

Markers of Severity During Severe Infections

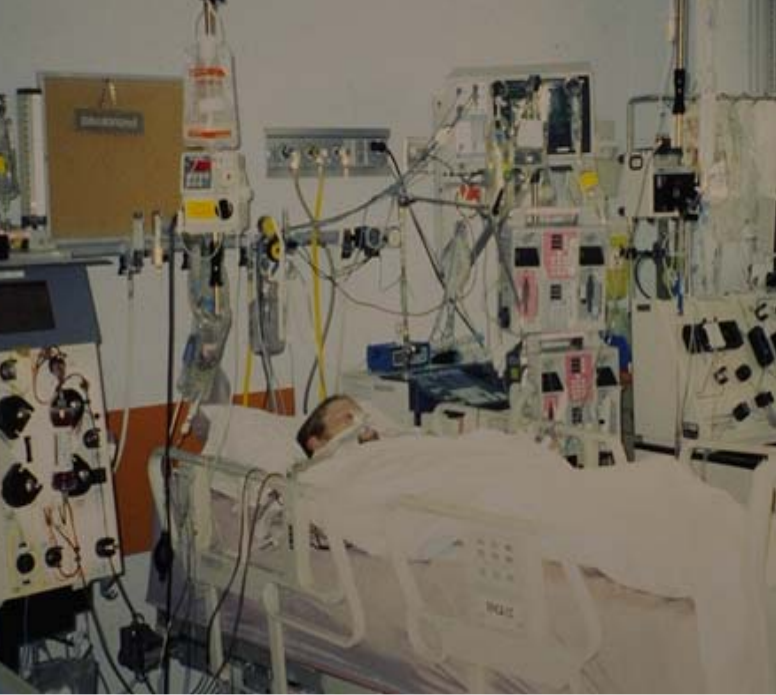
John C. Marshall, MD FRCSC



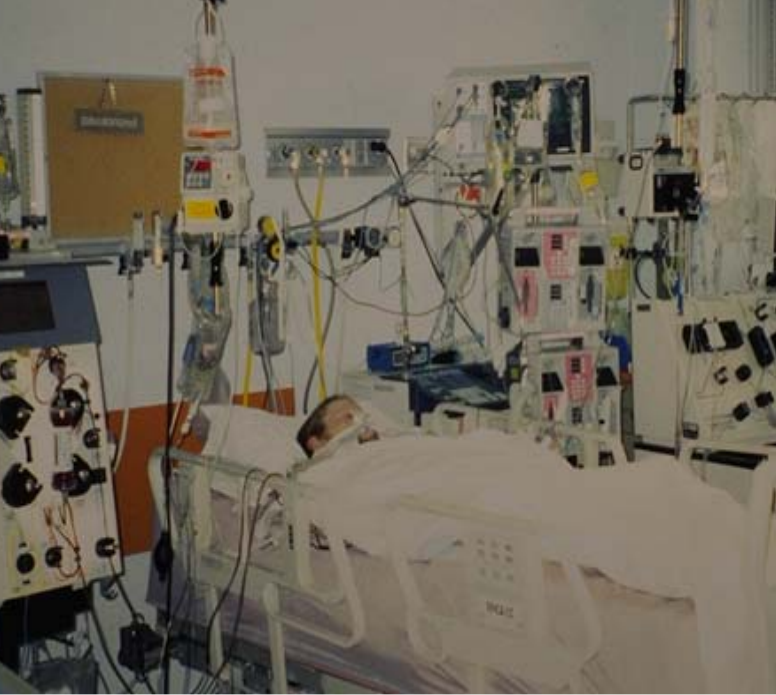
International Conference on Surgical
Infections, Stockholm Sweden

September 7, 2006



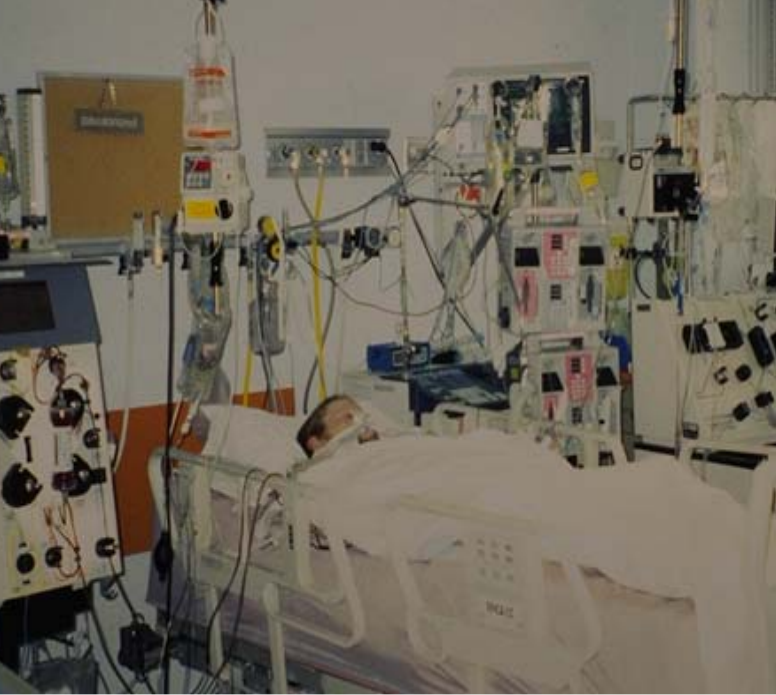


- **37 year old man**
- **Necrotizing pancreatitis**
- **ICU day 6**
- **Increased FIO₂**
- **Temperature 38.1°C**



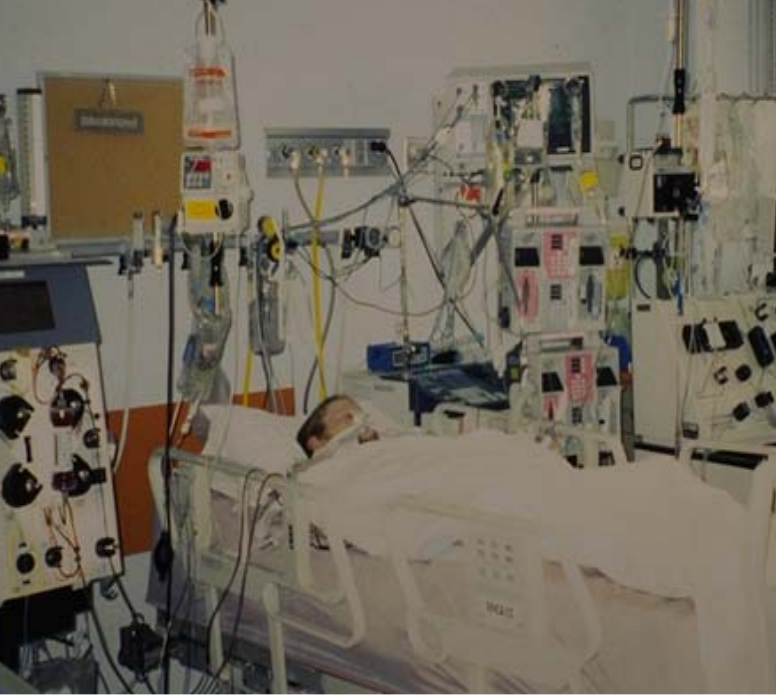
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- **Is he infected?**
- **What is the source?**
- **What is the organism?**
- **What else can we do?**



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- 37 year old man
- Necrotizing pancreatitis
- ICU day 6
- Increased FIO_2
- Temperature $38.1^{\circ}C$

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Markers of Inflammation

White blood cell count
C reactive protein
Endotoxin
Procalcitonin
Interleukin-6
Neopterin
Glucan
Mannan
Enterobacterial common antigen
Bacterial DNA
Bacterial lipoprotein
Interleukin-1
Interleukin-1 ra
Interleukin 8
Interleukin 12
Interleukin 10
Interleukin 18
Tumor necrosis factor
TGF beta
Leptin
MIF
HMG-1
Alpha MSH
Alpha-1 anti-trypsin
Prealbumin
Fibrinogen

Nitric oxide
Ceramide
Elastase
Myeloperoxidase
Lactoferrin
Troponin I
Intestinal fatty acid binding protein
Carbohydrate deficient transferrin
Hydrogen peroxide
Conjugated dienes
Fibrinogen degradation products
Von Willebrand's factor
D-dimers
Thrombomodulin
Fibrinopeptide A
PAI-1
F1+2
TAT Complexes
Protein C
Cortisol
rT3

.... and many,
many more

Biomarker

“ ... a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention”



Marker

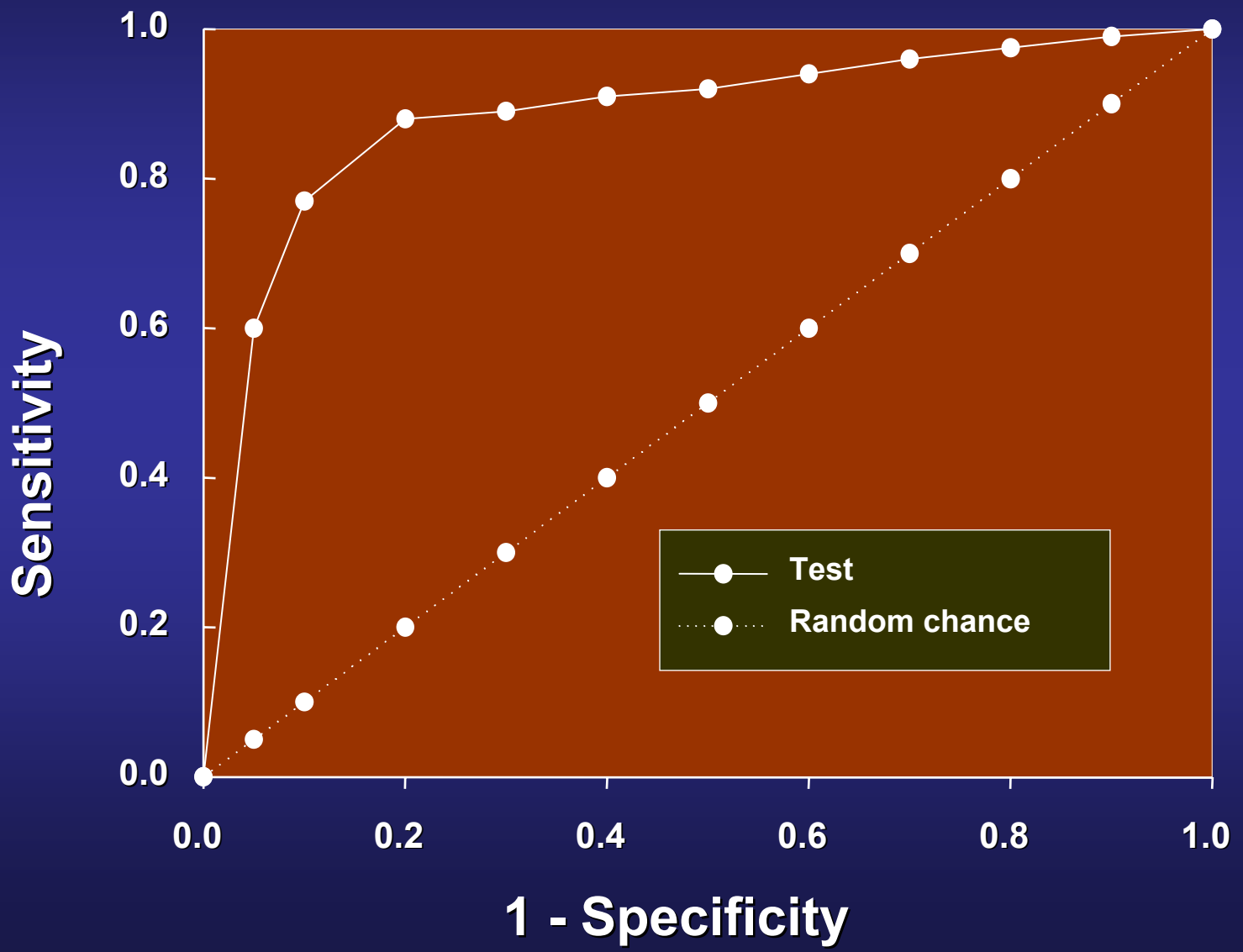
Population

Biomarker

A biologic measure that identifies the presence of a pathologic state or process, quantifies its severity, and/or predicts the effects of a given intervention on outcome.

- Diagnosis**
- Prognosis**
- Response to therapy**

Receiver Operating Characteristics (ROC) Curve



Likelihood Ratio

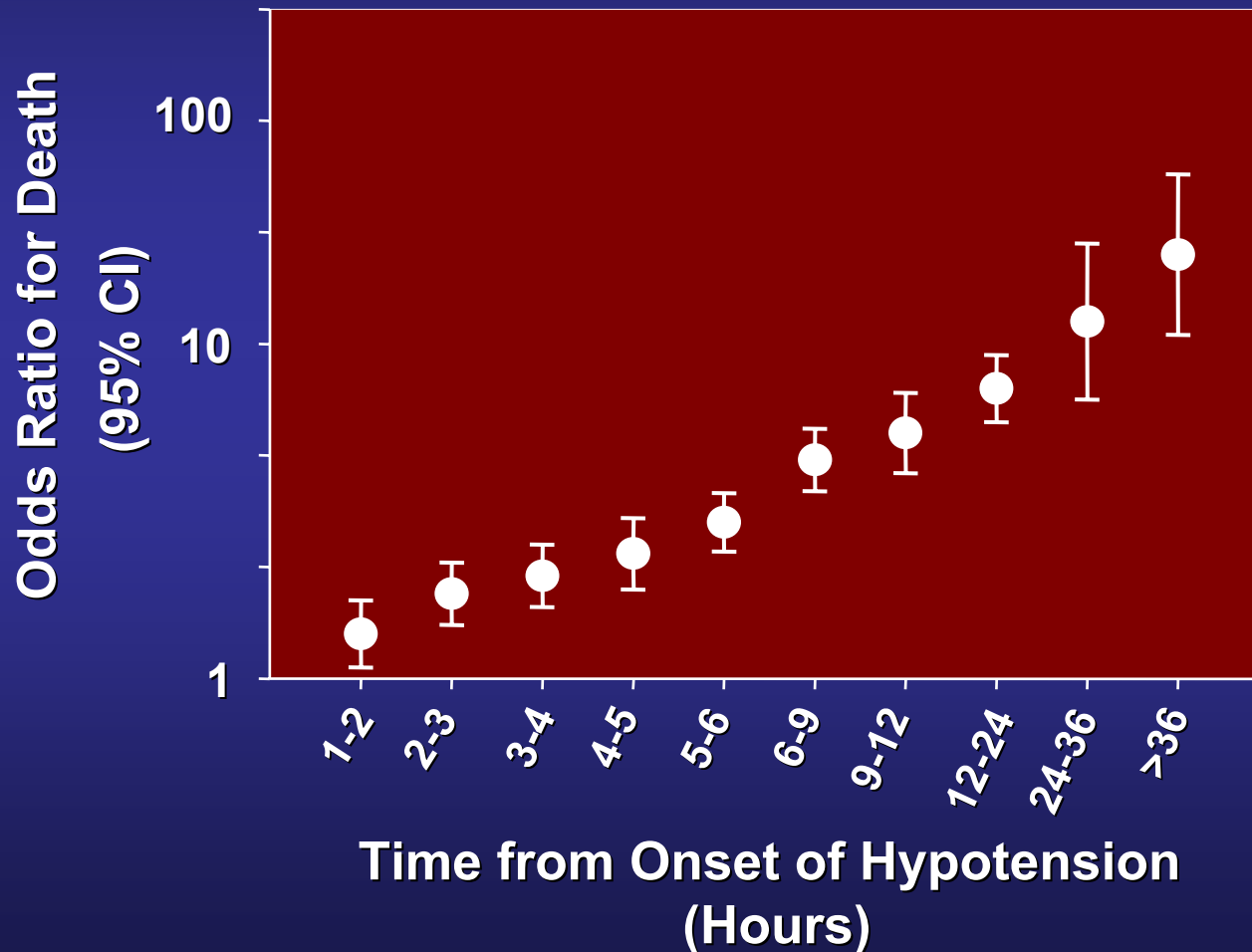




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Time to Appropriate Antimicrobials and Mortality in Septic Shock



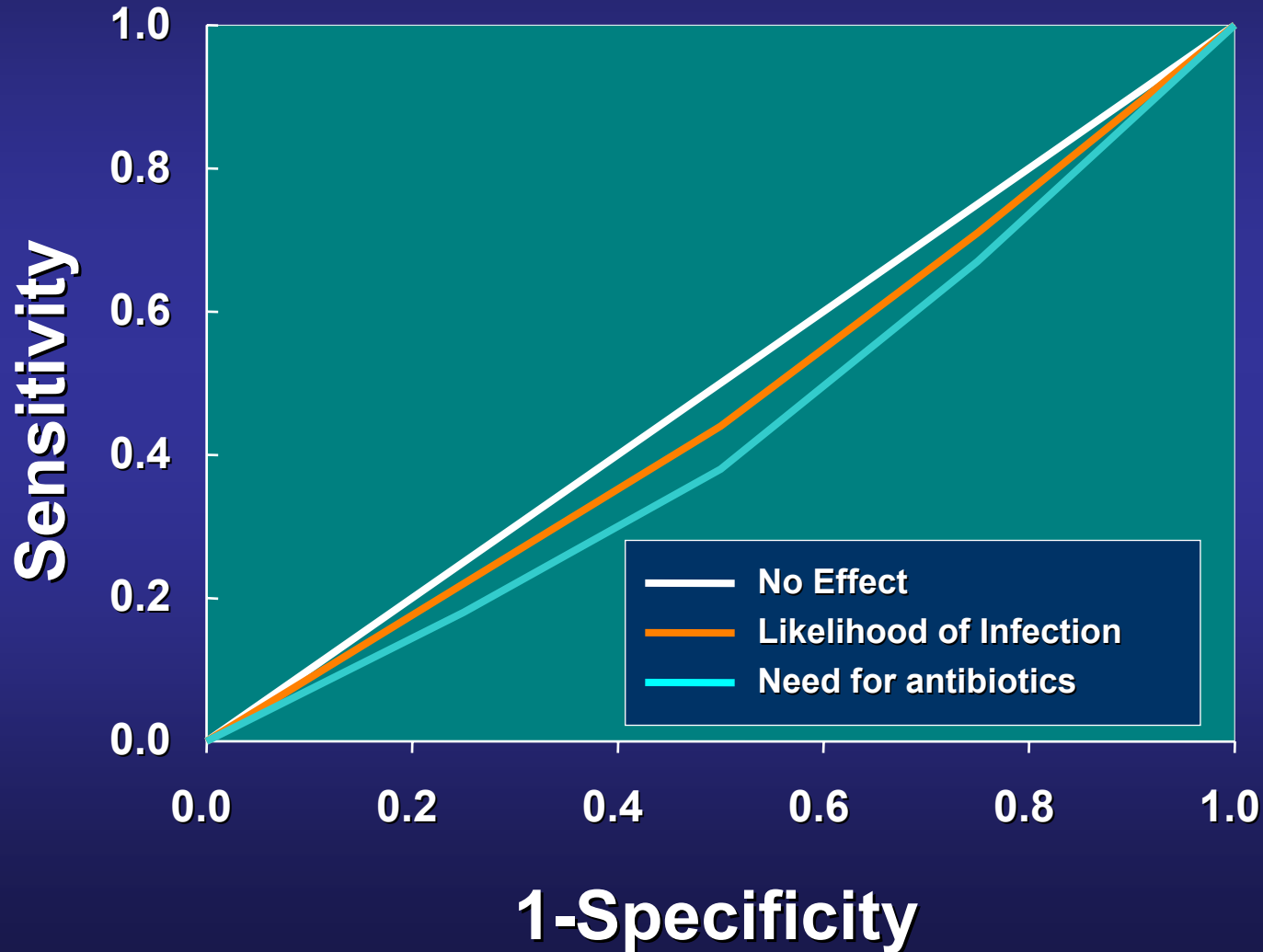
Risk Factors for Death in 549 Patients with *S. aureus* Infection

	OR	95% CI
Vasopressor use	5.49	(4.08-7.38)
Age (per year)	1.03	(1.02-1.04)
Inappropriate initial antibiotics	1.92	(1.48-2.50)

Randomized Trials of Antibiotic Minimization

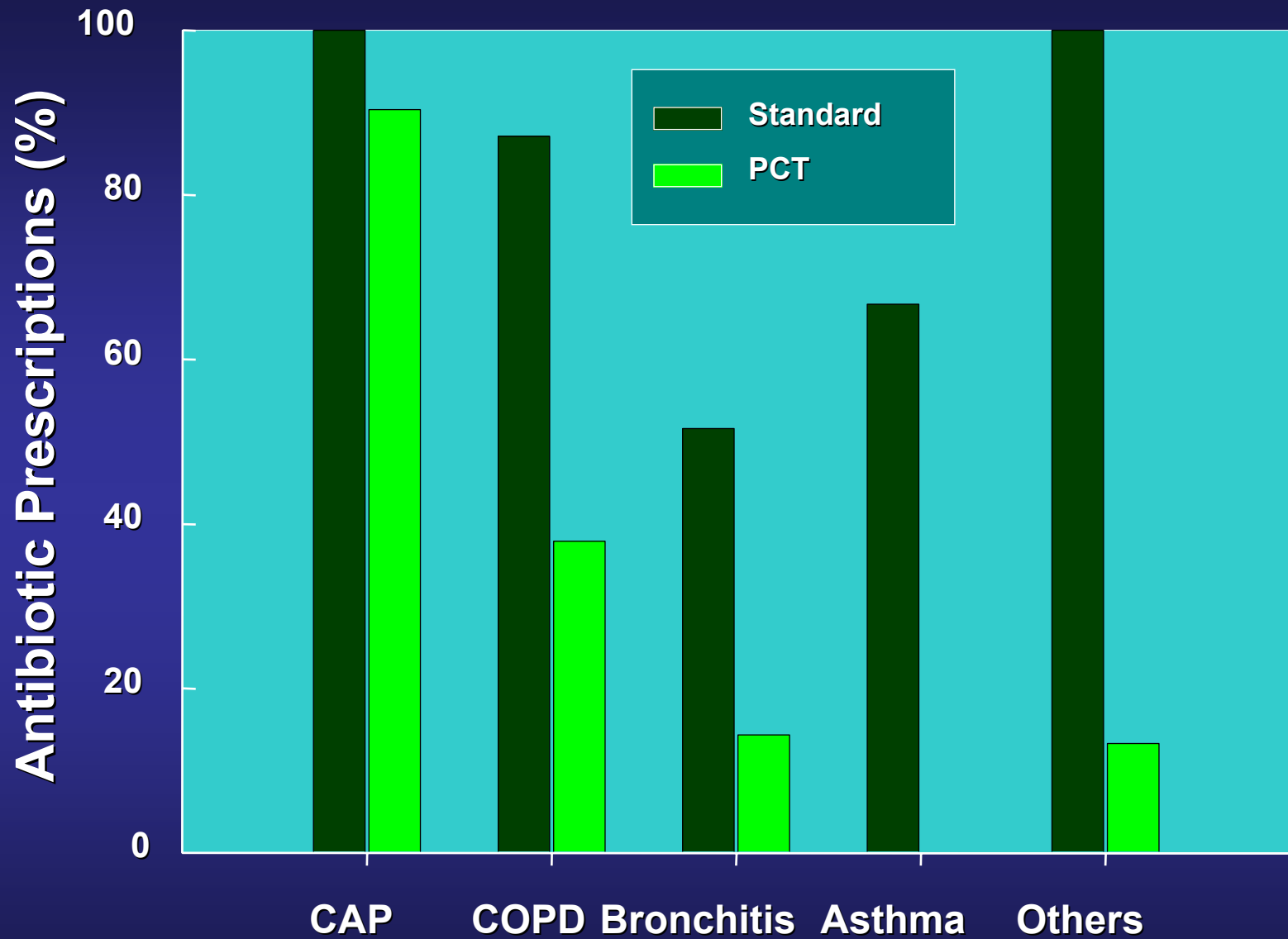
	Control	Restrictive	p.
Singh 2000 (Resistance)	35%	15%	0.02
Fagon 2000 (Mortality)	25.8%	16.2%	0.02
Chastre 2003 (Resistance)	62.0%	42.1%	0.04

Accuracy of Clinical Diagnosis



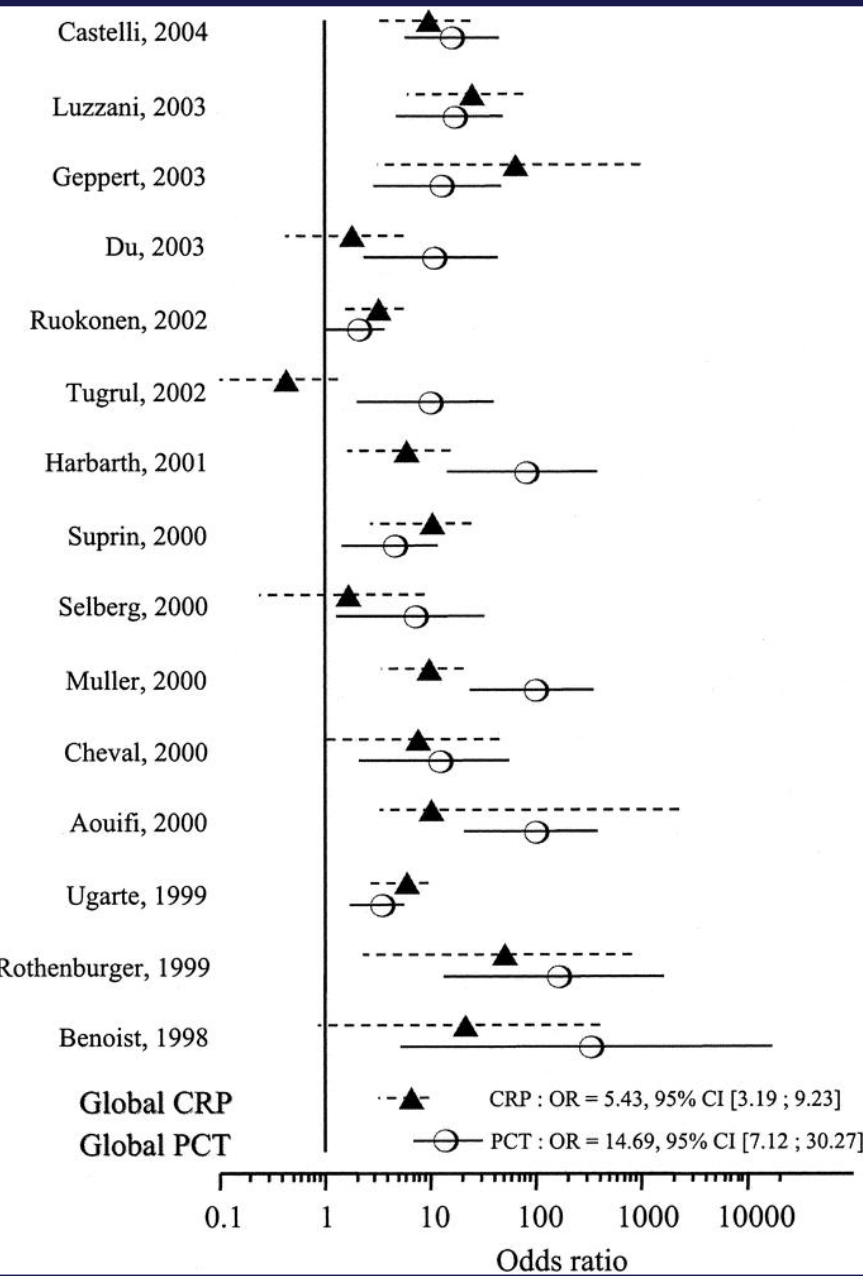
Neutrophil Parameters in the Diagnosis of Infection

	Sensitivity	Specificity	L.R.
PMN CD64	94.1%	84.9%	6.24
PMN Count	79.4%	46.8%	1.49
Band count	87.5%	43.5%	1.55



- Christ-Crain *Lancet* 363:600, 2004

Procalcitonin (PCT) and C-Reactive Protein (CRP) in the Diagnosis of Infection in Patients with SIRS



Absence of Endotoxemia During First 48 Hours of ICU Stay Rules Out Infection

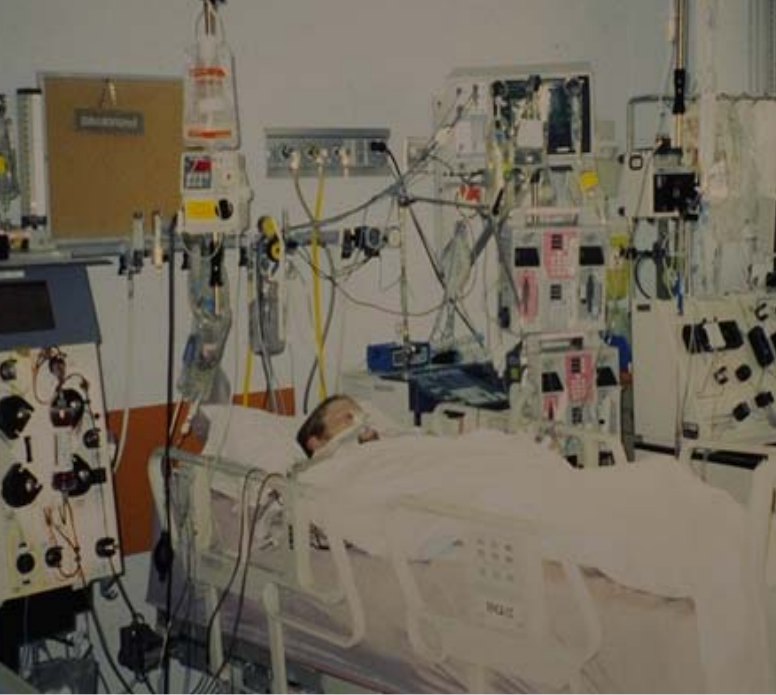
Negative Predictive Value:

97% (93 – 100)

Sensitivity:

85% (69 – 100)

Likelihood Ratio: 0.49



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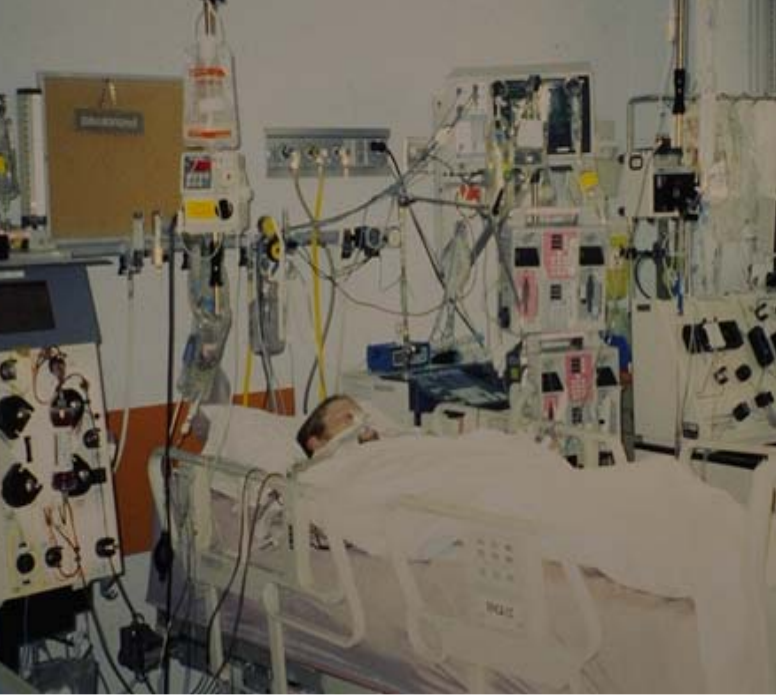
BAL TREM-1 in Diagnosis of Pneumonia

148 ventilated patients

CAP	38
VAP	46
No pneumonia	64

Sensitivity 98% **Specificity 90%**

Likelihood ratio 10.38



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Endotoxemia Predicts Infection

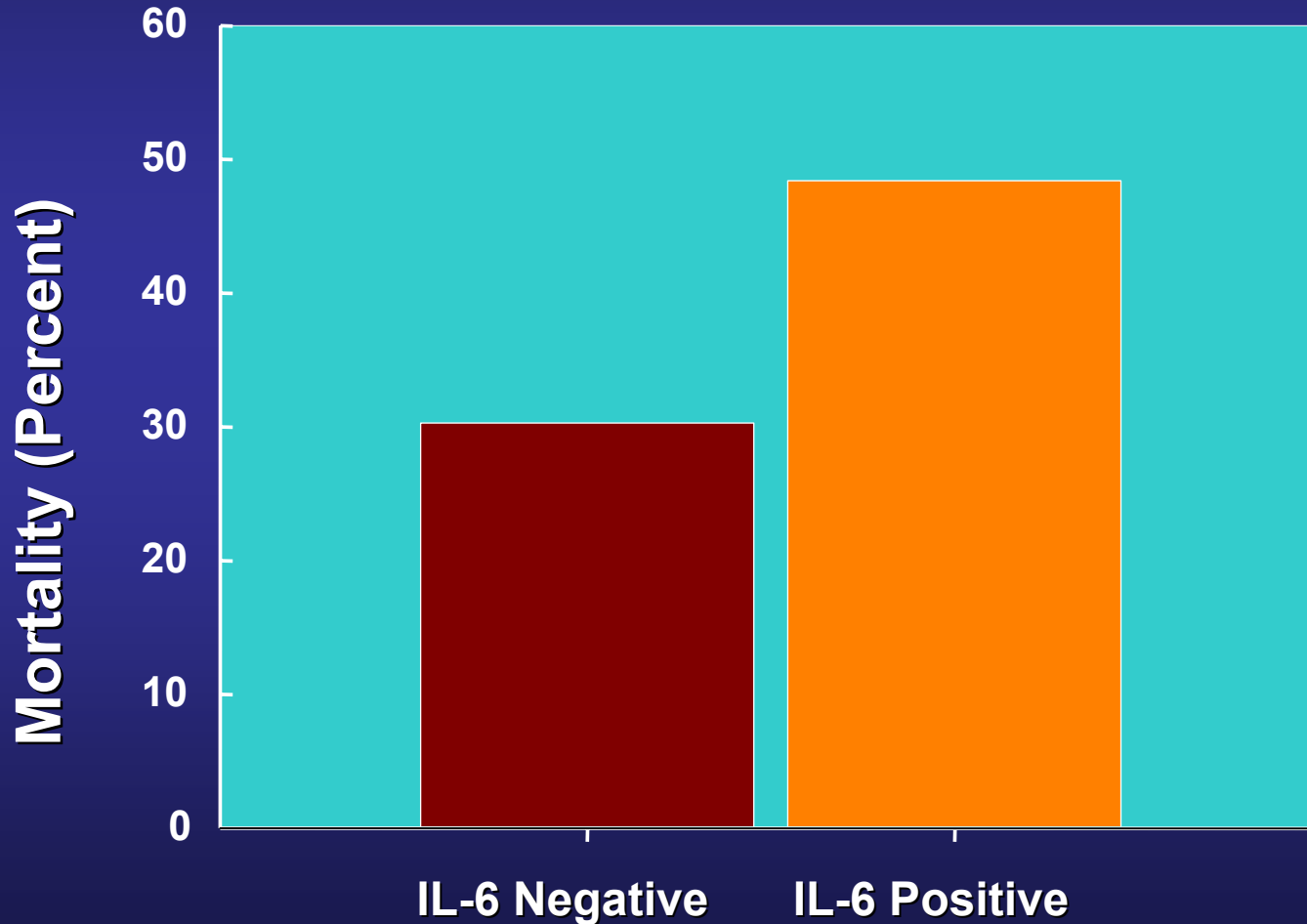
	Odds Ratio (95% CI)	
EA	0.4 - 0.6	>0.6
Any infection	3.1 (1.4-6.8)	3.2 (1.5-7.1)
Gram negative	2.7 (0.7-11.6)	6.4 (1.8-23.3)



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Elevated IL-6 Predicts Increased Risk of Death (N=4)



Impact of Source Control in Patients with Low IL-6 Levels

Source Control

Mortality

Adequate

(N=545)

126 (23.1%)

Inadequate

(N=121)

48 (39.7%)*

*** p<0.001**

Impact of Source Control in Patients with High IL-6 Levels

Source Control

Mortality

Adequate

(N=419)

177 (42.3%)

Inadequate

(N=85)

40 (47.1%)*

*** p=0.49**

Procalcitonin Levels Permit Earlier Discontinuation of Antibiotics in CAP

Antibiotics on Admission	85 vs 99%*
Total Antibiotic Exposure	0.52 (0.48-0.55)*
Duration of Therapy	5 vs 12 days*

***All p<0.001**

Tumor Necrosis Factor α

G \rightarrow A; -308 (Promoter)

Author	Disease	Cases	Controls	p.
Nadel	Meningococccemia (deaths)	0.56	0.29	0.03
Mira	Septic shock (deaths)	0.52	0.24	0.008
Tang	Septic shock (deaths)	0.40	0.08	<0.05

The G-308A TNF promoter polymorphism is associated with a favorable response to infliximab or etanercept in rheumatoid arthritis ...

- **Mugnier *Arthritis Rheum* 48:1849, 2003**
- **Balog *Pathobiology* 71:274, 2004**
- **Criswell *Arthritis Rheum* 50:2750, 2004**
- **Padyukov *Ann Rheum Dis* 62:526, 2003**
- **Martinez *Arthritis Rheum* 50:1077, 2004**

Conclusions

- **Multiple markers correlate with severity**
- **PCT and CRP can diagnose bacterial infection, and PCT can guide therapy**
- **Endotoxin levels may exclude diagnosis of Gram-negative infection**
- **Science of biomarkers in sepsis is underdeveloped, and need is great**



Thank you!!!