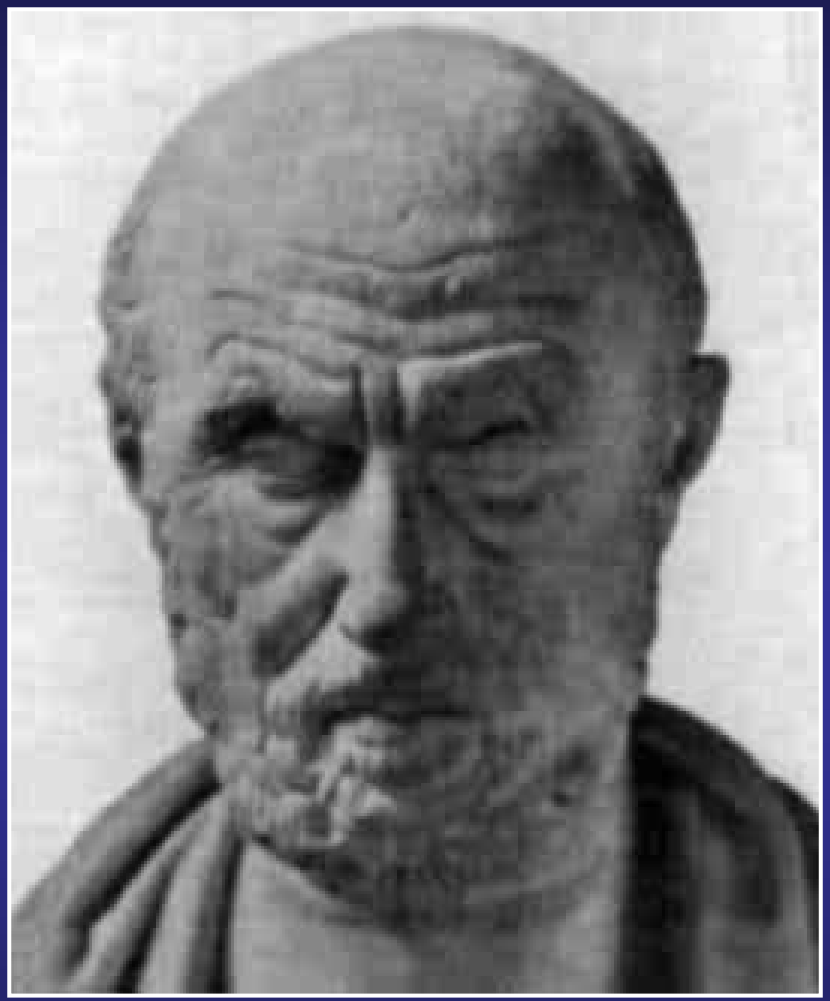
Sepsis

John C. Marshall, MD FRCSC

CAPRA
Toronto, Ontario
April 20, 2009

St. Michael's Hospital

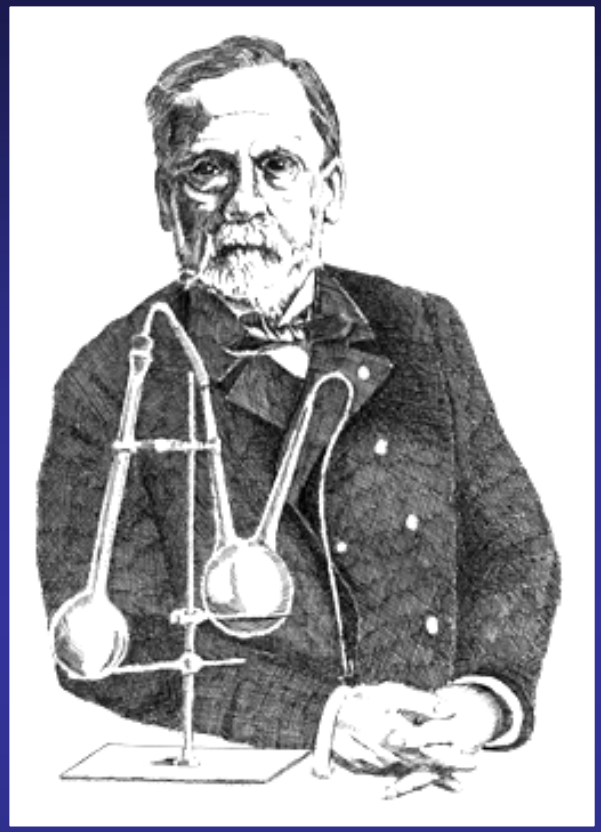
University of Toronto



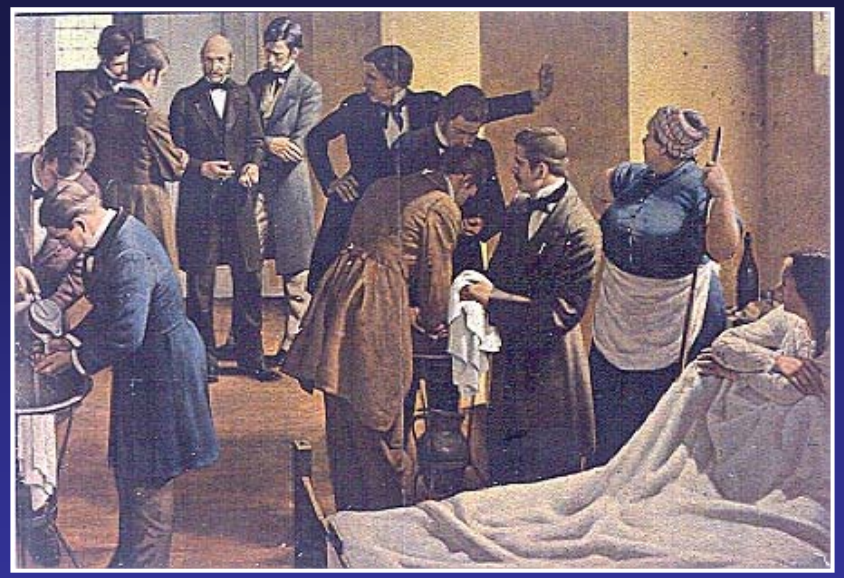
Hippocrates
460 – 370 BC

Sepsis

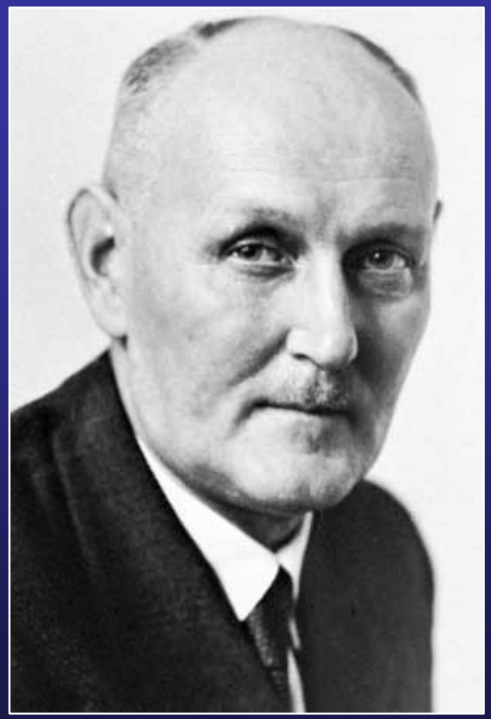
Pepsis



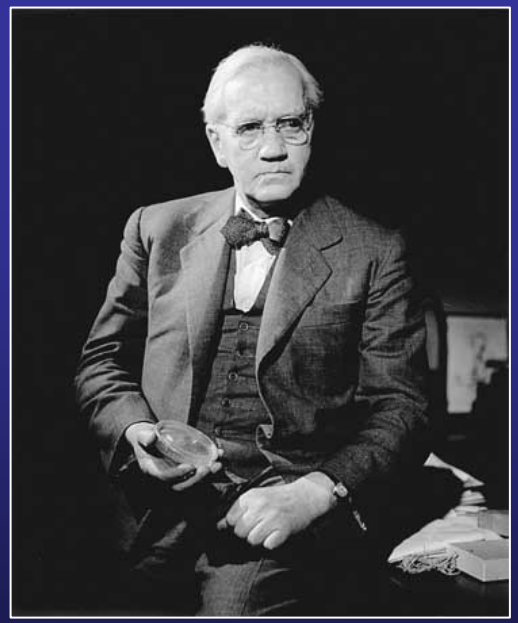
Louis Pasteur
1822 - 1895



Ignace Semmelweiss

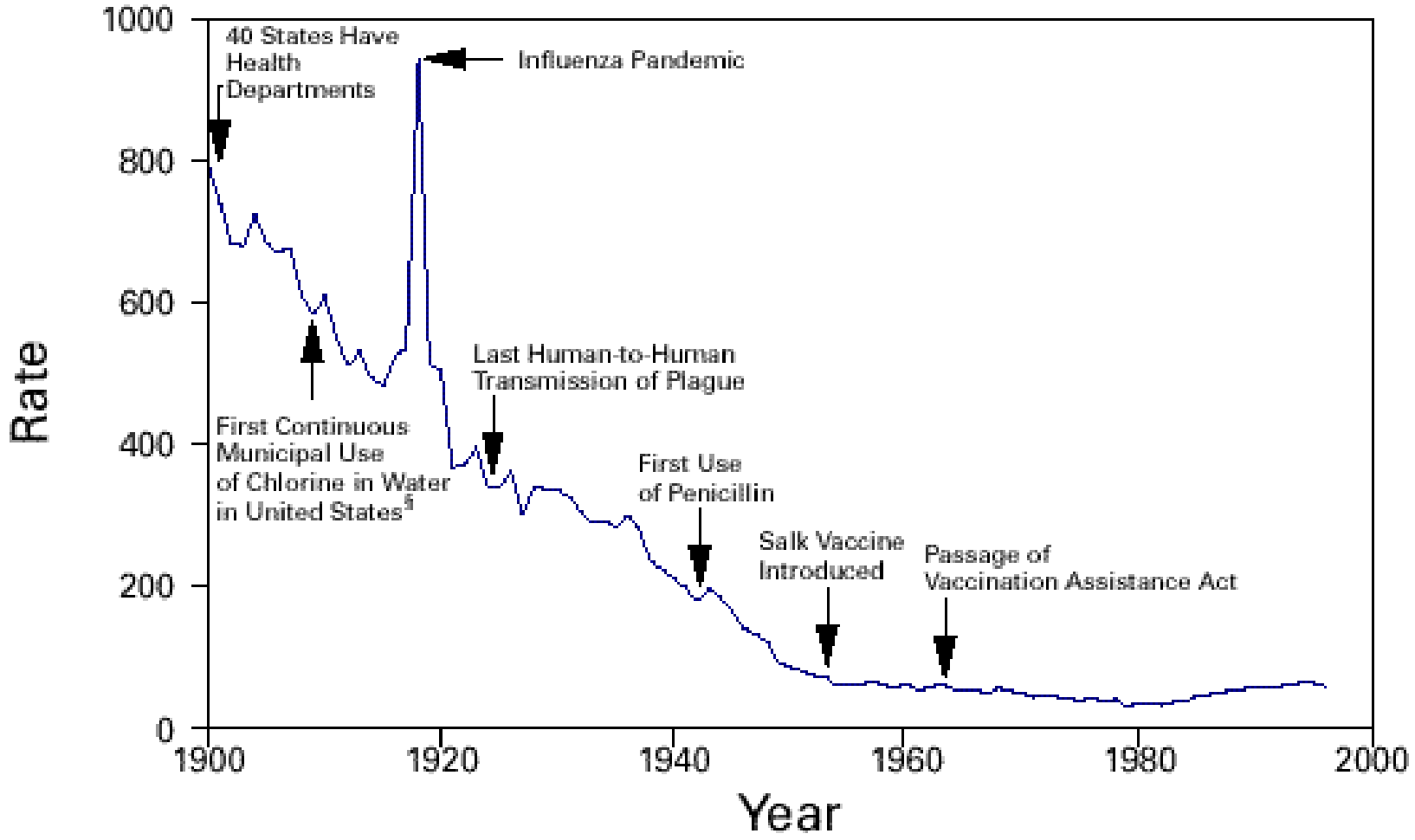


Gerhard Domagk



Alexander Fleming

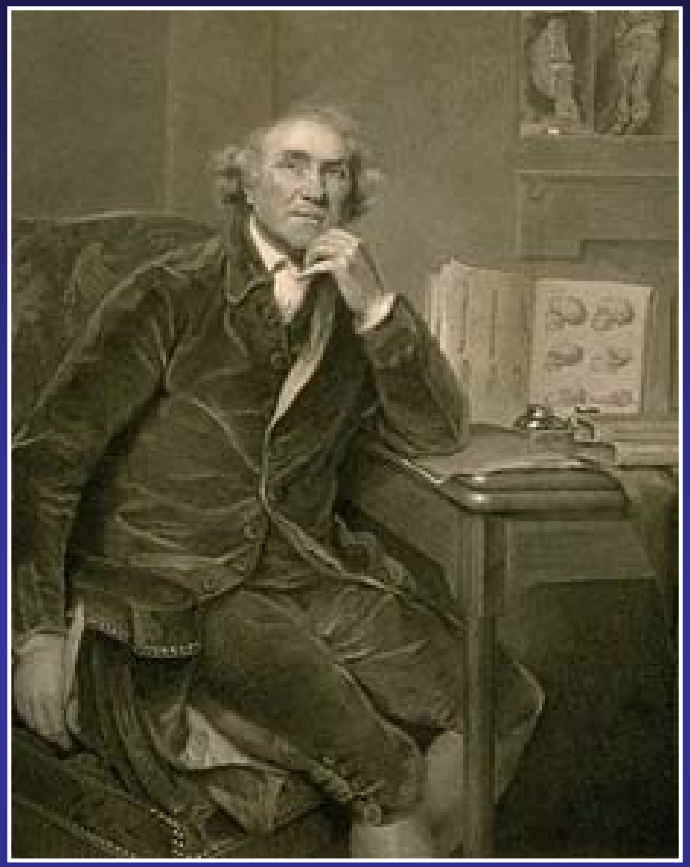
FIGURE 1. Crude death rate* for infectious diseases — United States, 1900–1996†



*Per 100,000 population per year.

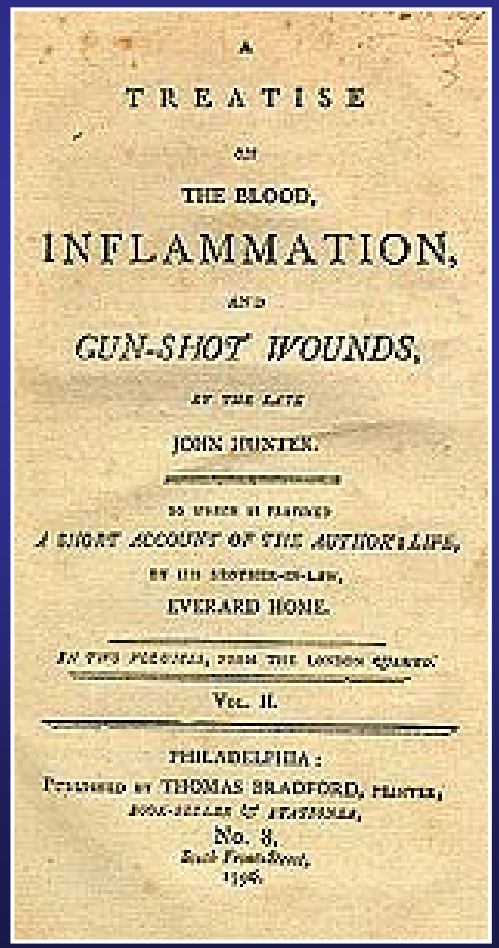
†Adapted from Armstrong GL, Conn LA, Pinner RW. Trends in infectious disease mortality in the United States during the 20th century. JAMA 1999:281;61–6.

§American Water Works Association. Water chlorination principles and practices: AWWA manual M20. Denver, Colorado: American Water Works Association, 1973.



John Hunter
1728 - 1793

"… both the disposition and the means of cure…"



A

TREATISE

ON

THE BLOOD,

INFLAMMATION,

AND

GUN-SHOT WOUNDS,

BY THE LATE

JOHN HUNTER.

TO WHICH IS PREFIXED

A SHORT ACCOUNT OF THE AUTHOR'S LIFE,

BY HIS BROTHER-IN-LAW,

EVERARD HOME.

IN TWO VOLUMES, FROM THE LONDON EDITION.

Vol. II.

PHILADELPHIA:

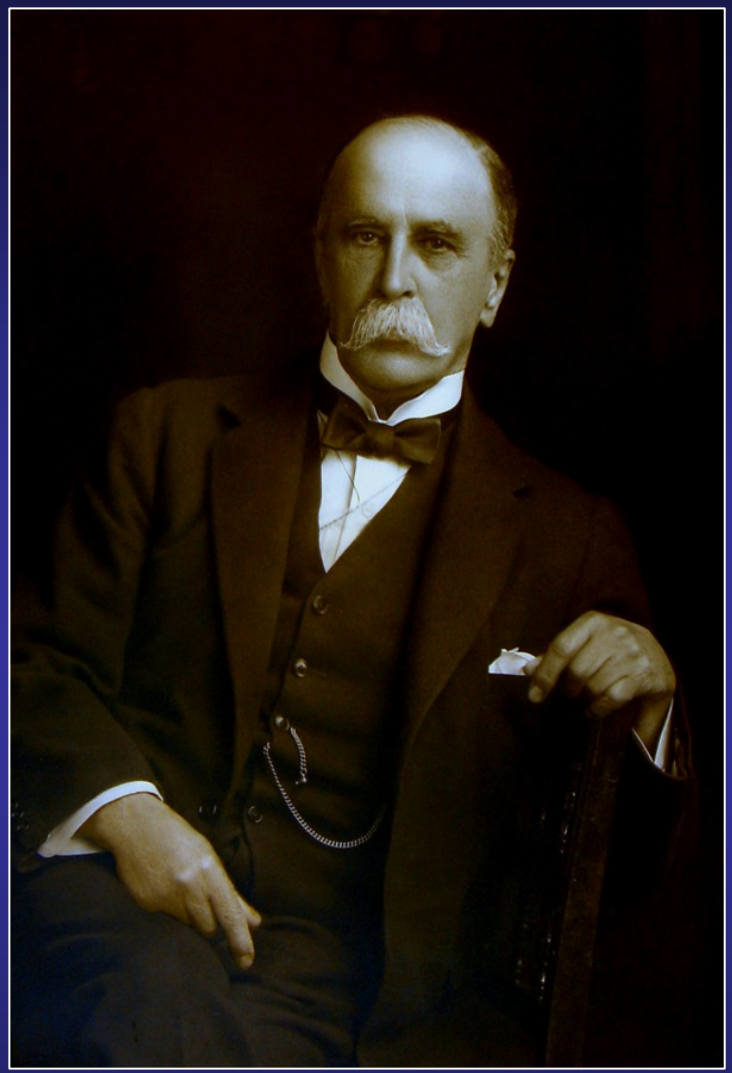
PUBLISHED BY THOMAS BRADFORD, PRINTER,

BOOK-SELLER & STATIONER,

No. 8,

South Front-Street,

1794.



William Osler

"Except on few occasions, the patient appears to die from the body's response to infection rather than from it …"

Richard Pfeiffer

An extract of the cell wall of *Vibrio cholera*:

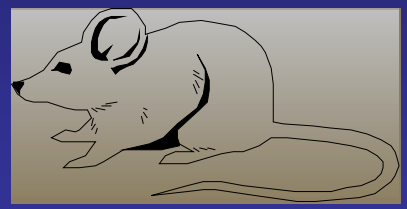
Endotoxin

- 1894

Susceptibility to LPS is Transferred with Bone Marrow Cells

C3H HeJ

(Resistant)



C3H HeN

(Sensitive)

- Michalek, *J.Infect.Dis.* 141:55, 1980

Susceptibility to LPS is Transferred with Bone Marrow Cells

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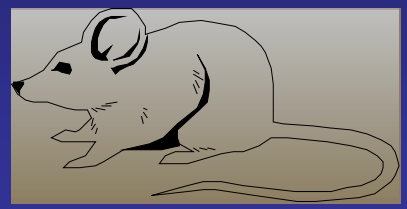

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IRRADIATION

CROSSOVER BONE MARROW TRANSPLANT

+ LPS

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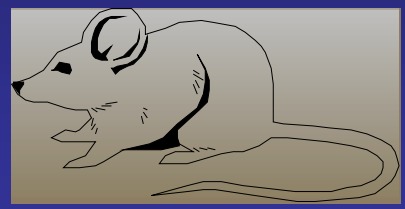

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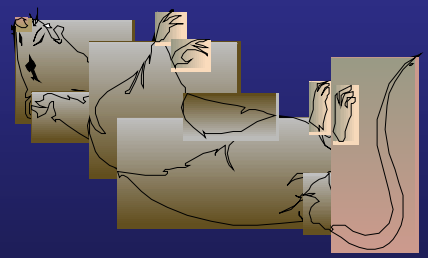


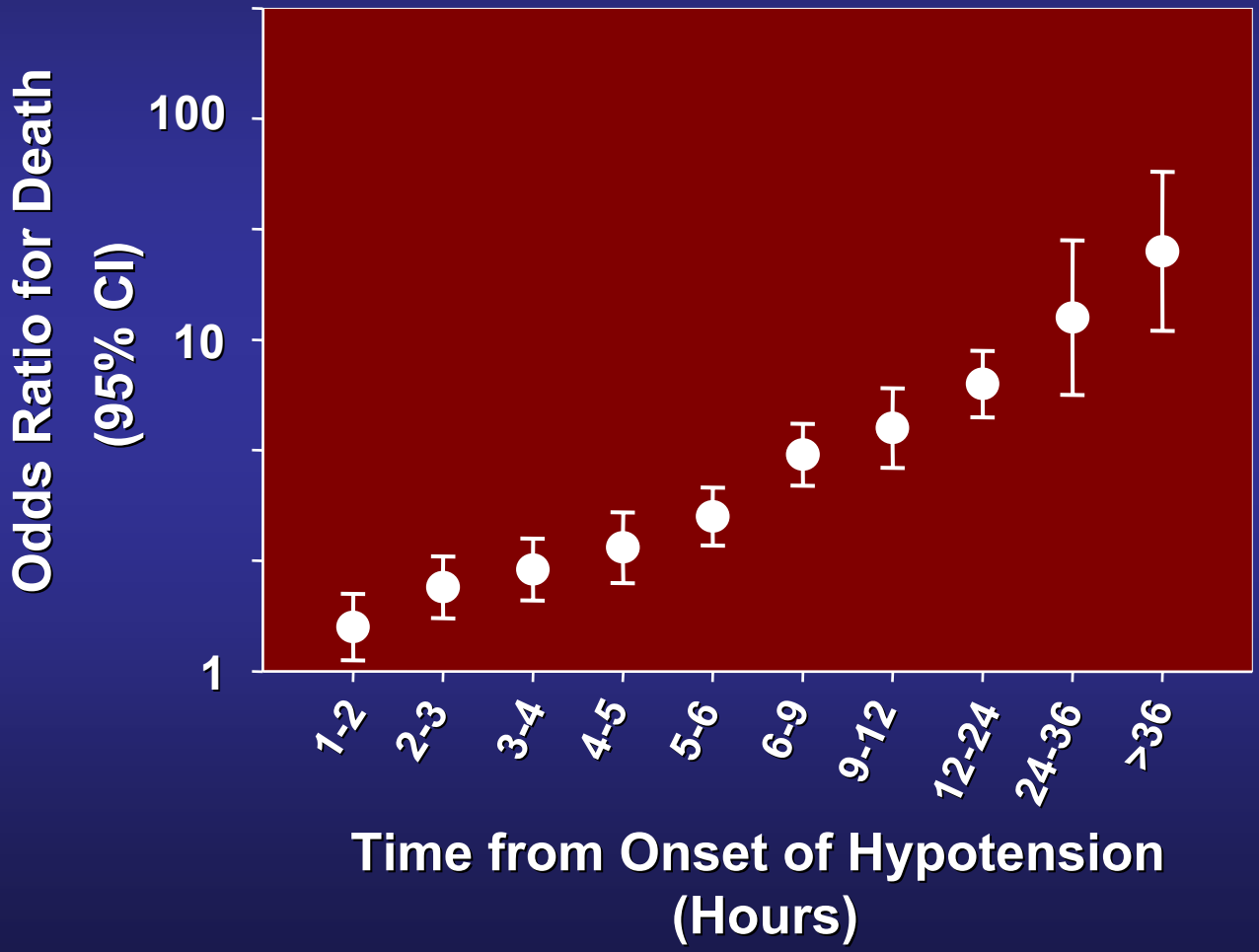
HeN Marrow Die

+ LPS

HeJ Marrow Live

- Michalek, *J.Infect.Dis.* 141:55, 1980

Impact of Delayed Antibiotic Therapy on Clinical Outcome



-Kumar, *Crit Care Med 34:1589, 2006*

Impact of Source Control in 1170 Patients with Sepsis

28 Day Mortality		
Adequate	Inadequate	p.
31.4% (303/964)	42.7% (88/206)	0.003
Odds Ratio 0.61 (0.45-0.83)		

Treatment of infection is necessary, but not sufficient, for the successful management of sepsis

Impact of Infection on ICU Outcome

Infectious Status	ICU Stay (Days)	Mortality Percent	p.
None (N=123)	3.7±0.1	3.3	….
Primary Infection (N=56)	7.1±1.0	19.6	0.03
ICU-Acquired (N=51)	11.2±1.2	23.5	0.002

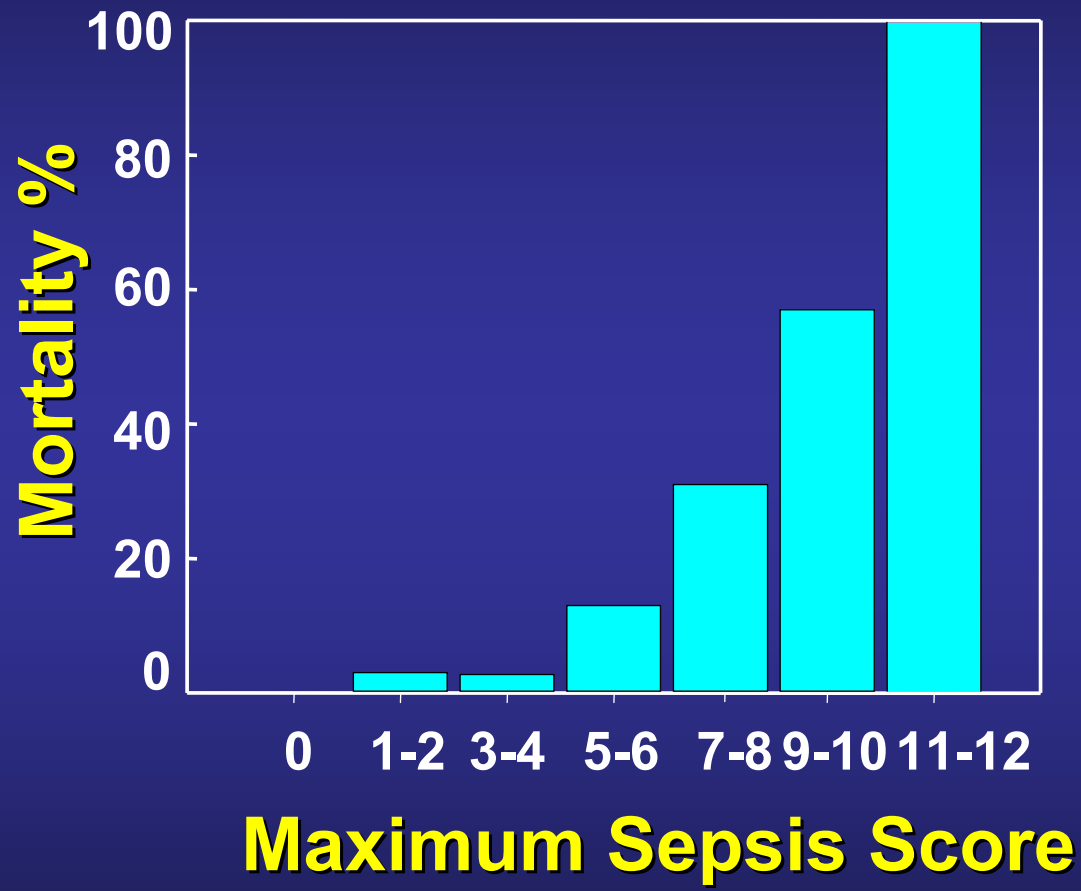
- Marshall & Sweeney *Arch Surg* 125:17, 1990

Sepsis Score

- Temperature
- White count
- Insulin requirements
- Cardiac output/SVR
- Change in GCS

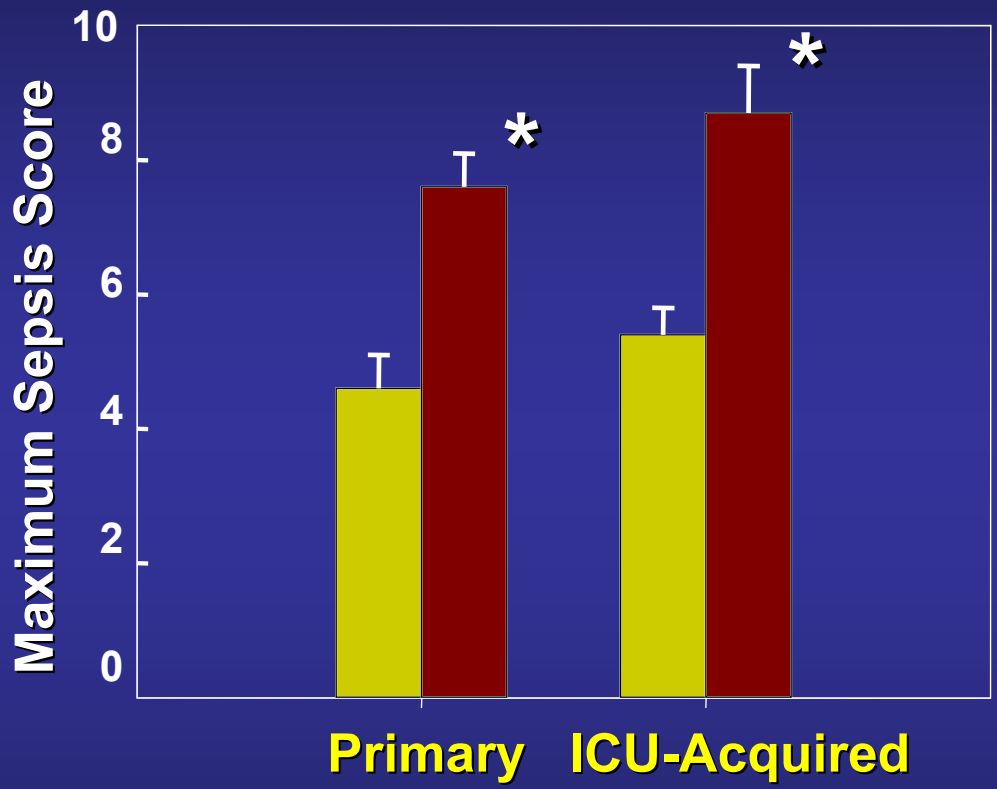
- Each scored 0-3
- Maximum score 15
- Scores calculated daily

Impact of Sepsis on ICU Outcome



- Marshall & Sweeney *Arch Surg* 125:17, 1990

Sepsis Scores in Patients with Infection



- Marshall & Sweeney *Arch Surg* 125:17, 1990

Infections in Patients with Sepsis Scores =>7

	% of Patients		
	Survivors	Non-Survivors	p.
Infection			
Primary	38.1	46.7	NS
ICU-Acquired	76.2	60	NS
None	14.3	13.2	NS
Pneumonia	47.6	53.3	NS
Peritonitis	33.3	40	NS
Bacteremia	42.9	20	NS
Sepsis Score	7.7±0.2	8.9±0.4	<0.01

- Marshall & Sweeney *Arch Surg* 125:17, 1990

Why did he die?

Sepsis

Uncontrolled infection

↓

Excessive inflammation

↓

Immune suppression

↓

Organ dysfunction

↓

Death

Why did he die?

Sepsis

?

Susceptibility to LPS is Transferred with Bone Marrow Cells

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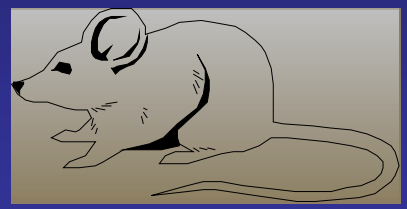
(Resistant)



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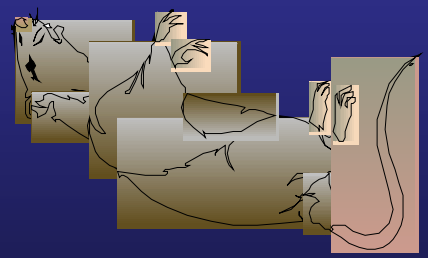

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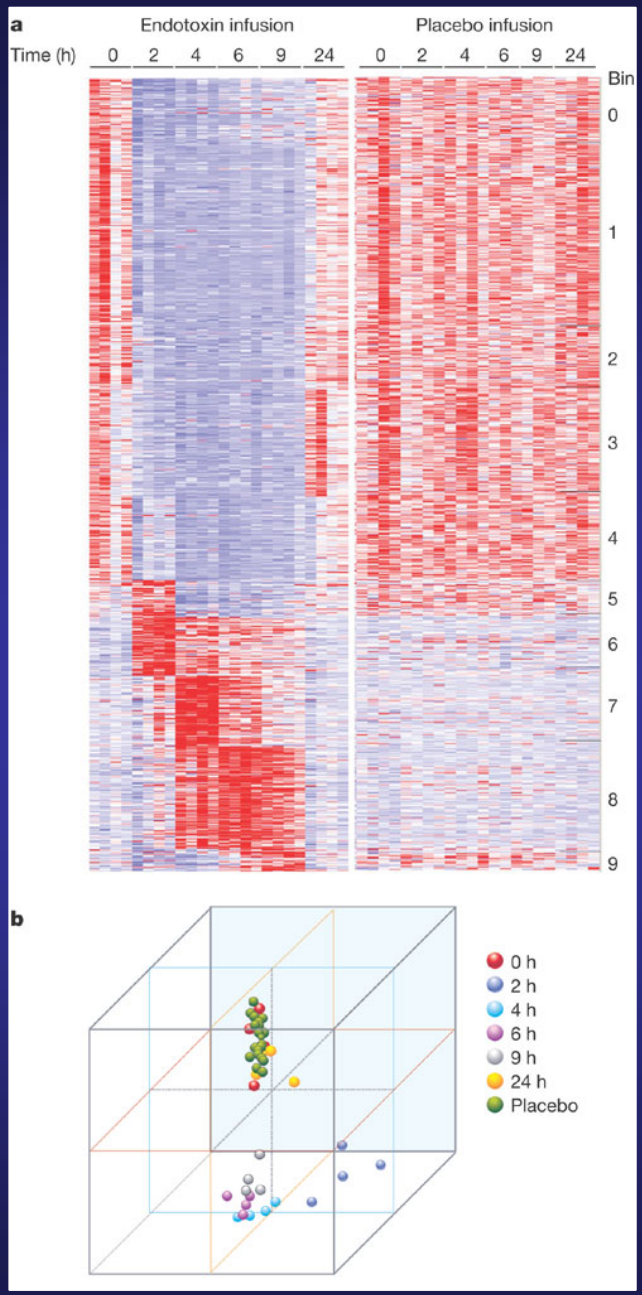


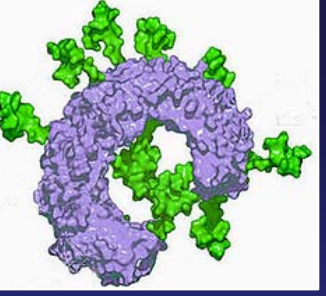
LPS challenge in human volunteers causes altered expression of 3714 distinct genes.

- Calvano, *Nature* 437:1032, 2005

Mediators of Lethality in Murine Endotoxemia

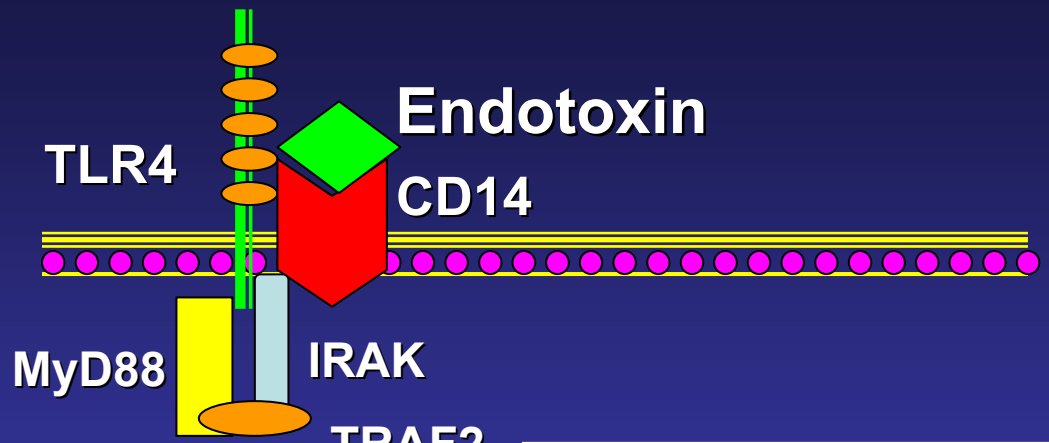
Cytokines	IL-1, IL-12, IL-18 TNF, IFNγ, TGFβ, LIF,MIF, G-CSF, HMGB-1, MIP-1α, MFP-14, LBP, PTH-RP IL-1ra, IL-4, IL-10, IL-13, IFNα, HGF, LIF, CRP, MCP-1, BPI, CAP18, TSG-14, VLDL, VIP, C3, C4, melatonin
Receptors	TNFr p55, IL-1r, PAFr, LECAM-1, TREM-1, LDLr, CD11a, CD14 VIPr, Adenosine A3r
Non-proteins	PAF, PLA_2 Vitamin B12, Vitamin D3
Signal transduction	hck, COX-2, p38, jnk, NFκB, iNOS, caspase-3 Stat4, Stat6, IκB, HSP70, hemoxygenase
Coagulation Factors	PAI 1, Tissue Factor TFPI, APC

- Marshall *Nature Rev Drug Disc* 2:391, 2003



Toll-like Receptors

TLR2	Lipoteichoic acid, bacterial lipoprotein, Injured tissue
TLR3	Double-stranded RNA
TLR4	Endotoxin, elastase, heparan, HSP60, oxidized phospholipids
TLR5	Flagellin
TLR6	*Mycoplasma* lipopeptide
TLR7	Imiquod, viral DNA
TLR8	Viral DNA, single-strand RNA
TLR9	Bacterial DNA



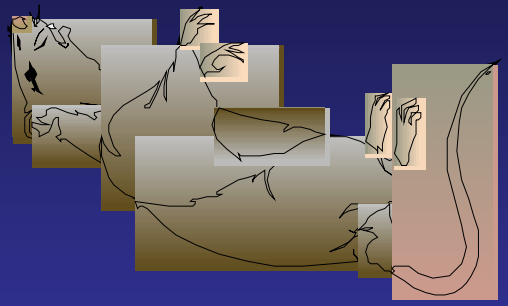
MAP Kinases: Erk, p38, Jnk
PI3 Kinase

NFkB

Pro-inflammatory genes:
IL-1, TNF

PAF, Nitric oxide,
Coagulation

Tissue ischemia,
Cell necrosis,
Apoptosis



???

Corticosteroids Reduce Mortality in Septic Shock (N=172)

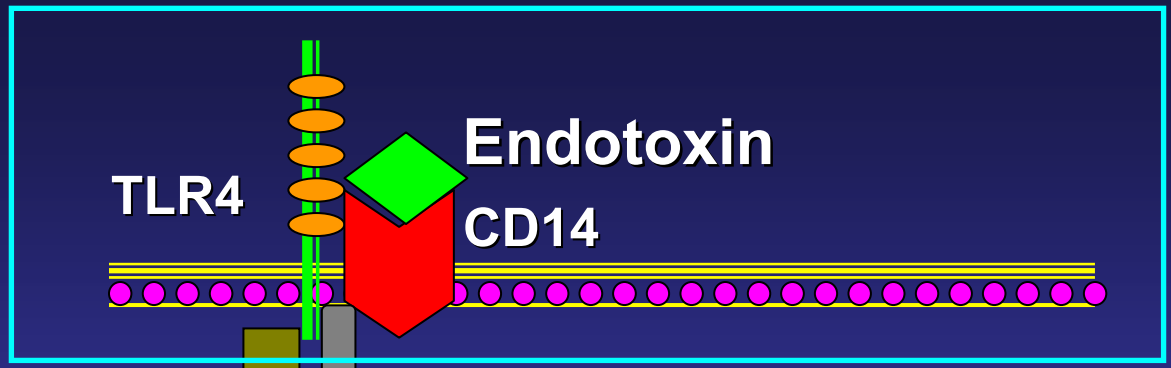
	30 Day Mortality
Control	38.4%
Methylprednisolone	11.6%
Dexamethasone	9.3%

- Shumer, *Ann Surg* 184:333, 1976

Effect of J5 Anti-serum in Gram Negative Bacteremia (N=304)

	Mortality		
	Placebo	J5	p.
Positive blood cultures	38%	24%	0.041
Hypotension	52%	32%	0.028
Shock	76%	46%	0.009

- Ziegler, *N.Engl.J.Med.* 307:1225, 1982



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IL-1, TNF

PAF, Nitric oxide,
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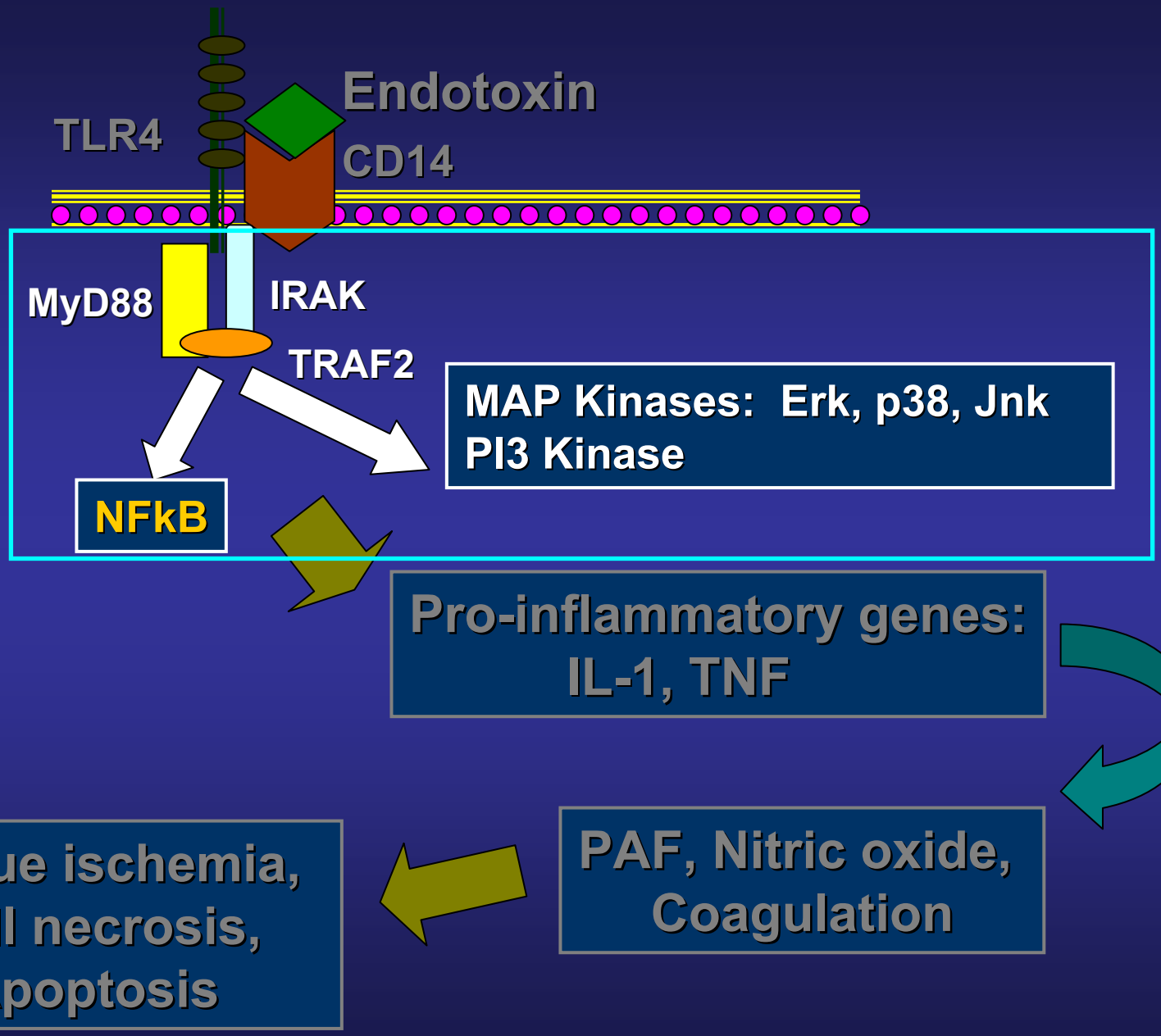
Tissue ischemia,
Cell necrosis,
Apoptosis

Therapies Targeting Endotoxin

TLR4 Antagonists	E5564 (Eisai) Others
CD14 Antagonists	IC14
Anti-LPS Strategies	Antibodies: J5, HA-1A, E5 $rBPI_{21}$ Polymyxin B dextran HDL, taurolidine Alkaline phosphatase Lipid emulsion Extracorporeal removal


Endotoxin
TLR4
CD14
MyD88
IRAK
TRAF2
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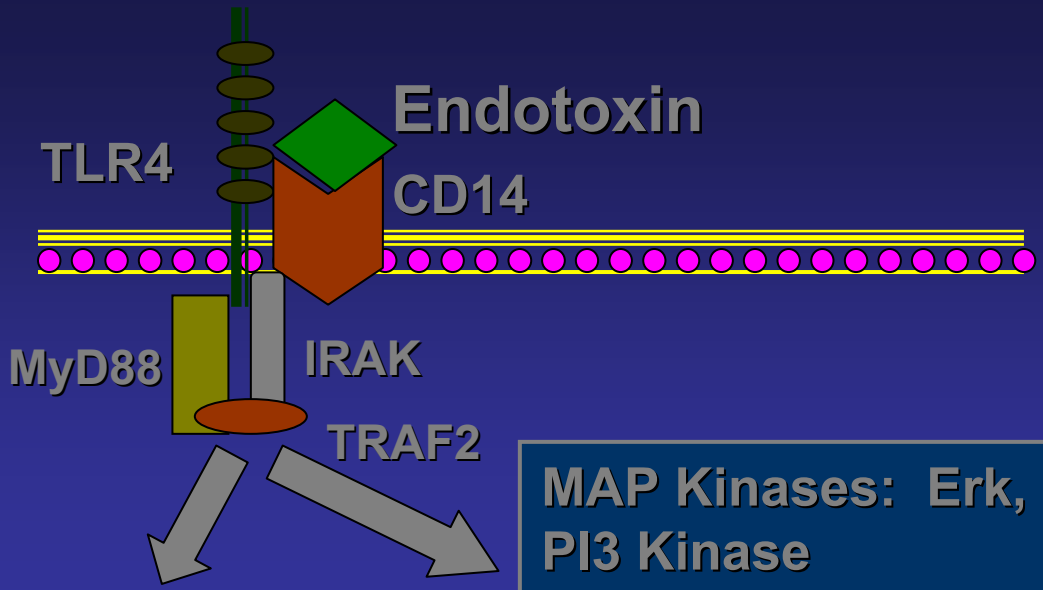

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Neutralization of Pro-Inflammatory Cytokines in Sepsis

Interleukin-1 Receptor Antagonist

3 Studies; 1688 patients

28 Day Mortality

Odds Ratio: 0.80 (0.65-0.99)

p=0.04

Neutralization of Pro-Inflammatory Cytokines in Sepsis

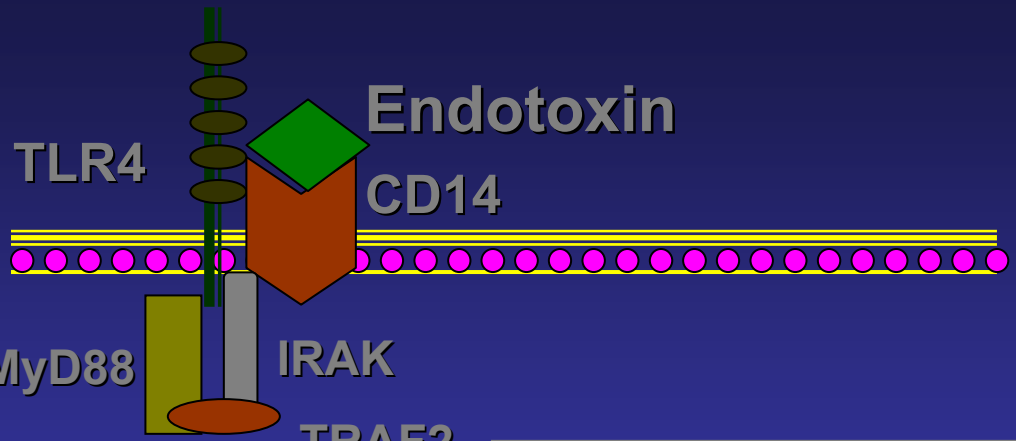
Anti-TNF Antibodies

8 Studies; 6500 patients

28 Day Mortality

Odds Ratio: 0.93 (0.87-0.99)

p=0.02



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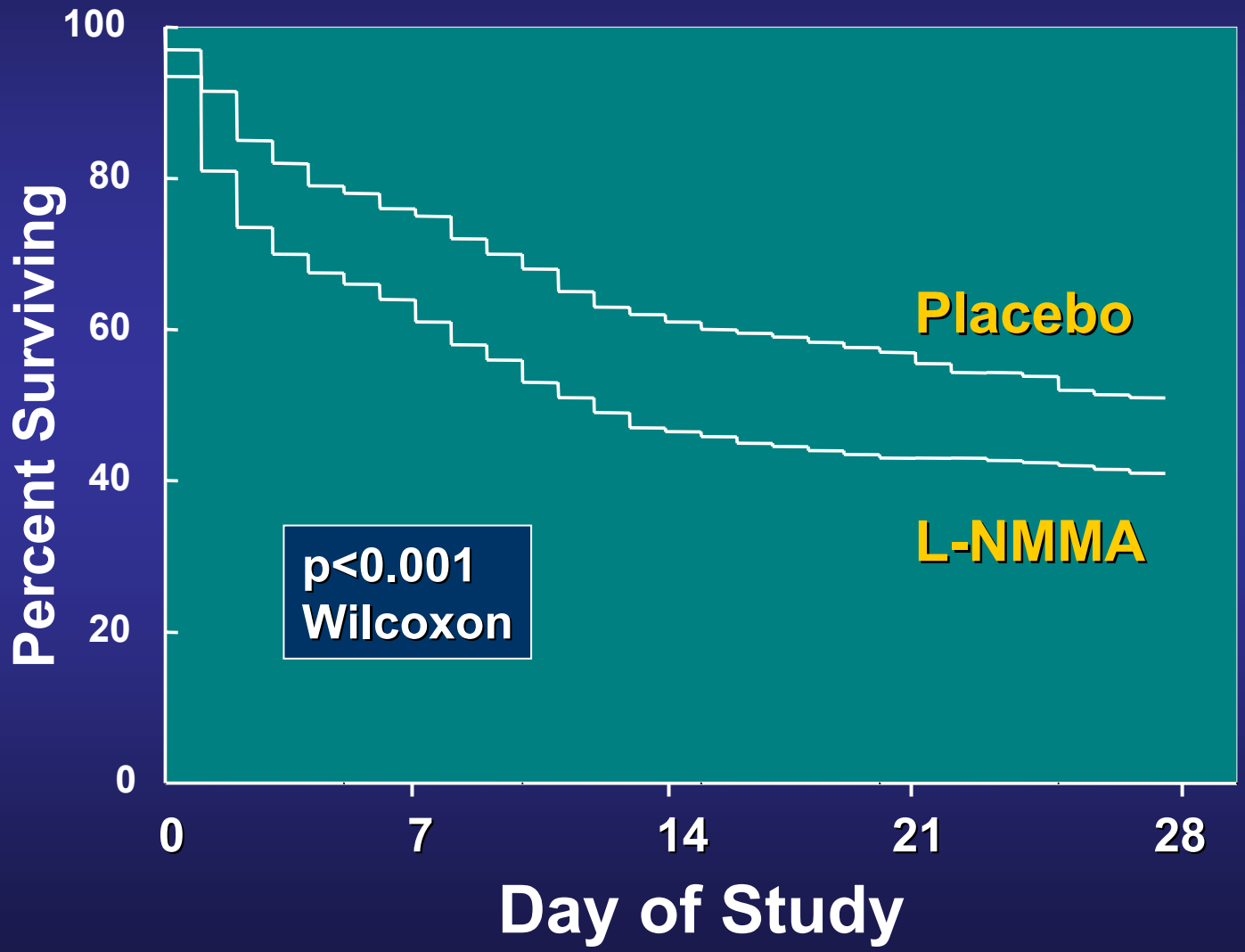
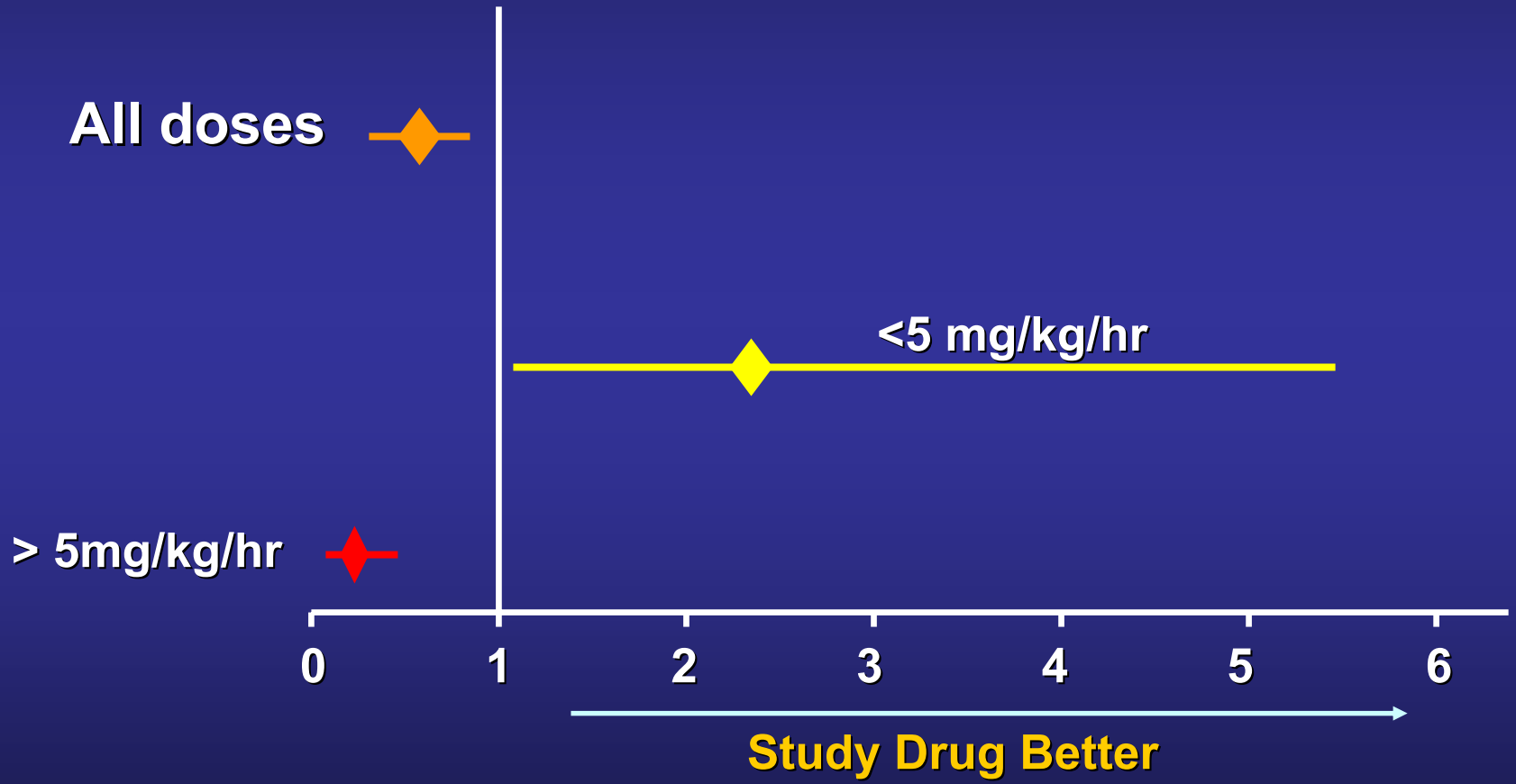
Effects of L-NMMA on Survival in Septic Shock



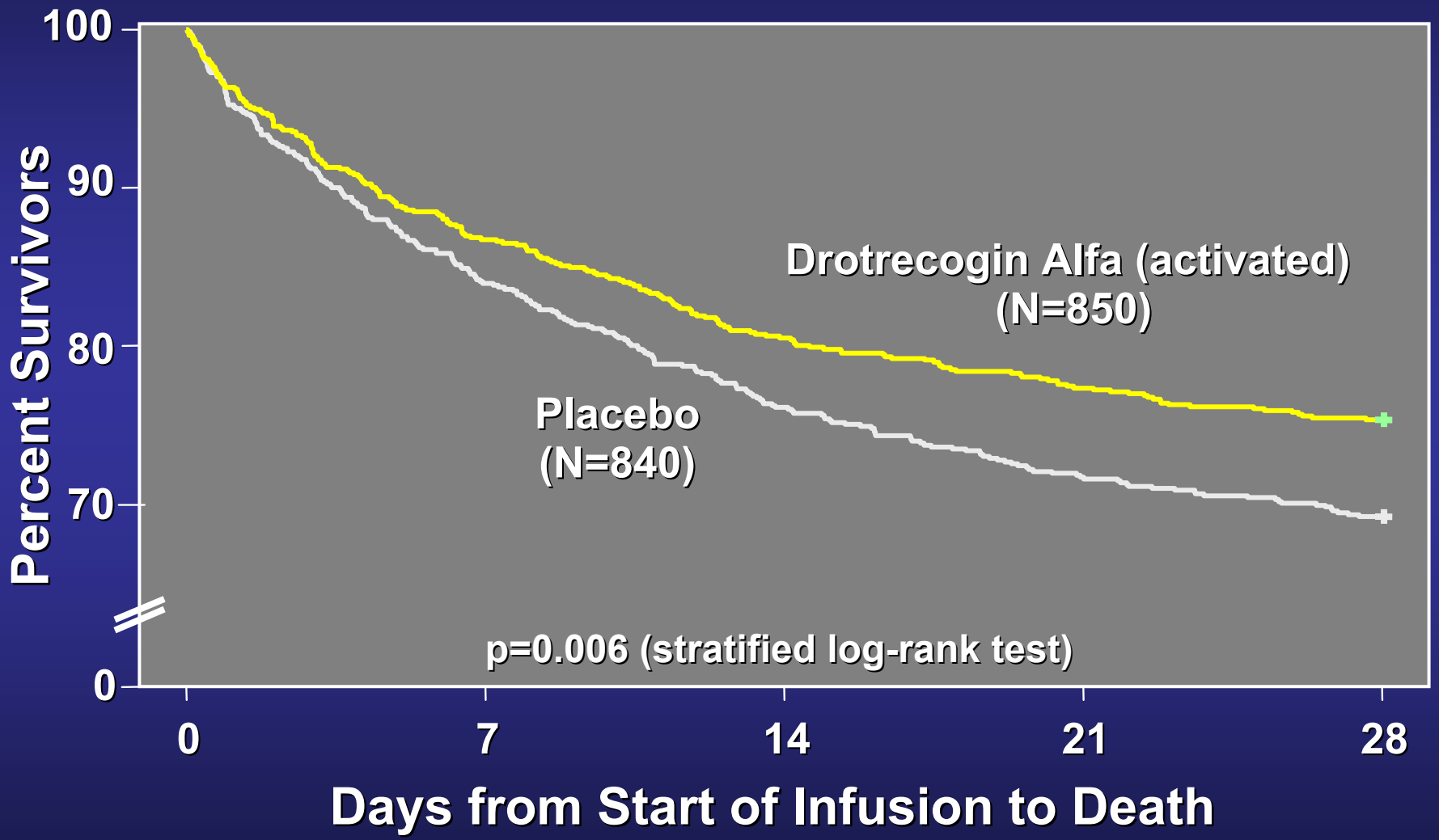
- Lopez, *Crit Care Med* 32:21, 2004

Dose-dependent Effects of L-NMMA on Survival

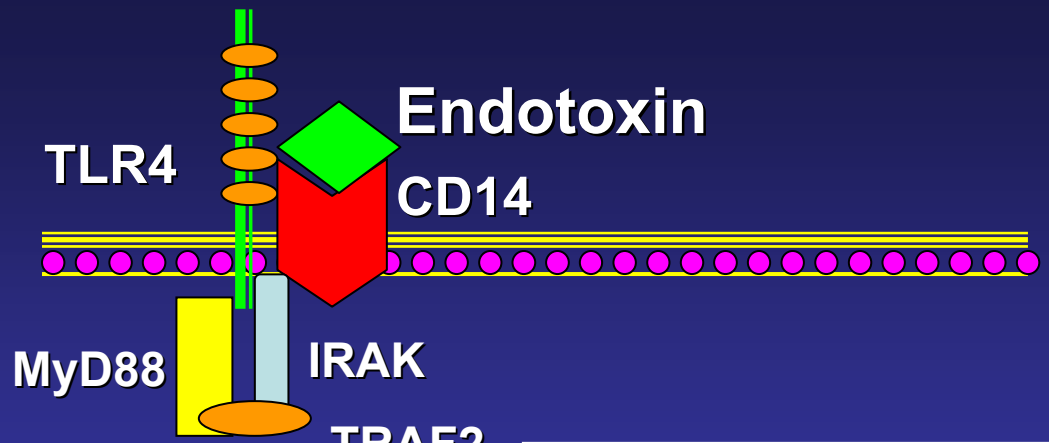


- Lopez, *Crit Care Med* 32:21, 2004

PROWESS: DrotAA Improved Survival



- Bernard et al; *NEJM* 344:649, 2001



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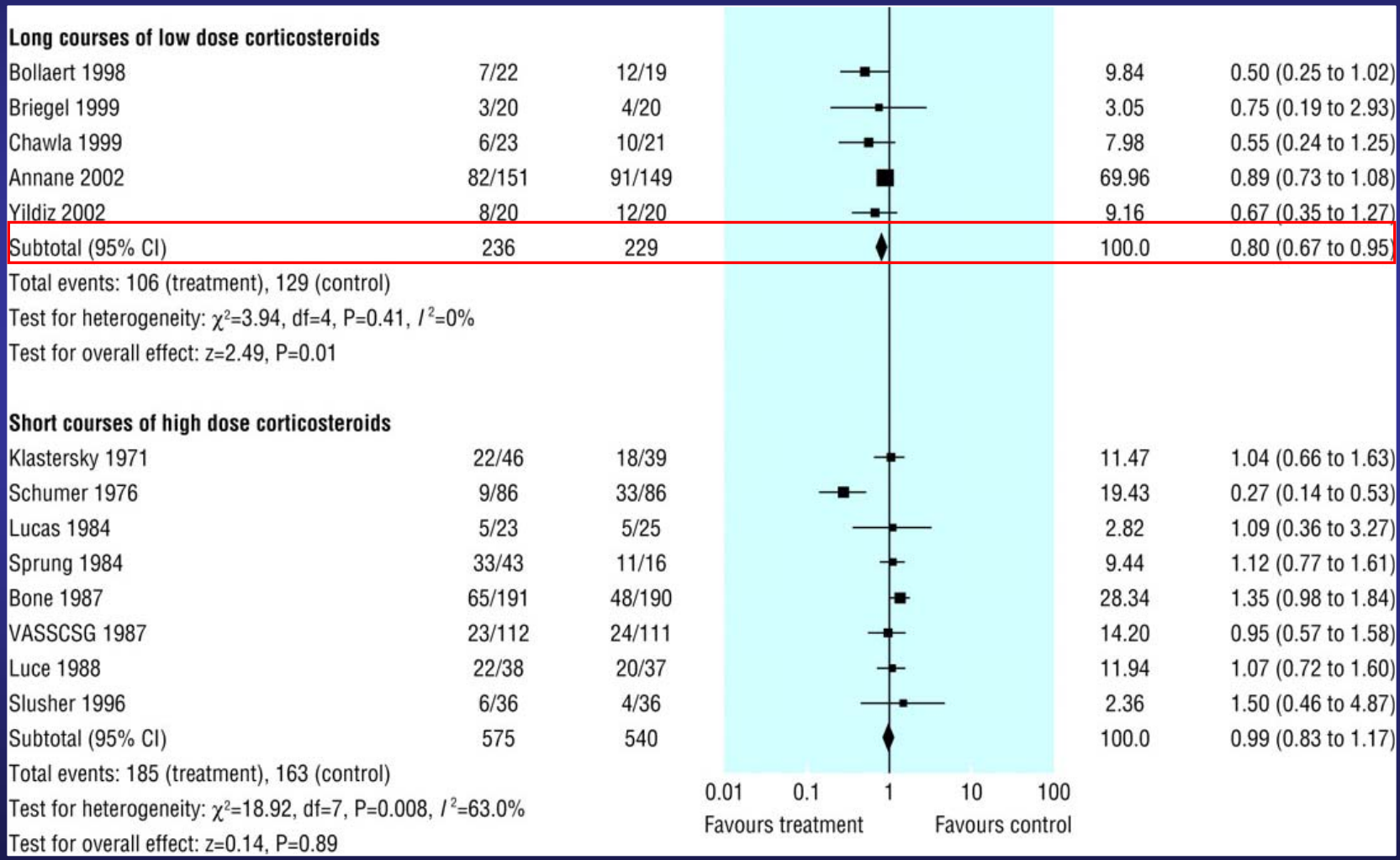
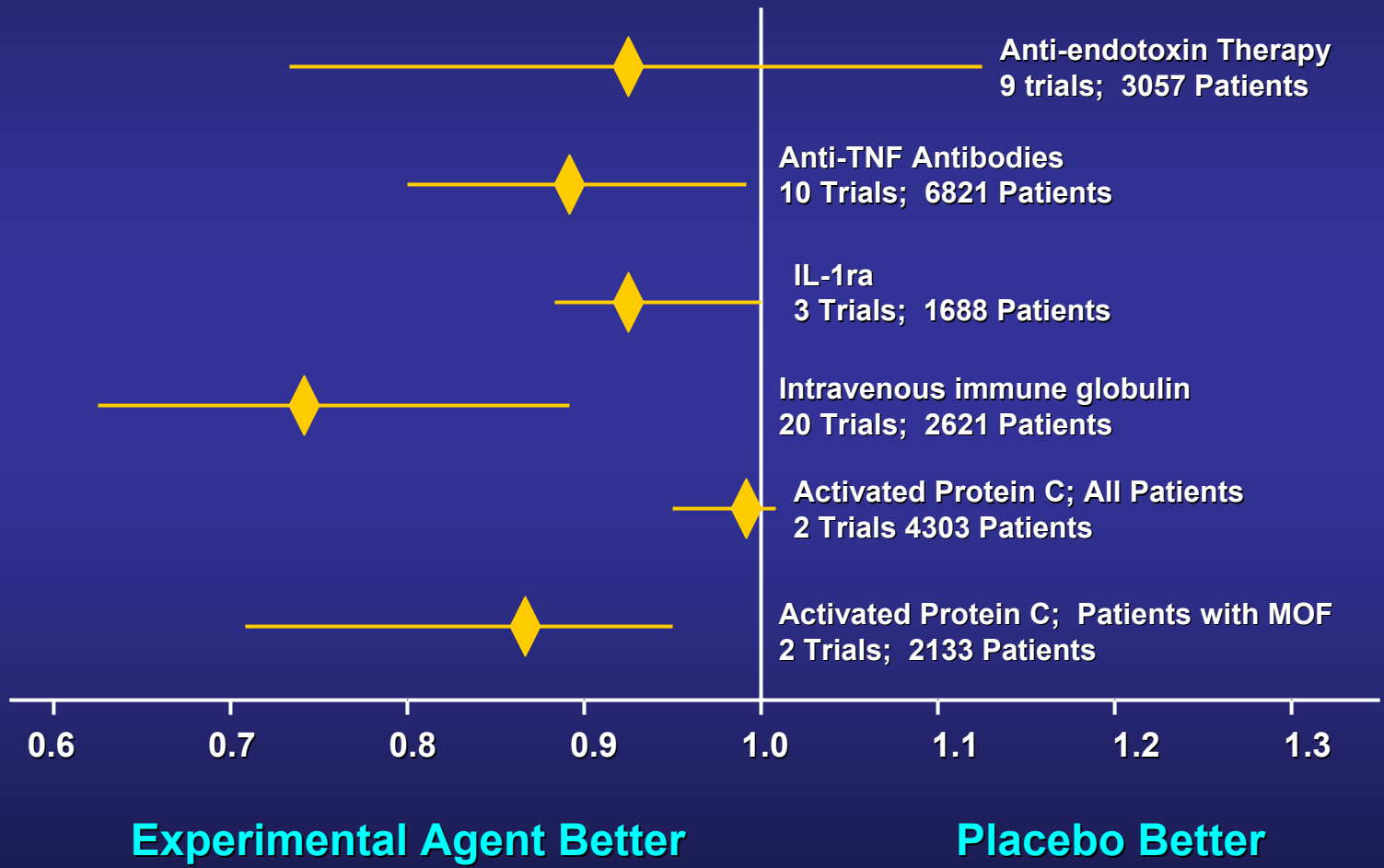
Corticosteroids in Septic Shock: A Meta-analysis



Long courses of low dose corticosteroids				
Bollaert 1998	7/22	12/19	9.84	0.50 (0.25 to 1.02)
Briegel 1999	3/20	4/20	3.05	0.75 (0.19 to 2.93)
Chawla 1999	6/23	10/21	7.98	0.55 (0.24 to 1.25)
Annane 2002	82/151	91/149	69.96	0.89 (0.73 to 1.08)
Yildiz 2002	8/20	12/20	9.16	0.67 (0.35 to 1.27)
Subtotal (95% CI)	236	229	100.0	0.80 (0.67 to 0.95)
Total events: 106 (treatment), 129 (control)				
Test for heterogeneity: χ^2=3.94, df=4, P=0.41, I^2=0%				
Test for overall effect: z=2.49, P=0.01				
Short courses of high dose corticosteroids				
Klastersky 1971	22/46	18/39	11.47	1.04 (0.66 to 1.63)
Schumer 1976	9/86	33/86	19.43	0.27 (0.14 to 0.53)
Lucas 1984	5/23	5/25	2.82	1.09 (0.36 to 3.27)
Sprung 1984	33/43	11/16	9.44	1.12 (0.77 to 1.61)
Bone 1987	65/191	48/190	28.34	1.35 (0.98 to 1.84)
VASSCSG 1987	23/112	24/111	14.20	0.95 (0.57 to 1.58)
Luce 1988	22/38	20/37	11.94	1.07 (0.72 to 1.60)
Slusher 1996	6/36	4/36	2.36	1.50 (0.46 to 4.87)
Subtotal (95% CI)	575	540	100.0	0.99 (0.83 to 1.17)
Total events: 185 (treatment), 163 (control)				
Test for heterogeneity: χ^2=18.92, df=7, P=0.008, I^2=63.0%				
Test for overall effect: z=0.14, P=0.89				

Annane D *BMJ* 2004;329:480

Adjuvant Therapy in Sepsis



But …

- Impact is modest
- Indications for use poorly defined

Sepsis Syndrome
(Bone et al; 1987)

Suspected or proven infection, in association with:

- Tachycardia
- Tachypnea
- Hyper- or hypothermia
- Dysfunction of one or more organs

Sepsis Syndrome

- 24 year old man with penetrating injury to colon
- 86 year old woman with CHF and Enterococcal UTI
- 51 year old man with COPD exacerbation; *Candida* in sputum

An Alternate Model for Sepsis Research

- A generic clinical phenotype
- Therapy-specific entry criteria
- Severity staging

An Alternate Model for Sepsis Research

- A generic clinical phenotype
- Therapy-specific entry criteria
- Severity staging

What is the Clinical Phenotype?

- Elevated heart rate
- Rapid respiratory rate
- Temperature changes
- Altered white cell count

The Cardinal Signs of Inflammation

- Rubor
- Calor
- Dolor
- Tumor
- Functio laesa

Galen of Pergamon
129 – 210 AD

Rubor	Hypotension, oliguria
Calor	Fever
Dolor	Confusion, drowsiness, pain
Tumor	Edema, dyspnea
Functio laesa	Organ dysfunction, coagulopathy

An Alternate Model for Sepsis Research

- A generic clinical phenotype
- Therapy-specific entry criteria
- Severity staging

Cytokine Levels in Human Sepsis

	Median (pg/ml)	Range
TNF	83	7 – 57,151
IL-6	965	8 – 1,553,435
IL-8	2130	16 – 651,338

- MONARCS, Unpublished

An Alternate Model for Sepsis Research

- A generic clinical phenotype
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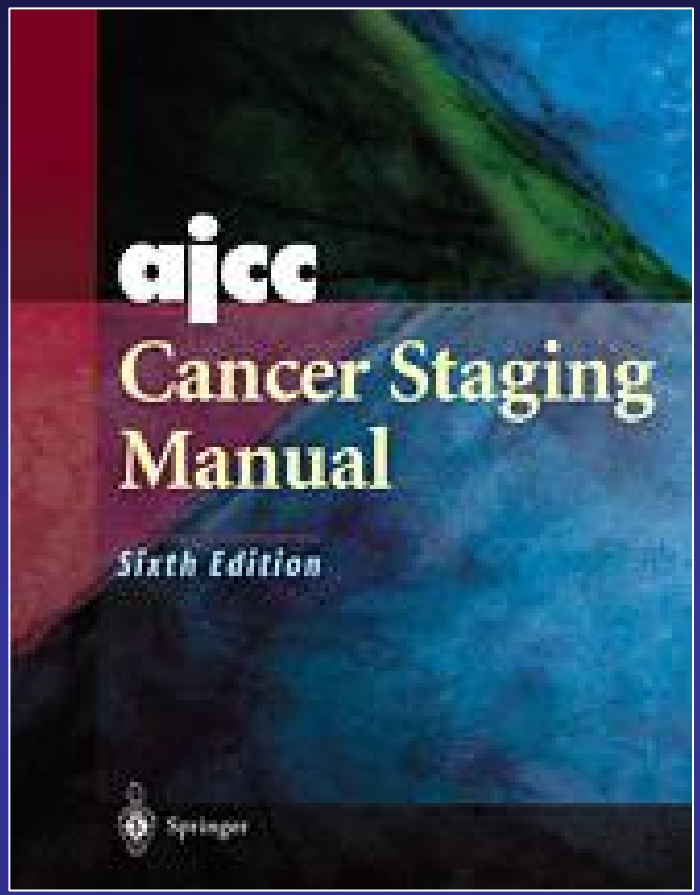
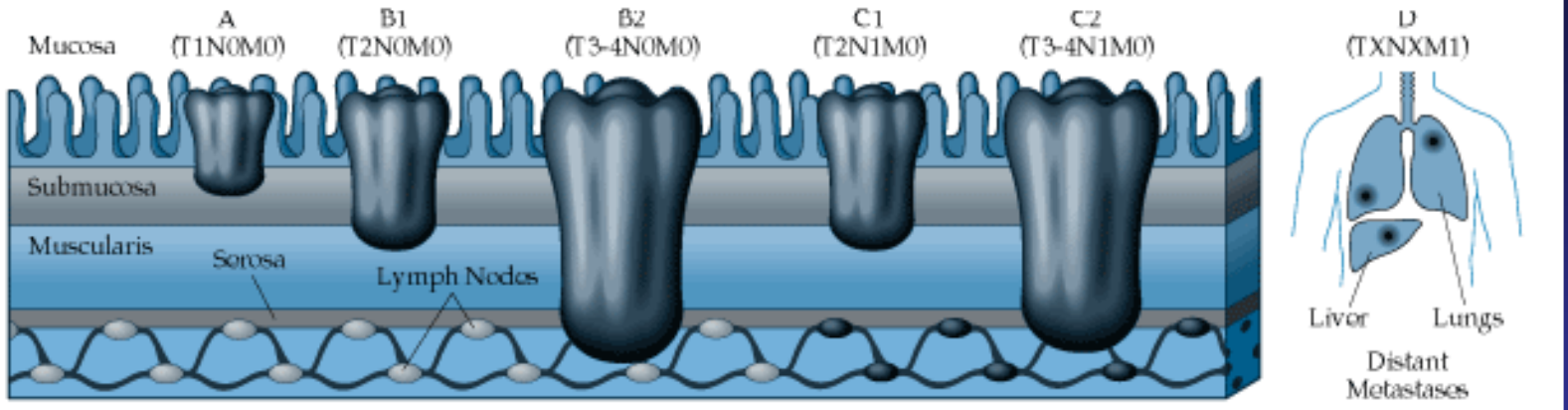
- Severity staging



Cancer staging stratifies by:

- **Prognosis**
- **Potential to respond to treatment**



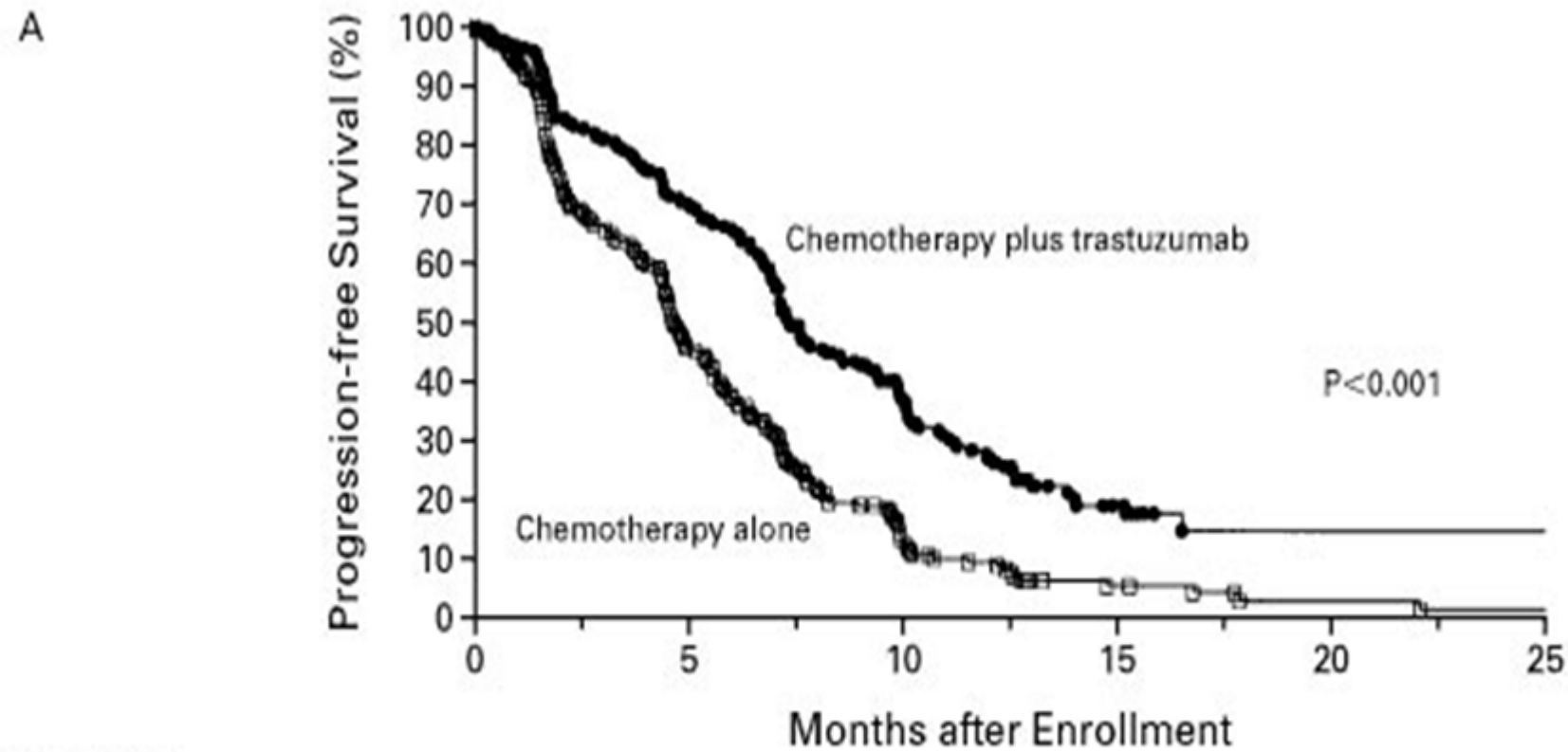
Staging of and Prognosis for Colorectal Cancer

Insult	Inflammatory Response		Organ Dysfunction
Infection	Adaptive	Injurious	Inflammation
Injury, Ischemia			Iatrogenic

- Histologically confirmed, completely excised breast cancer
- Her2 overexpression by immunohistochemistry or FISH
- Tumor >1 cm; node positive or node negative

- Romond, *N Engl J Med 353:1673, 2005*

Trastuzumab Improves Disease-Free Survival in HER2 Positive Breast Cancer



No. at Risk				
Chemotherapy plus trastuzumab	235	152	63	15
Chemotherapy alone	234	103	25	6

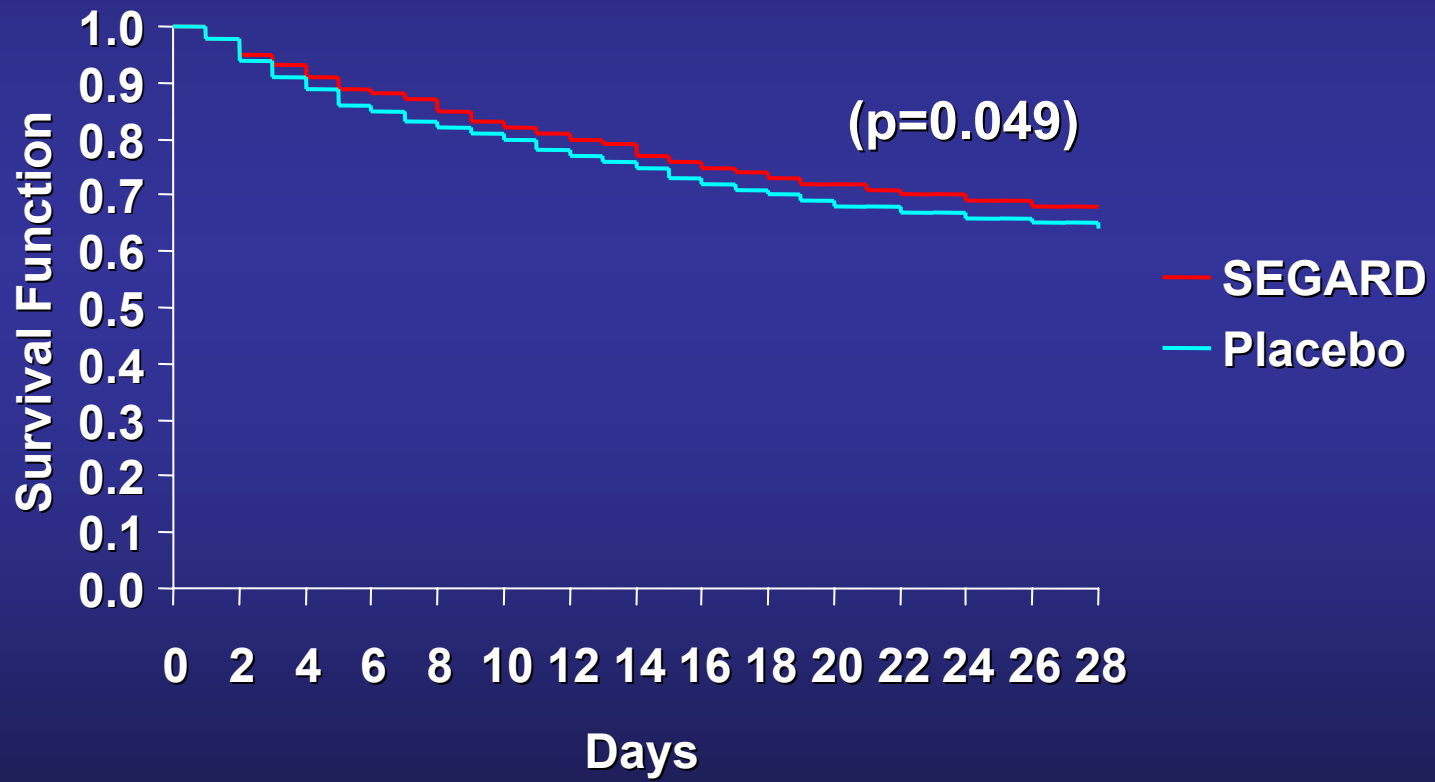
- Slamon, *N Engl J Med 344:783, 2001*

The PIRO Concept

- Predisposition
- Insult
- Response
- Organ dysfunction

- Crit Care Med 31:1250, 2003

Effects of Neutralization of TNF with MAK 195F on 28 Day All-cause Mortality



"Genetic and environmental influences on premature death in adult adoptees"

- Sorensen TI et al; *N Engl J Med* 318:727, 1988

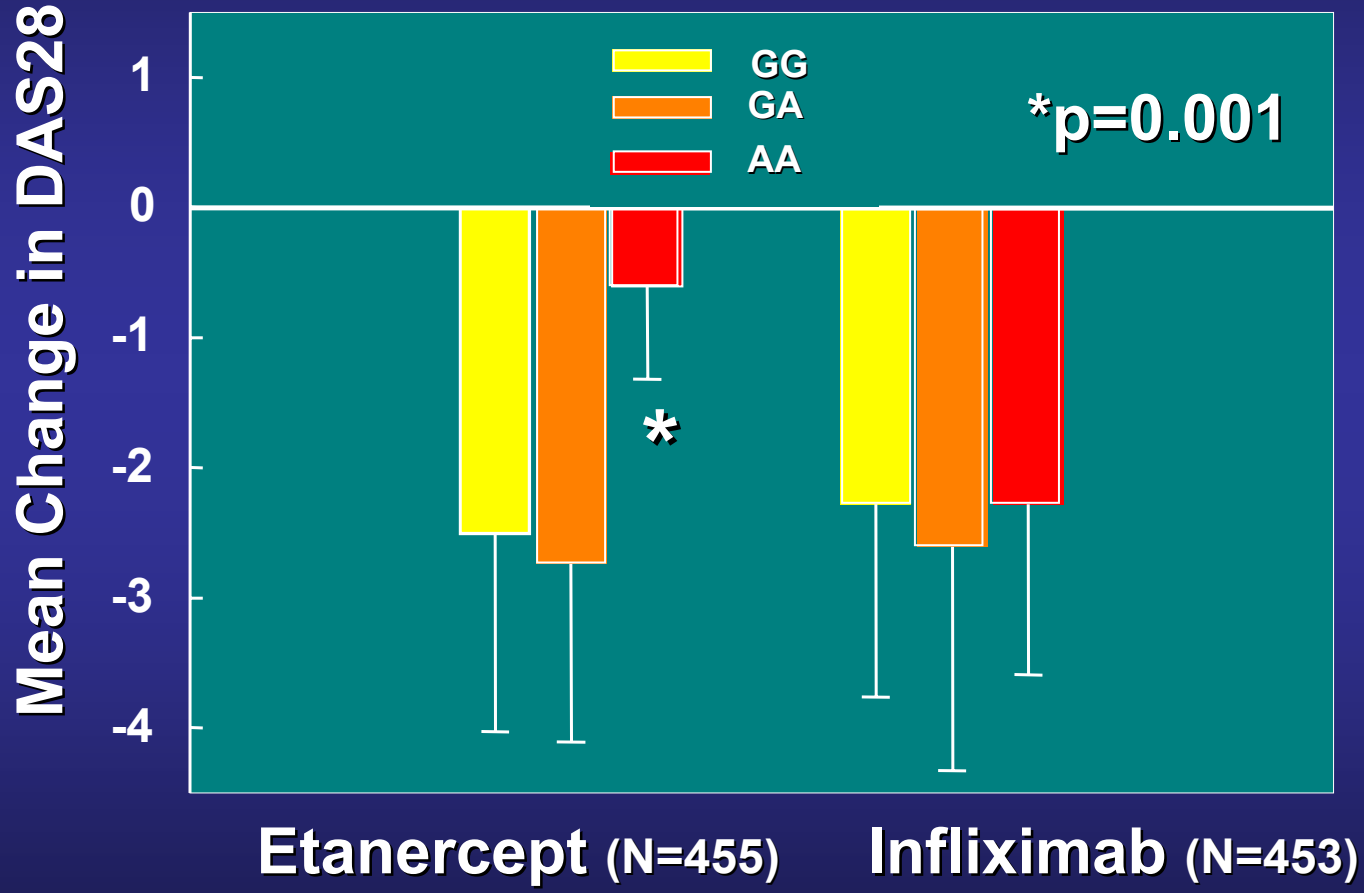
- 960 Danish families
- Children born 1924 – 1926
- Early adoption into biologically unrelated family
- Early deaths in children and parents

Risk of Death: Cause of Death of Biologic Parent

	RR	95% CI
All causes	1.71	1.14 – 2.57
Natural causes	1.98	1.25 – 3.12
Infection	5.81	2.47 – 13.7
Cardiovascular	4.52	1.32 – 15.4
Cancer	1.19	0.16 – 8.99

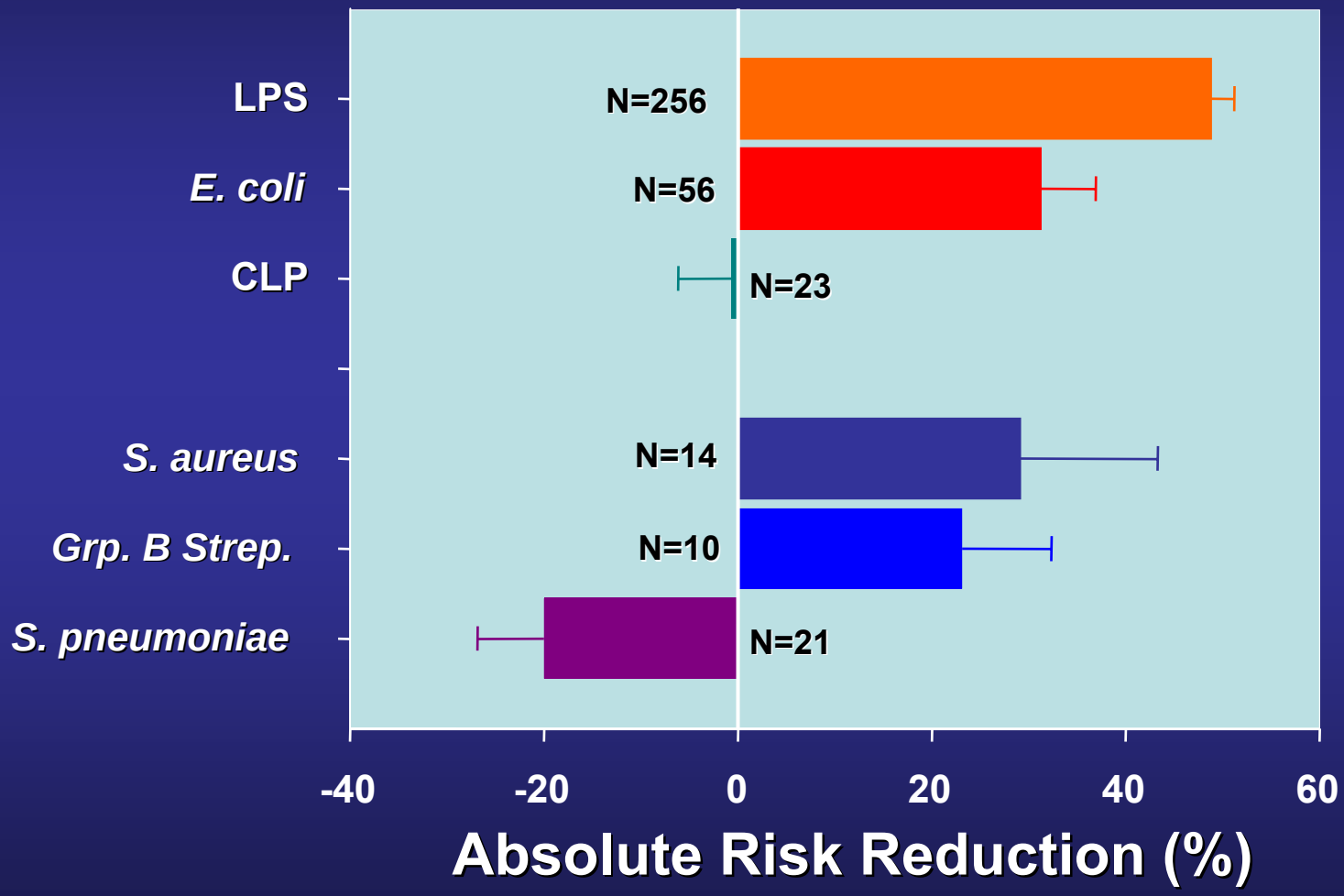
- Sorensen et al *N Engl J Med* 318:727, 1988

The TNF -308A/G Polymorphism Modifies the Response to Anti-TNF Therapy

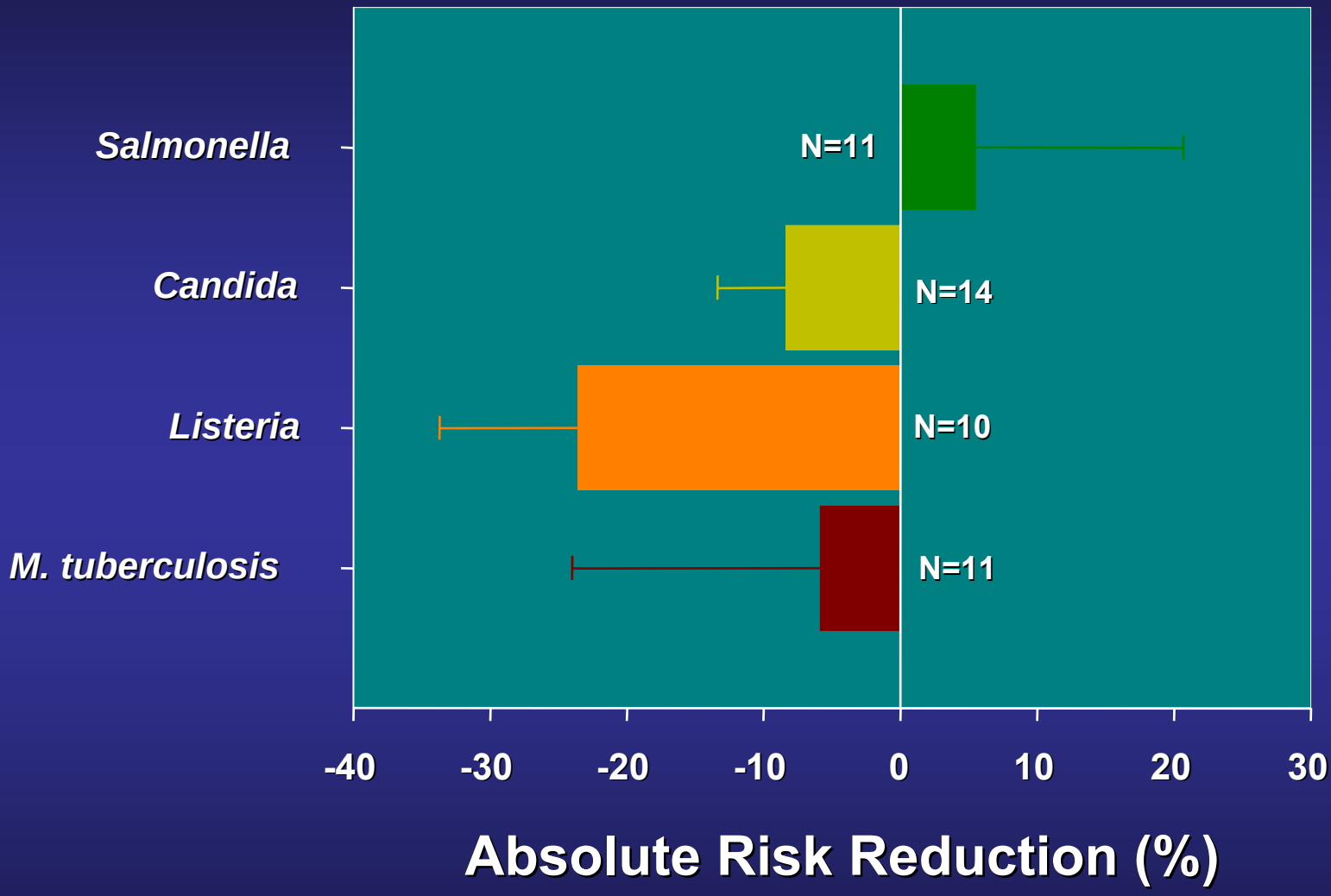


- Maxwell, *Hum Mol Genet* 17:3532, 2008

Influence of Infectious Challenge on Response to Neutralization of TNFα

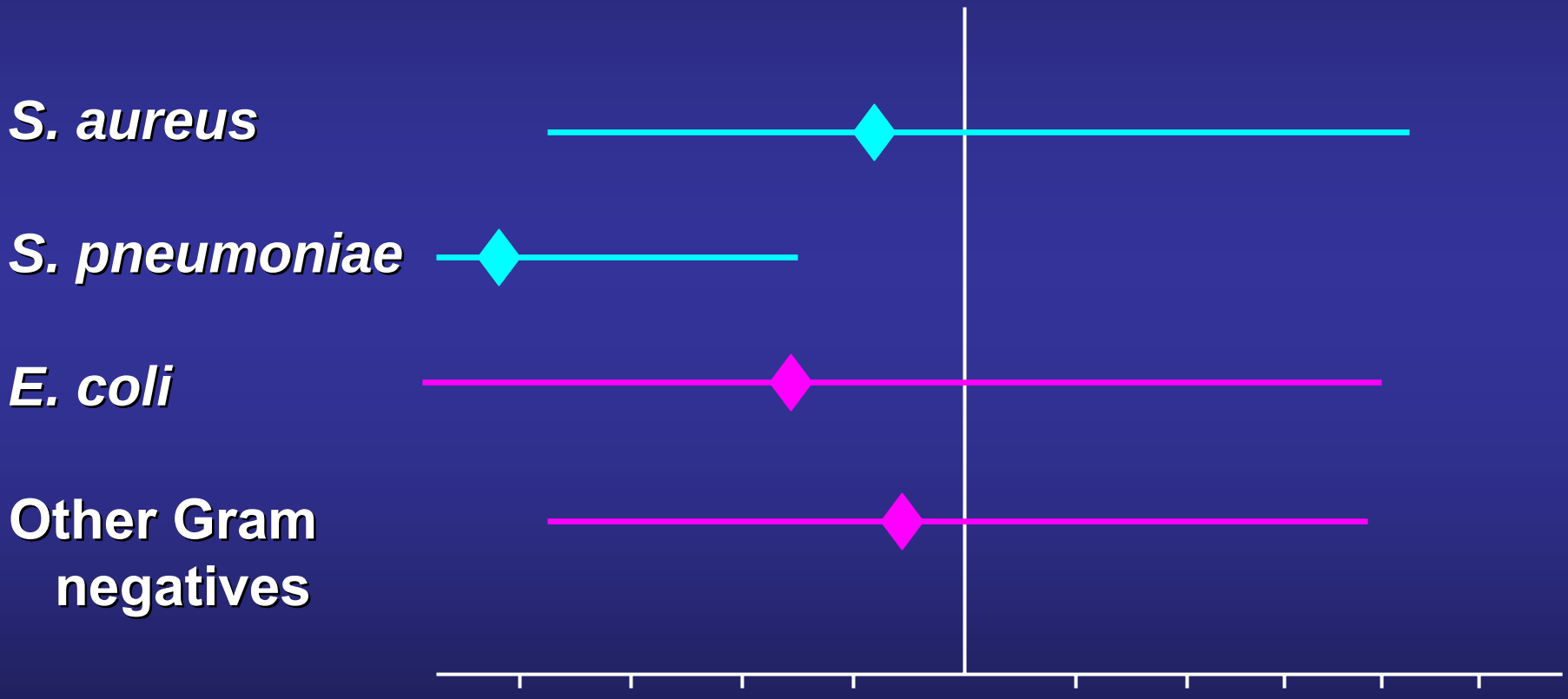


- Lorente & Marshall, *Shock* 24 (Suppl):107, 2005



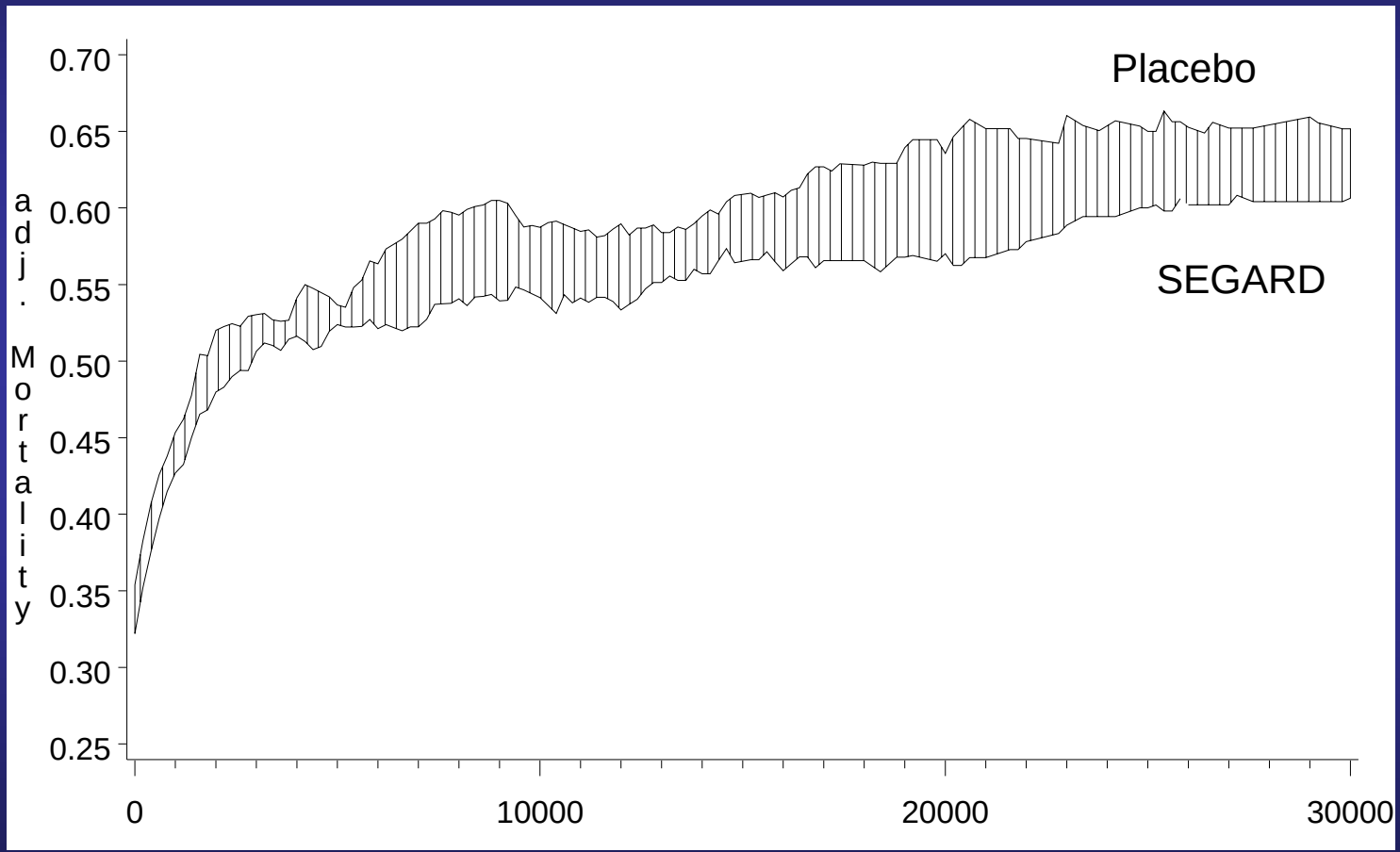
- Lorente & Marshall, *Shock* 24 (Suppl):107, 2005

Response to Drotrecogin α by Causative Organism



Opal et al; *Clin Infect Dis 37:50, 2003*

Probability of Mortality by Baseline IL-6 Level

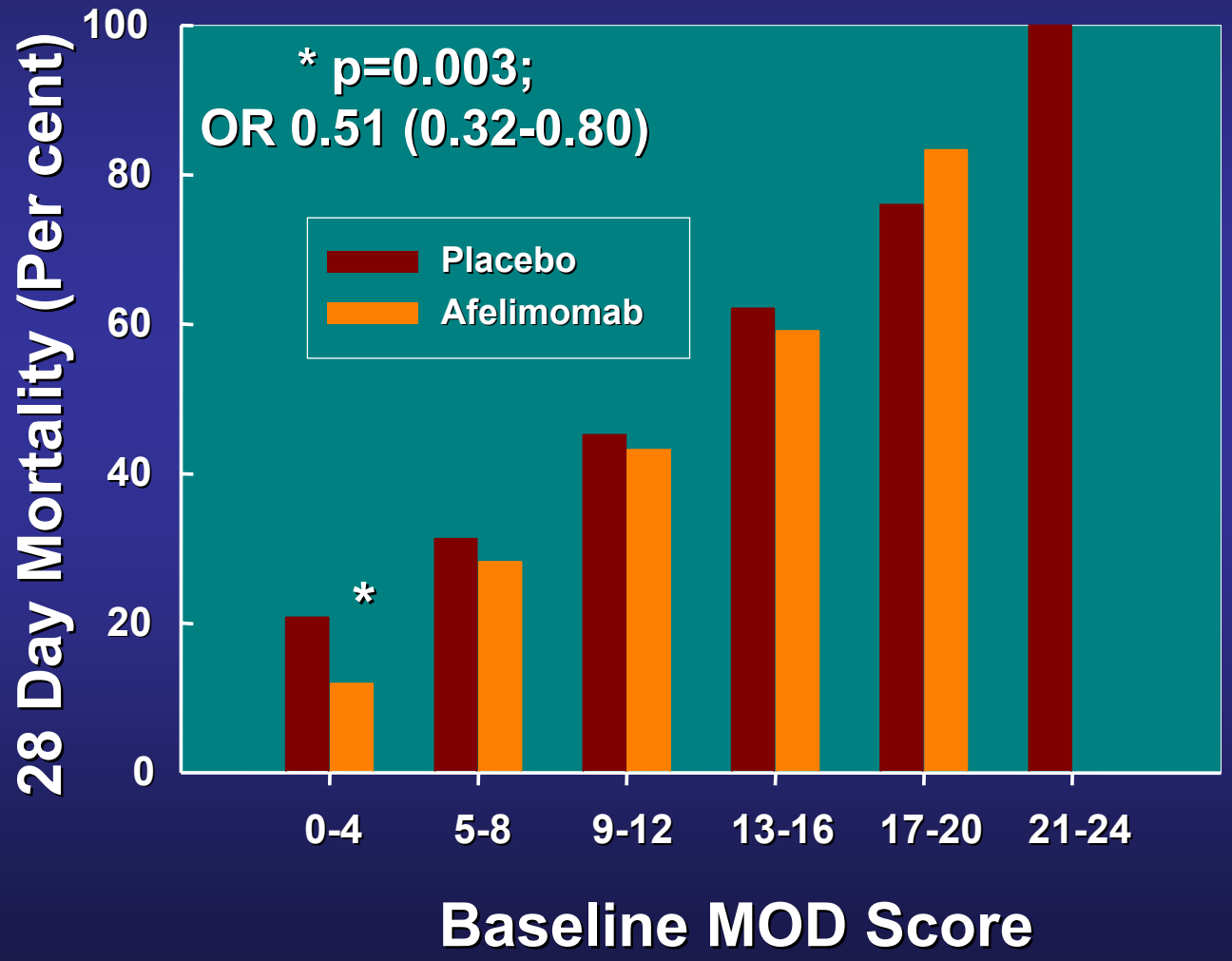


Impact of Organ Dysfunction on Response to Antibiotics

	ICU Mortality		
	Adequate	Inadequate	p.
LOD > 4 (N=72)	21/36 (59%)	20/36 (56%)	0.81
LOD ≤ 4 (N=70)	2/27 (7%)	16/43 (37%)	0.006

- Clec'h, *Intensive Care Med* 30:1327, 2004

Anti-TNF is Most Efficacious in Patients without Organ Dysfunction



The Next Anti-TNF Trial

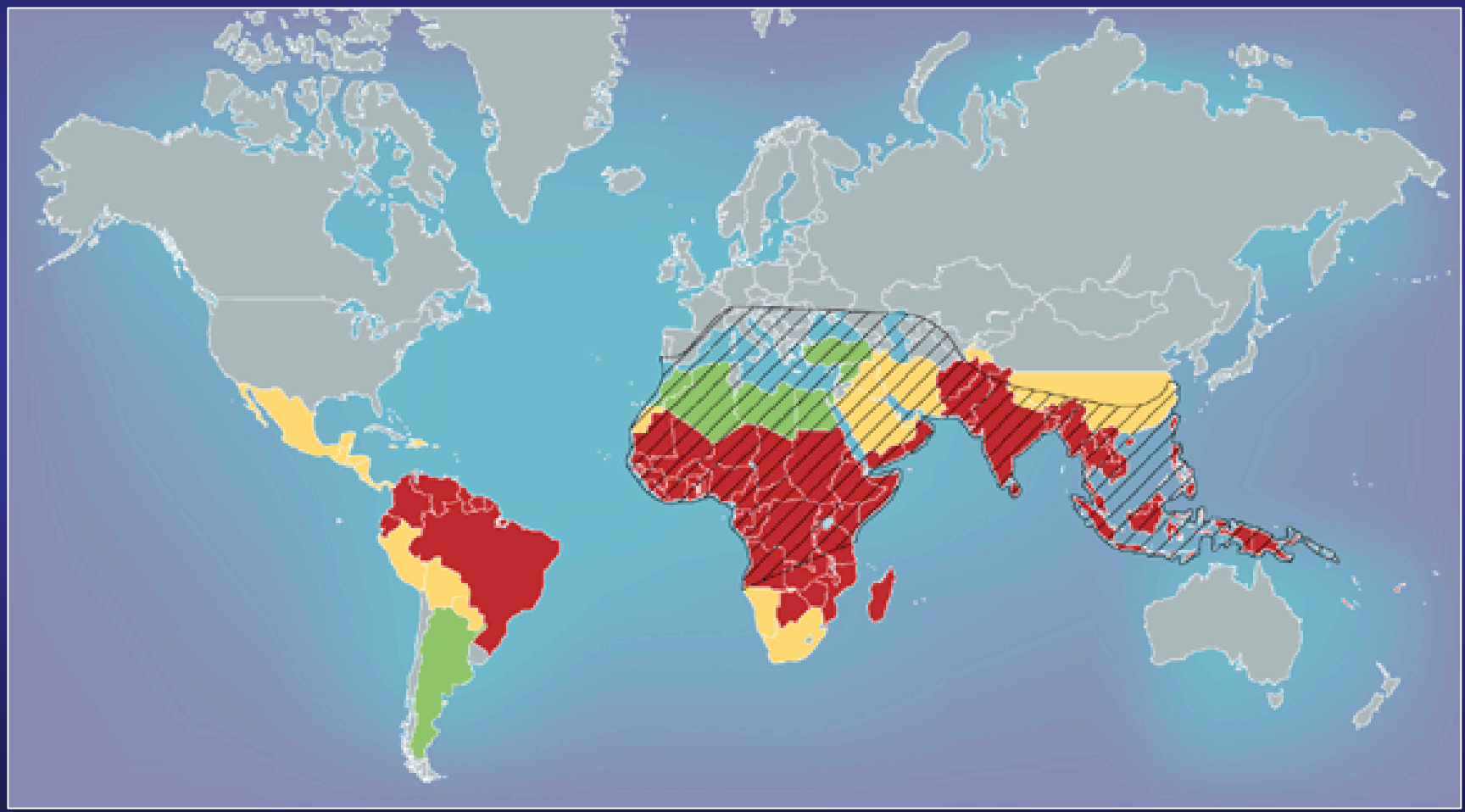
P: -308A promoter polymorphism

I: Acutely ill patient, exclude patients with fungal infection or CAP

R: Elevated IL-6

0: MOD/SOFA Score $\leq$ 8

Polymorphisms in the Hemoglobin Gene Arise in Regions Where Malaria is Endemic



Sepsis is the Leading Cause of Preventable Death

- Infection in the developed world
- Tuberculosis
- Malaria
- Childhood diarrhea
- HIV/AIDS

Surviving Sepsis Campaign

A global program to reduce mortality rates in severe sepsis

ESICM, ISF and SCCM

Partially funded by unrestricted educational grants from Baxter, Edwards, Philips and Lilly

Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock

R. Phillip Dellinger, MD; Jean M. Carlet, MD; Henry Masur, MD; Herwig Gerlach, MD, PhD; Thierry Calandra, MD; Jonathan Cohen, MD; Juan Gea-Banacloche, MD, PhD; Didier Keh, MD; John C. Marshall, MD; Margaret M. Parker, MD; Graham Ramsay, MD; Janice L. Zimmerman, MD; Jean-Louis Vincent, MD, PhD; Mitchell M. Levy, MD; for the Surviving Sepsis Campaign Management Guidelines Committee

Sponsoring Organizations: American Association of Critical-Care Nurses, American College of Chest Physicians, American College of Emergency Physicians, American Thoracic Society, Australian and New Zealand Intensive Care Society, European Society of Clinical Microbiology and Infectious Diseases, European Society of Intensive Care Medicine, European Respiratory Society, International Sepsis Forum, Society of Critical Care Medicine, Surgical Infection Society.

Objective: In 2003, critical care and infectious disease experts representing 11 international organizations developed management guidelines for severe sepsis and septic shock that would be of practical use for the bedside clinician, under the auspices of the

for death; with resolution of tissue hypoperfusion and in the absence of coronary artery disease or acute hemorrhage, targeting a hemoglobin of 7–9 g/dL; appropriate use of fresh frozen plasma and platelets; a low tidal volume and limitation of inspiratory plateau pressure strategy for

- *Crit Care Med* 32:858, 2004

Surviving Sepsis Campaign

- Global process change initiative based on “sepsis bundles”
- 15,022 patients enrolled
- 7% absolute, 5.4% relative mortality reduction ($p<0.001$)

The Future

- International large, unbiased natural history studies
- Clinical and biochemical characterization
- Extensive interdisciplinary collaboration
- Industry and peer review funding

Thank you!!