Sepsis: Etiology, pathophysiology and survival

Michelle Harkins, MD

Objectives

- Define the spectrum of disease from SIRS to septic shock
- Review the epidemiology and factors that effect the severity of disease
- Outline the pathophysiology of sepsis
- Discuss treatment guidelines for therapy
- Review UNM mortality data with the sepsis protocol

SIRS Definition

- Widespread inflammatory response to a variety of severe clinical insults.
- Clinically recognized by the presence of 2 or more of the following:
  - Temperature >38C or < 36C
  - Heart Rate >90
  - Respiratory Rate > 20 or PaCO2 <32
  - WBC > 12,000, < 4000 or > 10% immature forms

Sepsis

- SIRS criteria + evidence of infection, or:
  - White cells in normally sterile body fluid
  - Perforated viscus
  - Radiographic evidence of pneumonia
  - Syndrome associated with a high risk of infection

Severe Sepsis

- **Sepsis criteria + evidence of organ dysfunction, including:**
  - CV: Systolic BP ≤ 90 mmHg, MAP ≤ 70 mm Hg for at least 1 hour despite volume resuscitation, or the use of vasopressors.
  - Renal: Urine output < 0.5 ml/kg body weight/hr for 1 hour despite volume resuscitation
  - Pulmonary: PaO2/FiO2 ≤ 250 if other organ dysfunction present or ≤ 200 if the lung is the only dysfunctional organ.
  - Hematologic: Platelet count ≤ 80K or decreased by 50% in 3 days
  - Metabolic: pH ≤ 7.3 and plasma lactate > 1.5 x upper normal

Organ System Involvement

- Circulation
  - Hypotension, increases in microvascular permeability
- Lung
  - Pulmonary Edema, hypoxemia
- GI tract
  - Translocation of bacteria, Liver Failure
- Nervous System
  - Encephalopathy, Critical Illness Polyneuropathy
- Hematologic
  - DIC, coagulopathy
- Kidney
  - Acute Tubular Necrosis, renal failure

Sepsis Epidemiology

- "Severe Sepsis" is the leading cause of death in (non coronary) ICU
- Sepsis accounts for 40% ICU expenditures
- Sepsis cases increasing @ 1.5% yearly (750,000)
- Septic Shock is sepsis with hypotension despite fluid resuscitation with perfusion abnormalities.

- ***Mortality***
  - ***Sepsis: 30% - 50%***
  - ***Septic Shock: 50% - 60%***

Natural history of sepsis Prospective study (n=2527)

Syndrome	ARF (%)	ARDS (%)
Sepsis		
1 criteria	9	2
2 criteria	13	3
3 criteria	19	6
Severe sepsis		
Culture (+)	23	8
Culture (-)	16	4
Septic shock		
Culture (+)	51	18
Culture (-)	38	18

Rangel-Frausto et al JAMA, 1995

Normal Response

- TNF release self-stimulating (autocrine process)
- Cytokine levels further increase by release of inflammatory mediators IL-1, platelet activating factor, IL-2, IL-6, IL-8, IL-10, IFN, eicosanoids.
- Continued activation of PMNs, macrophages (paracrine process).
- Clearing of bacteria, debris then tissue repair.
- PMN rolling, adhesion, diapedesis, chemotaxis, phagocytosis and bacterial killing highly controlled and localized.

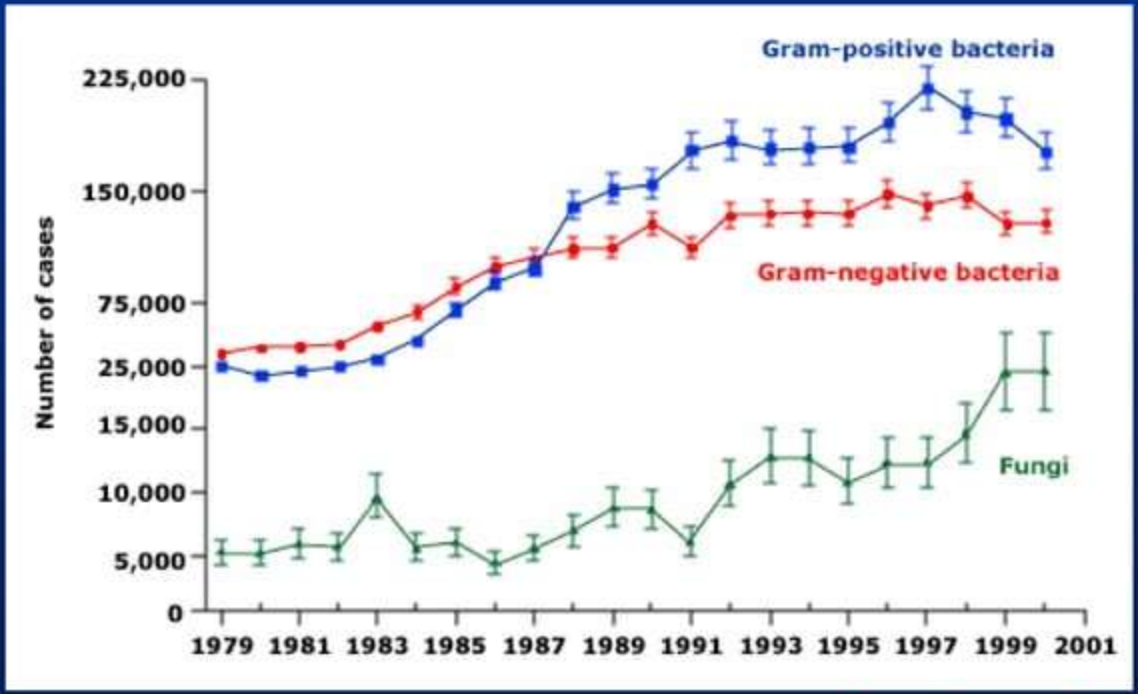
- Systemic pro-inflammatory reactions
  - Endothelial damage, microvascular dysfunction, impaired tissue oxygenation
- Excessive anti-inflammatory response
- Sepsis: auto-destructive process allowing normal responses to infection/injury to involve normal tissues

Pathogenesis of Sepsis

- Proinflammatory Cytokines
  - TNF-α and IL-1
- Bacterial Factors
- Complement Activation
- Cellular Injury
- Hypoxia
- Direct Cytotoxicity
- Apoptosis

Bacterial Factors

- LPS, cell wall components and bacterial products such as *Staph* enterotoxin, TSS toxin-1
- *Candida* species, *Pseudomonas, Klebsiella, Enterobacter* and *Serratia* are predictors of the clinical parameters associated with shock.

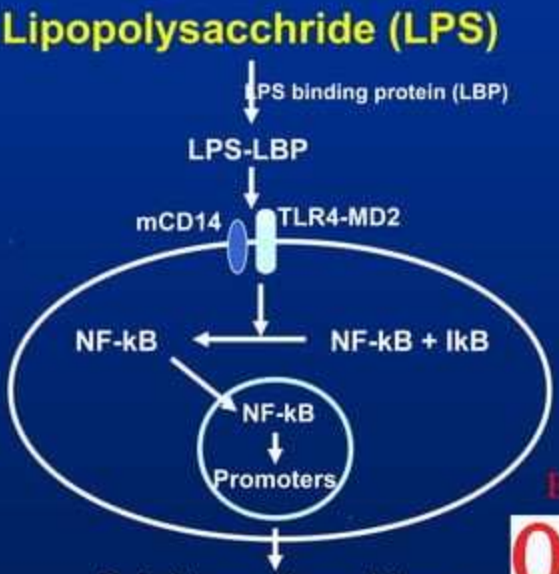


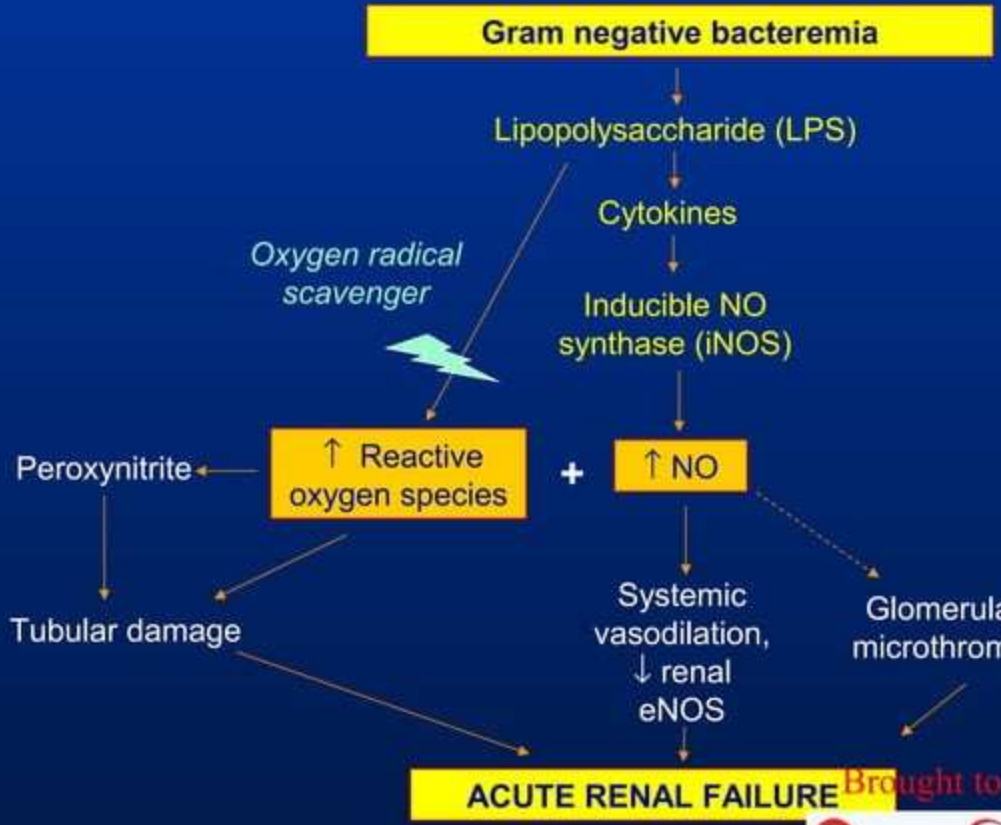
Martin et al, NEJM 2003; 348:1546

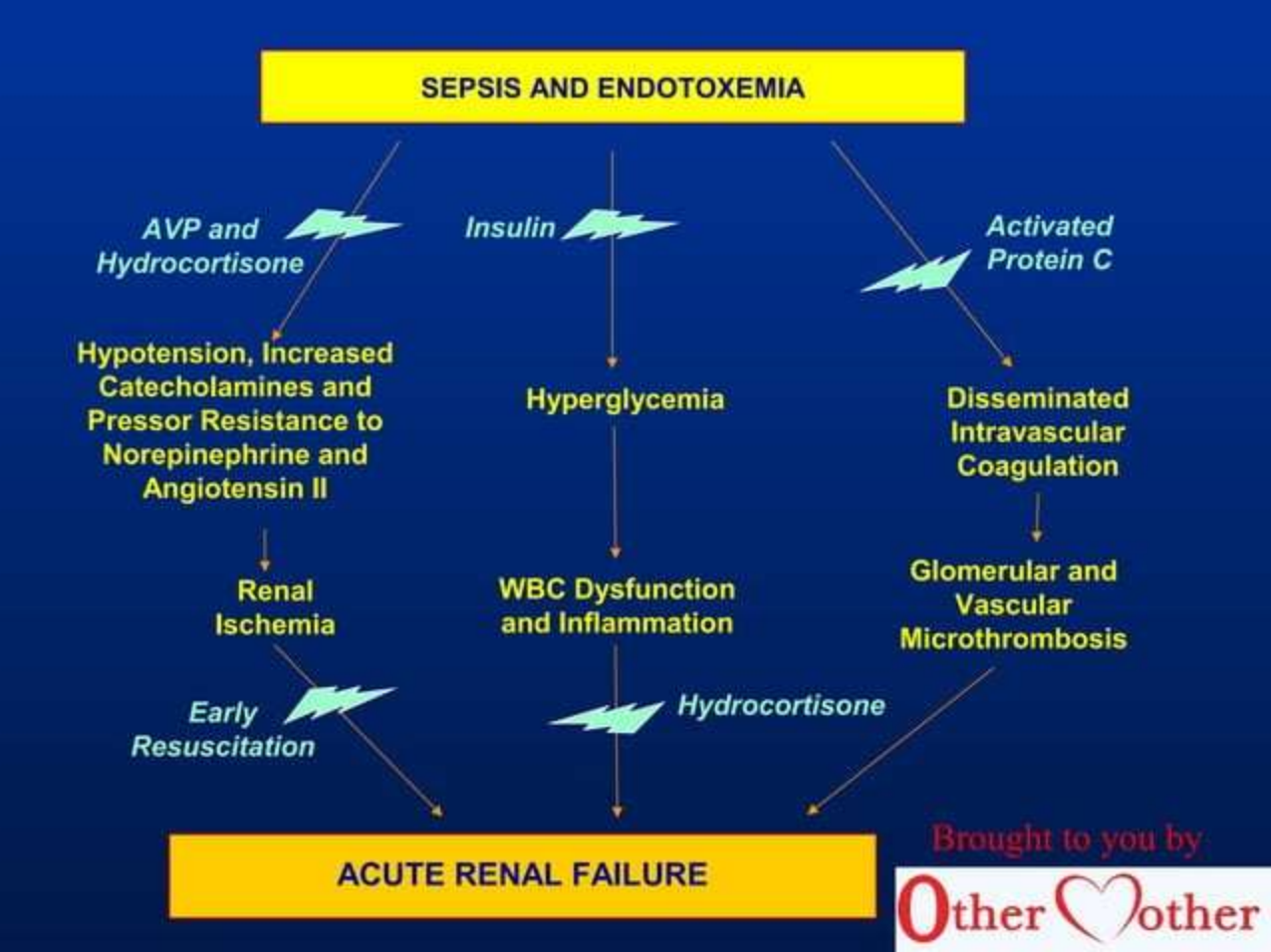
Endotoxin

- A lipopolysaccharide found in GN bacterial cell walls
- When infused into humans, mimics sepsis
- Activates the complement and coagulation systems
- Septic patients demonstrate endotoxemia and levels correlate with organ dysfunction

Cellular Events During Gram Negative Bacteremia






SEPSIS AND ENDOTOXEMIA
AVP and Hydrocortisone
Insulin
Activated Protein C
Hypotension, Increased Catecholamines and Pressor Resistance to Norepinephrine and Angiotensin II
Hyperglycemia
Disseminated Intravascular Coagulation
Renal Ischemia
WBC Dysfunction and Inflammation
Glomerular and Vascular Microthrombosis
Early Resuscitation
Hydrocortisone
ACUTE RENAL FAILURE
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Other other

Who is at risk for Sepsis?

- Patients with + blood cultures
- Comorbidities causing host-defense depression: AIDS, renal or liver failure, neoplasms
- Middle-aged, elderly

Characteristics that influence outcome

- Lack of febrile response
- Leukopenia
- Offending Organism
- Site of infection
- Nosocomial infections
- Shock and organ dysfunction

What do we have to offer these patients?

- Antibiotics
- IV Fluids
- Vasoactive agents
- Source control
- Steroid therapy (adrenal insufficiency)
- Activated protein C
- Ventilatory Strategies
- Glycemic control

Failed therapies

- Corticosteroids—high dose methylprednisolone
  - Bone et al. NEJM 1987;317:653
- Anti-endotoxin antibodies
  - Zieglar et al. NEJM 1991;324;429
- TNF antagonists—soluble TNF receptor
  - Fisher et al. NEJM 1996;334:1697
- Ibuprofen
  - Bernard et al. NEJM 1997;336:912

Treatment of Sepsis

- Early aggressive fluid resuscitation
- Antibiotics early
- Inotropes for BP support (Dopamine, vasopressin, norepinephrine)
- ? Hydrocortisone for adrenal insufficiency
- Tight glycemic control
- Possibly activated Protein C (Xigris)

Fluid Therapy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit

The SAFE Study Investigators*

- No mortality difference between colloid vs. crystalloid
- In severe sepsis patients (N=1218): mortality 35.3% (NS) vs. 30.7% (alb)… 95% CI .74-1.02 p=0.09

Antibiotics

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

Anand Kumar, MD; Daniel Roberts, MD; Kenneth E. Wood, DO; Bruce Light, MD; Joseph E. Parrillo, MD; Satendra Sharma, MD; Robert Suppes, BSc; Daniel Feinstein, MD; Sergio Zanotti, MD; Leo Taiberg, MD; David Gurka, MD; Aseem Kumar, PhD; Mary Cheang, MSc

- Abx within 1 hr hypotension: *79.9% survival*
- Survival decreased *7.6%* with each hour of delay
- Mortality increased by 2nd hour post hypotension
- Time to initiation of Antibiotics was the single strongest predictor of outcome

Antibiotics

Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis*

Jose Garnacho-Montero, MD, PhD; Jose Luis Garcia-Garmendia, MD, PhD; Ana Barrero-Almodovar, MD; Francisco J. Jimenez-Jimenez, MD, PhD; Carmen Perez-Paredes, MD; Carlos Ortiz-Leyba, MD, PhD

- Predictors of in hospital mortality:
  - SOFA scores
  - Respiratory failure within 24 hrs.
  - **Inadequate Empiric Antimicrobial Therapy**

- Independent Variables related to administration of inadequate Abx…
  - **Fungal Infection & previous Abx within the last month**

Vasopressor Therapy

Circulating Vasopressin Levels in Septic Shock

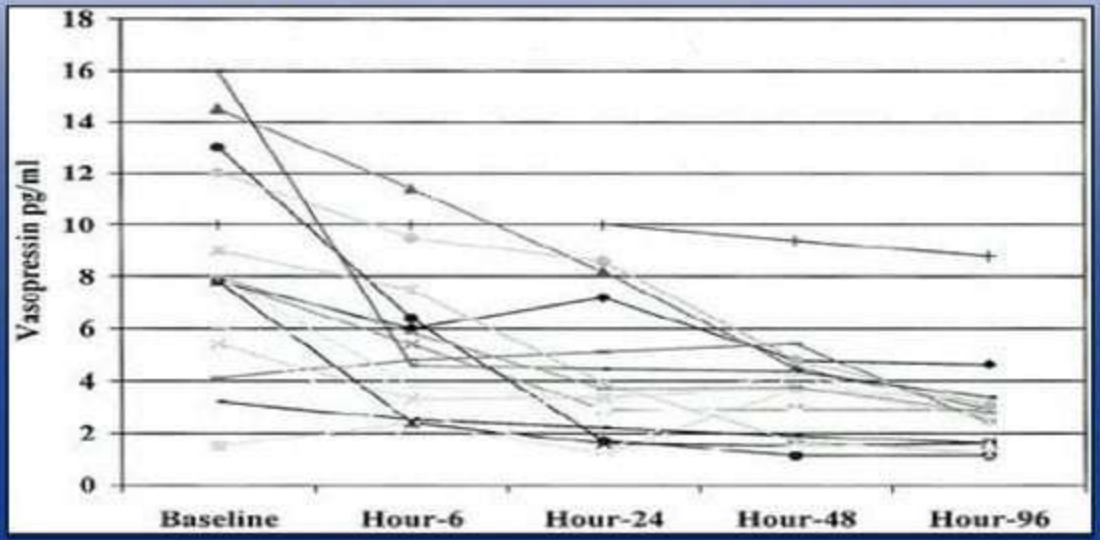


Figure 2, page 1755 reproduced with permission from Sharshar T, Blanchard A, Paillard M, et al. Circulating vasopressin levels in septic shock. *Crit Care Med* 2003; 31:1752-1758

Steroids

JAMA
The Journal of the American Medical Association

Volume 288(7) 21 August 2002 p 862–871

Effect of Treatment With Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patients With Septic Shock

[Caring for the Critically Ill Patient]

Annane, Djillali MD, PhD; Sébille, Véronique PhD; Charpentier, Claire MD; Bollaert, Pierre-Edouard MD, PhD; François, Bruno MD; Korach, Jean-Michel MD; Capellier, Gilles MD, PhD; Cohen, Yves MD, PhD; Azoulay, Elie MD; Troché, Gilles MD; Chaumet-Riffaut, Philippe MD; Bellissant, Eric MD, PhD

- Steroids for non-responders reduced mortality 10% without an increase in adverse events
- **Repeat studies have not supported routinely testing for relative adrenal insufficiency**

Surviving Sepsis Campaign

Surviving Sepsis

A global program to:

Reduce mortality rates in severe sepsis

Surviving Sepsis Campaign

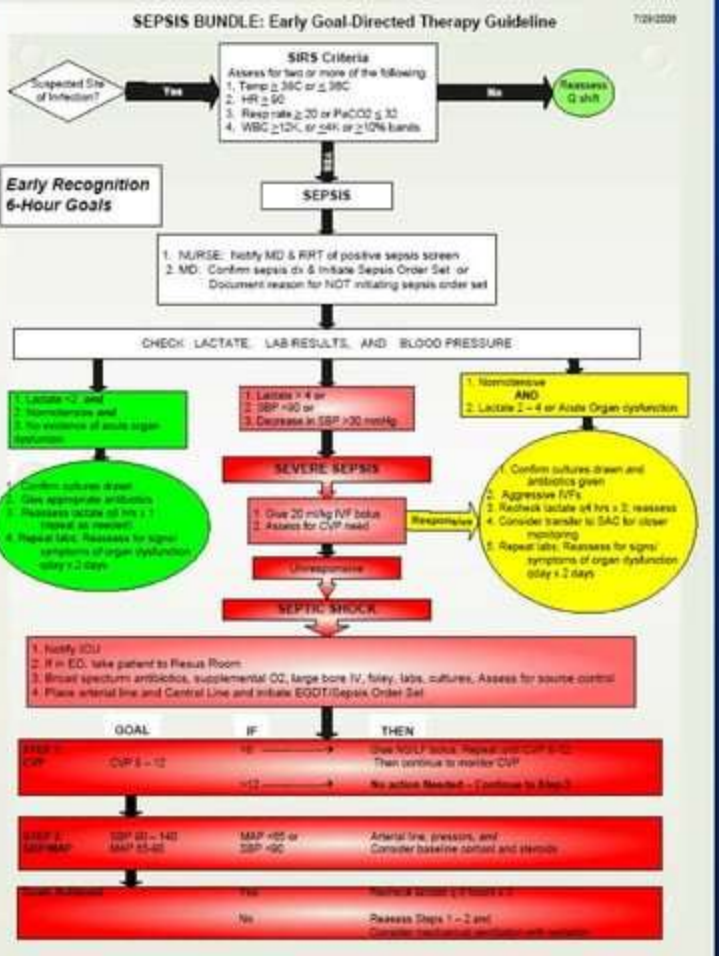
Sponsoring Organizations

- 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

Surviving Sepsis Implementation: "Care Bundles"

- ***6 Hour Sepsis Bundle***
  1. Measure serum lactate
  2. Blood cultures prior to Abx
  3. Broad spectrum Abx (3hrs)
  4. If hypotensive or lactate>4
     - ❑ Fluid bolus
     - ❑ Vasopressors for MAP≥ 65
  1. If persistent BP<65 or Lactate >4
     - ❑ Achieve CVP>8
     - ❑ SVO_2>65

- ***24 Hour Bundle***
  1. Steroids as needed
  2. APC if indicated
  3. Tight glycemic control
  4. Maintain plateau pressure <30



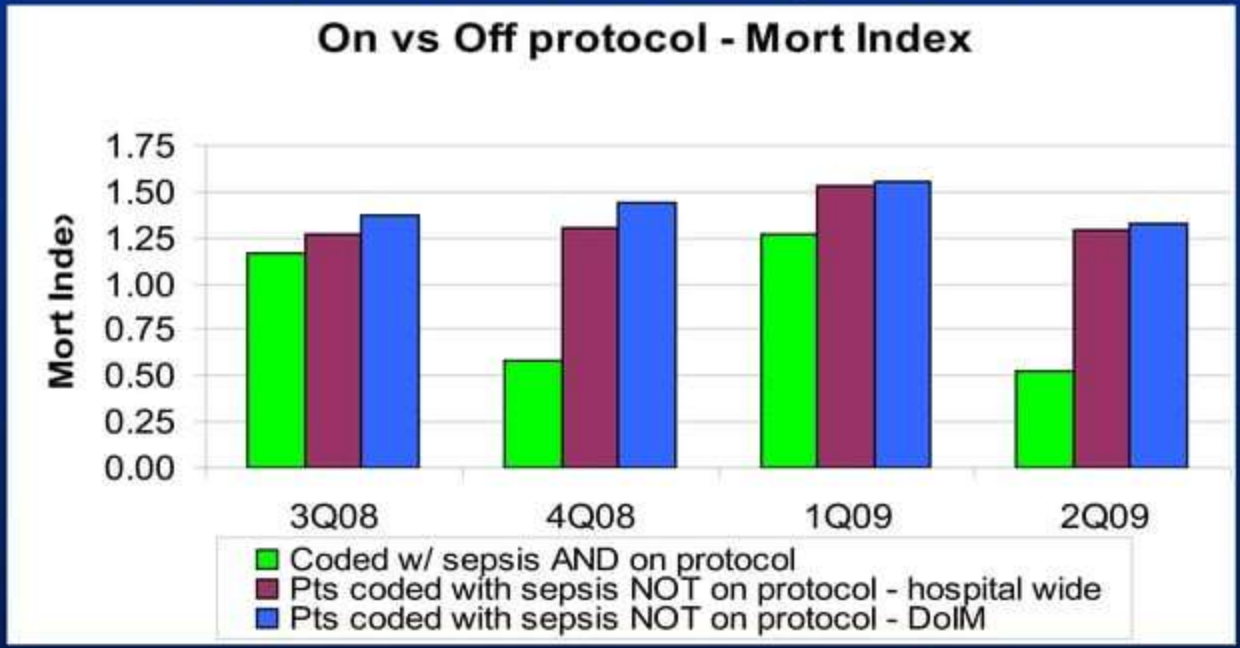
Sepsis Resuscitation Bundle

- The following steps should be completed as soon as possible (within 6 hours) after identification of a patient that has a positive SIRS screening
- Serum lactate measured
- Blood Cultures obtained

  Appropriate antibiotics administered
- If Lactate >4, SBP<90 or SBP decreased >30 mm Hg (Severe Sepsis):
- Give 20 ml/kg IVF bolus and assess need for CVP monitoring
- If responsive to fluids
  - continue aggressive IVFs as indicated
  - recheck lactate q 4 hours X 3
  - consider SAC transfer
- If unresponsive to fluids
  - Transfer to MICU

- Place arterial and central lines
  - Repeat fluid bolus 0.5-1L until CVP 8-12 mm Hg
- Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure ≥ 65 mmHg

Sepsis Pts Mortality Index



2Q2009 - only includes April & May discharges

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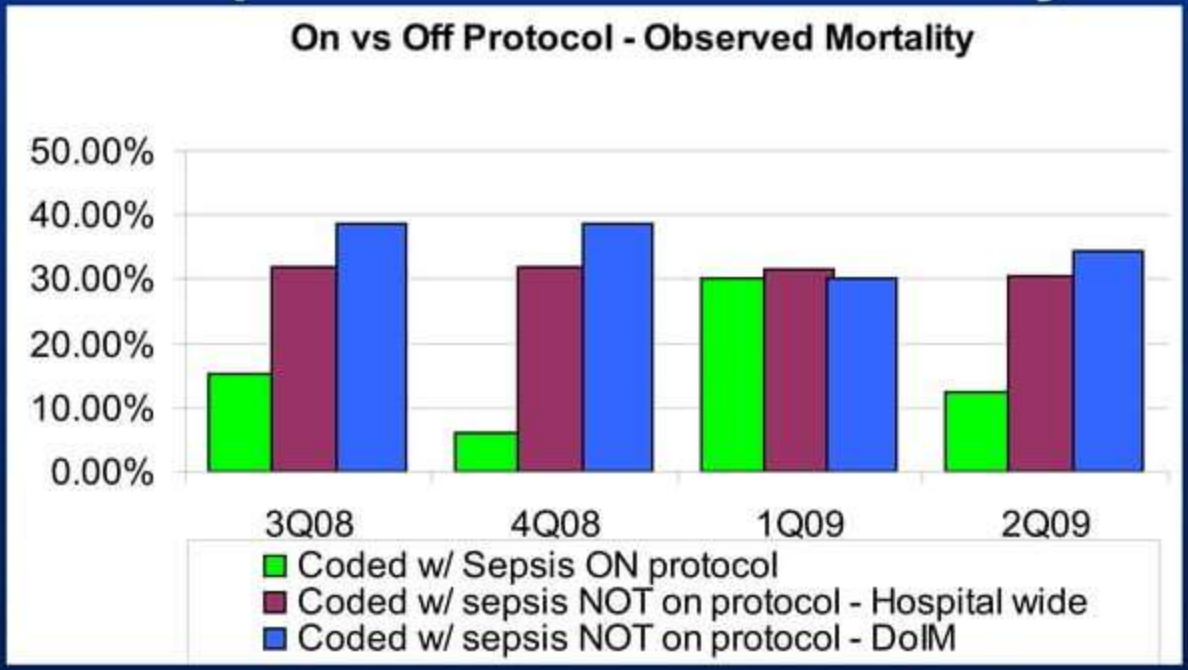
Sepsis Pts Observed Mortality



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Our views have increased the mark of the 10,000

- Thank you viewers
- Looking forward for franchise,

  collaboration, partners.

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