


Biomarkers in Critical Care Medicine

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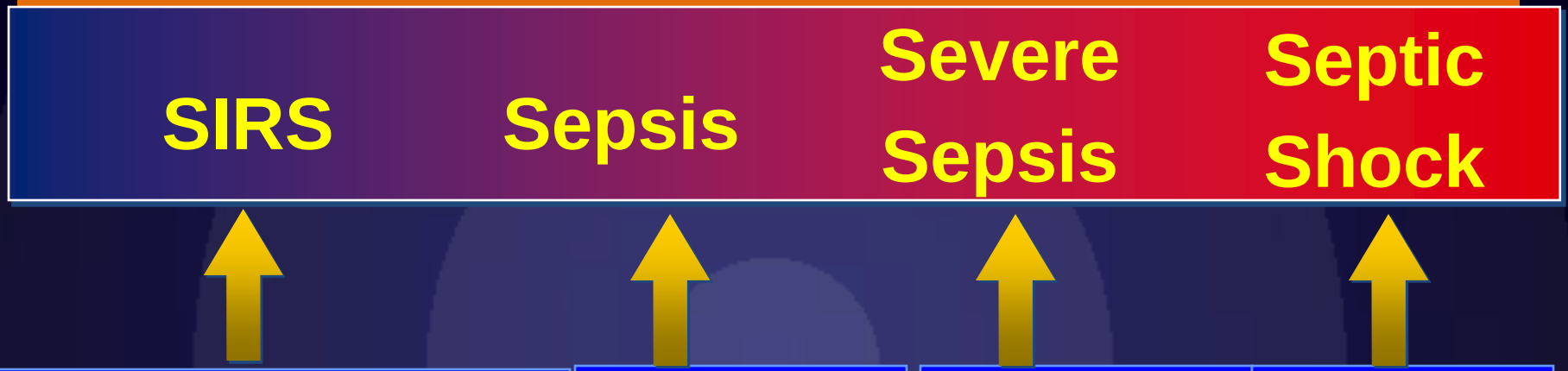
Contents

1. Sepsis
2. Biomarkers in Sepsis
   - Physiologic parameters
   - CRP, PCT, and others
3. Biomarkers in ALI
4. Biomarkers in AKI & Cardiac stress

The Sepsis Continuum



- A clinical response arising from a nonspecific insult, with ≥2 of the following:
  - T >38°C or <36°C
  - HR >90 beats/min
  - RR >20/min
  - WBC >12,000/mm^3 or <4,000/mm^3 or >10% bands

SIRS with a presumed or confirmed infectious process

Sepsis with organ failure

Refractory hypotension

SIRS = systemic inflammatory response syndrome

Crit Care Med 1992;20:864–74

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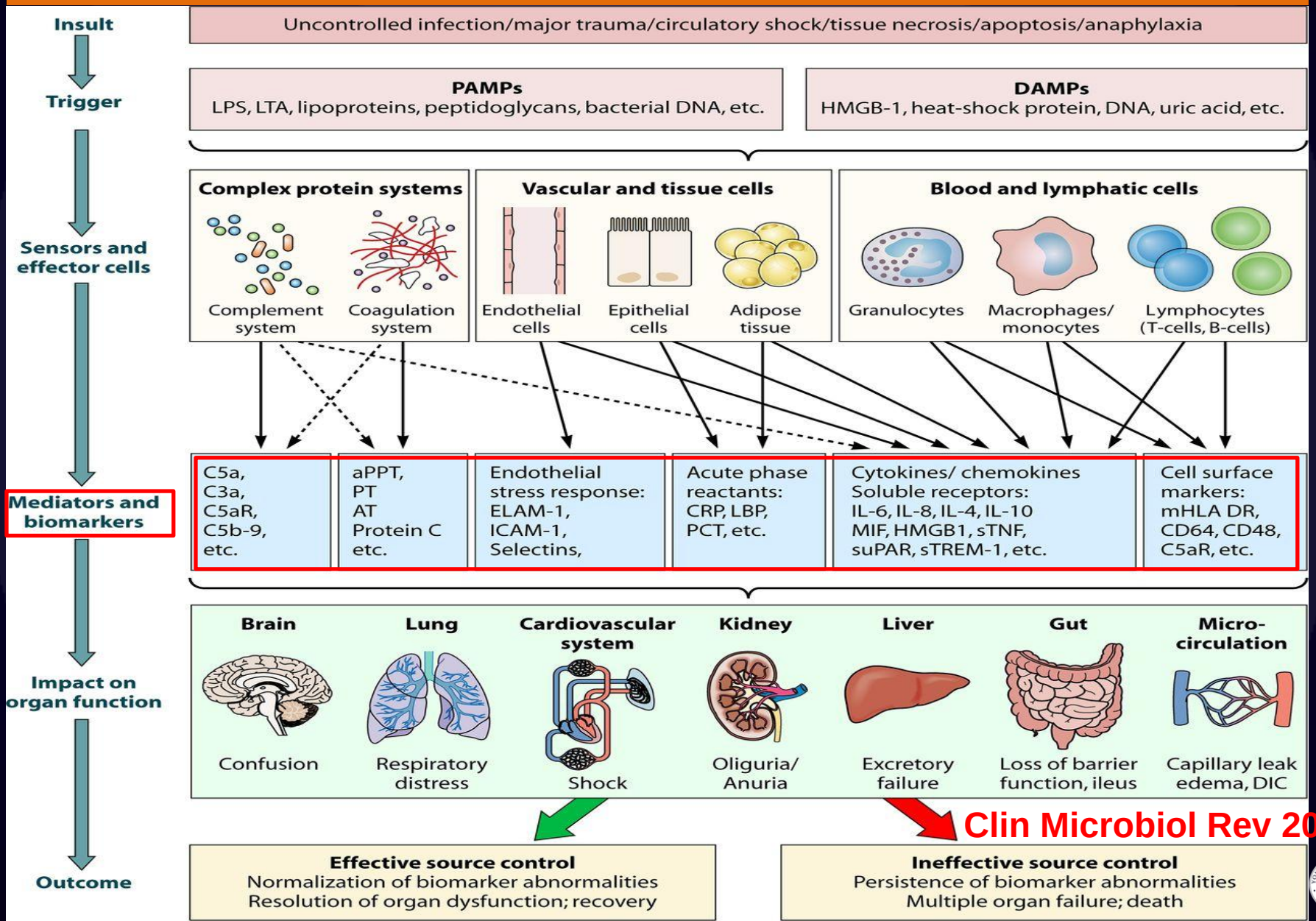
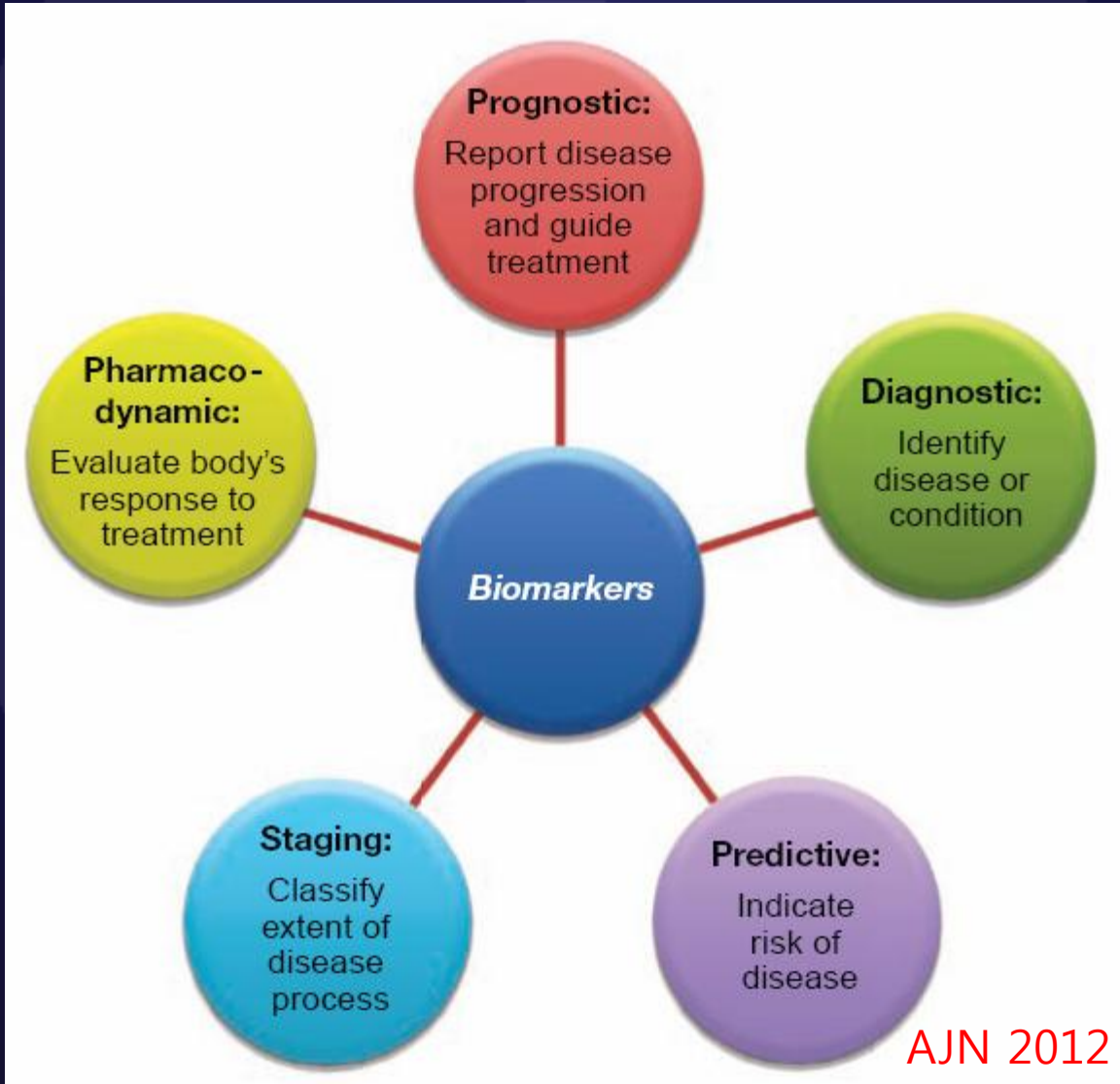
The inflammatory response



Clin Microbiol Rev 2012

Uses of Biomarkers



AJN 2012

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Ideal Biomarkers

- Acceptable to patient
- Stability in vivo and vitro
- Adequate analytical sensitivity (functional sensitivity)
- Good degree in reproducibility and accuracy
- Easy to perform
- Short analytical turnaround time
- Complete automation of assay
- International standardized
- Low cost
- Low biological variation
- Reference range and cutoff values tested for gender, age, and ethnicity dependence
- Good diagnostic and prognostic accuracy
- Favorable cost-benefit ratio

CCLM 2013

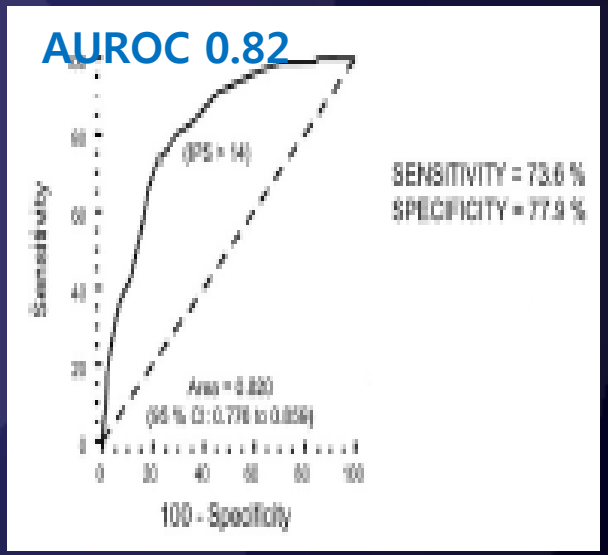
Physiologic Parameters in Sepsis

Study	Risk Evaluated	Independent Parameters
Infection probability score[26]	Infection in ICU	HR >140 beats/min BT >37°C
IMPACT[27]	Sepsis in ICU	BT ≥38°C MAP <70 mmHg
Jaimes et al[28]	Bacteremia in hospitalized patients	HR ≥90 beats/min BT ≥37.8°C
Falguera et al[29]	Bacteremia in community-acquired pneumonia	HR ≥125 beats/min RR >30 cycles/min SAP <90 mmHg
RISSC, European Sepsis Database[41]	Severe sepsis or shock in septic patients	HR ≥120 beats/min SAP <110 mmHg BT ≥38.2°C
MEDS score[42]	Mortality in patients with infection in the ED	SAP <90 mmHg RR >20 cycles/min or pulse oximetry <90% or the need for O_2 supplementation
Varela et al[47]	Mortality in patients with multiorgan failure	BT entropy

Crit Care Clin 2011

IPS (ICU)

	IPS Points						
	0	1	2	3	6	8	12
BT, °C	≤37.5		>37.5				
HR, beats/min	≤80					81–140	>140
RR, breaths/min	≤25	>25					
WBC, $\times 10^3/mm^3$	5–12	>12		<5			
CRP, mg/dL	≤6				>6		
SOFA score	≤5		>5				



CCM 2003

CRP as a Biomarker in Sepsis

Study	No.	Setting	CRP cutoff value (mg/L, ug/mL)	Sensitivity (%)	Specificity (%)
Diagnosis					
Ugarte et al, 1999	190	ICU	79	67.6	61.3
Povoa et al, 2005	112	ICU	87	93.4	86.1
Sierra et al, 2004	125	ICU	80	94.3	87.3
Povoa et al, 2006	63	ICU	Variation >41	92.1	71.4
Therapeutic guide					
Yentis et al, 1995	32	ICU	25% decrease	97	95
Schmit et al, 2008	50	ICU	Increase ≥22 at 48 hrs (ineffective initial anti-bi otics)	77	67
Lisboa et al, 2008	68	ICU VAP	96 hrs/base ratio < 0.8 (appropriate)	77	87
Prognosis					
Lobo et al, 2003	313	ICU	>100	More organ failure	Higher Mortality
Menendez et al, 2008	453	CAP	>219 Crit Care Clin 2011	More treat ment failure	

Eosinopenia in Sepsis

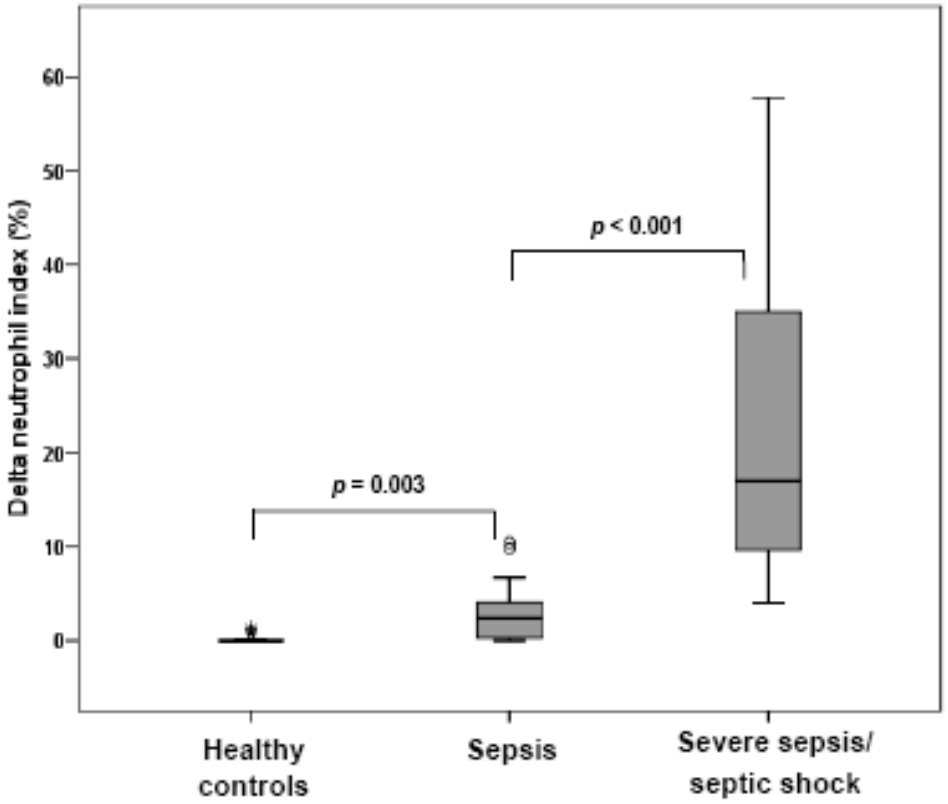
Crit Care 2008

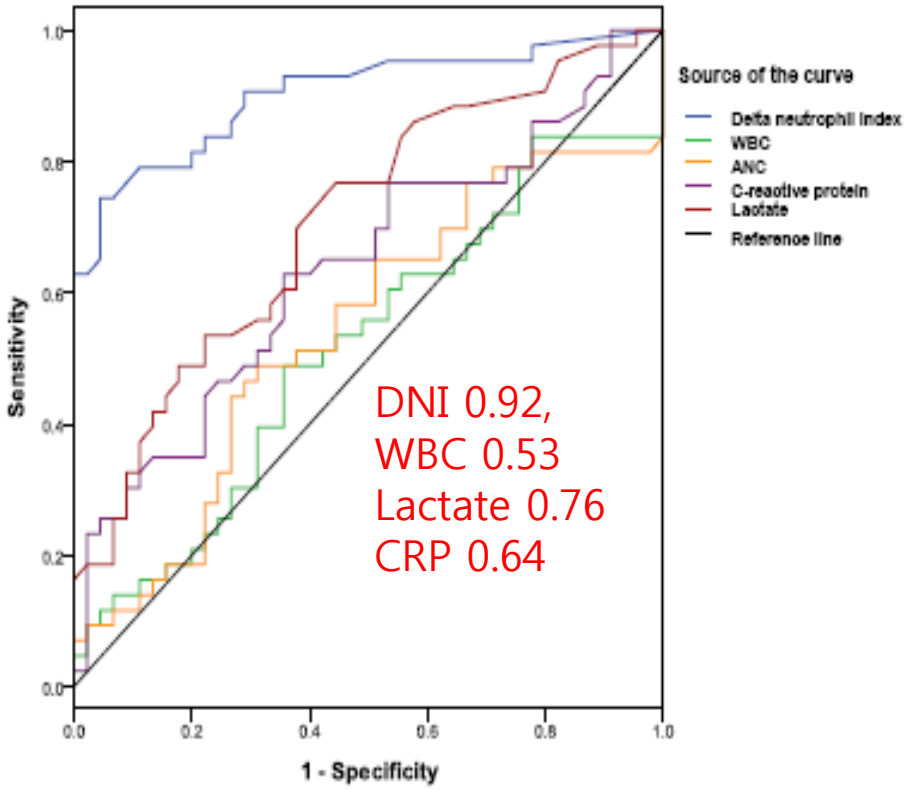
Diagnostic performance of the eosinophil count and the C-reactive protein level in the prediction of sepsis on intensive care unit admission

Variable	Noninfection versus infection		SIRS versus infection	
	C-reactive protein level	Eosinophil cell count	C-reactive protein level	Eosinophil cell count
Cutoff value	>70 mg/l	<50 cells/mm^3	>80 mg/l	<40 cells/mm^3
Sensitivity (%)	68 (59 to 76)	80 (71 to 86)	68 (59 to 79)	80 (71 to 86)
Specificity (%)	61 (47 to 74)	91 (79 to 96)	55 (32 to 76)	80 (55 to 93)
Positive likelihood ratio	1.77 (1.25 to 2.51)	9.12 (3.9 to 21)	1.52 (0.92 to 2.50)	4.00 (1.65 to 9.65)
Negative likelihood ratio	0.52 (0.39 to 0.69)	0.21 (0.15 to 0.31)	0.57 (0.41 to 0.81)	0.25 (0.17 to 0.36)
Area under the receiver operating characteristic curve	0.77 (0.70 to 0.84)	0.89 (0.83 to 0.94)	0.77 (0.67 to 0.87)	0.84 (0.74 to 0.94)

Delta Neutrophil Index (DNI)

DNI (the difference in leukocyte sub-fractions identified by myeloperoxidase and nuclear lobularity channels) = circulating immature granulocytes





Park BH et al, BMC Infect Dis 2011

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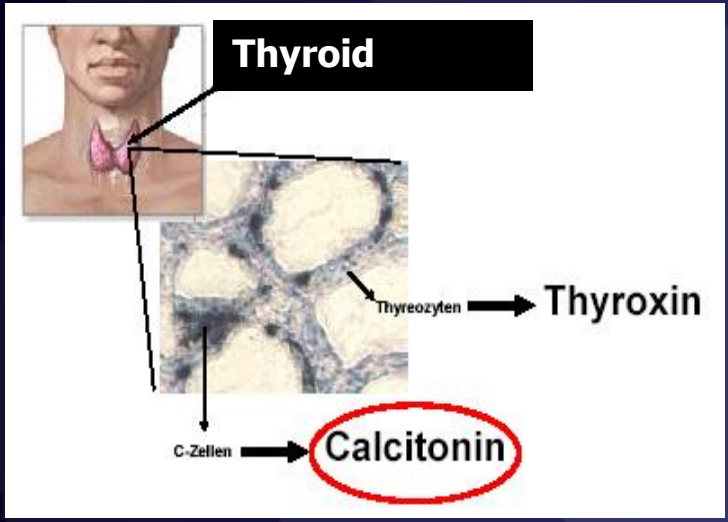
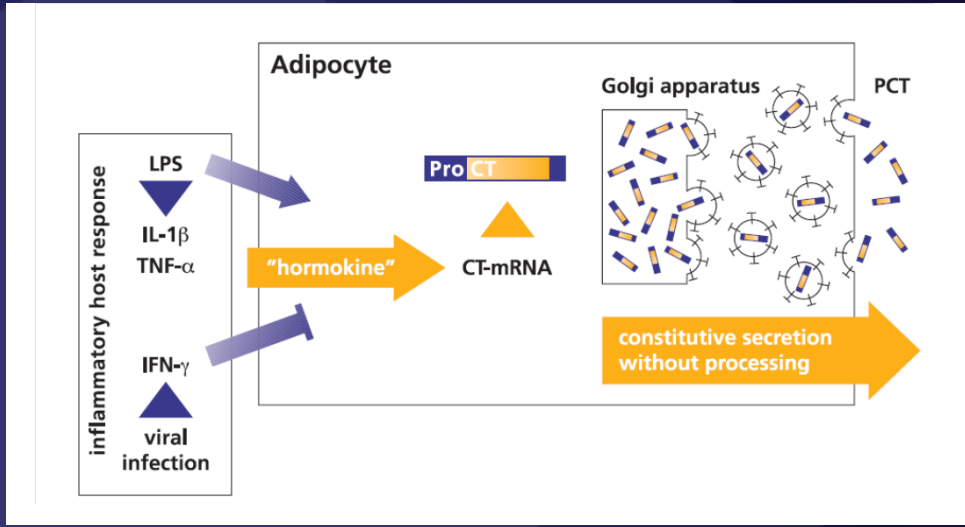
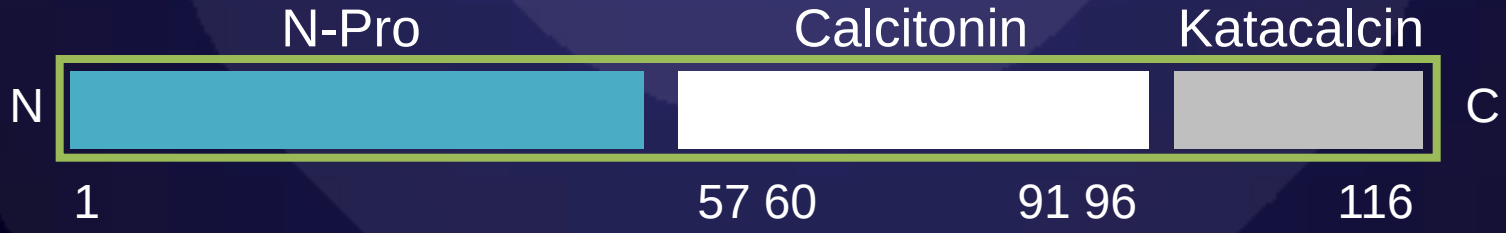
PCT – normally an intermediate product in the synthesis of Calcitonin



Normally in the synthesis of Calcitonin



Bacterial infection stimulates PCT production



LOW PCT values in the blood of healthy persons: 0.0467 ng/ml; median = 0.0127 ng/ml

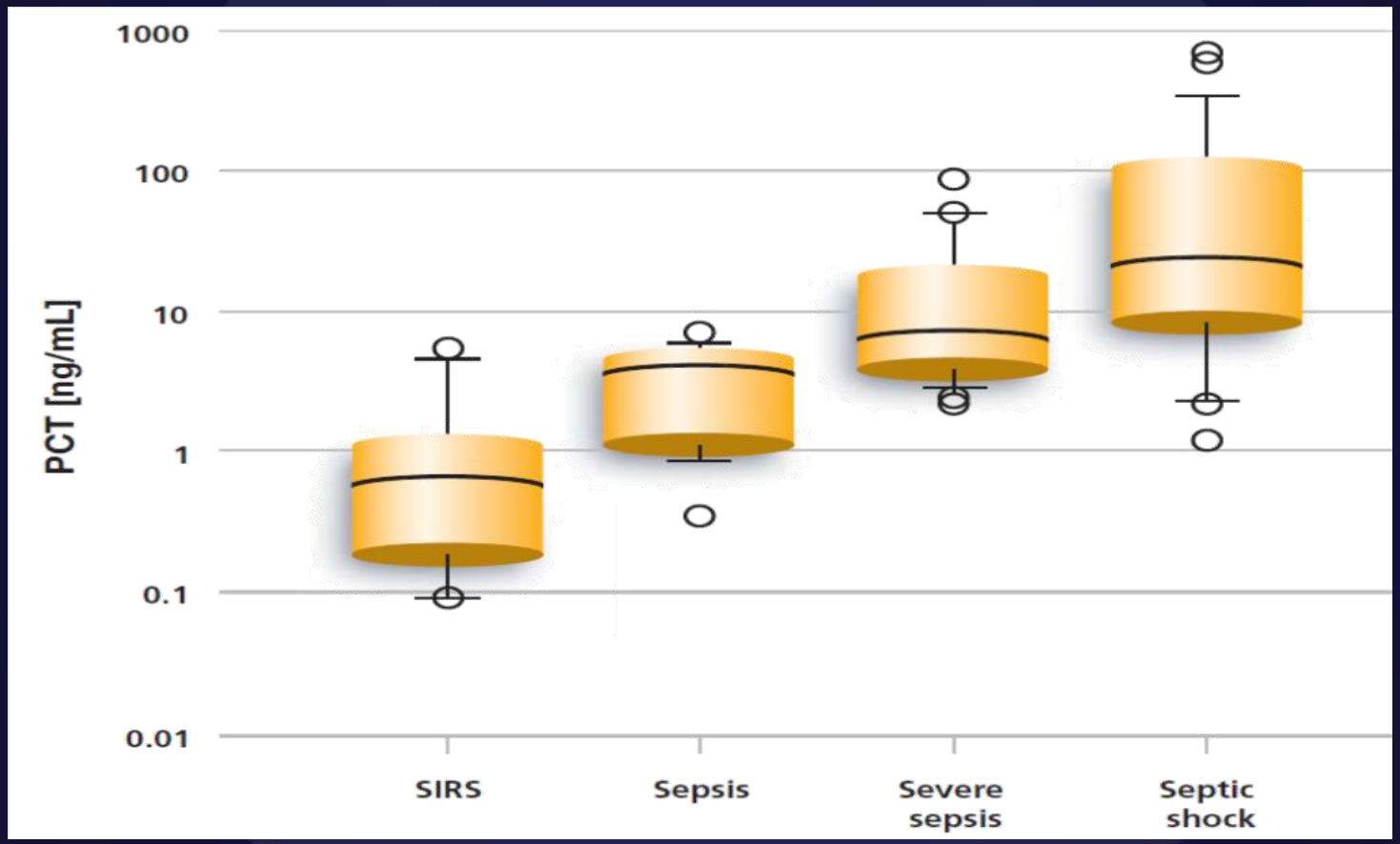
Morgenthaler et al, Clin Lab 2002;48: 263-270

PCT as a Biomarker in Sepsis

Aim of the Study	Findings
PCT levels in patients with sepsis, severe sepsis, and septic shock	PCT is significantly elevated in patients with sepsis, severe sepsis, and septic shock. Especially high concentrations were found in patients with severe stages of the disease (severe sepsis, septic shock)
PCT in severe bacterial infection	PCT levels were significantly higher in patients with bacterial infection than in those with viral and fungal infections and sepsis
PCT as a marker for effectiveness of source control and prognosis	PCT levels decline by successful measures of source control, and sustained elevated PCT levels are associated with poor prognosis. This finding was demonstrated in adult and pediatric patients with sepsis, VAP, and CAP
Usefulness of PCT for antibiotic stewardship	PCT-guided antibiotic therapy may result in a 20%–70% decrease in antibiotic exposure without a negative effect on patient outcome

Crit Care Clin 2011

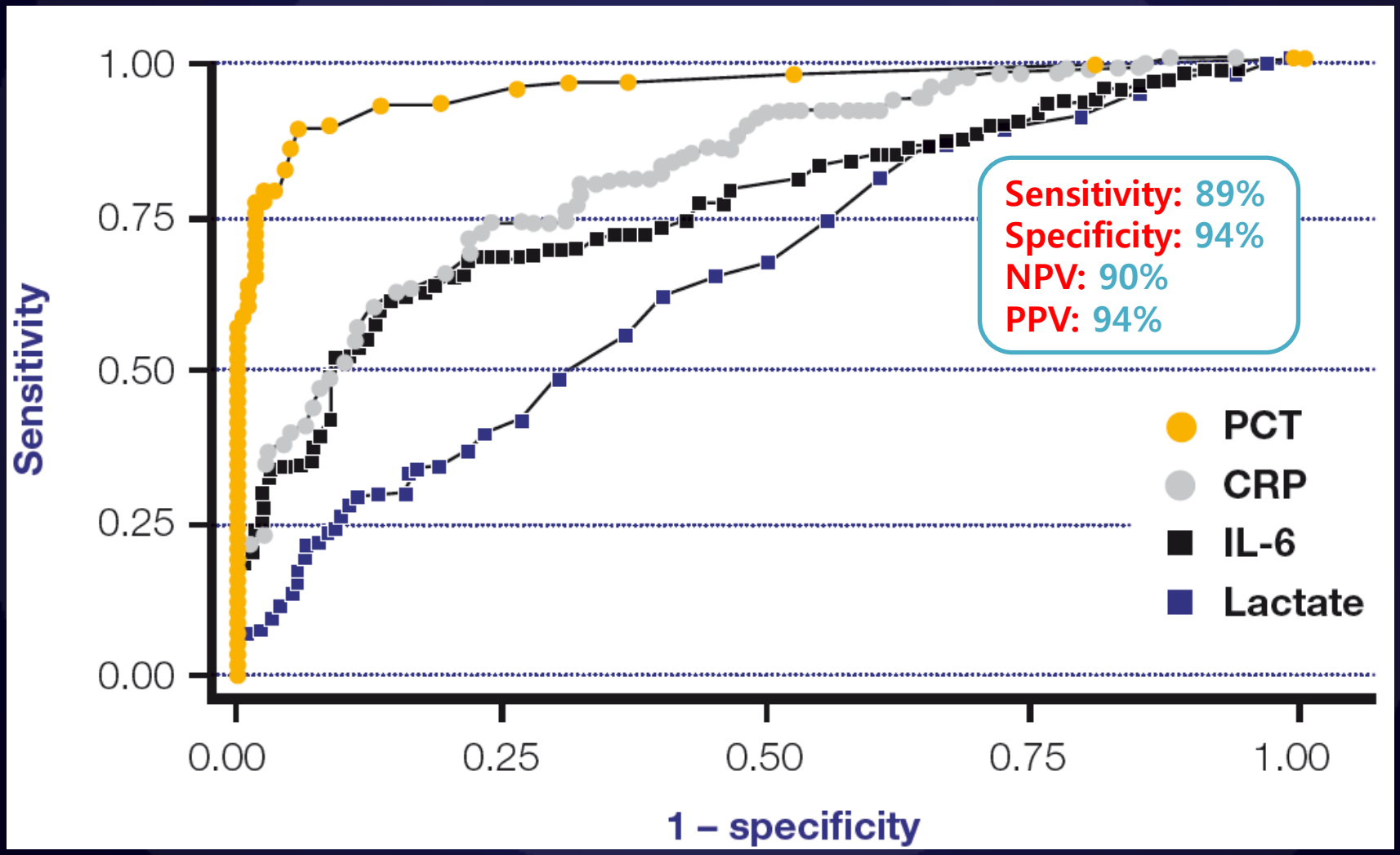
PCT as a Marker of Sepsis Severity



In healthy people, PCT concentration are found below 0.05 ng/ml

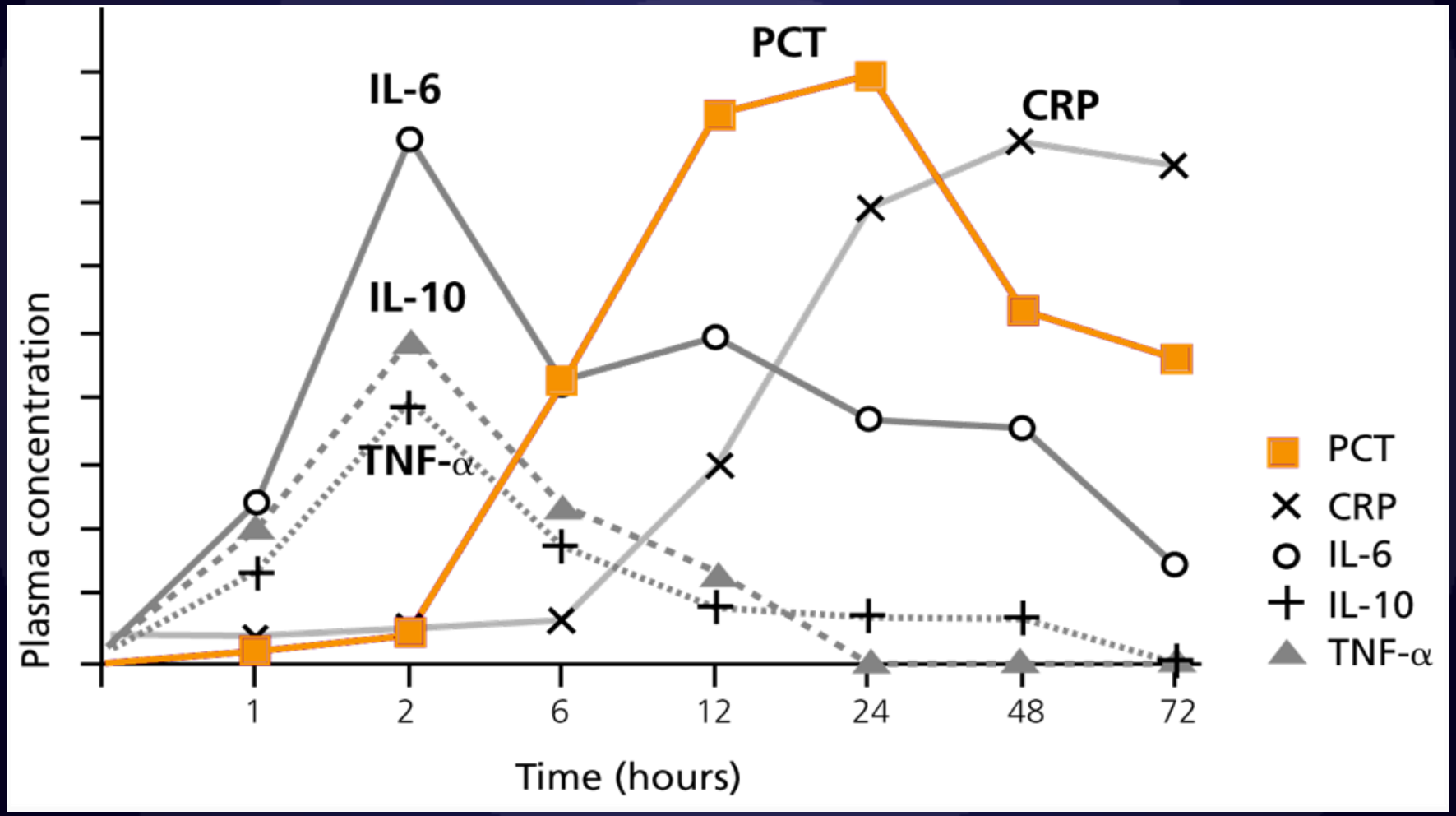
Harbarth S et al, AJRCCM 2001;164: 396-402
Meisner M et al, Critical Care 1999;3:45-50
Krüger S et al, ERJ 2008;31:349–55

Diagnostic Accuracy of PCT Compared to other Biomarkers in Sepsis



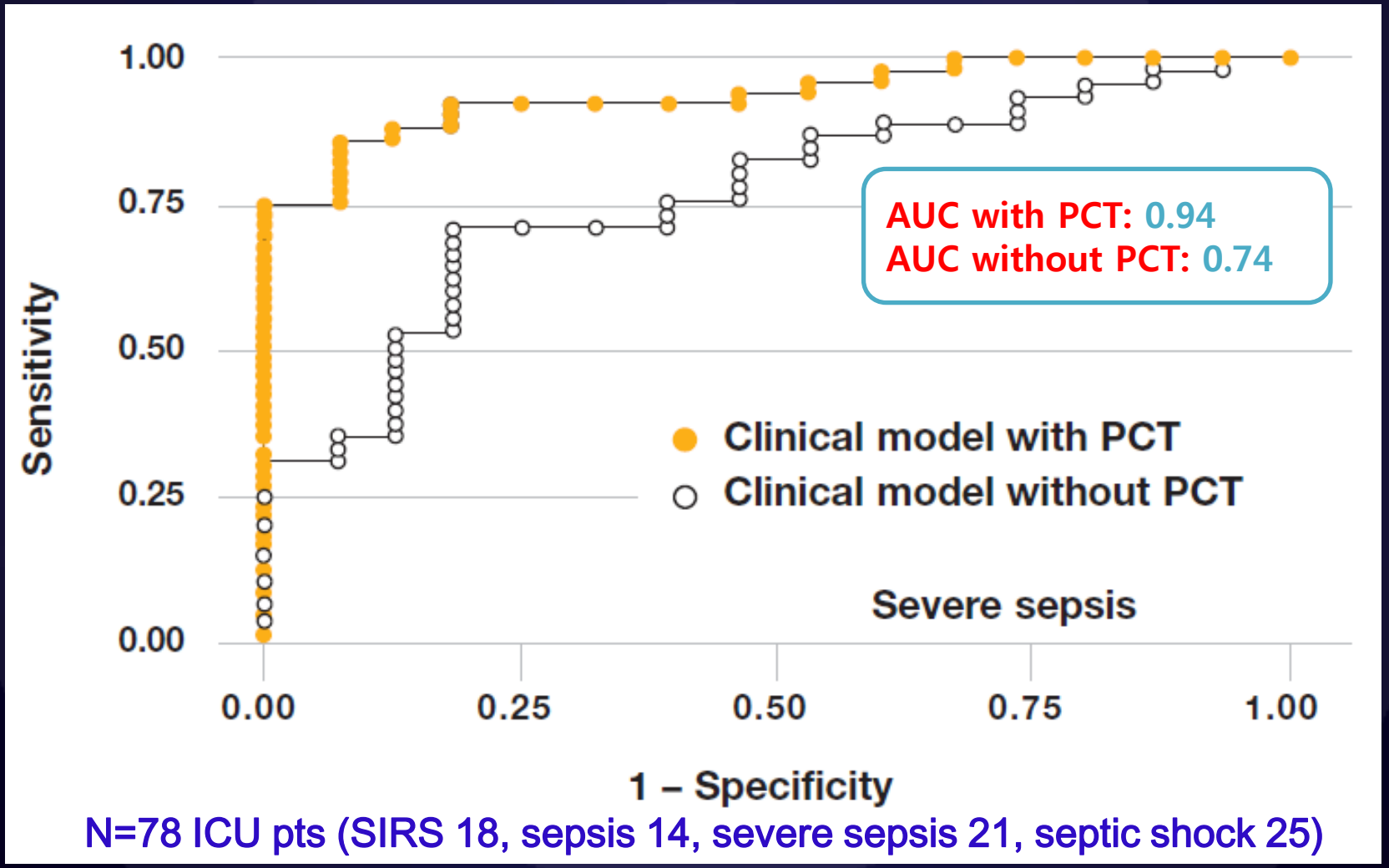
Simon L, Clin Infect Dis 2004;39:206-17

PCT Kinectisc in Sepsis



Brunkhorst FM, ICM 1998;24:888-92

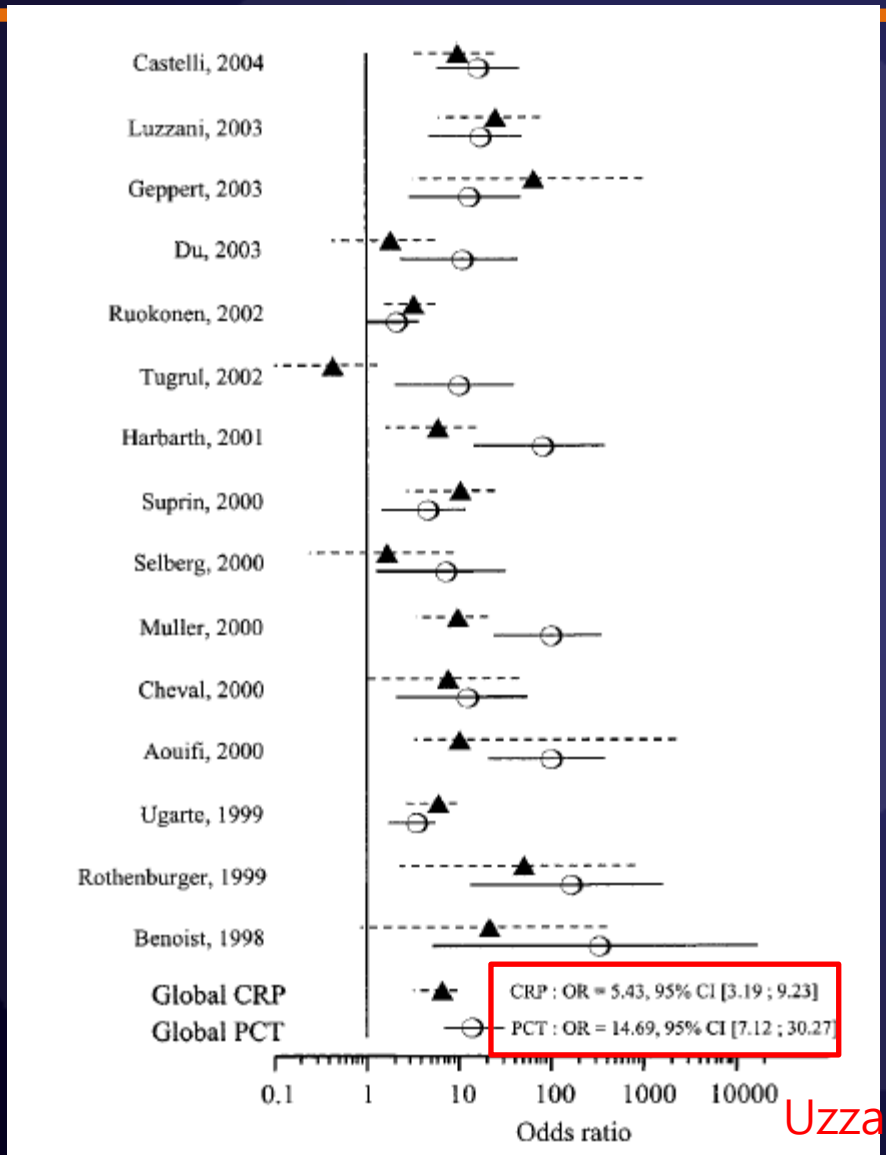
PCT plus Clinical Assessment Improves the Accuracy of Early Sepsis

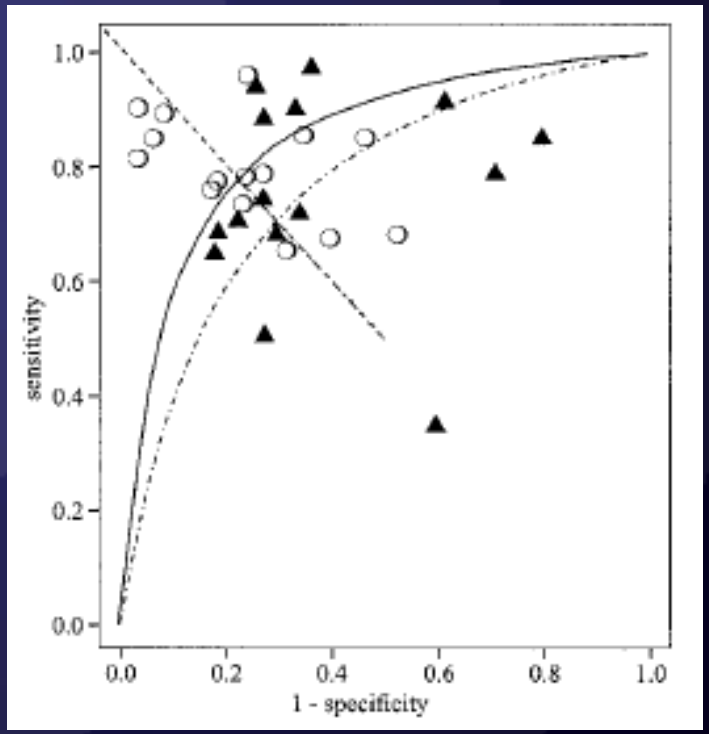


N=78 ICU pts (SIRS 18, sepsis 14, severe sepsis 21, septic shock 25)

Harbarth S, AJRCCM 2001;164:396-402

Comparison of PCT & CRP





Uzzan B et al, CCM 2006;34:1996

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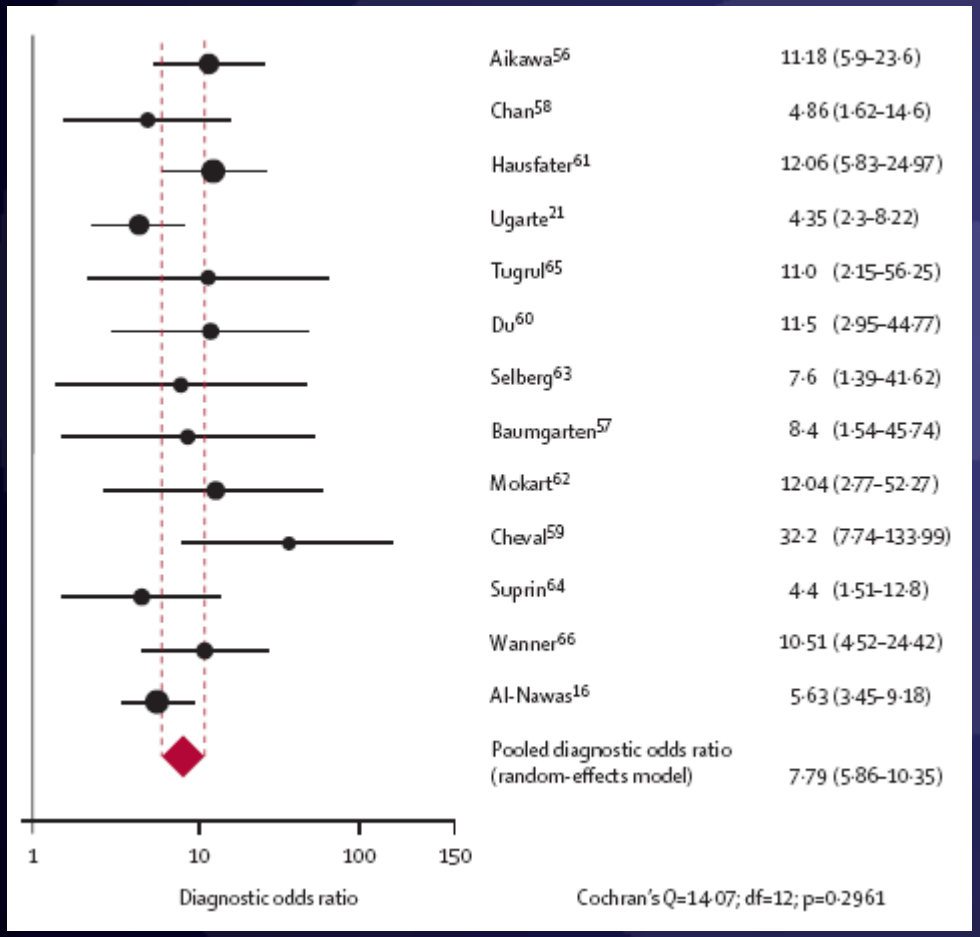
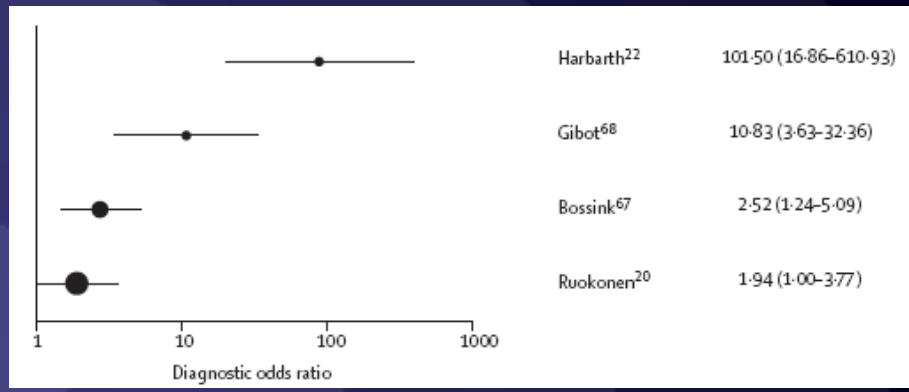
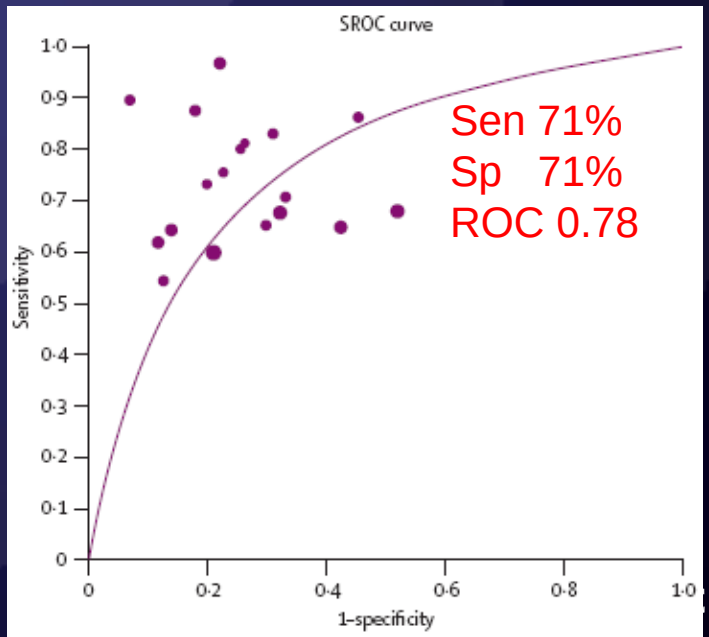
PCT for Sepsis: Meta-analysis

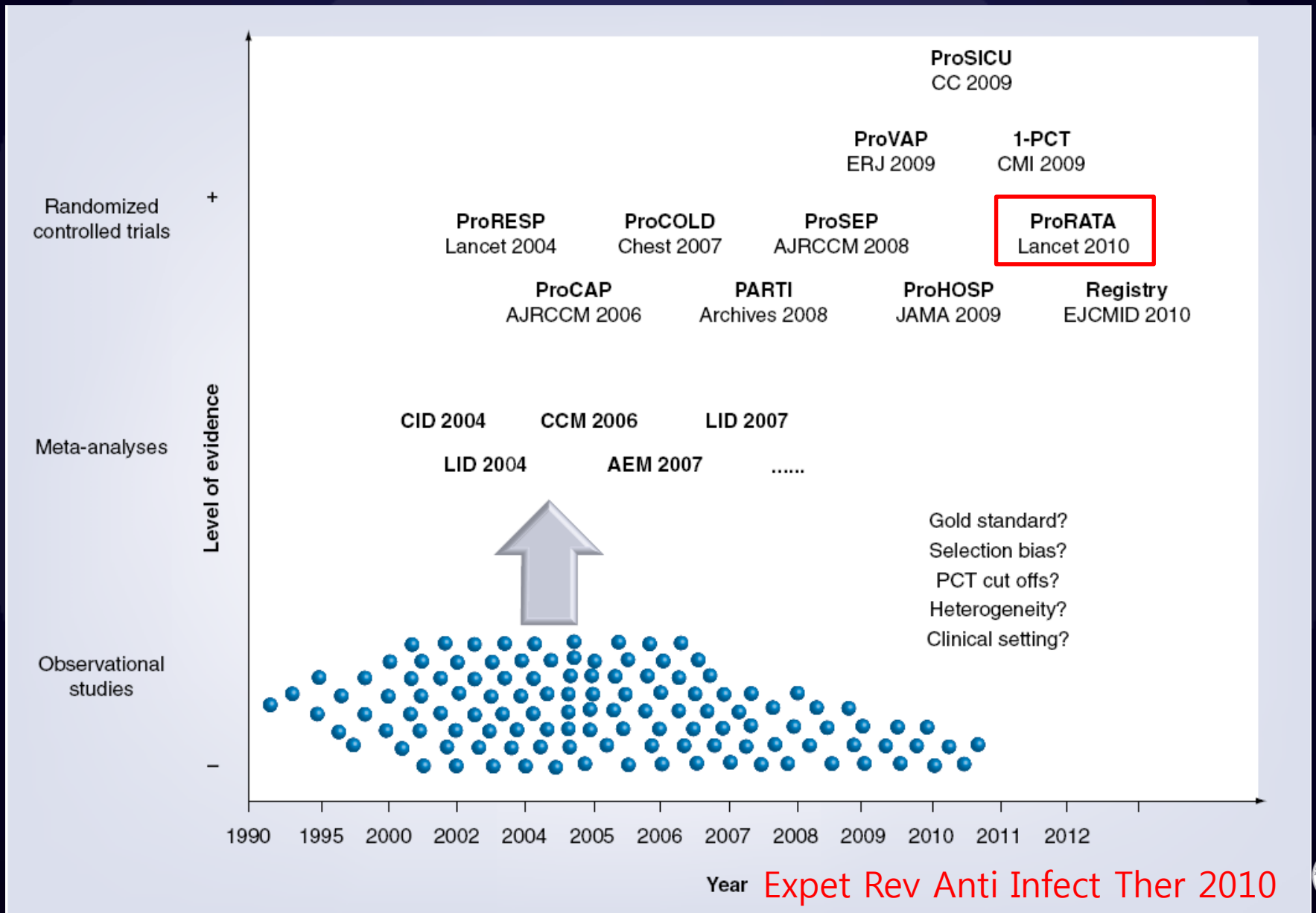






Tang et al, Lancet Infect Dis 2007;7:210-7

PCT-guided Antibiotic Tx



Expet Rev Anti Infect Ther 2010

PCT-guided Antibiotics Stewardship in ProRATA Study

Lancet 2010

N=630 ICU pts

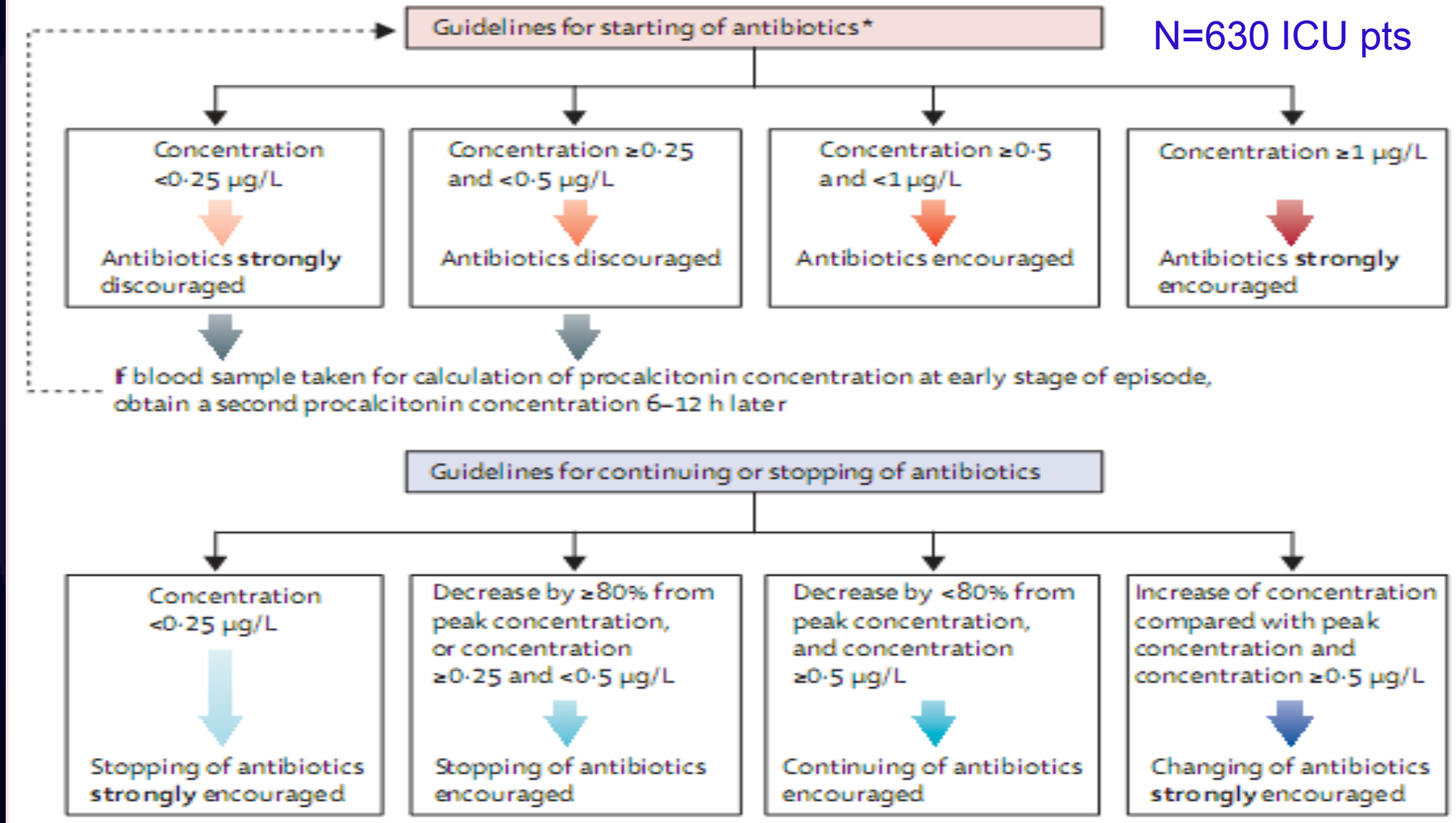
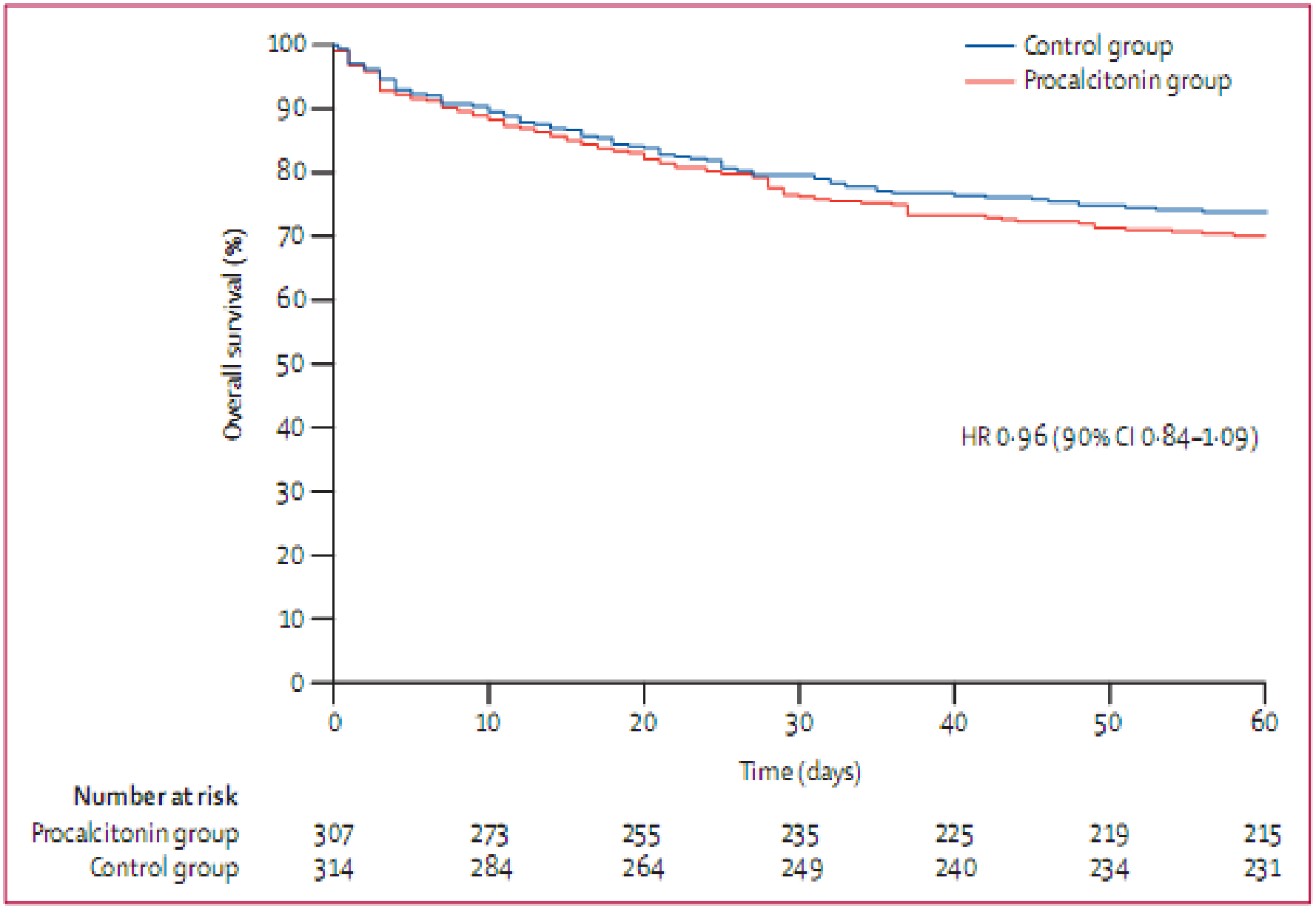


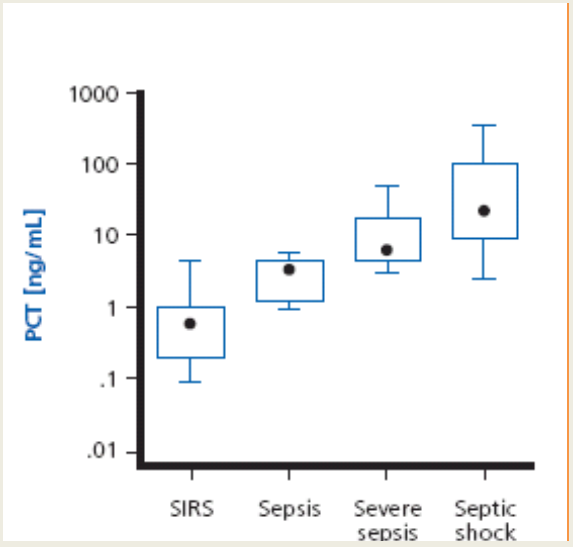
Figure 1: Guidelines for starting, continuing, or stopping of antibiotics according to procalcitonin concentrations

PCT-guided Antibiotics Stewardship

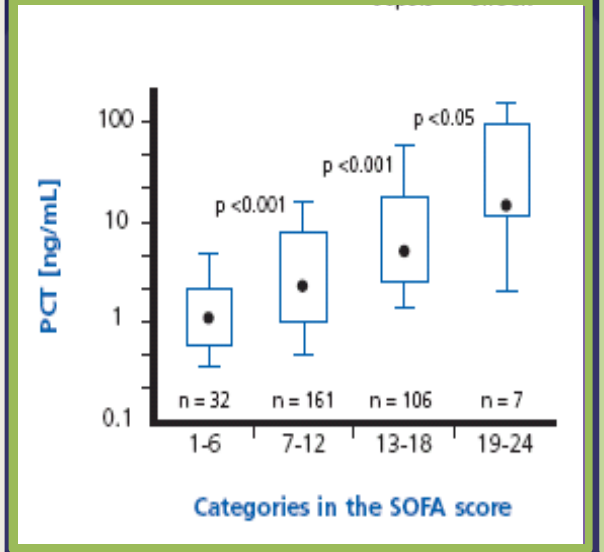


PCT as a Prognostic Biomarkers

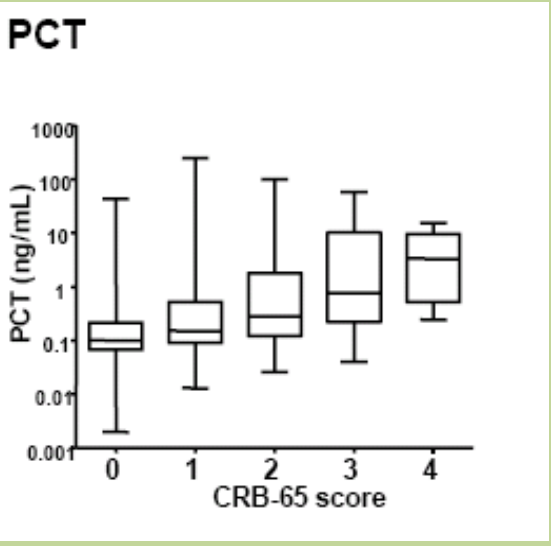
Sepsis



Organ Dysfunction



Pneumonia



Organ dysfunction status	PCT (mean ± SE; ng/mL)
Patients not progressing to MODS	4.47 ± 1.22
ARDS	10.48 ± 4.77
ARDS plus ARF	8.08 ± 2.25
ARDS plus ARF plus DIC	32.72 ± 13.41
ARDS plus ARF plus DIC plus HF	43.35 ± 20.98

ICM 2002

False +/-tive results of PCT

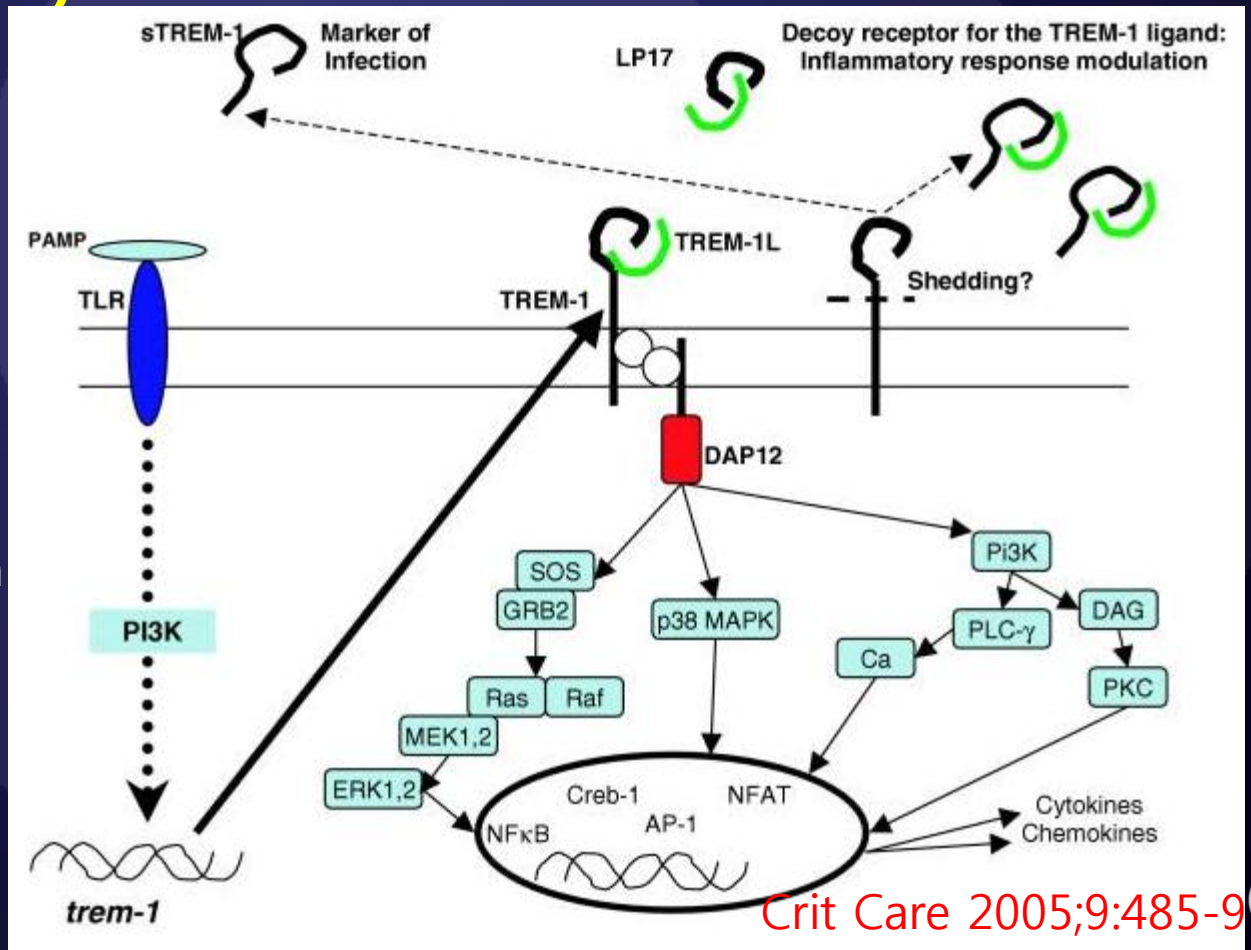
False-positive	False-negative
Acute respiratory distress syndromes	Early infections
Acute graft-versus-host disease	Localised infections
Falciparum malariae infections	Sub-acute bacterial endocarditis
Systemic fungal infections	
Mechanical and surgical trauma	
Chemical pneumonitis	
Severe burns and heat strokes, pancreatitis	
Familial Mediterranean fever	
Malignancies—medullary thyroid cancer, small-cell-cancer of the lung, liver metastasis, carcinoid tumours, and paraneoplastic syndromes,	
Treatment with T cell antibodies, granulocyte transfusions, anti-thymocyte globulin administration, therapeutic TNFα administration for melanoma, etc.	
Newborns	

Sankar V & Webster NR, J Anesth 2012 e-pub

Potential Biomarkers in Sepsis

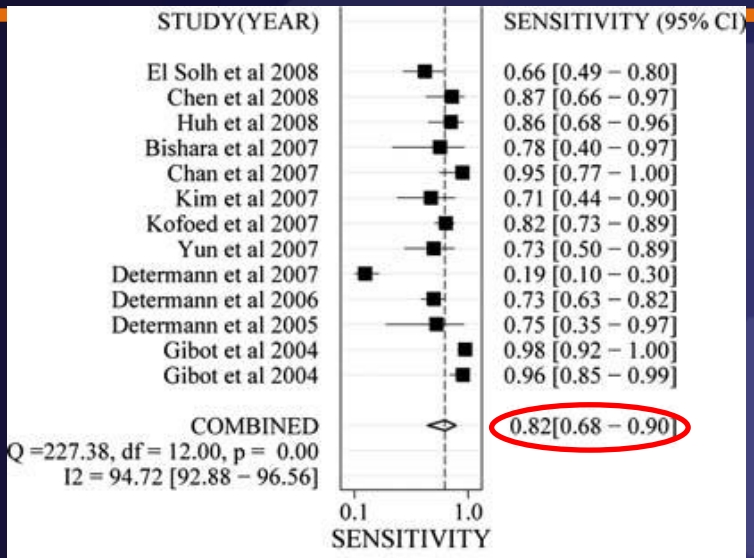
- ✓ **sTREM-1 (Soluble Triggering Receptor Expressed on Myeloid cells-1)**

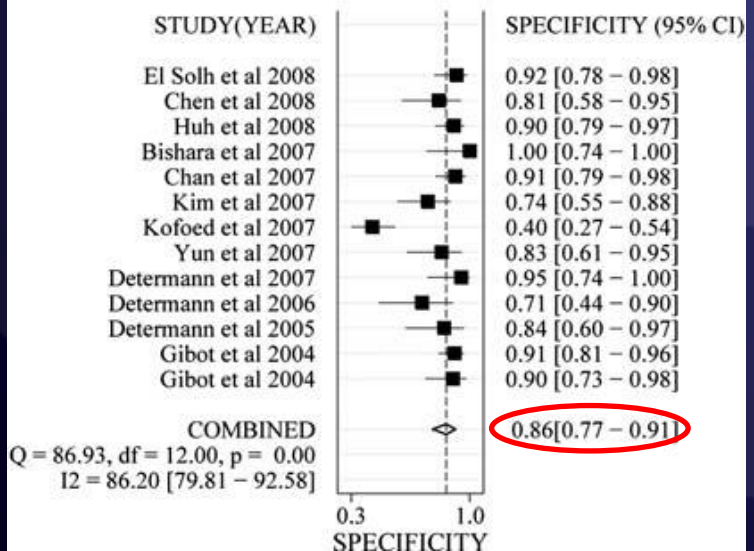
1. Cell surface receptor on neutrophils & MQs
2. Innate immunity
3. Amplify inflammation and bacterial infection
4. Therapeutic modulation of TREM-1 with LP17

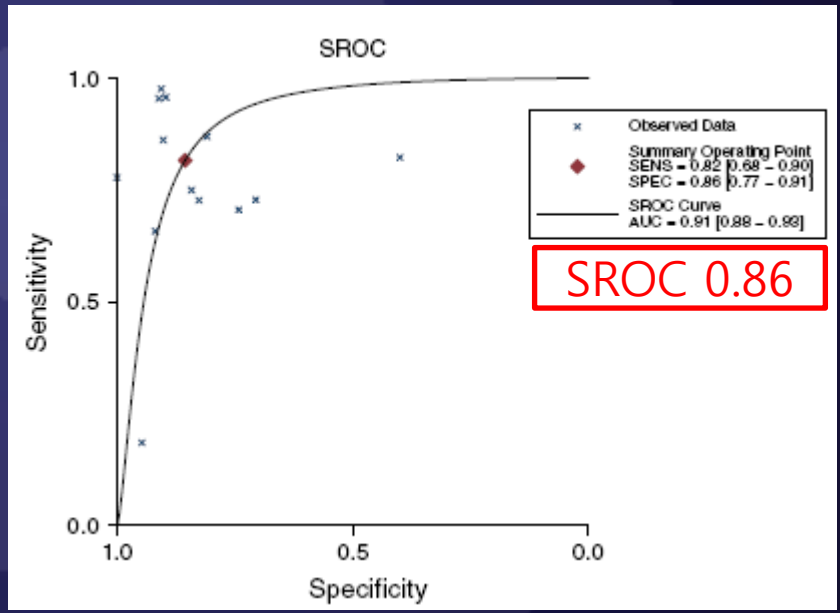


Crit Care 2005;9:485-9

Meta-analysis of sTREM-1







Jiyong J et al, ICM 2009;35:587-95

Panel of Biomarkers

Reference	Setting	No.	Biomarkers	Sensitivity (%)	Specificity (%)	Cutoff	AUC
Tsalik EL et al, 2012	ER; septicemia	336	PCT	18～68	63～97	0.1～3.05 ng/mL	0.72
			IL-6	14～58	67～96	40～500 pg/mL	069
			CRP	43～90	33～88	40～100 mg/mL	0.75
Harbarth S et al, 2001	ICU; infection/SIRS	78	PCT	97	78	1.1 ng/mL	0.92
			IL-6	67	72	200 pg/mL	0.75
			IL-8	63	78	30 pg/mL	0.71
Delannoy B et al, 2009	Cardiac surgery; sepsis/SIRS	32	BPW	100	93	0.465%T/s	0.95
			PCT	-	-	-	0.70
			CRP	-	-	-	0.66
Zakariah An et al, 2008	ICU; sepsis (adm/dur)	200	BPW	79/81	92/76	0.075%T/s	0.83
			PCT	83/83	79/75	1 ng/mL	-
			BPW＋PCT	79/81	95/94	-	-
Kofoed K et al, 2007	ER; CAP/SIRS	161	suPAR	35	67	2.7 ng/mL	0.50
			sTREM-1	82	40	3.5 ng/mL	0.61
			MIF	80	47	0.81 ng/mL	0.63
			PCT	80	58	0.28 ng/mL	0.72
			Neut count	64	74	8.5×10^9 cells/L	0.74
			CRP	86	60	59 ug/mL	0.81
			Composite 6 marker test	88	78	-	0.88
Gibot S et al, 2012	ICU; sepsis	379	sTREM-1	53.2	86.3	755 pg/mL	0.73
			PCT	83.1	84.9	1.55 ng/mL	0.91
			CD64 Index	84.4	95.2	1.62	0.95
			Bioscore with 3 markers	0 sepsis unlikely	-	2 or 3 sepsis likely	0.95

Benefits & Limitations of Sepsis Diagnostic Tools

Microbiology (Blood Culture)	Standard of care, time to result, ?Sens., ? Spec.
Imaging (X-Ray, Hr-CT)	Availability, costs, variability of source detection
Molecular Biological Testing	Availability, costs, time to results
Biopsy	Invasive, relatively expensive
Biomarker Testing (PCT)	Easy to measure, not invasive, relatively inexpensive
C-Reactive Protein (CRP)	Slow kinetics , high impact of inflammation (specificity), suppressed by corticosteroids, relatively inexpensive

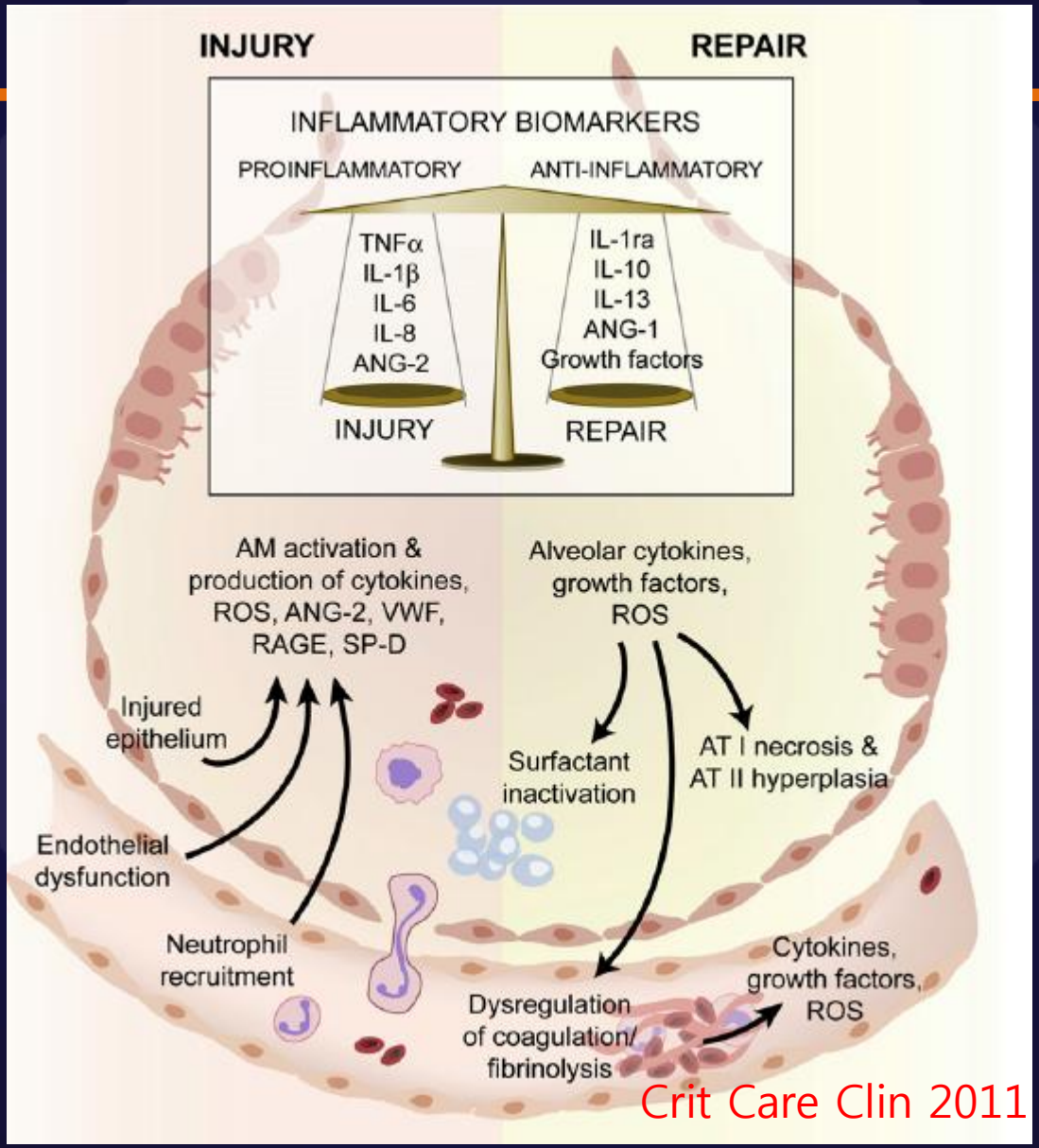
Endpoints in Biomarkers Research in ALI

- ✓ Diagnosis of ALI in high risk patients
- ✓ Discriminate hydrostatic vs permeability edema
- ✓ Different outcome (prognosis)
- ✓ Different treatment response

  → clinically short- & long-term mortality

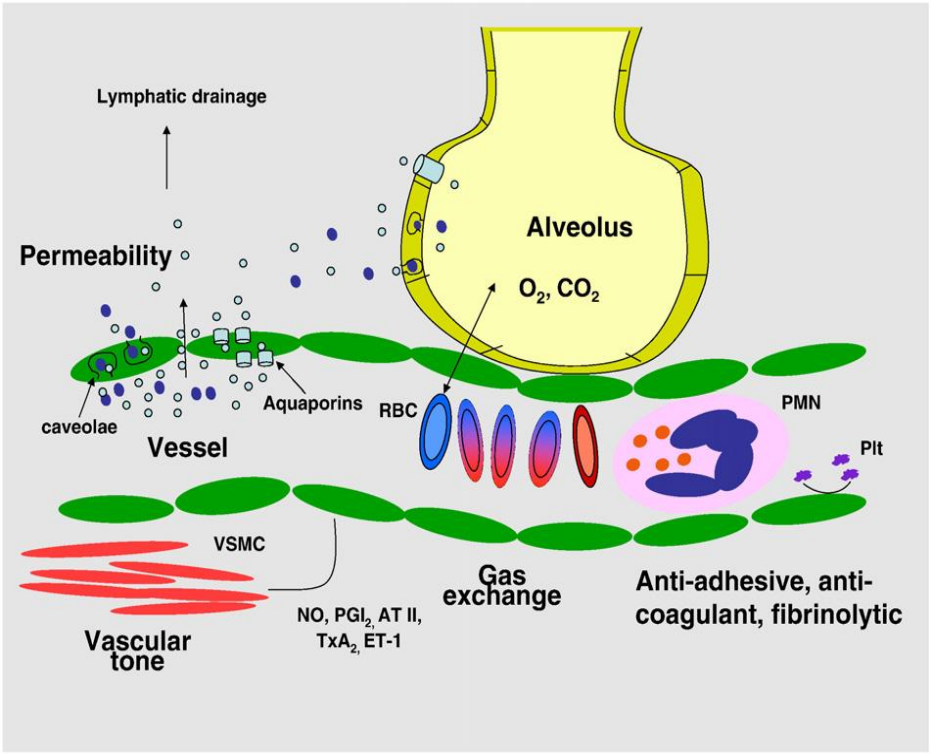
- ✓ Plasma/serum, BALF, pulmonary edema fluid, urine, exhaled breath condensate

Biomarkers in Injury & Repair of ALI

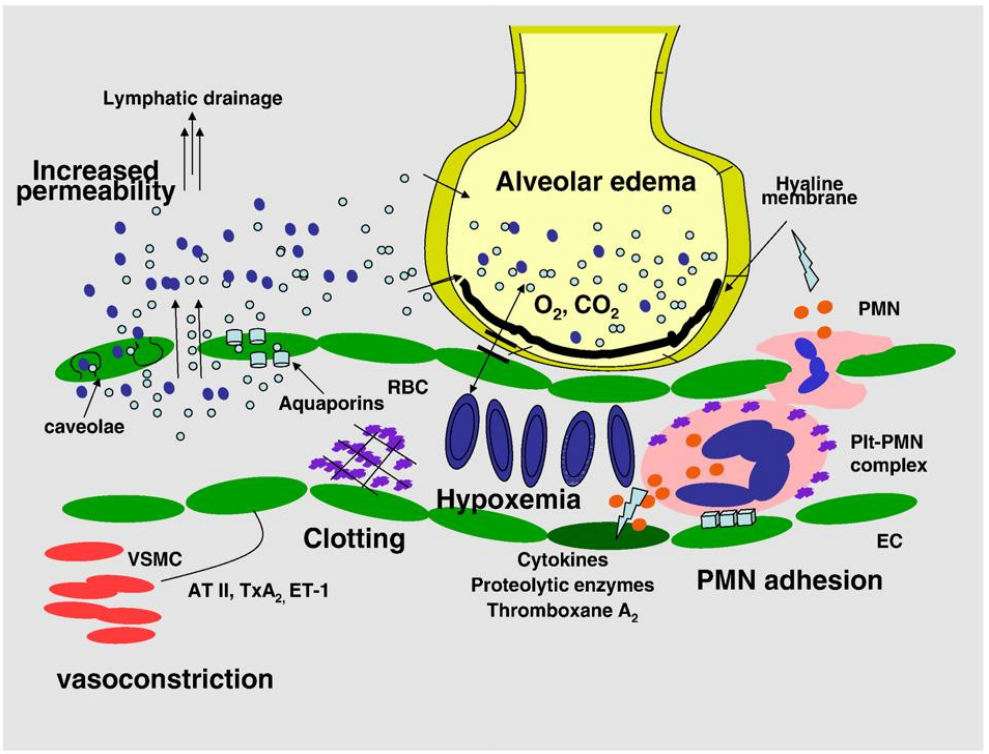


Crit Care Clin 2011

Endothelial Cell Function in ALI



Normal endothelial cell function



Endothelial cell responses in ALI

Maniatis NA et al, Vascul Pharmacol 2008;49:119-33

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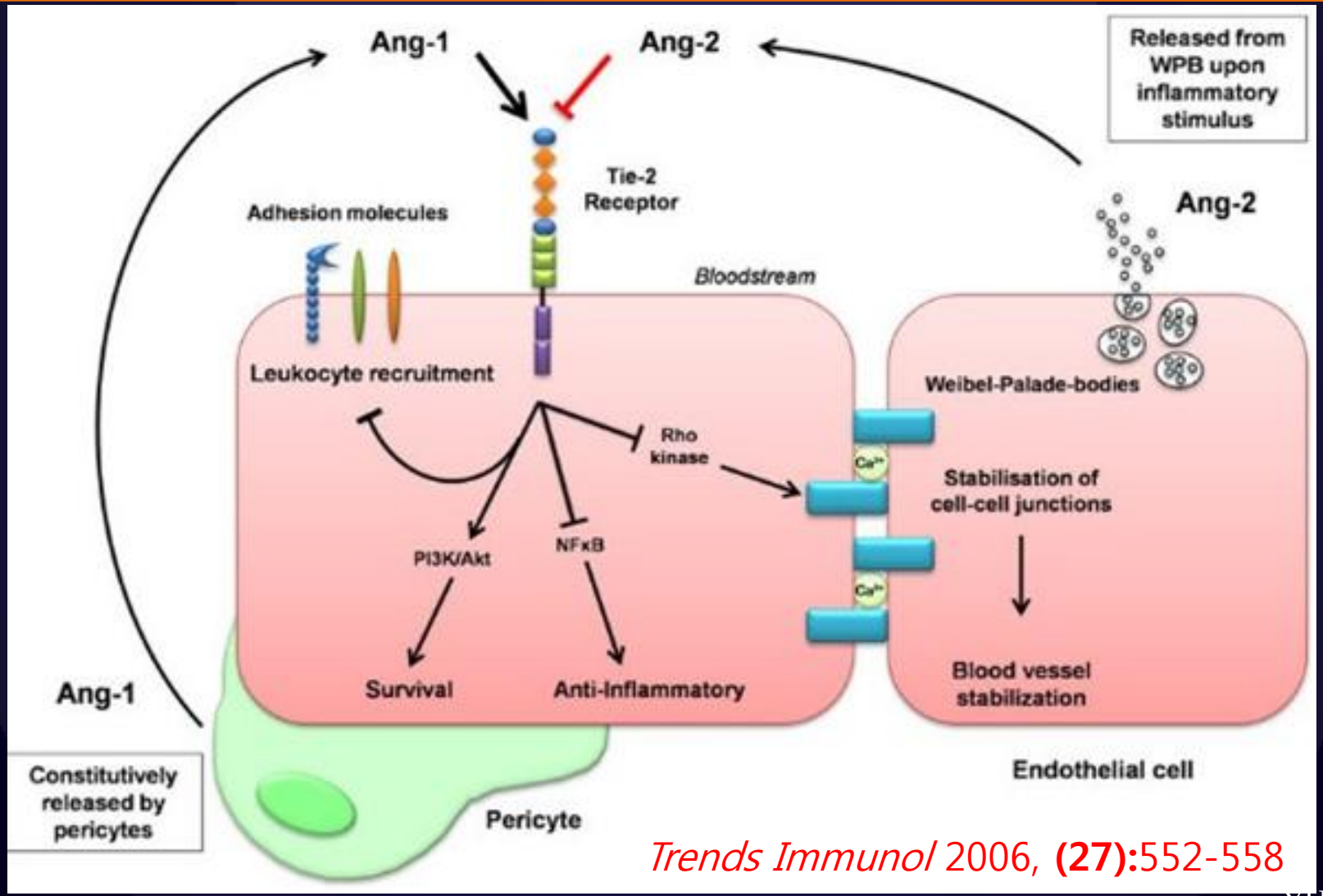
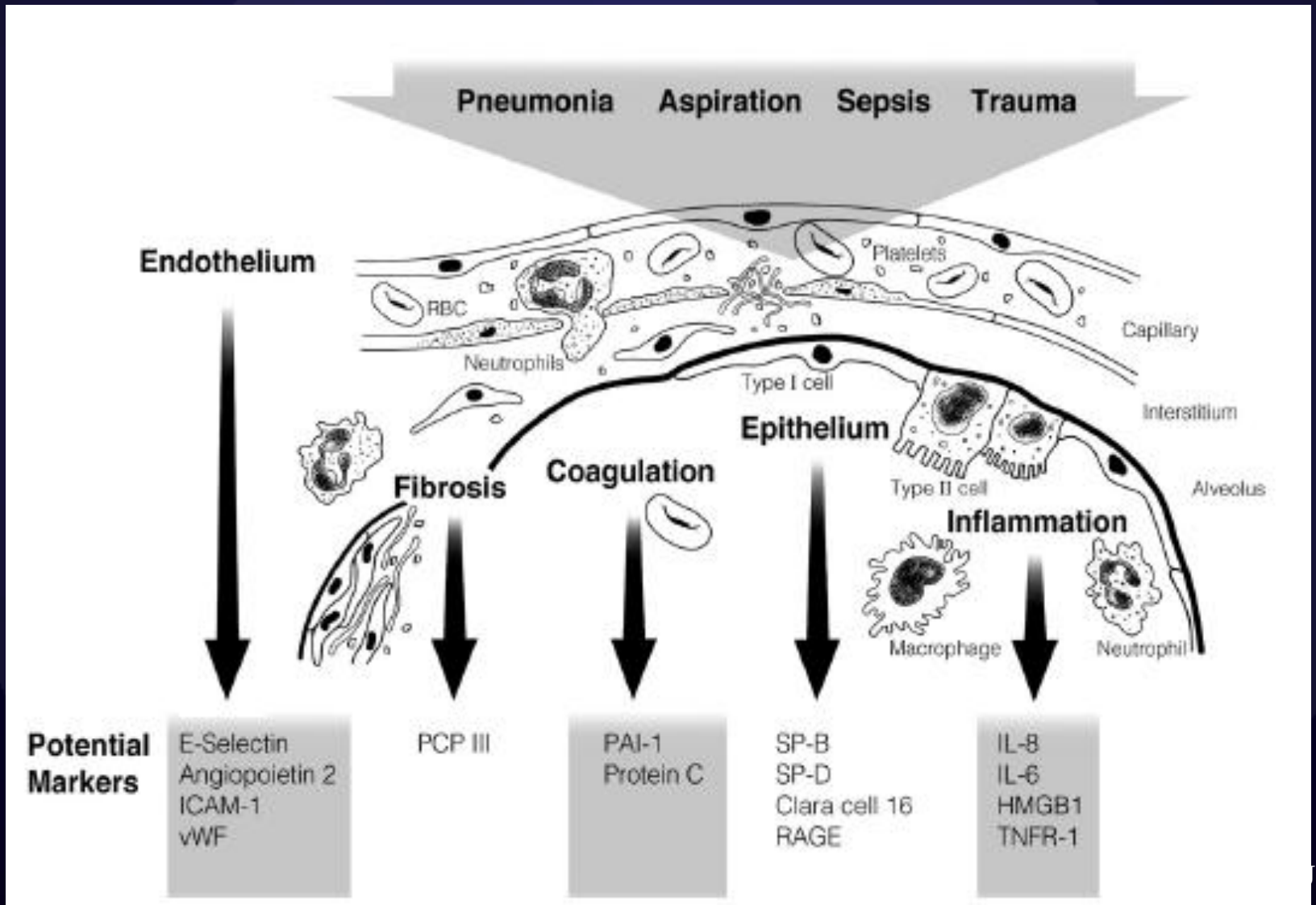
Ang-Tie system in ALI



Trends Immunol 2006, **(27):**552-558

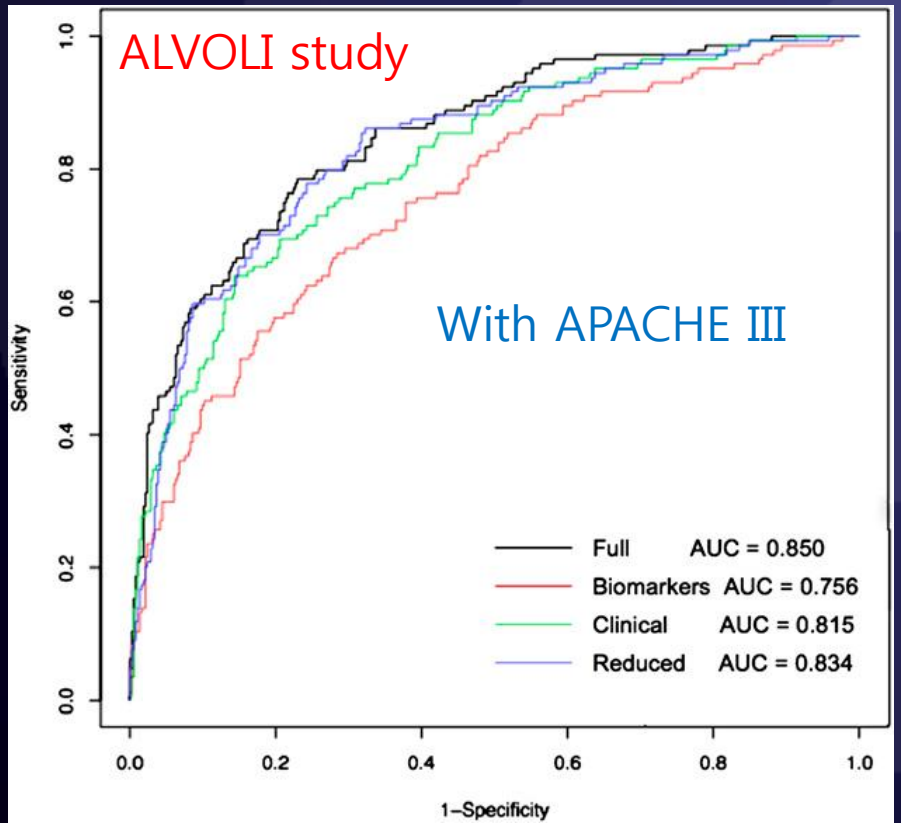
Biomarkers in Injury & Repair of ALI

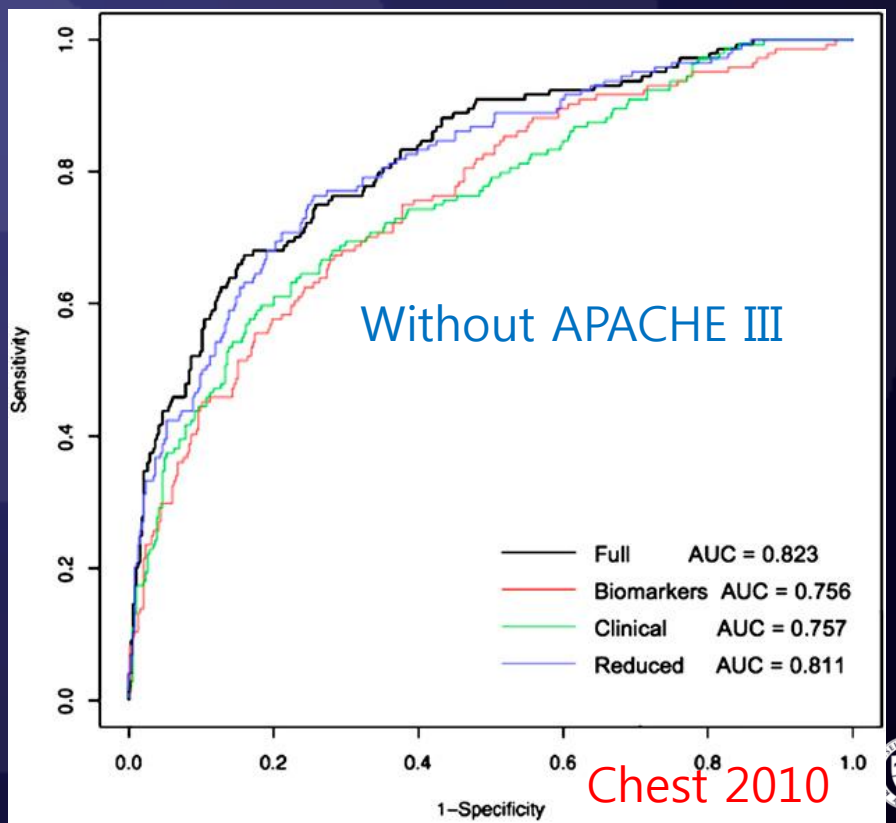
Crit Care Clin 2011



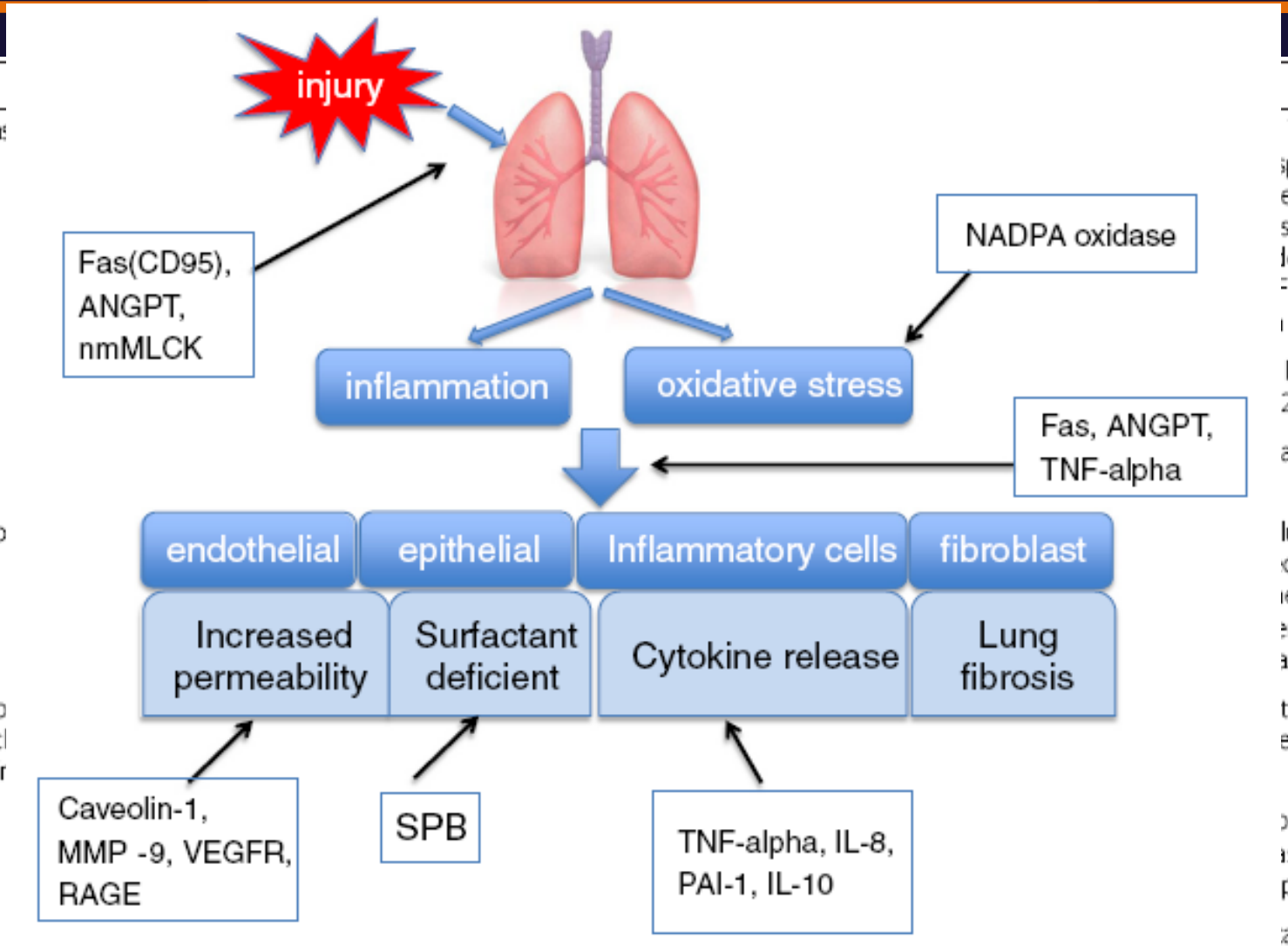
Combining Biomarkers

Biomarker	No.	Alive (n = 384)	Dead (n = 144)	Overall (N = 528)	*P* Value
IL-6, pg/mL	521 (381/140)	209 (92-610)	322 (103-1,670)	244 (94-742)	.004
IL-8, pg/mL	528	35 (13-74)	64 (13-255)	40 (13-98)	< .001
TNFR, pg/mL	528	3,668 (2,478-6,872)	6,914 (3,291-12,917)	4,283 (2,604-8,484)	< .001
PROTC, % control	528	82 (49-127)	68 (36-102)	78 (45-121)	.011
PAI-1, ng/mL	524 (381/143)	54 (29-110)	111 (34-233)	60 (30-143)	< .001
ICAM, ng/mL	528	854 (581-1,280)	1,072 (774-1,536)	924 (605-1,384)	< .001
SP-D, ng/mL	510 (372/138)	92 (49-192)	124 (55-317)	101 (50-217)	.010
VWF, % control	528	370 (223-553)	477 (292-732)	394 (247-624)	< .001

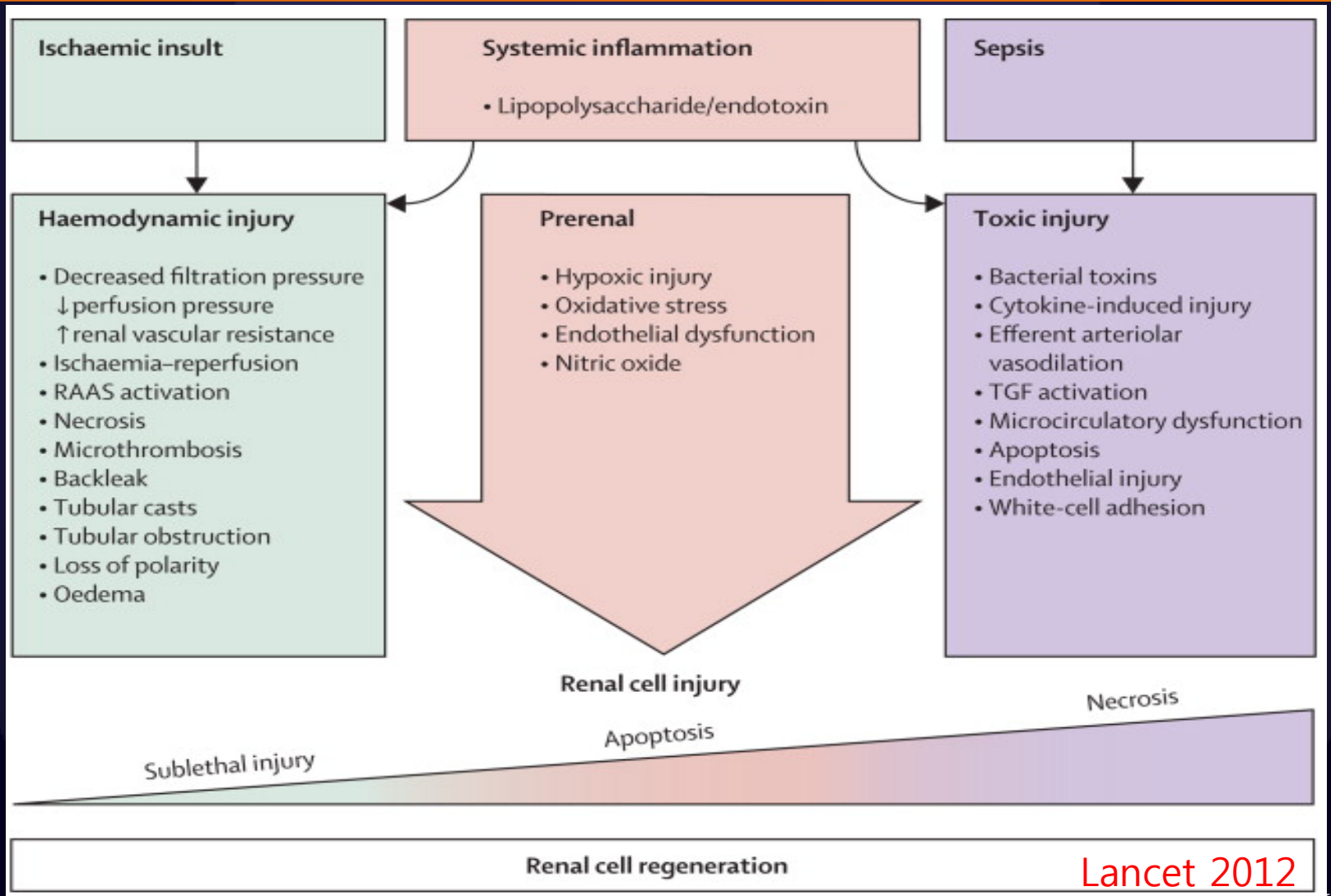




Potential biomarkers in ALI/ARDS

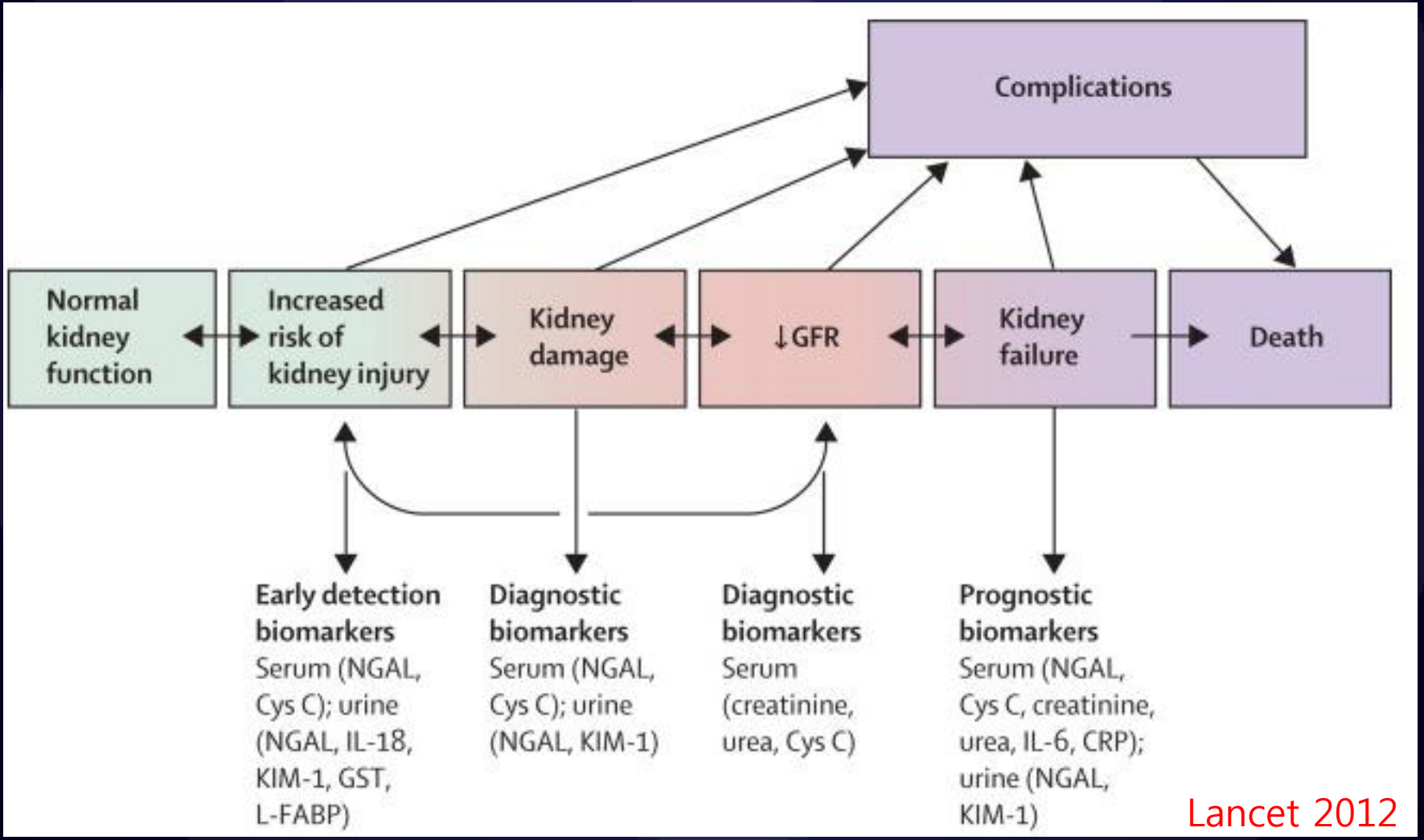


Sepsis-induced AKI



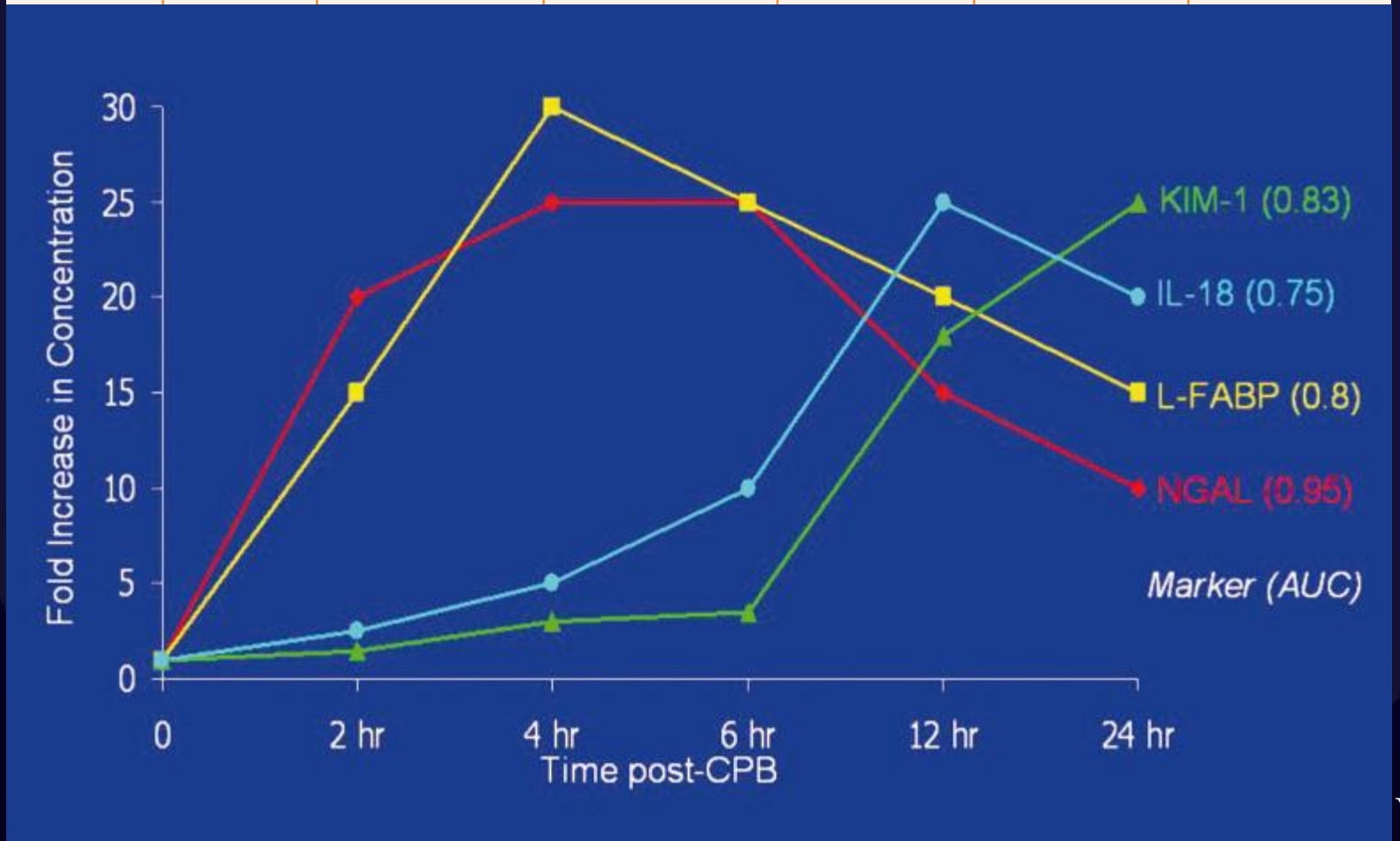
Lancet 2012

Biomarkers in AKI

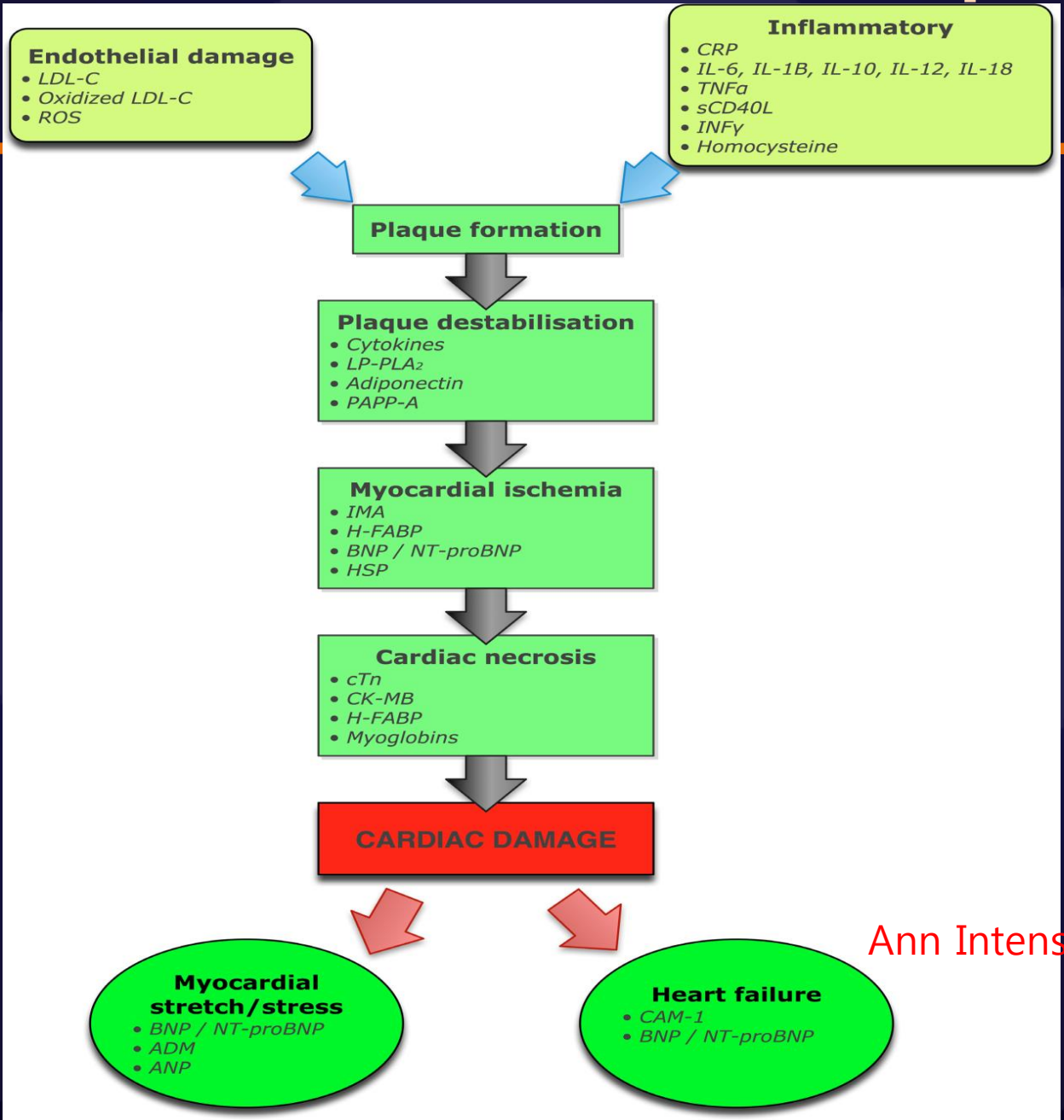


Lancet 2012

Biomarker name	Sample source	Cardiopulmonary bypass (CPB)	Contrast administration	Critical care setting	Kidney transplant (tx)	Commercial assay
NGAL	Urine	<2 h post-CPB	2 h post-contrast	48 h pre-AKI	12-24 h post-tx	ELISA, ARCHITECT[#]
IL-18	Urine	6 h post CPB	Not increased	48 h pre-AKI	12-24 h post-tx	ELISA
KIM-1	Urine	12 h post CPB	Not tested	Not tested	Not tested	ELISA
L-FABP	Urine	4 h post-CPB	24 h post-contrast	Not tested	Not tested	ELISA
NL	Plasma	<2 h post-CPB	2 h post-contrast	48 h pre-AKI	Not tested	ELISA, Triage[*]



Cardiac Biomarkers in Sepsis



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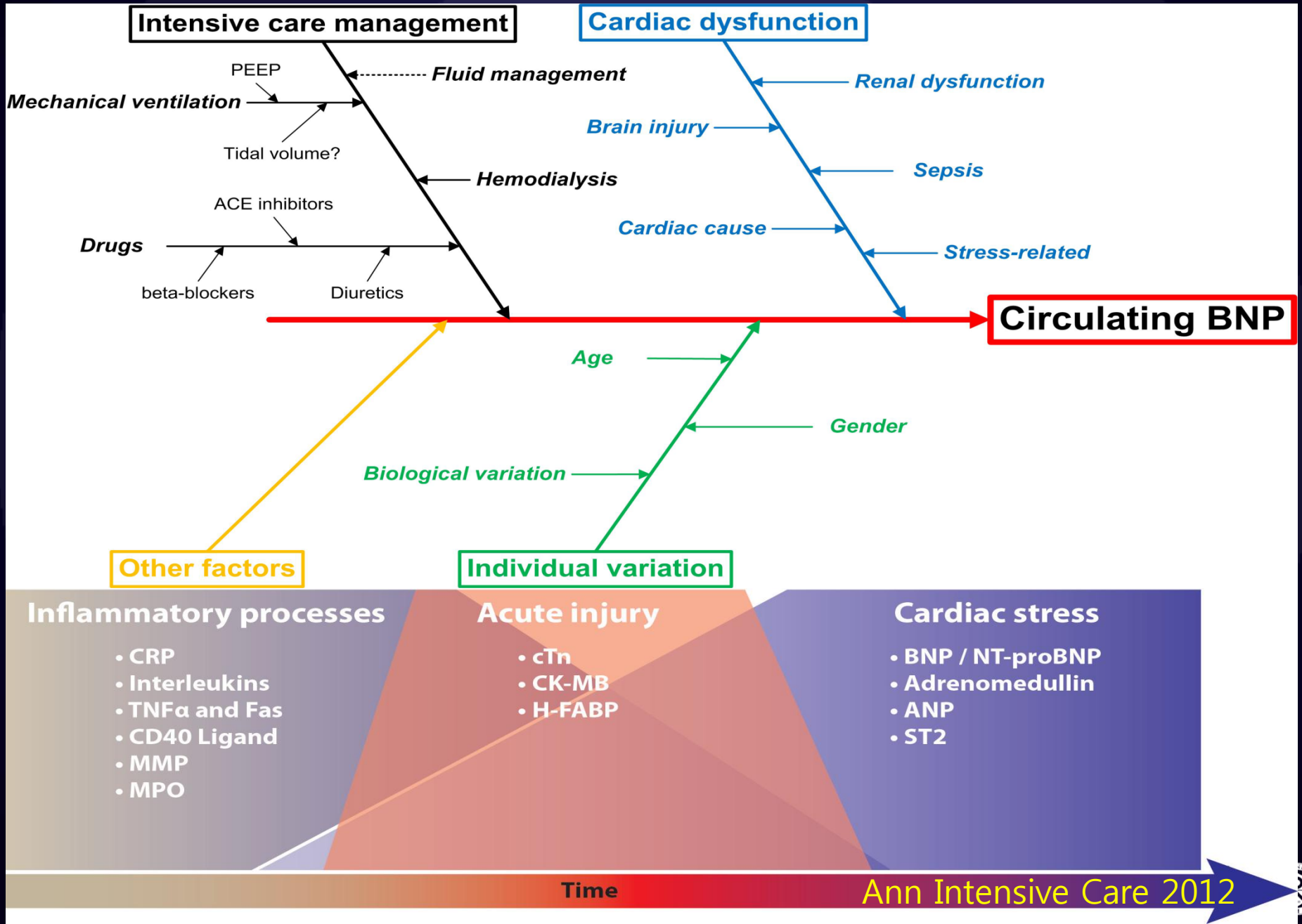
Cardiac Stress and BNP



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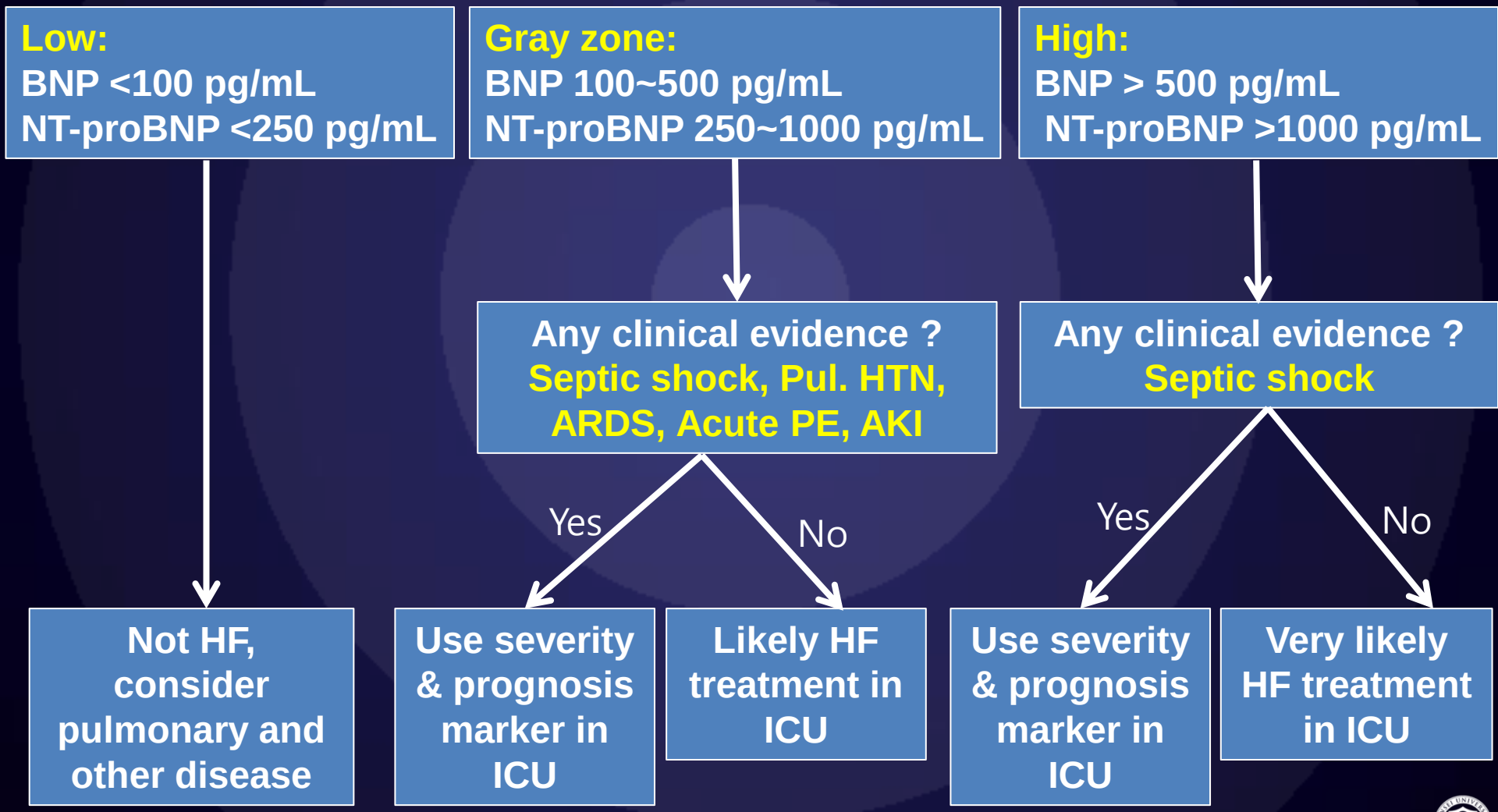
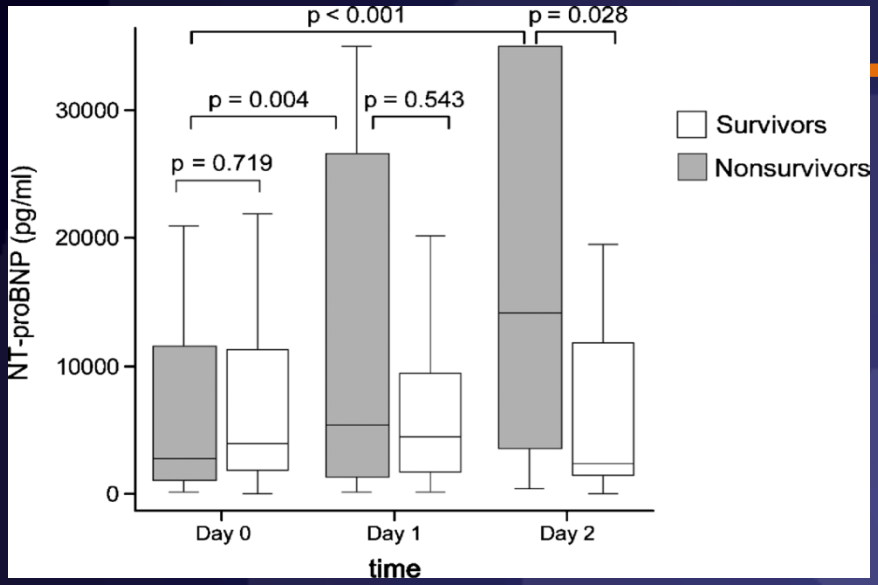
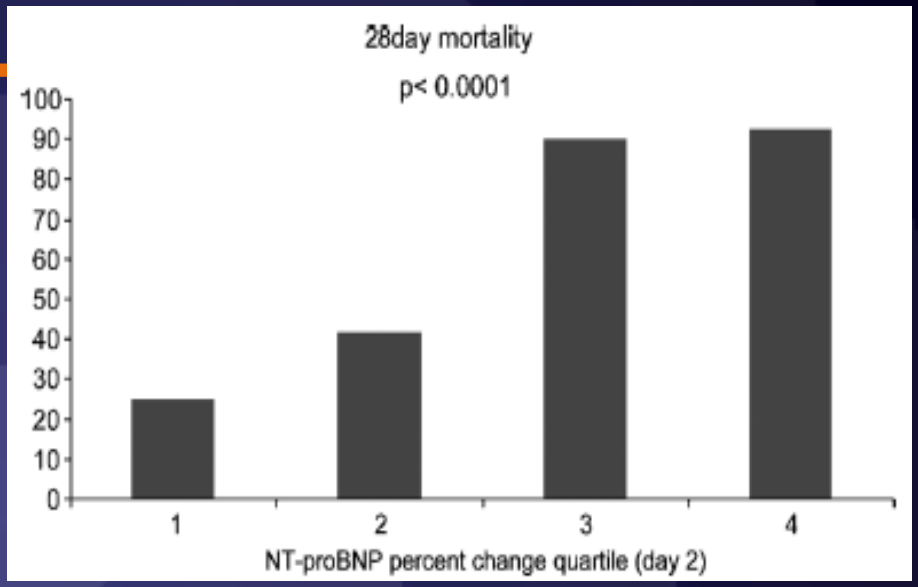
BNP or NT-proBNP in ICU

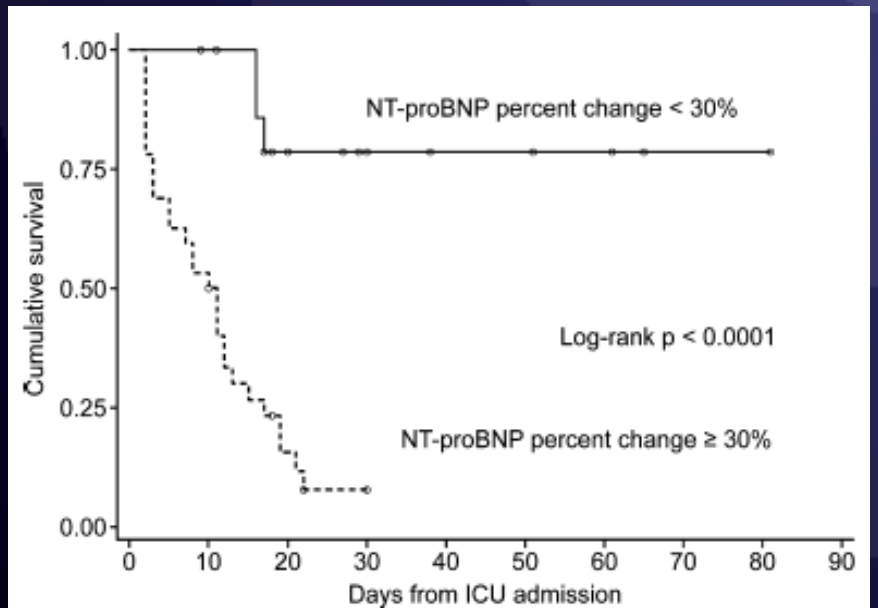


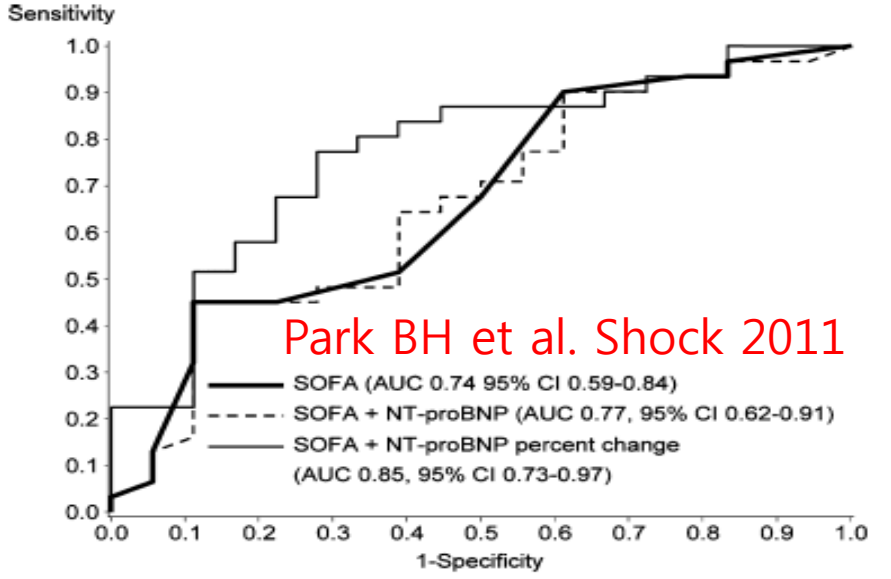
CCM 2005 YUMC

NT-proBNP in ALI/ARDS with Septic Shock

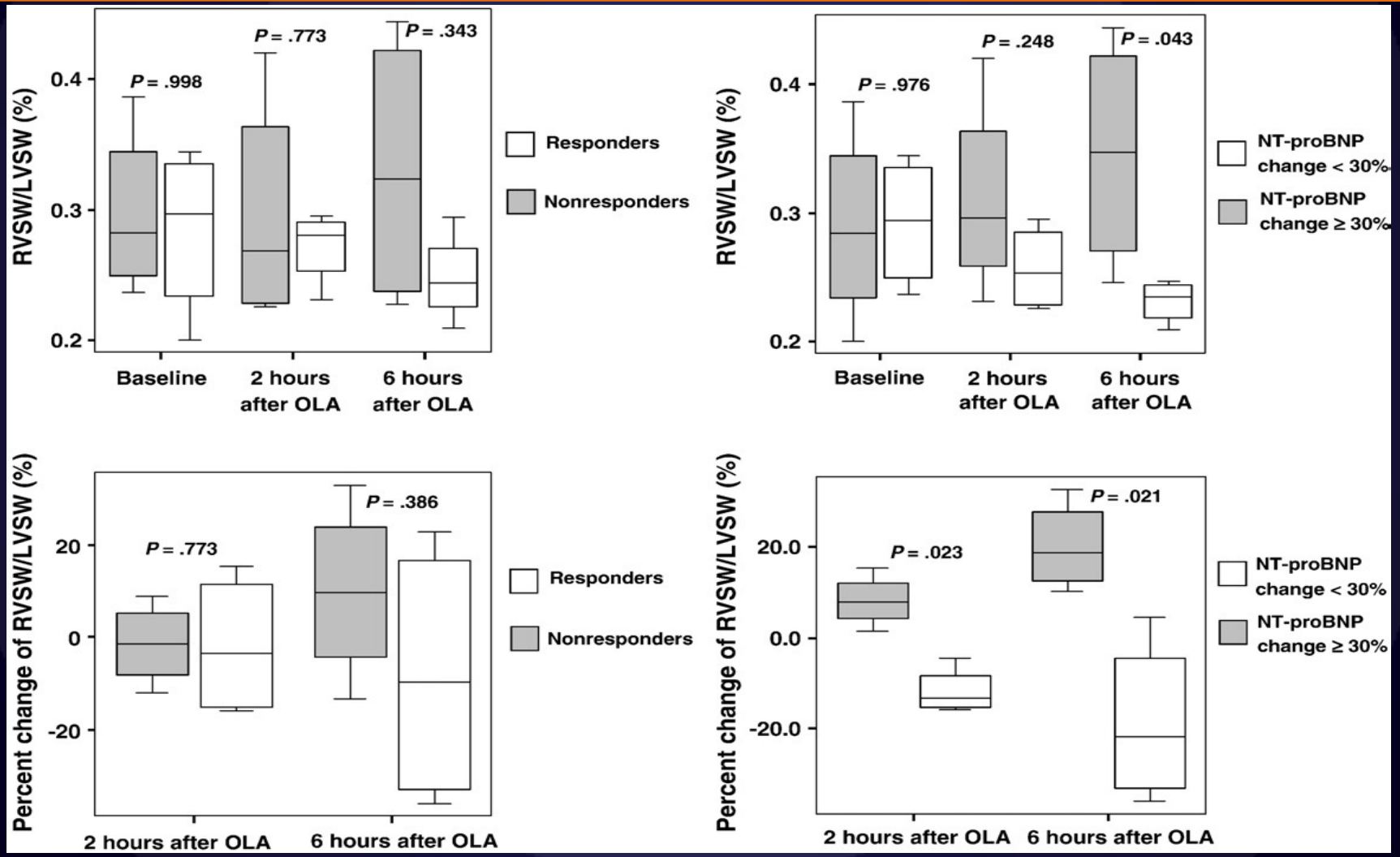






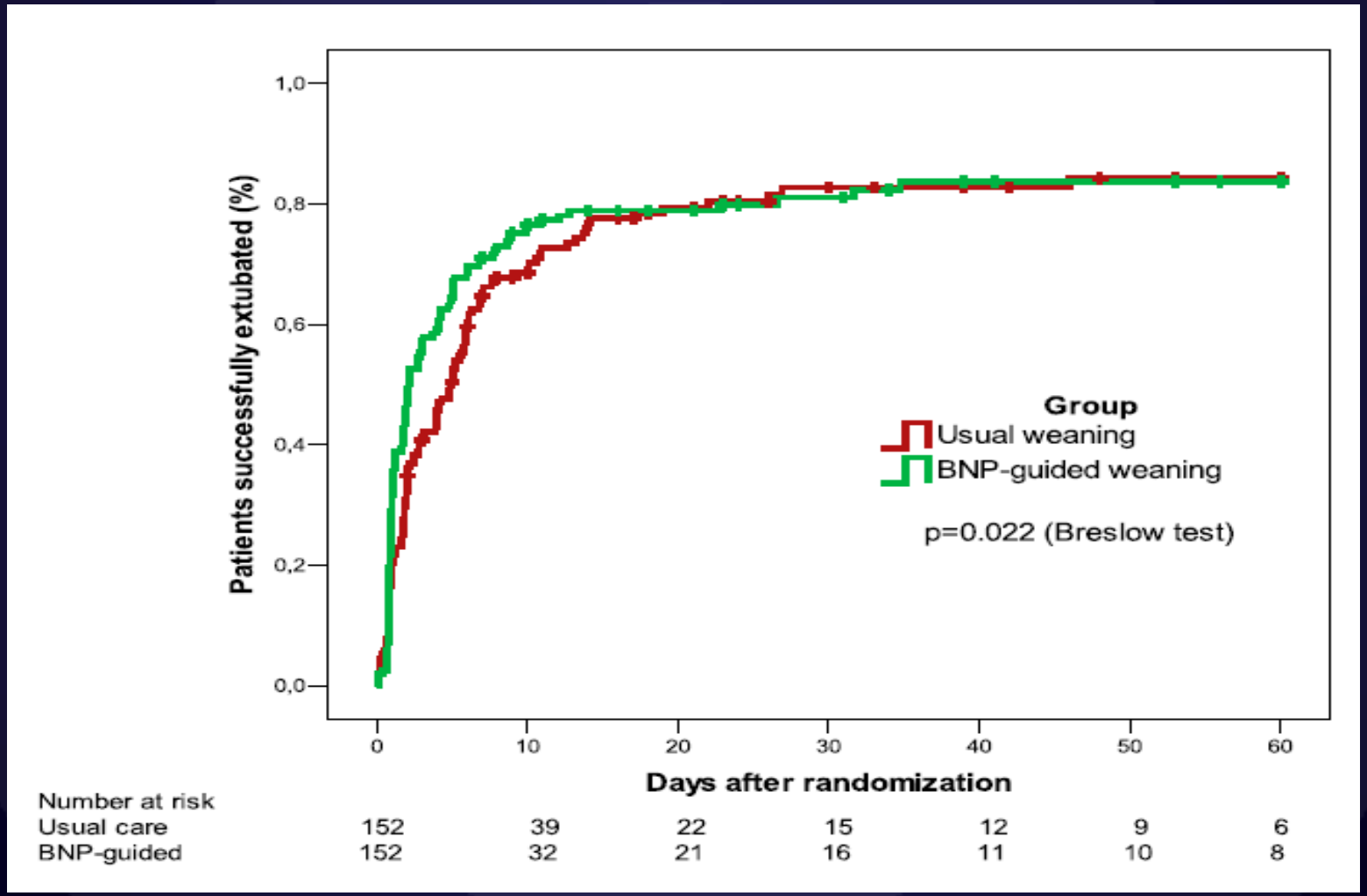


NT-proBNP in ALI/ARDS



Park BH et al, J Crit Care 2011

BNP-guided Weaning



AJRCCM 2012;186:1256

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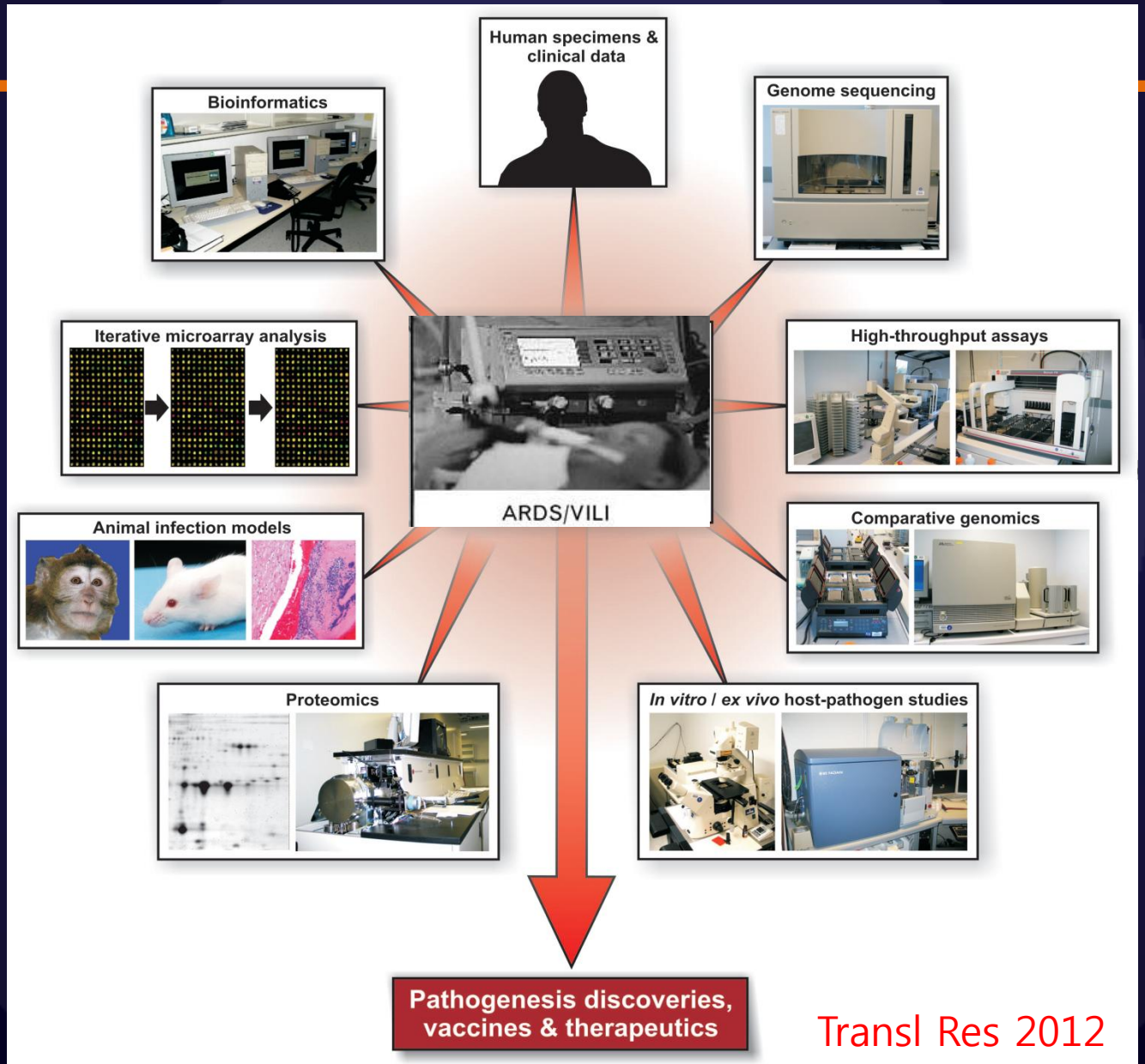
Future Biomarkers



Transl Res 2012

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Conclusions

- ✓ Biologic system is so complex and multifunctional
- ✓ No single perfect biomarker
- ✓ Combining clinical markers & panels of biomarkers
- ✓ Improve understanding of pathogenesis
- ✓ Identify novel targets for therapeutic interventions
- ✓ In future genomic, bioinformatic, and proteomic researches will be identify new biomarkers
- ✓ Provide tailor therapy