IMMUNO-INFLAMMATORY ASPECTS OF SEPTIC SYNDROME

1/ DEFINITIONS

2/ FREQUENCY

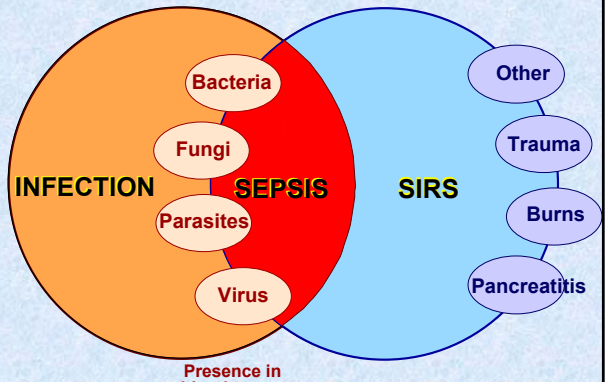
3/ CYTOKINE INDUCTION & DETECTION

4/ DELETERIOUS EFFECTS

5/ ANTI-INFLAMMATORY REACTION

6/ IMMUNOSUPPRESSION

7/ THERAPEUTICAL APPROACHES



DEFINITIONS[1-3]

BACTERIEMIA	Presence of alive bacteria within the blood stream
ENDOTOXINEMIA	Presence of LPS within the blood stream
SEPTICEMIA	Presence of microbes or their toxins in the blood
SYSTEMIC INFLAMMATORY RESPONSE SYNDROME [SIRS] † 10 - 17 % [3]	Two or more of the following parameters : - fevre (> 38°C) or hypothermia (< 36°C) - tachypnia (> 24 breaths/min.) - tachycardia (> 90 beats/min) - leucocytosis (> 12 000/mm3) ou leucopenia (< 4 000 mm3)
† 16 % **SEPSIS**	SIRS of ascertained or suspected infectious origin
† 20 % **SEVERE SEPSIS**	Sepsis with one, more organ failure
† 46 % **SEPTIC SHOCK**	Sepsis with hypotension (systolic arterial pressure < 90 or 40 mm Hg lower than normal SAP of the patient) non responsive to fluid rehabilitation, and organ failure

1 American College of Chest Physicians / Society of Critical Care Medicine Consensus Conference Committe. Definition for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit. Care Med.* 1992, 20, 864-74.

2 Bone RC Gram-negative sepsis: a dilemna of modern medicine. *Clin. Microbiol. Rev.* 1993, 6, 57-68

3 Rangel-Frausto et al. The natural history of the systemic inflammatory response syndrome (n = 3708). *JAMA* 1995, 273, 117-23

ENDOTOXEMIA IN PATIENTS WITH SEPTIS SYNDROME

Casey et al. Ann.Intern.Med. 1993,119,771 — n = 97, detectable LPS : 89%

	Control	Gram negative infection NO bacteremia	Gram negative bacteremia	Gram positive bacteremia
LPS (EU/ml)	0.04	4.7 ± 1.8	3.6 ± 0.7	2.7 ± 0.6

Guidet et al. Chest 1994,106,1194 — n = 93, detectable LPS : 47%

Gram negative infection	No Gram negative infection	Gram negative bacteremia	Gram positive bacteremia
67 %	28 %	73%	11%

DETECTION OF CIRCULATING BACTERIAL SUPERANTIGEN AND LYMPHOTOXIN-α IN PATIENTS WITH STREPTOCOCCAL TOXIC-SHOCK SYNDROME

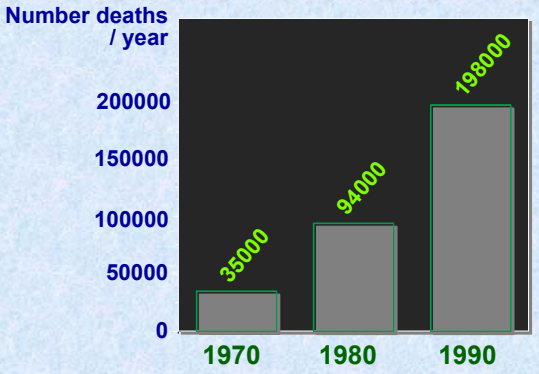
Sriskandan et al. Lancet 1996, 348, 1315

SURVIVAL	2/4	
SERUM SPEA	3/4	54 - 1039 pg/ml
SERUM LTα	3/4	0.3 - 28 ng/ml

FAMOUS PEOPLE WHO DIED OF SEPSIS

Lucrèce BORGIA	1519	puerperal septicaemia
Jean-Baptiste LULLY	1687	injury of the foot
Ignaz SEMMELWEIS	1865	injury of a finger
Gioacchino ROSSINI	1868	surgical wound
Georges BIZET	1875	severe sepsis
Edouard MANET	1883	leg amputation
Heinrich HERTZ	1894	dental abcess
Gustav MAHLER	1911	heart infection
Alexander SKRJABIN	1915	abcess of the lip

DEATH FROM SEPTIC SHOCK IN THE U.S.A.



THE EPIDEMIOLOGY OF SEVERE SEPSIS IN USA

D. Angus et al. Crit. Care Med. 2001

7 large states in USA
847 hospitals
6,621,559 hospital discharge records in Jan - Dec. 1995
192.980 severe sepsis

ESTIMATES

751,00 CASES

3.3 CASES PER 1000 POPULATION

2.26 CASES PER 100 HOSPITAL DISCHARGES

28.6% MORTALITY
(215.000 DEATHS → 9.3% DEATHS IN USA ≅ acute myocardial infarction)

MEAN AGE : 63.8 YEARS

49.6 % MALE

44% RESPIRATORY

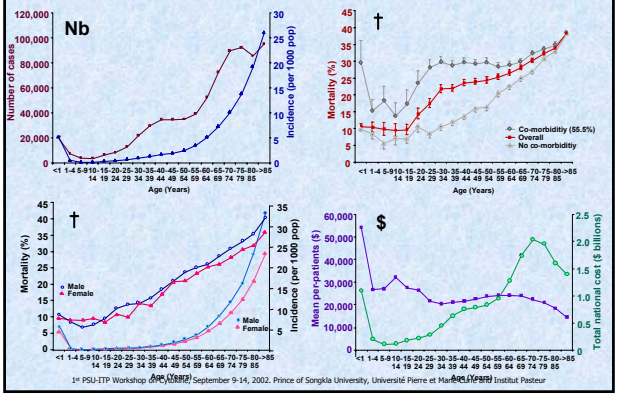
51% ICU

AVERAGE COST : 22.100 US $

PROJECTIONS :
GROWTH AT 1.5% / ANNUM
→ 1,110,000 CASES IN 2020

THE EPIDEMIOLOGY OF SEVERE SEPSIS IN USA

D. Angus et al. Crit. Care Med. 2001



NOSOCOMIAL INFECTIONS AFTER SURGERY

Crabtree et al. Shock 2002, 17, 258

	Mulholland 1975	Verkkala 1987	Rebollo 1996	Crabtree 2000
Lungs	28%	11%	26%	23%
Surgical site	28%	63%	53%	19%
Urine	23%	21%	16%	18%
Bloostream	9%	2%	6%	17%
Other	12%	4%	0%	23%
RATE (/100 admissions)	13.2	22.6	12.4	23.8

Bacteremia and severe sepsis in adults : a multicenter prospective survey in ICU and wards of 24 Hospitals

Brun-Buisson et al. Am. J. Respir. Crit. Care Med. 1996, 154, 617

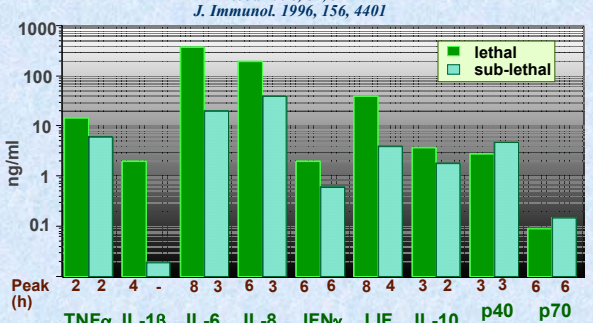
85 750 admissions	Bacteriemia	Severe sepsis
Hospitals	9.8 ‰	6.0 ‰
I.C.U.	69 ‰	119 ‰
Mortality (D28)	25 %	54 %

microbes	
Escherichia coli	23%
Staphyl. aureus	20% *
Strept pneumon.	9 %
Pseud. aeruginosa	6 %
coag neg *Staph.*	6 %
Klebsiella	5 %
Fungal infections	2 % *

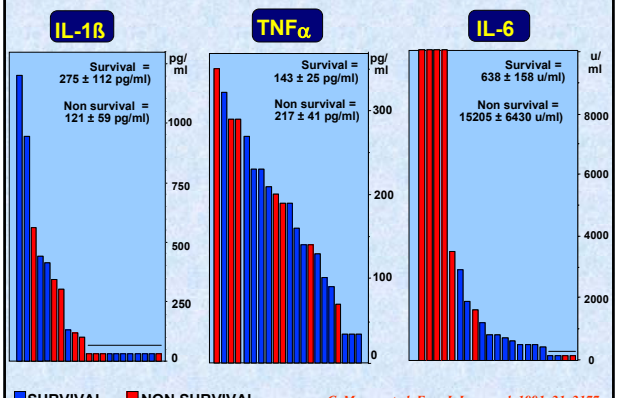
* linked with high mortality

RELEASE OF CYTOKINES IN BABOONS IN EXPERIMENTAL ESCHERICHIA COLI SHOCK

Jansen et al.
Blood 1996, 87, 5144
J. Immunol. 1996, 156, 4401



Exacerbated production of pro-inflammatory cytokines

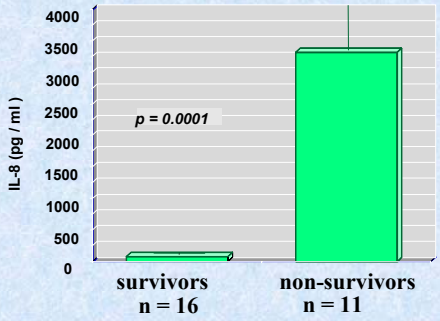


C. Munoz et al. Eur. J. Immunol. 1991, 21, 2177

Exacerbated production of pro-inflammatory cytokines

PLASMA LEVELS OF IL-8 WITHIN 48 hr OF ADMISSION

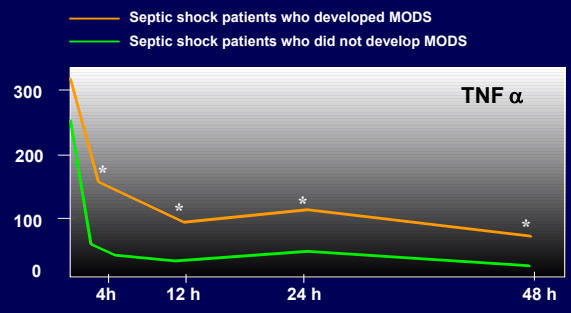
27 patients with sepsis syndrome



Marty et al. Crit. Care Med. 1994, 22, 673

THE PERSISTENCE OF TNF (AND IL-6) IN THE SERUM RATHER THAN THE PEAK LEVELS CORRELATES WITH MODS DEVELOPMENT AND PREDICTS A POOR OUTCOME

Pinsky et al. Chest 1993,103,565



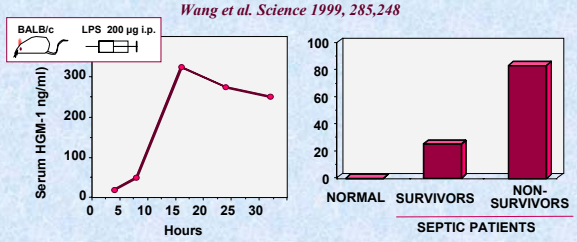
HMG-1

High Mobility group nonhistone chromosomal protein

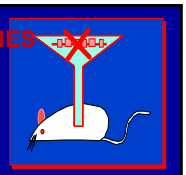
HGM-1 is a higly conserved (>95% identity between rodent and humans) nuclear protein that binds to cruciform DNA. It exists as a membrane form ("amphoterin" and as extracellular form which interacts with plasminogen and tissue typ plasminogen activator (t-PA)

HGM-1 IS A LATE MEDIATOR OF ENDOTOXIN LETHALITY IN MICE

Wang et al. Science 1999, 285,248



THE PRO-INFLAMMATORY CYTOKINES



KO MICE	ENDOTOXIN SHOCK: LPS + GalNH2	ENDOTOXIN SHOCK: LPS	RESULTS	
TNF R I	√		Enhanced Resistance	Pfeffer et al. 1993 Cell 73 457
TNF R I		√	No change	Rother et al. 1993 Nature 364, 798
TNFα / Lα	√		Enhanced Resistance	Eugster et al. 1996 Int. Immunol. 8, 23
TNFα / Lα		√	No change	Amiot et al. 1997 Mol. Med. 3, 863
IFNγ R	√		Enhanced Resistance	Car et al. 1994 J.Exp.Med. 179, 1437
I C E		√	Enhanced Resistance	Li et al. 1995 Cell 80, 401

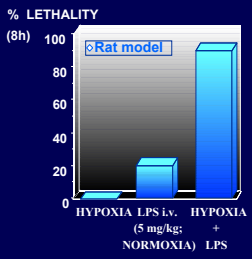
CYTOKINE & CYTOKINE RECEPTOR DEFICIENT MICE AND ENDOTOXIN SHOCK

(high LPS doses in the absence of GalNH2)

SIMILAR SUSCEPTIBILITY	FasL	*Heumann et al. J.Inflamm.1997, 47, 173*
	IL-1β	*Fantuzzi et al. J.Immunol. 1996, 157, 291*
	IL-6	*Fattori et al. J.Exp.Med. 1994, 180, 1243*
	TNF R I	*Rother et al. Nature 1993, 364, 798*
	TNFα /LTα	*Amiot et al. 1997 (submitted)*
REDUCED SUSCEPTIBILITY	ICE	*Li et al. Cell 1995, 80, 401*
	GM-CSF	*Basu etal. J. Immunol. 1997,159,1412*
ENHANCED SUSCEPTIBILITY	IL-1ra	*Hirsch et al. PNAS 1996,93,11008*
	IL-10	*Berg et al. J.Clin.Invest. 1995,96,2339*

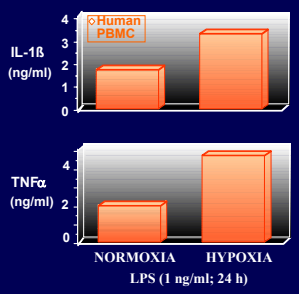
A SYNERGY EXISTS BETWEEN HYPOXAEMIA AND ENDOTOXAEMIA ON THE DEVELOPMENT OF LETHAL ORGAN FAILURE

Gerlach et al.
Eur. J. Anaesth. 1993,10,273



HYPOXIA INCREASES PRODUCTION OF IL-1 AND TNF BY PBMC TRIGGERED BY LPS

Ghezzi et al.
Cytokine 1991,3,189



Exacerbated production of pro-inflammatory cytokines

Exacerbated production of anti-inflammatory cytokines

Neisseria meningitidis SEPTICEMIA + SHOCK

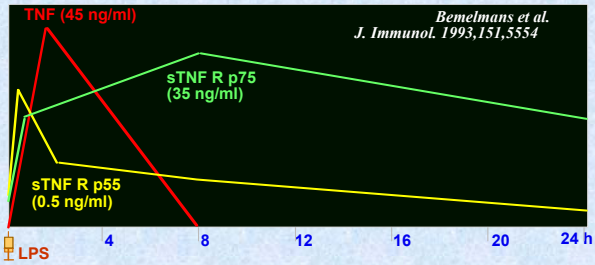
♀ 62 years DIC, ARDS, Died within 8 h after admission in I.C.U.

Circulating cytokines (pg/ml)

IL-1β	IL-1α	TNFα	IL-1ra	IL-10	TGFβ
25	40	420	1 525 400	2360	15 480
IFN γ	IL-8		sTNF R I	s TNF R II	
<50	63 515		43 500	142 340	

IL-6
1 122 400

IN VIVO RELEASE OF TNF AND s TNF R in a murine model



	TNF	s TNF R p55	s TNF R p75
Anti - IFN γ (T - 24h) + LPS	↓	↓	↑
IL-1 ra (T0,4,8,12 h) + LPS	≅	≅	≅
LIF (T - 24 h) + LPS	↓	↑	≅

LPS-INDUCED IL-10 CONTROLS TNF AND IFNγ PRODUCTION DURING MURINE ENDOTOXEMIA

Marchand et al. Eur.J.Immunol.1994,24,1167

Detectable plasma cytokines

LPS	mAb (t-2h)	TNF (U/ml) 90 min	IFNγ (U/ml) 6 hr
100 µg	Control	5040 ± 2282	0.8 ± 0.3
	Anti-IL-10	47214 ± 15667	4.6 ± 1.2

EXACERBATED PRODUCTION OF ANTI-INFLAMMATORY CYTOKINES

ELEVATED LEVELS OF CIRCULATING TGFβ1 IN PATIENTS WITH SEPSIS SYNDROME

Healthy donors (n=21)	Sepsis patients (n=26)	
13.0 ± 1.4 ng/ml	27.0 ± 4.5	*p = 0.01*
(4.8 - 26.6)	(2.9 -102.4)	Normal plasma

C. Marie et al. Ann. Intern. Med. 1996, 125, 520

ELEVATED LEVELS OF CIRCULATING TGFβ1 IN PATIENTS WITH TRAUMA

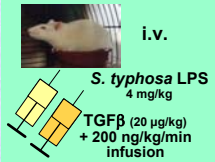
An elevated level of TGFβ1 was found in the plasma during the 10 days of the survey.

Adib-Conquy et al. J. Leuk. Biol. 2001, 70, 30

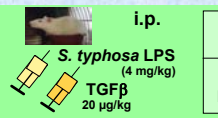
BENEFICIAL EFFECTS OF ANTI-INFLAMMATORY CYTOKINES

IN VIVO EFFECT OF TGFβ ON LPS-INDUCED HYPOTENSION & LETHALITY

Perrella et al. PNAS 1996, 93, 2054



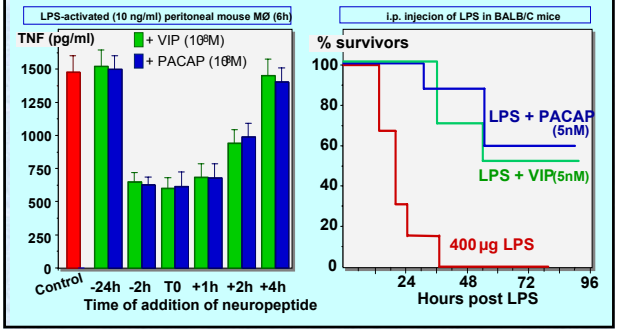
	Mean arterial pressure 120 min (mm Hg)	Survival 150 min.
0	110	100%
LPS	40	35%
LPS + TGFβ	100	90%



	iNOS mRNA			
	Heart	Kidney	Liver	Lung
LPS		100%		
LPS + TGFβ	37%	20%	10%	50%

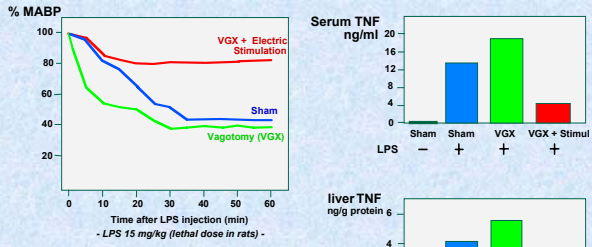
NEUROPEPTIDES VIP (vasoactive intestinal peptide) and PACAP (pituitary adenylate cyclase-activating polypeptide) INHIBIT LPS-INDUCED TNF AND PROTECT FROM LETHAL ENDOTOXEMIA

Delgado et al. J. Immunol. 1999, 162, 1200 & 2358

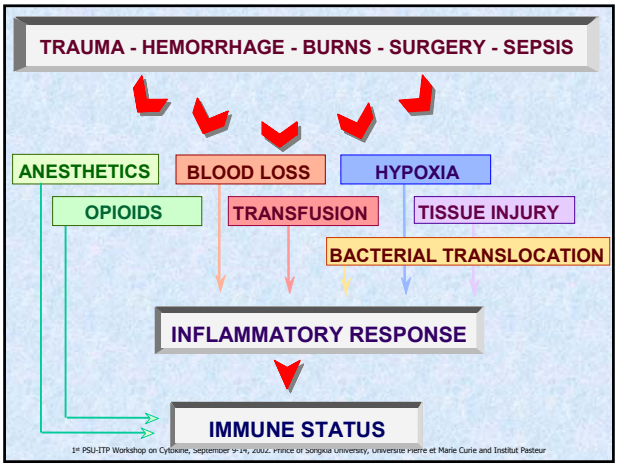


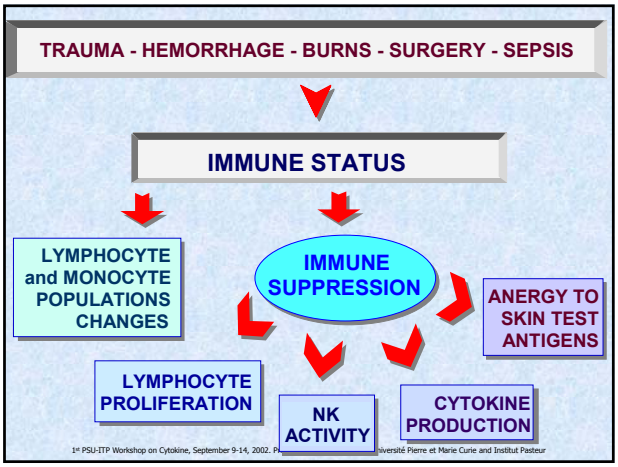
VAGUS NERVE STIMULATION ATTENUATES THE SYSTEMIC INFLAMMATORY RESPONSE TO ENDOTOXIN

Borovikova et al. Nature 2000, 405, 458



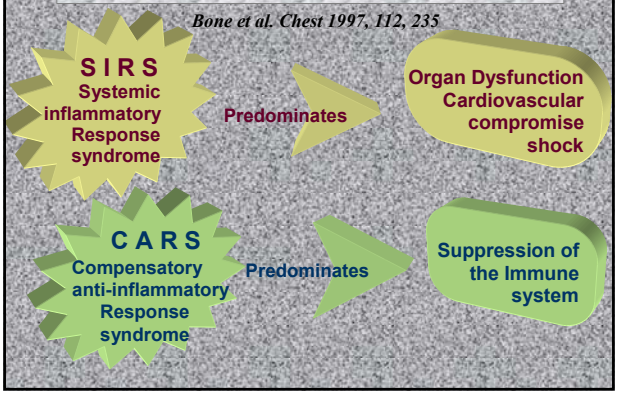
Acetylcholine, the principle vagal neurotransmitter, significantly attenuated the release of pro-inflammatory but not anti-inflammatory cytokines

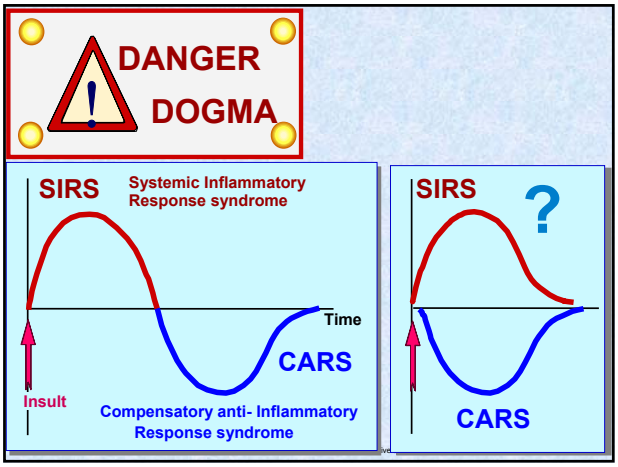




SEPSIS : A NEW HYPOTHESIS FOR PATHOGENESIS OF THE DISEASE PROCESS

Bone et al. Chest 1997, 112, 235





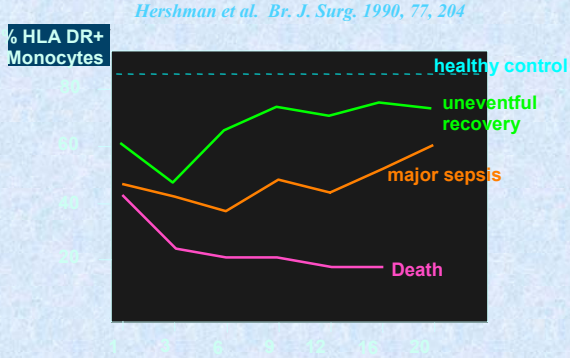
DELAYED HYPERSENSITIVITY SKIN TEST RESPONSE IN SURGICAL PATIENTS

Christou et al. Can. J. Surg. 1984, 28, 39

Patients who were anergic to a battery of 5 skin test antigens had a two-fold higher risk of post-operative infection than those who reacted to two or more antigens and were more than 5 fold more likely to die during the post-operative period

MONOCYTE HLA-DR EXPRESSION IN TRAUMA PATIENTS

Hershman et al. Br. J. Surg. 1990, 77, 204



NATURAL KILLER CELL ACTIVITY IN PATIENTS WITH SEPTIC SHOCK

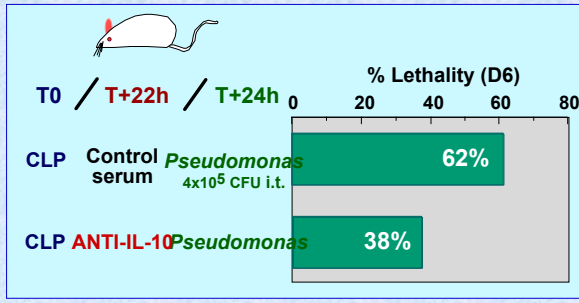
Maturana et al. 1991 J. Crit. Care 6, 42	Effector : target cell ratios 10:1	20:1	40:1
Control (n = 10)	19.6 ± 6 %	31.0 ± 6.5 %	49.5 ± 5.5 %
Patients with septic shock (n = 11)	0.6 ± 0.2 %	2.9 ± 1.0 %	9.5 ± 2.8 %

Puente et al. 1993 Int. J. Clin. Pharmacol. Ther. Toxicol. 31, 271	Effector : target cell ratio = 30:1 Baseline	IFNα 2h 37°C	IL-2 2h 37°C
Control (n = 20)	20.6 ± 16.6	37.6 ± 19.6	34.6 ± 13,8
Patients with septic shock (n = 15)	9.1 ± 7.8	12.6 ± 11.9	10.2 ± 8.5

Immunosuppression

IL-10 MEDIATES SEPSIS-INDUCED IMMUNOSUPPRESSION

Steinhauser et al. J. Immunol. 1999, 162, 392



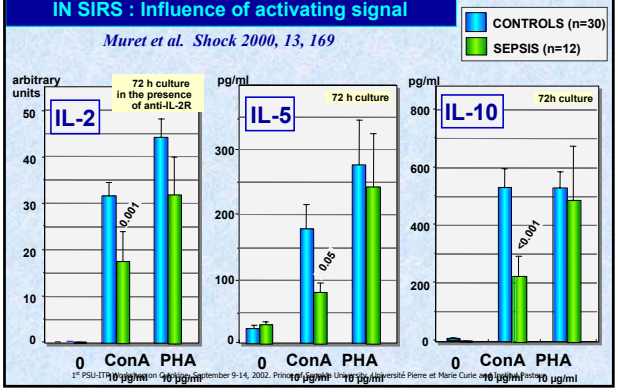
DECREASED *EX VIVO* CYTOKINE PRODUCTION IN HUMAN PERIPHERAL BLOOD MONONUCLEAR CELLS

CYTOKINE	ACTIVATORS	References
IL-2	PHA	Wood et al. *Ann Surg.* 1984, 200, 311
IFNγ	LPS ± IL-12	Ertel et al. *Blood* 1997,89,1612
IL-2 IL-5 IL-10	ConA but neither PHA nor anti-CD3	Muret et al. *Shock* 2000, 13, 169

Immunosuppression

BOTH Th1 & Th2 RESPONSES ARE REDUCED IN SIRS : Influence of activating signal

Muret et al. Shock 2000, 13, 169



DECREASED *EX VIVO* CYTOKINE PRODUCTION IN HUMAN SEP

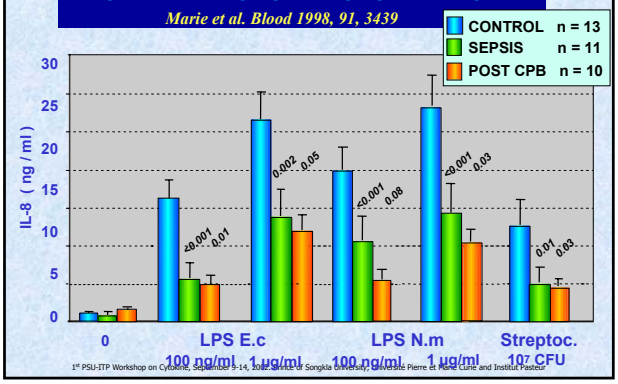
NEUTROPHILS

CYTOKINE	ACTIVATORS	References
IL-1β	LPS but not Staphylococcus	McCall et al. *J.Clin.Invest.* 1993, 91, 853
IL-8	LPS and Streptococcus	Marie et al. *Blood* 1998, 91, 3439
sIL-1ra	LPS and Streptococcus	Marie et al. *Crit. Care Med. 2000, 28, 2277*

Immunosuppression

REDUCED EX VIVO IL-8 PRODUCTION BY PMN IN SEPTIC AND NON-SEPTIC SIRS PATIENTS

Marie et al. Blood 1998, 91, 3439



1st PSU-ITP Workshop on Cytokine, September 9-14, 2002, Service of Songkla University, Universite Pierre et Marie Curie and Institut Pasteur

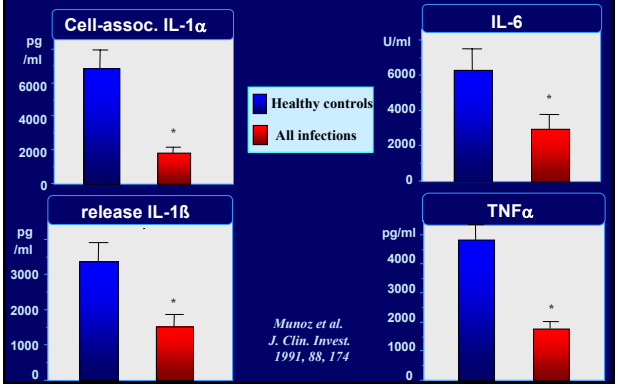
DECREASED *EX VIVO* CYTOKINE PRODUCTION IN HUMAN SE

MONOCYTES

CYTOKINE	ASSAYS	ACTIVATORS	References
IL-1	Monocytes P.B.M.C.	Silica LPS	Luger et al. *Crit.Care Med.* 1986,14,458 Helminen et al. *Scand.J.Infect.* 1990,22,105
IL-1α, IL-1β, IL-6, TNFα	Monocytes	LPS Streptococcus SEB	Muñoz et al. *J.Clin.Invest.* 1991,88,174 Cavaillon et al. *Endot. Res.* 1993,2,275 Astiz et al. J.Lab.Clin.Med.1996
TNFα	Alveolar MØ	LPS	Simpson et al. *Crit.Care Med.* 1991,19,1060
IL-1β, IL-6, TNFα *but not IL-1ra*	Whole Blood	LPS	Sekatrian et al. *Arch.Surg.* 1994,129,187 van Deuren et al. *J.Infect.Dis.* 1994,169,157 Marchant et al. *J.Clin.Immunol.* 1995,15,266 Ertel et al. *Blood* 1995,85,1341
IL-10	Whole Blood PMBC HLA DR+ low	LPS	Marchant et al. *J.Clin.Immunol.* 1995,15,266 Randow et al. *J.Exp.Med.* 1995,181,1887
IL-12	Whole Blood	LPS & SAC ± IFNγ	Ertel et al. *Blood* 1997,89,1612

Immunosuppression

HYPORESPONSIVENESS OF MONOCYTES OF SEPTIC PATIENTS UPON LPS STIMULATION

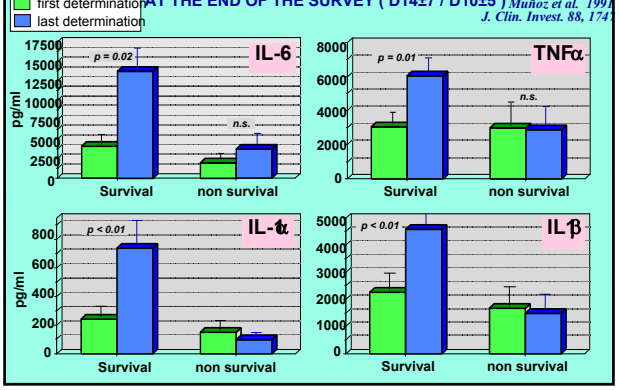


Munoz et al. J. Clin. Invest. 1991, 88, 174

Immunosuppression

LPS-INDUCED CYTOKINE PRODUCTION AT ADMISSION IN THE ICU AND AT THE END OF THE SURVEY (D14±7 / D10±5)

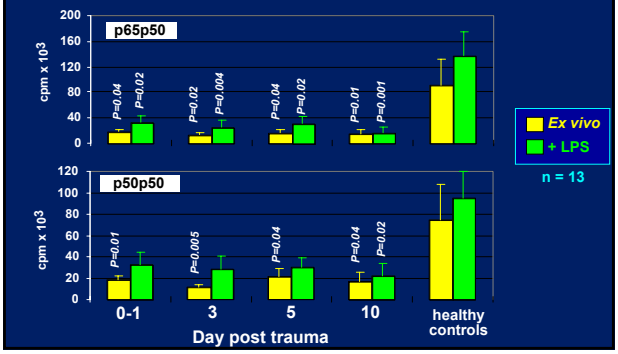
Muñoz et al. 1991 J. Clin. Invest. 88, 174



Immunosuppression

QUANTIFICATION BY PHOSPHORIMAGER ® OF p65p50 and p50p50 FORMS OF NF- κB IN NUCLEUS OF PBMC OF TRAUMA PATIENTS

Adib-Conquy et al. J. Leuk. Biol. 2001, 70, 30



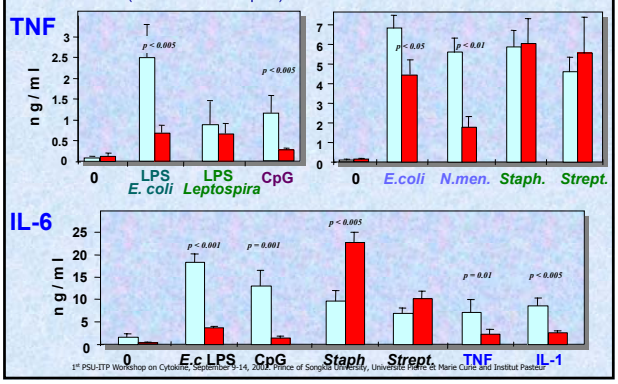
IMMUNOSUPPRESSION ASSESSED BY EX VIVO CYTOKINE PRODUCTION IS NOT A GENERALIZED PHENOMENON

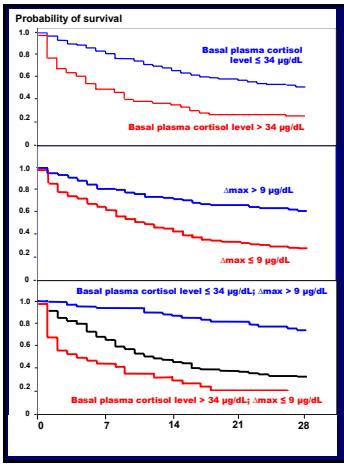
Cavaillon et al. J. Endotoxin Res. 2001, 7, 85

Not a generalized phenomenon

HEALTHY CONTROLS
TRAUMA PATIENTS
n = 11 - 23

EX VIVO CYTOKINE PRODUCTION
(Whole blood samples)





CLINICAL RELEVANCE

Cortisol levels and corticotropin response in septic shock

Annane et al. JAMA 2000, 283, 1038

One third of septic shock patients had high levels of basal cortisol

More than half of patients had adrenal insufficiency

SEPSIS

The first use of human monoclonal antibody in human

ANTI-LPS

HA-1A Centoxin®

Teng N et al.
Protection against Gram negative bacteremia and endotoxemia with human monoclonal IgM antibodies.
Proc Natl Acad Sci USA 1985, 82, 1790

Ziegler et al.
Treatment of Gram negative bacteremia and septic shock with HA-1A human monoclonal antibody against endotoxin.
New Engl J Med 1991, 324, 429

Treatment	28 DAYS MORTALITY		
	Sepsis n = 543	Gram neg. bacteremia n = 197	Gram neg. bact. + choc n = 101
PLACEBO	43%	49%	57%
HA-1A	39%	30%	33%
	ns	*p = 0.014*	*p = 0.017*

SEPSIS

The sad and costly story of theanti-LPS humanmonoclonal antibody

ANTI-LPS

HA-1A Centoxin®

The FDA required a second study, started in USA on July 1992.

nov. 91 : Start of use of Centoxin in French hospitals (cost : 3000 $)

nov. 92 : 1158 bought samples / 551 used

janv. 93 : The product is withdrawn after the results of the interim US study

proposed mechanism :

Clearance of LPS-IgM complexes by erythrocytes after complement activation

? ? ?

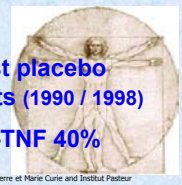
Warren S, Amato S, Fitting C, Black KM, Loiselle PM, Pasternack MS, Cavaillon J-M.
Assessment of ability of murine and human anti-lipid A monoclonal antibodies to bind and neutralize lipopolysaccharide
J Exp Med 1993, 177, 89

Is TNF responsible of the deleterious effects observed during sepsis ?

ANTI-TNF STUDIES

Beutler et al.
Passive immunization against cachectin/tumor necrosis factor protects mice from lethal effects of endotoxin
Science 1985, 229, 869

Tracey et al.
Anti-cachectin/TNF monoclonal antibodies prevent septic shock during lethal bacteraemia
Nature 1987, 330, 662



8 multicentric double blind against placebo Studies (1990 / 1998) : 4132 patients (1990 / 1998)

Mortality day : Placebo 41% / anti-TNF 40%

TREATMENT OF SEPTIC SHOCK WITH THE TYPE II TNF RECEPTOR - Fcγ1 FUSION PROTEIN

Fisher et al. New Engl. J. Med. 1996, 334, 1697

Treatment	n	28 day - Mortality n	%
placebo	33	10	30
0.15 mg/kg	30	9	30
0.45 mg/kg	29	14	48
1.5 mg/kg	49	26	53

p = 0.02

Protective effect of 55 but not 75 kDa S TNF R - IgG fusion proteins in a model of Gram negative sepsis

Evans et al. 1994 J.Exp.Med. 180,2173

T-30min: sTNF R - IgG1 i.v.
T0: 3x10^8 CFU *E. coli* i.v. (LD_{90})
T+2h, T+5h, (T24, T48, T72)x 2 : Gentamicin 1 mg/kg

Survival T+72h

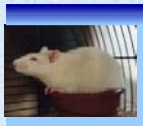
p75 sTNF R -IgG1 250 µg	p75 sTNF R -IgG1 250 µg + anti-TNF T+4h	p55 sTNF R -IgG1 50 µg	p55 sTNF R -IgG1 200 µg
30%	80%	45%	77%

1/2 life complex : p75 sTNF R -IgG1 / TNFα : 7 min
p55 sTNF R -IgG1 / TNFα : 8 h

Are TNF and IL-1 responsible of the deleterious effects observed during sepsis ?

COMBINED INHIBITION OF IL-1 and TNF IN RAT ENDOTOXEMIA

Russel et al. J. Infect. Dis. 1995,171,1528



LPS 25 mg/kg i.v.

% survival

IL-1ra (mg/kg)	PEG-(rsTNF R I)2 (mg/kg) 0	0.5	3
0	8	0	41
10	0	50	83
50	0	83	100

THE EFFECTS OF IBUPROFEN ON THE PHYSIOLOGY AND SURVIVAL OF PATIENTS WITH SEPSIS

Bernard et al. New England J. med. 1997, 336, 912

	IBUPROFEN (n=224) *vs* PLACEBO (n=231)
URINARY LEVELS OF PROSTACYCLIN AND THROMBOXANE	p < 0.05
TEMPERATURE	p < 0.001
HEART RATE	p < 0.001
BLOOD LACTATE	p = 0.2
INCIDENCE & DURATION OF SHOCK AND ARDS	ns
MORTALITY	37% *vs* 40%

DRUG	Nb patients (Nb studies)
Anti-endotoxin	
HA-1A	2742 (2)
E5	2437 (3)
Interleukin-1 receptor antagonist	1688 (3)
Anti-TNF monoclonal antibodies	
murine anti-TNF	3414 (3)
murine Fab '2	607 (3)
TNF receptor fusion proteins	
p75 TNF R	141 (1)
p55 TNF R	1838 (2)
Platelet activating factor antagonists	930 (2)
COX inhibitor (ibuprofen)	514 (3)
Bradykinin antagonist	755 (2)
	15 066 patients

HEMOFILTRATION IN HUMAN SEPSIS

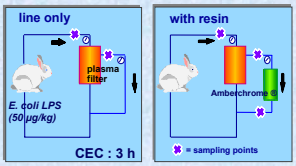
Hoffmann et al. Kidney Intern. 1995, 48, 1563

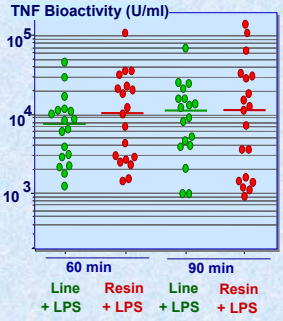
	afferent line T0	afferent line T+60min	Ultrafiltrate T+60min
IL-1β (pg/ml)	66	63	nd
IL-6 (U/ml)	1091	1127	<dl
IL-8 (pg/ml)	1439	1447	604
TNFα (U/ml)	33	29	<dl
$C3a_{desarg}$ (ng/ml)	677	545 **	104
$C5a_{desarg}$ (ng/ml)	27	26	0.2

Is life compatible with high levels of circulating TNF ?

COUPLED PLASMA FILTRATION-ADSORPTION IN A RABBIT MODEL OF ENDOTOXIC SHOCK

Tetta et al. Crit. Care Med. 2000, 28, 1526





	MAP (mm Hg) - 60 min -	Survival - 8 days -
Line	59 ± 0.9	70 %
Resin	58 ± 12	80 %
Line + LPS	36 ± 0.3	25 %
Resin + LPS	51 ± 11	79 %

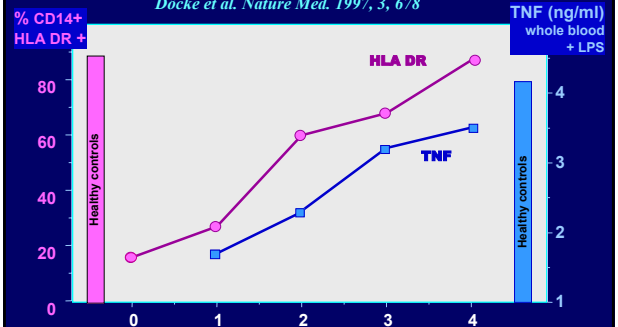
THE PRESENCE OF HIGH LEVEL OF TNF MAY BE ASSOCIATED WITH SURVIVAL

Prince o

CLINICAL RELEVANCE

Monocyte deactivation in septic patients : restoration by IFNγ treatment

Döcke et al. Nature Med. 1997, 3, 678



EFFECTS OF CORTICOSTEROIDS IN PATIENTS WITH SEVERE SEPSIS OR SEPTIC SHOCK

		Overal survival (treated vs placebo)
Sprung et al. New Engl. J. Med. 1984, 311, 1137	n = 59 methylprednisolone dexamethasone	n.s.
Bone et al. New Engl. J. Med. 1987, 317, 653	n = 382 methylprednisolone	n.s.
Vet. Adm. Study group New Engl. J. Med. 1987, 317, 659	n = 223 methylprednisolone	n.s.

LOW DOSE OF STEROIDS IN SEPTIC SHOCK

D. Annane et al. 2000

Hydrocortisone i.v. 50 mg every 6h

Fludrocortisone per os, 50 µg every day

Versus placebo - 7 days

n = 299 patients

ACTH test for adrenal insuficiency associated with sepsis

ACTH non-responder : p = 0.024 (ACTH responder p = 0.07)

Steroids save one life / 10 patients

1st PSU-ITP Workshop on Cytokine, September 9-14, 2002. Prince of Songkla University, Université Pierre et Marie Curie and Institut Pasteur

SPECIFIC INHIBITION OF COAGULATION & SEPSIS

ANTITHROMBINE III (ATIII)

Meta-analysis of three European placebo controlled randomized studies (n = 122)

22.9% reduction in 30-day all cause mortality in the ATIII treated group (ns)

significant reduction in the length of ICU stay

recombinant human ACTIVATED PROTEIN C (rhAPC)

Phase II trial of 131 patients with severe sepsis

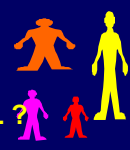
MORTALITY : high dose = 21%

placebo = 34 % *(p=0.2)*

- i.e. 40% relative risk reduction -

1st PSU-ITP Workshop on Cytokine, September 9-14, 2002. Prince of Songkla University, Université Pierre et Marie Curie and Institut Pasteur

SEPSIS THERAPY



ARE MICE A GOOD MODEL ?

Homogeneity	Heterogeneity
Same sex	Men and Women
Healthy	Underlying diseases
Young	Old
Pre-treatment	Post-treatment
low sensitivity to LPS	High sensitivity to LPS
Injection of LPS	Infection
	Intensive care, antibiotherap