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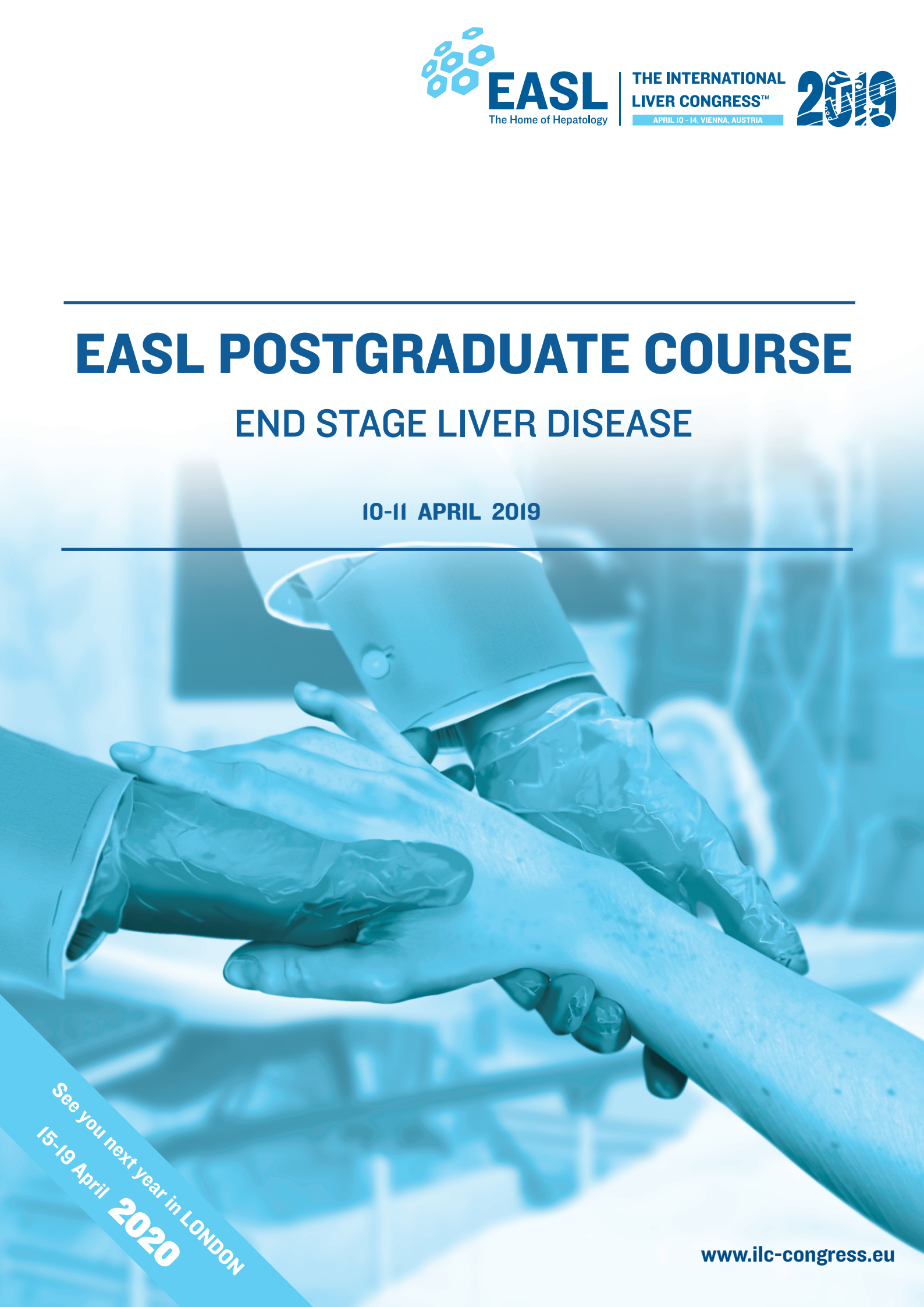
EASL POSTGRADUATE COURSE

END STAGE LIVER DISEASE

10-11 APRIL 2019



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MAT METABOLISM, ALCOHOL & TOXICITY

VH VIRAL HEPATITIS

CA CHOLESTASIS & AUTOIMMUNE

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Fields

- Liver transplant and surgery
- Public health
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- Imaging and interventional

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Welcome message from the course organisers

On behalf of the European Association for the Study of the Liver (EASL), we are delighted to welcome you to Vienna for the ILC 2019 PGC course on “End stage liver disease”.

In recent years, there has been growing interest in the mechanisms and management of end stage liver diseases. A new entity termed-acute-on chronic liver failure (ACLF), a syndrome characterized by the development of organ failures other than the liver and which is associated with high mortality rates has been defined. Some of the complex interactions between cirrhosis and other organs/ systems have been clarified. Mechanisms involved in the progression to end stage cirrhosis including bacterial infections, systemic inflammation and coagulation changes have been extensively explored. Therapeutic options such as rescue transplantation which was not used in the past in patients with end stage cirrhosis and organ failures because of being considered too sick are now increasingly used. Pushing the limits of transplantation in patients with organ failures is now widely accepted in selected cases.

During this postgraduate course, experts will discuss new tools in the diagnosis of cirrhosis and portal hypertension, new insights in bleeding and thrombosis, the growing impact of comorbidities, management of bacterial infections in the context of multi-drug resistance, revisited definitions of acute kidney injury in cirrhosis, new options in the management of encephalopathy, ACLF and transplantation in the sickest patients. Importantly, as organs other than the liver are involved in the progression of chronic liver disease, a multidisciplinary approach is needed. We have deliberately included experts coming from specialties other than hepatology but with a strong implication in the management of liver disease in the course to expand the scope of presentations and discussions. In order to make the program more interactive with the audience, the backbone of the sessions will be a clinical case presentation.

The organizers and the faculty wish you an enjoyable time in Vienna and they hope you find the course informative and interactive.

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Schedule

WEDNESDAY 10 April 2019

Diagnosis of cirrhosis and portal hypertension: non-invasive or invasive tests?

Chairs:
Tilman SAUERBRUCH, *Germany*
Annalisa BERZIGOTTI, *Switzerland*
François DURAND, *France*
Pere GINÈS, *Spain*

11:30-11:35	**Opening and presentation of the PGC** Annalisa BERZIGOTTI, *Switzerland* François DURAND, *France* Pere GINÈS, *Spain*
11:35-11:45	**Presentation of the clinical case and key questions regarding the challenge** Isabel GRAUPERA, *Spain*
11:45-12:05	**Are serum markers and liver stiffness tests sufficient to diagnose cirrhosis?** Laurent CASTERA, *France*
12:05-12:25	**Imaging diagnosis of cirrhosis** Valérie VILGRAIN, *France*
12:25-12:45	**Information provided by liver biopsy in the diagnosis of cirrhosis** Ian WANLESS, *Canada*
12:45-13:05	**Hepatic venous pressure measurement and splanchnic hemodynamics** Virginia HERNANDEZ-GEA, *Spain*
13:05-13:30	**Panel discussion**
13:30-14:00	**Lunch**

Bleeding and thrombosis

Chairs:
Jaime BOSCH, *Spain*
Annalisa BERZIGOTTI, *Switzerland*

14:00-14:05	**Presentation of the clinical case and key questions regarding the challenge** Mattias MANDORFER, *Austria*
14:05-14:20	**Prevention of variceal bleeding and medical management of acute variceal bleeding** Juan-Carlos GARCIA-PAGAN, *Spain*

14:20-14:35	**When to use TIPS in gastrointestinal bleeding?** Karel CACA, *Germany*
14:35-14:50	**Coagulation changes in cirrhosis: from bleeding to prothrombotic state** Marco SENZOLO, *Italy*
14:50-15:05	**Portal vein thrombosis in cirrhosis: who should be treated and how?** Erica VILLA, *Italy*
15:05-15:30	**Panel discussion**
15:30-16:00	**Coffee break**

Cirrhosis and Comorbidities

Chairs:
Frank LAMMERT, *Germany*
François DURAND, *France*

16:00-16:05	**Presentation of the clinical case and key questions regarding the challenge** Matthew ARMSTRONG, *United Kingdom*
16:05-16:20	**Assessment and relevance of sarcopenia and frailty** Shira ZELBER-SAGI, *Israel*
16:20-16:35	**Cardiovascular comorbidities in cirrhosis: the emerging burden of NASH** Josh LEVITSKY, *United States*
16:35-16:50	**Management of diabetes in patients with cirrhosis: which treatments, which targets?** Chris BYRNE, *United Kingdom*
16:50-17:05	**Indications for and access to transplantation in patients with comorbidities** Julie HEIMBACH, *United States*
17:05-17:30	**Panel discussion**

THURSDAY 11 April 2019

Managing bacterial infections and impaired renal function

Chairs:
Manuela MERLI, *Italy*
Pere GINÈS, *Spain*

08:30-08:40	**Presentation of the clinical case and key questions regarding the challenge** Elisa POSE, *Spain*
08:40-08:55	**Epidemiology of bacterial infections in cirrhosis and resistance to antibiotics worldwide** Salvatore PIANO, *Italy*

08:55-09:10	**Optimal use of antibiotics in patients with cirrhosis: which type of infection, which antibiotic(s), which dose?** Guadalupe GARCIA-TSAO, *United States*
09:10-09:25	**Acute kidney injury in cirrhosis: redefining the syndromes** Claire FRANCOZ, *France*
09:25-09:40	**Management of hepatorenal syndrome** Elsa SOLÀ, *Spain*
09:40-10:00	**Panel discussion**
10:00-10:30	**Coffee break**

Hepatic encephalopathy and ACLF in end-stage liver disease

Chairs:
Paolo ANGELI, *Italy*
Annalisa BERZIGOTTI, *Switzerland*
François DURAND, *France*
Pere GINÈS, *Spain*

10:30-10:40	**Presentation of the clinical case and key questions regarding the challenge** Sarah RAEVENS, *Belgium*
10:40-10:55	**New options in the treatment of hepatic encephalopathy: from lactulose to non-absorbable antibiotics** Sara MONTAGNESE, *Italy*
10:55-11:10	**ACLF: From pathogenesis to prognosis** Rafael BAÑARES, *Spain*
11:10-11:25	**Management of ACLF in the ICU and the role of liver support systems** Constantine KARVELLAS, *Canada*
11:25-11:40	**Rescue liver transplantation in patients with ACLF: where are the limits?** Patrick S. KAMATH, *United States*
11:40-12:00	**Panel discussion**

Abbreviations and acronyms

AASLD	American Association for the Study of the Liver
ACLD	advanced chronic liver disease
AD	acute decompensation
ALD	alcohol-related liver disease
ALF	acute liver failure
ALT	alanine aminotransferase
AKI	acute kidney injury
ACLF	acute on chronic liver failure
APRI	AST to platelet ratio index
ARFI	acoustic radiation force impulse imaging
AST	aspartate aminotransferase
ATN	acute tubular necrosis
BCAA	branched-chain amino acids
BIA	bioelectrical impedance analysis
BMI	body mass index
CLIF_C ACLF	Chronic Liver Failure ACLF score
CKD	chronic kidney diseases
CRE	carbapenem resistant *Enterobacteriaceae*
CSPH	clinically significant portal hypertension
CVD	cardiovascular disease
CPD	collagen proportionate area
CT	computed tomography
CVP	central venous pressure
DAMPs	damage-associated molecular patterns
DIC	diffuse intravascular coagulation
DOACs	direct oral anticoagulants
DVT	deep vein thrombosis
DXA	dual energy X-ray absorptiometry
EASL	European Association for the Study of the Liver
ECLS	extracorporeal liver support
EcV	ectopic varices
EDR	extensively drug resistant
ESBL	extended spectrum beta-lactamase
FHVP	free hepatic venous pressure
GFR	glomerular filtration rate
HAT	hepatic artery thrombosis
HCC	hepatocellular carcinoma
HE	hepatic encephalopathy
HPS	hepato-pulmonary syndrome
HR	hazard ratio
HRS	hepatorenal syndrome
HVPG	hepatic venous pressure gradient
ICA	International Club of Ascites
ICH	Intracranial hypertension
ICU	intensive care unit
INR	international normalized ratio
ISMN	isosorbide mononitrate
KIM 1	kidney injury molecule
KPC	*Klebsiella pneumoniae* carbapenemase
L-FABP	liver-fatty-acid binding protein
LOLA	L-ornithine L-aspartate
LS	liver stiffness
LT	liver transplantation
MARS	molecular adsorbent recirculating system

MELD	Model for End-stage Liver Disease score
MAMC	mid-arm muscle circumference
MDR	multi-drug resistant
MRE	magnetic resonance elastography
MRSA	methicillin resistant *Staphylococcus aureus*
MRI	magnetic resonance imaging
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NGAL	neutrophil gelatinase-associated lipocalin
NSBB	non-selective beta-blockers
OF	organ failure
OXA	oxacillinase
PAMPs	pathogen-associated molecular patterns
PEEP	positive end expiratory pressure
PH	portal hypertension
pSWE	point shear wave elastography
PVT	portal vein thrombosis
RAAS	renin angiotensin aldosterone system
RRT	renal replacement therapy
SBP	spontaneous bacterial peritonitis
sCr	serum creatinine
SMI	skeletal muscle index
SOFA	Sequential Organ Failure Assessment
SPPB	Short Physical Performance Battery
SS	spleen stiffness
SSTI	skin and soft tissues infections
T2DM	type 2 diabetes mellitus
TE	transient elastrography
TFPI	tissue factor pathway inhibitor
TIPS	transjugular intrahepatic portosystemic shunt
TSF	triceps skin fold
UO	urine output
US	ultrasound
UTI	urinary tract infection
VKA	vitamin K antagonists
VSE	vancomycin susceptible *Enterococci*
VTE	venous thromboembolism
VRE	vancomycin resistant *Enterococci*
vWf	von Willebrand factor
WHVP	wedged hepatic venous pressure
2D-SWE	2-D shear-wave elastography

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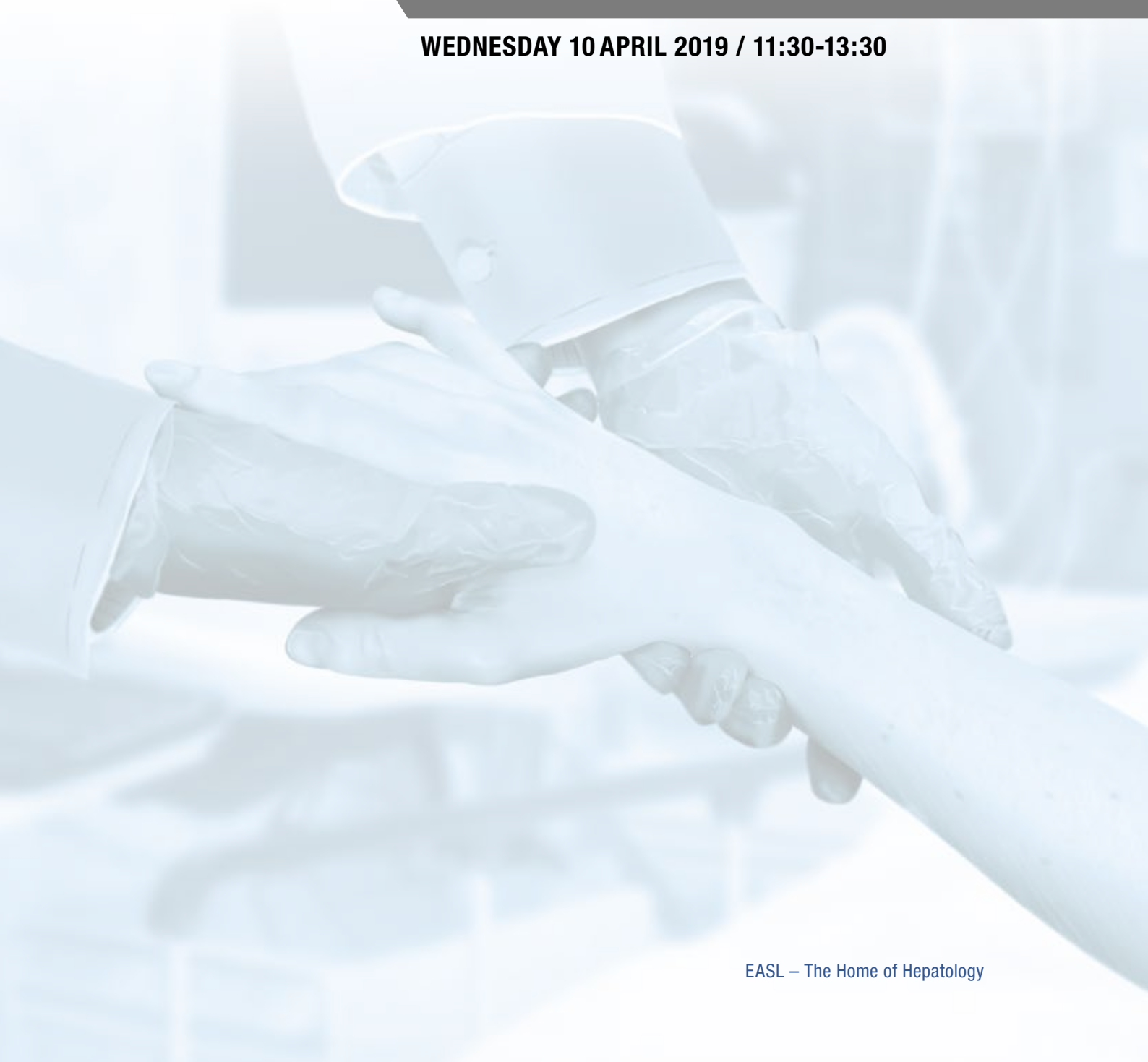
SESSION 1
DIAGNOSIS OF CIRRHOSIS AND PORTAL HYPERTENSION: NON-INVASIVE OR INVASIVE TESTS?

WEDNESDAY 10 APRIL 2019 / 11:30-13:30



Session 1

Are serum markers and liver stiffness tests sufficient to diagnose cirrhosis?

Laurent Castera

Dept of Hepatology, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris,

INSERM UMR 1149-CRI, University Denis Diderot Paris-7, Clichy, *Paris, France*

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Take-home messages

- Non-invasive tests must always be interpreted critically, according to the context of use (setting: primary health care or tertiary referral centre and clinical context), considering the recommended quality criteria for each test and its possible pitfalls.
- Limitations include cost and limited availability for patented serum markers, and operator experience and obesity for transient elastography.
- Among serum markers, the most validated tests are APRI, FIB-4 and NFS for non-patented and FibroTest® for patented tests.
- As for liver stiffness measurement, transient elastography is the most validated and accurate technique for diagnosing cirrhosis (better at ruling out than ruling in), outperforming serum markers.
- Non-invasive tests (transient elastography >> serum markers) are recommended as first-line for detecting cirrhosis before starting antiviral treatment in patients with viral hepatitis.
- Sequential algorithms combining serum markers as a first step, and liver stiffness measurement using transient elastography as the second step, appear to be a reasonable approach in patients with NAFLD, given the magnitude of the epidemic.

Introduction

Early detection of compensated cirrhosis is critical in the management and surveillance of patients with chronic liver disease. For many years, liver biopsy has been considered the “gold standard” for evaluating hepatic fibrosis. However, liver biopsy is an invasive procedure with rare but potentially life-threatening complications and prone to sampling errors. These limitations, as well as the availability of powerful antiviral agents, have rapidly decreased the use of liver biopsy for detecting cirrhosis in patients with chronic viral hepatitis and has led to the development of non-invasive methods. Finally, given the magnitude of the non-alcoholic fatty liver disease (NAFLD) epidemic, liver biopsy is unrealistic and non-invasive tests are more appropriate. They are now widely used in clinical practice and recommended by international and EASL guidelines [1-5].

Currently available non-invasive methods

Among the currently available non-invasive methods, there are two distinct approaches: i) a “biological” approach based on the dosage of serum markers of fibrosis; and ii) a “physical” approach based on the measurement of liver stiffness, using either ultrasound (US) or magnetic resonance (MR)-based elastography techniques. Although complementary, these two approaches are based on different rationale and conception: liver stiffness is related to elasticity, which corresponds to a genuine and intrinsic physical property of liver parenchyma, whereas serum biomarkers are combinations of several, not strictly liver-specific blood, parameters optimised to mimic fibrosis stages as assessed by liver biopsy.

Serum markers of liver fibrosis

Many serum markers have been developed and evaluated for their ability to detect cirrhosis in patients with chronic liver disease. They are summarised in Table 1. Their respective advantages and limitations are summarised in Table 2. Non-patented scores are cost-free, easy to calculate and almost available everywhere, whereas patented tests are commercially available proprietary formula.

Table 1. Currently available serum markers for non-invasive diagnosis of cirrhosis in patients with chronic liver disease, adapted from [1].

PATENTED
Enhanced Liver Fibrosis (ELF®) test (Siemens Healthcare Diagnostics Inc., USA) formula combining age, hyaluronate, MMP-3 and TIMP-1
Fibrometers® (Echosens, Paris, France) formula combining platelet count, prothrombin index, AST, α-2-macroglobulin, hyaluronate, urea and age
FibroTest® (Biopredictive, Paris, France) formula combining α-2-macroglobulin, GGT, apolipoprotein A1, haptoglobin, total bilirubin, age and gender
Hepascore (PathWest, University of Western Australia, Australia) formula combining bilirubin, GGT, hyaluronate, α-2-macroglobulin, age and gender
NON-PATENTED
AST: ALT ratio = AST (U/L)/ALT (U/L)
AST to Platelet Ratio (APRI) = AST (/ULN)/platelet (10^9/L) x 100
BARD score (BMI ≥28 = 1; AST/ALT ratio >0.8 = 2; Diabetes = 1; Score >2, odds ratio for advanced fibrosis = 17)
FIB-4 = age (years) x AST [U/L]/(platelets [10^9/L] x (ALT [U/L])$^{1/2}$
Forns Index = 7.811 - 3.131 x ln(platelet count) + 0.781 x ln(GGT) + 3.467 x ln(age) - 0.014 x (cholesterol)
Gotebörg University Cirrhosis Index (GUCI) = AST x prothrombin-INR x 100/platelet
HALT-C model = - 3.66 - 0.00995 x platelets (10^3/ml) + 0.008 x serum TIMP-1 + 1.42 x log (hyaluronate)
Lok index = - 5.56 - 0.0089 x platelet (10^3/mm^3) + 1.26 x AST/ALT ratio = 5.27 x INR
NAFLD Fibrosis Score (NFS) = (-1.675 + 0.037 x age (yrs) + 0.094 x BMI (kg/m^2) + 1.13 x IFG/diabetes (yes = 1, no = 0) + 0.99 x AST/ALT ratio - 0.013 x platelet count (×10^9/L) - 0.66 x albumin [g/dl])

AST, aspartate aminotransferase; ALT, alanine aminotransferase; BMI, body mass index; GGT, gamma-glutamyl-transferase; INR, international normalized ratio; MMP-3, matrix metalloproteinase-3; TIMP-1, tissue inhibitors of metalloproteinases-1.

Table 2. Respective advantages and limitations of currently available non-invasive methods in patients with chronic liver disease (adapted from [1]).

SERUM MARKERS	MEASUREMENT OF LIVER STIFFNESS			
	Transient elastography	**ARFI (pSWE)**	**2D-SWE**	**MR elastography**
ADVANTAGES				
Good reproducibility High applicability (95%) No cost and wide availability (non-patented) Well-validated Can be performed in a primary health care setting	Most widely used and validated technique: standard to be beaten Point-of-care technique Can be performed by nurses High range of values (2-75 kPa) Quality criteria well defined (IQR/M <30%) Good reproducibility High performance for cirrhosis Quantification of steatosis (CAP) Low failure rate in obese patients when using XL probe (3%)	Can be implemented on a regular US machine ROI smaller than TE but location chosen by the operator Higher applicability than TE (ascites and obesity) Performance equivalent to TE for cirrhosis	Can be implemented on a regular US machine ROI can be adjusted in size and location and chosen by the operator High range of values (2-150 kPa) Good applicability Performance equivalent to TE for cirrhosis	Can be implemented on regular MRI machine Examination of the whole liver Higher applicability than TE (ascites and obesity) High performance for cirrhosis

LIMITATIONS				
Non-specific of the liver	Requires a dedicated device	Unable to discriminate between intermediate stages of fibrosis	Further validation warranted	Further validation warranted especially in comparison with TE
Unable to discriminate between intermediate stages of fibrosis	ROI cannot be chosen	Units (m/sec) different from that of TE (kPa)	Unable to discriminate between intermediate stages of fibrosis	Small range of values (2-11 kPa)
Performance not as good as TE for cirrhosis	Unable to discriminate between intermediate stages of fibrosis	Narrow range of values (0.5-4.4 m/sec)	Quality criteria not well-defined	Not applicable in case of iron overload
Cost and limited availability (patented)	Applicability (80%) lower than serum markers: (obesity, ascites, operator experience)	Quality criteria not well defined	Cannot be performed by nurses	Time-consuming
Limitations (haemolysis, Gilbert syndrome, inflammation…)	False positive in case of acute hepatitis, cholestasis, liver congestion, food intake and excessive alcohol intake	Cannot be performed by nurses		Limited availability
				Costly

ARFI, acoustic radiation force impulse imaging; pSWE, point shear wave elastography; 2D-SWE, (2-D) shear-wave elastography; MR, magnetic resonance; US, ultrasound; TE, transient elastography; ROI, region of interest.

Liver stiffness measurement

Transient elastography (TE) was the first commercially available US-based elastography method developed for the measurement of liver stiffness, using a dedicated device (FibroScan®, Echosens, Paris, France). Several other liver elasticity-based imaging techniques challenging TE have been developed, including point shear-wave elastography (pSWE), also known as acoustic radiation force impulse imaging (ARFI), (2-D) shear-wave elastography (2D-SWE) and magnetic resonance elastography (MRE) [6]. Their respective advantages and limitations are summarised in Table 2. The main limitation of TE in clinical practice is its limited applicability in cases of obesity. Confounding factors for liver stiffness, whatever the technique, include inflammation (transaminases >5 x ULN), liver congestion, food intake and extrahepatic cholestasis. Procedures should be performed using a standardised protocol in fasting patients (for at least 2 hours).

Diagnostic performances of non-invasive methods for diagnosing cirrhosis

Serum biomarkers of fibrosis

Among non-patented tests, the aspartate aminotransferase to platelet ratio index (APRI) and the Fibrosis-4 (FIB-4) in viral hepatitis and NAFLD, and the NAFLD fibrosis score (NFS) in NAFLD, have all been the extensively studied and validated with evidence-based large meta-analyses, including several thousands of patients reporting AUROCs for diagnosing cirrhosis, ranging from 0.73 to 0.85 (Table 3). They all perform better at ruling out than ruling in cirrhosis with a high negative predictive value (>90%).

As for patented tests, FibroTest® has been the most extensively studied, mainly in patients with viral hepatitis. However, all patented tests lack external validation and meta-analyses independent from the developers are very few. When compared with non-patented tests, patented tests offer a slight improvement in their accuracy, but their widespread application is limited by cost and availability. Importantly, it should be stressed that these tests are poorly validated in alcohol-related liver disease (ALD).

Table 3. Diagnostic performances (meta-analyses) of serum markers and different elastography techniques for cirrhosis taking liver biopsy as a reference.

Serum markers	Aetiology	Patients (n)	Cut-offs	AUROC	Sensitivity (%)	Specificity (%)
Non-patented						
APRI	HBV	8773	1.0-2.0	0.73	66-31	74-89
	HCV	4548	1.0-2.0	0.83	76-46	72-91
	NAFLD	2327	1.0-2.0	0.76	63	78
FIB-4	HBV	6068	1.05-2.65	0.84	87-64	65-86
	NAFLD	1872	3.25	0.85	77	83
NFS	NAFLD	1830	-0.014	0.83	80	81

Serum markers	Aetiology	Patients (n)	Cut-offs	AUROC	Sensitivity (%)	Specificity (%)
Patented						
FibroTest®	HBV	2494	0.74	0.87	62	91
Liver stiffness						
US-based elastography						
TE	HBV	4386	9.0-16.9 kPa	0.93	86	87
	CLD (HCV)	8206	13.0 kPa	0.94	91	89
	NAFLD	1780	10.3-11.3 kPa	0.94	88	86
	ALD	1026	18.6 kPa	0.91	84	85
ARFI	HBV/HCV	2691	2.42 m/sec	0.91	86	84
2D-SWE	HBV	400	11.5 kPa	0.95	80	93
	HCV	379	13.0 kPa	0.93	86	88
	NAFLD	156	13.0 kPa	0.92	75	88
MR-based elastography						
MRE	HBV	1470	4.6 kPa	0.97	89	92
	NAFLD	340	4.1-6.7 kPa	0.97	87	93

ARFI, acoustic radiation force impulse imaging; CLD, chronic liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; MRE, magnetic resonance elastography; NAFLD, non-alcoholic fatty liver disease; NFS, NAFLD fibrosis score; pSWE, point shear wave elastography; TE, transient elastography; US, ultrasound; 2D-SWE, (2-D) shear-wave elastography.

Liver stiffness measurement

The diagnostic accuracy of TE for cirrhosis is based on large meta-analyses including several thousands of patients both in viral hepatitis and NAFLD [7,8] and considered excellent (AUROCs 0.93–0.96) with sensitivities and specificities of 84–91% and 85–89%, respectively (Table 3). However, a meta-analysis based on individual data is still awaited. Actually, TE is better at ruling out, rather than ruling in liver cirrhosis (with a negative predictive value higher than 90%). Different cut-offs have been proposed for different causes of liver diseases (hepatitis C [HCV] and B virus [HBV], NAFLD and ALD) but no consensus has been reached. As shown in Table 3, cut-offs for cirrhosis ranged from 9.0 kPa in HBV to 18.6 kPa in ALD. This may be related to the so-called spectrum bias, depending on the uneven distribution of different fibrosis stages in different cohorts. For instance, in ALD cohorts, the prevalence of cirrhosis is usually higher (40-50%) than in HBV (10-20%). Also, cut-offs in ALD should be adjusted according to transaminase levels and ongoing alcohol intake. In that respect, the 2015 Baveno VI consensus workshop recommended a diagnosis of compensated liver cirrhosis in asymptomatic patients using TE, if liver stiffness values are repeatedly (two different days, fasting) >15 kPa [9]. When compared head-to-head with serum markers, TE outperforms all of them.

ARFI performance for diagnosing cirrhosis has been evaluated mainly in viral hepatitis with high accuracy (AUROC 0.91) and cut-off of 2.42 m/sec [10]. When compared with TE, ARFI has

equivalent results. 2D-SWE has been evaluated in a single meta-analysis, based on individual data in 1340 patients with chronic liver disease, reporting a high accuracy (AUROCs 0.93-0.95) for cirrhosis with an optimal cut-off of 13.5 kPa. When compared to TE in this meta-analysis, no significant difference was found, if the quality criteria of TE were respected.

As for MRE, the evidence is based on a few hundred patients, but with excellent accuracy (97%) for diagnosing cirrhosis. However, widespread use of this method will depend on cost and availability. Finally, it should be kept in mind that cut-offs for cirrhosis are system specific.

Use in clinical practice

Identifying cirrhosis in patients with viral hepatitis

The EASL clinical practice guidelines recommend that all patients with chronic hepatitis B or C should be assessed for liver disease severity before antiviral therapy using non-invasive tests as first-line [2,3]. Identifying patients with cirrhosis is of particular importance, as the duration of the treatment of HCV patients with direct-acting antiviral agents depends on the stage of fibrosis. In HBV patients with cirrhosis, treatment by analogs should not be stopped. Finally, a post-treatment follow-up for portal hypertension and hepatocellular carcinoma is recommended in HBV and HCV patients with non-invasive test values in the range of liver cirrhosis. In case of unexplained discordance or suspected additional aetiologies of liver disease, a liver biopsy is still recommended [2,3].

Identifying cirrhosis in patients with NAFLD

In patients with suspected NAFLD (presence of steatosis on US or abnormal liver tests [transaminases/gamma-glutamyl-transferases] in patients with risk factors such as obesity, type 2 diabetes or metabolic syndrome), non-invasive tests can be used in clinical practice for risk stratification. Whatever the approach, serum markers or liver stiffness measurement, each modality is most reliable in excluding the presence of cirrhosis. As shown in Figure 1, the choice of non-invasive tools to be used should be guided by local availability and context of use [8]. In the primary health care setting, simple inexpensive and widely available serum markers, such as FIB-4 or NFS, should be used as first-line for ruling out advanced fibrosis-cirrhosis, due to high negative predictive value (>90%). Patients with low risk of having advanced fibrosis-cirrhosis do not need further assessment. Those with intermediate and high risk should be addressed to a referral centre for further assessment. Patented serum markers (FibroTest®, Fibrometer® or ELF®) could be considered in patients with intermediate risk according to local availability. Otherwise TE, as the most widely available and best evaluated point-of-care technique, appears to be the tool of choice, although ARFI and SWE are becoming increasingly available. XL probe should be used in patients with skin-liver capsule distance >25 mm in order to minimise the TE failure rate (<7%). Patients at low risk of having advanced fibrosis-cirrhosis should be offered lifestyle modifications and re-evaluation after 1 year. Those with an intermediate or high risk of having advanced fibrosis-cirrhosis should be considered for liver biopsy. However, confounders should be carefully excluded to minimise the risk of false positives. In case of TE failure, despite the use of XL probe or high BMI ($\geq$35 kg/m^2), alternative techniques such as MRE or SWE/ARFI may be considered according to local availability.

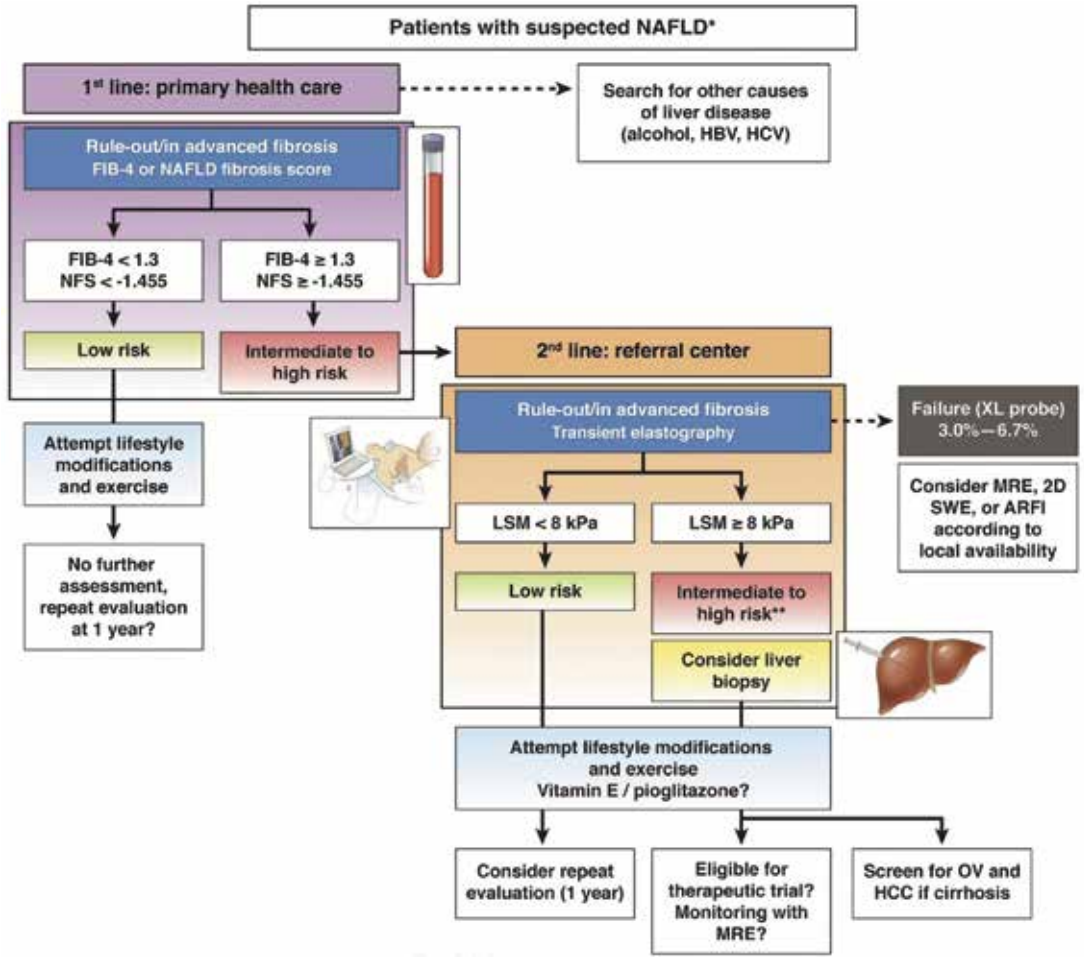

Figure 1. A suggested algorithm for the use of non-invasive tests for risk stratification of patients with suspected NAFLD in clinical practice (taken from [8]). NAFLD, non-alcoholic fatty liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; FIB-4, Fibrosis-4 score; NFS, NAFLD fibrosis score; LSM, liver stiffness measure; MRE, magnetic resonance elastography; 2D-SWE, 2-D shear wave elastography; ARFI, acoustic radiation force impulse imaging; OV, oesophageal varices.

References

[References in **BOLD** are required reading]

1. **EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol. 2015 Jul;63(1):237-64.**
2. EASL Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017 Aug;67(2):370-98.
3. EASL Recommendations on Treatment of Hepatitis C 2018. J Hepatol. 2018 Aug;69(2):461-511.
4. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016 Jun;64(6):1388-402.

5. EASL clinical practical guidelines: management of alcoholic liver disease. J Hepatol. 2012 Aug;57(2):399-420.

6. Friedrich-Rust M, Poynard T, Castera L. Critical comparison of elastography methods to assess chronic liver disease. Nat Rev Gastroenterol Hepatol. 2016 Jul;13(7):402-11.

7. Castera L. Noninvasive methods to assess liver disease in patients with hepatitis B or C. Gastroenterology. 2012 May;142(6):1293-302 e4.

8. Castera L, Friedrich-Rust M, Loomba R. Noninvasive assessment in patients with nonalcoholic fatty liver disease. Gastroenterology. 2019: Jan 17. pii: S0016-5085(19)30051-4.

9. de Franchis R, Baveno VIF. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. J Hepatol. 2015 Sep;63(3):743-52.

10. Kennedy P, Wagner M, Castera L, et al. Quantitative Elastography Methods in Liver Disease: Current Evidence and Future Directions. Radiology. 2018 Mar;286(3):738-63.

Imaging diagnosis of cirrhosis

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Take-home message

- Imaging (ultrasound, computed tomography, and magnetic resonance imaging) can non-invasively diagnose cirrhosis.
- Imaging findings are either morphological or quantitative, imaging-based elastography being a key technique.

Imaging of cirrhosis

"Cirrhosis" derives from a Greek word, meaning tawny, and was initially used to describe the gross appearance of the chronically diseased and dysfunctional liver [1]. Cirrhosis is defined as a diffuse process characterised by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules. Because the natural history of cirrhosis has changed significantly, and liver fibrosis may regress, the International Liver Pathology Study Group suggests discontinuing the use of the term cirrhosis. Anyhow, the term cirrhosis is still widely used.

Although the definition of cirrhosis is based on histology, ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) alone are often used to diagnose cirrhosis. All these imaging modalities show a variety of findings associated either to cirrhosis or to portal hypertension. In this chapter, we will describe the imaging findings. Classically they have been qualitative, but novel imaging techniques provide interesting quantitative data.

Morphologic findings

Distorted liver architecture

The coarseness of the liver parenchyma can be seen on US, CT, or MRI. It is related to the presence of micro regenerative nodules surrounded by fibrosis. MRI is more sensitive than US and CT to detect architectural changes. The best MR sequences are fat-suppressed T2-w and delayed contrast-enhanced T1-w showing hypointense nodules and fibrotic bands that are hyperintense on T2 and show enhancement on the delayed phase.

Nodular liver surface

Nodular liver surface results from the effects of fibrosis and the regenerative nodules on the capsule. This sign is best seen on US with a high-frequency probe. Colli *et al.* have described three stages: no irregularity, slight surface irregularity, and pronounced surface irregularity [2]. Several automatic methods have recently been used to quantify liver surface with high diagnostic performance on US or CT. Using semiautomatic measurements of liver surface nodularity on CT, Pickhardt *et al.* showed a sensitivity and specificity for diagnosing advanced fibrosis (>F3) of 89% and 84%, and for diagnosing cirrhosis of 98% and 85% [3].

Morphologic changes of the liver

Typically, the morphologic changes of the liver seen in cirrhosis are hypertrophy of segment 1 (caudate lobe) and hypotrophy of segment 4, the latter being considered as an early sign of cirrhosis. These changes are possibly related to changes in portal venous flow.

Lafortune *et al.* reported a mean (± SD) transversal diameter of segment 4 of 43 ± 8 mm in patients with healthy livers and 28 ± 9 mm in cirrhotic patients using US [4]. In their work, a cut-off point for the prediction of cirrhosis greater than 30 mm had a specificity of 100%. However, these measurements have been obtained using US and cannot be extrapolated to CT or MRI.

Segment I can be measured in different ways: the ratio between segment I and the left liver lobe on a sagittal plane or the ratio between segment I and the right liver on an axial plane. However, these measurements can be inaccurate because the other liver segments might change too [5].

These typical changes might also be associated with hypertrophy of the left liver lobe and atrophy of the right liver.

Other findings described in cirrhosis:

- a posterior hepatic notch sign is seen as a sharp indentation on the posteroinferior liver surface between the caudate and right lobes on an axial plane, probably caused by enlargement of segment I and atrophy of the right liver [6,7].
- An enlargement of the hilar periportal space seen on transverse images, as a widened distance (>10 mm) with increased thickness of the hilar periportal fat. This is measured as the distance between the anterior wall of the right portal vein and the posterior edge of segment IV. The line of measurement is made perpendicular to the midpoint of the anterior wall of the right portal vein [8-10].
- Splenomegaly is secondary to the increase of splenic venous pressure. The spleen should be measured through the hilum on a coronal plane. On US, a cut-off of 11.2 cm has been considered to be diagnostic of cirrhosis [11].
- Ascites. Although ascites can be a sign of cirrhosis, it is more likely to be a sign of hepatic decompensation.
- Gallbladder wall thickening may be seen in many other conditions, such as viral hepatitis and acute cholecystitis [12].
- Peribiliary cysts are cystic dilatation of the extramural glands in the periductal connective tissue. They do not communicate with the biliary tree. Peribiliary cysts are more commonly found in the hilum and the left lobe.

Hemodynamic findings

Vascular abnormalities in cirrhosis, such as the development of portocaval collaterals, can be explored by US, CT or MRI but Doppler US is best for showing hemodynamic changes.

Some of these changes are the consequence of portal hypertension:

- Increased portal vein diameter. It is considered enlarged beyond 12 mm in diameter. Yet, the diameter of the portal vein is not proportional to the degree of portal hypertension.
- Decreased portal velocity. In healthy patients, the mean of the maximal portal vein velocity is higher than 18 cm/s, and the mean of the mean portal vein velocity is higher than 10 cm/s [13]. Yet, many parameters should be taken into consideration to get an accurate measurement.
- Portosystemic collateral veins. Depiction of these veins is specific of portal hypertension. Collateral vessels can use several pathways to reach the systemic circulation via the superior or inferior

vena cava. The most common territories are gastroesophageal, splenorenal (direct or indirect), paraumbilical vein and perirectal. CT is the best tool for identifying ectopic varices.

Some other hemodynamic changes related to cirrhosis itself:

- Demodulation of the hepatic venous flow on Doppler US. The original triphasic modulation of the hepatic venous flow, which reflects cardiac activity, is progressively demodulated in cirrhosis [14]. In patients with chronic liver diseases, the reverse flow (due to atrial systole) first disappears and later the hepatic venous flow is completely demodulated and monophasic.
- Increased arterial hepatic flow. Both an increase in hepatic arterial resistance index and hepatic arterial blood flow have been reported in cirrhotic patients [15].

Elastography techniques

Imaging-based elastography is an emerging technology that uses imaging to non-invasively assess mechanical tissue properties. Elastography techniques have evolved significantly over the last decades and have now been implemented on clinical US and MR systems [16]. They assess stiffness indirectly by measuring the speed of shear waves propagating in the tissue of interest. The underlying concept is that shear-wave speed is related to tissue stiffness: shear waves travel faster in stiff tissues and slower in soft tissues. Shear waves may be generated by applying a mechanical vibration to the surface of the body or by focusing an acoustic radiation force (acoustic push pulse) inside the tissue. Some US-based techniques use mechanical vibration for shear-wave generation, whereas others use acoustic radiation force. Commercial MRI-based techniques use only the former.

Ultrasound elastography

The different techniques can be classified in:

- Point shear-wave elastography: the shear-wave speed is measured in a region of interest (ROI). The location of the ROI is defined on a B-mode image. It has been first developed by Siemens Healthcare using acoustic radiation force impulse technology, frequently named ARFI.
- 2D shear-wave elastography. First developed by Supersonic Imagine (shear-wave elastography, SWE) and recently many companies have developed this approach. SWE generates a quantitative parametric map displaying the shear wave-speed.

The diagnostic performance of US elastography techniques is close and often better than that obtained with FibroScan® [17-20].

MR elastography

With MRE, mechanical waves are produced by a transducer placed against the lower ribs of the patient. The speed of the waves is then measured by motion-sensitised MRE sequences. Compared to US, MRE allows analysing a larger proportion of the liver, which may potentially reduce sampling variability. Only one commercial elastography package (Resoundant) is being adopted for clinical implementation by the major MRI scanner manufacturers, which enables reproducibility of results.

MRE, at least, equals US elastometry in diagnostic performance, but with a better reproducibility [21]. Importantly, the values are much lower than with US elastography with a cut-off value around 6 kPa for cirrhosis. Interestingly, the failure rate for MRE is low (5.6%) [22].

Indeed, there are advantages and drawbacks of these two techniques. US elastography techniques are relatively inexpensive, portable, and increasingly available while providing good diagnostic accuracy but may be unreliable in obese patients and those with narrow intercostal spaces. MR elastography

offers excellent diagnostic accuracy that probably slightly exceeds that of US-based techniques, but quality may be degraded in patients with marked iron deposition, and cost and availability might be an issue.

Combined criteria for the diagnosis of cirrhosis

Although imaging features of liver fibrosis and cirrhosis can be seen on CT and MRI, US is the main tool used in clinical practice for the diagnosis of fibrosis and cirrhosis. Among the previously described features, nodular liver surface, increased spleen length, and demodulation of the hepatic vein appear to be the most accurate for diagnosing severe fibrosis. In a large series of patients with chronic liver disease, the association of ≥2 of these imaging features had 49% sensitivity and 87% specificity [23].

In another study, the same authors confirmed that the same imaging findings (nodular liver surface, increased spleen length, and demodulation of the hepatic vein) were independently associated with severe fibrosis. Moreover, they showed that when at least one of these imaging was seen, liver stiffness measurement ≥9.5 kPa increased the specificity for the diagnosis of severe liver fibrosis from 36% to 73% with a slight decrease of the sensitivity [24]. In other words, US elastography improves the accuracy of Doppler US for the detection of severe fibrosis and better identifies the patients that need to be referred to hepatologists. Similarly, other studies have shown that better prediction rates are achieved by combining Doppler US with non-invasive markers and liver stiffness [25].

Venkatesh *et al.* have retrospectively compared the morphological features of the liver (liver parenchyma texture, surface nodularity, liver volume changes and signs of portal hypertension) on MRI with MRE for the detection of significant fibrosis and cirrhosis [26]. Overall, MRE was superior to MRI for the non-invasive diagnosis of significant liver fibrosis and cirrhosis.

Other quantitative techniques

Although most of these techniques are not used routinely for the diagnosis of cirrhosis, they provide interesting information.

Texture analysis

Liver fibrosis leads to changes in the texture of the parenchyma that may be assessed using computer-based texture analysis for quantitative measurement on US, CT or MRI.

Perfusion imaging

On perfusion imaging (US, CT, and MRI), liver signal enhancement after injection of contrast agents is used to assess liver function. Changes in semiquantitative or quantitative parameters may be related to liver fibrosis stages.

Multiparametric MRI

- Diffusion-weighted MRI provides information on the Brownian motion of water molecules in each imaging voxel. Diffusion is restricted with higher fibrosis stages. Diffusion of water molecules is typically measured on a dedicated MRI sequence by applying diffusion gradients.
- The uptake of hepatobiliary MR contrast agents may be used as a surrogate marker of liver function, which decreases with higher fibrosis stages. Two hepatobiliary contrast agents are available, gadoxetate disodium and gadobenate dimeglumine, whose uptake depends on the

expression of transporters, related to the function of hepatocytes. These can be used to assess liver function by acquiring images before contrast injection and on hepatobiliary phase.

- T1ρ: The spin-lattice relaxation time in the rotating frame (T1ρ) increases with higher fibrosis stages [27].

Correlation between imaging and disease severity

In the early stages of liver disease, liver hypertrophy related to inflammation is common. In metabolic liver disease, steatosis also leads to hypertrophy. However, as the disease deteriorates, the liver tends to become hypotrophic, and decompensated cirrhosis is usually associated with global atrophy. Many studies have tried to correlate changes in liver volumetry with prognosis.

It has been reported that remodelling of the liver could be associated with prognosis. In a follow-up study with MRI, progressive atrophy of the right hepatic lobe and the medial segment correlated with the progression of clinical severity of cirrhosis, whereas the increased size of the caudate lobe and the lateral segment correlated with stability [28].

Several studies have analysed liver volume to spleen volume ratio. Feng *et al.* have shown that total liver volume/splenic volume ratio was accurate in discriminating between mild and moderate/severe cirrhosis and could be used for predicting complications of cirrhosis [29].

Chen *et al.* have demonstrated that the right liver volume/splenic volume ratio was the best non-invasive factor for the discrimination of liver cirrhosis between Child-Pugh class A and B (AUC = 0.725), between A and C (AUC = 0.975), and between B and C (AUC = 0.876) [30].

Others have analysed the liver to abdominal area ratio and have demonstrated that this ratio, MELD, and MELD-Na were independently associated with the progression to death/liver transplantation [31]. Quantitative MRI has been used recently to assess the severity of cirrhosis. Different approaches such as hepatobiliary phase and liver T1 mapping has shown to be significantly correlated with Child-Pugh score and MELD score [32,33].

Pitfalls in the non-invasive diagnosis of cirrhosis

Non-cirrhotic liver conditions can lead to morphologic changes in the liver that mimic cirrhosis. These changes may be due to obstruction of the major portal or hepatic veins, biliary obstruction, or more diffuse non-cirrhotic chronic liver diseases.

Venous or biliary obstruction

The association between hepatic lobar atrophy and ipsilateral portal vein obstruction is well known and has been described in patients with isolated portal vein obstruction or those with cholangiocarcinoma, resulting in both portal vein and biliary obstruction [34]. In the latter, portal vein obstruction seems to be the dominant factor in the development of lobar atrophy. Atrophy of the area involved is associated with compensatory hypertrophy and/or hyperplasia of the non-affected liver (atrophy-hypertrophy complex). Biliary obstruction may also induce ipsilateral liver atrophy, especially if it is chronic, but this is usually less pronounced than the combination of portal vein and biliary obstruction.

Diffuse non-cirrhotic chronic liver diseases

Morphologic changes of the liver mimicking cirrhosis are present in several non-cirrhotic liver diseases, most of them of vascular or biliary origin [35].

Cavernous transformation of the portal vein

It occurs as a result of complete extrahepatic portal vein obstruction and is seen as multiple collateral veins in the porta hepatis. Atrophy of the right liver, hypertrophy of the caudate lobe, and signs of portal hypertension are confusing and can mimic cirrhosis. However, the atrophy-hypertrophy complex is different from cirrhosis because hypertrophy is central (segment VI and I) as a result of maintained portal inflow and peripheral atrophy (right liver and left liver lobe) [36]. Moreover, nodularity of the hepatic contour is usually not present. Imaging features also include direct signs of complete portal vein.

Budd-Chiari syndrome is characterised by hepatic venous outflow obstruction in the absence of right-sided heart failure or constrictive pericarditis, which occurs in the small or large hepatic veins or the suprahepatic portion of the inferior vena cava. As mentioned above, hepatic venous obstruction can result in ipsilateral atrophy. On the other hand, adaptive mechanisms include the development of a collateral hepatic venovenous circulation to divert the outflow circulation by bypassing the obstruction and connecting blocked territories to contiguous, well-drained territories. Thus, atrophy will appear in the obstructed liver segments, and hypertrophy will be seen in liver segments where hepatic venous outflow is not altered. In most cases, the segment I is preserved. The diagnosis of Budd-Chiari syndrome is further supported by visualising direct anomalies of the hepatic veins and the collateral circulation.

Congenital hepatic fibrosis is a developmental malformation that belongs to the family of hepatic ductal plate malformations, resulting in a persistent additional embryonic bile duct structure in the portal tracts. Congenital hepatic fibrosis is usually associated with autosomal recessive polycystic kidney diseases, which together represent the most common hepatorenal fibrocystic diseases. Morphologic abnormalities of the liver (segmental hypertrophy or atrophy) are found in most patients, most frequently atrophy of the right liver and hypertrophy of the left liver lobe and the caudate lobe mimicking cirrhosis. Interestingly, segment IV is normal sized or enlarged [37]. Besides the morphologic changes of the liver, other abnormalities such as renal and biliary disorders that are not found in patients with cirrhosis are highly suggestive of this diagnosis.

Obliterative portal venopathy, also known as idiopathic portal hypertension and hepatoportal sclerosis, is one of the diseases that most closely mimics cirrhosis because portal hypertension is a key finding and in advanced cases, the imaging findings of liver nodularity and atrophy are indistinguishable from those of cirrhosis. Fortunately, certain findings help differentiate between obliterative portal venopathy and cirrhosis: intra- or extrahepatic portal vein anomalies (acute or chronic, complete or partial obstruction, stenosis or lack of visibility and mural calcifications) are mainly observed in patients with obliterative portal venopathy, whereas a nodular liver surface is rarely found [38].

On rare occasions, other conditions can mimic cirrhosis: liver metastases inducing pseudocirrhosis, acute liver failure (liver atrophy and liver surface nodularity can be seen up to 43%), posttherapeutic morphologic changes in the liver.

In summary, imaging (US, CT, and MRI) plays an important role in the diagnosis of cirrhosis. While in the past, most imaging findings were morphological, novel imaging is more quantitative, and imaging-based elastography is a key technique. Yet, no imaging findings are 100% specific, and differentials must be known. When the diagnosis remains doubtful, liver biopsy is indicated.

References

[References in **BOLD** are required reading]

1. Hytiroglou P, Snover DC, Alves V, Balabaud C, Bhathal PS, Bioulac-Sage P, et al. Beyond "cirrhosis": a proposal from the International Liver Pathology Study Group. Am J Clin Pathol 2012; 137:5-9.
2. Colli A, Fraquelli M, Andreoletti M, Marino B, Zuccoli E, Conte D. Severe liver fibrosis or cirrhosis: accuracy of US for detection--analysis of 300 cases. Radiology 2003; 227:89-94.
3. Pickhardt PJ, Malecki K, Kloke J, Lubner MG. Accuracy of Liver Surface Nodularity Quantification on MDCT as a Noninvasive Biomarker for Staging Hepatic Fibrosis. AJR Am J Roentgenol 2016; 207:1194-1199.
4. Lafortune M, Matricardi L, Denys A, Favret M, Dery R, Pomier-Layrargues G. Segment 4 (the quadrate lobe): a barometer of cirrhotic liver disease at US. Radiology 1998; 206:157-160.
5. Hess CF, Schmiedl U, Koelbel G, Knecht R, Kurtz B. Diagnosis of liver cirrhosis with US: receiver-operating characteristic analysis of multidimensional caudate lobe indexes. Radiology 1989; 171:349-351.
6. Ito K, Mitchell DG, Kim MJ, Awaya H, Koike S, Matsunaga N. Right posterior hepatic notch sign: a simple diagnostic MR finding of cirrhosis. J Magn Reson Imaging 2003; 18:561-566.
7. Tan KC. The right posterior hepatic notch sign. Radiology 2008; 248:317-318.
8. Ito K, Mitchell DG, Gabata T. Enlargement of hilar periportal space: a sign of early cirrhosis at MR imaging. J Magn Reson Imaging 2000; 11:136-140.
9. Ito K, Mitchell DG. Hepatic morphologic changes in cirrhosis: MR imaging findings. Abdom Imaging 2000; 25:456-461.
10. Tan KC. Enlargement of the hilar periportal space. Radiology 2008; 248:699-700.
11. Aube C, Winkfield B, Oberti F, Vuillemin E, Rousselet MC, Caron C, et al. New Doppler ultrasound signs improve the non-invasive diagnosis of cirrhosis or severe liver fibrosis. Eur J Gastroenterol Hepatol 2004; 16:743-751.
12. **Aube C, Bazeries P, Lebigot J, Cartier V, Boursier J. Liver fibrosis, cirrhosis, and cirrhosis-related nodules: Imaging diagnosis and surveillance. Diagn Interv Imaging 2017; 98:455-468.**
13. Zironi G, Gaiani S, Fenyves D, Rigamonti A, Bolondi L, Barbara L. Value of measurement of mean portal flow velocity by Doppler flowmetry in the diagnosis of portal hypertension. J Hepatol 1992; 16:298-303.
14. Arda K, Ofelli M, Calikoglu U, Olcer T, Cumhur T. Hepatic vein Doppler waveform changes in early stage (Child-Pugh A) chronic parenchymal liver disease. J Clin Ultrasound 1997; 25:15-19.
15. Colli A, Cocciolo M, Mumoli N, Cattalini N, Fraquelli M, Conte D. Hepatic artery resistance in alcoholic liver disease. Hepatology 1998; 28:1182-1186.
16. Tang A, Cloutier G, Szeverenyi NM, Sirlin CB. Ultrasound Elastography and MR Elastography for Assessing Liver Fibrosis: Part 1, Principles and Techniques. AJR Am J Roentgenol 2015; 205:22-32.

17. Guibal A, Renosi G, Rode A, Scoazec JY, Guillaud O, Chardon L, et al. Shear wave elastography: An accurate technique to stage liver fibrosis in chronic liver diseases. Diagn Interv Imaging 2016; 97:91-99.

18. Friedrich-Rust M, Nierhoff J, Lupsor M, Sporea I, Fierbinteanu-Braticevici C, Strobel D, et al. Performance of Acoustic Radiation Force Impulse imaging for the staging of liver fibrosis: a pooled meta-analysis. J Viral Hepat 2012; 19:e212-219.

19. Cassinotto C, Lapuyade B, Mouries A, Hiriart JB, Verginiol J, Gaye D, et al. Non-invasive assessment of liver fibrosis with impulse elastography: comparison of Supersonic Shear Imaging with ARFI and FibroScan(R). J Hepatol 2014; 61:550-557.

20. Cassinotto C, Boursier J, de Ledinghen V, Lebigot J, Lapuyade B, Cales P, et al. Liver stiffness in nonalcoholic fatty liver disease: A comparison of supersonic shear imaging, FibroScan, and ARFI with liver biopsy. Hepatology 2016; 63:1817-1827.

21. Yoon JH, Lee JM, Joo I, Lee ES, Sohn JY, Jang SK, et al. Hepatic fibrosis: prospective comparison of MR elastography and US shear-wave elastography for evaluation. Radiology 2014; 273:772-782.

22. Yin M, Glaser KJ, Talwalkar JA, Chen J, Manduca A, Ehman RL. Hepatic MR Elastography: Clinical Performance in a Series of 1377 Consecutive Examinations. Radiology 2016; 278:114-124.

23. Lignon G, Boursier J, Delumeau S, Michalak-Provost S, Lebigot J, Oberti F, et al. Screening for significant chronic liver disease by using three simple ultrasound parameters. Eur J Radiol 2015; 84:1466-1472.

24. Delahaye J, Bazeries P, Lannes A, Lebigot J, Cartier V, Oberti F, et al. Doppler ultrasonography devices, including elastography, allow for accurate diagnosis of severe liver fibrosis. Eur J Radiol 2018; 108:133-139.

25. Alempijevic T, Zec S, Nikolic V, Veljkovic A, Stojanovic Z, Matovic V, et al. Doppler ultrasonography combined with transient elastography improves the non-invasive assessment of fibrosis in patients with chronic liver diseases. Med Ultrason 2017; 19:7-15.

26. Venkatesh SK, Yin M, Takahashi N, Glockner JF, Talwalkar JA, Ehman RL. Non-invasive detection of liver fibrosis: MR imaging features vs. MR elastography. Abdom Imaging 2015; 40:766-775.

27. Petitclerc L, Sebastiani G, Gilbert G, Cloutier G, Tang A. Liver fibrosis: Review of current imaging and MRI quantification techniques. J Magn Reson Imaging 2016; 45:1276-1295.

28. Ito K, Mitchell DG, Hann HW, Outwater EK, Kim Y, Fujita T, et al. Progressive viral-induced cirrhosis: serial MR imaging findings and clinical correlation. Radiology 1998; 207:729-735.

29. Feng LM, Lei SJ, Zeng X, Wang PQ, Chen RT, Wang J, et al. The evaluation of non-invasive multi-slice spiral computed tomography-based indices for the diagnosis and prognosis prediction of liver cirrhosis. J Dig Dis 2017; 18:472-479.

30. Chen XL, Chen TW, Zhang XM, Li ZL, Zeng NL, Li T, et al. Quantitative assessment of the presence and severity of cirrhosis in patients with hepatitis B using right liver lobe volume and spleen size measured at magnetic resonance imaging. PLoS One 2014; 9:e89973.

31. Cross TJ, Joseph M, Fernando RA, Farrell C, Mitchell JD. The liver to abdominal area ratio (LAAR): a novel imaging score for prognostication in cirrhosis. Aliment Pharmacol Ther 2013; 38:1385-1394.

32. Cassinotto C, Feldis M, Vergniol J, Mouries A, Cochet H, Lapuyade B, et al. MR relaxometry in chronic liver diseases: Comparison of T1 mapping, T2 mapping, and diffusion-weighted imaging for assessing cirrhosis diagnosis and severity. Eur J Radiol 2015; 84:1459-1465.

33. Ding Y, Rao SX, Chen C, Li R, Zeng MS. Assessing liver function in patients with HBV-related HCC: a comparison of T(1) mapping on Gd-EOB-DTPA-enhanced MR imaging with DWI. Eur Radiol 2015; 25:1392-1398.

34. Hann LE, Getrajdman GI, Brown KT, Bach AM, Teitcher JB, Fong Y, et al. Hepatic lobar atrophy: association with ipsilateral portal vein obstruction. AJR Am J Roentgenol 1996; 167:1017-1021.

35. Vilgrain V, Lagadec M, Ronot M. Pitfalls in Liver Imaging. Radiology 2016; 278:34-51.

36. Vilgrain V, Condat B, Bureau C, Hakimé A, Plessier A, Cazals-Hatem D, et al. Atrophy-hypertrophy complex in patients with cavernous transformation of the portal vein: CT evaluation. Radiology 2006; 241:149-155.

37. Zeitoun D, Brancatelli G, Colombat M, Federle MP, Valla D, Wu T, et al. Congenital hepatic fibrosis: CT findings in 18 adults. Radiology 2004; 231:109-116.

38. Glatard AS, Hillaire S, d'Assignies G, Cazals-Hatem D, Plessier A, Valla DC, et al. Obliterative portal venopathy: findings at CT imaging. Radiology 2012; 263:741-750.

Session 1

Information obtained from liver biopsy in the diagnosis of cirrhosis

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Take-home messages

- A large component of "fibrosis" is a condensation of pre-existing collagenous structures caused by collapse (parenchymal extinction). This phenomenon is documented by an increased number of infrastructure elements (especially ducts and arteries) per unit tissue area.
- Method for staging should be quantitative, allowing a more objective and accurate assessment of biopsies. This is important in documenting response to therapy with sequential biopsies.
- Biopsy size is important for preventing sampling error.
- Stage (e.g. diagnosis of cirrhosis) is a small part of what can be learned from liver biopsy. Other parameters provide additional clues to the physiological state of the liver, with prognostic and therapeutic significance. The most important are:
  - Inflammation and congestion. These cause sinusoidal and venous injury that accelerates the progression of parenchymal extinction.
  - Capillarisation. This indicates severely elevated tissue pressure, a response to venous obliteration.
  - Budding, or lack of budding. These are indicators of the regenerative capacity of the liver.

Introduction

Liver biopsies present highly detailed visual images of the parenchyma including many features that cannot be demonstrated with non-invasive tests. Routine stains, such as hematoxylin and eosin show general architecture and hepatocyte health. Various chemical and immunochemical stains highlight features, such as deposition of collagen, iron, copper, bile, alpha-1-antitrypsin and amyloid. Reactive and neoplastic cellular infiltrates can be distinguished. Other features including duct and vessel injury, congestion, regenerative states can be identified and quantified. All of this information is important in the diagnosis and management of patients with liver disease.

In this presentation, staging and the diagnosis of cirrhosis will be emphasised. Staging is an estimation of the severity of architectural degradation and "fibrosis" in comparison with normal and "end-stage" liver disease, commonly called cirrhosis.

Vascular disease in the pathogenesis and regression of chronic liver disease

An introduction to the pathogenesis is necessary to be able to interpret histologic staging systems. Chronic hepatitis, with or without cirrhosis, shows obliteration of hepatic veins and portal veins of small-to-medium size. These lesions are usually secondary to inflammatory injury directed at hepatocytes. The vascular lesions are largely responsible for the ischemic amplification of hepatocyte injury, secondary collapse, and fibrosis [1]. Progression of stage correlates closely with the progression of vascular obstruction [2]. The vascular injury is initiated by local sinusoidal endothelial damage that

progresses to adjacent veins, possibly exacerbated by thrombosis [3]. In late-stage disease, sinusoidal injury continues because of elevated tissue pressure and associated congestion.

Fibrosis is the term applied to the apparent accumulation of newly synthesised collagen. The term is also applied to various derangements of hepatic architecture. Removal of numerous contiguous hepatocytes is followed by focal tissue collapse (parenchymal extinction). This collapse leads to an approximation of pre-existing portal tracts and hepatic veins causing increased collagen concentration in the form of fibrous septa typical of cirrhosis. The relative importance of collapsed infrastructure collagen and newly synthesised collagen in the genesis of cirrhosis is under investigation.

Regression refers to the lowering of the stage with time, usually after control of the aetiologic process [4]. Most patients show regression after cessation of alcohol intake, viral suppression, or removal of iron by phlebotomy [5]. This regression may be explained in part by the re-population and re-expansion of collapsed tissue by progenitor-cell-derived buds [6]. Thus, a healthy regenerative capacity is important for regression to occur [7].

Staging and diagnosis of cirrhosis

Stage of disease is determined by a subjective semi-quantitative assessment of multiple parameters including portal fibrosis, sinusoidal fibrosis, and fibrous septa with curved contours. The thickness of the septa is a parameter in some systems. Several systems for defining stages have been widely used (Fig. 1).

The Laennec staging system was proposed in 2000 [8], noting that the histologic appearance of cirrhosis varied greatly in severity and that this correlated with clinical severity. The Laennec system is based on the METAVIR system with the addition of subdivision of cirrhosis (stage 4) into grades 4A, 4B, and 4C, based on the width of the septa and size of regenerative nodules. This refinement recognises that clinical prognosis is vastly different for patients with different subdivisions of cirrhosis, roughly in parallel with the Child-Pugh clinical classification. This broader spectrum of histologic derangement allows improved documentation of regression of “fibrosis” after viral suppression and other therapies.

All semiquantitative systems require the consideration of several histological parameters to create a composite summary. This diagnostic process is highly subjective and depends greatly on training and experience, as well as the biopsy size. Although each stage is given a number implying a quantitative value, these stages are categories with only semi-quantitative underpinnings.

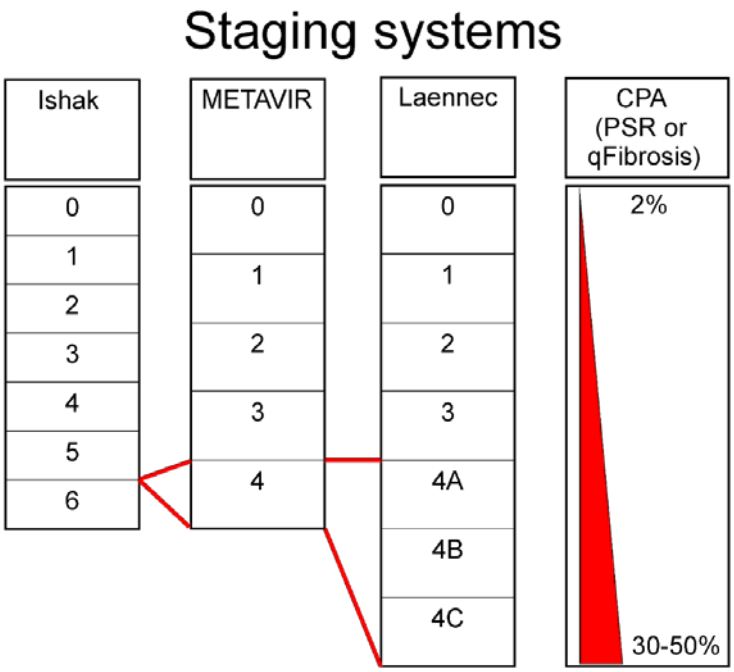

Figure 1. Diagram to show major differences between frequently used staging systems.

Digital imaging analysis

To overcome these difficulties, quantitative digital image analysis was introduced in 1997 by Kage *et al.* and was widely adopted [9,10]. These quantitative methods removed much of the interobserver variability associated with staging of liver biopsies [11,12].

The method uses digital images of tissue stained with Azan, reticulin, or picrosirius-red. The images are segmented so that pixels occupied by collagen can be counted by computer and usually expressed as the per cent of all tissue pixels. The resulting collagen proportionate area (CPA) documents the collagen concentration in the tissue. If a digital slide scanner is not available, digital camera photographs can be stitched with a free program called ICE (Microsoft Windows website). ImageJ software (NIH website) is useful for segmenting and counting collagen pixels.

A newer method capitalises on the physical property of collagen fibres to produce fluorescent signals by second harmonic generation (SHG) [14]. Capturing these signals provides a specific and quantitative image of collagen, recorded as qFibrosis, that gives data comparable to that of pircosirius-red stained tissue. Because the method does not require prior staining, the tissue sections can be used for further studies.

A novel interpretation of histologic staging points to future advances

Collagen concentration in cirrhosis has been shown to be increased 6-10-fold over normal. The tissue collapse found in cirrhosis is also associated with a 6-10-fold increase in the number of portal tracts per unit area. Because portal structures are associated with a large percentage of the collagen of normal liver, much of the increased collagen concentration in cirrhosis may be a reflection of tissue collapse [13].

An obvious extension of these observations is that artery or duct number per unit area can be used to stage biopsies. This is the basis of the forthcoming proposal for a new staging system. Two additional parameters will be included in this system, including CD34-positivity of sinusoidal endothelium (capillarisation) and bud-derived regenerative activity.

Capillarisation indicates severely elevated tissue pressure, a response to venous obliteration. This parameter is thus an easy marker for venous obstruction which is difficult to evaluate directly.

Regeneration can be detected by KI-67 counts but is more easily documented by the presence of CK19-positive cells that are numerous in bud-derived parenchyma. Healthy budding is seen in septa that are re-populating with new hepatocytes. Septa with loss of regenerative capacity lack buds [7]. Thus, the state of budding is a measure of the regenerative capacity of the liver. Active budding is a good indication that the disease is regressing.

Other features of regression

In addition to active budding, there are several histologic parameters that suggest regression is occurring [4]. These include thin or perforated septa, split or isolated collagen bundles in portal stroma, septa, or parenchyma, and growth of hepatocytes within portal and periportal collagen.

Problems with staging: sampling error and interobserver variation

All tissue-based analysis is limited by sample size. Optimum needle biopsy length is >2 cm, although 1.5 cm is usually adequate. Interobserver variation depends on training. Digital image analysis demonstrates less variation because computer programs perform many of the decisions otherwise required of the observer. Measurements are more objective and usually involve only a single parameter of interest.

Clinical use of staging

Monitoring the histological response to therapy requires the comparison of biopsies, so the final opinion depends on the accuracy of two or more evaluations. Accuracy is improved if all biopsies are reviewed simultaneously by the same observer. The pathologist can then decide on the level of confidence that can be assigned to the assessment, based on the quality of the specimens.

The correct choice of staging system or technique is essential. Systems prior to 2000 were not designed to record the severity of severity, so that the progression and regression of established cirrhosis could seldom be documented histologically with sequential biopsies. Severity subdivision also improves the clinical utility of staging, since it can assess prognosis in the cirrhotic range of disease.

Parameters that evaluate activity (inflammation, necrosis, and congestion), as well as capillarisation and regeneration, have important prognostic value and should be considered along with stage.

Non-invasive surrogate parameters for “staging”

As stage is defined by histological parameters, examination of a biopsy is required. Non-invasive techniques can visualise a different set of parameters, such as lobar size, nodularity of the capsular contour, and heterogeneity of ultrasound signals, that correlate sufficiently with histologic stage to guide clinical practice in most, but not all, situations.

References

[References in **BOLD** are required reading]

1. Wanless IR, Huang W-Y. Vascular disorders. In: Burt AD, Portmann BC, Ferrell L, editors. MacSween's Pathology of the Liver. 6th ed. Edinburgh: Churchill-Livingstone-Elsevier; 2012. p. 601-43.
2. Wanless IR, Shiota K. The pathogenesis of nonalcoholic steatohepatitis and other fatty liver diseases: a four-step model including the role of lipid release and hepatic venular obstruction in the progression to cirrhosis. Semin Liver Dis. 2004;24(1):99-106.
3. Wanless IR, Wong F, Blendis LM, Greig P, Heathcote EJ, Levy G. Hepatic and portal vein thrombosis in cirrhosis: possible role in development of parenchymal extinction and portal hypertension. Hepatology. 1995;21(5):1238-47.
4. Wanless IR, Nakashima E, Sherman M. Regression of human cirrhosis: morphologic features and the genesis of incomplete septal cirrhosis. Arch Pathol Lab Med. 2000;124:1599-607.
5. Asselah T, Marcellin P, Bedossa P. Improving performance of liver biopsy in fibrosis assessment. J Hepatol. 2014;61(2):193-5.
6. Stueck AE, Wanless IR. Hepatocyte buds derived from progenitor cells repopulate regions of parenchymal extinction in human cirrhosis. Hepatology. 2015;61(5):1696-707.
7. Wanless I, Stueck A. The mechanism of irreversibility of late stage cirrhosis. J Hepatology. 2018;68:S692.
8. **Kim SU, Oh HJ, Wanless IR, Lee S, Han KH, Park YN. The Laennec staging system for histological sub-classification of cirrhosis is useful for stratification of prognosis in patients with liver cirrhosis. J Hepatol. 2012;57(3):556-63.**
9. Kage M, Shimamatu K, Nakashima E, Kojiro M, Inoue O, Yano M. Long-term evolution of fibrosis from chronic hepatitis to cirrhosis in patients with hepatitis C: morphometric analysis of repeated biopsies. Hepatology. 1997;25(4):1028-31.
10. Pilette C, Rousselet MC, Bedossa P, Chappard D, Oberti F, Rifflet H, et al. Histopathological evaluation of liver fibrosis: quantitative image analysis vs semi-quantitative scores. Comparison with serum markers. J Hepatol. 1998;28(3):439-46.
11. **Standish RA, Cholongitas E, Dhillon A, Burroughs AK, Dhillon AP. An appraisal of the histopathological assessment of liver fibrosis. Gut. 2006;55(4):569-78.**
12. Shiha G, Ibrahim A, Helmy A, Sarin SK, Omata M, Kumar A, et al. Asian-Pacific Association for the Study of the Liver (APASL) consensus guidelines on invasive and non-invasive assessment of hepatic fibrosis: a 2016 update. Hepatol Int. 2017;11(1):1-30.
13. Wanless IR, Ravi PY. Importance of tissue collapse and unmasking of reticulin on the assessment of fibrosis in acute and chronic liver disease. Hepatology. 2016;2016:63.
14. Xu S, Wang Y, Tai DCS, Wang S, Cheng CL, Peng Q, et al. qFibrosis: a fully-quantitative innovative method incorporating histological features to facilitate accurate fibrosis scoring in animal model and chronic hepatitis B patients. J Hepatol. 2014;61(2):260-9.

Hepatic venous pressure measurement and splanchnic hemodynamics

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Take-home messages

- Hepatic vein catheterisation is the gold standard technique for evaluating portal hypertension.
- Hepatic venous pressure gradient is a surrogate marker of prognosis providing information regarding the risk of mortality and clinical decompensation.
- Hemodynamic response is the best marker for the treatment's response.
- Non-invasive markers might help in the initial evaluation of portal hypertension.

Introduction

Development of portal hypertension (PH) is a hallmark in the natural history of liver diseases both due to cirrhosis or non-cirrhosis aetiology. The presence of PH represents the start point of the disease, and its increase correlates with the development of clinical decompensations and prognosis deterioration. Inversely, decreases in portal pressure correlates with better outcome and lower risk of decompensation. PH measurement represents an accurate surrogate marker for prognosis.

PH is defined as a pathological increase in portal venous pressure. Under normal circumstances, the portal perfusion pressure of the liver (pressure gradient between portal vein and inferior vena cava, so-called portal pressure gradient) ranges from 1 to 5 mmHg. PH arises when portocaval pressure gradient increases above 5 mmHg, and it can be easily evaluated via hepatic vein catheterisation and hepatic venous pressure gradient (HVPG) measurement.

As in any other vascular territory, according to Ohm's law, portal pressure increases may be due to an increase in outflow resistance and/or portal venous inflow. In cirrhosis, the most common cause of PH in Western countries is outflow resistance, found in the hepatic parenchyma at the sinusoids (intrahepatic PH). However, obstructions in the splenic, mesenteric or portal vein can cause prehepatic PH whereas obstruction in the hepatic or inferior cava vein may impair venous outflow and cause post-hepatic PH [1].

In cirrhosis, the initial mechanism leading to PH is an increase in the intrahepatic vascular resistance to portal flow due to architectural distortion caused by extracellular matrix deposition and endothelial dysfunction. A sustained increase in portal pressure transmits backwards to patent normal portosystemic anastomoses and provokes dilatation and derivation of portal blood to systemic circulation bypassing the liver (portosystemic shunt). The second important player in PH development is splanchnic vasodilation that provokes increased portal flow. In advance stages of the disease, disequilibrium between endothelial vasodilators and vasoconstrictors and activation of neurohumoral systems cause systemic vasodilation leading to hyperdynamic circulatory state.

Hepatic vein catheterisation is the gold standard technique to measure PH, allows classification of PH and during the same procedure right heart catheterisation can be easily added to evaluate both hepatic and systemic hemodynamics fully.

The technique

HVPG represents the difference between the wedged hepatic venous pressure (WHVP) and the free hepatic venous pressure (FHVP). HVPG value closely correlates with the portocaval pressure gradient that in healthy adults is <6 mmHg. WHVP is measured by occluding a main hepatic vein; occlusion stops the blood flow and the blood stuck transmits the pressure to the preceding territory, the sinusoids. Therefore, WHVP equals sinusoidal pressure, not portal pressure. However, in cirrhosis, resistance is located at the sinusoids, and WHVP accurately correlates with portal pressure. FHVP measures the pressure in the hepatic vein when the catheter lies free, and the vein is not occluded.

HVPG is extremely useful in liver disease diagnosis and evaluating prognosis, but its measurement requires precision and methodical care. Hepatic vein catheterisation is performed under non-invasive vital sign monitoring and local anaesthesia. Ultrasonographic guidance reduces the risk and complications of the local puncture and should be used if available. Using fluoroscopic control, a catheter is moved from the jugular vein to the hepatic vein. FHVP is measured in the hepatic vein confirming that the catheter is "free", at 2-4 cm from its opening into the inferior vena cava. FHVP and not the inferior vena cava or right atrium pressure should be used to calculate HVPG as it correlates better with clinical outcome. WHVP is measured by occluding the hepatic vein, preferably with a catheter balloon than occluding a small and distal vein with the catheter. WHVP should be measured when the value remains stable (usually >40 s) and a minimum of two measurements, preferably three is recommended. Sedation significantly alters portal pressure measurement and should be avoided whenever possible; a maximum dose of 0.02 mg/kg midazolam has been proven not to interfere and can be securely used.

Important cut-off values of HVPG in the natural history of cirrhosis and correlation with outcome (Table 1)

HVPG >5 mmHg diagnoses PH, and it is the earliest and most important consequence of cirrhosis. Worsening of PH correlates with the appearance of clinical decompensations. Indeed, an HVPG ≥10 mmHg is necessary for varices to form [2], and it is the best predictor of clinical decompensation [3,4], and hepatocellular carcinoma [5]. Therefore, in patients with compensated cirrhosis, achieving the 10 mmHg threshold indicates an increased risk of decompensation, and is termed clinically significant portal hypertension (CSPH).

Variceal haemorrhage needs an HVPG ≥12 mmHg to occur [2], and importantly if HVPG decreases to less than 12 mmHg variceal bleeding is totally prevented [6,7].

In patients with previously decompensated cirrhosis, HVPG ≥16 mmHg correlates with poor outcome and risk of death [8]. HVPG ≥20 mmHg, in the setting of acute variceal bleeding, identifies patients with high risk of failure, rebleeding and mortality. In patients with acute alcoholic hepatitis, HVPG >22 mmHg measured early during hospitalisation is associated with a higher risk of death.

Table 1. Prognostic HVPG values in patients with cirrhosis.

HVPG cut-off value	Clinical significance
≥10 mmHg	Risk of varices formation, clinical decompensation and HCC
≥12 mmHg	Risk of variceal haemorrhage
≥16 mmHg	Risk of mortality in decompensated patients
≥20 mmHg	Risk of treatment failure and mortality in AVB
≥22 mmHg	Risk of mortality in AAH

HCC, hepatocellular carcinoma; AVB, acute variceal bleeding; AAH, acute alcoholic hepatitis.

How to interpret changes in HVPG?

Changes in HVPG during follow-up induced either by pharmacological treatment or due to an improvement in liver disease are associated with a better outcome and decreased the development of PH complications.

A reduction of HVPG ≥10% decreases the risk of varices formation and ascites development in patients with compensated cirrhosis. In patients with varices and no previous bleeding, a reduction in HVPG ≥10% reduces the risk of first variceal bleeding.

In patients surviving a variceal bleeding episode, a decrease in HVPG ≥20% from baseline or to 12 mmHg or less (good hemodynamic response) protects from rebleeding, reduces the risk of other PH-related complications and improves survival [9].

Hemodynamic response is the best marker for the treatment's response and achieving good hemodynamic response should be the aim treating PH.

Invasive HVPG *vs.* non-invasive markers: when does it help?

Although HVPG is the best surrogate marker of prognosis in patients with cirrhosis, it is only available and/or performed with adequate standards in a few centres of expertise. Therefore, the capacity of several non-invasive diagnostic methods to predict prognosis has been evaluated. They may help to rule out the presence of CSPH and/or the presence of oesophageal varices in patients with compensated chronic liver disease, at least as a first approach and guide the need of further evaluation with HVPG measurement and upper gastrointestinal endoscopy.

One of the simplest methods to detect PH is through the finding of portocollateral circulation (recanalised paraumbilical vein or spontaneous splenorenal circulation) in the imaging tests or the presence of a reversal of flow within the portal system using ultrasound. They are pathognomonic signs of PH, however, their absence does not rule out CSPH.

Assessment of liver stiffness (LS) by transient elastography (TE) has demonstrated a good capacity to discriminate patients with or without the presence of CSPH. Most studies identified values above 20-25 kPa as the best LS cut-off to detect CSPH with an accuracy of over 90%. LS values have an excellent correlation for HVPG values below 10–12 mmHg but not for values above 12 mmHg, suggesting that beyond a certain degree of portal pressure, the development of PH becomes at least partially independent from the degree of fibrosis and other factors, such as hyperdynamic circulation or splanchnic vasodilatation, which may play an important role. Accordingly, TE is unlikely to be useful in

monitoring the hemodynamic response to drug therapy, mostly mediated by decreasing the splanchnic blood flow. Interestingly, available data suggests that after anti-viral therapy in patients with hepatitis C virus-related cirrhosis and CSPH, changes in LS did not correlate with HVPG, and cut-off values were not reliable in ruling out CSPH after achieving sustained virologic response.

Spleen stiffness (SS) is a novel parameter which might reflect portal pressure better than LS. A close correlation between SS and the degree of PH has been shown that even improves when combining SS and LS measurements. Moreover, SS <54 kPa has been identified as a factor which predicts a low risk of decompensation in two years. However, TE device (Fibroscan) is optimised for LS measurements, and its technical limitations reduce its applicability and diagnostic value. Therefore, newer sonoelastographic methods (like point shear-wave elastography, two-dimensional real-time shear-wave elastography, magnetic resonance elastography) seem to facilitate SS measurement, allowing higher applicability and similar accuracy in the prediction of CSPH or predicting the presence of oesophageal varices.

Several biological parameters have been proposed for the non-invasive detection of CSPH, including prothrombin time, score combining platelet count and total bilirubin, or FibroTest, Forns Index, APRI, etc. but they are not reliable enough for assessing HPVG or to predict the presence of CSPH itself.

However, the combination of different non-invasive tools improves the accuracy of single tests. In particular, the combination of the 3 simple methods (LS, spleen size, and platelet count) can accurately rule out CSPH and high-risk oesophageal varices in patients with compensated chronic liver disease [10]. Based on these observations, the latest Baveno V consensus proposed that endoscopy could be safely avoided in patients with compensated chronic liver disease with LS <20 kPa determined with TE and platelet count above 150,000/mm^3 because they were very unlikely to have a high risk of oesophageal varices.

References

[References in **BOLD** are required reading]

1. **Bosch J, Abraldes JG, Berzigotti A, García-Pagan JC. The clinical use of HVPG measurements in chronic liver disease. Nat Rev Gastroenterol Hepatol 2009;6(10): 573-582.**
2. Garcia-Tsao G, Groszmann RJ, Fisher RL, Conn HO, Atterbury CE, Glickman M. Portal pressure, presence of gastroesophageal varices and variceal bleeding. Hepatology 1985;5(3): 419-424.
3. Groszmann RJ, Garcia-Tsao G, Bosch J, Grace ND, Burroughs AK, Planas R et al. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. N Engl J Med 2005;353(21): 2254-2261.
4. Ripoll C, Groszmann R, Garcia-Tsao G, Grace N, Burroughs A, Planas R, et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. Gastroenterology 2007 Aug;133(2):481-8.
5. Ripoll C, Groszmann RJ, Garcia-Tsao G, Bosch J, Grace N, Burroughs A, et al. Hepatic venous pressure gradient predicts development of hepatocellular carcinoma independently of severity of cirrhosis. J Hepatol. 2009;50(5): 923-928.
6. Groszmann RJ, Bosch J, Grace ND, Conn HO, Garcia-Tsao G, Navasa M et al. Hemodynamic events in a prospective randomized trial of propranolol versus placebo in the prevention of a first variceal hemorrhage. Gastroenterology 1990;99(5): 1401-1407.

7. Feu F, García-Pagán JC, Bosch J, Luca A, Terés J, Escorsell A, et al. Relation between portal pressure response to pharmacotherapy and risk of recurrent variceal haemorrhage in patients with cirrhosis. Lancet 1995;346(8982): 1056-1059.

8. Merkel C, Bolognesi M, Bellon S, Zuin R, Noventa F, Finucci G, et al. (1992). Prognostic usefulness of hepatic vein catheterization in patients with cirrhosis and esophageal varices. Gastroenterology 1992;102(3): 973-979.

9. D'Amico G, Garcia-Pagan JC, Luca A, Bosch J. Hepatic vein pressure gradient reduction and prevention of variceal bleeding in cirrhosis: a systematic review. Gastroenterology 2006;131(5): 1611-1624.

10. Berzigotti A, Seijo S, Arena U, Abraldes JG, Vizzutti F, García-Pagán JC, et al. (2013). Elastography, spleen size, and platelet count identify portal hypertension in patients with compensated cirrhosis. Gastroenterology 2013;144(1): 102-111 e101.


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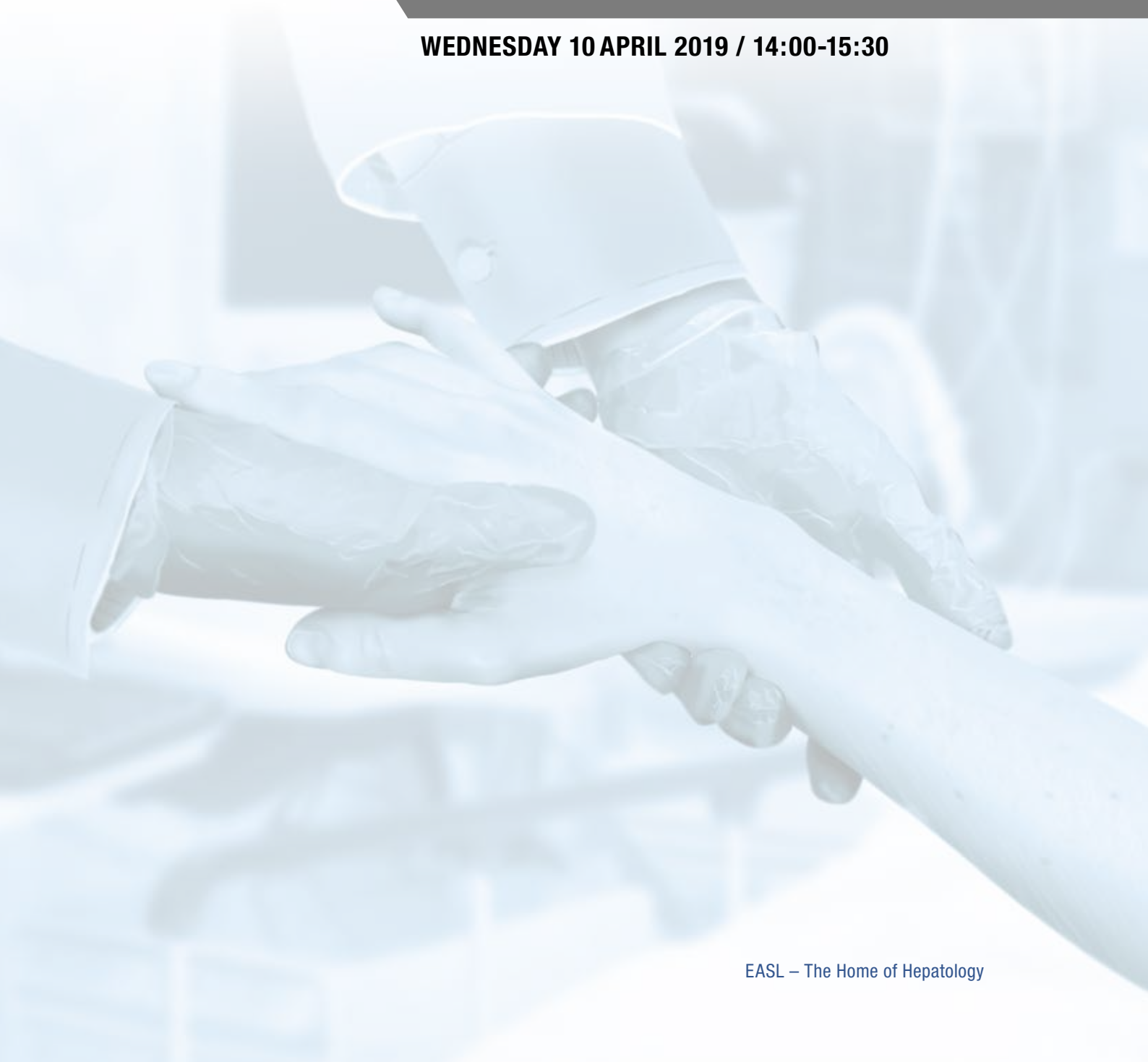
SESSION 2
BLEEDING AND THROMBOSIS

WEDNESDAY 10 APRIL 2019 / 14:00-15:30



Prevention of variceal bleeding and medical management of acute variceal bleeding

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Take-home messages

- In patients with compensated advanced chronic liver disease and clinically significant portal hypertension, the aim of therapy should be to prevent clinical decompensation. The use of non-selective beta-blockers ([NSBB] propranolol or carvedilol) may prevent decompensation (mainly ascites) and liver-related death especially in patients exhibiting at one year of treatment a decrease in HVPG >10% from baseline or <10 mmHg.
- Primary prophylaxis with NSBB (propranolol, nadolol, carvedilol) or endoscopic band ligation (EBL) must be initiated when the patient develops medium-large varices or small varices with red wall signs or in Child-Pugh C patients.
- Despite following current recommendations for acute variceal bleeding, up to 10–20% of patients present with refractory variceal bleeding. It is in this high-risk subgroup of patients where the use of a pre-emptive transjugular intrahepatic portosystemic shunting early after diagnosis of these patients with high-risk acute variceal bleeding improves survival.
- Combination therapy (drug + EBL) is significantly more effective than EBL or drug therapy alone (propranolol or nadolol +/- isosorbide-5-mononitrate) in preventing recurrent gastrointestinal haemorrhage. Pharmacological therapy with NSBB seems to be the more important part of the combination therapy.
- NSBB + EBL + statin is a highly promising therapeutic strategy for the prevention of rebleeding that would need further assessment.
- Current evidence does not support the harmful effect of NSBBs in most patients with decompensated cirrhosis. In these patients, especially in those with refractory ascites or spontaneous bacterial peritonitis, the dose of NSBBs should be carefully titrated, and high doses should be avoided.

Pre-primary prophylaxis

It is currently recommended that in compensated advanced chronic liver disease (ACLD) without clinically significant portal hypertension (CSPH) the aim of therapy should be preventing the development of CSPH, which is best achieved by treating the specific cause of cirrhosis and by supporting healthy lifestyle habits [1]. CSPH is defined as a hepatic venous pressure gradient (HVPG) ≥10 mmHg and is considered the threshold value for the development of varices and clinical decompensation.

A large, multicentre, randomised, placebo-controlled trial in patients with compensated ACLD without gastroesophageal varices showed no differences between placebo and non-selective beta-blockers (NSBB) in preventing the development of varices (pre-primary prophylaxis) [2]. However, this study included patients with and without CSPH, and since the response to NSBB is different between these groups [3], the negative results of this study cannot be generalised.

In patients with compensated ACLD and CSPH, the aim of therapy should be to prevent clinical decompensation. A recent prospective multicentre double-blind randomised controlled trial (RCT), in patients with compensated ACLD, CSPH but without high-risk oesophageal varices (no varices or small varices without red signs), showed that the use of NSBB (propranolol or carvedilol) was associated with a significant reduction in the incidence of decompensation (mainly ascites) or liver-related death. NSBB were particularly successful in the subgroup of patients with small varices and ACLD of non-alcoholic aetiology (Fig. 1) [4].

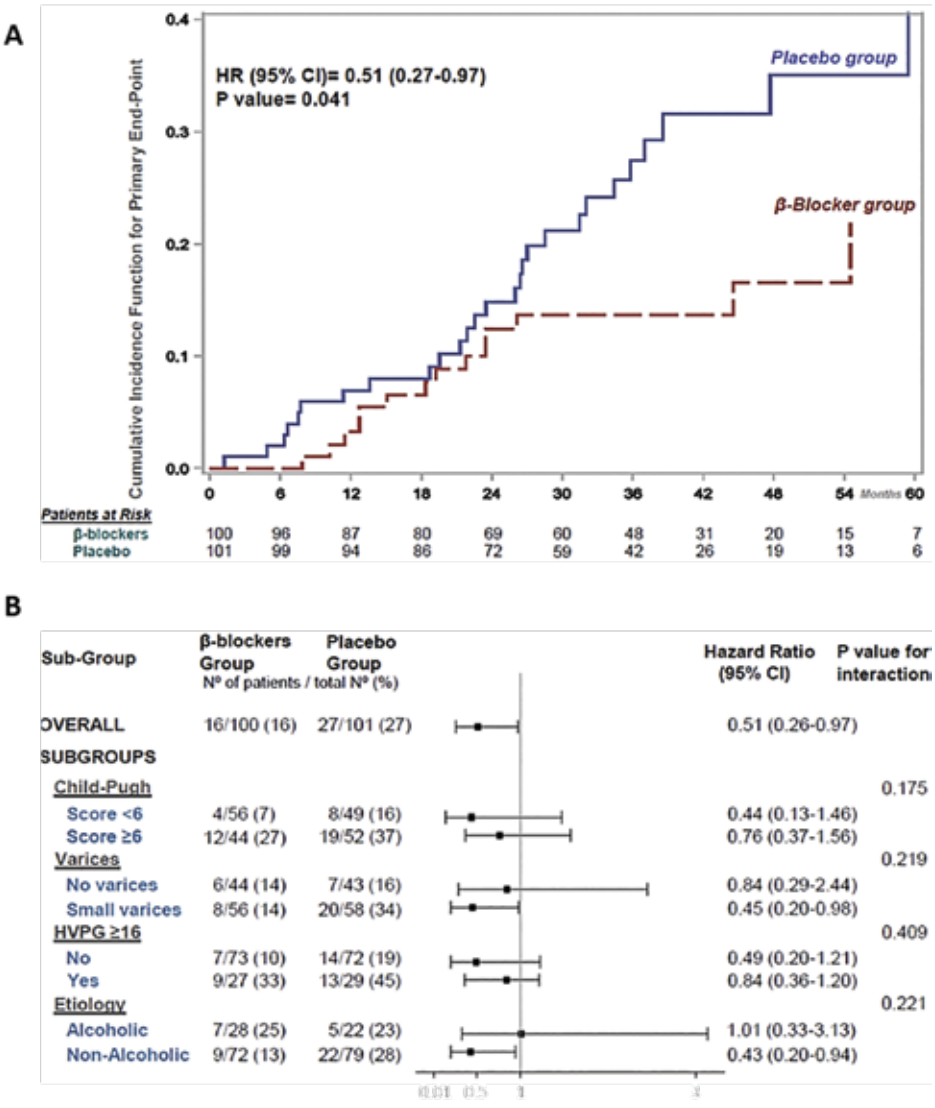

Figure 1. The use of NSBB. (A) Cumulative incidence of developing decompensation and/or death during follow-up in patients treated with beta-blockers *vs.* placebo. The risk was significantly lower in the NSBB-group than in the placebo group. (B) Forest plots of the benefit of NSBB therapy was consistent across pre-specified subgroups and appeared to be particularly pronounced in patients with small varices and in patients with non-alcoholic cirrhosis [4].

These results, that are in accordance with a recent RCT showing that carvedilol prevented the progression from small to large varices [5], recommend to initiate treatment with NSBB, preferably

carvedilol, in patients with ACLD once CSPH is detected. However, the incidence of decompensation or death was just reduced in those patients who had, at 1-year of follow-up, a decrease in HVPG >10% from baseline or <10 mmHg. No effect was shown in patients without such decreases in HVPG (57% of the population evaluated). These data suggest that, in patients not exhibiting such HVPG response, NSBB may not be required.

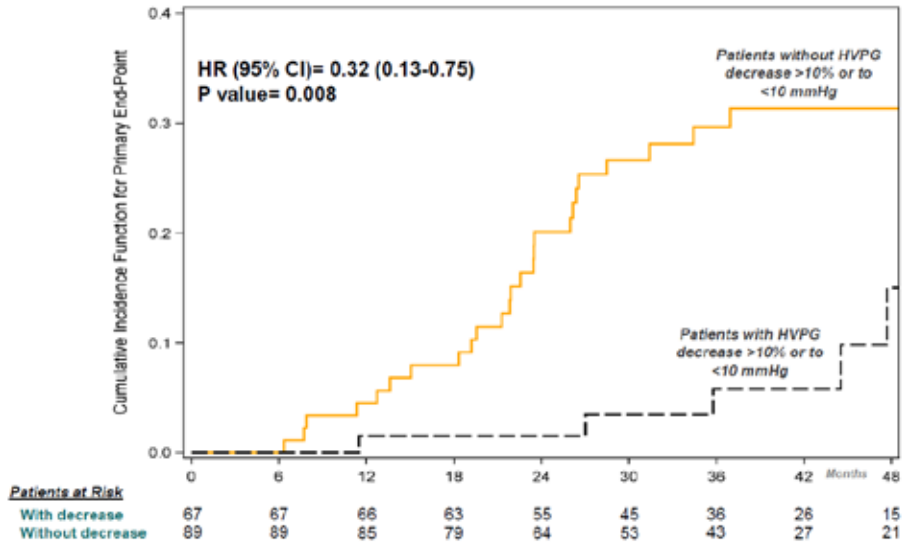

Figure 2. Cumulative incidence of decompensation and/or death in patients who at 1 year had a decrease in HVPG >10% from baseline or <10 mmHg *vs.* patients without such HVPG response [4].

Preventing first bleeding from oesophageal varices

Screening for oesophageal varices

Before 2015, expert consensus documents recommended that, at the time of diagnosis, all patients with cirrhosis (diagnosed either by liver biopsy or by liver elastography >12-15 kPa) should be screened with endoscopy [6] to detect gastroesophageal varices (GEV) that require treatment. However, a large number of those patients did not have GEV. Therefore, to avoid unnecessary endoscopies, in 2015 the selection criteria to undergo screening endoscopy in fully compensated patients was restricted to patients with elastography stiffness values >20 kPa or a platelet count below $150x10^9$/L and/or imaging study showing collaterals [7,8] indicating a higher risk of having varices. If GEV are not found at this initial endoscopy, follow-up endoscopies should be performed. Depending on the estimated risk of GEV to appear, in patients with advanced liver failure (Child-Pugh B and C), follow-up evaluation should be performed every year, while in patients with less severe disease, follow-up endoscopy should be performed every 2 years if there is an ongoing active disease or every 3 years if the disease is inactive [7,8].

Primary prophylaxis

Primary prophylaxis with NSBB (propranolol, nadolol, carvedilol) or endoscopic band ligation (EBL) must be initiated (see below) when the patient develops medium to large varices or small varices

with red wall signs or in Child-Pugh C patients [7]. No follow-up endoscopy is needed once NSBB are started, as these drugs should be maintained life-long. As previously mentioned, in patients with compensated cirrhosis and small varices without red signs, NSBB can prevent decompensation. However, if no treatment is initiated, surveillance endoscopy to evaluate a possible increase in size must be scheduled at one year if the disease remains active or every 2 years if inactive [4].

NSBB *vs.* EBL for primary prophylaxis

Propranolol and nadolol block the beta-1 adrenergic receptors in the heart and the peripheral beta-2 adrenergic receptors. Beta-1 blockade of cardiac receptors reduces heart rate and cardiac output and subsequently decreases flow into the splanchnic circulation. Beta-2 blockade leads to unopposed alpha-1 adrenergic activity that causes splanchnic vasoconstriction and a reduction of the portal inflow. Both effects contribute to the reduction in portal pressure [9]. Beyond reducing portal pressure, NSBB also have other beneficial effects in cirrhosis, such as reducing bacterial translocation and spontaneous bacterial peritonitis (SBP) due to the shortening of intestinal transit time and decreased bacterial overgrowth. Treatment with NSBB must be gradually stepped up until maximal tolerated dose (240 mg for propranolol, 160 mg for nadolol) or when heart rate is below 55 bpm or systolic blood pressure <100 mmHg. The goal is to reduce HVPG to $\leq$12 mmHg, or $\geq$20% from baseline protects from variceal haemorrhage [10,11] and also decreases the incidence of clinical decompensation and improves survival [12]. However, only 40-50% of the patients achieve such a hemodynamic response. Combination therapy with vasodilators (isosorbide 5-mononitrate or prazosin) enhances the reduction of HVPG in up to a third of non-responders [13]. However, these combinations are rarely used for primary prophylaxis. This is not the case for carvedilol. Carvedilol is an NSBB that also has some vasodilatation activity by blocking the alpha-1 adrenergic receptors. Carvedilol is more powerful in reducing HVPG than propranolol or nadolol and achieves a good hemodynamic response (HVPG reduction >20% from baseline or below 12 mmHg) in nearly 75% of cases [14,15,16]. Carvedilol has its maximal effects on portal pressure at low doses (12.5 mg per day) that are better tolerated than effective doses of traditional NSBB. Because of these advantages, carvedilol is becoming the most used NSBB for the management of portal hypertension in compensated cirrhosis. However, more data is required for its safety in decompensated patients with ascites.

EBL is performed every 3-4 weeks until eradication is achieved. Once varices are eradicated (usually after a mean of 2-3 sessions but there is high variability ranging from 1 to more than 10 sessions) follow-up endoscopies must be scheduled to evaluate the possible reappearance of the varices. These follow-up endoscopies are usually scheduled every 3 months and then every 6 months. If varices reappear, new EBL sessions must be done to re-eradicate them. EBL may cause significant side effects, such as bleeding from post-EBL ulcers.

Several RCT and meta-analysis of the RCTs have compared NSBB with EBL for primary prophylaxis. Briefly, these studies indicate that EBL is associated with a lower incidence of first variceal haemorrhage without significant differences in mortality [17,18]. Side effects were more frequent with NSBB but more severe with EBL. A recent network meta-analysis, combining direct evidence from RCTs with head-to-head comparison of interventions with indirect evidence from RCTs that compare different interventions with a common comparator, included 32 RCT with more than 3000 patients with cirrhosis and large oesophageal varices supported the use of NSBB as the preferred initial approach for primary prophylaxis. This recommendation was based on their findings showing that NSBB monotherapy may decrease all-cause mortality and the risk of first variceal bleeding with less severe complications than EBL. Authors of the study recommended to reserve EBL for patients with contraindications or who develop side effects after using NSBB [19]. This conclusion was, however, challenged by an accompanying editorial to the original article [20] that stated the presented evidence

was not strong enough to make this suggestion and concluded still using EBL, NSBB or carvedilol for primary prophylaxis are adequate options and that choices should be based on patients preferences after full explanation of the different alternatives.

Another strategy could be to combine drugs plus EBL. However, all randomised studies and meta-analyses comparing the combination of NSBB plus EBL *vs.* EBL alone in primary prophylaxis have failed to show a clear benefit from combination therapy, with a predicted a higher number of adverse events in the combination therapy group [21]. Therefore, currently combined therapy is not recommended for primary prophylaxis.

Medical management of acute variceal bleeding

Acute variceal bleeding (AVB) is the most severe and life-threatening complication of portal hypertension. We will focus on the goals of the treatment in AVB, namely: the control of the AVB episode and the prevention of bleeding-related complications.

General measures

The initial ABC (Airway, Breathing, Circulation) of resuscitation should be applied with the aim of maintaining aerobic metabolism and restoring an appropriate oxygen transport to the tissues. At least two large catheters should be placed to allow rapid volume expansion, usually with crystalloids. A central catheter is also recommended to closely monitor the volemic status of the patient avoiding either severe hypovolemia causing renal failure or hypervolemia. In addition, orotracheal intubation must be done if there's any depression of consciousness (i.e. hepatic encephalopathy). An exquisite balance must be maintained to restore and maintain hemodynamic stability avoiding overexpansion, which may increase portal pressure, impair clot formation and increase the risk of further bleeding. In fact, a certain degree of hypovolemia and hypotension promotes the activation of the endogenous vasoactive system leading to splanchnic vasoconstriction and, therefore, reduced portal blood flow and pressure. A restrictive packed red blood cell transfusion strategy improves survival in Child-Pugh A & B patients. Therefore, patients should be transfused when haemoglobin drops below 7 g/dl aiming at a target level of 7-8 g/dl. Exceptions, such as massive bleeding and cardiovascular co-morbidities (acute coronary syndrome, symptomatic peripheral vasculopathy, stroke, etc.) or conditions precluding an adequate physiological response to acute anaemia should be considered. Antibiotics significantly reduce the incidence of bacterial infections and improve survival in patients with AVB. Therefore, antibiotic prophylaxis is considered an integral part of therapy for patients with cirrhosis presenting with AVB and should be instituted from admission as the presence of bacterial infections is an independent predictor of failure to control bleeding and death. Oral quinolones (norfloxacin 400 mg b.i.d orally or by nasogastric tube for at least 7 days) or intravenous ceftriaxone (1 g daily for 7 days) in high-risk patients (those with ascites, severe malnutrition, encephalopathy or bilirubin >3 mg/dl), as well as in hospital settings with high prevalence of quinolone-resistant bacterial infections and in patients on previous quinolone prophylaxis can be used.

Aspiration pneumonia is the most common infection in AVB. Inhalation of blood or gastric content is especially common in patients with hepatic encephalopathy, especially during hematemesis, upper endoscopy, oesophageal tamponade and application of endoscopic treatment. In addition to aspiration pneumonia, AVB patients may develop SBP, urinary tract infection and spontaneous bacteraemia. Enteric pathogens are the most commonly involved microorganisms.

Specific haemostatic therapy

Current recommendations for AVB entail the combination of a pharmacological vasoactive agent (e.g., terlipressin, somatostatin, somatostatin analog) and endoscopic treatment (EBL or sclerotherapy could be used in those rare cases where it is not possible to perform band ligation). Early (pre-emptive) transjugular intrahepatic portosystemic shunting (TIPS) should be considered in patients at high-risk of treatment failure (HVPG $\geq$20 mmHg and/or Child-Pugh C patients <14 points and Child-Pugh B with active bleeding during endoscopy) after initial pharmacological and endoscopic therapy or at any moment as a rescue therapy.

Intensive care management, together with the use of combination treatment with endoscopic therapy, vasoactive drugs, careful replacement of volemia and antibiotics, has shown to reduce the 6-week mortality of AVB to about 15%. Despite this standard of care therapy, up to 10–20% of patients present with refractory variceal bleeding and require further intensive management. It is in this subgroup of patients where the mortality of the bleeding episode mostly accumulates. Indeed, even with the use of rescue TIPS, mortality in this population varies between 30 and 50% and accounts for 90% of deaths related to AVB. Several variables, such as the degree of liver failure or the severity of portal hypertension, identify patients at high-risk of treatment failure or early rebleeding. This has prompted the use of pre-emptive TIPS early after diagnosis of AVB if patients have variables predicting a high-risk of treatment failure (see in other chapters of the syllabus).

Prevention of recurrent bleeding from oesophageal varices

Patients who recover from the first episode of AVB have a high-risk of rebleeding (60% in the first year), with a mortality of up to 33%. Therapy to prevent rebleeding is therefore mandatory in these patients and should be established before the patient is discharged from hospital. Several meta-analyses have demonstrated that combination therapy (drug + EBL) is significantly more effective than EBL or drug therapy alone (propranolol or nadolol +/- isosorbide-5-mononitrate) in preventing recurrent gastrointestinal haemorrhage, but without a clear effect on survival. However, these studies did not take into consideration the cirrhosis stage. A recent individual patient meta-analysis including 3 RCTs comparing EBL + NSBB *vs.* NSBB alone and 4 RCTs comparing EBL + NSBB *vs.* EBL alone showed that in patients with compensated cirrhosis (Child-Pugh A) combination therapy (EBL + NSBB) is better than either alone preventing rebleeding but with no significant improvement in survival. However, in Child-Pugh B or C patients adding EBL does not improve rebleeding rate or survival in comparison to NSBB alone. On the contrary, adding NSBB to EBL in this population of patients reduced rebleeding and improved survival in comparison to EBL alone. Figure 3 shows the survival probability according to treatment and Child-Pugh class with a combination of EVL and BB *vs.* BB alone or *vs.* EVL alone. Thus, pharmacological therapy with NSBB is the more important part of the combination therapy. In most included studies, NSBB were associated to isosorbide-5-mononitrate, and it is well known that although it is associated to a slightly higher rate of side effects, the combination of NSBBs plus low-dose isosorbide mononitrate (ISMN) has a greater portal pressure-reducing effect than NSBBs alone. Nevertheless, in a meta-analysis, the combination of NSBBs and ISMN was not significantly better than NSBBs alone preventing rebleeding or decreasing mortality [22].

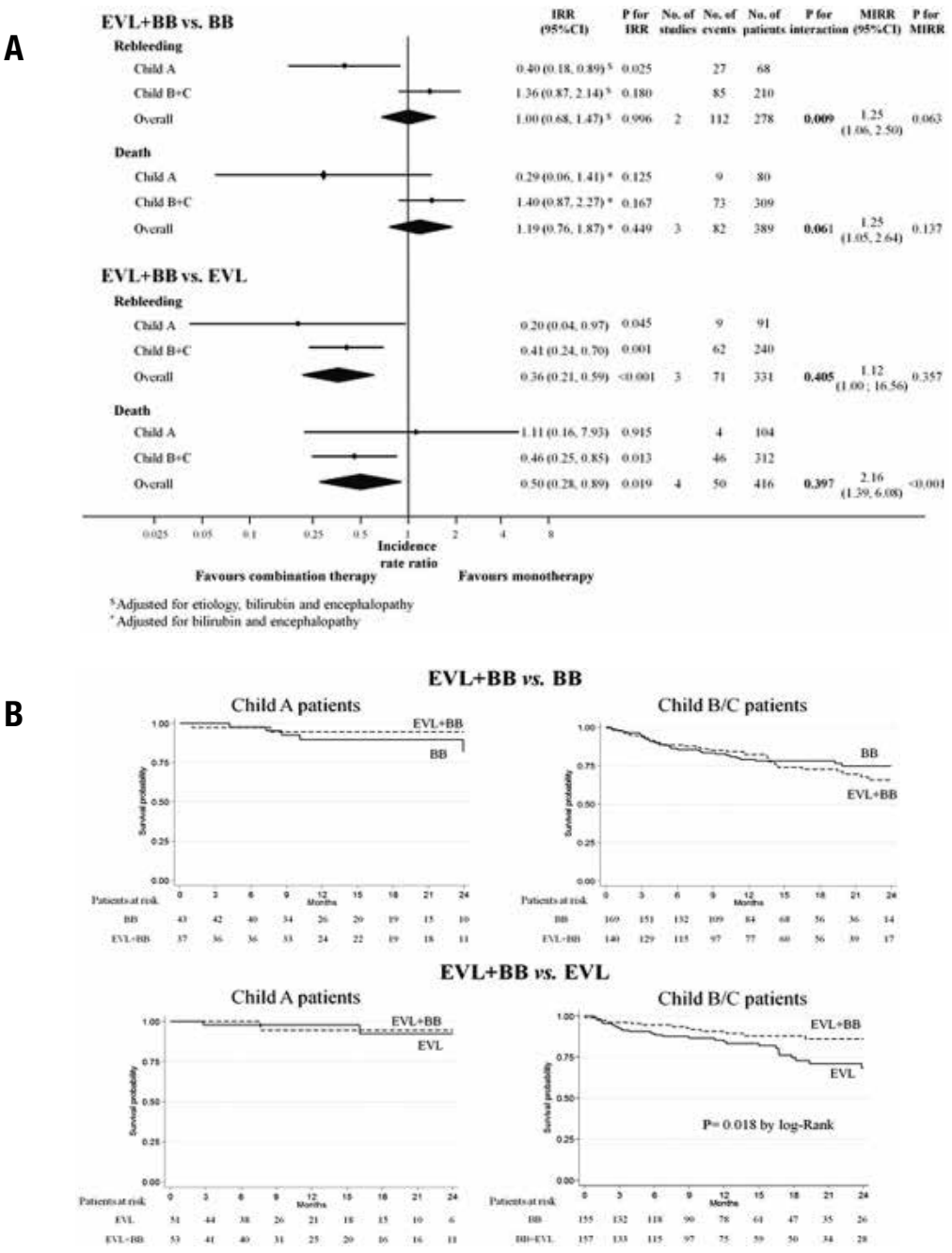

Figure 3. Survival probability according to treatment and Child-Pugh class with the combination of endoscopic variceal ligation (EVL) and beta-blockers (BB) *vs.* BB alone (A) or *vs.* EVL alone (B), as estimated by Kaplan-Meier [23].

Carvedilol has shown similar efficacy at preventing rebleeding and survival to EBL [24] or NSBB + ISMN [25]. Although, as far as we know, this combination has never been compared, it seems rational that the combination of carvedilol with EBL could be another effective drug + EBL strategy for secondary prophylaxis. In most studies, carvedilol is used at a dose increased if tolerated from 6.25 to 12.5 mg day. Higher doses of carvedilol, particularly at doses ≥25 mg/day, may decrease arterial pressure [15] and should not be used in patients with refractory/difficult to control ascites.

A recent multicentre, placebo-controlled RCT showed that the addition of simvastatin to EBL + NSBB (40 mg/day) was not associated with a significant reduction in rebleeding (compared to those administered a placebo), but was associated with a significant improvement in survival, mainly related to a decrease in deaths from rebleeding or infections [26]. Therefore, this combination (NSBB + EBL + statin) is a highly promising therapeutic strategy that would need further assessment.

Should we monitor beta-blockers?

The lowest bleeding or rebleeding rates are observed in patients who are HVPG responders (defined as a reduction in HVPG below 12 mmHg or >20% from baseline) [27]. In addition, this HVPG response is associated with a lower risk to develop other complications of portal hypertension and a better survival. The acute hemodynamic response to beta-blockers can also be used to predict the long-term risk of bleeding. An HVPG reduction >10% from baseline is the best target to define a response associated with a good long-term outcome [28]. The acute HVPG response to propranolol would be a more cost-effective strategy than the chronic evaluation of HVPG response and might be useful to guide therapeutic decisions in these patients. All the studies mentioned above set the rationale for the use of hemodynamic response as the therapeutic target in the drug therapy of portal hypertension and opened the possibility to use these hemodynamic criteria to tailor the treatment of portal hypertension by measuring the individual portal pressure response to therapy. Bleeding risk in HVPG-responders is extremely low, even lower than that achieved using surgical shunts or TIPS. Consequently, in these patients, it is unlikely that adding a further treatment (i.e. EBL) will result in a greater efficacy but may increase the number of adverse events. Efforts at improving therapy should focus on HVPG non-responders. However, data on how to improve the outcome of this high-risk population is scanty, and it is not yet known what the best option for patients without an adequate HVPG response to drug therapy is. Indeed, shifting to or adding EBL to these patients seems not to be associated with a marked improvement in outcomes. These data suggest that HVPG non-responders may require more effective and aggressive therapy to reduce the high rebleeding risk in these patients (46-65% in a recent survey). However, this needs to be carefully explored in adequately designed studies.

Deleterious effects of NSBBs

As previously mentioned, most NSBB side effects (hypotension, fatigue, weakness) may be managed by adjusting the dose. However, up to 15-20% of patients may have absolute or relative contraindications to NSBB or develop side effects severe enough that would require NSBB withdrawal.

A topic raising a lot of discussions in recent years is the use of NSBB in patients with ascites and in those with difficult to treat or refractory ascites [29,30]. Observational studies raised concerns regarding the use of NSBBs in patients with refractory ascites due to the finding of increased mortality [30] or of a greater incidence of post-paracentesis circulatory dysfunction [31]. A retrospective study showed that NSBBs improved survival in patients with ascites, but in a sub-analysis limited to those surviving an episode of SBP, NSBBs worsened survival and had a higher risk of hepatorenal syndrome [32].

These concepts have been challenged by three subsequent studies assessing large cohorts of patients with ascites [33,34,35], which have shown either no differences [34] or even improved survival [33,35] in patients treated with NSBBs, including patients with refractory ascites. An additional study showed that ongoing treatment with NSBBs was associated with improved survival in patients with acute-on-chronic liver failure [36].

The discrepancies might have been influenced by the use of unusually high doses of NSBBs in the initial studies, as suggested by two recent publications, showing that in patients with decompensated cirrhosis, doses of propranolol ≥160 mg/day were associated with worse survival, whereas doses up to 160 mg/day were associated with improved survival [35]. The second study showed similar findings in patients with SBP: doses <160 mg/day of propranolol were associated with improved survival after adjustment for confounders, whereas doses of 160 mg/day or above were not [37]. It is important to note that doses of propranolol of 160 mg or above (or of >80 mg/day if using nadolol) are very rarely (if ever) required in decompensated cirrhosis if the recommended titration steps for adjusting propranolol dosage are adhered to.

In summary, current evidence does not support a harmful effect of NSBBs in most patients with decompensated cirrhosis. In these patients, especially in those with refractory ascites or SBP, the dose of NSBBs should be carefully titrated and high doses should be avoided. Also, this last group of patients need careful monitoring and the NSBB dose reduced (or discontinued) with the development of severe hypotension (systolic blood pressure <90 mmHg), hyponatremia (serum sodium <130 mEq/L), or unexplained deterioration of renal function [7]. NSBBs might be reintroduced after correction of renal function/circulatory state. Monitoring for NSBB in these situations needs to be even more cautious if using carvedilol because, as previously mentioned, this drug may produce more accentuated hypotension.

Management of ectopic varices

Ectopic varices (EcV) are dilated portosystemic venous collaterals located outside of the gastro-oesophageal region. The rectum and the duodenum are the most common sites for EcV, but they can be present along the whole intestinal tract and especially in peristomal locations. Ectopic variceal bleeding is rare and accounts for only 1 to 5% of all variceal bleedings [38]. However, when present, EcV have a 4-fold increased risk of bleeding when compared with oesophageal varices and can have a mortality rate as high as 40% [38]. At present, there is no consensus on the best diagnostic workup and therapeutic strategies [39].

Treatment described depends on the localisation of the EcV, and includes stomal revision, mucocutaneous disconnection, variceal suture ligation and sclerotherapy. These methods may only serve to temporise the bleeding and are usually associated with a high-risk of recurrent bleeding [38,40]. TIPS has been advocated as the treatment of choice in patients with underlying liver cirrhosis, but the debate of whether to manage these varices by decompression with a TIPS, or other portosystemic shunts, *vs.* transvenous obliteration is unresolved. The rebleed rates after TIPS decompression are 20-40%. The rebleed rates after transvenous obliteration and the mortality rate at 3-6 months are 30-40% and 50-60%, respectively [40]. Several publications have addressed the role of TIPS to treat bleeding from EcV in cirrhotic patients with portal hypertension not responsive to conservative or endoscopic management [38]. Since EcV may rebleed despite a reduction of the portosystemic pressure gradient <12 mmHg or alternatively despite a 25–50% drop of baseline gradient, adding embolisation to TIPS could be useful to control bleeding of EcV.

References

1. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. Lancet 2014;383:1749–61.
2. Groszmann RJ, Garcia-Tsao G, Bosch J, Grace ND, Burroughs AK, Planas R, et al. Beta-Blockers to Prevent Gastroesophageal Varices in Patients with Cirrhosis. N Engl J Med 2005;353:2254–61.
3. Villanueva C, Albillos A, Genescà J, Abraldes JG, Calleja JL, Aracil C, et al. Development of hyperdynamic circulation and response to beta-blockers in compensated cirrhosis with portal hypertension. Hepatology 2016;63:197–206.
4. Villanueva C, Albillos A, Genescà J, Garcia-Pagán J-C, Calleja JL, Aracil C, et al. β-blockers to prevent the decompensation of cirrhosis in patients with clinically significant portal hypertension. Lancet 2018: In press.
5. Bhardwaj A, Kedarisetty CK, Vashishtha C, Bhadoria AS, Jindal A, Kumar G, et al. Carvedilol delays the progression of small oesophageal varices in patients with cirrhosis: a randomised placebo-controlled trial. Gut 2016;66:1838–43.
6. Merkel C, Marin R, Angeli P, Zanella P, Felder M, Bernardinello E, et al. A placebo-controlled clinical trial of nadolol in the prophylaxis of growth of small esophageal varices in cirrhosis. Gastroenterology 2004;127:476–84.
7. Franchis R De, Baveno V Faculty. Expanding consensus in portal hypertension. Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. J Hepatol 2015;63:743–52.
8. Jakab SS, Garcia-Tsao G. Screening and Surveillance of Varices in Patients With Cirrhosis. Clin Gastroenterol Hepatol 2019;17:26–9.
9. D'Amico G, Pagliaro L, Bosch J. Pharmacological treatment of portal hypertension: an evidence-based approach. Semin Liver Dis 1999;19:475–505.
10. Feu F, García-Pagán JC, Bosch J, Luca A, Escorsell A, Rodés J, et al. Relation between portal pressure response to pharmacotherapy and risk of recurrent variceal haemorrhage in patients with cirrhosis. Lancet 1995;346:1056–9.
11. D'Amico G, Garcia-Pagan JC, Luca A, Bosch J. Hepatic Vein Pressure Gradient Reduction and Prevention of Variceal Bleeding in Cirrhosis: A Systematic Review. Gastroenterology 2006;131:1611–24.
12. Reiberger T, Ulbrich G, Ferlitsch A, Payer BA, Schwabl P, Pinter M, et al. Carvedilol for primary prophylaxis of variceal bleeding in cirrhotic patients with haemodynamic non-response to propranolol. Gut 2013;62:1634–41.
13. García-Pagán JC, Morillas R, Bañares R, Albillos A, Villanueva C, Vila C, et al. Propranolol plus placebo versus propranolol plus isosorbide-5-mononitrate in the prevention of a first variceal bleed: A double-blind RCT. Hepatology 2003;37:1260–6.
14. Bosch J. Carvedilol for portal hypertension in patients with cirrhosis. Hepatology 2010;51:2214–8.
15. Sinagra E, Perricone G, D'Amico M, Tinè F, D'Amico G. Systematic review with meta-analysis: The haemodynamic effects of carvedilol compared with propranolol for portal hypertension in cirrhosis. Aliment Pharmacol Ther 2014;39:557–68.

16. Reiberger T, Ulbrich G, Ferlitsch A, Payer BA, Schwabl P, Pinter M, et al. Carvedilol for primary prophylaxis of variceal bleeding in cirrhotic patients with haemodynamic non-response to propranolol. Gut 2013;62:1634–41.

17. Abraldes J, Angermayr B, Bosch J. The management of portal hypertension. Clin Liver Dis 2005;9:685–713.

18. Gluud LL, Krag A. Banding ligation versus beta-blockers for primary prevention in œsophageal varices in adults. Cochrane Database Syst Rev 2012;8:CD004544.

19. Sharma M, Singh S, Desai V, Shah VH, Kamath PS, Murad MH, et al. Comparison of Therapies for Primary Prevention of Esophageal Variceal Bleeding: A Systematic Review and Network Meta-analysis. Hepatology 2018.

20. Laine L. Interventions for primary prevention of esophageal variceal bleeding. Hepatology 2018.

21. Sarin SK, Wadhawan M, Agarwal SR, Tyagi P, Sharma BC. Endoscopic variceal ligation plus propranolol versus endoscopic variceal ligation alone in primary prophylaxis of variceal bleeding. Am J Gastroenterol 2005;100:797–804.

22. Gluud LL, Langholz E, Krag A. Meta-analysis: Isosorbide-mononitrate alone or with either beta-blockers or endoscopic therapy for the management of oesophageal varices. Aliment Pharmacol Ther 2010;32:859–71.

23. Albillos A, Zamora J, Martínez J, Arroyo D, Ahmad I, De-la-Peña J, et al. Stratifying risk in the prevention of recurrent variceal hemorrhage: Results of an individual patient meta-analysis. Hepatology 2017;66:1219–31.

24. Stanley AJ, Dickson S, Hayes PC, Forrest EH, Mills PR, Tripathi D, et al. Multicentre randomised controlled study comparing carvedilol with variceal band ligation in the prevention of variceal rebleeding. J Hepatol 2014;61:1014–9.

25. Lo GH, Chen WC, Wang HM, Yu HC. Randomized, controlled trial of carvedilol versus nadolol plus isosorbide mononitrate for the prevention of variceal rebleeding. J Gastroenterol Hepatol 2012;27:1681–7.

26. Abraldes JG, Villanueva C, Aracil C, Turnes J, Hernandez-Guerra M, Genesca J, et al. Addition of Simvastatin to Standard Therapy for the Prevention of Variceal Rebleeding Does Not Reduce Rebleeding but Increases Survival in Patients with Cirrhosis. Gastroenterology 2016;150:1160–1170e3.

27. Bosch J, García-Pagán J. Prevention of variceal rebleeding. Lancet 2003;361:952–4.

28. Villanueva C, Aracil C, Colomo A, Hernández-Gea V, López-Balaguer JM, Alvarez-Urturi C, et al. Acute Hemodynamic Response to beta-Blockers and Prediction of Long-term Outcome in Primary Prophylaxis of Variceal Bleeding. Gastroenterology 2009;137:119–28.

29. Noronha Ferreira C, Seijo S, Plessier A, Silva-Junior G, Turon F, Rautou PE, et al. Natural history and management of esophagogastric varices in chronic noncirrhotic, nontumoral portal vein thrombosis. Hepatology 2016;63:1640–50.

30. Sersté T, Melot C, Francoz C, Durand F, Rautou P-E, Valla D, et al. Deleterious effects of beta-blockers on survival in patients with cirrhosis and refractory ascites. Hepatology 2010;52: 1017–22.

31. Sersté T, Francoz C, Durand F, Rautou PE, Melot C, Valla D, et al. Beta-blockers cause paracentesis-induced circulatory dysfunction in patients with cirrhosis and refractory ascites: A cross-over study. J Hepatol 2011;55:794–9.

32. Mandorfer M, Bota S, Schwabl P, Bucsics T, Pfisterer N, Kruzik M, et al. Nonselective beta-blockers increase risk for hepatorenal syndrome and death in patients with cirrhosis and spontaneous bacterial peritonitis. Gastroenterology 2014;146:1680–90.

33. Leithead JA, Rajoriya N, Tehami N, Hodson J, Gunson BK, Tripathi D, et al. Non-selective beta-blockers are associated with improved survival in patients with ascites listed for liver transplantation. Gut 2015;64:1111–9.

34. Bossen L, Krag A, Vilstrup H, Watson H, Jepsen P. Nonselective beta-blockers do not affect mortality in cirrhosis patients with ascites: Post Hoc analysis of three randomized controlled trials with 1198 patients. Hepatology 2016;63:1968–76.

35. Bang UC, Benfield T, Hyldstrup L, Jensen J-EB, Bendtsen F. Effect of propranolol on survival in patients with decompensated cirrhosis: A nationwide study based Danish patient registers. Liver Int 2016;36:1304–12.

36. Mookerjee RP, Pavesi M, Thomsen KL, Mehta G, MacNaughtan J, Bendtsen F, et al. Treatment with non-selective beta blockers is associated with reduced severity of systemic inflammation and improved survival of patients with acute-on-chronic liver failure. J Hepatol 2016;64: 574–82.

37. Madsen B, Nielsen K, Fialla A, Krag A. Keep the sick from harm in spontaneous bacterial peritonitis: Dose of beta blockers matters. J Hepatol 2016;64:1455–6.

38. Kwok ACH, Wang F, Maher R, Harrington T, Gananadha S, Hugh TJ, et al. The role of minimally invasive percutaneous embolisation technique in the management of bleeding stomal varices. J Gastrointest Surg 2013;17:1327–30.

39. Struyve M, Robaeys G. Ectopic variceal bleeding due to portosystemic shunt via dilated mesenteric veins and a varicous left ovarian vein: case report and literature review of ectopic varices. Acta Gastroenterol Belg n.d.;80:388–95.

40. Saad WEA, Lippert A, Saad NE, Caldwell S. Ectopic varices: anatomical classification, hemodynamic classification, and hemodynamic-based management. Tech Vasc Interv Radiol 2013;16:158–75.

Coagulation changes in cirrhosis: from bleeding to prothrombotic state

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Take-home messages

- Patients with cirrhosis have profound alterations in coagulation pathways leading to an altered haemostatic balance, which is specific for every patient and is influenced by the stage of liver disease and superimposed conditions. This equilibrium can be acutely tipped towards haemorrhagic and thrombotic complications.
- Invasive procedures increase the risk of bleeding complications in patients with cirrhosis compared to the non-cirrhotic population, especially during surgery or therapeutic endoscopy. Supplementation with platelets to obtain a threshold of about 60-70 x 10^9/L could reduce this risk in thrombocytopenic patients, although evidence is weak. Whole blood coagulation viscoelastic tests may be promising in this field.
- During acute bleeding, it is important to avoid volume overload (if correlated with portal hypertension), dilutional coagulopathy and to replenish coagulation factors and fibrinogen if patients have prolonged bleeding or worsening of accelerated intravascular coagulation. In this setting, seek advice from a haematologist with experience in viscoelastic tests.
- The interaction between the coagulation cascade and liver injury is multifaceted. Anticoagulation seems to be promising in reducing portal hypertension, and decompensation episodes in cirrhosis and further trials are needed.

The balance of coagulation/anticoagulation

The liver synthesises most coagulation factors and their inhibitors, except for von Willebrand factor (vWf). Liver failure is accompanied by multiple changes in the haemostatic system because of reduced plasma levels of procoagulative and anticoagulative clotting factors synthesised by the intact liver. Therefore, the haemostatic system is in a delicate balance between prothrombotic and antithrombotic processes, aimed at preventing excessive blood loss from injured vessels and spontaneous thrombosis. Moreover, during liver failure, there is a reduced capacity to clear activated haemostatic proteins and protein inhibitor complexes from the circulation. Thus, the global effect of liver disease with regard to haemostasis is complex, in which patients with advanced liver disease can experience severe bleeding or even thrombotic complications. Finally, when marked portal hypertension develops with secondary splenomegaly, thrombocytopenia develops due to splenic sequestration, but thrombocytopenia may also be due to decreased hepatic thrombopoietin synthesis haemostasis [1].

Primary haemostasis

Abnormalities in both number and function of platelets are common in patients with liver disease and contribute to the impaired haemostasis seen in these patients. About 70% of patients with chronic liver disease develop thrombocytopenia, which is usually mild to moderate (70-90 x 10^9/L) and worsens with disease progression and increased hypersplenism, which increases platelet sequestration [2].

Severe thrombocytopenia defined as platelet count less than 20 x 10^9/L occurs in only 1% of patients. Thrombocytopenia has not been associated with an increased risk of bleeding from oesophageal varices (i.e. structural bleeding) or other sources, and although only a few studies are evaluating this, it is correlated with blood loss during surgery (i.e. haemostatic bleeding). The synthetic function of the liver is essential for platelet production via thrombopoietin, which regulates platelet production in the bone marrow. Although thrombopoietin is increased in patients with thrombocytopenia due to a homeostatic response, this occurs to a lesser degree with severe or chronic liver diseases compared to those individuals with a normal liver [3]. In addition, a low platelet production from the bone marrow in cirrhotic patients has also been shown. Hepatitis C virus acute viral infection, alcohol abuse and folate deficiency can all result in some myelosuppression further lowering platelet counts. Consumption coagulopathy is not common in cirrhosis, and even if diffuse intravascular coagulation (DIC) is present at a chronic low level, it does not influence platelet count. Thrombocytopenia may also be triggered by immune-mediated mechanisms due to an increase production from B cells of antibody-binding platelet surface antigen GPIIb-IIIa and GPIb/I, which has been shown in viral-related cirrhosis B and C and cholestatic liver diseases (primary biliary cirrhosis, primary sclerosing cholangitis). Platelet aggregation in response to ADP, arachidonic acid, collagen and thrombin is subnormal, probably due to a defective signal transduction mechanism [2]. Intrinsic defects and abnormal plasma factors have also been shown to contribute to platelet function abnormalities. One study showed that although *in vitro* platelet adhesion to subendothelial structures under conditions of flow is substantially reduced, this was fully attributable to the reduced platelet count and reduced haematocrit in these patients [4]. These recent findings could be explained by the activation of platelet adhesion by thrombin, which is increased in cirrhosis and elevated levels of vWf, especially its high molecular multimeric forms [4]. Cholestatic liver diseases, which can demonstrate a normal or hypercoagulable state by thromboelastography (TEG) [5], have normal or hyperactive platelet function when assessed by platelet function assay (PFA-100) closure time and flow cytometric study of receptors. When the platelet number is too low, both cytometry or aggregation studies may be difficult to interpret. TEG is a global test of clot formation and dissolution, measuring both platelet function and number by maximum amplitude parameter and can be used to assess platelet function. Experiments calculating platelets from patients with cirrhosis compared with healthy controls show that a level around 50-60 x 10^9/L is the relative level for adequate thrombin generation [6].

Coagulation cascade

Fibrinogen and factors II, V, VII, IX, X, XI and XII are synthesised in the liver [7]; vWf is synthesised by the endothelium [8]. Factor VIII is synthesised mainly by the hepatic sinusoidal endothelial cells and also by endothelial and non-parenchymal cells in the kidney, spleen, lungs and brain. Thus, the plasma concentration of factor VIII, which is one of the most prominent procoagulant factors, is not decreased with liver disease, but it has been shown to be increased [9]. This occurs possibly because of increased endothelial synthesis and reduced clearance via low-density lipoprotein receptor-related protein and increased vWf. However, the biological activity of the synthesised molecule is lower than the plasma concentration.

Vitamin K is an essential cofactor for the production of biologically active forms of the coagulation factors II, VII, IX and X. It promotes hepatic post-ribosomal conversion of certain glutamic acid residues in the protein precursors, to γ-carboxyglutamic acid. These active forms of the clotting factors chelate calcium at the γ-carboxyglutamic acid site resulting in effective haemostatic function. In chronic liver disease, the γ-carboxylation is impaired due to a deficiency or antagonism of vitamin K, and inert precursors are synthesised (known as Proteins Induced by Vitamin K Absence [PIVKA]) and released into the bloodstream. The clinical significance of these precursors is not clear. In cholestasis,

a reduction of vitamin K absorption from the small intestine due to decreased bile salt production can be compensated with administering parenteral vitamin K 10 mg daily for 24-48 hours, but in parenchymal liver disease, decreased levels of coagulation factors are dependent on a decreased synthesis, so that there is no improvement with vitamin K administration. This therapeutic trial can be used to assess the eventual vitamin K deficit. Higher plasma des-γ-carboxy (PIVKA) prothrombin concentrations are found in patients with hepatocellular carcinoma, due to local production by tumour cells [10]. This abnormal prothrombin is thought to be a growth factor for this tumour and to be associated with poor prognosis [11]. The decreased production of procoagulant factors is mostly counterbalanced by a decreased production of anticoagulant proteins, such as protein C, protein S, protein Z, protein Z-dependent protease inhibitor, antithrombin (AT), heparin cofactor II and a2-macroglobulin, which are all produced by the liver. It has recently been established that protein S acts as a cofactor for tissue factor pathway inhibitor (TFPI) in the downregulation of thrombin generation and, TFPI/protein S anticoagulant system is functionally impaired in patients with cirrhosis [12]. As shown in Table 1, these studies have either shown a normo- or hypercoagulable state.

Table 1. Studies showing either hypo-normo-hypercoagulability in cirrhosis.

	Pro-haemostatic drivers	Anti-haemostatic drivers	Studies showing hypo- or hypercoagulability
Primary haemostasis	Elevated levels of vWf Low levels of ADAMTS13	Thrombocytopenia Functional platelet defects	Demonstrated platelet function defects Platelet adhesion normal under flow condition Platelet hyperfunction
Secondary haemostasis	Low anticoagulants levels: protein C, protein S, antithrombin, protein Z, protein Z dependent protease inhibitor, heparin cofactor II, alfa macroglobulin. High procoagulant factor VIII. Impaired TFPI-protein S anticoagulant system	Low procoagulant factors: fibrinogen, factor II, V, VII, IX, X, XI	Normocoagulability in acute liver failure patients Normocoagulability and hypercogulability in patients with cirrhosis Normal hypercoagulability in patients with ACLF
Tertiary haemostasis	Low levels of plasminogen High levels of PAI-1	High levels of tPA Low levels of TAFI, factor XIII and alfa-2-antiplasmin	Hypofibrinolysis in patients with acute liver failure Normofibrinolysis and hyperfibrinolysis in cirrhosis

ACLF, acute on chronic liver failure; PAI-1, plasminogen activator inhibitor-1; TFPI, tissue factor pathway inhibitor; tPA, tissue plasminogen activator; TAFI, thrombin-activatable fibrinolysis inhibitor; vWf, von Willebrand factor.

Plasma fibrinogen is an acute-phase reactant and remains normal or increased in patients with liver disease. Lower levels due to decreased synthesis, above 100 mg/dl, have been reported only in patients with very severe liver disease. However, as this synthesised form is a non-functional dysfibrinogen, about 60-70% of patients with liver disease have non-functional forms of fibrinogen due to increased activity of sialyltransferase expressed by immature hepatocytes generated during hepatic injury. This leads to low molecular weight fibrinogen with abnormal α chains and higher sialic acid content [13]. This counterbalances the high fibrinogen concentrations found in patients with chronic hepatitis, cholestatic jaundice and hepatocellular carcinoma, which does not result in increased clotting ability. Clinically, this results in an abnormal thrombin time, despite almost normal prothrombin time (PT) and partial thromboplastin time (PTT), with an apparently normal concentration of fibrinogen. This abnormality is reversed following recovery of liver function and after liver transplantation.

Changes in the fibrinolytic system

All the proteins involved in fibrinolysis, except for tissue plasminogen activator (tPA) and plasminogen activator inhibitor-1 (PAI-1) are synthesised in the liver, and indeed reduced plasma levels of plasminogen α2-antiplasmin, histidine-rich glycoprotein, factor XIII, and thrombin-activatable fibrinolysis inhibitor (TAFI) are documented in patients with liver cirrhosis. Conversely, tPA levels are increased in liver disease, due to decreased clearance, whereas it's inhibitor PAI-1 is normal or only slightly increased in plasma. Therefore, insufficient inhibitor concentrations account for the overall increased fibrinolysis. Hyperfibrinolysis is correlated with the severity of liver dysfunction in cirrhosis as assessed by Child-Pugh score. Increased levels of D-dimers, prothrombin fragments 1+2 (F1+2), fibrin degradation products and plasmin-α2-antiplasmin complexes are found. Many studies using different methodologies demonstrate hyperfibrinolysis (TEG), diluted whole blood clot lysis assay and euglobulin clot lysis time, however not all of the studies are concordant, and the role of hyperfibrinolysis in the risk of bleeding has not been clearly demonstrated, except for a single study indicating a risk of variceal bleeding [14].

Rebalanced coagulation: bleeding & thrombosis risk

Despite the rebalanced system, there are a variety of perturbations that can predispose a liver disease patient to bleeding or clotting. The synthesis of clotting factors can drop as low as 20% with the progression of liver disease; active compensatory mechanism may be low in stress situations. These conditions are not static and can change in acute decompensation, variceal bleeding, sepsis or uraemia, leading to acute changes of haemostatic balance. The clinical challenge is identifying which condition is present when the patient is deteriorating if bleeding or thrombosis is present before these occur [15].

Thus, despite the profound haemostatic alterations, the haemostatic system appears to be rebalanced in patients with liver disease [16]. However, this balance is far more precarious and potentially unstable compared with the haemostatic balance in healthy individuals, which explains the occurrence of both bleeding and thrombotic complications in these patients.

In fact, there are a variety of disturbances that can predispose a liver disease patient to either bleeding or thrombosis (Fig. 1). For instance, the development of renal failure is common in advanced liver disease, and this usually leads to a bleeding tendency as a result of acquired platelet dysfunction, abnormal platelet-vessel wall interaction and anaemia. Another important and often coexisting modulator of haemostasis is the appearance of bacterial infections. Endotoxins may inhibit platelet function by prostacyclin production and enhancement of nitric oxide and inhibit coagulation by stimulating the generation of heparin-like substances. Bacterial infection may thus increase the risk of initiation and fail to control bleeding. However, some investigators also suspect a potential direct effect

of endotoxin in the activation of the clotting cascade, leading to disseminated intravascular coagulation. Indeed, during endotoxemia or sepsis, endotoxin induces tissue factor expression in macrophages or endothelial cells, possibly contributing to the development of disseminated intravascular coagulation [17].

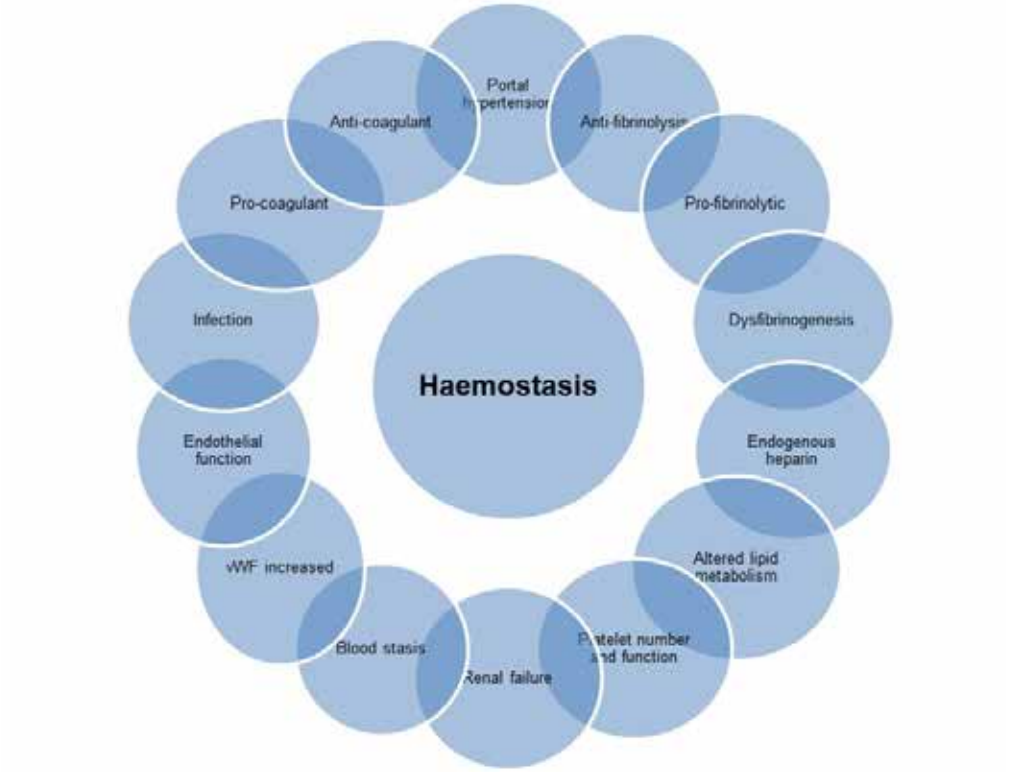

Figure 1. Factors affecting haemostasis in cirrhosis.

Using TEG, 20 cirrhotic patients who experienced early rebleeding were found to have worsening TEG parameters the day before rebleeding. Moreover, patients with bacterial infection have worse TEG parameters, which can be corrected *in vitro* by heparinase I, which can cleave heparin-like substances. The presence of heparin-like substances is associated in some with increased anti-Xa activity. Heparin-like substances have been detected hours after variceal bleeding. Based on this evidence, the hypothesis has been suggested that endotoxins and inflammation due to infection can release heparinoids from the endothelium and mast cells. One study, as yet not repeated, showed increased heparan sulphate concentrations in patients with variceal bleeding compared to patients without [18]. Moreover, sepsis can cause platelet function impairment, decreasing platelet number and aggregability, due to increased nitric oxide production. Cytokines, in particular IL6 and TNF-alfa released during infection, can trigger DIC with hyperfibrinolysis. Nowadays, there is increasing recognition of the various thrombotic complications that may occur in patients with liver diseases. Indeed, portal vein thrombosis (PVT) is a common occurrence in patients with cirrhosis, occurring in up to 26% of cirrhotic patients with end-stage liver disease [19]. Furthermore, the occurrence of venous thrombosis is also not uncommon in patients with liver disease. In fact, some studies have even suggested a significantly higher relative risk of venous thrombosis in these patients. The incidence of thrombosis in liver disease is possibly underreported because of nonspecific symptoms of deep vein thrombosis and pulmonary embolism and clinicians paying less attention to the possibility of thrombosis in these patients.

How to prevent bleeding with invasive procedures and when?

A frequent clinical need is predicting bleeding during or after procedures. Historically, PT and platelet count have been used to assess the risk of bleeding prior to invasive procedures. Patients with cirrhosis have increased mortality and morbidity during surgery [20], mainly due to increased bleeding in 60% of cases. Early studies linked PT to this risk during surgery (PT prolongation >1.5 and >2.5 seconds associated with 47% and 87% mortality, respectively). Hence, platelet count $<50 \times 10^9$/L and PT >3 seconds have been considered relative contraindications to elective surgery. In addition, portal hypertension and collateral veins increase the risk of bleeding during surgical dissection. Recently, the severity of liver disease has been shown to be correlated with the risk of bleeding complications during brain surgery with a mortality of up to 63% in Child-Pugh C patients and mortality after cardiac surgery [21]. A paper by Giannini *et al.* demonstrated an increased risk of bleeding following invasive procedures in patients with platelet count less than 75×10^9/L (10/32 versus 0/18, p = 0.008) [22]. Patients with end-stage liver disease had a 7-fold incidence of bleeding with 8% correlated mortality. Although high-risk procedures, such as complex surgery, are related to a higher risk of bleeding, the Child-Pugh class, severe portal hypertension, MELD score and comorbidities were the only factors correlating with mortality [23].

Many studies have shown the lack of a direct correlation between international normalisation ratio (INR) and procedural bleeding in varies procedures, such as percutaneous, laparoscopic and transjugular liver biopsy, paracentesis and thoracentesis, endoscopic polypectomy, percutaneous gastrostomy, dental extraction, percutaneous renal biopsy, central venous catheter placement, arteriography and coronary artery catheterisation (Table 2). For this reason, some recent guidelines for the American and Italian association for the study of the liver have recommended not to use INR to measure the bleeding risk before invasive procedures. Blood platelet count seems to correlate with the risk of bleeding only at its bottom. And an experimental study using TG with platelet count derived by cirrhotic patients demonstrated a normal TG with platelet count around 70,000/Ul.

Table 2. Post-procedural bleeding in cirrhotic patients and correlation with platelets count and INR values (modified from [40]).

Paracentesis	0.3%-3%	No	No
Thoracentesis	2%	Unknown	Unknown
Percutaneous liver biopsy	0.5%	Yes	Likely
Transjugular liver biopsy	<1%	No	No
Dentistry	2.9%	No	No
Endoscopic variceal ligation	3%-7.3%	No	No
Endoscopic polipectomy	3%-12.4%	No	No
Percutaneous ablation of HCC	1%	Unknown	Unknown
OLT		No	No
Liver surgery	3.9%-6.6%	No	No
Cholecystectomy	2.9%-10%	No	No
Hernioplasty	2.3%-10.8%	No	No
Cardiac Surgery	11%-16%	No	No

HCC, hepatocellular carcinoma; OLT, orthotopic liver transplantation.

Hyperfibrinolysis and clotting activation, due to increased tPA levels have been described in patients undergoing liver resection [24]. However, another study performed in patients undergoing laparoscopic liver biopsy failed to demonstrate any correlation between the risk of bleeding evaluated at the hepatic puncture site and coagulation tests, thus the degree of injury may be the important factor.

The risk of bleeding from variceal ulcers after variceal band ligation correlates only with the severity of the liver disease, but not with conventional coagulation tests nor TEG parameters [25].

During minor procedures, such as thoracentesis, paracentesis or lumbar puncture performed in patients with liver disease, there are no firm guidelines as to the haemostatic threshold for performing these tests. The largest review on 608 patients who underwent paracentesis or thoracentesis with mild coagulation abnormalities showed 0.2% of patients had excessive bleeding requiring transfusion and 0.02% mortality. There was no correlation with PT, PTT, platelet count and the risk of bleeding. In another study, performed in 200 patients with cirrhosis with INR $\geq$3 and platelet count $\geq$19,000/mm^3 who underwent paracentesis, no complications were seen, regardless of baseline INR and platelet count [26].

Bleeding after dental extraction occurred in about 3% of procedures even with INR greater than 3 and platelet count <30,000/mm^3. Local use of tranexamic acid (TXA) could be beneficial because the oral cavity is a hyperfibrinolytic area.

A contraindication to the procedure is clinically evident in DIC or fibrinolysis whereas it is impossible using evidence-based techniques currently available to establish “safe” coagulation tests for these procedures. Equally, if not more importantly, is to limit such procedures in circumstances which the perceived benefit of the procedure is clearly greater than the risk.

Fibrinogen levels are indirect markers of clotting capacity and clot breakdown; however, levels of fibrinogen have been reported to be variable amongst cirrhotic patients and correlation between bleeding and fibrinogen have been reported as not consistent in non-liver transplant candidates, except for patients with DIC. Fibrinogen is also an acute phase reactant protein, therefore, may be highly variable.

A recent study explored the role of fibrinogen on the risk of post-band ligation ulceration, and found a correlation between levels of fibrinogen below 179 mg/dl [27], although events were few and further confirmations are needed.

A single prospective trial evaluated the utility of viscoelastic tests in guiding transfusion in cirrhosis patients outside of the transplantation setting. In this study, cirrhosis patients with INR >1.8 or platelet count <50 x 10^3/ml were randomised to TEG-guided transfusion versus SOC transfusion support prior to undergoing invasive procedures. Patients underwent a variety of procedures, which were both high and low risk for bleeding. One-hundred per cent of patients in the SOC group received a transfusion of either fresh frozen plasma (FFP) or platelets versus 16% of patients in the TEG-guided group. This difference was largely driven by FFP use, with 53% of the SOC group receiving FFP versus 0% in the TEG group. Red blood cell transfusion was comparable in both groups, and there was no survival difference at 90 days. While a reduction in transfusion in the TEG-guided group was demonstrated, the standard of care transfusion goals in this study was relatively aggressive, particularly with an INR goal of 1.8, and may not reflect current practices. Furthermore, the low rates of bleeding in both arms argue strongly for the addition of a control arm evaluating the outcome of no prophylactic transfusion prior to procedures [28].

Contribution of the coagulation specialist in the treatment of bleeding

In actively bleeding patients, in whom bleeding is related to defective haemostasis, resuscitation with platelet transfusion, fibrinogen concentrate, or cryoprecipitate is indicated. However, aside from the standard coagulation test, it is difficult to address specific transfusion requirements for a single acute bleeding cirrhotic patient.

Generally, to avoid dilutional coagulopathy, 1 FFP unit recommended every 4 units of blood, however, if the bleeding is portal hypertensive-related, the increase of resuscitations volume has been shown to increase bleeding itself in rats and increase mortality in Child-Pugh B patients during gastrointestinal bleeding [29] (Fig. 2).

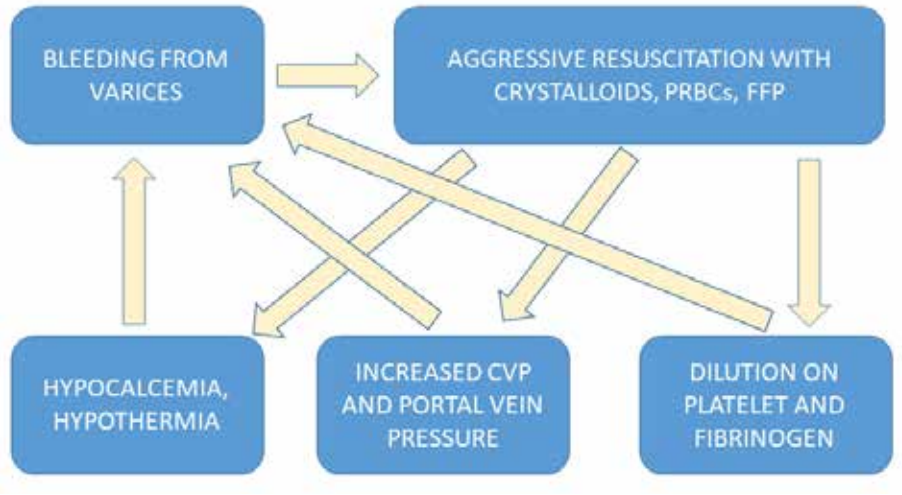

Figure 2. Bleeding related to defective haemostasis. CVP, central venous pressure FFP, fresh frozen plasma; PRBCs, packed red blood cells.

An alternative to blood products is the use of coagulation factors concentrate, with 3 or 4 factors and fibrinogen. Concerns have been raised in previous years due to the lack of anticoagulant factors in a three-factor concentrate and possible risk of thrombotic complications.

Data regarding fibrinogen derived from non-cirrhotic trauma patients showed levels greater than 200 mg/dl were correlated with better haemostasis. Although based on very limited data values, below 120 g/L in active bleeding cirrhotic patients have historically required correction. Restitution can be done by using cryoprecipitates or fibrinogen concentrated derived from a similar process of plasma cryoprecipitation. However, there are no definitive studies which justify the widespread use with elevated costs.

Cirrhosis poses a difficult setting because in diffuse bleeding, accelerated intravascular coagulation may be exacerbated or consumption coagulopathy is present. In sepsis, viscoelastic testing identifies alterations in the coagulation system that contribute to organ system dysfunction. An observational study by Brenner *et al.* showed that septic patients with disseminated intravascular coagulation (DIC) have hypocoagulable profiles, whereas septic patients without DIC have hypercoagulable profiles [30]. A critically ill patient with multiple organ failure and clinical suspicion of sepsis showed clear signs of a coagulopathy, characterised by a low platelet count, prolonged global coagulation tests and increased D-dimer.

Numerous studies have evaluated the utility of TEG and rotational thromboelastometry (ROTEM) in chronic liver disease outside of liver transplantation (Fig. 3).

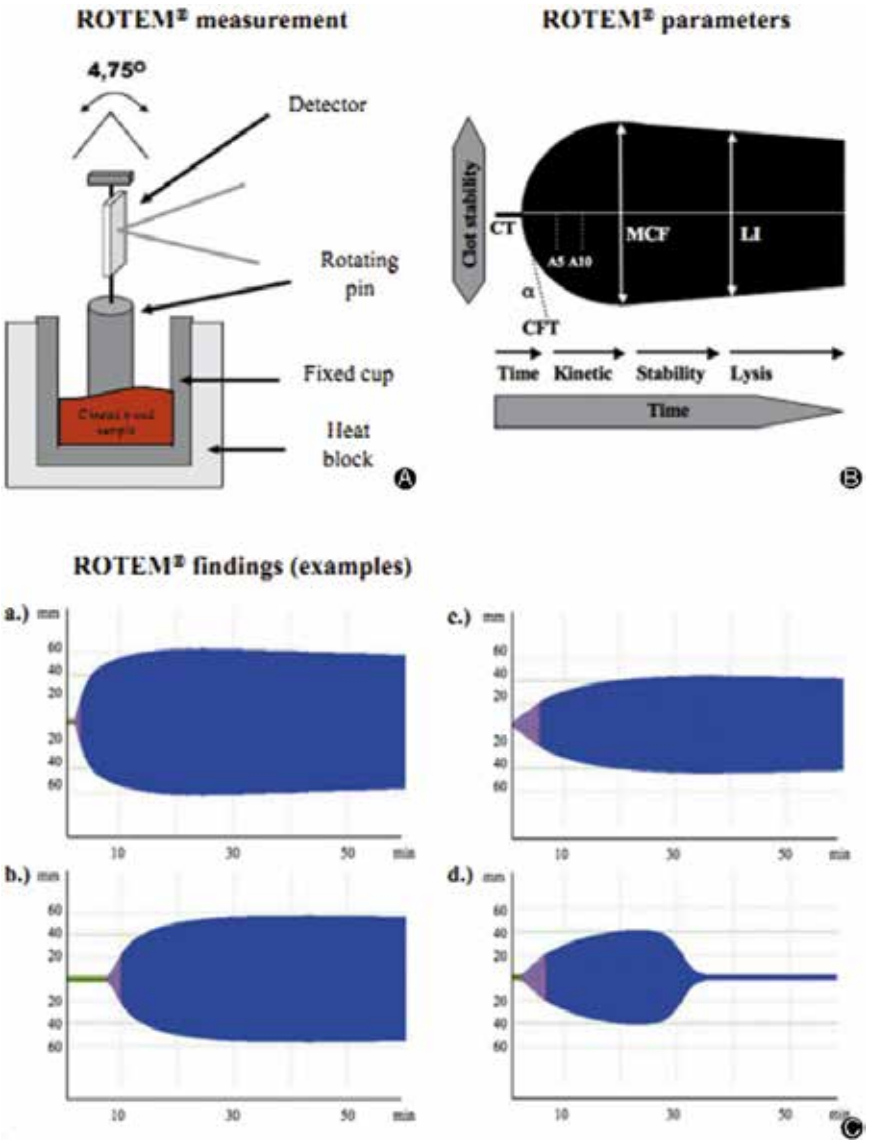

Figure 3. Example of a viscoelastic testing assay via rotational thromboelastometry (ROTEM®). (A) displays the measurement. A rotating pin is entered into a cup containing the citrated blood sample including a coagulation activator. Once the coagulation process is initiated, the clot builds up and increases the resistance against the rotating pin. The degree of resistance is translated into a curve signal. (B) Depiction of the different parameters of the ROTEM® test. A ¼ alpha angle (indicates the dynamics of the clotting process); CT ¼ clotting time (indicates the speed of the clotting process until clot initiation begins); CFT ¼ clot formation time (indicates the time until a sufficient clot has been generated); MCF ¼ maximum clot firmness (indicates the stability of the clot); LI ¼ lysis index (indicates fibrinolysis). Results are provided at 5 (A5) and 10 (A10) minutes after test initiation. (C) Shows typical test results: a) normal clotting; b) delayed clotting (coagulation factor deficit); c) reduced clot strength (fibrinogen deficit), and d) fibrinolysis. Taken from Maegele *et al.* 2017.

Many of these studies have evaluated thromboelastrography alongside traditional coagulation testing and markers of prognosis in cirrhosis patients, in an effort to delineate prognostic value and use of thromboelastrography for identifying bleeding and clotting risks in this group. Thromboelastrography

has also been used to characterise coagulation in chronic liver disease. In acute bleeders, an updated review included a total of 17 studies (1493 patients), of which, only one was in the setting of liver transplantation. The study concluded that TEG or ROTEM-guided transfusion practice appeared to reduce overall bleeding. In TEG/ROTEM-guided transfusion management groups compared to transfusion management guided by any other method, there was also a statistically significant decrease in the proportion of patients transfused with packed red blood cell (pRBC) plasma platelets, overall plasma or platelet transfusion for haemostasis, and fewer patients with dialysis-dependent renal failure [31].

However, data is lacking in this clinical setting for cirrhosis. A recent randomised controlled trial on the use of TEG to address blood products transfusion during acute variceal bleeding (presented as an abstract) showed a significant reduction in the number of FFP and platelet count transfused in the TEG group, and increased re-bleeding rates in standard of care versus TEG groups at 5 days (13.6% *vs.* 0%). Traditional models of coagulation emphasise linear coagulation pathways, which imply that deficiency of any factor would mandate replacement of that same factor. This model was developed to understand patients with severe deficiency of a single clotting factor, such as haemophilia. It may not work as well for critically ill patients, who often have numerous, moderate factor deficiencies. TEG suggests an alternative viewpoint, suggesting a greater degree of flexibility, redundancy, and synergism between different components of coagulation. For example, clot strength seems to reflect both platelet count and fibrinogen level. Thus, to a certain extent, a high fibrinogen level may compensate for low platelet count or vice versa [32]. Moving forward, it may be worth re-considering our strategy for blood product repletion. Our current strategy of repleting every component to an individual target (to achieve a roughly euboxic coagulation panel) is effective, but perhaps not ideal. For example, it might be safer to target a supra-normal fibrinogen level, while tolerating permissive thrombocytopenia and focus on a TEG-based coagulation target (e.g. adequate clot strength as measured by the maximum amplitude). Platelet dysfunction is widely reported in liver disease and cirrhosis, but specific dysfunctions cannot reliably be predicted; viscoelastic tests can detect specific platelet dysfunction during persistent bleeding. In fact, fibrin degradation products competitively inhibit the ADP receptors on platelets.

One function of the liver is to eliminate proteins involved in fibrinolysis (e.g. endogenous tPA). With worsening cirrhosis, these proteins accumulate in the blood leading to hyperfibrinolysis in perhaps 30-50% of patients [14]. Unfortunately, TEG may be insensitive to this hyperfibrinolysis (e.g. endogenous tPA loses activity within minutes of drawing the patient's blood). TXA, a fibrinolysis inhibitor, should be well suited to this situation. TXA shows promise in upper gastrointestinal bleeding, with the most recent Cochrane Review suggesting a mortality benefit (RR 0.6, 95% CI 0.42-0.87). In liver transplant surgery, a meta-analysis of randomised controlled trials found that TXA is safe and effective in reducing blood loss.

Fibrinogen is commonly overlooked, but it shouldn't be. The entire point of the coagulation cascade is the activation of fibrinogen so that it can form a clot. The yellow strands holding together this clot are made out of fibrinogen: with progressive cirrhosis, fibrinogen levels often decrease. Among patients undergoing liver transplantation, fibrinogen supplementation reduced the requirement for platelets, pRBCs, and FFP. Recent guidelines suggest targeting a fibrinogen level of >150-200 mg/dl, an increase compared to prior recommendations to target a fibrinogen level of >100 mg/dl. During major bleeding, fibrinogen is the first clotting factor to reach critically low levels below the normal physiological level of around 2 to 4 g/L, which is associated with increased bleeding, coagulopathy, and in turn, worsened clinical outcomes. Fibrinogen is an independent predictor of mortality in major trauma patients. In cirrhotic patients, the only modification that can be seen if it is used during prolonged bleeding is a prolongation of PTT. A separate study comparing standard fibrinogen measurement methods

(i.e., Clauss method and thrombin clotting time) with ROTEM FIBTEM in patients with cirrhosis suggested that FIBTEM is a promising alternative to standard plasma fibrinogen measurement in cirrhotic patients, especially in evaluating fibrin polymerisation disorders in these patients [34]. The use of modified thromboelastographic tests sensitive to fibrinogen can, therefore, reveal the need of fibrinogen supplementation because hypofibrinogenemia is not correlated directly with a reduction of the clot maximum amplitude as there is a temporary contribution of platelets.

Possible role of anticoagulation to prevent complications of cirrhosis

The interaction between the coagulation cascade and liver injury is multifaceted. Modified view of coagulation in cirrhosis in recent years has shifted the attention of clinicians on the possible role of anticoagulation in preventing decompensation of cirrhosis. Epidemiological studies have demonstrated that prothrombotic conditions promote liver fibrosis. Secondly, tissue factor and fibrin have been shown to be upregulated within fibrotic livers, which is in keeping with a role for vascular dysfunction in fibrogenesis. Thirdly, in addition to its role in activating fibrinogen, thrombin has been shown to mediate the cellular activation of macrophages, platelets and hepatic stellate cells via cleavage of the protease-activated receptor, PAR-1, and polymorphisms in the *PAR-1* gene have been shown to influence the rates of hepatic fibrosis.

Moreover, a recent study explored the role of FXa, showing that FXa promotes stellate cell contractility and activation. Early inhibition of coagulation using a FXa inhibitor significantly reduces murine liver fibrosis and may be a viable treatment for liver fibrosis in patients [35].

The progression of fibrosis and prothrombotic status has been linked in many experimental studies in murine models of acute hepatitis infection, which was demonstrated during acute liver damage that a clotting-like process was able to attract inflammatory and matric-producing cells. Anstee *et al.* showed that factor V mutation significantly contributes to fibrosis formation on CCl_4-treated rats. ADAMTS13 mutation is associated with the formation of microthrombosis in steatosis, and local activation of coagulation contributes to inflammation and fibrosis in non-alcoholic fatty liver disease (NAFLD) rat models [36].

In advance liver disease, although not recent, the landmark studies by Wanless demonstrated a close relationship between local procoagulative status and progression of liver damage. His anatomo-pathological study showed the presence of intimal fibrosis highly suggestive of healed hepatic vein or PVT in at least 70% and 36% of the livers, respectively. The distribution of hepatic vein lesions was patchy and largely confined to veins between 0.1 and 3 mm in diameter, suggesting a multifocal origin in small veins. Portal vein lesions were more uniform throughout the liver, suggesting the origin to be in large veins which propagate to the small veins.

Nearby areas are characterised by the irreversible loss of hepatocytes and their replacement with fibrous tissue (named parenchymal extinction). PVT is found in up to 40% of cirrhotic livers examined at transplantation [37]. Once cirrhosis has developed, the hepatic blood flow is chaotic and sluggish. Portal vein flow may be biphasic or continuously retrograde. In addition, loss of anticoagulant function and prothrombotic effects of sepsis and cholestasis may contribute to the increased risk of thrombosis of the hepatic and portal vein.

Therapeutic use of anticoagulation in this clinical setting has been explored first in *in vitro* experimental studies, in which heparin has been shown to inhibit protein expression of type I collagen and fibronectin. Heparins were demonstrated to suppress hepatic fibrosis in experimental models of acute liver damage and to significantly decrease portal pressure mainly due to a decrease in hepatic vascular resistance. Moreover, a reduction in fibrin deposition was observed in enoxaparin-treated rats, suggesting reduced intrahepatic microthrombosis [35].

New anticoagulants (direct-acting anticoagulants) have shown in rat models to decrease intrahepatic vascular resistances by reducing vascular resistances and also suppress genes correlated with lipid metabolism in NAFLD models, suggesting a role of thrombin in liver damage in NASH. This may not be true in late-stage liver disease as hypothesised in a negative study (Fig. 4).

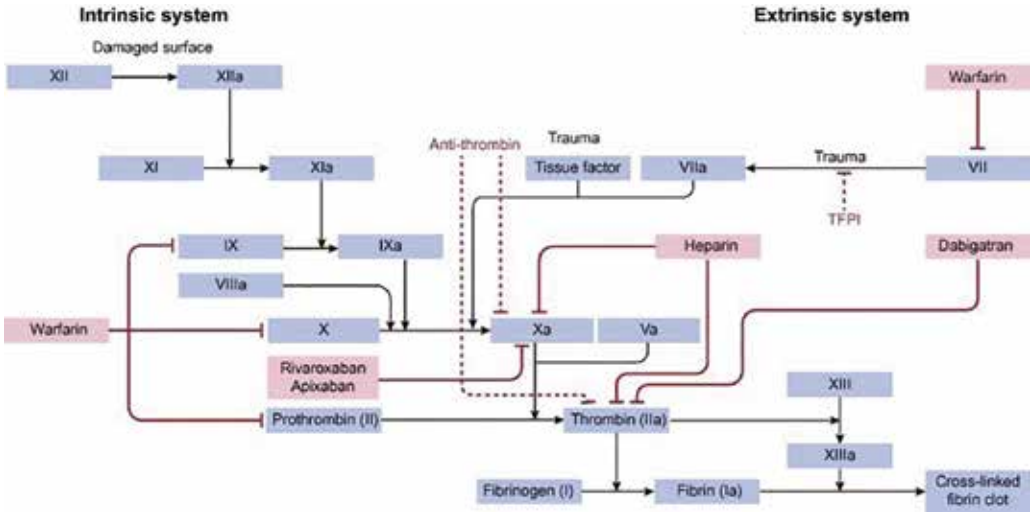

Figure 4. Effects of anticoagulants on coagulation cascade [39].

Human studies confirmed that thrombin could stimulate proliferation of cultured hepatic stellate cells, correlates with more advanced liver fibrosis in chronic hepatitis C and B virus infection. Anstee confirmed in experimental studies that factor V Leiden mutation was associated with more aggressive fibrosis, which has been further shown with G20210A mutations [36].

Additionally, a Dutch population-based cohort study identified the presence of factor V Leiden or prothrombin G202010A mutations as independent risk factors for a liver stiffness score of $\geq$8.0 kPa on transient elastography [38]. These evidence lead to studies which explored the therapeutic role of anticoagulation in liver disease. A study with short-term treatment with heparin and low molecular weight heparin (LMWH) in chronic hepatitis B virus infection showed amelioration of alanine aminotransferase levels and a reduction of hyaluronic and type IV collagen compared to controls.

In a single-centre, randomised controlled trial, the use of prophylactic enoxaparin, a LMWH, was evaluated in 70 patients with Child-Pugh B or C cirrhosis, to determine whether the incidence of PVT could be reduced. Patients were randomised to treatment with 4000 IU of enoxaparin for 48 weeks, or to the control group who received standard treatment (without anticoagulation). At 48 weeks, no patient randomised to the enoxaparin group had developed a PVT *vs.* 16.6% of the control group. Furthermore, there was a significant reduction in the occurrence or recurrence of liver decompensation (defined as the development of ascites, encephalopathy, spontaneous bacterial peritonitis or portal hypertensive bleeding) in the enoxaparin group *vs.* the control group (11.7% *vs.* 59.4%). Additionally, there was an increased transplant-free survival in the enoxaparin-treated arm. The improvement in liver decompensation and survival may have been related, in part, to the prevention of PVT, but this alone cannot explain the effect. The authors had suggested a possible additional protective effect on the intestinal microcirculation [19]. The beneficial effects on both fibrosis and portal pressures may, in part, explain the efficacy of anticoagulation in preventing decompensation in patients with cirrhosis. Further studies exploring the benefits of anticoagulation in this setting are required.

References

[References in **BOLD** are required reading]

1. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. N Engl J Med. 2011 Jul 14;365(2):147-56
2. Violi, F., Basili, S., Raparelli, V., Chowdary, P., Gatt, A., Burroughs, A.K. Patients with liver cirrhosis suffer from primary haemostatic defects?. Fact or fiction J Hepatol. 2011;55:1415–1427
3. Panasiuk A, Prokopowicz D, Zak J, Panasiuk B. Reticulated platelets as a marker of megakaryopoiesis in liver cirrhosis; relation to thrombopoietin and hepatocyte growth factor serum concentration. Hepatogastroenterology 2004 Jul;51(58):1124-8
4. Lisman T, Adelmeijer J, de Groot PG, Janssen HL, Leebeek FW. No evidence for an intrinsic platelet defect in patients with liver cirrhosis--studies under flow conditions. J Thromb Haemost 2006 Sep;4(9):2070-2
5. Ben-Ari Z, Panagou M, Patch D, Bates S, Osman E, Pasi J, Burroughs A. Hypercoagulability in patients with primary biliary cirrhosis and primary sclerosing cholangitis evaluated by thrombelastography. J Hepatol. 1997 Mar;26(3):554-9
6. Tripodi A, Primignani M, Chantarangkul V, Clerici M, Dell'Era A, Fabris F, et al. Thrombin generation in patients with cirrhosis: the role of platelets. Hepatology. 2006 Aug;44(2):440-5
7. Kelly DA, Summerfield JA. Hemostasis in liver disease. Semin Liver Dis 1987 Aug;7(3):182-91
8. Ferro D, Quintarelli C, Lattuada A, Leo R, Alessandroni M, Mannucci PM, et al. High plasma levels of von Willebrand factor as a marker of endothelial perturbation in cirrhosis: relationship to endotoxemia. Hepatology 1996 Jun;23(6):1377-83
9. Wion KL, Kelly D, Summerfield JA, Tuddenham EG, Lawn RM. Distribution of factor VIII mRNA and antigen in human liver and other tissues. Nature 1985 Oct 24;317(6039):726-9
10. Blanchard RA, Furie BC, Jorgensen M, Kruger SF, Furie B. Acquired vitamin K-dependent carboxylation deficiency in liver disease. N Engl J Med 1981 Jul 30;305(5):242-8.
11. Weitz IC, Liebman HA. Des-gamma-carboxy (abnormal) prothrombin and hepatocellular carcinoma: a critical review. Hepatology 1993 Oct;18(4):990-7
12. Potze W, Arshad F, Adelmeijer J, Blokzijl H, van den Berg AP, Meijers JC, et al. Decreased tissue factor pathway inhibitor (TFPI)-dependent anticoagulant capacity in patients with cirrhosis who have decreased protein S but normal TFPI plasma levels. Br J Haematol. 2013 Sep;162(6):819-26
13. Francis JL, Armstrong DJ. Fibrinogen-bound sialic acid levels in the dysfibrinogenaemia of liver disease. Haemostasis 1982;11(4):215-22
14. Leebeek FW, Rijken DC. The Fibrinolytic Status in Liver Diseases. Semin Thromb Hemost. 2015 Jul;41(5):474-80
15. **Intagliata NM, Argo CK, Stine JG, Lisman T, Caldwell SH, Violi F; faculty of the 7th International Coagulation in Liver Disease. Concepts and Controversies in Haemostasis and Thrombosis Associated with Liver Disease: Proceedings of the 7th International Coagulation in Liver Disease Conference. Thromb Haemost. 2018 Aug;118(8):1491-1506.**

16. Tripodi A, Salerno F, Chantarangkul V, Clerici M, Cazzaniga M, Primignani M, Mannuccio Mannucci P. Evidence of normal thrombin generation in cirrhosis despite abnormal conventional coagulation tests. Hepatology. 2005 Mar;41(3):553-8

17. Thalheimer U, Triantos CK, Samonakis DN, Patch D, Burroughs AK. Infection, coagulation, and variceal bleeding in cirrhosis. Gut. 2005 Apr;54(4):556-63

18. Senzolo M, Cholongitas E, Thalheimer U, Riddell A, Agarwal S, Mallett S, et al. Heparin-like effect in liver disease and liver transplantation. Clin Liver Dis. 2009 Feb;13(1):43-53.

19. Villa E, Cammà C, Marietta M, Luongo M, Critelli R, Colopi S, et al. Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. Gastroenterology. 2012 Nov;143(5):1253-1260

20. Perkins L, Jeffries M, Patel T. Utility of preoperative scores for predicting morbidity after cholecystectomy in patients with cirrhosis. Clin Gastroenterol Hepatol 2004 Dec;2(12):1123-8

21. Chen CC, Hsu PW, Lee ST, Chang CN, Wei KC, Wu CT, et al. Brain surgery in patients with liver cirrhosis. J Neurosurg 2012 May 25

22. Giannini EG, Greco A, Marenco S, Andorno E, Valente U, Savarino V. Incidence of bleeding following invasive procedures in patients with thrombocytopenia and advanced liver disease. Clin Gastroenterol Hepatol. 2010;8:899–902

23. Bhangui P, Laurent A, Amathieu R, Azoulay D. Assessment of risk for non-hepatic surgery in cirrhotic patients. J Hepatol. 2012 Oct;57(4):874-84

24. Meijer C, Wiezer MJ, Hack CE, Boelens PG, Wedel NI, Meijer S, et al. Coagulopathy following major liver resection: the effect of rBPI21 and the role of decreased synthesis of regulating proteins by the liver. Shock 2001 Apr;15(4):261-71

25. Vieira da Rocha EC, D'Amico EA, Caldwell SH, Flores da Rocha TR, Soares E Silva CS, et al. A prospective study of conventional and expanded coagulation indices in predicting ulcer bleeding after variceal band ligation. Clin Gastroenterol Hepatol 2009 Sep;7(9):988-93

26. Pache I, Bilodeau M. Severe haemorrhage following abdominal paracentesis for ascites in patients with liver disease. Aliment Pharmacol Ther 2005 Mar 1;21(5):525-9.

27. Giannini EG, Giambruno E, Brunacci M, Plaz Torres MC, Furnari M, Bodini et al. Low Fibrinogen Levels Are Associated with Bleeding After Varices Ligation in Thrombocytopenic Cirrhotic Patients. Ann Hepatol. 2018 Jun5;17(5):830-835

28. De Pietri L, Bianchini M, Montalti R, De Maria N, Di Maira T, Begliomini B, et al. Thrombelastography-guided blood product use before invasive procedures in cirrhosis with severe coagulopathy: A randomized, controlled trial. Hepatology. 2016 Feb;63(2):566-73.

29. Villanueva C, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, Aracil C, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med. 2013 Jan 3;368(1):11-21

30. Brenner T, Schmidt K, Delang M, Mehrabi A, Bruckner T, Lichtenstern C, et al. Viscoelastic and aggregometric point-of-care testing inpatients with septic shock – cross-links between inflammation and haemostasis. Acta Anaesthesiol Scand. 2012 Nov;56(10):1277-90

31. Afshari A, Wikkelsø A, Brok J, Møller AM, Wetterslev J. Thrombelastography (TEG) or thromboelastometry (ROTEM) to monitor haemotherapy versus usual care in patients with massive transfusion. Cochrane Database Syst Rev. 2011 Mar16;(3):CD007871

32. Blasi A, Calvo A, Prado V, Reverter E, Reverter JC, Hernández-Tejero M, et al. Coagulation Failure in Patients With Acute-on-Chronic Liver Failure and Decompensated Cirrhosis: Beyond the International Normalized Ratio. Hepatology. 2018 Dec;68(6):2325-2337.

33. Bennett C, Klingenberg SL, Langholz E, Gluud LL. Tranexamic acid for upper gastrointestinal bleeding. Cochrane Database Syst Rev. 2014 Nov 21;(11)

34. Vucelic D, Jesic R, Jovicic S, Zivotic M, Grubor N, Trajkovic G, et al. Comparison of standard fibrinogen measurement methods withfibrin clot firmness assessed by thromboelastometry in patients with cirrhosis.Thromb Res. 2015 Jun;135(6):1124-30s.

35. Turco L, Schepis F, Villa E. The Role of Anticoagulation in Treating Portal Hypertension. Curr Hepatol Rep. 2018;17(3):200-208.

36. Anstee QM, Dhar A, Thursz MR. The role of hypercoagulability in liver fibrogenesis. Clin Res Hepatol Gastroenterol. 2011 Sep;35(8-9):526-33.

37. Wanless IR, Wong F, Blendis LM, Greig P, Heathcote EJ, Levy G. Hepatic and portal vein thrombosis in cirrhosis: possible role in development of parenchymal extinction and portal hypertension. Hepatology. 1995 May;21(5):1238-47.

38. Plompen EP, Darwish Murad S, Hansen BE, Loth DW, Schouten JN, Taimr P, et al. Prothrombotic genetic risk factors are associated with an increased risk of liver fibrosis in the general population: The Rotterdam Study. J Hepatol. 2015 Dec;63(6):1459-65.

39. Dhar A, Mullish BH, Thursz MR. Anticoagulation in chronic liver disease. J Hepatol. 2017 Jun;66(6):1313-1326.

40. Under the auspices of the Italian Association for the Study of Liver Diseases (AISF) and the Italian Society of Internal Medicine (SIMI). Hemostatic balance in patients with liver cirrhosis: Report of a consensus conference. Dig Liver Dis. 2016 May;48(5):455-467.

Portal vein thrombosis in cirrhosis: Who should be treated and how?

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Take-home messages

- Coagulative balance in patients with compensated liver cirrhosis is close to normal, and bleeding (predominantly variceal) is usually the consequence of worsening portal hypertension.
- Worsening of chronic liver function is associated with progressive coagulative imbalance, tipping more towards a thrombophilic rather than haemorrhagic condition.
- Thrombotic complications are not primarily responsible for worsening chronic liver disease; they should be viewed as one of the different indicators of its progression.
- Influence of portal vein thrombosis (PVT) on liver transplantation is moderate: long-term survival is not affected, while short-term survival (less than 1 year) is worse in patients with PVT at liver transplantation.
- Transplant benefit for patients with PVT *vs.* those without is MELD >13 *vs.* MELD >11, respectively: this should be carefully considered when listing a patient.
- Treatment with anticoagulants (LMWH or VKAs) obtains PVT recanalisation more often than no treatment; it lowers thrombosis progression and risk of variceal bleeding.
- Anticoagulation, even in the setting of advanced cirrhosis, is safe and does not require intensive monitoring.

Portal vein thrombosis in cirrhosis: who should be treated and how?

Haemostasis is a complex physiological process, which causes bleeding to stop within a damaged vessel, an occurrence which is fundamental for the vessels to maintain its role, i.e. to provide oxygen and nutrients to major organs by means of continuous blood flow. Haemostasis is the result of the delicate balance between the reactions leading toward blood clot formation and the activation of the anticoagulation system. This depends on the equilibrium between procoagulant and anticoagulant proteins. The liver produces the majority of these factors. In patients with liver cirrhosis, as there is a proportional decrease in the synthesis of both pro- and anti-coagulant factors, this balance, although more fragile, is maintained at least until the patient is in a compensated state. When liver function deteriorates, or when events like infection or acute kidney insufficiency occur, there is a progressive alteration in blood test recordings, although the real coagulative performance is still maintained for a longer time. Recent evidence indicates that patients with liver disease are prone to develop thrombotic rather than haemorrhagic complications (the latter being due to increasing portal hypertension, not to coagulopathy). This applies both to venous thromboembolism (VTE) or venous thrombotic events (deep vein thrombosis [DVT], or portal vein thrombosis [PVT]).

1. Prevalence of and risk factors for portal vein thrombosis in cirrhosis (focus on candidates for transplantation)

Prevalence

The prevalence and incidence of extrahepatic PVT are notably different depending on the type of PVT (complete or partial: in about 75% of patients, portal vein thrombi occupy only a portion of the portal venous lumen), type of study (cross-sectional or prospective) and severity of liver disease of the cohort studied.

Reported prevalence ranges from 0.5% to 26%. This wide range reflects the heterogeneity of the population studied, in terms of aetiology, stage of disease, age, gender, risk factors, and diagnostic method used, etc. In the transplant setting, figures for PVT found at intervention, are often, but not always, in the higher range, reflecting more advanced stage of disease of patients on the waiting list. Figures ranging from 2% to 13% are reported for patients while on the waiting list, whereas figures as high as 36% have been reported at explant (reviewed in Verbeek *et al.*) [1]. Data obtained at the time of transplant, carry the obvious bias of registering incident data at that time, thus missing patients that are not suitable candidates for liver transplant (LT) or delisted for worsening conditions.

Prospective studies, although in limited number [2-5], provide more accurate information, both as incidence and influence on natural history of disease (discussed in the next paragraph). Two prospective studies enrolled patients with mostly Child-Pugh A cirrhosis. Nery *et al.* [2] observed a PVT incidence of about 5% and 11% at 1 and 5 years, respectively. Noronha Ferreira *et al.* [3] reported an incidence of 3% at 1 year and 7% at 3 years. The other two studies [4,5] evaluated patients in Child-Pugh class B/C. Villa *et al.* [4] observed a PVT incidence of 16.6% in the first year and 27.7% at two years, while Maruyama *et al.* [5] reported a cumulative incidence of 12.8%, 20%, and 38.7% at 1, 5, and 8-10 years, respectively (Fig. 1).

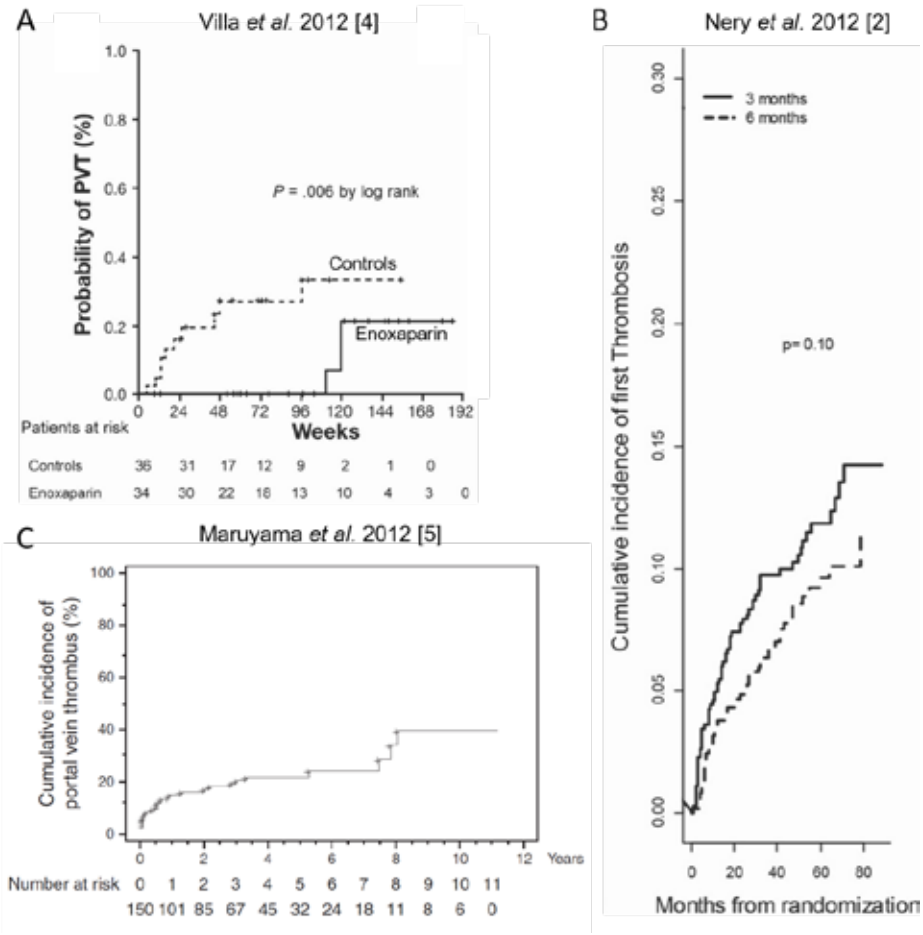

Figure 1. PVT incidence in three prospective studies [2,4,5].

Spontaneous portal vein recanalisation is a recognised event, occurring in highly variable proportion, from 5 to almost 60% of cases. Higher percentages of recanalisation have been registered in patients with Child-Pugh class A although several reports indicate that recanalisation can also occur in more advanced conditions.

Risk factors

A long list of factors has been implicated in PVT pathogenesis. The most relevant and frequent are acquired (Child-Pugh B-C, decompensated disease stage, presence of moderate/severe portal hypertension, previous variceal bleeding, reduced portal vein flow velocity, endoscopic treatment of varices*, abdominal surgery*, injury to the portal venous system [surgical portosystemic shunting, TIPS]*, liver cancer or cancer of other organs, sepsis, platelet count*, Philadelphia-negative myeloproliferative disease). Congenital risk factors (protein C & S deficiency, antithrombin [AT] deficiency, factor V Leiden mutation, mutation 20210A of prothrombin gene, mutation C667T MTHFR) are much less frequent and therefore play a minor role (asterisks indicate risk factors with a more significant relationship with PVT).

AT deficiency has low prevalence (0.02-0.2%) but carries a high-risk of thrombosis; in contrast, C667T *MTHFR* mutation has a high prevalence (2-4%) but is associated with a low risk of thrombosis.

Despite recent knowledge of increased thrombophilic features of non-alcoholic steatohepatitis (NASH)-associated chronic liver disease (CLD), risk for thrombotic complication seems to be not higher than in other aetiologies. There is, however, a single report in the transplant setting, that reports NASH as an independent risk factor for PVT at LT together with Hispanic race, older age and higher MELD score [6].

On the whole, the main risk factor for PVT resides in the progressive increase in the severity of the liver disease, which is characterised by modifications of the coagulative balance, by anatomical alterations, and eventually by the decrease of the portal blood flow, all of which contribute to the increased propensity to thrombosis.

2. Does portal vein thrombosis contribute further to the deterioration or is it a surrogate marker of disease severity?

The role of PVT in the natural history of CLD is easy to define as the question of which came first, the chicken or the egg. Its impact on the outcome of cirrhosis has not been investigated systematically. Older studies, all retrospective or cross-sectional bar two, attributed to a negative impact of PVT on the course of liver disease. An association with higher risk of variceal bleeding was more evident than the impact on survival. More recent prospective studies have partially modified this picture. An ongoing prospective study in 232 patients with cirrhosis without hepatocellular carcinoma and 77% in Child-Pugh A [3], demonstrates LT-free survival rates at 1 and 3 years very similar between patients who developed superficial venous thrombosis compared to those who did not. Maruyama *et al.* [5] showed that patients who developed PVT had more advanced stage of disease (lower albumin levels, more severe ascites, larger spleen size) than those who do not develop PVT. A long follow-up (more than 10 years) did not demonstrate a significant difference in the incidence of variceal haemorrhage in the post-treatment recurrent bleeding and, most importantly, in survival between the two groups.

In the transplant setting, the negative influence of PVT on outcome has been recently reconsidered. In a series of more than 22,000 patients from the Scientific Registry of Transplant Recipients, Englesbe *et al.* [7] showed that the presence of PVT was associated with a significantly higher adjusted post-transplant mortality, but only during the first year after LT. Considering the whole period of observation, transplant benefit was not significantly different for patients with PVT versus those without PVT, although there was a shift in the benefit curve, the threshold for patients without PVT being MELD 11 and that for those with PVT being MELD 13 (Fig. 2).

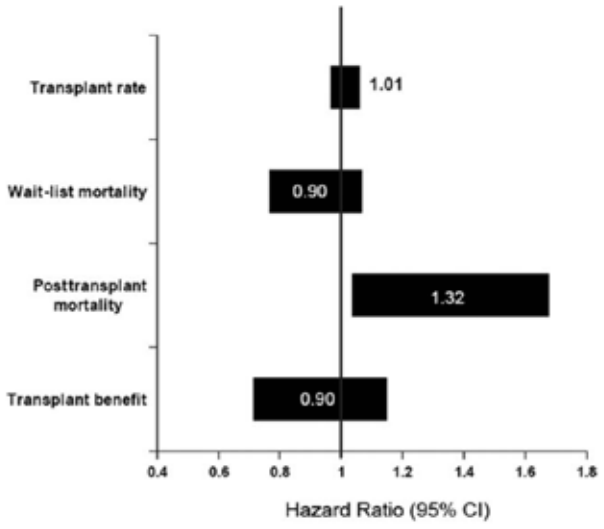

Figure 2. Covariate-adjusted effect of PVT on transplant rate, waiting list mortality, post-transplant mortality, and transplant benefit in the total cohort of patients, irrespective of the length of follow-up (taken from [7]).

These data fit with those reported by several other authors (including one on 63,182 recipients from UNOS database) who identified PVT as an independent risk factor for early post-transplant thrombosis of the hepatic artery. A recent updated meta-analysis of the PVT impact on LT outcome confirmed the negative impact on early outcome with decreasing influence during follow-up (Fig. 3) [8].

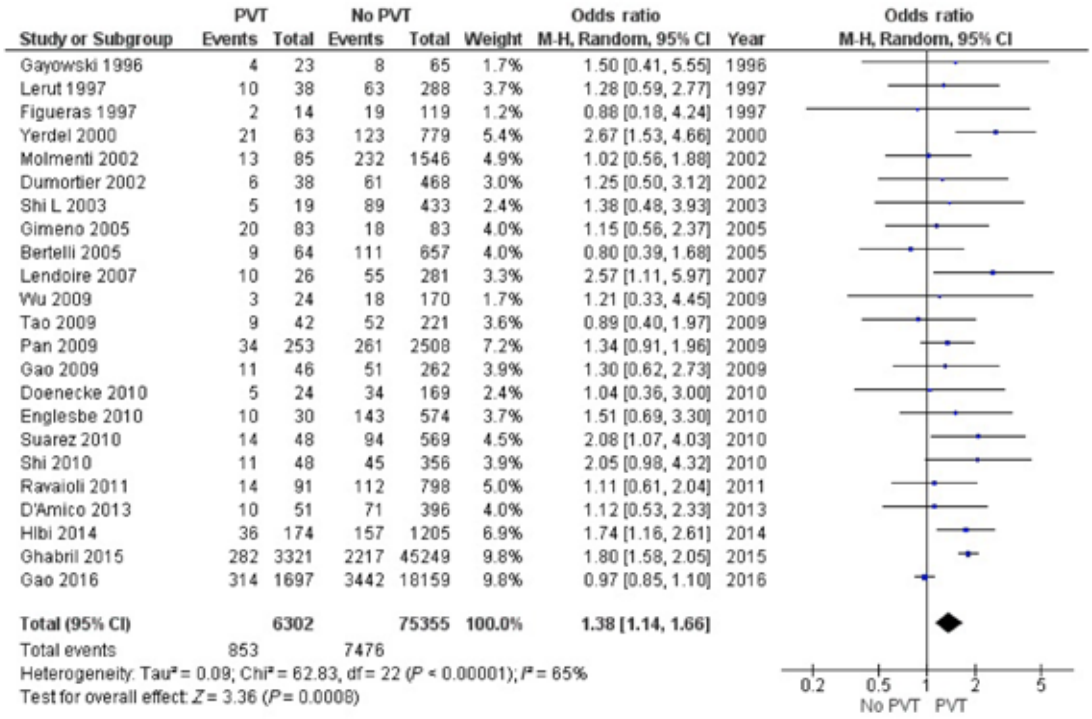

Figure 3. Forest plot shows there was a significant increase in 1-year mortality in liver transplant recipients with portal vein thrombosis (PVT) when compared to recipients without PVT (taken from [8]).

Interestingly, a clear-cut difference was noted, both in early (30 days) and late (1-year) mortality between patients with complete or partial PVT (Fig. 4, 5) [8].

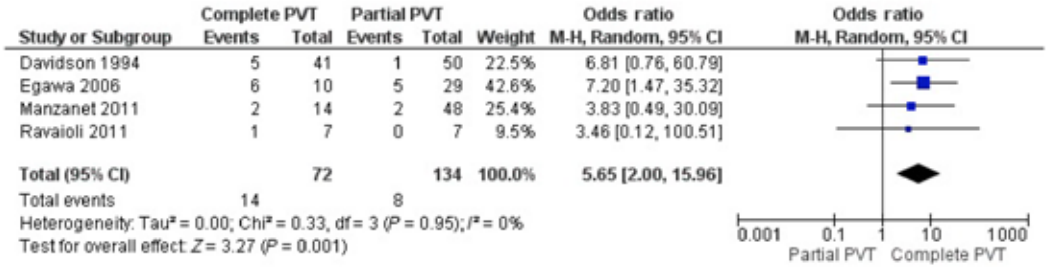

Figure 4. 30-day mortality in recipients with partial versus complete portal vein thrombosis (PVT). Forest plot shows a significant increase in short-term (30-days) mortality in liver transplant recipients with complete PVT *vs.* recipients with partial PVT (taken from [8]).

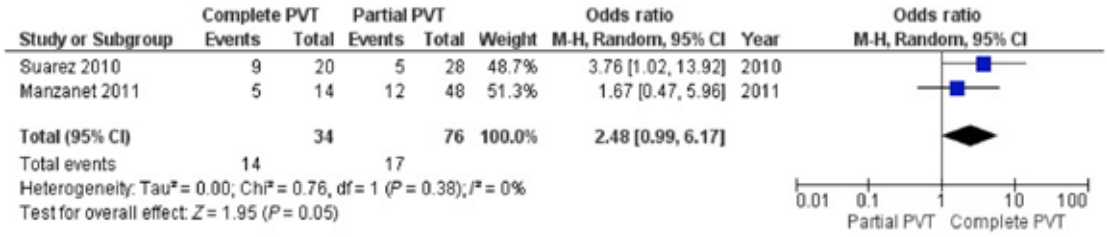

Figure 5. 1-year mortality in recipients with partial versus complete portal vein thrombosis (PVT). Forest plot shows there was a significant increase in mortality in liver transplant recipients with complete PVT when compared to recipients with partial PVT, although it was at an inferior limit of statistical significance.

Overall, it appears that PVT is one of the different indicators of progressive CLD. An indication supporting this view comes from the prospective study on anticoagulation for PVT prevention. Enoxaparin not only prevented PVT but also decompensation, likely by improving intestinal microcirculation, inhibiting bacterial translocation with resultant lower systemic inflammation. In this view, PVT and decompensation have similar expressions of a rapidly worsening portal hypertension.

3. Who should be treated and how?

It is clear from the paragraphs above that the decision of treating PVT implicates much wider reasoning than the simple thrombotic occurrence *per se.* If one accepts that PVT is one among several other factors linked to the progression of liver disease, treatment should take this wider landscape into account.

There is no doubt that acute symptomatic PVT should be treated, and treatment should be started as soon as possible. EASL guidelines recommend low molecular weight heparin (LMWH) treatment at a weight-adjusted dose for acute PVT in patients with cirrhosis [9]. The sooner the treatment, the better the outcome. Several data indicate that reasonable chances of recanalisation do not follow anticoagulation after 6 months of PVT occurrence. On the other hand, successful treatment of acute symptomatic PVT is associated with an improvement in the course of the disease and with facilitated control of other complications linked with portal hypertension without significant side effects [10].

LMWH is the treatment of choice unless significant renal impairment is present. Unfractionated heparin (UFH) does not have any added advantage in term of therapeutic effect and can be more difficult to handle. Experience with direct oral anticoagulants (DOAC) is still limited, as the use of these drugs in patients with cirrhosis is quite recent. Anticoagulation should be prolonged for 6 months, with either LMWH or vitamin K antagonists (VKA). Currently, evidence-based data on long-term anticoagulation are missing. Only a few reports from small patients' series are available. While safety is confirmed, it is not clear whether there is a real advantage in comparing retreatment in cases of recurrence.

Less evidence is available on the advantage of treating asymptomatic and/or incomplete PVT of unknown duration, especially in view of the reported spontaneous progression or regression and its uncertain influence on the disease course.

In case a patient on an active waiting list for LT develops PVT, anticoagulation can be safely used as it does not negatively impact transplant. On the contrary, recanalisation may favourably impact on LT complications, as PVT at surgery has been identified as an independent risk factor for early and late hepatic artery thrombosis (HAT) after LT. Heparin use at cross-clamp was associated with a lower HAT risk. In the LT setting, the thrombophilic shift can pose more problems than bleeding. This has brought attention to perioperative thromboprophylaxis in order to try to decrease morbidity and mortality associated with this feature.

4. How to monitor anticoagulation in advanced cirrhosis?

Monitoring anticoagulation in advanced cirrhosis has lately become less troublesome than in the past, in light of the modified understanding of the coagulative balance in CLD (Table 1).

Table 1. Summary of pros and cons of anticoagulants in cirrhotic patients (taken from [13]).

Anticoagulation Agents	Pros	Cons
LMWH	• Good safety profile in patients with cirrhosis and DVT/PVT • Experience up to 2 years in prophylaxis treatment for PVT • Anticoagulant effect is rapidly reversible in case of hemorrhagic complications	• Inconvenient and associated with poor compliance • Renal adjustments may be tricky • Acts on antithrombin • Heparin-induced thrombocytopenia (HIT) • Cannot use anti-Xa to estimate therapeutic effect
UFH	• Potential option in patients with concomitant renal failure • Anticoagulant effect is rapidly reversible in case of hemorrhagic complications	• Cannot be used practically and conveniently for long-term treatment • Higher potential for HIT
Fondaparinux	• Option for patients with HIT	• Acts on antithrombin • Accumulation in renal and liver disease • Inconvenient and associated with poor compliance • Limited data exist in the use of fondaparinux in cirrhotic patients
Warfarin	• Oral mode of administration • Supratherapeutic level is reversible	• Requires close monitoring • Cannot distinguish between INR resulting from warfarin vs cirrhosis • Altered metabolism as a result of liver dysfunction • Drug-drug interactions • Drug-food interactions
Direct factor Xa inhibitors: rivaroxaban and apixaban; direct thrombin inhibitors: dabigatran	• No monitoring required • Oral mode of administration	• Contraindicated because of lack of data—patients with cirrhosis were excluded from clinical trials

Anti-Xa, antifactory Xa; DVT, deep-vein thrombosis; LMWH, low-molecular weight heparin; PVT, portal vein thrombosis; UFH, unfractionated heparin.

LMWH – Is the treatment of choice for the treatment of PVT in patients with cirrhosis, is given subcutaneously once or twice daily in a fixed dose for thromboprophylaxis and a weight-adjusted dose for therapeutic purposes. LMWH does not require anti-Xa levels monitoring for dose adjustment. Its safety, both at prophylactic and therapeutic dosages, and in the setting of emergency or elective endoscopy for portal hypertension has been repeatedly shown [4,10-12].

UFH – Is an alternative in cirrhotic patients for shorter-term use and in cases of severe renal insufficiency. UFH requires laboratory monitoring by the activated partial thromboplastin time (APTT). Its use carries a higher risk of heparin-induced thrombocytopenia. For both LMWH and UFH, the anticoagulant effect is rapidly reversible in case of haemorrhagic complications.

VKAs – Oral VKA are other commonly used alternatives to heparins. Their efficacy and safety derive from longstanding experience in their use. VKAs require constant monitoring, which can be sometimes difficult as the prothrombin time (PT)-INR test was set up in patients without liver disease. This, together with the spontaneous PT prolongation in patients with liver cirrhosis, makes monitoring not straightforward. In patients listed for LT, VKAs interfere with MELD calculation.

DOACs – There is still limited experience with DOACs in cirrhosis. However, after the initial caution due to the exclusion of patients with cirrhosis from registrative studies, several reports, although in small patients' series, have been published. From these initial studies, it seems that DOAC are safe and can be used without the need for monitoring.

References

[References in **BOLD** are required reading]

1. Verbeek TA, Stine JG, Saner FH, Bezinover D. Hypercoagulability in End-stage Liver Disease: Review of Epidemiology, Etiology, and Management. Transplant Direct. 2018;4:e403.
2. Nery F, Chevret S, Condat B, de Raucourt E, Boudaoud L, Rautou PE, et al. Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire. Causes and consequences of portal vein thrombosis in 1,243 patients with cirrhosis: results of a longitudinal study. Hepatology. 2015;61:660-7.
3. Noronha Ferreira C, Coretz-Pinto H, Velosa J, Ferreira P, Dias M et al. Meld Score and Beta Blockers Are Independent Risk Factors for Development of Non-Tumoral Splanchnic Vein Thrombosis in Patients with Cirrhosis Which However Does Not Significantly Affect Decompensations of Cirrhosis or OLT Free Survival. Hepatology 2018; 68:1158A (Suppl).
4. Villa E, Cammà C, Marietta M, Luongo M, Critelli R, Colopi S, et al. Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. Gastroenterology. 2012;143:1253-1260.e4.
5. Maruyama H, Okugawa H, Takahashi M, Yokosuka O. De novo portal vein thrombosis in virus-related cirrhosis: predictive factors and long-term outcomes. Am J Gastroenterol. 2013;108:568-74.
6. Stine JG, Shah NL, Argo CK, Pelletier SJ, Caldwell SH, Northup PG. Increased risk of portal vein thrombosis in patients with cirrhosis due to nonalcoholic steatohepatitis. Liver Transpl. 2015 Aug;21(8):1016-21.
7. **Englesbe MJ, Schaubel DE, Cai S, Guidinger MK, Merion RM. Portal vein thrombosis and liver transplant survival benefit. Liver Transpl. 2010;16:999-1005.**

8. Zanetto A, Rodriguez-Kastro KI, Germani G, Ferrarese A, Cillo U, Burra P, Senzolo M. Mortality in liver transplant recipients with portal vein thrombosis - an updated meta-analysis. Transpl Int. 2018 Dec;31(12):1318-1329.

9. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Vascular diseases of the liver. J Hepatol. 2016;64:179-202.

10. Loffredo L, Pastori D, Farcomeni A, Violi F. Effects of Anticoagulants in Patients With Cirrhosis and Portal Vein Thrombosis: A Systematic Review and Meta-analysis. Gastroenterology. 2017;153:480-487.e1.

11. Cerini F, Gonzalez JM, Torres F, et al. Impact of anticoagulation on upper-gastrointestinal bleeding in cirrhosis. A retrospective multicenter study. Hepatology 2015;62:575–583.

12. Bianchini M, Cavani G, Bonaccorso A, et al Low molecular weight heparin does not increase bleeding and mortality post-endoscopic variceal band ligation in cirrhotic patients. Liver Int. 2018;38:1253-1262.

13. Ha NB, Regal RE. Anticoagulation in Patients With Cirrhosis: Caught Between a Rock-Liver and a Hard Place. Ann Pharmacother. 2016 May;50(5):402-9.


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SESSION 3
CIRRHOSIS AND COMORBIDITIES

WEDNESDAY 10 APRIL 2019 / 16:00-17:30

Assessment and relevance of sarcopenia and frailty

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Take-home message

- Sarcopenia is one of the most common complications of cirrhosis, leading to functional deterioration and frailty.
- Sarcopenia may also occur in obese patients, but due to the coexistence of obesity, it might be overlooked.
- Sarcopenia and frailty predict lower survival in patients with cirrhosis and patients undergoing liver transplantation, independent of the Model for End-Stage Liver Disease (MELD) score.
- Limitations of the MELD score include its failure to assess the nutritional and functional status of cirrhotic patients.
- Patients with a low MELD score and sarcopenia may be under prioritised.
- Adding sarcopenia to the MELD score is controversial since the added predictive value is modest and inconsistent.
- Dietary and moderate exercise interventions in patients with cirrhosis are consistently beneficial and safe, but large long-term studies are needed.
- All patients with cirrhosis should be encouraged to exercise, provided with practical advice appropriate to their abilities, and always accompanied by nutritional intervention.

Malnutrition is a common burden in liver cirrhosis, occurring in 20% of patients with compensated cirrhosis and more than 50% of patients with decompensated liver disease. Sarcopenia is defined by a progressive decline in skeletal muscle mass and function and is associated with a higher rate of complications, such as susceptibility to infections, hepatic encephalopathy and ascites. Sarcopenia independently predicts lower survival in patients with cirrhosis and patients undergoing liver transplantation [1]. Depletion of muscle mass also occurs in patients who are overweight or obese, mostly in non-alcoholic steatohepatitis (NASH) – cirrhosis; however, sarcopenia may be overlooked due to the coexistence of obesity. Obesity and sarcopenic obesity worsens the prognosis of patients with liver cirrhosis [2-4]. Moreover, post-transplant obesity and metabolic syndrome are common, in fact, weight gain after transplantation has been considered to be primarily due to an increase in the adipose tissue, with a concomitant loss in skeletal muscle [5,6].

How to measure malnutrition, sarcopenia and frailty?

Screening and assessment of malnutrition

Given the worse prognosis associated with malnutrition, all patients with advanced chronic liver disease are advised to undergo a rapid nutritional screen, and those at risk of malnutrition should complete a more detailed nutritional assessment to confirm the presence and severity of malnutrition [7], in order to actively manage this complication. A comprehensive summary of this topic can be found in the EASL Clinical Practice Guidelines on nutrition in chronic liver disease [1]. The recommended process

of nutritional screening and assessment in patients with cirrhosis is summarised in these guidelines (Fig. 1). Briefly, there are several possible tools to classify which patients are at risk for malnutrition. However, most were not validated in cirrhotic patients, and are prone to bias in case of fluid retention. The Royal Free Hospital-Nutritional Prioritizing Tool (RFH-NPT) score was reported to correlate with the severity of disease, clinical complications and survival [8]. It is advisable that patients who are at risk of malnutrition during screening undergo a detailed nutritional assessment for the diagnosis of malnutrition.

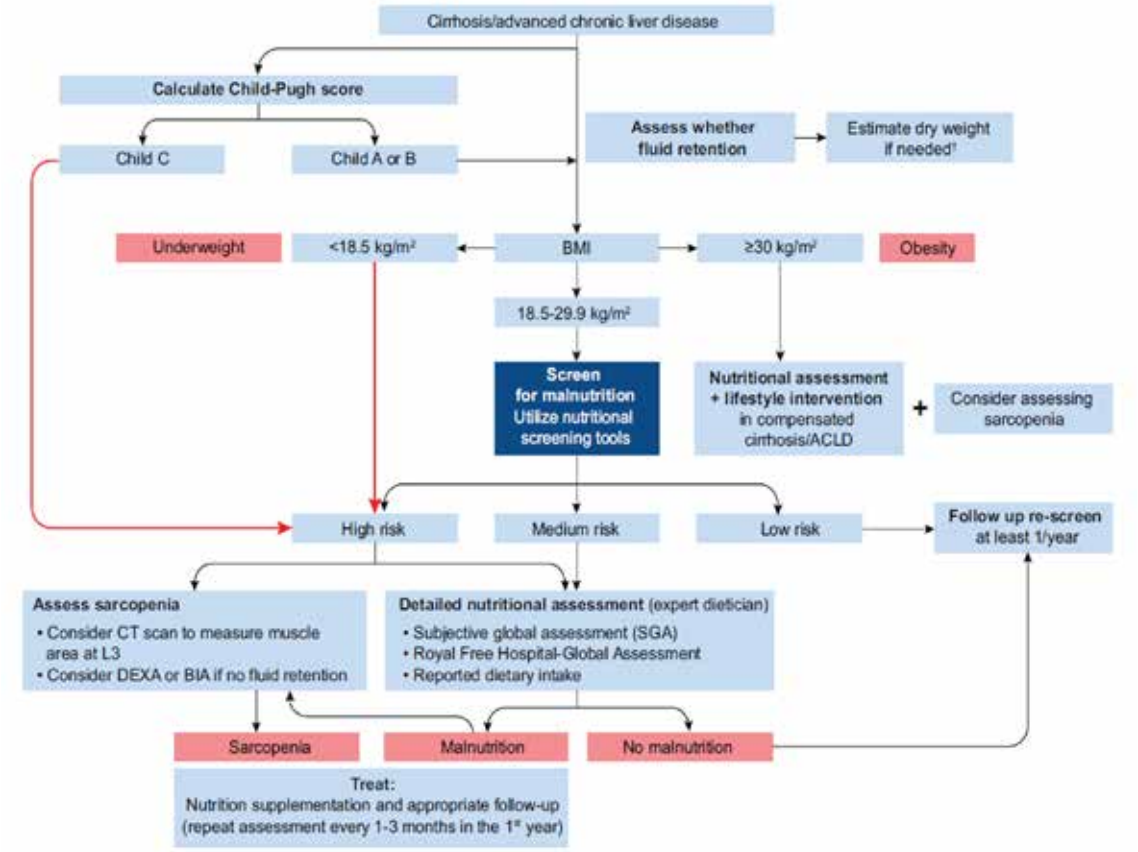

Figure 1. Nutritional screening and assessment in patients with cirrhosis [1]. †In a case of fluid retention, body weight should be corrected by evaluating the patient's dry weight by post-paracentesis body weight or weight recorded before fluid retention if available, or by subtracting a percentage of weight based upon severity of ascites (mild, 5%; moderate, 10%; severe, 15%), with an additional 5% subtracted if bilateral pedal oedema is present. BIA, bioelectrical impedance analysis; BMI, body mass index; CT, computed tomography; DEXA; dual-energy X-ray absorptiometry.

The components of a detailed nutritional assessment include evaluation of muscle mass, muscle contractile function, frailty and utilisation of global assessment tools, as described in brief below.

Sarcopenia and frailty: how to assess

Sarcopenia is a major component of malnutrition. Direct quantification of skeletal muscle mass requires cross-sectional imaging [9]. Computed tomographic (CT) image analysis at L3 vertebra is recognised as the most accurate technique to quantify muscle loss; abdominal skeletal muscle area at L3 is normalised to height to calculate the Skeletal Muscle Index (SMI) (cm^2/m^2). The routine use of CT imaging analysis, especially repeated assessments, is limited in clinical practice due to

cost and exposure to radiation. However, since CT scan is frequently available in cirrhotic patients (as a second-line imaging for screening hepatocellular carcinoma, for evaluation for liver transplant and evaluation of vascular shunts or portal vein thrombosis), it can be utilised at least once for the assessment of sarcopenia. Suggested cut-off values to define sarcopenia by CT were derived from a multicentre study of cirrhotic patients on the liver transplant list and were based on clinical outcomes (<50 cm^2/m^2 for men and <39 cm^2/m^2 for women) [10], but need to be further validated.

Body mass assessment can also be performed by simple bedside anthropometric methods including mid-arm muscle circumference (MAMC) defined as:

MAMC = MAC (cm) – [3.14 x TSF (cm)]

(mid-arm circumference [MAC]; triceps skin fold [TSF]). These are simple to perform, rapid, low cost, not affected by the presence of fluid retention, and have a demonstrated prognostic value for mortality among cirrhotic patients. Whole body dual energy X-ray absorptiometry (DXA) allows the measurement of bone mineral density, fat mass and fat-free mass, but cost and logistics are limiting its use. Tetrapolar bioelectrical impedance analysis (BIA) is low cost, portable modality, however it is inaccurate in the presence of fluid retention.

Skeletal muscle contractile function is not a direct measure of muscle mass but has been used as a measure of sarcopenia. Handgrip strength is a simple, inexpensive, and reliable method to detect malnutrition in cirrhotic patients with predictive capabilities of major complications and mortality [11,12].

Measures of frailty, defined as a patient's vulnerability to stress, decreased physiologic reserve and functional status deficits can also be used in the assessment of cirrhotic patients [13]. The most extensively validated tool is the Fried Frailty Phenotype, consisting of five components, including unintentional weight loss, low physical activity, exhaustion, slow gait speed, and weak handgrip strength. According to Fried, a score of 3 to 5 is defined as frail, 1 to 2 as pre-frail, and 0 is non-frail. The Short Physical Performance Battery (SPPB) consists of timed repeated chair stands, balance testing, and a timed 13-ft walk. SPPB predicts transplant waitlist mortality [12].

Global assessment tools in cirrhosis

The Royal Free Hospital-Global Assessment (RFH-GA) [14], used to determine nutritional status in patients with cirrhosis is reproducible, correlates with other measures of body composition and predicts survival and post-transplant complications. Patients are stratified into one of three categories based on their dry weight-based body mass index (BMI), MAMC, and dietary intake; adequately nourished, moderately malnourished (or suspected to be), or severely malnourished. The limitations of this tool include the time requirements and the need for trained personnel for consistent results.

Evidence that sarcopenia and frailty are predictive of mortality independent of MELD score

A recent meta-analysis included nineteen studies (3803 patients), which defined sarcopenia by CT-assessed skeletal muscle mass. The prevalence of sarcopenia ranged from 22% to 70% across studies. The pooled hazard ratios of sarcopenia were 1.84 (95% confidence interval 1.11–3.05) and 1.72 (95% confidence interval 0.99–3.00) for post-transplantation and waiting-list mortality, respectively, independent of MELD score. There also seemed to be a higher complication rate, particularly infections, among sarcopenic patients, but the evidence was less robust [15] (see Fig. 2). In addition, a recent study emphasised the even greater importance of sarcopenia in the prediction

of mortality in compensated/early decompensated cirrhosis. In 452 patients with cirrhosis (42% with sarcopenia) during a median follow-up period of 21.2 months, sarcopenia was generally associated with higher mortality (HR = 2.253, 95% CI 1.442–3.519), adjusting for MELD score and Child–Pugh score. The impact of sarcopenia was more pronounced and significant in patients with MELD score <15 or Child–Pugh score class A/B [16].

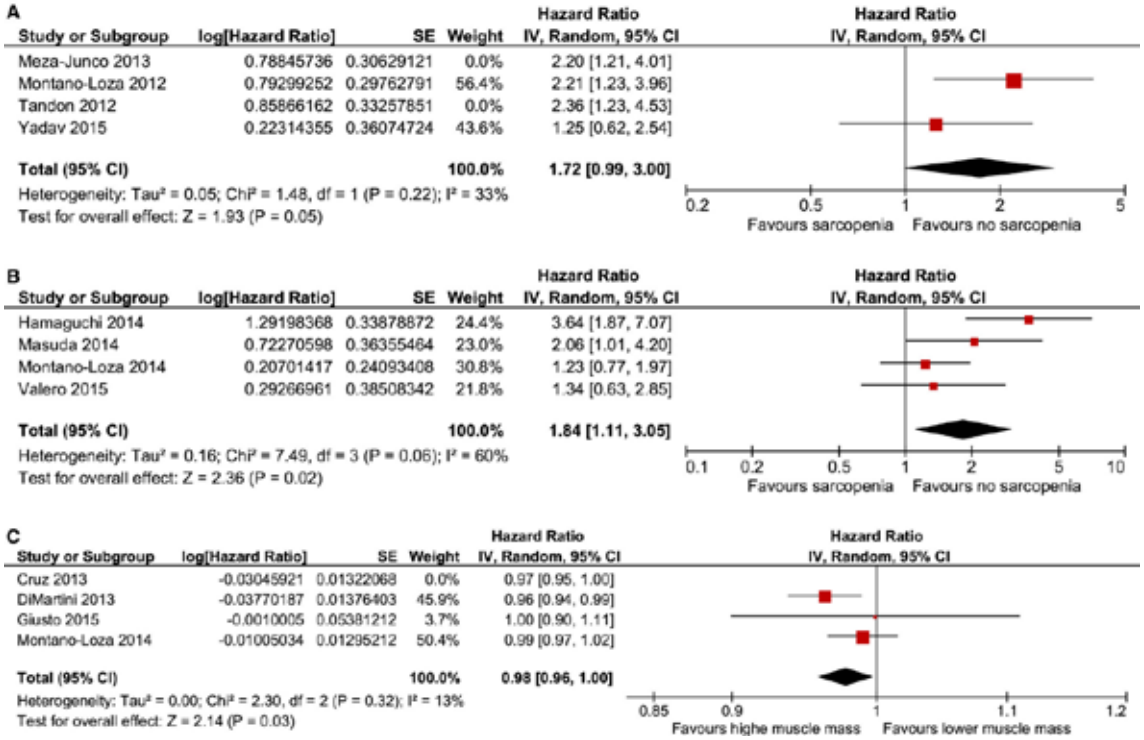

Figure 2. Forest plots of the association between sarcopenia and survival [15]. (A) Forest plot showing studies that reported the association between sarcopenia and waiting list mortality. (B) Forest plot showing studies that reported the association between sarcopenia and post-transplantation mortality. (C) Forest plot showing studies that reported the association between skeletal muscle mass and post-transplantation survival.

Frailty has consistently been shown to be a critical determinant of liver transplant outcomes, including hospitalisations, and mortality both before and after liver transplantation. An increase in the Fried Frailty score was demonstrated to be associated with increased risk of waitlist mortality, even with the adjustment for MELD [17]. The Liver Frailty Index, consisting of handgrip strength, chair stands, and balance testing, was derived specifically to capture the construct of physical frailty in liver transplant candidates, calculated as:

(-0.330 * gender-adjusted grip strength kg) + (-2.529 * number of chair stands per second) + (-0.040 * balance time sec) + 6.

The Liver Frailty Index strongly predicted waitlist mortality in a large cohort of patients [18] and, in fact, predicted more accurately than the Model for End-Stage Liver Disease–sodium (MELD-Na) score. The American Society of Transplantation advocates the use of the Liver Frailty Index in the baseline and longitudinal assessments of liver transplant patients to standardise incorporation of frailty into centre-level transplant decision-making [13]. A calculator of this score can be found in the following link: http://liverfrailtyindex.ucsf.edu.

Should sarcopenia and frailty be incorporated in prognostic scores in cirrhosis and how?

The lack of an objective parameter reflecting the nutritional and functional status of cirrhotic patients is a drawback of the MELD score. Consequently, patients with a low MELD score, but with sarcopenia or frailty may be under-prioritised. Therefore, the question arises if sarcopenia can be a useful addition to the MELD score to improve organ allocation and reduce waiting list mortality.

In the study of Durand *et al.* [19], transversal psoas muscle thickness/height (TPMT/height (mm/m)) was predictive of waiting list mortality, independent of the MELD score or MELD-Na score. A score combining MELD and TPMT/height was computed as follows:

MELD-psoas = (0.20 * MELD) - (0.08 * [TPMT/height]) + 2.

The discrimination for waiting list mortality of MELD-psoas score in all patients (c-statistics 0.82) was only mildly superior to that of the MELD score (c-statistics 0.80) and similar to that of the MELD-Na Score. The discrimination of the MELD-psoas area score was mildly superior to the MELD score and MELD-Na score in patients with a MELD score $\leq$25 or refractory ascites [19]. Similar findings were also reported in the study by Montano-Loza, in which a MELD-sarcopenia score was derived as follows:

MELD-Sarcopenia = MELD + 10.35 * Sarcopenia.

Overall, the c-statistics for 3-month mortality were similar; 0.82 for MELD and 0.85 for MELD-Sarcopenia. However, c-statistics for 3-month mortality in patients with MELD <15 were significantly higher for MELD-sarcopenia compared with MELD (0.85 *vs.* 0.69), suggesting that inclusion of sarcopenia is associated with improved prediction of mortality primarily in patients with low MELD scores [20] (see Fig. 3A, obtained from [21]). An external validation of this prognostic index was recently performed by van Vugt *et al.* in the Eurotransplant registry. However, in contrast to the previous study, the discriminative performance of the MELD-sarcopenia score (c-statistics 0.82) for 3-month mortality was slightly lower than MELD score alone (c-statistics 0.84), indicating that incorporating sarcopenia into the MELD score had no added value. The discriminative performance of the MELD-sarcopenia score among patients with MELD <15 was not presented [22]. Further external validation of the proposed scores is needed to understand their clinical usefulness. The main problems that impedes the inclusion of CT-assessed sarcopenia in predictive scores include the variability of the methods for assessment in different centres, lack of consensus regarding cut-off values and unfeasibility of sequential monitoring. In contrast to the MELD score, which is a parameter that is easier to assess and can be assessed repeatedly over a prolonged period.

As for frailty, the Liver Frailty Index, mentioned above [18], had a lower prognostic value for waitlist mortality at 3-months as compared to the one of the MELD-Na (c-statistic of 0.76 *vs.* 0.80). The combination of MELD-Na and the frailty index together resulted in a slightly higher c-statistic of 0.82 [18] (see Fig. 3B, obtained from [21]).

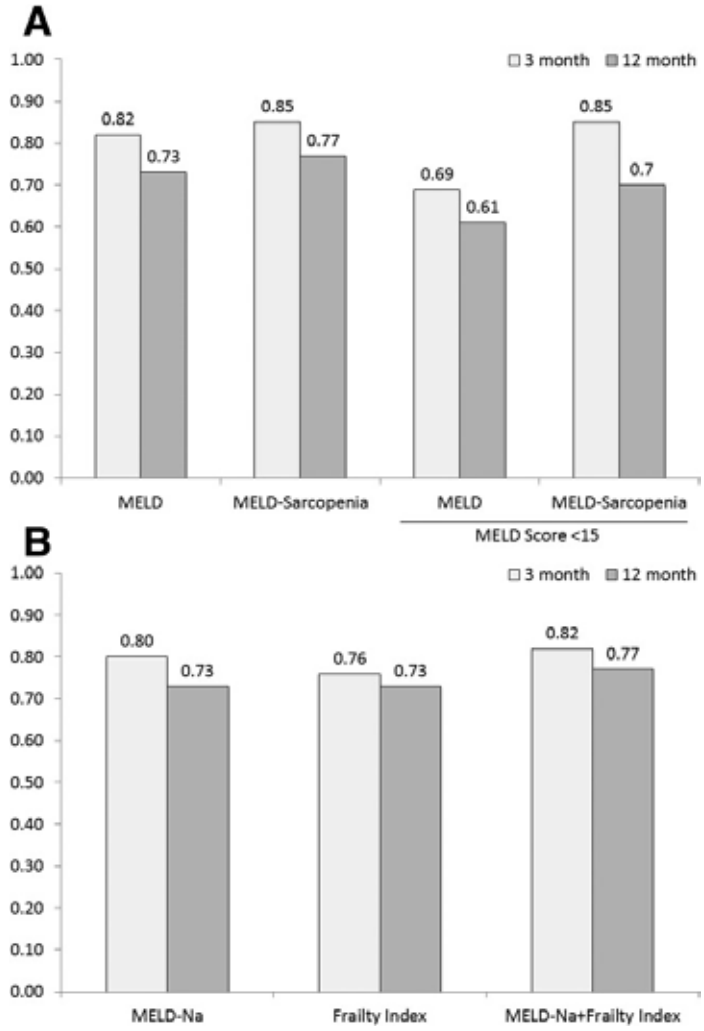

Figure 3. C-statistics for 3- and 12-month mortality prediction [21] (A) in patients with chronic liver disease comparing the use of MELD score and MELD-sarcopenia in the whole cohort (n = 669) and in those with a MELD score <15 (n = 438); and (B) in patients listed for LT comparing MELD-Na, the frailty index score, and its combination (n = 536).

Would improvement in sarcopenia and frailty by nutrition and exercise improve outcomes?

Nutritional support

Cirrhosis contributes to sarcopenia since it is a state of accelerated starvation, in which protein synthesis is decreased, and gluconeogenesis from amino acids is increased. The accelerated starvation is aggravated by reduced dietary intake due to a variety of factors including dysgeusia, anorexia of chronic disease, salt restricted food that is not tasty, portal hypertension that contributes to impaired gut motility, decreased nutrient absorption and protein-losing enteropathy [23]. Additional factors that result in decreased dietary intake include inappropriate dietary protein restriction, hospitalisation with periods of fasting for diagnostic and therapeutic procedures, encephalopathy and gastrointestinal bleeding [1]. Nutritional intervention improves survival and quality of life [24]. Dietary management should be implemented for every sarcopenic patient, with regular follow-up to evaluate response, preferably by a dedicated nutritional team [21].

The recently published EASL Clinical Practice Guidelines on nutrition in chronic liver disease provides a comprehensive review of the recommended nutritional and physical activity approach (recommendations by level of evidence are depicted in Table 1) [1]. The approach of the majority of nutritional interventions in cirrhosis is to supply at least 35 kcal kg^{-1} d^{-1}, and the recommended protein intake is 1.2–1.5 g/kg.BW/d to prevent loss of muscle mass and reverse muscle loss in those who are sarcopenic. Avoidance of fasting is important in preventing accelerated starvation state, by eating every 4-6 hours. Since the longest inter-meal duration is at night, the adoption of breakfast and a late evening snack to shorten the period of fasting is recommended. A late night snack containing complex carbohydrates as well as protein reduces lipid oxidation, improves nitrogen balance, reduces skeletal muscle proteolysis, increases muscle mass, reduces hepatic encephalopathy and improves quality of life; however, a reduction in mortality or need for transplantation have not been reported [25,26].

Table 1. Approach to sarcopenia in patients with liver cirrhosis, recommendations from the EASL Clinical Practice Guidelines on nutrition in chronic liver disease [1].

Recommendations	Grade* of evidence and strength of recommendation
Nutritional counselling should be performed in cirrhotic patients with malnutrition, when possible by a multidisciplinary team, helping patients to achieve adequate caloric and protein intake.	II-2, C2
Optimal daily energy intake should not be lower than the recommended 35 kcal/kg. actual BW/d (in nonobese individuals).	II-2, B1
Optimal daily protein intake should not be lower than the recommended 1.2–1.5 g/kg. actual BW/d.	II-2, B1
Include late evening oral nutritional supplementation and breakfast in dietary regimen of malnourished decompensated cirrhotic patients.	II-1, B1
BCAA supplements and leucine enriched amino acid supplements should be considered in decompensated cirrhotic patients when adequate nitrogen intake is not achieved by oral diet.	II-1, C1
In patients with malnutrition and cirrhosis who are unable to achieve adequate dietary intake with the oral diet (even with oral supplements), a period of enteral nutrition is recommended.	II-1, B1
Patients with cirrhosis, whenever possible, can be encouraged to avoid hypomobility and to progressively increase physical activity to prevent and/or ameliorate sarcopenia.	II-1, C2
Implement a nutritional and lifestyle program to achieve progressive weight loss (>5–10%) in obese cirrhotic patients (BMI >30 kg/m^2 corrected for water retention).	II-2, C1
A tailored, moderately hypocaloric (-500–800 kcal/d) diet, including adequate protein intake (>1.5 g proteins/kg.ideal BW/d) can be adopted to achieve weight loss without compromising protein stores in obese cirrhotic patients.	II-1, C2

*According to the GRADE scoring system.

In practical terms, when addressing the topic of nutrition with patients with cirrhosis, it is advisable to keep it simple. Meeting nutritional targets in patients with cirrhosis is challenging since the patients are burdened with a high degree of physical and psychological symptoms, medication complexity, and disability [27]. A suggested approach, combining nutritional education, and motivation and behavioural skills, is depicted in Figure 4.

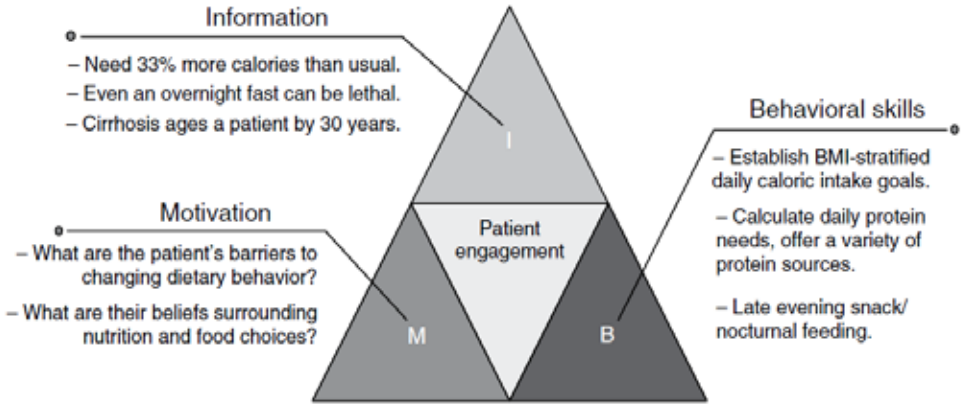

Figure 4. Framework for approaching nutritional counseling in patients with cirrhosis, based on the Information-Motivation-Behavioural Skills model for behavioral change [27].

In addition, short, practical dietary advice for bedside or outpatient clinic use can be found in Table 2, with an emphasis on avoiding unnecessary nutritional limitations and restrictions that are not evidence-based [1]. Regarding the obese patient with compensated cirrhosis, a reduction of body weight through lifestyle intervention including nutritional therapy and supervised moderate-intensity physical exercise may prevent clinical decompensation and improve clinical outcomes, such as reduction of portal pressure [2,28]. Dietary intake should guarantee moderate caloric restriction while ensuring adequate protein consumption needed to maintain muscle mass, due to the potential risk of worsening of sarcopenia during weight loss interventions.

Table 2. Short, practical dietary advice for bedside or outpatient clinic use [1].

• Most of what you have heard/read on the relationship between food and the liver has limited scientific evidence to support it. Generally, healthy eating of a variety of foods is advisable to all patients.
• Virtually no food other than alcohol does actually damage the liver and/or is genuinely contraindicated in patients with chronic liver disease.
• In most patients with chronic liver disease, eating an adequate amount of calories and protein is much more important than avoiding specific types of food, so it is important that you have a good, varied diet that you enjoy.
• You should try to split your food intake into 3 main meals (breakfast, lunch and dinner) and 3 snacks (mid-morning, mid-afternoon, late evening). The late-evening snack is the most important, as it covers the long interval between dinner and breakfast.
• You should try to eat as much vegetables and fruit as you can. If you feel that this makes you feel bloated, and that it makes you eat less, please report to your doctor or dietician.

- You should try not to add too much salt to your food. It may take some time to adjust, but it usually gets easier with time. However, if you keep feeling that this makes your food unpleasant to eat, and that it makes you eat less, please report to your doctor or dietician.
- A limited proportion of patients with liver disease have a complication called hepatic encephalopathy, which may make them tolerate animal protein (meat) less well than vegetable protein (beans, peas etc) and dairy proteins. Before you make any changes to your protein intake, you should always ask your doctor or dietician. Please do not reduce your total protein intake as it is not advisable in cirrhosis.
- Some patients with liver disease have other diseases, for example diabetes or overweight/obesity, which require dietary adjustments. Please remember to tell your doctor about all your illnesses and about any dietary advice you have already received from other doctors, nurses or dieticians.

Exercise and physical activity

The pathogenesis of sarcopenia and frailty in patients with cirrhosis includes a low level of physical activity in parallel with accelerated muscle protein breakdown [13]. Physical activity and exercise are anabolic stimuli that can improve muscle mass and function. Although long-term data in cirrhosis are lacking and most trials are small sample size, consistent benefits of exercise have been demonstrated including improvement in: aerobic capacity, muscle mass and strength, health-related quality of life and hepatic venous pressure gradient [28-31]. A combination of resistance and aerobic exercise would probably be beneficial, avoiding abdominal workouts [28,32]. Most patients with cirrhosis are sedentary; therefore, whenever possible should be encouraged to avoid hypomobility. Exercise must be tailored to the patient's ability, beginning with moderate intensity and maintained for the long-term to prevent and/or ameliorate sarcopenia [1]. Two recent comprehensive reviews on exercise in cirrhosis generally agree on the importance, benefit, safety (demonstrated also in a recent meta-analysis) and applicability of moderate intensity exercise in these patients, and provide practical advice [21,33,34]. Patients with cirrhosis on the transplant waiting list are advised, if possible, to perform 30-60-minute exercise sessions combining both aerobic and resistance training to achieve $\geq$150 minutes/week, along with a parallel increase in activities of daily living [21]. Long-term studies are needed to test whether improvement in muscle mass and/or muscle function improve clinical outcomes (lower the risk of decompensation, reduce hospital readmissions, decrease the length of hospital stay and improve survival) [1].

References

[Reference in **BOLD** are required reading]

1. **European Association for the Study of the Liver. EASL Clinical Practice Guidelines on nutrition in chronic liver disease. J Hepatol 2019;70:172-93.**
2. Berzigotti A, Garcia-Tsao G, Bosch J, Grace ND, Burroughs AK, Morillas R, Escorsell A, et al. Obesity is an independent risk factor for clinical decompensation in patients with cirrhosis. Hepatology 2011;54:555-61.
3. Montano-Loza AJ, Angulo P, Meza-Junco J, Prado CM, Sawyer MB, Beaumont C, Esfandiari N, et al. Sarcopenic obesity and myosteatosis are associated with higher mortality in patients with cirrhosis. J Cachexia Sarcopenia Muscle 2016;7:126-35.

4. Nishikawa H, Nishiguchi S. Sarcopenia and Sarcopenic Obesity Are Prognostic Factors for Overall Survival in Patients with Cirrhosis. Intern Med 2016;55:855-6.

5. Dasarathy S. Posttransplant sarcopenia: an underrecognized early consequence of liver transplantation. Dig Dis Sci 2013;58:3103-11.

6. Choudhary NS, Saigal S, Saraf N, Mohanka R, Rastogi A, Goja S, Menon PB, et al. Sarcopenic obesity with metabolic syndrome: a newly recognized entity following living donor liver transplantation. Clin Transplant 2015;29:211-5.

7. Tandon P, Raman M, Mourtzakis M, Merli M. A practical approach to nutritional screening and assessment in cirrhosis. Hepatology 2017;65:1044-57.

8. Borhofen SM, Gerner C, Lehmann J, Fimmers R, Gortzen J, Hey B, Geiser F, et al. The Royal Free Hospital-Nutritional Prioritizing Tool Is an Independent Predictor of Deterioration of Liver Function and Survival in Cirrhosis. Dig Dis Sci 2016;61:1735-43.

9. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing 2010;39:412-23.

10. Carey EJ, Lai JC, Wang CW, Dasarathy S, Lobach I, Montano-Loza AJ, Dunn MA, et al. A multicenter study to define sarcopenia in patients with end-stage liver disease. Liver Transpl 2017;23:625-33.

11. Tandon P, Tangri N, Thomas L, Zenith L, Shaikh T, Carbonneau M, Ma M, et al. A Rapid Bedside Screen to Predict Unplanned Hospitalization and Death in Outpatients With Cirrhosis: A Prospective Evaluation of the Clinical Frailty Scale. Am J Gastroenterol 2016;111:1759-67.

12. Wang CW, Feng S, Covinsky KE, Hayssen H, Zhou LQ, Yeh BM, Lai JC. A Comparison of Muscle Function, Mass, and Quality in Liver Transplant Candidates: Results From the Functional Assessment in Liver Transplantation Study. Transplantation 2016;100:1692-8.

13. Kobashigawa J, Dadhania D, Bhorade S, Adey D, Berger J, Bhat G, Budev M, et al. Report from the American Society of Transplantation on frailty in solid organ transplantation. Am J Transplant 2018. [Epub ahead of print]

14. 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.

15. van Vugt JL, Levolger S, de Bruin RW, van Rosmalen J, Metselaar HJ, JN IJ. Systematic Review and Meta-Analysis of the Impact of Computed Tomography-Assessed Skeletal Muscle Mass on Outcome in Patients Awaiting or Undergoing Liver Transplantation. Am J Transplant 2016;16:2277-92.

16. Kang SH, Jeong WK, Baik SK, Cha SH, Kim MY. Impact of sarcopenia on prognostic value of cirrhosis: going beyond the hepatic venous pressure gradient and MELD score. J Cachexia Sarcopenia Muscle 2018;9:860-70.

17. Lai JC, Feng S, Terrault NA, Lizaola B, Hayssen H, Covinsky K. Frailty predicts waitlist mortality in liver transplant candidates. Am J Transplant 2014;14:1870-9.

18. Lai JC, Covinsky KE, Dodge JL, Boscardin WJ, Segev DL, Roberts JP, Feng S. Development of a novel frailty index to predict mortality in patients with end-stage liver disease. Hepatology 2017;66:564-74.

19. Durand F, Buyse S, Francoz C, Laouenan C, Bruno O, Belghiti J, Moreau R, et al. Prognostic value of muscle atrophy in cirrhosis using psoas muscle thickness on computed tomography. J Hepatol 2014;60:1151-7.

20. Montano-Loza AJ, Duarte-Rojo A, Meza-Junco J, Baracos VE, Sawyer MB, Pang JX, Beaumont C, et al. Inclusion of Sarcopenia Within MELD (MELD-Sarcopenia) and the Prediction of Mortality in Patients With Cirrhosis. Clin Transl Gastroenterol 2015;6:e102.

21. Duarte-Rojo A, Ruiz-Margain A, Montano-Loza AJ, Macias-Rodriguez RU, Ferrando A, Kim WR. Exercise and physical activity for patients with end-stage liver disease: Improving functional status and sarcopenia while on the transplant waiting list. Liver Transpl 2018;24:122-39.

22. van Vugt JLA, Alferink LJM, Buettner S, Gaspersz MP, Bot D, Darwish Murad S, Feshtali S, et al. A model including sarcopenia surpasses the MELD score in predicting waiting list mortality in cirrhotic liver transplant candidates: a competing risk analysis in a national cohort. J Hepatol 2017.

23. Dasarathy S, Merli M. Sarcopenia from mechanism to diagnosis and treatment in liver disease. Journal of hepatology 2016;65:1232-44.

24. Iwasa M, Iwata K, Hara N, Hattori A, Ishidome M, Sekoguchi-Fujikawa N, Mifuji-Moroka R, et al. Nutrition therapy using a multidisciplinary team improves survival rates in patients with liver cirrhosis. Nutrition 2013;29:1418-21.

25. Plank LD, Gane EJ, Peng S, Muthu C, Mathur S, Gillanders L, McIlroy K, et al. Nocturnal nutritional supplementation improves total body protein status of patients with liver cirrhosis: a randomized 12-month trial. Hepatology 2008;48:557-66.

26. Tsien CD, McCullough AJ, Dasarathy S. Late evening snack: exploiting a period of anabolic opportunity in cirrhosis. Journal of gastroenterology and hepatology 2012;27:430-41.

27. Lai JC, Tandon P. How I Approach It: Improving Nutritional Status in Patients With Cirrhosis. Am J Gastroenterol 2018;113:1574-76.

28. Berzigotti A, Albillos A, Villanueva C, Genesca J, Ardevol A, Augustin S, Calleja JL, 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.

29. Kruger C, McNeely ML, Bailey RJ, Yavari M, Abraldes JG, Carbonneau M, Newnham K, et al. Home Exercise Training Improves Exercise Capacity in Cirrhosis Patients: Role of Exercise Adherence. Sci Rep 2018;8:99.

30. Berzigotti A, Saran U, Dufour JF. Physical activity and liver diseases. Hepatology 2016;63:1026-40.

31. Zenith L, Meena N, Ramadi A, Yavari M, Harvey A, Carbonneau M, Ma M, et al. Eight weeks of exercise training increases aerobic capacity and muscle mass and reduces fatigue in patients with cirrhosis. Clin Gastroenterol Hepatol 2014;12:1920-6 e2.

32. Macias-Rodriguez RU, Ilarraza-Lomeli H, Ruiz-Margain A, Ponce-de-Leon-Rosales S, Vargas-Vorackova F, Garcia-Flores O, Torre A, et al. Changes in Hepatic Venous Pressure Gradient Induced by Physical Exercise in Cirrhosis: Results of a Pilot Randomized Open Clinical Trial. Clin Transl Gastroenterol 2016;7:e180.

33. Tandon P, Ismond KP, Riess K, Duarte-Rojo A, Al-Judaibi B, Dunn MA, Holman J, et al. Exercise in cirrhosis: Translating evidence and experience to practice. J Hepatol 2018;69:1164-77.

34. Aamann L, Dam G, Rinnov AR, Vilstrup H, Gluud LL. Physical exercise for people with cirrhosis. Cochrane Database Syst Rev 2018;12:CD012678.

Cardiovascular comorbidities in cirrhosis: The emerging burden of NASH

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Session 3

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Take-home messages

- Non-alcoholic fatty liver disease (NAFLD), particularly non-alcoholic steatohepatitis (NASH), should now be considered an independent risk factor for cardiovascular disease (CVD).
- In pre- and post-liver transplant patients, NASH carries a high risk of CVD events and mortality.
- Management of patients with cirrhosis and NAFLD is fairly similar to the general population with some exceptions: avoiding the use of statins in decompensated liver disease, use of non-cardioselective beta-blockers to treat portal and arterial hypertension and avoiding obesity surgery in patients with portal hypertension.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a systemic disorder associated with diabetes, renal and cardiovascular diseases (CVD) [1]. There appears to be a clear tie between NAFLD and atherosclerotic CVD, suggesting that NAFLD should be included as an independent risk factor [2]. Patients with NAFLD have a higher risk of death from a CVD-related cause compared to a liver-related one. A subset of more progressive NAFLD, non-alcoholic steatohepatitis (NASH), has a particularly high risk of morbidity and mortality. Several societies have published guidelines that have emphasised the link between NAFLD and CVD in non-cirrhotic, cirrhotic, and post-liver transplant patients [1,3-5].

Prevalence of cardiovascular disease in patients with NASH

Patients with NAFLD have several known risk factors for CVD, such as diabetes, hypertension, dyslipidemia, chronic kidney disease and obesity. While it is unclear if NAFLD itself is associated with or is causal in the development of CVD, several lines of evidence support the latter (Fig. 1). For ischemic heart disease, persons with NAFLD have a higher prevalence of unstable coronary plaques, impaired endothelial function, and subclinical atherosclerosis (calcified and non-calcified plaques). As such, ischemic heart disease is highly prevalent among those with NAFLD compared to those without it [6].

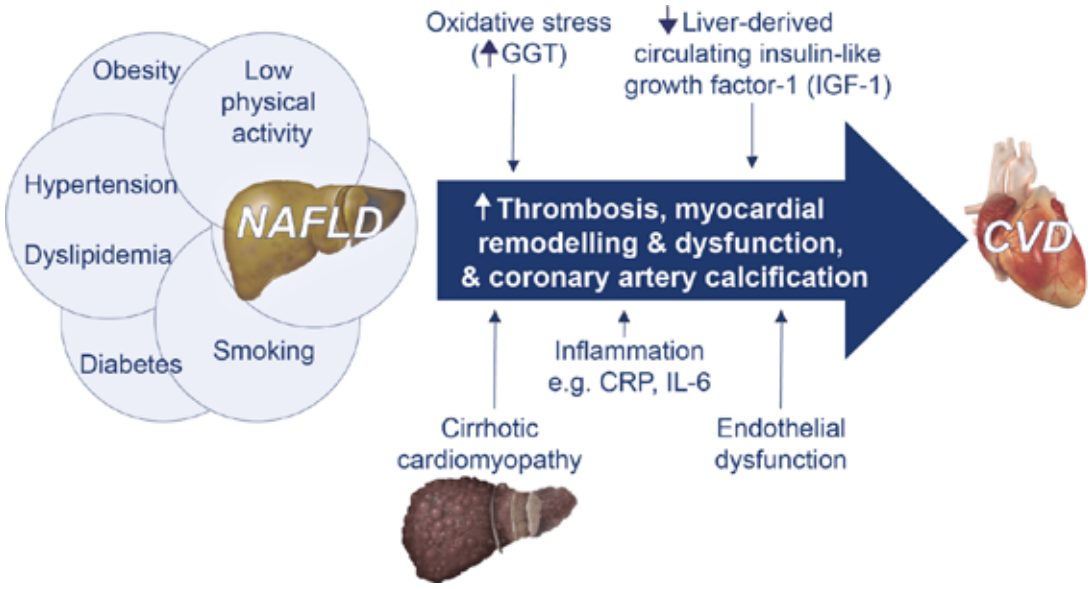

Figure 1. Proposed pathophysiology of cardiovascular disease and liver disease. NAFLD, non-alcoholic fatty liver disease; CVD, cardiovascular disease; GGT, gamma-glutamyl-transferase; CRP, C-reactive protein; IL, interleukin.

Studies have shown that NAFLD is also associated with subclinical changes in myocardial structure and function [7]. A recent large prospective population-based cohort demonstrated that computed tomography-diagnosed NAFLD was associated with subclinical myocardial remodeling, supporting the link between heart failure and preserved ejection fraction [8]. NAFLD is associated with altered cardiac energy metabolism, myocardial insulin resistance, impaired diastolic function and abnormal left ventricular structure. Finally, NAFLD has been independently associated with dysrhythmia, including atrial fibrillation, prolonged QTc interval and cardiac autonomic dysfunction.

Impact of cardiovascular disease and cirrhosis on mortality

Multiple studies have demonstrated a relationship between biopsy or imaging-proven NAFLD and the risk of developing CVD events. This may have to do with the stage of NAFLD and progression to NASH or more advanced fibrosis. For example, NHANES 1988–94 data showed that ultrasound-diagnosed NAFLD did not predict the risk of all-cause or cardiovascular-specific mortality [6]. However, NAFLD with advanced hepatic fibrosis (e.g., NASH) in this population was associated with a 70% increased risk of all-cause mortality, which was mainly from CVD. Thus, fibrosis stage is a key predictor of CV events among patients with NAFLD.

This is particularly prevalent in liver transplant recipients in which NASH is associated with an increased risk of post-operative CVD events and CVD-related mortality compared to other indications. Nearly a third of liver transplant recipients have a CVD complication after liver transplantation (LT). In the last 20 years, CVD mortality after LT has essentially doubled and CVD is a leading cause of early and late mortality [9]. These CVD complications are potentially preventable with early diagnosis and intervention, and it is clear that patients with NAFLD should be carefully screened for CVD to avoid future complications, with or without LT.

Prevention and treatment of cardiovascular comorbidities in cirrhosis

Based on these strong links, most societies have suggested that NAFLD by itself, regardless of other known risk factors, identifies a subset of patients with a higher risk of CVD mortality and morbidity over time, and thus recommends a thorough cardiovascular risk assessment [1,3-5]. Appropriate screening for hypertension, diabetes, and dyslipidemia is recommended in NAFLD patients, and medical optimisation is strongly recommended. Awareness of these increased risks among patients with NAFLD should lead practitioners to emphasise lifestyle modifications (i.e., physical activity, weight loss, smoking cessation) and pharmaceutical treatments (i.e., insulin sensitisers, lipid-lowering agents) to impact the manifestations of NAFLD. In general, management and treatment of CVD in patients with NAFLD with or without cirrhosis parallel the general population at risk. However, the following should be emphasised that is specific to the cirrhosis population:

- A multidisciplinary approach is recommended to establish a risk minimisation strategy (endocrinology and nutrition, psychology, cardiology, hepatology, nephrology, surgery, anesthesiology) [5].
- Patients with Child-Pugh A/B NASH cirrhosis and cardiovascular comorbidities should be considered for aspirin and statin therapy. However, it not known if the benefit of aspirin and statin therapy on prevention of CVD outcomes in the general population holds true in patients with cirrhosis, and statin therapy has risks associated with muscle-related events in patients with decompensated cirrhosis (e.g., Child-Pugh C), and thus relatively contraindicated in this population. Other risk factors for statin muscle-related adverse events include genetic factors, ethnicity, older age, female sex, low body mass index, hypothyroidism, hypertension, vitamin D deficiency, statin type and dose, polypharmacy, impaired kidney function, and alcohol or drug abuse – all of which may be highly prevalent in decompensated cirrhosis. That said, studies have established the safety of statins in patients with liver disease, including those with compensated cirrhosis. Thus, judicious use of these medications in patients with cirrhosis, with reduction in doses or use of statins with greater safety profile in this population (pravastatin, fluvastatin, or pitavastatin > rosuvastatin or lovastatin > atorvastatin), is advised. Simvastatin is relatively contraindicated in cirrhosis and liver transplant candidates given its poor efficacy for CVD prevention, potential drug-drug interactions (e.g., calcineurin inhibitors) and unfavourable safety profile.
- Screening and treating diabetes in patients with NASH is mandatory, preferentially using insulin sensitisers which could have additional beneficial effects in NASH. GLP-1 agonists should be considered as a first-line agent (e.g., liraglutide) beneficial for patients with type 2 diabetes and also early clinical trial data showing improvement in NAFLD. As randomised trials have not shown the benefit of metformin in NASH, guidelines have not recommended its use specifically for NASH. Pioglitazone showed improvement in liver histology in NASH and might be a reasonable option, but has the risk of weight gain and heart failure exacerbation.
- For hypertension, a non-cardioselective beta-blocker (e.g., carvedilol > nadolol or propranolol) is the ideal choice to treat both hypertension and portal hypertension. When beta-blockers are indicated for CVD prevention or treatment, cardioselective beta-blockers (e.g. metoprolol) may be preferred, or alternatively angiotensin-converting-enzyme or angiotensin-receptor blockers.
- Regarding obesity, a 7-10% weight loss may result in an improvement of histology and is the current target of therapy. Combination of dietary restriction and aerobic exercise/resistance training are the most effective approaches. While weight loss surgeries should not be performed in patients with portal hypertension, sleeve gastrectomy is currently the preferred approach in patients undergoing or soon after LT.

- An abnormal non-invasive test or a high pre-test probability of coronary artery disease should prompt consideration for coronary angiography. Coronary revascularisation should be considered in liver transplant candidates with obstructive coronary artery disease if the extent of coronary artery disease contraindicates transplantation [5].

References

[References in **BOLD** are required reading]

1. **Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, Harrison SA, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67:328-357.**
2. Targher G, Byrne CD, Lonardo A, Zoppini G, Barbui C. Non-alcoholic fatty liver disease and risk of incident cardiovascular disease: A meta-analysis. J Hepatol 2016;65:589-600.
3. **European Association for the Study of the L, European Association for the Study of D, European Association for the Study of O. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016;64:1388-1402.**
4. Burra P, Berenguer M, Pomfret E. The ILTS Consensus Conference on NAFLD/NASH and liver transplantation. Transplantation 2019 Jan;103(1):19-21.
5. **VanWagner LB, Harinstein ME, Runo JR, Darling C, Serper M, Hall S, Kobashigawa JA, et al. Multidisciplinary approach to cardiac and pulmonary vascular disease risk assessment in liver transplantation: An evaluation of the evidence and consensus recommendations. Am J Transplant 2018;18:30-42.**
6. Stepanova M, Younossi ZM. Independent association between nonalcoholic fatty liver disease and cardiovascular disease in the US population. Clin Gastroenterol Hepatol 2012;10:646-650.
7. Lee YH, Kim KJ, Yoo ME, Kim G, Yoon HJ, Jo K, Youn JC, et al. Association of non-alcoholic steatohepatitis with subclinical myocardial dysfunction in non-cirrhotic patients. J Hepatol 2017. pii: S0168-8278(17)32448-0.
8. VanWagner LB, Wilcox JE, Colangelo LA, Lloyd-Jones DM, Carr JJ, Lima JA, Lewis CE, et al. Association of nonalcoholic fatty liver disease with subclinical myocardial remodeling and dysfunction: A population-based study. Hepatology 2015. Sep;62(3):773-83.
9. VanWagner LB, Serper M, Kang R, Levitsky J, Hohmann S, Abecassis M, Skaro A, et al. Factors Associated With Major Adverse Cardiovascular Events After Liver Transplantation Among a National Sample. Am J Transplant 2016;16:2684-2694.

Management of diabetes in patients with cirrhosis: Which treatments, which targets?

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Session 3

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Take-home messages

- Patients with cirrhosis and type 2 diabetes (T2DM) are at increased risk of cardiovascular disease and non-liver cancer mortality, compared to subjects with T2DM who did not have liver disease.
- Patients with diabetes are at an increased risk of a range of different bacterial infections and patients with poor glycaemic control are particularly at risk of bacterial peritonitis and the development of septicaemia.
- Bacteraemia or septicaemia increases insulin resistance and causes hyperglycaemia.
- Recovery from infection improves insulin sensitivity necessitating a review of glucose-lowering medications and dosages.
- When considering which drug to choose to manage hyperglycaemia in patients with diabetes and cirrhosis, it is important to formally assess the level of liver dysfunction (and use of the Child-Pugh criteria are useful).
- Use of insulin is often the easiest and safest treatment for managing fluctuating glucose concentrations in patients with diabetes and cirrhosis requiring hospitalisation.

Introduction

Non-alcoholic fatty liver disease (NAFLD) was first described in 1980 with the description of 20 patients with non-alcoholic steatohepatitis (NASH) of unknown cause. The biopsy specimens were characterised by the presence of striking fatty changes with evidence of lobular hepatitis, focal necrosis with mixed inflammatory infiltrates, and, in most instances, Mallory bodies. Evidence of fibrosis was found in most specimens, and cirrhosis was diagnosed in biopsy tissue from three patients. The disease was more common in women. Most patients were moderately obese, and many patients had obesity-associated diseases, such as diabetes mellitus and cholelithiasis.

Changes in the prevalence of diabetes in patients with cirrhosis with the growing prevalence of NASH

NASH represents the harmful progressive form of liver disease within the spectrum of NAFLD that increases the risk of cirrhosis and hepatocellular carcinoma (HCC), and while there has been a decline in NASH-related hospital admissions in the UK in people without diabetes over the last two decades, rates have increased in people with diabetes. Since the 1980s, the burden of liver disease has increased dramatically, and NAFLD is thought to affect at least 25-30% of adults in developed countries and up to 70-90% of people with obesity or type 2 diabetes (T2DM). Importantly, T2DM also increases the risks of hospital admission and death from all common chronic liver diseases [1]. Prevalence of NAFLD, one of the two most common chronic liver diseases, is increasing as a consequence of increased obesity prevalence, and obesity is an extremely common risk factor

for T2DM. T2DM is a risk factor for liver fibrosis and cirrhosis and increases the risk of cirrhosis by 2- to 2.5-fold. NAFLD is associated with increased risk of extrahepatic complications including T2DM, chronic kidney disease and cardiovascular disease (CVD) and crucially, similar proportions of people with NAFLD die from CVD as from liver disease. Patients with T2DM are not only at an increased risk of the complications of NAFLD, but T2DM increases the risk of all chronic liver diseases that can lead to cirrhosis. The prevalence of NAFLD is much higher in patients with T2DM (ranging from approximately 50-75%), and patients with T2DM and NAFLD are also more likely to develop the more advanced forms of NAFLD, such as NASH, advanced fibrosis, cirrhosis, and in some cases HCC. We have recently performed a retrospective cohort study by using linked population-based routine data from diabetes registry, hospital, cancer, and death records for people aged 40–89 years diagnosed with T2DM in Scotland between 2004 and 2013, and who had one or more hospital admission records. Liver disease and outcomes were identified by using ICD-9 and ICD-10 codes. We estimated hazard ratios (HR) from Cox proportional hazards regression models, adjusting for key risk factors. A total of 134,368 people with T2DM (1707 with alcoholic liver disease [ALD] and 1452 with NAFLD) were studied, with a mean follow-up of 4.3 years for CVD and 4.7 years for mortality. Among those with ALD, NAFLD, or without liver disease hospital records there were 378, 320, and 21,873 CVD events; 268, 176, and 15,101 cancers; and 724, 221, and 16,203 deaths were reported, respectively. For ALD and NAFLD, respectively, adjusted HR (95% CIs) compared with the group with no record of liver disease were 1.59 (1.43, 1.76) and 1.70 (1.52, 1.90) for CVD, 40.3 (28.8, 56.5) and 19.12 (11.71, 31.2) for HCC, 1.28 (1.12, 1.47) and 1.10 (0.94, 1.29) for non-HCC cancer, and 4.86 (4.50, 5.24) and 1.60 (1.40, 1.83) for all-cause mortality. Thus, in this cohort, both NAFLD and ALD similarly increased the risk of CVD, cancer and all-cause mortality in people with T2DM [2]. Importantly, because of the study design in this analysis and the fact that subjects were required to have a hospital admission or died from liver disease, it is plausible to assume that both subjects with NAFLD and ALD had relatively severe liver disease. We have recently extended this work further. We have analysed data in the subgroup of individuals with NAFLD who had a diagnosis of liver fibrosis, cirrhosis, sclerosis or portal hypertension (unpublished). Of 1998 subjects with a diagnosis of NAFLD, 715 subjects had a diagnosis of cirrhosis, fibrosis, sclerosis or portal hypertension. In this group, the fully adjusted HR (95% CIs) for incident or recurrent CVD events occurring after a diagnosis of diabetes was 1.57 (1.36, 1.80) and for CVD mortality was 1.78 (1.31, 2.42). Interestingly, the fully adjusted HR (95% CIs) for cancer mortality (excluding HCC) was also increased 1.60 (1.21, 2.10). Thus, these data are shown in Table 1 suggest for the first time that patients with cirrhosis and T2DM are at increased risk of CVD and non-liver cancer mortality, compared to subjects with T2DM who did not have liver disease.

Table 1. Associations between history of hospital admission with non-alcoholic fatty liver disease (NAFLD) or its sub-groups, and all-cause mortality, cause-specific mortality, and cardiovascular disease (CVD) events among 134,368 people with type 2 diabetes with one or more hospital admission records and no record of other chronic liver diseases aged 40-89 years in Scotland from 2004-2013.

	Hazard ratios (95% CI)		
Outcome	Whole NAFLD group [a] (n = 1998)	Fatty liver / NASH sub-group [a,b] (n = 1283)	Cirrhosis / fibrosis/ Sclerosis/ PH sub-group [a,c] (n = 715)
Incident or recurrent CVD event after diagnosis of diabetes	1.62 (1.47, 1.77)	1.66 (1.47, 1.87)	1.57 (1.36, 1.80)
All-cause mortality	2.11 (1.92, 2.32)	1.29 (1.10, 1.51)	3.20 (2.84, 3.60)
CVD mortality	1.39 (1.10, 1.74)	1.10 (0.78, 1.54)	1.78 (1.31, 2.42)
HCC mortality	41.89 (27.1, 64.8)	2.42 (0.33, 17.5)	90.81 (58.0, 142.1)
Cancer mortality (excluding HCC)	1.15 (0.92, 1.42)	0.81 (0.58, 1.13)	1.60 (1.21, 2.10)
Other causes of death	3.16 (2.77, 3.59)	1.89 (1.52, 2.35)	4.82 (4.11, 5.64)

[a] Hazard ratios reflect comparison to people with type 2 diabetes, history of one or more hospital admissions, complete data and no history of chronic liver disease.

[b] Sub-group based on people with specific mention of fatty liver/non-alcoholic steatohepatitis (NASH) without mention of fibrosis, sclerosis, cirrhosis or portal hypertension (PH) in hospital records.

[c] Sub-group based on people with mention of fibrosis, sclerosis, cirrhosis or PH in hospital records.

Poor glycaemic control in patients with diabetes may also directly accelerate liver fibrosis and the development of cirrhosis. Hepatic stellate cells promote liver fibrosis through extra cellular matrix production and reduced extra cellular matrix degradation. Glucose and insulin have profibrogenic properties on hepatic stellate cells and incubation of hepatic stellate cells with high glucose or insulin levels lead to an overexpression of key profibrogenic gene connective tissue growth factor *(CTGF)*. Hyperglycaemia and oxidative stress contribute to the accumulation of advanced-glycation-end (AGE) products and functional receptors for AGE products are overexpressed in activated hepatic stellate cells. This upregulation of receptors for AGE products suggests that insulin and hyperglycaemia may also activate hepatic stellate cells through the ligation of AGE products on their receptors. Apoptosis is a form of cell death characterised by the formation of membrane-bound apoptotic bodies and apoptosis is an important phenomenon in the progression of liver fibrosis [3]. Indirect data suggest that diabetes might promote fibrosis through apoptosis. Perhaps the dysregulation of the insulin receptor pathway, associated with insulin resistance, promotes liver cell apoptosis. In patients with NASH, plasma cytokeratin 18 substrate which is a biomarker of liver apoptosis, is associated with liver fibrosis.

For people with and without diabetes, the liver plays a key role in glucose homeostasis. In the fed state the liver stores glycogen and glycogen synthesis is stimulated by insulin, whereas during fasting the

liver produces glucose through glycogenolysis and gluconeogenesis [4]. Consequently, in considering the use of glucose-lowering therapy to treat hyperglycaemia in patients with diabetes, it is important to bear in mind the severity of the liver disease and the relative health of the liver. It is also important to consider the health of other organs that influence glucose metabolism such as the adrenal glands because, for example, the adrenal gland produces counter regulatory hormones to insulin, such as glucocorticoid hormones, and these hormones can have a profound effect to stimulate hepatic gluconeogenesis and increase hepatic glucose output.

Glucose metabolism in patients with cirrhosis and insulin resistance

Insulin stimulates glycogen synthesis in the liver, but in patients with insulin resistance and T2DM there is a decreased capacity to synthesise glycogen. With hepatic lipid accumulation, there is an accumulation of lipid synthesis intermediaries, such as hepatic diacylglycerol (DAG), which has the potential to activate protein kinase C-ε (PKC-ε), impairing insulin receptor activation (causing hepatic insulin resistance) and impairing insulin-stimulated glycogen synthesis [5]. In addition to hepatic insulin resistance, peripheral insulin resistance (usually due to obesity) indirectly influences hepatic glucose and lipid metabolism by increasing flux of substrates that promote lipogenesis (fatty acids) and gluconeogenesis (glycerol and fatty acid-derived acetyl-CoA, an allosteric activator of pyruvate carboxylase in the gluconeogenic pathway). The liver has a limited capacity to store glycogen, and in patients with cirrhosis, liver glycogen levels are further decreased. The majority of patients with cirrhosis have glucose intolerance, and the presence of diabetes adversely affects prognosis in this patient group. The main feature of blood glucose dynamics in patients with chronic liver disease is marked fluctuations in blood glucose levels, and the presence of cirrhosis is associated with an increase in the amplitude of the change in glucose concentration over 24 hours. In patients with cirrhosis and splenomegaly, HbA1c concentrations may not accurately reflect blood glucose concentrations due to the shorter lifespan of the red blood cells.

Nocturnal hypoglycaemia and post-prandial hyperglycaemia are often features of chronic liver disease, and it is uncertain whether these problems are worse in patients with cirrhosis. Hyperinsulinaemia may occur with hepatic cell damage or portal-systemic shunting as the rate at which insulin is metabolised is reduced in patients with chronic liver disease. That said, despite peripheral hyperinsulinaemia portal insulin levels are low in patients with chronic liver disease who have portal-systemic shunting.

Possible implications of diabetes leading to complications of cirrhosis

Patients with diabetes are at an increased risk of bacterial infection due to impaired neutrophil function and decreased T cell-mediated immune responses. Subjects with poor glycaemic control are particularly at risk of bacterial peritonitis and the development of septicaemia. Diabetes is also associated with refractory cirrhosis [6] and with the development of ascites in patients with cirrhosis independently of the severity of liver dysfunction [7]. Patients with cirrhosis are also at an increased risk of bacterial infections compared to the general population, and patients with decompensated cirrhosis are at even greater risk. Although the mechanisms for increased susceptibility to infection are unclear, decreased neutrophil and also monocyte function has been implicated, as well as potential complement C3 and C4 deficiencies. There is a downregulation of monocyte leucocyte antigen-DR expression (and subsequent impaired antigen presentation ability) and impairment of macrophage Fc gamma receptor-mediated clearance of antibody-coated bacteria. The most common infection is spontaneous bacterial peritonitis, followed by urinary tract infection, and pneumonia. The usual causative organisms are Gram-negative *E. coli* and Gram-positive cocci. Although spontaneous bacterial peritonitis is rare in

patients with diabetes (who do not have cirrhosis), urinary tract infections and pneumonia are common infections in this patient group. That said, the combined influence of poorly controlled diabetes in a patient with decompensated cirrhosis is a parlous situation, and such patients are at very high risk of life-threatening bacterial infection.

Development of ascites is a complex process, but it has been linked to circulatory disturbance, renal dysfunction and sodium retention. In patients with diabetes, it is plausible that similar changes occur within the liver vasculature as in the kidney. Patients with diabetes are at risk of renal microangiopathy, and hypertension, hyperglycaemia and smoking are all risk factors for microvascular renal disease for which the first manifestation is usually the presence of microalbuminuria. Early in the development of microvascular disease, there is thickening of the glomerular basement membrane, and it is plausible that factors affecting the kidney could also affect the hepatic sinusoid. Stellate cell activation and matrix formation that underpins the development of cirrhosis leads to a disruption of the integrity and function of the hepatic sinusoid, and an increase in sinusoidal pressure can potentially result in portal hypertension.

With the development of bacterial peritonitis, ascites and septicaemia patients with diabetes and cirrhosis are at considerable risk of a massive cytokine response ('cytokine storm'), which converts responses that are normally directed at fighting infection into a damaging inflammatory response. For all patients with cirrhosis, this is potentially life-threatening with the possibility of worsening liver function, renal failure and circulatory collapse. For patients who also have diabetes, the stress response will cause insulin resistance, because of the release of counter-regulatory hormones that antagonise insulin action. The adrenal gland plays a large part in this stress response with the secretion of hormones, such as adrenaline and glucocorticoids (cortisol). If pancreatic beta cells are unable to respond (with the release of insulin) to counteract the effects of these stress hormones, unopposed glucagon activity in the liver results in a) marked increases in hepatic glucose output, and b) unopposed lipolysis in adipose tissue and consequent increased hepatic beta-oxidation and ketogenesis. The end result can be diabetic ketoacidosis that will result in patient death unless this devastating situation can be treated quickly and reversed. Mortality rates in such patients are exceptionally high, and patients will need intensive therapy if they are to survive. For those patients with severe liver dysfunction, extreme care is needed to correct glucose concentrations. As the patient recovers and the infection is treated, with a reduction in the stress response and improving insulin sensitivity, there is considerable potential for insulin-induced hypoglycaemia. Such patients may have a very diminished capacity to increase hepatic gluconeogenesis due to a marked deterioration in hepatic synthetic capability. The inability to produce sufficient hepatic glucose, compounded by relative adrenal insufficiency that is common in patients with cirrhosis and septic shock, may result in patients being 'over-treated' at addressing insulin levels, resulting in severe hypoglycaemia.

How to use oral hypoglycaemic medication and insulin in patients with cirrhosis. What are the targets?

Before considering the management of hyperglycaemia in patients with diabetes and cirrhosis, it is important to consider whether the patient has type 1 or type 2 diabetes (as the two most frequent types of diabetes mellitus). Patients with type 1 diabetes almost without exception have very little or no insulin secretory capability, due to autoimmune-mediated catastrophic destruction of beta cells. As a consequence, all patients with type 1 diabetes require replacement insulin therapy. Insulin is usually administered in the form of exogenous insulin injections. Insulin therapies are very varied but in brief can be divided into short-acting insulins, acting immediately and lasting 2-3 hours; long-acting insulin administered once or twice daily; and mixed insulins, administered twice or three times daily. Mixed

preparations of insulin are administered via a single device, and these insulins are formulations of different ratios of short- and longer-acting insulins. Typical mixed preparations may have a fixed ratio of, for example, 30% short-acting insulin and 70% long-acting insulin. Most modern insulins are within pre-filled cartridges that fit into a 'pen device', similar to a cartridge fountain ink pen. Patients can change the needles on their insulin pen device on a regular basis and 'dial' up and inject the required number of units of insulin. For most patients, the dose of insulin is modified regularly according to measurements of capillary glucose concentrations from finger-prick testing of blood.

If patients with diabetes and cirrhosis require hospitalisation due to severe illness from their diabetes, cirrhosis or incidental other disease, glucose control is best achieved with an 'insulin sliding scale', where intravenous short-acting insulin is administered via a pump, and the rate of insulin administration is titrated according to blood glucose concentration that can be measured at the point of care. It may be possible to manage some patients with T2DM and cirrhosis who are relatively well with oral medication (assuming the level of deterioration of pancreatic beta cell dysfunction is not too severe). It is very important to consider which oral treatments are safe and which should not be prescribed because of safety concerns. Table 2 shows the common treatments that are frequently used in the management of hyperglycaemia in patients with diabetes and includes whether they are safe in patients with liver disease or whether they should be avoided.

Table 2. Potential treatments for diabetes in patients with cirrhosis.

Treatments*	Usefulness for diabetes and cirrhosis	Side effects
Lifestyle	Maybe useful	May worsen malnutrition common
Metformin	Useful	Caution with eGFR <45 ml/min. Avoid with eGFR <30 ml/min
PPAR-gamma agonists	Maybe useful but caution with liver failure	Avoid with Child-Pugh A, B, or C
Secretagogues Sulphonylureas	Avoid	Major risk of hypoglycaemia with worsening liver function
Incretin modifiers	Useful	Nausea
Glucosidase inhibitors	Maybe useful with encephalopathy	Diarrhoea/flatulence
Insulin	Useful	Hypoglycaemia with worsening liver function

*All treatments can be used in patients with type 2 diabetes. Only insulin should be used in patients with type 1 diabetes and possibly metformin if the patient is obese.

eGFR, estimated glomerular filtration rate.

Two licensed drugs for the management of patients with T2DM, a peroxisome proliferator-activated receptor gamma (PPARγ) agonist, pioglitazone, and the glucagon-like peptide-1 agonist (GLP-1) agonist, liraglutide that produces substantial weight loss, have been shown to be effective in decreasing liver fibrosis in patients with NASH. Currently, three sets of guidelines from the UK, Europe and USA recommend pioglitazone or high dose vitamin E for the treatment of NASH. Extensive use of pioglitazone to treat T2DM has established its safety. The generic pioglitazone costs to the NHS are only ~£1.15 per patient per month. Pioglitazone targets both adipose tissue metabolism and inflammation, acting through the transcription factor PPAR-gamma. Pioglitazone treatment results in histological resolution of NASH in ~50% of patients, regardless of diabetes status, and the mean effect for the response to pioglitazone (defined as resolution of NASH from three key trials), was 51% (95% CI; 42, 60). However, for patients showing signs of cirrhosis, pioglitazone therapy should be avoided. There is concern that the drug may be inadequately metabolised by a liver with deteriorating function, and thus the potential for resulting drug toxicity caused by over dosage.

When considering which drug to choose to manage hyperglycaemia in patients with diabetes and cirrhosis, it is important to formally assess the level of liver dysfunction, and use of the Child-Pugh criteria are useful in that regard (Table 3). The Child-Pugh classification (see Table 3) is a simple easy to use classification and can be used to assess liver dysfunction in patients with chronic liver disease [8,9].

Table 3. Assessment of liver disease severity and liver dysfunction in patients with diabetes. The Child-Pugh classification to assess liver disease function.

	1 point	2 points	3 points
Child-Pugh score parameters			
Serum bilirubin micromoles/L (mg/dl)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin (mg/dl)	>35	28-35	<28
International Normalized Ratio	<1.70	1.71-2.20	>2.20
Ascites	None	None with medication	Persistent
Hepatic encephalopathy	None	Grade I-II (or none with treatment)	Grade III-IV (or persistent)

Child-Pugh score A = 5-6 points; B = 7-9 points; C = ≥10 points

All drugs used for the management of hyperglycaemia are probably safe in patients with mild liver dysfunction (i.e. Child-Pugh A). In contrast, drugs that are metabolised in the liver, or that place the patient at considerable risk of hypoglycaemia (insulin excepted), should be avoided in patients with Child-Pugh B and C, who have more severe liver dysfunction.

Over time, regardless of deteriorating liver function, pancreatic beta cell dysfunction tends to deteriorate in patients with T2DM. Thus, it is not uncommon for there to be a therapeutic need to intensify the dose, number, or type of glucose-lowering medication. Sometimes patients with T2DM ultimately require treatment with insulin in order to ameliorate hyperglycaemia, avoid diabetic ketoacidosis and attenuate the risk of microvascular complications. Whereas the increased risk of macrovascular complications is strongly associated with increased low-density lipoprotein cholesterol

concentration and hypertension, increased risk of microvascular complications are more strongly associated with hyperglycaemia. Although in patients with diabetes, who do not have serious liver disease, the clinician might aim for HbA1c concentrations of ~55 mmol/mol (in a patient treated with insulin) to optimise the risk of microvascular complications, such a level of glycaemic control could be very unsafe in patients with severe liver dysfunction due to cirrhosis. The risk of severe hypoglycaemic reactions with that level of glycaemic control would offset any potential benefit from having a low risk of microvascular complications. Because it is uncertain what the optimum level of glycaemic control should be for patients with diabetes and severe liver dysfunction, it is important to adopt a pragmatic approach to managing glucose levels, in order to keep the patient safe and optimise the overall risk to benefit ratio. While higher levels of glucose concentrations resulting in HbA1c concentrations of $\geq$55 mmol/mol, may result in a slightly higher risk of development of microvascular complications than HbA1c concentrations of <55 mmol/mol, it is important to aim for HbA1c concentrations in the 55 to 70 mmol/mol range. Any small increase in the risk of microvascular disease due to higher glucose concentrations is outweighed by not putting the patient at risk of catastrophic, life-threatening hypoglycaemia.

In summary, this syllabus has discussed the significant prevalence of diabetes in patients with cirrhosis; the metabolism of glucose in patients with cirrhosis; the implications of diabetes for complications of cirrhosis and the use of diabetes-specific medications and targets for patients with diabetes and cirrhosis.

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References

[References in **BOLD** are required reading]

1. Wild SH, Morling JR, McAllister DA, Kerssens J, Fischbacher C, Parkes J, Roderick PJ, et al. Type 2 diabetes and risk of hospital admission or death for chronic liver diseases. J Hepatol 2016;64:1358-1364.
2. Wild SH, Walker JJ, Morling JR, McAllister DA, Colhoun HM, Farran B, McGurnaghan S, et al. Cardiovascular Disease, Cancer, and Mortality Among People With Type 2 Diabetes and Alcoholic or Nonalcoholic Fatty Liver Disease Hospital Admission. Diabetes Care 2018;41:341-347.
3. Malhi H, Guicciardi ME, Gores GJ. Hepatocyte death: a clear and present danger. Physiol Rev 2010;90:1165-1194.
4. **Elkrief L, Rautou PE, Sarin S, Valla D, Paradis V, Moreau R. Diabetes mellitus in patients with cirrhosis: clinical implications and management. Liver Int 2016;36:936-948.**
5. **Samuel VT, Shulman GI. Nonalcoholic Fatty Liver Disease as a Nexus of Metabolic and Hepatic Diseases. Cell Metab 2018;27:22-41.**
6. Moreau R, Delegue P, Pessione F, Hillaire S, Durand F, Lebrec D, Valla DC. Clinical characteristics and outcome of patients with cirrhosis and refractory ascites. Liver Int 2004;24:457-464.

7. Elkrief L, Chouinard P, Bendersky N, Hajage D, Larroque B, Babany G, Kutala B, et al. Diabetes mellitus is an independent prognostic factor for major liver-related outcomes in patients with cirrhosis and chronic hepatitis C. Hepatology 2014;60:823-831.

8. Papatheodoridis GV, Cholongitas E, Dimitriadou E, Touloumi G, Sevastianos V, Archimandritis AJ. MELD vs Child-Pugh and creatinine-modified Child-Pugh score for predicting survival in patients with decompensated cirrhosis. World J Gastroenterol 2005;11:3099-3104.

9. Peng Y, Qi X, Guo X. Child-Pugh Versus MELD Score for the Assessment of Prognosis in Liver Cirrhosis: A Systematic Review and Meta-Analysis of Observational Studies. Medicine (Baltimore) 2016;95:e2877.

Indications for and access to transplantation in patients with comorbidities

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Take-home messages

- In the United States and many other countries, liver allograft allocation is based on the Model for End-Stage Liver Disease (MELD) score, which was updated in the United States to include serum sodium (MELD-Na) in 2016.
- MELD-Na is highly predictive of waitlist mortality at 3 months (c-statistic of 0.878) and accurately ranks the most medically urgent patients awaiting transplantation.
- Weaknesses of MELD-based system: the need for MELD exceptions, the disadvantage to women, urgency-based models prioritise sickest patients (more renal failure, potentially more frailty and sarcopenia).
- Development of a utility-based model of allocation, as opposed to an urgency-based allocation model, is challenging and limited published data are available.
- Co morbid conditions of sarcopenia, frailty and renal failure are related to advanced disease severity, as prioritised by an urgency-based model, impact both waitlist and post-transplant survival. Interventions to reduce the impact of these co morbidities are needed.
- Obesity is an additional comorbidity, unrelated to the allocation system, yet that may also impact long-term post-transplant outcomes

Objectives:

1. Discuss the pros and cons of MELD allocation system.
2. Discuss the impact of comorbidities (obesity, sarcopenia, frailty, renal failure) on the access to orthotopic liver transplantation and outcome of transplantation.

Liver transplantation is the standard of care for the treatment of decompensated liver disease. Ideally, transplant could be offered to every medically-suitable patient when they need it, though the critical shortage of available liver allografts requires that there is a system of allocation which determines priority for transplantation. Currently, in the United States, approximately 13% of waitlisted patients die without being transplanted, and 19% are removed from the list mostly because they have become too ill to undergo transplantation [1]. Organ allocation is dependent upon the remarkable altruism of donor families. There is a high degree of morbidity and mortality for patients with end-stage liver disease awaiting transplantation. In order for the donor families and waitlisted patients to have trust in the allocation system, it is imperative that it be transparent and fair, balancing the need to select patients who are both the most medically urgent and likely to have a benefit from the transplantation.

The Model for End-Stage Liver Disease (MELD) score was first developed as a model to aid in the selection of patients for trans-hepatic portosystemic shunt placement and was subsequently determined to be predictive of mortality overall in patients with end-stage liver disease. The MELD score was adopted for liver allocation in the United States in 2002 after an analysis using data on waitlisted patients demonstrated that MELD was able to accurately rank candidates according to the risk of waitlist mortality

with a c-statistic of 0.83 [2,3]. Prior to the MELD system, allocation in the United States was based on Child-Turcotte Pugh (CTP) scores and included three separate categories; status 1 for fulminant hepatic failure, status 2A for patients in the intensive care unit and status 2B (hepatocellular carcinoma [HCC] within Milan criteria, or CTP score >7 with associated complications), and status 3. The problem was that the system defaulted to waiting time within these broad categories, instead of disease severity. Plus, it was difficult to monitor and audit the subjective components of the CTP score (ascites, encephalopathy), as well as ICU admission criteria used to justify 2A status. The MELD allocation system was updated in 2016 to include sodium (MELD-Na; Fig. 1), which resulted in an improved discrimination with a c-statistic of 0.87 [4]. Under a MELD-based allocation system, patients with a complication of cirrhosis which impacts their survival and is not accounted for by the MELD system, such as HCC or hepato-pulmonary syndrome (HPS) will need to be assigned a MELD score (a MELD exception score) in order to access transplantation. The system of MELD score exceptions has likely contributed to the steady rise in median MELD at transplant seen in the United States [5].

Candidates (who are at least 12 years old):

0.957 x Log(creatinine mg/dl) + 0.378 x Log(bilirubin mg/dl) + 1.120 x Log(INR) + 0.643

If the initial MELD score is greater than 11, the MELD score is then re-calculated as follows:

MELD = MELD(i) +1.32*(137-Na) - [0.033*MELD(i)*(137-Na)]

Fig. 1. MELD-Na formula currently used for liver allocation used in the United States.

Another problem specifically related to the MELD allocation system is the fact that women are disadvantaged by the system. This is primarily due to decreased muscle mass which results in a lower serum creatinine level for women versus men with the same degree of renal impairment as determined by a measured glomerular filtrate rate using a technique such as an iothalamate clearance. This, in combination with reduced height and lower incidence of HCC and thus fewer HCC exceptions (historically associated with higher access to transplantation), has led to a persistent disparity in access to transplant for women versus men [6,7].

While MELD and MELD-Na are robust predictors of waitlist outcomes, they are not very predictive of post-transplant survival. Alternative systems have been sought which optimally could select patients with long-term post-transplant benefit, however because of the large number of factors that influence outcomes (recipient and donor characteristics, plus centre-related factors), a system which can accurately select not only the patient with a high-risk of waitlist mortality but also with the best chance of long-term survival has been challenging. Net Benefit is a system proposed by the group from the University of Michigan, which was considered by the UNOS/OPTN Liver Intestine committee as an alternative to MELD allocation but ultimately not adopted [8]. It was a complex formula which included variables that need to be collected and entered for each listed patient at each score renewal, the majority of the predictability of the model remained on the pre-transplant side of the equation, and the benefit was only calculated out to 3 years of post-transplant survival. A system proposed in the United Kingdom called UKELD was developed with a similar performance as MELD-Na, but is again, largely predictive of pre-transplant survival [9]. Several other systems have been proposed including HCC-MELD, MELD-HCC, and deMELD, which attempted to incorporate the characteristics of waitlisted candidates with HCC in order to develop a system which can function both for patients with and without HCC, considering not only the risk of waitlist drop-out but also prioritising longer-term survival [10,11]. Thus far, none of these systems have been widely adopted.

In addition to concerns about with the use of the MELD system not prioritising long-term outcomes, concerns have been noted about changes in the waitlisted population. With the persistent and severe organ shortage as well as an ageing population, patients are waiting longer at higher MELD scores for transplantation and are older at the time of transplantation. This has led to the need to consider liver transplant candidates who may be a different risk category than they were at the time of their original transplant assessment. Renal failure from prolonged hepato-renal syndrome, as well as acute tubular necrosis may develop, leading to the consideration of liver-kidney transplantation [12]. In response to these concerns, a revised liver-kidney allocation policy has been adopted in the United States, which not only includes specific eligibility criteria for kidney transplantation in the setting of combined liver-kidney transplant but also includes a safety net policy in cases where patients do not experience recovery of renal function post-liver transplantation. Candidates, especially older candidates or those with refractory ascites, are at risk of becoming increasingly frail while awaiting transplantation. Sarcopenia is a specific condition of reduced skeletal muscle mass seen in frail patients, which can be accurately measured by cross-sectional imaging and is predictive of waitlist and post-transplant survival [11]. Various frailty assessment tools have also been developed, and their utility in the transplant population is an area of active investigation (Fig. 2) [14,15]. In addition to determining the impact and optimal method of assessing frailty, there is considerable interest in intervention studies to determine if outcomes can be improved.

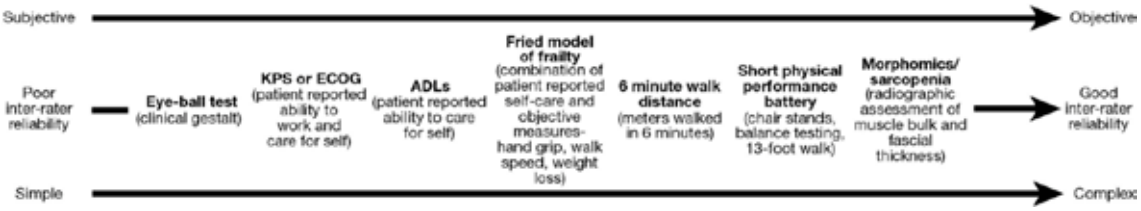

Fig. 2. Flow chart demonstrating attributes of available performance/frailty metrics for patients with cirrhosis, taken from Tapper and Su, 2016 [15].

Separate from the challenges related to the MELD allocation system is the impact of the obesity epidemic. More than a third of the United States population is obese, which has contributed to the rapidly rising incidence of obesity-related liver disease and a steady rise in the number of patients who require liver transplantation for non-alcoholic steatohepatitis (NASH). Though outcomes of liver transplantation may be similar in well-selected obese versus non-obese patients, complication rates for liver transplantation in obese patients may be higher, and patients are less likely to be listed and be transplanted once listed. Long-term post-liver transplantation outcomes may be affected by obesity-related complications, such as recurrent NASH, diabetes, heart disease and cancer. Weight loss may reduce the risk of recurrent NASH and may also affect other obesity-related complications but achieving weight loss is challenging. Bariatric surgery may be effective for selected patients, though the optimal timing is an area of active investigation [16]. Importantly, bariatric surgery is not an option prior to liver transplantation in patients with decompensated liver disease.

In conclusion, MELD-based allocation systems allow the selection of the most urgent candidates. However, in addition to the ongoing challenges of the MELD system related to handling exceptions and the disparity in access to transplant for women, new challenges related to the demographics of the aging population combined with prolonged waiting times at higher and higher disease acuity, plus the obesity epidemic and related increased incidence of NASH has led to increasing challenges of optimal patient selection, and the need to develop strategies to address this challenges.

References

[References in **BOLD** are required reading]

1. **Kim WR, Lake JR, J. M. Smith JM et al. OPTN/SRTR 2016 Annual Data Report: Liver. Am J Transplant. 2018 Jan;18 Suppl 1:172-253.**
2. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464–470.
3. **Wiesner R, Edwards E, Freeman R, et al. Model for End-Stage Liver Disease (MELD) and Allocation of Donor Livers. Gastroenterology 2003;124:91–96.***
4. Leise MD, Kim WR, Kremers WK et al. A revised model for end-stage liver disease optimizes prediction of mortality among patients awaiting liver transplantation. Gastroenterology. 2011 Jun;140(7):1952-60
5. Northup PG, Intagliata NM, Shah NL, et al. Excess mortality on the liver transplant waiting list: unintended policy consequences and model for end-stage liver disease (MELD) inflation. Hepatology 2015;61:285–291
6. Mathur AK, Schaubel DE, Gong Q, et al. Sex-based disparities in liver transplant rates in the United States. Am J Transplant 2011;11:1435–1443.
7. Myers RP, Shaheen AA, Aspinall AI, et al. Gender, renal function, and outcomes on the liver transplant waiting list: assessment of revised MELD including estimated glomerular filtration rate. J Hepatol 2011;54:462–470.
8. Schaubel DE, Guidinger MK, Biggins SW, et al. Survival benefit- based deceased-donor liver allocation. Am J Transplant 2009; 9(4 Pt 2): 970–981.
9. Barber K, Madden S, Allen J, et al. Elective liver transplant list mortality: development of a United Kingdom end-stage liver disease score. Transplantation 2011;92:469–476.
10. Vitale A, Volk ML, De Feo TM, et al. A method for establishing allocation equity among patients with and without hepatocellular carcinoma on a common liver transplant waiting list. J Hepatol 2013;60:290–297.
11. Toso C, Mazzaferro V, Bruix J, Freeman R, Mentha G, Majno P. Toward a better liver graft allocation that accounts for candidates with and without hepatocellular carcinoma. Am J Transplant. 2014;14(10):2221-7.
12. Sharma P, Schaubel DE, Guidinger MK, et al. Impact of MELD-based allocation on end-stage renal disease after liver transplantation. Am J Transplant 2011;11:2372–2378.
13. Englesbe MJ, Patel SP, He K, et al. Sarcopenia and mortality after liver transplantation. J Am Coll Surg. 2010;211(2):271-8.
14. **Lai JC, Covinsky KE, Dodge JL, et al. Development of a novel frailty index to predict mortality in patients with end-stage liver disease. Hepatology. 2017;66(2):564-574.**
15. **Tapper EB and Su GL. Does Karnofsky Performance Status of Patients With Cirrhosis on the Transplant Waitlist Meet the Eyeball Test? Clin Gastroenterol Hepatol. 2016;14(8):1196-8***
16. Zamora-Valdes D, Watt KD, Kellogg TA, et al. Long-term outcomes of patients undergoing simultaneous liver transplantation and sleeve gastrectomy. Hepatology.2018 ;68(2):485-495.

SESSION 4
MANAGING BACTERIAL INFECTIONS AND IMPAIRED RENAL FUNCTION

THURSDAY 11 APRIL 2019 / 8:30-10:00

Epidemiology of bacterial infections in cirrhosis and resistance to antibiotics worldwide

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Take-home messages

- Mortality due to bacterial infections and sepsis is increasing in patients with cirrhosis.
- Multi-drug resistant (MDR) bacteria are spreading worldwide, limiting the efficacy of antibiotic treatment.
- There are relevant regional differences in the prevalence of MDR bacteria which are very common in Asia (in India, extensively drug-resistant bacteria are very common).
- Empirical antibiotic treatment strategies should be based on local epidemiology.
- While waiting for new antibiotics, any effort should be made to reduce the spread of MDR bacteria in cirrhosis.

Introduction

Patients with cirrhosis have a high risk of developing infections and sepsis, which is almost doubled when compared to patients hospitalised for other diseases [1]. The reason for this high prevalence is related to several factors, namely cirrhosis-associated immune dysfunction, increased intestinal permeability, quantity and quality changes in gut microbiota, contributing to a pathological bacterial translocation from the gut to the systemic circulation, and genetic predisposition [2]. The prevalence of bacterial infections in hospitalised patients with cirrhosis ranges between 25-50% [3,4]. In addition, about 20% of infected patients may develop second infections during the hospitalisation [5]. About 60% of these infections are diagnosed at admission (within 48 hours), while 30-40% are nosocomial. About one-half of infections diagnosed at admission are health-care associated, i.e. occurring in patients recently discharged from the hospital or residents in long-term care facilities. The most common types of infection in cirrhotic patients are urinary tract infection (UTI; 23-41%) and spontaneous bacterial peritonitis (SBP; 20-35%), followed by pneumonia (8-14%), spontaneous bacteraemia (8-21%), and skin and soft tissues infections (SSTIs; 6-13%;). Infections in patients with cirrhosis are mainly due to bacteria, and only a small amount (3-7%) is sustained by fungi. Pneumonia, spontaneous bacteraemia and SSTIs are more frequently sustained by Gram-positive bacteria, while UTIs are more frequently caused by Gram-negative bacteria. In SBP, Gram-negative bacteria are more prevalent, but recently the rate of Gram-positive bacteria involved in SBP has increased. Among Gram-negative bacteria, *Enterobacteriaceæ* (e.g. *Escherichia coli, Klebsiella pneumoniae* etc.) are the most common pathogens responsible for infections in patients with cirrhosis. Among Gram-positive bacteria, *Staphylococci, Streptococci* and *Enterococci* are those more frequently involved.

The onset of bacterial infections has been associated with the occurrence of severe complications, such as acute kidney injury (AKI), hepatic encephalopathy and organ failures, conferring high short-term mortality [6]. Bacterial infections increase mortality risk in any stage of the liver disease, from compensated to decompensated cirrhosis and also in acute-on-chronic liver failure [7–9]. Remarkably, the risk of dying from sepsis has significantly increased in hospitalised patients with

cirrhosis during the last 20 years (Fig. 1) [10]. The spread of multi-drug resistant (MDR) bacteria has been considered, at least in part, responsible for the increase of mortality observed in patients with cirrhosis. MDR bacteria are bacteria resistant to at least one agent in three or more antimicrobial categories, while extensively drug-resistant (XDR) bacteria are a subgroup of MDR bacteria, which are resistant to at least one agent in all but two or fewer antimicrobial categories [11]. Indeed, MDR and XDR bacterial infections are more difficult to treat, being less responsive to empirical antibiotic treatment and associated with a risk of developing septic shock, transfer to the intensive care unit and short-term mortality [6,12,13]. Thus, bacterial infections and MDR bacteria are a relevant concern in patients with cirrhosis. The purpose of this chapter is to review the epidemiology of bacterial infections, mechanisms of antibiotic resistance and the epidemiology of MDR bacterial infections in patients with cirrhosis.

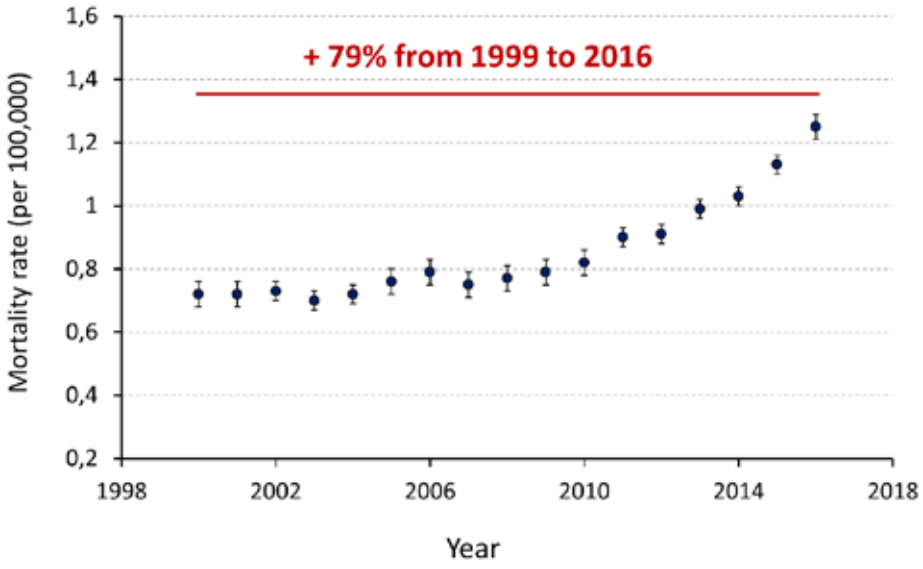

Figure 1. Age-adjusted death rates attributable to cirrhosis and sepsis per 100,000 inhabitants in U.S., each year from 1999 to 2016 (adapted from [10]).

Overview of the mechanisms of antibiotic resistance

Bacteria have developed several antibiotic resistance mechanisms, which can be summarised into the following categories: a) antibiotic modification/degradation; b) antibiotic efflux pumps; c) antibiotic sequestration; and d) target modification [14] (Table 1).

Table 1. Antibiotic options for MDR bacteria.

Antibiotic	Target organism	Mechanism of action
Old antibiotics		
Vancomycin	MRSA, VSE	Inhibition of cell wall synthesis in Gram+ bacteria (bactericidal)
Linezolid	MRSA, VRE	Inhibition of bacterial protein synthesis (bacteriostatic)
Daptomycin	MRSA, VRE	Insertion in cell membranes and creation of holes with rapid depolarisation (bactericidal)
Carbapenems	ESBL + *Enterobacteriaceæ* *Pseudomonas aeruginosa*	Inhibition of cell wall synthesis (bactericidal)
Colistin	CRE, *Pseudomonas aeruginosa*	Solubilisation and degradation of cell wall (bactericidal)
Tigecycline	MRSA, VRE, ESBL + *Enterobacteriaceæ* Some strains of CRE	Inhibition of bacterial protein synthesis (bacteriostatic)
Novel antibiotics		
Tedizolid	MRSA, VRE	Inhibition of bacterial protein synthesis (bacteriostatic)
Dalbavancin	MRSA, VSE	Inhibition of cell wall synthesis in Gram+ bacteria (bactericidal)
Delafloxacin	MRSA	Inhibition of bacterial DNA topoisomerase IV and DNA gyrase (bactericidal)
Omadacycline	MRSA	Inhibition of bacterial protein synthesis (bacteriostatic)
Ceftolozane/ tazobactam	ESBL + *Enterobacteriaceæ* *Pseudomonas aeruginosa*	Inhibition of cell wall synthesis (bactericidal)
Ceftazidime/ avibactam	ESBL+ Enterobacteriaceæ CRE (KPC and OXA-48)	Inhibition of cell wall synthesis, inhibition of carbapenemases (bactericidal)
Meropenem/ varbobactam	ESBL+ Enterobacteriaceæ CRE (KPC)	Inhibition of cell wall synthesis, inhibition of carbapenemases (bactericidal)
Eravacycline	MRSA, VRE, ESBL + *Enterobacteriaceæ* CRE, *Acinetobacter*	Inhibition of bacterial protein synthesis (bacteriostatic)

CRE, carbapenem resistant *Enterobacteriaceae*; ESBL, extended spectrum beta-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; MRSA, methicillin resistant *Staphylococcus aureus*; OXA, oxacillinase; VSE, vancomycin susceptible *Enterococci*; VRE, vancomycin resistant *Enterococci*.

Antibiotic modification/degradation

Antibiotic modification is a frequent mechanism used by bacteria to confer resistance against aminoglycosides. It involves the activity of enzymes, such as N-acetyl transferases, O-phosphotransferases, and O-adenyltransferases, which add acetyl, phosphate, or adenyl groups to aminoglycosides reducing their antimicrobial activity. Resistance to beta-lactams is usually due to antibiotic-hydrolysing enzymes known as beta-lactamases. Beta-lactamases are one of the most clinically relevant mechanisms of antibiotic resistance in human health and particularly in patients with cirrhosis. According to Ambler's classification, beta-lactams are generally grouped into four classes (A,B,C,D) based on their amino acid sequence and use of a catalytic serine or zinc ion. Class A includes serine proteases, such as penicillinases (which generally hydrolyse only penicillin), extended-spectrum beta-lactamases (ESBL, which also hydrolyse cephalosporins) and Klebsiella pneumoniae carbapenemase (KPC, which hydrolyses penicillin, cephalosporins and carbapenems). Class B includes metallo-beta-lactamases that require a bivalent metal ion, usually zinc, for activity. This group exhibits broad-spectrum hydrolysis including all beta-lactams, even carbapenems. New-Delhi metallo-beta-lactamase (NDM-1) and Verona integron-encoded metallo-beta-lactamase (VIM) are part of this group. Group C includes cephalosporinases, which exhibits greater hydrolysis for cephalosporins in comparison to benzylpenicillin and the most known of this group is Amp-C beta-lactamases. Finally, Group D includes the oxacillinases (OXA), enzymes able to hydrolyse cloxacillin or oxacillin, which is a wide group of beta-lactamase and some can hydrolyse carbapenem, such as OXA-48.

Antibiotic efflux pumps

Antibiotic efflux pumps remove the antibiotic from the cell using energy from ATP hydrolysis or proton gradients. Normally, each efflux pump involves the import or export of only one specific substrate. However, examples of multidrug exporters have been found.

Antibiotic sequestration

Sequestration involves the function of drug-binding proteins, which prevent the antibiotic from reaching its target.

Target modification

Target modification acts as a mechanism against several classes of antibiotics, including beta-lactams, glycopeptides, macrolides, lincosamides, and streptogramins, and aminoglycosides. Target modification includes various target alterations, such as alterations in the peptidoglycan precursors (for example, in the case of glycopeptides), or synthesis of alternate low-affinity targets (such as penicillin binding protein) that reduce or completely block antibiotics (beta-lactams) from associating with the target. The classic example of target modification is seen in methicillin-resistance *Staphylococcus aureus* (MRSA), where resistance to beta-lactams is conferred by an exogenous penicillin-binding protein (PBP2a), whose transpeptidase domain is insensitive to the action of several different beta-lactams.

Antibiotic resistance can be intrinsic or acquired. Intrinsic resistances are usually chromosome-encoded and include non-specific efflux pumps, antibiotic-inactivating enzymes, or mechanisms that serve as permeability barriers. An example of intrinsic resistance is the one related to vancomycin in Gram-negative bacteria, which results from the permeability barrier imposed by the outer membrane. Another example is the intrinsic resistance to cephalosporins in *Enterococci*, which involves the expression of a low-affinity penicillin-binding protein that binds weakly to cephalosporins. The acquired resistance mechanisms usually involve a horizontal gene transfer and include plasmid-

encoded specific efflux pumps and enzymes that can modify the antibiotic or the target of the antibiotic. The mechanisms by which the resistance genes are transferred to clinical isolates could occur by a variety of routes. One important route involves direct transfer from environmental bacteria (found in bodies of water, aquaculture, livestock animals, wildlife, and plants) to clinical isolates [14].

Epidemiology and risk factors of MDR bacteria in patients with cirrhosis throughout the world

As mentioned previously, the prevalence of MDR bacteria is increasing in patients with cirrhosis, although it is very heterogeneous among different centres and countries [6,12,15,16].

As mentioned previously, the prevalence of MDR bacteria is increasing in patients with cirrhosis, although it is very heterogeneous among different centres and countries [6,12,15,16].

Recently, the International Club of Ascites planned a multicentre intercontinental study (GLOBAL study) to assess the prevalence and the type of MDR infections in patients with cirrhosis. Relevant differences in the prevalence of MDR bacteria were found among different countries, ranging from more than 70% in India to about 20% in North America (Fig. 2) [6]. Data coming from the CANONIC study confirmed significant differences in the prevalence of MDR bacteria in different countries in Europe, with changing patterns in the most recent series, with a higher prevalence of MDR in Southern and Eastern Europe [16]. Most common MDR bacteria in patients with cirrhosis are ESBL-producing *Enterobacteriaceae*, MRSA and vancomycin-resistant *Enterococci* [5,6,16,17]. More recently, the spread of carbapenem-resistant *Enterobacteriaceae* (CRE) has been described also in patients with cirrhosis, being very common in India.

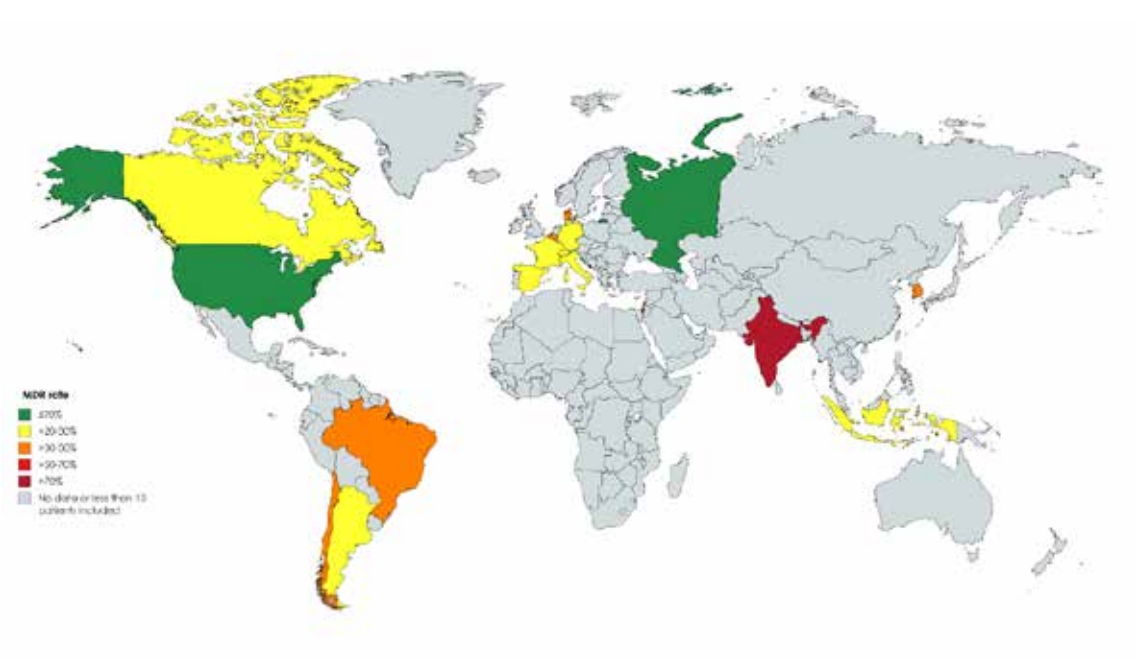

Figure 2. Prevalence of multidrug-resistant bacteria across the world. Different colours represent different rate in the prevalence of MDR bacterial infections. Relevant differences were found in the prevalence of MDR among the different countries. MDR, multidrug resistant. Modified from [6].

Risk factors for MDR bacterial infections are: previous exposure to antibiotics, nosocomial infections and previous infections due to MDR bacteria [13,17,18]. In some series, also healthcare-associated infections were found to be a risk factor for MDR infections [6,13].

The role of quinolone prophylaxis in inducing the development of antibiotic resistance may be very relevant [13,17,18], driving opinion leaders to suggest caution about their use in clinical practice [19]. However, more recently three studies questioned previous findings. Quinolones prophylaxis was not found to be associated with MDR infections in the GLOBAL study cohort and the CANONIC study cohort (although only 7 patients received norfloxacin in the latter) [6,16], and in a large randomised controlled trial in France, patients receiving norfloxacin did not have a higher rate of MDR bacteria than those receiving placebo [20]. Finally, it should be recognised that in high-risk patients, norfloxacin prophylaxis improves survival [20,21]. Thus, while waiting for non-antibiotic options for SBP prophylaxis, quinolones should be still used in high-risk patients, as suggested by the most recent guidelines [22].

Antibiotic options for MDR bacteria

The most important measure to improve the outcomes of infections in cirrhosis is the administration of an adequate empirical antibiotic treatment [6,9]. Indeed, an effective empirical antibiotic treatment of MDR infections ensures similar clinical outcomes than infections due to multi-susceptible bacteria [6]. The proper selection of antibiotic treatment should be based on several variables, namely: a) severity of infections; b) local epidemiology; c) type of infection; d) risk factors for MDR bacteria; e) safety of antibiotics; f) pharmacokinetic/pharmacodynamic of antibiotics and will be discussed in detail in another chapter of this syllabus. However, antibiotic options for MDR bacteria will be discussed in this section (Table 1).

Approved antibiotic options for MDR bacteria

As far as new antibiotic options for MDR bacteria is concerned, it should be recognised that new drugs are currently available for treating both Gram-positive and Gram-negative MDR.

As to the former, MRSA can be safely treated with vancomycin, daptomycin and linezolid, while linezolid and daptomycin are both effective in treating vancomycin-susceptible *Enterococci* (VRE) infections, although the latter is approved only for SSTIs and bloodstream infections. However, daptomycin has been effectively used in combination with meropenem for treating nosocomial SBP [23]. More recently, new drugs have been approved for clinical use. Tedizolid is an oxazolidinone-class antibiotic active against MRSA and VRE and has been approved for the treatment of SSTIs. Also, dalbavancin, a second-generation lipoglycopeptide antibiotic active against MRSA, has been approved for the treatment of SSTIs. Delafloxacin is a fluoroquinolone active against MRSA and approved for the treatment of SSTIs. Omadacycline is a modernised tetracycline, designed to overcome tetracycline resistance, it is active against MRSA and is approved for the treatment of pneumonia and SSTIs.

As for Gram-negative MDR organisms, carbapenem still represents the first-line treatment for ESBL-producing *Enterobacteriaceae*. Piperacillin/tazobactam can be considered an alternative only in UTIs, because in bloodstream infections it is less effective than carbapenems [24]. Ceftolozane-tazobactam is a new antibiotic effective against ESBL-producing *Enterobacteriaceae*, which represents an alternative to carbapenems. It is also highly effective against MDR *Pseudomonas Aeruginosa*. Ceftolozane-tazobactam is currently approved for the treatment of complicated UTIs and intra-abdominal infections, while phase 3 clinical trials are ongoing in pneumonia.

Ceftazidime-avibactam is a combination of third-generation cephalosporins and a new beta-lactamase inhibitor specifically designed for treating CRE. Avibactam inhibits carbapenemases, such as KPC and OXA-48, allowing the activity of ceftazidime. Remarkably, avibactam is not active against metallo-beta-lactamases, such as NDM-1 and VIM, which are the most common type of carbapenemases in India.

It is active against almost all *Enterobacteriaceae*, and it is approved for treating complicated UTIs and intra-abdominal infections.

Meropenem varbobactam combines a carbapenem and a beta-lactamase inhibitor, which inhibits the activity of KPC. However, it is not effective against metallo-beta-lactamases and OXA-48-producing *Enterobacteriaceae*. Meropenem varbobactam is currently approved for the treatment of complicated UTIs.

Eravacycline is a tetracycline antibiotic closely related to tigecycline; it is active against both Gram-positive (MRSA and VRE) and Gram-negative MDR (ESBL-producing *Enterobacteriaceae* and CRE). It has been recently approved for treating complicated intra-abdominal infections.

Plazomicin has just been approved for treating complicated UTIs, and it is active against CRE, however, it is an aminoglycoside, a class of antibiotic that is usually not recommended in patients with cirrhosis.

It is worth noting that all these antibiotics have not been tested in patients with cirrhosis and their efficacy/safety profile should be further investigated.

Antibiotics under investigation

Lefamulin is a member of a novel class of antibiotic, named pleuromutilins. It inhibits protein synthesis in bacteria by binding to the peptidyl transferase component of the 50S subunit of ribosomes. It is active against MRSA and macrolide-resistant Gram-positive bacteria and is under investigation for the treatment of SSTIs and community-acquired pneumonia.

Relebactam is a novel carbapenemase inhibitor that is effective against KPC. However, it is not effective against metallo-beta-lactamases and OXA-48. It is under investigation for the treatment of intra-abdominal infections, pneumonia and UTIs.

Cefiderocol is a siderophore cephalosporin, which has a unique mechanism of cell entry. Cefiderocol forms a chelated complex with ferric iron that facilitates its crossing of the outer membrane of Gram-negative bacilli using the receptor-mediated bacterial iron transport system. It is probably the most promising antibiotic against MDR Gram-negative bacteria, being effective *in vitro* against CRE, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Remarkably, cefiderocol has shown *in vitro* antimicrobial activity even in metallo-beta-lactamases and OXA-48-producing strains.

Strategies to prevent the spread of MDR bacteria

Any effort should be made to prevent the spread of MDR bacteria in patients with cirrhosis, as well as in the general population. Strategies to avoid the selection of MDR bacteria involves antimicrobial stewardship, early identification of carriers of MDR bacteria, the limitation of antibiotic use in human and non-human settings and stringent rules for eliminating antibiotics in the environment (Table 2) [6,12]. The antimicrobial stewardship involves the implementation of strategies aimed at rationalising antibiotic use, summarised as follows: a) use of broad-spectrum antibiotics only for patients at high-risk of MDR bacteria; b) use antibiotics at high dose for a short period of time; c) de-escalate antibiotics when antimicrobial susceptibility tests are available; d) limit antibiotic prophylaxis to evidence-based indications. In high-risk patients (such as those coming from another hospital, or

nursing home residency, or those with a previous MDR isolate), an active screening (rectal and nasal swabs) for colonisation with MDR bacteria may be useful. It allows to identify the carriers of MDR bacteria and to apply contact precautions and hand hygiene to prevent transmission to other patients. Another important measure to reduce the selection of MDR bacteria is to limit the over-the-counter access to antibiotics. Finally, the use of antibiotics in livestock to increase production should be prohibited because it can select MDR bacteria, which can be transmitted to human [25]. Finally, lack of regulations governing the waste of expired antibiotics and/or the wastewater treatment plants serving antibiotic manufacturing facilities can increase the antibiotic pressure in the environment, facilitating the development of MDR bacteria and the transfer of resistant genes into human pathogens. Thus, the fight against MDR bacteria should involve all the stakeholders, physicians, regulators, government, patients and mass media.

Table 2. Principles for avoiding the spread of multi-drug resistant bacteria.

What to do	Why
Spare broad-spectrum antibiotics for the most severe patients or those with risk factors for MDR bacteria	Broad-spectrum antibiotics are not more effective than narrower spectrum antibiotics in patients with susceptible bacteria
Use antibiotics at a high dose for a short time	7-10 days antibiotic course is sufficient for most infections
De-escalate antibiotics (if possible) when antibiogram is available	De-escalation is safe and reduces the exposure to broad-spectrum antibiotics
Antibiotic prophylaxis should be reserved to patients with evidence-based indications	Antibiotic prophylaxis improves patients' outcomes but can increase the risk of MDR infections
Surveillance for MDR bacteria carrier	Rectal or nasal swab may be useful in patients with several risk factors
Contact precautions in patients with MDR bacterial infections and or MDR bacteria carrier	The use of contact precautions may reduce the spread of bacteria to other patients
Limitation of over-the-counter access to antibiotics	The access to antibiotics without prescription may cause a non-appropriate use
Limitation of the use of antibiotics in livestock	They increase antibiotic pressure and the development of resistant bacteria in animals, which can be transferred to humans
Regulation of waste of expired antibiotics and water treatment plants serving antibiotic manufacturing facilities	The diffusion of antibiotics in the environment can facilitate the selection of MDR bacteria and the potential transfer of resistant genes to human pathogens

MDR, multi-drug resistant.

References

[References in **BOLD** are required reading]

1. Foreman MG, Mannino DM, Moss M. Cirrhosis as a risk factor for sepsis and death: Analysis of the National Hospital Discharge Survey. Chest 2003;124:1016–20.
2. Piano S, Brocca A, Mareso S, Angeli P. Infections complicating cirrhosis. Liver Int 2018;38:126–33.
3. Fasolato S, Angeli P, Dallagnese L, Maresio G, Zola E, Mazza E, et al. Renal failure and bacterial infections in patients with cirrhosis: Epidemiology and clinical features. Hepatology 2007;45:223–9.
4. Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology 2013;144:1426–1437.e9.
5. Bajaj JS, O'Leary JG, Reddy KR, Wong F, Olson JC, Subramanian RM, et al. Second infections independently increase mortality in hospitalized patients with cirrhosis: The north American Consortium for the study of end-stage liver disease (NACSELD) experience. Hepatology 2012;56:2328–35.
6. **Piano S, Singh V, Caraceni P, Maiwall R, Alessandria C, Fernandez J, et al. Epidemiology and Effects of Bacterial Infections in Patients With Cirrhosis Worldwide. Gastroenterology 2018. pii: S0016-5085(18)35402-7.**
7. Nahon P, Lescat M, Layese R, Bourcier V, Talmat N, Allam S, et al. Bacterial infection in compensated viral cirrhosis impairs 5-year survival (ANRS CO12 CirVir prospective cohort). Gut 2017;66:330–41.
8. Dionigi E, Garcovich M, Borzio M, Leandro G, Majumdar A, Tsami A, et al. Bacterial Infections Change Natural History of Cirrhosis Irrespective of Liver Disease Severity. Am J Gastroenterol 2017;112:588–96.
9. Fernández J, Acevedo J, Wiest R, Gustot T, Amoros A, Deulofeu C, et al. Bacterial and fungal infections in acute-on-chronic liver failure: prevalence, characteristics and impact on prognosis. Gut 2018;67:1870–80.
10. Tapper EB, Parikh ND. Mortality due to cirrhosis and liver cancer in the United States, 1999-2016: observational study. BMJ 2018;362:k2817.
11. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: An international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012;18:268–81.
12. **Fernández J, Bert F, Nicolas-Chanoine M-H. The challenges of multi-drug-resistance in hepatology. J Hepatol 2016;65:1043–54.**
13. Merli M, Lucidi C, Di Gregorio V, Falcone M, Giannelli V, Lattanzi B, et al. The Spread of Multi Drug Resistant Infections Is Leading to an Increase in the Empirical Antibiotic Treatment Failure in Cirrhosis: A Prospective Survey. PLoS One 2015;10:e0127448.
14. Peterson E, Kaur P. Antibiotic Resistance Mechanisms in Bacteria: Relationships Between Resistance Determinants of Antibiotic Producers, Environmental Bacteria, and Clinical Pathogens. Front Microbiol 2018;9:2928.

15. Zhao R, Ma J, Li P, Fang H, Sun S, Wu W, et al. Multidrug-resistant bacterial infections in cirrhotic patients: an epidemiological study. Expert Rev Gastroenterol Hepatol 2018:1–8. [Epub ahead of print]

16. Fernández J, Prado V, Trebicka J, Amoros A, Gustot T, Wiest R, et al. Multidrug-resistant bacterial infections in patients with decompensated cirrhosis and with acute-on-chronic liver failure in Europe. J Hepatol 2018. pii: S0168-8278(18)32511-X.

17. Fernández J, Acevedo J, Castro M, Garcia O, Rodríguez de Lope C, Roca D, et al. Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: A prospective study. Hepatology 2012;55:1551–61.

18. Tandon P, DeLisle A, Topal JE, Garcia-Tsao G. High Prevalence of Antibiotic-Resistant Bacterial Infections Among Patients With Cirrhosis at a US Liver Center. Clin Gastroenterol Hepatol 2012;10:1291–8.

19. Fernández J, Tandon P, Mensa J, Garcia-Tsao G. Antibiotic prophylaxis in cirrhosis: Good and bad. Hepatology 2016;63:2019–31.

20. Moreau R, Elkrief L, Bureau C, Perarnau J-M, Thévenot T, Saliba F, et al. Effects of Long-term Norfloxacin Therapy in Patients with Advanced Cirrhosis. Gastroenterology 2018;155(6):1816-1827.e9.

21. Fernández J, Navasa M, Planas R, Montoliu S, Monfort D, Soriano G, et al. Primary Prophylaxis of Spontaneous Bacterial Peritonitis Delays Hepatorenal Syndrome and Improves Survival in Cirrhosis. Gastroenterology 2007;133:818–24.

22. Angeli P, Bernardi M, Villanueva C, Francoz C, Mookerjee RP, Trebicka J, et al. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018;69:406–60.

23. Piano S, Fasolato S, Salinas F, Romano A, Tonon M, Morando F, et al. The empirical antibiotic treatment of nosocomial spontaneous bacterial peritonitis: Results of a randomized, controlled clinical trial. Hepatology 2016;63:1299–309.

24. Harris PNA, Tambyah PA, Lye TC, Mo Y, Lee TH, Yilmaz M, et al. Effect of piperacillin-tazobactam vs meropenem on 30-day mortality for patients with E coli or Klebsiella pneumoniæ bloodstream infection and ceftriaxone resistance: A randomized clinical trial. JAMA 2018;320:984–94.

25. Hammerum AM, Larsen J, Andersen VD, Lester CH, Skytte TSS, Hansen F, et al. Characterization of extended-spectrum β-lactamase (ESBL)-producing Escherichia coli obtained from Danish pigs, pig farmers and their families from farms with high or no consumption of third- or fourth-generation cephalosporins. J Antimicrob Chemother 2014;69:2650–7.

Optimal use of antibiotics in patients with cirrhosis: Which type of infection, which antibiotic(s), which dose?

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Take-home messages

- Bacterial infections are a complication of cirrhosis that may occur in compensated and decompensated patients and are associated with high mortality.
- The most common are the "spontaneous" infections, such as spontaneous bacterial peritonitis, which are increasingly being caused by multi-drug resistant organisms.
- Timely and appropriate empirical antibiotic therapy is essential and requires a high degree of suspicion, identification of the source of infection and causative organism, and recognition of setting in which infection occurs.
- Albumin use prevents the progression of renal dysfunction in this setting.

Bacterial infections in cirrhosis

About a third of hospitalised patients with cirrhosis are diagnosed as having a bacterial infection, the most common being the "spontaneous" infections, such as spontaneous bacterial peritonitis (SBP) and spontaneous bacteraemia [1]. Non-SBP infections constitute a heterogeneous group regarding clinical course and prognosis with endocarditis, secondary peritonitis, and pneumonia being associated with a worse prognosis [2].

Bacterial infections are the most common precipitants of decompensation and acute-on-chronic liver failure in cirrhosis. Mortality is consequently greater in patients with cirrhosis who develop a bacterial infection, independent of the severity of liver disease [3].

Because timely antibiotic therapy is essential in reducing mortality, a high degree of suspicion for the presence of infection is essential. Up to one-third of patients with SBP or other bacterial infections may be entirely asymptomatic or present with only hepatic encephalopathy and/or renal dysfunction. Therefore, a diagnostic paracentesis to rule out SBP should be performed in any patient with ascites, who is hospitalised emergently, independent of the presence of symptoms (e.g. fever, abdominal pain). Delays in the performance of diagnostic paracentesis has been shown to result in progressively higher mortality from SBP [4]. A bacterial infection should be suspected and investigated in any patient presenting with acute development of encephalopathy, kidney injury or jaundice, in which case blood and urine cultures, and chest X-ray should be performed in addition to diagnostic paracentesis. In the presence of hypotension, infectious workup should be accelerated in any of the above settings as mortality from septic shock increases by 10% with every hour delay in initiating antibiotics [5].

Although C-reactive protein and pro-calcitonin have been proposed as markers of early detection of infections, they are associated with a high rate of false-negative results [6].

Which antibiotics for which infection?

Spontaneous infections in cirrhosis are mostly mono-bacterial, and bacteria implicated are mostly Gram-negative enteric organisms. Empiric antibiotic therapy for SBP should be initiated as soon as the diagnosis is established (an ascites polymorphonuclear count >250/mm^3), even before ascitic fluid culture results become available and should be also initiated in cases where there is a high suspicion for infection as outlined above. Because it is important to identify a causative organism, in case there is a lack of response to the initial empirical antibiotic and because bacteria are isolated from ascites in only 40–50% of cases, blood cultures should always be obtained prior to starting empirical antibiotic therapy for SBP.

Recommended first-line empirical antibiotic therapy for SBP was previously a third-generation cephalosporin (e.g. cefotaxime, ceftriaxone). However, the epidemiology of bacterial infections in cirrhosis has been changing due to the emergence of multi-drug resistant (MDR) bacteria (resistant to 3 or more of the main antibiotic families, including beta-lactams) and have led to a lack of response to initial empirical antibiotic and higher mortality [7]. Infections due to MDR in cirrhosis have been increasing in the U.S. [8] and Europe [9]. In a recent multicentre prospective intercontinental study, 42% of infected patients with cirrhosis (n = 1302) were infected with MDR or with extensively drug-resistant bacteria [10].

Patients that are most likely to harbour an MDR infection are those with a nosocomial infection (i.e. hospitalised patient that develops infection >48 hours after hospitalisation), those exposed to a healthcare environment or who have received beta-lactams 3 months prior or those with a history of infection with an MDR organism [1,10].

In these patients, initial antibiotic therapy should be based on extended-spectrum antibiotics: piperacillin/tazobactam in areas of low prevalence of MDR, carbapenem (with or without glycopeptide or daptomycin or linezolid) in areas with high prevalence of MDR organisms [11,12]. Third-generation cephalosporins are recommended as the first-line antibiotic treatment for community-acquired SBP in countries with low rates of bacterial resistance.

Because of the increasing failure rate of initial antibiotic therapy, it is essential to repeat a diagnostic paracentesis within 48 hours. A decrease in the absolute neutrophil count by <25% from baseline indicates failure and should lead to broadening of antibiotic spectrum and investigations to rule out secondary peritonitis.

The development of infections due to MDR organisms is becoming a serious problem in patients with cirrhosis, and therefore antibiotic stewardship is essential, consisting of treating only patients who are most likely to be infected, starting with wide-spectrum antibiotics only in high-risk settings, rapidly de-escalating them and using them for short periods. Aminoglycosides should be avoided, as they are associated with a high incidence of renal toxicity in patients with cirrhosis.

Use of albumin in infections

Renal dysfunction is the main predictor of death in patients with SBP [13]. In a landmark randomised controlled trial, renal dysfunction was significantly lower in patients randomised to albumin (*vs.* placebo) as was mortality during hospitalisation and at 90 days [14]. Patients that were more likely to benefit from albumin were those who had evidence of renal or liver dysfunction at the time of diagnosis of SBP (BUN >30 mg/dl, and/or creatinine >1 mg/dl, and/or a serum bilirubin >4 mg/dl), indicating that the main effect of intravenous albumin was in preventing the progression of acute kidney injury (AKI) associated with SBP.

Although in patients with infections other than SBP, intravenous albumin did not improve survival in two open-label studies, both a low incidence of renal dysfunction and death. Because a recent study has shown that the main predictor of death in non-SBP infections is the presence of renal dysfunction [2], it would appear sensible to administer albumin in patients with SBP and with non-SBP infections who present with AKI as recommended for any patient with cirrhosis who develops AKI, as indicated in Ascites Club criteria [15].

The recommended dose of intravenous albumin in patients with SBP based on the study by Sort *et al.* is arbitrary (1.5 g/kg at day 1, and 1 g/kg at day 3) [12], other schedules/doses have not been investigated. Again, it would make sense to guide albumin administration on the presence/course of AKI in both SBP and non-SBP infections as recommended by the Ascites Club [15].

References

[References in **BOLD** are required reading]

1. **Fernandez J, Acevedo J, Castro M, Garcia O, de Lope CR, Roca D, et al. Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: a prospective study. Hepatology 2012;55(5):1551-1561.**
2. Fernandez J, Acevedo J, Prado V, Mercado M, Castro M, Pavesi M, et al. Clinical course and short-term mortality of cirrhotic patients with infections other than spontaneous bacterial peritonitis. Liver Int 2017;37(3):385-395.
3. Dionigi E, Garcovich M, Borzio M, Leandro G, Majumdar A, Tsami A, et al. Bacterial Infections Change Natural History of Cirrhosis Irrespective of Liver Disease Severity. Am J Gastroenterol 2017;112(4):588-596.
4. Kim JJ, Tsukamoto MM, Mathur AK, Ghomri YM, Hou LA, Sheibani S, et al. Delayed paracentesis is associated with increased in-hospital mortality in patients with spontaneous bacterial peritonitis. Am J Gastroenterol 2014;109(9):1436-1442.
5. Arabi YM, Dara SI, Memish Z, Al Abdulkareem A, Tamim HM, Al-Shirawi N, et al. Antimicrobial therapeutic determinants of outcomes from septic shock among patients with cirrhosis. Hepatology 2012;56(6):2305-2315.
6. Papp M, Vitalis Z, Altorjay I, Tornai I, Udvardy M, Harsfalvi J, et al. Acute phase proteins in the diagnosis and prediction of cirrhosis associated bacterial infections. Liver Int 2012;32(4):603-611.
7. **Jalan R, Fernandez J, Wiest R, Schnabl B, Moreau R, Angeli P, et al. Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013. J Hepatol 2014;60(6):1310-1324.**
8. Singal AK, Salameh H, Kamath PS. Prevalence and in-hospital mortality trends of infections among patients with cirrhosis: a nationwide study of hospitalised patients in the United States. Aliment Pharmacol Ther 2014;40(1):105-112.
9. Fernandez J, Prado V, Trebicka J, Amoros A, Gustot T, Wiest R, et al. Multidrug-resistant bacterial infections in patients with decompensated cirrhosis and with acute-on-chronic liver failure in Europe. J Hepatol 2018. pii: S0168-8278(18)32511-X. [Epub ahead of print]

10. Piano S, Singh V, Caraceni P, Maiwall R, Alessandria C, Fernandez J, et al. Epidemiology and Effects of Bacterial Infections in Patients With Cirrhosis Worldwide. Gastroenterology 2018. pii: S0016-5085(18)35402-7. [Epub ahead of print]

11. Piano S, Fasolato S, Salinas F, Romano A, Tonon M, Morando F, et al. The empirical antibiotic treatment of nosocomial spontaneous bacterial peritonitis: Results of a randomized, controlled clinical trial. Hepatology 2016;Apr;63(4):1299-309

12. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018;69(2):406-460.

13. Tandon P, Garcia-Tsao G. Renal dysfunction is the most important independent predictor of mortality in cirrhotic patients with spontaneous bacterial peritonitis. Clin Gastroenterol Hepatol 2011;9(3):260-265.

14. Sort P, Navasa M, Arroyo V, Aldeguer X, Planas R, Ruiz-del-Arbol L, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med 1999;341:403-409.

15. Angeli P, Gines P, Wong F, Bernardi M, Boyer TD, Gerbes A, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: Revised consensus recommendations of the International Club of Ascites. J Hepatol 2015;62(4):968-974.

Acute kidney injury in cirrhosis: Redefining the syndromes

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Take-home messages

- Acute kidney injury (AKI) corresponds to an abrupt reduction in excretory kidney function, whatever the cause.
- The classification and staging of AKI should be based on the International Club of Ascites. However, the role of urine output may be underestimated.
- Precipitating factors of AKI are common and include bleeding, sepsis and nephrotoxic drugs.
- Prolonged kidney hypoperfusion during hepatorenal syndrome may result in acute tubular necrosis (ATN), but in almost all cases, ATN is not documented since biopsy is impractical.
- In a substantial proportion of patients with advanced cirrhosis, hepatorenal syndrome and ATN may represent a continuum rather than two distinct entities.
- Irrespective of the phenotype of AKI, a central objective in the future is to develop tools to determine the potential for renal recovery in patients with cirrhosis and AKI. In this setting, the assessment of kidney fibrosis seems promising.

Emerging concepts on acute kidney injury in the general population

Several new concepts in the field of renal dysfunction have emerged during the last decade, including new definitions, classification and pathophysiology.

The term “acute renal failure” has been abandoned and replaced by “Acute Kidney Injury” (AKI), emphasising the fact that a continuum of changes exists in AKI and that functional and/or structural changes exist before a sufficient loss in kidney function results in overt “failure”, a condition characterised by a drop in glomerular filtration rate and an increase in serum creatinine (sCr) (Fig. 1) [1].

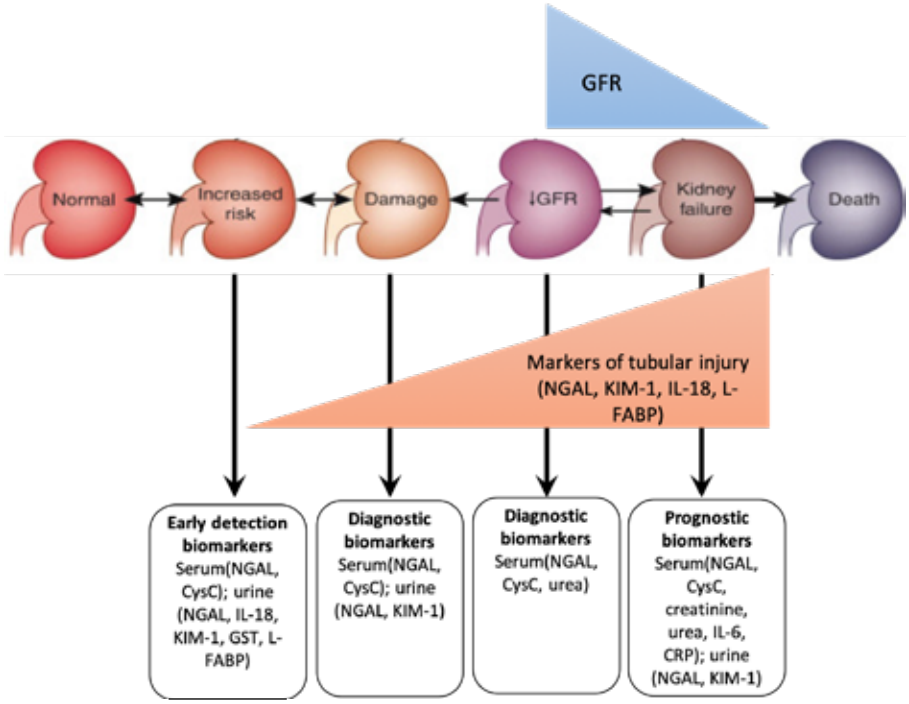

Figure 1. Evolution of AKI. Injury begins before excretory function is lost (before decreased glomerular filtration rate, [GFR]) and may progress to the organ death. Several biomarkers may be useful at (1) predicting impaired kidney function at an earlier stage, (2) making a diagnosis of AKI and (3) assessing the prognosis (adapted from [1]). CRP, C reactive protein; CysC, cystatin C; GST, glutathione-S-transferase; IL-6, interleukin 6; IL-18, interleukin 18; KIM-1, kidney injury molecule 1; L-FABP, liver fatty-acid-binding-protein; NGAL, neutrophil gelatinase-associated lipocalin.

The concept of AKI also illustrates a continuum in terms of prognosis according to different phenotypes and different underlying conditions. Even a small increase in sCr may be associated with increased mortality in some circumstances. To better reflect this continuum, a new classification of AKI (Acute Kidney Injury Network [AKIN]) has been proposed (Table 1) [2]. In addition, classic phenotypes of AKI including prerenal failure and intrarenal failure, have been revisited and the terms primary and secondary AKI have been proposed. Primary AKI are rare diseases that correspond to intrinsic parenchymal diseases of the kidney (glomerulonephritis and vasculitis). By contrast, secondary AKI result from prerenal factors, such as shock, sepsis or nephrotoxic drugs. Secondary AKI are frequent, especially in critically ill patients, with a prevalence ranging from 50 to 60%. Any of the factors inducing AKI initiate a cascade of events, resulting in impaired kidney microcirculation, activation of inflammatory pathways and tubular cell injury. Tubular cells indeed are the most susceptible to ischemia. Pre-existing chronic kidney changes and/or pre-existing impaired kidney function are predisposing factors for deterioration after an initial insult. Acute tubular necrosis (ATN) is one of the most common phenotypes of AKI. It is characterised by a rapid increase in sCr following hypotension and/or sepsis and/or nephrotoxic agents, decreased urine output (UO), elevated urinary sodium concentration and urinary granular casts. However, ATN may be misleading. ATN is basically defined by specific histological changes, which are almost always unavailable, especially in an emergency context. Kidney biopsy is invasive and impractical in this context. In addition, it is unlikely that systematic kidney biopsy would help improve the management of patients with a clinical diagnosis of ATN which has a high potential for recovery. Overall, a clinical diagnosis of ATN should be interpreted with caution.

Table 1. Current definitions and staging of Acute Kidney Injury in patients without cirrhosis and with cirrhosis [2, 6].

	Patients without cirrhosis	Patients with cirrhosis
Baseline sCr	First sCr measured	A value of sCr obtained in the previous 3 months, when available, can be used as baseline sCr. In patients with more than one value within the previous 3 months, the value closest to the admission time to the hospital should be used. In patients without a previous sCr value, the sCr on admission should be used as baseline
AKI	Increase sCr ≥0.3 mg/dl within 48 hrs, or increase sCr ≥1.5 x baseline within 48 hours, or Urinary output <0.5 ml/kg/h x 6 hrs	• Increase in sCr ≥0.3 mg/dl (≥26.5 µmol/L) within 48 hours, or • A percentage increase sCr ≥50% from baseline which is known, or presumed, to have occurred 7 days before
Staging	**Serum creatinine criteria**	
	Stage 1: increase in sCr ≥0.3 mg/dl (26.5 µmol/L) or an increase in sCr ≥1.5-fold to 2-fold from baseline	**Stage 1**: increase in sCr ≥0.3 mg/dl (26.5 µmol/L) or an increase in sCr ≥1.5-fold to 2-fold from baseline
	1A: peak level of sCr <1.5 mg/dl (133 µmol/L)	**1A**: peak level of sCr <1.5 mg/dl (133 µmol/L)
	1B: peak level of sCr ≥1.5 mg/dl (133 µmol/L)	**1B**: peak level of sCr ≥1.5 mg/dl (133 µmol/L)
	Stage 2: increase in sCr >2-fold to 3-fold from baseline	**Stage 2**: increase in sCr >2-fold to 3-fold from baseline
	Stage 3: increase of sCr >3-fold from baseline or sCr ≥4.0 mg/dl (353.6 µmol/L) with an acute increase ≥0.3 mg/dl (26.5 µmol/L) or initiation of renal replacement therapy	**Stage 3**: increase of sCr >3-fold from baseline or sCr ≥4.0 mg/dl (353.6 µmol/L) with an acute increase ≥0.3 mg/dl (26.5 µmol/L) or initiation of renal replacement therapy
	Urine output criteria	
	Stage 1: <0.5 ml/kg/hr x 6-12 hrs	
	Stage 2: <0.5 ml/kg/hr x 12 hrs	
	Stage 3: <0.3 ml/kg/hr x 24 hr or anuria x 12 hrs	

sCr, serum creatinine.

Several biomarkers have emerged to assess the course of AKI (Fig. 1). These biomarkers provide different information concerning kidney injury. Serum cystatin C concentrations, as well as sCr, reflect changes in glomerular filtration rate whereas neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule (KIM 1) and liver-fatty-acid binding protein (L-FABP) are markers of tubular cell injury. These biomarkers may be useful at (i) predicting impaired kidney function at an earlier stage during AKI (before an sCr increase), (ii) making a diagnosis of AKI, and (iii) better assessing the prognosis. However, in the general population, to what extent biomarkers help clearly categorise different phenotypes and whether categorising phenotypes through biomarkers improves management and outcomes needs to be clarified. Again, the different phenotypes of secondary AKI should be seen as a continuum rather than distinct entities.

There is accumulating evidence that AKI and chronic kidney diseases (CKD) are interconnected [3]. Firstly, a number of risk factors predispose to both AKI and CKD. These risk factors include advanced age, diabetes mellitus and metabolic syndrome. Secondly, about 10% of patients who develop AKI will progress to end-stage CKD after a few weeks or months. The mechanisms leading to a progression from AKI to CKD include impaired tubular cells regeneration with progression to kidney fibrosis and end-stage kidney disease. Factors associated with maladaptive repair following tubular cell injury include advanced age, previous episodes of AKI, underlying CKD, prolonged kidney hypoxia, oxidative stress, mitochondrial dysfunction and DNA damage [4].

Acute kidney injury in patients with cirrhosis

Advanced cirrhosis is a condition characterised by portal hypertension, splanchnic vasodilatation, hyperkinetic state and central hypovolemia. In response to central hypovolemia, mechanisms involved in vasoconstriction (sympathetic nervous system) and in reabsorption of salt and water (renin-angiotensin aldosterone system [RAAS] and antidiuretic hormone) are activated. Activation of RAAS contributes to renal vasoconstriction which, up to a certain level, is compensated by an increase in cardiac output. However, kidney hypoperfusion is a key factor leading to acute renal failure (and possibly to CKD) in cirrhosis. In the most advanced stages of cirrhosis, especially in patients with refractory ascites, cardiac output tends to decrease, and hyperkinetic state no longer compensates renal vasoconstriction. Renal perfusion decreases with a drop in the glomerular filtration rate. In addition to systemic and splanchnic circulatory changes associated with portal hypertension, cirrhosis is characterised by a state of chronic systemic inflammation leading to kidney microcirculatory changes [5].

Until recently, acute renal failure in cirrhosis corresponded to prerenal failure, ATN or type-1 hepatorenal syndrome (HRS). Type-1 HRS was considered as an acute renal failure, while type-2 HRS corresponded to chronic kidney disease. In recent years, the term AKI in cirrhosis has been adopted and redefined with the aims of (i) identifying acutely impaired renal function at an earlier stage, (ii) incorporating HRS, into the different phenotypes of AKI (HRS-AKI) and (iii) better staging disease severity.

Definition, classification and staging of AKI in cirrhosis have undergone significant changes over the past years. In 2015, the International Club of Ascites (ICA) proposed the use of a definition of AKI based on the Kidney Disease Improving Global Outcomes (KDIGO) sCr criteria, namely the percentage increase in sCr compared to baseline sCr, with the removal of an absolute sCr cut-off value (1.5 mg/dl) (Table 1) [6]. By definition, AKI corresponds to an increase in sCr $\geq$0.3 mg/dl or $\geq$50% from baseline sCr in less than 48 hours. Baseline sCr corresponds to sCr within the previous 3 months if available. If not, admission sCr is used as the reference (Table 1). Changes in the definition of AKI

in patients with cirrhosis has led to changes in the definition of type1-HRS, now termed as HRS-AKI and defined as stage 2 or 3 AKI, that fulfils all other diagnostic criteria of HRS. Since then, ICA criteria have been validated to predict mortality in numerous studies of hospitalised patients with cirrhosis including those in intensive care units.

Even though these new definitions and classifications clearly improved our ability to recognise AKI at an early stage in cirrhosis, to initiate appropriate therapy (i.e., vasoconstrictors in HRS-AKI) and to assess prognosis, there are still substantial limitations [7].

Oliguria, which is one of the KDIGO criteria, was not included in the current ICA definition of AKI in patients with cirrhosis since patients with cirrhosis are frequently oliguric at baseline. However, UO has been found to be a sensitive and early marker for AKI in ICU patients, including those with cirrhosis, and to be associated with worse outcomes [8]. Therefore, regardless of any rise in sCr, a decrease in UO may be reconsidered in the future.

While prerenal AKI and HRS-AKI are supposed to be functional in nature, by definition, ATN is defined by intrinsic kidney changes. Due to a better understanding of the pathophysiology of cirrhosis, new concepts challenge the classical view of AKI phenotypes. For instance, it has been suggested that HRS-AKI does not exclude tubular lesions and that ATN may result from unrecognised and/or untreated prerenal failure with prolonged hypoperfusion leading to ischemic injury. In some patients, HRS-AKI and ATN may be a continuum rather than two distinct entities. In addition, in patients with decompensated cirrhosis and AKI corresponding to the definition of HRS, there are often precipitating factors, which are also found in patients with ATN, such as hypovolemia, infection and/or systemic inflammatory response syndrome. All of these factors precipitate renal hypoperfusion.

The ICA recently proposed an algorithm to help manage AKI (See next chapter, Fig. 1). The general principles are a rapid diagnosis of AKI, the control of precipitating factors (withdrawal of nephrotoxic drugs, NSAIDs and diuretics, beta blockers, screening and treatment of infections) and plasma volume expansion. As shown in Figure 1, in the next chapter, vasoconstrictors are only given in patients with stage 2 or 3 AKI meeting criteria of HRS, after two consecutive days of albumin infusion and no response to albumin infusion, the prerequisite to make a diagnosis of HRS-AKI. In nephrology and critical care, early management of AKI is crucial to improving the outcome, both in terms of renal recovery and improvement of survival. In patients with cirrhosis, a low level of sCr at the initiation of terlipressin has been associated with a higher likelihood of resolution of HRS and better survival as compared to higher levels. Finally, no study has reported a detrimental effect on renal function of terlipressin in non-responders. An interval of 48 hours between diagnosis of AKI and initiation of vasopressors in those who are eventually categorised in the HRS-AKI group means delayed initiation of therapy. These data raise the issue of whether earlier administration of terlipressin in combination with albumin could improve the prognosis of HRS in cirrhosis.

In candidates for liver transplantation, central issues are to predict reversibility of impaired renal function and, in those with a potential for renal recovery, to predict to which extent renal function may improve after liver transplantation alone. The treatment of choice in patients with HRS-AKI is liver transplantation and, in theory, renal function is fully reversible after transplantation. However, several series have shown that mean sCr after liver transplantation is higher in patients transplanted with HRS-AKI as compared to patients without HRS-AKI at transplantation.

In patients with AKI, several consensus meetings have proposed criteria to perform simultaneous liver-kidney transplantation rather than liver transplantation alone, based on a high probability of non-renal recovery post-transplantation [9]. However, neither centre nor national guidelines predict kidney recovery with sufficient accuracy. Therefore, the current allocation system allows listing for simultaneous liver-kidney transplantation based on subjective clinical judgment. Alternative criteria for predicting the reversibility or irreversibility of AKI after transplantation, such as biomarkers, are clearly needed to allow more accurate allocation of kidney grafts and avoid "futile" kidney transplantation in patients with a high potential for renal recovery.

None of the conventional biomarkers (fractional excretion of filtered sodium, fractional excretion of filtered urea, proteinuria) can accurately determine the phenotype of AKI in advanced cirrhosis. In the last decade, several biomarkers have been assessed in patients with cirrhosis. Markers of tubular injury (NGAL, KIM-1, IL-18, L-FABP) have been the most extensively studied since they reflect the earliest markers of ischemia-related events. Levels of all these biomarkers seem to be higher in ATN compared to other phenotypes of AKI. However, substantial overlap exists between the different phenotypes and no clear cut-off values have been defined yet. In addition, most of these biomarkers are also increased in CKD.

The prevalence of underlying CKD in patients with cirrhosis who develop AKI ("acute-on-chronic kidney disease") is unknown. However, it can be reasonably assumed that patients with advanced cirrhosis frequently have chronic kidney changes due to comorbidities (e.g., diabetes and hypertension) and/or specific causes of CKD (e.g., IgA nephropathy, viral-induced glomerulopathy). Finally, evidence for close interconnections between AKI and CKD emerged recently in the general population [3]. These interconnections are likely to exist in patients with cirrhosis. Since patients with end-stage cirrhosis are prone to develop repeated episodes of AKI as a consequence of events, such as sepsis, hypovolemia, paracentesis-induced circulatory changes, and HRS, it can be suspected that these patients with repeated episodes AKI eventually develop irreversible chronic kidney changes [10].

Irrespective of the phenotype of AKI, an objective is to develop tools to determine the potential for renal recovery in patients with cirrhosis and AKI. Since kidney biopsy is difficult to perform in patients with advanced cirrhosis, the challenge in the future will be to develop non-invasive markers of irreversible kidney lesions, namely biomarkers of fibrosis.

References

[References in **BOLD** are required reading]

1. Bellomo R, Kellum JA, Ronco C. Acute kidney injury. Lancet 2012;380:756-766.

2. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11:R31.

3. Chawla LS, Eggers PW, Star RA, Kimmel PL. Acute kidney injury and chronic kidney disease as interconnected syndromes. N Engl J Med 2014;371:58-66.

4. Ferenbach DA, Bonventre JV. Mechanisms of maladaptive repair after AKI leading to accelerated kidney ageing and CKD. Nat Rev Nephrol 2015;11:264-276.

5. Wong F. The evolving concept of acute kidney injury in patients with cirrhosis. Nat Rev Gastroenterol Hepatol 2015;12:711-719.

6. Angeli P, Gines P, Wong F, Bernardi M, Boyer TD, Gerbes A, Moreau R, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. J Hepatol 2015;62:968-974.

7. European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018;69:406-460.

8. Amathieu R, Al-Khafaji A, Sileanu FE, Foldes E, DeSensi R, Hilmi I, Kellum JA. Significance of oliguria in critically ill patients with chronic liver disease. Hepatology 2017;66:1592-1600.

9. Nadim MK, Sung RS, Davis CL, Andreoni KA, Biggins SW, Danovitch GM, Feng S, et al. Simultaneous liver-kidney transplantation summit: current state and future directions. Am J Transplant 2012;12:2901-2908.

10. Francoz C, Nadim MK, Durand F. Kidney biomarkers in cirrhosis. J Hepatol 2016;65:809-824.

Management of hepatorenal syndrome

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Take-home messages

- The diagnostic criteria of hepatorenal syndrome (HRS) have been recently modified according to the new definition and diagnostic criteria of acute kidney injury (AKI) in cirrhosis proposed by the International Club of Ascites.
- According to the new diagnostic criteria, a cut-off value of serum creatinine is no longer required for the diagnosis of HRS. In this context, HRS will be diagnosed earlier, and treatment will be started at lower serum creatinine values compared with the classical diagnostic criteria.
- First-line pharmacological treatment for the management of HRS-AKI is the combination of vasoconstrictors and albumin. Terlipressin and albumin is the treatment of choice when available. In countries where terlipressin is not available, treatment with noradrenaline plus albumin is considered an alternative therapy.
- Besides systemic circulatory dysfunction, systemic inflammation appears to play an important role in the pathophysiology of HRS-AKI and may have a negative impact on treatment response.

Introduction

Hepatorenal syndrome (HRS) is a unique type of kidney failure that develops in patients with advanced cirrhosis and is associated with very poor outcomes [1]. Traditionally, HRS was considered exclusively of functional origin as a consequence of marked renal vasoconstriction secondary to the systemic circulatory dysfunction occurring in patients with advanced cirrhosis [1]. Nonetheless, in recent years the new theory of the pathophysiology of decompensated cirrhosis has been modified, including not only the arterial vasodilation theory but also the existence of chronic systemic inflammation as the main drivers of disease progression and the development of complications [2]. In this context, it is currently accepted that the pathophysiology of HRS may include both hemodynamic and inflammatory changes as the key factors in the pathophysiology of the syndrome [1-3]. The diagnostic criteria of HRS have been recently modified leading to changes in the diagnosis and management of the syndrome [3,4]. This chapter will summarise updated information on the management of HRS in the setting of the new definition and diagnostic criteria.

New considerations in the diagnosis of hepatorenal syndrome

As described in the previous chapter, the definition of acute kidney injury (AKI) in cirrhosis has been recently modified and is currently based on the International Club of Ascites-AKI (ICA-AKI) criteria (Table 1) [4].

Table 1. New diagnostic criteria of acute kidney injury (AKI) according to the ICA-AKI consensus and AKI stages, including the proposed modification of AKI stage 1.

Definition of AKI	
Increase in sCr ≥0.3 mg/dl (≥26.5 µmol/L) within 48 hours; or, a percentage increase in sCr ≥50% from baseline which is known, or presumed to have occurred within 7 days prior.	
AKI stages	
AKI 1	Increase in sCr ≥0.3 mg/dl (26.5 µmol/L) or an increase in sCr ≥1.5-fold to 2-fold from baseline. ***AKI 1a:** sCr at diagnosis <1.5 mg/dl ***AKI 1b:** sCr at diagnosis ≥1.5 mg/dl
AKI 2	Increase in sCr >2-fold to 3-fold from baseline.
AKI 3	Increase of sCr >3-fold from baseline or sCr ≥4.0 mg/dl (353.6 µmol/L) with an acute increase ≥0.3 mg/dl (26.5 µmol/L) or initiation of renal replacement therapy.

AKI, acute kidney injury; sCr serum creatinine.

These new definitions have also led to changes in the diagnostic criteria of HRS, currently named HRS-AKI. Importantly, the only change that was made with respect to the classical diagnostic criteria was the removal of the cut-off value of serum creatinine (sCr). Experts agreed that the cut-off value of sCr for diagnosis of HRS-AKI should be removed to allow earlier identification of the syndrome. Therefore, according to the new criteria, HRS-AKI is defined by AKI stage 2 or 3 or by the progression of the initial AKI stage despite general therapeutic measures in patients who meet all other diagnostic criteria of HRS provided by the previous definition, irrespective of sCr value at diagnosis [4] (Table 2).

Table 2. Diagnostic criteria for hepatorenal syndrome type of acute kidney injury (HRS-AKI).

Diagnostic criteria of HRS-AKI
Cirrhosis and ascites
Diagnosis of AKI according to ICA-AKI criteria: increase in sCr ≥0.3 mg/dl within 48 hours
Absence of shock
No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin (1 g per kg of body weight)
No current or recent use of nephrotoxic drugs (NSAIDs, aminoglycosides, iodinated contrast media, etc.)

Diagnostic criteria of HRS-AKI
No macroscopic signs of structural kidney injury, defined as:
- absence of proteinuria (>500 mg/day)
- absence of microhematuria (>50 RBCs per high power field),
- normal findings on renal ultrasonography

Traditionally HRS has been classified into two entities according to the severity and progression of kidney failure: type-1 HRS and type-2 HRS. The definition of the two different types of HRS was based on the time frame and the level of sCr increase. In the revised definition, these two terms are no longer used. Type-1 HRS, which traditionally represented the "acute" form of HRS, now corresponds to HRS-AKI. In contrast, the previously named type-2 HRS is not included in the current concept of AKI-HRS, because it is not an acute but rather a chronic impairment of kidney function. This term now includes patients with renal impairment that fulfil criteria of HRS but not of AKI and is considered a form of chronic kidney disease (HRS-CKD) characteristic of cirrhosis [3,4]. Nonetheless, it should be noted that although HRS-AKI is the current accepted terminology, type-1 HRS is still widely used in daily clinical practice. This chapter will focus on the management of HRS-AKI.

Management of hepatorenal syndrome

The goal of the management of HRS-AKI, particularly in those patients awaiting liver transplantation, is the normalisation of kidney function [1,3,4]. HRS-AKI should be treated as soon as possible, as higher sCr values have been associated with a lower probability of response. Patients can be treated on a regular ward, but the decision to transfer patients to an intensive or intermediate care unit should be individually based. Patients should be closely monitored for early detection of possible associated complications, particularly bacterial infections and side effects of pharmacological treatment. Intravenous fluids should be administered with caution to prevent pulmonary oedema and the development/or further impairment of hypervolemic hyponatremia. The use of a central venous catheter is recommended to monitor central venous pressure in patients who are going to receive pharmacological treatment considering that treatment includes intravenous albumin. The use of a bladder catheter is not necessary in all cases because it is associated with an increased risk of urinary tract infections. Therefore, its use is recommended only in patients with marked oliguria [1,3].

Specific treatment

Vasoconstrictors and albumin

First-line pharmacological treatment for the management of HRS-AKI is the administration of vasoconstrictors associated with intravenous albumin [1,3,4]. Vasoconstrictor drugs used for the management of HRS-AKI are vasopressin analogues, such as terlipressin, and alpha-adrenergic agonists, such as noradrenaline and midodrine [1,3,4-8]. Most of the existing evidence is related to the use of terlipressin and albumin. It is important to remark that evidence available so far is derived from studies including patients with type-1 HRS defined according to the classical definition. To date, there are still no studies reported assessing the efficacy of vasoconstrictors and albumin in patients with HRS defined according to the new HRS-AKI criteria.

Terlipressin

Results from randomised controlled trials and systematic reviews indicate that treatment with terlipressin and albumin is associated with significant improvement of kidney function in approximately 40-70% of patients with type-1 HRS (including complete and partial responders) and that treatment is associated with improved survival [3-5].

Traditionally, terlipressin has been administered as repeated intravenous (i.v.) boluses. The classical scheme recommended starting terlipressin at a dose of 1 mg/4-6 h. If after 3 days of treatment there is no improvement of kidney function, defined as a reduction of sCr of more than 25% from pre-treatment value, the dose should be increased up to 2 mg/4-6 h [3]. Nonetheless, recently a randomised controlled trial compared the safety and efficacy of terlipressin given by continuous intravenous infusion versus i.v. boluses. This study showed that the percentage of response to treatment was not significantly different between patients treated with continuous i.v. infusion versus patients treated with i.v. boluses (76% *vs.* 65%, respectively; p = NS). However, the mean daily effective dose of terlipressin was significantly lower in the group treated with continuous infusion compared to the group treated with i.v. boluses and the rate of adverse events were also significantly lower in the group of patients treated with continuous intravenous infusion, compared to the group of patients treated with i.v. boluses (35% *vs.* 62%, respectively; p <0.025). Therefore, these results suggest that terlipressin given by continuous i.v. infusion is better tolerated and is effective at lower doses than terlipressin given by i.v. boluses [6]. Nonetheless, patients receiving treatment with terlipressin should be monitored closely for early detection of potential side effects, as terlipressin is a very intense vasoconstrictor that may lead to ischemic or cardiovascular effects. The frequency of adverse events leading to treatment withdrawal is of approximately 20% [1,3]. The most common side effects of terlipressin include abdominal pain, diarrhoea, cardiovascular ischaemic complications and circulatory overload, with frequencies of up to 40% when terlipressin is administered as i.v. bolus. In patients presenting serious adverse events, treatment should be discontinued. If adverse events are not severe, it could be considered to maintain terlipressin at lower doses, but close monitoring of these patients should be performed.

Finally, it should be noted that in contrast to previous trials, the recently published REVERSE trial performed in North America, which is the largest randomised, placebo-controlled, double-blind study aimed at assessing the efficacy of terlipressin in type-1 HRS did not show significant differences between terlipressin and placebo in the reversal of type-1 HRS. However, the study described a greater improvement in kidney function in patients treated with terlipressin, and survival was highly correlated with changes in sCr levels [7]. The main reasons that could explain these differences are first, that the duration of treatment with terlipressin was relatively short in this study as up to one-third of patients received ≤3 days of treatment and, second, that there was a high use of competitive treatments, such as renal replacement therapy (RRT) and liver transplantation [7]. However, continued analysis of patients included in the REVRSE trial as well as in a previous trial in North America (OT-0401) demonstrated that treatment with terlipressin plus albumin in patients with type-1 HRS resulted in a significantly higher rate of HRS reversal compared to that of patients who received albumin alone.

During treatment with terlipressin, patients must receive concomitant treatment with i.v. albumin at a dose of 1 g/kg body weight the first day followed by 20-40 g/day [1,3,4]. If patients have high central venous pressure levels during treatment, with values above 15 mmHg, i.v. albumin should be temporarily discontinued.

Other vasoconstrictors

Vasoconstrictors other than terlipressin represent an alternative pharmacological treatment in countries where terlipressin is not available. These include i.v. noradrenaline and oral midodrine plus subcutaneous octreotide, in both cases associated with i.v. albumin at the same dose recommended for treatment with terlipressin [1,3,8].

Noradrenaline appears to be an effective alternative for the management of type-1 HRS in countries where terlipressin is not available [3,8]. In contrast to terlipressin, noradrenaline always requires a central venous line to be administered. A randomised controlled trial compared the efficacy and safety of treatment with terlipressin *vs.* noradrenaline for patients with type-1 HRS, it showed that approximately 40% of patients responded to treatment in both groups and the adverse event profile was also similar [8]. In a recent meta-analysis, noradrenaline appeared to be as effective and safe as terlipressin for the management of type-1 HRS and represents a good alternative treatment. However, the number of patients treated with noradrenaline is still small, and a recent systematic review and network meta-analysis showed low-quality evidence supporting the use of noradrenaline to reduce mortality and reverse the HRS.

The combination of oral midodrine plus subcutaneous octreotide together with albumin has also been shown to improve kidney function in patients with type-1 HRS. Two proof-of-concept studies that investigated the effects of treatment with midodrine plus octreotide in patients with type-1 HRS showed that kidney function significantly improved in patients treated with midodrine plus octreotide compared to controls. However, a randomised controlled trial that compared the safety and efficacy of midodrine and octreotide *vs.* terlipressin showed that response to treatment was significantly higher in those patients receiving terlipressin compared to the group receiving midodrine and octreotide. Therefore, midodrine plus octreotide could be considered an option only when terlipressin and noradrenaline are not available [3].

Duration of treatment

Treatment with terlipressin or noradrenaline should be continued until a complete response to therapy or for a maximum of 14 days. According to the new definition, complete response to therapy is defined as the return of sCr to a value within 0.3 mg/dl (26.5 µmol/L) of the baseline value. In contrast, a partial response is defined as the regression of AKI stage with a reduction of sCr to ≥0.3 mg/dl (26.5 µmol/L) above the baseline value [3,4].

Liver transplantation

Liver transplantation is the treatment of choice for patients with HRS-AKI as it represents the definitive treatment of the underlying liver disease. HRS-AKI is reversible after liver transplantation; therefore, liver transplant alone is preferred to combined liver-kidney transplant [1,3]. Combined liver-kidney transplant should only be considered in patients who have either a CKD in the following conditions: a) estimated glomerular filtration rate ([GFR], using MDRD6 equation) ≤40 ml/min or measured GFR using iothalamate clearance ≤30 ml/min, b) proteinuria ≥2 g a day, c) kidney biopsy showing >30% global glomerulosclerosis or >30% interstitial fibrosis, or d) inherited metabolic disease, or an HRS-AKI refractory to drug therapy, which has required RRT for more than 4 weeks or with GFR ≤35 ml/min or measured GFR ≤25 ml/min ≥4 weeks, and thus who have a low probability of kidney function recovery [3].

Considering the poor prognosis of patients with HRS-AKI, these patients should be given high priority for a transplant. The use of the Model for End-Stage Liver Disease (MELD) score as the system for

organ allocation allows giving high priority to these patients. However, it is important to emphasise that in order to avoid a reduction in MELD score in patients who respond to pharmacological treatment with vasoconstrictors and albumin, it has been suggested to maintain the MELD score calculated with the sCr value before treatment while these patients are on the waiting list.

Other therapeutic options

There is not enough evidence demonstrating the efficacy of other therapeutic options for the management of HRS-AKI. Transjugular intrahepatic portosystemic shunt (TIPS) has been proposed as an alternative therapy because it reduces portal pressure leading to an improvement of circulatory dysfunction. However, the applicability of TIPS in patients with AKI-HRS, who have very advanced liver disease, is limited because many patients have contraindications for the insertion of TIPS [1,3].

RRT is not recommended as a first-line treatment in patients with HRS-AKI, as there are no studies specifically investigating its efficacy in this setting. RRT can be used as a rescue treatment in patients with HRS-AKI who do not respond to treatment with vasoconstrictors and who develop criteria for emergent RRT (i.e., hypervolemia, hyperkalaemia, metabolic acidosis). However, clinical experience indicates that the development of criteria leading to the indication of RRT is not common in patients with HRS-AKI, at least when treatment is started at early stages and soon after diagnosis [1,3].

Alternative dialysis methods, such as the use of the molecular adsorbent recirculating system (MARS®), or fractionated plasma separation and adsorption (Prometheus®), have been proposed as alternative methods for the management of HRS-AKI. These methods are based on the clearance of several substances from the circulation, including endogenous vasodilators, and appear to have some potential beneficial effects, but data is still limited, and results are not conclusive [1,3]. Thus, further studies are needed to define their role as therapeutic alternatives for HRS.

New algorithm for the management of HRS-AKI

A new algorithm for the management of HRS-AKI has been recently proposed, based on the new ICA-AKI criteria (Fig. 1) [4]. In all patients where HRS-AKI is suspected, precipitating factors of AKI should be identified and treated, including screening and treatment of infections. In addition, all nephrotoxic drugs, such as vasodilators or NSAIDs should be withdrawn, and diuretics and beta-blockers should also be discontinued. Importantly, all patients with AKI stage ≥1B should receive 20% albumin solution at a dose of 1 g of albumin/kg of body weight (with a maximum of 100 g of albumin) for two consecutive days. If patients do not respond to volume expansion with albumin and meet all other HRS criteria (Table 2) provided by the previous definition, treatment with vasoconstrictors and albumin should be started [3,4].

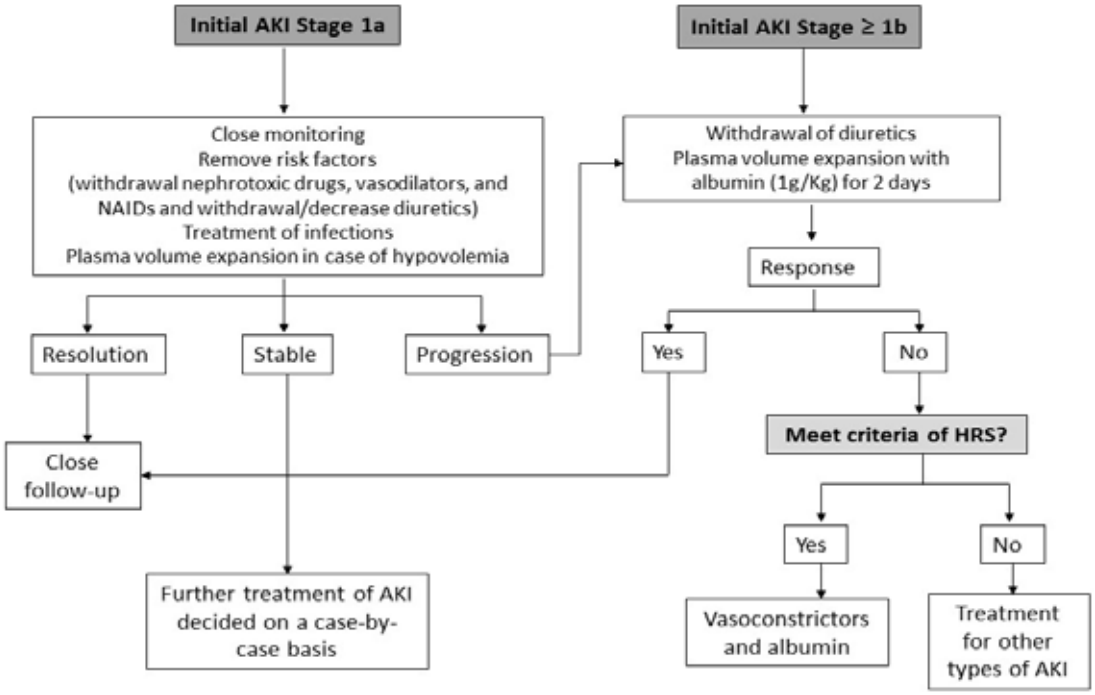

Figure 1. Algorithm for the management of HRS-AKI according to the new ICA-AKI criteria and proposed by current EASL guidelines. Adapted from [2]. AKI, acute kidney injury; HRS, hepatorenal syndrome.

It is important to remark that using this algorithm treatment with vasoconstrictors and albumin will be started earlier compared to when using classical type-1 HRS diagnostic criteria because there is no need to reach the cut-off level of sCr of 2.5 mg/dl. Therefore, treatment will be initiated with lower sCr values. Considering that the baseline sCr at the initiation of pharmacological therapy is a predictive factor of treatment response, this new strategy should lead to a higher probability of response. However, to date, no studies are investigating the efficacy and safety profile of the use of vasoconstrictors and albumin in patients with HRS using the new ICA-AKI criteria. Therefore, treatment should be closely monitored, and prospective studies are needed to assess the efficacy and safety of this approach.

Predictive factors of response to therapy

Several studies have shown that baseline sCr at the time of starting therapy is an independent predictive factor of treatment response, with higher sCr values associated with lower probability of response [1,3]. In addition, bilirubin and mean arterial pressure by reflecting liver function and systemic hemodynamics, respectively, have been also described as independent predictive factors of response to therapy. There is data showing that serum bilirubin <10 mmHg and an increase in mean arterial pressure ≥5 mmHg at day 3 of treatment are associated with a higher probability of response [1,3].

Impact of inflammation in response to therapy

There is growing evidence showing that decompensated cirrhosis is associated with a marked inflammatory response that increases in parallel with the progression of the disease [2]. Systemic inflammation is particularly marked in patients with acute-on-chronic liver failure (ACLF), a syndrome

characterised by acute decompensation of the disease associated with organ failures. In fact, the degree of systemic inflammation as assessed by the levels of proinflammatory cytokines and other inflammatory mediators has been related to the number of organ failures and, therefore, to the ACLF grade. It is known that systemic inflammation can induce organ failure either by reducing organ perfusion or by direct cell and tissue damage by inflammatory mediators [2]. Therefore, as described above it is currently hypothesised that systemic inflammation plays a role in the pathophysiology of AKI-HRS [1,2]. However, until recently data assessing the inflammatory response in these patients and its effects in response to treatment was lacking.

A recent study that investigated the inflammatory response in patients with HRS-AKI by evaluating a large number of cytokines describes that HRS-AKI is characterised by a marked inflammatory state as reflected by a significant increase in several proinflammatory cytokines (i.e., IL-6, IL-8, TNFα, VCAM-1) compared to patients with hypovolemia-induced AKI and patients without AKI. Interestingly, the presence of this inflammatory state was independent of the presence of concomitant bacterial infections or ACLF, thus confirming that systemic inflammation plays a role in the pathophysiology of HRS [9].

In addition, recent data show that the presence and the severity of ACLF, a syndrome characterised by a marked systemic inflammatory state, also has an important impact on treatment response to HRS-AKI. This study showed that patients with grade 3 ACLF (the most severe stage of ACLF) have a significantly lower probability of response to treatment compared to patients with ACLF grades 1 or 2 (29% in ACLF-3, compared to 60% and 48% in ACLF-1 and ACLF-2, respectively; $p < 0.001$) [10]. Although both systemic inflammation and systemic circulatory dysfunction play a role in the pathogenesis of ACLF (and HRS-AKI), it is currently suggested that systemic inflammation is the main driver of this syndrome. In this setting, this study suggests that in patients with ACLF-1 and HRS, who have a moderate increase in systemic inflammation over the chronic inflammation of decompensated cirrhosis, systemic circulatory dysfunction may have a significant role in ACLF and HRS development. Therefore, these patients may be more likely to respond to terlipressin and albumin. In contrast, systemic inflammation is significantly more intense in patients with ACLF-2 and particularly with ACLF-3. The predominant mechanism in the pathophysiology of ACLF and HRS in these patients might be systemic inflammation, leading to a generalised increase in microcirculatory and mitochondrial dysfunction and cell death; disorders that cannot be reversed by improving systemic circulatory function with terlipressin and albumin [10].

Future research

HRS has always been considered an interesting topic of research in the field of complications of cirrhosis. Given the new diagnostic criteria and changes in the understanding of the pathophysiology of decompensated cirrhosis, new questions arise that need to be addressed in the near future:

(1) According to the new definition and algorithm, patients with HRS-AKI will be treated earlier and at lower sCr values than patients treated with the classical definition of type-1 HRS. To date, there is no data on the impact of the new algorithm on the management of HRS-AKI with respect to response rate, adverse events and patient outcomes. All these issues should be addressed in future prospective studies to confirm whether the new therapeutic approach is associated with an improved response rate and outcomes.

(2) Response rate to vasoconstrictors and albumin in patients with HRS ranges from 40 to 70% approximately (including complete and partial response). Therefore, there is still a relevant percentage of patients with no response to the treatment of choice. Treatment with vasoconstrictors and albumin

targets systemic circulatory dysfunction, which has been traditionally known to be the main driver of HRS. However, as described above, it is currently accepted that systemic inflammation may play a relevant role on the pathophysiology of HRS-AKI and may have an impact on response to treatment. In this context, new treatment strategies should be investigated for patients with HRS-AKI, with special interest including systemic inflammation as a potential new target.

(3) Finally, the role of new biomarkers of kidney tubular damage in the differential diagnosis and predicting response to treatment in patients with HRS-AKI should also be further investigated (see previous chapter).

References

1. Angeli P, Ginès P, Wong F, Bernardi M, Boyer TD, Gerbes A, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. J Hepatol 2015; 62: 968-974.

   *** Revised consensus of the International Club of Ascites describing the new definition and diagnostic criteria of AKI and HRS-AKI in patients with cirrhosis.*

2. Angeli P, Bernardi M, Villanueva C, Francoz C, Mookerjee RP, Trebicka J, et al. EASL clinical practice guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018; 69: 406-60.

   *** Recently published new EASL clinical practice guidelines for the management of patients with decompensated cirrhosis. These guidelines include the accepted definition and algorithm for the management of HRS-AKI and an updated summary of the available therapeutic options.*

3. Bernardi M, Moreau R, Angeli P, Schnabl B, Arroyo V. Mechanisms of decompensation and organ failure in cirrhosis: from peripheral arterial vasodilation to systemic inflammation hypothesis. J Hepatol 2015; 63: 1272-84.

4. Ginès P, Solà E, Angeli P, Wong F, Nadim MK, Kamath PS. Hepatorenal syndrome. Nat Rev Dis Primers 2018; 4(1): 23.

   ***The most recent and complete review focused on hepatorenal syndrome. This review includes updated information on the definition and diagnostic criteria, pathophysiology and management of HRS.*

5. Gluud LL, Kristensen K, Kristensen E, Krag A. Systematic review of randomized trials on vasoconstrictor drugs for hepatorenal syndrome. Hepatology 2010; 51: 219-226.

6. Boyer TD, Sanyal AJ, Wong F, Frederick RT, Lake JR, O'Leary JG, et al. Terlipressin Plus Albumin Is More Effective Than Albumin Alone in Improving Renal Function in Patients With Cirrhosis and Hepatorenal Syndrome Type 1. Gastroenterology 2016;150:1579-1589.e2

7. Cavallin M, Piano S, Romano A, Fasolato S, Frigo AC, Benetti G, et al. Terlipressin given as continuous intravenous infusion versus intravenous boluses in the treatment of hepatorenal syndrome: a randomized controlled study. Hepatology 2016; 63: 983-992.

8. Alessandria C, Ottobrelli A, Debernardi-Venon W, Todros L, Cerenzia MT, Martini S, et al. Noradrenalin vs terlipressin in patients with hepatorenal syndrome: a prospective, randomized, unblinded, pilot study. J Hepatol 2007;47:499-505.

9. Solé C, Solà E, Huelin P, Carol M, Moreira R, Cereijo U, et al. Characterization of inflammatory response in hepatorenal syndrome: relationship with kidney outcome and survival. Liver Int 2018; Dec 29. doi: 10.1111/liv.14037. [Epub ahead of print].

10. Piano S, Schmidt HH, Ariza X, Amoros A, Romano A, Hüsing-Kabar A, et al. Association Between Grade of Acute on Chronic Liver Failure and Response to Terlipressin and Albumin in Patients With Hepatorenal Syndrome. Clin Gastroenterol Hepatol 2018; 16: 1792-1800.e3.

SESSION 5
HEPATIC ENCEPHALOPATHY AND ACLF IN END-STAGE LIVER DISEASE

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New options in the treatment of hepatic encephalopathy: from lactulose to non-absorbable antibiotics

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Take-home messages

- Hepatic encephalopathy (HE) should be classified based on: i) the underlying condition leading to HE; ii) the severity of mental alteration; iii) the time-course of mental alteration; and iv) the precipitating and facilitating events.
- Venous blood ammonia has a high negative predictive value in relation to the diagnosis of overt HE (OHE) (i.e. there is no OHE without hyperammonaemia, while documented hyperammonaemia does not necessarily imply that the patient is symptomatic).
- Once there is a working diagnosis of OHE, every effort should be made to identify facilitating and precipitating events.
- Primary prophylaxis for the prevention of OHE is not required, with the exception of rapid removal of blood from the gastrointestinal tract after an upper gastrointestinal bleed.
- An episode of OHE, spontaneous or precipitated, should be actively treated. Once resolved, non-absorbable disaccharides represent the first choice treatment for the secondary prophylaxis of OHE. Rifaximin should be added to non-absorbable disaccharides in patients with recurrent OHE, i.e. those who have developed a second episode of OHE within 6 months of the first one.

Definition

Hepatic encephalopathy (HE) is a brain dysfunction caused by liver failure and/or portal-systemic blood shunting that produces a spectrum of neurological/psychiatric abnormalities ranging from subclinical alterations to coma.

Pathophysiology

Both liver failure and portal-systemic shunting produce encephalopathy in humans, as well as in experimental models. Encephalopathy can be induced by the administration of ammonia salts in patients with cirrhosis [1], the administration of ammonia salts or urea precursors in dogs with a surgical portal-systemic shunt, and meat feeding in dogs with surgical portal-systemic shunt [2]. Encephalopathy is reversed by using oral non-absorbable disaccharides and antibiotics, both acting on gut bacteria, and by portal-systemic shunt reduction. These findings support the view that HE is caused by liver failure and/or portal-systemic shunting, as well as by nitrogen metabolism and gut content, including the gut microbiota and its interaction with food. It is therefore reasonable to qualify this kind of encephalopathy as “hepatic encephalopathy”.

Several gut-derived substances may have neurotoxic effects, including ammonia, mercaptans, benzodiazepine-like substances, and indole. Plasma ammonia, in addition to its direct effect on the brain, is likely to be a marker of the presence of other toxic nitrogenous substances produced by the gut microbiota. For example, the levels of ammonia and indole are correlated because the origin of

these substances is similar. Other sites that play a role in determining plasma ammonia levels are the kidneys, which have ammoniogenic properties, the urinary tract, where ammonia can be released from urea by the action of urease-containing bacteria, and the muscles, which can utilise ammonia for glutamine synthesis, thus explaining why sarcopenia is a risk factor for HE. Protein breakdown and the consequent amino acid oxidation in fasting conditions can also contribute to hyperammonaemia. Finally, any systemic condition increasing pro-inflammatory cytokines, causing hyponatremia or alkalaemia can become sensitised to the action of ammonia.

An increase in cellular water content is observed in the brain in HE, and in extracellular water content in acute liver failure (ALF) [3] and acute on chronic liver failure (ACLF) [4]. These correlate with clinical findings to a varying extent. The increase in blood ammonia facilitates the entrance of ammonia in the brain with first-order kinetics and can explain, at least in part, the neurological findings. Ammonia drives:

- An increase in glutamine synthesis in astrocytes, the entrance of glutamine into the mitochondria, plus oxidative and nitrosative stress.
- Activation of microglia and induction of neuroinflammation.
- Impairment in brain energy metabolism via inhibition of ketoglutarate dehydrogenase and pyruvate dehydrogenase, with consequent tricarboxylic acid cycle dysfunction, increased glycolytic activity and lactate production.
- Interference with glutamatergic and GABAergic neurotransmission.
- Interference with inhibitory and excitatory mechanisms of neurotransmission, due to the similarity in dimension and charge between the ammonium and potassium ions.

In addition, there is some evidence for alterations in serotoninergic, histaminergic and dopaminergic neurotransmission in HE [5]. Hyperintense globus pallidus/basal ganglia on T1-weighted magnetic resonance imaging is frequently observed in patients with HE and are related to brain manganese deposition [6]. Manganese is neurotoxic and can impair dopaminergic neurotransmission. However, the hyperintensity of globus pallidus/basal ganglia is poorly related, if at all, to the cognitive symptoms of HE. Alterations of the blood-brain barrier have been reported in ALF and severe ACLF. In these conditions, they may concur to the development of brain oedema and intracranial hypertension (ICH), with the risk of death caused by cerebellar tonsil herniation. This event is very rare in ACLF, while it is more common in ALF [7].

Classification

HE should be classified based on 4 items:

1. the underlying condition leading to HE;
2. the severity of mental alteration;
3. the time-course of mental alteration;
4. the precipitating and facilitating events.

1. In "type A" HE, ALF is recognised as the clinical setting for HE onset. Intracranial hemodynamic alterations, as well as brain barrier alterations and astrocyte swelling cause ICH. This can lead to death because of cerebellar tonsil herniation.

   In "type B" HE, portal-systemic shunting alone is the cause of HE development. In "type C" HE, both liver failure and portal-systemic shunting are at the basis of HE.

Recently, a distinction between patients with and without ACLF has been suggested. HE in patients with ACLF has more severe prognostic value [8], intercellular brain oedema parallels the severity of symptoms [4], and ICH has been reported, albeit rarely. In patients with ACLF, massive inflammation causing damage to the blood-brain barrier and injuries to the brain derived from multiorgan failure and drug treatments can be present. This may cause a mixed form of metabolic encephalopathy, for which personalised treatment might be preferable [9].

2. The severity of mental impairment also has prognostic [8] and management implications. Comatose patients require airway protection, and agitated patients require sedation. HE has been traditionally split into overt (clinically detectable neurological/psychiatric abnormalities; OHE) and minimal (abnormalities on neuropsychological or neurophysiological testing; MHE) [10]. As the clinical diagnosis of mild forms of OHE is heavily operator-dependent, it has been suggested [11, 12] that HE is qualified as overt when at least temporal disorientation and/or flapping tremor are detected (grade II according to the West Haven criteria [13]). In contrast, grade I HE abnormalities [13], which are usually appreciated by caregivers or physicians who are well acquainted with the patient, are grouped with abnormalities on testing (MHE) and qualified as covert HE (CHE). Thus, a diagnosis of CHE requires testing and cannot be solely clinical [12]. OHE can be graded according to the AASLD/EASL operative definitions [11,14] while CHE does not have a universally accepted diagnostic tool. The animal naming test (ANT) [15] is a simple and costless approach to quantify mental function in non-disoriented subjects and can be recommended for everyday practice. For centres highly motivated in screening for the presence of MHE, more accurate tools are the PHES score, the critical flicker frequency and the EEG, possibly quantified. Computerised tests assessing attention, working memory or inhibition can also be used in highly skilled asymptomatic patients [11,14].

3. The time course and in particular the frequency of relapse has prognostic value in patients with HE, and is a guide for prophylactic treatment. In terms of its time-course, HE is qualified as episodic (1 bout over 6 months), recurrent (2 or more bouts over 6 months) or persistent (in between bouts the patient's performance never returns to baseline).

4. The precipitating (infection, gastrointestinal bleeding, diuretic overdose, electrolyte disorder, constipation) [11] and facilitating events (spontaneous or surgical portal-systemic shunts, or transjugular intrahepatic portosystemic shunt [TIPS]) are relevant to support the diagnosis. Their prevention (i.e. bleeding prophylaxis, avoidance of constipation, diuretic treatment tapering, etc.) reduces the risk of HE bouts. In all instances, information on the existence of surgical portal-systemic shunts should be acquired.

The response to treatment is useful to confirm the diagnosis and, if effective, to guide treatment choices in case of relapse.

General management principles of type C, OHE

The management of OHE is based on four general principles: i) initiation of care of patients with altered consciousness; ii) identification and treatment of alternative and co-existing causes of altered mental status; iii) identification and correction of precipitating factors; and iv) commencement of empirical ammonia-lowering treatment [11,14]. Patients with grades III and IV OHE according to the West Haven criteria [13] who are at risk or unable to protect their airways, should ideally be managed in an intensive care setting. A nasogastric tube can be used to administer drugs which are only available/known to work by mouth formulations in patients who are unable to swallow or appear to be at risk of aspiration. The identification and control of precipitating factors is of paramount importance, as it can cure a significant proportion of patients with a bout of OHE. The most commonly used

drugs for the subsequent commencement of empirical treatment are non-absorbable disaccharides, such as lactulose, and non-absorbable antibiotics, such as rifaximin. Other agents, for which the available evidence is anecdotal, include intravenous branched-chain amino acids (BCAAs), intravenous L-ornithine L-aspartate (LOLA), probiotics, and other antibiotics. Given that OHE is a predictor of death and that its appearance generally marks a worsening in both hepatic function and prognosis [16], after a first bout of OHE the patient should be referred to a liver transplant centre.

Primary prophylaxis of OHE is not generally recommended, with the exception of the rapid removal of blood from the gastrointestinal tract after an upper gastrointestinal bleed, for example with lactulose or mannitol by mouth.

In contrast, secondary prophylaxis is important, as once a patient has experienced a bout of OHE, the likelihood of further episodes is high and is one of the main causes of re-admission into hospital and health-related expenses [17]. Secondary OHE prophylaxis should be started with a non-absorbable disaccharide (i.e. lactulose or lactitol) [18]. The laxative effect of non-absorbable disaccharides varies considerably in the population, so it is reasonable to start with 20 ml of syrup (or the equivalent in granules) twice daily, and then proceed by titrating the drug in order to obtain 2-3 soft stools per day. In the course of a few weeks, the patient generally adjusts and manages to avoid both constipation and diarrhoea.

If OHE becomes recurrent (i.e. more than one bout within six months), the addition of the non-absorbable antibiotic rifaximin is useful in maintaining remission, as documented in a multicentre, multinational trial of rifaximin versus placebo in patients who had had two previous bouts of OHE, 91% of whom were already on lactulose [19].

The management of patients with highly recurrent or persistent HE is extremely challenging. This form of HE is common in patients with large, spontaneous portal-systemic shunts, which should be always sought for, and those who have undergone TIPS. Shunt embolisation/closure can be considered in patients with demonstrated, accessible portal-systemic shunts. A recent retrospective study including 43 patients with OHE refractory to conventional therapy who underwent Coil-Assisted Retrograde Transvenous Obliteration [20] showed significant improvement in 91% of cases, 67% with complete resolution during a median follow-up of 755 days. Another prospective study evaluated technical and clinical outcomes of Plug-Assisted Retrograde Transvenous Obliteration for the treatment of HE [21]; none of the patients developed HE episodes during the follow-up, Child-Pugh score improved in 40% of cases and worsening ascites or varices were observed in 23% and 26%, respectively.

When related to TIPS, persistent/highly recurrent HE can be treated by reducing or occluding the stent. TIPS should probably be revised when a causal relationship between the shunt and HE is suspected, when HE occurs within a few weeks or months after TIPS, or when the procedure leads to a significant reduction in portal-systemic gradient, supporting the hypothesis that the excessive portal blood diversion is responsible for HE. TIPS should not be revised in patients with persistent HE due to liver failure. At any rate, as the complications of portal hypertension may recur as a consequence of shunt reduction, the decision to revise always requires a careful evaluation of risks and benefits.

Highly recurrent and persistent HE, together with those forms of HE with prominent motor dysfunction, also represent a clinical scenario where combination treatment is often necessary and can be probably tested on a case-to-case basis, even in the absence of hard evidence. The drugs to consider are BCAAs, probiotics, LOLA, non-ureic nitrogen scavengers (i.e. sodium benzoate, sodium phenylbutyrate, glycerol phenylbutyrate and ornithine phenylacetate) and albumin, together with faecal transplantation and modifications in the amount and sources of dietary protein [14,22].

Liver transplantation is the ultimate therapeutic option for persistent/highly recurrent HE and patients with prominent HE-related motor dysfunction (i.e. hepatic myelopathy) [23]. Prioritisation of these patients is currently based on liver function and could therefore underestimate their risk of mortality and hospitalisation. Therefore, it is important to weigh the prognostic impact of persistent/highly recurrent HE in patients on the waiting list for transplantation, possibly adding a quantitative or clinical HE parameter to the available scoring systems [24,25]. However, this issue remains under debate. Finally, it is crucial that all significant shunts are closed during transplantation, to avoid post-transplant type B HE.

References

[References in **BOLD** are required reading]

1. Van Caulert C DC, Halff M. Troubles provoques par l'ingestion de sels ammoniacaux chez l'homme atteint de cirrhose de Laennec. Comptes Rendus Soc Biol. 1932:739-40.
2. Balo J KB. The encephalitis of dogs with Eck fistula fed on meat. Arch Pathol. 1932;13:80-7.
3. Aggarwal S, Kramer D, Yonas H, Obrist W, Kang Y, Martin M, et al. Cerebral hemodynamic and metabolic changes in fulminant hepatic failure: a retrospective study. Hepatology. 1994;19:80-7.
4. Gupta T, Dhiman RK, Ahuja CK, Agrawal S, Chopra M, Kalra N, et al. Characterization of Cerebral Edema in Acute-on-Chronic Liver Failure. J Clin Exp Hepatol. 2017;7:190-7.
5. Lozeva V, Montgomery JA, Tuomisto L, Rocheleau B, Pannunzio M, Huet PM, et al. Increased brain serotonin turnover correlates with the degree of shunting and hyperammonemia in rats following variable portal vein stenosis. J Hepatol. 2004;40:742-8.
6. Rose C, Butterworth RF, Zayed J, Normandin L, Todd K, Michalak A, et al. Manganese deposition in basal ganglia structures results from both portal-systemic shunting and liver dysfunction. Gastroenterology. 1999;117:640-4.
7. Joshi D, O'Grady J, Patel A, Shawcross D, Connor S, Deasy N, et al. Cerebral oedema is rare in acute-on-chronic liver failure patients presenting with high-grade hepatic encephalopathy. Liver Int. 2014;34:362-6.
8. Cordoba J, Ventura-Cots M, Simon-Talero M, Amoros A, Pavesi M, Vilstrup H, et al. Characteristics, risk factors, and mortality of cirrhotic patients hospitalized for hepatic encephalopathy with and without acute-on-chronic liver failure (ACLF). J Hepatol. 2014;60:275-81.
9. Weiss N, Barbier Saint Hilaire P, Colsch B, Isnard F, Attala S, Schaefer A, et al. Cerebrospinal fluid metabolomics highlights dysregulation of energy metabolism in overt hepatic encephalopathy. J Hepatol. 2016;65:1120-30.
10. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy--definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. Hepatology. 2002;35:716-21.
11. Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology. 2014;60:715-35.
12. Bajaj JS, Cordoba J, Mullen KD, Amodio P, Shawcross DL, Butterworth RF, 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.

13. Conn HO, Leevy CM, Vlahcevic ZR, Rodgers JB, Maddrey WC, Seeff L, et al. Comparison of lactulose and neomycin in the treatment of chronic portal-systemic encephalopathy. A double blind controlled trial. Gastroenterology. 1977;72:573-83.

14. Montagnese S, Russo FP, Amodio P, Burra P, Gasbarrini A, Loguercio C, Marchesini G, Merli M, Ponziani FR, Riggio O, Scarpignato C. Hepatic Encephalopathy 2018: a Clinical Practice Guideline by the Italian Association for the Study of the Liver (AISF). Dig. Liver Dis. 2018;51(2):190-205.

15. Campagna F, Montagnese S, Ridola L, Senzolo M, Schiff S, De Rui M, et al. The animal naming test: An easy tool for the assessment of hepatic encephalopathy. Hepatology. 2017;66:198-208.

16. 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.

17. Di Pascoli M, Ceranto E, De Nardi P, Donato D, Gatta A, Angeli P, et al. Hospitalizations Due to Cirrhosis: Clinical Aspects in a Large Cohort of Italian Patients and Cost Analysis Report. Dig Dis. 2017;35:433-8.

18. Sharma BC, Sharma P, Agrawal A, Sarin SK. Secondary prophylaxis of hepatic encephalopathy: an open-label randomized controlled trial of lactulose versus placebo. Gastroenterology. 2009;137:885-91.

19. Bass NM, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB, et al. Rifaximin treatment in hepatic encephalopathy. N Engl J Med. 2010;362:1071-81.

20. Lee EW, Saab S, Kaldas F, Fletcher S, Busuttil RW, Durazo F, et al. Coil-Assisted Retrograde Transvenous Obliteration (CARTO): An Alternative Treatment Option for Refractory Hepatic Encephalopathy. Am J Gastroenterol. 2018;113:1187-96.

21. Gwon DI, Kim YH, Ko GY, Kim JW, Ko HK, Kim JH, et al. Vascular Plug-Assisted Retrograde Transvenous Obliteration for the Treatment of Gastric Varices and Hepatic Encephalopathy: A Prospective Multicenter Study. J Vasc Interv Radiol. 2015;26:1589-95.

22. EASL Clinical Practice Guidelines (CPG) on nutrition in chronic liver disease. Collaborators: Merli M, Berzigotti A, Zelber-Sagi S, Dasarathy S, Montagnese S, Genton L, Plauth M, Parés A. J Hepatol. 2018;70(1):172-193.

23. Baccarani U, Zola E, Adani GL, Cavalletti M, Schiff S, Cagnin A, et al. Reversal of hepatic myelopathy after liver transplantation: fifteen plus one. Liver Transpl. 2010;16:1336-7.

24. Montagnese S, De Rui M, Schiff S, Ceranto E, Valenti P, Angeli P, et al. Prognostic benefit of the addition of a quantitative index of hepatic encephalopathy to the MELD score: the MELD-EEG. Liver Int. 2015;35:58-64.

25. Lucidi C, Ginanni Corradini S, Abraldes JG, Merli M, Tandon P, Ferri F, et al. Hepatic encephalopathy expands the predictivity of model for end-stage liver disease in liver transplant setting: Evidence by means of 2 independent cohorts. Liver Transpl. 2016;22:1333-42.

Acute on chronic liver failure: From pathogenesis to prognosis

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Take-home messages

- Acute on chronic liver failure (ACLF) is a frequent syndrome in patients with cirrhosis, is clinically different from acute decompensation and is associated with a relevant risk of short-term death.
- Besides the different definitions of ACLF, its recognition and prognostic evaluation are essential in patients with decompensated cirrhosis.
- The pathogenesis of ACLF is clearly different from the observed in patients with acute decompensation; the exacerbation of systemic inflammation and the dysregulation of the immune response are critical in the pathogenesis of ACLF.
- ACLF is a highly dynamic condition, especially during the first days. Prognosis correlates better with the clinical course within the first 3 to 7 days than with ACLF grade at diagnosis.

The concept of ACLF

Chronic advanced liver disease has two well-defined stages commonly designed as compensated and decompensated cirrhosis. The transition between these two phases occurs when the patient develops complications such as ascites, hepatic encephalopathy, infection and/or variceal bleeding. Decompensated stage is associated with decreased survival (mean survival of 3 to 5 years) and is characterised by a slow but progressive deterioration of liver function and organ dysfunction. Importantly, a sub-group of patients with decompensated cirrhosis may develop a distinct syndrome characterised by rapid deterioration of liver function associated to the development of organ failure/s (OF; hepatic and extrahepatic) and high short-term mortality. The latter situation is usually known as acute on chronic liver failure (ACLF) [1]. However, there is not a universally accepted definition for ACLF, probably because of the different precipitating events and prevalence of underlying liver diseases in different settings. Currently, there are three major definitions. The Asia-Pacific Association for the study of the Liver (APASL) defines ACLF as an "acute hepatic insult manifesting as jaundice (serum bilirubin $\geq$5 mg/dl) and coagulopathy (INR $\geq$1.5 or prothrombin activity <40%) complicated within 28 days by clinical ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease" [2]. This definition was based on a consensus conference and comprises of cirrhotic and non-cirrhotic patients without a previous history of decompensation that develops liver failure after a precipitating event, which causes a direct effect on the liver. The major advantage of the APASL definition is that it identifies patients before the development of extrahepatic OF and, therefore, may allow early intervention. The North American Consortium for Study of End-Stage Liver Disease (NACSELD) proposed an alternative definition based on the results of a prospective study that included decompensated patients with bacterial infection who developed extrahepatic OF [3]. The European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) defined ACLF according to the results of the CANONIC study [4]. The CANONIC study was a multinational European prospective study specifically designed to describe the concept, precipitating events, diagnostic

criteria, natural history and prognosis of ACLF in a large series of patients admitted to hospital with acute decompensation (AD) of cirrhosis. The study was comprised of 1343 consecutive patients from 29 hospitals. According to this study, ACLF is defined as a specific syndrome characterised by AD of cirrhosis associated with OF and high short-term mortality (predefined as a 28-day mortality >15%). The presence of OF was assessed by a modified version of the Sequential Organ Failure Assessment score (SOFA), called CLIF-SOFA score. A simplified version of the CLIF-SOFA, the CLIF Consortium Organ Failure score (CLIF-C OF) (Table 1) was developed later for the definition of OF [5].

Table 1. The CLIF-C Organ Failure score system. Shaded areas denote the threshold for defining organ failures. ACLF grade 1 (ACLF-1): patients with single kidney failure, patients with non-renal organ failure plus renal dysfunction (creatinine 1.5–1.9 mg/dl) and/or brain dysfunction (grade 1–2 HE). ACLF-2: patients with two organ failures. ACLF-3: patients with three or more organ failures.

Organ/system	Sub score = 1	Sub score = 2	Sub score = 3
Liver	Bilirubin <6 mg/dl	Bilirubin <6 mg/dl and <12 mg/dl	Bilirubin >12 mg/dl
Kidney	Creatinine <2 mg/dl	Creatinine >2 mg/dl and <3.5 mg/dl	Creatinine >3.5 mg/dl or renal replacement
Brain (West-Haven grade for hepatic encephalopathy)	Grade 0	Grade 1-2	Grade 3-4
Coagulation	INR <2.0	INR >2.0 and <2.5	INR >2.5
Circulatory	MAP <70 mmHg	MAP <70 mmHg	Use of vasopressors
Respiratory PaO_2/FiO_2	>300	<300 and >200	<200
or SpO_2/FiO_2	or >357	or >214 and <357	or <214

HE, hepatic encephalopathy; INR, international normalized ratio; MAP, mean arterial pressure; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; SpO_2, pulse oximetric saturation.

ACLF is a frequent complication in patients with cirrhosis and represents a major healthcare problem worldwide. In the CANONIC study, the prevalence of the syndrome in patients with acutely decompensated cirrhosis was 30%; twenty per cent of patients presented ACLF at hospital admission, and 10% of the patients with no ACLF at admission developed it during hospitalisation. ACLF (as defined by the CANONIC study) has also been described as a prevalent syndrome in Asia (20 to 70%), North America (41,6%) and South America (24 to 37%).

Precipitating events of ACLF can be classified as hepatic (i.e. viral hepatitis, drug-induced liver injury, excessive alcohol intake) or extrahepatic (i.e. bacterial infection, gastrointestinal bleeding, major surgery). Importantly, precipitating events vary according to geographical areas. The most common precipitating events in Asia are reactivation of chronic HBV, acute viral hepatitis (A or E), alcoholic hepatitis and infections. In the West, the most common precipitating events are alcoholic hepatitis and bacterial infections; importantly, there is no recognisable precipitating event in a considerable proportion of patients.

Mechanisms of ACLF: Role of inflammation and immunity

The precise mechanisms associated with the development and prognosis of ACLF are not completely understood. However, several studies clearly indicate that the exacerbation of systemic inflammation and circulatory dysfunction already present in patients with AD plays a major role. In this setting, the presence of proinflammatory molecules (pathogen-associated molecular patterns; PAMPs) associated to the disruption of gut barrier, and the release of damage-associated molecular patterns (DAMPs), mainly derived from the injured liver, are critical in the initial stimulation of immune system. In the CANONIC study, a close relationship between clinical markers of inflammation (C-reactive protein and leukocyte count) and the presence and severity of ACLF was observed [4]. More precisely, ACLF develops when a further increase in inflammatory mediators is observed [6]; interestingly, the frequency, severity and clinical course of ACLF seems to be strongly associated with the intensity of inflammatory changes as assessed by the elevation of IL-8 and IL-6 levels. Importantly, the profile of cytokine response characteristically affected in ACLF mainly suggest an alteration in the innate immune response. Furthermore, the uncontrolled systemic inflammation associated to ACLF leads to host damage, loss of cell function, cell death and organ dysfunction. It should be noted that the progression from AD to ACLF seems to be associated with an increase in non-apoptotic cell death and that the severity of cell death is related to relevant clinical findings such as the predisposing factor, the precipitating illness, the severity of systemic inflammation and the type and number of organ failures [7].

Importantly, the presence of two polymorphisms in the *IL-1* gene cluster, that encode for the most important cytokines of the inflammatory process: IL-1a, IL-1b, and IL- 1ra, strongly influence the susceptibility for the development of ACLF and its prognosis [8], thus suggesting the possibility of a more personalised approach for the prognosis and therapy of ACLF patients.

Finally, a recent study has described that monocytes in patients with ACLF show an upregulated pattern of immunosuppressive parameters that compromised its antibacterial and antigen-presenting properties, findings that are not present in monocytes of patients with AD. Furthermore, when healthy monocytes are cultured in ACLF plasma, they mimic the immunosuppressive profile observed in patients [9]. Altogether, these findings strongly indicate that the pathogenesis of ACLF is distinct to the observed in AD and is mainly associated with an exacerbated inflammation and alteration of immune response. Furthermore, its precise knowledge may help in the design of new, specific therapies for the management of ACLF.

ACLF prognosis according to organ failure

Recognition and staging of OFs is essential in prognosis assessment. Patients with decompensated cirrhosis can be stratified into four groups of severity according to the number and type of OF:

- No ACLF.
- ACLF grade 1:
  - Patients with single kidney failure;
  - Single non-kidney OF and renal dysfunction (creatinine ranging from 1.50 to 1.99 mg/dl) and/or brain dysfunction (West-Haven grade 1-2 hepatic encephalopathy).
- ACLF grade 2: two OF.
- ACLF grade 3: three or more OF.

Data from the CANONIC study reports kidney failure as the most prevalent OF in ACLF grade 1. For ACLF grade 2, liver failure is the most prevalent followed by kidney, brain and coagulation failure.

For ACLF grade 3, the prevalence of all OFs is high [1]. Among patients with ACLF, 51% had ACLF grade 1, 35% had ACLF grade 2, and 13% had ACLF grade 3. Besides providing the diagnosis of the syndrome, these criteria also provide data for rapid prognostic information, with the ACLF grade associated with different mortality rates. The CLIF-C ACLF score is a prognostic model developed and validated to improve the prognostic ability of ACLF grades [5]. This model incorporates the CLIF-C OF score, the age and the white blood cell count, and was validated using prospective data from a series of patients not included in the CANONIC study. The CLIF-C ACLF score provided a significantly better estimate of the risk of death at 28 days, 90 days, 6 months and 12 months compared with the Model for End-Stage Liver Disease (MELD) score, the MELD-sodium score and the Child-Pugh score. Compared with the CLIFC ACLF score, the MELD score underestimated the risk of death of patients by 20–30%, implying that organ allocation for transplantations using the MELD score seriously disadvantages patients with ACLF.

ACLF is a dynamic and potentially reversible syndrome [10]. Data from the CANONIC study show that evolution within the first 3-7 days following the diagnosis of ACLF is extremely important to predict clinical course since resolution, improvement or worsening of ACLF occur within this early time period in most patients. Importantly, the final grade of ACLF will be defined within the first 3-7 days after diagnosis in 81% of patients. Furthermore, prognosis correlates better with the clinical course than with ACLF grade at diagnosis. For instance, at days 3-7 from presentation, approximately 50% of patients with ACLF grade 1 will present resolution of ACLF, with a consequent low 28-day mortality rate (<10%). In addition, 25% of patients with ACLF grade 1 will remain unchanged, with a 28-day mortality rate of 24%. By contrast, approximately 25% of patients with ACLF grade 1 progress to ACLF grade 2 or ACLF grade 3, bringing the mortality rates to 53% and 88%, respectively.

Therefore, prognostic scores need to be dynamic so that they can be updated sequentially on a daily basis. This regular assessment may be useful to identify a response to an intervention or a guide to determine whether further interventions are likely to be futile. CLIF-C ACLF score computed at 3-7 days and 8-15 days after ACLF diagnosis predicted 28-day and 90-day mortality to be significantly better than the CLIF-C ACLFs at diagnosis.

Another interesting point is the influence of ACLF in response to conventional therapy in different settings; thus, the response to terlipressin plus albumin for the treatment of hepatorenal syndrome (HRS) is lower in patients with HRS and concomitant ACLF as compared with the observed response in patients with HRS without ACLF [11]. Similarly, the response to steroids in severe alcoholic hepatitis was lower in patients who simultaneously had ACLF [12].

Predictive factors for ACLF in patients with cirrhosis

According to the results of the CANONIC study, ACLF was the initial manifestation of decompensated cirrhosis in 23% of patients. These patients without prior history of decompensation were younger, more-frequently alcoholics, had more-severe systemic inflammation, greater ACLF grade and higher short-term mortality (42% versus 30%) than patients with ACLF with prior history of AD. These results highlight the importance of alcohol abuse as a precipitating event of ACLF in patients with previously compensated advanced liver disease.

Nonetheless, neither aetiology nor precipitating events seem to impact mortality, suggesting that OF is the main risk factor of mortality. In a retrospective study from China in patients who predominantly had HBV-related cirrhosis patients with hepatic precipitants, such as reactivation of HBV, had a short-term (28-day and 90-day) mortality similar to patients with an extrahepatic precipitant, such as infection. This pattern was also observed in a second Chinese study in patients with cirrhosis due

to chronic HBV infection who developed ACLF. The 28-day and 90-day mortality rates for any given grade of ACLF in this study were similar to those reported by the CANONIC study.

The CLIF-C AD score was developed for prognostication in patients with AD without ACLF. Variables that were found to be independently associated with survival were age, serum sodium level, serum creatinine level, white blood cell count and international normalised ratio. These generated a score between 0 and 100, which was significantly more accurate in predicting prognosis than the MELD, MELD-sodium and Child-Pugh scores. Patients with a CLIF-C AD score of <45 had a 28-day mortality rate of <3%, and this category might identify a group of patients who could be discharged early from the hospital. Conversely, patients with a CLIF-C AD score of >60 were at high risk of progression to full-blown ACLF and had a 28-day mortality rate of approximately 20%, indicating that this is probably a 'pre-ACLF' group. (CLIF-OF, CLIF-C ACLF and CLIF-C AD Scores can be calculated online at www.clifresearch.com/ToolsCalculators.aspx)

However, the precise predictive factors for the development of ACLF in patients with decompensated cirrhosis are not fully elucidated. The PREDICT study, currently under development, has been designed to answer this critical question.

References

[References in **BOLD** are required reading]

1. **Arroyo V, Moreau R, Kamath PS, Jalan R, Gines P, Nevens F, et al. Acute-on-chronic liver failure in cirrhosis. Nat Rev Dis Primers. 2016;2:16041.**
2. Sarin SK, Kumar A, Almeida JA, Chawla YK, Fan ST, Garg H, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the study of the liver (APASL). Hepatol Int. 2009;3:269-82.
3. Bajaj JS, O'Leary JG, Reddy KR, Wong F, Biggins SW, Patton H, et al.. Survival in infection-related acute-on-chronic liver failure is defined by extrahepatic organ failures. Hepatology. 2014;60:250-6.
4. **Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology. 2013;144:1426-37, 1437 e1-9.**
5. **Jalan R, Saliba F, Pavesi M, Amoros A, Moreau R, Gines P, et al. Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. J Hepatol. 2014;61:1038-47.**
6. Claria J, Stauber RE, Coenraad MJ, Moreau R, Jalan R, Pavesi M, et al. Systemic inflammation in decompensated cirrhosis: Characterization and role in acute-on-chronic liver failure. Hepatology. 2016;64:1249-64.
7. Macdonald S, Andreola F, Bachtiger P, Amoros A, Pavesi M, Mookerjee R, et al. Cell death markers in patients with cirrhosis and acute decompensation. Hepatology. 2018;67:989-1002.
8. Alcaraz-Quiles J, Titos E, Casulleras M, Pavesi M, Lopez-Vicario C, Rius B, et al. Polymorphisms in the IL-1 gene cluster influence systemic inflammation in patients at risk for acute-on-chronic liver failure. Hepatology. 2017;65:202-216.

9. Korf H, du Plessis J, van Pelt J, De Groote S, Cassiman D, Verbeke L, et al. Inhibition of glutamine synthetase in monocytes from patients with acute-on-chronic liver failure resuscitates their antibacterial and inflammatory capacity. Gut. 2018. pii: gutjnl-2018-316888. [Epub ahead of print].

10. Gustot T, Fernandez J, Garcia E, Morando F, Caraceni P, Alessandria C, et al. Clinical Course of acute-on-chronic liver failure syndrome and effects on prognosis. Hepatology. 2015;62:243-52.

11. Gustot T and Moreau R. Acute-on-chronic liver failure vs. traditional acute decompensation of cirrhosis. J Hepatol. 2018;69:1384-1393.

12. Serste T, Cornillie A, Njimi H, Pavesi M, Arroyo V, Putignano A, et al. The prognostic value of acute-on-chronic liver failure during the course of severe alcoholic hepatitis. J Hepatol. 2018;69:318-324.

Management of acute on chronic liver failure (ACLF) in the intensive care unit and the role of liver support systems

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Take-home messages

- The hyperdynamic circulatory state typical of cirrhosis includes a high cardiac output with low systemic vascular resistance and may mask cirrhotic cardiomyopathy.
- Consider a mean arterial pressure of 65 mmHg. Norepinephrine is recommended as the first-line vasopressor in acute on chronic liver failure (ACLF) patients with shock, unresponsive to fluid/albumin resuscitation.
- In the ACLF patient with septic shock, a thorough evaluation should be promptly followed by antibiotic administration, since each hour delay impairs outcome.
- Currently, there is no evidence to support the routine use of extracorporeal liver support in ACLF patients in intensive care units.
- In high-risk ACLF patients (e.g. CLIF-C ACLF >70) who are ineligible for transplant and who do not respond to short-term therapy (72 hours), consideration should be given to placing ceilings on critical care support, and a re-evaluation of goals of care should be strongly considered in collaboration with palliative care services.

Introduction

Cirrhosis is a progressive disease in the vast majority of cases. Given the natural history of liver failure, advancing liver disease frequently results in progressive multisystem organ dysfunction, which culminating in intensive care support in many patients (acute on chronic liver failure [ACLF]). The focus of this review is to highlight the common complications of cirrhosis occurring in critically ill ACLF patients and our approach to management.

Cardiovascular abnormalities

Both circulatory and cardiac abnormalities may develop in patients with cirrhosis (Fig. 1) [1]. Portal hypertension induces progressive systemic and splanchnic vasodilation mediated by nitric oxide and other vasoactive molecules, which in turn leads to a hyperdynamic state. The hyperdynamic circulatory state typical of cirrhosis includes a high cardiac output with low systemic vascular resistance and decreased arterial blood pressure. Low effective circulating volume results in the activation of the neurohormonal axis with associated sodium and water retention and increases in heart rate. In addition to the circulatory abnormalities, cirrhotic cardiomyopathy occurs in approximately 40-50% of patients. For ACLF patients with circulatory shock, arterial catheters are recommended for the guidance of resuscitative efforts. Central venous access is also recommended as both an aid for assessment of hemodynamic status (e.g. measurement of central venous pressure [CVP]) and a route for vasoactive medications. Dynamic measures of volume and circulatory function such as echocardiography,

changes in CVP in response to fluid challenge, and passive leg raise are likely superior in assessing hemodynamic status as compared to static measures. While resuscitation end-points have not been systematically studied in patients with ACLF, a goal mean arterial blood pressure of 60-65 mmHg should be considered. Volume expansion with pH balanced crystalloid solutions (e.g. Hartmann's/ Ringer's lactate), or concentrated albumin (25% 100 cc prn) is appropriate with fluid choice being guided by the patient's clinical status. Albumin has proven in spontaneous bacterial peritonitis, after large volume paracentesis, and in hepatorenal syndrome [2].

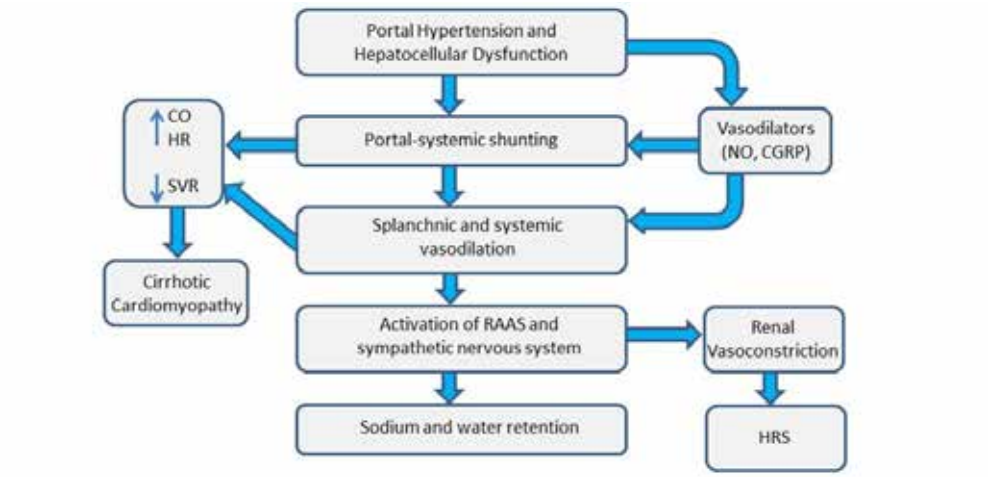

Figure 1. Circulator abnormalities in cirrhosis (taken from [1]). Circulatory abnormalities in cirrhosis, in advancing liver disease, progressive fibrosis and hepatocellular dysfunction result in the development of portal-systemic shunting. Increasing levels of vasodilators further exacerbate circulatory abnormalities leading to hyperdynamic circulatory changes and the development of cardiac dysfunction (cirrhotic cardiomyopathy). These circulatory changes also result in renal blood flow abnormalities and hepatorenal syndrome (HRS). NO, nitric oxide; CGRP, calcitonin-gene peptide; CO, cardiac output; HR, heart rate; SVR, systemic vascular resistance.

In patients with persistent shock, norepinephrine is the recommended first-line agent as it is associated with fewer adverse events. Vasopressin or terlipressin may be used as second-line agents and have demonstrated improvement in hemodynamics in patients with cirrhosis [3]. Adrenal insufficiency is common in critically ill cirrhotic patients and should be considered in cases of refractory shock [4]. In patients where adrenal insufficiency is suspected, it is our practice to administer hydrocortisone 200 mg i.v. in 4 divided doses. Non-selective beta-blockers (NSBB) should be discontinued in ACLF/ cirrhotic patients admitted to the intensive care unit (ICU) with shock, renal failure, or persistent hypotension. The presence of hypotension and vasopressor usage is not necessarily an absolute contraindication when proceeding with transplantation in a patient awaiting liver transplantation (LT). Depending on centre expertise, patients on vasopressor agents at low- or mid-range doses and who have room for up-titration, may be considered for surgery after thoughtful evaluation with the principal team members including surgeons, anesthesiologists, and intensivists.

Pulmonary disorders

Pulmonary complications in the ACLF patient can be broadly categorised into two categories: acute respiratory failure, e.g. pneumonia, acute lung injury, or hepatic hydrothorax; and respiratory complications that are a direct consequence of cirrhosis, such as portopulmonary hypertension

and hepatopulmonary syndrome. Decreased thoracic compliance occurs in the presence of tense abdominal ascites, chest wall oedema, and hepatic hydrothorax and may complicate mechanical ventilation. Given the paucity of studies in ACLF patients, and it is recommended to use a lung protective ventilation strategy using low tidal volume ventilation and positive end-expiratory pressure (PEEP) to maintain appropriate oxygenation [5]. In patients with unexplained hypoxia and/or evidence of pulmonary hypertension on echocardiography, diagnostic studies to evaluate for hepatopulmonary syndrome and portopulmonary hypertension should be considered. These studies may include contrast echocardiography, use of pulmonary artery catheterisation, and/or micro-aggregated albumin shunt studies.

Neurological dysfunction

The approach to neurological dysfunction in the ACLF patient should be aimed at treating possible precipitating factors and evaluate the response to ammonia lowering therapies. In patients who fail to respond to standard treatments, or in patients whose hepatic encephalopathy (HE) onset is particularly abrupt or severe, brain imaging is indicated. An electroencephalogram may also be considered to exclude other causes of altered mental status in patients who fail to respond to standard therapy. Serum ammonia levels may be used to aid in the differentiation of HE from other neurological conditions, the finding of a normal serum ammonia level should prompt a search for alternative neurologic abnormalities.

For patients with advanced HE with a Glasgow coma score of $\leq$8, endotracheal intubation is recommended for airway protection. In patients who are intubated only for depressed mental status, avoidance of sedation is recommended. For patients who require mechanical ventilation for respiratory failure, usage of short-acting agents, such as fentanyl (25-200 µg/hour) or propofol (50-150 mcg/kg/min) should be considered. Avoidance of benzodiazepines is recommended as these agents precipitate more pronounced neurocognitive impairment. Specific therapies for HE are utilised in conjunction with concomitant treatment of possible precipitating factors, e.g. gastrointestinal bleeding or infection. Lactulose has long been the cornerstone of therapy for HE, despite large randomised trials. In the ICU, titration to number of stools can be difficult, particularly when rectal tubes are utilised, care must be used to avoid profuse stool output as this may result in significant electrolyte abnormalities and thus may worsen encephalopathy. In addition, caution must be used when administering lactulose in a critically ill patient, ileus and or bowel obstruction are contraindications to oral administration. A recent study comparing lactulose to polyethylene glycol (PEG-3350) bowel irrigation solution demonstrated a shorter time to improvement in HE and a trend towards shorter hospital stay in the PEG-3350 group. PEG-3350 has attractive qualities, including ease of use and lack of fermentation that may decrease risk of bowel distention and ileus. Rifaximin, a minimally absorbed antibiotic, has demonstrated efficacy in prevention of HE-related events including hospitalisations. Consider rifaximin in ACLF patients in the ICU with HE dosed at 550 mg BID.

Septic shock in ACLF in the ICU

Given the rates of antimicrobial prophylaxis are increasing in cirrhosis, increasing rates of ACLF patients are presenting with septic shock/bacteraemia from Gram-negatives (50-60%) and multidrug-resistant pathogens. If severe sepsis is suspected, a thorough evaluation should be promptly followed by antibiotic administration, since each hour delay impairs outcome [6]. In patients with clinical improvement within 48-72 hours and a known pathogen, immediate tailoring of antibiotics is recommended. In patients without clinical improvement, consider antifungal therapy and computed tomography. ACLF patients

are at a higher risk for fungal infections likely due to significant immunologic impairment, increased intestinal permeability, frequent use of corticosteroids, malnutrition and performance of invasive procedures. In patients with multifocal candida colonisation with clinical risk factors for infection but who remains in stable condition, pre-emptive therapy is not indicated. Antifungal therapy should be considered in ACLF patients with two positive cultures from different sites, isolated positive blood culture and in septic patients without improvement for 48 hours. Consider echinocandins (micafungin 50-100 mg i.v. daily; caspofungin 70 mg then 50 mg i.v. daily; anidulafungin 200 mg then 100 mg i.v. daily) as first-line therapy in this setting. Antifungal prophylaxis (fluconazole 400 mg i.v. daily) may be used in ACLF patients without clinical improvement in high prevalence areas or in those with multiple risk factors for infection (corticosteroid use, prolonged microbial use, central venous catheter, total parenteral nutrition, high APACHE score, renal replacement therapy, or malnutrition), particularly while awaiting LT.

Artificial liver support

Artificial (non-biological) extracorporeal liver support (ECLS) devices aim to preserve hepatic function and mitigate or limit the progression of multiorgan failure until either hepatic recovery or liver transplant occurs. Current artificial ECLS devices differ primarily in selectivity of the membrane utilised; dialysis-based techniques (MARS) combine renal replacement therapy with albumin dialysis (MARS) and a highly selective (<50 kDa) filter in contrast to plasmapheresis (HVP)/plasma separation and filtration (Prometheus) techniques, which are less selective (~250 kDa). Bioartificial ECLS systems incorporate a bioreactor containing various forms of hepatocytes to provide synthetic functions. Summaries of key ECLS trials are shown in Table 1. Artificial and bioartificial ECLS devices have demonstrated biochemical improvement in ACLF patients in small studies and in those patients with HE, but their effects have failed to correlate with a survival benefit in larger methodologically robust studies [7]. In the largest prospective study of MARS (n = 189, RELIEF trial), while there were significant biochemical (bilirubin, p = 0.001) improvements and a more frequent improvement in HE (from grade II-IV to grade 0-I; 62.5% versus 38.2%; p = 0.07) was observed in the MARS group, there were no statistically significant differences in 28-day mortality (~60% in both groups, p = NS) [7]. Based on the current literature, routine use of ECLS as the standard of care in ACLF patients as a bridge to transplant cannot be recommended at this time.

Table 1. Evidence for extracorporeal liver support in acute on chronic liver failure. Biochemical improvements: Statistically significant reduction in bilirubin, bile acids, creatinine, ammonia

STUDY	(N)	ECLS Type	Biochemical improvement	Hemodynamic improvement	Hepatic encephalopathy improvement	Survival advantage (ECLS *vs.* SMT)
Artificial						
Mitzner *et al.* [11]	13	MARS	Yes	Yes	No	Yes (37.5% *vs.* 0% at 7 d)

STUDY	(N)	ECLS Type	Biochemical improvement	Hemodynamic improvement	Hepatic encephalopathy improvement	Survival advantage (ECLS *vs.* SMT)
Artificial						
Heemann *et al.* [12]	24	MARS	Yes	Yes	Yes	Yes (90% *vs.* 55% at 30 d)
Laleman *et al.* [13]	18	MARS/ Prometheus	Yes	No	N/A	N/A
Hassanein *et al.* [14]	70	MARS	Yes	N/A	Yes	N/A
Kribben *et al.* [15]	143	Prometheus	Yes	N/A	N/A	No
Banares *et al.* [7]	189	MARS	Yes	N/A	Yes	No
Bioartificial						
Thompson *et al.* [16]	203	ELAD	N/A	N/A	N/A	No (59% *vs.* 62% at 90 d)

ECLS, extracorporeal liver support; ELAD, extracorporeal liver assist device; MARS, molecular adsorbent recirculating system; N/A: not assessed; SMT, standard method of treatment.

Aggressive versus palliative care in ACLF in the ICU

Organ failure scores, such as the CLIF-C ACLF score (and ACLF grade) appear to identify ACLF patients with poor prognosis [8]. While outcomes in ACLF patients admitted to ICU are generally improving, mortality remains high, particularly in those patients with septic shock and multiorgan failure. In a study of 867 ACLF patients admitted to the ICUs in North America and in Europe, increasing ACLF grade on admission day and at day 3 was associated with increased mortality at 90 days [9]. A CLIF-C ACLF score of >70 on ICU admission was associated with 90% mortality at day 90 (Fig. 2). Patients who improve clinically post-ICU admission (reflected be decreased ACLF grade) at day 3 demonstrated better outcomes at 28 and 90 days than those who did not.

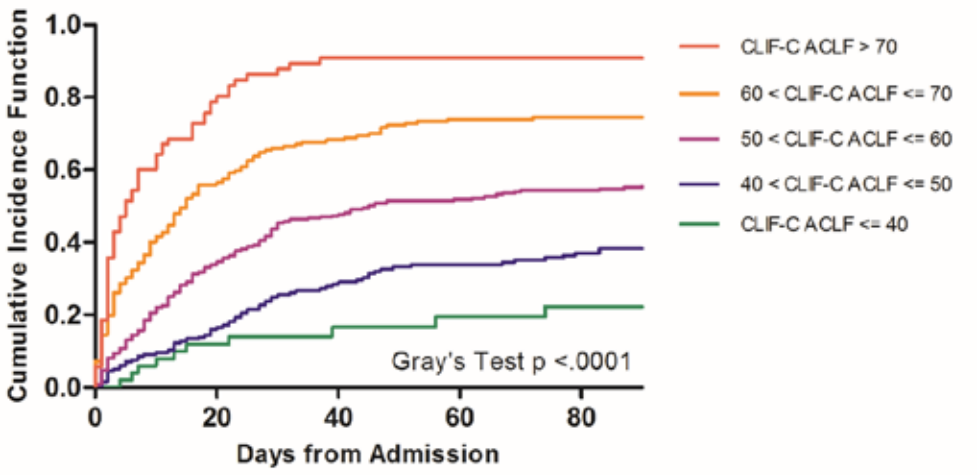

Figure 2. Cumulative incidence function for 90-day mortality in the presence of transplant by CLIF-C ACLF on ICU admission in 867 patients with ACLF (taken from [9]).

In ACLF patients who are ineligible for transplant and who do not respond to short-term therapy (72 hours), consideration should be given by placing ceilings on critical care support, and a re-evaluation of goals of care should be strongly considered. Poonja and colleagues demonstrated in a retrospective cohort of 102 cirrhotic patients declined for transplant, that goals of care were only documented in 29% of patients [10]. Scores such as the CLIF-C ACLF score, which is available on a mobile platform (ACLF calculator), may provide assistance in having appropriate discussions earlier in ACLF patients either prior to initiating life support or after deterioration despite organ support. Incorporation of palliative care in the ICU may decrease unnecessary and futile use of life support while potentially improving patient and family satisfaction.

References

1. Olson JC, Karvellas CJ. Critical care management of the patient with cirrhosis awaiting liver transplant in the intensive care unit. Liver Transpl 2017;23:1465-1476.
2. Ortega R, Gines P, Uriz J, Cardenas A, Calahorra B, De Las Heras D, Guevara M, et al. Terlipressin therapy with and without albumin for patients with hepatorenal syndrome: results of a prospective, nonrandomized study. Hepatology 2002;36:941-948.
3. Choudhury A, Kedarisetty CK, Vashishtha C, Saini D, Kumar S, Maiwall R, Sharma MK, et al. A randomized trial comparing terlipressin and noradrenaline in patients with cirrhosis and septic shock. Liver Int 2017;37:552-561.
4. Fernandez J, Escorsell A, Zabalza M, Felipe V, Navasa M, Mas A, Lacy AM, et al. Adrenal insufficiency in patients with cirrhosis and septic shock: Effect of treatment with hydrocortisone on survival. Hepatology 2006;44:1288-1295.
5. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med 2000;342:1301-1308.
6. Arabi YM, Dara SI, Memish Z, Al Abdulkareem A, Tamim HM, Al-Shirawi N, Parrillo JE, et al. Antimicrobial therapeutic determinants of outcomes from septic shock among patients with cirrhosis. Hepatology 2012;56:2305-2315.

7. Bañares R, Nevens F, Larsen FS, Jalan R, Albillos A, Dollinger M, Saliba F, et al. Extracorporeal albumin dialysis with the molecular adsorbent recirculating system in acute-on-chronic liver failure: The RELIEF trial. Hepatology 2013;57:1153-1162.

8. Jalan R, Saliba F, Pavesi M, Amoros A, Moreau R, Gines P, Levesque E, et al. Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. J Hepatol 2014;61:1038-1047.

9. Karvellas CJ, Garcia-Lopez E, Fernandez J, Saliba F, Sy E, Jalan R, Pavesi M, et al. Dynamic Prognostication in Critically Ill Cirrhotic Patients With Multiorgan Failure in ICUs in Europe and North America: A Multicenter Analysis. Crit Care Med 2018;46:1783-1791.

10. Poonja Z, Brisebois A, van Zanten SV, Tandon P, Meeberg G, Karvellas CJ. Patients with cirrhosis and denied liver transplants rarely receive adequate palliative care or appropriate management. Clin Gastroenterol Hepatol 2014;12:692-698.

11. Mitzner SR, Stange J, Klammt S, Risler T, Erley CM, Bader BD, Berger ED, et al. Improvement of hepatorenal syndrome with extracorporeal albumin dialysis mars: Results of a prospective, randomized, controlled clinical trial. Liver Transplantation 2000;6:277-286.

12. Heemann U, Treichel U, Loock J, Philipp T, Gerken G, Malago M, Klammt S, et al. Albumin dialysis in cirrhosis with superimposed acute liver injury: A prospective, controlled study. Hepatology 2002;36:949-958.

13. Laleman W, Wilmer A, Evenepoel P, Elst IV, Zeegers M, Zaman Z, Verslype C, et al. Effect of the molecular adsorbent recirculating system and Prometheus devices on systemic haemodynamics and vasoactive agents in patients with acute-on-chronic alcoholic liver failure. Crit Care 2006;10:R108.

14. Hassanein TI, Tofteng F, Brown RS, Jr., McGuire B, Lynch P, Mehta R, Larsen FS, et al. Randomized controlled study of extracorporeal albumin dialysis for hepatic encephalopathy in advanced cirrhosis. Hepatology 2007;46:1853-1862.

15. Kribben A, Gerken G, Haag S, Herget–Rosenthal S, Treichel U, Betz C, Sarrazin C, et al. Effects of Fractionated Plasma Separation and Adsorption on Survival in Patients With Acute-on-Chronic Liver Failure. Gastroenterology 2012;142:782-789.e783.

16. Thompson J, Jones N, Al-Khafaji A, Malik S, Reich D, Munoz S, MacNicholas R, et al. Extracorporeal cellular therapy (ELAD) in severe alcoholic hepatitis: A multinational, prospective, controlled, randomized trial. Liver Transplantation 2018;24:380-393.

Rescue liver transplantation in patients with ACLF: where are the limits?

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Take-home messages

- The mortality rate of patients with acute on chronic liver failure (ACLF) on the transplant waiting list has been reported to be as high as 50%, compared with 15% mortality rate for patients listed for other indications.
- Highly selected patients with ACLF have favourable outcomes with liver transplantation.
- There are currently no validated, objective, "futility scores" to determine which patients should be excluded from liver transplantation.
- Liver transplantation for patients with ACLF is controversial and requires further prospective evaluation to determine which factors are predictive of better post-transplant survival.

Increasing prevalence of critically ill cirrhotic patients on the waiting list

Acute on chronic liver failure (ACLF) describes an acute deterioration in the clinical status of patients with cirrhosis, which portends high morbidity and mortality. Several definitions of ACLF have been proposed by different authors and societies without consensus thus far [1-5]. For this discussion, we will define ACLF according to the criteria suggested by the European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) Consortium. Based on the results of the CANONIC study, a prospective, multi-centre European observational study of 1343 patients hospitalised for an acute decompensation of cirrhosis [3], the EASL-CLIF Consortium defined ACLF as the development of acute decompensation of cirrhosis (as indicated by ascites, encephalopathy, gastrointestinal bleeding, and/or bacterial infection) associated with either a single organ failure or multiple organ failures.

The definition of ACLF led to its recognition as a major worldwide medical problem. While geographical variation exists, studies suggest a prevalence of 24-34% in patients hospitalised with complications of cirrhosis [3, 6]. The CANONIC study reported a 28-day mortality of 32.8% in patients with ACLF without liver transplantation. This far exceeds a 28-day mortality rate of 1.9% in patients with decompensated cirrhosis without ACLF [3]. A multi-centre survival analysis of ACLF in the United States which used the North American Consortium for the Study of End-Stage Liver Disease (NACSELD) criteria (defined as two or more extrahepatic organ failures) found that 30-day survival worsened with the number of extrahepatic organ failures [7]. This study reported a 30-day survival of 92% with no extrahepatic organ failures, 72.6% with one, 51.3% with two, 36% with three, and only 23% with four. A recent study of the healthcare burden of ACLF in the United States revealed that the number of hospitalisations for ACLF increased 6-fold from 2001 to 2011, while hospitalisations for cirrhosis doubled over the same time frame [8]. The costs associated with hospitalisations for ACLF increased 5-fold over this time period, and the inpatient mortality rate for ACLF averaged 50%.

Results of transplantation in patients with ACLF

Liver transplantation, therefore, remains the definitive therapeutic option for patients with ACLF. However, the process of transplantation requires optimisation in patients with ACLF as the rapid progression of ACLF often leaves a limited period for transplant evaluation, selection, and eligibility [9,10]. The mortality rate of patients with ACLF on the transplant waiting list has been reported as 50%, compared with 15% mortality rate for patients listed for other indications [11]. However, studies suggest that the 5-year survival of selected patients transplanted for ACLF ranges from 74% and 90%, which is similar to the survival of patients undergoing transplantation for other indications [11-14,15].

Liver transplantation is controversial for patients with ACLF with 3 or more failing organs (ACLF-3). Data from the United Network for Organ Sharing from 2005 through to 2016 demonstrated that patients with ACLF-3 were more likely to die or be removed from the waitlist, regardless of MELD-Na score, compared to the other ACLF groups. There were 6381 patients with ACLF-3 at the time of transplant. Patients with an ACLF-3 score and MELD-Na score below 25 were at the highest risk (43.8% at 28 days) [16].

Impact of age and comorbidities

In the NACSELD study among patients with infection-related ACLF, 41% of patients were delisted for liver transplantation. MELD scores were highest in those who were delisted/died and were lowest in those remaining listed (25.07, 24.26, 17.59, respectively; $p < 0.001$) [17]. Those who were delisted or died, rather than those who underwent transplantation or were awaiting transplantation, had the highest proportion of 3 or 4 organ failures at hospitalisation versus those transplanted or those continuing to await liver transplantation (38%, 11%, and 3%, respectively; $p = 0.004$). For those who were delisted or died, underwent transplantation, or were awaiting transplantation, organ failures were dominated by respiratory (41%, 17%, and 3%, respectively; $p < 0.001$) and circulatory failures (42%, 16%, and 3%, respectively; $p < 0.001$). Liver transplantation-listed patients with end-stage liver disease and infection have a 42% risk of delisting/death within a 6-month period following admission. The number of organ failures was highly predictive of the risk for delisting/death.

In a UNOS study, the probability of survival for more than 30 days in those with three or more organ failures was less than 8%. However, among patients transplanted within 30 days, the survival at one-year ranged from 84% with three organ failures to 81% with 5-6 organ failures [18].

In another UNOS database study, mechanical ventilation at liver transplantation (hazard ratio [HR]), donor risk index above 1.7 (HR, 1.22), and liver transplantation within 30 days of listing (HR, 0.89) are independently associated with survival for 1-year after liver transplantation [16].

Can we define a limit above which transplantation is futile?

Futile transplantation is transplantation that is “pointless”. Essentially this means outcome with transplantation will be poor. Liver transplantation requires careful selection at all levels of evaluation. Data are typically derived from patients listed for liver transplantation. Such patients are selected and do not represent the broad cadre of all patients with end-stage liver disease. Even among listed patients, not all are eventually transplanted. In fact, only approximately 50% of listed patients are transplanted, the rest have died, are too sick to transplant, or continue to wait for a transplant. There are also major subjective elements in the selection of patients, the most common being the “eye-ball test”. Assessment of frailty and sarcopenia is a step in the right direction in making an objective

assessment of suitability for transplantation. The only definite way of determining transplant futility is from a randomised trial such that a MELD or ACLF score can be obtained that determines transplant futility. Current data that are largely retrospective suggest that carefully selected patients with MELD score ≥35 or ACLF-3 may have a reasonably good post-transplant survival. The corollary to this is that the majority of patients with ACLF-3 or MELD scores in the 40 range may not do well with a transplant.

References

1. Sarin SK, Kedarisetty CK, Abbas Z, Amarapurkar D, Bihari C, Chan AC, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the Study of the Liver (APASL) 2014. Hepatol Int 2014;8:453-71.
2. Sarin SK, Kumar A, Almeida JA, Chawla YK, Fan ST, Garg H, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the study of the liver (APASL). Hepatol Int 2009;3:269-82.
3. Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology 2013;144:1426-37, 1437 e1-9.
4. Bajaj JS, O'Leary JG, Reddy KR, Wong F, Biggins SW, Patton H, et al. Survival in infection-related acute-on-chronic liver failure is defined by extrahepatic organ failures. Hepatology 2014;60:250-6.
5. Jalan R, Gines P, Olson JC, Mookerjee RP, Moreau R, Garcia-Tsao G, et al. Acute-on chronic liver failure. J Hepatol 2012;57:1336-48.
6. Silva PE, Fayad L, Lazzarotto C, Ronsoni MF, Bazzo ML, Colombo BS, et al. Single-centre validation of the EASL-CLIF consortium definition of acute-on-chronic liver failure and CLIF-SOFA for prediction of mortality in cirrhosis. Liver Int 2015;35:1516-23.
7. O'Leary JG, Reddy KR, Garcia-Tsao G, Biggins SW, Wong F, Fallon MB, et al. NACSELD acute-on-chronic liver failure (NACSELD-ACLF) score predicts 30-day survival in hospitalized patients with cirrhosis. Hepatology 2018;67:2367-2374.
8. Allen AM, Kim WR, Moriarty JP, Shah ND, Larson JJ, Kamath PS. Time trends in the health care burden and mortality of acute on chronic liver failure in the United States. Hepatology 2016;64:2165-2172.
9. Arroyo V, Moreau R, Kamath PS, Jalan R, Gines P, Nevens F, et al. Acute-on-chronic liver failure in cirrhosis. Nat Rev Dis Primers 2016;2:16041.
10. Putignano A, Gustot T. New concepts in acute-on-chronic liver failure: Implications for liver transplantation. Liver Transpl 2017;23:234-243.
11. Finkenstedt A, Nachbaur K, Zoller H, Joannidis M, Pratschke J, Graziadei IW, Vogel W. Acute-on-chronic liver failure: excellent outcomes after liver transplantation but high mortality on the wait list. Liver Transpl 2013;19:879-86.
12. Gustot T, Fernandez J, Garcia E, Morando F, Caraceni P, Alessandria C, et al. Clinical Course of acute-on-chronic liver failure syndrome and effects on prognosis. Hepatology 2015;62:243-52.

13. Sharma P, Schaubel DE, Gong Q, Guidinger M, Merion RM. End-stage liver disease candidates at the highest model for end-stage liver disease scores have higher wait-list mortality than status-1A candidates. Hepatology 2012;55:192-8.

14. Chan AC, Fan ST. Criteria for liver transplantation in ACLF and outcome. Hepatol Int 2015;9:355-9.

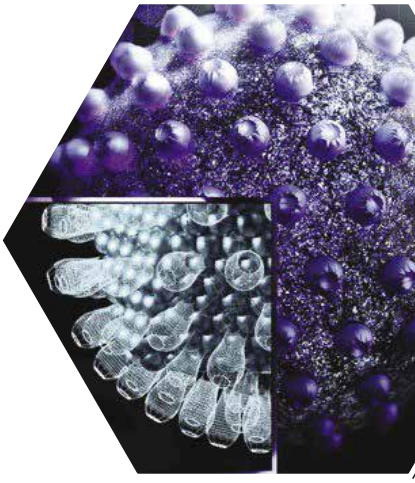
15. Reddy MS, Rajalingam R, Rela M. Liver transplantation in acute-on-chronic liver failure: lessons learnt from acute liver failure setting. Hepatol Int 2015;9:508-13.

16. Sundaram V, Jalan R, Wu T, Volk ML, Asrani SK, Klein AS, Wong RJ. Factors Associated with Survival of Patients With Severe Acute on Chronic Liver Failure Before and After Liver Transplantation. Gastroenterology 2018. pii: S0016-5085(18)35405-2. [Epub ahead of print].

17. Reddy KR, O'Leary JG, Kamath PS, Fallon MB, Biggins SW, Wong F, et al. High risk of delisting or death in liver transplant candidates following infections: Results from the North American Consortium for the Study of End-Stage Liver Disease. Liver Transpl 2015;21:881-8.

18. Thuluvath PJ, Thuluvath AJ, Hanish S, Savva Y. Liver transplantation in patients with multiple organ failures: Feasibility and outcomes. J Hepatol 2018;69:1047-1056.

Notes



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