

# Recent Advances and Current Concepts in the Diagnosis and Monitoring of Sepsis

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## *The Clinical Definitions*

Systemic Inflammatory Response (SIRS) is a clinical response arising from a non-specific insult

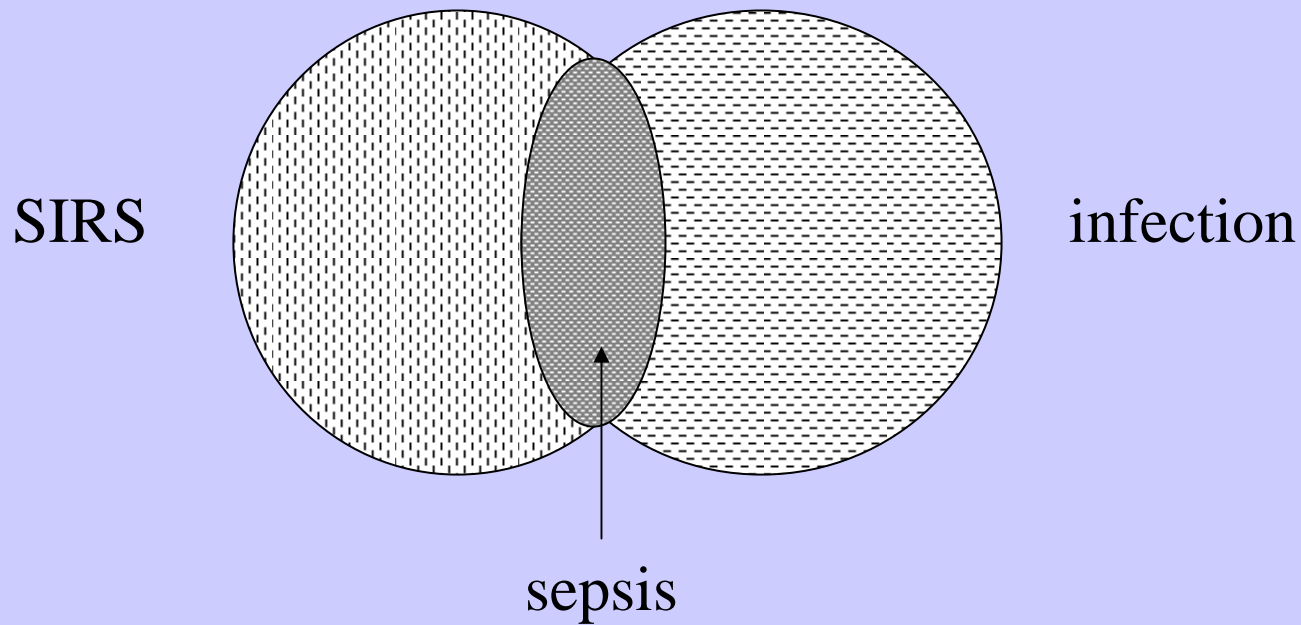
*2 or more of the following conditions:*

1. temp above 38°C or below 36°C
2. heart rate >90 beats/min
3. respiratory rate >20/min or PaCO<sub>2</sub> < 32 mm Hg
4. WBC: > 12,000 cells/mm<sup>3</sup>, < 4,000 cells/mm<sup>3</sup> or immature (band) forms >10%

*(ACCP/SCCM; 1992 Consensus Statement on definitions. Crit Care Med; 20:864)*

SEPSIS is SIRS associated with a confirmed infectious process.

spectrum: sepsis → severe sepsis → septic shock



- Sepsis is a major clinical problem
  - High numbers
  - Morbidity and mortality

# Diagnosis: Bacterial (ID) Methods

## Phenotypic ID methods:

not reliable for all pathogens or take too long to be clinically relevant

## Molecular

- nucleic acid sequencing; Concordance excellent with phenotypic ID; Results in 1-2 days
- Fluorescent in situ hybridization assays (PNA-FISH)
- Direct specimen multiplex PCR; useful for MRSA
- Microchip analysis for identification and antibiotic susceptibility

# Why Biomarkers of Sepsis

- Sepsis must be diagnosed early to effectively improve patient therapy; use of empiric and inappropriate Ab Tx
- Clinical signs of sepsis are not very specific (i.e. fever or leukocytosis) and mimic other conditions including SIRS

We need markers for

- diagnosis → to identify patients in whom antimicrobial Tx is likely to be of benefit
- prognosis → to provide estimates of patient risk for outcomes including LOS and mortality
- severity of illness; may be useful as a variable in organisation of studies and clinical trials
- monitoring → response to therapy; trends using serial measurements

*objective markers vs clinical impression*

# Biology of Sepsis

The protective action of the Innate immune response

Rapid

Based on non-clonally distributed receptors that recognise molecular patterns found in microbes

✓ pathogen-associated molecular patterns

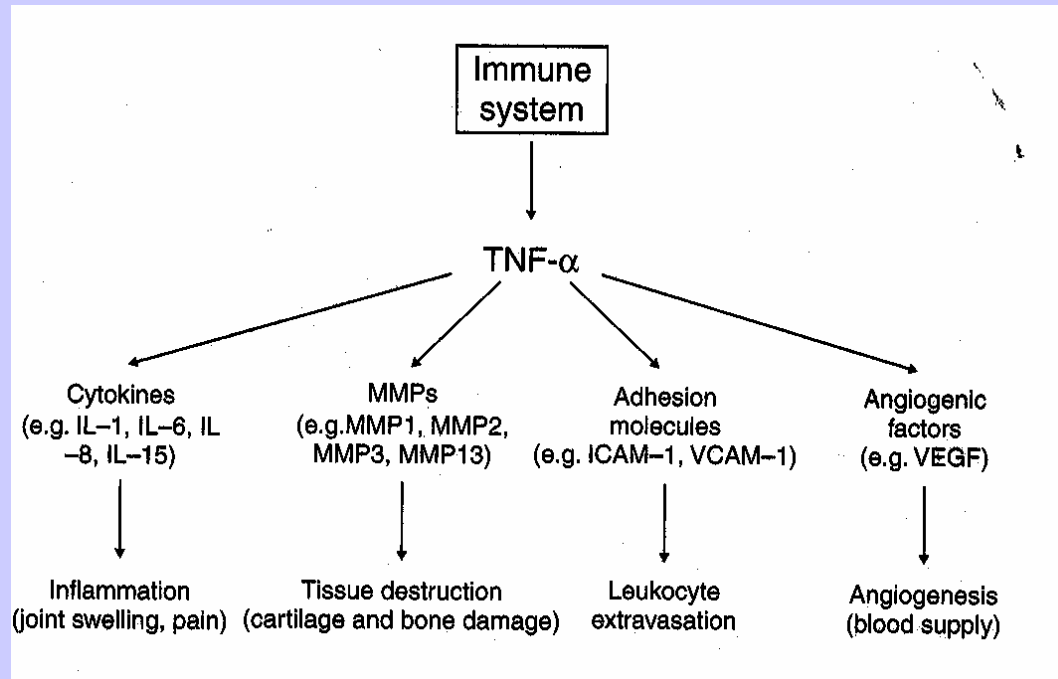
LPS (endotoxin), cell wall components: non-bacterial molecules

✓ pattern recognition receptors

➤ germ-line encoded

➤ expressed on many effector (cells) of the IMS

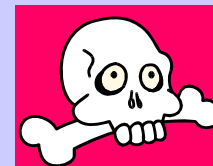
✓ Cellular and non-cellular responses



*Normal response of the innate immune system to infection → inflammatory cascade*

This response

- is normally un-noticed
- if prolonged and un-regulated → SIRS/sepsis  
→ pathological



## The pathophysiology of the innate response

- cellular activation: monocytes, macrophages, dendritic cells ⇒ phagocytosis/degradation/opsonisation
- up-regulation of specific cell markers and receptors
- release of mediators: cytokines, acute phase proteins,
- complement pathway activation; mannan binding lectin
- up-regulation/release of specific reactants or intermediates: lipopolysaccharide binding protein (LBP), protein C

*suggests potential markers*

## Cell counts

- total WBC counts, differentials, platelets
- used in many early studies

## Flow cytometry for specific markers of cell types and activation

- use of multiple fluorescent probes enhances specificity of analysis
- quantitative

Neutrophil CD64 →sepsis in Emergency Department

Patients *Davis et al. Arch Pathol Lab Med, 2006;130:654*

CD64 (and IL8) early markers of severity and outcome

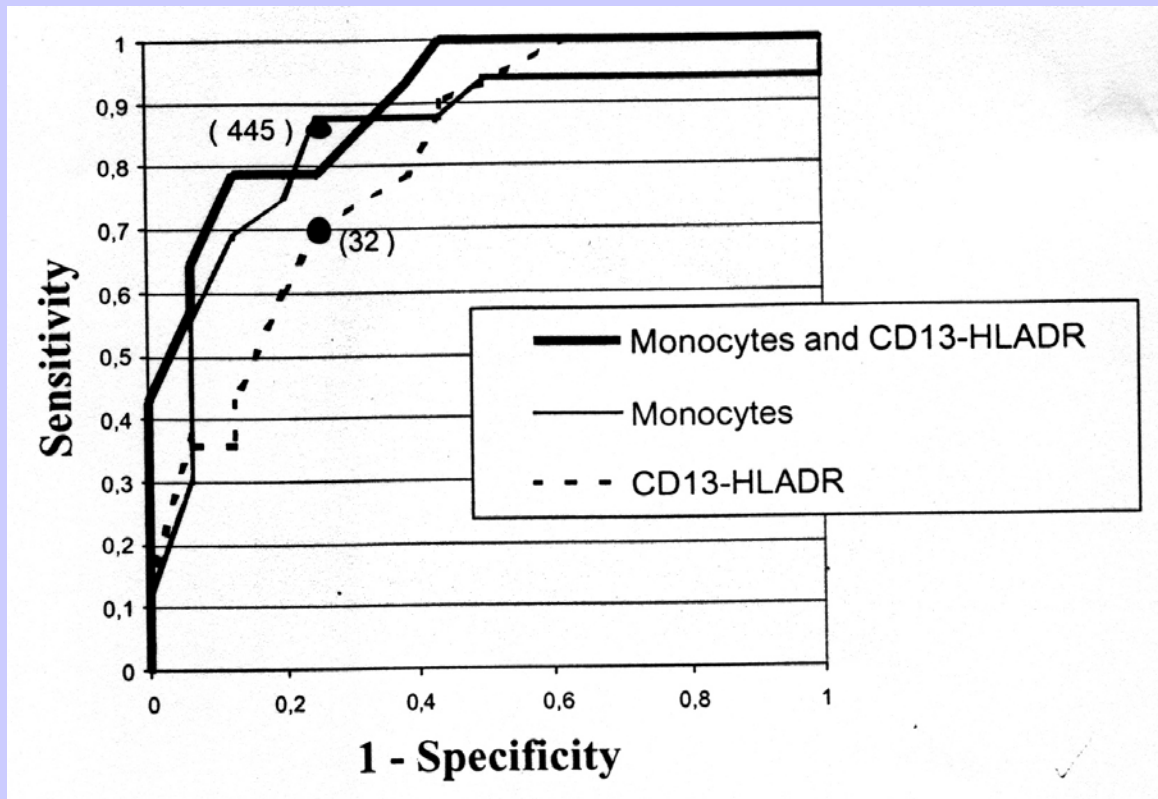
*Livaditi et al, Cytokine 2006*

Diagnosis of sepsis in VLBW infants

neutrophils: CD11b: adhesion molecule; CD64: phagocytosis;  
upregulated by bacterial/endotoxin;

both peaked with active infection; CD64 much better

*(PC Ng et al. Pediatr Res, 2002; 51:296-303)*



Prognostic significance for total monocyte count, subpopulations; t =48hrs. Survival; adults

AUC - Monos+ CD13-HLADR = 0.918

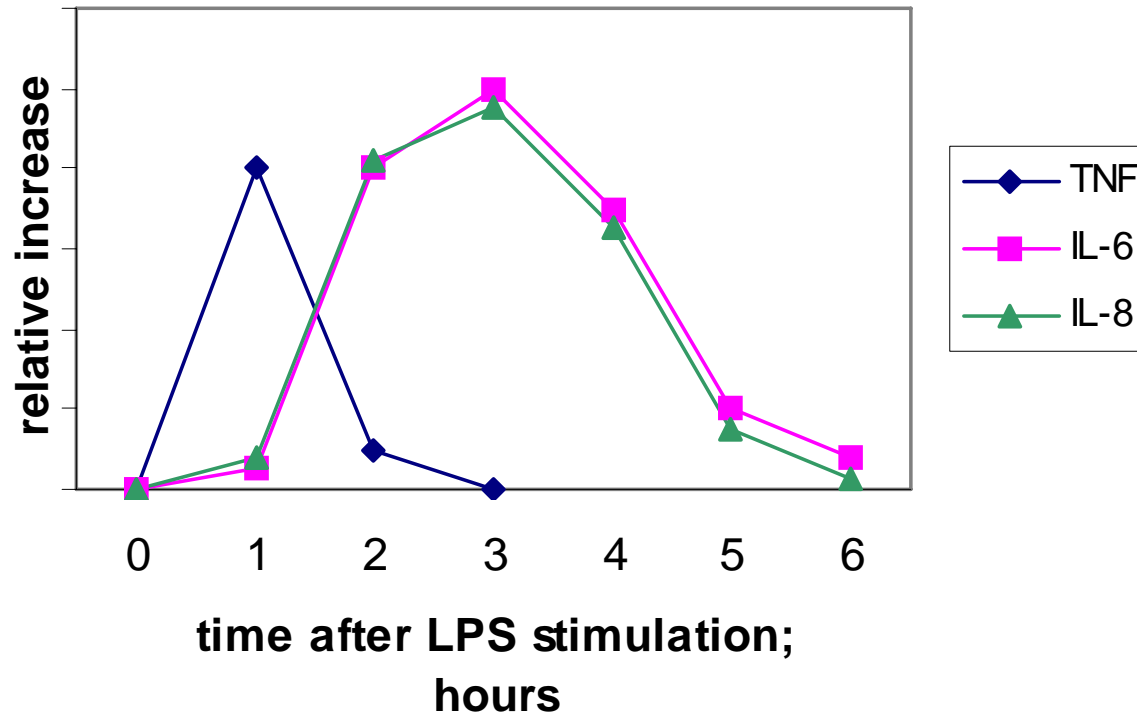
*(from Sáenz et al, Intensive Care Med. 2001; 27:970. ©, reproduced with permission)*

# Cytokines

- small proteins; secreted by various cells
- regulate cellular activation, differentiation and proliferation
- regulate the inflammatory response;
  - pro- or anti-inflammatory (immunosuppressive)
- *smaalll* amounts necessary; *large amounts are harmful (dysregulated release)*

TNF $\alpha$ , IL-1, IL-6, IL-8, IL-10,

## time course of cytokine release



- adults; IL-6 ↑ in non-survivors;  
initial level correlated with duration of survival;  
problem → definition of an optimal cut-off value  
(*Calandra et al, 1991; Amer J Med, 91:23*)
- adults; ↑IL-8 correlated with fatal outcome; more  
specific than IL-6 (*Murty et al, 1992*)
- - ↑ concentrations of IL-10 → associated with  
adverse clinical outcomes including non-survival  
- action of IL-10 as an immunosuppressant  
*Oberholzer et al, 2002; Review; Crit Care Med, 30(1,Suppl):S58*

- Use of immunostaining and flow cytometry for quantitation of intracellular concentrations of cytokines
  - Fumeaux et al, Intensive Care Med 2004

# cytokine/chemokine profile in CLP model of sepsis (*Osuchowski et al, 2006*)

Altered homeostasis with

- Early mixed pro- and anti-inflammatory response
- Final compensatory anti-inflammatory response with excessive anti-inflammatory mediator release and activity

Initial inflammatory response correlates with early mortality (not late sepsis mortality)

*Significance of Th1 versus Th2 cellular response*

Review of cytokines in neonates noted marked variability in results (*Mehr & Doyle, 2000; Pediatr Infect Dis J, 19:879*)

Similar conclusions can be drawn from an examination of the literature pertaining to adults and children; for diagnosis or outcome prediction

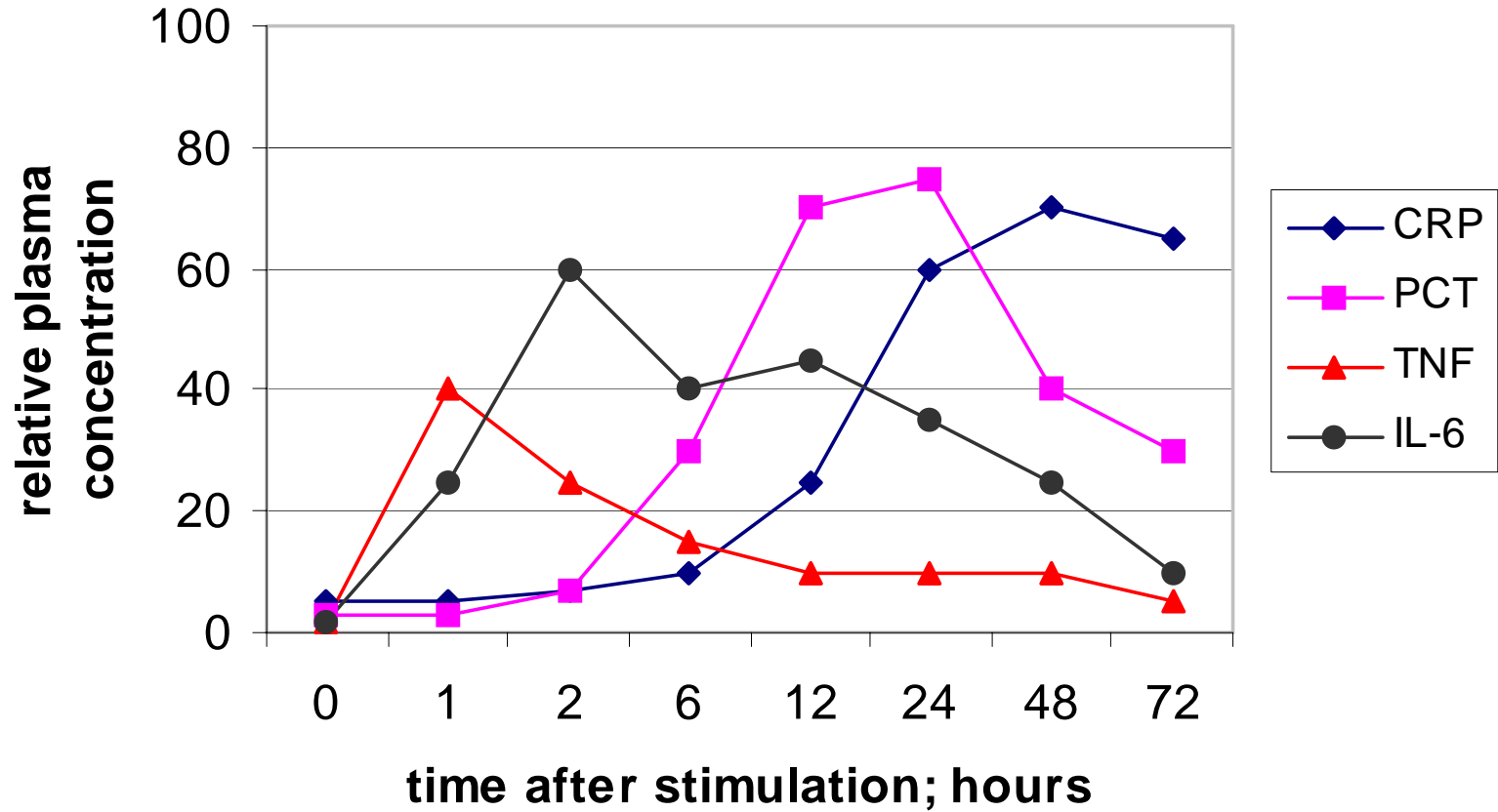
Problems include

- sensitivity and specificity: overlapping results
- variable correlation with disease severity and outcome
- threshold values

# CRP

- acute phase protein; synthesised in liver; IL-6 (and IL-1 and TNFa) stimulate synthesis via action on promoter
- binds bacterial polysaccharide, chromatin
- activates the classical complement pathway
- increased in the immune inflammatory response; especially in bacterial (vs viral) infection

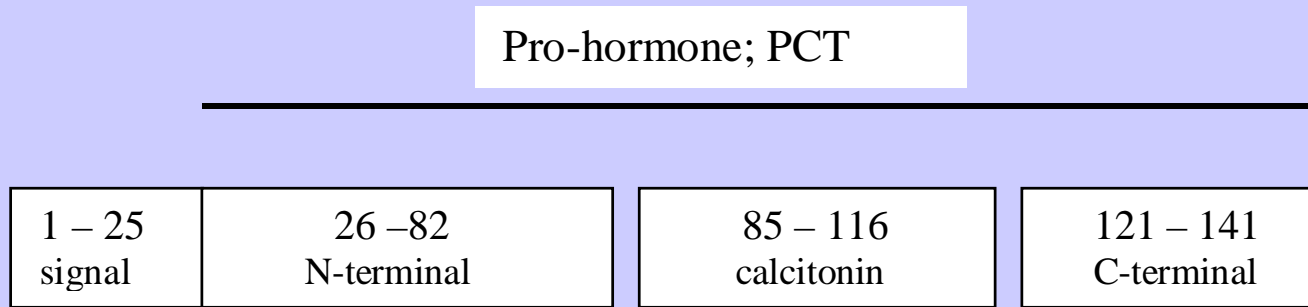
### time course of release



*few studies on CRP alone*

- In adult patients with SIRS, CRP was useful in diagnosing infection; compared to WBC (*Reyn et al, 2002; Crit Care Med, 30:529*)
- Use of CRP and cytokines for the diagnosis of late onset neonatal sepsis; CRP best; combination CRP + IL-6 at different times gives better PPV and NPV; can be used as a tool for discontinuation of Ab Tx (*Ng et al, 1997; Arch Dis Child, 77:F221*)

- Procalcitonin (PCT): the prohormone form of calcitonin; synthesis → C cells in thyroid



- In the course of a study on pediatric burn patients → increased serum PCT was shown to be a specific marker of sepsis in a pediatric population (*Assicot et al, 1993; Lancet, 341:515*)
- since then → numerous studies

- PCT distinguishes between bacterial and viral infections or other distress states in children; more discriminatory than CRP and IL-6 (*Gendrel et al, 1996; J Pediatr 128:570. Gendrel et al, 1999; Pediatr Inf Dis J 18:875*)

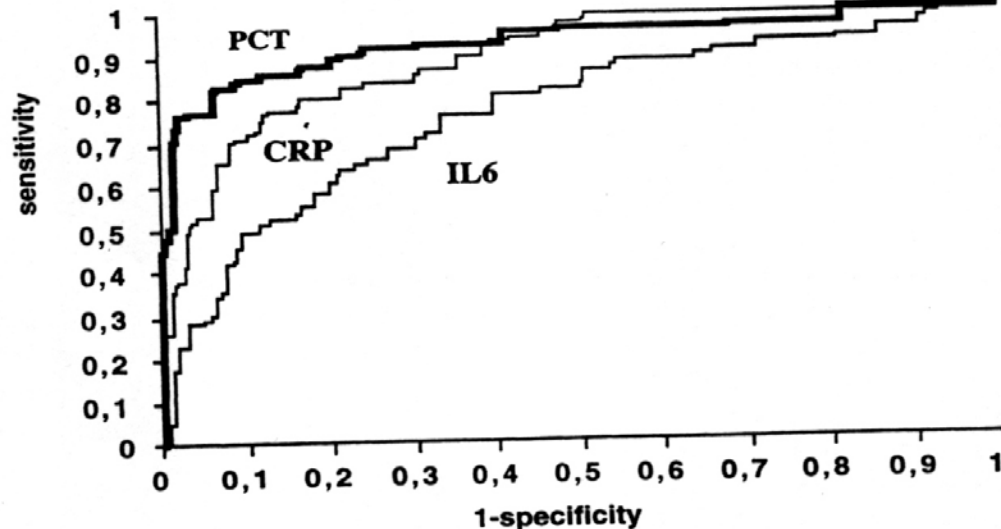
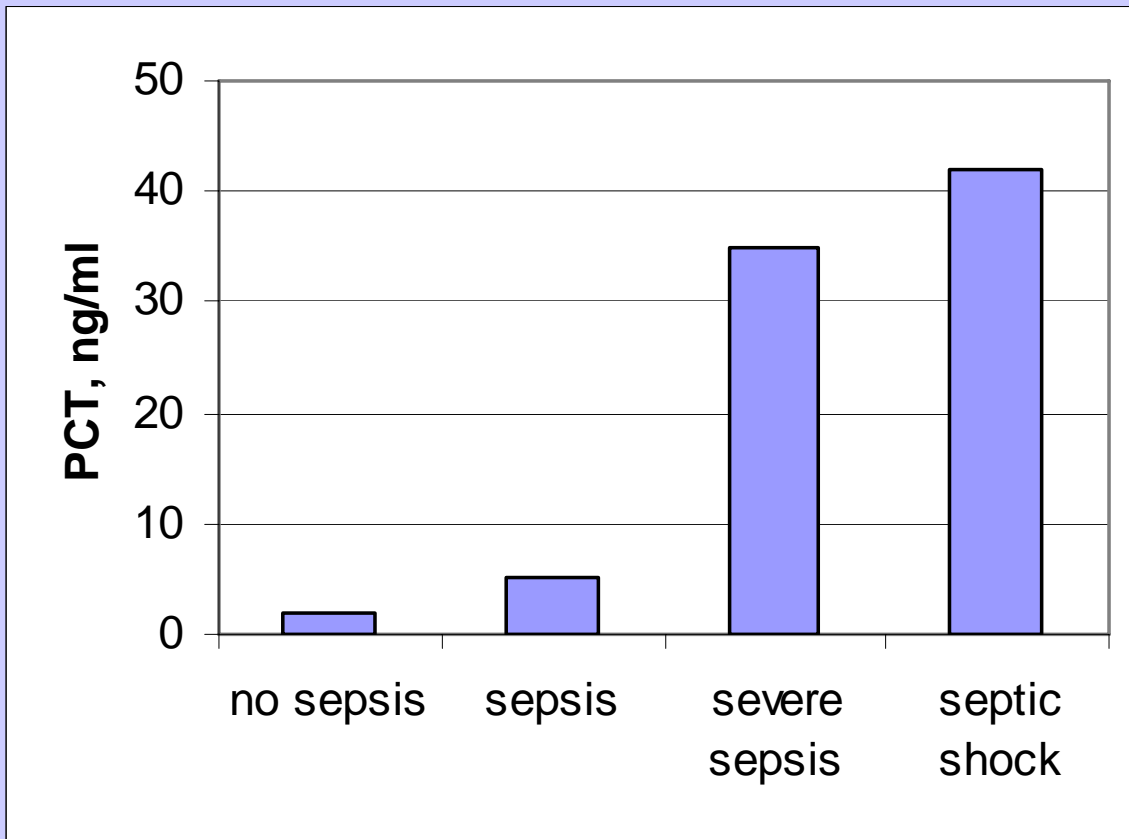


FIG. 2. ROC curves for PCT, CRP and IL-6 for discrimination between bacterial and viral infections.



*Data from Zeni et al , 1994; Clin Intens Care, 5(Suppl. 2):89*

- PCT is increased markedly in septic states
- levels seem to correlate with severity of infection and therapeutic response
- calcitonin is always normal in these conditions
- site of synthesis → liver, ? PBMNC
- ? signal that regulates incomplete proteolysis
- ? stimulation by LPS/sepsis-related cytokines
- ? function: may mediate the inflammatory response particularly in bacterial sepsis

## PCT is a well-established biomarker of sepsis

- Indicator of bacterial infection
- Indicator of the severity of the systemic inflammatory response (SIRS)
- Monitor progression of infection in sepsis and septic shock
- Follow responsiveness to antibiotic treatment
- PCT test recently cleared by FDA as ‘an aid in the risk assessment of critically ill patients on their first ICU day for sepsis and progression to septic shock’
- No outcome studies of routine clinical use of PCT have been done in important clinical settings (i.e. ICU or Emergency)

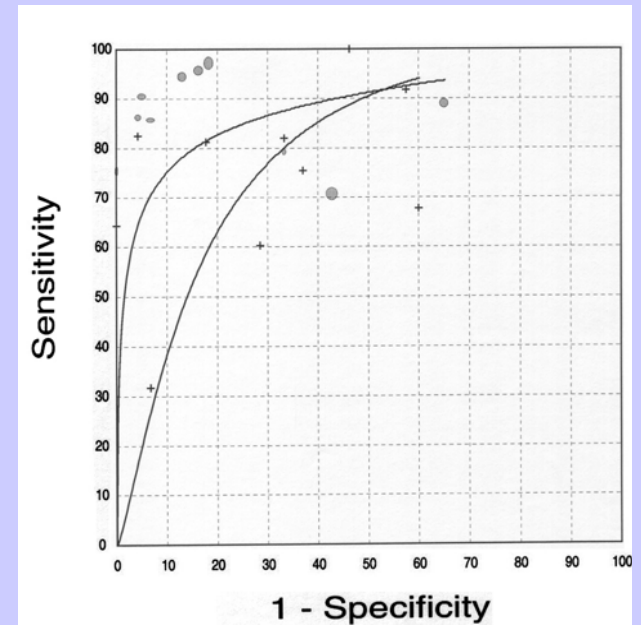
*(D. Church, 2006)*

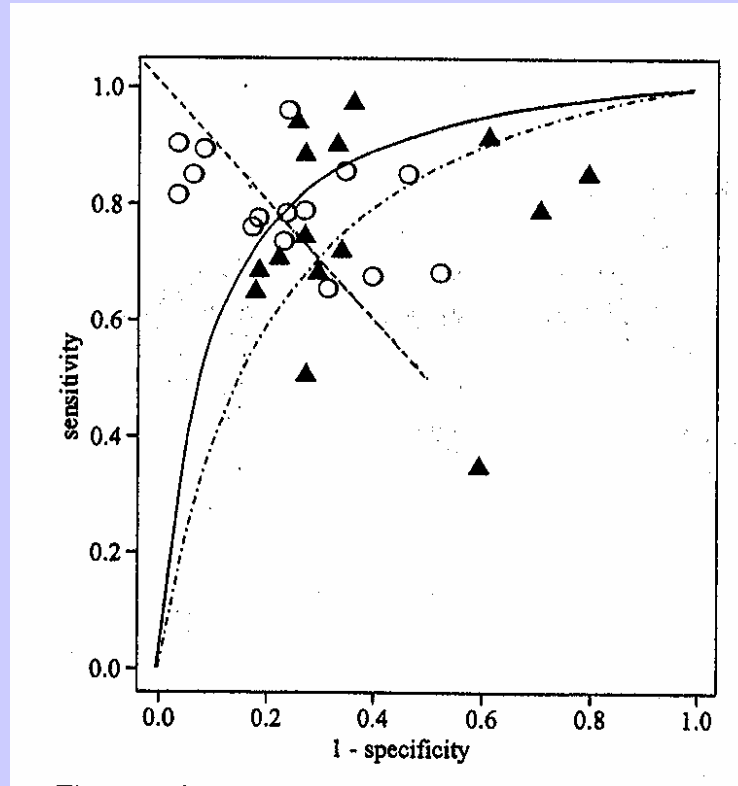
## PCT versus CRP

- variable utility for diagnosis and for prediction of severity and outcome
- the threshold (cut-off) value is somewhat variable especially for PCT
- both are normally absent or present at very low serum levels
- analytical methods

	Bacterial	v. non-inf	bacterial	v. viral
	sens	spec	sens	spec
PCT	0.87 (0.79-0.92)	0.83 (0.68-0.92)	0.90 (0.86-0.93)	0.76 (0.52-0.90)
CRP	0.72 (0.62-0.80)	0.76 (0.63-0.85)	0.62 (0.51-0.72)	0.94 (0.78-0.98)

*Meta-analysis, n = 12, 1490 patients with SIRS; Dx only. Summary ROC curve. Simon et al;*





*Uzzan et al. Crit Care Med 2006*

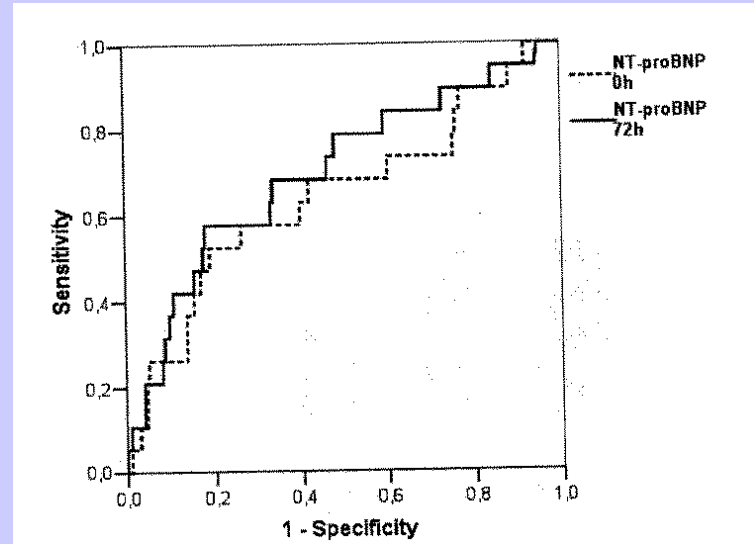
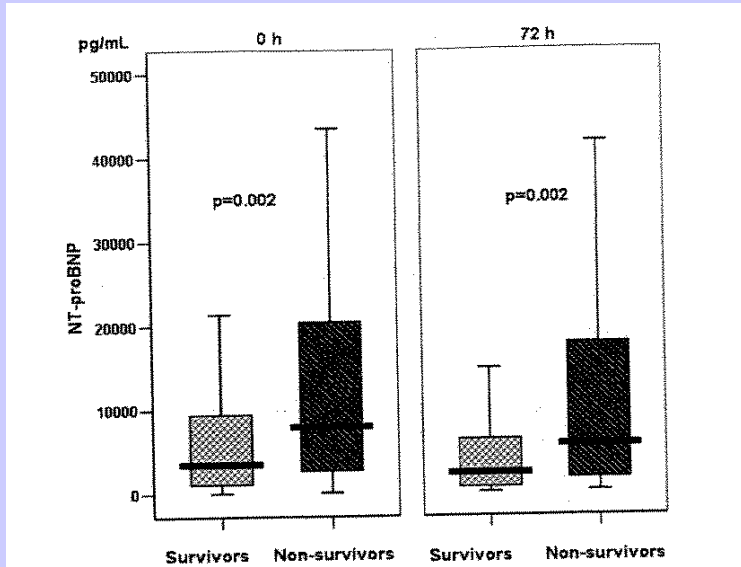
Other potential markers

# Lactate

- Elevations of lactate frequently accompany severe illnesses; includes sepsis and septic shock
- Hyperlactatemia → marker of severity of the stress response
- Degree of elevation correlates; predictor of outcome → prognosis
- Use serial measurements rather than single determination

# NT-Pro BNP in patients w. severe sepsis, septic shock

*Varpula et al, CCM, 2007*

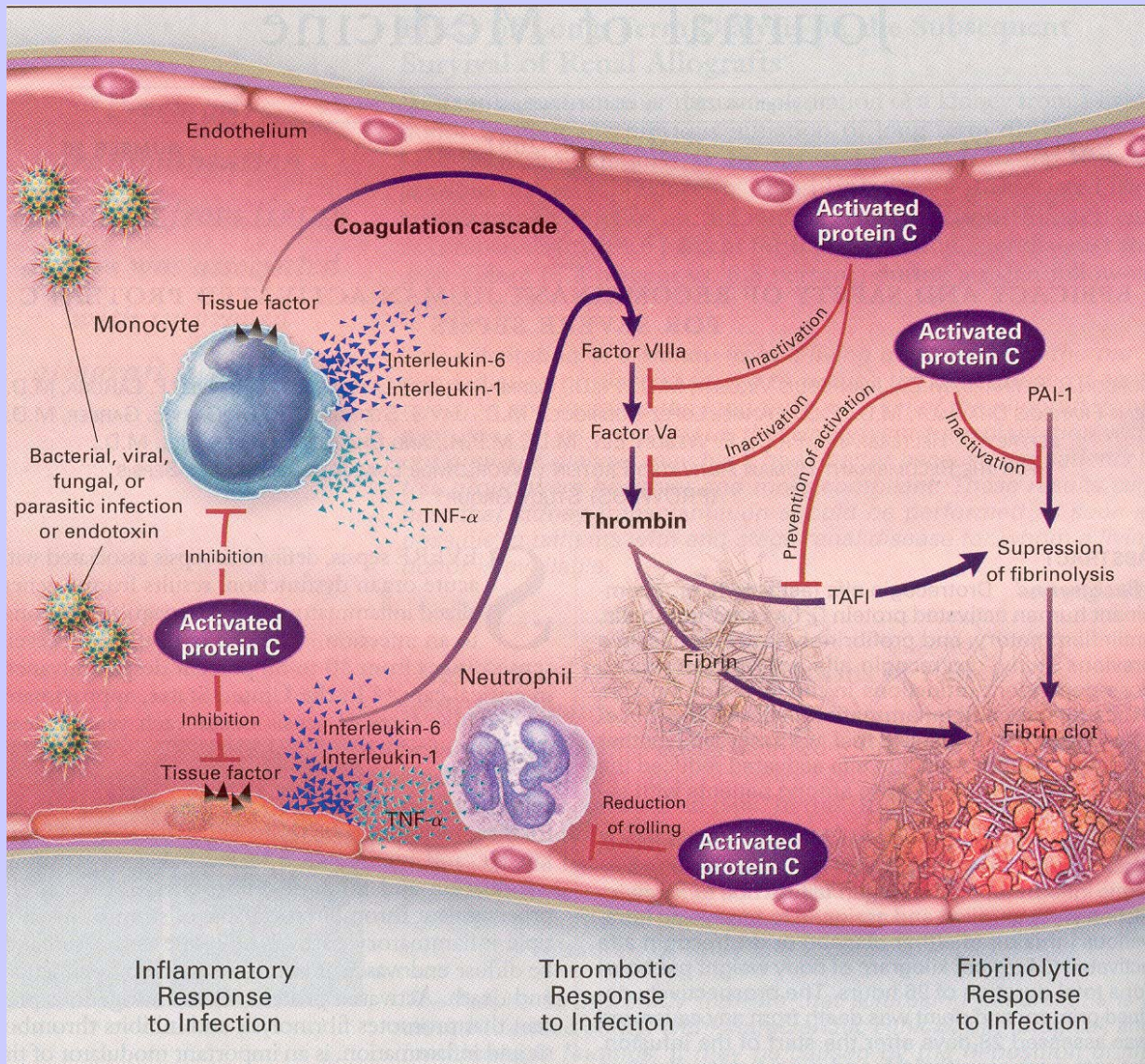


## Controversy:

Variability of characteristics of these patients wrt cardiac function and Tx;

LVD, myocardial wall tension

Catecholamines and other cardio/vasoactive drugs on board



- (Activated) protein C
  - a major regulator of hemostasis;
  - down-regulates coagulation activation cascade
  
- sepsis → activation of clotting system with abnormal coagulation and fibrinolysis
  - acquired deficiency of protein C

- Serial protein C determination may be useful in the diagnosis or monitoring of sepsis (*Boldt et al, 2000; Crit Care Med, 28:445*)
- ↓ protein C correlated with mortality in sepsis (*Mesters et al, Crit Care Med, 28:2209; Macias & Nelson, 2004*)
- Protein C levels may serve as a useful prognostic indicator of outcome in sepsis (*Fisher & Yan, 2000; review in Crit Care Med, 28(Suppl.):S49*)

Complement C3a: adults; SIRS versus sepsis (culture +);  
C3a, PCT and IL-6 higher in patients with sepsis;  
C3a also predicted outcome ; “score” slightly better  
(*Selberg et al, 2000; Crit Care Med, 28:2793*)

	sens	spec	AUC
C3a	86	80	0.90
PCT, >3.3 ng/ml	86	54	0.82
IL-6	86	54	0.78
CRP, >60 mg/L	86	18	0.67
Score (PCT + C3a)	90	80	0.93

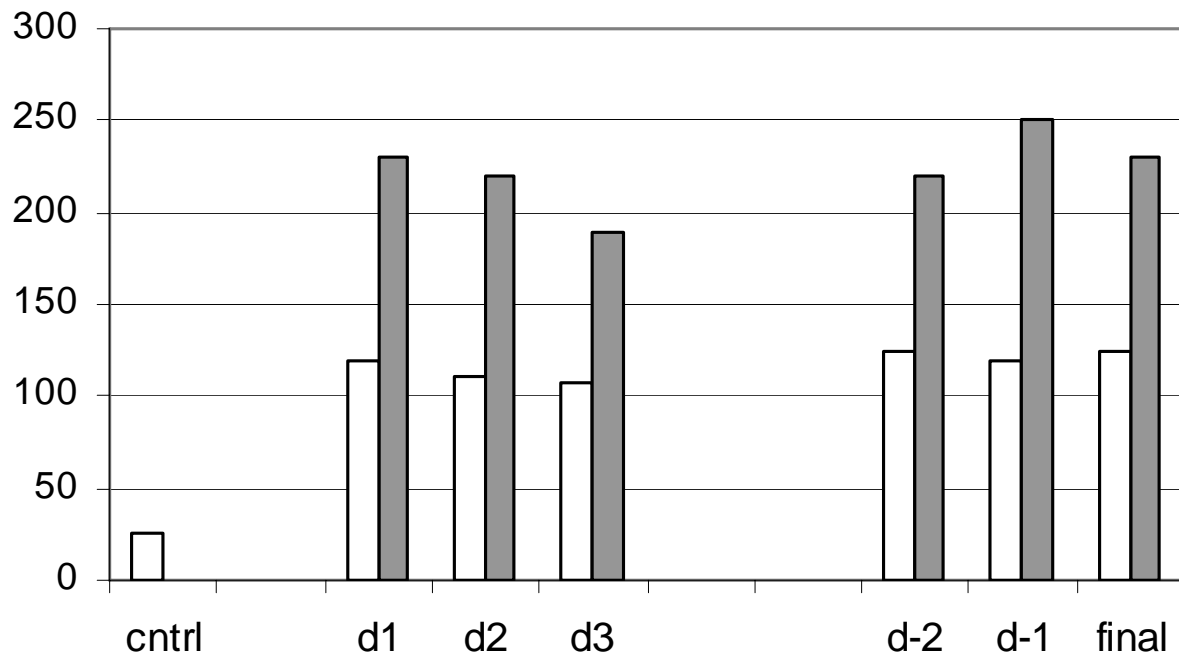
## Calcitonin gene related peptide (CGRP)

Alternate splicing of the gene for calcitonin

- a neuropeptide; sensory afferent nerves in most tissues; receptors on many cell types  
causes vasodilation; immunomodulation (↓)
- release stimulated by endotoxic shock (LPS), PGs, etc
- ↑ in patients with sepsis  
extent of rise correlates with outcome
- ? Is CGRP an early marker of sepsis

### **CGRP in sepsis patients; survivors, non-survivors.**

*(Beer et al, Crit Care Med, 2002; 30:1794)*



## Bactericidal/Permeability Increasing protein (BPI)

- released from activated PMNLs
- alters permeability of bacterial cell membranes
- inhibits the biological effects of LPS by preventing LPS/host receptor interaction; thus effect is opposite to that of LBP
  
- levels ↑ in sepsis but did not correlate well with outcome (*Rintala et al, 2000; Intensive Care Med, 26:1248*)

## Endotoxin (LPS)

- component of cell wall of Gram-negative bacteria
- stimulates the immune/inflammatory response
- Endotoxin Activity assay

study of ICU patients (n = 857)

sens of 85% and spec of 44% for the Dx of  
Gm-ve infection

*(Marshall et al. J Inf Dis 2004, 190:527)*

→ a marker of severity of infection

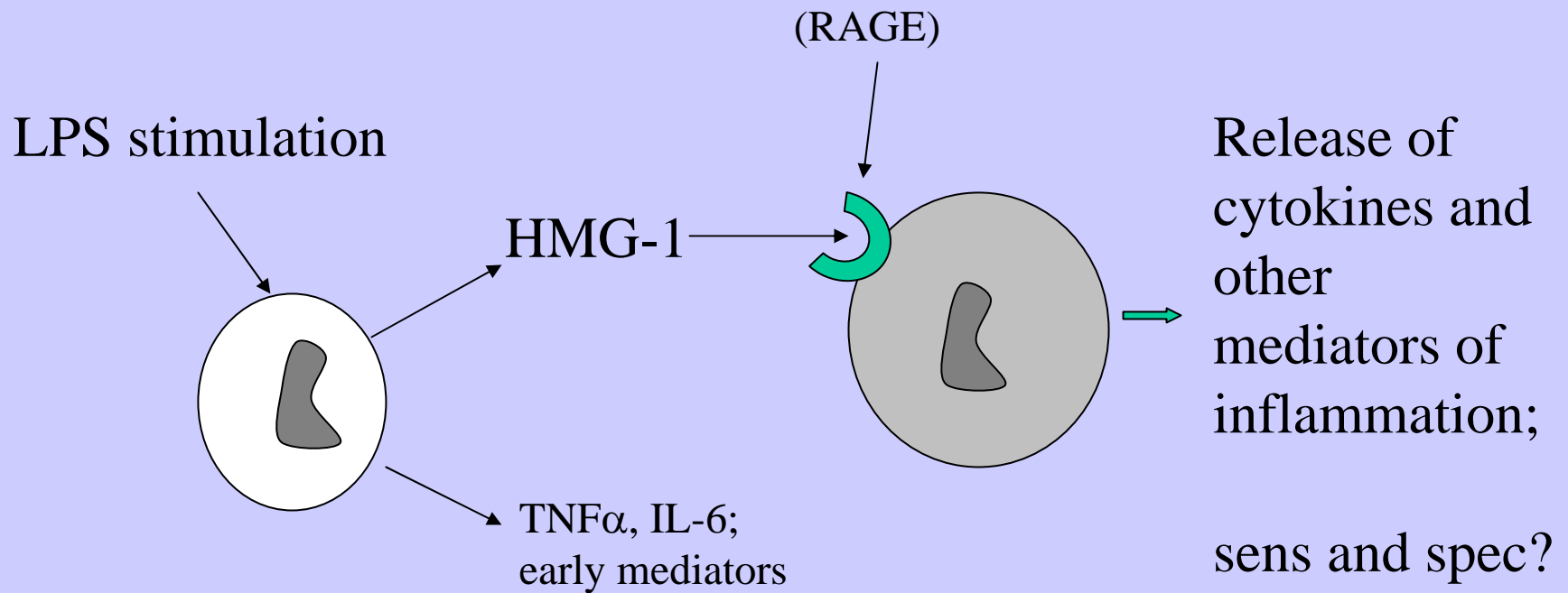
→ a prognostic marker

→ a marker for the success of Tx; to ID patients  
likely to benefit from anti-endotoxin Tx

→ Gm -ve infections only ?

## High mobility group 1 protein (HMG-1)

- a macrophage-derived (non-histone chromosomal) protein
- released late (>8 hours) after stimulation by LPS, TNF $\alpha$ , IL-1 $\beta$
- → a late mediator of endotoxemia by stimulating the release of pro-inflammatory cytokines from MNCs/macrophages



- not detectable in serum of normals
- $\uparrow\uparrow\uparrow$  in critically ill patients with sepsis
- higher in non-survivors

*(Wang et al, 2001; Am J Respir Crit Care Med 164:1768)*

# Macrophage migration inhibitory factor (MIF)

- bacterial infection (LPS)
  - T cells, macrophages → inflammatory mediators
  - pituitary cells → ACTH → corticosteroids
    - immunosuppressive
- stimulation of both cell types → MIF release (12.5 kDa) (LPS, exotoxin, corticosteroids)
  - ↓ immunosuppressive effect of corticosteroids
  - thus has pro-inflammatory actions
  - MIF  $\longleftrightarrow$  TNF $\alpha$  secretion (*loop effect*)

- high levels of MIF detected in patients with sepsis and septic shock  
(*Calandra, 2003; review; Scand J Infect Dis, 35:573*)
- MIF serves as a general marker for systemic inflammation in septic and non-septic critical illness; but
  - does not differentiate between infectious and non-infectious causes
  - does not discriminate for severity(*Lehman et al, 2001; Intensive Care Med, 27:1412*)

# Toll-like receptors

Act as sensors of the PAMPs of microbes, triggering the host defense via the innate immune system

- TLR1 – 10 in humans
- ✓ TLR2 Gram-pos markers → peptidoglycan
- ✓ TLR4 Gram-neg markers → LPS

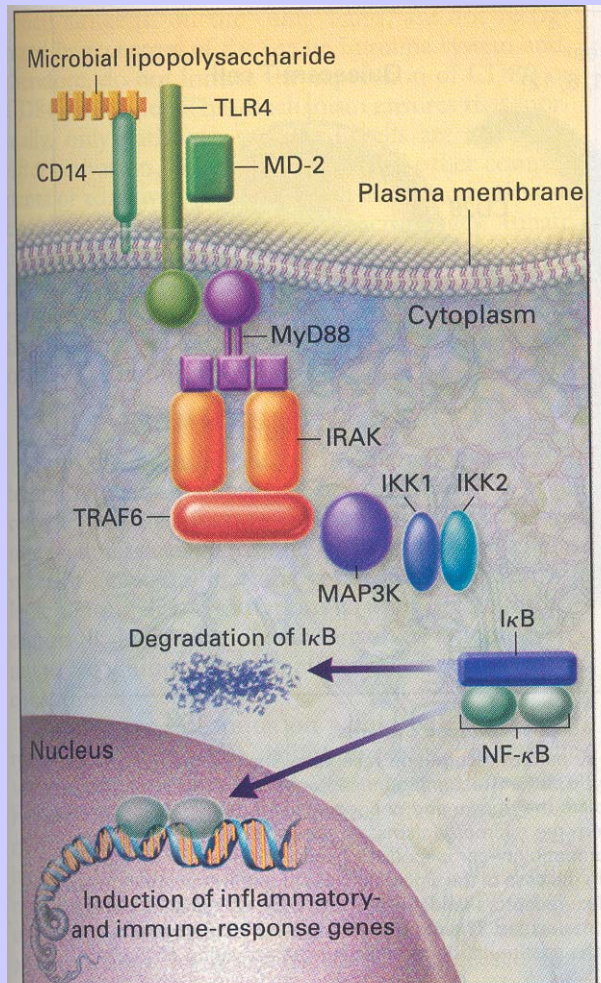
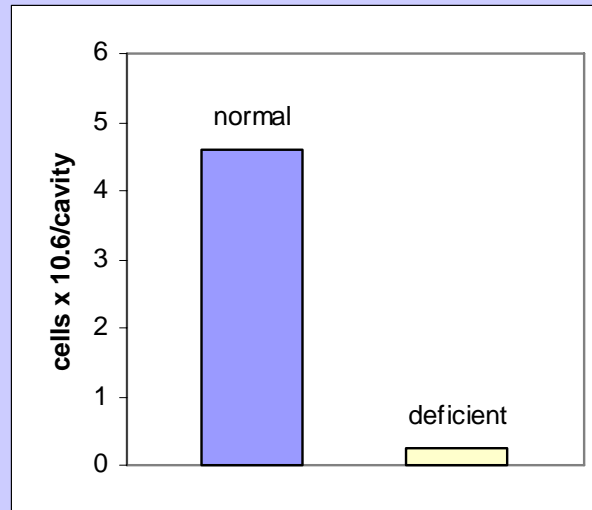
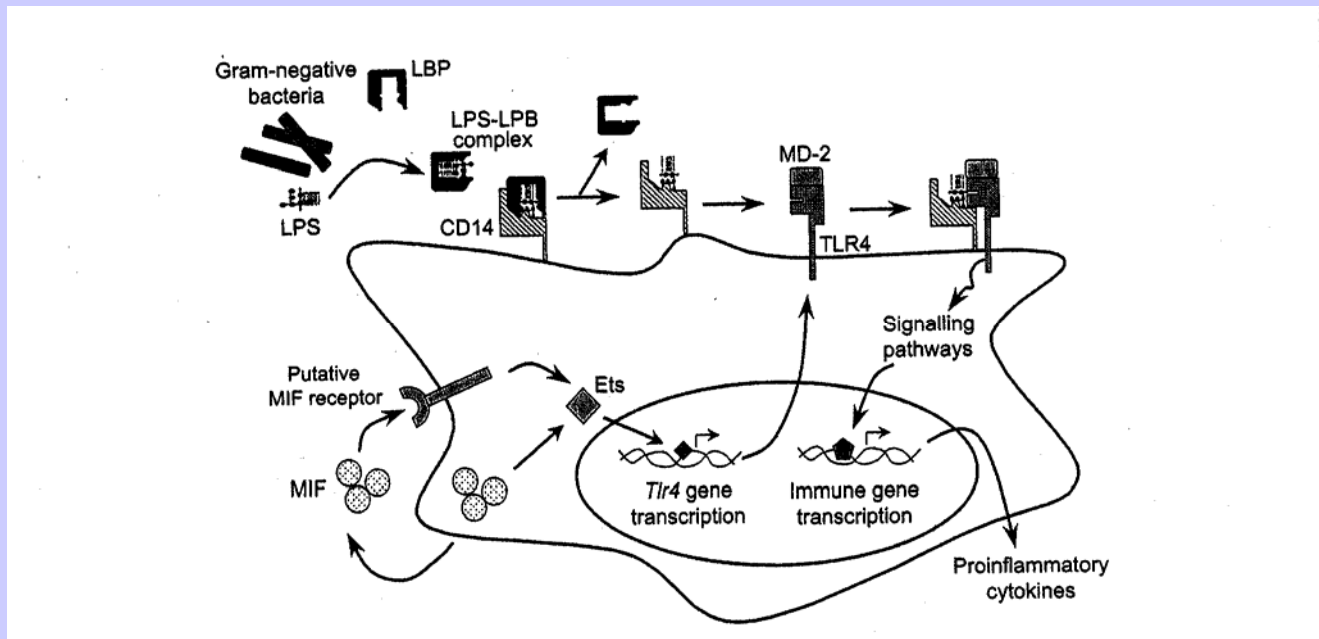


Figure 2. The Signaling Pathway of Toll-like Receptors.

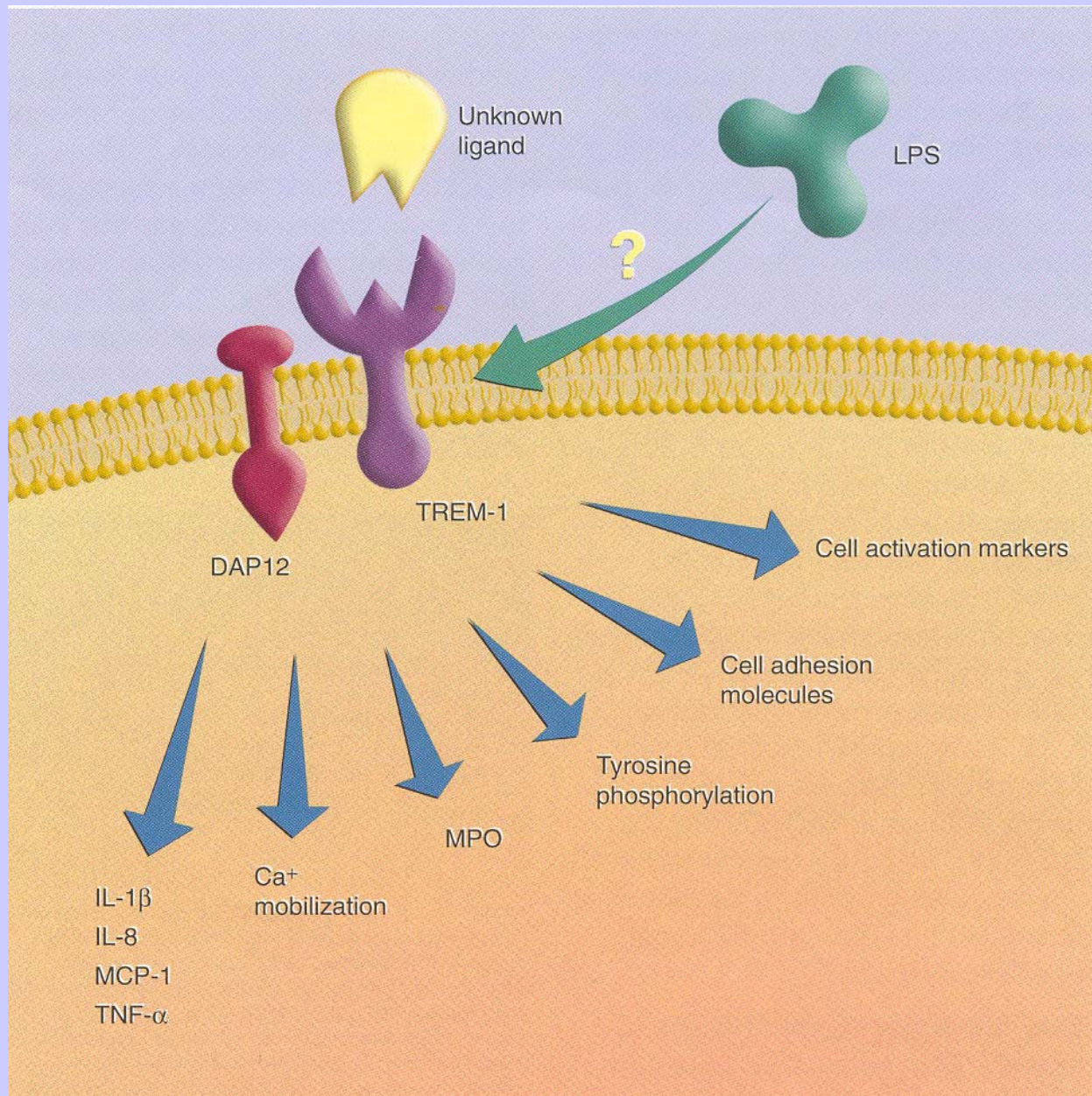
Deficient TLR4 signalling leads to impairment of neutrophil migration in polymicrobial sepsis  
(Alves –Filio et al, Crit Care Med 2006)



- Model of sepsis in TLR4 deficient and TLR4 normal mice.
- Impaired migration diminishes normal protective responses:
  - ↓ systemic levels of cytokines, MIP-2,
- Results in high mortality



*Calandra et al, 2003; JID*



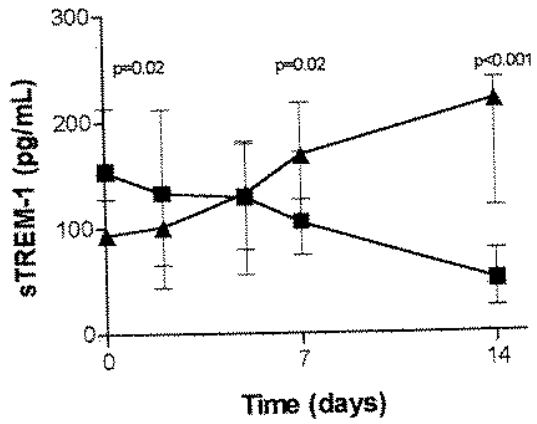
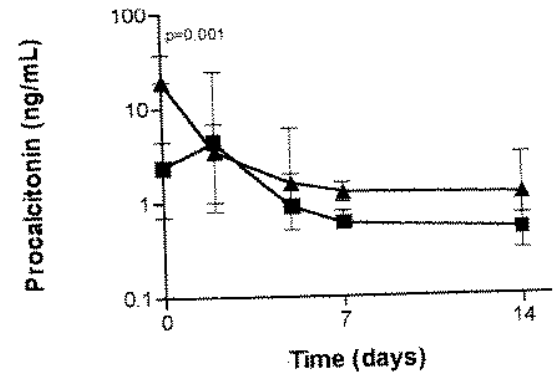
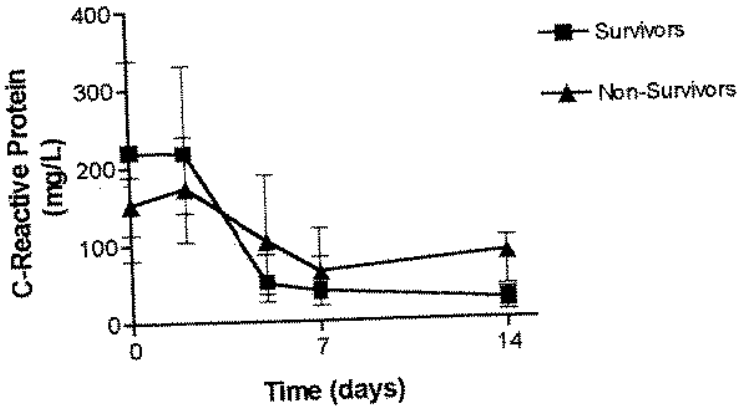
## Triggering receptor expressed on myeloid cells (TREM)

- IgG superfamily member
  - infection → up-regulation of TREM-1 on neutrophils, monocytes
  - activation of TREM-1 triggers proinflammatory responses including cytokine release, MPO release, etc (see figure)
- net effect is to amplify the acute inflammatory response (via TLR)

*(Bouchon et al, 2001; Nature 410:1103)*

- ? Does TREM-1 interact *in vivo* with microbial products, including LPS
- A soluble form of TREM (sTREM-1) has been identified in serum samples from patients with septic shock but not from controls
  - a potential marker
  - immunomodulatory actions
  - potential therapeutic agent

*(Gibot et al, J Exp Med 2004; 200:1419)*



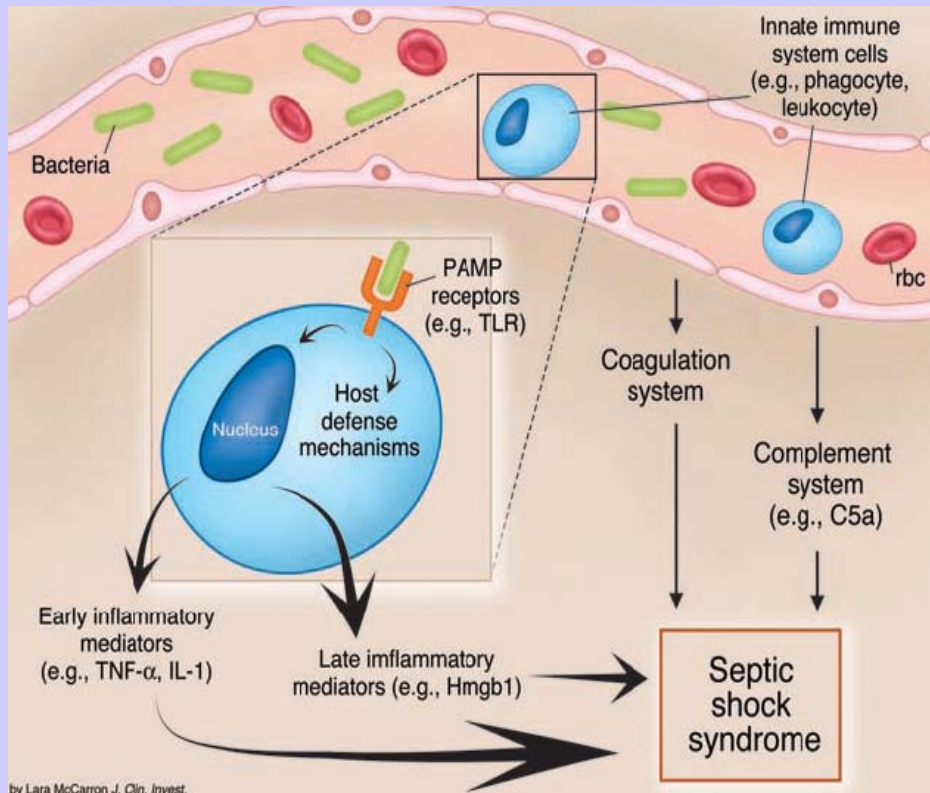
↓ Plasma sTREM → favourable outcome

Baseline sTREM may be a predictor of outcome

*Gibot et al, CCM, 2007*

# Multiple Markers

# Towards a Panel Approach



- Sepsis is a complex disease with multiple pathways.
- Multiple markers define disease and transitions more comprehensively.
- Multi-marker panels can aid in differential diagnosis and better define therapy.

*(E.P. Rivers; Henry Ford Hospital and Biosite. 2005; with permission)*

# LPS Binding protein - LBP

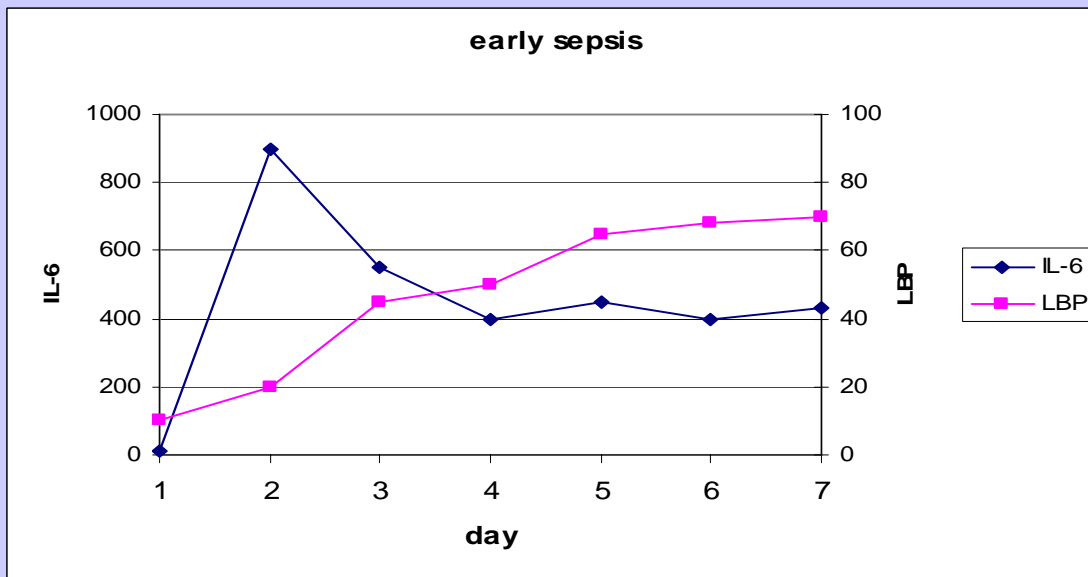
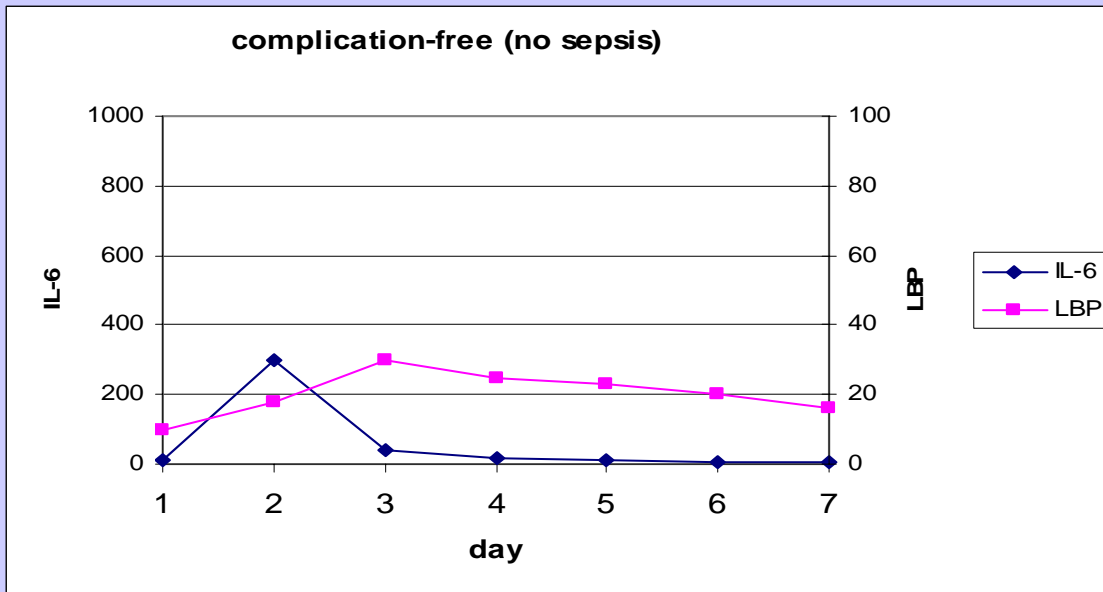
⇒ acute phase protein

⇒ + CD14 interaction → macrophage activation and cytokine release

- ↑ levels shown in children and adults with sepsis
- diagnostic accuracy neonates and children;

AUC:	LBP	IL-6	PCT	CRP
	0.90	0.67	0.67	0.84
	(0.79-0.96)	(0.54 - 0.79)	(0.53-0.78)	(0.57-0.89)

*(Pavcnik-Arnol et al; Intensive Care Med, online; May 2004)*



# Multiple Marker (MMX) concept

- 50 biomarkers tested by immunoassay →
  - Pro- and anti-inflammation, coagulation and fibrinolysis, apoptosis, vasoregulation, organ and tissue dysfunction; weighted
- A search engine based on optimization of the ROC AUC used to select a panel of markers
- Results optimized to give a Multi-Marker Index (MMX) value;
- Provides a single composite value; more accurate Dx tool

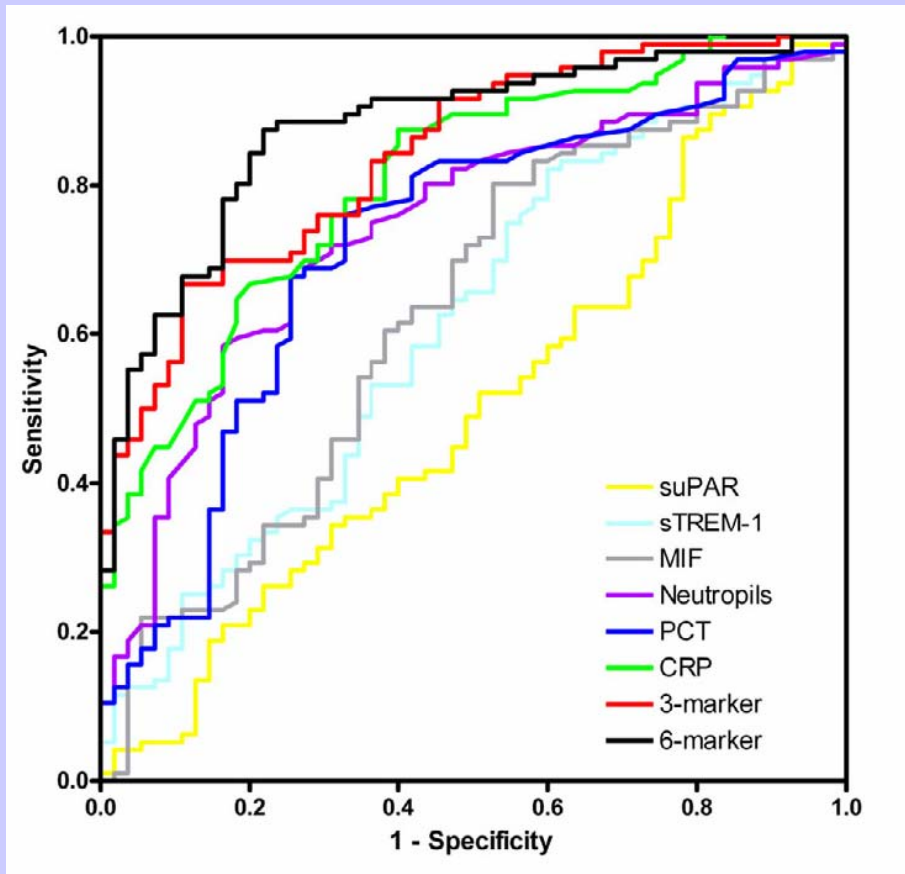
*(E.P. Rivers; Biosite. 2005; with permission)*

# ROC AUC (95% CI)\*

## A PANEL OF SIX BIOMARKERS - Interim Analysis \*

Condition	Sepsis Panel MMX	CRP	IL-6
All sepsis (sepsis, severe sepsis, septic shock)	0.76 (0.70-0.82)	0.62 (0.54-0.70)	0.64 (0.57-0.71)
All sepsis w/ positive blood culture	0.85 (0.79-0.92)	0.69 (0.59-0.79)	0.69 (0.59-0.80)
Severe sepsis	0.89 (0.83-0.95)	0.63 (0.53-0.74)	0.66 (0.55-0.77)
Septic shock	0.95 (0.91-0.99)	0.71 (0.57-0.85)	0.63 (0.45-0.82)

\*This chart illustrates research as of October 2005. Product in Development



600 patients  
 Dx of community  
 acquired infections;  
 $\geq 2$  SIRS criteria

151 patients  
 enrolled; 96 with  
 bacterial infection

*Kristian Kofoed, Ove Andersen, Gitte Kronborg, et al;*  
*Critical Care 2007, 11:R38 (doi:10.1186/cc5723)*

ICU patients: SIRS → sepsis

Protein profiling using Mass Spec

→ 134 proteins significantly different

- 32 complement and coagulation cascade
- 10 classic complement pathway
- 8 lectin-binding complement pathway

These pathways were all statistically significantly over-represented in the sepsis only group

*(Lissauer et al, J Trauma, 2007)*

Genetics  
and  
Genomics

# Use of forward genetics

- reverse genetics: gene to phenotype eg cytokines
- Forward genetics – phenotype to gene; the mutations that cause phenotype eg TLRs
- Sepsis is a complex process – innate immune system
- Scrips - Use of mutant mice; mostly ex vivo screening  
→ phagocytosis, microbial killing, macrophage response to LPS
- In vivo – mutation that selectively prevents LPS signalling but does not involve any of the “core” components of the TLR pathway

*(Beutler et al, JID, 2003)*

# Differential gene expression

*(Yu et al, 2004; Am J Respir Crit Care Med, 169:1135)*

liver cells, septic mice; cDNA microarray

- 4.8% of 6,144 genes differentially regulated
- most were common for gm-ve, gm+ve bacteria; some (17 genes) were specific; suggests early differences with a common final pathway
  - ↑ MHC molecules: CD36, CD39, CD82
  - ↓ ATIII, anti-inflammatory enzymes,  
↓ SOD ( ↑ oxidative stress, counter-regulatory)

## Gene chip technology

- Expression patterns of subsets of genes from tissues of known phenotypes
- Construction of prediction rules
- Use for phenotype prediction
  
- Mice CLP model; patients with sepsis ( $\pm$ )

Genes involved inflammation, apoptosis, regulation of signal transduction

*(Chung et al, 2006, J AM Coll Surgeons)*

# FDA/NIH/PhRMA Biomarker Consortium

## **Biomarker Consortium Mission Statement**

- Develop promising biomarkers for research, medical, and/or regulatory uses and to improve understanding of the biology of health and disease
- Develop evidence that will facilitate guidance on the use and qualification of biomarkers for specific diseases and their treatment
- Inform the regulatory framework for evaluating biomarkers and enable guidance on their use and qualification
- Promote dialogue across sectors to increase understanding of each sector's priorities for biomarker development

We need markers for

- diagnosis → to identify patients in whom antimicrobial Tx is likely to be of benefit
- prognosis → to provide estimates of patient risk for outcomes including LOS and mortality
- severity of illness; may be useful as a variable in organisation of studies and clinical trials
- monitoring → response to therapy; trends using serial measurements

*objective markers vs clinical impression*

## factors influencing the results of evaluations

- definitions: criteria for the diagnosis of sepsis; culture –ve, +ve
- selection of patient groups: diagnosis
- disease spectrum → severe sepsis, etc
- age
- gender
- genetics
- test methods: various; performance; TAT

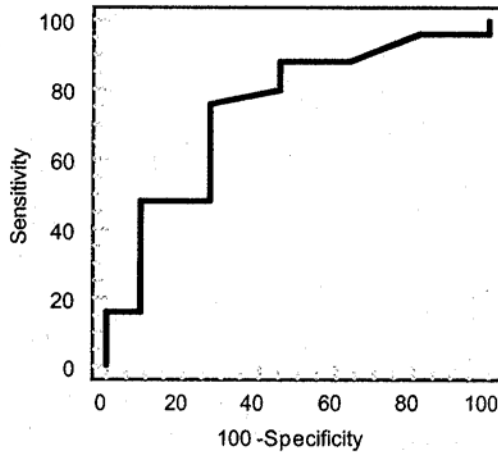


Figure 3. Receiver operating characteristic curve of serum procalcitonin levels for prediction of prognosis in medical patients with septic shock.

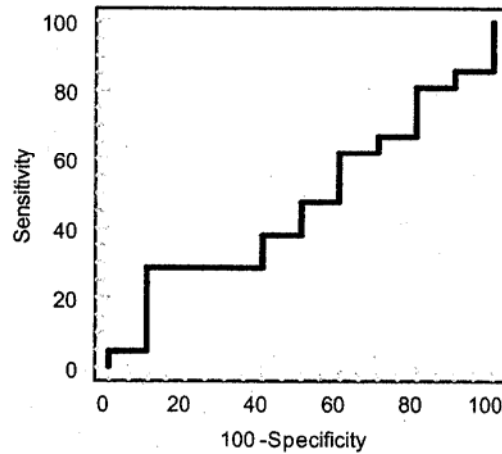


Figure 4. Receiver operating characteristic curve of serum procalcitonin levels for prediction of prognosis in surgical patients with septic shock.

## Age as a factor

- adults and children
- neonates

early onset versus late onset sepsis

*(perinatal versus post natal - nosocomial)*

- variations in « normal » neonatal biology in the first hours and days of life; compared to older children and adults many parameters have varying norms at this period

# GENETICS

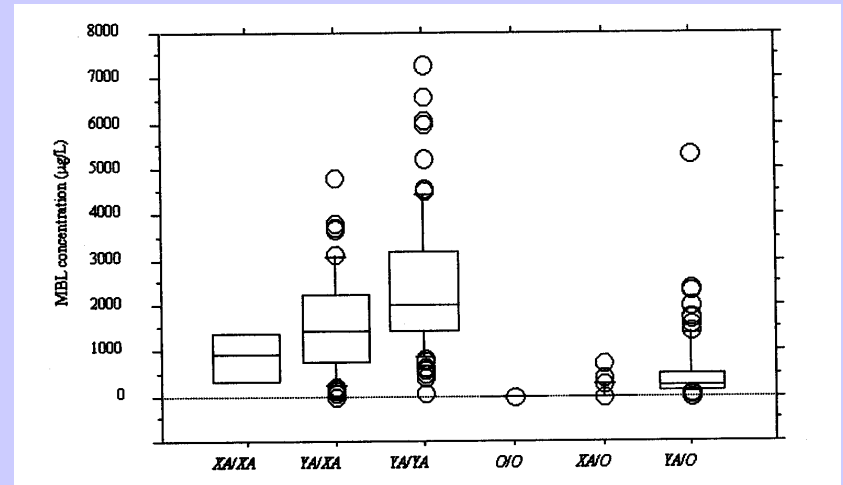
Host genetic variation can influence the activation of the immune system in sepsis

Gene polymorphisms do have a role in the susceptibility to infection and severity of response; usually via effect on immune/inflammatory response system (*Lin & Albertson, 2004; Crit Care Med, 32:569*)

## Mannose Binding Lectin (MBL)

- variant alleles in sepsis
- ↑ risk of fatal outcome noted in patients carrying variant alleles

*(Garred et al. 2003; J Inf Dis, with permission)*



TLR4 mutations are associated with an increased incidence of Gram-neg infections in critically ill patients

*(Agnese et al, JID, 2002)*

So what do we have ?

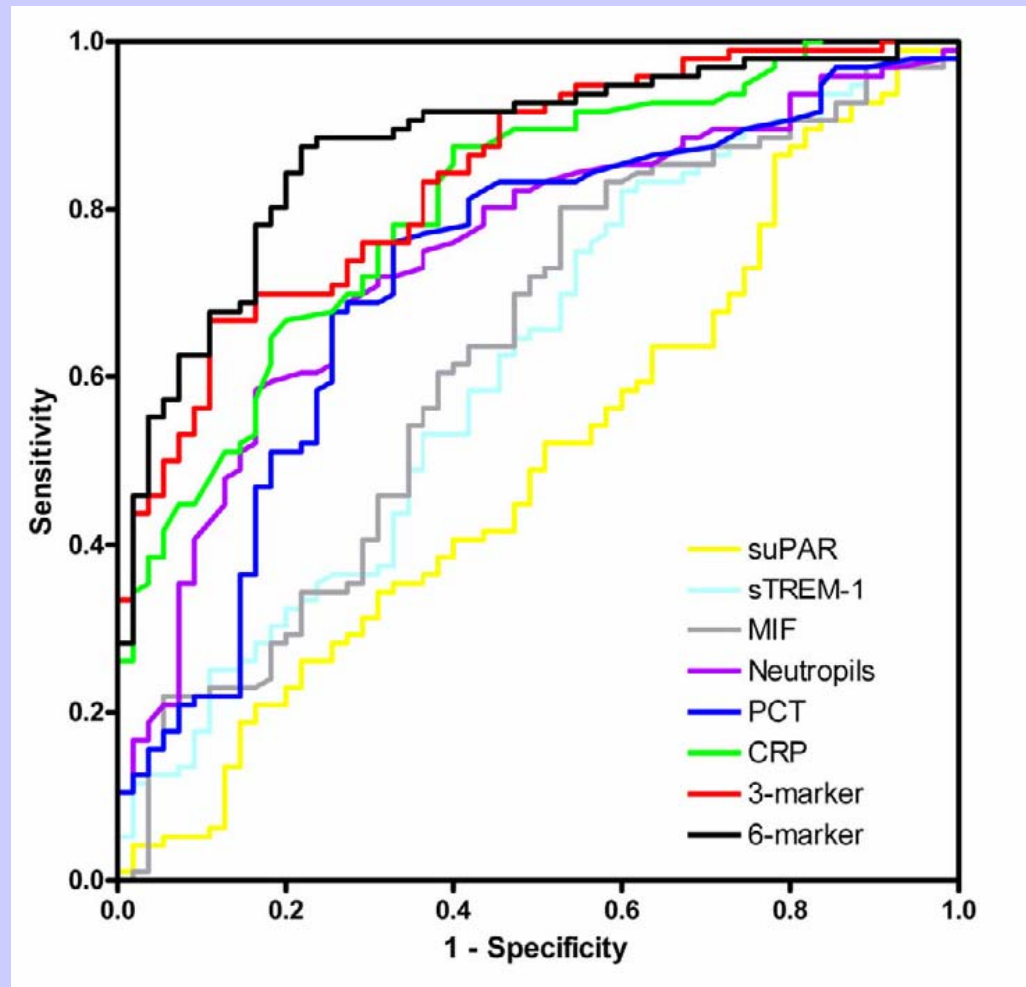
Many studies → various markers → variable performance

→ insufficient ability to discriminate in the face of a critical clinical situation

# Finding/selecting markers

- knowledge of pathophysiology of a complex response process
- fortuitous: PCT
- evaluation of combinations of markers
- targeted search: use of microarrays

*Kristian Kofoed, Ove Andersen, Gitte Kronborg, et al;  
Critical Care 2007, 11:R38 (doi:10.1186/cc5723)*



## Highlights some of problems in sepsis studies

- Cause/clinical Dx: Community vs hospital acquired infection/sepsis
- Criteria include CRP and neutrophil count; selection bias
- Classification of sepsis: documented infection; bacterial infection of unknown origin; viral and fungal sources
- Timing of sampling – some after antibiotic Tx begun
- Data manipulation: Linear combination vs quadratics

# Using multiple markers

The real (mathematically derived) predictive value of a set of biomarkers may not necessarily improve in direct relation to the number of markers

- *Data from the Framingham Heart study → multiple biomarkers only add modest value to the predictive value of traditional risk markers (BNP and UA/10)*

Effect of

- Marker selection – traditional or well known
- Selected patient population
- Statistical model (ROC AUC – the C statistic)

*(NEJM 2006)*

- test cut-off value must be as sensitive as possible to ensure that truly infected patients are diagnosed; patient with a FP result does not die of sepsis
- the NPV must be as high as possible to permit the decision that Ab Tx in a patient with a neg test is unnecessary
- maximal sensitivity = lower specificity and lower overall accuracy

Mehr & Doyle (2000; *Pediatr Infect Dis J*, 19:879):  
review of cytokines in neonates

# CONCLUSIONS

1. Activation of the Innate Immune system, in response to bacterial infection, results in a series of inflammatory responses effected by various mediators.
2. Dysregulation of this immune/inflammatory response results in sepsis
3. Our knowledge of this response system, at all levels, forms the basis of the search for reliable laboratory markers for diagnosis and monitoring.

Our work is not yet done

## Goal-directed therapy

Use of CRP and PCT results to guide treatment

→ withhold or discontinue antibiotic Tx

→ cost/benefit studies

- Effect of PCT-guided treatment on antibiotic use and outcome in lower respiratory tract infection. (*Christ-Crain et al. Lancet 2004, 363:600*)
- Measurement of IL-8 in combination with CRP reduced unnecessary antibiotic therapy in newborn infants. (*Franz et al. Pediatrics 2004, 114:1*)

## The Epidemiology of Sepsis; the numbers

1. In USA annually >500,000 cases; mortality = 35%
2. 1979 - 2000 ↑incidence; in-hospital mortality ↓  
however total no. of deaths ↑ (*Martin et al.NEJM, 2003*)
3. PICU @ HSJ: incidence of SIRS = 82%;  
28% of these have sepsis diagnosed
4. ICU-Acquired Bloodstream Infections (BSI) → the isolation of a pathogenic organisms from at least one blood culture set 48h or more after admission
  - Affects approx 1/20 ICU patients
  - Increases the length of ICU stay
  - An independent risk factor for death

(*Laupland et al, Critical Care Medicine 2002;30:2462-2467*).

## new criteria for the diagnosis of sepsis:

⇒ infection documented or suspected, and some of the following

- general variables (fever, heart rate, etc)
- inflammatory variables: cell counts, CRP, PCT
- hemodynamic variables
- organ dysfunction variables

*(Levy et al, 2003. The 2001 International Sepsis Definitions Conference. Crit Care Med, 31:1250)*

essentially accepts “culture negative” sepsis