

## Surviving Sepsis: Are we?

The 7<sup>th</sup> National Emergency  
Medicine Congress  
Antalya, Turkey

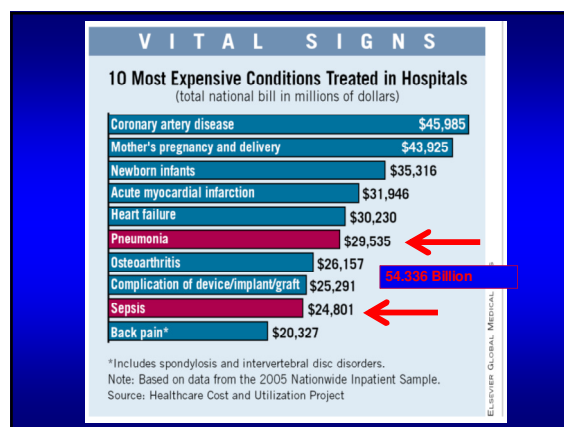
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Department of Surgery  
UTSW

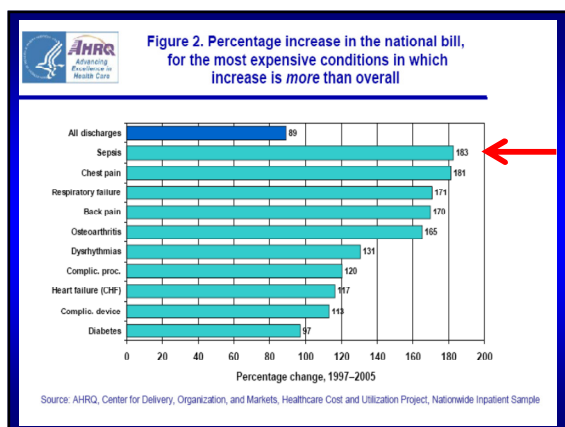


## Severe Sepsis: A Significant Healthcare Challenge

- Major cause of morbidity and mortality worldwide
  - Leading cause of death in noncoronary ICU (US)<sup>1</sup>
  - 10th leading cause of death overall (US)<sup>2\*</sup>
- More than 750,000 cases of severe sepsis in the US annually<sup>3</sup>
- In the US, more than 500 patients die of severe sepsis daily<sup>3†</sup>

\* Based on data for septicemia  
† Reflects hospital-wide cases of severe sepsis as defined by infection in the presence of organ dysfunction  
1. Sands KE, Bates DW, Lanken PN, et al. Epidemiology of sepsis syndrome in 8 academic medical centers. JAMA 1997;278:234-40.  
2. National Vital Statistics Reports, 2006.  
3. Angus DC, Linde-Zwirble WJ, Lickler J, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome and associated costs of care. Crit Care Med 2001;29:1303-10.





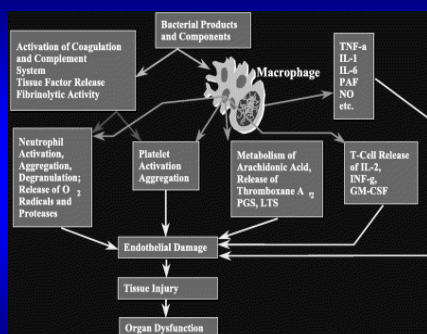
## What is sepsis ?

The poisoning of the system by the introduction of putrescent material into the blood.

- Webster's Dictionary (1913)

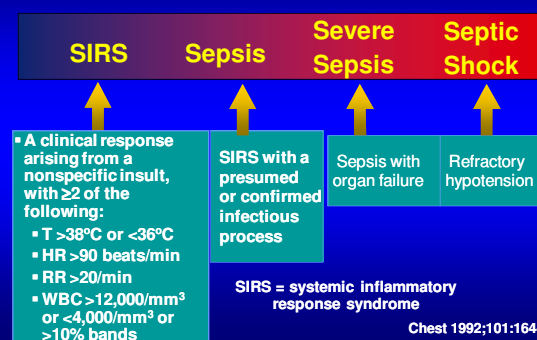


## The SEPSIS CASCADE



Balk, adapted from R Bone

## The Sepsis Continuum



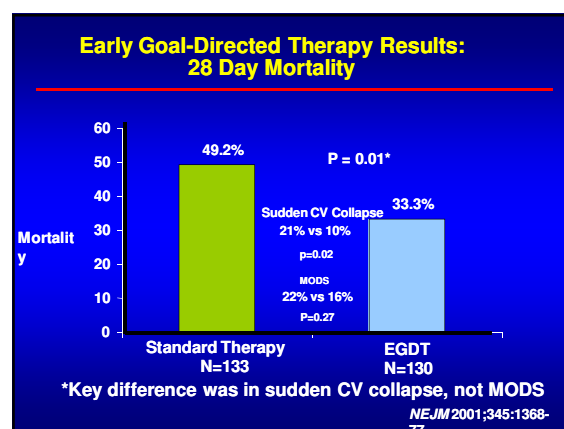
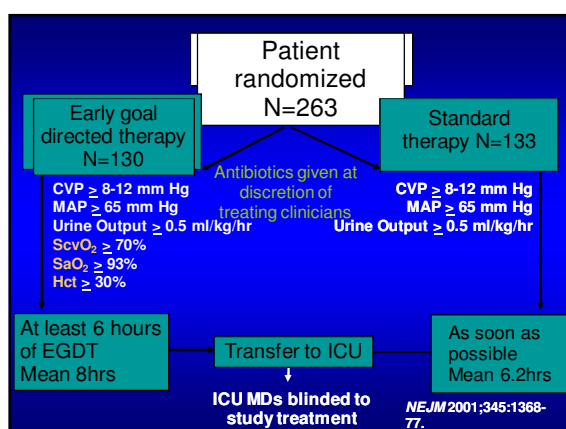
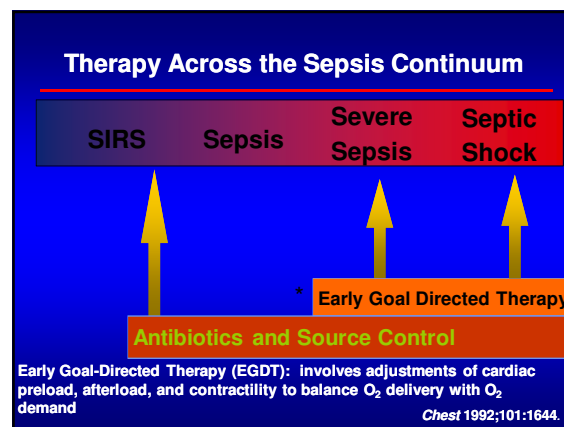
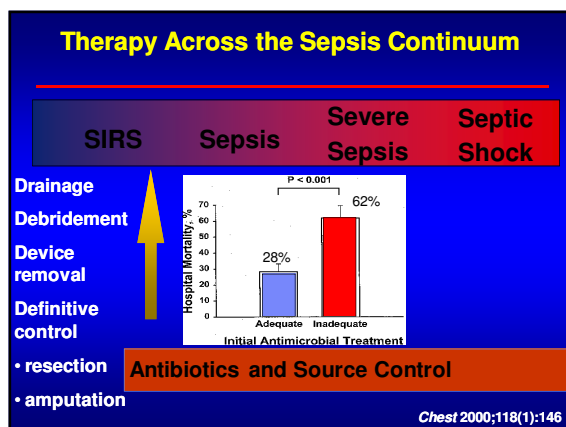
## Sepsis: A Major Cause of ICU Death

- More than 750,000 cases of severe sepsis in the US each year
- Mortality about 20% (recent decline)
- Total cost of \$17 billion each year
- Incidence is projected to increase by 1.5% yearly
- Although prognosis has improved, because of increased incidence, actual deaths will increase

## Sepsis is a Significant Healthcare Challenge

- Major cause of morbidity and mortality worldwide
  - leading cause of death in non-coronary ICU (US)
  - 13th leading cause of death overall (US)
- More than 1.5 million cases of severe sepsis in OECD countries annually (estimated)
- More than 750,000 cases of severe sepsis in US annually
- Health care costs of severe sepsis estimated at \$17 billion annually (US)
- Striking increase in incidence expected in the next decade

Sands KE et al. JAMA. 1997;278:234-40; †Based on data for septicemia. ‡Murphy SL. National Vital Statistics Reports. †Angus DC et al. Crit Care Med. 2001; reflects hospital-wide cases of severe sepsis as defined by infection in the presence of organ failure.



## Surviving Sepsis

A global program to:  
Reduce mortality rates in severe sepsis

## 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

## Guidelines Committee\*

Dellinger (RP)	Ramsay	Harvey	Sprung
Carlet	Zimmerman	Hazelzet	Torres
Masur	Beale	Hollenberg	Vendor
Gerlach	Bonten	Jorgensen	Bennet
Levy	Brun-Buisson	Maier	Bochud
Vincent	Carcillo	Maki	Cariou
Calandra	Cordonnier	Marini	Murphy
Cohen	Dellinger (EP)	Opal	Nitsun
Gea-Banacloche	Dhainaut	Osborn	Szokol
Keh	Finch	Parrillo	Trzeciak
Marshall	Finfer	Rhodes	Visonneau
Parker	Fourrier	Sevransky	

\*Primary investigators from recently performed positive trials with implications for septic patients excluded from committee selection.

## Initial Resuscitation

### Goals during first 6 hours:

- Central venous pressure: 8–12 mm Hg
- Mean arterial pressure  $\geq$  65 mm Hg
- Urine output  $\geq$  0.5 mL kg<sup>-1</sup>/hr<sup>-1</sup>
- Central venous (superior vena cava) or mixed venous oxygen [SvO<sub>2</sub>] saturation  $\geq$  70%

Grade B

## Initial Resuscitation

### Goals during first 6 hours:

- Central venous or mixed venous O<sub>2</sub> sat  $<$  70% after CVP of 8–12 mm Hg
  - Packed RBCs to Hct 30%
  - Dobutamine to max 20 µg/kg/min

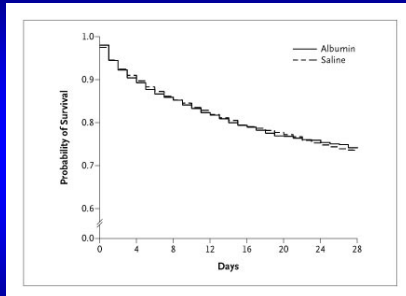
Grade B

## SAFE Study

- In a randomized, controlled trial conducted in 16 ICUs in Australia and New Zealand 6997 patients were randomized to receive either saline or 4% albumin for fluid resuscitation
- The albumin group received less fluid volume, but required more transfusion in the first 48h

NEJM 2004; 350:2247

### Kaplan-Meier Estimates of the Probability of Survival



The SAFE Study Investigators, N Engl J Med 2004;350:2247-2256

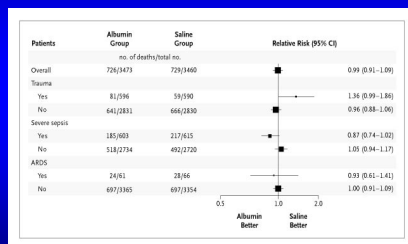
Primary Endpoint was 28 day mortality



## SAFE STUDY

There were also no differences in duration of mechanical ventilation or ICU stay, development of single or multiple organ failure or duration of hospitalization.

### Relative Risk of Death from Any Cause among All the Patients and among the Patients in the Six Predefined Subgroups



The SAFE Study Investigators, N Engl J Med 2004;350:2247-2256



## Fluid Therapy

- Fluid resuscitation may consist of natural or artificial colloids or crystalloids.

Grade C

## Vasopressin and Septic Shock

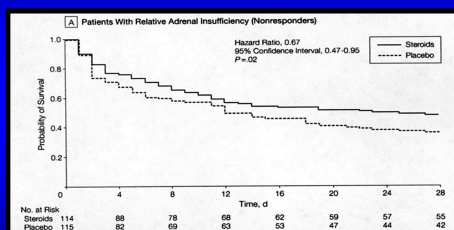
- Versus cardiogenic shock
- Decreases or eliminates requirements of traditional pressors
- As a pure vasopressor expected to decrease cardiac output

## Vasopressors—Vasopressin

- Not a replacement for norepinephrine or dopamine as a first-line agent
- Consider in refractory shock despite high-dose conventional vasopressors
- If used, administer at 0.01-0.04 units/minute in adults

Grade E

## Steroid Therapy



Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002; 288:862-871

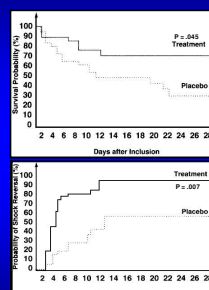


Figure 2 and Figure 3, page 648, reproduced with permission from Bellani F, Chazotte C, Levy B, et al. Reversal of late septic shock with supraphysiologic doses of hydrocortisone. *Crit Care Med* 1999; 28:545-550

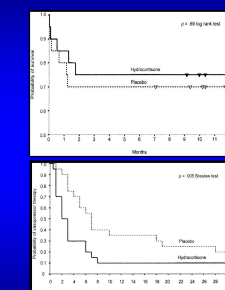


Figure 2 and Figure 3, page 727, reproduced with permission from Bregel J, Fors H, Heller M, et al. Stress doses of hydrocortisone reverse hyperdynamic septic shock: A prospective, randomized, double-blind, single-center study. *Crit Care Med* 1999; 27:723-732

## Steroids

- Treat patients who still require vasopressors despite fluid replacement with hydrocortisone 200-300 mg/day, for 7 days in three or four divided doses or by continuous infusion.

Grade C

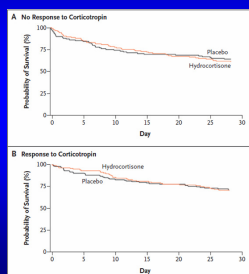
## Severe Sepsis – Role of Steroids – CORTICUS

### CORTICUS trial

- 500 adults with septic shock (onset < 72 hrs)
- Randomized to:
  - Hydrocortisone (50 mg Q6h for 5 days, then tapered over 6 days) vs. placebo
- All patients underwent corticotropin testing
- Excluded individuals with a life expectancy of < 24 hrs

NEJM 2008;358:111-24

## Severe Sepsis – Role of Steroids – CORTICUS



- 28-day mortality same in both groups regardless of response to corticotropin

- BP improved more quickly with steroids, but steroid recipients had more infections

NEJM 2008;358:111-24

## Severe Sepsis – Role of Steroids – CORTICUS

### Conclusion:

- 2008 guideline “Surviving Sepsis Campaign”
  - Weak grade 2C recommendation: Give steroids “only if BP poorly responsive to fluids and vasopressors”
  - This was based on differences between CORTICUS and a prior trial (*JAMA* 2002;288:862)
  - Do not base decisions on corticotropin testing



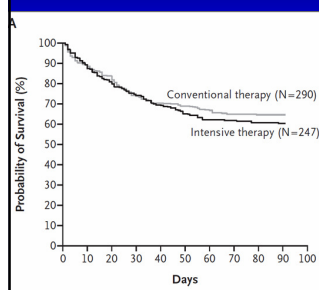
## Severe Sepsis – Role of Insulin – VISEP

NEJM 2008;358:125-39

- No previous trials of intensive insulin for severe sepsis
- VISEP:
  - Approximately 500 pts with severe sepsis
  - randomized to:
    - intensive insulin (initiate when glucose > 110; target 80-110) vs.
    - standard insulin (initiate when glucose > 200; target 180-200)

## Severe Sepsis – Role of Insulin – VISEP

NEJM 2008;358:125-39



- Mean gluc: 112 vs. 151 mg/dl
- Trial was stopped early
- No significant difference in mortality at 28 or 90 dys
- Hypoglycemia: 17 vs. 4%\*
- ARF: 31 vs. 27%\*

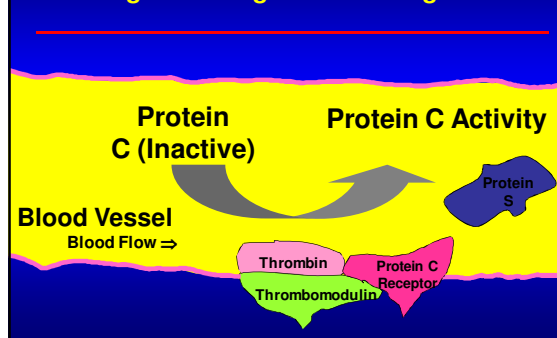
## Severe Sepsis – Role of Insulin – VISEP

NEJM 2008;358:125-39

### Conclusion:

- 2008 guideline “Surviving Sepsis Campaign”
  - Suggests keeping glucose < 150 mg/dl (grade 2C – weak, low quality evidence)

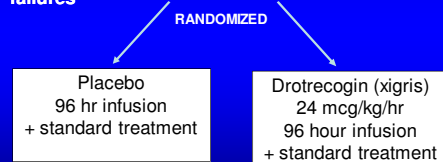
## Human Activated Protein C Endogenous Regulator of Coagulation



## PROWESS Study Design

1690 Patients :

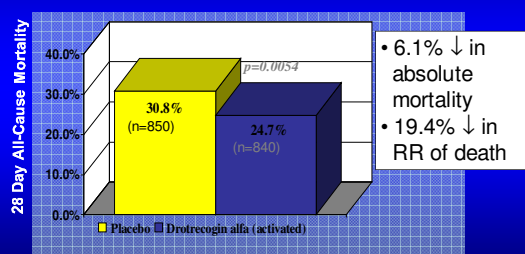
- Known or suspected infection
- $\geq 3$  of the SIRS criteria
- $\geq 1$  acute (< 24hr in duration) organ failures



Primary Endpoint: All-Cause Mortality at 28 days

## PROWESS Results

### Primary Stratified Intention-to-Treat Analysis

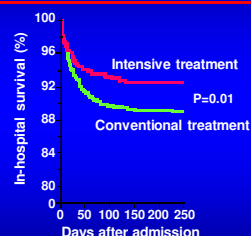


- 6.1% ↓ in absolute mortality
- 19.4% ↓ in RR of death

NEJM 2001;344:699-709.

### The Role of Intensive Insulin Therapy in the Critically Ill

- At 12 months, intensive insulin therapy reduced mortality by 3.4% ( $P<0.04$ )



van den Borgh G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001;345:1359-67

### Economic Implications of an Evidence-based Sepsis Protocol: Can We Improve Outcomes and Lower Costs?

#### Objective

- To determine financial impact of a sepsis protocol designed for use in the ED

#### Design

- Analysis of results from recent prospective study comparing outcomes in patients with septic shock before and after initiation of sepsis protocol

#### Setting

- Academic, tertiary care hospital in US

Shorr AF et al. *Crit Care Med*. 2007;35:1257-1262.

### Subjects

- Adults (n=120) who sequentially presented to ED with septic shock, specifically:
  - At least two systemic inflammatory response syndrome (SIRS) criteria
  - Known or suspected infection (based on radiologic imaging and clinical suspicion)
  - Shock requiring both fluid resuscitation and vasopressor administration

Shorr AF et al. *Crit Care Med*. 2007;35:1257-1262.

### Median Costs per Patient for Treating Sepsis

	Median per-patient cost	Range	p-value
Before protocol initiation	\$21,985	\$3,610–99,795	0.008
After protocol initiation	\$16,103	\$3,445–102,440	

- Median saving of \$5,882
  - 18.3% more survivors following protocol initiation
- Receipt of care under the protocol associated with decreased costs

Shorr AF et al. *Crit Care Med*. 2007;35:1257-1262.

### Costs Among Survivors

- Survivors
  - Pre-protocol 51.7%, post-protocol 70.0% ( $p=0.04$ )

Median total costs among survivors varied significantly following protocol initiation

	Pre-protocol		Post-protocol		p-value
	Median	Range	Median	Range	
Median total costs	\$21,985	\$3,610–99,795	\$16,103	\$3,445–102,440	0.008
Hospital LOS	13 days	3–37 days	8 days	2–35 days	0.001

LOS = length of stay

Shorr AF et al. *Crit Care Med*. 2007;35:1257-1262.

### Summary of Results

- Post-protocol, savings of ~\$6,000/patient observed
  - Translated into total cost difference of \$573,000 between the two groups
- Post-protocol, ICU costs reduced by ~35% ( $p=0.026$ ) and ward costs fell by 30% ( $p=0.033$ )
- Protocol resulted in a reduction in overall hospital LOS of 5 days ( $p=0.023$ )
- Pre-protocol, 28-day mortality rate was 48.3% vs. 30.0% following protocol initiation ( $p=0.040$ )

ICU, intensive care unit; LOS, length of stay

Shorr AF et al. *Crit Care Med*. 2007;35:1257-1262.



## Contact Information

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**Thank You**