Managing cirrhosis with limited resources: perspectives from sub-Saharan Africa

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Cirrhosis represents the end stage of chronic liver disease. Sub-Saharan Africa, a resource-constrained region, has a high burden of chronic liver disease, with causes including chronic viral hepatitis, excessive alcohol use, and metabolic dysfunction-associated steatotic liver disease (MASLD), the risk of which is burgeoning. The development of liver cirrhosis predicts for morbidity and mortality, driven by both liver dysfunction and the consequences of portal hypertension. Compensated cirrhosis portends a better prognosis than decompensated cirrhosis, highlighting the need for the early diagnosis of cirrhosis and its causes. With resource challenges, the diagnosis and management of cirrhosis is demanding, but less costly and less invasive interventions with substantial benefits, ranging from simple blood tests to transient elastography, are feasible in such settings. Simple interventions are also available to manage the complex manifestations of decompensation, such as β blockers in variceal bleeding prophylaxis, salt restriction and appropriate diuretic use in ascites, and lactulose and generic rifaximin in hepatic encephalopathy. Ultimately, managing the underlying causative factors of liver disease is key in improving prognosis. Management demands expanded policy interventions to increase screening and treatment for hepatitis B and C and reduce alcohol use and the metabolic factors driving MASLD. Furthermore, the skills needed for more specialised interventions, such as transjugular intrahepatic portosystemic shunt procedures and even liver transplantation, warrant planning, increased capacity, and support for regional centres of excellence. Such centres are already being developed in sub-Saharan Africa, demonstrating what can be achieved with dedicated initiatives and individuals.

Introduction

Cirrhosis represents the end stage of chronic liver disease and is the leading cause of liver-related morbidity and mortality worldwide.[1] It is a histological diagnosis defined by the presence of nodules of regenerating hepatocytes surrounded by fibrous tissue.[2] Several clinical, biochemical, and haematological features can suggest cirrhosis, and non-invasive biomarkers have now effectively replaced liver biopsies in diagnosing cirrhosis.[3] The natural history of cirrhosis has two defined stages. First, compensated cirrhosis defines the period from the onset or diagnosis of cirrhosis to the first potential major complication. The prognosis of compensated cirrhosis is good, with a median survival exceeding 12 years.[4] The development of jaundice, ascites, variceal haemorrhage, or hepatic encephalopathy marks the transition from a compensated to a decompensated state (the second stage); prognosis becomes poorer, with a median survival of 3–5 years.[5] The transition from compensated to decompensated cirrhosis occurs at a rate of about 5–7% per year.[4] Approximately 58% of people with cirrhosis decompensate in 10 years, and ascites is the most common presentation.[6] Overall survival for people with compensated and decompensated cirrhosis, respectively, is 87% (95% CI 86·1–88·4) versus 75% (72·5–77·3) at 1 year, and 67% (64·5–68·5) versus 45% (42·1–48·7) at 5 years.[7] Conventionally, when defining decompensated cirrhosis, the Child–Pugh scoring system is used to grade severity, with serum albumin, bilirubin, prothrombin time, and the presence of ascites and hepatic encephalopathy as criteria.[8] The MELD score and now the MELD-Na (sodium) score, which use bilirubin, creatinine, prothrombin time, and (now) sodium as variables, are predictive of mortality and the need for liver transplantation in people with advanced liver disease.[9,10] In the USA in 2016, expenditure associated with managing liver disease was US$32·5 billion (95% CI 27·0–40·4 billion), with two-thirds spent on inpatient or emergency department care.[11] This cost increased by 4% point per year from 1996 to 2016, primarily driven by hospital-based services.

Managing liver cirrhosis and its complications in resource-limited settings is particularly challenging. Sub-Saharan Africa, with a population of 1·2 billion people and a substantial burden of chronic liver disease, is one such resource-limited region. Health expenditure per capita is approximately only $95·40 per year,[12] representing less than 2% of the average spent in high-income countries. Compounding this gap in expenditure is a health-care workforce shortage, with 2·9 physicians and 18·9 nurses per 10 000 population compared with a global mean of 16·7 physicians and 38·6 nurses per 10 000 population.[13] In this context, and from a sub-Saharan African perspective, this Review addresses, with available evidence, the epidemiology, causes, diagnosis, and best-practice management of liver cirrhosis.

Global epidemiology of cirrhosis

Compensated cirrhosis is asymptomatic so its prevalence is probably underestimated. The most accurate epidemiological data are for decompensated cirrhosis. Cirrhosis is the 11th leading cause of death worldwide and the tenth leading cause of death in Africa.[1] In 2017, cirrhosis caused more than 1·32 million deaths (95% uncertainty interval [UI] 1·27–1·45 million; 440 000 deaths [416 000–518 000; 33·3%] among women and 883 000 [838 000–967 000; 66·7%] among men).[14] Deaths due to cirrhosis constituted

	Hepatitis B		Hepatitis C		Alcohol-related liver disease		Metabolic dysfunction-associated steatotic liver disease		Other	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Global	31·5%	24·0%	25·5%	26·7%	27·3%	20·6%	7·7%	11·3%	8·0%	17·3%
Western sub-Saharan Africa	50·4%	45·7%	7·9%	7·6%	22·8%	13·4%	5·5%	7·7%	13·3%	25·5%
Central sub-Saharan Africa	33·2%	26·2%	32·5%	31·9%	18·6%	12·3%	5·0%	7·2%	10·7%	22·4%
Eastern sub-Saharan Africa	28·4%	21·7%	28·8%	29·1%	22·7%	16·3%	6·2%	8·3%	13·8%	24·6%
Southern sub-Saharan Africa	23·1%	19·7%	34·5%	32·9%	22·0%	15·6%	9·4%	9·7%	11·0%	22·1%

Adapted from the Global Burden of Diseases, Injuries, and Risk Factors Study 2017.[14] Male and female designation is according to documented sex.

Table 1: **Proportion of deaths in 2017 due to different causes of cirrhosis**

2·4% (95% UI 2·3–2·6) of total deaths globally in 2017 compared with 1·9% (1·8–2·0) in 1990. Despite an increase in the number of deaths, the age-standardised death rate decreased from 21·0 deaths per 100 000 population (95% UI 19·2–22·3) in 1990 to 16·5 deaths per 100 000 population (15·8–18·1) in 2017 and was lowest in high-income super-regions of the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2017 during this time.[14] Causes of cirrhosis vary in different regions of the world.[14] Decompensated cirrhosis accounts for a substantial proportion of liver-related morbidity, mortality, and resource use; therefore, prevention of cirrhosis through treatment of its causes is essential, notably in resource-limited settings.

Cirrhosis epidemiology in sub-Saharan Africa

GBD 2017 indicated that sub-Saharan Africa had the highest cirrhosis-related age-standardised death rate in the GBD super-regions at 32·2 deaths per 100 000 population (95% UI 25·8–38·6), compared with the global rate of 16·5 deaths per 100 000 population (15·8–18·1).[14] Age-standardised death rates in 2017 in the different sub-Saharan African regions were 35·8 deaths per 100 000 population (23·9–49·9) in western sub-Saharan Africa, 34·8 deaths per 100 000 population (26·4–42·2) in eastern sub-Saharan Africa, 34·3 deaths per 100 000 population (25·9–45·2) in central sub-Saharan Africa, and 11·6 deaths per 100 000 population (9·7–13·5) in southern sub-Saharan Africa. The global age-standardised disability-adjusted life-year (DALY) rate in 2017 was 510·7 per 100 000 population (95% UI 487·6–557·1). Across most regions of sub-Saharan Africa it was higher: 1018·9 DALYs per 100 000 population (795·5–1312·6) in central sub-Saharan Africa; 1001·9 DALYs per 100 000 population (684·4–1404·1) in western sub-Saharan Africa; 917·5 DALYs per 100 000 population (707·6–1105·0 in eastern sub-Saharan Africa; and 341·3 DALYs per 100 000 population (284·8–399·9) in southern sub-Saharan Africa.[14]

In 2017, chronic hepatitis C virus (HCV) infection was the most frequent cause of cirrhosis-related death in central, eastern, and southern sub-Saharan Africa (32·4%, 28·9%, and 33·9% of deaths, respectively).[14] Hepatitis B virus (HBV) infection was the second leading cause of cirrhosis-related death in central (31·2%), eastern (25·9%), and southern (21·9%) sub-Saharan Africa and the most frequent cause in western sub-Saharan Africa (48·9% of cirrhosis-related deaths). The proportion of deaths from HCV was much lower in this region at 7·8% (table 1). Other causes of cirrhosis included autoimmune liver diseases, toxin-induced acute liver failure related to use of traditional medicine, Khat ingestion, and vascular liver diseases. Overall, age-standardised prevalence per 100 000 population for compensated and decompensated cirrhosis was highest in western sub-Saharan Africa and lowest in southern sub-Saharan Africa (table 2).[14]

	Compensated cirrhosis	Decompensated cirrhosis
Global	1395·0 (1323·5–1470·5)	132·5 (128·6–136·2)
Western sub-Saharan Africa	1883·5 (1756·6–2010·9)	147·5 (143·3–151·9)
Eastern sub-Saharan Africa	1836·2 (1717·9–1958·3)	128·6 (124·8–132·4)
Central sub-Saharan Africa	1765·8 (1649·4–1885·5)	131·8 (127·8–136·1)
Southern sub-Saharan Africa	1029·0 (963·0–1096·8)	82·7 (80·4–85·0)

Data are prevalence per 100 000 population (95% UI). Adapted from the Global Burden of Diseases, Injuries, and Risk Factors Study 2017.[14] UI=uncertainty interval.

Table 2: **Age-standardised prevalence per 100 000 population for compensated and decompensated cirrhosis in 2017**

Causes of cirrhosis in sub-Saharan Africa

The frequencies of the various causes of compensated and decompensated cirrhosis are listed in table 3 for the different regions of sub-Saharan Africa.[14]

HBV

In the WHO African region, 82·3 million (95% UI 62·1–114·7 million) people are chronically infected with HBV. Of these people, only 1·8 million (1·4 –2·5 million) are diagnosed, with 110 000 (51 000–130 000) on treatment.[15] Approximately 4·3 million children younger than 5 years are HBsAg-positive and at higher risk of cirrhosis and hepatocellular carcinoma in early adulthood.[15–17] A 2020 systematic review and meta-analysis (22 cohorts across 13 countries, comprising 13 cohorts [3204 patients] with chronic HBV monoinfection and nine cohorts

	Compensated cirrhosis	Decompensated cirrhosis
Global		
Hepatitis B virus	32·6%	27·9%
Hepatitis C virus	24·7%	24·8%
Alcohol-related liver disease	21·0%	23·1%
MASLD	8·4%	8·6%
Other	13·3%	15·5%
Western sub-Saharan Africa		
Hepatitis B virus	39·3%	34·5%
Hepatitis C virus	11·2%	9·9%
Alcohol-related liver disease	13·6%	12·2%
MASLD	5·9%	5·4%
Other	30·0%	38·0%
Eastern sub-Saharan Africa		
Hepatitis B virus	21·2%	18·3%
Hepatitis C virus	29·3%	25·7%
Alcohol-related liver disease	13·7%	12·2%
MASLD	5·8%	5·4%
Other	30·0%	38·5%
Central sub-Saharan Africa		
Hepatitis B virus	30·7%	26·8%
Hepatitis C virus	25·2%	22·2%
Alcohol-related liver disease	11·8%	10·6%
MASLD	5·1%	4·7%
Other	27·2%	35·8%
Southern sub-Saharan Africa		
Hepatitis B virus	19·8%	17·3%
Hepatitis C virus	22·8%	20·0%
Alcohol-related liver disease	16·9%	15·3%
MASLD	10·2%	9·7%
Other	30·3%	37·7%

Adapted from the Global Burden of Diseases, Injuries, and Risk Factors Study 2017.[14] MASLD=metabolic dysfunction-associated steatotic liver disease.

Table 3: **Attributable frequencies of compensated and decompensated cirrhosis causes in 2017**

[688 patients] with HIV–HBV coinfection) assessed the prevalence of HBV-related cirrhosis in sub-Saharan Africa.[18] The pooled prevalence was 4·1% (95% CI 2·6–6·4) in primary care compared with 12·7% (8·6–18·3) in referral or tertiary care facilities (adjusted odds ratio [OR] 0·29, 95% CI 0·15–0·56).[18] Cofactors increasing the risk of HBV-related cirrhosis are untreated HIV–HBV or HBV–hepatitis D virus (HDV) coinfection.[19] HBV–HDV coinfection can progress to cirrhosis within 5 years.[20]

The greatest burden of HIV–HBV coinfection, with an estimated 1·9 million cases, is in sub-Saharan Africa.[15] The estimated prevalence of HDV coinfection in sub-Saharan Africa was 8·39% (95% CI 4·73–12·85) between 1995 and 2016, equating to approximately 9 million people.[21] The highest pooled seroprevalence in populations with liver disease was 37·77% (12·13–67·54) in central Africa followed by 9·57% (2·31–20·43) in west Africa.[21]

HCV

Despite the availability of curative antiviral therapy, only around 500 000 (95% UI 400 000–630 000) of the estimated 9 million (6–15 million) people infected with HCV in the WHO African region know their status.[22] A fraction of this number, or 23 000 (7700–29 000) people, have accessed therapy. Direct-acting antiviral therapies, where available, are either paid for out of pocket or through scarce state-funded programmes.[22] Countries, such as Rwanda, have initiated HCV elimination programmes,[23] and Ghana initiated an Egyptian-supported HCV elimination programme in 2023 (the Ghana HEAT Project).[24] Approximately 6·0% of people with HIV in sub-Saharan Africa have HCV coinfection, with rates varying from nearly 7·0% in western sub-Saharan Africa to 4·5% in southeast sub-Saharan Africa.[25] People with HIV–HCV coinfection have a three-fold greater risk of liver disease progression to cirrhosis than people monoinfected with HCV.[26] HIV-directed antiretroviral therapy attenuates the high rate of progression to cirrhosis, but the rate of disease progression in HIV–HCV coinfection continues to exceed that observed with HCV monoinfection.[27]

Alcohol

Median per-capita alcohol consumption in the WHO African region is estimated at 6·3 L per annum, with consumption increasing.[28] Commensurate with this increasing consumption, rates of alcohol-related liver disease, both directly and as a cofactor for cirrhosis, are rising.[12]

Metabolic dysfunction-associated steatotic liver disease

The prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) is estimated to be 13·5% for the general population in sub-Saharan Africa, but this value is likely to be an underestimate, considering the rising prevalence of obesity and type 2 diabetes across all regions of sub-Saharan Africa.[29,30] The prevalence of people with MASLD regularly using alcohol is increasing, and, according to studies outside of Africa, this combination constitutes a cumulative risk for the development of cirrhosis.[31,32] Multiple components of the metabolic syndrome independently affect the risk for severe liver disease. Alcohol use, at consumption levels less than the amount to define alcohol-related liver disease, is associated with increased liver disease severity in individuals with metabolic syndrome.[33]

Similarly, MASLD is increasing in prevalence among individuals with viral hepatitis.[34] In a study of 401 people with biopsy-proven MASLD, 179 of whom had HBV infection, a total of 83 pairs were successfully matched via propensity score matching. HBV infection (*vs* no HBV infection) was associated with a higher risk of liver fibrosis in people with MASLD (OR 3·140, 95% CI 1·479–6·663; p=0·003).[35] On multivariate regression analysis, hypertension (OR 2·640, 95% CI 1·091–6·368;

p=0·031), type 2 diabetes (4·939, 1·121–21·796; p=0·035), and elevated γ-glutamyl transferase concentrations (3·980, 1·735–9·132; p=0·001) were risk factors for liver fibrosis in the group with MASLD and HBV.[35] There are no data available from Africa on the interaction between MASLD and viral hepatitis.

Schistosomiasis as a cofactor for portal hypertension

Africa accounts for up to 90% of the global schistosomiasis burden, with an estimated 280 000 deaths annually.[36] Approximately 54 million people are infected with *Schistosoma mansoni*, the predominant cause of intestinal schistosomiasis in Africa. The pathophysiology involves inflammatory or fibrotic portal-obstructive vascular changes, with perihilar fibrosis leading to presinusoidal portal hypertension. The effect is non-cirrhotic portal hypertension with varices that leads to an estimated 130 000 annual deaths from upper gastrointestinal bleeding in people with schistosomiasis.[37] Schistosomiasis with concomitant chronic hepatitis B or C infection, causes advanced liver disease and worsens the outcome, with an increased mortality rate through an increased incidence of cirrhosis and hepatocellular carcinoma.[38]

Diagnosing cirrhosis and clinically significant portal hypertension

Diagnosing cirrhosis early and identifying clinically significant portal hypertension is key to potentially arresting the progression of disease and preventing complications. The gold standard diagnostic approach for clinically significant portal hypertension is demonstrating a gradient between the portal vein and hepatic vein (hepatic venous pressure gradient [HVPG]) of 10 mm Hg or higher, the threshold above which complications of portal hypertension develop. This approach is neither realistic, nor readily available or practised in many centres, especially in resource-limited settings. For real-world settings, we suggest a simple algorithm to diagnose cirrhosis (figure), thereby reducing the need for invasive investigations. This algorithm is especially applicable in resource-poor settings, where diagnoses can be strongly suggested by complete histories, physical examinations, and simple blood tests. Most patients with cirrhosis in sub-Saharan Africa present with decompensated cirrhosis, so clinically significant portal hypertension is implied and neither measurement of HVPG, nor a liver biopsy, would alter the diagnosis.

Biomarker-based tests used to rule in and rule out advanced liver fibrosis or cirrhosis are an important clinical decision-making tool. Table 4 denotes the cutoff values for a range of non-invasive tests. Among these tests, the aspartate aminotransferase (AST) to platelet ratio index (APRI) and fibrosis-4 (FIB-4) index are simple, inexpensive, and easy to calculate. The FIB-4 index, which uses age, alanine aminotransferase concentration,

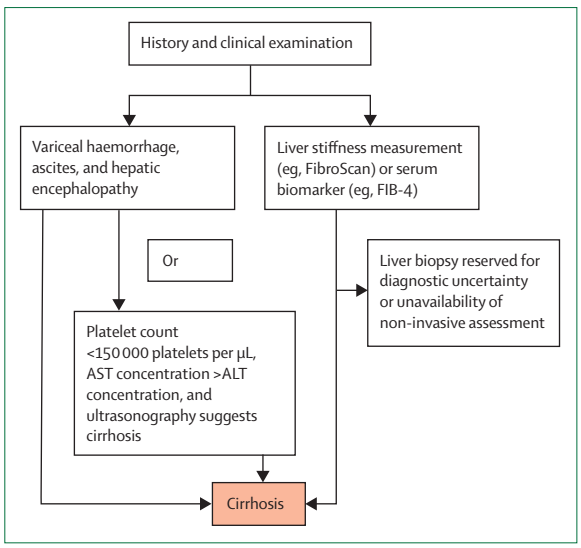

Figure: **A proposed algorithm for diagnosing cirrhosis in resource-limited settings**
ALT=alanine aminotransferase. AST=aspartate aminotransferase. FIB-4=fibrosis-4 index.

AST concentration, and platelet count, has been validated in HCV monoinfection, HCV–HIV coinfection, and MASLD.[45] For hepatitis C, a FIB-4 value of greater than 3·25 has a 97% specificity and a positive predictive value of 65% for advanced fibrosis.[46] The APRI score uses AST concentration and platelet count and has been validated in both chronic HBV and HCV infection.[47] A value of 0·5 or lower rules out clinically significant fibrosis and cirrhosis, and a value of 1·5 or higher rules in clinically significant fibrosis. An important concern is that biomarkers, in addition to other non-invasive assessments, have not been specifically validated in populations in sub-Saharan Africa. Data suggest that WHO-recommended cutoff values for APRI in people with chronic HBV in sub-Saharan Africa are not appropriate, with the cirrhosis threshold of greater than 2·0 set too high.[48] In sub-Saharan Africa, an APRI rule-in threshold of more than 0·65 (set for transient elastography liver stiffness measurement [LSM] >12·2 kPa) had a sensitivity of 56·2% and a specificity of 90·0% for predicting cirrhosis. A rule-out threshold of less than 0·36 had a sensitivity of 80·6% and a specificity of 64·3%.

Ultrasonography of the liver and portal vein allows for non-invasive assessment of the liver and portal circulation with portable technology. Ultrasonography enables direct imaging of the liver, hepatocellular carcinoma screening and diagnosis, and doppler examination of the portal vein and hepatic veins. Certain features, such as liver size and morphology, can point towards cirrhosis, whereas assessment of portal vein velocity and splenic size can signify portal hypertension. The presence of ascites is a surrogate for advanced hepatic fibrosis and the presence of clinically significant portal hypertension. In advanced fibrosis, hepatic vein waveforms change from a triphasic

	APRI* (low cutoff value)	APRI (high cutoff value)	FIB-4 (single cutoff value)	FIB-4 (low cutoff value)	FIB-4 (high cutoff value)	2D-SWE	VCTE	NFS
Hepatitis B[39–41]								
Clinically significant fibrosis (≥stage F2)	0·5	1·5	1·45	..	..	>7·91 kPa	>7–9 kPa	..
Sensitivity, % (95% CI)	78% (71–84)	36% (28–45)	..	..	..	88% (83–91)	76% (71–80)	..
Specificity, % (95% CI)	60% (50–69)	92% (90–95)	..	..	..	83% (78–88)	82% (75–87)	..
Cirrhosis (≥stage F4)	1·0	2·0	3·25	..	..	≥11·5 kPa	>11–14 kPa	..
Sensitivity, % (95% CI)	65% (55–73)	35% (22–49)	..	..	..	79·9% (41·4–100·0)	86% (81–90)	..
Specificity, % (95% CI)	75% (70–80)	89% (81–94)	..	..	..	93·3% (87·6–97·6)	87% (83–90)	..
Hepatitis C[41–43]								
Clinically significant fibrosis (≥stage F2)	0·5	1·5	..	1·45	3·25	>7·1 kPa	>7·1 kPa	..
Sensitivity, % (95% CI)	82% (77–86)	39% (32–47)	..	89% (79–95)	59% (43–73)	94·7% (85·1–99·9)	64% (50–70)	..
Specificity, % (95% CI)	57% (49–65)	92% (89–94)	..	42% (25–61)	74% (56–87)	52·0% (27·2–76·5)	87% (80–91)	..
Cirrhosis (≥stage F4)	1·0	2·0	..	..	..	>10·1 kPa	>12·5 kPa	..
Sensitivity, % (95% CI)	77% (73–81)	48% (41–56)	..	..	..	85·8% (74·0–95·1)	72% (72–77)	..
Specificity, % (95% CI)	78% (74–81)	94% (91–95)	..	..	..	87·8% (72·5–98·1)	80% (85–90)	..
MASLD[41,44]								
Clinically significant fibrosis (≥stage F2)	..	..	≥1·30	..	..	>7·1 kPa	≥8 kPa	>1·45
Sensitivity, % (95% CI)	..	..	76% (66–83)	..	..	93·8% (84·6–99·5)	90% (83–85)	76% (66–83)
Specificity, % (95% CI)	..	..	53% (40–66)	..	..	52·0% (23·0–80·4)	50% (37–63)	53% (40–66)
Advanced fibrosis or cirrhosis (≥stage F3)	..	..	≥2·67	..	..	≥9·2 kPa	≥12 kPa	≥0·68
Sensitivity, % (95% CI)	..	..	82% (69–91)	..	..	75·3% (45·2–97·5)	98% (90–100)	94% (85–99)
Specificity, % (95% CI)	..	..	43% (34–53)	..	..	87·8% (78·0–95·5)	36% (27–45)	16% (10–24)

Stages follow the METAVIR staging system. Available sensitivity and specificity values are indicated. 2D-SWE=two-dimensional shear-wave elastography. APRI=aspartate aminotransferase to platelet ratio index. FIB-4=fibrosis-4 index. MASLD=metabolic dysfunction-associated steatotic liver disease. NFS=Non-alcoholic fatty liver disease Fibrosis Score. VCTE=vibration-controlled transient elastography (eg, FibroScan). *APRI scores unique to sub-Saharan Africa are noted in this Review.

Table 4: **Disease-specific optimal cutoff values for non-invasive tests of clinically significant liver fibrosis or cirrhosis**

waveform to a biphasic or monophasic waveform.[49] A damping index (DI), as calculated by the minimum velocity/maximum velocity of downward hepatic venous flow, suggests high accuracy with an area under the receiver operating characteristic (AUROC) of 0·86 for the prediction of severe portal hypertension (HVPG ≥12 mm Hg), with a sensitivity of 75·9% and specificity of 81·8%, and positive and negative predictive values of 91·1% and 58·1%, respectively.[50] CT, more than MRI, has improved sensitivity and specificity for detecting small (sensitivity 58–89%, specificity 68–82%) and large (sensitivity 65–100%, specificity 97–100%) oesophageal varices. However, CT and MRI are expensive and access in sub-Saharan Africa is limited.[51]

For non-invasive real-time assessment of liver fibrosis and clinically significant portal hypertension, LSM using transient elastography is accurate in identifying advanced hepatic fibrosis and allows for the early identification of clinically significant portal hypertension and thus the risk for hepatic decompensation and liver-related mortality. Cirrhosis is, strictly speaking, a diagnosis made histologically. However, non-invasive assessment by transient elastography is usually done in lieu of liver biopsy to assess hepatic fibrosis. There is an increased risk of liver-related complications and death with fibrosis METAVIR stages F3 (bridging fibrosis) and F4 (cirrhosis) versus F0 to F2.[52] The F3 and F4 stages are also recognised as a continuum rather than as distinct stages. Therefore, the term compensated advanced chronic liver disease is used for asymptomatic patients with F3 and F4 stages on LSM. Furthermore, among people with compensated advanced chronic liver disease, two stages are identified to dichotomise patients on the basis of the presence or absence of clinically significant portal hypertension. By the so-called rule of five, LSM of less than 5 kPa represents a liver without fibrosis, LSM of less than 10 kPa excludes compensated advanced chronic liver disease, LSM of 10–15 kPa is suggestive of compensated advanced chronic liver disease, LSM of greater than 15 kPa is highly suggestive of compensated advanced chronic liver disease, and LSM of 20–25 kPa in the presence of a platelet count of less than 150 000 platelets per µL or a LSM of 25 kPa or higher diagnose clinically significant portal hypertension.[53] Several factors can influence LSM, including cholestasis, hepatitis flares, elevated right-heart pressures, and increased BMI (>30 kg/m²). Spleen stiffness measurement using transient elastography (with a 100 Hz probe) in people with chronic viral hepatitis can be used to rule out (<21 kPa) and rule in (>50 kPa) clinically significant portal hypertension.[54] Spleen stiffness measurement (<40·9 kPa for ruling out and >49·9 kPa for ruling in) has been validated in patients with MASLD for diagnosing clinically significant portal hypertension, with an AUROC of 0·95.[55]

In general (and for a variety of aetiologies), an LSM of greater than 10 kPa suggests advanced chronic liver disease and an LSM of greater than 12 kPa has a greater than 90% accuracy in predicting cirrhosis.[56] Normative values are guided by the cause of the underlying disease. Ultrasound machines can have elastography functions, which are helpful for simultaneously delivering both investigations. Baveno VII guidance recommends vibration controlled transient elastography (VCTE; FibroScan, Echosens; Paris, France) for monitoring people with advanced chronic liver disease and identifying the need for variceal screening endoscopy.[53] There are 88 FibroScan machines available across several countries in sub-Saharan Africa (Hassan Al Sahmarani, Echosens, Paris, France, personal communication). The option of 2D shear-wave elastography with Aixplorer (Hologic; Marlborough, MA, USA) has also been suggested.[53] Where access to endoscopic variceal screening is poor or the use of non-selective β blockers is contraindicated, patients with an LSM of less than 20 kPa and a platelet count of greater than 150×10^9 platelets per L (150 000 platelets per µL) can have their LSM re-evaluated annually and a screening endoscopy done only when LSM increases or platelets decrease past these thresholds.[53]

The importance of managing the cause of cirrhosis

Managing the primary causal factor for cirrhosis to arrest, if not reverse, ongoing fibrosis and cirrhosis is crucial in resource-constrained settings. Management includes achieving a sustained virological response for people with chronic HCV infection, suppression of HBV infection (in the absence of HDV coinfection), alcohol abstinence in alcohol-related liver disease, and weight loss in patients with MASLD. Eliminating the underlying causal factor potentially reduces HVPG, and hence clinically significant portal hypertension and the risk of liver decompensation. Among patients with chronic HCV infection and decompensated cirrhosis who achieve a sustained virological response on direct-acting antivirals, European follow-up data show long-term improvement of liver function and subsequent delisting from transplantation in around a third of people.[57] The risk of decompensation after delisting was low. Data supporting the treatment of HBV infection in people with cirrhosis, even when decompensated, were reported more than two decades ago, showing improvement in liver function following the initiation of lamivudine.[58] A 5-year paired-biopsy study of tenofovir treatment in people with chronic HBV infection found that 304 (87%) of 348 participants had histological improvement, 176 (51%) had fibrosis regression, and, of the 96 patients with cirrhosis at baseline, 71 (74%) no longer had cirrhosis.[59] In a 2022 study, 171 (60%) of 283 patients with decompensated HBV-related cirrhosis treated with entecavir for 120 weeks had recompensation and a stable improvement in liver function tests, validating the Baveno VII definition of recompensation.[60]

Alcohol abstinence in patients with alcohol-related cirrhosis and clinically significant portal hypertension significantly reduces the risk of liver decompensation (adjusted hazard ratio [HR] 0·391, 95% CI 0·276–0·555; p<0·001) and liver-related (0·428, 0·263–0·697; p<0·001) and all-cause (0·453, 0·300–0·686; p<0·001) mortality.[61] Abstinence improves prognosis across all stages of alcohol-related cirrhosis.[61] Similarly, lifestyle modification, including dietary changes and exercise, with the primary goal of weight loss, remains a first-line intervention for people with MASLD.[62,63] A 16-week diet and moderate exercise intervention in individuals with overweight or obesity (BMI ≥26 kg/m²), portal hypertension, and compensated cirrhosis resulted in a significant reduction in bodyweight and HVPG.[64] No decompensation occurred during follow-up, and Child–Pugh and MELD scores were unchanged.

Prevention and management of the complications of cirrhosis

Variceal bleeding

Primary and secondary prophylaxis

Prevention of the complications of portal hypertension is best exemplified with non-selective β blockers in the primary and secondary prevention of variceal bleeding. Non-selective β blockers or variceal band ligation are the first-line treatment options in primary prevention of bleeding in patients with oesophageal varices, with similar reductions in bleeding outcomes.[65] The choice of therapy for primary prevention should be individualised, and, in resource-limited settings, this choice is principally dependent on endoscopic capacity, the availability of endoscopic equipment and accessories, and technical expertise. Non-selective β blockers alter the natural history of cirrhosis by reducing all-cause mortality and complications,[66] making these drugs a particularly attractive option for the primary prevention of variceal bleeding in resource-limited settings. They also have the secondary prevention benefit of reducing the risk of variceal rebleeding when administered alone or, preferably, in combination with variceal ligation. The most widely available and affordable non-selective β blocker is propranolol, which is given to patients with portal hypertension at doses of 10–40 mg twice daily (maximum daily dose 160–320 mg, although due to adverse effects, these doses are infrequent). Propranolol has been linked to depressive side-effects.[67] Nadolol, compared with propranolol, has the advantage of being renally cleared and is less lipid soluble, reducing the risk of depressive side-effects.[68] Carvedilol is currently the preferred alternative to propranolol, with its added α_1-blockade properties that reduce intrahepatic resistance.[69] Carvedilol is initiated at a dose of 3·125 mg twice daily, increasing to 6·25 mg twice daily. The usual maintenance dose is 12·5 mg daily. At this dose, carvedilol is more costly than propranolol, but this cost might be offset by the superior efficacy of carvediol in reducing HVPG.[68]

Dose escalation of carvedilol to 25 mg daily might occasionally be necessary (titrated to symptoms, pulse rate, and blood pressure). Data support the use of carvedilol over propranolol in secondary variceal rebleeding prophylaxis and preventing further risk of non-bleeding decompensation, as shown by superior reduction in HVPG.[69] The PREDESCI study[70] on using β blockers to prevent the decompensation of cirrhosis in patients with clinically significant portal hypertension recognised that the most relevant endpoint in compensated cirrhosis is the prevention of decompensation, rather than managing the complications of variceal bleeding. The study used HVPG measurements, which are impractical in most resource-limited settings, but it did show a significantly greater percentage decrease in HVPG with carvedilol versus propranolol (16% *vs* 10%).[70] A 2023 Bayesian re-analysis of the PREDESCI study confirmed the clinical benefit and substantial gain in decompensation-free life-years with the use of β blockers; thus, the use of carvedilol in patients with clinically significant portal hypertension can be recommended in resource-constrained environments.[71] The goal of β blocker therapy is to initially reduce resting heart rate by 25% or to approximately 55–60 beats per min. Patients can easily be taught how to measure their heart rates. Side-effects of β blockers include fatigue, hypotension, cold extremities, depression, and erectile dysfunction. At clinic visits, the dose of β blockers can be reduced if systolic blood pressure is less than 90 mm Hg or on the basis of symptoms. Non-selective β blockers are a useful and relatively cheap intervention in the management of people with cirrhosis. In people with ascites, their use is recommended, with dose reduction or discontinuation in those who develop symptomatic hypotension or acute kidney injury.

Statins might have a role in management, as their safety profile has been established and their potential benefits in cirrhosis have been described.[72] They potentially lower HVPG,[72] might slow the progression of liver disease,[73] and are associated with reduction in the incidence of hepatocellular carcinoma.[74] Statins are not contraindicated in patients with compensated cirrhosis; however, evidence based on clinically relevant and measurable outcomes is scarce.[75] In people with metabolic syndrome, MASLD, or other cardiovascular risk factors, statins are advised. Recent data comparing 12 months of simvastatin plus rifaximin with a placebo in people with decompensated cirrhosis, showed no benefit in reducing the risk of acute or chronic liver failure or death.[76] Additional data from December, 2023, comparing atorvastatin at a daily dose of 10–20 mg for 6 months with a placebo in a group of people with Child-Pugh class A, B or C, showed that the treatment was safe but that there was no difference in mortality, risk of liver-related complications, or HVPG.[77] Some anti-inflammatory benefits were noted.[77] If statins are used in people with decompensated cirrhosis, monitoring is required and a maximum dose of 20 mg per day of simvastatin is advised.[78,79] Rosuvastatin has a better pharmacokinetic profile in people with cirrhosis, however no data exist for any specific benefits.

Control of variceal bleeding

A comprehensive approach to variceal bleeding is beyond the scope of this Review. Acute bleeds require prompt attention and basic principles of resuscitation must be applied. Ideally, patients should be managed in an intensive or high-care environment, but this approach is not always feasible given low critical care availability. Resuscitation should not be delayed, but transfusion of red blood cells should be judicious and targeted to a haemoglobin concentration of 7–8 g/dL.[80] Vasoactive therapies (eg, octreotide and terlipressin) should be used for 2–5 days. Empirical intravenous antibiotics, such as ceftriaxone at a daily dose of 1 g intravenously, reduce the risk of infection and rebleeding; benefits are greater in people with Child–Pugh B or C disease, but, in the absence of evidence, these antibiotics should be provided irrespective of a person's Child–Pugh grade.[81] Before endoscopy, intravenous proton-pump inhibitors can be initiated, as up to 20% of upper gastrointestinal bleeds in cirrhosis are not related to varices.[82] Proton-pump inhibitors should be continued only if a compelling endoscopic reason for their continuation is found. Endoscopy is key to management, so transfer to a centre where endoscopy is available is best, given the scarce endoscopy services available in sub-Saharan Africa. For example, in eastern sub-Saharan Africa, there is an estimated rate of one endoscopist per 400 000–2 million population and one functional gastroscope per 400 000–1·3 million population.[83] Before transfer, upper gastrointestinal bleeding in a patient with cirrhosis should be regarded as a variceal bleed until proven otherwise. The empirical use of vasoactive therapies and intravenous proton-pump inhibitors before transfer is justified.

Ascites

The pathophysiological pathways of portal hypertension drive a reduction in effective systemic arterial volume, thereby stimulating a neurohumoral response, including the renin–angiotensin–aldosterone, sympathetic, and antidiuretic (or arginine-vasopressin) systems.[84] The result is sodium and water retention and ultimately the development of ascites, one of the cardinal presentations of liver decompensation. Ascites has a prevalence of roughly 20%, and an annual incidence of approximately 1–4%, in patients with cirrhosis.[85] A key therapeutic goal in ascites management is an improvement in the patient's health-related quality of life. The initial diagnostic paracentesis is done to establish whether the ascitic fluid is related to portal hypertension (high serum ascites albumin gradient [>11 g/L]) or peritoneal infection or inflammation or malignancy (low serum ascites albumin gradient [<11 g/L]). In the presence of a low serum ascites albumin gradient, infections (including tuberculosis) must be excluded.[86] Diagnostic paracentesis

is mandatory in all patients with worsening ascites and should include white blood cell total and differential counts to assess for spontaneous bacterial peritonitis (ascitic fluid neutrophil count >250 cells per µL).

Management of ascites

With chronic management, initial steps should include advice on salt restriction and the introduction of an aldosterone antagonist, such as spironolactone, and a loop diuretic, such as furosemide. Simple, sensible, and easy-to-understand guidance on avoiding foods containing high salt content should be provided to patients. Across sub-Saharan Africa, spices and food enhancements (many with high salt contents) are often used in cooking and the avoidance of these enhancers should be specifically explained to patients. A target of 5·0–6·5 g (87–113 mmol sodium) of salt per day is a realistic goal in the outpatient setting.[87] Three randomised controlled trials have yielded conflicting data on whether to start patients on a combination of spironolactone and furosemide or sequential monotherapy.[85] Patient heterogeneity in trials accounts for the lack of clarity. A reasonable recommendation on first presentation of moderate or grade 2 ascites, characterised by a mild symmetrical abdominal distension, is monotherapy with spironolactone (starting at a dose of 100 mg per day and titrating to 400 mg per day, over 2–4 weeks as tolerated). With an inadequate response, or with severe, grade 3 ascites at presentation, combination therapy with furosemide (starting at a dose of 40 mg per day and slowly titrating to 160 mg per day, over a 2–4-week period) is advised. The higher top-end dose range of these medications is seldom achieved because of renal, electrolyte, and encephalopathic adverse effects. Simple and non-costly measures to assess response are key. Weight loss should not exceed 0·5 kg per day in people without peripheral oedema, and 1 kg per day in those with peripheral oedema. Simply weighing an individual frequently achieves this valuable clinical assessment.[85] Gynaecomastia, an adverse effect of spironolactone, can be managed by switching to eplerenone. This switch is not generally feasible due to high costs and the relative unavailability of the drug in low-income and middle-income countries. Amiloride can be used instead of spironolactone, as it is less expensive and more available. Monitoring electrolytes and renal function after initiating diuretics, and at follow-up visits, is clinically prudent.

Large-volume paracentesis in combination with spironolactone and furosemide is the standard of care for managing large-volume and refractory ascites. Neurohumoral responses driving post-paracentesis circulatory dysfunction and renal impairment are not greatly activated following a single paracentesis of 5 L or less, supporting the fact that simultaneous volume replacement is not required.[88] However, one study concluded that albumin administration reduced complications in people with acute-on-chronic liver failure when 5 L of ascites or less was tapped.[89] A reasonable approach in resource-constrained environments might be that, with a paracentesis of 5 L or less, plasma expanders should be limited to people with acute-on-chronic decompensation. When more than 5 L of ascites is removed without plasma volume expansion, renal impairment, hyponatraemia, and post-paracentesis circulatory dysfunction can occur. Pooled risk ratio (RR) data from older studies show a tendency of albumin being beneficial (pooled RR 0·23, 95% CI 0·03–1·64).[85] A pooled analysis of ten studies established that people with cirrhosis who received albumin after large-volume paracentesis had no difference in their risk of renal dysfunction compared with people receiving a replacement plasma expander (pooled RR 1·11, 95% CI 0·58–2·14).[90] Although there are additional benefits to albumin use,[91] if albumin is unavailable or too costly, plasma expanders are a reasonable alternative. In local practice, products such as gelofusine (succinylated gelatine) and voluven (hydroxyethyl starch) are used, given that the costs of a 100–200 mL bottle of 20% human albumin range from $40 to $250. Failure to gain ascites control with salt restriction, diuretics, and large-volume paracentesis requires consideration of a transjugular intrahepatic portosystemic shunt. At 12 months post-procedure, transjugular intrahepatic portosystemic shunts control ascites better than large-volume paracentesis, and patients are more likely to be ascites-free.[92] Transjugular intrahepatic portosystemic shunts primarily have a role in life-threatening variceal bleeds and refractory ascites, although several other indications exist. Cardiac disease, liver cysts, or uncontrolled sepsis constitute the major contraindications to transjugular intrahepatic portosystemic shunts (appendix pp 1–2). However, transjugular intrahepatic portosystemic shunts are costly, require enormous skill, and are not available in most countries in sub-Saharan Africa.

See Online for appendix

Spontaneous bacterial peritonitis

Antibiotic therapy should be empirical and guided by local practice, with antibiogram-based adjustments if cultures are positive. In most instances, daily intravenous ceftriaxone, which is widely available, is the empirical therapy of choice for spontaneous bacterial peritonitis. Converting to oral antibiotics after 48 h is reasonable if the clinical scenario allows for this. Repeat diagnostic paracentesis 48 h after initiating antibiotics is recommended, and a less than 25% reduction in polymorphonuclear leukocyte count should prompt re-evaluation of antimicrobial choices. Repeat paracentesis is an inexpensive intervention to optimise spontaneous bacterial peritonitis care and reduces 30-day mortality and improves 30-day transplant-free survival.[93] Albumin infusion, at 1·5 g/kg of bodyweight, in patients with spontaneous bacterial peritonitis within 6 h of presentation to hospital reduces renal impairment and mortality. A meta-analysis showed a reduction of renal impairment in

patients with spontaneous bacterial peritonitis (pooled OR 0·21 [95% CI 0·11–0·42]) with albumin use.[94] The pooled OR for mortality was 0·34 (0·19–0·60) with albumin use, with ORs for mortality in individual trials ranging from 0·16 to 0·55. Emergent data suggest that long-term weekly albumin administration in people with cirrhosis and ascites might improve survival, prevent complications, aid in the management of ascites, and reduce hospitalisations.[91] However, intravenous albumin administration remains costly and is not readily available in many countries. Weekly albumin administration in all patients with cirrhosis cannot currently be recommended in sub-Saharan Africa. Prophylaxis for spontaneous bacterial peritonitis is controversial, and randomised controlled trial data for Child–Pugh C cirrhosis established that norfloxacin did not reduce 6-month mortality but did show a survival benefit in people with low-protein ascites.[95]

Hepatorenal syndrome

Two forms of hepatorenal syndrome (HRS) are recognised: hepatorenal syndrome causing acute kidney injury (HRS-AKI), representing acute impairment in renal function, and HRS-non-AKI, representing functional kidney injury that does not meet criteria for AKI for more than 7 days in the absence of other causes of kidney disease.[96] HRS-AKI, in which kidney histology is typical, is the result of marked vasoconstriction of the renal afferent arterioles driven by marked splanchnic arteriolar vasodilation, a reduction in effective arterial blood volume, and an activation of vasoconstrictor factors primarily due to the resulting renal hypoperfusion.[97] HRS-AKI is associated with high morbidity and mortality and a median survival of 3 months or less,[98] and can be triggered by spontaneous bacterial peritonitis. Diagnosing HRS is challenging and warrants the exclusion of underlying parenchymal kidney disease. This exclusion is particularly difficult in people with associated metabolic risk factors. In resource-limited settings, prevention of HRS-AKI through the judicious use of albumin and early antibiotics in patients with spontaneous bacterial peritonitis is key. Liver transplantation remains the only definitive intervention. In the absence of liver transplant availability or access, or as a bridging means, the use of vasoconstrictors, including norepinephrine, terlipressin, and a combination of midodrine plus octreotide, shows some treatment benefit. These vasoactive therapies reduce splanchnic or peripheral vasodilation or both, increase mean arterial pressure, downregulate renin–aldosterone and sympathetic activation, and improve kidney perfusion.[99] In a randomised placebo-controlled trial, terlipressin was superior for completely reversing HRS-AKI compared with placebo.[100] However, this benefit came at the expense of a greater number of adverse effects in the terlipressin group, including pulmonary oedema and respiratory failure. Terlipressin is best avoided in people with clinical evidence of intravascular volume overload. The use of renal replacement therapy is best used as a bridge to definitive intervention, such as liver transplantation. However, renal replacement therapy could be used when other probable causes of AKI are a concern (eg, acute tubular necrosis).[97] Realistically, in areas where critical care resources are constrained, interventions such as renal replacement therapy and other supportive measures are in short supply.

For more on the **EncephalApp Stroop Test** see https://encephalapp.com/

Hepatic encephalopathy

Hepatic encephalopathy is a reversible syndrome observed in patients with acute or chronic liver disease, characterised by a wide spectrum of neuropsychiatric abnormalities.[101] Along with ascites and variceal haemorrhage, hepatic encephalopathy is one of the most serious complications of decompensated liver cirrhosis. Severe (ie, West Haven grade 3 or grade 4) hepatic encephalopathy in people with cirrhosis is associated with a mortality of more than 50% within a year.[102] Cerebral oedema with oxidative stress, inflammation, hyperammonaemia, and resulting disturbances of cerebral function underlie the pathophysiology of hepatic encephalopathy. Ammonia is among several neurotoxic substances that cause impairment of excitatory neurotransmission. Ammonia crosses the blood–brain barrier, where astrocyte glutamine synthetase converts it and glutamate into glutamine. Glutamine acts as an osmolyte and causes cerebral oedema. Measuring serum ammonia is controversial. First, values vary, even in healthy individuals, and they are influenced by collection methods, laboratory processing, and the individual's sex.[103] A normal ammonia measurement in a confused patient with cirrhosis should direct attention to alternative diagnoses. Elevated ammonia concentrations alone should not be used to diagnose hepatic encephalopathy, unless there are symptoms consistent with the diagnosis.[104] Assays for ammonia measurements are not readily available in laboratories in sub-Saharan Africa, and treatment for hepatic encephalopathy should be promptly started on clinical grounds alone. Smartphone-based applications, such as the EncephalApp Stroop Test, are helpful at the bedside, but hepatic encephalopathy is essentially a clinical diagnosis and does not require ammonia measurements.

Grading of hepatic encephalopathy is conventionally done with the West Haven criteria, ranging from mild grade 1 encephalopathy to severe grade 4 encephalopathy.[105] Diminished awareness of one's environment and response to stimuli, impaired sleep–wake cycles, and somnolence during the day are characteristic of the earlier stages of this condition. Personality changes might also be evident. Covert or minimal hepatic encephalopathy, characterised by neurocognitive impairment in attention, vigilence, and integrative function and for which there is no obvious clinical manifestation, is diagnosed on the basis of atypical behaviour on psychometric tests.[106] The effect of hepatic encephalopathy on an individual's quality of life can be marked. Key to the management of hepatic encephalopathy is the

identification and management of triggering or precipitating factors. These factors include sedative drugs, alcohol use, gastrointestinal haemorrhage, infection, dehydration, electrolyte abnormalities, and constipation.

The liberal use of the non-absorbable disaccharide lactulose is the cornerstone of hepatic encephalopathy management. Lactulose decreases intestinal transit time, increases ammonia uptake by colonic flora, and acidifies intestinal pH, which changes the composition of the gut microbiome to favour non-urease-producing bacteria, thereby reducing intestinal production of ammonia.[107] Restricting protein is no longer advised in hepatic encephalopathy and should not be a reason to limit the protein content of diets (the requirements being 1·0–1·5 g of protein per kg bodyweight per day).[108] For recurrent hepatic encephalopathy, rifaximin (550 mg twice a day), which alters the composition of the gut microbiome, is used in combination with lactulose. This combination reduces the risk of encephalopathy by 58% and hospitalisation by 50%, factors influencing overall quality of life.[109] Apart from addressing aggravating factors (infection, bleeding, hypokalaemia, etc), lactulose and rifaximin are the major therapeutic options in resource-constrained environments. Rifaximin, an old drug with a new purpose, is costly. Generic rifaximin products are available in several east and central African countries. L-ornithine L-aspartate can be used in patients with a suboptimal response to lactulose and rifaximin as it lowers ammonia concentrations by providing an alternative substrate for the urea cycle.[110] However, L-ornithine L-aspartate is also costly and largely unavailable in sub-Saharan Africa.

Nutrition

Nutrition is a neglected, yet important, aspect in the management of liver disease. The traditional focus is on dietary restrictions (particularly protein), rather than enhancement. In people with cirrhosis, malnutrition is multifactorial and can broadly be divided into inadequate intake, increased metabolic processes, and malabsorption.[111] In low-resource settings, malnutrition related to cirrhosis might be compounded by a high prevalence of adult patients who are at nutritional risk, with 61% of hospitalised patients assessed to be at risk of malnutrition in selected hospitals in Ghana, Kenya, and South Africa.[112] Nutritional assessment and management should form part of the comprehensive management of people with cirrhosis and requires a multidisciplinary approach. A cirrhosis-specific tool for nutritional screening, the Royal Free Hospital-Nutritional Prioritizing Tool, is suited to low-resource settings because it does not require costly investigations.[113] Simply, people with Child–Pugh C liver disease or a BMI of less than 18·5 kg/m² are at high nutritional risk and need not undergo formal nutritional screening. Once patients have been established as being at nutritional risk, a detailed nutritional management plan (geared to locally available foods) and supplements are the next step. Key principles of management are to aim for a caloric intake of 35–40 kcal/kg per day, a protein intake of 1·0–1·5 g/kg per day (dry bodyweight), and frequent meals (six times a day), with a bedtime snack; there is no need to restrict protein.[114] In many countries, beans, legumes, and fish are the most affordable protein-rich foods.

Sarcopenia

Sarcopenia represents a decline in skeletal muscle mass and function and is associated with a high incidence of complications in people with cirrhosis.[115] The pathogenesis of sarcopenia is multifactorial and includes muscle catabolism, elevated ammonia concentrations, insulin resistance, reduced testosterone, reduced growth hormones, and systemic inflammation. In low-income and middle-income countries in sub-Saharan Africa, sarcopenia is potentiated by food insecurity, chronic undernutrition, little leisure time, and physical inactivity.[116–118] Protein-calorie malnutrition in people with cirrhosis and portal hypertension contributes to sarcopenia. Sarcopenia and progressive frailty increase an individual's clinical vulnerability and likelihood of adverse health outcomes, including the risk of falls with fractures, incident disability, exhaustion, weakness, low physical activity, anorexia, weight loss, cachexia, physical and cognitive impairments, frequent hospitalisation, and mortality.[119]

Formally assessing for sarcopenia in resource-constrained environments relies on clinical acumen and simple tools. Nutrition is best assessed by a nutritionist or dietitian, but this option might be limited by resource constraints. Simple tools to formally assess loss of muscle strength include the hand grip strength test and the chair stand test. The hand grip strength test records a mean value (in kg) of three consecutive measurements of a person's dominant arm when gripping a dynamometer. The chair stand test involves counting the number of times a person can rise to a full standing position and then sit down in 30 s without any help from their hands. Both tests assess lean muscle mass depletion and low muscle strength. Hand grip strength is an independent factor of mortality in men with cirrhosis.[120] Suggested cutoffs for these tests have not been studied in a sub-Saharan African population of patients with cirrhosis so their use is reasonable but lacks validation. Imaging, such as CT or MRI scanning, can measure skeletal muscle and visceral and subcutaneous fat content. Again, availability and appropriate normative parameters for sub-Saharan African populations should be considered. Dual-energy x-ray absorptiometry should form part of assessments to measure bone density and fracture risk. Country-specific fracture risk assessment scores are available for some countries in sub-Saharan Africa and can be used if dual-energy x-ray absorptiometry is unavailable.[121]

Managing sarcopenia is challenging, as it is a marker of advancing liver disease; the presence of sarcopenia

influences liver transplantation risk and outcomes. Several measures can be used to aid nutrition and maintain muscle integrity. A study looking at night-time snacking for patients with HBV-related cirrhosis showed improvements in markers of sarcopenia and malnutrition-related complications within 3 months of intervention.[122] A sensible approach is thus to advise a protein intake of 1·2–2·0 g/kg per day, regular meals, and late-evening snacks (with approximately 50 g of carbohydrate) to protect against protein catabolism.[123] Exercise resistance training or strength training with weight or resistance bands has benefits. A randomised trial of people with compensated cirrhosis found that 12 weeks of resistance training increased people's muscle strength, with beneficial effects on general performance measures, compared with not changing activity level.[124] Recommending easy-to-implement and cost-neutral measures can have substantial benefits.

A randomised placebo-controlled study of 101 men with cirrhosis and low testosterone found that testosterone supplementation improved muscle and bone mass, increased haemoglobin, and reduced fat mass and glycated haemoglobin.[125] In such patients, cautious supplementation seems reasonable. Supplementation with vitamin D might be an effective and safe treatment option for patients with decompensated cirrhosis. A small study of people receiving branched-chain amino acids suggested an increase in skeletal muscle volume and strength in people with cirrhosis who were supplemented with vitamin D3 at a dose of 2000 international units once daily for 12 months.[126]

Screening for hepatocellular carcinoma

α-Fetoprotein measurement and ultrasonography are the foundation of surveillance for hepatocellular carcinoma, with elevated α-fetoprotein concentrations being highly predictive for hepatocellular carcinoma in the presence of a liver mass. A normal α-fetoprotein concentration, as seen in approximately 20% of patients with hepatocellular carcinoma,[127] does not exclude hepatocellular carcinoma. α-Fetoprotein concentrations fluctuate, but with a higher cutoff (eg, >20 ng/mL), specificity improves at the expense of sensitivity.[128] A longitudinal rise in α-fetoprotein concentration in an individual patient might also predict hepatocellular carcinoma.[129] Ultrasonography is the most available and accessible radiological tool for hepatocellular carcinoma screening in sub-Saharan Africa. It is operator-dependent but is a readily attainable skill and can potentially be performed as a point-of-care test. Ultrasonography plus α-fetoprotein testing can detect early-stage hepatocellular carcinoma with a 63% sensitivity compared with 45% sensitivity for ultrasonography alone.[130] Ultrasound is best performed at 6-monthly intervals in patients with cirrhosis. The major issue for resource-constrained settings is the need for cross-sectional imaging if a lesion is detected on ultrasonography. A 2022 review of hepatocellular carcinoma in sub-Saharan Africa suggested several interventions to address the heterogeneous nature of the challenges in detecting hepatocellular carcinoma.[131] These interventions included approaches to address the scarcity of specialised care, creating centres of excellence to offer diagnostics and treatment, upskilling primary care practitioners, enhancing awareness and education, and, crucially, putting focus on primary hepatocellular carcinoma prevention.

Liver transplantation in sub-Saharan Africa

Liver transplantation, which has excellent 1-year and 5-year survival,[132] is the only therapeutic option for patients with end-stage chronic liver disease with decompensation or acute liver failure. Indications for transplantation have expanded to include oncological disease, such as hepatocellular carcinoma and colorectal metastases, and several metabolic diseases, especially in the paediatric population. Liver transplantation remains a highly complex intervention with several contraindications requiring potential candidates to be carefully evaluated (appendix pp 4–5). With few overall resources, liver transplantation in sub-Saharan Africa faces several challenges, including wide socioeconomic disparity, several countries without brain-death and organ-donation legislation, shortages of skilled medical or surgical personnel and facilities, an infectious disease burden, and insecure access to and monitoring of immunosuppression. The burden of liver disease in sub-Saharan Africa drives people with resources to travel elsewhere for living donor liver transplantation, at high cost. Long-term follow-up in these cases might be suboptimal as physicians in people's home countries might have little experience in managing liver transplantation.

In sub-Saharan Africa, to our knowledge, only South Africa has established adult and paediatric liver transplantation programmes. Investing in liver transplantation programmes, despite their cost, has its benefits, and several countries are currently doing so. In December, 2021, Côte d'Ivoire performed their first living donor liver transplantation in Abidjan[133]—pioneered by local surgeons, with support from an Egyptian transplantation team and WHO. Similarly, in Sudan in July, 2022, a local team, with support from India, performed the first living donor liver transplantation in the public sector at the Ibn Sina Hospital in Khartoum.[134] This initiative was supported by the Ministry of Health in Sudan. Establishing and sustaining transplantation programmes requires careful planning, with national governmental and institutional support being essential. Developing a range of staff—from transplantation surgeons to interventional radiologists and laboratory technicians—is crucial and would have considerable collateral benefits for institutions and health-care systems.[135] Legal frameworks and national oversight for organ donation and transplantation, appropriate training

of transplantation teams, and transparent and equitable criteria for organ allocation are important to establish before creating a transplantation programme. Well designed, sustainable, and supported transplantation programmes in sub-Saharan Africa, with equal access for all citizens, will be an important step towards curtailing transplantation tourism and organ trafficking.

Future directions—enhancing capacity to manage chronic liver disease

Focus has mostly been on optimising care for people with cirrhosis in settings with limited resources. However, it is important to simultaneously build capacity so that care can progressively improve. Such capacity building includes interventions, such as point-of-care ultrasonography, transient elastography (eg, FibroScan), interventional endoscopy, and radiology skills. The World Gastroenterology Organisation has played an important role in upskilling clinicians, establishing train the trainers programmes, all designed to disseminate teaching skills to gastroenterologists who hold training positions in their own countries. In Africa, the World Gastroenterology Organisation has established training centres in Egypt, Morocco, Nigeria, Malawi, Kenya, Ethiopia, and Sudan.[136] The Gastroenterology Foundation of South Africa has also provided real-time training in transient elastography and point-of-care ultrasonography to gastroenterology and hepatology trainees from several sub-Saharan African countries. An aspect warranting specific intervention is the upskilling of interventional radiologists to perform transjugular intrahepatic portosystemic shunt procedures, given the widespread need for this intervention in variceal bleeding and other portal hypertension complications. Project ECHO is being used extensively in sub-Saharan Africa to build collegial networks and disseminate knowledge and up-to-date treatment practices for the management of liver diseases.

The management of cirrhosis in resource-constrained environments rests on three key aspects: prevention; early detection; and the strengthening of health-care systems. Prevention is encompassed in the elimination of HBV and HCV infection through vaccination, strategies to prevent mother-to-child transmission, and widespread screening, testing, and treatment. Public health interventions to reduce excess alcohol consumption and increase awareness and prioritisation of screening for MASLD in people with metabolic risk factors as part of general wellness interventions are key. Case finding of people with advanced liver fibrosis is fundamental, as managing the underlying causes of liver disease limits the risk of developing clinically significant portal hypertension and decompensation. All these interventions require health system strengthening. This strengthening, in tandem with capacity-building programmes, needs to be supported and expanded across sub-Saharan Africa, taking time, resources, and will. However, much can be done with mostly inexpensive interventions to improve the care of patients with cirrhosis in sub-Saharan Africa.

Search strategy and selection criteria

References for this Review were identified through searches of PubMed with the search terms "cirrhosis", "cirrhosis aetiology", "portal hypertension", "ascites", "variceal bleeding", "sarcopenia", "HRS-AKI", "nutrition in liver disease", and "sub-Saharan Africa" from Jan 1, 2000, to Jan 5, 2023. Authors' own files were also used for searches. Only papers published in English were accessed, although French-language papers were used by CT. The final reference list was generated on the basis of originality and relevance to the Review.

Contributors

MWS conceptualised this Review and edited the final manuscript. All authors contributed to the development, insights, and perspectives for this Review and the literature review. In addition, PSK provided editorial support and literature review. CWS provided additional technical support, literature searches, and input.

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References

1 Huang DQ, Terrault NA, Tacke F, et al. Global epidemiology of cirrhosis—aetiology, trends and predictions. *Nat Rev Gastroenterol Hepatol* 2023; **20:** 388–98.
2 Pellicoro A, Ramachandran P, Iredale JP, Fallowfield JA. Liver fibrosis and repair: immune regulation of wound healing in a solid organ. *Nat Rev Immunol* 2014; **14:** 181–94.
3 Berzigotti A, Tsochatzis E, Boursier J, et al. EASL clinical practice guidelines on non-invasive tests for evaluation of liver disease severity and prognosis—2021 update. *J Hepatol* 2021; **75:** 659–89.
4 D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol* 2006; **44:** 217–31.
5 Arroyo V, Moreau R, Kamath PS, et al. Acute-on-chronic liver failure in cirrhosis. *Nat Rev Dis Primers* 2016; **2:** 16041.
6 Ginés P, Quintero E, Arroyo V, et al. Compensated cirrhosis: natural history and prognostic factors. *Hepatology* 1987; **7:** 122–28.
7 Fleming KM, Aithal GP, Card TR, West J. All-cause mortality in people with cirrhosis compared with the general population: a population-based cohort study. *Liver Int* 2012; **32:** 79–84.
8 Child CG, Turcotte JG. Surgery and portal hypertension. *Major Probl Clin Surg* 1964; **1:** 1–85.
9 Kamath PS, Kim WR. The model for end-stage liver disease (MELD). *Hepatology* 2007; **45:** 797–805.
10 Goudsmit BFJ, Putter H, Tushuizen ME, et al. Validation of the model for end-stage liver disease sodium (MELD–Na) score in the Eurotransplant region. *Am J Transplant* 2021; **21:** 229–40.
11 Devarbhavi H, Asrani SK, Arab JP, Nartey YA, Pose E, Kamath PS. Global burden of liver disease: 2023 update. *J Hepatol* 2023; **79:** 516–37.
12 Spearman CW, Sonderup MW. Health disparities in liver disease in sub-Saharan Africa. *Liver Int* 2015; **35:** 2063–71.
13 Haakenstad A, Irvine CMS, Knight M, et al. Measuring the availability of human resources for health and its relationship to universal health coverage for 204 countries and territories from 1990 to 2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2022; **399:** 2129–54.

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14 GBD 2017 Cirrhosis Collaborators. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol* 2020; **5:** 245–66.

15 WHO. Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021. Geneva: World Health Organization, 2021.

16 Shimakawa Y, Yan HJ, Tsuchiya N, Bottomley C, Hall AJ. Association of early age at establishment of chronic hepatitis B infection with persistent viral replication, liver cirrhosis and hepatocellular carcinoma: a systematic review. *PLoS One* 2013; **8:** e69430.

17 Shimakawa Y, Lemoine M, Njai HF, et al. Natural history of chronic HBV infection in West Africa: a longitudinal population-based study from The Gambia. *Gut* 2016; **65:** 2007–16.

18 Surial B, Wyser D, Béguelin C, Ramírez-Mena A, Rauch A, Wandeler G. Prevalence of liver cirrhosis in individuals with hepatitis B virus infection in sub-Saharan Africa: systematic review and meta-analysis. *Liver Int* 2021; **41:** 710–19.

19 Ioannou GN, Bryson CL, Weiss NS, Miller R, Scott JD, Boyko EJ. The prevalence of cirrhosis and hepatocellular carcinoma in patients with human immunodeficiency virus infection. *Hepatology* 2013; **57:** 249–57.

20 Miao Z, Zhang S, Ou X, et al. Estimating the global prevalence, disease progression, and clinical outcome of hepatitis delta virus infection. *J Infect Dis* 2020; **221:** 1677–87.

21 Stockdale AJ, Chaponda M, Beloukas A, et al. Prevalence of hepatitis D virus infection in sub-Saharan Africa: a systematic review and meta-analysis. *Lancet Glob Health* 2017; **5:** e992–1003.

22 Shah R, Agyei-Nkansah A, Alikah F, et al. Hepatitis C virus in sub-Saharan Africa: a long road to elimination. *Lancet Gastroenterol Hepatol* 2021; **6:** 693–94.

23 Nisingizwe MP, Makuza JD, Janjua NZ, et al. The cascade of care for hepatitis C treatment in Rwanda: a retrospective cohort study of the 2017–2019 mass screening and treatment campaign. *Viruses* 2023; **15:** 2023.

24 Coalition for Global Hepatitis Elimination. Ghana HEAT Project. Oct 16, 2023. https://www.globalhep.org/resources/heat-hepatitis-evaluation-amplify-testing-project/ghana-heat-project (accessed Nov 24, 2023).

25 Rao VB, Johari N, du Cros P, Messina J, Ford N, Cooke GS. Hepatitis C seroprevalence and HIV co-infection in sub-Saharan Africa: a systematic review and meta-analysis. *Lancet Infect Dis* 2015; **15:** 819–24.

26 Graham CS, Baden LR, Yu E, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. *Clin Infect Dis* 2001; **33:** 562–69.

27 Thein HH, Yi Q, Dore GJ, Krahn MD. Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis. *AIDS* 2008; **22:** 1979–91.

28 WHO. Global status report on alcohol and health 2018. Geneva: World Health Organization, 2018.

29 Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease—meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016; **64:** 73–84.

30 Spearman CW, Afihene M, Betiku O, et al. Epidemiology, risk factors, social determinants of health, and current management for non-alcoholic fatty liver disease in sub-Saharan Africa. *Lancet Gastroenterol Hepatol* 2021; **6:** 1036–46.

31 Ginès P, Krag A, Abraldes JG, Solà E, Fabrellas N, Kamath PS. Liver cirrhosis. *Lancet* 2021; **398:** 1359–76.

32 Idalsoaga F, Kulkarni AV, Mousa OY, Arrese M, Arab JP. Non-alcoholic fatty liver disease and alcohol-related liver disease: two intertwined entities. *Front Med (Lausanne)* 2020; **7:** 448.

33 Åberg F, Helenius-Hietala J, Puukka P, Färkkilä M, Jula A. Interaction between alcohol consumption and metabolic syndrome in predicting severe liver disease in the general population. *Hepatology* 2018; **67:** 2141–49.

34 van Kleef LA, Choi HSJ, Brouwer WP, et al. Metabolic dysfunction-associated fatty liver disease increases risk of adverse outcomes in patients with chronic hepatitis B. *JHEP Rep* 2021; **3:** 100350.

35 Lv H, Jiang Y, Zhu G, et al. Liver fibrosis is closely related to metabolic factors in metabolic associated fatty liver disease with hepatitis B virus infection. *Sci Rep* 2023; **13:** 1388.

36 George NS, David SC, Nabiryo M, et al. Addressing neglected tropical diseases in Africa: a health equity perspective. *Glob Health Res Policy* 2023; **8:** 30.

37 Aula OP, McManus DP, Jones MK, Gordon CA. Schistosomiasis with a focus on Africa. *Trop Med Infect Dis* 2021; **6:** 109.

38 Omar HH. Impact of chronic schistosomiasis and HBV/HCV co-infection on the liver: current perspectives. *Hepat Med* 2019; **11:** 131–36.

39 WHO. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva: World Health Organization, 2015.

40 Wei H, Jiang H-Y, Li M, Zhang T, Song B. Two-dimensional shear wave elastography for significant liver fibrosis in patients with chronic hepatitis B: a systematic review and meta-analysis. *Eur J Radiol* 2020; **124:** 108839.

41 Herrmann E, de Lédinghen V, Cassinotto C, et al. Assessment of biopsy-proven liver fibrosis by two-dimensional shear wave elastography: an individual patient data-based meta-analysis. *Hepatology* 2018; **67:** 260–72.

42 WHO. Guidelines for the care and treatment of persons diagnosed with chronic hepatitis c virus infection. Geneva: World Health Organization, 2018.

43 Pawlotsky J-M, Negro F, Aghemo A, et al. EASL recommendations on treatment of hepatitis C: final update of the series. *J Hepatol* 2020; **73:** 1170–218.

44 Kjaergaard M, Lindvig KP, Thorhauge KH, et al. Using the ELF test, FIB-4 and NAFLD fibrosis score to screen the population for liver disease. *J Hepatol* 2023; **79:** 277–86.

45 Vallet-Pichard A, Mallet V, Nalpas B, et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. Comparison with liver biopsy and fibrotest. *Hepatology* 2007; **46:** 32–36.

46 Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology* 2006; **43:** 1317–25.

47 Wai C-T, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology* 2003; **38:** 518–26.

48 Johannessen A, Stockdale AJ, Henrion MYR, et al. Systematic review and individual-patient-data meta-analysis of non-invasive fibrosis markers for chronic hepatitis B in Africa. *Nat Commun* 2023; **14:** 45.

49 Joseph T, Madhavan M, Devadas K, Ramakrishnannair VK. Doppler assessment of hepatic venous waves for predicting large varices in cirrhotic patients. *Saudi J Gastroenterol* 2011; **17:** 36–39.

50 Kim MY, Jeong WK, Baik SK. Invasive and non-invasive diagnosis of cirrhosis and portal hypertension. *World J Gastroenterol* 2014; **20:** 4300–15.

51 Lipp MJ, Broder A, Hudesman D, et al. Detection of esophageal varices using CT and MRI. *Dig Dis Sci* 2011; **56:** 2696–700.

52 Sanyal AJ, Van Natta ML, Clark J, et al. Prospective study of outcomes in adults with nonalcoholic fatty liver disease. *N Engl J Med* 2021; **385:** 1559–69.

53 de Franchis R, Bosch J, Garcia-Tsao G, et al. Baveno VII—renewing consensus in portal hypertension. *J Hepatol* 2022; **76:** 959–74.

54 Rigamonti C, Cittone MG, Manfredi GF, et al. High reproducibility of spleen stiffness measurement by vibration-controlled transient elastography with a spleen-dedicated module. *Hepatol Commun* 2022; **6:** 3006–14.

55 Odriozola A, Puente Á, Cuadrado A, et al. High accuracy of spleen stiffness measurement in diagnosing clinically significant portal hypertension in metabolic-associated fatty liver disease. *Liver Int* 2023; **43:** 1446–57.

56 Papatheodoridi M, Hiriart JB, Lupsor-Platon M, et al. Refining the Baveno VI elastography criteria for the definition of compensated advanced chronic liver disease. *J Hepatol* 2021; **74:** 1109–16.

57 Perricone G, Duvoux C, Berenguer M, et al. Delisting HCV-infected liver transplant candidates who improved after viral eradication: outcome 2 years after delisting. *Liver Int* 2018; **38:** 2170–77.

58 Villeneuve JP, Condreay LD, Willems B, et al. Lamivudine treatment for decompensated cirrhosis resulting from chronic hepatitis B. *Hepatology* 2000; **31:** 207–10.

59 Marcellin P, Gane E, Buti M, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. *Lancet* 2013; **381:** 468–75.

60 Wang Q, Zhao H, Deng Y, et al. Validation of Baveno VII criteria for recompensation in entecavir-treated patients with hepatitis B-related decompensated cirrhosis. *J Hepatol* 2022; **77:** 1564–72.

61 Hofer BS, Simbrunner B, Hartl L, et al. Alcohol abstinence improves prognosis across all stages of portal hypertension in alcohol-related cirrhosis. *Clin Gastroenterol Hepatol* 2023; **21:** 2308–17.

62 Younossi ZM, Corey KE, Lim JK. AGA Clinical practice update on lifestyle modification using diet and exercise to achieve weight loss in the management of nonalcoholic fatty liver disease: expert review. *Gastroenterology* 2021; **160:** 912–18.

63 Sheka AC, Adeyi O, Thompson J, Hameed B, Crawford PA, Ikramuddin S. Nonalcoholic steatohepatitis: a review. *JAMA* 2020; **323:** 1175–83.

64 Berzigotti A, Albillos A, Villanueva C, et al. Effects of an intensive lifestyle intervention program on portal hypertension in patients with cirrhosis and obesity: the SportDiet study. *Hepatology* 2017; **65:** 1293–305.

65 Gluud LL, Krag A. Banding ligation versus beta-blockers for primary prevention in oesophageal varices in adults. *Cochrane Database Syst Rev* 2012; **15:** CD004544.

66 Rodrigues SG, Mendoza YP, Bosch J. Beta-blockers in cirrhosis: Evidence-based indications and limitations. *JHEP Rep Innov Hepatol* 2019; **2:** 100063.

67 Patten SB. Propranolol and depression: evidence from the antihypertensive trials. *Can J Psychiatry* 1990; **35:** 257–59.

68 Jachs M, Hartl L, Simbrunner B, et al. Carvedilol achieves higher hemodynamic response and lower rebleeding rates than propranolol in secondary prophylaxis. *Clin Gastroenterol Hepatol* 2023; **21:** 2318–26.

69 Gupta V, Rawat R, Shalimar, Saraya A. Carvedilol versus propranolol effect on hepatic venous pressure gradient at 1 month in patients with index variceal bleed: RCT. *Hepatol Int* 2017; **11:** 181–87.

70 Villanueva C, Albillos A, Genescà J, et al. β blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2019; **393:** 1597–608.

71 Rowe IA, Villanueva C, Shearer JE, et al. Quantifying the benefit of non-selective beta-blockers in the prevention of hepatic decompensation: a Bayesian re-analysis of the PREDESCI trial. *Hepatology* 2023; **78:** 530–39.

72 Abraldes JG, Albillos A, Bañares R, et al. Simvastatin lowers portal pressure in patients with cirrhosis and portal hypertension: a randomized controlled trial. *Gastroenterology* 2009; **136:** 1651–58.

73 Kamal S, Khan MA, Seth A. Beneficial effects of statins on the rates of hepatic fibrosis, hepatic decompensation, and mortality in chronic liver disease: a systematic review and meta-analysis. *Am J Gastroenterol* 2017; **112:** 1495–505.

74 Zou B, Odden MC, Nguyen MH. Statin use and reduced hepatocellular carcinoma risk in patients with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol* 2023; **21:** 435–44.

75 Moctezuma-Velazquez C, Abraldes JG. The role of statins in cirrhosis. *Curr Treat Options Cardiovasc Med* 2022; **20:** 316–35.

76 Pose E, Jiménez C, Zaccherini G, et al. LBO-01—Simvastatin plus rifaximin to prevent ACLF in patients with decompensated cirrhosis. A randomised, double-blind, placebo-controlled, phase-3 trial: the liverhope efficacy trial. *J Hepatol* 2023; **78** (suppl 1): S10–11 (abstr).

77 Kronborg TM, Schierwagen R, Trošt K. Atorvastatin for patients with cirrhosis. A randomized, placebo-controlled trial. *Hepatol Commun* **7:** e0332.

78 Pose E, Napoleone L, Amin A, et al. Safety of two different doses of simvastatin plus rifaximin in decompensated cirrhosis (LIVERHOPE-SAFETY): a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Gastroenterol Hepatol* 2020; **5:** 31–41.

79 Pereira G. Statins in patients with cirrhosis: a note of caution in the middle of hope. *Dig Med Res* 2020; **3:** 3.

80 García-Pagán JC, Reverter E, Abraldes JG, Bosch J. Acute variceal bleeding. *Semin Respir Crit Care Med* 2012; **33:** 46–54.

81 Wu CK, Wang JH, Lee CH, et al. The outcome of prophylactic intravenous cefazolin and ceftriaxone in cirrhotic patients at different clinical stages of disease after endoscopic interventions for acute variceal hemorrhage. *PLoS One* 2013; **8:** e61666.

82 Ardevol A, Ibañez-Sanz G, Profitos J, et al. Survival of patients with cirrhosis and acute peptic ulcer bleeding compared with variceal bleeding using current first-line therapies. *Hepatology* 2018; **67:** 1458–71.

83 Mwachiro M, Topazian HM, Kayamba V, et al. Gastrointestinal endoscopy capacity in eastern Africa. *Endosc Int Open* 2021; **9:** E1827–36.

84 Iwakiri Y, Trebicka J. Portal hypertension in cirrhosis: pathophysiological mechanisms and therapy. *JHEP Rep Innov Hepatol* 2021; **3:** 100316.

85 Aithal GP, Palaniyappan N, China L, et al. Guidelines on the management of ascites in cirrhosis. *Gut* 2021; **70:** 9–29.

86 Benmassaoud A, Freeman SC, Roccarina D, et al. Treatment for ascites in adults with decompensated liver cirrhosis: a network meta-analysis. *Cochrane Database Syst Rev* 2020; **1:** CD013123.

87 Garcia-Tsao G. Chapter 18: ascites. In: Boyer TD, Manns MP, Sanyal AJ, eds. Zakim and Boyer's hepatology, 6th edn. Saint Louis: WB Saunders, 2012: 283–95.

88 Peltekian KM, Wong F, Liu PP, Logan AG, Sherman M, Blendis LM. Cardiovascular, renal, and neurohumoral responses to single large-volume paracentesis in patients with cirrhosis and diuretic-resistant ascites. *Am J Gastroenterol* 1997; **92:** 394–99.

89 Arora V, Vijayaraghavan R, Maiwall R, et al. Paracentesis-induced circulatory dysfunction with modest-volume paracentesis is partly ameliorated by albumin infusion in acute-on-chronic liver failure. *Hepatology* 2020; **72:** 1043–55.

90 Kütting F, Schubert J, Franklin J, et al. Insufficient evidence of benefit regarding mortality due to albumin substitution in HCC-free cirrhotic patients undergoing large volume paracentesis. *J Gastroenterol Hepatol* 2017; **32:** 327–38.

91 Bernardi M, Angeli P, Claria J, et al. Albumin in decompensated cirrhosis: new concepts and perspectives. *Gut* 2020; **69:** 1127–38.

92 Wong F. Management of refractory ascites. *Clin Mol Hepatol* 2023; **29:** 16–32.

93 Goel A, Biewald M, Huprikar S, Schiano T, Im GY. A real-world evaluation of repeat paracentesis-guided management of spontaneous bacterial peritonitis. *J Clin Gastroenterol* 2017; **51:** 278–84.

94 Salerno F, Navickis RJ, Wilkes MM. Albumin infusion improves outcomes of patients with spontaneous bacterial peritonitis: a meta-analysis of randomized trials. *Clin Gastroenterol Hepatol* 2013; **11:** 123–30.

95 Moreau R, Elkrief L, Bureau C, et al. Effects of long-term norfloxacin therapy in patients with advanced cirrhosis. *Gastroenterology* 2018; **155:** 1816–27.

96 Ginès P, Solà E, Angeli P, Wong F, Nadim MK, Kamath PS. Hepatorenal syndrome. *Nat Rev Dis Primers* 2018; **4:** 23.

97 Nadim MK, Garcia-Tsao G. Acute kidney injury in patients with cirrhosis. *N Engl J Med* 2023; **388:** 733–45.

98 Loftus M, Brown RS Jr, El-Farra NS, et al. Improving the management of hepatorenal syndrome-acute kidney injury using an updated guidance and a new treatment paradigm. *Gastroenterol Hepatol* 2023; **19:** 527–36.

99 Angeli P, Bernardi M, Villanueva C, et al. EASL clinical practice guidelines for the management of patients with decompensated cirrhosis. *J Hepatol* 2018; **69:** 406–60.

100 Wong F, Pappas SC, Curry MP, et al. Terlipressin plus albumin for the treatment of type 1 hepatorenal syndrome. *N Engl J Med* 2021; **384:** 818–28.

101 Häussinger D, Dhiman RK, Felipo V, et al. Hepatic encephalopathy. *Nat Rev Dis Primers* 2022; **8:** 43.

102 Fichet J, Mercier E, Genée O, et al. Prognosis and 1-year mortality of intensive care unit patients with severe hepatic encephalopathy. *J Crit Care* 2009; **24:** 364–70.

103 Wang J, Zhang Y, Xiang Z. Changes of plasma blood ammonia levels of Chinese healthy people and the establishment of reference intervals. *Clin Lab* 2023; **69**.

104 Bajaj JS, Lauridsen M, Tapper EB, et al. Important unresolved questions in the management of hepatic encephalopathy: an ISHEN consensus. *Am J Gastroenterol* 2020; **115:** 989–1002.

105 Bajaj JS, Cordoba J, Mullen KD, et al. Review article: the design of clinical trials in hepatic encephalopathy—an International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) consensus statement. *Aliment Pharmacol Ther* 2011; **33:** 739–47.

106 Kappus MR, Bajaj JS. Covert hepatic encephalopathy: not as minimal as you might think. *Clin Gastroenterol Hepatol* 2012; **10:** 1208–19.

107 Nardelli S, Gioia S, Faccioli J, Riggio O, Ridola L. Hepatic encephalopathy—recent advances in treatment and diagnosis. *Expert Rev Gastroenterol Hepatol* 2023; **17:** 225–35.

108 American Association for the Study of Liver Diseases. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. *J Hepatol* 2014; **61:** 642–59.

109 Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med* 2010; **362:** 1071–81.

110 Butterworth RF, McPhail MJW. L-ornithine L-aspartate (LOLA) for hepatic encephalopathy in cirrhosis: results of randomized controlled trials and meta-analyses. *Drugs* 2019; **79** (suppl 1)**:** 31–37.

111 Lalama MA, Saloum Y. Nutrition, fluid, and electrolytes in chronic liver disease. *Clin Liver Dis* 2016; **7:** 18–20.

112 Blaauw R, Achar E, Dolman RC, et al. The problem of hospital malnutrition in the African continent. *Nutrients* 2019; **11:** 2028.

113 Morgan MY, Madden AM, Soulsby CT, Morris RW. Derivation and validation of a new global method for assessing nutritional status in patients with cirrhosis. *Hepatology* 2006; **44:** 823–35.

114 Bischoff SC, Bernal W, Dasarathy S, et al. ESPEN practical guideline: clinical nutrition in liver disease. *Clin Nutr* 2020; **39:** 3533–62.

115 Ebadi M, Bhanji RA, Mazurak VC, Montano-Loza AJ. Sarcopenia in cirrhosis: from pathogenesis to interventions. *J Gastroenterol* 2019; **54:** 845–59.

116 Militao EMA, Salvador EM, Uthman OA, Vinberg S, Macassa G. Food insecurity and health outcomes other than malnutrition in southern Africa: a descriptive systematic review. *Int J Environ Res Public Health* 2022; **19:** 5082.

117 Beyene SD. The impact of food insecurity on health outcomes: empirical evidence from sub-Saharan African countries. *BMC Public Health* 2023; **23:** 338.

118 Guthold R, Louazani SA, Riley LM, et al. Physical activity in 22 African countries: results from the World Health Organization STEPwise approach to chronic disease risk factor surveillance. *Am J Prev Med* 2011; **41:** 52–60.

119 Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* 2019; **48:** 16–31.

120 Sinclair M, Chapman B, Hoermann R, et al. Handgrip strength adds more prognostic value to the model for end-stage liver disease score than imaging-based measures of muscle mass in men with cirrhosis. *Liver Transpl* 2019; **25:** 1480–87.

121 Johansson H, Dela SS, Cassim B, et al. FRAX-based fracture probabilities in South Africa. *Arch Osteoporos* 2021; **16:** 51.

122 Han Z, Li R, Zhong Z, Piao Y, Guo R. Clinical effect of nighttime snacking on patients with hepatitis B cirrhosis. *Front Nutr* 2023; **9:** 999462.

123 Dhaliwal A, Armstrong MJ. Sarcopenia in cirrhosis: a practical overview. *Clin Med* 2020; **20:** 489–92.

124 Aamann L, Dam G, Borre M, et al. Resistance training increases muscle strength and muscle size in patients with liver cirrhosis. *Clin Gastroenterol Hepatol* 2020; **18:** 1179–87.

125 Sinclair M, Grossmann M, Hoermann R, Angus PW, Gow PJ. Testosterone therapy increases muscle mass in men with cirrhosis and low testosterone: a randomised controlled trial. *J Hepatol* 2016; **65:** 906–13.

126 Okubo T, Atsukawa M, Tsubota A, et al. Effect of vitamin D supplementation on skeletal muscle volume and strength in patients with decompensated liver cirrhosis undergoing branched chain amino acids supplementation: a prospective, randomized, controlled pilot trial. *Nutrients* 2021; **13:** 1874.

127 Collier J, Sherman M. Screening for hepatocellular carcinoma. *Hepatology* 1998; **27:** 273–78.

128 Gupta S, Bent S, Kohlwes J. Test characteristics of alpha-fetoprotein for detecting hepatocellular carcinoma in patients with hepatitis C. A systematic review and critical analysis. *Ann Intern Med* 2003; **139:** 46–50.

129 Galle PR, Foerster F, Kudo M, et al. Biology and significance of alpha-fetoprotein in hepatocellular carcinoma. *Liver Int* 2019; **39:** 2214–29.

130 Tzartzeva K, Obi J, Rich NE. Surveillance imaging and alpha fetoprotein for early detection of hepatocellular carcinoma in patients with cirrhosis: a meta-analysis. *Gastroenterology* 2018; **154:** 1706–18.

131 Spearman CW, Dusheiko G, Jonas E, et al. Hepatocellular carcinoma: measures to improve the outlook in sub-Saharan Africa. *Lancet Gastroenterol Hepatol* 2022; **7:** 1036–48.

132 Lucey MR, Furuya KN, Foley DP. Liver transplantation. *N Engl J Med* 2023; **389:** 1888–900.

133 Awuah WA, Ng JC, Bulut HI, et al. The unmet need of organ transplantation in Africa. *Int J Surg* 2023; **109:** 519–20.

134 International Liver Transplantation Society. Setting up a liver transplant program in Sudan. International Liver Transplantation Society, Aug 12, 2022. https://ilts.org/news/setting-up-a-liver-transplant-program-in-sudan/ (accessed Dec 4, 2023).

135 Spearman CW, McCulloch MI. Challenges for paediatric transplantation in Africa. *Pediatr Transplant* 2014; **18:** 668–74.

136 World Gastroenterology Organisation. WGO training centres. World Gastroenterology Organisation, 2023. https://www.worldgastroenterology.org/education-and-training/training-centers. (accessed July 31, 2023).