

Best of EASL - Addis Ababa, Ethiopia 29 Sep to 01 Oct, 2016
Inaugural meeting of the Sub Saharan GI-Hepatology Working Group
Incorporating Best of AGA and Best of EASL

THE NEED OF A NEW PATHOPHYSIOLOGICAL CLASSIFICATION OF CIRRHOSIS

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The Current Perception of Chronic Liver Disease



Now There Are Many (Stages) Where Before There Was One: In Search of a Pathophysiological Classification of Cirrhosis

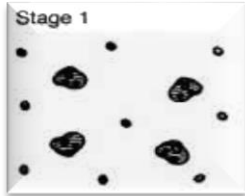
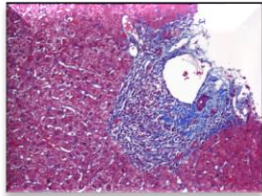
HEPATOLOGY, Vol. 51, No. 4, 2010

Guadalupe Garcia-Tsao,¹ and Scott Friedman,² John Iredale,³ and Massimo Pinzani⁴

	F1-F3		F4 (Cirrhosis)	
<u>Histological</u>				
<u>Clinical</u>	<i>Non-cirrhotic</i>	<i>Compensated</i>	<i>Compensated</i>	<i>Decompensated</i>
Symptoms	None	None (no varices)	None (varices present)	Ascites, VH, Encephalopathy
Sub-stage	-	Stage 1	Stage 2	Stages 3,4,5*
<u>Hemodynamic</u> (HVPG, mmHg)	>6	>10	>12	
<u>Biological</u>	<i>Fibrogenesis and Angiogenesis</i>	<i>Scar and X-linking</i>	<i>Thick (acellular) scar and nodules</i>	<i>Insoluble scar</i>

*G. D'Amico, AASLD 2011 PGC

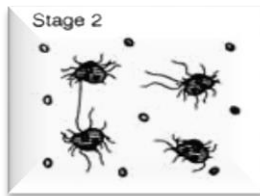
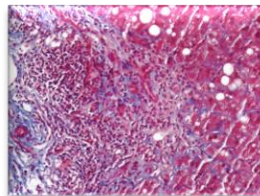
The Progression of Chronic Hepatitis C and the METAVIR Score



F1

PORTAL FIBROSIS

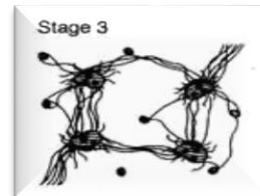
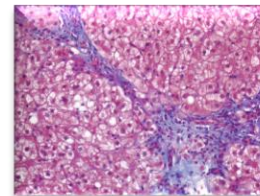
Mild fibrous expansion of portal tracts



F2

PERIportal FIBROSIS

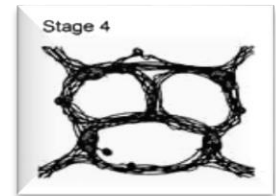
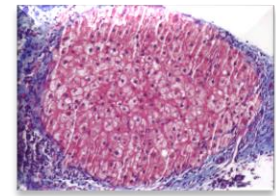
Rare portal-portal septa



F3

SEPTAL FIBROSIS

Portal-portal linkage



F4

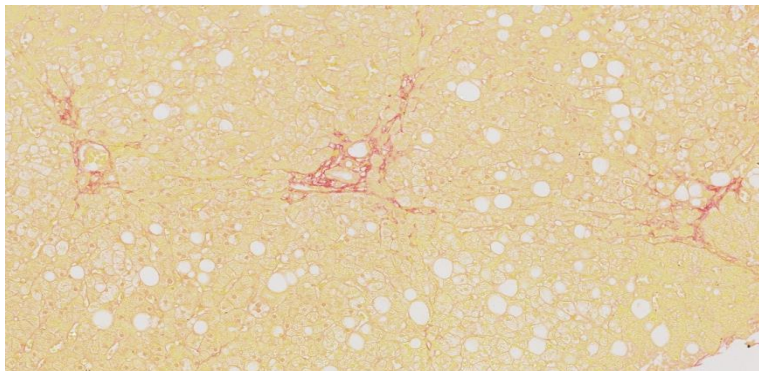
CIRRHOSIS

Bridging fibrosis and nodular regeneration

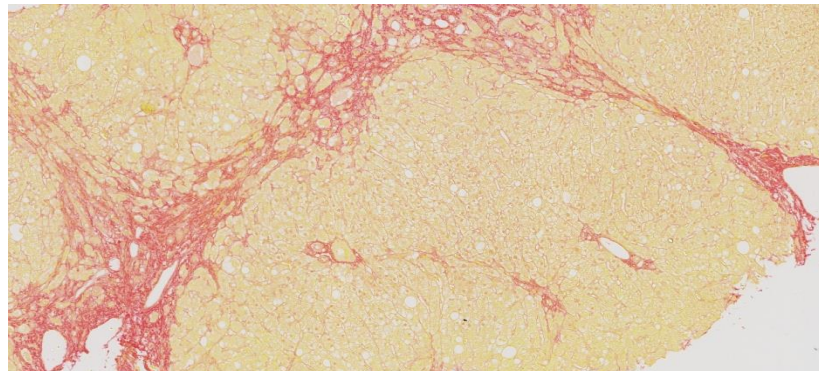
F4 is WRONGLY considered an END-STAGE

Collagen Proportionate Area (CPA)

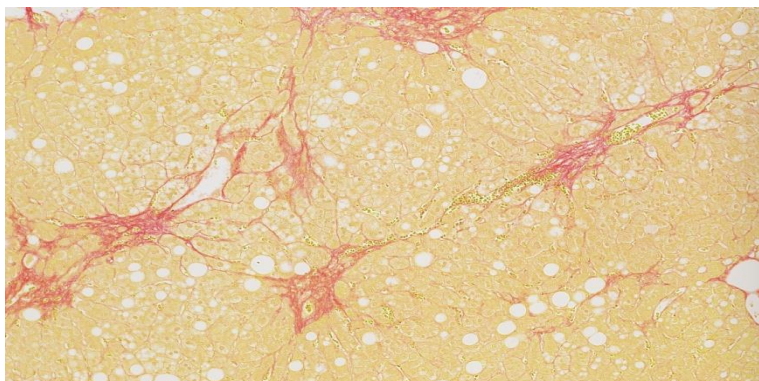
Courtesy of Andrew Hall, Liver Pathology Royal Free Hospital



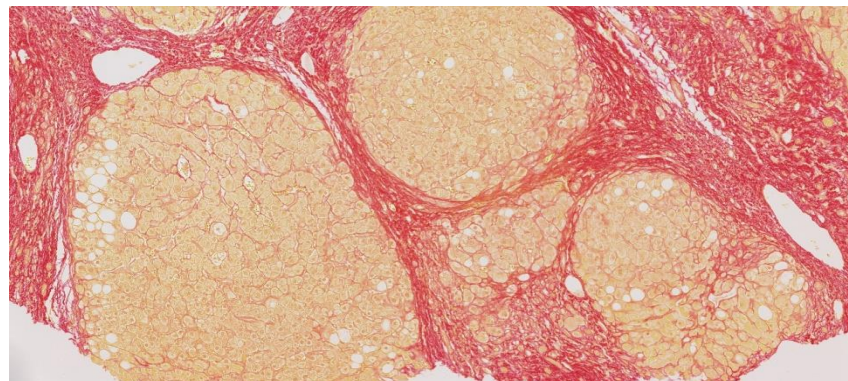
MILD: Ishak 1/2 CPA: 0.17%



SEVERE: Ishak 5 CPA: 11.3%



MODERATE: Ishak 3/4 CPA: 5.7%



VERY SEVERE: Ishak 6 CPA: 31%

The Diversity of Chronic Liver Diseases



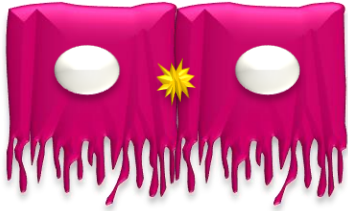
ETIOLOGY !!

Etiology has a relevant impact on disease progression (fibrogenesis) and regression (fibrolysis)

Different etiologies result in different patterns of fibrosis development

Etiology influences the prevailing pro-fibrogenic mechanism(s)

PREVALENT MECHANISMS OF FIBROGENESIS IN DIFFERENT CLDs

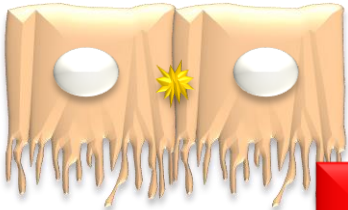


Chronic direct/indirect
damage (Viral, Autoimmune)



Chronic activation of the
wound healing process

Inflammation is a key feature of fibrogenesis

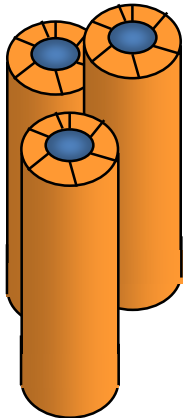


Chronic Toxic Damage and/or
metabolic overload (ETOH
Abuse, metals, steatohepatitis)



Oxidative stress

Fibrogenesis is, at least in part, independent of inflammation



Ductular reaction /
chronic cholestasis



**Role of bile acids/bile acid
receptors in the regulation of
inflammation?**

Oxidative Stress, “Pro-
inflammatory” Cholangiocytes,
Disturbance of the normal
Epithelial-Mesenchymal
Equilibrium (???)

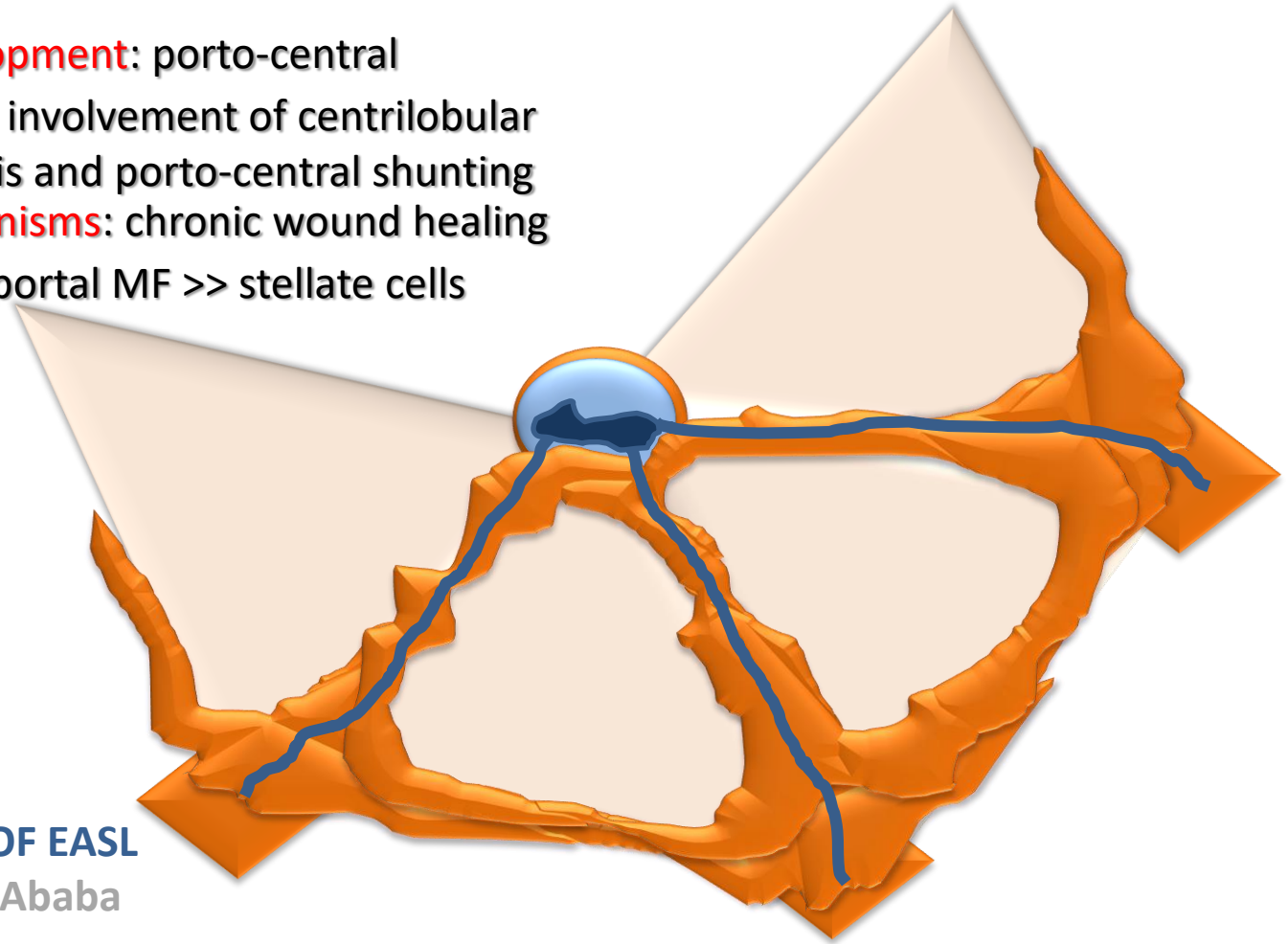
Post-Necrotic Fibrosis (e.g. Chronic HCV/HBV)

Pattern of Development: porto-central

Key Events: early involvement of centrilobular vein, angiogenesis and porto-central shunting

Prevalent Mechanisms: chronic wound healing

Fibrogenic cells: portal MF >> stellate cells



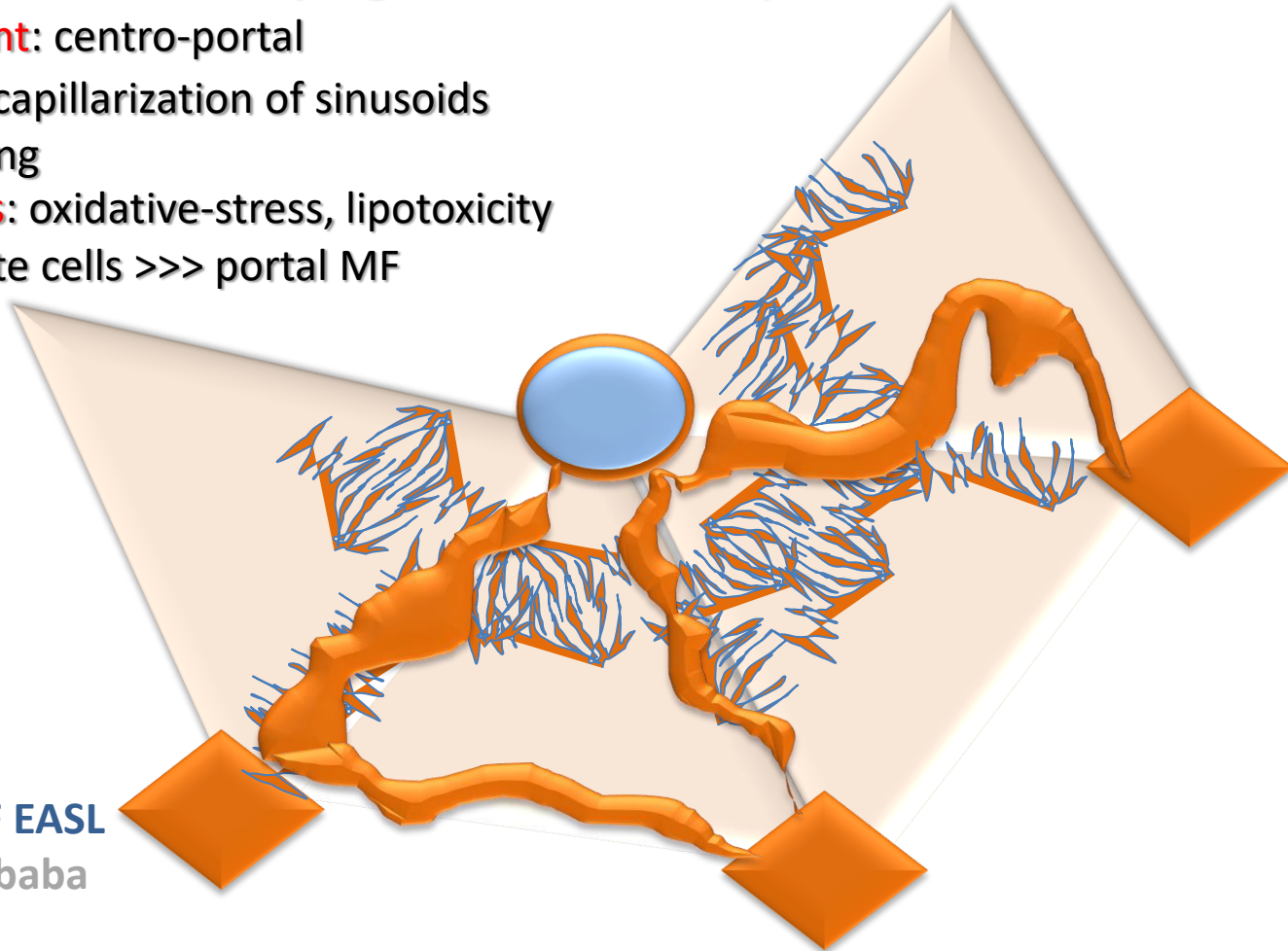
Pericellular Fibrosis and Capillarization of Sinusoids (e.g. ASH/NASH)

Pattern of Development: centro-portal

Key Events: extensive capillarization of sinusoids
precedes septal bridging

Prevalent Mechanisms: oxidative-stress, lipotoxicity

Fibrogenic cells: stellate cells >>> portal MF



The Diversity of Chronic Liver Diseases

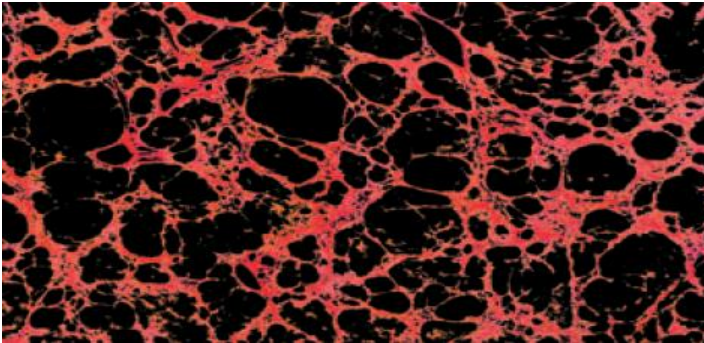
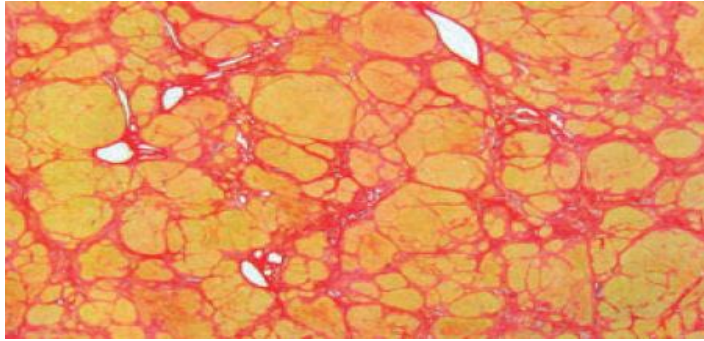


**ONE OR MANY
CIRRHOSIS ????**

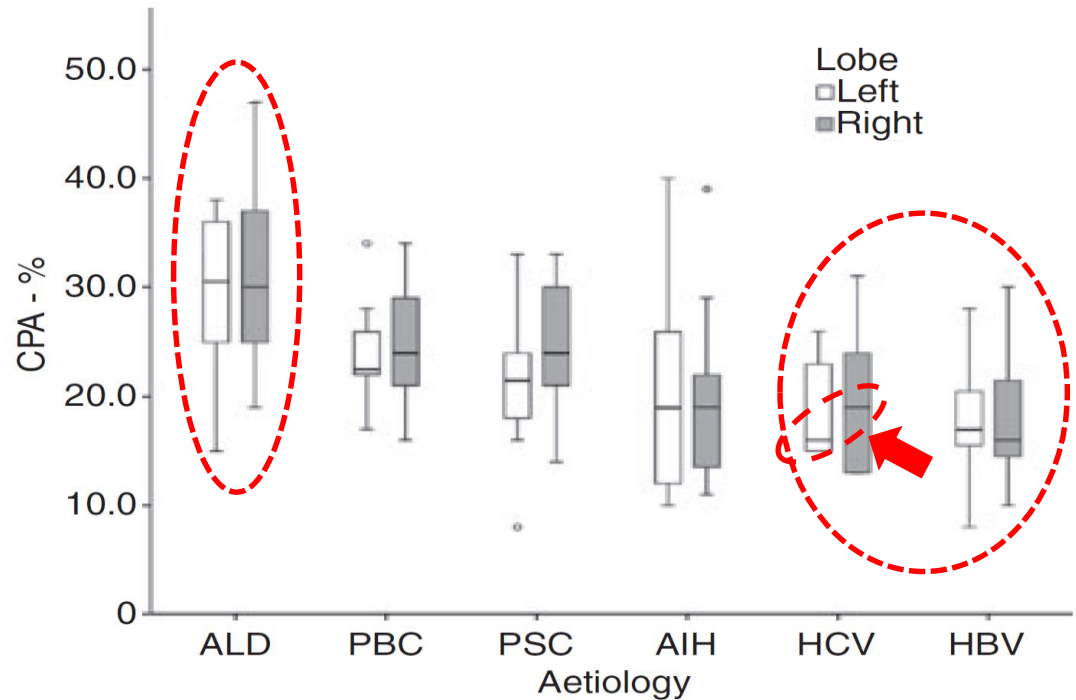
ETIOLOGY !!

Fibrosis Quantity and Distribution in Explanted Cirrhotic Liver Depending on Etiology

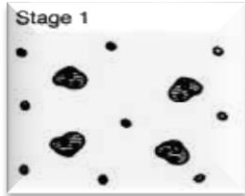
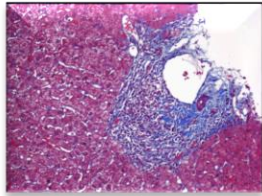
Hall A. et al., Histopathology 2012; 60:270-277



Measurement of Collagen
Proportionate Area (CPA)



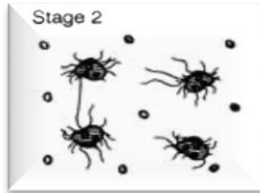
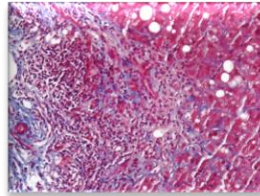
The Progression of Chronic Hepatitis C and the METAVIR Score



F1

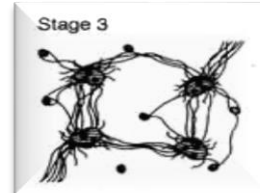
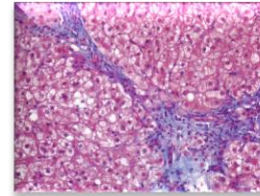
PORTAL FIBROSIS

Mild fibrous expansion of portal tracts



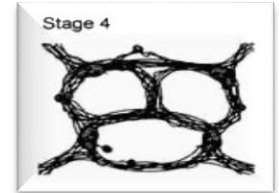
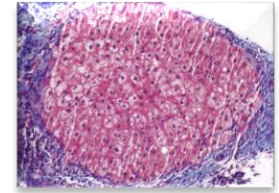
F2

Rare portal-portal septa



F3

Portal-portal links



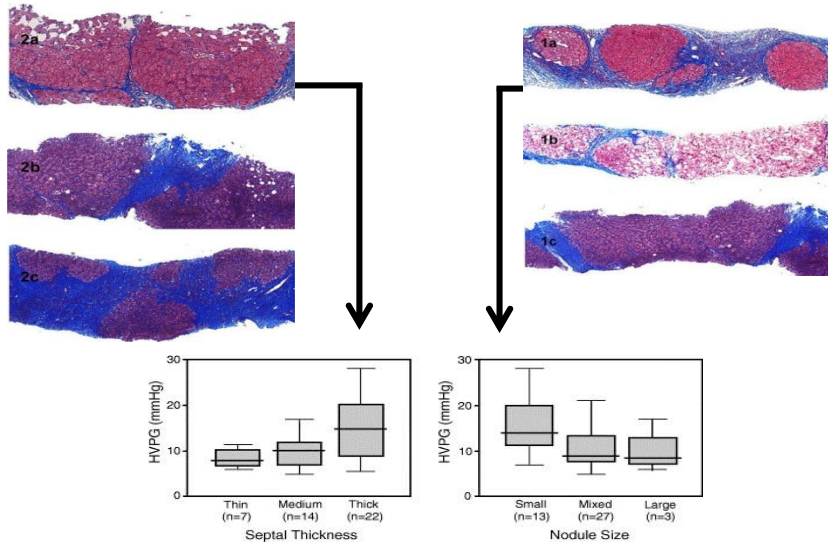
F4

CIRRHOSIS

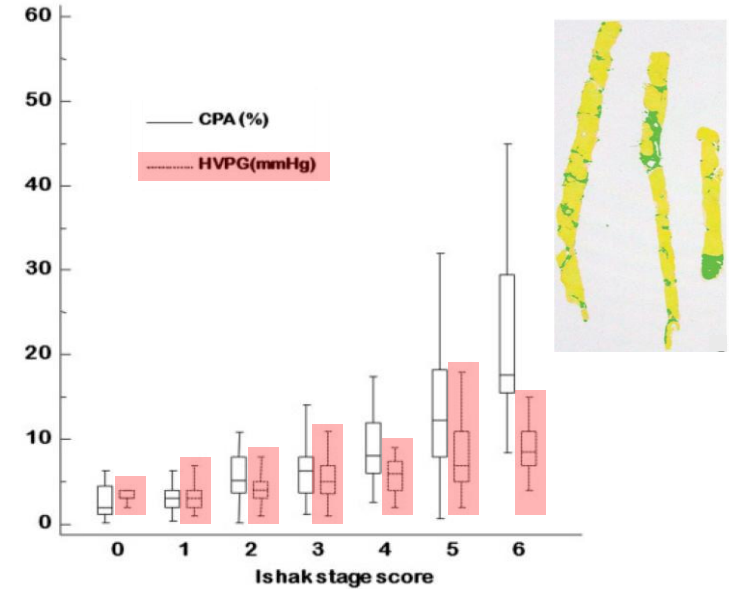
Bridging fibrosis and nodular regeneration

Beyond F4 !!

Morphology and Collagen Proportionate Area Correlate with Portal Hypertension



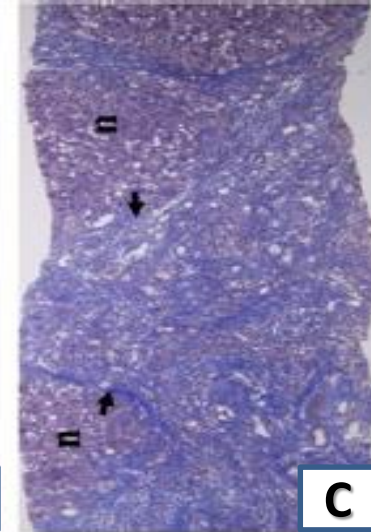
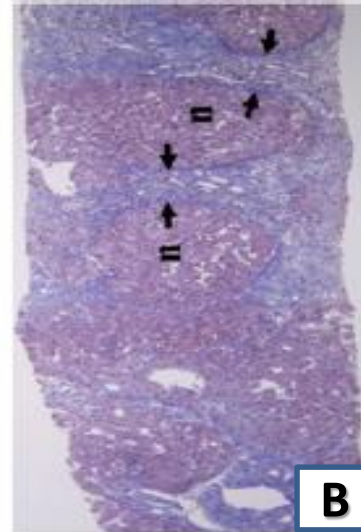
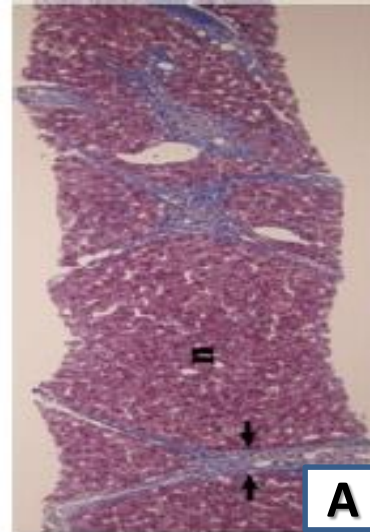
Nagula S et al., J. Hepatol. 2006; 44:111-117



Calvaruso V et al., Hepatology 2009; 49:1236-1244

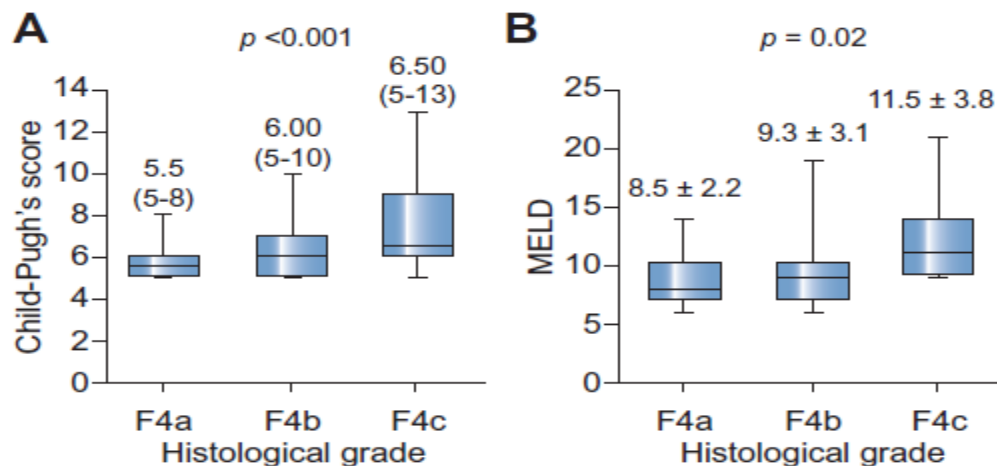
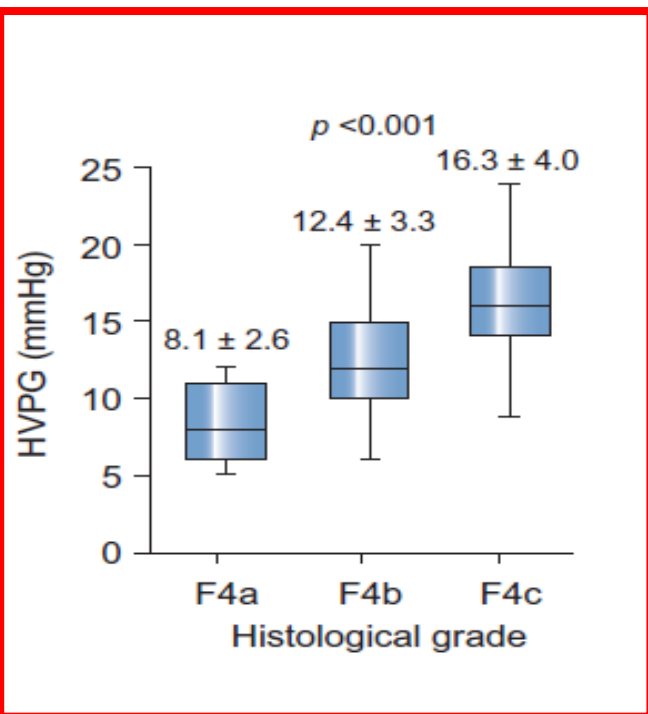


Stage	Name	Septa (thickness and number)	Criteria	score
0	No definite fibrosis			0
1	Minimal fibrosis	+/-	No septa or rare thin septum; may have portal expansion or mild sinusoidal fibrosis	1
2	Mild fibrosis	+	Occasional thin septa; may have portal expansion or mild sinusoidal fibrosis	2
3	Moderate fibrosis	++	Moderate thin septa; up to incomplete cirrhosis	3
4A	Cirrhosis, mild, definite, or probable	+++	Marked septation with rounded contours or visible nodules Most septa are thin (one broad septum allowed)	4
4B	Moderate cirrhosis	++++	At least two broad septa, but no very broad septa and less than half of biopsy length composed of minute nodules	5
4C	Severe cirrhosis	+++++	At least one very broad septum or more than half of biopsy length composed of minute nodules (micronodular cirrhosis)	6



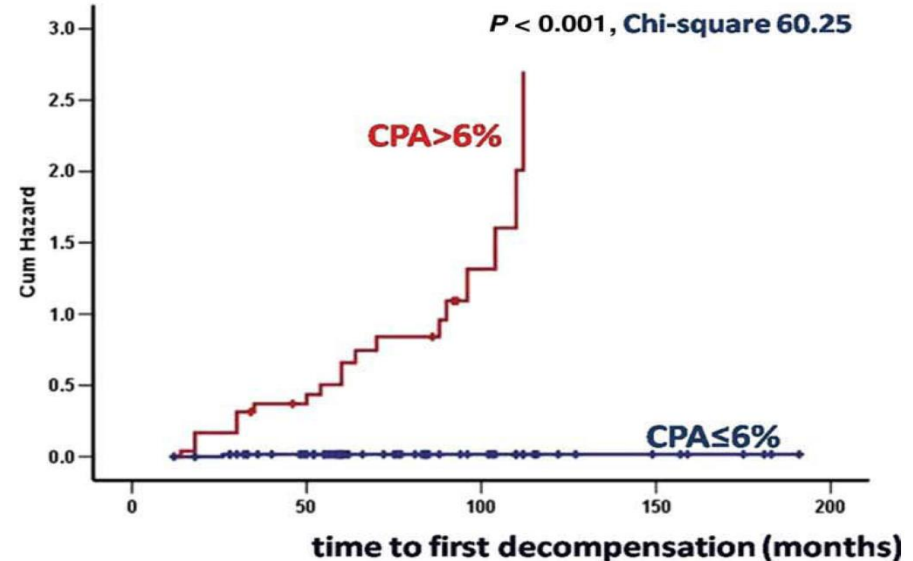
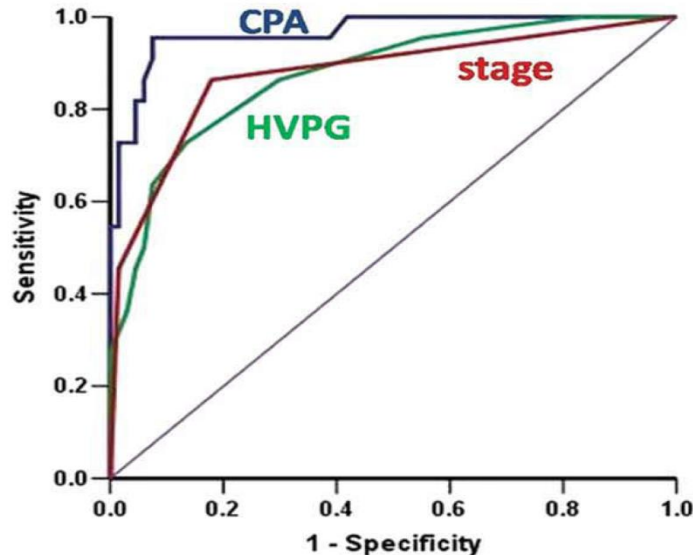
Histological subclassification of cirrhosis using the Laennec fibrosis scoring system correlates with clinical stage and grade of portal hypertension

Moon Young Kim^{1,†}, Mee Yon Cho^{2,†}, Soon Koo Baik^{1,*}, Hong Jun Park¹, Hyo Keun Jeon¹, Chong Kun Im¹, Chan Sik Won¹, Jae Woo Kim¹, Hyun Soo Kim¹, Sang Ok Kwon¹, Min Seob Eom², Seung Hwan Cha³, Young Ju Kim³, Sei Jin Chang⁴, Samuel S. Lee⁵



Digital Image Analysis of Liver Collagen Predicts Clinical Outcome of Recurrent Hepatitis C Virus 1 Year After Liver Transplantation

Pinelopi Manousou,^{1*} Amar P. Dhillon,^{2*} Graziela Isgro,¹ Vincenza Calvaruso,^{1,3} T.V. Luong,² Emmanuel Tsochatzis,¹ E. Xirouchakis,¹ G. Kalambokis,¹ Timothy J. Cross,¹ N. Rolando,¹ James O'Beirne,¹ David Patch,¹ D. Thornburn,¹ and Andrew K. Burroughs¹



Liver biopsy: 1 yr after OLT
Staging: Ishak's

Now There Are Many (Stages) Where Before There Was One: In Search of a Pathophysiological Classification of Cirrhosis

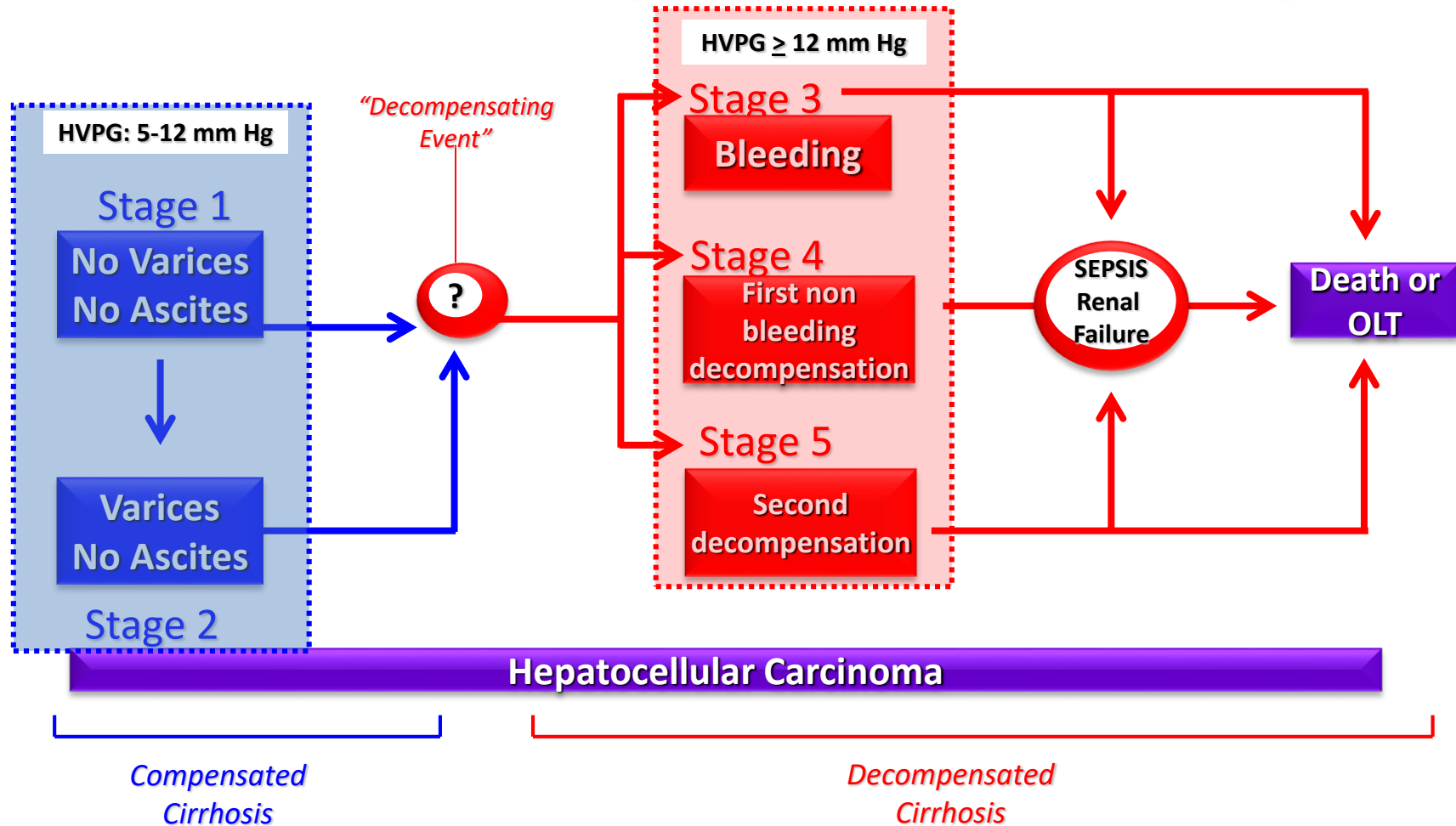
HEPATOLOGY, Vol. 51, No. 4, 2010

Guadalupe Garcia-Tsao,¹ and Scott Friedman,² John Iredale,³ and Massimo Pinzani⁴

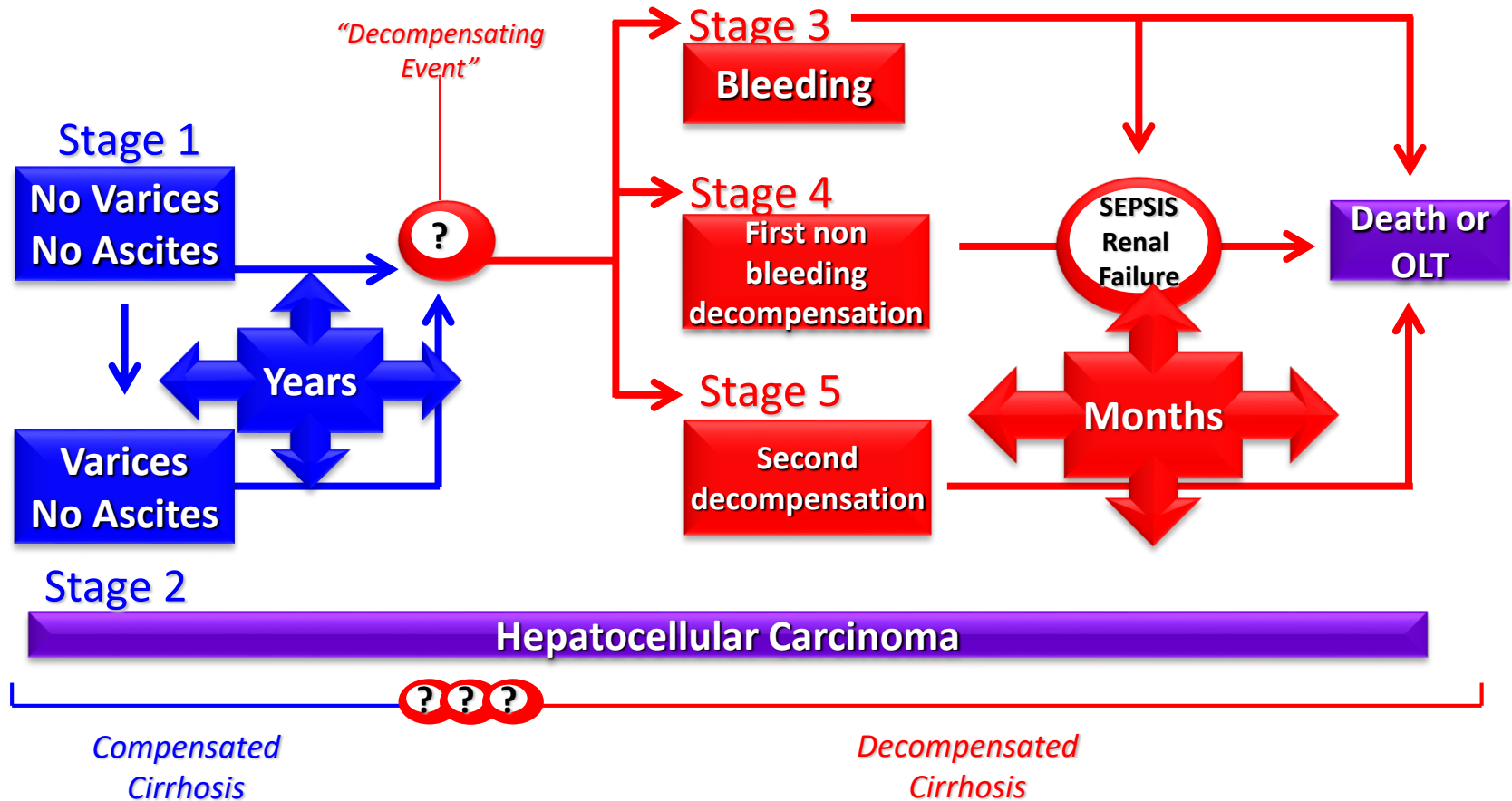
	F1-F3		F4 (Cirrhosis)	
<u>Histological</u>	<i>Non-cirrhotic</i>		<i>Compensated</i>	
<u>Clinical</u>	<i>None</i>		<i>Decompensated</i>	
Symptoms	None		None (varices present)	
Sub-stage	-		Stage 1	
<u>Hemodynamic</u> (HVPG, mmHg)	>6		>10	
<u>Biological</u>	<i>Fibrogenesis and Angiogenesis</i>		<i>Thick (acellular) scar and nodules</i>	
	<i>Scar and X-linking</i>		<i>Insoluble scar</i>	

*G. D'Amico, AASLD 2011 PGC

The Natural History of Cirrhosis: a Summary

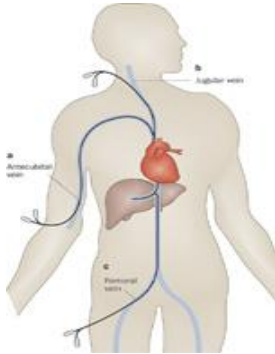


Compensated Cirrhosis a Clinical Stage with Very Limited Diagnostic Resources

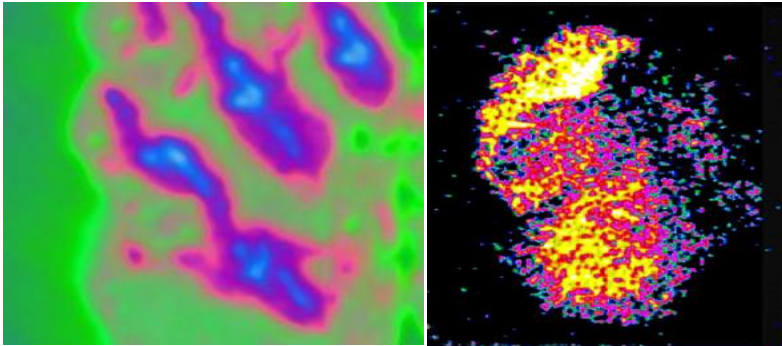




Clinical observation, tissue morphology



Measurement of portal pressure (HVPG) and liver tissue stiffness



Bio-imaging, functional imaging?

Now There Are Many (Stages) Where Before There Was One: In Search of a Pathophysiological Classification of Cirrhosis

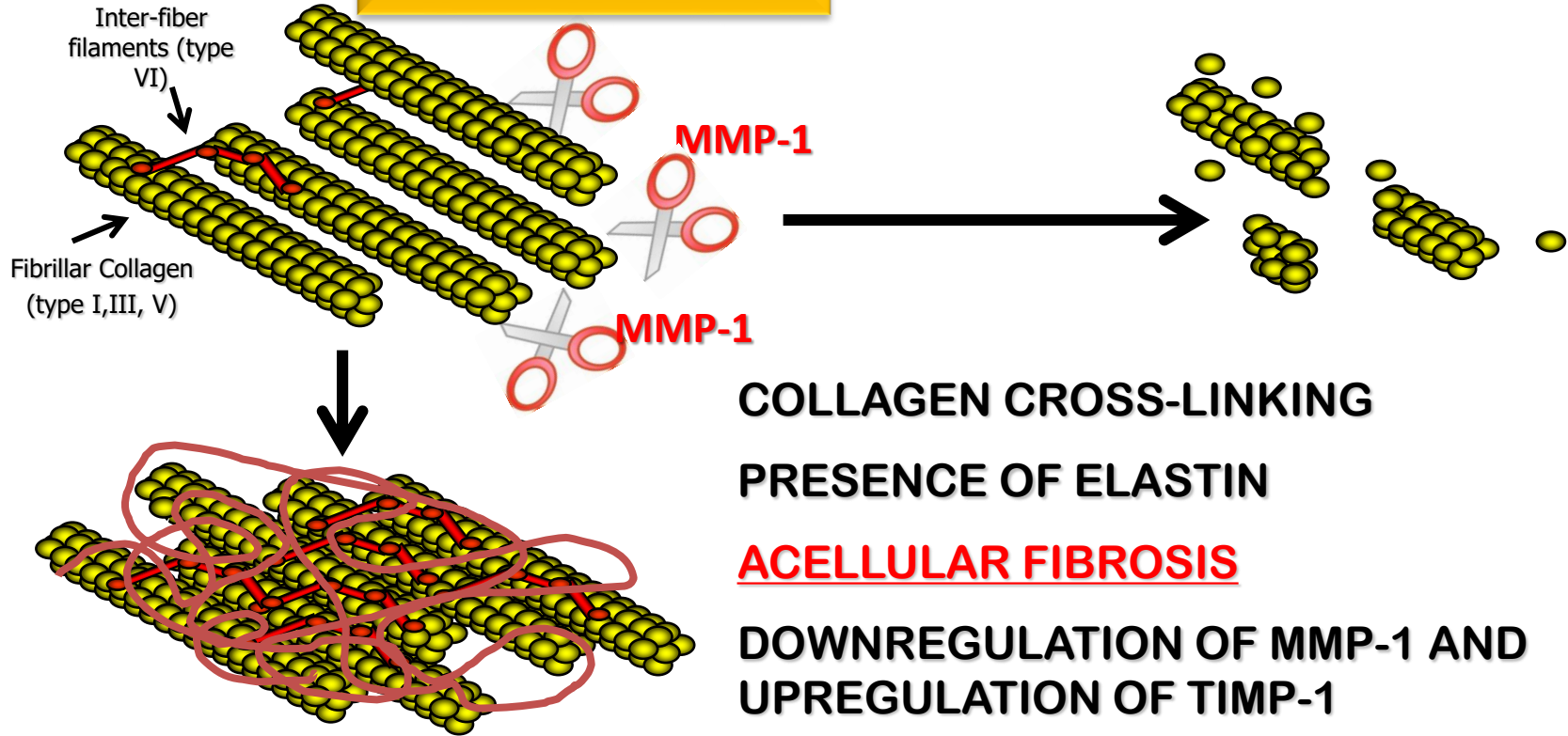
HEPATOLOGY, Vol. 51, No. 4, 2010

Guadalupe Garcia-Tsao,¹ and Scott Friedman,² John Iredale,³ and Massimo Pinzani⁴

	F1-F3		F4 (Cirrhosis)	
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<u>Clinical</u>	<i>Non-cirrhotic</i>	<i>Compensated</i>	<i>Compensated</i>	<i>Decompensated</i>
Symptoms	None	None (no varices)	None (varices present)	Ascites, VH, Encephalopathy
Sub-stage	-	Stage 1	Stage 2	Stages 3,4,5*
<u>Hemodynamic</u> (HVPG, mmHg)		>6	>10	>12
<u>Biological</u>	<i>Fibrogenesis and Angiogenesis</i>	<i>Scar and X-linking</i>	<i>Thick (acellular) scar and nodules</i>	<i>Insoluble scar</i>
	REVERSIBLE		PARTIALLY REVERSIBLE	
			IRREVERSIBLE	

Biochemical and Biological Evolution of Fibrillar Extracellular Matrix

EARLY FIBROSIS



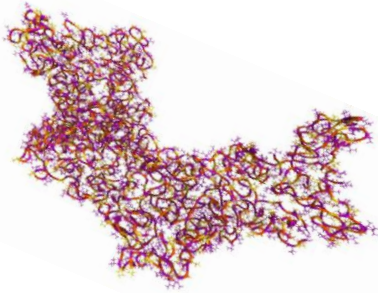
ESTABLISHED FIBROSIS

ACELLULAR FIBROSIS

DOWNREGULATION OF MMP-1 AND
UPREGULATION OF TIMP-1

INCREASE IN TISSUE RIGIDITY AND
TENSION

Elastin: a Marker of Fibrosis Aging and Irreversibility



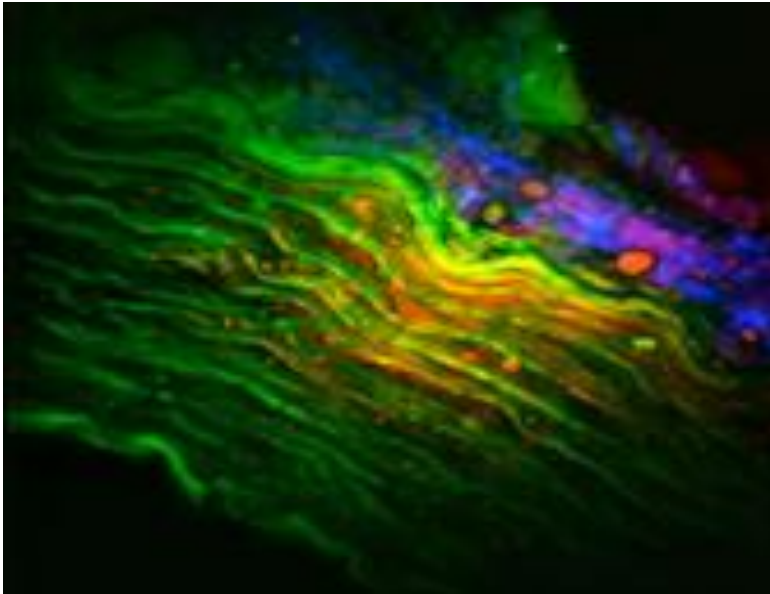
Non linear Optics (NLO)

Some NLO signals are intrinsically biochemically specific to extracellular matrix components. No need for staining!!

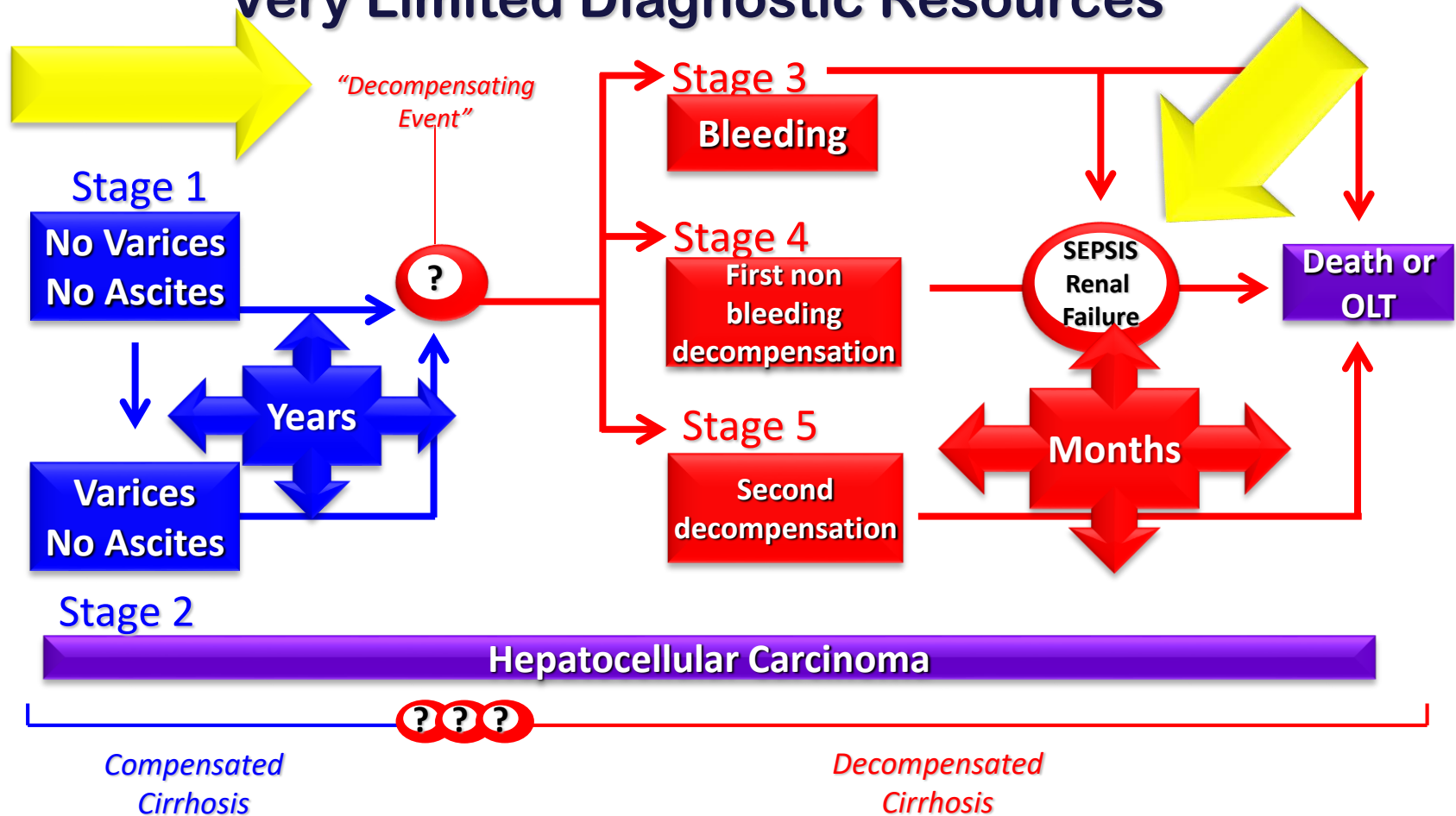
Examples include:

Strong TPEF originating from elastin fibers

Intense SHG from type-I fibrillar collagen



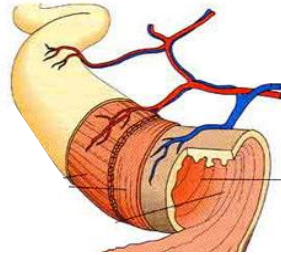
Compensated Cirrhosis a Clinical Stage with Very Limited Diagnostic Resources



Cirrhosis Causes Structural and Functional Changes in the Mucosa of the Small Intestine

CIRRHOSIS

Changes in Microbiota
Bacterial Overgrowth
Decreased Bile Acids
Mucosal Injury (ETOH)
Mesenteric Vein Congestion
Immunosuppression
Obesity/Overweight
High Fat Diet

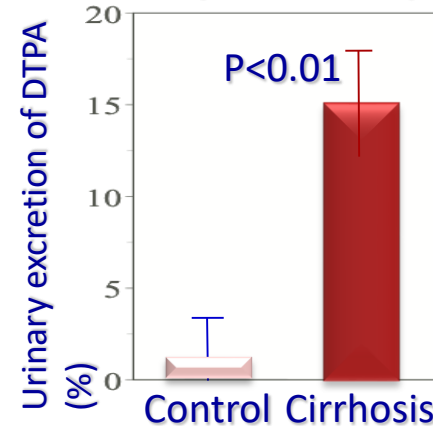


Increased *Pathogen-Associated Molecular Patterns* “PAMPs”
(i.e. LPS) in the portal circulation

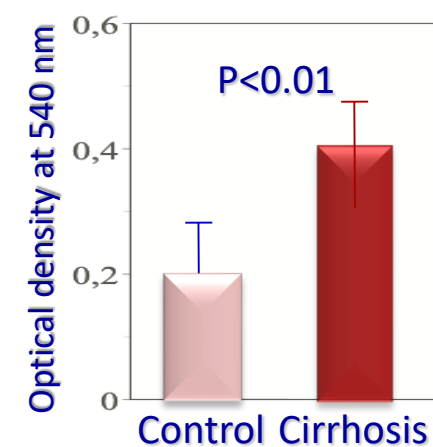
Functional abnormalities of the mucosa of the small intestine of rats with cirrhosis:

- oxidative stress, ↑ xanthine oxidase activity
- lipid peroxidation of brush border membrane
- ↑ sugar content of brush border membrane
- abnormal intestinal transport

Intestinal permeability



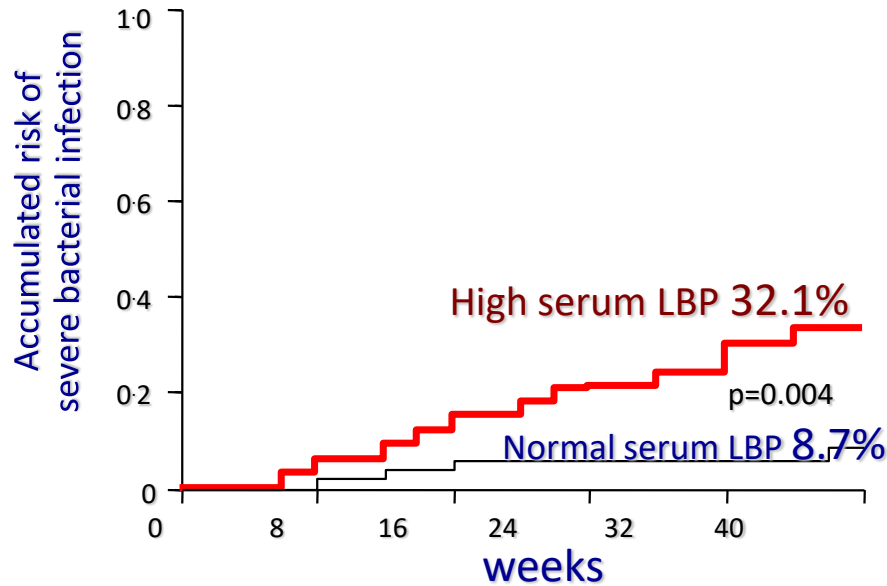
Bacterial adherence to BBM



Ramachandran A. et al. Hepatology 2002
Chiva M. et al. Eur J Gastroenterol Hepatol 2003
Perez-Páramo M et al. Hepatology 2003
Natarajan SK et al. Hepatology 2006

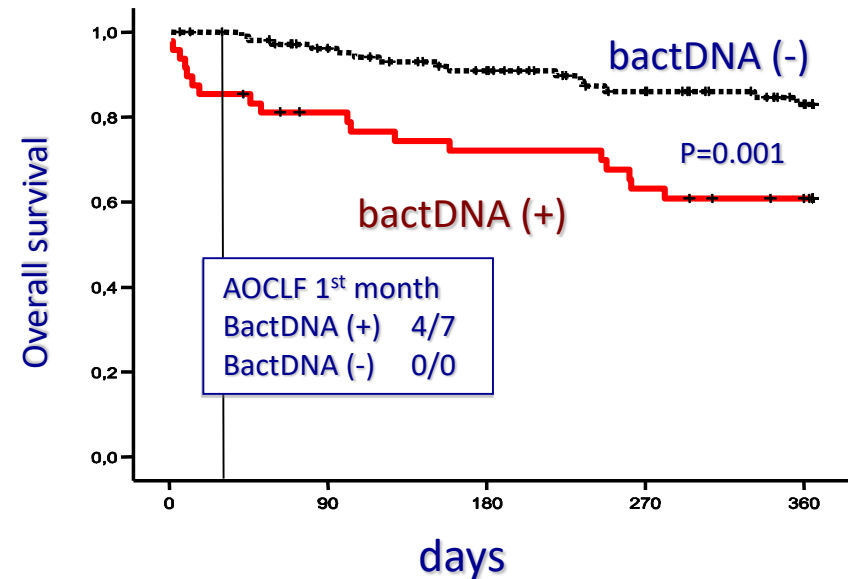
Different Outcome of Cirrhotic Patients with High LBP or Presence of bactDNA in Serum

Increased risk of spontaneous bacterial infection in patients with cirrhosis and high LBP



Albillos A et al. Lancet 2004

Increased risk of death, but not of SBP, in patients with cirrhosis and bacterial DNA



Zapater P et al. Hepatology 2008

Beyond “Cirrhosis”

A Proposal From the International Liver Pathology Study Group

Prodromos Hytioglou, MD,¹ Dale C. Snover, MD,² Venancio Alves, MD,³ Charles Balabaud, MD,⁴ Prithi S. Bhathal, MD,⁵ Paulette Bioulac-Sage, MD,⁶ James M. Crawford, MD,⁷ Amar P. Dhillon, MD,⁸ Linda Ferrell, MD,⁹ Maria Guido, MD,¹⁰ Yasuni Nakanuma, MD,¹¹ Valerie Paradis, MD,¹² Alberto Quaglia, MD,¹³ Neil D. Theise, MD,¹⁴ Swan N. Thung, MD,¹⁵ Wilson M.S. Tsui, MD,¹⁶ and Dirk J. van Leeuwen, MD¹⁷

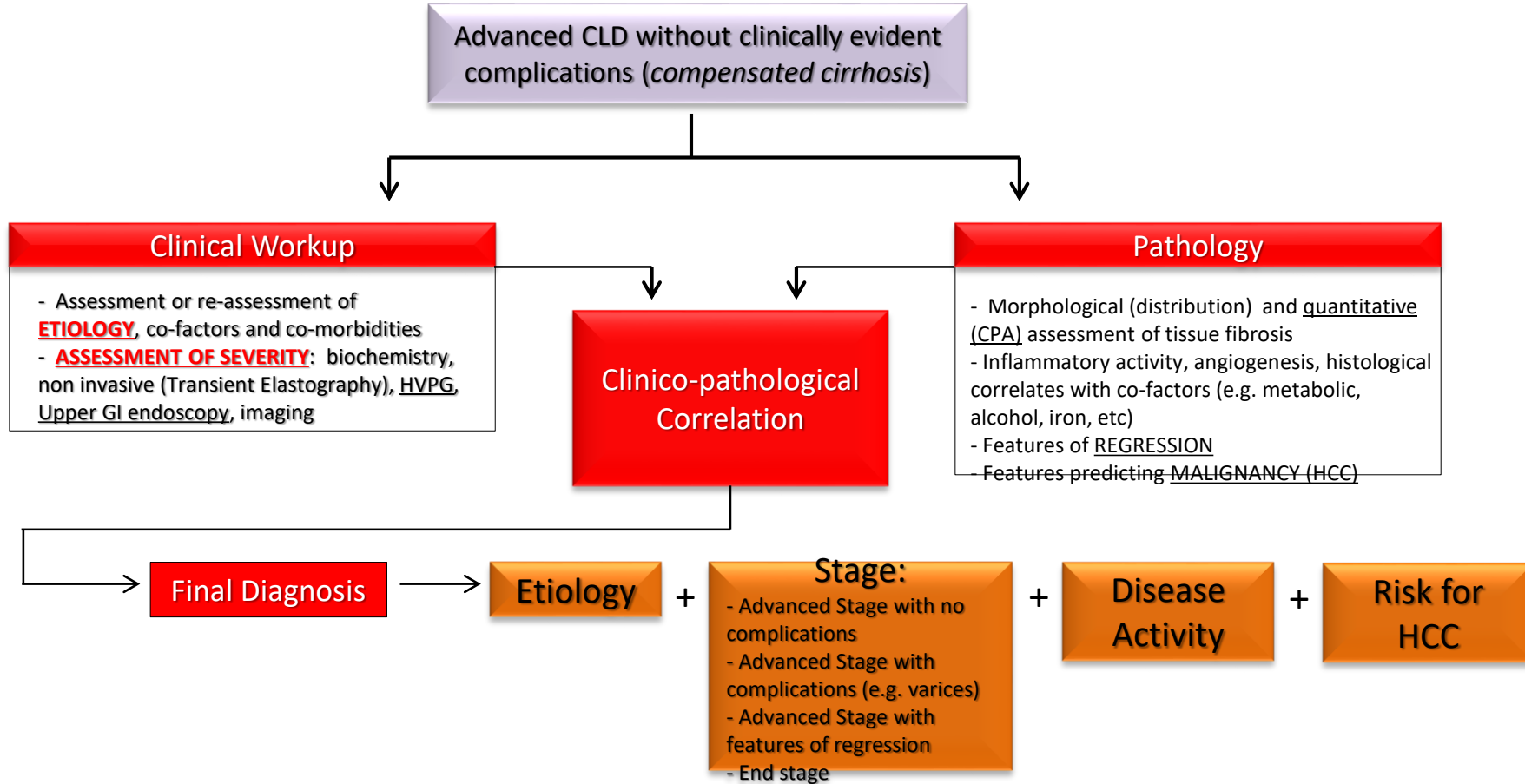


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Am J Clin Pathol 2012;137:5-9

DOI: 10.1309/AJCP2T2OHTAPBTMP

Beyond Cirrhosis.....





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