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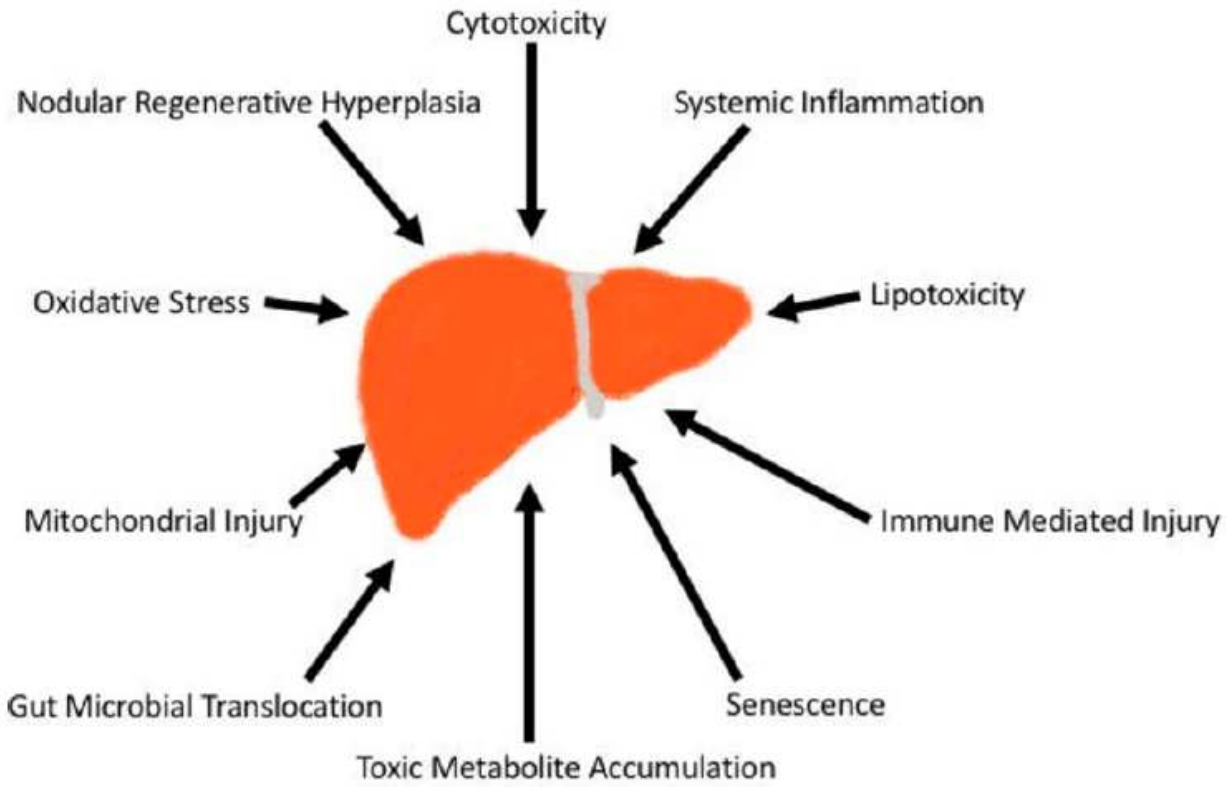
Sistema Socio Sanitario
Regione Lombardia

Evoluzione delle co-morbidità non infettive dopo eradicazione di HCV

Raffaele Bruno, MD

UNIVERSITÀ DI PAVIA


Cytotoxicity
Nodular Regenerative Hyperplasia
Systemic Inflammation
Oxidative Stress
Lipotoxicity
Mitochondrial Injury
Immune Mediated Injury
Gut Microbial Translocation
Senescence
Toxic Metabolite Accumulation

EDITORIAL

NAFLD

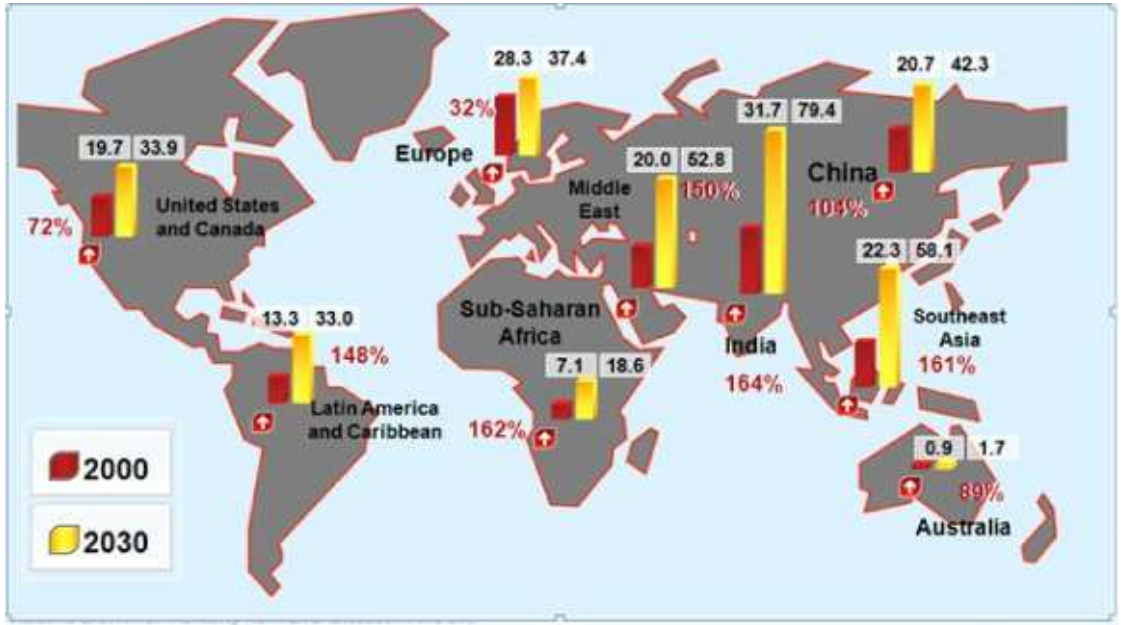
NAFLD—the next global epidemic

The future is fatty. Dramatic changes in the lifestyle and diet of the global population are fuelling a worldwide epidemic of obesity and the increasing prevalence of NAFLD. Experts now predict that the next epidemic in chronic liver disease will be a direct result of this increased incidence of obesity and NAFLD. *Nature Reviews Gastroenterology & Hepatology* therefore commissioned a special focus issue on NAFLD to provide a comprehensive overview that covers the breadth of basic, translational and clinical research on this important condition.

the environment (diet in particular) and, as discussed further by Wajahat Mehal, the gut microbiota.

From this improved understanding in pathogenesis, it is clear that NAFLD is a complex disease, with considerable variation in severity amongst individuals. In their Review, Quentin Anstee and Christopher Day discuss the underlying genetics of NAFLD and argue that genetic variation might account for the heterogeneity in disease phenotype and progression. Tackling the issue of progression, Anna Mae Diehl *et al.* provide explanations as to how NAFLD-related cirrhosis can ultimately progress

> "...NAFLD could almost be considered the human equivalent of foie gras..."



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Nature Reviews Gastroenterology & Hepatology 10, 621 (2013)

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The epidemiology of non-alcoholic fatty liver disease

Prevalence of NAFLD in different population in Europe

	Case Identification	Prevalence NAFLD
14 EU Countries	FLI	33% (adults)
Germany	US and LE	2% (36% in obese children)
Germany	US	30% (adults)
Greece	Histology	31% (adults)
Italy	US	26% (adults)
Italy	US	12.5% (adolescents)
Italy	US	44% (obese children)
Italy	US	69.5% (diabetic pts)
Romania	US	20% (adults)
Spain	US	25.8% (adults)
UK	US	46.2% (diabetic pts)

FLI, fatty liver index; US, ultrasound; LE, liver enzymes.

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Stefano Bellentani. Liver International 2017; 37 (Suppl. 1): 81–84

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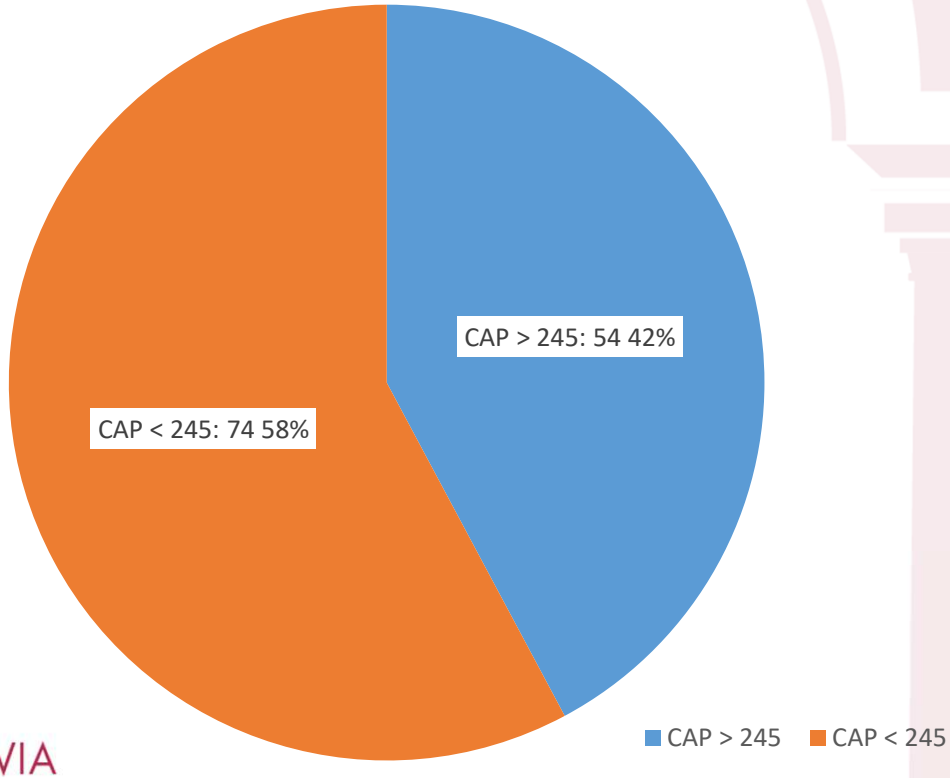
NAFLD, evaluated by Fibroscan Transient Elastography with Controlled Attenuation Parameter and considering a cut off of 245 dB/m is common among HIV patients of our cohort occurring with a prevalence of 42% (54/128).



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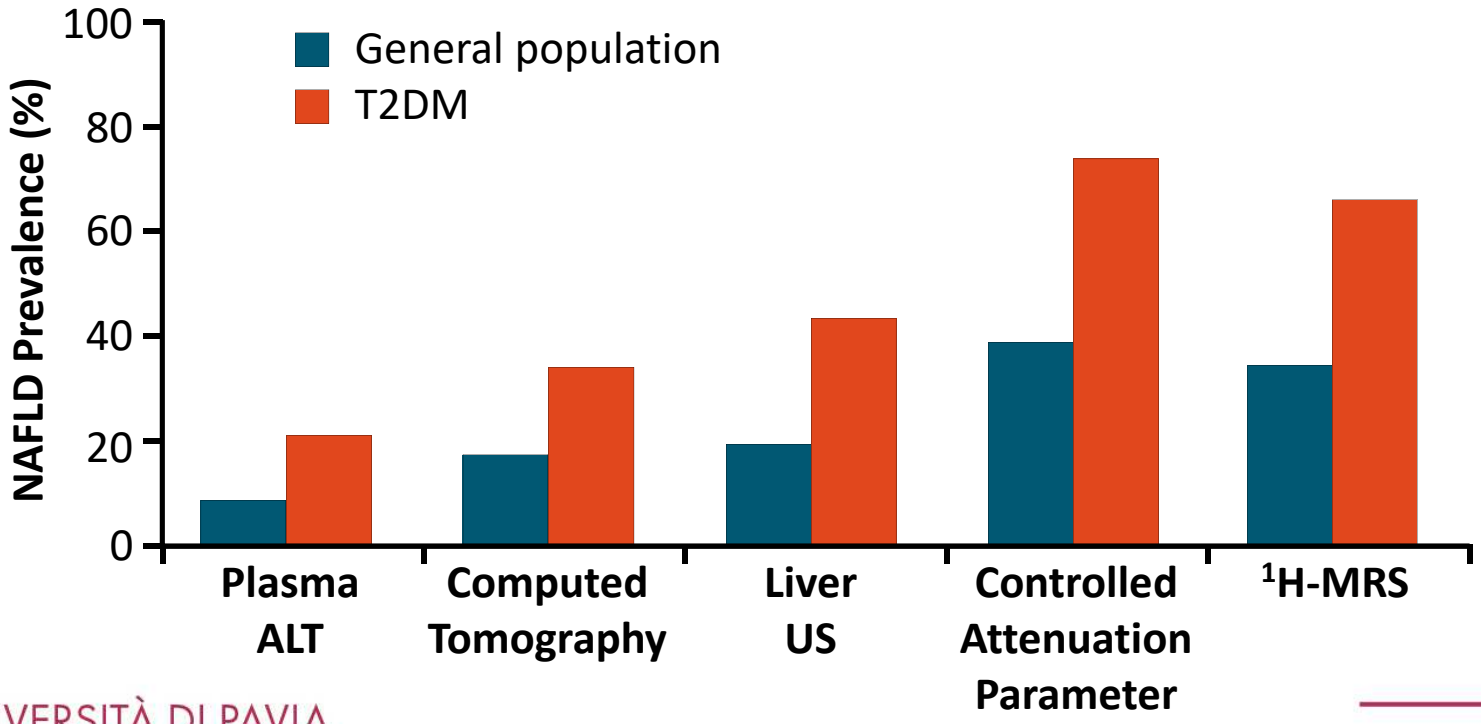
Prevalence of NAFLD in the general population and in patients with T2DM according to different diagnostic tools

The presence of T2DM significantly increases the prevalence of NAFLD in comparison of general population



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Bril. Diabetes Care. 2017;40:419.

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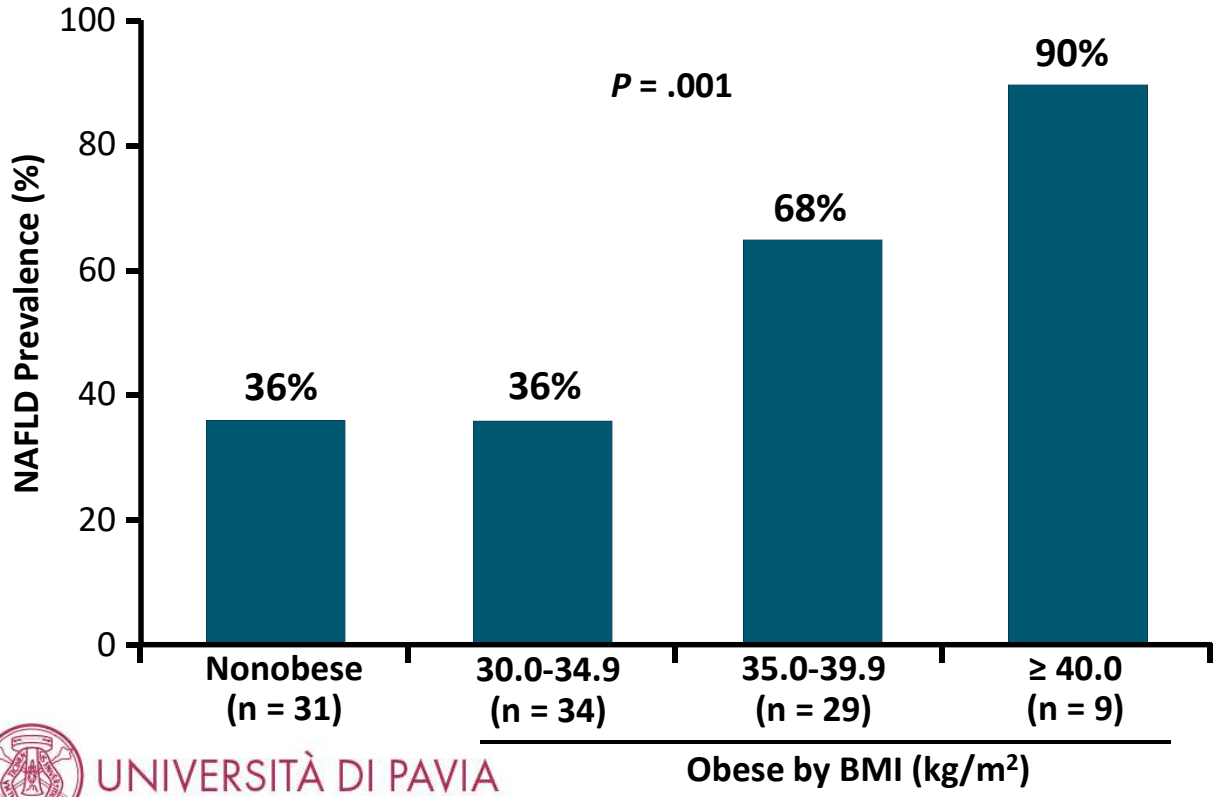
Prevalence of NAFLD in Patients With Type 2 diabetes and Normal Plasma AST or ALT

- The prevalence of NAFLD is higher also in overweight/obese patients with T2DM and normal aminotransferases. (N = 103)



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Portillo-Sanchez. J Clin Endocrinol Metab. 2015;100:2231. Stål. World J Gastroenterol. 2015;21:11077.

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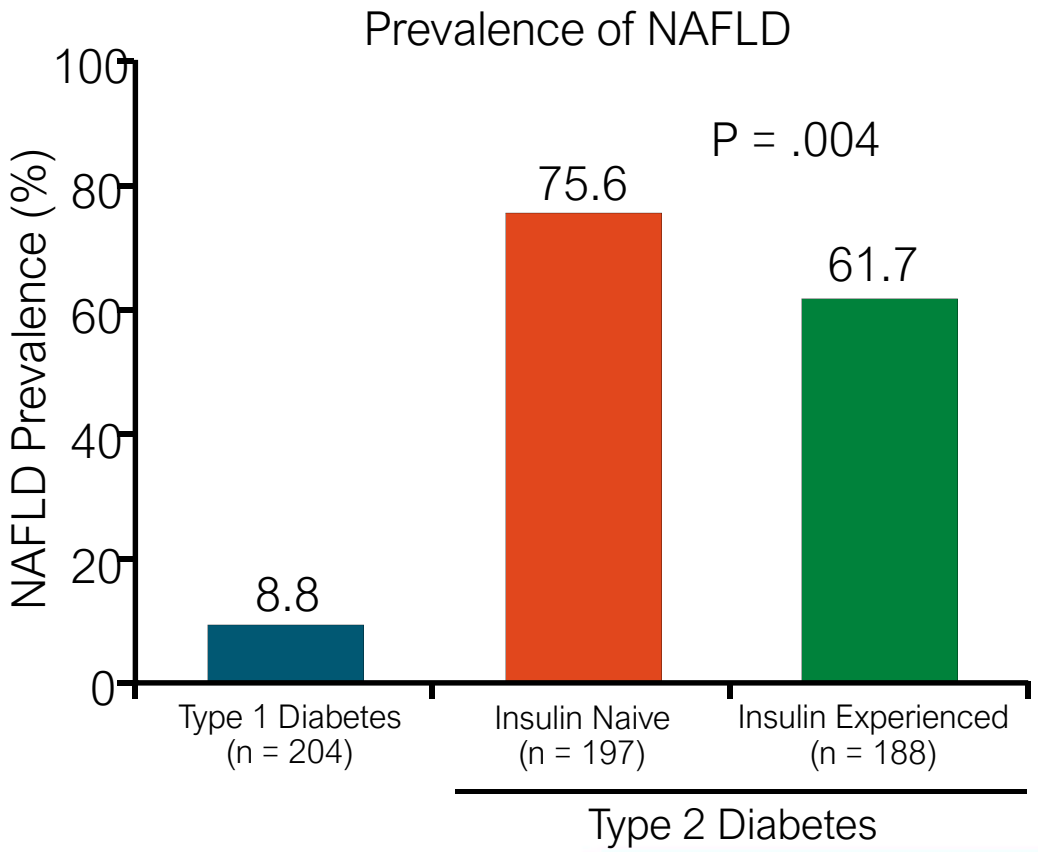
Prevalence of NAFLD in Patients With Type 1 and 2 Diabetes

- Post hoc analysis of baseline data from 4 phase III trials (N = 589)
- The prevalence of NAFLD is low in T1D patients but high in T2D patients
- NAFLD is more frequent in insulin-naïve T2D patients compared to those previously treated with insulin



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Cusi. Diabetes Obes Metab. 2017;19:1630.

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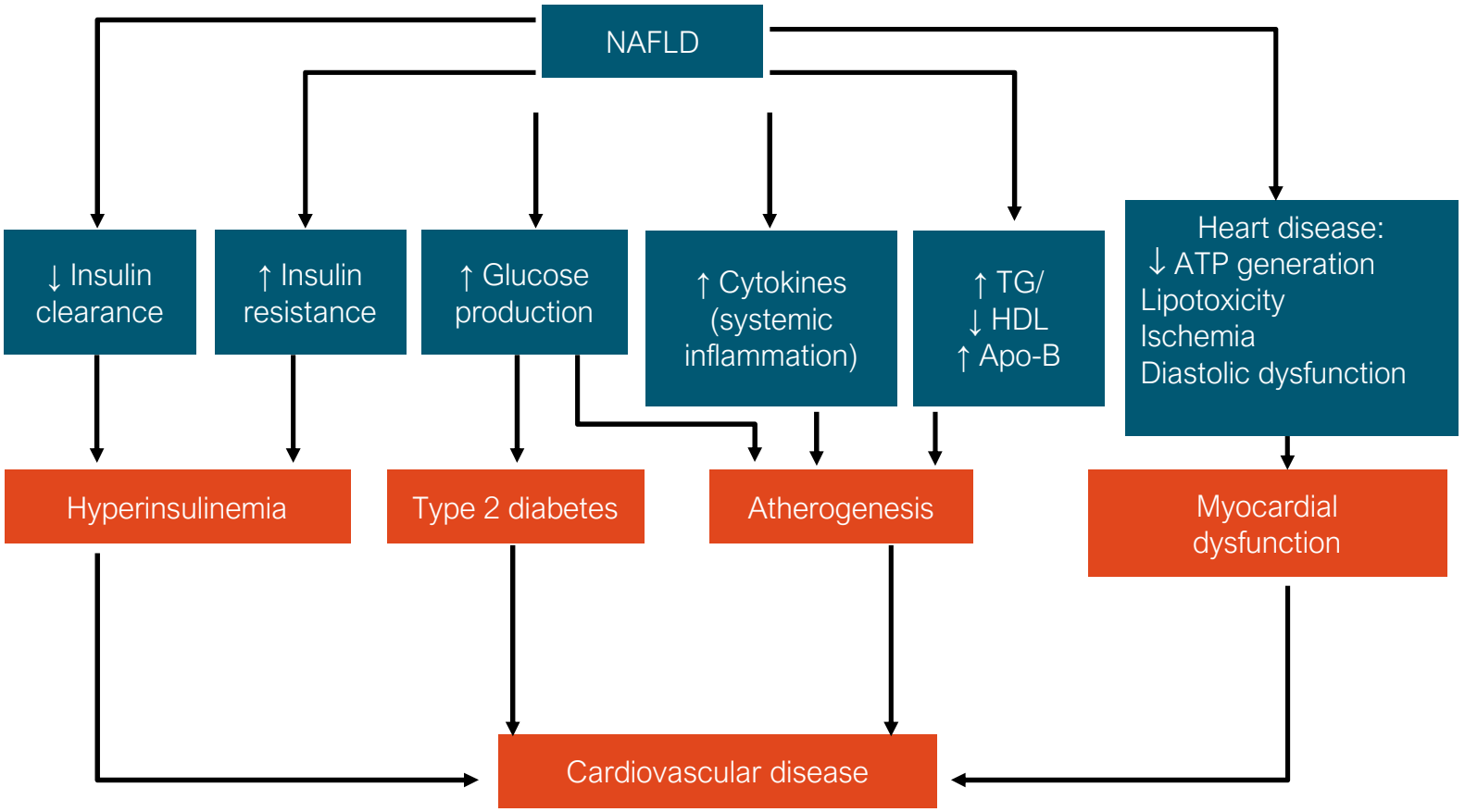
Metabolic Consequences of NAFLD



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Cusi. Gastroenterology. 2012;142:711.

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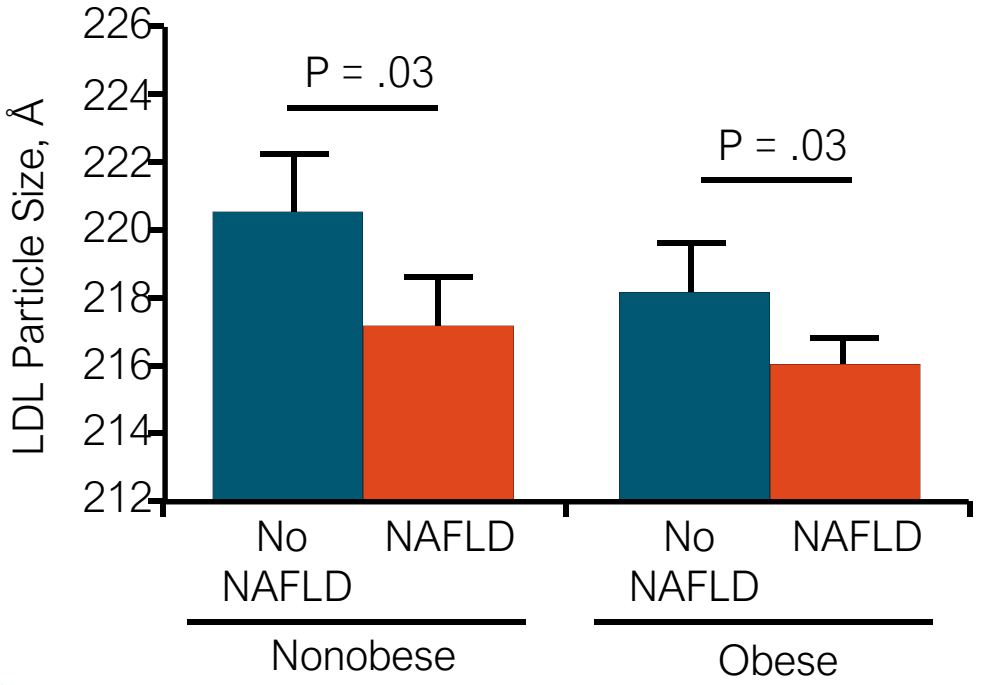
Hepatic Steatosis and Insulin Resistance, But Not Steatohepatitis, Promote Atherogenic Dyslipidemia in NAFLD.

- NAFLD was associated with a worse atherogenic lipoprotein profile (LDL Particle Size Is Reduced in NAFLD), regardless of similar body mass index and other clinical parameters



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Bril. J Clin Endocrinol Metab. 2016;101:644.

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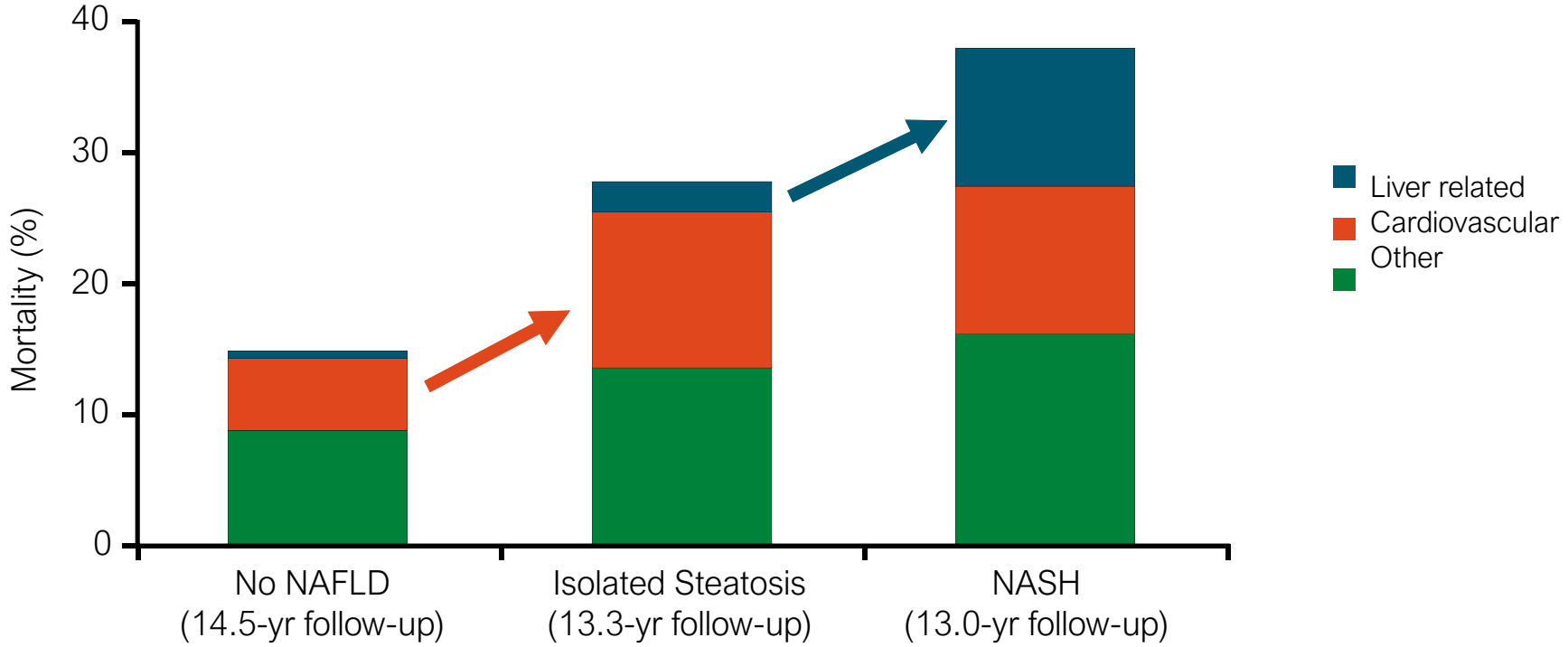
Mortality Risk Associated With Isolated Steatosis and NASH

- Analysis of all-cause mortality in 6 separate studies among patients without NAFLD vs with and without NASH
  - NAFLD determined by ultrasound; NASH determined by liver biopsy



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Bril. Endocrinol Metab Clin N Am. 2016;45:765.

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Genetic Risks for NAFLD

- Known: PNPLA3, others
- Unknown:
  - Family history of diabetes, even among people without diabetes, is associated with NASH and NAFLD fibrosis[2]
  - Increased odds of advanced cirrhosis in first-degree relatives of patients with NAFLD cirrhosis[1]

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1. Caussy. J Clin Invest. 2017;127:2697. 2. Loomba. Hepatology. 2012;56:943.

How to define an EUBIOTIC enterotype?

EU= good ***BIOS= life***

- **Composition:** ***Diversity***
  Richness
  Relative Abundance

- ***Our gut is a sophisticated ecosystem that is regulated by the logic of RELATIONAL HARMONY***
- ***Microbiota and Host live in a COOPERATIVE SYSTEMIC AGGREGATION MODEL***

EUBIOSIS

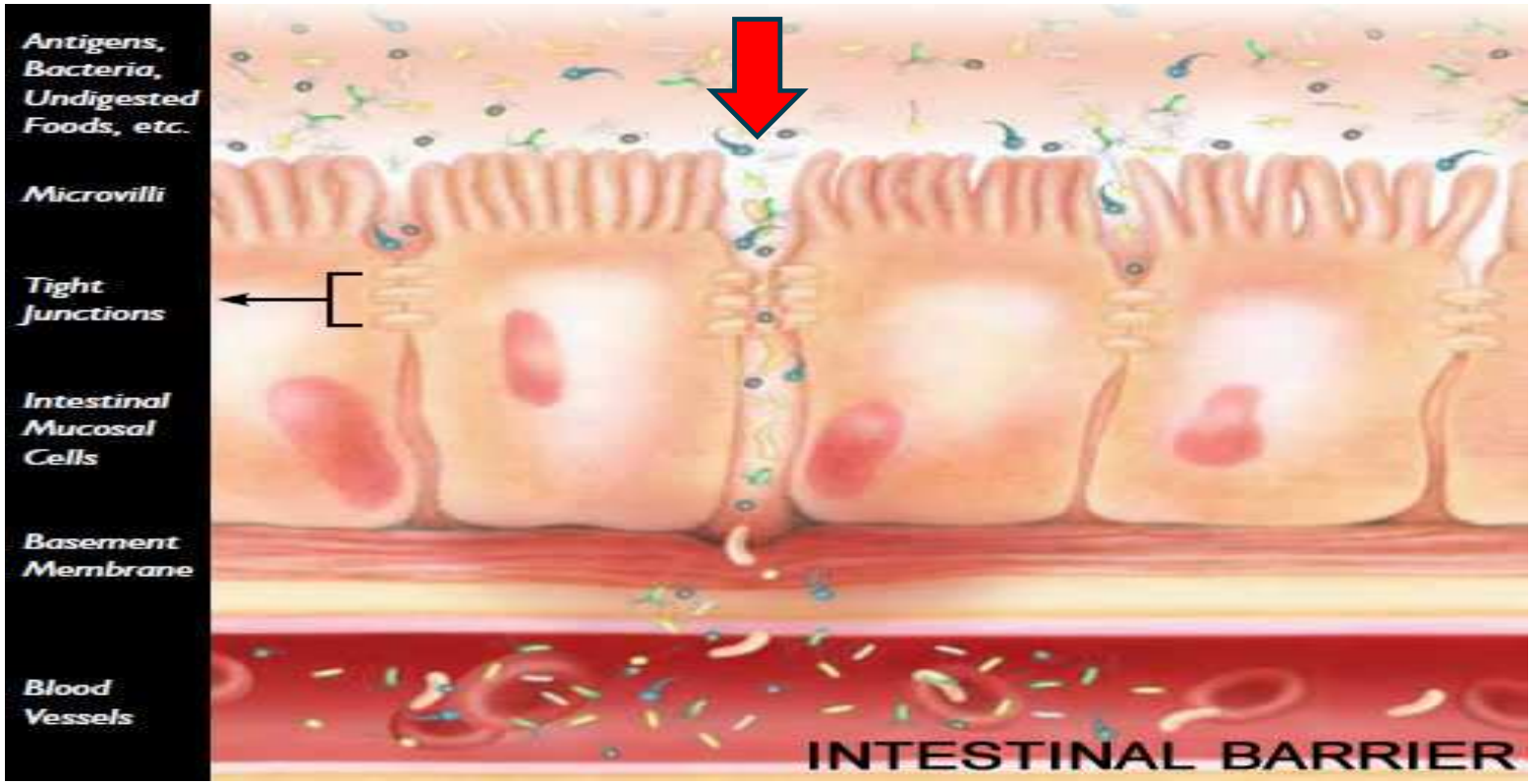
Failure of HOST-MICROBIOTA equilibrium

Quali-quantitative alterations of oral, esophageal, gastric, small bowel and/or colonic microbiota

DYSBIOSIS

Gut Barrier disfunction

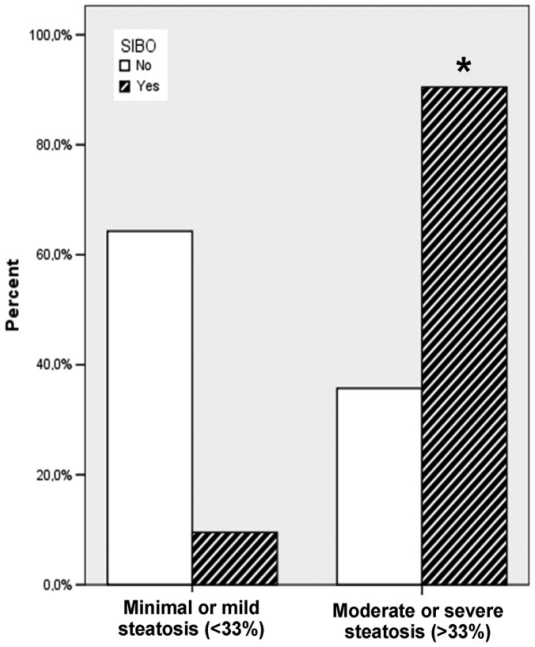
Intestinal permeability: Leaky gut

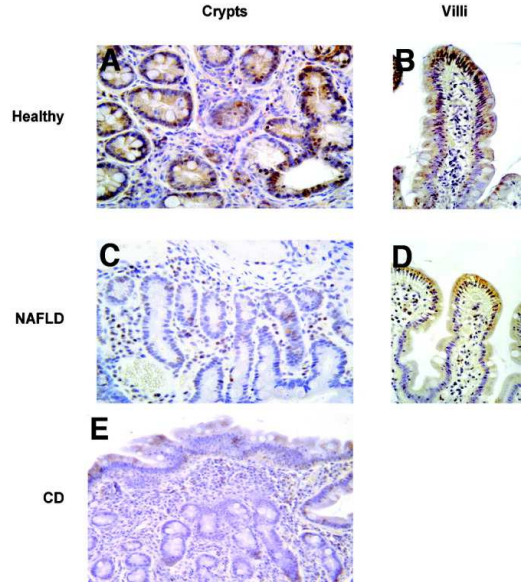


Increased Intestinal Permeability and Tight Junction Alterations in Nonalcoholic Fatty Liver Disease

Luca Miele,[1] Venanzio Valenza,[2*] Giuseppe La Torre,[3*] Massimo Montalto,[1*] Giovanni Cammarota,[1] Riccardo Ricci,[4] Roberta Mascianà,[1] Alessandra Forgione,[1] Maria L. Gabrieli,[1] Germano Perotti,[2] Fabio M. Vecchio,[4] Gianlodovico Rapaccini,[1] Giovanni Gasbarrini,[1] Chris P. Day,[5**] and Antonio Grieco[1**]

- NAFLD in humans is associated with increased gut permeability and that his abnormality is related to the increased prevalence of SIBO in these patients.
- The increased permeability appears to be caused by disruption of intercellular tight junctions in the intestine, and it may play an important role in the pathogenesis of hepatic fat deposition



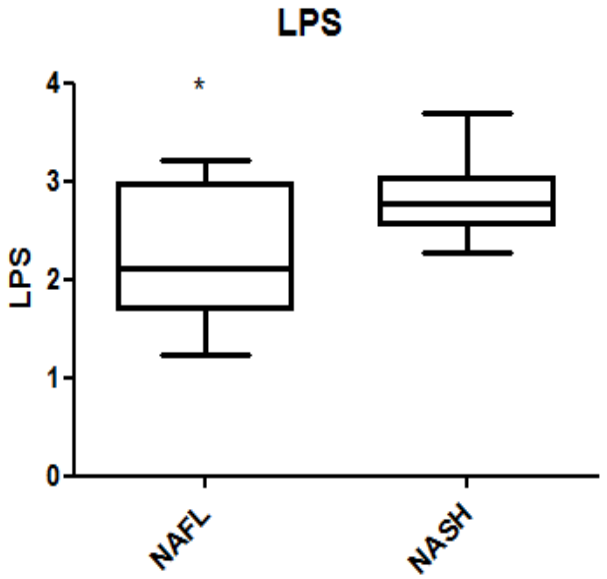


(HEPATOLOGY 2009;49:1877-1887.)

Intestinal permeability is increased in children with non-alcoholic fatty liver disease, and correlates with liver disease severity

Valentina Giorgio[a,1], Luca Miele[b,c,1], Luigi Principessa[d], Francesca Ferretti[a], Maria Pia Villa[d], Valentina Negro[d], Antonio Grieco[b], Anna Alisi[a], Valerio Nobili[a,*]

↑ Severity of NASH and LPS in children

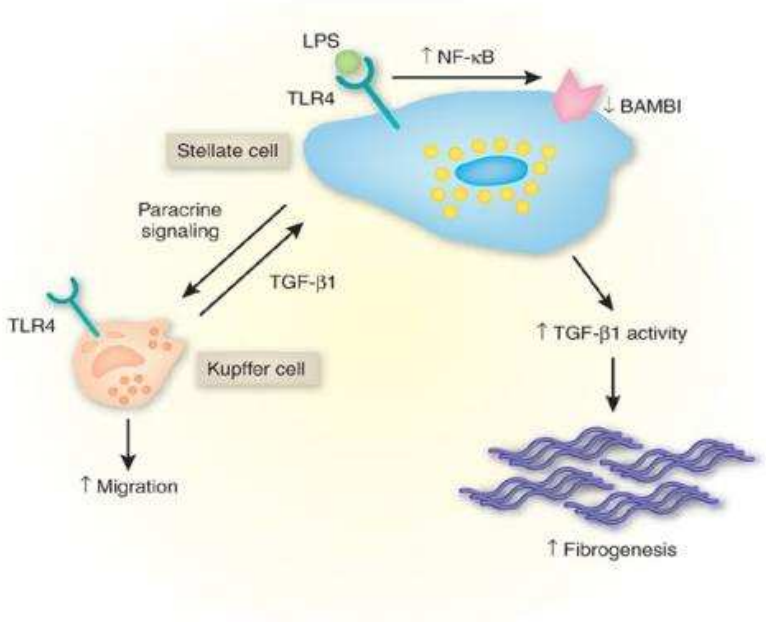


Digestive and Liver Disease xxx (2014) xxx–xxx

Translocation & NAFLD

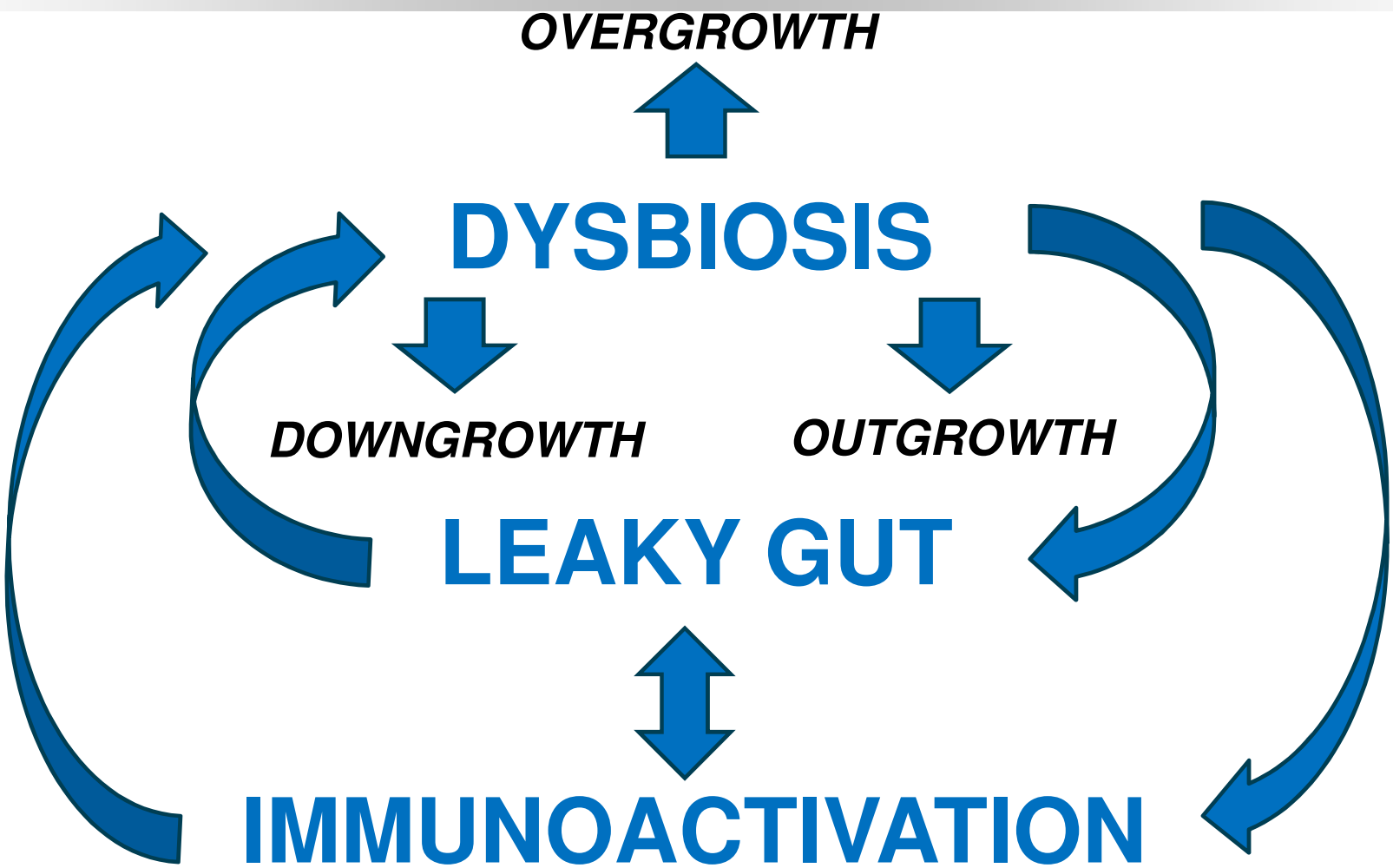
- Translocated microbial products might contribute to the pathogenesis of fatty liver disease by several mechanisms.

- Activation of Toll-like receptors (TLRs) on hepatic Kupffer cells and stellate cells to stimulate pro-inflammatory and profibrotic pathways via a range of cytokines.



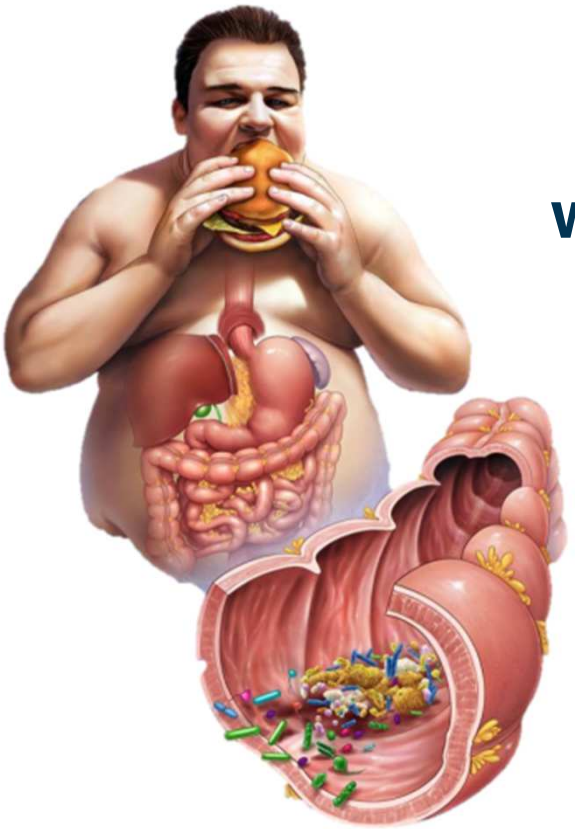
Lipopolysaccharide signaling through the Toll-like receptors downregulates an inhibitory pseudoreceptor of TGF-β, enhancing hepatic fibrosis and liver injury

Friedman SL. Nat Med 2007 - Saki et al. Nat Med 2007



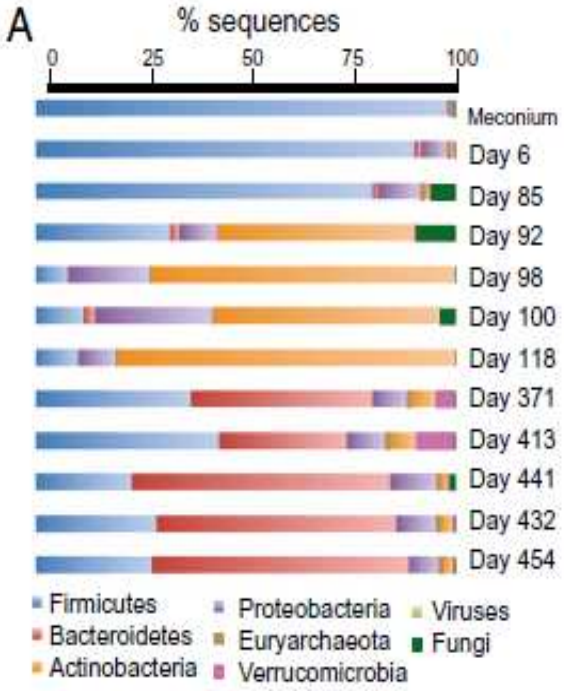
ENTEROPATHOGENIC SYNDROMES

Microbiota in NAFLD



which bacteria are involved?

At birth the human body is sterile



Vaginal microbiota (mother)

Fecal microbiota (mother)

Skin microbiota (mother/father/parents/babysitter)

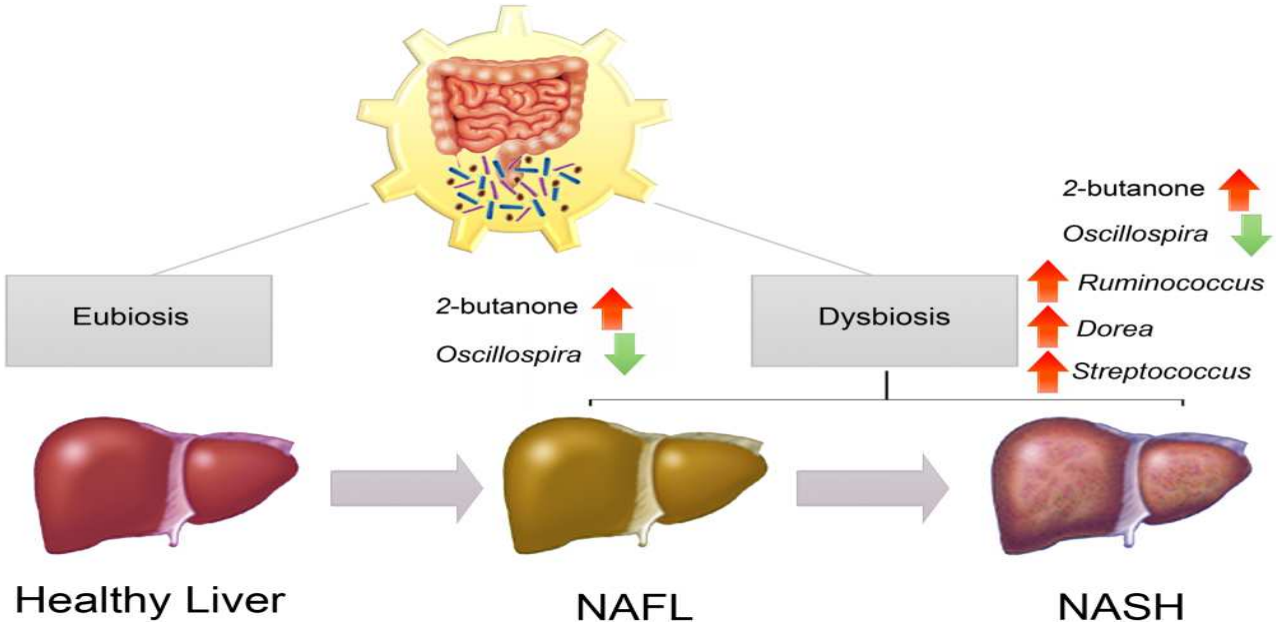
Diet

Ambient

Native CORE microbiota (8-36 months of life)

Gut Microbiota Profiling of Pediatric Nonalcoholic Fatty Liver Disease and Obese Patients Unveiled by an Integrated Meta-omics-Based Approach

Federica Del Chierico,[1*] Valerio Nobili,[2,3*] Pamela Vernocchi,[1] Alessandra Russo,[1] Cristiano De Stefanis,[3] Daniela Gnani,[3] Cesare Furlanello,[4] Alessandro Zandonà,[4] Paola Paci,[5,6] Giorgio Capuani,[7] Bruno Dallapiccola,[8] Alfredo Miccheli,[7] Anna Alisi,[3] and Lorenza Putignani[1,9]



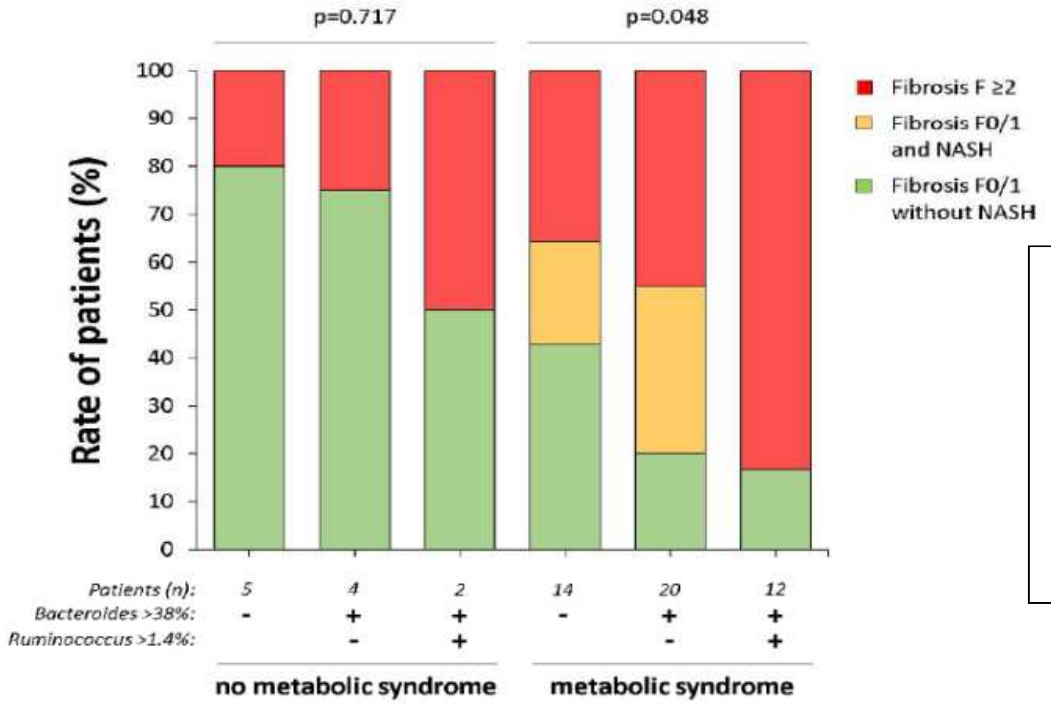
- The combination of a low abundance of *Oscillospira* with high levels of 2-butanone may be a specific intestinal profile for liver steatosis in children.
- The high relative abundance of Lachnospiraceae, *Ruminococcus*, and *Dorea* observed in pediatric patients with NASH suggests that changes in the gut microbiota are associated with disease severity.

HEPATOLOGY, VOL. 00, NO. 00, 2016

The Severity of Nonalcoholic Fatty Liver Disease Is Associated With Gut Dysbiosis and Shift in the Metabolic Function of the Gut Microbiota

Jérôme Boursier,[1,2] Olaf Mueller,[3] Matthieu Barret,[4] Mariana Machado,[5] Lionel Fizanne,[2] Felix Araujo-Perez,[6] Cynthia D. Guy,[7] Patrick C. Seed,[3,6] John F. Rawls,[3] Lawrence A. David,[3] Gilles Hunault,[2] Frédéric Oberti,[1,2] Paul Calès,[1,2] and Anna Mae Diehl[5]

HEPATOLOGY, VOL. 63, NO. 3, 2016

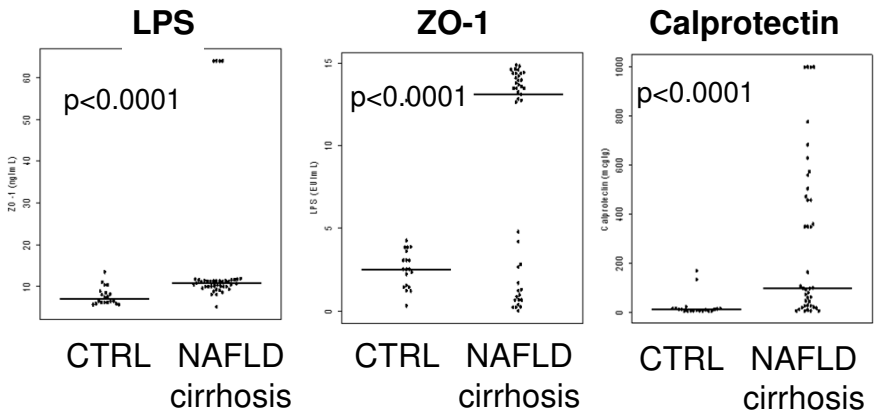


Bacteroides abundance was independently associated with NASH and Ruminococcus with F≥2 fibrosis

Stratification according to the abundance of these 2 bacteria generated 3 patient subgroups with increasing severity of NAFLD lesions

Hepatocellular Carcinoma Is Associated With Gut Microbiota Profile and Inflammation in Nonalcoholic Fatty Liver Disease

Francesca Romana Ponziani ,[1,*] Sherrie Bhoori,[2] Chiara Castelli,[3] Lorenza Putignani,[4,5] Licia Rivoltini,[3] Federica Del Chierico,[4] Maurizio Sanguinetti,[6] Daniele Morelli,[7] Francesco Paroni Sterbini,[6] Valentina Petito,[1] Sofia Reddel,[4] Riccardo Calvani,[8] Chiara Camisaschi,[3] Anna Picca,[8] Alessandra Tuccitto,[3] Antonio Gasbarrini,[1] Maurizio Pompili,[1,*] and Vincenzo Mazzaferro[2,*]



NAFLD cirrhotic patients have increased LPS, intestinal permeability (ZO-1), and calprotectin

↑ *Bacteroides*, Enterobacteriaceae, *Ruminococcus,* and

↓ decreased abundance of *Akkermansia*, *Methanobrevibacter* and *Dehalobacterium* compared to healthy controls.

Ponziani FR et al. Hepatology 2018

Characterization of Gut Microbiomes in Nonalcoholic Steatohepatitis (NASH) Patients: A Connection Between Endogenous Alcohol and NASH

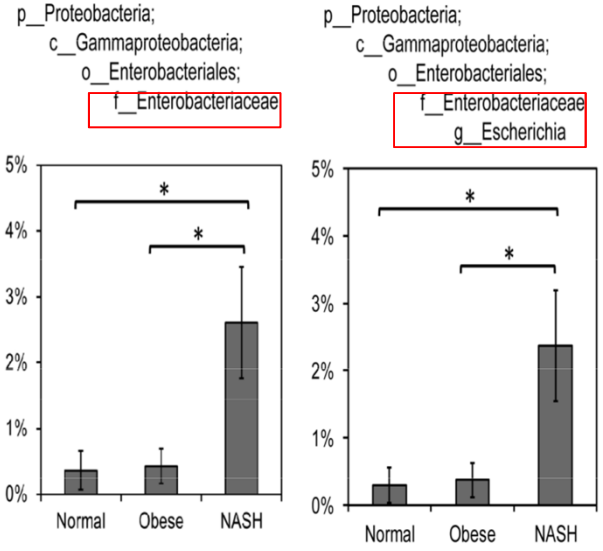
(HEPATOLOGY 2013;57:601-609)

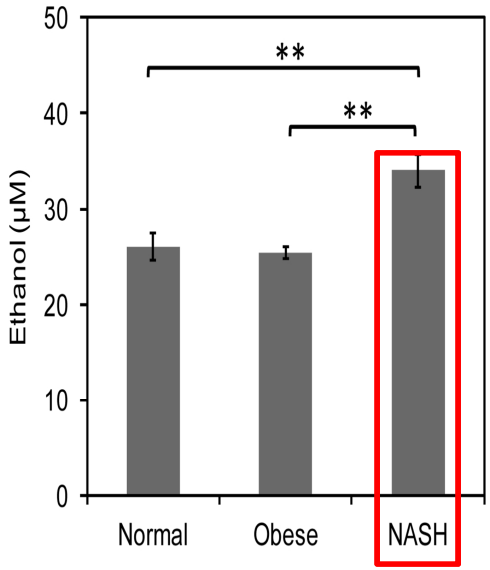
Lixin Zhu,[1] Susan S. Baker,[1] Chelsea Gill,[2] Wensheng Liu,[1] Razan Alkhouri,[1] Robert D. Baker,[1] and Steven R. Gill[2]

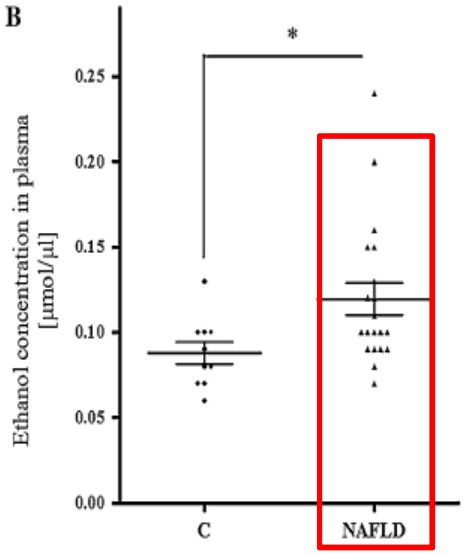
Nutrition, Intestinal Permeability, and Blood Ethanol Levels Are Altered in Patients with Nonalcoholic Fatty Liver Disease (NAFLD)

Dig Dis Sci (2012) 57:1932–1941

Valentina Volynets · Markus A. Küper · Stefan Strahl · Ina B. Maier · Astrid Spruss · Sabine Wagnerberger · Alfred Königsrainer · Stephan C. Bischoff · Ina Bergheim

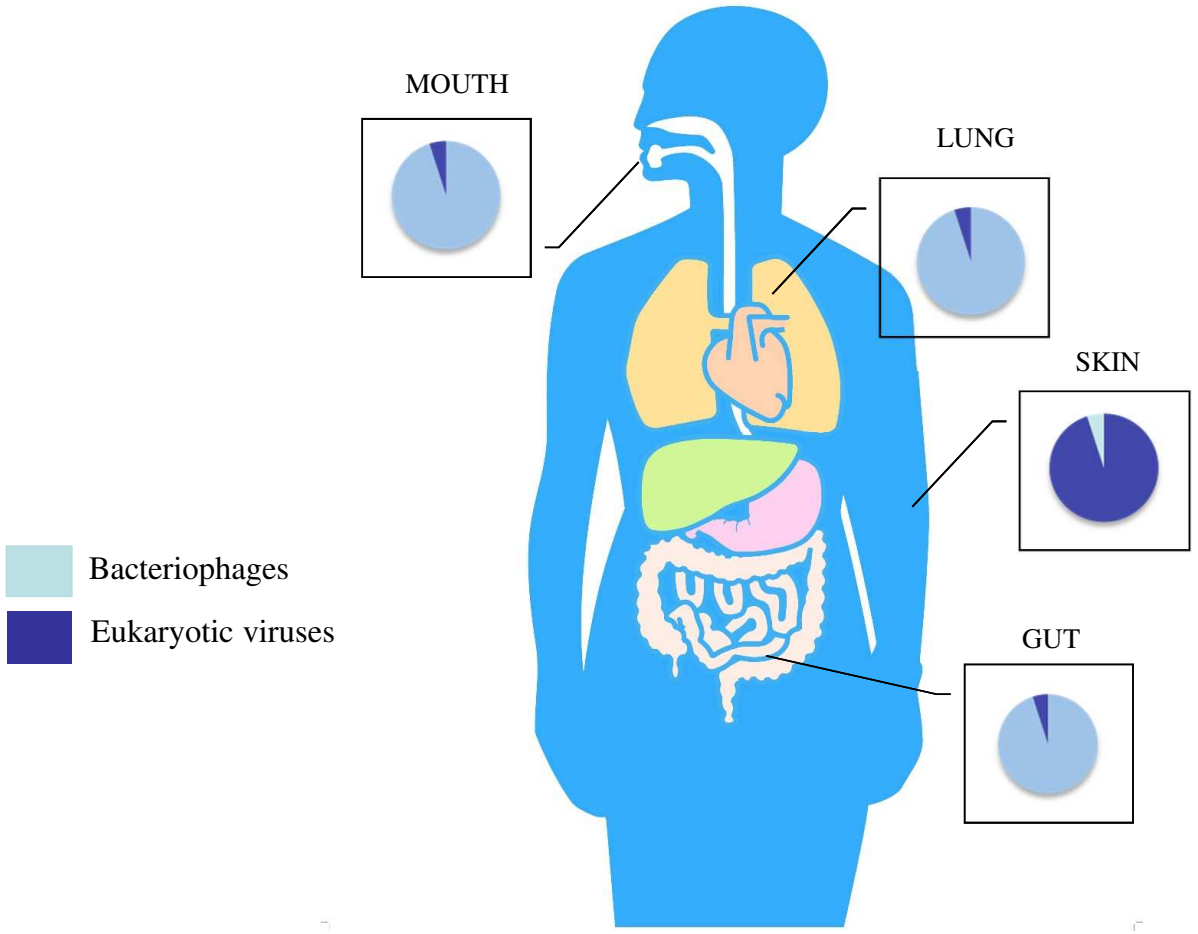






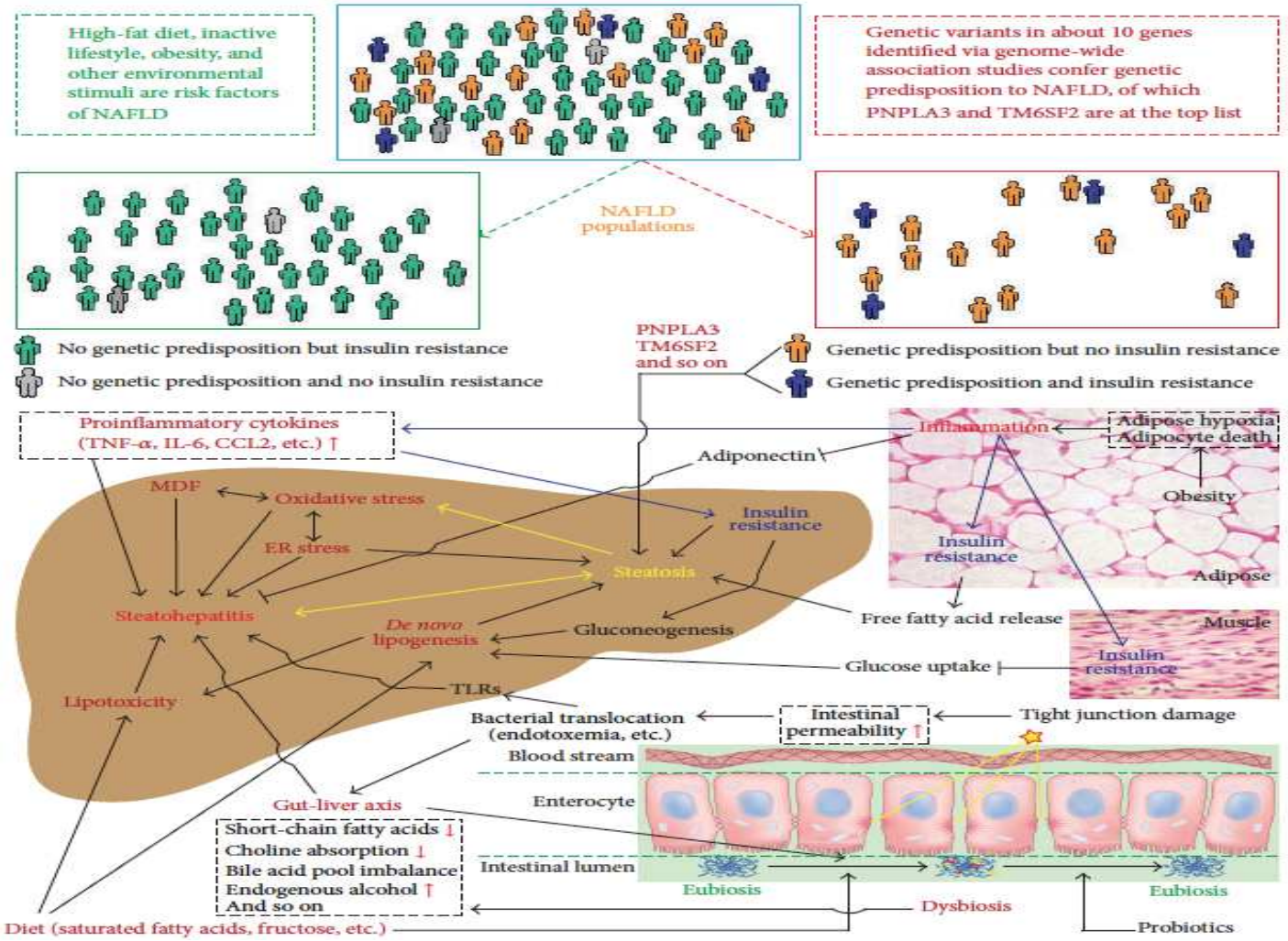
The increased abundance of alcohol-producing bacteria in NASH microbiomes, elevated blood-ethanol concentration in NASH patients, and the well-established role of alcohol metabolism in oxidative stress and, consequently, liver inflammation suggest a role for alcohol-producing microbiota in the pathogenesis of NASH

GUT - VIROME



Bruno R. et al. Beyond the gut bacterial microbiota: The gut virome - Journal of Medical Virology 88:1467–1472 (2016)

Overview at the pathogenesis of nonalcoholic fatty liver disease (NAFLD)



(+ gut microbiota)...

Is NAFLD also an "infectious" disease?

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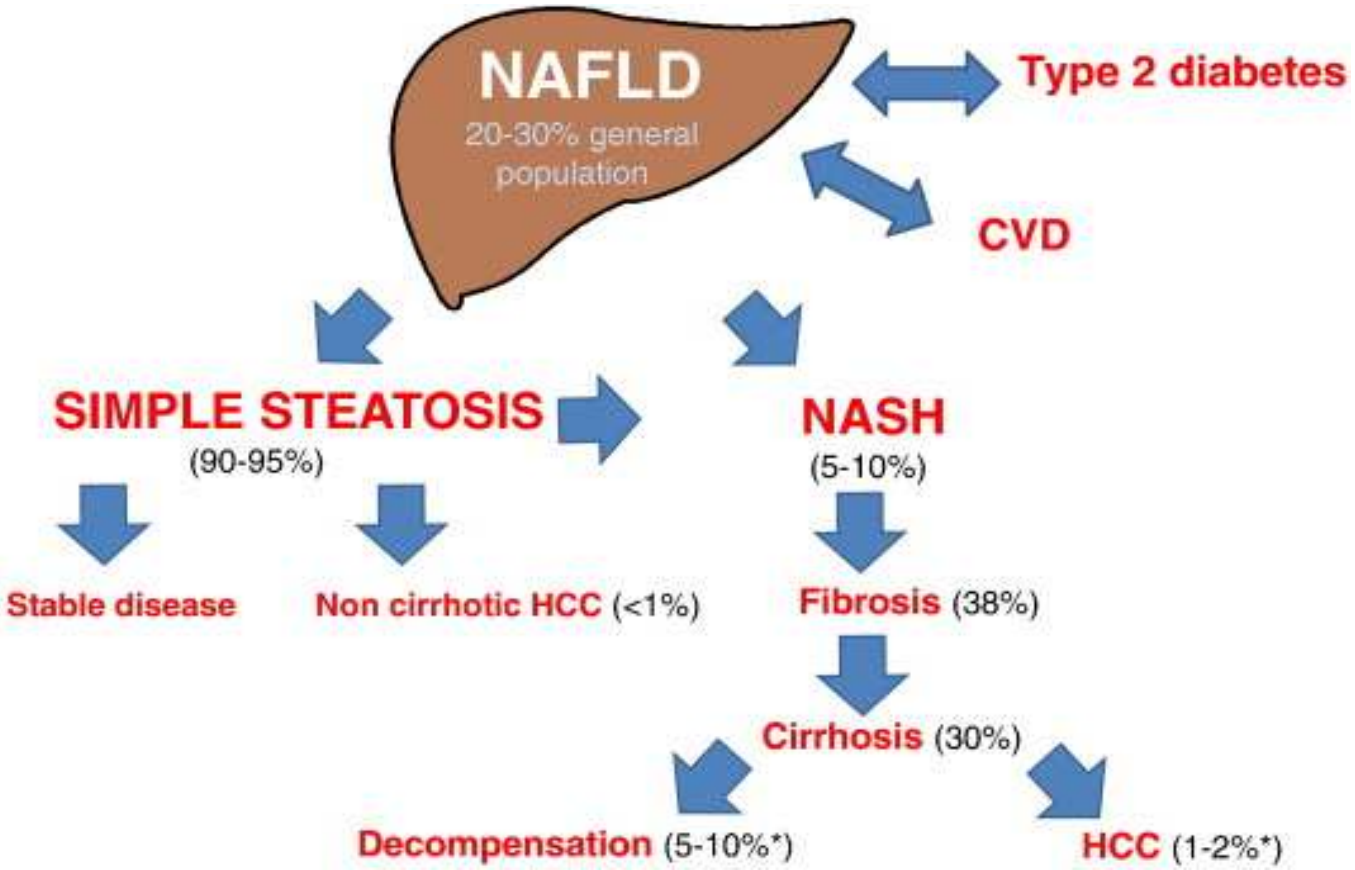
NATURAL HISTORY



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The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD); Metabolism, volume 65, Issue 8, August 2016, Pages 1038-1048

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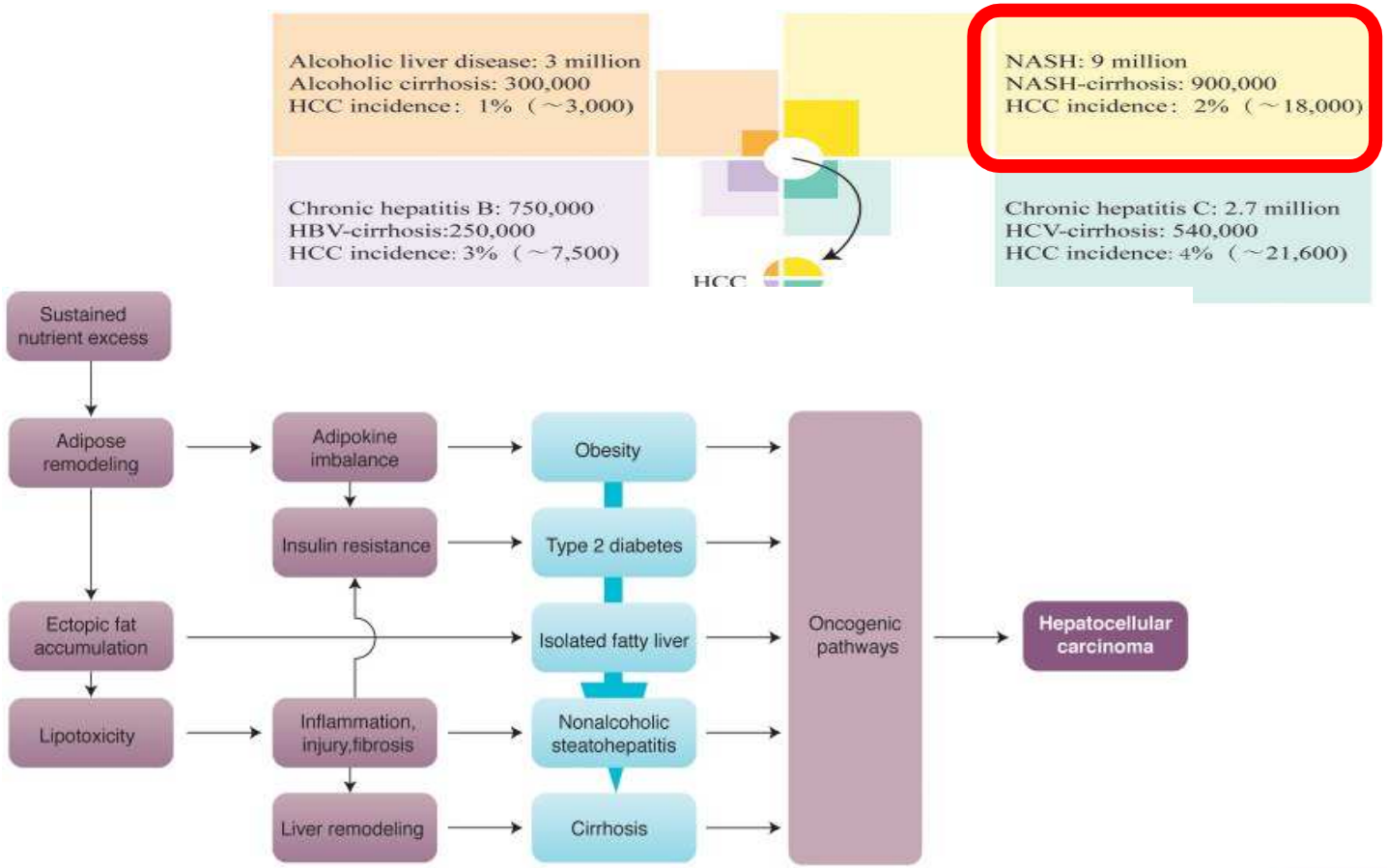
Disease burden of HCC by major etiologies in the USA



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Hepatocellular Carcinoma in Non-alcoholic Fatty Liver Disease: Epidemiology, Pathogenesis, and Prevention

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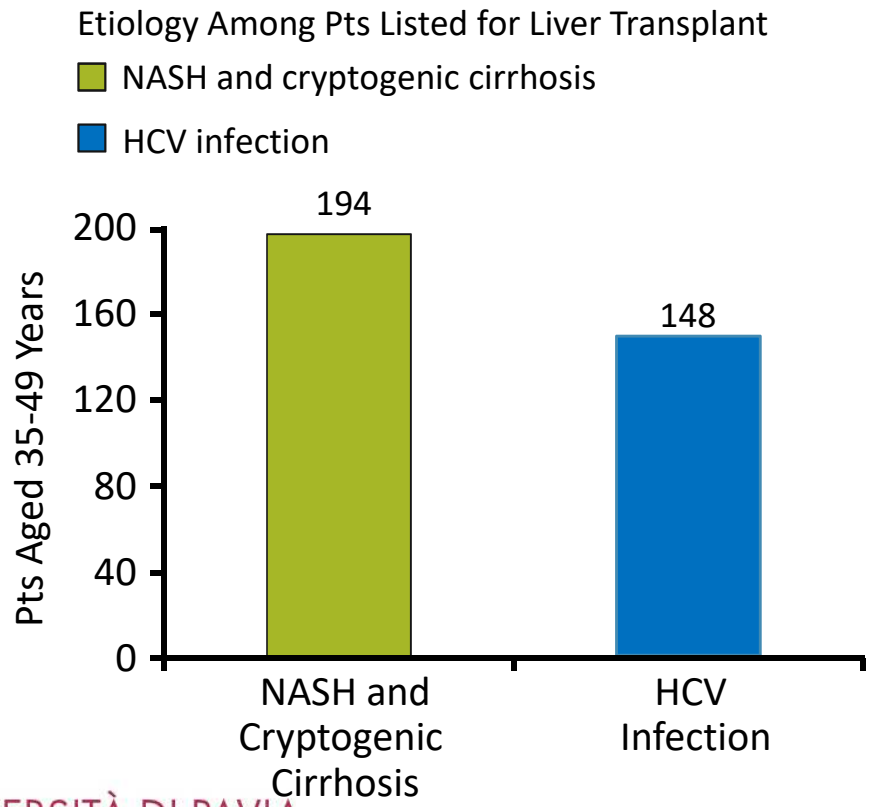
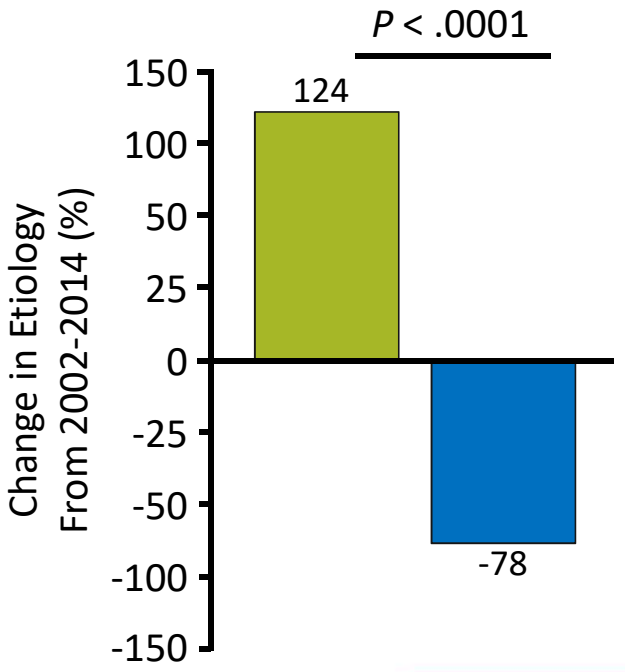
NASH: Number One Indication for Liver Transplant in Patients Aged < 50 Years

In 2015 registry of patients listed for liver transplant in US, NASH surpassed HCV infection





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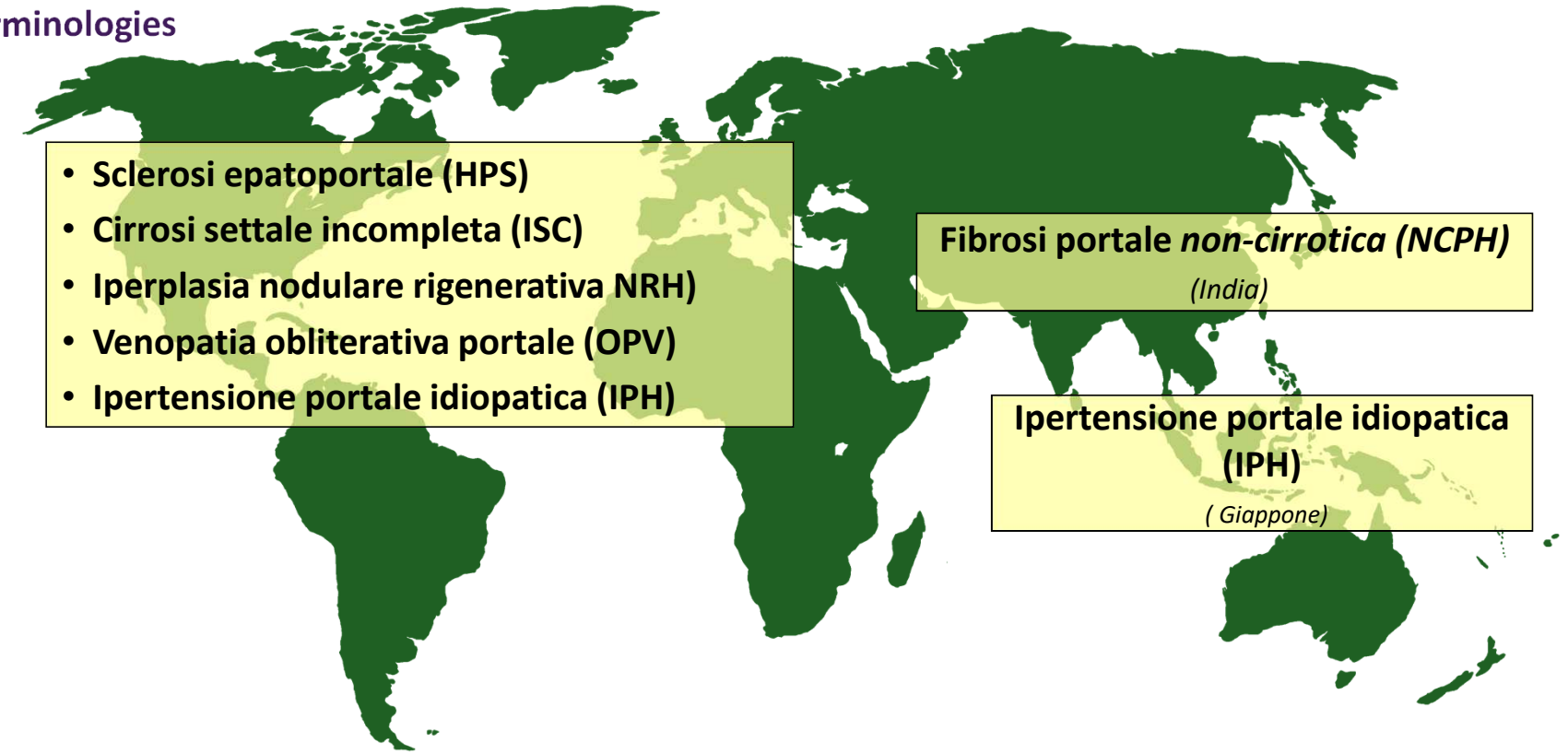
Banini BA, et al. ACG 2016. Abstract 46

Obliterative Portal Venopathy

Different Terminologies

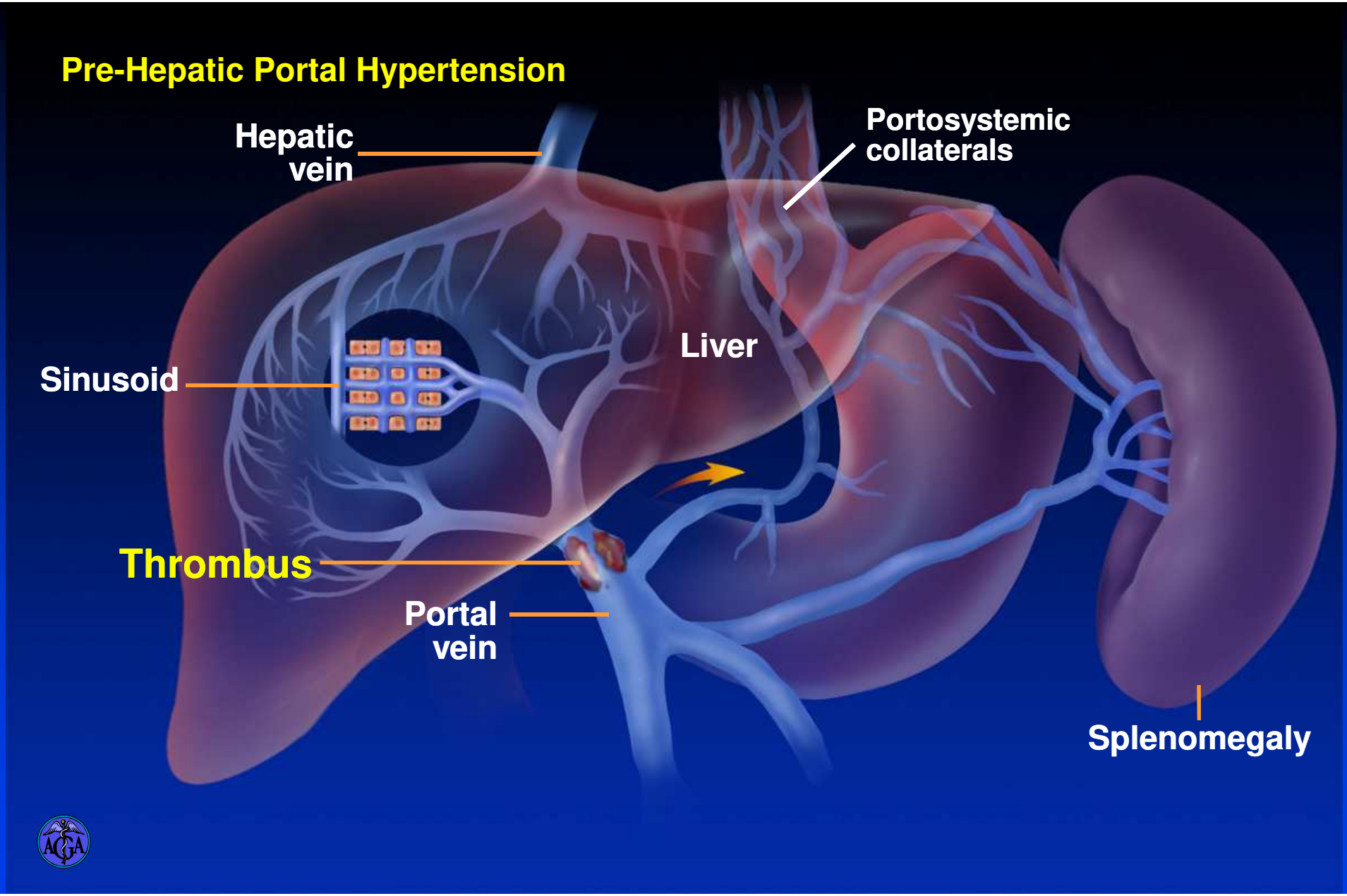


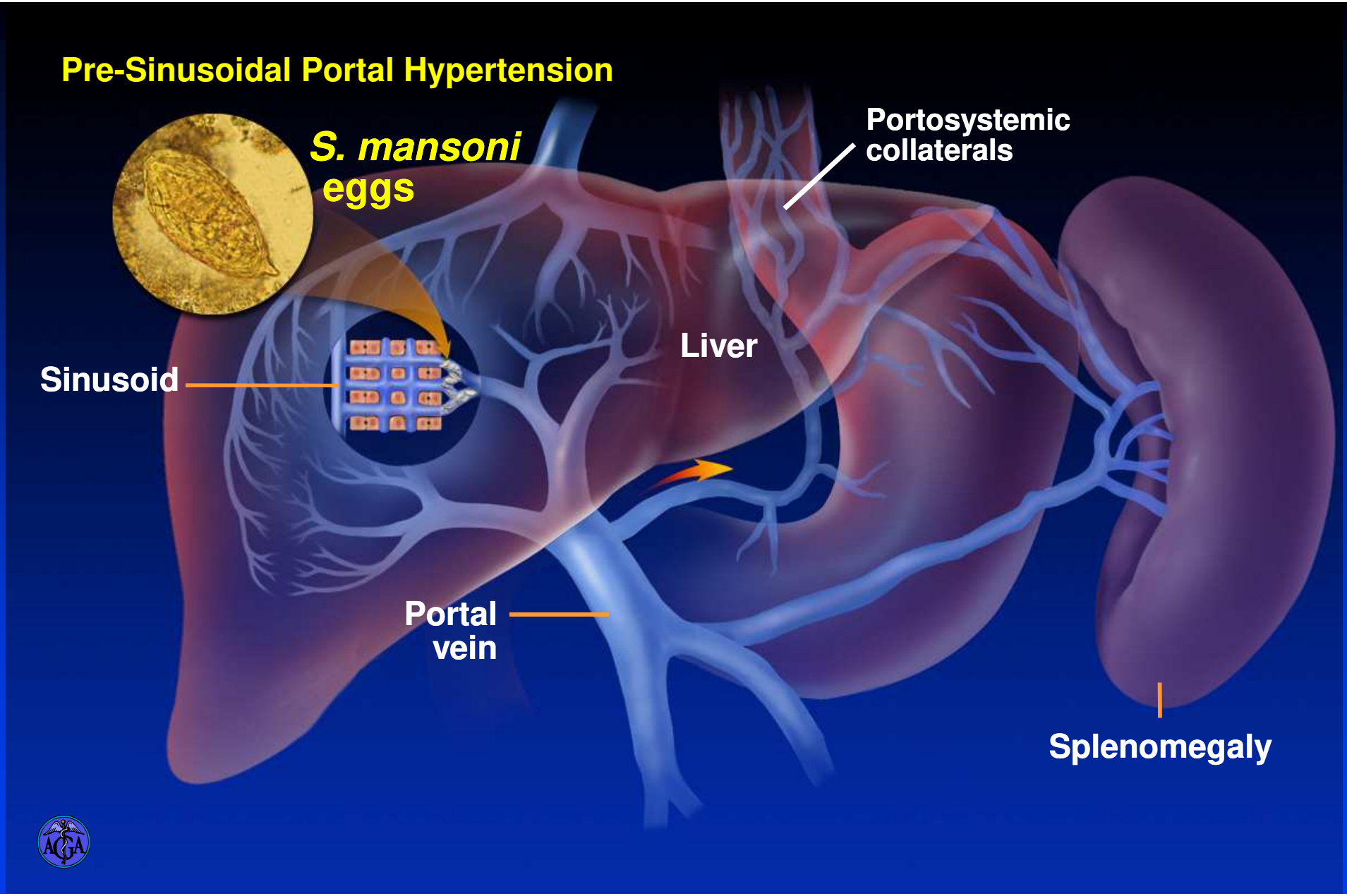
Confusing terminology in presence and/or absence of PH

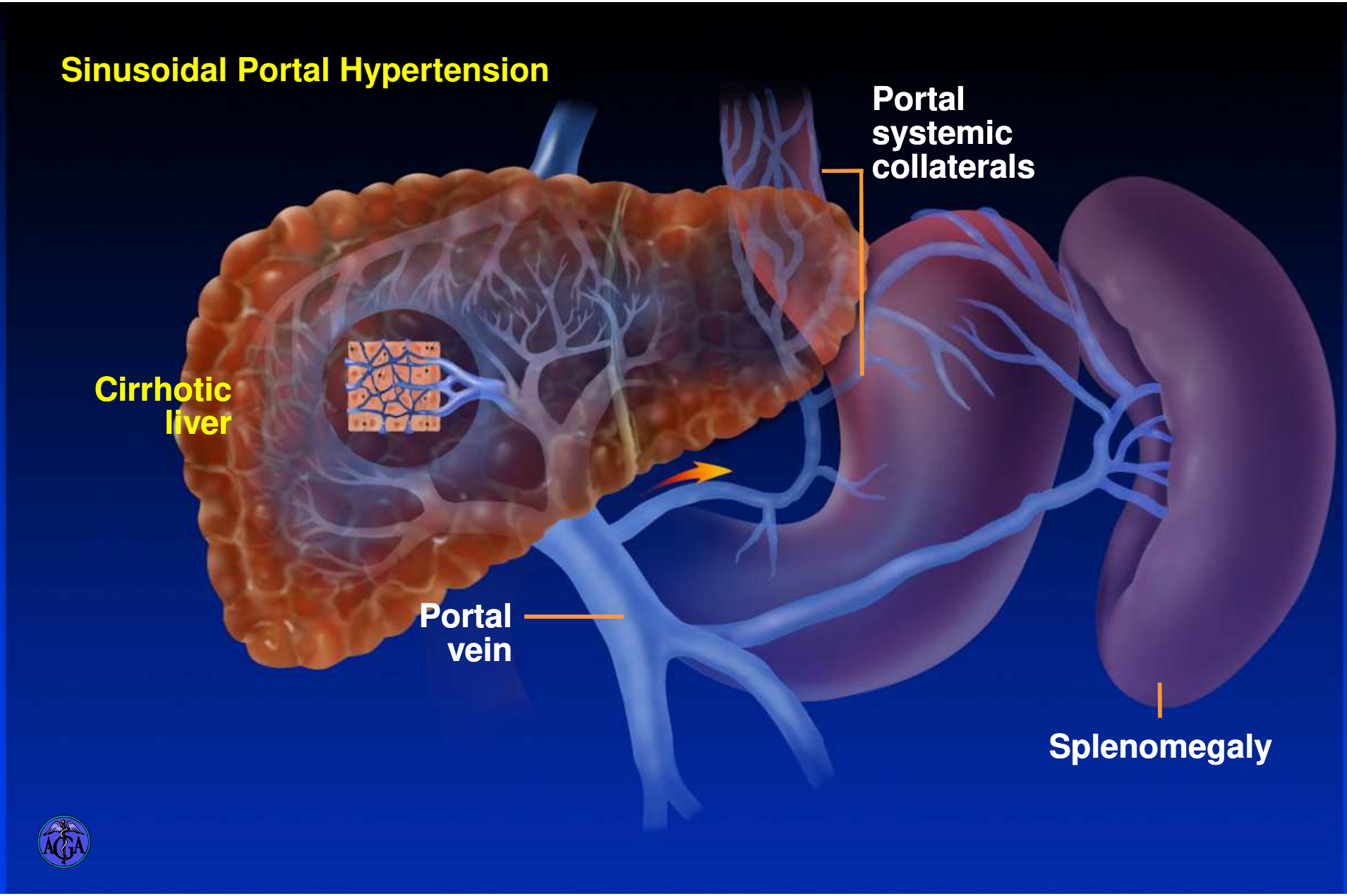
Schouten J et al: Hepatology 2011

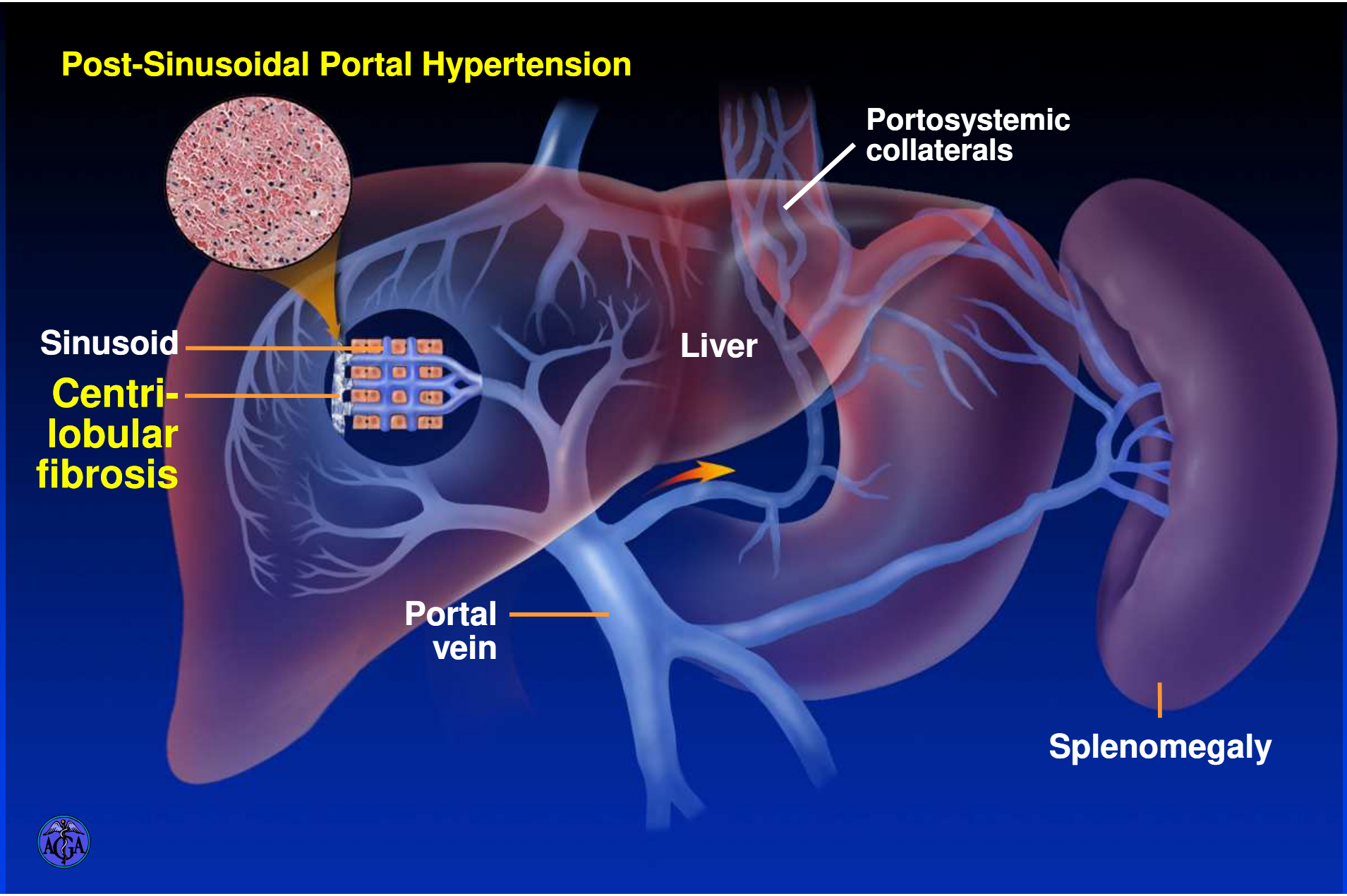
Portal Hypertension Is Classified According to the Site of Increased Resistance

Type	Example
Pre-hepatic	Portal or splenic vein thrombosis
Pre-sinusoidal	Schistosomiasis
Sinusoidal	Cirrhosis
Post-sinusoidal	Veno-occlusive disease
Post-hepatic	Budd-Chiari syndrome


Pre-Hepatic Portal Hypertension
Hepatic vein
Portosystemic collaterals
Liver
Sinusoid
Thrombus
Portal vein
Splenomegaly


Pre-Sinusoidal Portal Hypertension
S. mansoni eggs
Portosystemic collaterals
Sinusoid
Liver
Portal vein
Splenomegaly


Sinusoidal Portal Hypertension
Portal systemic collaterals
Cirrhotic liver
Portal vein
Splenomegaly


Post-Sinusoidal Portal Hypertension
Portosystemic collaterals
Sinusoid
Centri-lobular fibrosis
Liver
Portal vein
Splenomegaly

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Non-cirrhotic Portal Hypertension (NCPH)

- Maida et al. (2006) described a cohort of 17 HIV-infected patients with symptoms of portal hypertension in setting of didanosine (ddI) use
- Saifee et al. (2008) described a cohort of 11 HIV-infected patients with NCPH and correlated it to either ddI use and/or to a predisposing hypercoaguable state
- Kovari et al. (2009) conducted a nested case control study of 15 HIV-infected patients showing strong association between prolonged ddI exposure and NCPH
- Mendizabal et al. (2009) described 6 HIV-infected patients with NCPH in the setting of ddI use

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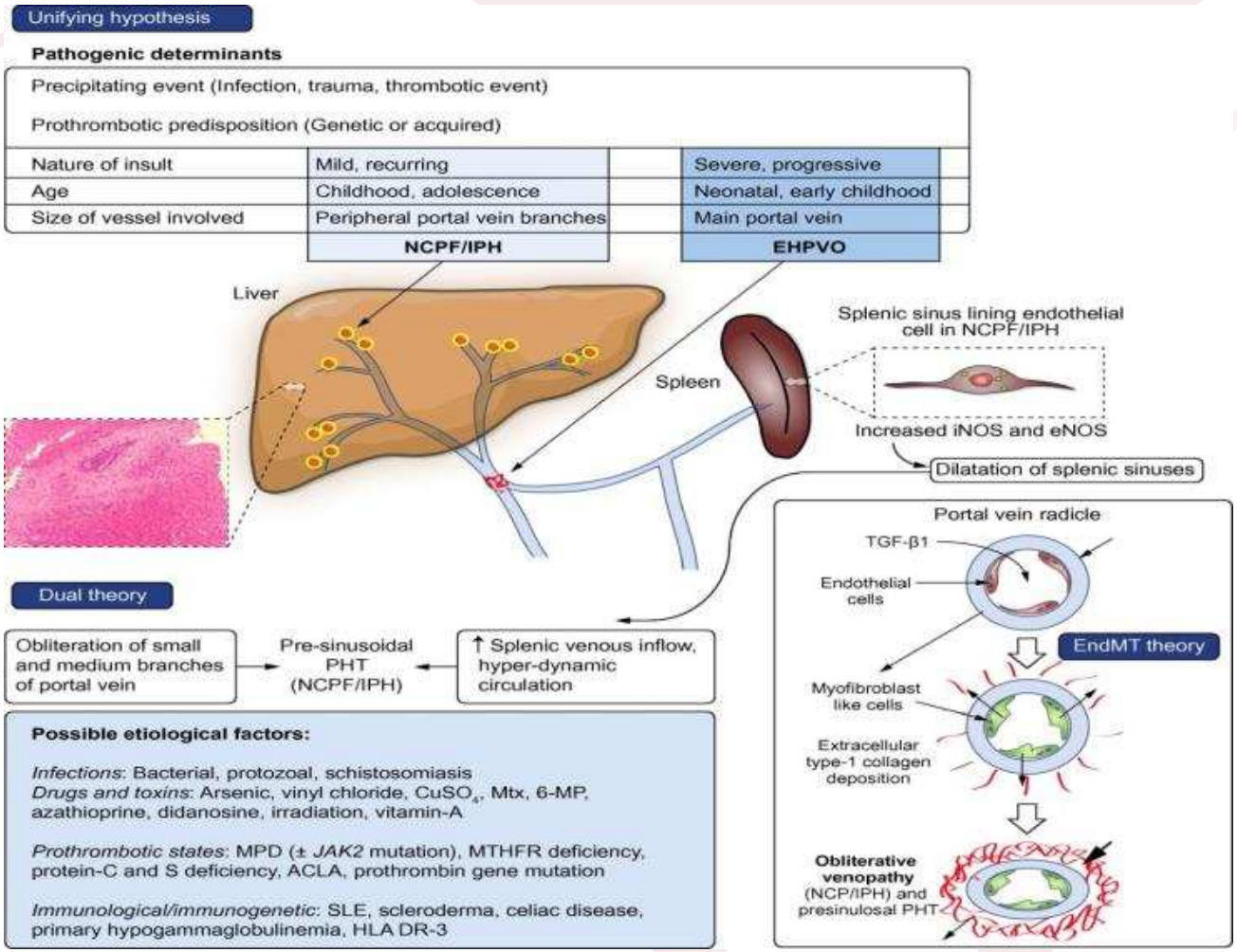
Pathogenetic theories for NCPF/IPH.

The *Unifying hypothesis* : A major thrombotic event occuring at a young age or later in life

The *dual theory* : increased splenic blood flow + intrahepatic obstruction (**obliterative venopathy**)



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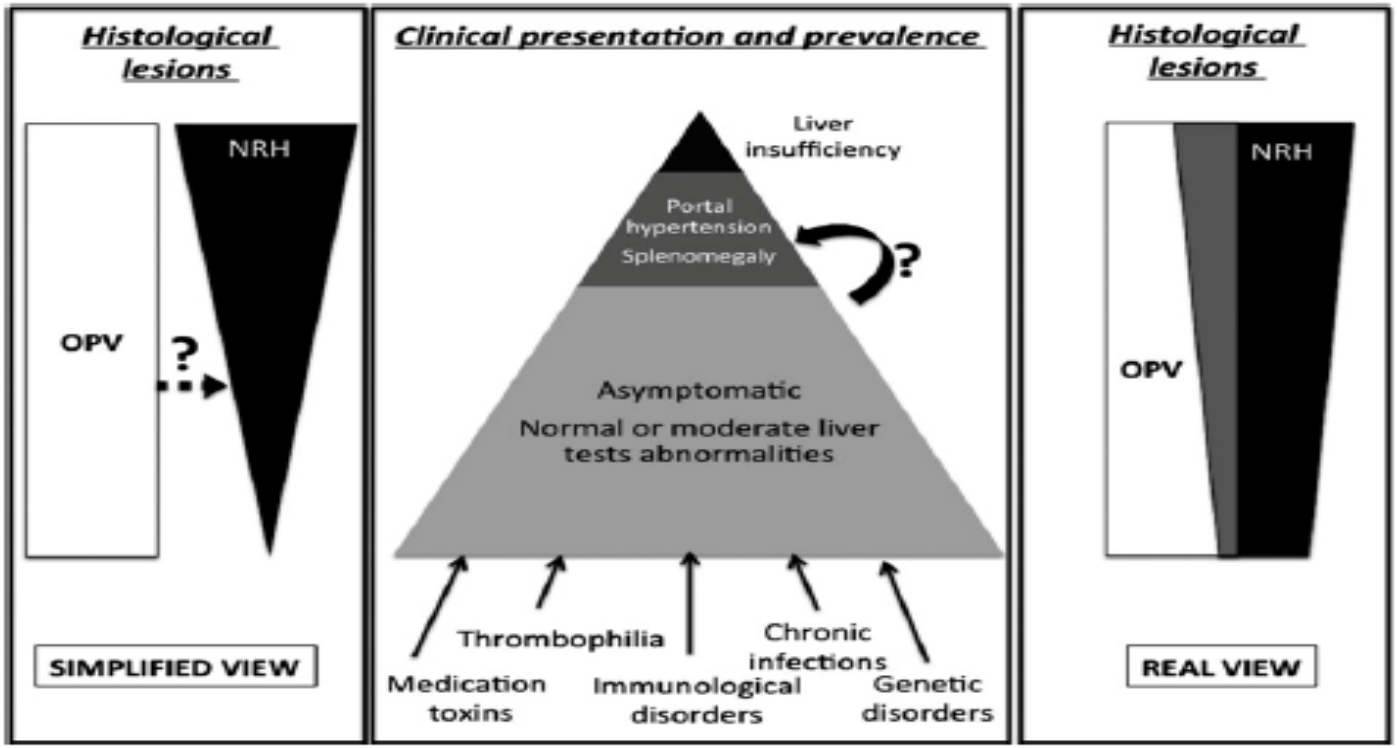
The obliterative portal venopathy 'iceberg'.



Idiopathic non-cirrhotic portal hypertension (INCPH)
obliterative portal venopathy(OPV),
nodular regenerative hyperplasia (NRH),

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Laure Elkrief1 and Pierre-Emmanuel Rautou

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obliterative portal venopathy(OPV),
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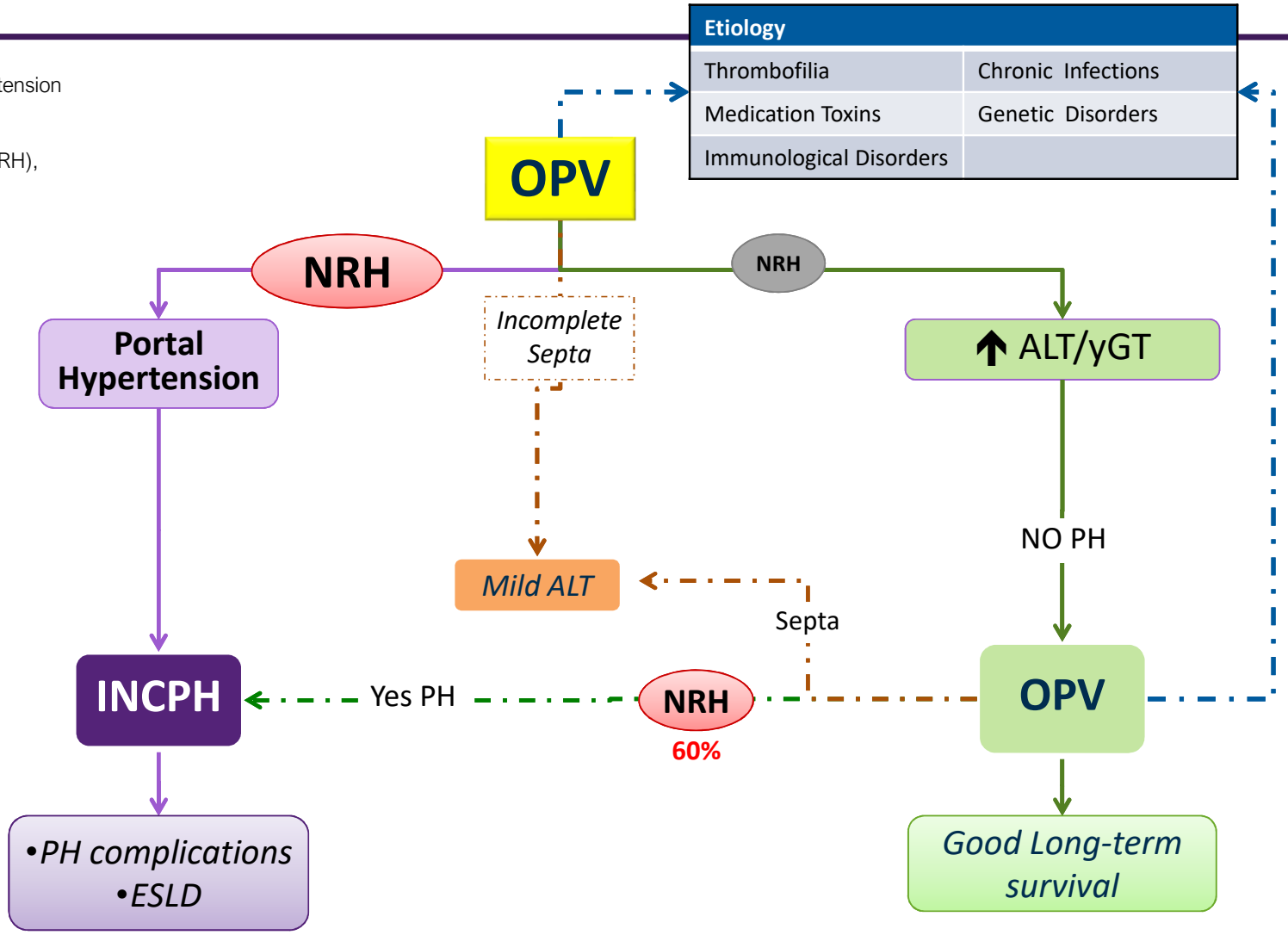
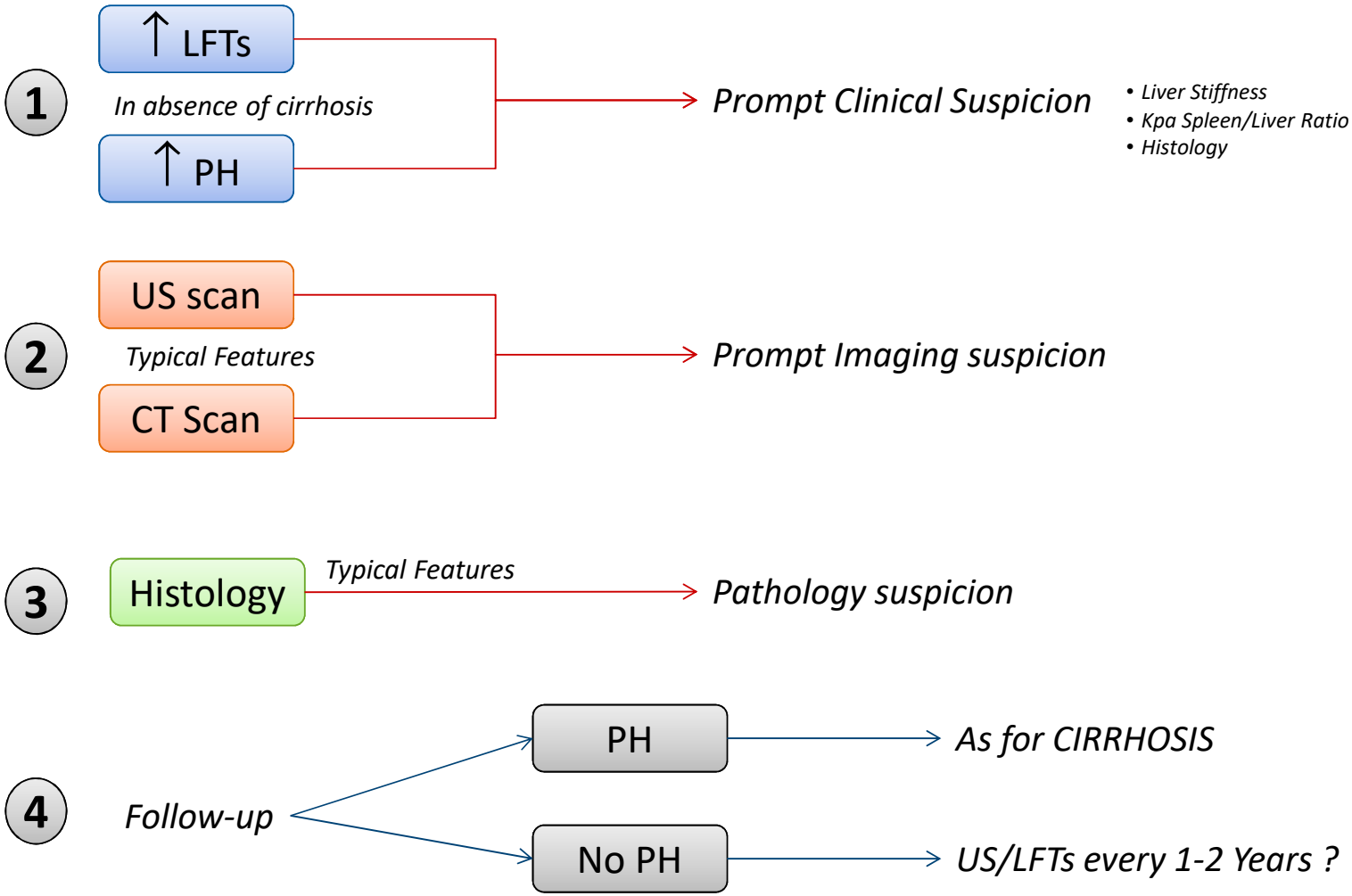


Take Home Messages



Si trova quello che si cerca

Ma si cerca ciò che si conosce

Anonimo