

Sepsis

Septic shock

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Occurrence of Severe Sepsis

- Annual incidence: ~750,000 cases in US
- 2.26 cases per 100 hospital discharges
- 51.1% received ICU care and 17.3% received IMC care
- Incidence and mortality increased with age
- Case fatality rate: 28%
- Economic burden
 - \$22,100 per case
 - ~\$16.7 billion nationally

Angus DC et al. 2001. Crit Care Med 29:1303-1310.

Reference Diseases

- Incidence in US (cases per 100,000)
 - AIDS¹ 17
 - Colon and rectal cancer² 48
 - Breast cancer² 112
 - Congestive heart failure³ ~196
 - Severe sepsis⁴ ~300
- Number of deaths in US each year
 - Acute myocardial infarction⁵ 218,000
 - Severe sepsis⁴ 215,000

¹Centers for Disease Control and Prevention. 2000. Incidence rate for 1999.

²American Cancer Society. 2001. Incidence rate for 1993-1997.

⁴Angus DC et al. 2001. Crit Care Med 29:1303-1310.

⁵National Center for Health Statistics. 2001.

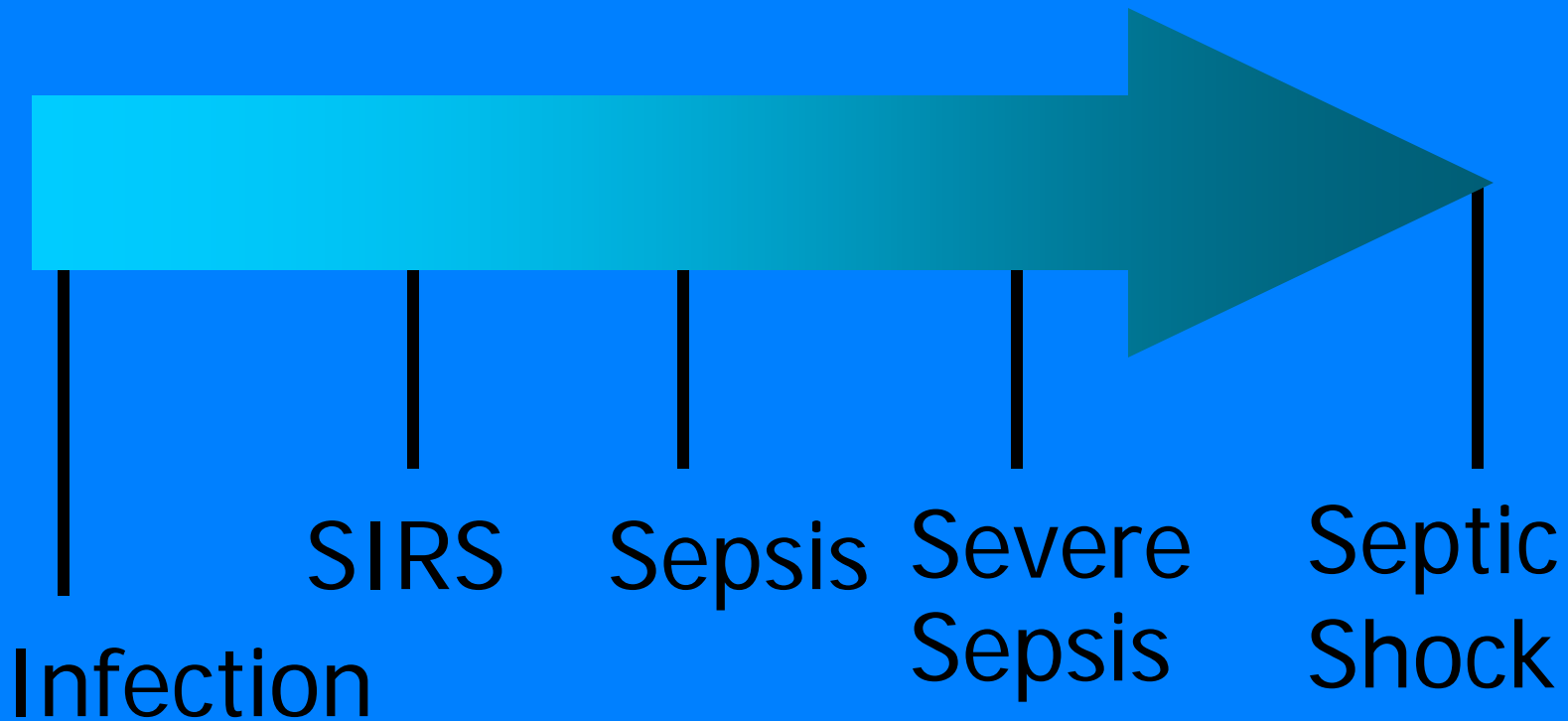
Sepsis on the Rise

- Incidence projected to rise during the next decade
 - Aging population especially in developed nations
 - Increased awareness and diagnosis
 - Immunocompromised patients e.g. cancer therapy, transplantation)
 - Invasive procedures (ventilators, catheters, prostheses)
 - Resistant pathogens

Angus DC et al. 2001. Crit Care Med 29:1303-1310.

Balk RA. 2000. Crit Care Clin 16(2):179-191

Definitions



Systemic Inflammatory Response Syndrome

- Systemic Inflammatory Response Syndrome (SIRS)--the beginning of illness

– ≥ 2 of the following:

- Temp $> 38^{\circ}\text{C}$ or $< 36^{\circ}\text{C}$
- Heart rate > 90 bpm
- Respiratory rate > 20 bpm
- WBC $> 12,000$, $< 4,000$ or bands $> 10\%$

Bone, et al. 1992. Chest 101:1644-1655

Sepsis

- Sepsis
 - SIRS + infection
- Severe sepsis
 - Sepsis with organ dysfunction, hypoperfusion or hypotension
- Septic Shock
 - Sepsis with hypotension and perfusion abnormalities despite adequate volume replacement

Mortality from Sepsis

Martin NEJM 2003

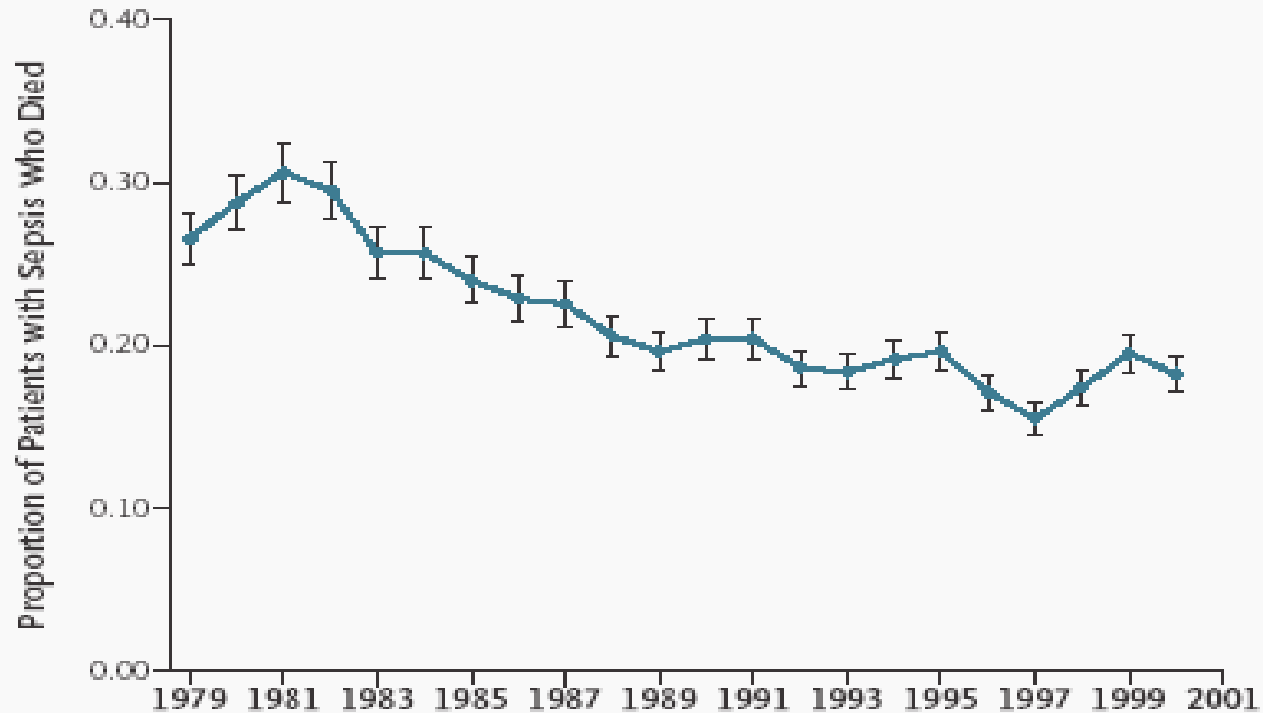


Figure 4. Overall In-Hospital Mortality Rate among Patients Hospitalized for Sepsis, 1979–2000.

Mortality averaged 27.8 percent during the first six years of the study and 17.9 percent during the last six years. The I bars represent the standard error.

Changes in the Documented Causes of Sepsis

Martin NEJM 2003

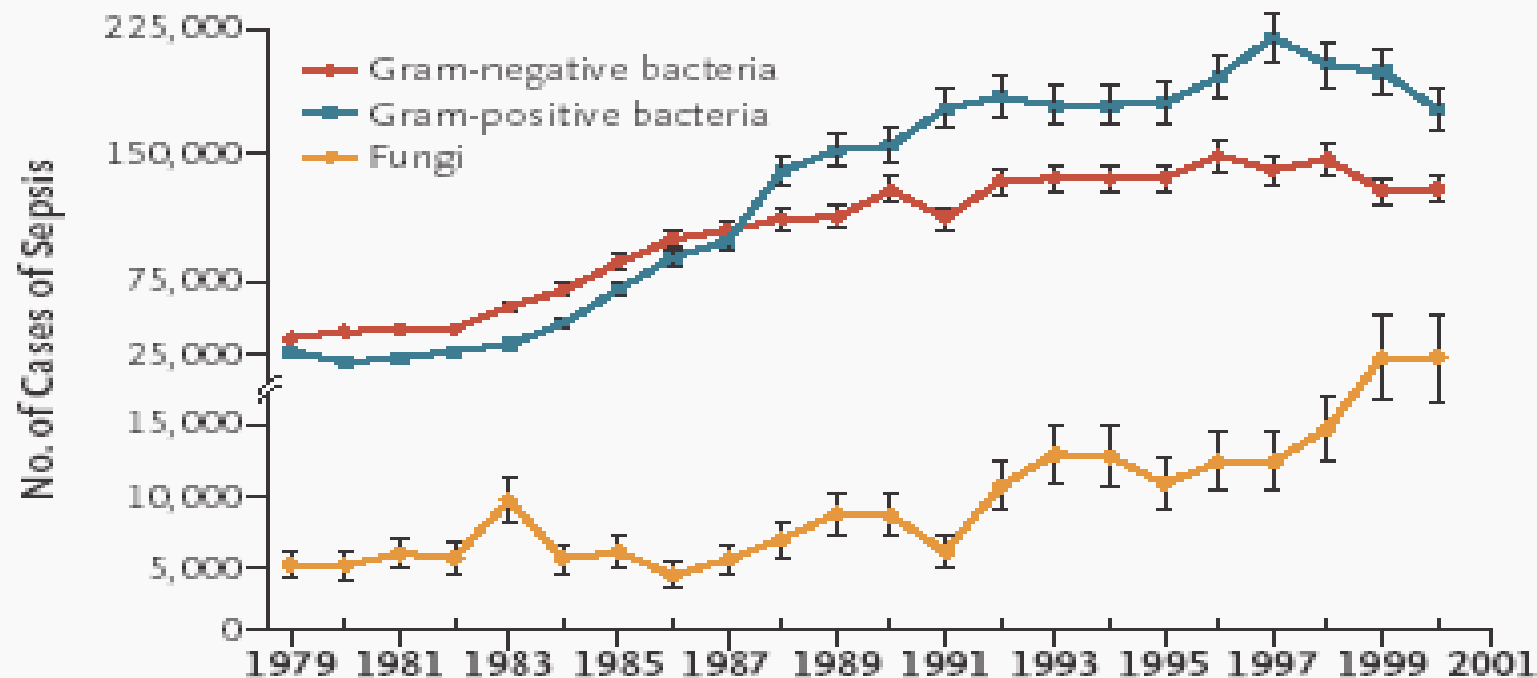


Figure 3. Numbers of Cases of Sepsis in the United States, According to the Causative Organism, 1979–2000.

Points represent the number of cases for the given year, and I bars the standard error.

Why do people die from Sepsis?

- Very few organisms produce toxins that cause death directly
 - Diphtheria
 - Tetanus, botulism
 - *Pseudomonas aeruginosa* ?
- Death from sepsis is mainly due to inflammation

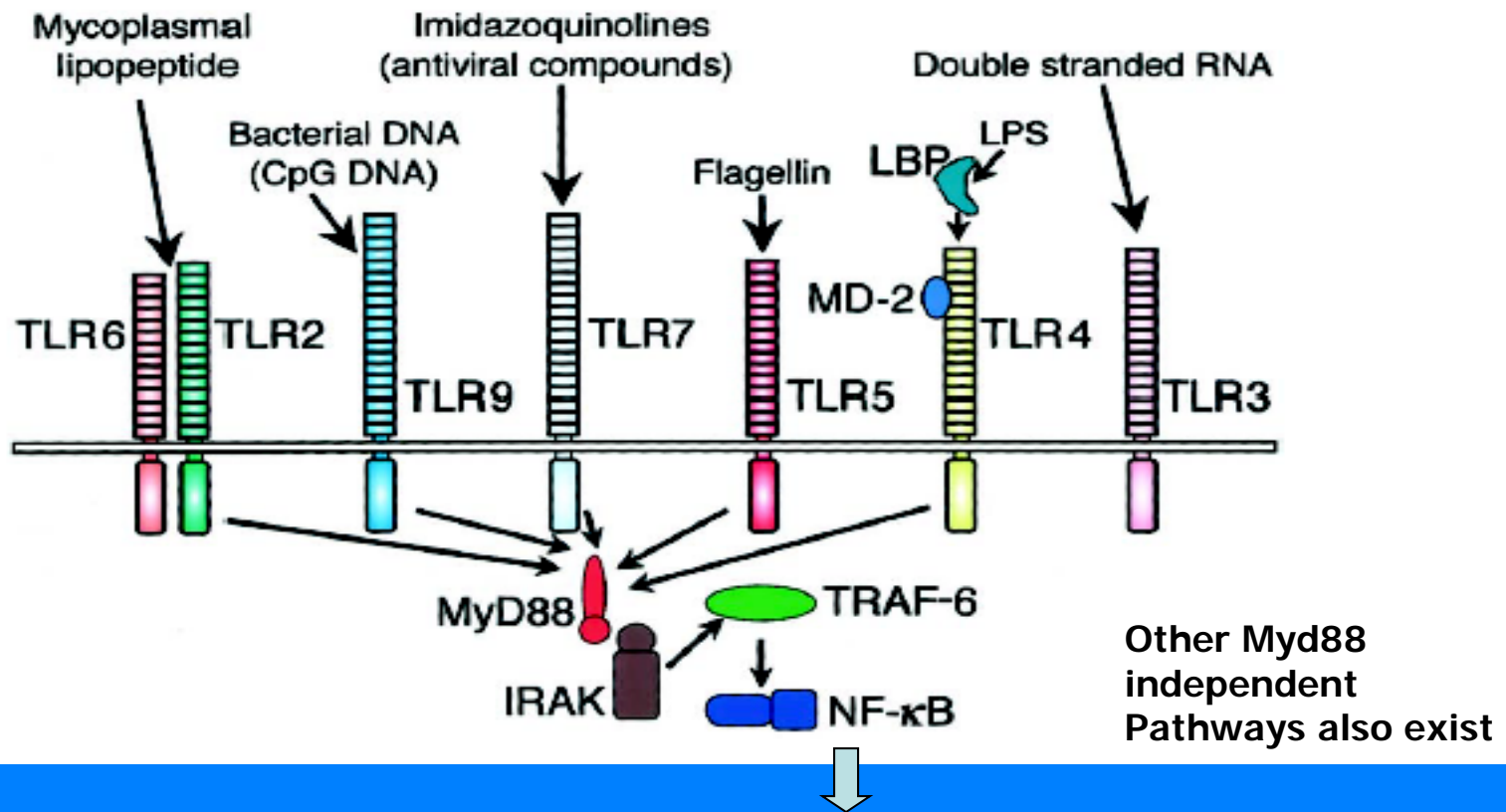
Pathogenesis of Sepsis

- A wide variety of microorganisms cause sepsis
- How--there must be some common mechanism
- Interaction of specific Pathogen Associated Molecular Patterns (PAMPs) with Toll-like receptors (Tlrs)
- **PAMPs** - highly conserved parts of microbial molecules on organisms-Lps, peptidoglycan, flagellin
- **Tlrs** -ancient receptors conserved on animal and plant cells
- Sepsis may also caused by interactions of super antigens with receptors on T- cells e.g. **some staphylococcal and streptococcal toxins**

Innate Immune response → Sepsis

- Interaction of a **microbial signature** with a toll-like receptor leads to activation of innate immune mechanisms
 - Message sent to nucleus resulting in transcription of repressed genes
 - Antimicrobial peptide (DEFENSINS) synthesis and release which can kill most organisms
 - Release of Mediators of inflammation - cytokines, chemokines
 - PMN leucocytes come into the site of inflammation to phagocytize organisms--release enzymes
 - Normally protective but either overwhelmed by bacterial inocula or some type of dysregulation leads to severe SEPSIS

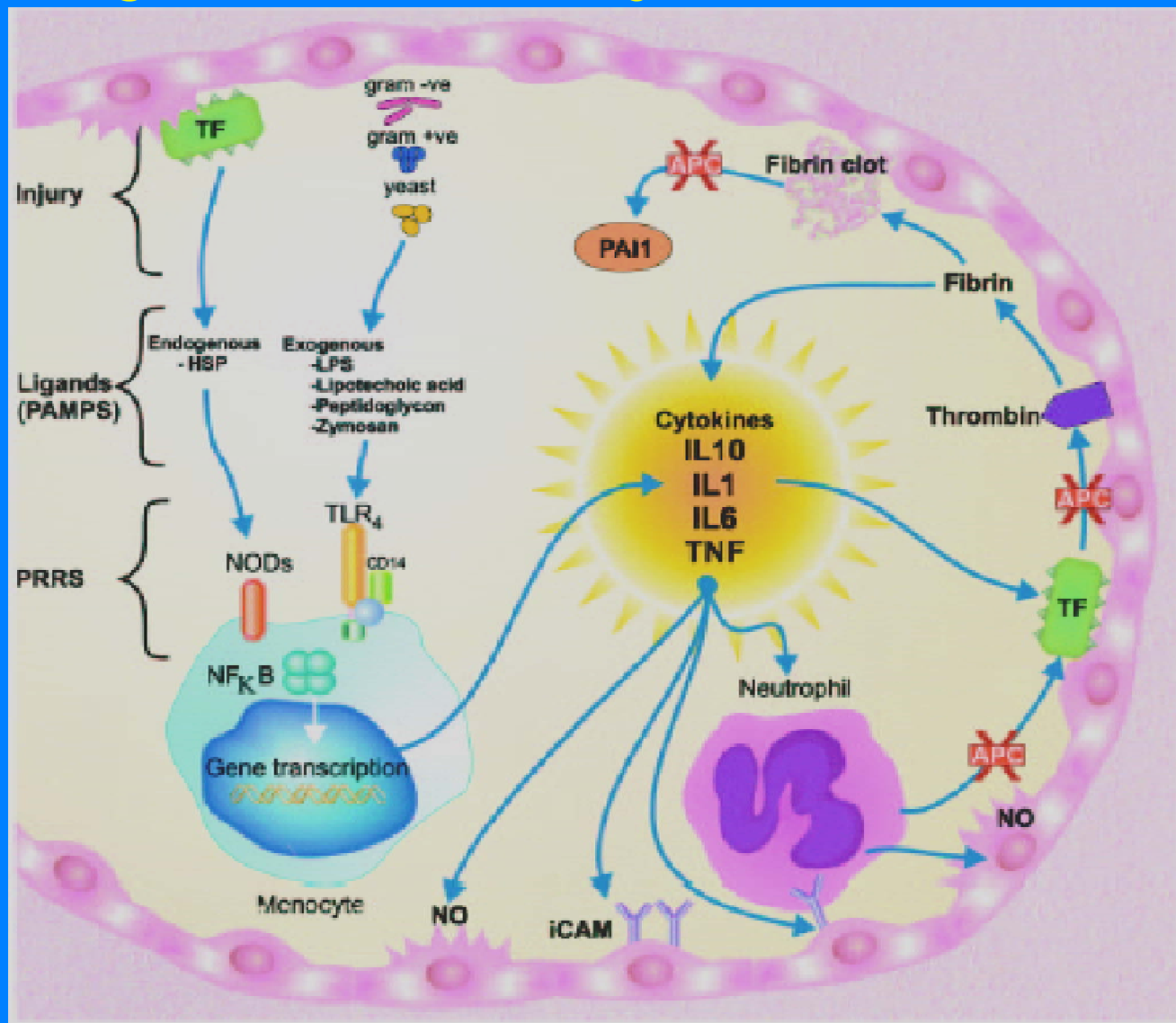
Microbial substances and recognition by TLR family of receptors



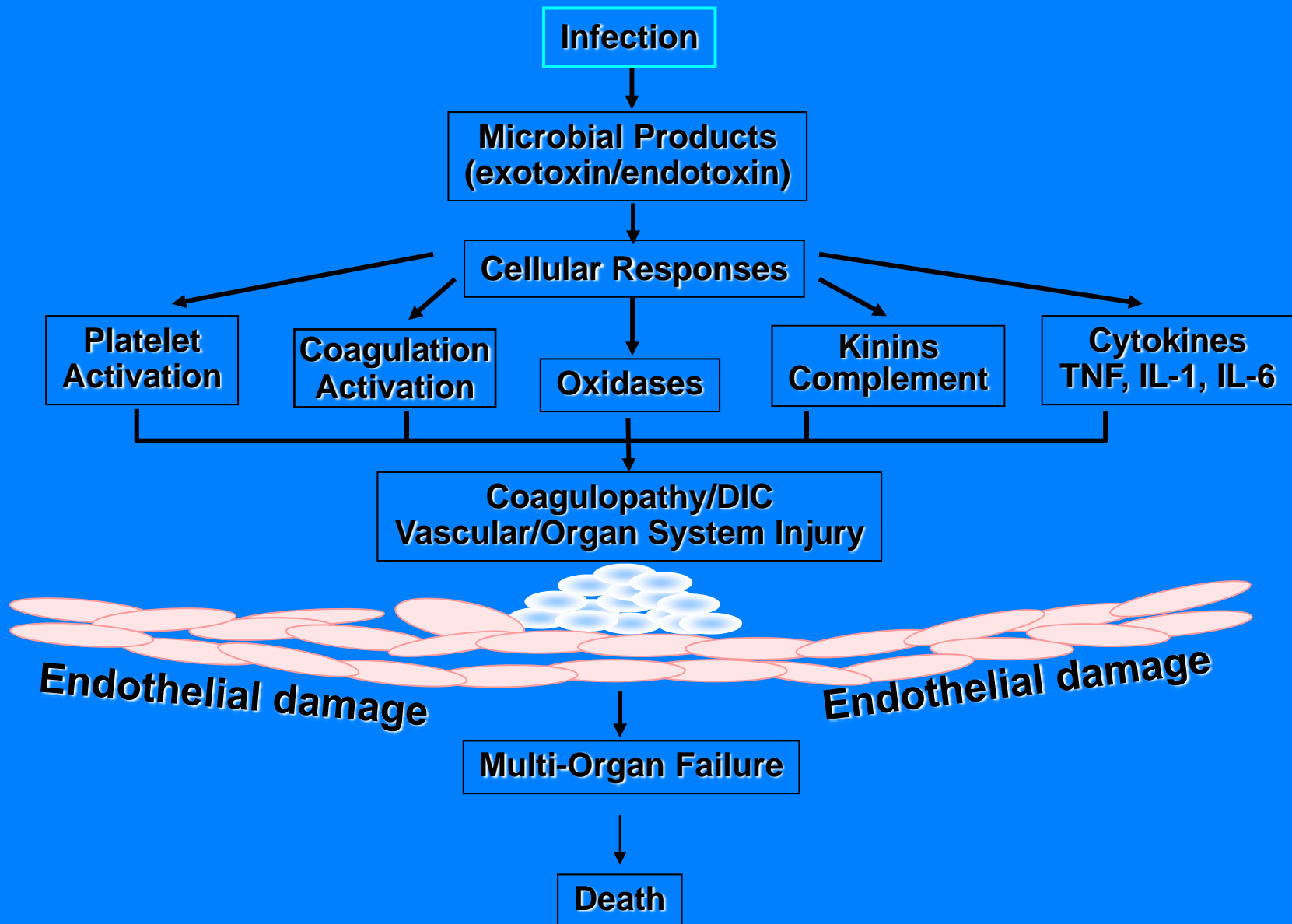
Adapted from Akira and Hashino,
Osaka University
J Infect Dis 2003

Transcription of effector genes

Synthesis and release of Effector molecules leading to the SEPSIS syndrome and shock



Pathogenesis of Severe Sepsis



Survivors according to systemic response

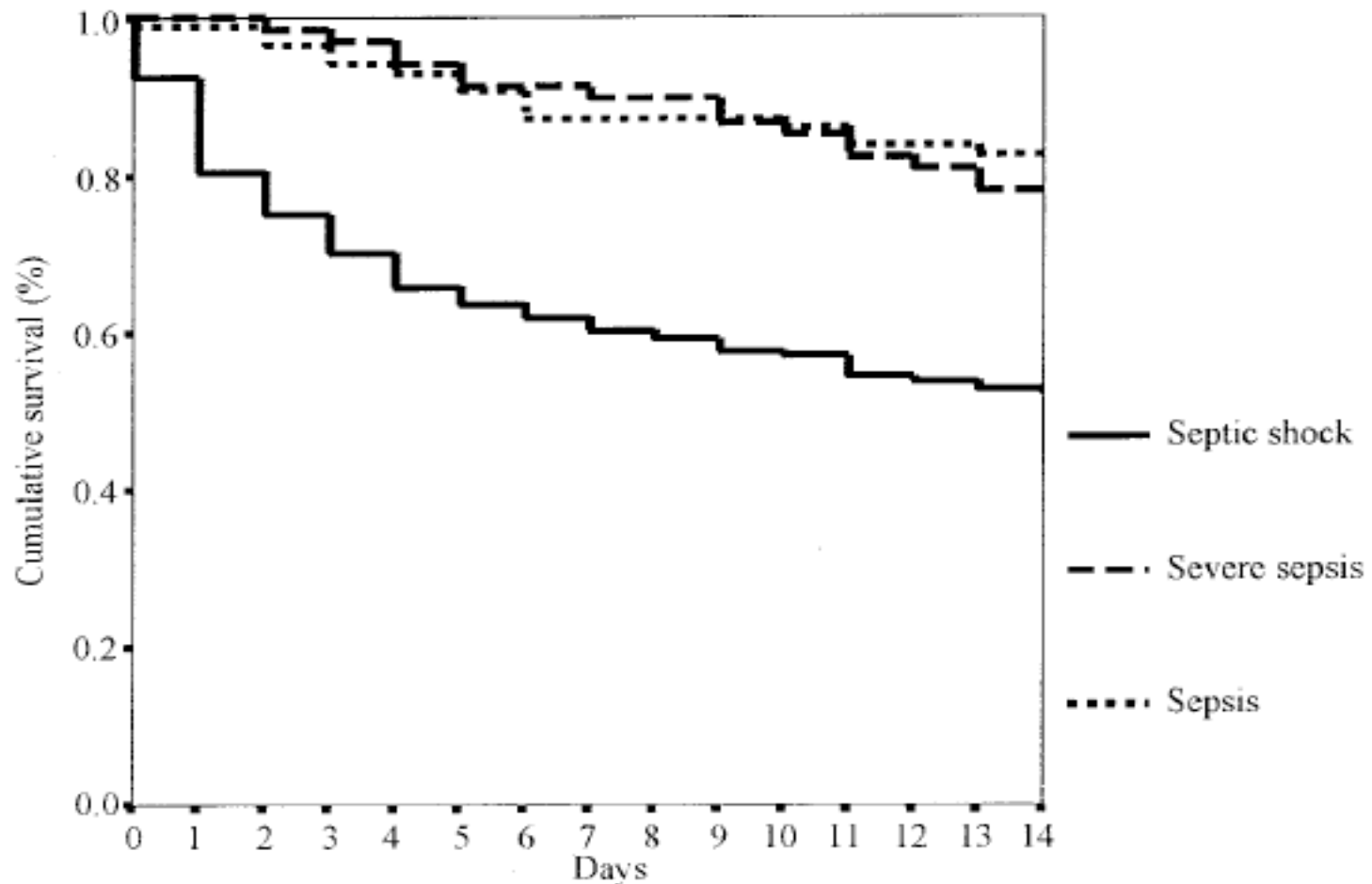


FIGURE 1. Proportion of survivors according to systemic response (log-rank test, $p = 0.01$).

Most Effective therapies

- Early recognition of preshock- tachynea leading to respiratory alkalosis
 - Low P_{CO_2} , $pH > 7.45$
- Lots of intravenous Fluids
- Antibiotics
- Effective antibiotics
- Timely administration of Effective antibiotics

Hospital mortality and adequacy of initial antimicrobial therapy of blood stream infections

Ibrahim
Chest 2000

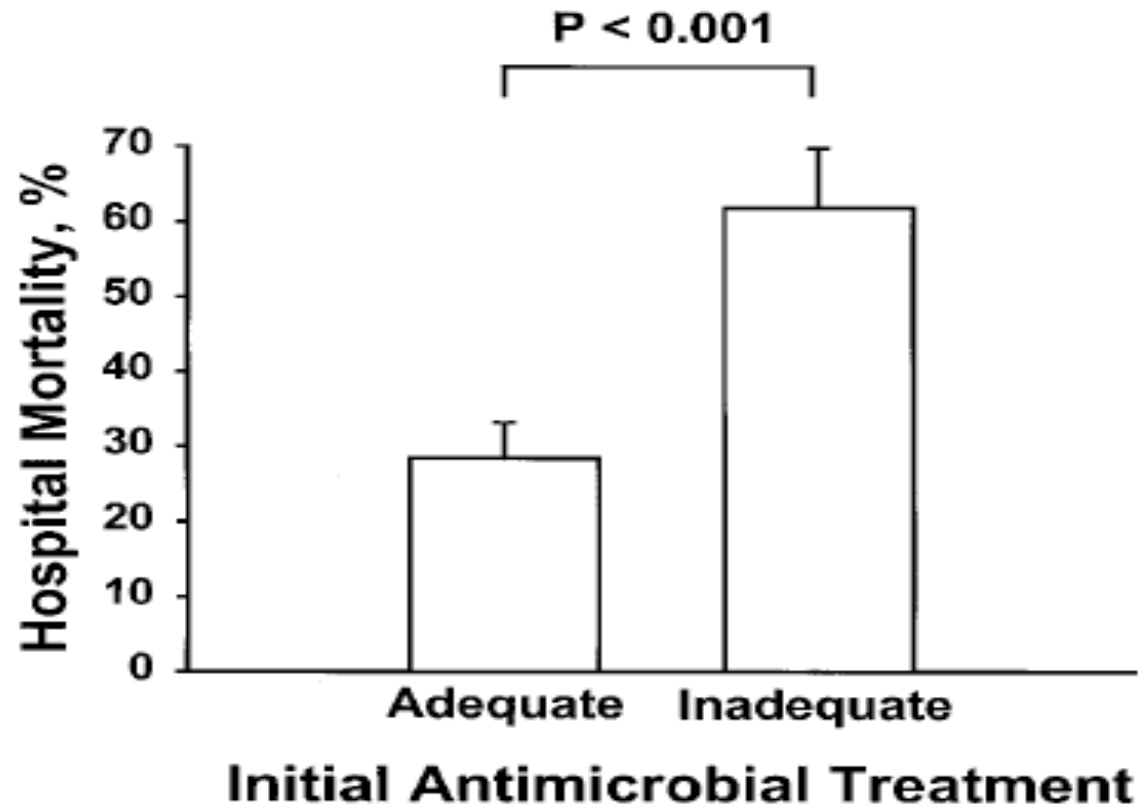


FIGURE 1. Hospital mortality according to the adequacy of the initial antimicrobial treatment prescribed for bloodstream infections. Upper 95% CIs are shown.

Effect of Antibiotics on Survival from Sepsis acquired in the community

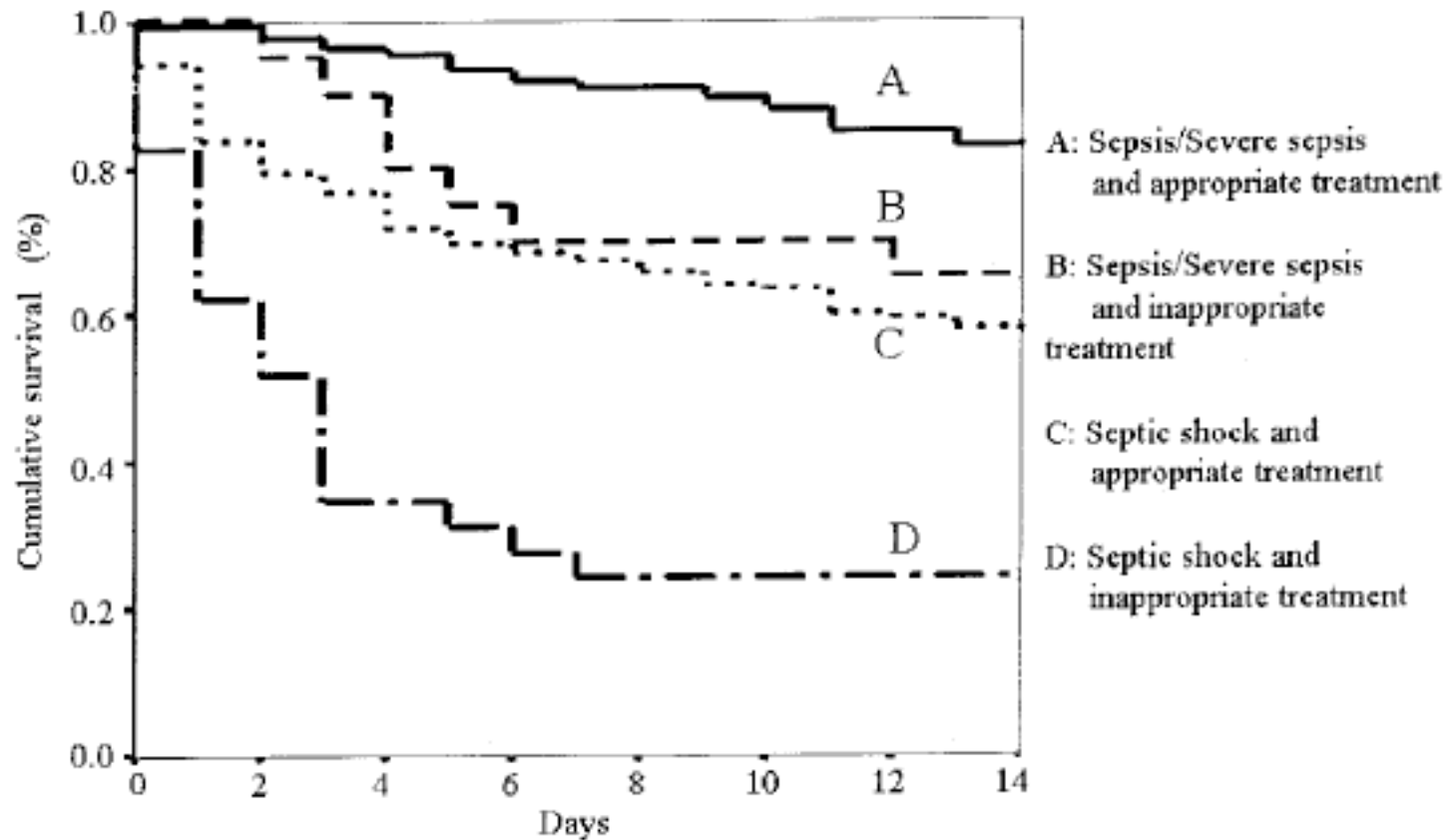


FIGURE 2. Survival rate according to the presence of shock and empiric antibiotic treatment (log-rank test, $p < 0.001$).

Survival dependent on severity of illness

Table 4—Correlation Between Survival Time and Empiric Appropriate Treatment According to Severity of Illness at ICU Admission (APACHE II Score)*

APACHE II Score	Appropriate Treatment		Inappropriate Treatment		Attributable Mortality, %	p Value
	Patients, No	Survival Rate, %	Patients, No	Survival Rate, %		
0-14 (n = 93)	84	80.7	9	70.0	10.7	NS
15-24 (n = 162)	136	63.6	26	28.6	35	0.001
≥ 25 (n = 84)	70	41.8	14	0	41.8	0.004
Overall (n = 339)	290	63	49	30.6	32.4	0.001

*NS = not significant.

Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock*

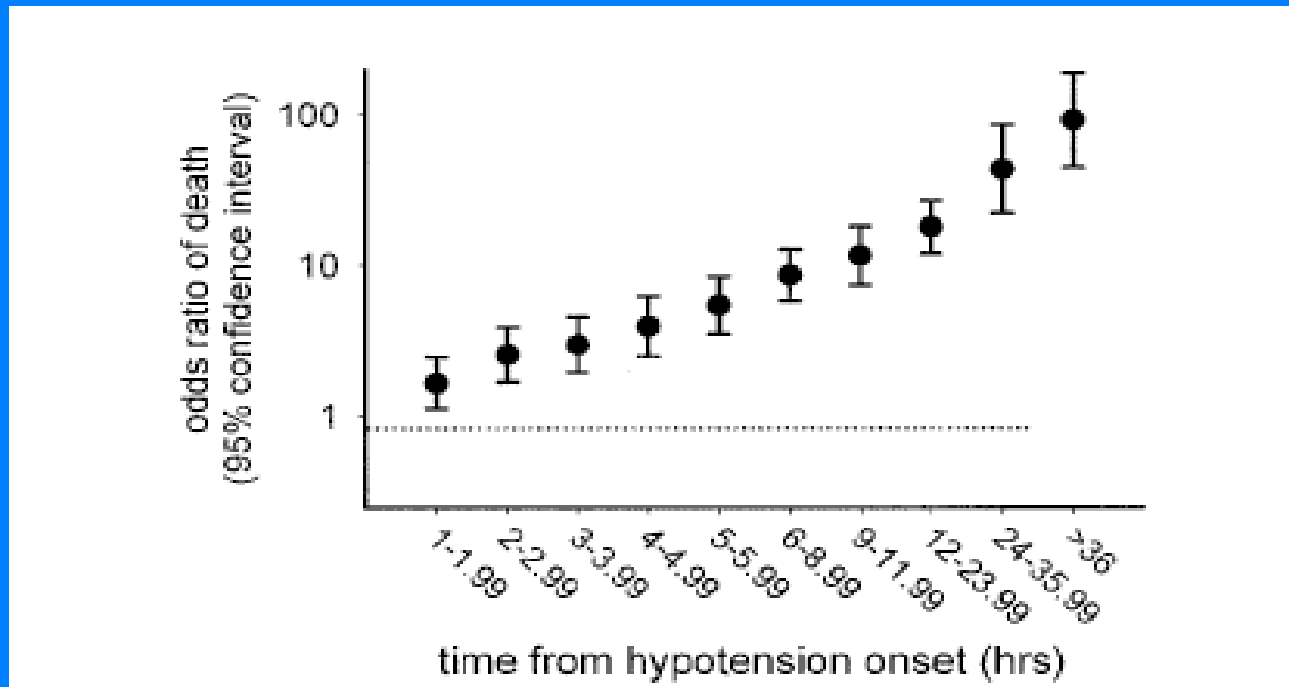


Figure 2. Mortality risk (expressed as adjusted odds ratio of death) with increasing delays in initiation of effective antimicrobial therapy. Bars represent 95% confidence interval. An increased risk of death is already present by the second hour after hypotension onset (compared with the first hour after hypotension). The risk of death continues to climb, though, to >36 hrs after hypotension onset.

Anand et al. Crit.Care Med 2006 (2150 patients)

Each hour of delay increased mortality by 7.6% in the first 6 hours

Mortality and Antibiotic therapy- univariate analysis

Monotherapy vs.combination for gram neg. bacteremia--2124 patients

Leibovici et al. AAC 2004

Antibiotic treatment	<u>No. of patients who died/total no. of patients (%)</u>	
	Empirical treatment	Definitive treatment
<u>Inappropriate treatment</u>	228/670 (34)	52/205 (25)
<u>Appropriate treatment</u>		
β -Lactam	131/789 (17)	109/816 (13)
Aminoglycoside	59/249 (24)	44/193 (23)
Aminoglycoside plus β -lactam	62/327 (19)	67/442 (15)
Others	26/89 (29)	41/222 (18)

Major Risk factors for mortality other than antibiotic treatment in patients with gram-negative bacteremia^a

(Leibovici 1997)

Risk factor	Survivors (<i>n</i> =1,652)	Patients who died(<i>n</i> =513)
Age (yr) ^b	60	74
Underlying disorder (% of patients)		
Steroid treatment	12.1	21.6
Neutropenia	8.6	14.1
Overt malignancy	20.9	32.0
Hospital infection (% of patients)	33.4	54.8
Unknown bacteremia (% of patients)	16.8	33.7
<i>Pseudomonas</i> sp. (% of patients)	13.9	22.0
Septic shock (% of patients)	3.2	32.8

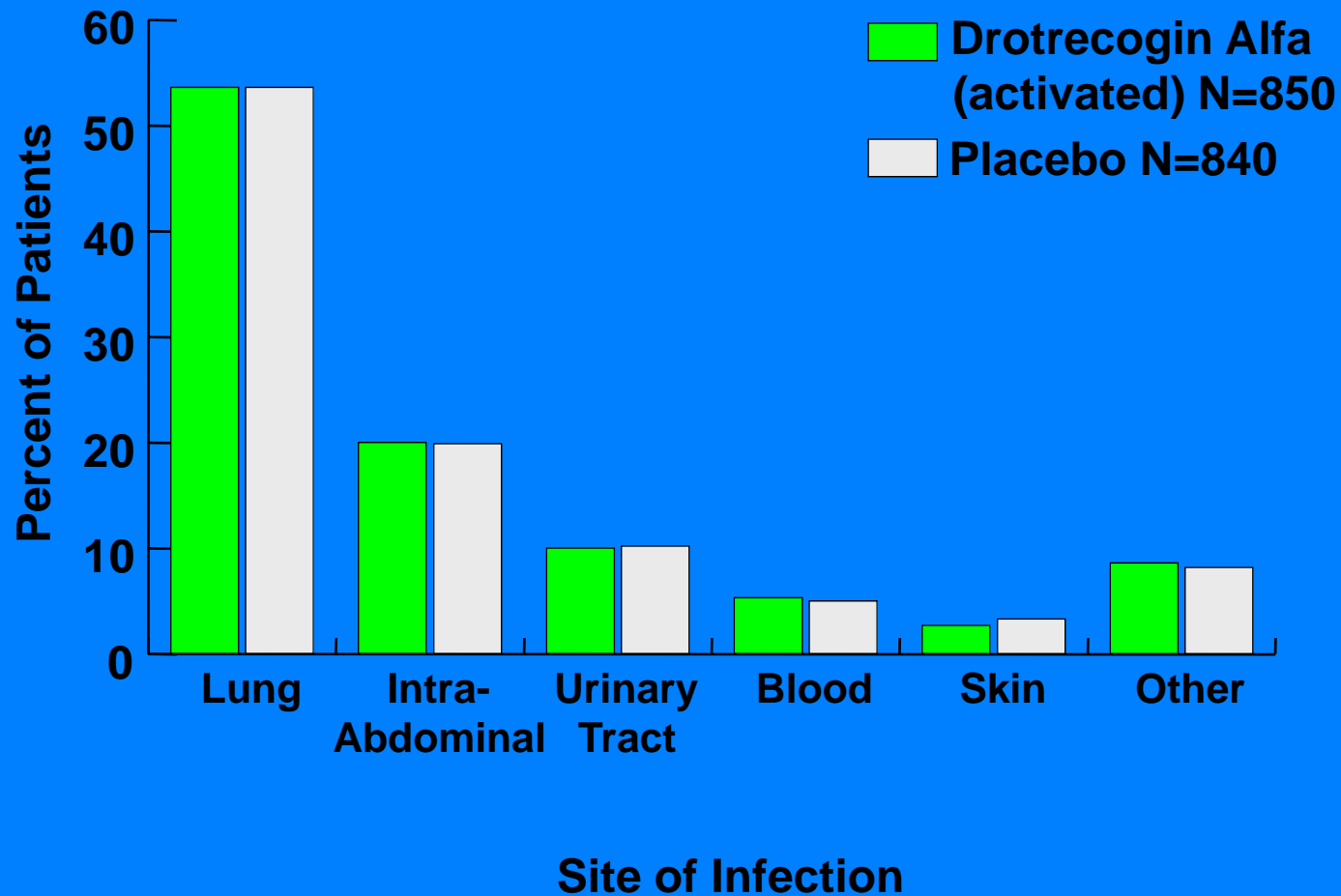
^a All comparisons are statistically significant (*P* # 0.0001).

^b Values are medians.

Choosing the RIGHT antibiotic in Sepsis

- Site of Infection, if known it helps to limit choices
 - intraabdominal, or necrotizing soft tissue infection needs anaerobic coverage.
 - Skin infections require gram positive coverage
- Lung most common site of documented infection-*P. aeruginosa*, *S. aureus*,
- Know resistance picture in hospital
 - ESBLs, *P. aeruginosa*, choose best drugs against these
- Know resistance in community if sepsis is community acquired - *S. aureus*, *S. pneumoniae*, *E.coli*
- **Give the antibiotic as soon as possible**

Primary Sites of Infection in a recent large study of Septic shock

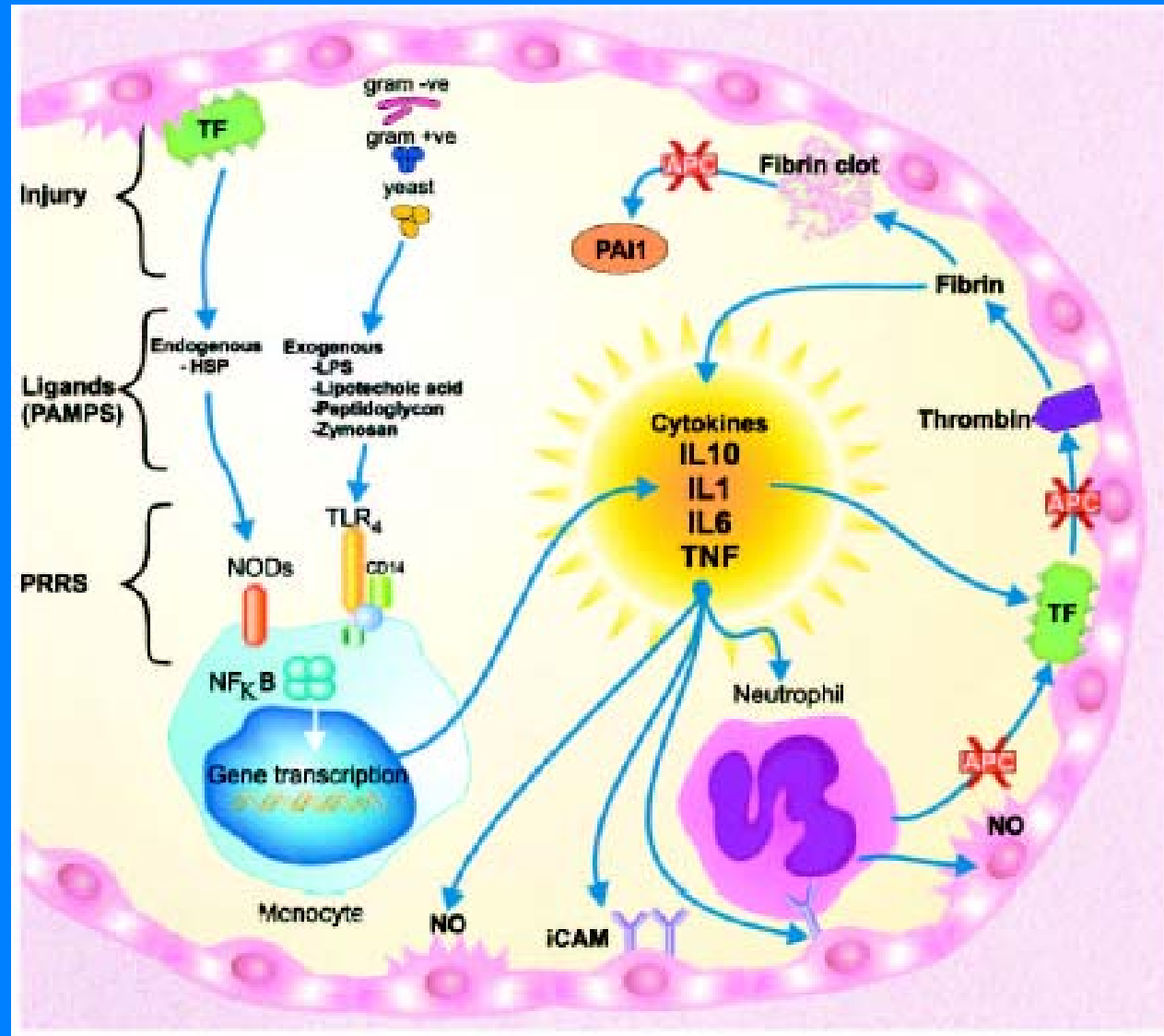


Antibiotic Choices

- Given the world wide resistance issues the most effective antibiotic choices to cover gram negatives would be
 - Fourth generation cephalosporins ± aminoglycoside (Geographic location)
 - Carbapenems ± aminoglycoside (Pseudomonas resistance during therapy of Lung infections)
 - Pip-Tazobactam + an aminoglycoside (Esbl resistance)
- If the incidence of MRSA is high and gram positive coverage is needed, add an anti Staphylococcal agent --Vanco, Teicoplanin

Effector mechanism based non antibiotic therapy - adjuncts to antibiotic therapy for patients in Septic Shock

IL-1
TNF
APC



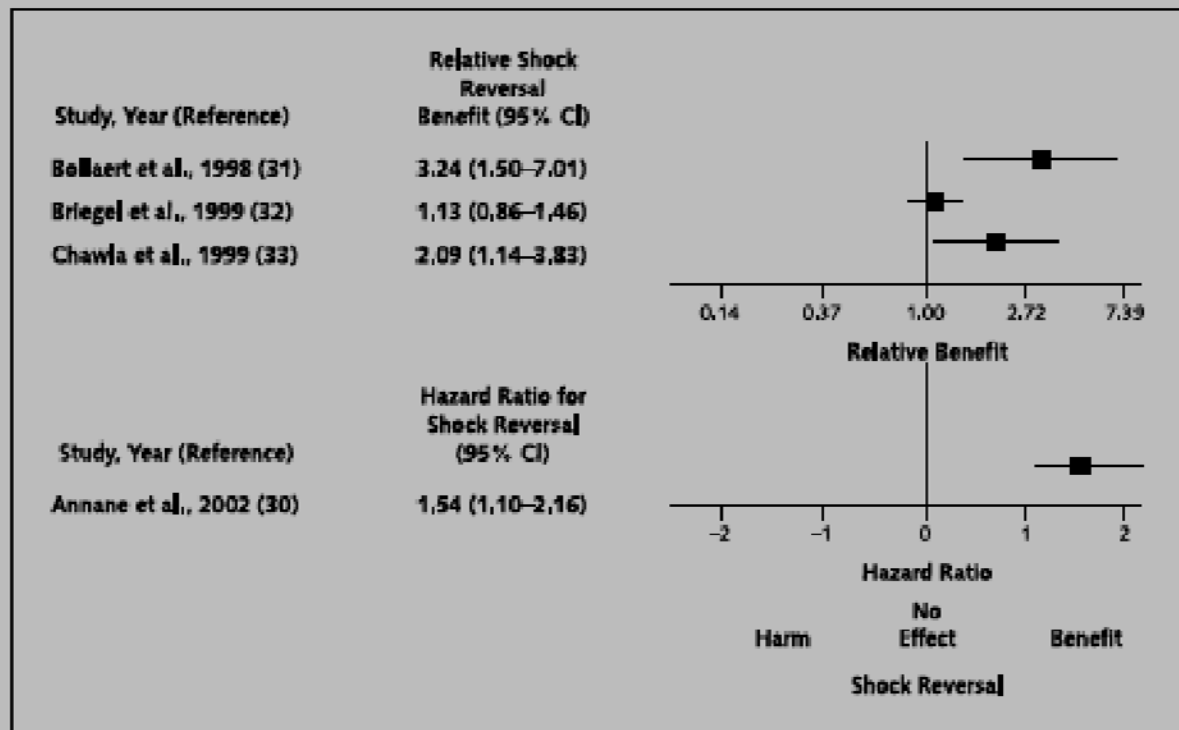
Non antibiotic therapy of septic shock

TABLE 7. Randomized controlled trials of immunotherapy in sepsis and septic shock*

Type of trial	No. of trials	Total no. of patients	Mortality (%) in patients receiving:	
			Placebo	Therapy
Anti-endotoxin	4	2,010	35	35
Anti-IL-1R	3	1,898	35	31
Anti-bradykinin	2	755	36	39
Anti-PAF	2	870	50	45
Anti-TNF	8	4,132	41	40
Soluble TNF-R	2	688	38	40
NSAIDS	3	514	40	37
Steroids	9	1,267	35	39
Activated protein C	1	1,690	31	25
All studies	33	13,824	38	37

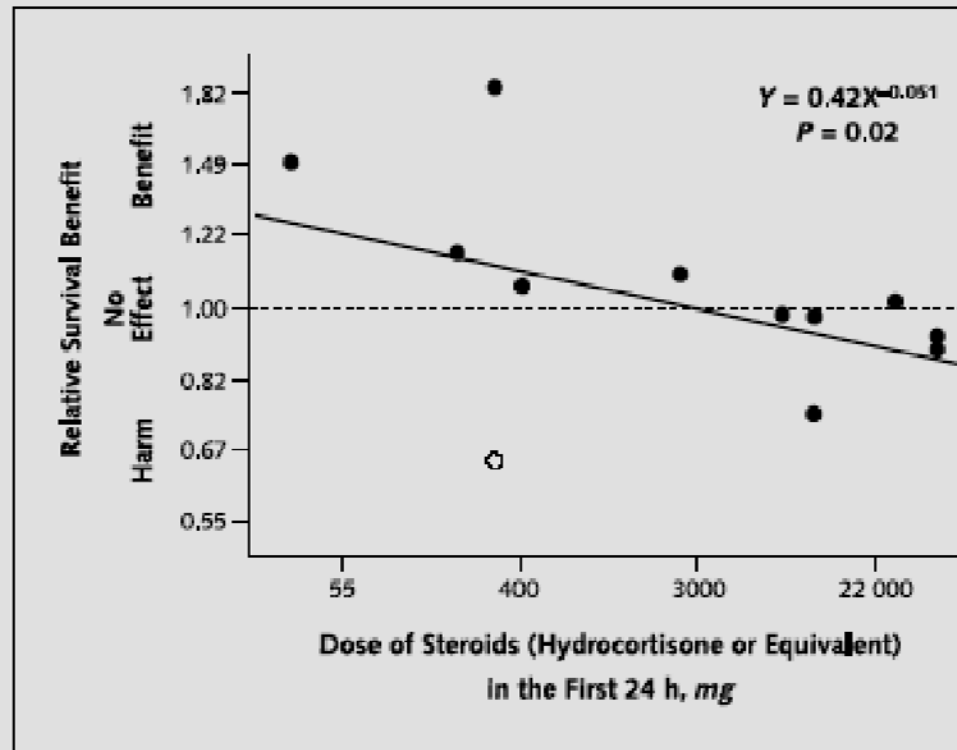
2002 opinion

Figure 4. Effects of steroids on shock reversal.



The relative benefit (95% CI) and the hazard ratio (with 95% CI) of shock reversal for the sepsis trials published after 1997 are presented. Of note, in 3 of the 4 studies, the discontinuation of vasopressor therapy with steroid treatment statistically significantly improved. In the fourth trial, the effect of steroid therapy on vasopressor discontinuation was similar to the effect in the other trials ($I^2 = 0\%$; $P > 0.2$).

Figure 3. Effects of steroid dose on survival.



The relationship between the dose of steroids administered in the first 24 hours after enrollment in a sepsis trial and relative survival benefit (*black circles*) is presented. There is a linear relationship (that is, the relative

2004 opinion

REVIEW | Dose Effects of Steroids on Survival in Sepsis

Context

Do high and low doses of glucocorticoids affect clinical outcomes differently in patients with sepsis?

Contribution

In this meta-analysis, 8 randomized, controlled trials published before 1989 showed that glucocorticoids worsened survival of patients with sepsis, while 5 recent trials showed that glucocorticoids improved survival. Recent trials administered glucocorticoids later, for longer periods, and in lower doses than earlier trials.

Implications

Short courses of high-dose glucocorticoids harm patients with sepsis while 5- to 7-day courses of physiologic doses equivalent to 200 to 300 mg of hydrocortisone daily benefit patients with sepsis.

—The Editors

Reversal of shock in response to steroids

Kaplan–Meier Curves for the Time to Reversal of Shock.

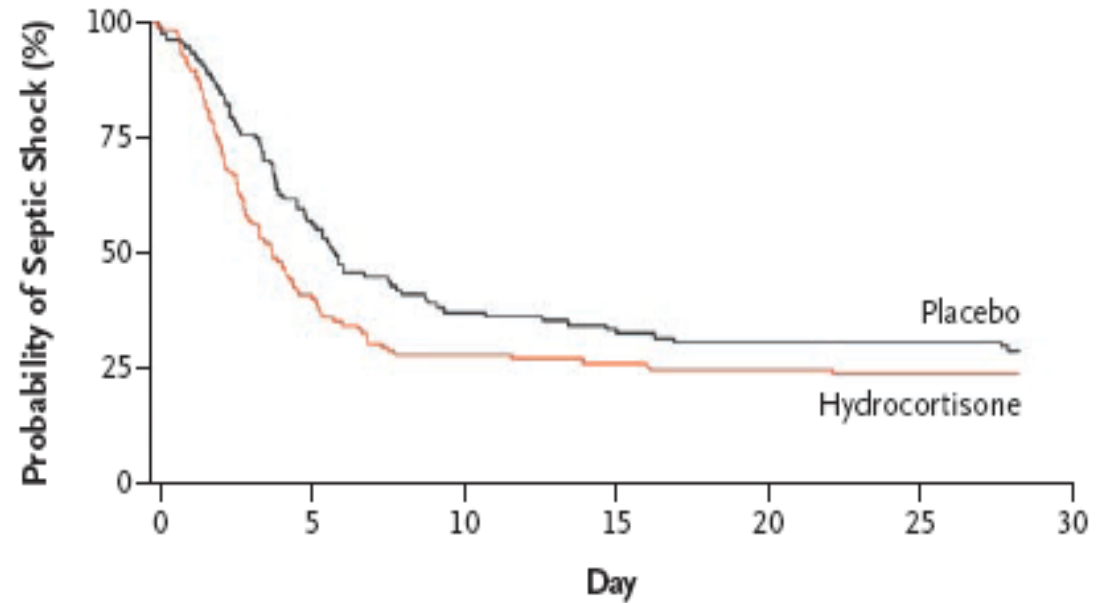
For the comparison between patients with septic shock who received hydrocortisone

and those who received placebo, $P = 0.06$ for patients who did not

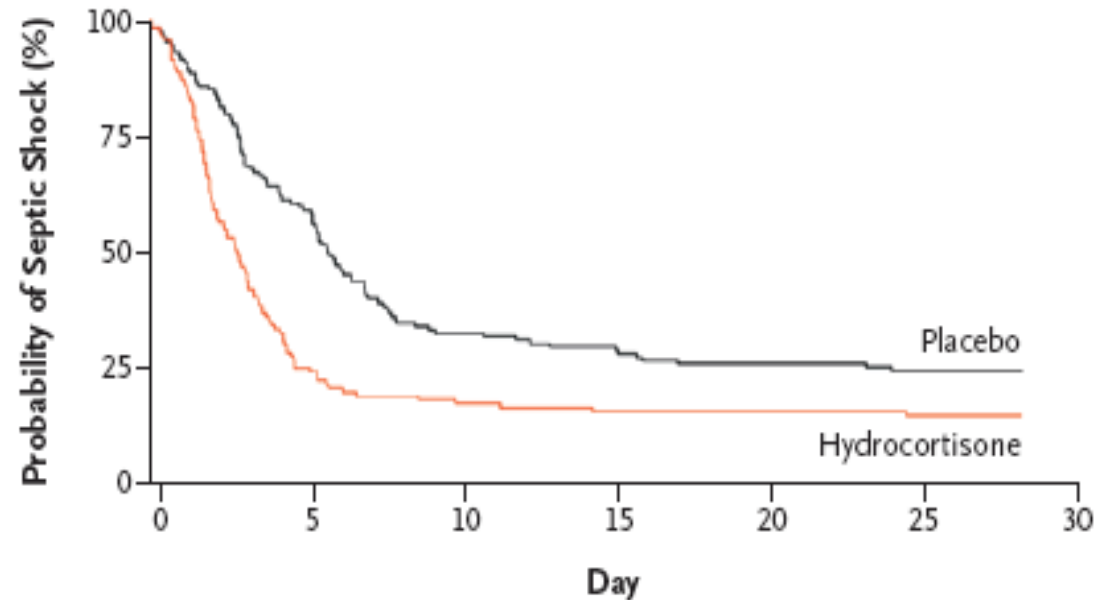
have a response to a corticotropin test (Panel A) and $P < 0.001$ for patients who had a response to corticotropin (Panel B)

Hydrocortisone therapy for septic Shock. NEJM 2008

A No Response to Corticotropin



B Response to Corticotropin



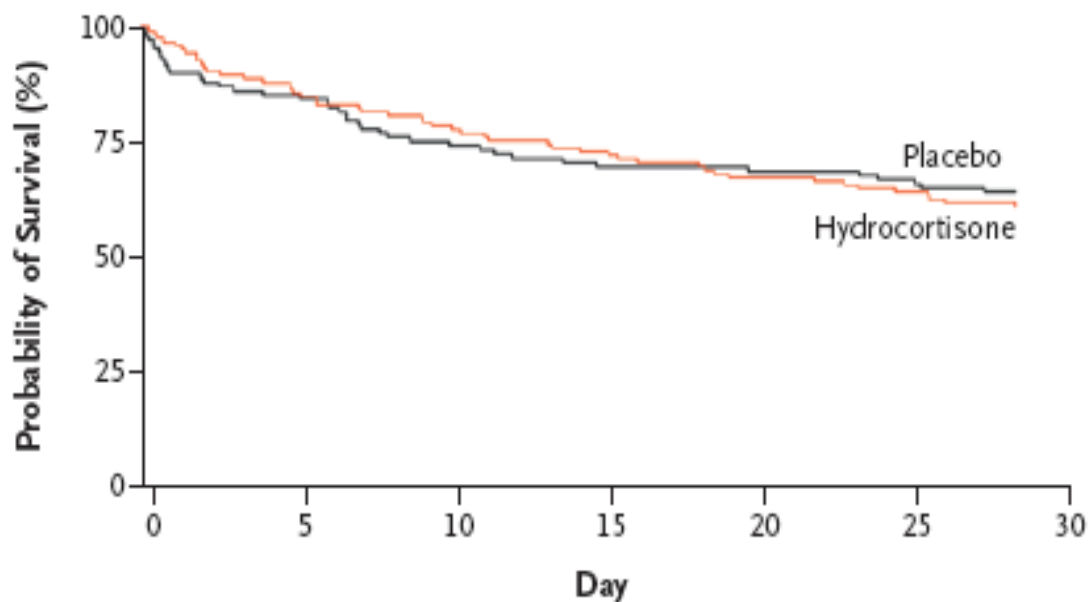
Survival at 28 days in response to steroids

Kaplan–Meier Curves for Survival at 28 Days.

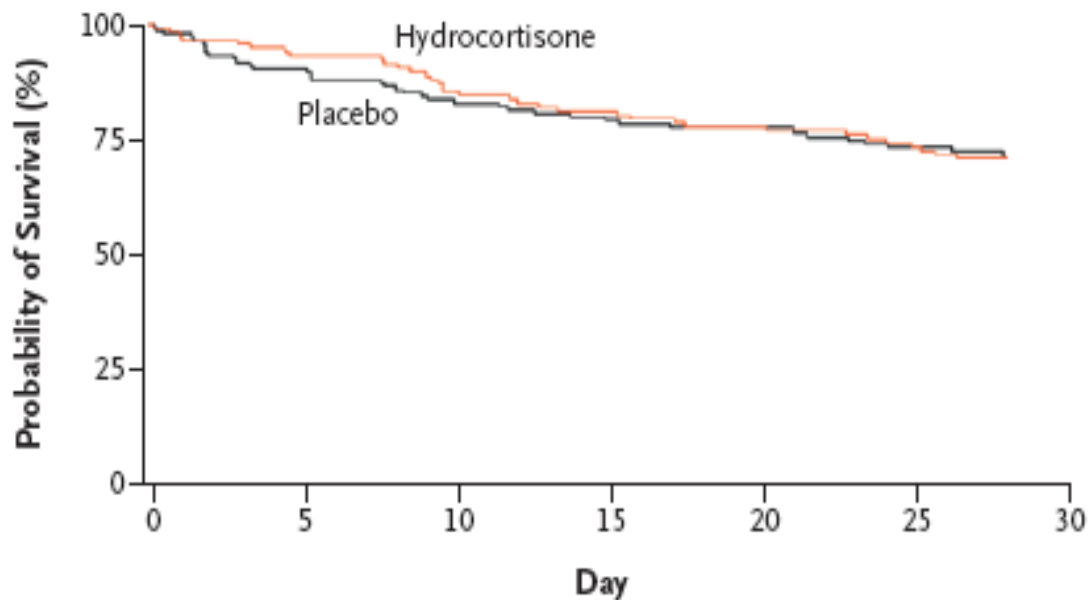
For the comparison between patients with septic shock who received hydrocortisone and those who received placebo, there was no significant difference among those who did not have a response to a corticotropin test (Panel A), those who had a response to corticotropin (Panel B).

Hydrocortisone therapy for septic Shock. NEJM 2008

A No Response to Corticotropin



B Response to Corticotropin



Optimum therapy of Sepsis and Shock

- Antibiotics remain the most critical choice to be made
 - TIMELY-reduces mortality
 - EFFECTIVE, BROAD SPECTRUM-reduces mortality
 - DIFFERENT antibiotics for different patients
 - *P. aeruginosa* continues to be associated with highest mortality
 - Resistance issues need to be kept in mind
 - A large number of patients with the sepsis syndrome will not have an organism cultured but should be treated with antibiotics
- Prevent the development of septic shock - fluids and Right antibiotics