

**Sepsis chez les Malades
Atteints de Cirrhose.
Actualités sur l'Albumine**

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Dr. Richard Moreau

**INSERM U773, Centre de Recherche Biomédicale
Bichat-Beaujon CRB3 et Service d'Hépatologie,
Hôpital Beaujon, Clichy
rmoreau@bichat.inserm.fr**

In Cirrhosis, Bacterial Infection is a Common Cause of Acute-on-Chronic Liver Failure

Cirrhosis (n):	700,000
Acute-on-chronic LF (n):	100,000
Gram-negative bacteria-related:	Frequent
Mortality (n/yr)	
Overall:	10,000
Sepsis-related:	5-6,000
Hepatic replacement therapy:	NA*
Liver transplantation (n/yr):	~1,000

***Not available.**

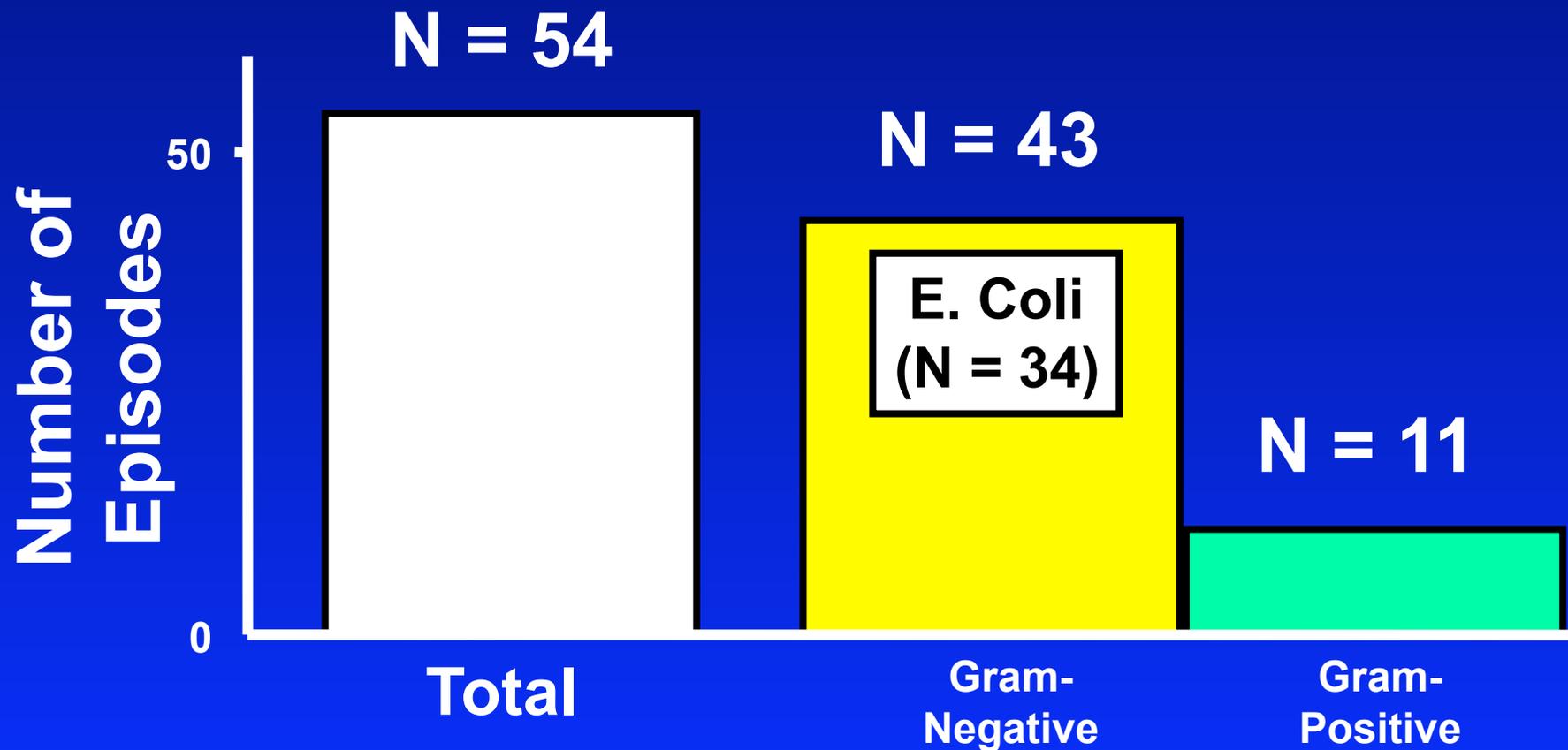
Definition of Sepsis

Infection
(Bacteria, Virus, Fungus)

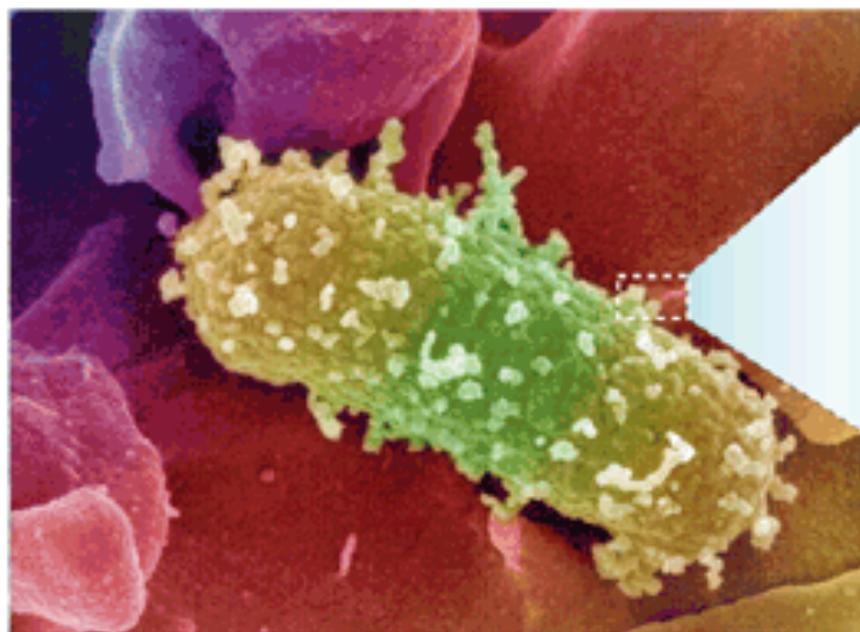
+

Host
Systemic Inflammatory
Response

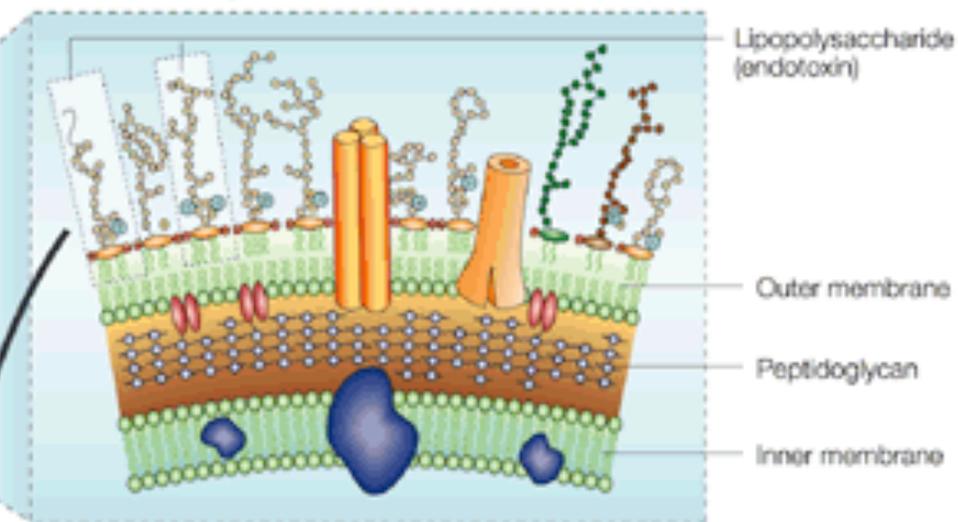
Spontaneous Bacterial Peritonitis (SBP) is The Paradigm of Bacterial Infection in Cirrhosis



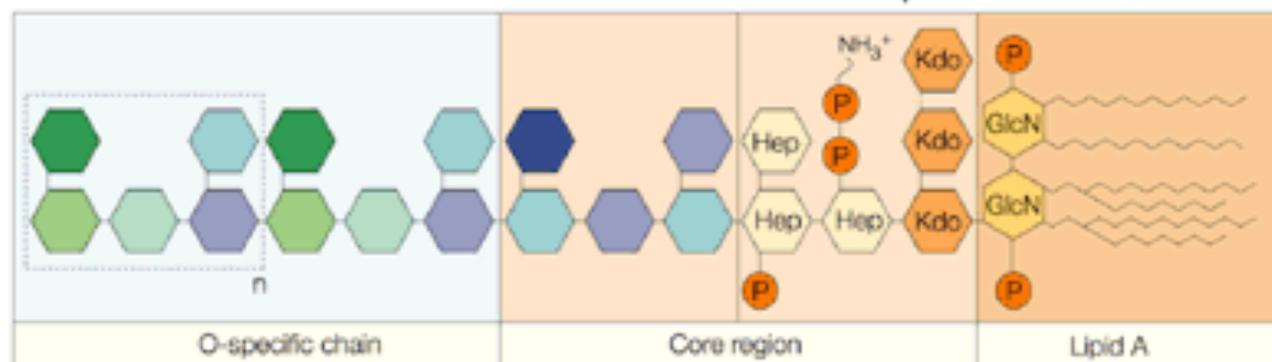
a Bacterial cell (*E. coli*)



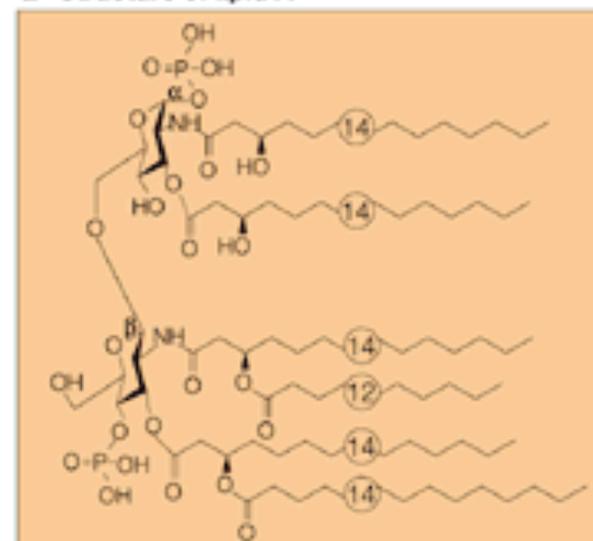
b Cell-wall organization



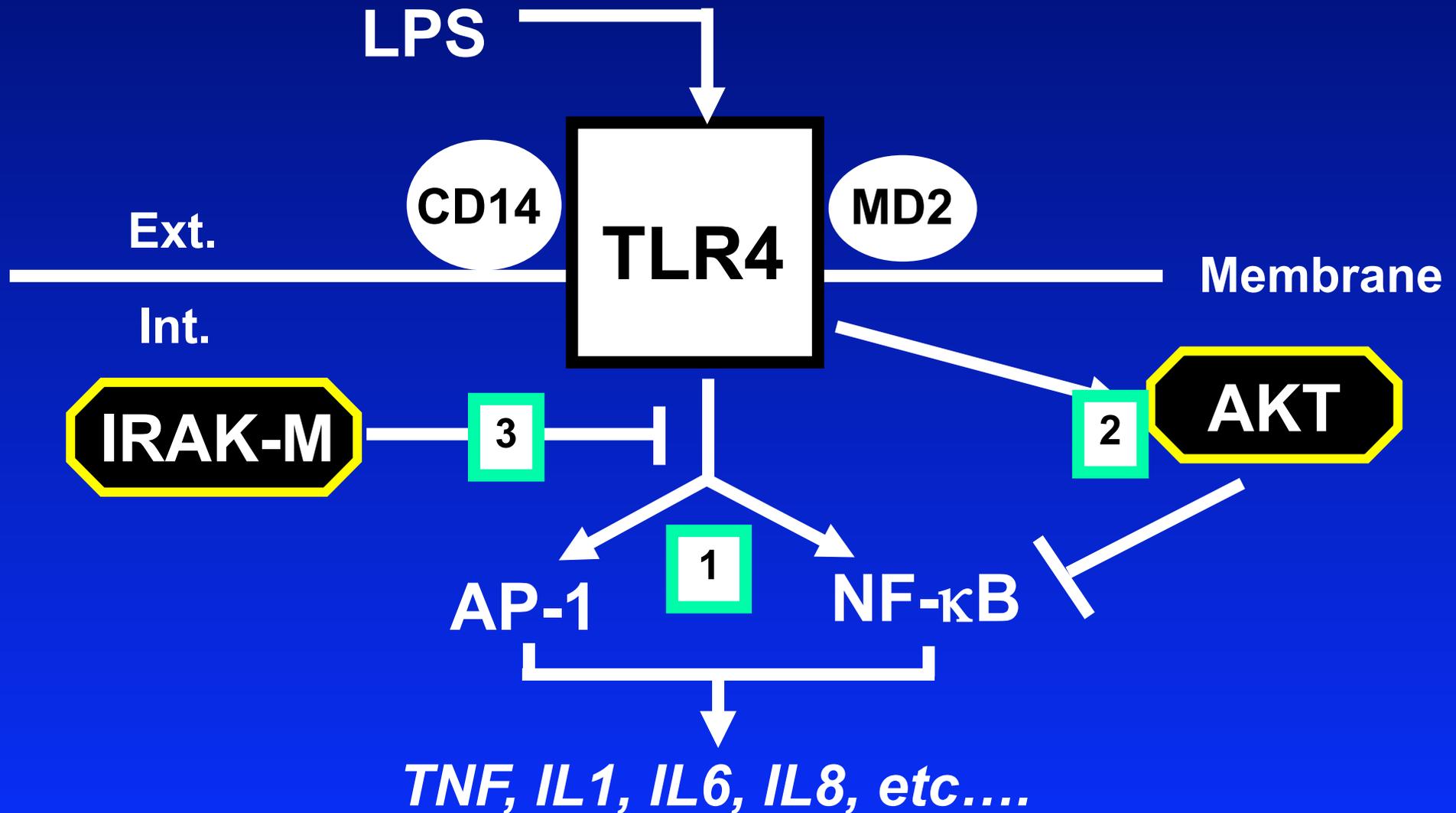
c Architecture of lipopolysaccharide



d Structure of lipid A

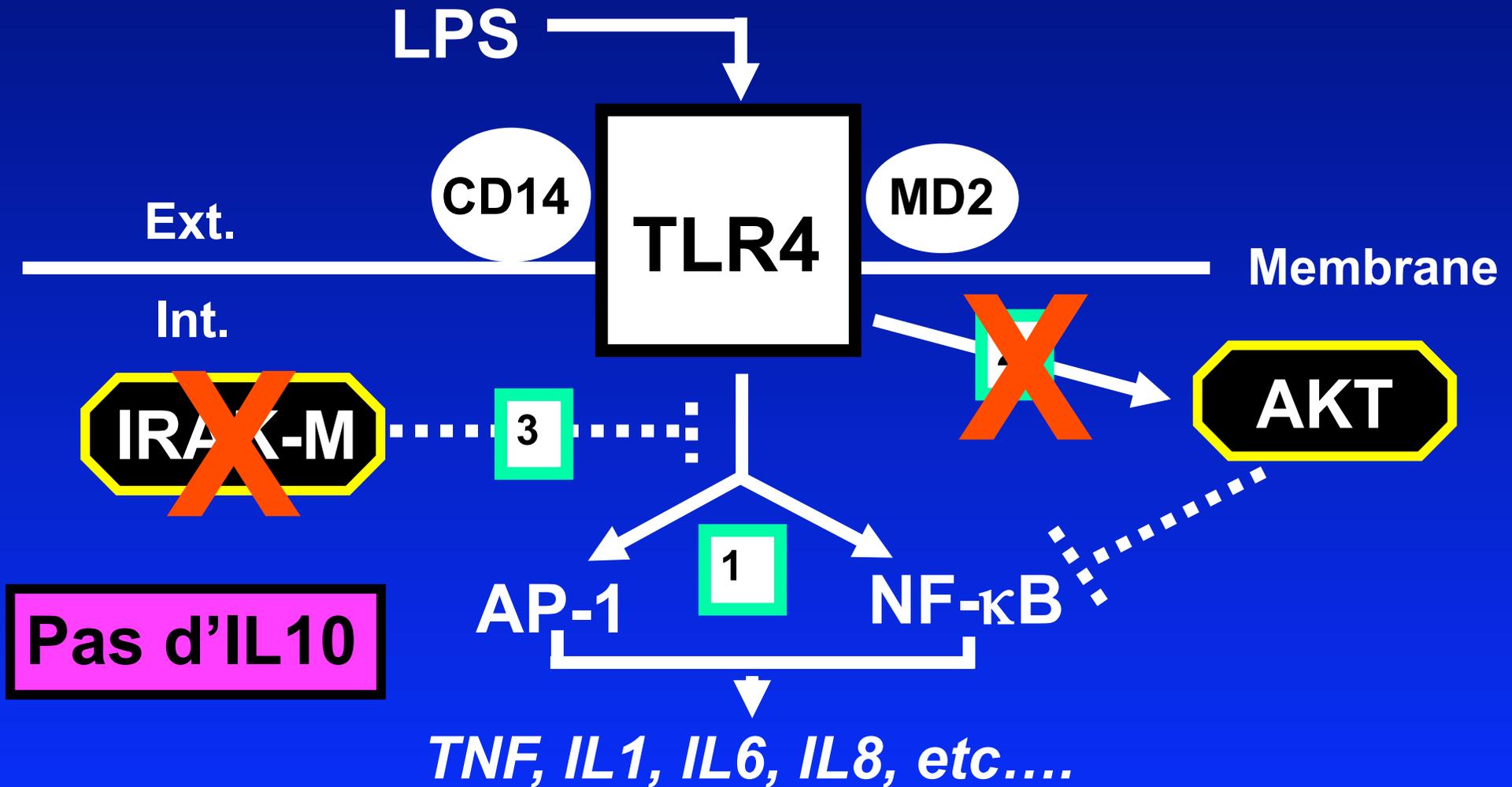


Réponse immunitaire innée dans les monocytes de sujets normaux



*GSK : glycogen synthase kinase. Martin et al. Nat Immunol 2005;6:777.

Réponse immunitaire innée dans les monocytes des malades atteints de cirrhose avancée



Gram-Negative Bacteria Byproducts (LPS)



*Monocytes/
macrophages*

Proinflammatory molecules

**Systemic
Inflammation**

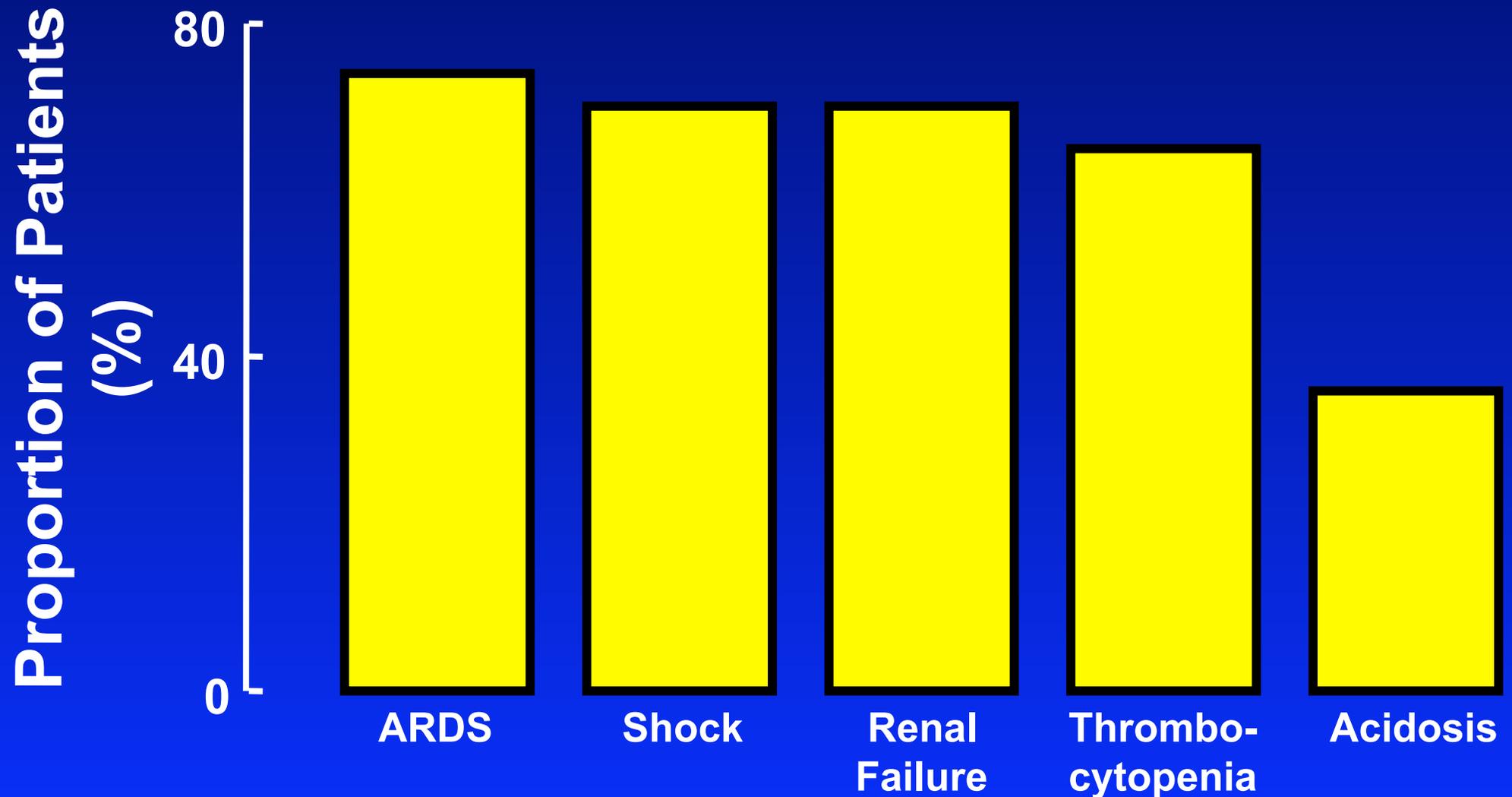
**Thrombin
Generation**

Organ/System Failures

Death

Bernard et al.
N Engl J Med
2001;344:699.

Extrahepatic Organ Failures in Patients With Cirrhosis and Severe Sepsis



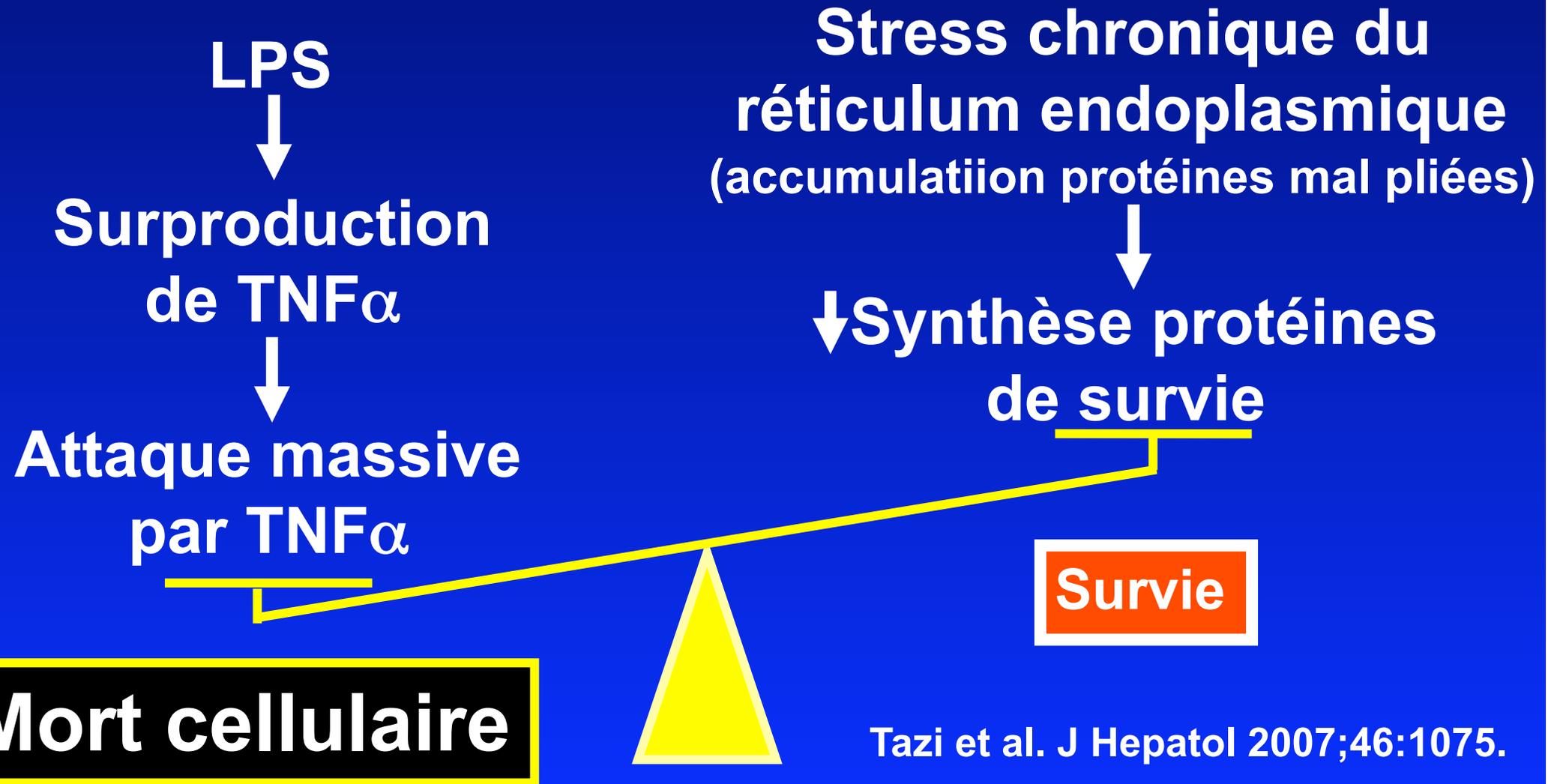
Plessier et al. Liver Int 2003;23:440.

Coagulation Disorders in Patients With Cirrhosis and Sepsis

Variable	Sepsis	Severe Sepsis
FVII+X (IU/mL)*	55	25**
FV (IU/mL)*	75	43**
FII (IU/mL)*	58	30**
Patients with soluble fibrin (%)	9	41**

*Mean. **P<0.05. Plessier et al. Liver Int 2003;23:440.

Apoptose hépatocytaire induite par LPS dans la cirrhose



Tazi et al. J Hepatol 2007;46:1075.

Septic Shock is More Severe in Cirrhotics Than in Noncirrhotics

Variable	Non cirrhotic	Cirrhotic
Hypotension	30%	80%
Liver failure	No	Severe
Mortality	30%	80%

*Bernard et al. N Engl J Med 2001;344:699-709.

**Plessier et al. Liver Int 2003;23:440-8.

**Nouvelles Approches
Thérapeutiques Dans la Cirrhose
Complicquée de Choc Septique**

A Nonrandomized Study of Hydrocortisone For Septic Shock in Patients With Cirrhosis

Variable	Untreated (N = 50)	Treated (N = 25)
	<i>Proportion (%)</i>	
Shock resolution	58	96*
ICU survival	38	68*
Hospital survival	32	64*

* $P < 0.05$. Fernandez et al. Hepatology 2006;44:1288.

Treatments That May Decrease Mortality in Noncirrhotic Patients With Severe Sepsis

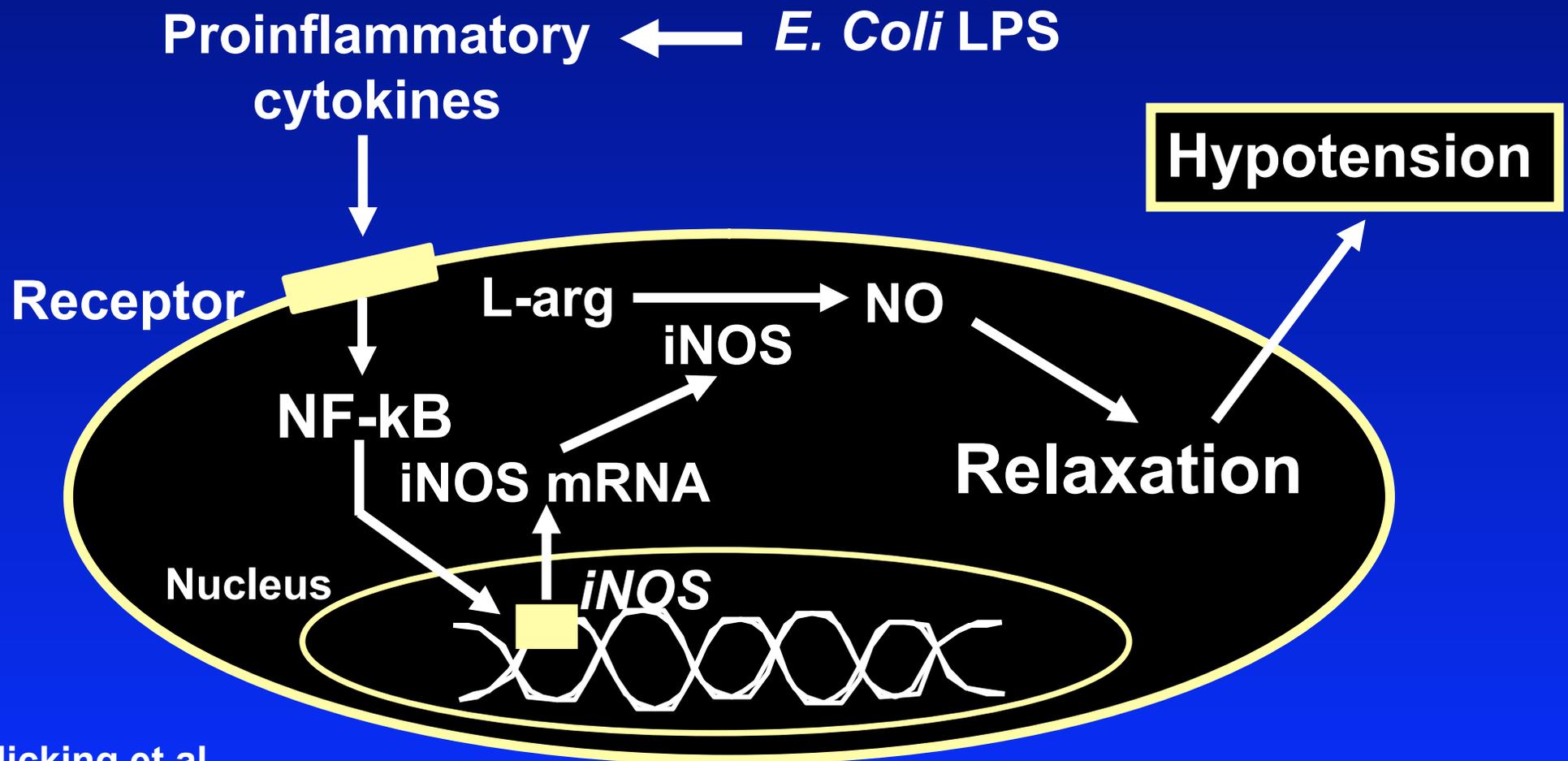
<u>Treatment</u>	<u>First Author (ref.)</u>
Antibody to TNF	Marshall (1)
IL-1 receptor antagonist	Marshall (1)
Activated protein C	Bernard (2)
Intensive insulin	Van den Berghe (3)
Hemodynamic therapy	Rivers (4)
Glucocorticoid	Annane (5)

(1) Nat Rev Drug Discov 2003;2:391. (2) N Engl J Med 2001;344:699.

(3) N Engl J Med 2001;345:1359. (4) N Engl J Med 2001;345:1368.

(5) JAMA 2002;288:862.

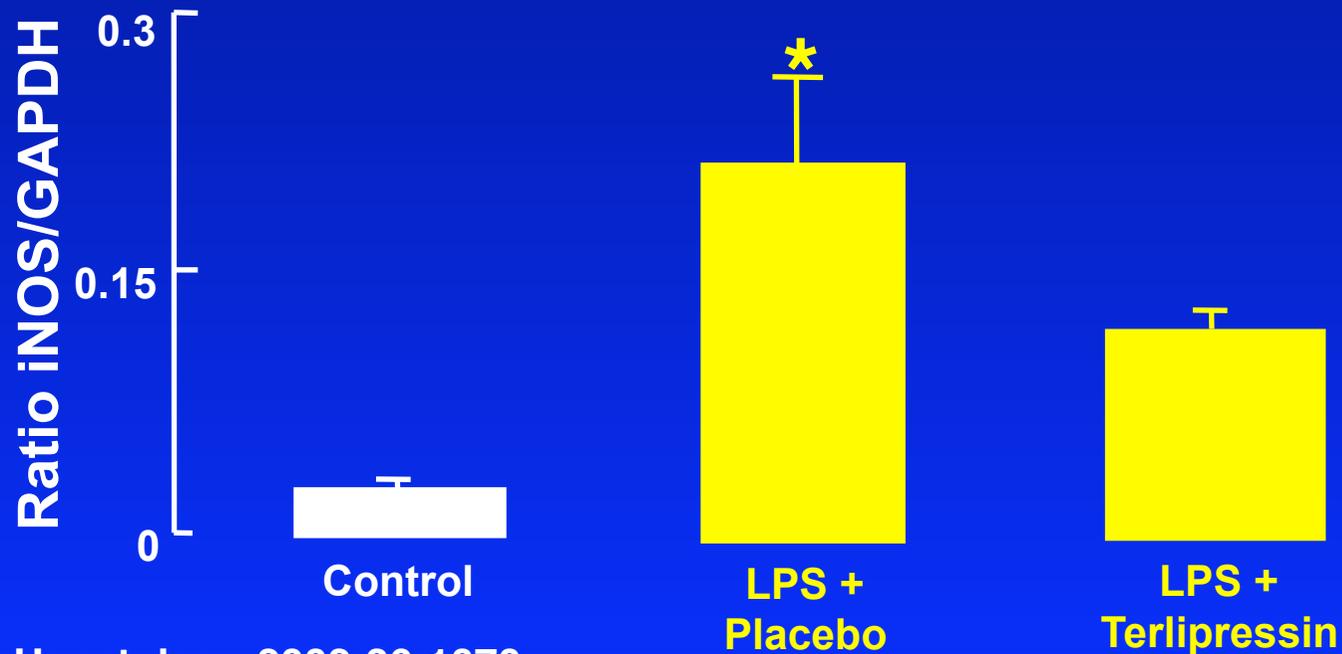
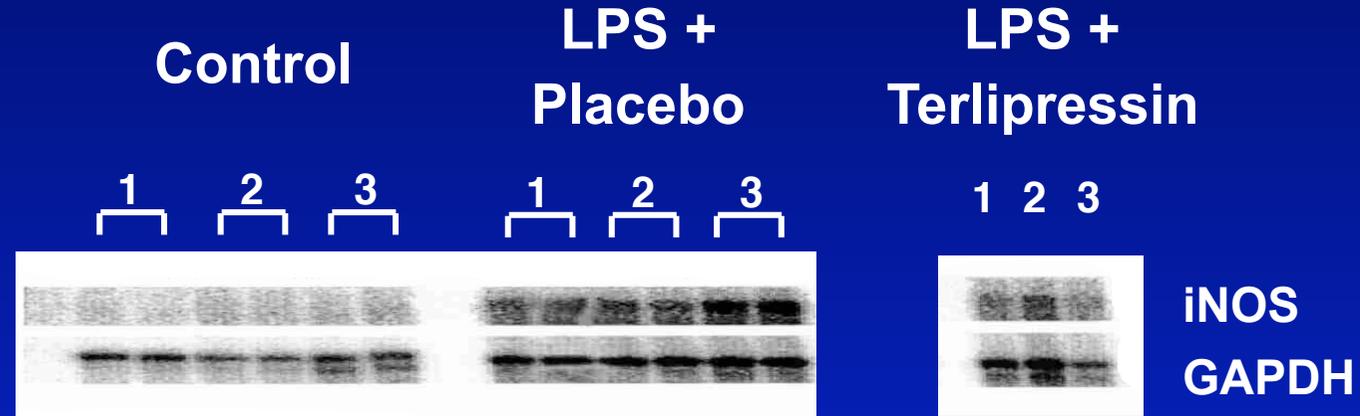
Innate Immune Response to LPS: Induction of Arterial iNOS



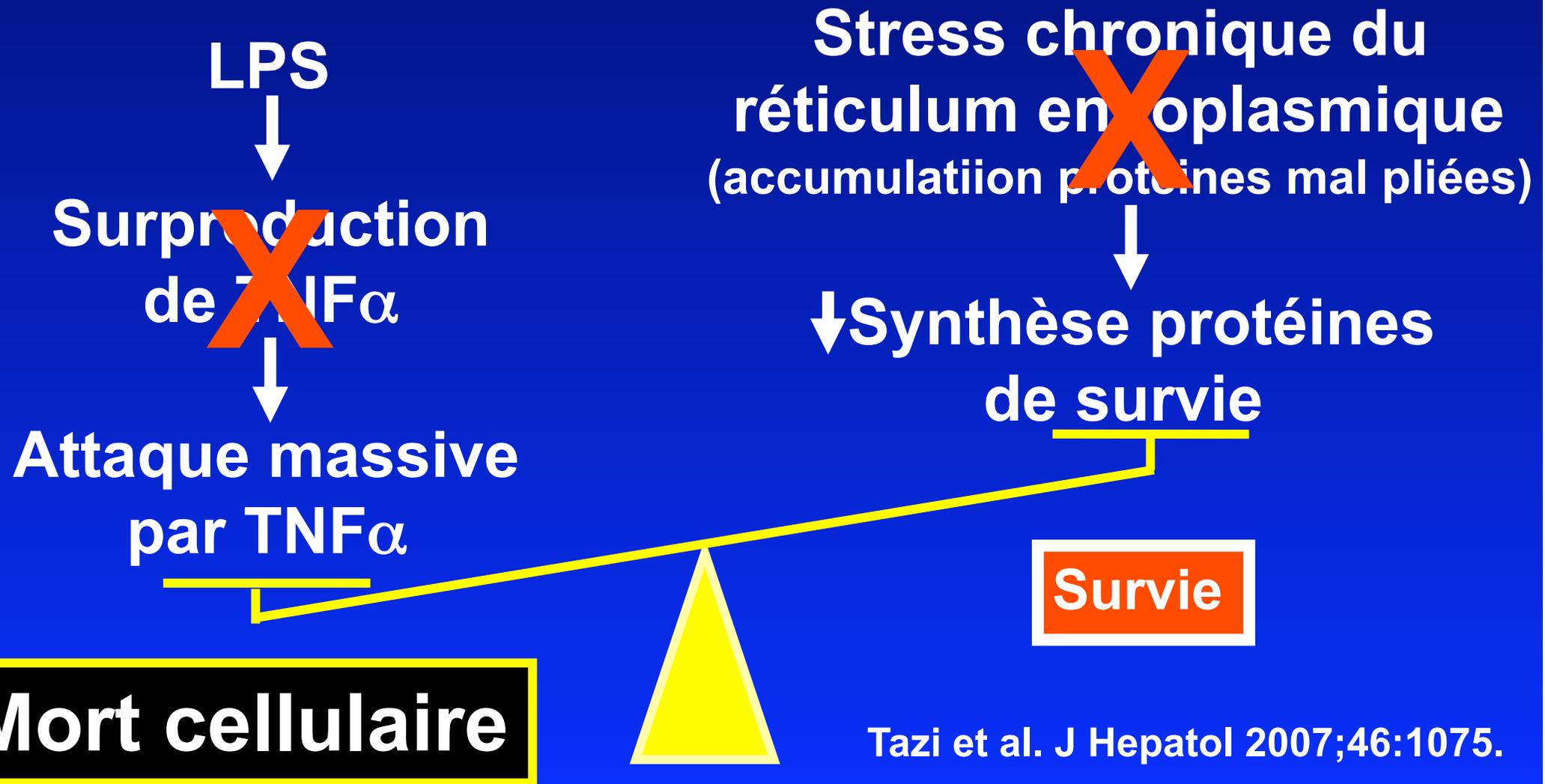
MacMicking et al.
Cell 1995;81:641-50.

Arterial smooth muscle cell

Terlipressin Inhibits *in Vivo* LPS-Induced *iNOS* mRNA in Cirrhotic Rat Aortas



Apoptose hépatocytaire induite par LPS dans la cirrhose



Archives of Biochemistry and Biophysics 408 (2002) 69–77

**Chronic liver and renal diseases
differently affect structure of human
serum albumin**

“...we analyzed infrared and Raman spectra of serum albumin isolated from healthy donors and patients with chronic uremia and cirrhosis...

The dramatic structural alterations of serum albumin (especially MISFOLDING) in cirrhosis may be caused by its oxidative modification and might underlie the decreased binding ability and changed body distribution of albumin.”

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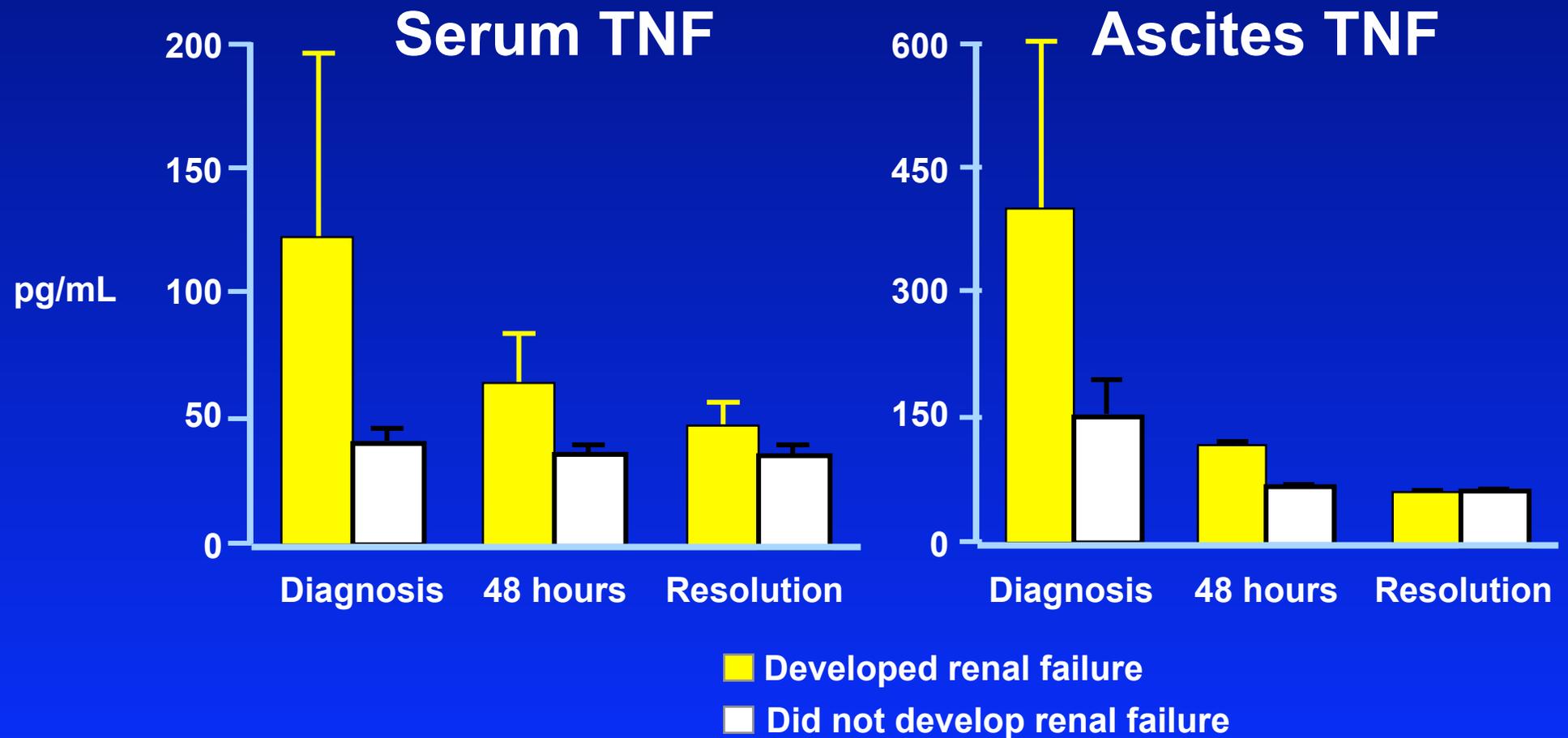
(1) Nat Rev Drug Discov 2003;2:391. (2) N Engl J Med 2001;344:699.

(3) N Engl J Med 2001;345:1359. (4) N Engl J Med 2001;345:1368.

(5) JAMA 2002;288:862.

**Sepsis-Induced
Acute Renal Failure
(in Patients Without
Shock)**

SBP-Induced Increases in Serum and Ascites Tumor Necrosis Factor (TNF) Levels Are associated With Development of Renal Failure



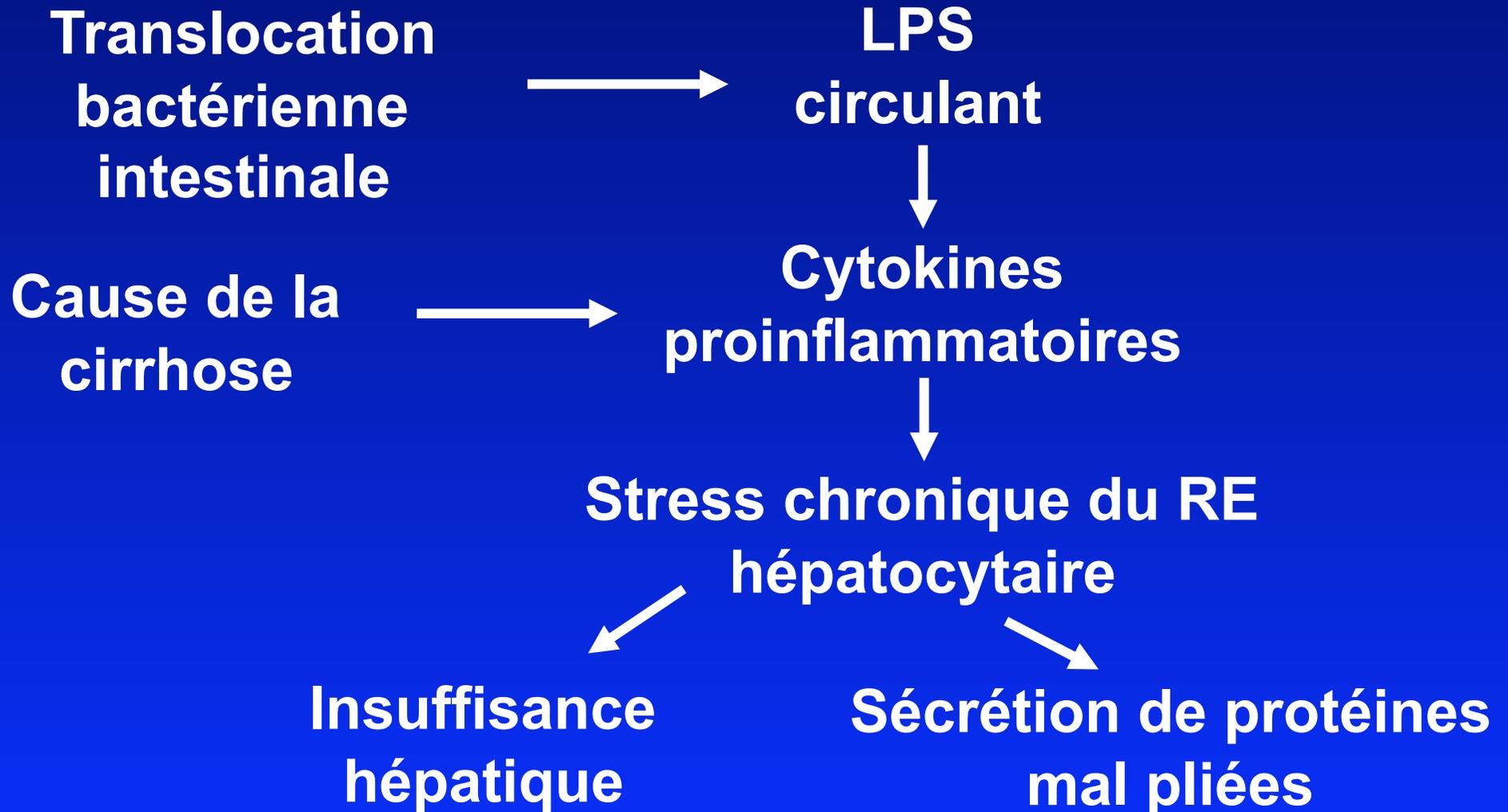
Navasa et al. Hepatology 1998; 27:1227.

Prevention of Acute Renal Failure in Patients With SBP

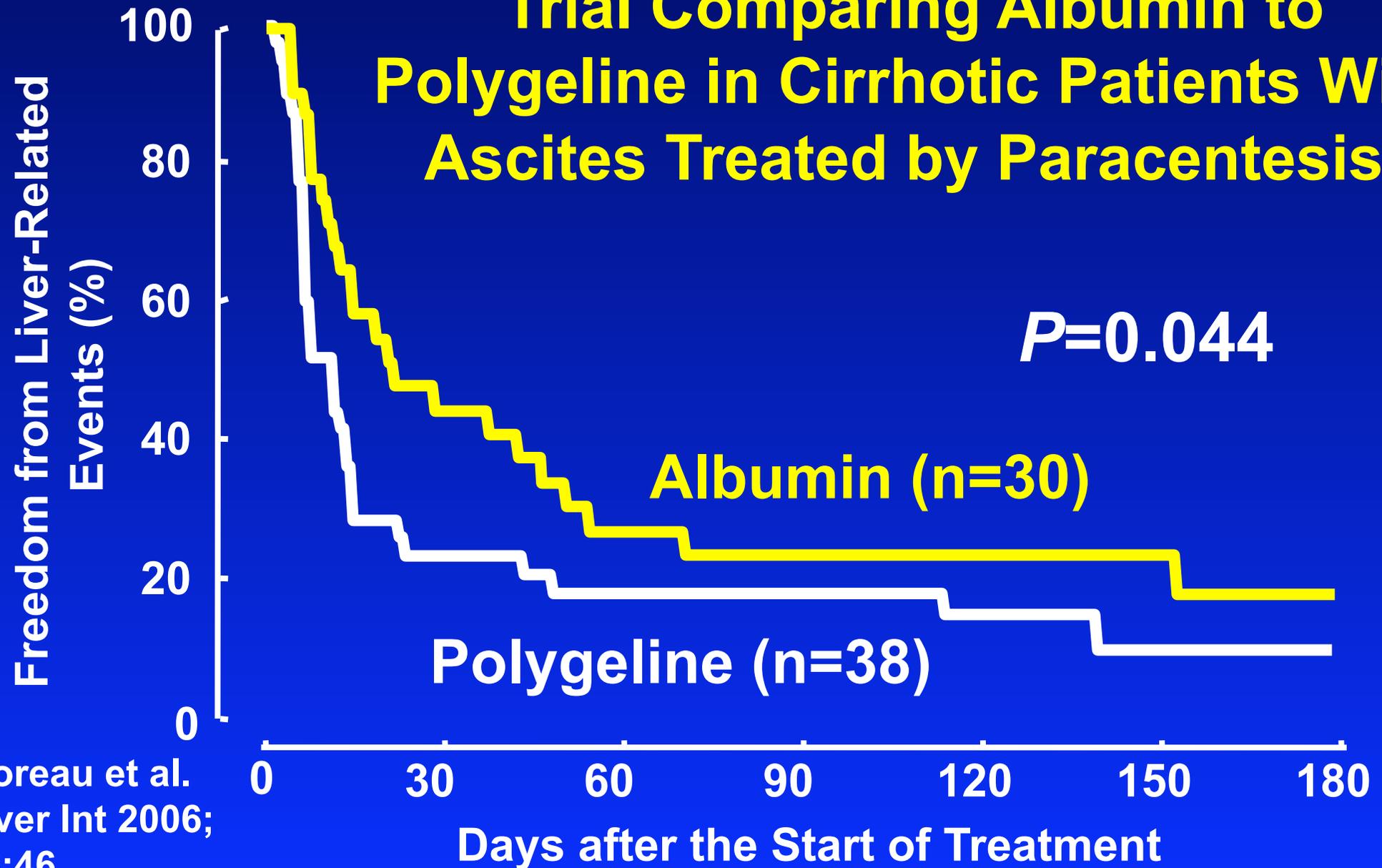
Variable	Cefotaxime Alone (N=63)	Cefotaxime + Albumin (N=63)
Resolution infection (%)	94	98
HRS (%)	33	10*
Death (%)		
In hospital	29	10*
At 3 months	41	22*

* $P < 0.05$. Sort et al. N Engl J Med 1999;341:103.

Scénario Pour la Cirrhose Décompensée Sans Infection Bactérienne en Cours



Randomized, Double-Blind, Pilot Trial Comparing Albumin to Polygeline in Cirrhotic Patients With Ascites Treated by Paracentesis



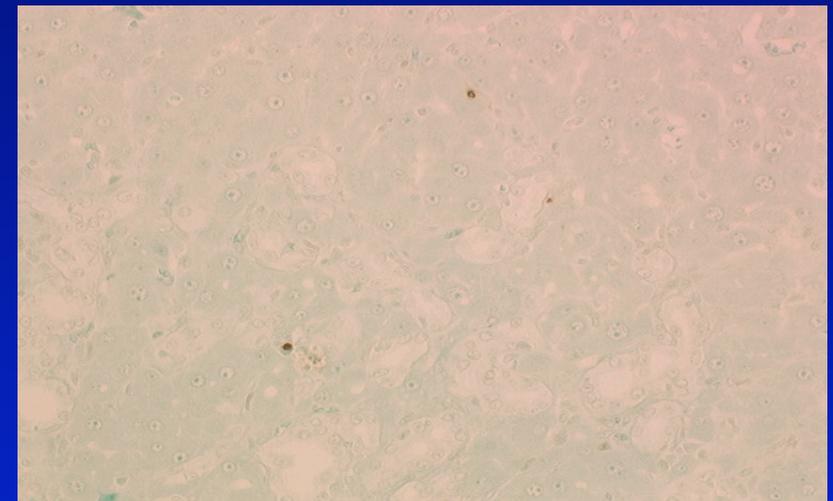
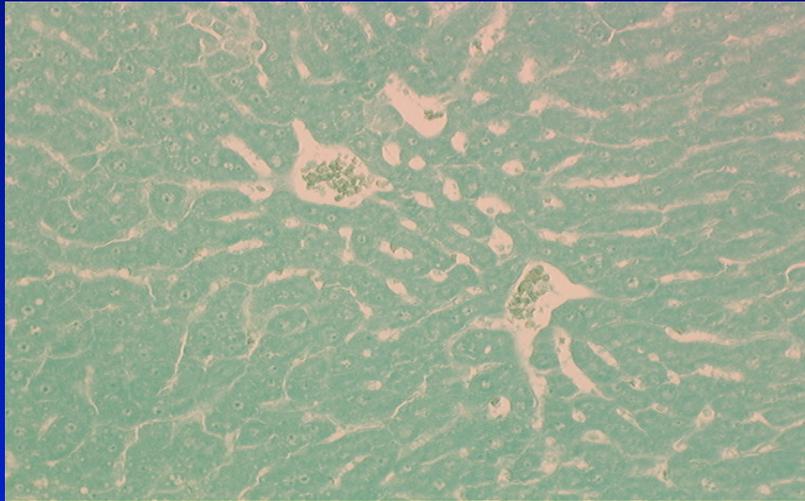
Moreau et al.
Liver Int 2006;
26:46.

LPS induit une apoptose dans le foie cirrhotique mais pas dans le foie normal

Normal

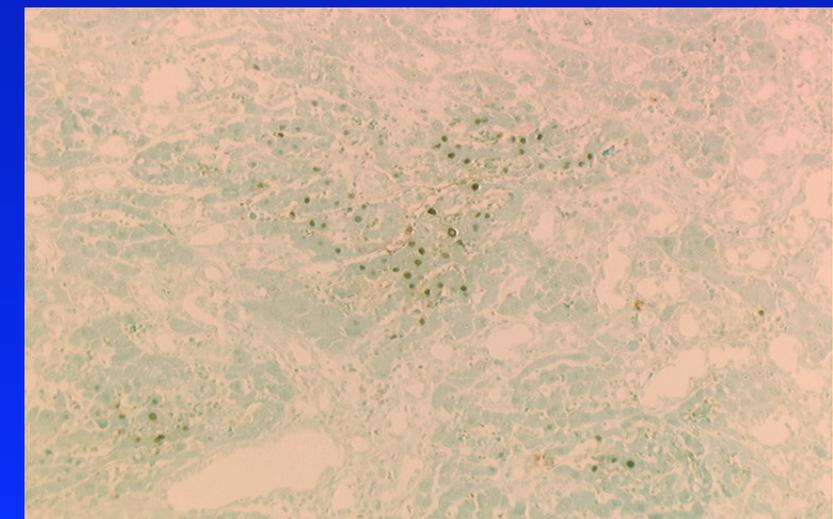
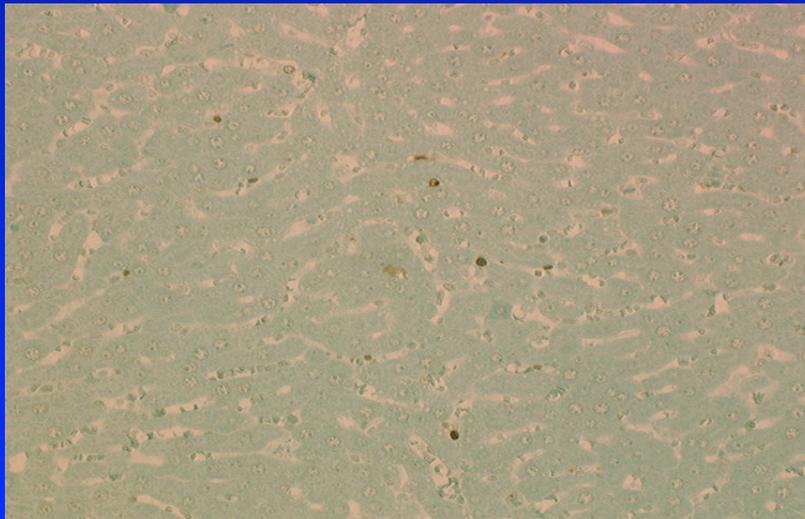
Cirrhose

Pas de
LPS



TUNEL

LPS



Tazi et al.
J Hepatol 2007;
46:1075.

Histoire naturelle de la maladie chronique du foie

