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ACLF Pathophysiology: Systemic Inflammation and Oxidative Stress

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Outline

- Two theories on ACLF pathophysiology
- How the 2 theories were addressed
- Examples of triggers

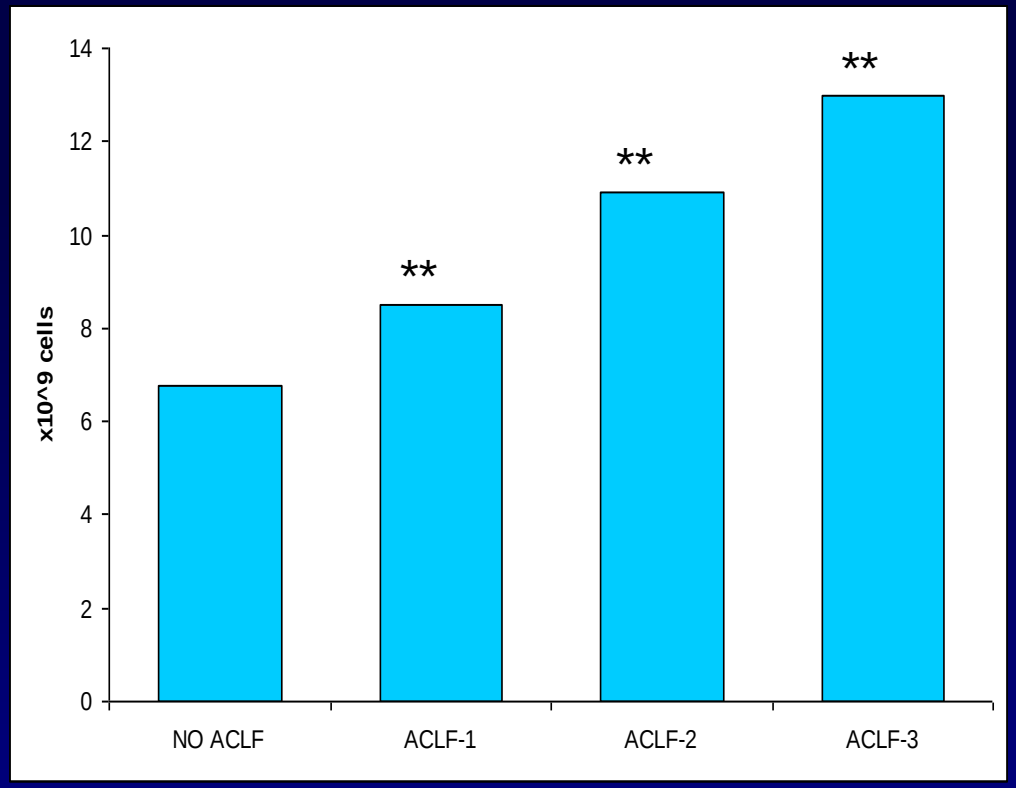
The “traditional” peripheral vasodilation theory

In cirrhosis, enhanced circulatory dysfunction causes “functional” organ failure (OF) that may progress to “organic” OF

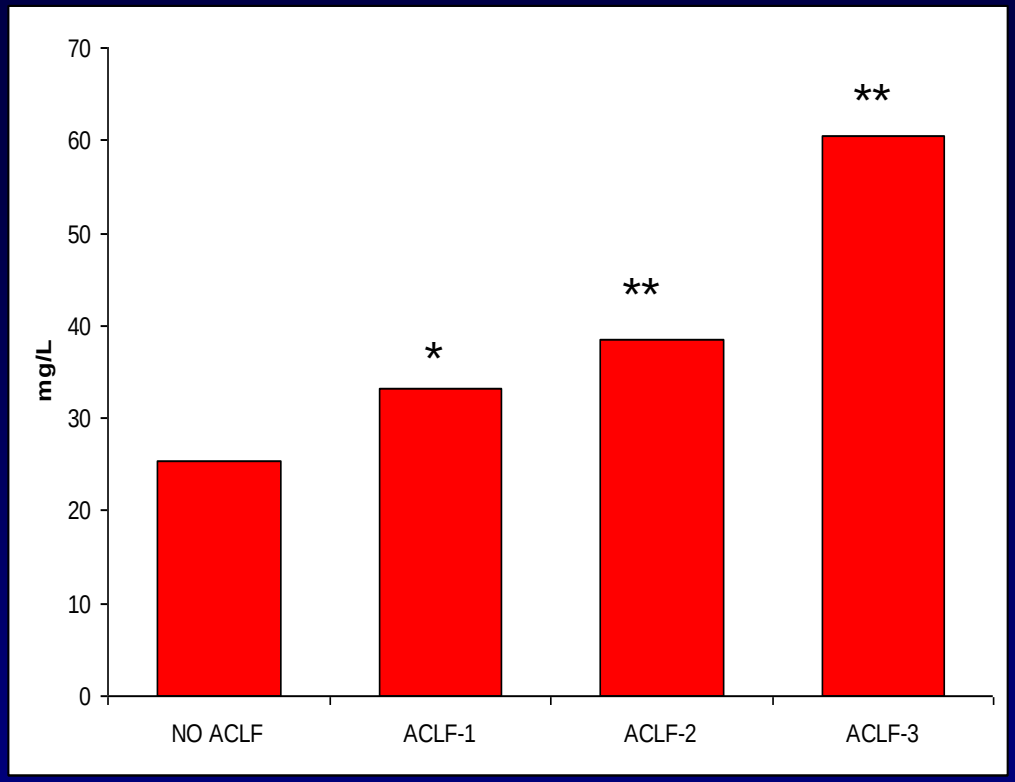
What we learnt with the CANONIC study

ACLF is Associated With Systemic Inflammation

White-cell count*



C-reactive Protein*



* p<0.05 with respect to No ACLF

** p<0.001 with respect to No ACLF

Moreau et al. Gastroenterology 2013;144:1426-37.

What we learnt
from immunologists:
Excessive systemic inflammation can cause tissue damage (immunopathology)

The “revisited” theory

In cirrhosis, systemic inflammation can drive the development of organ dysfunction/failure

Bernardi et al. J Hepatol 2015;63:1272-84.
Arroyo et al. Nat Rev Dis Primers 2016;2:1604

Outline

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- **How the 2 theories were addressed**
- Examples of triggers

The Study by Claria, Stauber et al. in CANONIC Patients

Tools	Markers of
Plasma renin & copeptin	Systemic circulatory dysfunction
29 plasma cytokines & chemokines	Systemic inflammation
Serum albumin redox (HNA2, Cys32)	Systemic oxidative stress

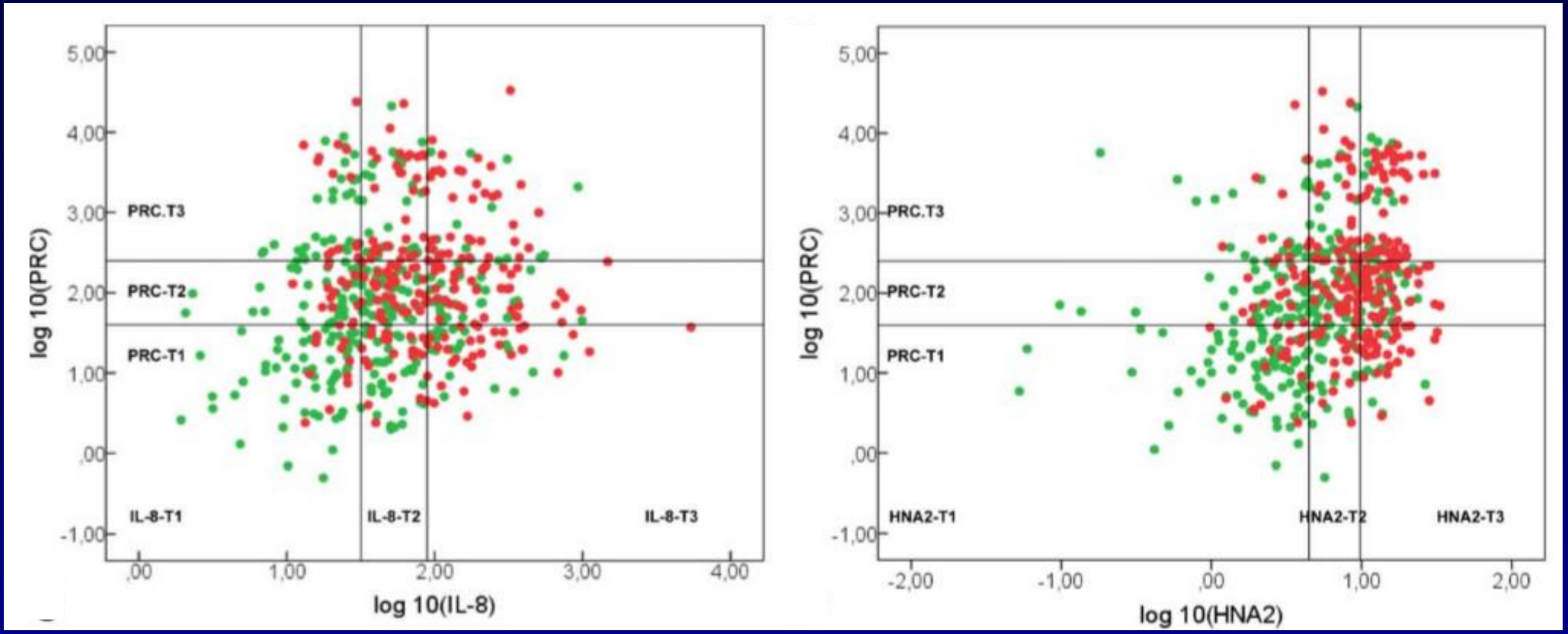
Hepatology 2016;64:1249-64.

The ACLF Landscape

Markers	Healthy Controls (N=40)	With AD, No ACLF (N=285)	With ACLF (N=237)	*P* value
Systemic circulatory dysfunction				
Renin (microIU/mL)	8 (6-17)	65 (17-242)	134 (36-378)	<0.001
Copeptin (pmol/L)	0 (0-10)	9 (3-23)	31 (13-61)	<0.001
Pro-inflammatory cytokines				
TNF-α (pg/mL)	9 (7-12)	20 (14-27)	29 (17-41)	<0.001
IL-6 (pg/mL)	0.3 (0.3-0.3)	21 (11-41)	39 (17-115)	<0.001
IL-8 (pg/mL)	1.6 (0.6-3.3)	37 (20-76)	84 (41-169)	<0.001
Anti-inflammatory cytokines				
IL-10 (pg/mL)	1.1 (0.4-1.1)	3.4 (1.1-9.2)	8.1 (2.1-29.9)	<0.001
IL-1ra (pg/mL)	7 (3-9)	10 (5-22)	23 (9-63)	<0.001
Albumin oxidation fractions				
HNA2 (%)	1.3 (0.3-1.9)	4.5 (2.5-8.8)	9.8 (5.6-14.8)	<0.001

Claria, Stauber et al. Hepatology 2016;64:1249-64.

Distribution of Markers at Baseline Among Patients with (red) and without (green) ACLF



Claria, Stauber et al. Hepatology 2016;64:1249-64.

Markers at Baseline According to ACLF Triggers

Markers	No trigger (N=94)	Bacterial infection/ No active alcoholism (N=63)	Active alcoholism/ No infection (N=28)	Bacterial infection/ active alcoholism (N=11)	*P* value
Renin (microIU/mL)	151 (50-474)	164 (28-447)	92 (31-295)	205 (112-998)	0.3
IL-6 (pg/mL)	30 (14-69)	72 (28-358)	37 (13-122)	83 (34-466)	<0.001
IL-8 (pg/mL)	64 (38-104)	92 (47-167)	211 (141-351)	158 (99-310)	<0.001
IL-10 (pg/mL)	6.2 (1.9-25.8)	17.8 (4.7-55)	8.3 (1.0-22.9)	24.5 (5.9-40.2)	0.08
IL-1ra (pg/mL)	19 (8-47)	41 (13-100)	16 (8-49)	25 (14-37)	0.17
HNA2 (%)	9.6 (5.1-14.8)	12.3 (8.-15)	8.6 (7.0-13.3)	10.3 (6.5-14)	0.06

Claria, Stauber et al. Hepatology 2016;64:1249-64.

Markers at Baseline Across ACLF Grades

Markers	ACLF-I (N=126)	ACLF-II (N=86)	ACLF-III (N=25)	*P* value
Systemic circulatory dysfunction				
Renin (microIU/mL)	169 (40-383)	114 (28-352)	87 (33-258)	0.8
Pro-inflammatory cytokines				
TNF-α (pg/mL)	30 (21-43)	26 (15-36)	32 (17-43)	0.03
IL-6 (pg/mL)	34 (18-96)	43 (13-106)	111 (32-355)	0.02
IL-8 (pg/mL)	62 (37-112)	97 (48-192)	144 (80-292)	<0.001
Anti-inflammatory cytokines				
IL-10 (pg/mL)	4.3 (1.1-17.9)	15.3 (5.5-41.5)	12.4 (6.6-40.8)	<0.001
IL-1ra (pg/mL)	17 (10-45)	26 (8-63)	49 (24-135)	0.02
Albumin oxidation fractions				
HNA2 (%)	9.5 (5.1-13.9)	9.8 (5.6-15.1)	11.1 (7.8-15.1)	0.2

Claria, Stauber et al. Hepatology 2016;64:1249-64.

Summary

- Patients with AD without ACLF have high baseline levels of inflammatory cytokines, HNA2, PRC and PCC. Patients with ACLF have much higher levels of these markers than patients without ACLF.
- The strength of association of ACLF with systemic inflammation and systemic oxidative stress is higher than with systemic circulatory dysfunction.
- Different cytokine profiles exist according to the ACLF trigger (active alcoholism, bacterial infection).
- Intensity of systemic inflammation, but not of systemic oxidative stress, is strongly associated with the frequency and severity of ACLF at enrollment.

Summary

- Patients with AD without ACLF have high baseline levels of inflammatory cytokines, HNA2, PRC and PCC. Patients with ACLF have much higher levels of these markers than patients without ACLF

These data support systemic inflammation as the primary driver of ACLF in cirrhosis

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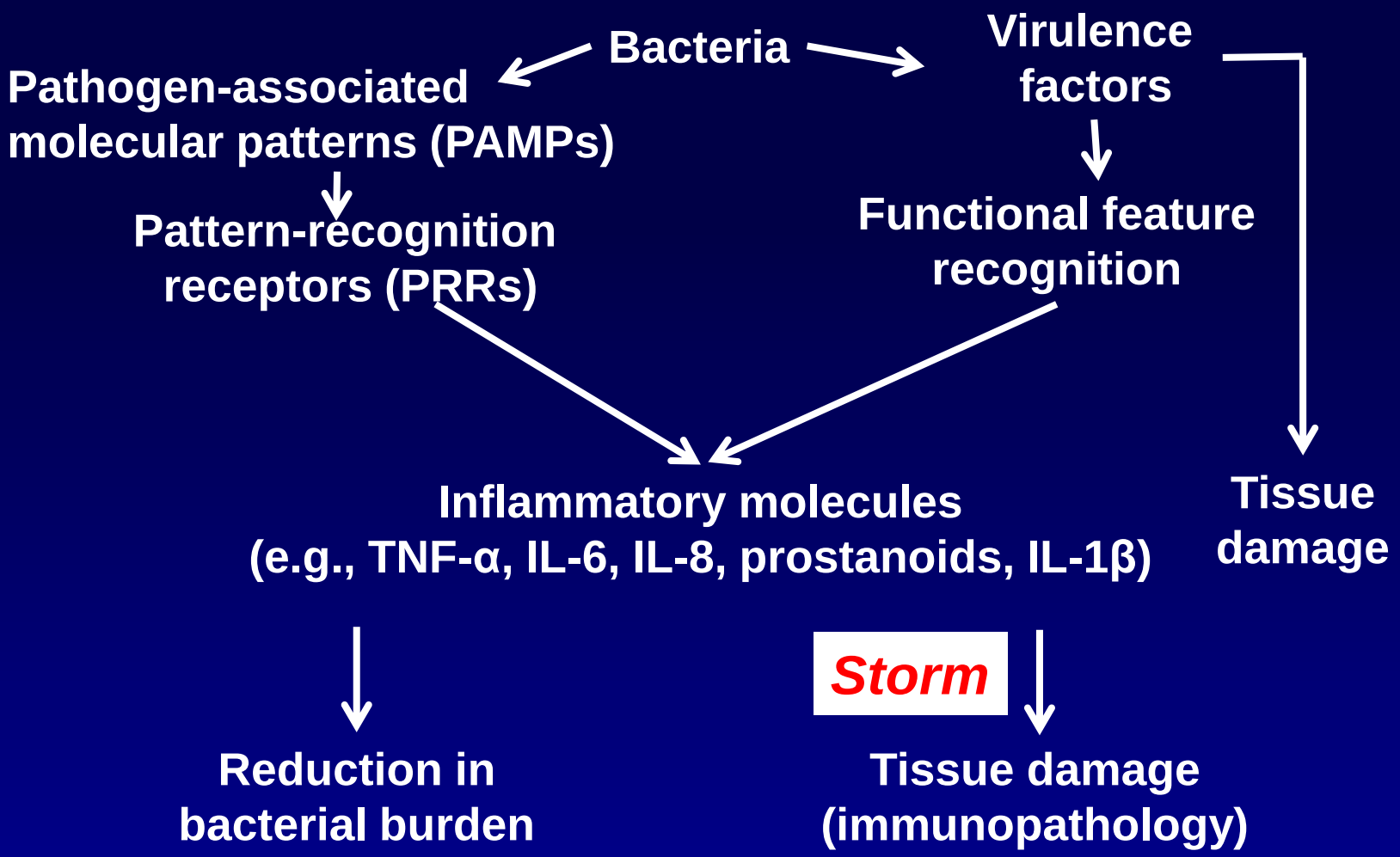
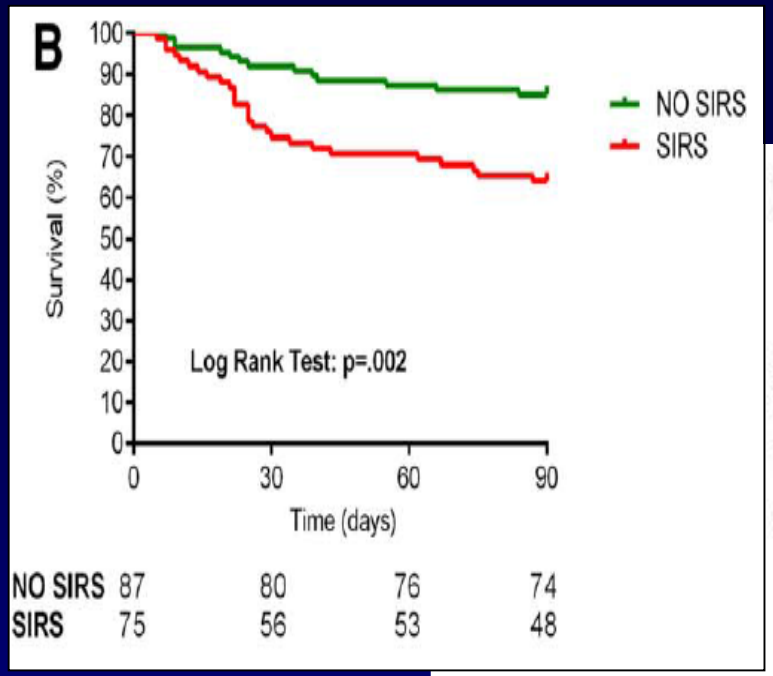
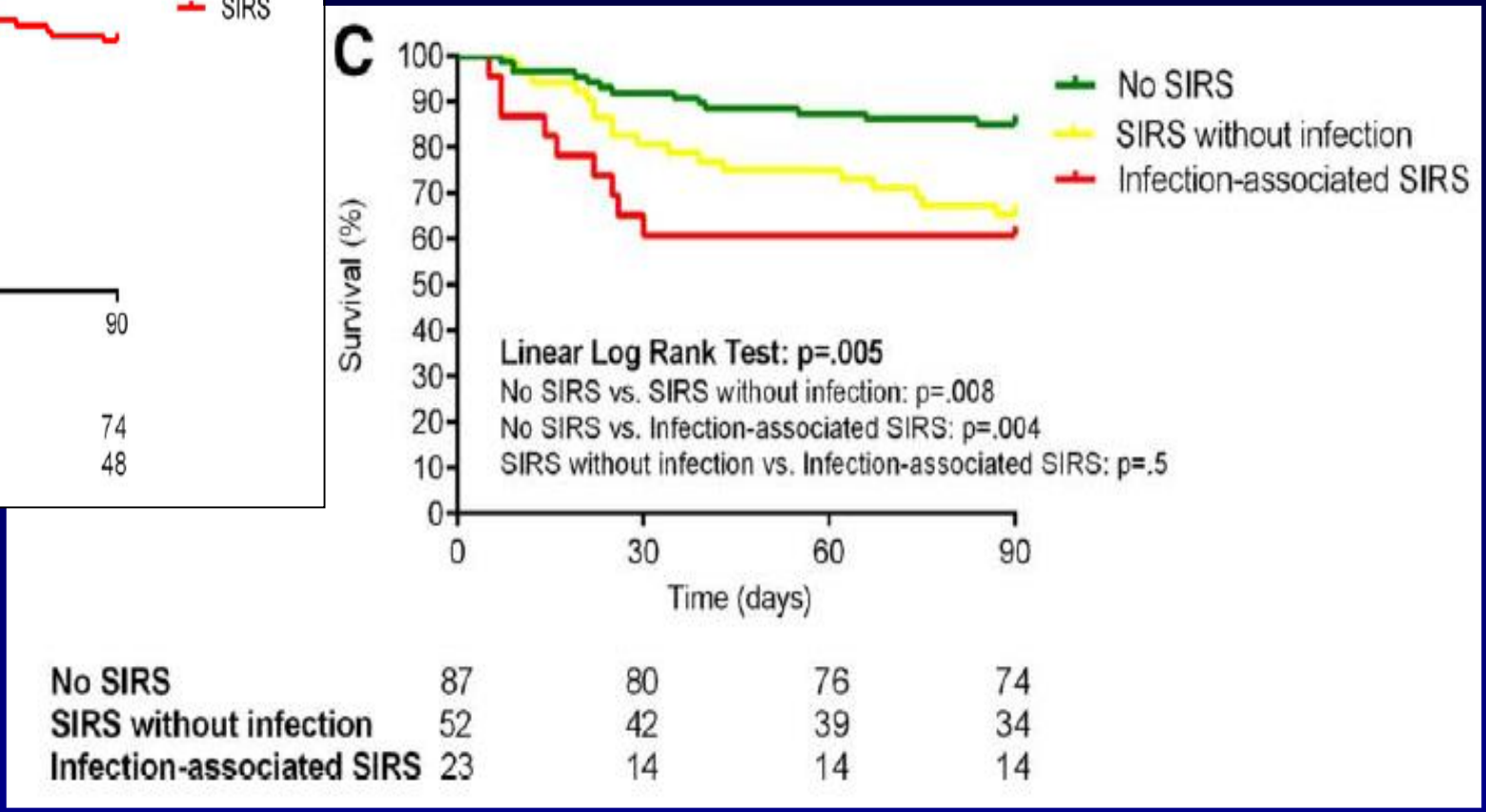
Mechanisms of Severe Bacterial Sepsis



Systemic Inflammation Predicts Outcome in Patients with Alcoholic Hepatitis





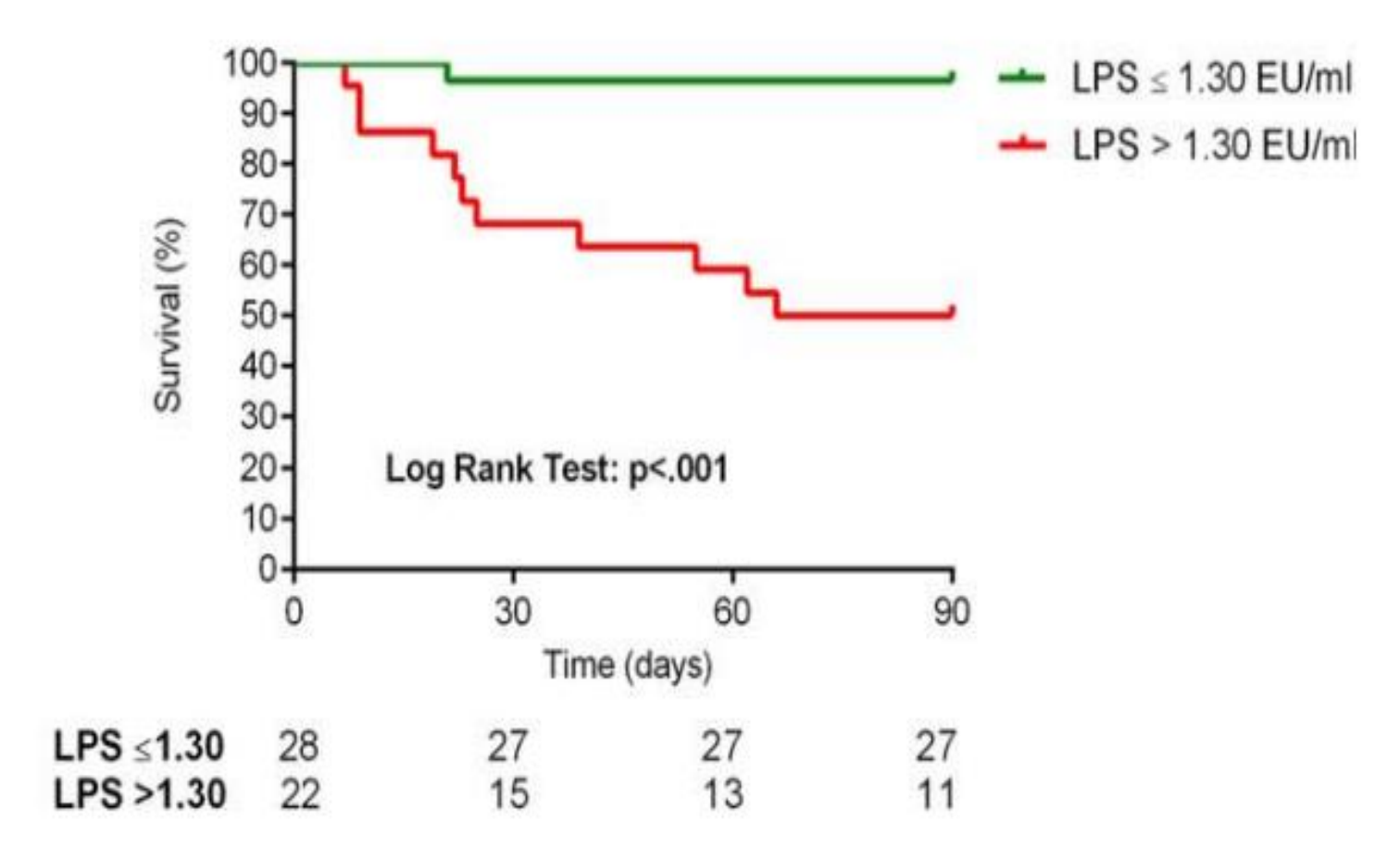
Michelena et al. Hepatology 2015;62:762-72.

Predictors of Multiorgan Failure in Patients with Alcoholic Hepatitis

Variable	OR	95% CI	*P*
Multivariate model 1 (only variables at admission)			
SIRS at admission	2.687	1.129-6.395	**0.025**
Infection at admission	1.591	0.590-4.289	0.358
Creatinine (mg/dL)	2.508	1.146-5.491	**0.021**
Bilirubin (mg/dL)	1.096	1.042-1.153	**<0.001**
Albumin (g/L)	0.956	0.864-1.059	0.393
INR	1.996	0.745-5.344	0.169
Multivariate model 2			
SIRS at admission	3.351	1.344-8.354	**0.009**
In-hospital infection	6.585	2.562-16.924	**<0.001**
Creatinine (mg/dL)	1.616	0.739-3.532	0.229
Bilirubin (mg/dL)	1.095	1.037-1.157	**0.001**
Albumin (g/L)	0.913	0.814-1.025	0.123
INR	1.531	0.526-4.457	0.435

Michelena et al. Hepatology 2015;62:762-72.

Endotoxemia Predicts Death in Patients with Alcoholic Hepatitis



Michelena et al. Hepatology 2015;62:762-72.

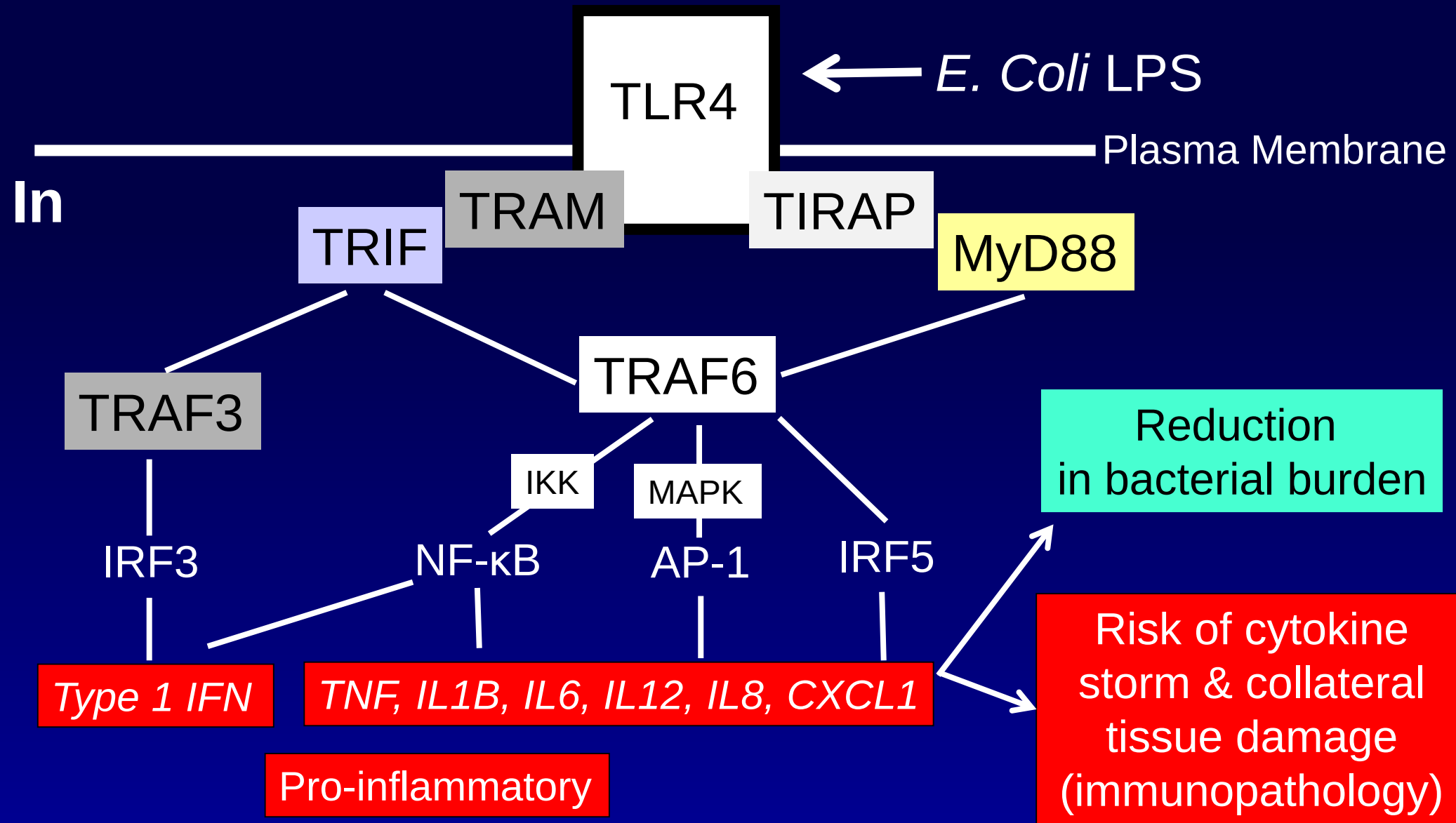
ACLF of 'Unknown Origin'

- No trigger in ~45% of ACLF
- Associated with inflammation
- Mechanism(s) for inflammation?
  - — Infection, not identified by culture?
  - — Translocation of bacterial pathogen-associated molecular patterns (PAMPs)?
  - — Metabolites produced by gut bacteria?
  - — Damage/danger-associated molecular patterns (DAMPs)?

Summary

- In bacterial infections, systemic inflammation can be a result of several mechanisms induced by PAMPs and virulence factors.
- In severe alcoholic hepatitis, independently of infection, bacterial PAMPs coming from the gut, may play a role in systemic inflammation and the development of ACLF.
- In ACLF with no identifiable triggers, the mechanism of systemic inflammation is unknown.

What we Learnt From Immunologists



Kawai and Akira. Nat Immunol 2010;11:373-84.