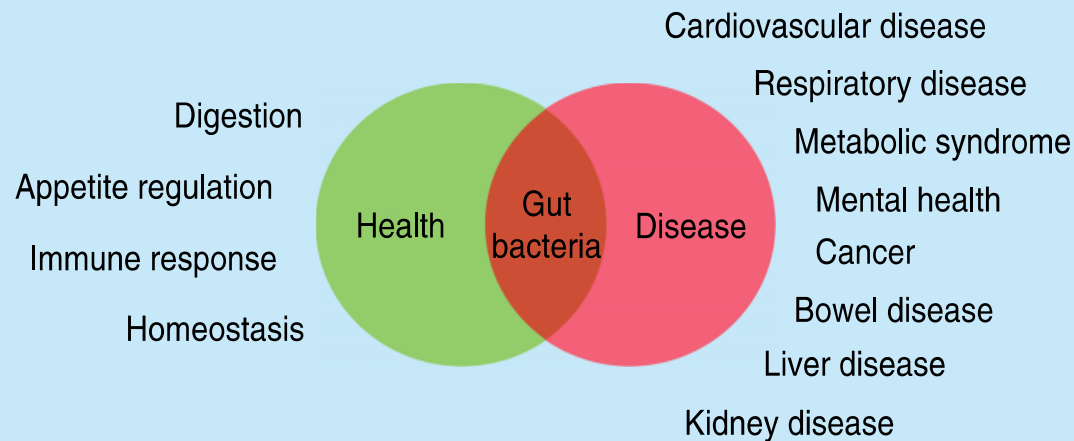


Probióticos en Hígado

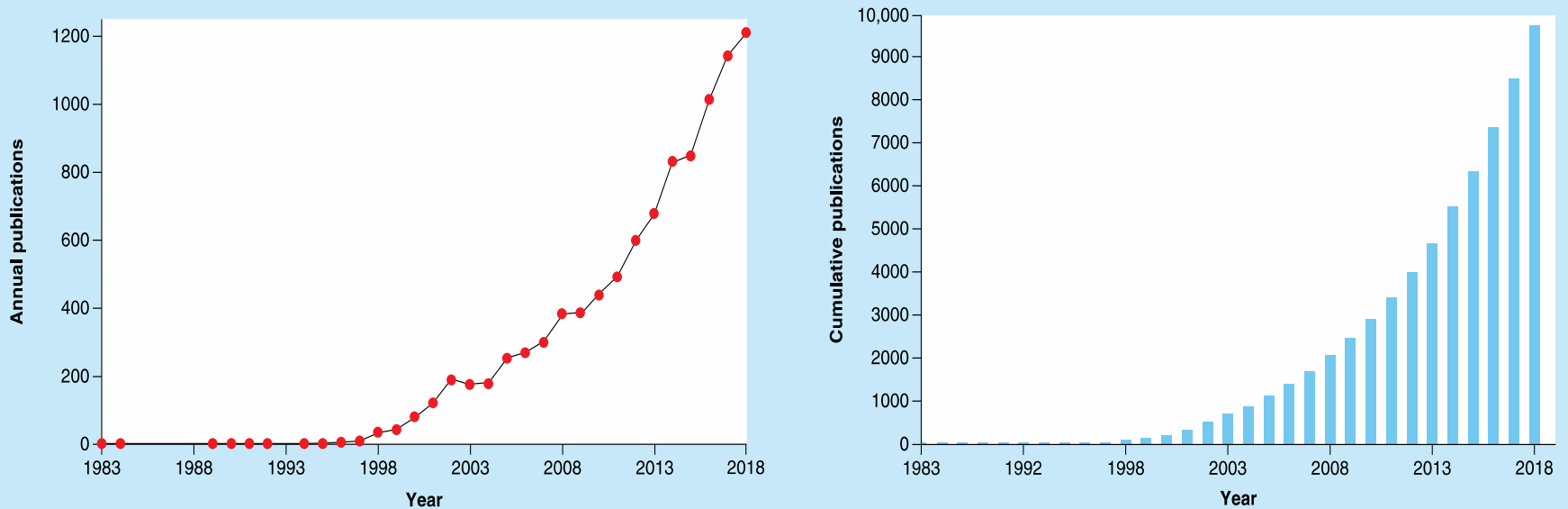
Fernando Cairo
fercairo@yahoo.com

Microbioma, el nuevo “organo metabólico”



En boom de investigación

Manuscritos Indexados en MEDLINE-Pubmed
(Probióticos and disease)



**15 Billones anuales - incremento 7%
/año**

Microbiota Saludable

Ecosistema compuesto por bacterias, protozoarios, hongos y virus

100 trillones de bacterias

80% Firmicutes 15% Bacteroidetes 2.5% Actinobacterias 1% Proteobacterias

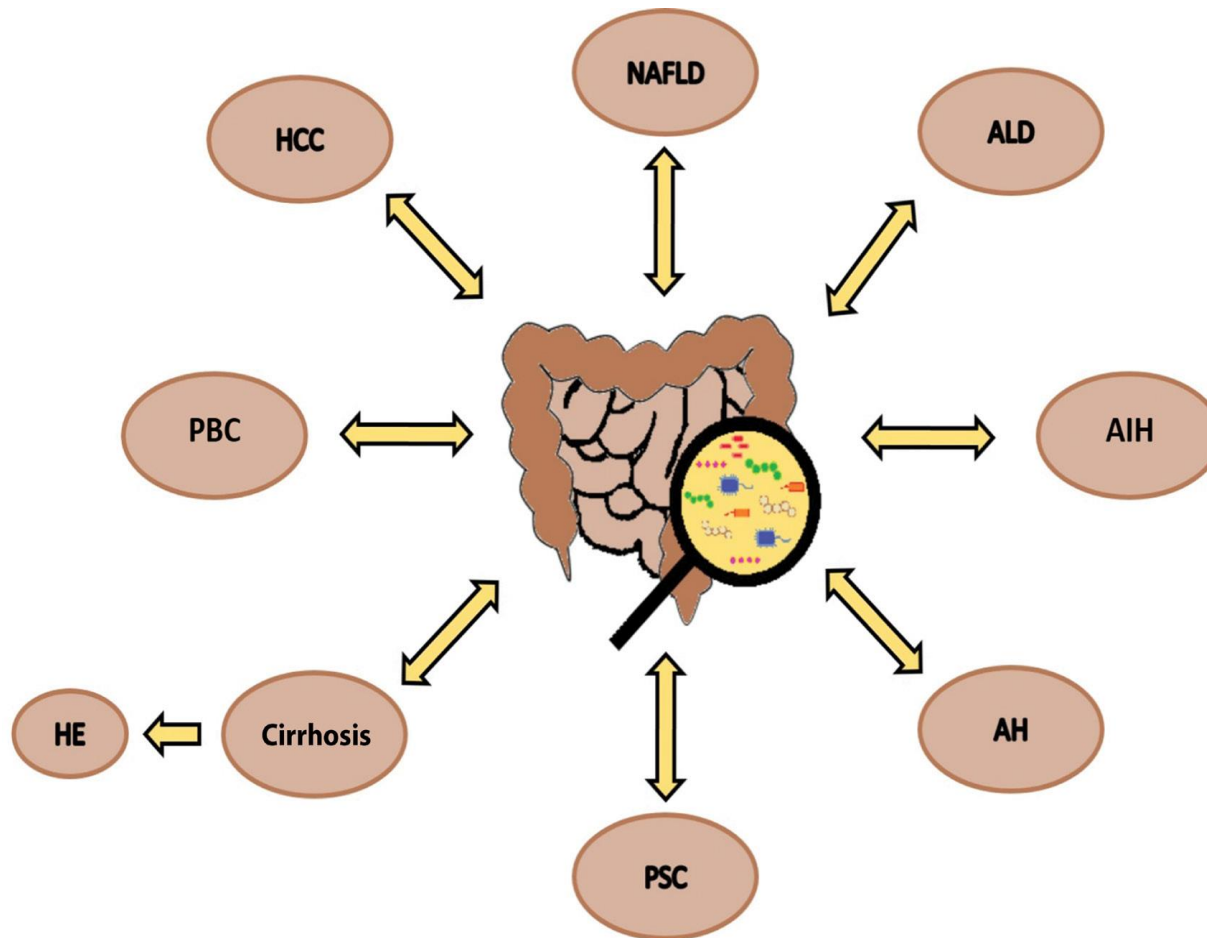
Ruminococcus
Clostridium
Eubacterias

Porphyromona
Prevotella

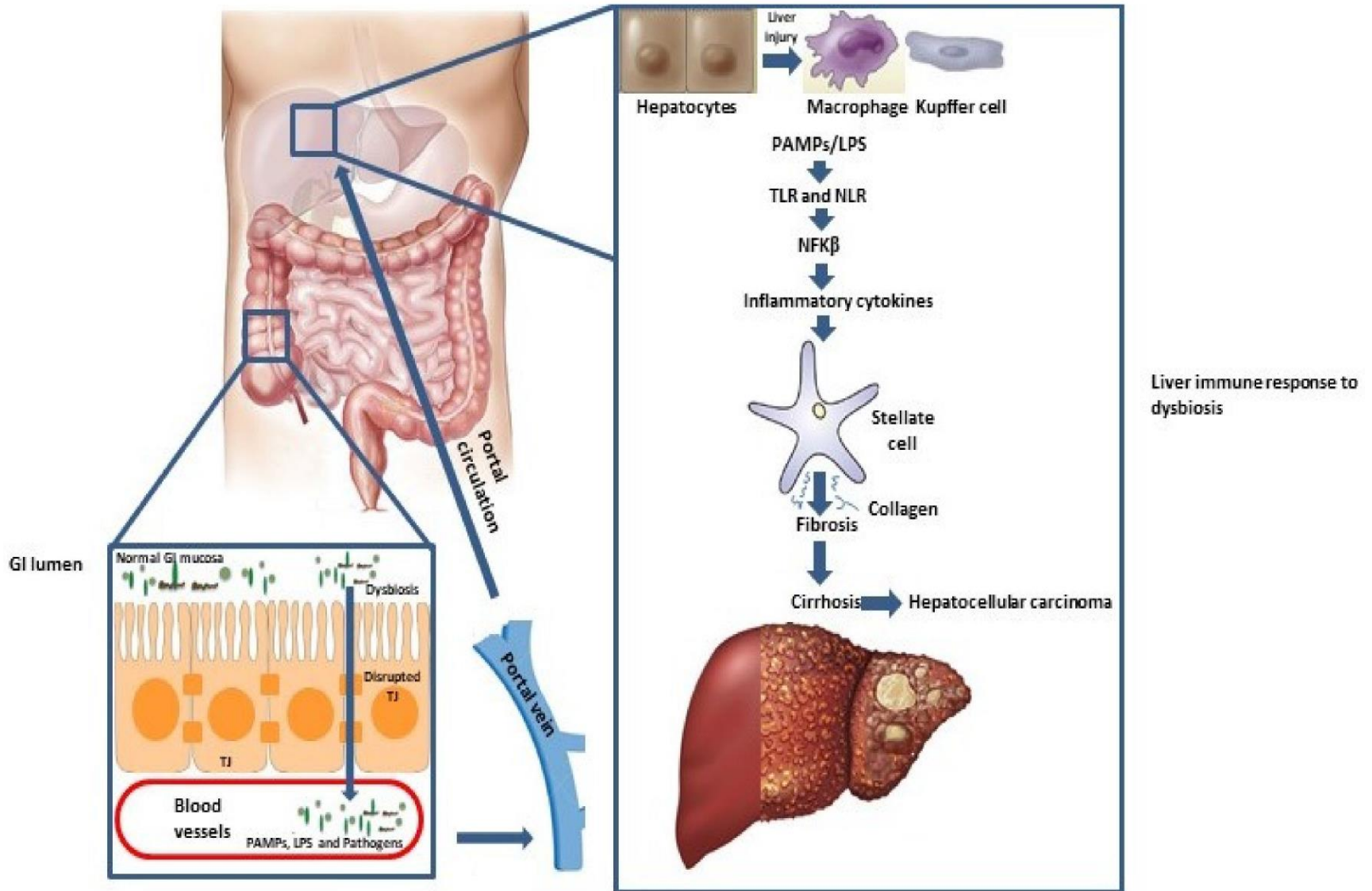
Bifidobacteria

Lactobacilos, Streptococcus, E coli

Eje intestino-hepático



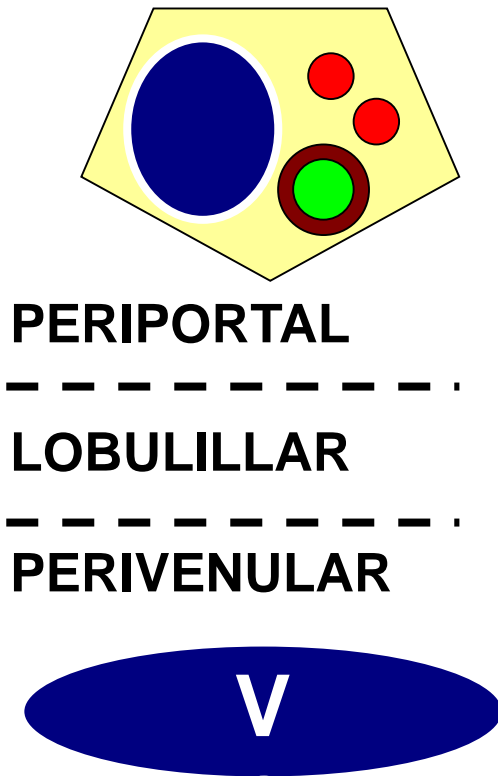
Disbiosis



Ultraestructura hepática

Células de Kupffer

¿Porque se distribuyen en zonas?



Flujo vascular

43%

28%

29%

- Célula presentadora de antígeno
- Detoxificación
- Regeneración

Eje Entero-Hepático

DISBIOSIS

Permeabilidad
Intestinal

Etanol

Colina

*Circulación
entero
hepática*

*Metabolismo
de ácidos
biliares*

Endotoxemia

LPS/Peptidogilcanos/flagelinas
PAMPS

Acetaldehído

Butirato

Péptido simil glucagón

Reducción de
producción de
ácidos grasos
de cadena
corta

TLRs/NLRs
Activación Cel.
Kupffer

Activación Cel.
Estrelladas

TGF- β

TNF- α IL-1/6

Fibrosis

Esteatosis

Aumento de
permeabilidad
intestinal.
Afectación de la
síntesis de IgA

Inflamación

**Daño de los
Hepatocitos**

Neoplasia

Correlación Bacteriana con Enfermedades Hepáticas

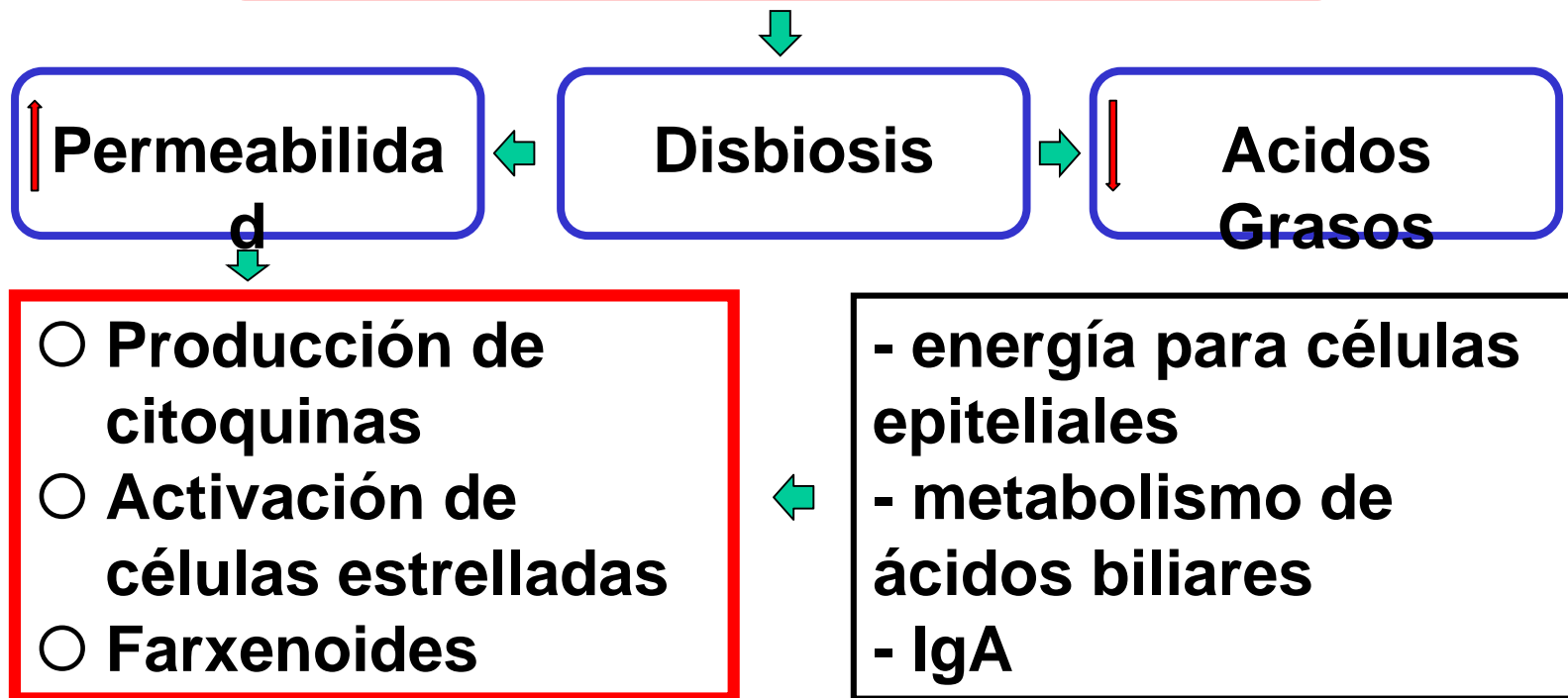
Enfermedad	Disbiosis
HBV	Cambio ratio Bifidobarteriaceae/Enterobacteriaceae Bajos niveles de Bifidobacterias y Lactobacillus
HBV cirrosis	Altos niveles de Enterococcus y enterobacteriaceae Descenso de bacteroidetes
HCV	Incremento de Proteobacteria Descenso de Bifidobacterium
HCC	Incremento de Prevotella Descenso de Lactobacillus
EPS	Incremento de E coli
ALD	Producción de amonio por bacterias productoras de ureasa (Klebsiella, Proteus)
NAFLD/NASH	Descenso de niveles de Butiraro (Clostridium)
CIRROSIS	Incremento de bacterias pro inflamatorias

Disbiosis en las Hepatitis Virales

- ◎ **Alteración en la producción de IgA (infección de linfocitos B gástricos)**
- ◎ **Modificación en las poblaciones bacterianas**
- ◎ **Aumento de proteobacterias**
- ◎ **Endotoxemia- Respuesta inflamatoria**
- ◎ **Progresión de fibrosis**
- ◎ **Mayor riesgo de HCC**

Disbiosis en consumo de Alcohol


Consumo crónico de Alcohol




Disbiosis en NASH

Obesidad

Diabetes



Reducción de síntesis de ácidos biliares
Cambio de poblaciones bacterianas
Producción etanol por metabolismo de azúcares (acetaldehído)



FARXENOIDES inactivos
-Inflamación
-Acumulación de triglicéridos intracelulares
-Aumenta resistencia insulínica

Disbiosis en Cirrosis

EPS

- Bacterias ureasa (+)
- Producción de amonio
- Endotoxina

PBE

- Permeabilidad intestinal
- Endotoxemia
- Bacteriemia

HCC

- Aflatoxina
- TLR4 proliferación celular
- Neovascular

Probióticos en Hígado

Disease	Therapeutic Option	References
NAFLD/NASH	-“VSL #3” (<i>Streptococcus thermophilus</i> , <i>Bifidobacterium breve</i> , <i>B. longum</i> , <i>B. infantis</i> , <i>Lactobacillus acidophilus</i> , <i>L. plantarum</i> , <i>L. paracasei</i> , <i>L. bulgaricus</i>) reduces liver injury	[61,62]
Cirrhosis	-Diet rich in fermented milk, vegetables, cereals, coffee, and tea is associated with a higher microbial diversity and lower risk for cirrhosis progression	[63]
HCC	-Probiotics can contribute to the inhibition of aflatoxin B-induced hepatocarcinogenesis, restore intestinal dysbiosis, reduce LPS levels and decrease tumor size -Probiotic fermented milk and chlorophyllin slow down tumor growth and volume for 40%	[58,99] [64]
HE	- <i>Lactobacillus</i> , <i>Bifidobacterium</i> , non-pathogenetic strains of <i>Escherichia coli</i> , <i>Clostridium butyricum</i> , <i>Streptococcus salivarius</i> , <i>Saccharomyces boulardii</i> and VSL#3 improve HE	[65–69]

Abbreviations: NAFLD, non-alcoholic fatty liver disease, HCC, hepatocellular carcinoma, HE, hepatic encephalopathy, and NASH, non-alcoholic steatohepatitis.

**Ivana Milosevic, et al. International Journal of Molecular Sciences
Gut-Liver Axis, Gut Microbiota, and Its Modulation in the Management of Liver
Diseases. 2019**

Probióticos en Hígado. Evidencia Cochrane

<i>Liver conditions</i>						
Lirussi et al. (2009) [45]	0	n/a	n/a	<ol style="list-style-type: none"> 1 All-cause mortality 2 Hepatic-related mortality 3 Radiological response and/or histological response 4 Biochemical response 5 Breath tests 6 Adverse events 7 Quality-of-life measures 8 Cost-effectiveness 	C	No randomized controlled trials fulfilling the inclusion criteria were found and the authors were unable to draw any conclusions about benefit or harm.
McGee et al. (2011) [46] ***	7	550	30–74	<ol style="list-style-type: none"> 1 All-cause mortality 2 Number of participants who did not recover 3 Adverse events 4 Quality of life 5 Change of or withdrawal from treatment 6 Number of participants with one or more episodes of sepsis 7 Change in plasma ammonia concentration 8 Duration of stay in hospital 	C	The authors were unable to draw any conclusions about benefit or harm.

* (A) the review indicated good evidence of benefit from probiotics; (B) the review indicated good evidence of no benefit from probiotics; (C) the review indicated that there was not sufficient available evidence to allow benefits from probiotics to be determined

** Review conclusions are based on GRADE assessment for the primary outcomes and for adverse events if GRADE was used in the review. For reviews that did not explicitly use GRADE, a summary of the amount and type of evidence from the “Effects of interventions” section was provided.

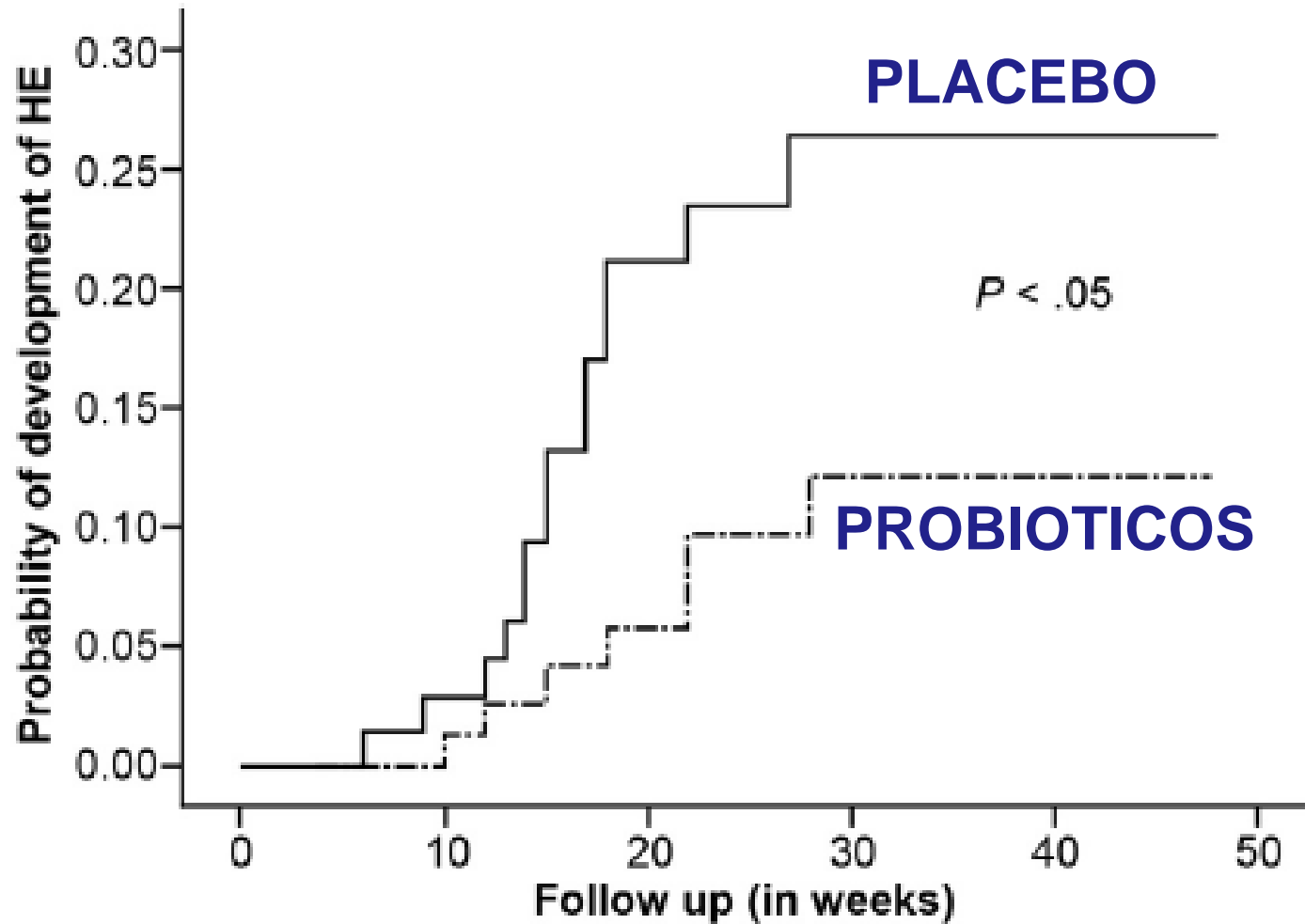
*** GRADE criteria used in the review.

Probióticos

**6 Trials- RTC hasta 2014
(496 pac incluidos)**

Desarrollo de EPS	0,0001
Mortalidad	ns
Niveles de Amonio	ns
Constipación	ns

Probióticos en EPS



Conclusiones

- © **Es necesario mayor cantidad de Trials**
- © **Clara asociación fisiopatogénica**
- © **Mayor impacto en NASH, Alcohol, EPS y cirrosis**
- © **No se reconoce cual es la mejor opción terapéutica**
- © **Se discute el riesgo de bacteriemia**