Innovations in the Care of Sepsis in the Emergency Service

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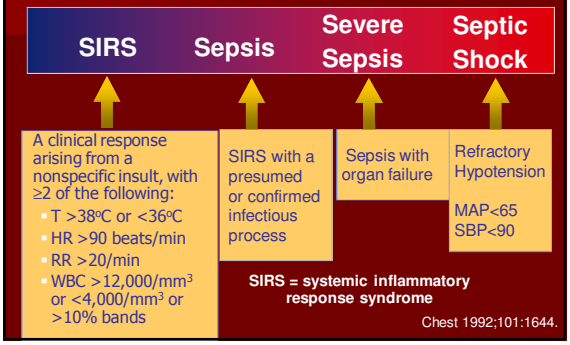
Major Cause of Death

- 750,000 cases of severe sepsis in the US each year
- Incidence will increase by 1.5% each year
- Sepsis in ED: 458,200 cases (61% of severe sepsis/septic shock)
- Mortality about 28.7% (215,000 deaths per year vs 180,000 deaths of AMI, 200,000 of lung or breast cancer)
- Economic cost of $16.7 billion per year

Comparable Global Epidemiology

- 95 cases per 100,000
  - 2 week surveillance
  - 206 French ICUs
- 95 cases per 100,000
  - 3 month survey
  - 23 Australian/New Zealand ICUs
- 51 cases per 100,000
  - England, Wales and Northern Ireland.

Sepsis Continuum



Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. Mikkelsen ME, et al. Crit Care Med. 2009 ;37(5):1670-7.

OBJECTIVE:

To test whether the association between initial serum lactate level and mortality in patients presenting to the emergency department (ED) with severe sepsis is independent of organ dysfunction and shock.

DESIGN:

Single-center cohort study. The primary outcome was 28-day mortality and the risk factor variable was initial venous lactate (mmol/L), categorized as low (< 2), intermediate (2-3.9), or high (> or = 4).

PATIENTS:

Eight hundred thirty adults admitted with severe sepsis in the ED.

CONCLUSIONS:

Initial serum lactate was associated with **mortality** independent of clinically apparent organ dysfunction and shock in patients admitted to the ED with severe sepsis. Both intermediate and high serum lactate levels were independently associated with mortality.

Early lactate clearance is associated with biomarkers of inflammation, coagulation, apoptosis, organ dysfunction and mortality in severe sepsis and septic shock
H Bryant Nguyen et al, Emanuel P Rivers group. Journal of Inflammation 2010, 7:6

- Lactate clearance=(Lactate ED Presentation - Lactate Hour 6) X 100 / Lactate ED Presentation
- Early lactate clearance (75.1 ± 7.1%) as a surrogate for the resolution of global tissue hypoxia is significantly associated with **decreased levels of biomarkers** (IL-1ra, IL-6, IL-8, IL-10, TNF-a, ICAM-1 , HMGB-1, D-Dimer, and caspase-3), **improvement in organ dysfunction** and **outcome** in severe sepsis and septic shock.

A prospective, multicenter derivation of a biomarker panel to assess risk of organ dysfunction, shock, and death in emergency department patients with suspected sepsis.
Shapiro NI et al. Crit Care Med. 2009;37(1):96-104.

OBJECTIVE:
To define a biomarker panel to predict organ dysfunction, shock, and in-hospital mortality in emergency department (ED) patients with suspected sepsis.

PATIENTS:
There were 971 patients enrolled. Inclusion criteria: 1) ED patients age > 18; 2) suspected infection or a serum lactate level > 2.5 mmol/L; and 3) two or more systemic inflammatory response syndrome criteria. Exclusion criteria: pregnancy, do-not-resuscitate status, or cardiac arrest.

CONCLUSIONS:
A biomarker panel of **neutrophil gelatinase-associated, lipocalin, interleukin-1ra, and Protein C** was predictive of severe sepsis, septic shock, and death in ED patients with suspected sepsis. Further study is warranted to prospectively validate the clinical utility of these biomarkers and the sepsis score in risk-stratifying patients with suspected sepsis.

Prognostic value of mortality in emergency department sepsis score, procalcitonin, and C-reactive protein in patients with sepsis at the emergency department.
Lee CC et al Shock. 2008 Mar;29(3):322-7.

- **Prospective observational study to compare the prognostic value of PCT on sepsis and compared with a validated score, Mortality in Emergency Department Sepsis (MEDS) score, and C-reactive protein (CRP) in the setting of ED of an urban, university-based medical center.**
- **Five hundred twenty-five consecutive adult patients admitted to the ED.**
- **Serum PCT and CRP were evaluated for each patient.**
- **The main outcome was early (5-day) and late (6- to 30-day) mortality.**
- **Overall, MEDS score has the best discriminative capability among the three tested markers. Under the best cutoff value, PCT was the most sensitive, and MEDS score was the most specific marker. We suggest further combining the information on PCT and MEDS score to enhance the accuracy in predicting ED sepsis mortality.**

Surviving Sepsis Campaign

- Launched in Fall 2002 as a collaborative effort of European Society of Intensive Care Medicine, the International Sepsis Forum, and the Society of Critical Care Medicine
- Goal: reduce sepsis mortality by 25% in the next 5 years
- Guidelines revealed at SCCM in Feb 2004
  - *Critical Care Medicine* March 2004 32(3):858-87.
  - Website: survivingsepsis.org

Early steps (6h-bundle)

- Fluid resuscitation (ED)
- Appropriate cultures prior to antibiotic administration (ED)
- Early targeted antibiotics and source control (ED)
- Use of vasopressors/inotropes when fluid resuscitation optimized (ED)

Late steps (24h-bundle)

- Evaluation for adrenal insufficiency (ICU)
- Stress dose corticosteroid administration (ICU, ED?)
- Recombinant human activated protein C (xigris) for severe sepsis (ICU, ED?)
- Low tidal volume mechanical ventilation for ARDS (ICU)
- Tight glucose control (ED, ICU)

Late steps (24h-bundle)

- Prophylaxis for DVT (ICU)
- Stress ulcer prophylaxis (ICU)
- Prevention of nosocomial pneumonia by elevation of head to 45 degrees (ICU)
- Facilitate extubation by daily interruption of sedation and early SBT (ICU)
- Narrowing of antibiotic spectrum when appropriate (ICU)

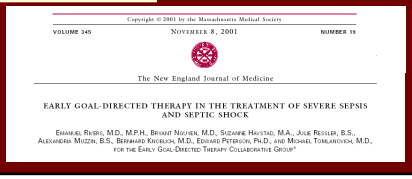
What is a Bundle?

Specifically selected care elements

- From evidence based guidelines
- Implemented together provide improved outcomes compared to individual elements alone

6 Hour Resuscitation Bundle

- Early Identification
- Early Antibiotics and Cultures
- Early Goal Directed Therapy



Infection Control

- Appropriate cultures prior to antibiotic administration
- Early targeted antibiotics and source control

Early Appropriate Antibiotics and Source Control

- Gram positive organisms have replaced gram negatives as the most common source of sepsis
- Lung (35%), abdomen (21%), Urinary tract (13%), skin and soft tissue (7%), other site (8%), unknown primary site (7%)
- Therapy targeted to the suspected site (eg, CAP, intra-abdominal source)
- Drainage, debridement and device removal as indicated

Although there are insufficient data to conclude that delays on the order of hours are deleterious, administration of antibiotics within the time of ED care and as soon as possible (within one hour) once there is reasonable suspicion of severe sepsis/septic shock will likely increase the chance of favorable outcome compared with later administration (Grade 1C and 1B)

Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Critical Care Medicine, 2008.

Association between timing of antibiotic administration and mortality from septic shock in patients treated with a quantitative resuscitation protocol. Puskarich MA et al. Crit Care Med. 2011

OBJECTIVE:
To determine the association between time to initial antibiotics and mortality of patients with septic shock treated with an emergency department-based early resuscitation protocol.

DESIGN:
Preplanned analysis of a multicenter randomized controlled trial of early sepsis resuscitation.

SETTING:
Three urban US emergency departments.

PATIENTS:
Adult patients with septic shock.

CONCLUSION:
In this large, prospective study of emergency department patients with septic shock, we found no increase in mortality with each hour delay to administration of antibiotics after triage. However, delay in antibiotics until after shock recognition was associated with increased mortality.

Empirical antimicrobial recommendations for adults patients

Unknown source:

Vancomycin (1g/12h) + Levofloxacin (750mg/24h) + Gentamicin (7mg/kg/24H)

Community acquired pneumonia:

Vancomycin (1g/12h) + levofloxacin (750mg/24h)

Meningitis:

Vancomycine (1g/12h) + ceftriaxone (2g/12h)

Urinary tract infection:

Piperacillin/Tazobactam (3.375g/6h) + Gentamicin (7mg/kg/24H)

Intrabdominal/pelvic infection:

Piperacillin/Tazobactam (3.375g/6h) + Gentamicin (7mg/kg/24H)

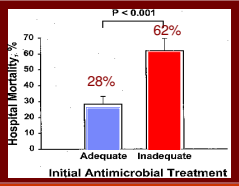
Skin and soft tissue infection/necrorizing infection:

Vancomycine (1g/12h) + Piperacillin/Tazobactam (3.375g/6h)+ Clindamycin 900mg/8h

Therapy Across the Sepsis Continuum

SIRS | Sepsis | Severe Sepsis | Septic Shock

- Drainage
- Debridement
- Device removal
- Definitive control
- • resection
- • amputation



Antibiotics and Source Control

Chest 2000;118(1):146
Chest 1992;101:1644.

Therapy Across the Sepsis Continuum

SIRS | Sepsis | Severe Sepsis | Septic Shock

* Early Goal Directed Therapy

Antibiotics and Source Control

Early Goal-Directed Therapy (EGDT): involves adjustments of cardiac preload, afterload, and contractility to balance O_2 delivery with O_2 demand

Chest 1992;101:1644.

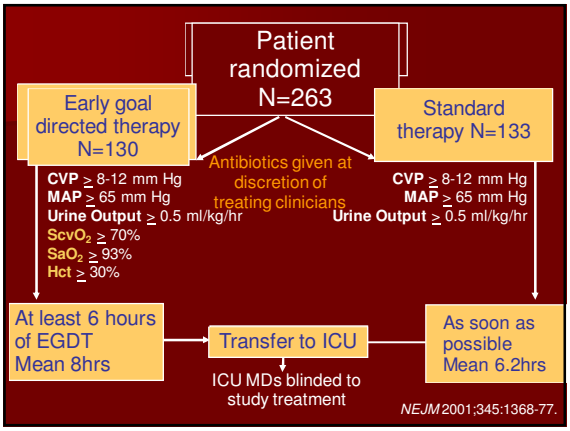
Goal Directed Therapy

Restore systemic oxygen delivery through a manipulation of preload (volume), afterload (blood pressure), and contractility (stroke volume) to preserve effective tissue perfusion while avoiding excessive increase in myocardial oxygen consumption and maintaining coronary perfusion pressure.

Administration of fluids, pressors and transfusion based upon targets for CVP, blood pressure, urine output, mixed venous oxygen saturation and hematocrit.

In patients with severe sepsis/septic shock, EGDT should be used as the first means of resuscitation within the first 6 hours, with simultaneous prioritization of appropriate empirical antimicrobials and source control (Grade 1C)

Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Critical Care Medicine, 2008.

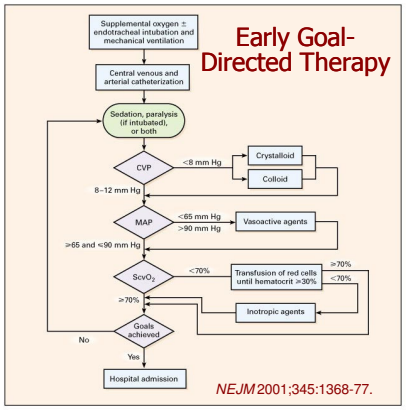


NEJM 2001;345:1368-77.

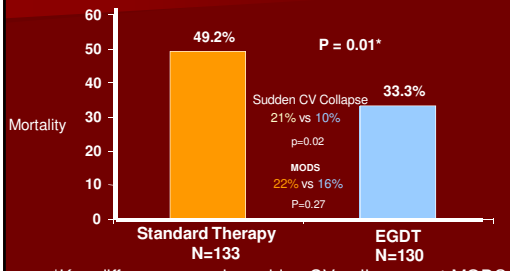
CVP: central venous pressure

MAP: mean arterial pressure

$ScvO_2$: central venous oxygen saturation



Early Goal-Directed Therapy Results: 28 Day Mortality



*Key difference was in sudden CV collapse, not MODS

NEJM 2001;345:1368-77.

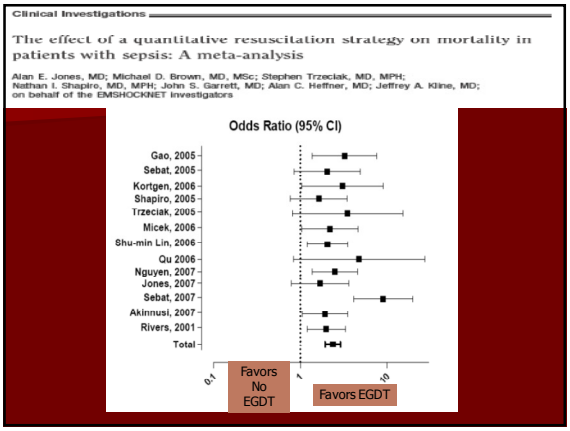
One year mortality of patients treated with an emergency department based early goal directed therapy protocol for severe sepsis and septic shock: a before and after study

Michael A Puskarich et al. *Critical Care 2009,* ***13:R167***

The primary outcome of 1 year mortality was observed in 39/79 (**49%**) pre-implementation subjects and 77/206 (**37%**) post-implementation subjects (difference 12%; *P = 0.04).*

Conclusions

Implementation of EGDT for the treatment of ED patients with severe sepsis and septic shock was associated with significantly lower mortality at one year.



Early Goal-directed Therapy (EGDT) for Severe Sepsis/Septic Shock: Which Components of Treatment are More Difficult to Implement in a Community-based Emergency Department?

O'Neill R, Morales J, Jule M. J Emerg Med. 2011 May 4.

BACKGROUND:

Early goal-directed therapy (EGDT) has been shown to reduce mortality in patients with severe sepsis/septic shock, however, implementation of this protocol in the emergency department (ED) is sometimes difficult.

OBJECTIVES:

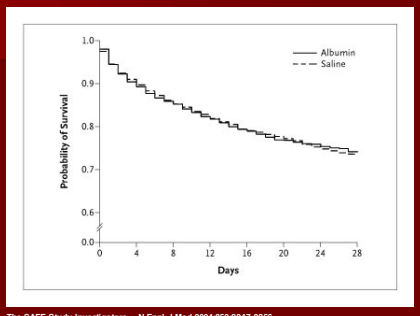
We evaluated our sepsis protocol to determine which EGDT elements were more difficult to implement in our community-based ED.

CONCLUSION:

In this community hospital, **arterial line placement**, **central venous pressure measurement**, and **central venous oxygen saturation measurement** were the most difficult elements of EGDT to implement. Patients who survived to hospital discharge were more likely to receive the crystalloid bolus.

Fluid Resuscitation

Crystalloids and colloids are equally effective in restoring intravascular volume



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

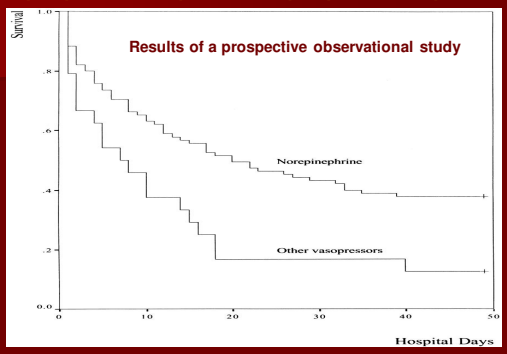
Primary Endpoint was 28 day mortality

The NEW ENGLAND JOURNAL of MEDICINE

What Pressors for Septic Shock ?

- Several non-randomized studies and one small prospective randomized study of dopamine vs norepinephrine for septic shock suggest that survival may be improved with the use of norepinephrine

Norepinephrine vs Dopamine+/_ Epinephrine in Septic Shock



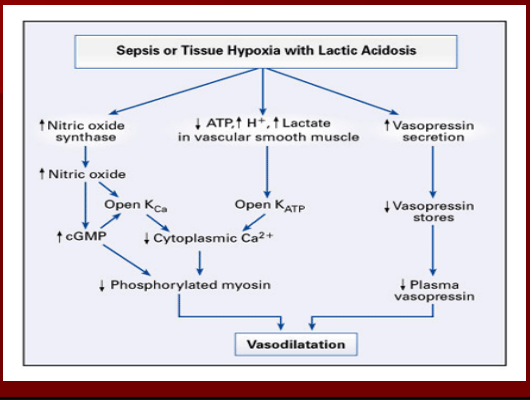
Claude, Critical Care Med 2000;28:2758

However

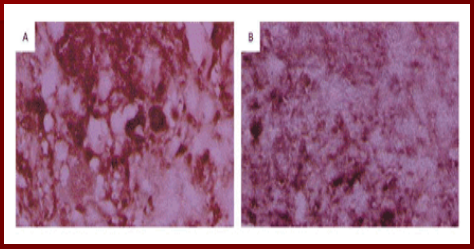
- If cardiac output is inadequate with norepinephrine, as indicated by a reduced mixed venous oxygen saturation, dobutamine may be added
- Vasopressin is emerging as a valuable addition to therapy for septic shock in patients with catecholamine refractory hypotension

Why Vasopressin ?

There is vasopressin deficiency in vasodilatory shock



VASOPRESSIN DEFICIENCY OCCURS IN SHOCK



A. Normal B. One hour of hemorrhagic shock

Why Vasopressin ?

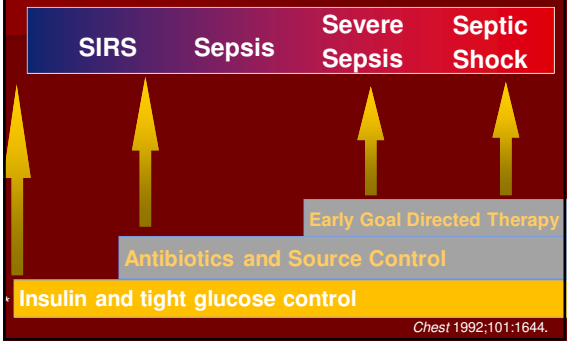
- Patients with septic shock have increased sensitivity to its pressor effects
- Vasopressin restores vascular tone in catecholamine resistant shock by several mechanisms including potentiation of adrenergic agents
- Low dose vasopressin increases urine output in septic patients, and increases creatinine clearance

BUT

Low-dose vasopressin did not reduce mortality rates as compared with norepinephrine among patients with septic shock who were treated with catecholamine vasopressors.

Russel JA et al: N Engl J Med, 2008

Therapy Across the Sepsis Continuum



Chest 1992;101:1644.

Glucose Control: Mechanisms

- Stress hyperglycemia is common in sepsis
- Glucose has pro-inflammatory effects
- Insulin resistance is common in sepsis
- Insulin has an anti-inflammatory effect, possibly via NOS.
- Benefit is likely related to both insulin itself and lowering of blood glucose

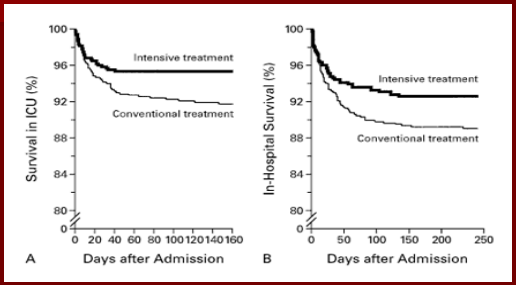
Intensive Insulin Therapy in Critically Ill Patients

Randomization

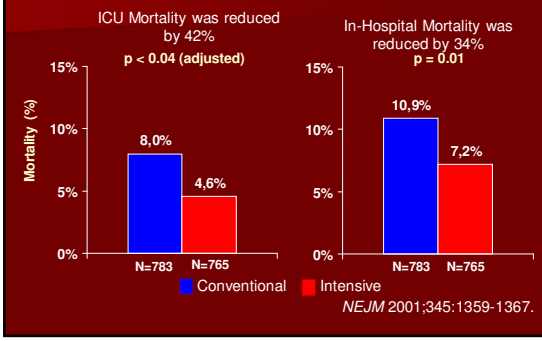
	Conventional	Intensive
Blood glucose level when insulin infusion was started	>215 mg/dL	>110 mg/dL
Infusion adjusted to maintain blood glucose	180 to 200 mg/dL (10.0 and 11.1 mmol/L)	80 to 110 mg/dL (4.4 to 6.1 mmol/L)
	39 % Received insulin	99% Received Insulin

van den Berghe G, et al. *NEJM* 2001;345:1359-1367.

Tight Glucose Control Improved Survival



Intensive Insulin Therapy in Critically Ill Patients: Mortality



NEJM 2001;345:1359-1367.

Tight Glucose Control

- Other dramatic effects: 46% decrease in bacteremias, 41% in acute renal failure requiring dialysis, 50% reduction in blood transfusion and a 44% decrease in critical illness polyneuropathy
- Patients with bacteremia had a mortality of 12.5% vs 29.5% and a decreased risk of MSOF

Institution of glycemic control is recommended (1B) with targeting a blood glucose < 150 mg/dL after initial stabilization (2C)

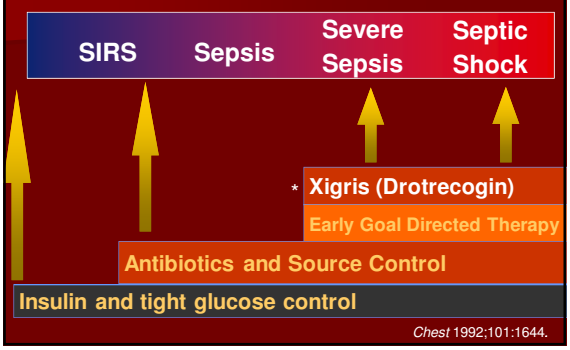
Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Critical Care Medicine, 2008.

BUT

The use of intensive insulin therapy placed critically ill patients with sepsis at increased risk for serious adverse events related to hypoglycemia.

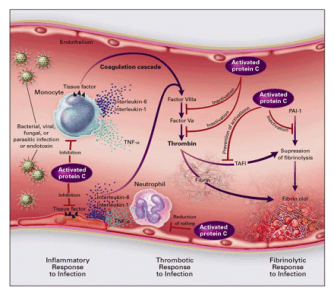
Brunkhorst FM et al. *NEJM* 2008.

Therapy Across the Sepsis Continuum



Chest 1992;101:1644.

Activated Protein C in Sepsis



Protein C:
1. Inactivates clotting factors limiting the generation of thrombin
2. Inhibits prodn of inflammatory cytokines

PROWESS Study Design

1690 Patients :
- Known or suspected infection
- ≥ 3 of the SIRS criteria
- ≥ 1 acute (< 24hr in duration) organ failures

RANDOMIZED

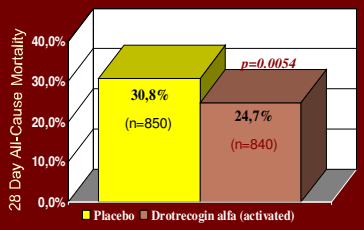
Placebo	Drotrecogin (xigris)
96 hr infusion + standard treatment	24 mcg/kg/hr 96 hour infusion + standard treatment

Primary Endpoint: All-Cause Mortality at 28 days

NEJM 2001;344:699-709.

PROWESS Results

Primary Stratified Intention-to-Treat Analysis



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

NEJM 2001;344:699-709.

Adverse Events with Drotrecogin alfa

TABLE 5. INCIDENCE OF SERIOUS ADVERSE EVENTS.

VARIABLE	PLACEBO GROUP (N=840)	DROTRECOGIN ALFA ACTIVATED GROUP (N=850)	P VALUE
	no. of patients (%)		
At least one serious adverse event	102 (12.1)	106 (12.5)	0.84
Serious bleeding event*	17 (2.0)	30 (3.5)	0.06
Gastrointestinal	9 (1.1)	9 (1.1)	
Intraabdominal	4 (0.5)	3 (0.4)	
Intrathoracic	1 (0.1)	6 (0.7)	
Retroperitoneal	0	4 (0.5)	
Intracranial	1 (0.1)	2 (0.2)	
Skin or soft tissue	0	2 (0.2)	
Genitourinary	0	2 (0.2)	
Source unidentified†	2 (0.2)	2 (0.2)	
Thrombotic events	25 (3.0)	17 (2.0)	0.20

*A serious bleeding event was defined as any intracranial hemorrhage, any life-threatening bleeding, any bleeding event classified as serious by the investigator, or any bleeding that required the administration of 3 units of packed red cells on two consecutive days.

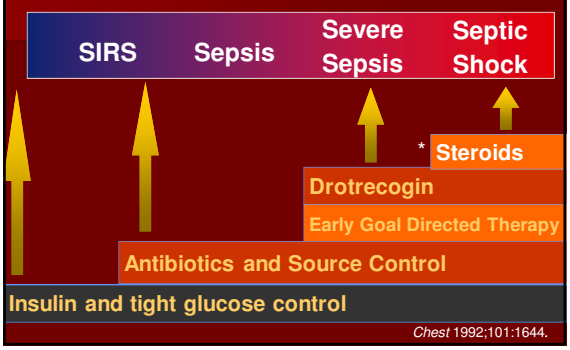
†These patients received 3 units of packed red cells on two consecutive days but had no identifiable source of bleeding.

« Patients who do not respond to institution of EGDT, antibiotics, and source control (ie, persistent hypotension, lactic acidosis, low ScvO2, or sepsis related dysfunction) and high risk of death, reflected by APACHE II score, should be considered for drotrecogin alfa (activated) administration » (Grade IIb)

Usually in ICU (24h-bundle) but in real life some patients stay more than 24 h in the ED!

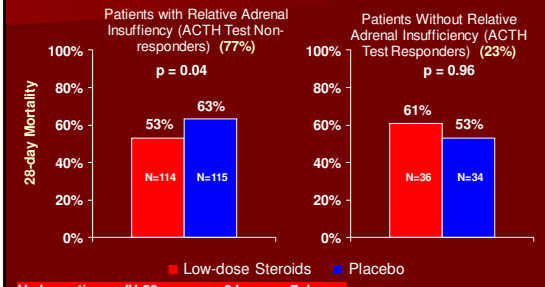
Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Critical Care Medicine, 2008.

Therapy Across the Sepsis Continuum



Chest 1992;101:1644.

Low Dose Steroid Treatment in Septic Shock: 28 Day Mortality (Non-responders vs. Responders)



Hydrocortisone IV 50mg every 6 hours x 7 days + Fludrocortisone 50mcg daily x 7 days

Annane D, et. al. *JAMA* 2002;288(7):862.

« Patients who have refractory shock (ie, require vasopressors after adequate volume resuscitation) or organ dysfunction and are receiving mechanical ventilation should have an adrenocorticotropic hormone-stimulation test and be given low-dose replacement corticosteroid therapy »

BUT

Hydrocortisone did not improve survival or reversal of shock in patients with septic shock, either overall or in patients who did not have a response to corticotropin, although hydrocortisone hastened reversal of shock in patients in whom shock was reversed.

Sprung CL et al. N Engl J Med 2008.

Corticosteroids in the Treatment of Severe Sepsis and Septic Shock in Adults

A Systematic Review. Djillali Annane et al. *JAMA. 2009;301(22):2362-2375*

Conclusions

Corticosteroid therapy has been used in varied doses for sepsis and related syndromes for more than 50 years, with no clear benefit on mortality. Since 1998, studies have consistently used prolonged low-dose corticosteroid therapy, and analysis of this subgroup suggests a beneficial drug effect on short-term mortality.

- 28-day mortality for treated vs control patients was 236/629 (**37.5%**) vs 264/599 (**44%**) (RR, 0.84; 95% CI, 0.72-0.97; *P=.02).* This treatment increased 28-day shock reversal (322/481 [**66.9%**] vs 276/471 [**58.6%**]; RR, 1.12; 95% CI, 1.02-1.23; *P=.02; I2=4%)*

SUMMARY: 6 - hour Severe Sepsis/ Septic Shock Bundle

- **Early Detection:**
  - Obtain serum lactate level.
- **Early Blood Cx/Antibiotics:**
  - within 3 hours of presentation. In fact during The first hour.
- **Early EGDT:**
  Hypotension (SBP < 90, MAP < 65) or lactate > 4 mmol/L:
  - initial fluid bolus 20-40 ml of crystalloid (or colloid equivalent) per kg of body weight.
- **Vasopressors:**
  - Hypotension not responding to fluid
  - Titrate to MAP > 65 mmHg.
- **Septic shock or lactate > 4 mmol/L:**
  - CVP and $ScvO_2$ measured.
  - CVP maintained >8 mmHg.
  - MAP maintain > 65 mmHg.
- **ScvO2<70%with CVP > 8 mmHg, MAP > 65 mmHg:**
  - PRBCs if hematocrit < 30%.
  - Inotropes.

The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. Mitchell M. Levy et al. Intensive Care Med (2010) 36:222–231.

- An analysis was conducted on data submitted from January 2005 through March 2008.
- Main results: Data from 15,022 subjects at 165 sites were analyzed.
  Compliance with the entire resuscitation bundle increased linearly from 10.9% in the first site quarter to 31.3% by the end of 2 years (P\0.0001).
- Unadjusted hospital mortality decreased from **37** to **30.8%** over 2 years (P = 0.001).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