

Management of Septic Shock

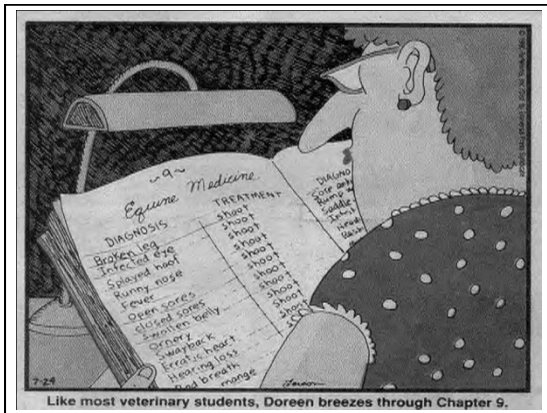
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A 62 year-old female presents to the ED with fever, cough, dyspnea. She has type 2 DM and COPD.

T 102, HR 130, RR 24, BP 100/50, SaO₂ = 94% on 6L. Breath sounds are decreased with egophony in the left base.

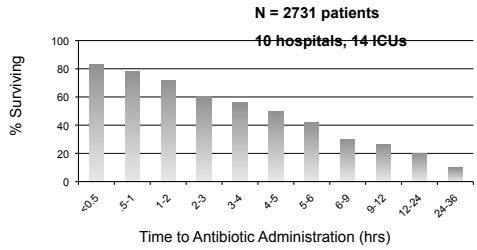
CXR shows LLL consolidation.

Wbc 18, Na 128, Creatinine 2.2, Lactate 2.1, Albumin 2.2

What is the next best step?

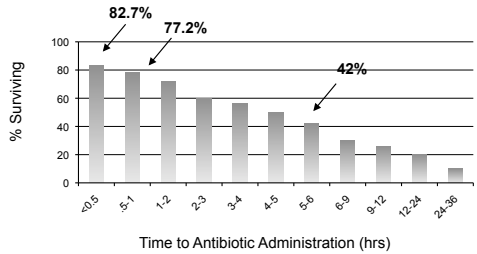
- A. Insert a central line and initiate early goal directed therapy
- B. Volume resuscitate with colloid (albumin or pentastarch)
- C. Give antibiotics to cover community acquired pneumonia
- D. Start norepinephrine to improve tissue perfusion

Prompt Administration of Antibiotics Saves Lives



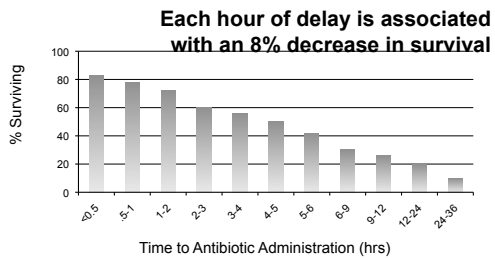
Kumar. Crit Care Med 2006

Prompt Administration of Antibiotics Saves Lives



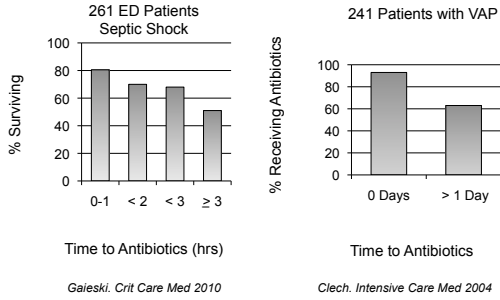
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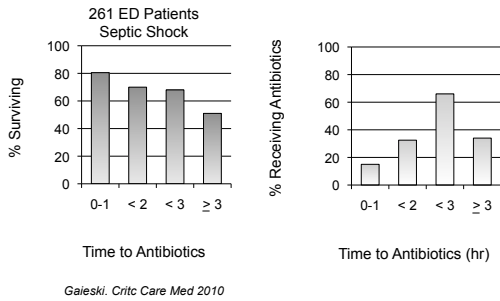


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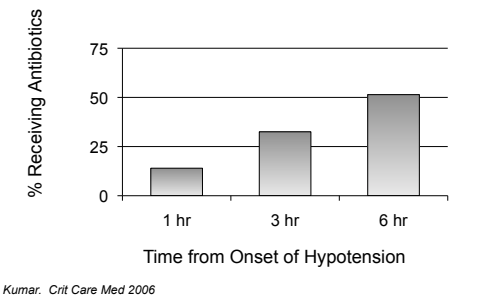
More Studies Demonstrating The Importance of Prompt Treatment With Antibiotics



Delay in Administration of Antibiotics is Common



Antibiotic Administration is Often Delayed



*Antibiotics For Septic Shock
Reasons for Delay*

1. Delay in making the diagnosis
2. Trying to get cultures first
 - Cultures are essential but as soon as antibiotics are ready, please give them
3. Transfer between units
4. Systems issues

*Antibiotics For Septic Shock
Systems Delay*

Systems Delay - Too many steps

1. Order written
2. Orders sent to pharmacy
3. Antibiotics mixed by pharmacy
4. Antibiotics delivered to unit
5. Antibiotics received by RN
6. Antibiotics hung

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Summary: Antibiotics for Sepsis



- Sepsis is an emergency!
- Early identification and treatment is crucial
- Get cultures and give antibiotics ASAP
- Make sure that all care providers understand the sense of urgency
- Give the most potent antibiotic first

You are called to the ED to admit a 62 year-old female with pneumonia and acute respiratory failure. She received prompt antibiotics as well as 3L of normal saline. Mechanical ventilation was initiated for hypoxemia. Norepinephrine has been started. Current BP is 88/40. The patient's daughter is an RN and asks about steroids.

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Which of the following is true regarding steroids?

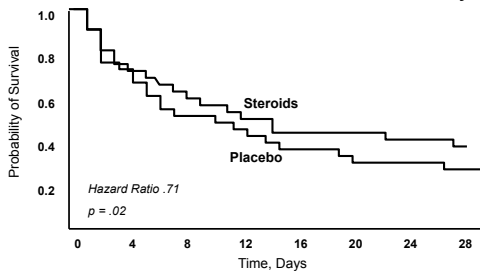
- A. Administration of steroids in this setting has a proven survival benefit.
- B. Administration of steroids to patients with septic shock accelerates time to shock resolution
- C. Baseline and ACTH-stimulated cortisol levels should be used to help guide therapy.
- D. All of the above

Effect of Treatment with Hydrocortisone on Mortality in Patients with Septic Shock *

- Design
 - Prospective, randomized, double-blind, placebo-controlled trial
 - 300 patients with septic shock
 - Randomized to treatment or placebo within 8 hours of developing shock
- Treatment Arms
 - Hydrocortisone 50 mg IV q6h + Fludrocortisone 50 mcg po q24 x 7 days
 - Placebo
- Data collection
 - Baseline cortisol level
 - Cortisol level 30 and 60 minutes after 250 mcg IV ACTH

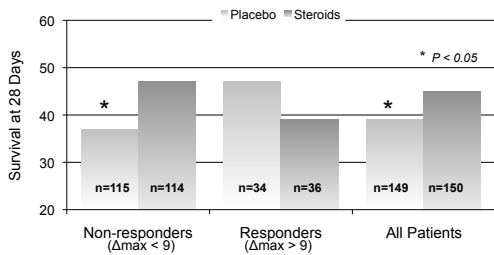
* Annane D. JAMA 2002; 288:862-871

Low Dose Steroids in Septic Shock Survival at 28 days



Annane, D. JAMA 2002;288:862-871.

Low Dose Steroids in Septic Shock Survival by Group

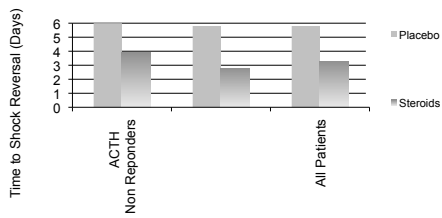


Corticosteroid Therapy of Septic Shock CORTICUS*

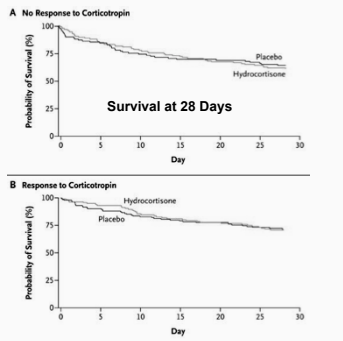
- Design
 - Randomized, double blind, placebo controlled trial (52 centers in Europe)
 - Designed to enroll 800 patients with severe sepsis or septic shock
 - Onset of shock within previous 72 hours (SBP < 90 despite adequate fluids or need for vasopressors for at least one hour and hypoperfusion or organ dysfunction)
- Treatment groups
 - Hydrocortisone 50 mg IV q6 hrs x 5d, then taper over 6 more days
 - Placebo
- Data collection
 - Baseline cortisol level
 - Cortisol level 60 minutes after 250 mcg IV ACTH
- Primary endpoint: 28 day mortality in corticotropin non-responders

Sprung CL. NEJM 2007;358:111-124

Time to Reversal of Shock



Sprung CL. NEJM 2007;358:111-124



Sprung CL. NEJM 2007;358:111-124

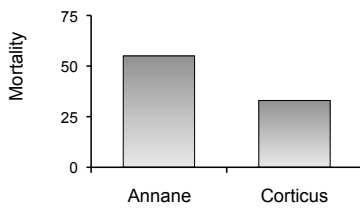
Was Annane Wrong?

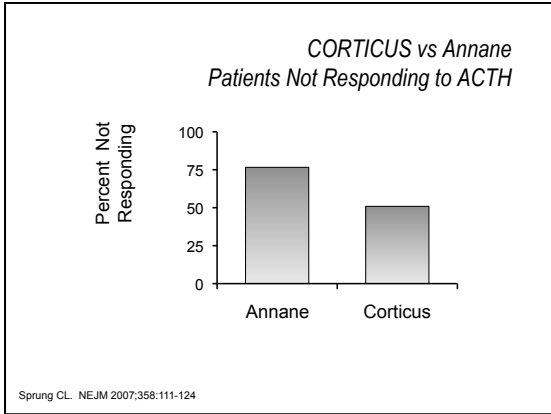
Corticosteroid Therapy in Septic Shock Annane versus CORTICUS

- Entry Criteria
 - Annane: SBP <90 for more than one hour despite fluids AND vasopressors
 - Corticus: SBP <90 despite fluid resuscitation OR need for vasopressors
- Time to enrollment
 - Annane: Under 8 hours after meeting entry criteria
 - Corticus: 72 hour window
- Treatment regimen:
 - Annane: Hydrocortisone and fludrocortisone for 7 days. No taper
 - Corticus: Hydrocortisone with taper over 11 days

Sprung CL. NEJM 2007;358:111-124
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CORTICUS vs Annane Mortality





CORTICUS Problems with Enrollment and Power

- Before the study, the investigators predicted that they needed sample size of 800 pts (400 per group) to have 80% power to detect a 10% decrease in mortality with baseline death rate of 50%.
- Death rate in control group was 31%. Only 500 patients enrolled. Thus, the study had a power of less than 35% to detect a 20% reduction in risk of death.
- Future study will need 2600 patients to detect a 15% reduction in mortality if baseline mortality is 35%

Steroids in Septic Shock Conclusions

- Corticosteroids improve time to shock resolution in patients with septic shock. They do not appear to improve survival in most patients
- Steroids are most effective when they are given early (< 8 hours) and when they are given to sicker patients (pressor dependent)
- We have no idea how to handle the ACTH stim test.

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Your patient with pneumonia and septic shock arrives in the ICU. She is now on 100% oxygen via the vent and CXR shows multilobar infiltrates. She remains on pressors. Laboratory values show a creatinine of 2.2, lactate 4.1, platelet count 42k. She has mild DIC.

What is the next best step?

- A. Place a pulmonary artery catheter to guide fluids
- B. Give albumin and lasix to remove lung water
- C. Initiate activated protein C infusion
- D. None of the above

*Efficacy and Safety of Recombinant Human Activated Protein C for Severe Sepsis (PROWESS)**

- Design
 - Randomized, double blind, placebo controlled trial (164 centers worldwide)
 - Designed to enroll 2280 patients with severe sepsis or septic shock
 - Sponsored by Eli Lilly (activated protein C = Xigris)
- Treatment groups
 - Drotrecogin alpha (APC) 24 mcg/kg/hr x 96 hour continuous infusion
 - Placebo
- Primary endpoint 28-day mortality
 - Data analysis based on age, protein C levels, disease severity (APACHE II)
 - Study stopped after 2nd interim analysis (1690 patients) due to significant drug benefit

* Bernard NEJM 2001;344:699-709

APACHE II
Acute Physiology and Chronic Health Evaluation

- Temperature
- Blood pressure
- Heart Rate
- Respiratory Rate
- pH or bicarbonate
- PaO₂ or (A-a) O₂
- Serum sodium
- Serum potassium
- Serum creatinine
- Hematocrit
- White blood cell count
- Glasgow Coma Score
- Age
- Chronic disease
- Score correlates directly with mortality
- www.globalrph.com/xigris

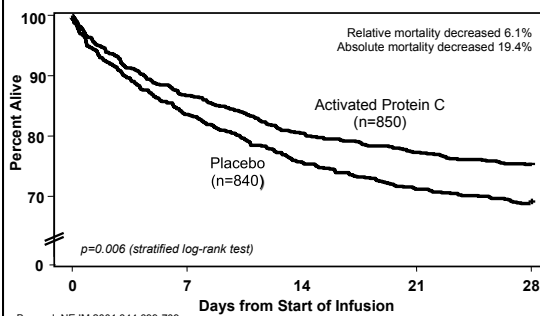
Knaus Crit Care Med 1985;13:818

PROWESS
Exclusion Criteria

- < 18 years of age
- > 135 kg
- Pregnancy, breastfeeding
- Neutropenia
- Chronic renal failure/dialysis
- Chronic liver failure
- Anticoagulant use
- Platelet count < 30,000/mm³
- Severe head trauma, intracranial surgery, or stroke in prior 3 months
- History of intracerebral AVM, cerebral aneurysm, or CNS mass lesion
- GI bleed in past 6 weeks
- Major surgery within previous 12 hours

Bernard NEJM 2001;344:699-709

28-Day All-Cause Mortality



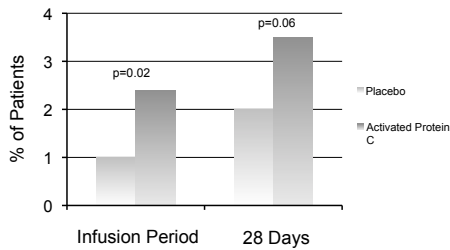
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PROWESS
Serious Bleeding Events

Serious bleeding event defined as:

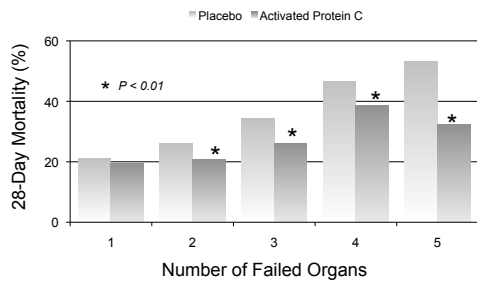
- Any intracranial hemorrhage
- Any life threatening bleed (at risk of death at time of event)
- ≥ 3 units of packed red blood cells/day for 2 consecutive days

PROWESS
Serious Bleeding Events

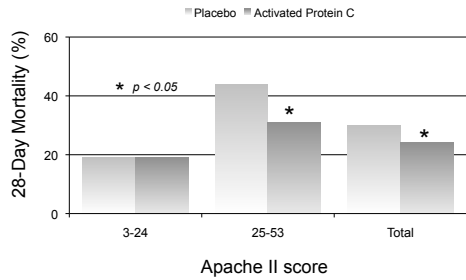


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Activated Protein C
Mortality by Number of Failed Organs



Activated Protein C Mortality by Apache II Score



Activated Protein C Conclusions

- Activated protein C reduces mortality in severe sepsis patients with acute organ dysfunction
- Indicated for patients with APACHE II > 25
 - 1 life saved for every 16 patients treated
 - 14% reduction in 28-day mortality
- Bleeding is major concern
 - Risk highest when platelet count is < 30 k
 - Patients with DIC and ARDS benefit most
- Stop infusion 2 hrs before surgery or an invasive procedure
- Restart 12 hrs after surgery and 2 hrs after less invasive procedures

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