 µg / hour, possibly preceded by a bolus of 50 µg, the benefit of which has not been demonstrated* | (National Agency for Accreditation and Evaluation in Health, 2004) | Not formally assessed – referenced a study | |
| Octreotide bolus 50 µg IV, infusion 50 µg h (600 µg/50, 4cc/h)* | (Rodrigues et al., 2020) | Not formally assessed | |
| Somatostatin dose :250 µg IV bolus followed by continuous infusion of 250 µg/h. | (Cheng *et al.*, 2009) | Not formally assessed | |
| Somatostatin dose: 250 µg / h, whether or not preceded by a bolus of 250 µg. | (National Agency for Accreditation and Evaluation in Health, 2004) | Not formally assessed | |

| | | | |
|---|---|---|---|
| Somatostatin bolus 250 µg IV, perfusion 250 µg/h | (Rodrigues et al., 2020) | Not formally assessed | |

*Recommendations made by guidelines just passing through Domain 3.

*Table 3-8 Recommendations for active variceal haemorrhage- vasoactive treatments. Abbreviations: µg= microgram, mg= milligram, IV= intravenous*

Of the five guidelines that recommend a combination of vasoactive drugs and endoscopic treatment for variceal haemorrhage, four have given this recommendation a strength of A1 or similar (Farooqi *et al.*, 2016; Schiavon *et al.*, 2019; Korean Association for the Study of the Liver (KASL), 2020; Bruno *et al.*, 2021). However, they differ in their Domain 3 scores, which range from red to green. As the quality of evidence behind this recommendation is mostly unanimous, and has also been supported by KASL (2020) who have rated green in Domain 3, this recommendation can be put forward.

The recommendation that states that vasoactive drug should be started when a variceal haemorrhage is suspected, is supported by nine guidelines. The strength behind this recommendation varies, where three of the guidelines that have rated green in Domain 3 have conflicting views (Dworzynski *et al.*, 2012; Nevens *et al.*, 2019; Korean Association for the Study of the Liver (KASL), 2020). KASL (2020) has graded this recommendation to be at A1. However, Dworzynski *et al* (2012) and Nevens *et al* (2019) have graded the evidence to be of low and moderate quality respectively. Three other guidelines, which are not associated with an organisational body, did not formally grade the recommendation (National Agency for Accreditation and Evaluation in Health, 2004; Lebrec, Vinel and Dupas, 2005; Rodrigues *et al.*, 2020). As the majority of the rigorously developed guidelines agree that the quality of evidence behind this general statement is sub-optimal, this recommendation cannot be put forward.

The choice of vasoactive drug differs amongst the guidelines. The three drugs that were recommended were: terlipressin, octreotide or somatostatin. Between the guidelines, there were some discrepancy amongst which drug to use first. Most of them chose terlipressin

and have added a different choice of drug e.g. octreotide or somatostatin. However, the quality of evidence and the Domain 3 ratings are generally variable, so most of them cannot be put forward. For example, five guidelines have said that terlipressin, somatostain or octreotide can be used (Lebrec, Vinel and Dupas, 2005; Cheng *et al.*, 2009; Rodrigues *et al.*, 2020; Yoshiji *et al.*, 2021; de Franchis *et al.*, 2022). De Franchis *et al* (2022) has given this recommendation a strength of A1, and has rated amber in Domain 3, whilst Yoshiji *et al* (2021) has given this a weak strength due to moderate quality evidence. Yoshiji *et al* (2021) has rated green in Domain 3. Due to the conflicting evidence quality regarding which drug to use first, this recommendation cannot be put forward.

There are two recommendations that can be put forward regarding the choice of drugs: terlipressin or somatostatin can be used (Tripathi *et al.*, 2015); terlipressin is the first choice of vasoactive drug (Dworzynski *et al.*, 2012; Nevens *et al.*, 2019; Siau *et al.*, 2020) All of these guidelines have rated green in Domain 3. There are some conflicting views regarding the later recommendation where Nevens et al (2019) and Siau *et al* (2020) have graded the recommendation to be A1 or similar, whilst Dworzynski *et al* (2012) appraised the evidence to be of low to moderate quality. On balance, the use of terlipressin and somatostatin can be put forward.

Dose specific recommendations were mostly isolated recommendations by guidelines that were appraised against Domain 3. Only Siau *et al* (2020), who rated green, was able to recommend that terlipressin should be given at a dose of 2mg four times daily, with a recommendation strength of A1 or similar and so, this can be put forward. The other guidelines did not grade the recommendations formally, and rated either red (National Agency for Accreditation and Evaluation in Health, 2004; Rodrigues *et al.*, 2020) or amber (Cheng *et al.*, 2009) in Domain 3.

#### *3.4.6.2 Antibiotic prophylaxis*

During a variceal haemorrhage, antibiotics can be prescribed to prevent infections which can cause the patient to deteriorate further. Five recommendations were proposed altogether (Table 3-9), and the commonest recommendations have been summarised in Figure 3-5.

- Antibiotics prophylaxis should be initiated and be given for 5-7 days.
- The choice of antibiotic is of the quinolone class, but if patients have resistant or have severe liver disease, they should be given ceftriaxone (which belongs to the cephalosporin class).
- Drug dosage for ceftriaxone is 1g in 24 hours.

*Figure 3-5 Summary of common recommendations that have been proposed by guidelines in the management of a variceal haemorrhage.*

| Therapy of choice | Which guideline supports this | Recommendation strength | Domain 3 quality appraisal assessment: |
|---|---|---|---|
| Antibiotic prophylaxis should be initiated and should have a duration of 5-7 days | (Korean Association for the Study of the Liver (KASL), 2020) | A1 – Quality of evidence: high, Strength of recommendation: strong | |
| | (de Franchis *et al.*, 2022) | A1 | |
| | (Tripathi *et al*., 2015) | A1 | |
| | (Dworzynski *et al.*, 2012) | The GRADE quality for the reviewed outcomes was generally low to very low. However, the GDG felt that these studies were well conducted given the difficulties of research in this acutely ill patient group. | |
| | (Perumalswami and Schiano, 2011) | Not formally assessed | |
| | (Bruno *et al.*, 2021) | quality of evidence: high strength of recommendation: strong | |
| | (Rodrigues et al., 2020) | Not formally assessed | |
| | (Siau et al., 2020) | Level of evidence: High Strength of recommendation: Strong | |
| | (Diaz-Brito, Cardoso and Sarmento, 2018) | Not formally assessed -referenced some studies | |
| Quinolone antibiotic should be given first, but if they have severe liver disease/local quinolone resistance, then ceftriaxone should be given | (de Franchis *et al.*, 2022) | D2 | |
| | (Rodrigues et al., 2020) | Not formally assessed | |
| Choice of Ab: ceftriaxone or quinolone | (Diaz-Brito, Cardoso and Sarmento, 2018) | Not formally assessed -some studies referenced | |

| | | | |
|---|---|---|---|
| Drug dosage of ceftriaxone:<br><br>Intravenous ceftriaxone 1 g/24 h for advanced liver disease | (de Franchis *et al.*, 2022) | A1 | |
| | (Rodrigues et al., 2020) | Not formally assessed | |
| | (Diaz-Brito, Cardoso and Sarmento, 2018) | Not formally assessed -referenced in some studies | |
| Quinolone dosage:<br><br>oral norfloxacin 400 mg every 12 h | (Diaz-Brito, Cardoso and Sarmento, 2018) | Not formally assessed -referenced some studies | |

*Table 3-9: Recommendations for active variceal haemorrhage- antibiotics prophylaxis.*

Nine guidelines have recommended that antibiotics should be started and should be used for 5-7 days. Of the six guidelines that did formally assess the evidence, five of the guidelines have made a recommendation of A1 or equivalent (Tripathi *et al.,* 2015; Korean Association for the Study of the Liver (KASL), 2020; Siau *et al.*, 2020; Bruno *et al.*, 2021; de Franchis *et al.*, 2022). Three of the guidelines were rated green (Tripathi *et al.*, 2015; Korean Association for the Study of the Liver (KASL), 2020; Siau *et al.*, 2020) whilst the rest were rated amber (Bruno *et al.*, 2021; de Franchis *et al.*, 2022). However, Dworzynski *et al* (2012) disagreed and graded the quality of evidence to be low. Despite this, the use of antibiotics for 5-7 days can be put forward as the majority of guidelines believe the strength to be of A1 or similar.

Despite nine guidelines recommending the use of antibiotics, only three guidelines indicate which antibiotics to use. They may have left this to the clinician's judgement and local antibiotic policies. If the antibiotics were specified by the guidelines, either quinolones or ceftriaxone were recommended. De Franchis *et al* (2022) and Rodrigues *et al* (2020) recommend the use of a quinolone if there is local antibiotic resistance or if the patient has severe liver disease. However, the evidence behind this recommendation is lacking, as de Franchis *et al* (2022), who rated amber, was the only guideline to grade the recommendation. This was graded to be weak with low quality evidence. Diaz-Brito, Cardoso and Sarmento (2018) have recommended that either ceftriaxone or quinolones can be used, but no formal grading method was used so it is difficult to appreciate the strength of this recommendation. Both of the recommendations regarding the choice of antibiotic cannot be put forward due to the absence of high quality evidence.

The three aforementioned guidelines specified the exact dosage of the medication (Diaz-Brito, Cardoso and Sarmento, 2018; Rodrigues *et al.*, 2020; de Franchis *et al.*, 2022). However, only de Franchis *et al* (2022) has graded the recommendation (at A1) which states that ceftriaxone should be given at 1g/24h. Despite the high strength and quality of evidence, the recommendations on antibiotic dosages cannot be put forward as de Franchis *et al* (2022) has rated amber in Domain 3.

#### *3.4.6.3 Time to endoscopy*

Endoscopy is the recommended diagnostic tool of choice to visualise and identify the cause of the upper gastrointestinal bleeding and perform definitive treatment. Though a variceal bleed can be suspected prior to diagnosis (through patient signs and symptoms), it is important confirm this so that suitable treatments can be offered for the patient. The time to endoscopy is defined as the time it takes for the patient to receive endoscopy from time of admission. The recommended time to endoscopy range from 6-48 hours (Table 3-10).

| Treatment of choice | Guidelines supporting the recommendation | Strength of recommendation | Domain 3 assessment |
|---|---|---|---|
| Time to endoscopy :<6 hours | (Lebrec, Vinel and Dupas, 2005) | Not formally assessed | |
| Time to endoscopy:<br>Ideally less than 6 hours, but up to 12 hours | (National Agency for Accreditation and Evaluation in Health, 2004) | Not formally assessed | |
| Time to endoscopy<br>Up to 12 hours | (de Franchis *et al.*, 2022) | B1 | |
| | (Hwang *et al.*, 2014) | Moderate quality | |
| | (Rodrigues *et al.*, 2020) | Not formally assessed | |
| | (Farooqi *et al.*, 2016) | 5D | |
| | (Diaz-Brito, Cardoso and Sarmento, 2018) | Not formally assessed | |
| Time to endoscopy in stable patients<br><br>Within 24 hours* | (Tripathi *et al*., 2015) | Level 2b, grade A | |
| | (Dworzynski *et al.*, 2012) | The available clinical evidence in relation to the timing of endoscopy for stable patients is predominantly of very low quality by GRADE criteria. Little clinical evidence is available which addresses the timing of endoscopy in unstable or high risk patients. That which is available is predominantly of very low quality. The economic analysis performed as part of the guideline development process is based upon NHS costs, models of care and representative UK audit data – and therefore directly applicable. However as it is based on observational data, it potentially has | |

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| | | serious limitations. Evidence based on many randomised trials. | |
| | (Bruno *et al.*, 2021) | Quality Of Evidence: Low<br>Strength Of Recommendation: Weak | |
| | (Siau et al., 2020) | Level of evidence: Weak<br>Level of recommendation: Strong<br>Bundle recommendation: Referral to ensure that endoscopy is performed within 24hours of presentation (100% agreement | |
| Within 48 hours* | (Cheng *et al.*, 2009) | Iia, C | |
| Patients that are unstable, endoscopy should be performed when it is safe to do so after resuscitation- they may need it urgently | (National Agency for Accreditation and Evaluation in Health, 2004) | Not formally assessed | |
| | (de Franchis *et al.*, 2022) | D1 | |
| | (Siau et al., 2020) | Level of evidence: Weak<br>Level of recommendation: Strong<br>Agreement: 90% | |
| | (Dworzynski *et al.*, 2012) | Little clinical evidence is available which addresses the timing of endoscopy in unstable or high risk patients. That which is available is predominantly of very low quality- using many RCTs for this recommendation. | |

*Recommendations made by guidelines passing through just Domain 3.

*Table 3-10: Recommendations for active variceal haemorrhage- time to endoscopy.*

13 guidelines have recommended different times to endoscopy, which range from 6-48h. However, the quality of evidence behind all of the recommendation are not of high quality, despite having varying strengths. As none of the recommendations are supported by high quality evidence, they cannot be put forward.

The commonest quoted time to endoscopy is 12 hours, recommended by five guidelines (Hwang *et al.*, 2014; Farooqi *et al.*, 2016; Diaz-Brito, Cardoso and Sarmento, 2018; Rodrigues *et al.*, 2020; de Franchis *et al.*, 2022). All of the UK guidelines recommend that endoscopy should be performed within 24 hours (Dworzynski *et al*., 2012; Tripathi *et al.*, 2015; Siau *et al.*, 2020). All of them have scored green in Domain 3 and acknowledge that the quality of evidence is moderate. But, despite this, Tripathi *et al* (2015) and Siau *et al* (2020) proposes the strength of the recommendation as strong. Dworzynski *et al* (2012) acknowledges that cost and resource availability was taken into account for this recommendation, which many of the other guidelines may have also done without specifying so.

In patients that are unstable, it has been recommended that endoscopy should be performed urgently (National Agency for Accreditation and Evaluation in Health, 2004; Dworzynski *et al*., 2012; Siau *et al.*, 2022). All of the papers except for National Agency for Accreditation and Evaluation in Health (2004), have appraised the quality of the evidence to be weak.

#### 3.4.6.4 Endoscopic treatment strategies

Endoscopic treatment is performed whilst the patient is undergoing a diagnostic endoscopy to identify the cause of the bleeding. Depending on the location of the varices, different management options are available (see section 1.6.3.2.1). There were 11 recommendations proposed (Table 3-11) and the commonest recommendations that were proposed are summarised in Figure 3-6.

- For oesophageal varices, VBL is the choice of treatment. If this is not available, sclerotherapy can also be used.
- VBL or endoscopic sclerotherapy can be used as treatment.
- For gastric varices, tissue adhesives in the form cyanoacrylate (CA) injections are the choice of treatment. This can also apply for cardio-fundal gastric varices.
- VBL or tissue adhesive can be used in bleeding from gastroesophageal varices type 1.
- If patient is still bleeding despite endoscopic and pharmacological treatment, balloon tamponade or Sengstaken-Blakemore tube can be used for up to 24 hours as a bridge therapy until definitive therapy.
- An alternative to SB tube is a self-expanding covered oesophageal metal stent, which is sometimes preferred.
- Prior to endoscopy, erythromycin (an antibiotic) can be given to improve the view on endoscopy.

*Figure 3-6: Summary of common recommendations that have been proposed by guidelines in the management of an acute variceal bleed.*

| Endoscopy treatment type: | Which guidelines support this | Strength of recommendation | Domain 3 assessment: |
|---|---|---|---|
| For oesophageal varices, VBL is the treatment of choice | (Nevens *et al.*, 2019) | Grade A (consistent level 1 studies [systematic review of randomized controlled trials (RCT) and RCT]) | |
| | (de Franchis *et al.*, 2022) | A:1 | |
| | (Tripathi *et al.*, 2015) | (level 1a, grade A) | |
| | (Hwang *et al.*, 2014) | Moderate quality | |
| | (Dworzynski *et al.*, 2012) | GRADE criteria the evidence on this question was low to very low. The GDG felt that these studies had generally been well performed given the difficulties inherent in any study of acutely ill patients such as these. | |
| | (Perumalswami and Schiano, 2011) | Not formally assessed -experience based | |
| | (National Agency for Accreditation and Evaluation in Health, 2004) | Not formally assessed | |
| | (Bruno *et al.*, 2021) | quality of evidence: high strength of recommendation: strong | |
| | (Schiavon *et al.*, 2019) | class 1 | |
| | (Farooqi *et al.*, 2016) | (1b;A); | |
| | (Lebrec, Vinel and Dupas, 2005) | Not formally assessed | |
| If VBL is not available, sclerotherapy can be done | (Perumalswami and Schiano, 2011) | Not formally assessed -experience based recommendation | |
| | (National Agency for Accreditation and Evaluation in Health, 2004) | Not formally assessed | |
| | (Schiavon *et al.*, 2019) | Class Iia | |
| | (Farooqi *et al.*, 2016) | (1b,A) | |
| | (Hwang *et al.*, 2014) | Moderate quality | |

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| VBL or Endoscopic injection sclerotherapy is proposed treatment | (Yoshiji *et al.*, 2021) | (Recommendation: weak, 100% agreed, evidence level C) C is low quality evidence | |
| For gastric varices, CA injection is the treatment of choice / tissue adhesives e.g. (e. g. N-butyl-cyanoacrylate/thrombin) | (de Franchis *et al.*, 2022) | A1 | |
| | (Hwang *et al.*, 2014) | Low quality | |
| | (Dworzynski *et al.*, 2012) | The grade of most of the studies that were used were very low- low quality studies to compare the efficacy of cyano vs TIPS to come to the conclusion that cyanoacrylate is the better option | |
| | (Cheng *et al.*, 2009) | Not formally assessed -references 2 studies | |
| | (Bruno *et al.*, 2021) | quality of evidence: low<br>strength of recommendation: strong | |
| | (Farooqi *et al.*, 2016) | 1b,A | |
| Specifically, for cardio-fundal varices, tissue adhesives is the choice of treatment | (Cheng *et al.*, 2009) | 1,B | |
| | (Schiavon *et al.*, 2019) | Class 1 | |
| VBL or tissue adhesive can be used in bleeding from gastroesophageal varices type 1* | (Schiavon *et al.*, 2019) | Class IIB | |
| | (Farooqi *et al.*, 2016) | 4;C | |
| | (de Franchis *et al.*, 2022) | D1 | |
| Repeat endoscopy in those that have initially failed endoscopic therapy | (Rodrigues *et al.*, 2020) | Not formally assessed | |
| | (Schiavon *et al.*, 2019) | Class Iib | |
| | (Farooqi *et al.*, 2016) | 2b,B | |
| If patient is still bleeding despite endoscopic and pharmacological treatment, balloon tamponade / SB tube can be used for up to 24h as a bridge therapy until definitive therapy | (Korean Association for the Study of the Liver (KASL), 2020) | B2 | |
| | (de Franchis *et al.*, 2022) | B1 | |
| | (Tripathi *et al*., 2015) | Level 2b, grade B | |
| | (Hwang *et al.*, 2014) | Very low quality | |
| | (Cheng *et al.*, 2009) | I,B | |

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| | (Rodrigues *et al.*, 2020) | III; 1 | |
| | (Farooqi *et al.*, 2016) | 5D | |
| An alternative to SB tube is an self-expanding covered oesophageal metal stents, which is sometimes preferred | (de Franchis *et al.*, 2022) | B1 | |
| | (Schiavon *et al.*, 2019) | Class 1 | |
| | (Farooqi *et al.*, 2016) | 4,C | |
| Erythromycin prior to endoscopy to have a better view on endoscopy: | (Nevens *et al.*, 2019) | Grade B (consistent level 2 or 3 studies or extrapolations from level 1 studies [systematic review of cohort studies, cohort studies, and low quality RCT] | |
| | (Nevens *et al.*, 2019) | Not formally assessed | |
| | (de Franchis *et al.*, 2022) | B1 | |
| | (Perumalswami and Schiano, 2011) | Not formally assessed | |
| | (National Agency for Accreditation and Evaluation in Health, 2004) | Not formally assessed | |
| | (Rodrigues *et al.*, 2020) | Not formally assessed | |
| Dosage of erythromycin:<br>250 mg of intravenous erythromycin over 30-120 minutes | (National Agency for Accreditation and Evaluation in Health, 2004) | Not formally assessed | |
| | (Rodrigues *et al.*, 2020) | Not formally assessed | |

*Recommendations made by guidelines just passing through Domain 3.

*Table 3-11: Recommendations for active variceal haemorrhage- endoscopic treatment options. Abbreviations: CA= cyanoacrylate, SB= Sengstaken-Blakemore.*

Eleven guidelines promote the use of VBL as the endoscopic treatment of choice for oesophageal varices. Six of the guidelines have given this a strength of A1 or similar (Tripathi *et al*., 2015; Farooqi *et al.*, 2016; Nevens *et al.*, 2019; Schiavon *et al.*, 2019; Bruno *et al.*, 2021; de Franchis *et al.*, 2022). The Domain 3 scores varies for the six guidelines, where Nevens *et al* (2019) and Tripathi *et al* (2015) were the only guidelines that have been rated green, whilst the other guidelines received an amber (n=3) or red (n=1) rating. The rest of the five guidelines, either graded the evidence to be moderate (Dworzynski *et al.*, 2012; Hwang *et al.*, 2014) or did not specify the grade (National Agency for Accreditation and Evaluation in Health, 2004; Lebrec, Vinel and Dupas, 2005; Perumalswami and Schiano, 2011). Dworzynski *et al* (2012) graded the quality of evidence as low and has speculated that this may be because it is difficult to perform studies if patients are acutely unwell. Guidelines published after 2014 all agree that the quality is at A1 standard or similar whilst guidelines published prior to this have given the evidence quality moderate/low. A reason for this may be that better quality evidence may have been published around 2014. As there are two guidelines that were rated green in Domain 3 that agree that the quality is A1 or similar, the recommendation stating that VBL is the choice of treatment for oesophageal varices can be put forward.

The recommendation that states that sclerotherapy can be performed if VBL is not available cannot be put forward, as the quality of evidence and Domain 3 ratings vary between those who formally assessed the evidence (Hwang *et al.*, 2014; Farooqi *et al.*, 2016; Schiavon *et al.*, 2019). Farooqi *et al* (2016) was the only guideline to grade this recommendation as high quality whilst Hwang *et al.*, (2014) and Schiavon *et al* (2019) have appraised the quality of the evidence to be moderate.

Three recommendations have been proposed for managing gastric varices by seven (33%) guidelines assessed against Domain 3. They differ because management options vary depending on the location of the gastric varices, but they all generally recommend tissue adhesives. One of the recommendations that did not specify the location of the gastric varix, proposed that gastric varices should be treated with tissue adhesives e.g. cyanoacrylate. The quality of evidence ranges from low to high and the Domain 3 ratings range from amber to green for the six guidelines that support this. Farooqi *et al* (2016) and de Franchis *et al* (2022) graded it to be of high strength due to high quality evidence, whilst Bruno *et al* (2021) has given this a strength of strong despite appraising the quality of evidence to be low. Dworzynski *et al* (2012), who is the only guideline to score green, appraised the quality to be very low. The used of tissue adhesives was recommended specifically for cardio-fundal varices by Cheng *et al* (2009) and Schiavon *et al* (2019), but the Domain 3 scores are amber and red respectively, so this recommendation cannot be put forward. For gastroesophageal varices type 1, three guidelines recommend using either VBL or tissue adhesives (Farooqi *et al.*, 2016; Schiavon *et al.*, 2019; de Franchis *et al.*, 2022). This was specifically made by only those assessed against Domain 3. The quality of evidence is moderate to poor, and the Domain 3 ratings range from red to amber. Despite the poor quality evidence, de Franchis *et al* (2022) makes a strong recommendation. None of the recommendations on gastric varices can be put forward due to conflicting opinions on the quality of evidence and the strength.

If a haemorrhage cannot be controlled, some guidelines specify that a second endoscopy should be attempted, whilst others say that balloon tamponade or oesophageal stents should be used. Repeating endoscopy has been favoured by three guidelines, but the evidence is of moderate quality so this recommendation cannot be put forward (Farooqi *et al.*, 2016; Schiavon *et al.*, 2019; Rodrigues *et al.*, 2020). The use of balloon tamponade has been recommended by seven

guidelines but the evidence quality is moderate to very low quality. Tripathi *et al* (2015) and KASL (2020) were rated green in Domain 3, and graded the quality to be moderate and strength to be weak. However, Cheng *et al* (2009) and de Franchis *et al* (2022), who were rated amber, recognise that the quality of evidence is moderate but have still given this a strong recommendation. Due to the conflicting views between guidelines that are of high and moderate quality, this recommendation cannot be put forward. Three newer guidelines have suggested the use of self-expanding oesophageal stent rather than a balloon tamponade in the management of a severe variceal haemorrhage (Farooqi *et al.*, 2016; Schiavon *et al.*, 2019; de Franchis *et al.*, 2022). The evidence quality varies between high (Schiavon *et al.*, 2019), moderate (de Franchis *et al.*, 2022) and low (Farooqi *et al.*, 2016). None of the guidelines have ratings of green in Domain 3. Due to the differences in quality of evidence around stenting, this recommendation cannot be put forward.

The use of erythromycin (an antibiotic that is indicated to improve the view of varices on endoscopy) was recommended by five guidelines but only two of them appraised them quality of evidence, which stated that they were of moderate standards (Nevens *et al.*, 2019; de Franchis *et al.*, 2022). Dosages of erythromycin (250mg over 30-120 min) were provided by two guidelines which did not grade the evidence behind this recommendation (National Agency for Accreditation and Evaluation in Health, 2004; Rodrigues *et al.*, 2020). As the evidence behind erythromycin is lacking, it cannot be recommended.

In summary, the only recommendation that can be put forward is the use of VBL in oesophageal varices. The recommendations for gastric varices are lacking evidence, and were not supported by rigorously developed guidelines.

#### 3.4.6.5 Post endoscopic treatment strategies

Patients that had a variceal haemorrhage could be at risk of rebleeding acutely within the week. This can occur despite the use of endoscopic and pharmacological treatments. Therefore, it may be appropriate to take a definitive treatment approach. There were eight recommendations proposed (Table 3-12) and the most common can be found in Figure 3-7.

- Transjugular intrahepatic portosystemic shunt (TIPS) can be offered to patients as a rescue therapy if they fail to respond to pharmacological and endoscopic therapy.
- TIPS can be given for gastric variceal haemorrhage if they fail to stop bleeding.
- Patients that are of Child Pugh Class A can have surgical interventions to stop bleeding.
- Patients of higher risk (Child Pugh Score Class B and C), can be considered for early TIPS (<72h), if the hospital has resources to do so.
- Balloon-occluded retrograde transvenous obliteration (BRTO) can be a treatment for patients with gastric varices.

*Figure 3-7: Summary of common recommendations that have been proposed by guidelines in managing an active variceal haemorrhage.*

| Recommendation | What paper supports this | Strength of the recommendation | Domain 3 assessment: |
|---|---|---|---|
| After endoscopic management, cross-sectional (MRI or CT) imaging with portal venous contrast phase should be obtained to determine vascular anatomy, including the presence or absence of portosystemic shunts and gastrorenal shunts | (de Franchis *et al.*, 2022) | D1 | |
| TIPS should be placed in patients with high risk of rebleeding as rescue therapy. This normally occurs as a result of failed pharmacology and endoscopic treatment | (Korean Association for the Study of the Liver (KASL), 2020) | A2-Quality of evidence: high, Strength of recommendation: weak | |
| | (Tripathi *et al.*, 2020) | (strong recommendation, moderate-quality evidence) | |
| | (de Franchis *et al.*, 2022) | B1 | |
| | (Tripathi *et al*., 2015) | (level 1a, grade A) | |
| | (Hwang *et al.*, 2014) | Moderate quality | |
| | (Dworzynski *et al.*, 2012) | Not formally assessed | |
| | (Perumalswami and Schiano, 2011) | Not formally assessed | |
| | (Cheng *et al.*, 2009) | Not formally assessed | |
| | (National Agency for Accreditation and Evaluation in Health, 2004) | Not formally assessed | |
| | (Bruno *et al.*, 2021) | quality of evidence: high strength of recommendation: strong | |
| | (Rodrigues *et al.*, 2020) | Not formally assessed | |
| | (Schiavon *et al.*, 2019) | Class I | |
| | (Farooqi *et al.*, 2016) | 1b;A | |
| | (Fagiuoli *et al.*, 2017) | 2bB | |
| | (Lebrec, Vinel and Dupas, 2005) | Not formally assessed | |
| | (Tripathi *et al*., 2015) | Level 3a, grade B | |

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|---|---|---|---|
| TIPS should be given to ongoing bleeding gastric varices if they do not respond to treatment | (Dworzynski *et al.*, 2012) 12) | The GRADE quality categories were noted. In general the GDG felt that these studies were well conducted given the difficulties of research in this acutely ill patient group. They noted however that the studies performed in the 1990's (those by Rossle and Sanyal) will have used uncovered stents not purposely designed for TIPS, and therefore may not reflect the benefits which can be achieved now. | |
| | (Fagiuoli *et al.*, 2017) | 2bB | |
| | (Perumalswami and Schiano, 2011) | Not formally assessed | |
| Surgical diversion / surgery is restricted to Child Turcotte Pugh (CTP) class A patients | (Tripathi *et al.*, 2015) | Level 1b, B | |
| | (Cheng *et al.*, 2009) | Not formally assessed | |
| | (Farooqi *et al.*, 2016) | 2b;B | |
| In patients who have CTP class C disease (C10-13) or MELD ≥19 or HVPG>20mmHg, and bleeding from oesophageal varices or GOV1 and GOV2 gastric varices and are haemodynamically stable, early or pre-emptive TIPSS should be considered within 72hours of a variceal bleed where local resources allow | (Tripathi *et al.*, 2020) | (weak recommendation, moderate quality of evidence) | |
| | (Nevens *et al.*, 2019) | Grade A (consistent level 1 studies [systematic review of randomized controlled trials (RCT) and RCT]) | |
| | (Korean Association for the Study of the Liver (KASL), 2020) | B2-Quality of evidence: moderate, Strength of recommendation: weak | |
| | (Tripathi *et al.*, 2015) | (level 1b, grade B) | |
| | (Cheng *et al.*, 2009) | Not formally assessed | |
| | (Bruno *et al.*, 2021) | quality of evidence: high strength of recommendation: strong | |
| | (Schiavon *et al.*, 2019) | Class IIA | |
| | (Farooqi *et al.*, 2016) | 1b;A | |

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|---|---|---|---|
| | (Fagiuoli *et al.*, 2017) | 1b;A | |
| BRTO can be used in the treatment for GOV.2/IGV1 in high risk patients | (Korean Association for the Study of the Liver (KASL), 2020) | B1-Quality of evidence: moderate, Strength of recommendation: strong | |
| | (de Franchis *et al.*, 2022) | D2 | |
| | (Fagiuoli *et al.*, 2017) | 5D | |
| | (Yoshiji *et al.*, 2021) | Recommendation: weak, 100% agreed, evidence level C) C is low quality evidence | |

*Table 3-12 Recommendations for active variceal haemorrhage- post-endoscopic treatments. Abbreviation: CT= computerised tomography, MRI= magnetic resonance imaging, GOV= gastro-oesophageal varices, IGV= isolated gastric varices, BRTO= balloon-occluded retrograde transvenous obliteration, HVPG= hepatic venous pressure gradient, TIPS= transjugular intrahepatic portosystemic shunt.*

The recommendation stating that imaging (MRI or CT) should be used after endoscopy is only supported by de Franchis *et al* (2022), who rated amber in Domain 3. Despite quoting the evidence to be of low quality, the recommendation strength is strong. As there is a clear discrepancy between the evidence and the strength, this recommendation cannot be put forward.

The use of TIPS has been recommended by many guidelines for different scenarios. For example, it has been recommended as a rescue therapy if previous treatments did not work. Of the 15 guidelines that recommend this, nine have formally graded the evidence, which ranges from moderate to high. Two BSG guidelines, both of which were rated green in Domain 3, have graded the use of TIPS differently (Tripathi *et al.*, 2015; Tripathi *et al.*, 2020). The earlier guideline, specifically written for the management of varices, graded it to be A1 or similar, whilst the latter (produced for the use of TIPS in cirrhotic patients) gave this a strong strength despite moderate quality evidence. This may be due to the release of newer evidence that may have proved TIPS to not be as beneficial as initially expected. Despite KASL (2020) publishing their guideline at similar times as Tripathi *et al* (2020), KASL graded the recommendation completely differently – weak strength despite high quality evidence. This could be because different organisations may have had access to different evidence. Despite the evidence quality being moderate to high, the conflicted grading between guidelines means that the use of TIPS as rescue therapy cannot be put forward.

Another indication for TIPS is specifically for bleeding gastric varices that are not responsive to treatment. This was recommended by four guidelines, where three of them graded the strength to be weak due to moderate quality evidence (Dworzynski *et al*., 2012; Fagiuoli *et al.,* 2017;

Tripathi *et al.*, 2020). A notable point that was raised by Dworzynski *et al* (2012) is that some of the studies that have been used to form the recommendation were made in the 1990s, and the difficulties that they had faced then may not be a problem currently e.g. access to resources.

Nine guidelines have been specific about what treatment to offer depending on the severity of the chronic liver disease. The Child-Turcotte-Pugh (CTP) and MELD NA scores can be used to identify the severity of liver disease (see section 4.3.4.2). In CTP class A patients, who have less severe disease, surgical diversion can be performed. This was recommended by three guidelines (Cheng *et al.*, 2009; Tripathi *et al.*, 2015; Farooqi *et al.*, 2016). Of the two guidelines that did formally assess the quality of evidence, Tripathi *et al* (2015) (who was rated green) graded it as a weak recommendation despite high quality evidence and Farooqi *et al* (2016) (who rated amber) has appraised the quality to be of moderate quality. Despite the guidelines being published at similar times, their grading of evidence is quite different. Those with severe liver disease, denoted at CPT class C, are recommended to have TIPS within 72h if at risk of bleeding by nine guidelines. Four guidelines have graded it A1 or similar (Farooqi *et al.*, 2016; Fagiuoli *et al*., 2017; Nevens *et al.*, 2019; Bruno *et al.*, 2021). However, the Domain 3 scores varied, where Nevens *et al* (2019) was rated green whilst the others were rated amber. Tripathi *et al* (2020) and Korean Association for the Study of the Liver (2020), who were rated green, agreed that the quality of the evidence is moderate and strength of the recommendation is weak. As the majority of the guidelines that were rated green in Domain 3 propose that the strength of the evidence is weak, the recommendations that are specific to the severity of liver disease cannot be put forward.

BRTO has been specifically recommended for different types of gastric varices. This is a relatively new therapy and has only been recommended by guidelines that have been published after 2017. BRTO has been indicated to be used as a rescue therapy for either isolated gastric varices

(IGV) or gastro-oesoephageal varices type 2 (GOV 2) (Fagiuoli*et al.*, 2017; Korean Association for the Study of the Liver (KASL), 2020; Yoshiji *et al.*, 2021; de Franchis *et al.*, 2022). The quality of evidence ranges from moderate to poor quality whilst the strength ranges from weak to strong. KASL (2020), who were rated green in Domain 3, is the only guideline to grade the recommendation as strong despite moderate quality guideline, whilst Yoshiji *et al* (2021) acknowledges that the strength should be weak due to weak evidence. The two other guidelines acknowledge that the quality of evdience is poor. Due to the overirding opinion that BRTO is supported by sub-optimal evidence, this recommendaiton cannot be put forward.

As there are conflicitng views on the evidence quality and the strength of the recommendation, none of the recommendations from this section can be put forward.

### 3.4.7 Secondary prophylaxis

In patients with varices, secondary prophylaxis can be given to prevent recurrent haemorrhage (see section 1.7.3.3). There are 20 recommendations proposed altogether but most of the recommendations for this section are stand-alone recommendations (Table 3-13). Some of the key recommendations that have been proposed by multiple guidelines are stated in Figure 3-8. The reason there are so many recommendations is because they relate to very specific scenarios rather than being high-level recommendations.

- Initiation of secondary prophylaxis upon discharge or day 6 from the index bleed.
- Secondary prophylaxis can be given in the combined form of NSBB and VBL.
- The choice of NSBB is propranolol or nadolol, and carvedilol is an alternative to this.
- Therapies can be maintained alone if patient cannot tolerate VBL/NSBB/carvedilol.
- VBL is superior to endoscopic sclerotherapy.

*Figure 3-8: Summary of common recommendations that have been proposed in managing an active variceal haemorrhage.*

| Secondary prophylaxis | Papers | Strength of the recommendation | Domain 3 appraisal assessment |
|---|---|---|---|
| Patient should receive secondary prophylaxis upon discharge or day six of index bleed. | (Korean Association for the Study of the Liver (KASL), 2020) | A1 | |
| | (Cheng *et al.*, 2009) | Not formally assessed | |
| | (Farooqi *et al.*, 2016) | 1a, A | |
| | (Diaz-Brito, Cardoso and Sarmento, 2018) | Not formally assessed | |
| Combination of NSBB and VBL is the choice of treatment for secondary prophylaxis | (Korean Association for the Study of the Liver (KASL), 2020) | A1 | |
| | (de Franchis *et al.*, 2022) | A1 | |
| | (Tripathi *et al.*, 2015) | (level 1a, grade A) | |
| | (Cheng *et al.*, 2009) | A1 | |
| | (Bruno *et al.*, 2021) | quality of evidence: high<br>strength of recommendation: strong | |
| | (Schiavon *et al.*, 2019) | class 1 | |
| | (Farooqi *et al.*, 2016) | 1a, A | |
| | (Reiberger and Mandorfer, 2017) | Not formally assessed | |
| The choice of NSBB is usually propranolol of nadolol. Carvedilol is an alternative* | (Tripathi *et al.*, 2015) | (level 1b, grade B) | |
| | (Farooqi *et al.*, 2016) | Not formally assessed | |
| NSBB can be considered for gastric varices* | (Tripathi *et al*., 2015) | Level 1b, grade b | |
| Carvedilol dose:<br>dose of 6.25 mg daily and increased to 6.25 mg twice<br>daily, if clinically tolerated* | (Farooqi *et al.*, 2016) | 1b,A | |
| In patients who cannot get/tolerate VBL or carvedilol or NSBB, any of these therapies can be maintained alone | (Korean Association for the Study of the Liver (KASL), 2020) | A1 | |
| | (de Franchis *et al.*, 2022) | A1 | |

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|---|---|---|---|
| | (Tripathi *et al*., 2015) | (level 1a, grade B) | |
| Intolerance to NSBB, perform monotherapy of VBL* | (Tripathi *et al*., 2015) | (level 1a, grade A). | |
| | (Farooqi *et al.*, 2016) | 5D | |
| | (Diaz-Brito, Cardoso and Sarmento, 2018) | Not formally assessed -one study referenced | |
| If intolerant to VBL, combination of pharmacotherapy should be initiated e.g. NSBB and ISMN | (Farooqi *et al.*, 2016) | 1a,A | |
| Endoscopic treatment: both VBL and sclerotherapy can be used for oesophageal varices* | (Yoshiji *et al.*, 2021) | (Recommendation: weak, 100% agreed, evidence level C<br>C is low quality evidence | |
| | (Cheng *et al.*, 2009) | A1 | |
| Endoscopic treatment of choice: cyanoacrylate injection as needed for GOV-2 and IGV* | (Tripathi *et al*., 2015) | (level 2b, grade B). | |
| | (Farooqi *et al.*, 2016) | 1b,A | |
| Perform VBL every 2-4 weeks until variceal eradication is achieved. | (Tripathi *et al*., 2015) | (level 1b, grade B) | |
| Repeat endoscopy at 1-8 week intervals for VBL till eradication* | (Hwang *et al.*, 2014) | Low quality | |
| Somatostatin analogues can be used in part of secondary prophylaxis* | (Cheng *et al.*, 2009) | Not formally assessed | |
| Small GOV1 can be treated with VBL and NSBB | (Schiavon *et al.*, 2019) | Class 1 | |
| If patient had no primary prophylaxis start them on NSBB and VBL* | (National Agency for Accreditation and Evaluation in Health, 2004) | Not formally assessed | |

| | | | |
|---|---|---|---|
| If patient had no primary prophylaxis start on either NSBB or VBL* | (Lebrec, Vinel and Dupas, 2005) | Not formally assessed | |
| Increase the dose of NSBB if dose is low in primary prophylaxis and VBL* | (National Agency for Accreditation and Evaluation in Health, 2004) | Not formally assessed | |
| If patient's dose was low in primary prophylaxis on NSBB, increase the dose or use VBL* | (Lebrec, Vinel and Dupas, 2005) | Not formally assessed | |
| If patient had VBL monotherapy for primary prophylaxis, move straight to TIPS is they at risk of bleeding* | (National Agency for Accreditation and Evaluation in Health, 2004) | Not formally assessed | |
| | (Lebrec, Vinel and Dupas, 2005) | Not formally assessed | |
| Patient has NSBB treatment failure and bleeds, start then on VBL* | (Lebrec, Vinel and Dupas, 2005) | Not formally assessed | |

*Recommendations made by those passing through just Domain 3.

*Table 3-13 Recommendations for secondary prophylaxis. Abbreviation: TIPS= transjugular intrahepatic portosystemic shunt, VBL= variceal band ligation, GOV 1= gastro-oesophageal varices type 1.*

The recommendation that states that patients should receive secondary prophylaxis upon discharge or day six after the index bleeding event was supported by four guidelines (Cheng *et al.*, 2009; Farooqi *et al.*, 2016; Diaz-Brito, Cardoso and Sarmento, 2018; Korean Association for the Study of the Liver (KASL), 2020). Only two of the guidelines formally assessed the evidence and graded it A1 or similar (Farooqi *et al.*, 2016; Korean Association for the Study of the Liver (KASL), 2020). As KASL (2020) was rated green in Domain 3, this recommendation can be put forward. Eight guidelines have specified that the secondary prophylaxis should be given as a combination of NSBB and VBL. Of the eight guidelines, seven of them have formally assessed the quality and graded it to be A1 or similar. This is one of the only recommendations where a majority of guidelines agree with the quality of evidence. Their Domain 3 ratings ranged from red to green. Reiberger and Mandorfer (2017) is the only guideline here to not formally assess the evidence, which is also reflected in their Domain 3 rating. As all guidelines graded the evidence to be A1 or similar, the administration of secondary prophylaxis after day 6 of index bleed can be put forward.

The choice of NSBB is similar to that of primary prophylaxis; propranolol and nadolol as first choice and carvedilol as second choice (Tripathi *et al.*, 2015; Farooqi *et al.*, 2016). Tripathi *et al* (2015) is the only guideline to formally assess this recommendation and grade it as weak, and thus, it cannot be put forward. NSBB was also recommended for the use of gastric varices by Tripathi *et al* (2015) but the recommendation is weak, so this cannot be put forward.

If patients were intolerant to one of the types of therapies e.g. VBL, carvedilol, propranolol or nadolol, they can be maintained alone. This was supported by three guidelines that all agreed that the quality of evidence was high (Tripathi *et al.*, 2015; Korean Association for the Study of the Liver (KASL), 2020; de Franchis *et al.*, 2022). However, Tripathi *et al* (2015) graded the

strength as weak whilst the others made a strong recommendation. Due to the fact that KASL (2020) and Tripathi *et al* (2015), who were both rated green, have conflicting views on the strength, this recommendation cannot be put forward. However, Tripathi *et al* (2015) also proposes that if the patient is specifically intolerant to NSBB, VBL can be performed at a grade of A1. Farooqi *et al* (2016) however grades this with an opposing quality of evidence, 5D (the lowest grade possible). As Tripathi *et al* (2015) produced a guidelines that is rigourously developed  than Farooqi *et al* (2016), the recommendation stating that VBL can be performed if there is intolerance to NSBB can be put forward as it based on high quality evidence.

There are recommendations specifically made for endoscopic treatment. For oesophageal varices, the use of VBL and sclerotherapy has been recommended (Cheng *et al.*, 2009; Yoshiji *et al.*, 2021). However, Yoshiji *et al* (2021), which was rated green in Domain 3, graded the recommendation to be weak due to low quality evidence which overrides the A1 grading by Cheng *et al* (2009) which was rated amber. The grading style is similarly seen for the recommendation promoting the use of cyanoacrylate for GOV2 and IGV, where Tripathi *et al* (2015) graded it to be weaker than what Farooqi *et al* (2016) graded it as. Despite the guidelines being produced around a similar time frame, they have different recommendation of strength.

Eradication of varices can take numerous endoscopic sessions. Two recommendations have been proposed for the specific time period, but they are both not graded highly so they cannot be put forward. Tripathi *et al* (2015) recommends that VBL should be performed every 2-4 weeks till eradication, whilst Hwang *et al* (2014) recommends that it should be performed in 1-8 week intervals.

There is an exhaustive list of single recommendations that have been supported by just one or two guidelines (Table 3-13). None of the recommendation have a quality of A1 or similar or are supported by guidelines that were rated green in Domain 3, and so none of them can be put forward. National Agency for Accreditation and Evaluation in Health (2004) and Lebrec, Vinel and Dupas (2005) have the most number of recommendations that are not supported by other guidelines in secondary prophylaxis. These recommendations are very patient scenario specific and are based on the treatment pathway that the patient had during primary prophylaxis. They have not graded the quality of the evidence and so it is difficult to ascertain how strong the recommendations are. They have also been rated red in Domain 3. Due to the general lack of evidence, the stand-alone recommendations cannot be put forward.

## 3.5 Discussion

### 3.5.1 Summary

In summary, there were 49 guidelines included in this systematic review. All underwent data extraction and Domain 1 appraisal using the AGREE II checklist. The Domain 1 scores that the guidelines received were coded to the traffic light system to indicate how well they performed. Twenty one guidelines that were rated amber or green in Domain 1 (Score and Purpose) passed to Domain 3 (Rigour of Development) quality appraisal and were again rated according the traffic light system. If the guidelines performed well and recommendations were made based on high quality evidence, these recommendations were put forward (Table 3-14).

#### *3.5.1.1 Summary of primary prophylaxis*

The recommendations that have been proposed by guidelines that have just been appraised against Domain 1 can be found in the appendix (Appendix 4). The recommendations proposed by guidelines passing to Domain 3 appraisal were presented in Table 3-6 and Table 3-7. Of the 24 recommendations that were proposed for primary prophylaxis, 10 of them can be put forward for the use in UK clinical practice (Table 3-14). Some of the recommendation that have been put forward include: NSBB should be used first for prophylaxis; small varices at risk should be treated with NSBB; propranolol should be prescribed at 40mg twice daily. The majority of the other recommendations could not be put forward as they were not supported by rigorously developed guidelines or high quality evidence. For instance, the recommendations on the doses of medications were not formally graded, so only the guidelines that did grade the evidence to be A1 or similar could have their recommendations put forward. The quality evidence is lacking for certain interventions and patient factors. In

patients with small varices, the interventions that were recommended have been graded to be of moderate quality. The reason why this may be is because literature is scarce. If trials were to analyse subgroups defined by the size of the varix, a meta-analysis of the results may be beneficial to draw conclusions on specific interventions.

#### *3.5.1.2 Summary of management of haemorrhage*

Variceal haemorrhage management consists of different steps. For this review, they were categorised as: vasoactive drugs; antibiotic prophylaxis; time to endoscopy; endoscopic treatment strategies; post-endoscopic treatment (Table 3-8 to Table 3-12).

***Vasoactive drugs:***

Of the 17 recommendation that were proposed by guidelines appraised against Domain 3, only four can be put forward (Table 3-14): endoscopic and vasoactive therapy is the choice of treatment for variceal haemorrhage; the first choice of vasoactive drugs is terlipressin; terlipressin or somatostatin can be used as vasoactive drugs; the dose of terlipressin is 2mg four times daily. The others cannot be put forward as their Domain 3 rating was less than a green and the quality of evidence was not high. The three drugs that were commonly recommended were: terlipressin, octreotide and somatostatin.

***Antibiotic prophylaxis***

There were five recommendations put forward by guidelines appraised against Domain 3, but only one recommendation can be put forward which states that antibiotic prophylaxis should be initiated and continued for five to seven days. This was graded to be A1 quality by five

guidelines and was supported by numerous guidelines that rated green in Domain 3. Only 9 of 21 guidelines commented on antibiotic prophylaxis.

***Time to endoscopy:***

The guidelines proposed times which ranged from 6-48 hours in stable patients. Though endoscopy timings were quoted by numerous guidelines, none of them could be put forward as the evidence quality was moderate or poor, even though guidelines that rated green in Domain 3 supported them. Despite this, some guidelines have given the strength of the recommendation as strong which suggests that expert opinion may have been a deciding factor for the strength. The commonest recommended time was 12 hours. However, all of the UK guidelines recommend that endoscopy should be performed within 24 hours, which may have been influenced by availability of service (including the number of staff that are available that have the skillset).

***Endoscopic treatment strategies:***

Despite there being eleven recommendations in this area, only one recommendation could be put forward which was that VBL is the choice of treatment for oesophageal varices. This was supported by eleven guidelines, and a majority agreed the quality to be A1 or similar. The recommendations proposed for gastric varices were limited and were generally of moderate quality.

***Post endoscopic treatment strategies:***

None of the recommendations that have been proposed for patients that are at risk of rebleeding acutely can be put forward as the evidence quality is generally lacking for all the interventions. TIPS and BRTO were the commonly recommended treatment for these patients. Despite TIPS being recommended by 16 guidelines, there were opposing quality of evidence between the guidelines that were rated green in Domain 3. BRTO is also a relatively new therapy that has been recommended by four guidelines, where all of them have been published after 2017. However, it seems that the quality of evidence is generally lacking. This could be because this is a newer therapy where the number of clinical trials and systematic reviews may be limited.

#### *3.5.1.3 Summary of secondary prophylaxis*

In this section, there were 24 recommendations but 15 of them were stand-alone recommendations proposed by only one guideline. Only three recommendations can be put forward: patients should receive secondary prophylaxis upon discharge; NSBB and VBL can be combined; if intolerant to NSBB, then VBL should be done. The quality of evidence for the stand-alone recommendations poor and so most of them have not been put forward. National Agency for Accreditation and Evaluation in Health (2004), and Lebrec, Vinel and Dupas (2005), which were rated red in Domain 3, made the most stand-alone recommendations. The quality of evidence was not formally assessed and so it is difficult to appreciate the strength of their recommendations.

#### 3.5.1.4 Recommendations that are being put forward:

| Treatment | Recommendations |
|---|---|
| **Primary prophylaxis** | Pharmacological or endoscopic treatment can be used as primary prophylaxis |
| | NSBB should be used first for prophylaxis, |
| | If the patient is intolerant to NSBB, then VBL should be performed. |
| | Small varices are at risk should be treated with primary prophylaxis with NSBB; |
| | Medium/large varices should be treated with primary prophylaxis, either with NSBB or VBL |
| | Propranolol is the first choice of NSBB |
| | The alternative to propranolol is nadolol or carvedilol |
| | Propranolol should be prescribed at a dose of 40mg twice daily |
| | Nadolol should be given at a dose of 40mg |
| | Carvedilol should be given at a dose of 3.125mg twice daily |
| **Active haemorrhage management** | Endoscopic and vasoactive therapy is the choice of treatment for variceal haemorrhage |
| | The first choice of vasoactive drugs is terlipressin |
| | Terlipressin or somatostatin can be used as vasoactive drugs |
| | The dose of terlipressin is 2mg four times daily |
| | Antibiotics prophylaxis should be initiated and continued for five to seven days |
| | VBL is the treatment of choice for oesophageal varices |
| **Secondary prophylaxis** | Patients should receive secondary prophylaxis upon discharge/from day 6 of index bleeding |
| | If the patient is intolerant to NSBB, then VBL should be performed |
| | NBSS and VBL can be used as a combination treatment |

*Table 3-14: The recommendations that are put forward by this review.*

### 3.5.2 The year of publication

The publication date ranges between 1990-2022. For all guidelines assessed against Domain 1 of the AGREE II checklist, the median year of publication was 2016, and mode was 2020. The guidelines assessed against Domain 3, were published at similar times (2004-2022, median 2017, mode 2020). Initially I hypothesised that newer guidelines were most likely to be rated amber or green against Domain 1. However, it does not seem that way because after 2004, there was no notable time trend in whether the papers passed through to Domain 3.

Seven papers, that were rated green on Domain 3, were published between 2012-2021 (median and mode 2020), and five of them were produced between 2019-2021. Though it seems that newer papers perform better in AGREE II, this cannot be extrapolated because there were numerous guidelines published between 2019-2022 that did not perform well. However, they were more likely to formally assess the evidence and be transparent with their methodology. Though older guidelines were less likely to do this, it cannot be concluded that they did not appraise the quality of evidence more than they did not document it within the publication. Newer guidelines have access to more, higher-quality evidence e.g., RCTs, which older guidelines may have not had. Older guidelines may have made more recommendations based on expert opinion. AGREE II was published after the older guidelines, so the newer guidelines were more likely to use it to create a guideline that will be rated well against this checklist.

### 3.5.3 Associated organisations

Of the included guidelines, 67% were written in association with multidisciplinary organisations, whilst the rest were written independently. It seems that guidelines were more

likely to be rated amber or green on Domain 1 if written alongside an organisation (71% of guidelines appraised against Domain 3 did so). Some of the notable organisations include: British Society of Gastroenterology (BSG), Pacific Association for the Study of the Liver and Korean Association for the Study of the Liver. The guidelines that were produced independently were less likely to pass to Domain 3 (56%). This could be due to not presenting the clinical questions to a high enough standard for Domain 1 and not having a standard set of methodology to follow that organisational bodies tend to provide (Gow and Chapman, 2001; Goshi and Stanley, 2005; D'Amico, Pagliaro and Bosch, 2008; Mellinger and Volk, 2013). Six out of seven papers that rated green in Domain 3 were written in association with an organisation.

It is also important to acknowledge that not all guidelines associated with organisational bodies passed through to Domain 3 (n=19). This includes guidelines produced by well-known bodies e.g. American Association for the Study of Liver Disease, European Association for the Study of the Liver, and American College of Radiology (Garcia-Tsao, Arun J. Sanyal, *et al.*, 2007; Angeli *et al.*, 2018; Kim *et al.*, 2020; Pinchot *et al.*, 2021). This was quite surprising, as some of these organisations have produced numerous guidelines that have been used globally by clinicians. It is important to acknowledge that these guidelines were excluded at Domain 1 as they did not clearly specify their aims, but had they done so, it might have been determined that they based their recommendations on good evidence. The methodology that I had followed for this review was strict and prioritised those performing better in Domain 1 to pass to Domain 3, which is a limitation of this review. Through this approach, I have missed out some recommendations that were proposed only by guidelines excluded after Domain 1 assessment. The recommendations were mostly on drug dosages, which are an addition to what the guidelines passing through Domain 3 propose. The quality of evidence for most were moderate to poor quality so they would have not been put forward anyway. The American

College of Radiology produced two guidelines, which did not pass to Domain 3, which have provided recommendations that are extremely patient-specific (Kim *et al.*, 2020; Pinchot *et al.*, 2021). For example, Kim *et al* (2020) recommend the use of BRTO in a cirrhotic patient, with a large gastrorenal shunt, bleeding from high flow gastric varices, with significant portal hypertension, and a MELD score of 14. All of the recommendations were based on specific scenarios. As they are very specific, it seems that they only apply to a small patient population group and so, they have not made much of a difference even if these recommendations were put forward. However, it should be highlighted that when comparing the recommendation that was proposed by guidelines in just Domain 1 and Domain 3 (Table 3-6 and Table 3-13, Appendix 4), most of the recommendations are the same, so the overall conclusions that I have arrived would not have differed. I attempted to find reviews that also followed a similar methodology to mine (prioritising domains and dropping guidelines if they did not meet a certain threshold, which is a suggestion put forward by AGREE II developers) but I could not find any. This could be because other reviews have approximately appraised 10 guidelines or less, which is much fewer than what I have done, so it easier for them to perform analysis using all of the domains (Blanco-Mavillard *et al.*, 2018; Gillespie *et al.*, 2018; Romeo *et al.*, 2019; Cui *et al.*, 2022).

### 3.5.4 What are the strongest guidelines?

If a guideline was rated green in Domain 3, they were deemed as high quality, as they have proven that that their rigour of development is of a good standard, defined by the AGREE II checklist. However, this is still a subjective observation as the scoring system is user-dependent. However, it was mitigated to some extent by calculating the average scores of the reviewers (Brouwers *et al.*, 2017).

There were seven guidelines that were produced of high standards in comparison other guidelines (Dworzynski *et al.*, 2012; Tripathi *et al.*, 2015; Nevens *et al.*, 2019; Korean Association for the Study of the Liver (KASL), 2020; Siau *et al.*, 2020; Tripathi *et al.*, 2020; Yoshiji *et al.*, 2021). The guideline by Nevens *et al.*, (2019) was the only guideline that was not written in association with an organisation. All of them were transparent with the methodological process of making recommendations, which highlighted that the rigour of development was much higher in comparison to other guidelines included in the review. Of those seven guidelines, the outstanding guideline was produced by NICE (Dworzynski *et al.*, 2012). The raw scores for Domain 1 and 3 were 94.4% and 70.8% respectively. The second highest raw score for Domain 3 was 43.8% (Yoshiji *et al.*, 2021), which shows the difference in quality between the NICE guidelines and the others which have also been rated green. The NICE guidelines had extensive detail about the quality of evidence for each recommendation and compared multiple studies to each other. However, as the document was very long, it was difficult to understand and extract information. They have produced a summary which is more comprehensible.

It is important to acknowledge that those guidelines that did not score highly in Domain 3 may have had a good methodological process but may not have reported this within the guideline document. This could be due to multiple reasons: strict word count proposed by the journal; lack of knowledge regarding the methodological process; changes in expectations about the transparency of guidelines over time. Another factor that must be considered is that AGREE II has very high expectations as it is very precise with what it wants. Domain 1 assessed for the guideline objectives, target population specifications and the presence of health questions. Most guidelines did poorly in Domain 1 as they did not mention the health questions; they used sub-headers rather than specifying questions. AGREE II also alluded that health questions

need not be in the form of a question, but can also be a statement. As a reviewer, it is difficult to gauge what a health question is if not made explicitly clear by the guideline, which may be the reason why most guidelines did not score well for that AGREE II item. Though it was difficult for most guidelines to meet the standards, future guidelines should aim to fulfil these criteria to be well-rounded, evidence based guidelines.

### 3.5.5 The quality of evidence

The quality of evidence for some of the interventions e.g. TIPS, time to endoscopy, gastric varices, BRTO, oesophageal stenting are generally poor or even lacking. It is important to note that despite the quality of evidence being poor for some of the interventions (e.g. TIPS), these interventions can still be performed as they are beneficial to patients. The reason for why the quality of evidence can lack for acute scenarios is because it may not be ethical or possible to perform randomised control trials in a patient that is acutely ill. For example: it may not be ethical to perform randomised control trials on patients with an acute variceal bleed to identify if the patient would benefit from having the TIPS procedure being performed, whilst also denying other patients TIPS treatment, which may have potentially been lifesaving. Another reason why the quality of evidence may be lacking (specifically for the use of BRTO and oesophageal stenting) is because some treatments are much newer and may have not had the chance to be evaluated by high quality clinical trials. These interventions may be beneficial despite having a lower quality evidence-base. For these interventions, consensus opinion can override the quality of evidence, as experts may be experienced enough to know which treatment strategies could be beneficial. This may be also the reason why the strength of some recommendations were strong despite the quality of evidence being weak or moderate.

Sometimes, clinicians will also have to make clinical decisions despite the absence of evidence- the review has demonstrated that most of the dosages for medications are not supported with any evidence. In these scenarios, it should not be assumed that a lack of evidence for a treatment is evidence that it is ineffective. Clinicians must instead dependend on their clinical judgement and experience to make a decision (Anderson, 2005). Patients will still need to be managed with pharmacological treatment despite the lack of evidence, which can still have a positive outcome for the patient.

### 3.5.6 Comparing it to other literature

A systematic review was published in 2014 that also appraised the quality of guidelines on the management of oesophageal and gastric varices (Rios *et al.*, 2014). The methodology that Rios *et al* (2014) followed is different to what I have done. Despite this, some of the findings that have been found are shared across both of the reviews, which is reassuring.

I retrieved 7355 titles from my search and included 49 guidelines in my review, whereas Rios et al retrieved 4612 titles and included 10 guidelines. There could be multiple reasons for this. Rios *et al* (2014) did not publish their full search strategy but had included the search terms that they used. They were similar to those I used for varices, but differed for clinical practice guidelines (Appendix 2). They had only used three search terms for guidelines, whilst I had four with added truncations to pick up other search terms. This could have contributed to Rios et al identifying fewer titles. Another reason for this is that Rios *et al* (2014) only used MEDLINE as their primary database to retrieve studies, whilst I had used MEDLINE, EMBASE, and Web of Science. Importantly, Rios *et al* (2014) only included guidelines if they were in English or Spanish, whilst I had translated all the included guidelines if possible, which were in

other languages such as French, German, Portuguese and Chinese. Added to this, I identified guidelines published since 2014.

A relative strength of Rios *et al* (2014) is that all ten guidelines were appraised against Domain 1 to 6 with three appraisers, whilst I had prioritised Domain 1 and 3 and they were appraised by 2 reviewers. Their methodology was much more rigorous and was probably better able to appreciate the guideline as a whole. However, Rios *et al* (2014) extracted the recommendations from guidelines if they scored above 50% in the Domains, and so the recommendations of only five guidelines were extracted. Whereas in my review, I performed data extraction on all of the 49 guidelines included. This is a strength of my review as it highlighted the differences in the recommendation quality between those guidelines that were rigorously produced and those that were not.

Both the reviews suggest that the guideline published by Dworzynski *et al* (2012) was the strongest guideline included. Rios *et al* (2014) scored the NICE guidelines 100% in Domain 1 and 98.1% Domain 3, whilst I scored them 94.4% and 70.8% respectively. I had scored the NICE guidelines lower in Domain 3 as they did not specify the methodological steps they took to propose recommendations, and also hinted that it may have been based on consensus opinion. They also did not specify how they would resolve disagreements regarding recommendations. This shows that there are obvious differences in the marking styles that the reviewers used for this review versus that by Rios *et al* (2014). It is tempting to say that my review may have been harsher with the marking, scores were generally lower for other guidelines too. This suggests that different reviewers can perceive the AGREE II manual differently, which can lead to subjective marking styles and scores. It is not clear whether this

might induce bias, for example if some reviewers are more likely to be more lenient in scoring guidelines produced by notable organisations.

Of the 10 guidelines that Rios *et al* (2014) reviewed, my review shared six of them. However, three of the six have been updated since then, and have been included in my review. For example, Rios *et al* (2014) included the older BSG guideline, whilst I used the updated version (Jalan and Hayes, 2000; Tripathi *et al.*, 2015). Rios *et al* (2014) scored Hayes and Jalan (2000), 88.6% and 28.5% for Domain 1 and 3 respectively, whereas I had scored the updated version 88.89% and 40.10% (Tripathi *et al.*, 2015). This suggests that the superseded version is more rigorously produced in comparison to older version. Tripathi *et al* (2015) has been explicitly clear that they used the AGREE II checklist as a guidance for formatting their guidelines. When Hayes and Jalan (2000) published their guideline, the AGREE instrument did not exist, and so it is understandable why the older guideline was less likely to perform well and be as transparent as AGREE II would like it to be. The four guidelines that were included in the review by Rios *et al* (2014) but not mine, were produced by organisations in countries such as Scotland, Mexico, and Malaysia. They have been archived, and so, they were not included in my review.

Both the reviews agree that the guidelines did not score highly in Domain 3 in comparison to Domain 1. This could be because the guidelines were not transparent on their literature search and the methodology they followed to create the recommendations. This suggests that there are specific areas in which all guidelines can improve their quality.

Rios *et al* (2014) have categorised their recommendations similarly to my review – "acute bleeding", "endoscopic failure", "primary prevention" and "secondary prevention". Both the reviews have found similar findings specifically regarding the management of active variceal haemorrhage, where guidelines strongly recommend the use of vasoactive drugs, endoscopic band ligation and antibiotics prophylaxis. There were recommendations e.g. on BRTO and oesophageal stenting that were only made in newer guidelines, so they were only included in my review. It is good to see that there have been some major advances in the treatment of varices within the space of eight years.

### 3.5.7 Strengths and Limitations of this review

Though a similar systematic review has been performed earlier, my systematic review has updated the findings using my inclusive criteria. Additionally, as I performed data extraction on all of the guidelines, regardless of quality, I was able to ascertain that some of recommendations were similar across different qualities of guideline.

One of the major limitations of this systematic review was that the quality of the guidelines was assessed using only two Domains of the AGREE II checklist, rather that all six of the Domains. If the guidelines were to have been assessed by all six Domains, this would have provided useful insight into how well-rounded the guidelines are. The Domains that were not assessed were stakeholder involvement, clarity of presentation, applicability and editorial independence. Due to the time constraints of this degree, I prioritised two Domains which were helpful in identifying how thorough the methodology of a guideline was. Applicability is a Domain that I would have prioritised next in order to assess if the guideline realistically gave recommendations for the specific healthcare system that it has targeted rather than being

idealistic. For example, the NICE guidelines factor in cost-benefit analysis and resource availability when recommending certain therapies, but I am unsure whether other organisations have done the same. There may have been a clear variation in the quality for this particular domain between those guidelines that have been produced with an associated organisation versus those that have been written independently. Assessment of stakeholder involvement is also important to see if the patient group's views were sought as well as including the relevant healthcare professionals that manage the condition. Even though all of the domains were not assessed, I did assess the guidelines included in the review against those domains that I considered to be the most important – those assessing its purpose and its rigour of development.

Another limitation of this review is that all of the title screening was performed by one reviewer. It is better to perform double-screening by two reviewers as this prevents studies from being potentially missed (Waffenschmidt *et al.*, 2019). The title screening had to be performed by one reviewer due to time constraints. It has been quoted in the literature that inexperienced reviewers are likely to miss 13% of studies whilst experienced reviewers are likely to miss 3% (Waffenschmidt *et al.*, 2019), and as I am relatively inexperienced, I could have missed some of the titles. To avoid this for the other parts of the screening process, the abstracts and full texts were screened by at least two reviewers, which is a strength. All data extraction and quality appraisal was checked by a second reviewer.

A further strength of the review is that all of the languages were included e.g. English, French, Chinese, German, Spanish, and Portuguese. They were translated using Google Translate or Microsoft Edge if the full paper was available online. The accuracy of these tools needs to be taken into account; one study recognised that the overall meaning of documents were

retained at 82.5% when using Google Translate (Taira *et al.*, 2021). For paper copies, it was difficult to translate them as their text would not be recognised online from an uploaded image. Google Lens was used to bypass this. This is an application on a mobile phone that is able to translate words on a paper from the original language to English in real time. These were used for nine of the paper copies. The accuracy of Google Lens for translating text has not explored, and so, it is difficult to ascertain the quality of the translations.

I extracted all of the data onto an excel spreadsheet. There were some difficulties with this as the guideline documents were quite long, e.g. the EASL guidelines was 55 pages (Angeli *et al.*, 2018). There is a greater potential for error when extracting long documents, in comparison to condensed or shorter documents. There were parts the document that were not relevant e.g. recommendations on other complications of ACLF. However, as the data extraction was checked by another reviewer, this could have potentially mitigated some of the errors that could have arisen.

AGREE II recommends that there should be at least 2 reviewers for critical appraisals but 4 reviewers are preferred (Brouwers *et al.*, 2017). However, this was not feasible due to time constraints, so I did what was realistically possible and accepted that there are limitations with this. I had split the papers in half for SM and RD, whilst I performed the quality appraisal for all the papers.

### 3.5.8 Implications of this research

This systematic review brings together all national and international guidelines on the treatment of varices in patients with ACLF, resulting in a summary set of evidence based

recommendations (Table 3-14). It has also highlighted commonly recommended treatment strategies that are not underpinned by adequate evidence. These findings could be used by clinicians as an easy access tool to understand where their practice is evidence based and where it is based only on expert opinion. However, as with any guideline, the recommendation from this review of guidelines cannot replace clinical judgement and individual risk assessment when treating patients.

This systematic review also showed what gaps are present for certain recommendations e.g. small varices, endoscopy timings, management of rebleed and the use of BRTO. This highlights areas where more research needs to be conducted so that future guidelines can be based on higher quality evidence.

### 3.5.9 Future research questions

This review has highlighted opportunities for future research, which can be categorised into four aspects. These are: potential changes to the AGREE II tool; guidelines should aiming to improve their reporting; guideline developers should specify health questions that are of higher calibre; high-quality primary research studies are needed in areas which lack evidence. Each is discussed in turn below.

This review has highlighted that only a small number of guidelines can be rated green against Domain 1 and 3 of the AGREE II checklist. It may be that AGREE II has high expectations and is specific. For example, when specifying the target population for Domain 1, most guidelines say 'cirrhotic patient' which is quite standard. However, AGREE II expects them to specify that they are an adult population. Most guidelines would not specify this, as most cirrhotic patients

are assumed to be adults unless specified. If AGREE II were to have accounted for this, the guidelines could have scored better.

Guideline developers should aim to improve their reporting as they did not perform well against the AGREE II tool. They did not specify enough information on fundamental factors such as target population, objectives and health questions.

This review has highlighted that there is a need primary research studies so that guidelines can use them to make a stronger recommendation. There are some topics that would benefit from this e.g. gastric varices, time to endoscopy and the use of BRTO in gastric varices.

## 3.6 Conclusion

In conclusion, this systematic review was able to show what the key recommendations are for primary prophylaxis, active variceal haemorrhage management and secondary prophylaxis. These can potentially be used by clinicians as a guide when treating ACLF patient with varices. In the next chapter, I will used these evidence based recommendations to conduct a service evaluation of care at UHNM for patients with an upper-gastrointestinal variceal haemorrhage.

# 4 A Service Evaluation of the Management of Patients Presenting with a Upper Gastro-intestinal Variceal Bleed at University Hospitals of the North Midlands NHS Trust (UHNM)

## 4.1 Introduction

Service evaluations use accepted standards of practice to assess the current performance of a service and so set targets for the specific health care organisation to improve the quality of care for the patients. The idea being to improve the quality of treatment and care for patients, which could potentially lead to favourable outcomes (Esposito and Dal Canton, 2014).

In the previous chapter, I identified the key recommendations and the strengths of the evidence underlying them in the management of upper-gastrointestinal varices in ACLF. In this chapter, I will use the standards relating to acute variceal bleeding to conduct a service evaluation and assess the performance of a local hospital, the Royal Stoke University Hospital, part of UHNM, in the management of variceal bleeding in ACLF.

Stoke-on-Trent has a higher rate of hospital admission in comparison to the national average for liver disease (The Foundation for Liver Research, 2014). UHNM is the main NHS Trust in Stoke-on-Trent so it would be reasonable to assume that the burden of liver disease would affect UHNM workload. By identifying the areas of potential improvement in clinical practice, it may be possible to improve outcomes for patients in the local area.

## 4.2 Aims

The overall aim of performing this service evaluation is to identify whether patients were managed according to relevant, evidence-based recommendations and whether guideline adherence was associated with patient characteristics and subsequent outcomes. If there are areas for potential improvement, these will be identified, and suggestions will be put forward.

## 4.3 Methods

### 4.3.1 Recommendations

The previous chapter identified evidence-based recommendations for the management of acute variceal haemorrhage (Table 4-1). Four of these recommendations will be used as the standards for this service evaluation (Table 4-2). The two recommendations that will not been used as standards for this service evaluation are 1) terlipressin should be given at a dose of 2 milligrams every four hours, and 2) the vasoactive drug of choice is terlipressin or somatostatin. First, the data available to me for this service evaluation had already been collected (see section 4.3.4) and did not contain the dosage of the medication. Therefore, I could not assess drug doses. Second, local UHNM guidelines state that terlipressin is the drug of choice and other vasoactive drugs are not used. Therefore, this standard was adapted to exclude somatostatin.

| **Treatment** | **Recommendation** |
|---|---|
| Active haemorrhage management | Endoscopic and vasoactive therapy is the choice of treatment for variceal haemorrhage. |
| | The first choice of vasoactive drugs is terlipressin. |

| | |
|---|---|
| | Terlipressin or somatostatin can be used as vasoactive drugs*. |
| | The dose of terlipressin is 2milligrams four times daily*. |
| | Antibiotics prophylaxis should be initiated and continued for five to seven days. |
| | Variceal band ligation is the treatment of choice for oesophageal varices. |

**These recommendations will not be used as standards for the service evaluation*

*Table 4-1: The recommendations that were put forward by the systematic review specifically for active variceal haemorrhage.*

- Terlipressin should be administered when variceal haemorrhage is suspected;
- Prophylactic antibiotics should be given to those with a variceal haemorrhage;
- Endoscopy should be performed within 24 hours in all patients with variceal haemorrhage;
- Variceal band ligation (VBL) is the choice of endotherapy for oesophageal varices.

*Table 4-2: Service evaluation criteria to be employed in this chapter*

These recommendations are the highest quality recommendations that have been put forward by the systematic review which clinical practice should aspire towards providing. However, UHNM would have not expected to be appraised against the recommendations that have been proposed by my review. UHNM follows trust-specific guidelines which are based on UK guidelines, and the UK guidelines all recommend the service evaluation standards. If patients were managed accordingly to the recommendations, this will be termed 'recommendation adherent'.

If the patient has been suspected to have a variceal bleed, according to these recommendations they should receive terlipressin, antibiotic prophylaxis and have an endoscopy. Performing endoscopy on patients with a suspected variceal haemorrhage has been recommended by most guidelines, and this is based on high quality evidence. However,

the strength for the specific timing from admission to endoscopy, as different countries/organisations recommend different times, is moderate. As the patients at UHNM are managed according to the UK guidelines, it would be reasonable to compare the patients against the specific timing of endoscopy that has been proposed by UK guidelines (Dworzynski, *et al.*, 2012; Tripathi *et al.*, 2015; Siau *et al.*, 2020). The UK guidelines have recommended that endoscopy should be performed within 24h and so, this is the timeframe that will be used to compare UHNM data. Variceal band ligation (VBL) has been recommended as the endotherapy of choice for oesophageal varices, so this will be used as a standard for patients with oesophageal varices.

### 4.3.2 Data

The data used in this chapter include patients admitted to UHNM with variceal UGI bleeding between 24/03/2019 to 21/03/2021. These data were collected from the clinical system iPortal (electronic patient record database at UHNM) by Dr R Desai with the help of the Hepatology clinical team. This was originally intended for the use in an audit comparing the treatment of patients with variceal haemorrhage before and during the COVID-19 pandemic. As the data are to be used in a service evaluation in this thesis, approval from the research ethics committee was not considered necessary.

#### *4.3.2.1 Secondary Data Analysis*

Analysis of an earlier project can be termed secondary data analysis (Donnellan and Lucas, 2013). Although this is not technically a secondary analysis of data and is a clinical service evaluation, it is helpful to consider concepts related to secondary data analysis in

understanding the quality and likely integrity of this data for use in this chapter. Dr Desai gathered the information from the clinical data that were routinely collected during the patient stay in the hospital. iPortal is the UHNM electronic patient records database that stores extensive confidential clinical information on clinical episodes, chronology of patient journey, outcome of hospital episode (death or discharge), discharge diagnosis, date, time and cause of death, results of investigations, discharge summaries, outpatient clinic letters, correspondence with other NHS organisations, reports of post mortem examinations, inquest and electronic copies of drug charts.

One of the main advantages of secondary data analysis is that it is much more time efficient. As my research degree is limited to one year, using pre-existing data which was collected for another audit was a practical and feasible decision. There are some disadvantages of secondary data analysis, which include the data not being specific to the particular project and so all preferred data may not be available (e.g. terlipressin dose) and there may be irrelevant information in the dataset. These irrelevant data will need to be filtered out. For this service evaluation, I removed some of the information that was not specific to my work. There may be bias from the person that collected the data, which may not only impact the initial project but could also impact the secondary project (Trinh, 2018). However, this disadvantage is unlikely to be relevant because the data were objective and collected from electronic patient records. Though the data cannot be subjectively perceived and can only be recorded as it is in the iPortal system, there is still a possibility that there could be errors. To increase understanding of data quality, I carried out some checks on the data, which will be detailed below.

### 4.3.3 Approval by the research ethics committee

Approval by the research ethics committee is required while conducting research that involves humans, their data or biomaterials. However, this part of my work is not a research project but a service evaluation because I am comparing the current clinical practice in a hospital against the published guidelines. I am not extrapolating these findings for a large-scale population or posing research questions. Therefore, I concluded that the approval from research ethics committee was not necessary.

### 4.3.4 Data collected

#### *4.3.4.1 Quality indicators*

To assess if recommendations were met, data were specifically needed on whether patients were administered terlipressin, antibiotic prophylaxis and timing of endoscopy. As terlipressin and antibiotics are both drugs, the administration of the drugs are recorded by doctors and nurses on the patient drug charts. The drug charts are also uploaded electronically upon completion of a clinical episode. Clinicians write discharge summaries when a patient is discharged which mentions what interventions (both pharmacological and endoscopic) were given to the patients. This is also uploaded to iPortal. As both the drug chart and the discharge summary may have the information, they were used for data extraction.

The time of endoscopy can be found on iPortal, when the endoscopist started the endoscopy session on the patient, and the date and time are recorded in dd.mm.yyyy hh:mm:ss. To assess the time of endoscopy, the time difference between arrival time and endoscopy time needs to be calculated. The arrival time to hospital can also be found in patients within the iPortal system when a relevant healthcare professions inputs that they have arrived at the hospital (also recorded with the date and time in hh:mm:ss). Both of these pieces of

information were imported into a Microsoft Excel spreadsheet, and the time was calculated between them to assess whether time to endoscopy was within 24 hours of admission.

#### *4.3.4.2 Patient characteristics*

*Personal details:*

The age (in years) and gender of the patient were recorded.

*The severity of liver disease:*

There are several scoring systems that can be used to assess the severity of liver disease. The two scoring systems that were used for the clinical service evaluation were: Model for End-Stage Liver Disease - Sodium (MELD-Na) and the Child-Turcotte-Pugh (CTP) class (see section 1.2.2.3). The relevant information e.g. blood test results and clinical signs were accessed through iPortal. The scores were calculated by using an online calculator (https://www.mdcalc.com).

As MELD-Na uses only biochemical parameters, whilst CTP class includes both biochemical and clinical parameters, the use of both of the scoring systems in this service evaluation is warranted, as they may show different associations with recommendation adherence and therefore provide additional insights into how current practice could be improved.

*Patients presenting outside of working hours*

Patients presenting outside Monday-Friday 9am-5pm were deemed to be presenting outside of hours. It is important to assess if this has an impact on whether patients received treatments or not. A well-documented phenomenon called the 'Weekend Effect' states that patient mortality can be impacted if patients present outside of working hours with an emergency (Clarke *et al.*, 2010). The factors that are most likely to explain this effect are staffing levels and access to multidisciplinary services (Cram *et al.*, 2004). It is valuable to determine whether this had an impact on patients at UHNM.

### 4.3.5 Checking for the quality of the data

Quality of the data needs to be assessed as I am performing secondary data analysis. I checked that all values were within realistic ranges and assessed levels of missingness in each variable. Missingness can be defined as the proportion of data that is missing from the dataset (Kang, 2013). I also checked, as far as possible, that the data had been transposed correctly from iPortal to the audit dataset. To do this, I checked for duplicates. I chose to compare the variables age, gender and date of admission. I planned a sensitivity analysis, whereby potential duplicates were removed and the analyses repeated (see section 4.4.7).

### 4.3.6 Statistical Analysis

The data were analysed using Stata version 17.0 (StataCorp, 2021). Stata is a statistical software that can be used for data manipulation and analysis. This was the preferred software in comparison to other software options available because it has "do" files. These are text files where commands can be saved, edited and rerun, ensuring reproducibility and transparency in analysis.

Data were described using appropriate summary statistics. Means and standard deviations were used for symmetrically distributed continuous variables and medians with first and third quartiles when the distribution was not symmetrical. Categorical variables were presented as numbers and percentages. Associations between recommendation adherence and patient characters were assessed using chi-square tests and t-tests as appropriate.

### 4.3.7 Patients with oesophageal varices

As the recommendations state that variceal band ligation is the choice of endotherapy for oesophageal patients. Patients with oesophageal varices only will form a subgroup in which this recommendation will be assessed. There are other patients with different varices and different co-morbidities e.g. gastric varices, portal hypertensive gastropathy, and gastric antral vascular ectasia, who will not be included in the patient group specifically for VBL as patients with oesophageal varices are the only specified population that have been recommended to have VBL. The oesophageal varices have been graded as: grade one, grade two and grade three in respect to their size. Within the dataset, if a patient has two grades of varices, the highest grade was used, as it is the most severe that will be prioritised for treatment. For example, patients that have both grade 1 and 2 varices, they were categorised as grade 2.

## 4.4 Results

### 4.4.1 Data quality

The quality of the data was checked to ensure gender and age fields were complete, and all of the values were within sensible clinical ranges. Four pairs of potentially duplicated records were identified (i.e. same age, gender and date of presentation). However, there were some characteristics that were different such as timings of endoscopy. These were not truly duplicated rows of data that could be deleted. Therefore, they were included in the main analysis. However, as it seemed possible that two patient records had been conflated or in some way combined, I performed sensitivity analysis removing all eight of these rows of to see if the results would be similar even if suspicious data were filtered out.

### 4.4.2 Patient characteristics data

Table 4-3 shows the characteristics of the 149 patients included in this service evaluation. The mean age of the patients was 57.1 years. 82 (55.0%) were male. The mean (standard deviation) MELD-Na score was 19.1 (7.9) and the commonest CPT class was B (n=65, 43.6%). 87 (58.39%) presented outside working hours.

| **Patient characteristics** | **Results** |
|---|---|
| **Number of Patients** | 149 |
| **Age in years, Mean (SD)** | 57.06 (14.61) |
| **Male n (%)** | 82 (55.03) |
| **MELDNa score, Mean (SD)** | 19.14 (7.91) |
| **CPT Class, n (%)**<br>**A**<br>**B**<br>**C** | <br>22 (14.77)<br>65 (43.62)<br>62 (41.61) |
| **Patients presenting outside of working hours, n (%)** | 87 (58.39) |

*Table 4-3 Characteristics of patients included in this service evaluation.*

*Abbreviations: n= number, SD= standard deviation, MELDNa= Model of End stage Liver Disease Sodium, CTP= Child-Turcotte-Pugh*

### 4.4.3 Patients managed with Terlipressin

At UHNM, 135 (91.22%) patients were treated with terlipressin whilst 13 (8.78%) were not (Table 4-4). The mean age of the patients that received terlipressin was 57.16 years, whilst those who did not had a mean age of 53.29 years. This difference was not statistically significant (p=0.41). There was no statistically significant difference in the proportion of males and females that did and did not receive terlipressin (p=0.27). Sicker patients, as defined by the MELD-Na score and CPT class were more likely to have been treated with terlipressin, but this difference was only significant for CPT class. CPT class A patients were over-represented the group that were not given terlipressin. There was no statistically significant difference between in the proportion of patients receiving terlipressin within an outside working hours (90.70% v 91.94% , p=0.79).

| **Patient characteristics** | **Patient managed with Terlipressin** | **Patient managed without Terlipressin** | **p value** |
|---|---|---|---|
| **Number of Patients, n (%)** | 135 (91.22) | 13 (8.78) | - |
| **Age in years, Mean (SD)** | 57.16 (14.45) | 53.69 (14.44) | 0.41 |
| **Sex, n (%)**<br>**Male**<br>**Female** | <br>73 (91.22)<br>62 (92.54) | <br>8 (8.78)<br>5 (7.46) | 0.27 |
| **MELDNa score, Mean (SD)** | 19.53 (7.85) | 15.77 (7.84) | 0.10 |
| **CPT Class, n (%)**<br>**A**<br>**B**<br>**C** | <br>15 (71.43)<br>61 (93.85)<br>59 (95.16) | <br>6 (28.57)<br>4 (6.15)<br>3 (4.84) | 0.002 |
| **Presenting within working hours, n (%)**<br>**Yes**<br>**No** | <br><br><br>78 (90.70)<br>57 (91.94) | <br><br><br>8 (9.30)<br>5 (8.06) | 0.79 |

*Table 4-4: The results of patients managed with and without terlipressin. [4].*

*Abbreviations: n= number, SD= standard deviation, MELDNa= Model of End stage Liver Disease Sodium, CTP= Child-Turcotte- Pugh. Statistical analysis: Chi-squared tests were used for gender, CPT class, presentation out of working hours. Student t- test was used for age and MELDNa scores.*

[4] There was one patient where the data were missing on whether they had received terlipressin or not.

### 4.4.4 Patients managed with prophylactic Antibiotics

There were 140 (94.0%) patients that were managed with prophylactic antibiotics, whilst 9 (6.0%) patients were not (Table 4-5). The mean ages of the patients that did and did not receive antibiotics were 57.3 and 52.9 years respectively. This difference was not statistically significant (p=0.38). There was no statistically significant difference in the proporitonof males and females that did and did not receive prophylactic antibiotics (p=0.43). Both of the severity scores suggest that patients with more severe liver disease were more likely to receive antibiotic treatment in comparison to those who's disease is less severe. However, this finding was only significant for CPT class (p=0.002). There was an over-representation of CPT class A patients not receiving antibiotic prophylaxis. There was no statistically significant difference between the proportion of patients presenting within and outside working hours who received prophylactic antibiotics (94.25% v 93.55%, p= 0.86).

| **Patient characteristics** | **Patient managed with Antibiotics** | **Patient managed without Antibiotics** | **p value** |
|---|---|---|---|
| **Number of Patients, n (%)** | 140 (93.95) | 9 (6.04) | - |
| **Age in years, Mean (SD)** | 57.34 (14.55) | 52.89 (15.80) | 0.38 |
| **Sex, n (%)**<br>**Male**<br>**Female** | <br>78 (95.12)<br>62 (92.54) | <br>4(4.88)<br>5 (7.46) | 0.43 |
| **MELDNa score, Mean (SD)** | 19.37 (7.87) | 15.56 (8.05) | 0.16 |
| **CPT Class, n (%)**<br>**A**<br>**B**<br>**C** | <br>17 (77.27)<br>63 (96.92)<br>60 (96.77) | <br>5(22.73)<br>2(3.08)<br>2(3.23) | 0.002 |
| **Presenting within working hours, n (%)**<br>**Yes** | <br>58 (93.55) | <br>4 (6.45) | 0.86 |

| | | | |
|---|---|---|---|
| **No** | 82 (94.25) | 5 (5.75) | |

*Table 4-5: The results of patients that were or were not managed with antibiotic prophylaxis.*

*Abbreviations: n= number, SD= standard deviation, MELDNa= Model of End stage Liver Disease Sodium, CTP= Child-Turcotte- Pugh. Statistical analysis: Chi-squared tests were used for gender, CPT class, presentation out of working hours. Student t- test was used for age and MELDNa scores.*

### 4.4.5 Patients managed with endoscopic therapy: performed within 24 or above 24 hours

There were 147 (98.7%) patients that received endoscopy. Endoscopy was performed within 24 hours in 40.82% of patients (Table 4-6). Most of the patient characteristics e.g. mean age, gender, and severity scores were not significantly associated with receiving endoscopy within 24 hours. The only statistically significant difference was between patients presenting within and outside working hours. Those presenting outside working hours were more likely to receive endoscopy within 24 hours than those presenting outside working hours (48.24% v 30.64%, p=0.032).

| **Patient characteristics** | **Patients with endoscopy< 24 hours** | **Patients with endoscopy> 24 hours** | **p value** |
|---|---|---|---|
| **Number of Patients, n (%)** | 60 (40.82) | 87 (59.18) | - |
| **Age in years, Mean (SD)** | 56.6 (12.84) | 57.26 (15.89) | 0.79 |
| **Sex, n (%)**<br>**Male**<br>**Female** | <br>31 (38.27)<br>29 (43.94) | <br>50 (61.73)<br>37 (56.06) | 0.49 |
| **MELDNa score, Mean (SD)** | 18.82 (7.56) | 19.45 (8.24) | 0.64 |
| **CPT Class, n (%)**<br>**A**<br>**B**<br>**C** | <br>7 (31.82)<br>28 (43.75)<br>25 (40.98) | <br>15 (68.18)<br>36 (56.25)<br>36 (59.02) | 0.62 |
| **Presenting within working hours, n (%)**<br>**Yes**<br>**No** | <br><br>19 (30.65)<br>41 (48.24) | <br><br>43 (69.35)<br>44 (51.76) | 0.032 |

*Table 4-6 The results of patients that were or were not managed with endoscopy within 24 hours.*

*Abbreviations: n= number, SD= standard deviation, MELDNa= Model of End stage Liver Disease Sodium, CTP= Child-Turcotte- Pugh. Statistical analysis: Chi-squared tests were used for gender, CPT class, presentation out of working hours. Student t- test was used for age and MELDNa scores.*

### 4.4.6 Patients that were managed with all three interventions in comparison to those that were not

Table 4-7 compares the data between patients that had all three recommended interventions in comparison to those that did not. Altogether, there were 56 (37.6%) patients that received all the therapies, whilst 93 (62.4%) did not. There was no statistically significant difference in for patient characteristics such as age, gender and severity scores between those receiving all three treatments and those not. 44.83% of patients presenting outside working hours received all three therapies compared to 27.52% presenting within working hours. This difference was statistically significant (p=0.031).

| **Patient characteristic** | **Patients that had all of the therapies** | **Patients that did not have all of the therapies** | **p value** |
|---|---|---|---|
| **Number of Patients, n (%)** | 56 (37.58) | 93 (62.42) | - |
| **Age in years, Mean (SD)** | 57 (1.65) | 57.11 (1.65) | 0.97 |
| **Sex, n (%)**<br>**Male**<br>**Female** | <br>29 (35.37)<br>27 (40.30) | <br>53 (64.63)<br>40 (59.70) | 0.54 |
| **MELDNa score, Mean (SD)** | 18.89 (7.40) | 19.29 (8.23) | 0.77 |
| **CPT Class, n (%)**<br>**A**<br>**B**<br>**C** | <br>5 (22.73)<br>27 (41.54)<br>24 (38.71) | <br>17 (77.27)<br>38 (58.46)<br>38 (61.29) | 0.28 |
| **Presenting within working hours, n (%)**<br>**Yes**<br>**No** | <br><br>17 (27.42)<br>39 (44.83) | <br><br>45 (72.58)<br>48 (55.17) | 0.031 |

*Table 4-7 The results of patients that were managed with all three therapies vs those that did not receive all three therapies.*

*Abbreviations: n= number, SD= standard deviation, MELDNa= Model of End stage Liver Disease Sodium, CTP= Child-Turcotte- Pugh. Statistical analysis: Chi-squared tests were used for gender, CPT class, presentation out of working hours. Student t- test was used for age and MELDNa scores.*

### 4.4.7 The patient characteristics with patients with oesophageal varices

Table 4-8 shows the characteristics of patients with oesophageal varices. There were 120 patients with oesophageal varices, with a mean age of 56.8 years. There were 64 (53.3%) males included for this evaluation. There were 31 (25.8%), 70 (58.3%) and 19 (15.8%) patients with grade one, two and three oesophageal varices respectively. The mean MELD-Na score was 19.3, with the commonest CPT class was B (45.3%).

| **Patient characteristics** | **Results** |
|---|---|
| **Number of Patients, n (%)** | 120 |
| **Age in years, Mean (SD)** | 56.75 (14.99) |
| **Male n (%)** | 64 (53.33) |
| **Patients with oesophageal varices, n (%)**<br><br>Patients with oesophageal varices grade 1 (%)<br>Patients with oesophageal varices grade 2<br>Patients with oesophageal varices grade 3 | 120<br>31 (25.83)<br>70 (58.33)<br>19 (15.83) |
| **MELDNa score, Mean (SD)** | 19.33 (7.80) |
| **CPT Class, n (%)**<br>**A**<br>**B**<br>**C** | <br>16 (13.33)<br>55 (45.83)<br>49 (40.83) |
| **Patients presenting outside of working hours, n (%)** | 71 (59.17) |

*Table 4-8 Characteristics of patients with oesophageal varices included in this service evaluation.*

*Abbreviations: n= number, SD= standard deviation, MELDNa= Model of End stage Liver Disease Sodium, CTP= Child-Turcotte- Pugh.*

### 4.4.8 Patients with oesophageal varices receiving Variceal Band Ligation (VBL)

There were a total of 120 patient with oesophageal varices (OV), who were eligible for VBL treatment (see Table 4-9). Of those, 88 (77.3%) received banding whilst 32 (26.7%) did not. Patient characteristics including mean age, gender, severity scores, and patients presenting in or out of hours were not significantly associated with receipt of VBL. Grade 1 varices are over-represented in the group of patients that did not receive banding (78.12%). Patients that have Grade 2 or 3 varices were more likely to receive banding (p<0.0001).

| **Patient characteristics** | **Patient had banding** | **Patient did not have banding** | **p value** |
|---|---|---|---|
| **Number of patients with oesophageal varices, n (%)** | 88 (73.33) | 32 (26.67) | - |
| **Age in years, Mean (SD)** | 55.95 (14.98) | 58.94 (15.06) | 0.34 |
| **Sex, n (%)**<br>**Male**<br>**Female** | <br>44 (68.75)<br>44 (78.57) | <br>20 (31.25)<br>12 (21.43) | 0.23 |
| **Number of patients with oesophageal varices, n (%)**<br>**Grade 1**<br>**Grade 2**<br>**Grade 3** | <br>6 (19.35)<br>65 (92.86)<br>17 (89.47) | <br>25 (80.65)<br>5 (7.14)<br>2 (10.53) | <0.0001 |
| **MELDNa score, Mean (SD)** | 19.20(7.61) | 19.69(8.42) | 0.77 |
| **CPT Class, n (%)**<br>**A**<br>**B**<br>**C** | <br>12 (75.00)<br>38 (69.09)<br>38 (77.55) | <br>4 (25.00)<br>17 (30.91)<br>11 (22.45) | 0.61 |
| **Presenting within working hours, n (%)**<br>**Yes**<br>**No** | <br>35 (71.43)<br>53 (74.65) | <br>12 (28.57)<br>18 (25.35) | 0.70 |

*Table 4-9: The results of patients with oesophageal varices receiving banding or not.*

*Abbreviations: n= number, SD= standard deviation, MELDNa= Model of End stage Liver Disease Sodium, CTP= Child-Turcotte- Pugh. Statistical analysis: Chi-squared tests were used for gender, CPT class, presentation out of working hours. Student t- test was used for age and MELDNa scores.*

### 4.4.9 Patients with oesophageal varices that were managed with all three interventions in comparison to those who did not

Of the 120 patients that had oesophageal varices, 46 (38.3%) received all of the four treatments, whilst 76 (61.7%) did not (see Table 4-10). There are only factors that were significantly associated with recipt of all four treatments: the grade of oesophageal varix and whether patients presented in or out of working hours. With regards to the grade of oesophageal varix, only a small proportion of patients with grade 1 varices had all four treatment (9.68% v 90.32%), whilst patients with grade 2 and 3 varices were more likely to receive treatment (44.29% v 55.71%, 63.16% v 36.84% respectively). Those presenting outside normal working hours were more likely to receive all four therapies (46.48%) than those presenting within working hours (26. 53%) (p= 0.03).

| **Patient characteristics** | **Patients, with oesophageal varices, that had all of the therapies** | **Patients, with oesophageal varices, that did not have all of the therapies (in respect to OV)** | **p value** |
|---|---|---|---|
| **Number of Patients, n (%)** | 46 (38.33) | 74 (61.67) | - |
| **Age in years, Mean (SD)** | 56.76 (12.87) | 56.74 (16.26) | 0.995 |
| **Sex, n (%)**<br>**Male**<br>**Female** | <br>22 (34.38)<br>24 (42.86) | <br>42 (65.62)<br>32 (57.14) | 0.34 |
| **Patients with oesophageal varices, n (%)**<br>**Grade 1**<br>**Grade 2**<br>**Grade 3** | <br><br><br>3 (9.68)<br>31(44.29)<br>12 (63.16) | <br><br><br>28 (90.32)<br>39 (55.71)<br>7 (36.84) | <0.001 |
| **MELDNa score, Mean (SD)** | 19.15 (7.14) | 19.45 (8.23) | 0.84 |
| **CPT Class, n (%)**<br>**A**<br>**B**<br>**C** | <br><br>4 (31.25)<br>22 (40.00)<br>19 (38.78) | <br><br>11 (68.75)<br>33 (60.00)<br>30 (61.22) | 0.82 |

| | | | |
|---|---|---|---|
| **Presenting within working hours, n (%)** | | | 0.03 |
| **Yes** | 13 (26.53) | 36 (73.47) | |
| **No** | 33 (46.48) | 38 (53.52) | |

*Table 4-10: The results of patients with oesophageal varices that received all of the treatments compared to those who did not.*

*Abbreviations: n= number, SD= standard deviation, MELDNa= Model of End stage Liver Disease Sodium, CTP= Child-Turcotte- Pugh. Statistical analysis: Chi-squared tests were used for gender, CPT class, presentation out of working hours. Student t- test was used for age and MELDNa scores.*

### 4.4.10 Sensitivity analyses for all patients

After removing eight potentially erroneous rows of data, 141 patients remained. Full results are shown in Appendix 5 and show that the same patterns remained in the data, and the same associations remained statistically significant.

After these eight rows of potential duplicates were removed, 114 patients with only oesophageal varices remained. The conclusions in this group were also the same as before removal of the potential duplicates.

## 4.5 Discussion

### 4.5.1 Summary

In summary, the four recommendations that were used to assess guideline adherence were: administration of terlipressin when a variceal haemorrhage is suspected; antibiotic prophylaxis when variceal haemorrhage is confirmed; perform endoscopy within 24 hours in patients with a variceal haemorrhage; and variceal band ligation is the treatment of choice of oesophageal varices. The level of adherence to these recommendations was as follows: 91.2% of patients received terlipressin; 94.0% of patients received prophylactic antibiotics; 40.8% of patients

received endoscopy within 24 hours; and 77.3% of patients with oesophageal varices received VBL. Only 37.6% of all patients with a variceal bleed received all of the three interventions (terlipressin, antibiotics and endoscopy), whilst 38.3% of patients with oesophageal varices received all four treatments. There were three patient characteristic that seemed to be associated with adherence. The first characteristic is CPT class where sicker patients were more likely to receive treatment. The second characteristic is patients presenting out of hours, where they were more likely to receive endoscopy within 24 hours in comparison to those presenting within hours. The third characteristic was grading of the varices where patients with smaller varices (grade one) were less likely to receive treatment.

### 4.5.2 Band ligation for oesophageal varices

In general, patients who did not have VBL were more likely to have grade one varices. Patients with grade 2 and 3 varices were more likely to receive VBL. This is likely to be because it is practically difficult to band grade 1 varices as they are small. Banding would have most likely been attempted when the patient did have endoscopy, but if they are too small to band, then they would have not received banding treatment. The guidelines state a blanket recommendation that oesophageal varices should be treated with VBL rather than specifying whether grading of the varix is a potential factor that should also be taken into account (Tripath *et al*., 2015; Angeli *et al.*, 2018; de Franchis *et al.*, 2022).

### 4.5.3 Explanation for patients presenting out of hours

The results demonstrated that the patients who presented out of working hours were more likely to receive endoscopy within 24 hours, which seems counterintuitive. This can be explained by the specific endoscopic schedules that are offered by the Royal Stoke Hospital.

Endoscopy lists for inpatients with bleeding are usually scheduled in the weekdays between 2pm-5pm. Patients presenting after 5pm are assessed either in the night or the next morning and are scheduled to have endoscopy on the next day's endoscopy list, which was usually within 24 hours of presentation. Patients presenting with upper GI bleeding during working hours who are stable, are usually not put on the same day endoscopy list and usually wait till the next day, which will likely be beyond 24 hours of their presentation. Unstable patients usually receive endoscopy as soon as practically possible, however I was unable to assess this here as the data regarding haemodynamic stability were not available.

### 4.5.4 Confounding by indication

Confounding by indication in this scenario can be described as how patients are treated depending on the severity of liver disease, which can potentially impact the outcome (Kyriacou and Lewis, 2016). This service evaluation has highlighted that if patients are more ill (highlighted by the severity of CPT class), they are more likely to receive terlipressin and antibiotic prophylaxis. As the CPT scoring system takes clinical signs into account, it may be more beneficial for doctors in some aspects to risk assess the patient. To be given a class of CPT B or C, there needs to be some signs of liver disease that can be clinically recognised e.g. ascites and hepatic encephalopathy. If these signs are recognised by a clinician, they are more likely to expect that the upper gastrointestinal bleed is from varices rather than other diseases e.g. ulcers. Hence, such patients with higher CPT scores are more likely to receive treatment for varices more quickly than in those who have liver disease but do not have clinical signs of liver disease, i.e. those with lower CPT scores.

### 4.5.5 Pre-endoscopy risk stratification:

There are risk stratification scores that are used by clinicians at the time of upper gastrointestinal bleed that can impact the time to endoscopy for the patient. There are several risk stratification scores but the commonest ones used in the UK are the Glasgow-Blatchford score and the Rockall score.

The Glasgow-Blatchford score can be used to predict the outcome of a patient that has a upper gastrointestinal bleed (Blatchford, Murray and Blatchford, 2000). The scoring system incorporates various biochemical results, clinical signs and past medical history in order to assess whether a patient is safe for discharge and can be managed as an out-patient. Some of the characteristics that are assessed include: haemoglobin level, urea levels, systolic blood pressure, melena, previous liver disease history, and the presence of heart failure (Blatchford, Murray and Blatchford, 2000). If the score is zero, the patient is deemed to be at very low risk, and is usually managed out of the hospital as an out-patient, and may not have their endoscopy assessment within a hospital stay. If the score is one or more, the clinician must use their clinical judgement to assess whether the patient will need urgent outpatient management, including endoscopic treatment (Custovic *et al.*, 2020). At UHNM, the Blatchford score is used in the emergency department and the acute medical unit in order to decide whether a patient needs to be managed as an inpatient or an outpatient. All the patients included in this evaluation were inpatients who had been admitted following emergency presentation of an acute upper gastro-intestinal bleed, so the Blatchford score may not necessarily play a role in the management of variceal bleeds in this service evaluation.

The Rockall score is another risk stratification score that is used to predict the mortality in patients with an UGI bleed (Rockall, 1998). The complete Rockall score can be calculated after endoscopy, but there is a pre-endoscopic Rockall score that can be calculated in patients prior to endoscopy. The pre-endoscopic Rockall score incorporates aspects such as age, blood pressure, heart rate and co-morbidities into its scoring system (Rockall, 1998). The complete Rockall score incorporates endoscopic findings and endoscopic diagnosis e.g. malignancy and a tear in the oesophagus. All of this information combined can be used to predict the risk of re-bleeding and mortality (Pang *et al.*, 2010). At UHNM, the Rockall score is often used in the assessment of non-variceal haemorrhage. This is because the factors considered in calculating the Rockall score are not specific for liver disease, portal hypertension or variceal haemorrhage. The endoscopic findings that have been listed in the Rockall score are more specific towards a peptic ulcer bleed or a gastrointestinal malignancy bleed rather than a variceal bleed. For these reasons, UHNM does not use this scoring system as part of the assessment of variceal bleeds.

### 4.5.6 Data quality

For my service evaluation, I made use of data that were collected for another service evaluation. This meant that the quality of the data were presumed. Ideally, I could have checked some or all of the collected data by comparing it to records from iPortal. This would have flagged up any errors and would have been similar to having two people performing data extraction, a technique known to improve data quality in comparison to one person (Buscemi *et al.*, 2006). To ensure that the data were as accurate as possible, I conducted a sensitivity analysis, by removing rows of data that could have been incorrect. The same conclusions were

drawn from the sensitivity analysis, increasing confidence that even if there were some errors in the data, the errors did not have an appreciable effect on the conclusions and the recommendations drawn.

### 4.5.7 Comparing the data

This service evaluation has not been performed at UHNM previously, so the conclusions cannot be compared to previous audit cycles to identify whether improvements have been made. Given the higher than average admission rate for chronic liver disease at UHNM, it would have been beneficial to find out the national CPT score and MELD-Na score, so that this can be compared against the patients at UHNM to see if the patients in Staffordshire have more severe liver disease in comparison to patients nationally (The Foundation for Liver Research, 2014). However, national data were not available.

A nationwide audit has been performed by Stanworth *et al* (2014), covering 212 UK hospitals and including 526 patients. They found that 44.1% of their patients had received vasopressors (this could be vasoactive drugs such as terlipressin, octreotide or somatostatin), and 27.4% recieved prophylactic antibiotics. In comparison to the national average, it seems that UHNM is better at meeting these targets as 91.22% and 93.95% received terlipressin and prophylactic antibiotics respectively. A reason that could explain this difference is that practices have improved since 2014, and so clinicians are able to treat their patients much more effectively than before.

Endoscopy timing is where UHNM performs lower in comparison to the national average. Stanworth *et al* (2014) found that 66% of the patients received endoscopy within 24 hours,

whereas in UHNM only 59.2% of patients received it within 24 hours. Another nationwide audit, that was specifically for patients with all cause of upper gastrointestinal bleeding, found that 74% of patients had endoscopy, and 50% of those patients received endoscopy within 24 hours (Hearnshaw *et al.*, 2010). Though the results of the nationwide audit conducted by Hearnshaw and colleagues may not be comparable to the service evaluation I conducted, it highlights that there need to be improvements nationally to meet the target of 24 hours. A reason why Stanworth *et al* (2014) found a higher average in patients having endoscopy within 24 hours in comparison to UHNM may include variations in endoscopy practices in different hospitals and changes in the health care provision between the two study periods. The impact of COVID-19 pandemic and the resulting pressures on the health care system may also have played a role. At UHNM emergency endoscopy facilities are available 24/7, however emergency endoscopy is undertaken only for patients with significant haemodynamic instability. Patients who are relative stable, usually have their endoscopy in the next available afternoon list, which may be beyond 24 hours of admission.

Stanworth *et al* (2014) has identified that 53% of patients with varices received banding, whilst 73.3% patients with oesophageal varices received banding at UHNM. However, the reason why Stanworth *et al* (2014) may have had a lower adherence is because they did not limit the population to patients with oesophageal varices, and have included all patients with upper variceal haemorrhage. This also includes patients with gastric varices, who may not necessarily be eligible for banding.

### 4.5.8 Recommendation choices

The service evaluation standards that were chosen for this review primarily came from what was put forward from the systematic review in Chapter 3. If I were to have chosen different service evaluation standards, this could have shown different results. As previously explained in section 4.3.1, the time that was chosen was 24 hours to endoscopy. This was chosen because this timing was widely promoted by UK guidelines (Dworzynski *et al.*, 2012; Tripathi *et al.*, 2015). However, it is important to note that the evidence behind these recommended times is lacking. Most of the guidelines have specified a specific time but also acknowledge that the evidence quality is sub-optimal.

There are different vasoactive drugs that can be given (Baik *et al.*, 2005). UHNM chooses to give terlipressin, which was also one of the recommended drugs that was put forward by the systematic review by the UK guidelines. There are different vasoactive drugs that are available such as octreotide and somatostatin. As there were no patients in our service evaluation that were treated with other vasopressors (than terlipressin), I was unable to study the outcome of treatment with those agents.

### 4.5.9 Improvements that can be made

I was able to show that there was an association between severity of liver disease, as defined by the CPT class, and receiving guideline adherent treatment. Patients with more severe disease by this measure, which includes overt clinical signs and symptoms such as ascites and encephalopathy were more likely to receive recommended therapies. It is understandable that clinicians may find it harder to differentiate the cause of an upper gastrointestinal bleed if the clinical signs of liver disease are lacking. There is an associated diagnostic delay with CPT class A patient as they do not present with signs of CLD. It would most likely be the first

presentation of chronic liver disease. Within the group of patients that did not receive terlipressin and antibiotic prophylaxis, there were 7 and 4 patients respectively of CPT class B and C. There may be scope for training admitting clinicians who are working in the emergency setting to improve skills in recognising the less overt clinical signs of liver disease, hence leading to appropriate use of terlipressin, antibiotics and referral to endoscopy.

Ideally, increasing the capacity for endoscopy units may be a solution so that more stable patients are likely to have endoscopy within 24 hours. However, this recommendation may be impractical due to the existing NHS pressures.

### 4.5.10 Feedback to UHNM

I have fed-back the results from the clinical service evaluation to some of the clinicians who are responsible for the care of the patient with variceal haemorrhages. I explained that UHNM has been optimal, and above the national average in the administration of terlipressin and antibiotic prophylaxis.

One of the main findings from this evaluation was that patients in CPT class A were less likely to receive guideline-adherent treatment. The clinicians were able to explain that from a clinical perspective that it is difficult to manage these patients as this is most likely to be the patient's first presentation of chronic liver disease, and that giving the treatment may not have an anticipated beneficial outcome. I was able to appreciate that though there is a statistically significant difference between groups in my analysis, there may not be clinically significant differences. One of my suggestions for UHNM was to recognise less overt clinical signs of chronic liver disease e.g. optimised history taking and physical examinations.

However, this may only be possible in patients that are of CPT class B and C who may exhibit these, and may not necessarily be beneficial for CPT class A.

Endoscopy was performed in 40% of the patients within 24 hours, and the clinicians were able to further explain that this figure may not improve unless there are more endoscopy suites open out of hours, which may not occur due to the limited resources within the NHS. However, they were able to reassure that if the patient is unstable and is in need of urgent endoscopy, they would perform an endoscopy regardless of time of presentation.

## 4.6 Conclusion

In conclusion, this service evaluation found that the level of adherence to recommendations from the systematic review has been acceptable, particularly when factoring resource availability as well. However, it should be considered that improving adherence to recommendations could lead to over-treatment. The treatment may not always be beneficial for the patient, but can increase risk of side effects, and health care costs (Ooi, 2020). A study has found that wasteful care can account for up to 30% of total health care costs (Grimshaw *et al.*, 2020). For instance, one of the standards used in the service evaluation states that endoscopy should be performed within 24 hours, but for this to occur, there needs to be better service delivery. This would be associated with costs such as keeping endoscopy suites open out of hours and having adequately trained staff out of hours. However, this may not necessarily be beneficial for a stable patient and would instead increase healthcare costs. So, this should be taken into consideration prior to treating individual patients and following guidelines to mitigate risks of potentially causing harm.

The next chapter will draw together the findings of this thesis and consider the implications for future research and clinical practice.

# 5 Discussion for the thesis

## 5.1 Introduction

Chronic liver disease has shown itself to be a growing problem in the UK in comparison to other pathologies (British Liver Trust, 2022). Acute on chronic liver failure is associated with a high 28-day mortality and can be associated with many complications such as variceal haemorrhage (Arroyo, Moreau and Jalan, 2020). Variceal haemorrhage is a medical emergency and is associated with a 30% mortality rate (Sharara and Rockey, 2001). A systematic review and a service evaluation have been completed as part of this thesis. The aim was to appraise the quality of the guidelines in the management of varices in patients with ACLF and use the most appropriate standards to assess the management of patients in a local liver service with higher than average rates of admission.

## 5.2 Summary

The systematic review identified 49 guidelines, of which 21 were assessed for the rigour of their recommendation development using the AGREE II checklist Domain 3. The recommendations covered three treatment scenarios: primary prophylaxis, acute haemorrhage management, and secondary prophylaxis. In total, 19 recommendations were put forward as they are supported by high quality evidence.

The quality of the primary prophylaxis recommendations were mixed. Of the 24 recommendations made in the included guidelines, only 10 of the recommendations could be put forward as they were supported by high quality evidence and written by rigorously developed guidelines. It should be noted that the majority of the recommendations for this section were written by Tripathi *et al* (2015). Examples of recommendations that were put forward for primary prophylaxis include: pharmacological or endoscopic therapy can be used; non-selective beta blocker (NSBB) should be used first; and propranolol is the first choice of NSBB. Generally, the recommendations for the dosage of medication lacked in evidence.

The recommendations that were put forward for active haemorrhage management were split according to the different therapy types offered to the patient e.g. vasoactive drugs, antibiotic prophylaxis, time to endoscopy, endoscopic therapy, and post-endoscopic therapy. Though there were many recommendations put forward by different guidelines, only six of them could be put forward following the review. Some of the key recommendations are: endoscopic and vasoactive therapy should be used in variceal haemorrhage, terlipressin is the choice of vasoactive drug, and antibiotic prophylaxis should be initiated.

There were 24 recommendations proposed specifically for secondary prophylaxis. Only two of them could be put forward: patients should receive secondary prophylaxis; NSBB and VBL can be used as combination treatment. Most of the recommendations in this section were stand-alone recommendations that were supported by one guideline and were of low to moderate quality, so they have not been put forward.

The service evaluation used four of the recommendations that were put forward from the systematic review to assess whether UHNM treated patients according to the recommendations I made following my systematic review. Though UHNM would have not anticipated that I would assess them against these standards, the four recommendations were all quoted by the UK guidelines, which is also what the local UHNM guidelines follow, and so, the standards that I have proposed and the ones that they use are similar. The standards that were used for the service evaluation were: administration of terlipressin when a variceal haemorrhage is suspected; antibiotic prophylaxis should be given in patients with variceal haemorrhage; perform endoscopy within 24h in patients with a variceal haemorrhage; and VBL is the endoscopic treatment of choice for oesophageal varices. In the UHNM cohort of patients that were included in the service evaluation, the adherence for terlipressin and antibiotics use were high (91.2% and 94.0% respectively). 40.82% of patients received endoscopy within 24h, and 73.3% of patients with oesophageal varices received banding. There were three statistically significant associations between clinical practice and patient characteristics: sicker patients (denoted by CPT class B and C) were more likely to receive terlipressin and antibiotics; patients presenting outside of working hours were more likely to receive endoscopy within 24h; and patients with grade one oesophageal varices were less likely to receive VBL treatment.

## 5.3 Comparing it to existing literature

A similar systematic review has been published by Rios *et al* (2014) that also appraised the quality of guidelines on varices. Rios *et al* (2014) had included a smaller number of guidelines in comparison to what I have, as they had a tighter inclusion criteria (e.g. only including guidelines that were in English or Spanish). This was an advantage of my review as I had 13 articles that I translated, which were helpful in identifying what recommendations have been proposed by different countries (some had passed through to Domain 3). As this current review is written eight years after the review by Rios *et al* (2014), updated versions of the guidelines were included in my review, and some of the updated guidelines have improved considerably in terms of their quality since their outdated version.

There are different quality appraisal tools that I could have used for this review. For this systematic review, I felt that AGREE II was the best tool to use as it incorporated parts of other quality appraisal tools and was very thorough (Brouwers *et al.*, 2017). In their systematic review, Siering *et al.*, 2013 considered AGREE II to be the most comprehensive quality appraisal there is specifically for assessing the transparency of the methodology. In this review, I have prioritised Domains 1 and 3 (which assess for the scope and purpose and rigour of development respectively), as they were the Domains that were most likely to show whether the guidelines was of a good standard or not. Siering *et al* (2013) suggest if applicability of the guidelines is of focus, the Guidelines Implementability Appraisal (GLIA) tool version 2.0 is more suitable (Kashyap *et al.*, 2011). Guideline implementability is an area that could have been assessed as it is important to see whether the recommendations that guidelines propose can actually be applied within a healthcare system. Siering *et al* (2013) has found that some guidelines failed to improve clinical practice or improve patient outcomes as they did not account for the obstacles and challenges that they could face in clinical practice

e.g. resource availability and costs. Guideline implementability could be measured by the adherence to guideline recommendation and see whether this improved patient outcomes (Siering *et al.*, 2013). Though the implementability of the included guidelines have not been formally assessed using AGREE II in this review, it generally seemed that some of the guidelines did not consider this. The majority of the guidelines recommended that TIPS should be used as a rescue therapy in patients that acutely re-bleed from varices or have a high risk of rebreeding from varices. A large multi-centre audit was performed in France to assess whether cirrhotic patients received TIPS if eligible for it (Thabut *et al.*, 2018). Of the 946 patients that were included in the audit, 35% of them were eligible for TIPS, but only 6.8% of them had the treatment (Thabut *et al.*, 2018). Though this audit was performed in France, it has been said that the UK follows a similar trend (Jairath, 2013; Tripathi *et al.*, 2020). One of the barriers to receiving TIPS therapy could be that TIPS can only be performed by interventional radiologists in a specialised centre to which patients usually need to be referred. These barriers should be taken into account and guideline developers should have a deeper understanding of the services that are available specifically for their country and how feasible certain interventions are. Guidelines should be based on realism whilst aspiring towards idealism.

Majority of guidelines suggest that endoscopy should be performed in conjunction with vasoactive drugs. This recommendation itself is a high quality recommendation. However, the quality of evidence behind the recommendation that mentioned specific timings to endoscopy was disappointing. Specific timings were proposed by most guidelines, where a majority of them recommended that endoscopy should be performed within 12h. Not all of the quoted timings have been supported by high quality evidence. All the UK guidelines quote that endoscopy should be performed within 24h (Dworzynski*et al.*, 2012; Tripathi*et al.*, 2020). NICE guidelines have given a detailed explanation of why they recommended that endoscopy

should be performed within 24 hours (Dworzynski*et al.*, 2012). They explained that this is based on numerous factors: there is no difference in mortality between those that had received endoscopy within 12 and 24 hours; the cost of implementing services that would be needed to perform endoscopy within 12h is high and would not be cost effective; and performing endoscopy within 24h can still allow for early discharge of patients and a reduced hospital stay. In comparison to the other included guidelines, NICE guidelines seem to place a higher priority on costs and resource availability.

Prevention of advanced liver disease relied on effective patient education and optimal primary prophylaxis (James and Liou, 2015; Hayward *et al.*, 2017). A study has found that many patients with chronic liver disease found it difficult to understand specific information about their pathology and what management options were available (Hayward *et al.*, 2017). This could potentially be a target of improvement for clinicians at UHMN to develop resources to enhance patient education.

## 5.4 Strengths and Limitations of the Thesis

There are numerous strengths of this thesis. The systematic review is the first to the best of my knowledge in this field to perform data extraction on all the included guidelines. In this process, I was able to appreciate how recommendations could differ according to the rigor of the development process. Additionally, language was not a barrier in this review, as any guideline was included if it could be translated. This resulted in numerous guidelines from

languages other than English being included, which gave an insight into the management practices that occur globally.

The service evaluation also had some strengths. This service evaluation has not previously been performed at UHNM, and I was able to do this as part of my thesis. I have been able to highlight that the level of adherence toward terlipressin and antibiotics have been acceptable, and that adherence can be improved for endoscopy.

A limitation of the systematic review was that there was one reviewer for title screening. Performing double screening with another reviewer could aid in preventing studies being missed (Waffenschmidt *et al.*, 2019). Data extraction was generally difficult as the guideline documents were very long, which meant that it took considerable time to filter through what was relevant and what was not for each guideline – potentially increasing the likelihood of errors.

A limitation of the service evaluation was that it was performed using secondary data. Verification of the collected data could have highlighted any errors that may have occurred. If I were to have checked the data using the electronic patient database, these errors could have been changed to the correct values, and sensitivity analysis may have not needed to be performed.

Another limitation of the service evaluation was that the sample size was small. There was a total of 149 patients included within the service evaluation, and 120 patients that had oesophageal varices. The smaller the sample size, the smaller the statistical power. As this is a

service evaluation and not a research project, a sample size calculation was not carried out, but it is possible that there was insufficient power to detect statistical differences between groups that could be considered clinically important. Further limitation of the service evaluation was the retrospective nature if data collection. The quality of the data depended on the information recorded on the electronic patient records at UHNM. Prospective identification of patients and data collection would have enhanced the quality of the study but this was not practical considering the fixed time schedule that I had to complete my MPhil.

## 5.5 Implications in clinical practice

Since the rise of evidence-based practice in the 1980s, clinical practice guidelines have been widely introduced (Graham, 2014). Guidelines propose recommendations that can be used by clinicians as guidance. Following the recommendations of guidelines has numerous benefits (Woolf *et al.*, 1999). They can improve patient outcome by promote the use of interventions that have proven to be beneficial, and can standardise care amongst different hospitals (Woolf *et al.*, 1999). They are a source of the latest evidence for clinicians, as they incorporate results from systematic reviews and randomised controlled trials, which clinicians can use to make their own judgement whilst considering the risks and benefits to their individual patients. Guidelines also can identify where there is missing evidence and can potentially recognise where there is a potential for service improvement (Woolf *et al.*, 1999; Brignardello-Petersen, Carrasco-Labra and Guyatt, 2021). However, there are some potential limitations that should also be considered with guidelines. The evidence that is used to make recommendations can be misleading and can be interpreted differently than intended (Woolf *et al.*, 1999). Another limitation is that expert opinion or consensus opinions can impact the recommendations made, when they should ideally be evidence-based. This was particularly seen in the guidelines that were included in this systematic review. There were some guidelines that were consensus

based that included leading experts as part of the guideline development groups (National Agency for Accreditation and Evaluation in Health, 2004; Narváez-Rivera *et al.*, 2013; Reiberger, Püspök, *et al.*, 2017; de Franchis *et al.*, 2022b). It is fair to say that the expert opinions may have had an impact on what recommendations should be put forward despite the evidence that is present. Some recommendations are based on expert opinion (commonly denoted as 5D in terms of strength and quality of evidence). Rios *et al* (2014), who also found this finding, inferred that consensus based guidelines may be more common in varices because the limited availability of evidence due to the acute nature of variceal bleeding. If there is better evidence based recommendations available (rather than expert opinion) they should be used instead (Ponce *et al.*, 2017).

Though following guidelines has many benefits for both the clinician and the patient, most of the time, they do specify that clinicians must use their clinical judgement in conjunction with the recommendations so that optimal care is achieved. Each patient is different and can present with different complications and co-morbidities which should all be taken into account when managing a patient. Most clinicians, especially junior clinicians who are yet to fully specialise, will use recommendations from guidelines but may not necessarily read about the evidence base behind each of the recommendations. They may not be able to interpret the formal assessment tool that is used for the recommendations. Even some of the specialty doctors within the field may not have a thorough understanding of what evidence is upcoming unless they have some academic background. Normally, hepatologists prescribe the treatment for primary and secondary prophylaxis for the patient. However, if the patient becomes intolerant to a certain medication e.g. propranolol, their general practitioner may have to change the dosage or change the medication. Variations in experience and understanding of

liver disease amongst different clinicians (e.g. general practitioners and emergency physicians) caring for patients with varices can potentially have an impact on patient outcomes.

To interpret and use a guideline effectively, there are various steps that can be taken. Some of the steps include (Brignardello-Petersen, Carrasco-Labra and Guyatt, 2021):

- identifying whether the recommendation are clear;
- whether the strength of the recommendation has been provided;
- whether the evidence behind the recommendation is transparent;
- looking at how the guideline development group came to the recommendation from the evidence;
- whether the specific recommendation applies to the patient that you are treating.

If these steps are taken, it could aid in better evidence based practice and improve patient outcomes.

## 5.6 How this has changed my views on medical practice

Completing both the systematic review and the service evaluation has helped me to develop my research skills profoundly. I have had little experience in academic medicine so far in my career and this was the first time I have undertaken a systematic review, and performed a service evaluation. This systematic review has aided my understanding into the rigour that is needed to produce academic work. By appraising the quality of guidelines that are written for the management of varices, I have now developed a much better understanding of the

guideline development process. I am able to appreciate where the limitations lie and why sometimes recommendations differ between guidelines. I also had initially thought that the evidence behind the recommendations would be high quality and had not considered that guideline developers would not formally assess the quality of evidence. I soon realised that the evidence quality is lacking around some topic areas e.g. small varices, BRTO, and endoscopic timings. This helped me realise the uncertainty in some areas but despite this, patients still need to be managed. Clinicians have to use their judgement, expert opinions and anecdotal evidence in order to treat the patient when high quality evidence-based treatment strategies are unavailable (Isaacs and Fitzgerald, 1999; Matthews, 2008). This is often expected in emergency situations where patients can acutely deteriorate, and be unresponsive to certain treatments, so the other options that are not conventionally used need to be attempted.

Additionally, doctors can potentially over-estimate the benefits of certain interventions, which could be harmful for the patient later after treatment is administered (which is also most often realised in hindsight) (Ralston and Schroeder, 2015). This is especially applicable for the treatment of small varices with primary prophylaxis. The evidence is of poor to moderate quality, but this recommendation is followed by clinicians. Though it may be somewhat beneficial, the treatment of them can increase the risk adverse events and have unwanted side effects for the patient (Merkel, 2003).

The process of completing a service evaluation has given me a deeper insight into the importance of constant evaluation to improve patient care. There is a sense of accountability that can be created from appraising practice against recognised standards and striving to better patient outcomes. By knowing what services are not meeting certain criteria, resources

can be better directed and be re-evaluated later on to assess if it was worth making the changes for.

## 5.7 Future research questions

Generally, it seemed that the quality of evidence for some interventions were not of the highest quality (e.g. TIPS, therapy for gastric and small oesophageal varices), which made it quite difficult to put most recommendations forward. It is also difficult to assess whether they will have a beneficial outcome for the patient. It is important that the quality of evidence improves overall so that it can be better identified if the interventions have a desirable effect with minimal uncertainty. The quality of the guideline itself has had an impact on whether recommendations can be put forward. Only eight guidelines have scored highly in Domain 3 (which assessed for rigour of development). 13 guidelines that passed into Domain 3 either received amber or red. 28 guidelines did not pass Domain 1 as they did not specify the health questions and objectives to a reasonable standard. If guidelines were to have been explicit with mentioning their objectives and be transparent with their methodology, they would have performed well across both Domains. This an improvement that all guidelines can make.

As the systematic review had identified guidelines over the span of nearly 3 decades, a potential requirement that guidelines should undergo is updating their material, or if it cannot be updated, they should be archived. Updating recommendations is important in maintaining the validity of guidelines (Vernooij *et al.*, 2014). A clinical practice guideline can act as a summary document for newer evidence and therapies that are potentially available for managing patients with a particular condition. It would be beneficial for clinical communities around the world (given guidelines are generally written by regional organisations) if guideline

developers regularly updated the systematic reviews underlying their recommendations, and hence avoid outdated clinical practices.

Further research into the management of small varices, role of early TIPS after the first episode of variceal bleeding, and the role of BRTO in gastric varices may likely lead to significant change to the outcomes for patients with liver disease.

## 5.8 Conclusion

In conclusion, the recommendations that were proposed by guidelines on the management of varices in CLD were identified and categorised as recommendations for primary prophylaxis, active haemorrhage management and secondary prophylaxis. The evidence behind the recommendations is variable, but 19 recommendations were put forward as high quality and evidence based. The systematic review was able to highlight that evidence quality was lacking in areas including small varices management, time to endoscopy and the use of BRTO in gastric varices.

Relevant high quality recommendations resulting from the systematic review were used as standards for a service evaluation of variceal bleeding in CLD at UHNM. The standards for the clinical service evaluation were based on whether the patient was given: terlipressin, antibiotic prophylaxis, endoscopy within 24 hours, and banding, if they had oesophageal varices. Generally, the level of adherence for terlipressin and antibiotics was high. Sicker patients were more likely to receive them. Additionally, patients presenting outside of working hours were more likely to receive endoscopy within 24 hours than those presenting in hours, possibly as a

result of endoscopy list timings at UHNM. Lastly, patients with grade one varices were less likely to receive band ligation. If there are continuous improvements made to improve the quality of guidelines, as well as the services at UHNM, this could lead to potentially favourable outcomes for patients in the future.

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# 6 Appendices

## Appendix 1: The protocol

Version 7, October 2019

### School of Medicine
### Systematic Review Protocol & Support Template

This template is primarily intended to help you plan your review in a systematic way. Keeping a record of all the reviews will also assist in planning the work of the Centre and ensuring adequate methodological support. Not all the information will be relevant to every review and items should be adapted to fit the type of review that is being undertaken.
The template has been updated to include all the items from the PRISMA-P checklist (http://www.prisma-statement.org/Extensions/Protocols.aspx). All systematic reviews should be registered with PROSPERO database (http://www.crd.york.ac.uk/PROSPERO/) unless the review is methodological.

**Please complete the form in as much detail as possible for your review and email to one of the SR Team:- Yemi (Opeyemi) Babatunde, o.babatunde@keele.ac.uk, Jo Jordan, j.jordan@keele.ac.uk, or Nadia Corp, n.corp@keele.ac.uk.**

| | |
|---|---|
| **Title of the review** | **A systematic review of international guidelines on the management of gastro oesophageal varices in acute on chronic liver failure.** |
| **First reviewer** | Saumiya Kesavan |
| **Other reviewers (with role/contribution in the review)** | Dr Sara Muller – supervisor<br>Dr Rajeev Desai- supervisor |
| **Clinical Portfolio Group** | |
| **Funding source** | Self-funded |
| **PROSPERO registration number** | Will get this done |

| | |
|---|---|
| **Amendments to the protocol** | |

## 1. Background to review

Brief introduction to the subject of the review, including rationale for undertaking the review and overall aim

Chronic liver disease (CLD) is a major cause of mortality in the UK. CLD can have multiple effects on various systems of the body and can lead to complications including upper gastrointestinal variceal bleeding. The management of these complications have been thoroughly studied to produce various guidelines. The aim of this is systematic review is to assess the quality of international guidelines in the management of gastro intestinal varices in acute on chronic liver disease

## 2. Specific objectives/questions the review will address

Varices:

- Identify the current published guidelines for the primary and secondary prophylactic treatment for upper gastrointestinal varices.
- Identify the current published guidelines for the management of acute upper gastrointestinal variceal haemorrhage
- Critically appraise the existing clinical practical guidelines to assess their quality based on the evidence that they have used to come to those recommendations in the treatment of upper gastrointestinal varices using the AGREE II checklist
- Compare and contrast the identified guideline recommendations (for prophylaxis and haemorrhage) and relate this to the quality of evidence used in generation of the individual guidelines.

## 3. a) Eligibility Criteria for including studies in the review

If the PICOS format does not fit the research question of interest, please split up the question into separate concepts and put one under each heading

| | |
|---|---|
| **i. Population, or participants and conditions of interest** | **Patients with acute on chronic liver disease** |

| | |
|---|---|
| ii. Interventions/Exposure/item of interest | **Varices is the exposure. Varices are the complications that can occur in people with acute on chronic liver disease. The potential relevant search terms to pick up varices will include: varic*, varix*, dilated blood vessel.** |
| iii. Comparisons or control groups, if any | **NA** |
| iv. Outcomes of interest | **NA** |
| v. Setting | **NA** |
| vi. Study designs | **Clinical guidelines will be used. The clinical guidelines should be evidenced-based and not opinion based. We will include studies that are backed by both systematic reviews and clinical evidence.** |

| **3. b) Criteria for excluding studies not covered in inclusion criteria**<br>Any specific populations excluded, date range, language, whether abstracts or full text available, etc |
|---|
| - **Paediatric guidelines**<br>- **If only the abstract is available**<br>- **Guidelines in other languages for which the research team cannot access appropriate translation**<br>- **Cover only other complications of liver disease such as hepatorenal syndrome, ascites**<br>- **Guidelines superseded by a newer version** |

| **4. Search methods** |
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| **Electronic databases & websites**<br><br>Please list all databases that are to be searched and include the interface (e.g. NHS HDAS, EBSCO, OVID etc) and date ranges searched for each.<br><br>**NB All search strategies should be reviewed by Jo Jordan or Nadia Corp BEFORE searching begins** | - MEDLINE via OVID<br>- EMBASE via OVID<br>- Web of Science (Science Citation Index only)<br>- TRIP Database for clinical guidelines.<br>- Epistemonikos for clinical guidelines. |

| | |
|---|---|
| **Other methods used for identifying relevant research**<br>ie contacting experts and reference checking, citation tracking | - Checking the references of included papers<br>- Conference abstracts to ascertain whether full paper is available<br><br>14/12/21: We may ask experts for their opinion regarding the inclusion of some of the papers. They may also have an idea what papers should be included that may necessarily not have been part of the search.<br><br>I will check websites of relevant professional organisations and include guidelines written in English :<br><br>- European association for the study of the liver (EASL)<br>- National institute of clinical excellence (NICE)<br>- American association for the study of liver disease (AASLD)<br>- Asian pacific association for the study of the liver (APASL)<br>- Armenian hepatological forum (AHF)<br>- Austrian society of gastroenterology and hepatology (OEGGH)<br>- Azerbaijan Gastroenterologists and Hepatologists association (AGHA)<br>- Byelorussian Gastroenterology association<br>- Belgian Association for the Study of the Liver (BASL)<br>- Association of Gastroenterologists and Hepatologists in Bosnia and Herzegovina<br>- Bulgarian society of gastroenterology<br>- Croatian Society of gastroenterology<br>- Czech Society of Hepatology (CSH)<br>- Danish gastroenterology and hepatology association (DSGH)<br>- Eesti Gastroenteroloogide Selts, Estonian Socity of Gastroneterology<br>- Finish Society of Gastroenterology<br>- Association Fracaise Pour l'Etude du Foie (AFEF)<br>- Georgian Hepatology Association<br>- German Association for the study of the liver (GASL)<br>- Hullenic Association for the study of the liver (HASL)<br>- Hungarian Liver Research society<br>- Irish society of Gastroenterology (ISG)<br>- Israel Association for the study of the liver diseases<br>- Associazione Italiana per lo Studio del Fegato (AISF)<br>- GastroHepato TransplantGroup Astana<br>- Latvian Association of Infectologists and Hepatologists<br>- Lithuanina Society of Gastroenterology<br>- Polish Association for the study of the liver (PASL)<br>- Associacao Poruguesa para o Estudo do Figado (APEF)<br>- Romanian Association for the study of the liver (ARSF)<br>- Russian Scientific Liver Society (RSLS)<br>- Hepatology section of the Serbian Medical Society<br>- Slovak Society of Hepatology<br>- Slovenian Society for Gastroenterology and Hepatology<br>- Asociacion Espanola para el Estudio del Higado (AEEH)<br>- Svensk Gastroenterologisk Förening (SGF)<br>- Swiss Association for the Study of the Liver (SASL)<br>- Nederlandse Vereniging voor Hepatologie Duth Society for Hepatology<br>- Turkish Association for the Study of the Liver (TASL)<br>- Ukraninan Association for the study of the liver disease (UASL)<br>- The British Association for the study of the liver (BASL) |
| **Journals hand searched**<br>If any are to be hand searched, please list which journals and date searched from, including a rationale. | NA |

**5. Methods of review**

| | |
|---|---|
| **How will search results be managed & documented?**<br>ie which reference management software, how duplicates dealt with | - Zotero can be used as a web-based bibliography. This will also be able to delete the duplicates/ near close matches. This will be then exported into Rayyan, a free software, that will help with the screening process- titles and abstract. |
| **Selection process**<br>Number of reviewers, how agreements to be reached and disagreements dealt with, etc. | The current selection criteria:<br>- Saumiya Kesavan will screen the titles initially by herself.<br>- There will be two reviewers past the title screening stage- Saumiya Kesavan and either Sara Muller or Rajeev Desai.<br>- At the abstract screening stage, any paper included by either reviewer will be retained.<br>- At the full text screening stage, any disagreements will be resolved through discussion. If agreement in not possible, the third reviewer will arbitrate |
| **Quality assessment**<br>Tools or checklists used with references or URLs, was this piloted? Is it to be carried out at same time as data extraction? | AGREE II – this is a quality appraisal tool that has been used extensively to appraise the quality of guidelines. The AGREE 2 checklist contains 6 domains. As the appraiser, we are allowed to prioritise the domains and assess their scores. This will be done at the same time as data extraction.<br><br>AGREE II developers suggest the use of a score of 70% or more on the most important domain (as defined by the review team) to take the guidelines forward for assessment of the other domains. This process will be modified slightly.<br>First, a three-stage process will be adopted. 1) Domain 1 (scope and purpose) will be used to ensure the guideline is relevant to the question posed, 2) Domain 3 (rigour of development) will be used to ensure only high quality, evidence-based guidelines are included in the final review. 3) Domains, 2, 4, 5,6 will be assessed in the remaining guidelines.<br>Second, scores will be used to help inform decisions and discussion between reviewers, but not as the sole basis on which to reject a guideline. Choices as to inclusion or exclusion of a guideline from the review based on Domain 1 and Domain 3 will be based on this discussion, which will be documented, and not only on a score over 70%. However, it is expected that the majority of included guidelines will score ≥70% on these domains and those excluded will score <70%. Where this is not the case, a detailed argument will be given.<br><br>AGREE II Domain 1 (scope and purpose) will be used to confirm the eligibility of the study for the review. Any guideline that does not clearly address the management of varices in liver disease will not be taken forward.<br><br>Domain 3 (rigour of development) will be used to further screen out low quality guidelines that were not based on a sufficiently rigorous review of the evidence and or on poor quality evidence.<br><br>Domains 2, 4, 5 and 6 will be completed for those guidelines remaining in the review after assessment against Domains 1 and 3. These will be used to enable the remaining reviews to be compared and contrasted more holistically in terms of quality. This will allow the review to feed into another objective of the MPhil project of which this systematic review is the first part – the highest quality guideline(s) will be used as an audit standard against which to compare local data.<br><br>The use of this checklist and associated data extraction, will be piloted by Saumiya Kesavan and Sara Muller against the British Gastroenterology Society (BSG) guidelines. |

| | |
|---|---|
| **How is data to be extracted?**<br>What information is to be collected on each included study? If databases or forms on Word or Excel are used, were these piloted and how is this recorded and by how many reviewers? | - A pilot of the data extraction will be carried out using the BSG guidelines. The data extraction will be done by two reviewers: Saumiya Kesavan and either Sara Muller or Rajeev Desai.<br>- For the data extracted, see appended document.<br>- Alongside of this, the quality appraisal will also be done using the AGREE 2 checklist.<br>- Data extraction will be done on the guidelines in accordance to the appended document which will have the header on them. |
| **Outcomes to be extracted & hierarchy/priority of measures**<br>ie which measure is preferred and if that is not available which is next in order of preference? | -<br><br>The focus of this review is on quality and identifying guidelines based on high quality evidence. However, for all guidelines retained after applying AGREE II Domain 1 (scope and purpose), the recommendations in the guidelines will be compared between those scoring highly on Domain 3 (and therefore retained for the other domains) and those scoring less highly and not assessed using the remaining AGREE II domains. Guidelines that are assessed against Domains 2, 4, 5 and 6 and scoring highly (using ≥70% as a guide, but at the discretion of the review team, with documenting of reasoning) will be compared in terms of their content against those guidelines scoring less highly on these domains. |
| **Narrative synthesis**<br>Details of what methods, how synthesis will be done and by whom. Is the Narrative Synthesis Framework to be used? | The narrative synthesis will be done by Saumiya Kesavan. The data will be **tabulated** so that comparisons can be made between the different clinical practice guidelines, based on factors such as: similarities, differences, strength of the data, and quality appraisal scores using the AGREE 2 checklist.<br><br>Although we will not look at subgroups of patients, we will break down the results by recommendations, and see what the overall popular recommendations are. With these recommendations, we will see which guidelines support this view and what their quality appraisal score is (AGREE 2). We will also be doing the same for the recommendations that are not as prominent, and see which guidelines support this and what their quality appraisal score is. |
| **Meta-analysis**<br>Details of what and how analysis and testing will be done. If no meta-analysis is to be conducted, please give reason. | NA |
| **Will the overall strength of evidence be assessed? If so, how?**<br>ie GRADE? | We will present the scores over the 6 domains in the AGREE 2 checklist for the guidelines that are included in the review. |

| **6. Presentation of results** | |
|---|---|
| **Outputs from review**<br>Papers and target journals, conference presentations, reports, etc | MPhil thesis<br>Publication and conference attendance:<br>- Midland Gastroenterology Society conference November 2022 (abstract in for summer of 2022).<br>- British Society of Gastroenterology annual conference (20-23 June 2022)<br>- United European Gastroenterology Week 2022 (October 8-11 2022) |

| 7. Timeline for review – when do you aim to complete each stage of the review | |
|---|---|
| **Protocol** | 30/09/2021 |
| **Literature searching** | 8/10/2021 (will do this alongside the protocol development) |
| **Screening search results** | 22/10/2021 |
| **Quality appraisal** | 31/01/2022 |
| **Data extraction** | 31/01/2022 |
| **Synthesis** | 31/03/2022 |
| **Writing up** | This should be done alongside the review |

## Appendix 2: The Search Strategy

| Concept 1 | Concept 2 | Concept 3 | Concept 4 |
|---|---|---|---|
| **Acute on chronic liver failure:** | **Ascites:** | **Varices:** | **Clinical practice Guidelines:** |
| Alternative terms:<br>• Liver<br>• Portal hypertension<br>• Fibrosis | Alternative terms:<br>• Abdominal fluid<br>• Fluid in the abdomen<br>• Abdominal oedema<br>• | Alternative terms:<br>• Dilated vessels | Alternative terms:<br>• Guideline<br>• Recommendation<br>• Clinical protocols<br>• Critical pathway |
| Possible truncations:<br>- Cirrho* (picks up cirrhosis and cirrhotic)<br>- Hepat* | Possible truncations:<br>-ascit* | Possible truncations:<br>- Varice* (will pick up all the other forms of varices) | Possible truncations:<br>- Guideline* |
| Quotation marks for:<br>- "Portal hypertension" | Quotation marks for:<br>All of them, unless you use ADJ | Quotation marks for:<br>• Gastric varices<br>• Gastro-oesophageal varices<br>• Dilated vessels | Quotation marks for:<br>- "clinical protocols" |

| | | | |
|---|---|---|---|
| Wildcard: finding changes in the spelling | Wildcard: finding changes in the spelling<br>- #edema | Wildcard: finding changes in the spelling<br>- #eosophageal | Wildcard: finding changes in the spelling |
| Thesaurus/ MESH:<br>Liver diseases<br>- Liver cirrhosis<br>- Hypertension, Portal<br><br>Liver failure<br>- Acute on chronic liver failure | Thesaurus/ MESH:<br>Chylous ascites<br>Ascitic fluid | Thesaurus/ MESH:<br>Esophageal and gastric varices | Thesaurus/ MESH:<br>Guideline (includes practice guideline)<br>Clinical protocols |

## Appendix 3: Blank Data Extraction form

| A | B | C | D | E | F |
|---|---|---|---|---|---|
| **TITLE** | **ORGANISATION** | **AUTHORS** | **DATE OF DEVELOPMENT** | **MAIN RECOMMENDATION** | **CONDITION OF RECOMMENDATION AND EVIDENCE** |
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## Appendix 4: Recommendations and strength of evidence that have been proposed by guidelines that only passed through Domain 1

### Recommendations for Primary Prophylaxis

| Recommendations | Which paper support it | Recommendation strength |
|---|---|---|
| Primary prophylaxis can be either pharmacological treatment or endoscopic treatment (in the form of VBL) for patients that have a risk of bleeding. | (Garcia-Tsao, Lim, and Members of Veterans Affairs Hepatitis C Resource Center Program, 2009) | Not formally assessed- has referenced an RCT |
| | (Fejfar, Vanasek, J. Lata, *et al.*, 2017) | Not formally assessed- referenced a couple of studies |
| | (Bosch, Juan G. Abraldes and Groszmann, 2003) | Not formally assessed |
| | (Chinese Society of Spleen and Portal Hypertension Surgery, 2019) | Not formally assessed |
| The treatment of choice should be NSBB, and if the patient is intolerant to the medication, elastic band ligation can be performed till variceal eradication. | (Rosolowski *et al.*, 2014) | Not formally assessed |
| | (Jaime Bosch *et al.*, 2012) | Not formally assessed |
| | (Farooqi *et al.*, 2007) | A1 |
| | (Reiberger, Puspok, *et al.*, 2017) | B1 |
| | (Angeli *et al.*, 2018) | III:1 |
| The NSBB of choices can be between propranolol, and nadolol | (Jaime Bosch *et al.*, 2012) | Grade A |
| | (Farooqi *et al.*, 2007) | A1 |
| If patient are intolerant to NSBB, ISMN should be used instead* | (Gow and Chapman, 2001) | Not formally assessed- referenced a meta-analysis |
| Carvedilol is more effective than propranolol* | (Reiberger, Puspok, *et al.*, 2017) | B1 |
| Dosage of the medication<br>Propranolol:<br>oral doses of 20-40 mg twice a day, titrated up to 160-320 mg/day to maintain heart rate between 55-60 beats per min and systolic blood pressure >90 mmHg* | (Bittencourt *et al.*, 2017) | Not formally assessed |

| Recommendations | Which paper support it | Recommendation strength |
|---|---|---|
| Dosage of propranolol:<br>10 mg/twice daily , titrated to the maximum tolerated dosage; | (Farooqi *et al.*, 2007) | A1 |
| Dosage of propranolol:<br>dose of 20 mg twice daily | (Garcia-Tsao, Lim, and Members of Veterans Affairs Hepatitis C Resource Center Program, 2009) | Not formally assessed |
| Dosage of propranolol: 20–40 mg twice daily with a maximum dosage of 160 mg/day* | (Reiberger, Puspok, *et al.*, 2017) | B1 |
| Carvedilol dosage: oral doses of 3.125 mg twice a day, and titrated to 6.25 mg twice a day. | (Bittencourt *et al.*, 2017) | Not formally assessed |
| | (Fejfar, Vanasek, J. Lata, *et al.*, 2017) | Not formally assessed |
| Carvedilol dosage: 6.25 mg once daily with a maximum dosage of 12.5 mg/day* | (Reiberger, Puspok, *et al.*, 2017) | B1 |
| Nadolol: 20–40 mg once daily* | (Garcia-Tsao, Lim, and Members of Veterans Affairs Hepatitis C Resource Center Program, 2009) | No reference |
| Small varices: those that are not at risk may be treated with NSBB. | (Garcia-Tsao, Lim, and Members of Veterans Affairs Hepatitis C Resource Center Program, 2009) | Not formally assessed – referenced a study |
| | (Garcia-Tsao, Arun J. Sanyal, *et al.*, 2007) | Class III, B |
| | (Reiberger, Puspok, *et al.*, 2017) | B1 |
| | (Fejfar, Vanasek, J. Lata, *et al.*, 2017) | Not formally assessed |
| Small varices that are at increased risk of bleeding should be treated with NSBB. E.g. red signs/Child-Pugh class B or C | (Bittencourt *et al.*, 2017) | Not formally assessed |
| | (Narváez-Rivera *et al.*, 2013) | Level 9 agreement |
| | (Rosolowski *et al.*, 2014) | Not formally assessed |
| | (Garcia-Tsao, Lim, and Members of Veterans Affairs Hepatitis C Resource Center Program, 2009) | Not formally assessed |
| | (Garcia-Tsao, Arun J. Sanyal, *et al.*, 2007) | Class IIa, C |
| | (Reiberger, Puspok, *et al.*, 2017) | A1 |

| Recommendations | Which paper support it | Recommendation strength |
|---|---|---|
| | (Angeli *et al.*, 2018) | III;1 |
| | (Fejfar, Vanasek, J. Lata, *et al.*, 2017) | Not formally assessed |
| Medium/large varices should be treated with primary prophylaxis, either with NSBB or band ligation. | (Bittencourt *et al.*, 2017) | Not formally assessed |
| | (Garcia-Tsao, Lim, and Members of Veterans Affairs Hepatitis C Resource Center Program, 2009) | No reference- based on expert opinion |
| | (Reiberger, Puspok, *et al.*, 2017) | A1 |
| | (Angeli *et al.*, 2018) | I:1 |
| Medium/large varices should be treated with primary prophylaxis, either with NSBB or band ligation **if high risk** of bleeding | (Garcia-Tsao, Lim, and Members of Veterans Affairs Hepatitis C Resource Center Program, 2009) | Not formally assessed |
| | (Farooqi *et al.*, 2007) | C1 |
| | (Garcia-Tsao, Arun J. Sanyal, *et al.*, 2007) | A1 |
| | (Mellinger and Volk, 2013) | A1 |
| Medium/large varices should be treated with primary prophylaxis, either with NSBB or band ligation if not high risk of bleeding | (Garcia-Tsao, Lim, and Members of Veterans Affairs Hepatitis C Resource Center Program, 2009) | Not formally assessed |
| | (Trebicka and Götz, 2018) | Not formally assessed |
| Medium or large varices should be treated initially with NSBB and if intolerant, they should have band ligation | (Narváez-Rivera *et al.*, 2013) | Level 9 of agreement |
| | (Rosolowski *et al.*, 2014) | Not formally assessed |
| | (Farooqi *et al.*, 2007) | A1 |
| | (Garcia-Tsao, Arun J. Sanyal, *et al.*, 2007) | A1 |
| | (Fejfar, Vanasek, J. Lata, *et al.*, 2017) | Not formally assessed |
| | (Bosch, Juan G. Abraldes and Groszmann, 2003) | Not formally assessed |
| | (Diaz-Brito, Cardoso and Sarmento, 2018) | Not formally assessed – referenced a study |
| | (Mellinger and Volk, 2013) | A1 |

*Recommendations made by guidelines just in Domain 1.

The primary prophylaxis management options that have been recommended by guidelines in just Domain 1. Abbreviations: VBL= variceal band ligation, NSBB= non-selective beta blocker, ISMN= isosorbide mononitrate, mg= milligrams.

## Recommendations for Active Variceal Haemorrhage

| Treatment | Which guidelines support it | Strength of guideline |
|---|---|---|
| Endoscopy and vasoactive treatment are the therapy of choice for variceal haemorrhage | (Narváez-Rivera *et al.*, 2013) | Level 9 of agreement |
| | (Jaime Bosch *et al.*, 2012) | Not formally assessed |
| | (Farooqi *et al.*, 2007) | A1 |
| | (Reiberger, Puspok, *et al.*, 2017) | A1 |
| | (Bosch, Juan G. Abraldes and Groszmann, 2003) | Evidence: 3 studies |
| | (Sarin *et al.*, 2011) | 1a;A |
| Vasoactive drug should be administered as soon as variceal haemorrhage is suspected and should be continued for 3-5 days | (Henry *et al.*, 2021) | Guidance, meta- analysis, RCT and comparative studies were referenced |
| | (Bittencourt *et al.*, 2017) | Not formally assessed |
| | (Fernandez, Aracil, Sola, Soriano, Cinta Cardona, *et al.*, 2016) | Not formally assessed |
| | (Narvaez-Rivera *et al.*, 2013) | Level 9 of agreement |
| | (Rosolowski *et al.*, 2014) | Not formally assessed |
| | (Jaime Bosch *et al.*, 2012) | Not formally assessed |
| | (Garcia-Tsao, Lim, and Members of Veterans Affairs Hepatitis C Resource Center Program, 2009) | Not formally assessed |
| | (Farooqi *et al.*, 2007) | Not formally assessed |
| | (Garcia-Tsao, Arun J Sanyal, *et al.*, 2007) | Class I, Level A |
| | (Reiberger, Puspok, *et al.*, 2017) | A1/A1 for duration |
| | (Angeli *et al.*, 2018) | I:1 |
| | (Fejfar, Vanasek, J Lata, *et al.*, 2017) | Not formally assessed |
| | (Bosch, Juan G. Abraldes and Groszmann, 2003) | Not formally assessed -referenced to RCT |
| | (Sarin *et al.*, 2011) | class 1A recommendations,/5D for duration |
| | (Mellinger and Volk, 2013) | class 1A recommendations (for both) |

| Treatment | Which guidelines support it | Strength of guideline |
|---|---|---|
| | (Trebicka and Götz, 2018) | Not formally assessed |
| | (Chinese Society of Spleen and Portal Hypertension Surgery, Chinese Society of Surgery and Chinese Medical Association, 2019) | Not formally assessed |
| | (D'Amico, Pagliaro and Bosch, 1999) | A1 |
| Drug choice: terlipressin,somatostatin, octreotide | (Bittencourt *et al.*, 2017) | Not formally assessed – referenced a Meta analysis |
| | (Jaime Bosch *et al.*, 2012) | Not formally assessed |
| | (Garcia-Tsao, Lim, and Members of Veterans Affairs Hepatitis C Resource Center Program, 2009) | Not formally assessed - RCTs referenced |
| | (Farooqi *et al.*, 2007) | Not formally assessed |
| | (Garcia-Tsao, Arun J Sanyal, *et al.*, 2007) | Class I, Level A |
| | (Angeli *et al.*, 2018) | I:1 |
| | (Gow and Chapman, 2001) | Not formally assessed – Referenced multiple RCTs |
| | (Mellinger and Volk, 2013) | Class 1A |
| | (Xu *et al.*, 2020) | Not formally assessed |
| Drug choice: terlipressin or somatostatin | (Fernandez, Aracil, Sola, Soriano, Cinta Cardona, *et al.*, 2016) | Not formally assessed |
| | (Reiberger, Puspok, *et al.*, 2017) | A1 |
| 1st Choice of vasoactive drug: terlipressin | (Narvaez-Rivera *et al.*, 2013) | Level 9 of agreement |
| | (Fejfar, Vanasek, J Lata, *et al.*, 2017) | Not formally assessed -referenced RCT, and SR. |
| | (Bosch, Juan G. Abraldes and Groszmann, 2003) | Not formally assessed -reference to RCT |
| | (Sarin *et al.*, 2011) | 5D |
| | (D'Amico, Pagliaro and Bosch, 1999) | A2 |
| | (Goshi and Stanley, 2005) | Not formally assessed |
| 2nd choice: somatostatin after terlipressin* | (D'Amico, Pagliaro and Bosch, 1999) | A2 |

| Treatment | Which guidelines support it | Strength of guideline |
|---|---|---|
| | | |
| | (Fejfar, Vanasek, J Lata, *et al.*, 2017) | Not formally assessed |
| 2nd choice: somatostatin or octreotide* | (Bosch, Juan G. Abraldes and Groszmann, 2003) | Not formally assessed -reference to a two guidelines (one of them which BOSCH wrote) |
| | (Sarin *et al.*, 2011) | 5D |
| 1st choice is octreotide: | (Henry *et al.*, 2021) | Not formally assessed -guidance, meta- analysis, RCT and comparative studies were referenced |
| Terlipressin dose:<br>TL should be administered as an intravenous bolus dose of 2 mg followed by 1-2 mg (depending on patient's weight) every 4 hours during the initial 48 hours after admission. The dose should be reduced to a maintenance dose of 1 mg every 4 hours* | (Bittencourt *et al.*, 2017) | Not formally assessed |
| Terlipressin: 2 mg/4 h intravenous bolus (1.5 mg in patients weighing between 50-70kg, 1mg in patients weighing less than 50 kg) during the first 48 h, and 1 mg/4 h until day 5* | (Fernandez, Aracil, Sola, Soriano, Cinta Cardona, *et al.*, 2016) | Not formally assessed |
| Terlipressin: 2mg/4h iv, reduce to 1mg /4h 24h after haemostasis | (Jaime Bosch *et al.*, 2012) | Not formally assessed |
| | (Farooqi *et al.*, 2007) | Not formally assessed |
| Terlipressin dose: initially a bolus of 2 mg every 4 h. If the patient does not bleed for 24h, bolus administration of 1 mg every 4 h should be continued for the next 24 h for up to 5 days. Continuous terlipressin infusion (initial dose of 2 mg/day; maximum 12 mg/day) can be used as well* | (Reiberger, Puspok, *et al.*, 2017) | Not formally assessed |
| Terlipressin 1-2 mg every 4 hours iv* | (Fejfar, Vanasek, J Lata, *et al.*, 2017) | Not formally assessed -referenced RCT and SR |
| | (Gow and Chapman, 2001) | 5D |

| Treatment | Which guidelines support it | Strength of guideline |
|---|---|---|
| Dose vasoactive drug: octreotide: Intravenous bolus of 50 mg (can be repeated in first hour if ongoing bleeding). Continuous intravenous infusion of octreotide 50 mg/h for 2–5 d * | (Henry *et al.*, 2021) | Not formally assessed – refered to guidance, meta- analysis, RCT and comparative studies were referenced |
| | (Jaime Bosch *et al.*, 2012) | Not formally assessed |
| Octreotide should be administered as an intravenous bolus dose of 50-100 µg followed by a continuous infusion of 50 µg/h * | (Bittencourt *et al.*, 2017) | Not formally assessed |
| Octreotide is administered as an initial IV bolus of 50 µg followed by a continuous infusion of 50 µg/h* | (Garcia-Tsao, Lim, and Members of Veterans Affairs Hepatitis C Resource Center Program, 2009) | Not formally assessed |
| Octreotide- 100 ug bolus followed by 25-50 ug per hour* | (Farooqi *et al.*, 2007) | Not formally assessed |
| Octreotide 50µg bolus iv, then continuously 25–50 µg/hour iv* | (Fejfar, Vanasek, J Lata, *et al.*, 2017) | Not formally assessed |
| Dose of the vasoactive drug: somatostatin: should be administered as an intravenous bolus dose of 250 µg followed by a continuous infusion of 250 µg/h* | (Bittencourt *et al.*, 2017) | Not formally assessed |
| | (Farooqi *et al.*, 2007) | Not formally assessed |
| Somatostatin: continuous IV infusion of 250µg / h (500µg/h if active bleeding) preceded by bolus of 250µg* | (Jaime Bosch *et al.*, 2012) | Not formally assessed |
| Somatostatin: 250 µg/h in continuous infusion. Boluses of 250 µg/h (can be repeated up to three times in the first 3 h). Patients with active bleeding can benefit from double doses (500 ug/h) * | (Fernandez, Aracil, Sola, Soriano, Cinta Cardona, *et al.*, 2016) | Not formally assessed |
| Initially a bolus of 500 µg, afterwards 500 µg/h (6 mg/50 mL, 4.2 mL/h) by continuous infusion | (Reiberger, Puspok, *et al.*, 2017) | Not formally assessed |

| Treatment | Which guidelines support it | Strength of guideline |
|---|---|---|
| Somatostatin 250 µg bolus iv, then continuously 250–500 µg/hour iv* | (Fejfar, Vanasek, J Lata, *et al.*, 2017) | Not formally assessed |

Active haemorrhage management options that have been recommended by guidelines in just Domain 1. Abbreviations: µg= microgram, mg= milligram, iv= intravenous

| Therapy of choice | Which guideline supports this | Recommendation strength |
|---|---|---|
| Antibiotic prophylaxis should be initiated and should have a duration of 5-7 days | (Henry *et al.*, 2021) | Not formally assessed -referenced to a SR |
| | (Bittencourt *et al.*, 2017) | Not formally assessed |
| | (Rosolowski *et al.*, 2014) | Not formally assessed |
| | (Jaume Bosch *et al.*, 2012) | Not formally assessed |
| | (Garcia-Tsao, Lim, and Members of Veterans Affairs Hepatitis C Resource Center Program, 2009) | Not formally assessed -referenced an RCT |
| | (Farooqi *et al.*, 2007) | A1 |
| | (Garcia-Tsao, Arun J Sanyal, *et al.*, 2007) | A1 |
| | (Reiberger, Puspok, *et al.*, 2017) | A1 |
| | (Angeli *et al.*, 2018) | I:1 |
| | (Bosch, Juan G. Abraldes and Groszmann, 2003) | Not formally assessed -referenced a consensus document |
| | (Gow and Chapman, 2001) | Not formally assessed -referenced a meta-analysis |
| | (Sarin *et al.*, 2011) | 1a A |
| | (Mellinger and Volk, 2013) | class 1A recommendations, |
| | (Goshi and Stanley, 2005) | Not formally assessed |

| Therapy of choice | Which guideline supports this | Recommendation strength |
|---|---|---|
| | (Trebicka and Götz, 2018) | Not formally assessed |
| | (Chinese Society of Spleen and Portal Hypertension Surgery, 2019) | Not formally assessed |
| Quinolone antibiotic should be given first, but if they have severe liver disease/local quinolone resistance, then ceftriaxone should be given | (Garcia-Tsao, Arun J Sanyal, *et al.*, 2007) | A1 |
| | (Angeli *et al.*, 2018) | I:1 |
| | (Garcia-Tsao, Lim, and Members of Veterans Affairs Hepatitis C Resource Center Program, 2009) | Not formally assessed – referenced RCT |
| | (Jaume Bosch *et al.*, 2012) | Not formally assessed |
| Choice of antibiotics 1st line : ceftriaxone * | (Henry *et al.*, 2021) | Not formally assessed -(Goshi and Stanley, 2005)referenced to a SR |
| | (Farooqi *et al.*, 2007) | C1 |
| | (Sarin *et al.*, 2011) | 1Aa |
| | (Goshi and Stanley, 2005) | Not formally assessed |
| Choice of antibiotics 1st line : quinolone * | (Bosch, Juan G. Abraldes and Groszmann, 2003) | Not formally assessed -consensus document referenced |
| Choice of Ab: ceftriaxone or quinolone | (Rosolowski *et al.*, 2014) | Not formally assessed |
| | (Mellinger and Volk, 2013) | class 1A recommendations |
| Drug dosage of ceftriaxone:<br><br>Intravenous ceftriaxone 1 g/24 h for advanced liver disease | (Narváez-Rivera *et al.*, 2013) | Level 9 of agreement |
| | (Bittencourt *et al.*, 2017) | Not formally assessed |
| | (Garcia-Tsao, Lim, and Members of Veterans Affairs Hepatitis C Resource Center Program, 2009) | Not formally assessed -referenced RCT |
| | (Garcia-Tsao, Arun J Sanyal, *et al.*, 2007) | B1 |
| | (Angeli *et al.*, 2018) | I:1 |
| | (Sarin *et al.*, 2011) | 1Aa |
| | (Goshi and Stanley, 2005) | Not formally assessed |
| Quinolone dosage: | (Narváez-Rivera *et al.*, 2013) | Level 9 of agreement |

| Therapy of choice | Which guideline supports this | Recommendation strength |
|---|---|---|
| oral norfloxacin 400 mg every 12 h | | |
| | (Bittencourt *et al.*, 2017) | Not formally assessed |
| | (Garcia-Tsao, Arun J Sanyal, *et al.*, 2007) | A1 |
| | (Angeli *et al.*, 2018) | I:1 |
| | (Bosch, Juan G. Abraldes and Groszmann, 2003) | Not formally assessed -referenced a consensus document |

*Recommendations made in guidelines only assessed against Domain 1

Active haemorrhage management options that have been recommended by guidelines in just Domain 1. Abbreviations: mg= milligram.

| Treatment of choice | Guidelines supporting the recommendation | Strength of recommendation |
|---|---|---|
| Time to endoscopy :<6h | (Sarin *et al.*, 2011)(Sarin *et al.*, 2011) | 5D |
| Time to endoscopy:<br>Ideally less than 6h, but up to 12h | (Fernandez, Aracil, Sola, Soriano, Cinta Cardona, *et al.*, 2016) | Not formally assessed |
| | (Reiberger, Puspok, *et al.*, 2017) | C1 |
| | (Fejfar, Vanasek, J. Lata, *et al.*, 2017) | Not formally assessed -referenced guidelines |
| | (Cales *et al.*, 1991) | Not formally assessed |
| Time to endoscopy<br>(Bittencourt *et al.*, 2017)Up to 12h | (Henry *et al.*, 2021) | Not formally assessed – referenced guideline and guidance |
| | (Bittencourt *et al.*, 2017) | Not formally assessed |
| | (Narváez-Rivera *et al.*, 2013) | Level 9 of agreement |
| | (Rosolowski *et al.*, 2014) | Not formally assessed |
| | (Jaime Bosch *et al.*, 2012) | Not formally assessed |
| | (Angeli *et al.*, 2018) | II- 2:1 |
| | (Trebicka and Götz, 2018) | Not formally assessed |
| | (Garcia-Tsao, Arun J Sanyal, *et al.*, 2007) | A1 |
| | (Mellinger and Volk, 2013) | A1 |
| Patients that are unstable, endoscopy should be performed when it is safe to do so after resuscitation- they may need it urgently | (Garcia-Tsao, Lim, and Members of Veterans Affairs Hepatitis C Resource Center Program, 2009) | Not formally assessed |
| | (Farooqi *et al.*, 2007) | C1 |

Active haemorrhage management options that have been recommended by guidelines in just Domain 1.

| Endoscopy treatment type: | Which guidelines support this | Strength of recommendation |
|---|---|---|
| For oesophageal varices, VBL is the treatment of choice | (Bittencourt *et al.*, 2017) | Not formally assessed |
| | (Fernandez, Aracil, Sola, Soriano, Cardona, *et al.*, 2016) | Not formally assessed - referenced guideline |
| | (Narváez-Rivera *et al.*, 2013) | Level 9 of agreement |
| | (Rosolowski *et al.*, 2014) | Not formally assessed |
| | (Garcia-Tsao, Lim, and Members of Veterans Affairs Hepatitis C Resource Center Program, 2009) | Referenced to a RCT |
| | (Farooqi *et al.*, 2007) | A1 |
| | (Reiberger, Puspok, *et al.*, 2017) | A1 |
| | (Angeli *et al.*, 2018) | I:1 |
| | (Goshi and Stanley, 2005) | Not formally assessed |
| | (Fejfar, Vanasek, J. Lata, *et al.*, 2017) | Not formally assessed |
| | (Bosch, Juan G Abraldes and Groszmann, 2003) | Not formally assessed |
| | (Sarin *et al.*, 2011) | 1a,A |
| If VBL is not available, sclerotherapy can be done | | Not formally assessed |
| | (Fernandez, Aracil, Sola, Soriano, Cardona, *et al.*, 2016) | Not formally assessed |
| | (Garcia-Tsao, Lim, and Members of Veterans Affairs Hepatitis C Resource Center Program, 2009) | Not formally assessed -referenced to a RCT |
| | (Farooqi *et al.*, 2007) | A1 |
| | (Fejfar, Vanasek, J. Lata, *et al.*, 2017) | Not formally assessed |
| | (Sarin *et al.*, 2011) | 5D |
| Endoscopic sclerotherapy can be considered as a next step after vasoactive treatment therapy failure * | (D'Amico, Pagliaro and Bosch, 1999) | A1 - Quality of evidence: high, Strength of recommendation: strong |
| VBL or sclerotherapy is proposed treatment | (Gow and Chapman, 2001) | Not formally assessed |
| | (Mellinger and Volk, 2013) | class 1A recommendations, |

| Endoscopy treatment type: | Which guidelines support this | Strength of recommendation |
|---|---|---|
| | | which are based on multiple, high-quality, randomized, controlled trials or meta-analyses. |
| | (Chinese Society of Spleen and Portal Hypertension Surgery, 2019) | Not formally assessed |
| VBL or tissue adhesive as a treatment for varices* | (Trebicka and Götz, 2018) | Not formally assessed |
| For gastric varices, CA injection is the treatment of choice / tissue adhesives e.g. (e. g. N-butyl-cyanoacrylate/thrombin) | (Henry *et al.*, 2021) | Not formally assessed -reference RCT |
| | (Rosolowski *et al.*, 2014) | Not formally assessed |
| | (Farooqi *et al.*, 2007) | A1 |
| | (Farooqi *et al.*, 2016) | 1b,A |
| | (Bosch, Juan G Abraldes and Groszmann, 2003) | Not formally assessed |
| | (Sarin *et al.*, 2011) | 1bA |
| GOV1 can be treated with VBL* | (Narváez-Rivera *et al.*, 2013) | Level of agreement 9: expert opinions |
| | (Henry *et al.*, 2021) | Not formally assessed- RCTs referenced |
| Specifically, for cardio-fundal varices, tissue adhesives is the choice of treatment | (Henry *et al.*, 2021) | Not formally assessed |
| | (Garcia-Tsao, Lim, and Members of Veterans Affairs Hepatitis C Resource Center Program, 2009) | Not formally assessed -referenced 2 RCTs |
| | (Garcia-Tsao, Arun J Sanyal, *et al.*, 2007) | Class 1, level B |
| | (Reiberger, Puspok, *et al.*, 2017) | A1 |
| Repeat endoscopy in those that have initially failed endoscopic therapy | (Farooqi *et al.*, 2007) | (Recommendation grade BI) |
| | (Sarin *et al.*, 2011) | 5D |
| If patient is still bleeding despite endoscopic and pharmacological treatment, balloon tamponade / SB tube can be used for up to 24 hours as a bridge therapy until definitive therapy | (Bittencourt *et al.*, 2017) | Not formally assessed |
| | (Narváez-Rivera *et al.*, 2013) | Level 9 of agreement |
| | (Rosolowski *et al.*, 2014) | Not formally assessed |
| | (Jaime Bosch *et al.*, 2012) | Not formally assessed |

| Endoscopy treatment type: | Which guidelines support this | Strength of recommendation |
|---|---|---|
| | Garcia-Tsao, Lim, and Members of Veterans Affairs Hepatitis C Resource Center Program, 2009) | Not formally assessed -referenced one study |
| | (Farooqi *et al.*, 2007) | Class 1, level B |
| | (Garcia-Tsao, Arun J Sanyal, *et al.*, 2007) | Not formally assessed |
| | (Angeli *et al.*, 2018) | Not formally assessed |
| | (Fejfar *et al.*, 2017) | 5,D |
| | (Gow and Chapman, 2001) | Not formally assessed |
| | (Xu *et al.*, 2020) | Not formally assessed |
| | (Cales *et al.*, 1991) | Not formally assessed |
| | (Goshi and Stanley, 2005) | Not formally assessed |
| | (Trebicka and Götz, 2018) | Not formally assessed |
| Sengstaken-Blakemore tube for only 12h* | (Sarin *et al.*, 2011) | 1b B |
| An alternative to Sengstaken-Blakemore tube is an self-expanding covered oesophageal metal stents, which is sometimes preferred | (Bittencourt *et al.*, 2017) | Not formally assessed |
| | (Reiberger, Puspok, *et al.*, 2017) | B1 |
| | (Angeli *et al.*, 2018) | I;2 |
| | (Fejfar, Vanasek, J. Lata, *et al.*, 2017) | Not formally assessed- reference to: guideline, RCT and a study |
| | (Spaander *et al.*, 2021) | Strong recommendation, moderate quality evidence |
| Erythromycin prior to endoscopy to have a better view on endoscopy: | (Henry *et al.*, 2021) | Not formally assessed - RCT and guideline referenced |
| | (Jaime Bosch *et al.*, 2012) | Not formally assessed |
| | (Reiberger, Puspok, *et al.*, 2017) | A1 |
| | (Angeli *et al.*, 2018) | I: 2 |
| | (Fejfar, Vanasek, J. Lata, *et al.*, 2017) | Not formally assessed -guideline reference |
| | (Sarin *et al.*, 2011) | 2b,B |
| | (Trebicka and Götz, 2018) | Not formally assessed |
| | (Bittencourt *et al.*, 2017) | Not formally assessed |

| Endoscopy treatment type: | Which guidelines support this | Strength of recommendation |
|---|---|---|
| Erythromycin prior to endoscopy to have a better view on endoscopy: | (Henry *et al.*, 2021) | Not formally assessed -RCT referenced |
| | (Reiberger, Puspok, *et al.*, 2017) | A1 |
| | (Angeli *et al.*, 2018) | I:2 |
| | (Fejfar, Vanasek, J. Lata, *et al.*, 2017) | Not formally assessed – referenced a guideline |
| Erythromycin 125mg iv bolus 30min before* | (Jaime Bosch *et al.*, 2012) | Not formally assessed |

*Recommendations made in guidelines only assessed against Domain 1

Active haemorrhage management options that have been recommended by guidelines in just Domain 1. Abbreviations: VBL= variceal band ligation, CA= cyanoacrylate, GOV1= gastro-oesophageal varices type 1.

| Recommendation | What paper supports this | Strength of the recommendation |
|---|---|---|
| After endoscopic management, cross-sectional (MRI or CT) imaging with portal venous contrast phase should be obtained to determine vascular anatomy, including the presence or absence of portosystemic shunts and gastrorenal shunts | (Henry *et al.*, 2021) | Not formally assessed- expert opinion based |
| TIPS should be placed in patients with high risk of rebleeding as rescue therapy. This normally occurs as a result of failed pharmacology and endoscopic treatment. | (Fernandez, Aracil, Sola, Soriano, Cardona, *et al.*, 2016) | Not formally assessed |
| | (Narváez-Rivera *et al.*, 2013) | Level of agreement 9 |
| | (Jaume Bosch *et al.*, 2012) | GR: C |
| | (Garcia-Tsao, Lim, and Members of Veterans Affairs Hepatitis C Resource Center Program, 2009) | Not formally assessed - referenced 2 meta-analysis |
| | (Garcia-Tsao, Arun J Sanyal, *et al.*, 2007) | Class I, Level C (strong recommendation with weak evidence) |
| | (Angeli *et al.*, 2018) | I:1 |
| | (Fejfar, Vanasek, J. Lata, *et al.*, 2017) | Not formally assessed - referenced 2 guidelines |
| | (Boyer and Haskal, 2010) | Evidence I |
| | (Bosch, Juan G. Abraldes and Groszmann, 2003) | Not formally assessed |
| | (Gow and Chapman, 2001) | Not formally assessed |
| | (Sarin *et al.*, 2011) | 2aB |
| | (Goshi and Stanley, 2005) | Not formally assessed |
| | (Trebicka and Götz, 2018) | Not formally assessed |
| TIPS should be given to ongoing bleeding gastric varices if they do not respond to treatment | (Bittencourt *et al.*, 2017) | Not formally assessed |
| | (Boyer and Haskal, 2010) | Evidence II-3 |
| | (Bosch, Juan G. Abraldes and Groszmann, 2003) | Not formally assessed |
| | (Sarin *et al.*, 2011) | 2bB |
| Surgical diversion and surgery is restricted to child A patient | (Garcia-Tsao, Lim, and Members of Veterans Affairs Hepatitis C Resource Center Program, 2009) | Not formally assessed - referenced 2 studies |

| Recommendation | What paper supports this | Strength of the recommendation |
|---|---|---|
| | (Garcia-Tsao, Arun J Sanyal, *et al.*, 2007) | Class I, level A |
| | (Bosch, Juan G. Abraldes and Groszmann, 2003) | Not formally assessed |
| | (Sarin *et al.*, 2011) | 1bA |
| | (Farooqi *et al.*, 2007) | A1 |
| | (Bittencourt *et al.*, 2017) | Not formally assessed |
| In patients who have Child's C disease (C10-13) or MELD ≥19 or HVPG>20mmHg, and bleeding from oesophageal varices or GOV1 and GOV2 gastric varices and are haemodynamically stable, early or pre-emptive TIPSS should be considered within 72hours of a variceal bleed where local resources allow. | (Reiberger, Puspok, *et al.*, 2017) | A1 - oesophageal varices specifically |
| | (Reiberger, Puspok, *et al.*, 2017) | B1- for GOV2 and IGV1 |
| | (Garcia-Tsao, Arun J Sanyal, *et al.*, 2007) | Class I, level A |
| | (Angeli *et al.*, 2018) | I:2 |
| | (Fejfar, Vanasek, J. Lata, *et al.*, 2017) | Not formally assessed -referenced 3 different studies |
| | (Sarin *et al.*, 2011) | 1b;A |
| | (Xu *et al.*, 2020) | Not formally assessed |
| BRTO is a safe endovascular technique for GV if there are no comorbidities associated with PTHN for the presence of a gastrorenal shunt* | (Henry *et al.*, 2021) | Not formally assessed -references simple studies |
| | (Angeli *et al.*, 2018) | III;2 |
| | (Sarin *et al.*, 2011) | 2bB |
| BRTO can be used in the treatment for GOV.2/IGV1 in high risk patients | (Reiberger, Puspok, *et al.*, 2017) | B2 |

Active haemorrhage management options that have been recommended by guidelines in just Domain 1. Abbreviations: MRI= magnetic resonance imaging, CT= computerised tomongraphy, TIPS= transjugular intrahepatic portosystemic shunt, HVPG= hepatic venous pressure gradient, GOV1= gastro-oesophageal varices type 1, GOV2: = gastro-oesophageal varices type 2, BRTO= balloon occluded retrograde transvenous obliteration, GV= gastric varices, PTHN= portal hypertension, IGV1= isolated gastric varices type 1.

| Recommendation | What paper supports this | Strength of the recommendation |
|---|---|---|
| Cirrhotic patient with active bleeding from large high flow gastric varices, significant portal hypertension, and a MELD score of 14. CT demonstrates a large gastrorenal shunt<br>Procedure: Balloon- occluded retrograde transvenous obliteration (BRTO)* | (Kim *et al.*, 2020) | Strength of Evidence: STRONG<br>Rating: 8<br>Appropriateness scale: Usually appropriate |
| Cirrhotic patient with active bleeding from large high flow gastric varices, significant portal hypertension, and a MELD score of 14. CT demonstrates a large gastrorenal shunt.<br><br>Procedure: Endoscopic management* | (Kim *et al.*, 2020) | Strength of Evidence: STRONG<br>Rating: 8<br>Appropriateness scale: Usually appropriate |
| Cirrhotic patient with active bleeding from large high flow gastric varices, significant portal hypertension, and a MELD score of 14. CT demonstrates a large gastrorenal shunt.<br><br>Procedure: TIPS* | (Kim *et al.*, 2020) | Strength of Evidence: STRONG<br>Rating: 8<br>Appropriateness scale: Usually appropriate |
| Cirrhotic patient with active bleeding from large high flow gastric varices, significant portal hypertension, and a MELD score of 14. CT demonstrates a large gastrorenal shunt.<br><br>Procedure: Partial Splenic Embolization* | (Kim *et al.*, 2020) | Strength of Evidence: STRONG<br>Rating: 5<br>Appropriateness scale: May be appropriate |
| Cirrhotic patient with active bleeding from large high flow gastric varices, significant portal hypertension, and a MELD score of 14. CT demonstrates a large gastrorenal shunt. | (Kim *et al.*, 2020) | Strength of Evidence: STRONG<br>Rating: 4<br>Appropriateness scale: May be appropriate |

| Recommendation | What paper supports this | Strength of the recommendation |
|---|---|---|
| Procedure: Surgical management* | | |
| Cirrhotic patient with bleeding from large high flow gastric varices with a MELD score of 20. CT demonstrates a large gastrorenal shunt.<br><br>Procedure: BRTO* | (Kim *et al.*, 2020) | Strength of Evidence: Limited<br>Rating: 8<br>Appropriateness scale: Usually appropriate |
| Cirrhotic patient with bleeding from large high flow gastric varices with a MELD score of 20. CT demonstrates a large gastrorenal shunt.<br><br>Procedure: Endoscopic management* | (Kim *et al.*, 2020) | Strength of Evidence: Strong<br>Rating: 8<br>Appropriateness scale: Usually appropriate |
| Cirrhotic patient with bleeding from large high flow gastric varices with a MELD score of 20. CT demonstrates a large gastrorenal shunt.<br><br>Procedure: TIPS* | (Kim *et al.*, 2020) | Strength of Evidence: Limited<br>Rating: 6<br>Appropriateness scale: May be appropriate |
| Cirrhotic patient with bleeding from large high flow gastric varices with a MELD score of 20. CT demonstrates a large gastrorenal shunt.<br><br>Procedure: Partial splenic embolization* | (Kim *et al.*, 2020) | Strength of Evidence: Limited<br>Rating: 5<br>Appropriateness scale: May be appropriate |
| Cirrhotic patient with bleeding from large high flow gastric varices with a MELD score of 20. CT demonstrates a large gastrorenal shunt.<br><br>Procedure: Surgical Management* | (Kim *et al.*, 2020) | Strength of Evidence: Strong<br>Rating: 5<br>Appropriateness scale: May be appropriate |
| Cirrhotic patient bleeding from small, low flow gastric varices and moderate ascites with a MELD | (Kim *et al.*, 2020) | Strength of Evidence: Limited<br>Rating: 8<br>Appropriateness scale: Usually appropriate |

| Recommendation | What paper supports this | Strength of the recommendation |
|---|---|---|
| score of 18. MRI does not demonstrate a gastrorenal shunt.<br><br>Procedure: Endoscopic Management* | | |
| Cirrhotic patient bleeding from small, low flow gastric varices and moderate ascites with a MELD score of 18. MRI does not demonstrate a gastrorenal shunt.<br><br>Procedure: TIPS* | (Kim *et al.*, 2020) | Strength of Evidence: Limited<br>Rating: 7<br>Appropriateness scale: Usually appropriate |
| Cirrhotic patient bleeding from small, low flow gastric varices and moderate ascites with a MELD score of 18. MRI does not demonstrate a gastrorenal shunt.<br><br>Procedure: Partial splenic embolization* | (Kim *et al.*, 2020) | Strength of Evidence: Limited<br>Rating: 5<br>Appropriateness scale: May be appropriate |
| Cirrhotic patient bleeding from small, low flow gastric varices and moderate ascites with a MELD score of 18. MRI does not demonstrate a gastrorenal shunt.<br><br>Procedure: Surgical Management* | (Kim *et al.*, 2020) | Strength of Evidence: Strong<br>Rating: 4<br>Appropriateness scale: May be appropriate |
| Cirrhotic patient bleeding from large, high flow gastric varices with hepatic encephalopathy and a MELD score of 18. MRI demonstrates a large gastrorenal shunt<br><br>Procedure: BRTO* | (Kim *et al.*, 2020) | Strength of Evidence: Strong<br>Rating: 8<br>Appropriateness scale: Usually appropriate |

| Recommendation | What paper supports this | Strength of the recommendation |
|---|---|---|
| Cirrhotic patient bleeding from large, high flow gastric varices with hepatic encephalopathy and a MELD score of 18. MRI demonstrates a large gastrorenal shunt<br><br>Procedure: endoscopic management* | (Kim *et al.*, 2020) | Strength of Evidence: Limited<br>Rating: 8<br>Appropriateness scale: Usually appropriate |
| Cirrhotic patient bleeding from large, high flow gastric varices with hepatic encephalopathy and a MELD score of 18. MRI demonstrates a large gastrorenal shunt<br><br>Procedure: TIPS* | (Kim *et al.*, 2020) | Strength of Evidence: Limited<br>Rating: 4<br>Appropriateness scale: May be appropriate |
| Cirrhotic patient bleeding from large, high flow gastric varices with hepatic encephalopathy and a MELD score of 18. MRI demonstrates a large gastrorenal shunt<br><br>Procedure: Partial Splenic Embolization* | (Kim *et al.*, 2020) | Strength of Evidence: Strong<br>Rating: 5<br>Appropriateness scale: May be appropriate |
| Cirrhotic patient bleeding from large, high flow gastric varices with hepatic encephalopathy and a MELD score of 18. MRI demonstrates a large gastrorenal shunt<br><br>Procedure: Surgical Management* | (Kim *et al.*, 2020) | Strength of Evidence: Limited<br>Rating: 4<br>Appropriateness scale: May be appropriate |
| Cirrhotic patient bleeding from oesophageal varices and gastric varices not amenable to endoscopic management with a MELD score of 13 and a hepatic wedge pressure of 22 mmHg. CT demonstrates a small gastrorenal shunt. | (Kim *et al.*, 2020) | Strength of Evidence: Strong<br>Rating: 9<br>Appropriateness scale: Usually appropriate |

| Recommendation | What paper supports this | Strength of the recommendation |
|---|---|---|
| Procedure: TIPS* | | |
| Cirrhotic patient bleeding from oesophageal varices and gastric varices not amenable to endoscopic management with a MELD score of 13 and a hepatic wedge pressure of 22 mmHg. CT demonstrates a small gastrorenal shunt.<br><br>Procedure: Partial Splenic embolization* | (Kim *et al.*, 2020) | Strength of Evidence: Limited<br>Rating: 5<br>Appropriateness scale: may be appropriate |
| Cirrhotic patient bleeding from oesophageal varices and gastric varices not amenable to endoscopic management with a MELD score of 13 and a hepatic wedge pressure of 22 mmHg. CT demonstrates a small gastrorenal shunt.<br><br>Procedure: Surgical Management* | (Kim *et al.*, 2020) | Strength of Evidence: Limited<br>Rating: 5<br>Appropriateness scale: May be appropriate |
| Cirrhotic patient bleeding from large high flow gastric varices with a MELD score of 12 and a hepatic wedge pressure of 10 mmHg. MRI demonstrates a large gastrorenal shunt.<br><br>Procedure: BRTO* | (Kim *et al.*, 2020) | Strength of Evidence: Limited<br>Rating: 8<br>Appropriateness scale: Usually appropriate |
| Cirrhotic patient bleeding from large high flow gastric varices with a MELD score of 12 and a hepatic wedge pressure of 10 mmHg. MRI demonstrates a large gastrorenal shunt.<br><br>Procedure: Endoscopic Management* | (Kim *et al.*, 2020) | Strength of Evidence: Limited<br>Rating: 7<br>Appropriateness scale: Usually appropriate |
| Cirrhotic patient bleeding from large high flow gastric varices with a MELD score of 12 and a | (Kim *et al.*, 2020) | Strength of Evidence: Limited<br>Rating: 7<br>Appropriateness scale: Usually appropriate |

| Recommendation | What paper supports this | Strength of the recommendation |
|---|---|---|
| hepatic wedge pressure of 10 mmHg. MRI demonstrates a large gastrorenal shunt.<br><br>Procedure: TIPS* | | |
| Cirrhotic patient bleeding from large high flow gastric varices with a MELD score of 12 and a hepatic wedge pressure of 10 mmHg. MRI demonstrates a large gastrorenal shunt.<br><br>Procedure: Partial splenic embolization* | (Kim *et al.*, 2020) | Strength of Evidence: Limited<br>Rating: 5<br>Appropriateness scale: May be appropriate |
| Cirrhotic patient bleeding from large high flow gastric varices with a MELD score of 12 and a hepatic wedge pressure of 10 mmHg. MRI demonstrates a large gastrorenal shunt.<br><br>Procedure: surgical management* | (Kim *et al.*, 2020) | Strength of Evidence: Limited<br>Rating: 5<br>Appropriateness scale: May be appropriate |
| Acute variceal bleeding. Child-Pugh class B, cirrhotic with active oesophageal variceal haemorrhage, MELD 12.<br>previously treated with octreotide and variceal ligation on three prior occasions, no encephalopathy.<br><br>Therapy:<br><br>Endoscopic management, medical therapy with vasoactive drugs, Transjugular intrahepatic portosystemic shunt * | (Pinchot *et al.*, 2021) | Usually appropriate |

| Recommendation | What paper supports this | Strength of the recommendation |
|---|---|---|
| Acute variceal bleeding. Child-Pugh class C, cirrhotic with active oesophageal and junctional variceal haemorrhage,<br>previously treated with octreotide and endoscopic sclerotherapy, MELD 17, intermittent mild hepatic encephalopathy<br>managed as an outpatient with nutritional support<br><br>Therapy:<br><br>Endoscopic management, Medical therapy with vasoactive drugs, Transjugular intrahepatic portosystemic shunt* | (Pinchot *et al.*, 2021) | Usually appropriate |
| Acute variceal bleeding. Child-Pugh class C, cirrhotic with active oesophageal and junctional variceal haemorrhage,<br>previously treated with octreotide and endoscopic sclerotherapy, MELD 17, intermittent mild hepatic encephalopathy<br>managed as an outpatient with nutritional support<br><br>Therapy:<br>Coated oesophageal self-expandable metal stent, Surgical shunt* | (Pinchot *et al.*, 2021) | May be appropriate |
| Acute variceal bleeding. Child-Pugh class C, cirrhotic with hepatocellular carcinoma, branch portal vein tumour | (Pinchot *et al.*, 2021) | Usually appropriate |

| Recommendation | What paper supports this | Strength of the recommendation |
|---|---|---|
| thrombus, and active oesophageal and gastroesophageal type 1 (GOV1) variceal haemorrhage, MELD 24.<br><br>Therapy:<br><br>Medical therapy with vasoactive drugs, Percutaneous transhepatic embolization, endoscopic management * | | |
| Acute variceal bleeding. Child-Pugh class C, cirrhotic with hepatocellular carcinoma, branch portal vein tumour<br>thrombus, and active oesophageal and gastroesophageal type 1 (GOV1) variceal haemorrhage, MELD 24.<br><br>Therapy:<br><br>Coated oesophageal self-expandable metal stent, Transjugular intrahepatic portosystemic shunt* | (Pinchot *et al.*, 2021) | May be appropriate |

*Recommendations made by guidelines only assessed against Domain 1.

Active haemorrhage management options that have been recommended by guidelines in just Domain 1. Abbreviations:CT= computerised tomongraphy, TIPS= transjugular intrahepatic portosystemic shunt, BRTO= balloon occluded retrograde transvenous obliteration.

## Recommendations for Secondary Prophylaxis

| Secondary prophylaxis treatment | Guidelines | Strength of the recommendation |
|---|---|---|
| Patient should receive secondary prophylaxis upon discharge or day six of index bleed. | (Narváez-Rivera *et al.*, 2013) | Level 9 of agreement |
| | (Jaime Bosch *et al.*, 2012) | Grade A |
| | (Farooqi *et al.*, 2007) | A1 |
| | (Garcia-Tsao, Arun J Sanyal, *et al.*, 2007) | A1 |
| | (Mellinger and Volk, 2013) | A1 |
| | (Chinese Society of Spleen and Portal Hypertension Surgery, 2019) | Not formally assessed |
| Combination of NSBB and VBL is the choice of treatment for secondary prophylaxis | (Bittencourt *et al.*, 2017) | Not formally assessed |
| | (Narváez-Rivera *et al.*, 2013) | Level 9 of agreement |
| | (Rosolowski *et al.*, 2014) | Not formally assessed |
| | (Jaime Bosch *et al.*, 2012) | Grade A |
| | (Garcia-Tsao, Lim, and Members of Veterans Affairs Hepatitis C Resource Center Program, 2009) | Not formally assessed -referenced meta-analysis, and RCTs |
| | (Farooqi *et al.*, 2007) | A1 |
| | (Garcia-Tsao, Arun J Sanyal, *et al.*, 2007) | A1 |
| | (Reiberger, Puspok, *et al.*, 2017) | A2 |

| Secondary prophylaxis treatment | Guidelines | Strength of the recommendation |
|---|---|---|
| | (Angeli *et al.*, 2018) | I:1 |
| | (Fejfar, Vanasek, J. Lata, *et al.*, 2017) | Not formally assessed -referenced a couple of studies |
| | (Gow and Chapman, 2001) | Not formally assessed |
| | (Mellinger and Volk, 2013) | A1 |
| | (Trebicka and Götz, 2018) | Not formally assessed |
| | (Chinese Society of Spleen and Portal Hypertension Surgery, 2019) | Not formally assessed |
| Either NSBB or VBL can be used* | (Bosch, Juan G. Abraldes and Groszmann, 2003) | Not formally assessed -references a couple of studies |
| If the patient did not have primary prophylaxis previously , start the patient on NSBB | (D'Amico, Pagliaro and Bosch, 1999) | A1 |
| If there is NSBB failure, start them on both VBL and NSBB* | (D'Amico, Pagliaro and Bosch, 1999) | A1 |
| The choice of NSBB is usually propranolol or nadolol. Carvedilol is an alternative | (Bittencourt *et al.*, 2017) | No reference |
| In patients who cannot get/tolerate VBL or carvedilol or NSBB, any of these therapies can be maintained alone | (Trebicka and Götz, 2018) | Not formally assessed |
| If intolerant to VBL, combination of pharmacotherapy should be initiated e.g. NSBB and ISMN | (Garcia-Tsao, Lim, and Members of Veterans Affairs Hepatitis C Resource Center Program, 2009) | Not formally assessed -referenced RCTs |
| Propranolol should be administered in initial oral doses of 20-40 mg twice a day, titrated up to 160-320 mg/day<br><br>Dosage 80–160 mg/day * | (Bittencourt *et al.*, 2017) | Not formally assessed |
| | (Reiberger, Puspok, *et al.*, 2017) | A2 |

| Secondary prophylaxis treatment | Guidelines | Strength of the recommendation |
|---|---|---|
| NSBBs non-responders in secondary prophylaxis require close VBL intervals (every 2–4 weeks) till eradication. It can be used alone* | (Reiberger, Puspok, *et al.*, 2017) | A2 |
| NSBB intolerance, start on VBL | (D'Amico, Pagliaro and Bosch, 1999) | A1 |
| VBL is superior to sclerotherapy in secondary prophylaxis* | (Narváez-Rivera *et al.*, 2013) | Level 9 of agreement |
| | (Farooqi *et al.*, 2007) | B1 |
| | (Gow and Chapman, 2001) | Not formally assessed -referenced a meta-analysis |
| | (D'Amico, Pagliaro and Bosch, 1999) | A1 |
| VBL: performed every 2-4 weeks until variceal eradication is achieved. | (Bittencourt *et al.*, 2017) | Not formally assessed |
| | (Rosolowski *et al.*, 2014) | Not formally assessed |
| | (Farooqi *et al.*, 2007) | A1 |
| | (Garcia-Tsao, Arun J Sanyal, *et al.*, 2007) | C1 |
| | (Reiberger, Puspok, *et al.*, 2017) | Not formally assessed |
| On endoscopy, gastric varices should be treated prior to oesophageal varices* | (Reiberger, Puspok, *et al.*, 2017) | C1 |
| Either NSBBs in combination with repeated cyanoacrylate glue applications in cases of gastric varices* | (Reiberger, Puspok, *et al.*, 2017) | B1 |
| Small GOV1 can be treated with VBL and NSBB* | (Reiberger, Puspok, *et al.*, 2017) | B2 |

*Recommendations made by guidelines only assessed against Domain 1.

Active haemorrhage management options that have been recommended by guidelines in just Domain 1. Abbreviations: NSBB= non-selective beta blocker, VBL= variceal band ligation, GOV1= gastro-oesophageal varices type 1, ISMN= isosorbide mononitrate, mg= milligrams.

## Appendix 5: The results of the sensitivity analysis for the service evaluation

### Patient characteristic data

| Patient characteristics | Results |
|---|---|
| **Number of Patients, n (%)** | 141 |
| **Age in years, Mean (SD)** | 57.35 (14.71) |
| **Male n (%)** | 78 (55.32) |
| **MELDNa score, Mean (SD)** | 18.83 (7.91) |
| **CPT Class, n (%)**<br>**A**<br>**B**<br>**C** | <br>22 (15.60)<br>63 (44.68)<br>56 (39.72) |
| **Patients presenting outside of working hours, n (%)** | 83 (58.87) |

### Patients managed with Terlipressin

| Patient characteristics | Patient managed with Terlipressin | Patient managed without Terlipressin | p value |
|---|---|---|---|
| **Number of Patients, n (%)** | 127 (90.71) | 13 (9.29) | - |
| **Age in years, Mean (SD)** | 57.48 (14.54) | 53.69 (14.44) | 0.37 |
| **Male n (%)** | 69 (89.61) | 8 (10.39) | 0.62 |
| **MELDNa score, Mean (SD)** | 19.21 (7.87) | 15.77 (7.84) | 0.14 |
| **CPT Class, n (%)**<br>**A**<br>**B**<br>**C** | <br>15 (71.43)<br>59 (93.65)<br>53 (91.38) | <br>6 (28.57)<br>4 (6.35)<br>3 (5.38) | 0.004 |
| **Patients presenting outside of working hours, n (%)** | 74(90.24) | 8 (9.76) | 0.82 |

### Patients managed with Prophylactic Antibiotics

| Patient characteristics | Patient managed with Antibiotics | Patient managed without Antibiotics | p value |
|---|---|---|---|
| **Number of Patients, n (%)** | 132 (93.62) | 9 (6.38) | - |
| **Age in years, Mean (SD)** | 57.66 (14.64) | 52.89 (15.80) | 0.35 |
| **Male n (%)** | 74 (98.87) | 4 (5.13) | 0.50 |
| **MELDNa score, Mean (SD)** | 19.05(7.88) | 15.56 (8.05) | 0.20 |
| **CPT Class, n (%)**<br>**A**<br>**B** | <br>17 (77.27)<br>61 (96.83) | <br>5(22.73)<br>2(3.17) | 0.003 |

| | | | |
|---|---|---|---|
| **C** | 54 (96.43) | 2(3.57) | |
| **Patients presenting outside of working hours, n (%)** | 78 (93.98) | 5 (6.02) | 0.84 |

## Patients managed with endoscopic therapy: performed within 24 or above 24 hours

| **Patient characteristics** | **Patients with endoscopy< 24 hours** | **Patients with endoscopy> 24 hours** | **p value** |
|---|---|---|---|
| **Number of Patients, n (%)** | 59 (42.45) | 80 (57.55) | - |
| **Age in years, Mean (SD)** | 56.81 (12.84) | 57.63 (16.15) | 0.75 |
| **Male n (%)** | 30 (38.96) | 47 (61.04) | 0.35 |
| **MELDNa score, Mean (SD)** | 18.84 (7.61) | 18.9(8.24) | 0.97 |
| **CPT Class, n (%)**<br>**A**<br>**B**<br>**C** | <br>7 (31.82)<br>27 (43.55)<br>25 (45.45) | <br>15 (68.18)<br>35 (56.45)<br>30 (55.55) | 0.54 |
| **Patients presenting outside of working hours, n (%)** | 40 (49.38) | 41 (50.62) | 0.051 |

## Patients that have been managed with all three interventions in comparison to those that did not

| **Patient characteristics** | **Patients that had all of the therapies** | **Patients that did not have all of the therapies** | **p value** |
|---|---|---|---|
| **Number of Patients, n (%)** | 55 (39.01) | 86 (60.99) | - |
| **Age in years, Mean (SD)** | 57.24 (12.35) | 57.43 (16.10) | 0.94 |
| **Male n (%)** | 28 (35.90) | 50 (64.10) | 0.40 |
| **MELDNa score, Mean (SD)** | 18.93 (7.47) | 18.77(8.22) | 0.91 |
| **CPT Class, n (%)**<br>**A**<br>**B**<br>**C** | <br>5 (22.73)<br>26 (41.27)<br>24 (42.86) | <br>17 (77.27)<br>37 (58.73)<br>32 (57.14) | 0.23 |
| **Patients presenting outside of working hours, n (%)** | 38 (45.78) | 45 (54.22) | 0.048 |

## Patient characteristic data for patients with oesophageal varices

| Patient characteristics | Results |
|---|---|
| **Number of Patients, n (%)** | 114 |
| **Age in years, Mean (SD)** | 57.12 (15.12) |
| **Male n (%)** | 61 (53.51) |
| **Patients with oesophageal varices, n (%)**<br><br>Patients with oesophageal varices grade 1 (%)<br>Patients with oesophageal varices grade 2<br>Patients with oesophageal varices grade 3 | <br><br>30 (26.32)<br>65 (57.02)<br>19 (16.67) |
| **MELDNa score, Mean (SD)** | 18.96 (7.74) |
| **CPT Class, n (%)**<br>**A**<br>**B**<br>**C** | <br>16 (14.04)<br>54 (47.37)<br>44 (38.60) |
| **Patients presenting outside of working hours, n (%)** | 68 (59.65) |

## Patients with oesophageal varices managed with banding

| Patient characteristics | Patient had banding | Patient did not have banding | p value |
|---|---|---|---|
| **Number of patients with oesophageal varices, n (%)** | 84 (73.68) | 30 (26.32) | / |
| **Age in years, Mean (SD)** | 56.17 (15.08) | 59.73 (15.23) | 0.27 |
| **Male n (%)** | 41 (67.21) | 20 (32.79) | 0.092 |
| **Number of patients with oesophageal varices, n (%)**<br>**Grade 1**<br>**Grade 2** | <br>6 (20.00)<br>61 (93.85) | <br>24(80.00)<br>4 (6.15) | <br><0.001 |

| | | | |
|---|---|---|---|
| **Grade 3** | 17 (89.47) | 2 (10.53) | |
| **MELDNa score, Mean (SD)** | 19 (7.69) | 18.87 (8.03) | 0.94 |
| **CPT Class, n (%)**<br>**A**<br>**B**<br>**C** | <br>12 (75.00)<br>37 (68.52)<br>35 (79.55) | <br>4 (25.00)<br>17(31.48)<br>9 (20.45) | <br>0.46 |
| **Patients presenting outside of working hours, n (%)** | 50 (73.53) | 18 (26.32) | 0.964 |

## Patients with oesophageal varices that have or have not received all four therapies

| **Patient characteristics** | **OV patients that had all of the therapies** | **OV patients that did not have all of the therapies** | **p value** |
|---|---|---|---|
| **Number of Patients, n (%)** | 45(39.47) | 69 (60.53) | - |
| **Age in years, Mean (SD)** | 57.04 (12.87) | 57.14 (16.53) | 0.97 |
| **Male n (%)** | 21 (29.57) | 50 (70.43) | 0.24 |
| **Patients with oesophageal varices, n (%)**<br>**Grade 1**<br>**Grade 2**<br>**Grade 3** | <br>3 (10)<br><br>30 (46.15)<br><br>12 (63.16) | <br>27 (90)<br><br>35 (53.85)<br><br>7 (36.84) | <br><br><0.001 |
| **MELDNa score, Mean (SD)** | 19.2 (7.21) | 18.81 (8.12) | 0.79 |
| **CPT Class, n (%)**<br>**A**<br>**B**<br>**C** | <br>5 (31.25)<br>21 (38.89)<br>19 (43.18) | <br>11 (68.75)<br>33 (61.12)<br>25 (56.82) | <br>0.7 |
| **Patients presenting outside of working hours, n (%)** | 32 (47.06) | 36 (52.94) | 0.04 |