MANAGEMENT OF SEPSIS: WHAT HAVE WE LEARNED SINCE EGDT?

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PETER S. MARSHALL, MD MPH graduated from Yale College in 1991 and went on to the University of Connecticut to complete his MD in 1995. He then completed internal medicine training in 1998 at Yale-New Haven Hospital (YNHH). For four years Dr. Marshall was employed as a hospitalist / educator at the Hospital of Saint Raphael (HSR): now the Saint Raphael Campus of YNHH. While at the HSR, in addition to clinical and teaching duties, Dr. Marshall acted as corporate compliance officer for the Department of Medicine. From 2002 to 2005 Dr. Marshall completed training in Pulmonary & Critical Care Medicine at the Yale School of Medicine (YSM). During that time he completed an MPH in chronic disease epidemiology. He then joined Pulmonary Associates in Allentown, PA where he was the medical director of Respiratory Care for Lehigh Valley Hospital. In 2008 Dr. Marshall returned to the Yale School of Medicine and is currently an Assistant Professor. Since returning to YSM / YNHH, Dr. Marshall has directed the institution of a therapeutic hypothermia program and is currently involved in building a Tele-ICU program and PE response team. He continues to attend in the Medical Intensive Care unit and Medical Step-down Unit. He also sees pulmonary outpatients and inpatient consults. Currently, he is the Medical Director for the largest respiratory care department in the country (over 160 RTs) and also functions as the Medical Director of the Medical Step-Down Unit. Dr. Marshall has published several review articles and has spoken at both ATS and ACCP international meetings. He has been a member of NAMDRC since 2011 and is grateful for the opportunity to appear on the ballot.

OBJECTIVES:
Participants should be better able to:

1. Examine evidence behind selected current Surviving Sepsis Recommendations;
2. Examine the role of Procalcitonin in caring for patients with severe sepsis and septic shock;
3. Examine the role of protocols in the care of patients with severe sepsis and septic shock.
Septic Shock: What’s New Since EGDT?

NAMDRC ANNUAL CONFERENCE
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Outline

• Update regarding definitions and clinical criteria – “hot off the presses”
• Update in early detection / screening
• Update in Resuscitation
• Update in protocol driven care
Disclosure

• I have no financial disclosures as it relates to the content of this presentation.

• I have no conflicts of interest related to the content of this presentation.

**Question # 1**: Does the presence of altered mental status support the diagnosis of . . .

A) Sepsis  
B) Severe sepsis  
C) Septic shock  
D) All of the above
### TABLE 1. Diagnostic Criteria for Sepsis

**Infection, documented or suspected, and some of the following:**

<table>
<thead>
<tr>
<th>General variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (&gt;38.3°C)</td>
</tr>
<tr>
<td>Hypothermia (core temperature &lt;36°C)</td>
</tr>
<tr>
<td>Heart rate &gt; 90/min or more than two so above the normal value for age</td>
</tr>
<tr>
<td>Tachypnea</td>
</tr>
<tr>
<td>Altered mental status</td>
</tr>
<tr>
<td>Significant edema or positive fluid balance (&gt;20 mL/kg over 24 hr)</td>
</tr>
<tr>
<td>Hyperglycemia (plasma glucose &gt;140 mg/dL or &gt;7.7 mmol/L) in the absence of diabetes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inflammatory variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytosis (WBC count &gt; 12,000 µL⁻¹)</td>
</tr>
<tr>
<td>Leukopenia (WBC count &lt; 4000 µL⁻¹)</td>
</tr>
<tr>
<td>Normal WBC count with greater than 10% immature forms</td>
</tr>
<tr>
<td>Plasma C-reactive protein more than two so above the normal value</td>
</tr>
<tr>
<td>Plasma procalcitonin more than two so above the normal value</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hemodynamic variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial hypotension (SBP &lt;90 mm Hg, MAP &lt;70 mm Hg, or an SBP decrease &gt;40 mm Hg in adults or less than two so below normal for age)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Organ dysfunction variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial hypoxemia (PaO₂/FIO₂ &lt; 300)</td>
</tr>
<tr>
<td>Acute oliguria (urine output &lt;0.5 mL/kg/hr for at least 2 hrs despite adequate fluid resuscitation)</td>
</tr>
<tr>
<td>Creatinine increase &gt;0.5 mg/dL or 4.4 µmol/L</td>
</tr>
<tr>
<td>Coagulation abnormalities (INR &gt;1.5 or aPTT &gt; 60 s)</td>
</tr>
<tr>
<td>Leus (absent bowel sounds)</td>
</tr>
<tr>
<td>Thrombocytopenia (platelet count &lt; 100,000 µL⁻¹)</td>
</tr>
<tr>
<td>Hyperbilirubinemia (plasma total bilirubin &gt; 4 mg/dL or 70 µmol/L)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tissue perfusion variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlactatemia &gt; 1 mmol/L</td>
</tr>
<tr>
<td>Decreased capillary refill or metting</td>
</tr>
</tbody>
</table>

### TABLE 2. Severe Sepsis

**Severe sepsis definition = sepsis-induced tissue hypoperfusion or organ dysfunction (any of the following thought to be due to the infection)**

<table>
<thead>
<tr>
<th>Sepsis-induced hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate above upper limits laboratory normal</td>
</tr>
</tbody>
</table>

| Urine output < 0.5 mL/kg/hr for more than 2 hrs despite adequate fluid resuscitation |

| Acute lung injury with PaCO₂/FIO₂ < 250 in the absence of pneumonia as infection source |

| Acute lung injury with PaCO₂/FIO₂ < 200 in the presence of pneumonia as infection source |

| Creatinine > 2.0 mg/dL (178.8 µmol/L) |

| Bilirubin > 2 mg/dL (34.2 µmol/L) |

| Platelet count < 100,000 µL |

| Coagulopathy (international normalized ratio > 1.5) |
Defining sepsis, severe sepsis and septic shock

• Sepsis circa 1991:
  • Results from host’s systemic inflammatory response syndrome (SIRS) to infection
  • Severe sepsis: sepsis accompanied by organ dysfunction
  • Septic shock: sepsis – induced hypotension despite adequate fluid resuscitation

• Sepsis circa 2001:
  • Expansion of SIRS (clinical) criteria
  • No change in definitions

• Problems
  • 2 or more SIRS criteria are non-specific
  • Changes do not necessarily reflect an abnormal or dysregulated response
  • 12 % of patients in one cohort had infection and new organ failure but did not have 2 SIRS criteria, yet had significant mortality and morbidity
  • Definition of shock varies greatly → variability in clinical outcomes because of variability in clinical variables and cut-offs

Singer et al Jama v315 2016

Revision of 2008 surviving sepsis campaign

• Surviving sepsis campaign (SSC): International guidelines for management of severe sepsis and septic shock: 2012

• Three Hour Bundle
  • Lactate level
  • BLC prior to abx
  • Broad spectrum abx
  • 30 mL / Kg crystalloid for hypotension or LA > 4.0

• Six Hour Bundle
  • CVP 8 – 12
  • MAP > 65
  • U.O. 0.5 mL/kg/hr
  • SvO2 > 65 or ScvO2 > 70
  • Lactate levels elevated at outset → target efforts to lower

Crit Care Med v41 2013
### SSC 2012: Specific Interventions and Grades of Evidence

<table>
<thead>
<tr>
<th>Grade 1A</th>
<th>Grade 1B</th>
<th>Grade 1C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose control protocol (&lt; 180)</td>
<td>Antibiotics within 1 hour</td>
<td>Avoid Paralysis in absence of severe ARDS</td>
</tr>
<tr>
<td>SBT Protocol</td>
<td>De-escalate antibiotics</td>
<td>Consider limiting support</td>
</tr>
<tr>
<td>Sedation Holiday Protocol</td>
<td>Resuscitation with crystalloid</td>
<td>30 cc/kg IBW bolus</td>
</tr>
<tr>
<td>Protective ventilator strategy*</td>
<td>Avoid hetastarch</td>
<td>Culture before antibiotics</td>
</tr>
<tr>
<td>No renal dose DA</td>
<td>Norepinephrine first line pressor</td>
<td>Early source identification</td>
</tr>
<tr>
<td>No high-dose steroids</td>
<td>Dobutamine for systolic dysfunction</td>
<td>Avoid phenylephrine</td>
</tr>
<tr>
<td></td>
<td>Avoid bicarbonate</td>
<td>Early source control</td>
</tr>
<tr>
<td></td>
<td>DVT/PUD prophylaxis</td>
<td>Sepsis screens</td>
</tr>
</tbody>
</table>

### Screening for sepsis and performance improvement

- Screen potentially infected individuals for severe sepsis
- Rationale: Early intervention dependent upon early identification
- Early initiation of evidence based care improves outcomes and reduced sepsis related mortality
Validation of a Screening Tool for the Early Identification of Sepsis

- Used simple screening tool that RNs applied
- If reached a threshold, an LIP was asked to more thorough evaluation
- Evidenced based care applied asap if indicated
- Compared mortality from severe sepsis before and after intervention
- Compared mortality from severe sepsis with other units

Moore et al; Journal of Trauma v66 2009

Bedside Nurse Screening Tool

RESULTS

Moore et al; Journal of Trauma v66 2009
Automated sepsis screening

• Sepsis – Clinical syndrome not amenable to automated diagnosis. Screen with use of EMR and centralized staff (Tele-ICU).
  • Use IT to apply screening tools (high sensitivity, low / moderate specificity) at defined intervals, “cast a wide net several times per day”
  • Clinicians make the final diagnosis from among positive “screens”
  • Rincon et al performed approximately 194 screens / day to find 5 new cases of severe sepsis:
    → Bedside staff avoid sifting through gigabytes of data; info presented in a useful format to facilitate diagnosis
    → Diagnosis of the disease earlier; avoid multi-organ failure or death
    → Using only 1 intensivist and 2 – 3 RNs – while covering 100 to 120 ICU patients

Which screening tool should we use?

• Assessment of clinical criteria for sepsis
  • SOFA, qSOFA, SIRS, LODS
  • 1.3 Million EHR encounters (from 12 hospitals in southwestern PA) from patients w/ suspected infection
  • Jan 2010 to Dec 2012
  • Compared ability of screening tools to predict poor outcomes

• Confirmatory analysis
  • 700,000 outpatient encounters – US and non-US hospitals
  • Jan 2008 to Dec 2013
Screening tools: SOFA, qSOFA, LODS and SIRS

<table>
<thead>
<tr>
<th>SIRS (range 0 – 4)</th>
<th>SOFA (0 – 24)</th>
<th>LODs (0 – 22)</th>
<th>qSOFA (0 – 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>P / F</td>
<td>P / F</td>
<td>RR</td>
</tr>
<tr>
<td>WBC / bands</td>
<td>GCS</td>
<td>GCS</td>
<td>GCS</td>
</tr>
<tr>
<td>Pulse</td>
<td>MAP</td>
<td>SBP</td>
<td>SBP</td>
</tr>
<tr>
<td>Temp</td>
<td>Vasopressors</td>
<td>HR</td>
<td></td>
</tr>
<tr>
<td>pCO2</td>
<td>Cr / U.O.</td>
<td>Cr/U.O. / BUN</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bili</td>
<td>Bili</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plt</td>
<td>Plt</td>
<td></td>
</tr>
<tr>
<td></td>
<td>WBC</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>PT</td>
</tr>
</tbody>
</table>

AUC Analysis – Validation set

In-Hospital Mortality

<table>
<thead>
<tr>
<th>Assessment Tool</th>
<th>ICU</th>
<th>Non-ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIRS</td>
<td>0.64</td>
<td>0.76</td>
</tr>
<tr>
<td>SOFA</td>
<td><strong>0.74</strong></td>
<td>0.79</td>
</tr>
<tr>
<td>LODS</td>
<td><strong>0.75</strong></td>
<td>0.81</td>
</tr>
<tr>
<td>qSOFA</td>
<td>0.66</td>
<td><strong>0.81</strong></td>
</tr>
</tbody>
</table>

CONCLUSIONS:
1) Among ICU patients, SOFA and LODS had similar predictive capability despite greater complexity of LODS
2) Among Non-ICU patients the qSOFA had statistically greater predictive power for in-hospital mortality than SIRS or SOFA. qSOFA ideal screening tool.
3) Q-SOFA is simple and can be rapidly calculated without blood tests.
New definition & clinical criteria for sepsis and septic shock - Proposed

- Sepsis – Suspected or documented infection and life threatening organ dysfunction caused by a dysregulated host response to infection.
  
  Clinical variables:
  1) Acute rise in SOFA >= 2 points (use of SOFA as surrogate for organ dysfunction)

- Severe sepsis has less meaning now

- Septic shock - Subset of sepsis where circulatory and cellular metabolic abnormalities are profound enough to substantially increase risk of death
  
  Clinical variables to describe:
  1) MAP (< 65)
  2) Need for vasopressor therapy despite adequate resuscitation
  3) Lactate (> 2.0)

Singer et al Jama v315 2016

Operationalization of clinical criteria identifying patients with sepsis and septic shock
**Question # 2:** In a patient presenting with pneumonia, procalcitonin can . . .

- A) Help differentiate pure influenza pneumonia from influenza with bacterial superinfection.
- B) Not assist in predicting adverse events in patients with pneumonia.
- C) Reliably differentiate between SIRS and Sepsis in a critically ill patient.
- D) Not be used as a diagnostic criteria for sepsis.

**Procalcitonin**

- 116-amino acid peptide
- Pre-cursor to hormone calcitonin
  - Involved in calcium homeostasis
  - Produced by para-follicular C-cells of thyroid and neuroendocrine cells of lung and intestine
  - Rises in pro-calcitonin during infection do not affect Calcium levels
- Biomarker elevated in infection (especially bacterial) and inflammation: SIRS vs Sepsis
- Not supposed to be elevated as significantly in non-infectious inflammation or viral illness
- Use in patients with renal failure more complex as baseline levels higher
  - Pro-Calcitonin is dialyzed
Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis

• Estimated the diagnostic accuracy of procalcitonin in sepsis diagnosis in critically ill patients
• 18 studies were included
• Mean sensitivity 71% (95% CI 67–76)
• Mean specificity 71% (95% CI 67–76)
• AUC 0·78 (95% CI 0·73–0·83)
• CONCLUSION: Procalcitonin cannot reliably differentiate sepsis from non-infectious causes of SIRS in critically ill adult patients. This may differ from population at large or non-ICU populations

Benjamin et al, Lancet Infect Dis vol 7 2007

Prognostic value of procalcitonin in community-acquired pneumonia

• Assessed performance of PCT overall, stratified into four predefined procalcitonin tiers (<0.1, 0.1–0.25, >0.25–0.5, >0.5 μg·L⁻¹)
  • Stratified by Pneumonia Severity Index (PSI) and CURB-65
  • GOAL: To predict all-cause mortality and adverse events within 30 days follow-up in 925 CAP patients.
• RESULTS
  • Initial PCT levels performed only moderately for mortality prediction (area under the curve (AUC) 0.60
  • Follow-up measurements on days 3, 5 and 7 showed better prognostic performance (AUCs 0.61, 0.68 and 0.73)
  • For prediction of adverse events, the AUC was 0.66 and PCT significantly improved the PSI (from 0.67 to 0.71) and the CURB-65 (from 0.64 to 0.70)
• Conclusion: PCT was helpful during follow-up and for prediction of adverse events and, thereby, improved the PSI and CURB65 scores. Most helpful when combined with these prediction rules

Schuetz et al Eur Respir J, v37 2011
Can procalcitonin help identify associated bacterial infection in patients with severe influenza pneumonia? A multicenter study

- Retrospective observational study during 2009 H1N1 pandemic
- Compared PCT levels between influenza associated and not associated with a bacterial co-infection

- RESULTS:
  - 103 flu A patients not receiving prior abx → 48 had documented bacterial co-infection

Cuquemelle et al, Intensive Care Medicine v37 May 2011

Conclusions:
PCT may help discriminate viral from mixed pneumonia during the influenza season. Levels of PCT less than 0.8 μg/l combined with clinical judgment suggest that bacterial infection is unlikely. PCT had better operating characteristics than CRP.
Can procalcitonin tests aid in identifying bacterial infections associated with influenza pneumonia? A systematic review and meta-analysis

- Six studies; 137 patients with co-infection, 381 cases without

- RESULTS
  - Mean sensitivity = 0.84 (95% CI 0.75 – 0.90)
  - Mean specificity = 0.65 (95% CI 0.58 – 0.69)

- CONCLUSIONS:
  - PCT tests have a high sensitivity, particularly for ICU patients. It can be used as a suitable rule-out test (good negative likelihood ratio)
  - PCT has low specificity for identifying secondary bacterial infections among patients with influenza. It cannot be used as a standalone rule-in test.

Meng-Huan wu et al; Influenza Other Respir Viruses. v7 2013

Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis

- 30 studies (3244 patients)

- RESULTS:
  - Mean sensitivity 0.77 (95% CI 0.72 – 0.81)
  - Mean specificity 0.79 (95% CI 0.81 – 0.88)
  - AUC 0.85 (95% CI 0.81 – 0.88)

- CONCLUSION:
  - Procalcitonin is a helpful biomarker for early diagnosis of sepsis in critically ill patients.
  - Results of the test must be interpreted carefully in the context of medical history, physical examination, and microbiological assessment

Wacker et al; The Lancet – Infectious Diseases V13, May 2013
**Question # 3**: Use of albumin with crystalloid versus crystalloid alone for resuscitation may worsen 90 day mortality in patients with septic shock.

- A) Statement TRUE
- B) Statement FALSE

**Question # 4**: Targeting the lactic acid instead of the ScvO2 during resuscitation of a patient with septic shock may result in ...

- A) Reduced ICU LOS
- B) Increased mortality
- C) Increased hospital LOS
- D) Similar rates of organ failure
- E) Increased ventilator free days
Which Fluids? CRYSITMAS study.

- 6% HES 130/0.4 and NaCl 0.9% for HDS in patients with severe sepsis
- Prospective, multicenter, active-controlled, double-blind, randomized study in the ICU

**RESULTS:**

- Less HES used to reach HDS vs. NaCl (mean difference = -331±1,033, 95% CI -640 to -21, P = 0.0185).
- ICU and hospital LOS, and area under the curve of SOFA score were comparable.
- Acute renal failure occurred in 24 (24.5%) and 19 (20%) patients for HES and NaCl, respectively (P = 0.454).
- No difference in mortality, coagulation, or pruritus up to 90 days after treatment initiation.

**CONCLUSIONS:**

- Significantly less volume required to achieve HDS for HES vs. NaCl in the initial phase of fluid resuscitation in severe sepsis
- No difference in adverse events

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**Hydroxyethyl Starch 130/0.42 versus Ringer’s Acetate in Severe Sepsis (6 S TRIAL)**

- N = 798, severe sepsis
- Multi-center, RCT, double blind of HES versus LR
- Used up to 33 cc / kg IBW per day
- Primary outcomes were death or ARF

**RESULTS:**

- RR of death 1.17 in HES versus LR (p = 0.03)
- RR of RRT 1.35 in HES versus LR (p = 0.04)

**CONCLUSIONS:**

HES 130/0.42 group had an increased risk of death at day 90 and were more likely to require renal-replacement therapy
Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care (CHEST TRIAL)

- N = 7000
- Multi-center, blinded, RCT
- HES versus saline
- Outcomes:
  - Primary outcome was 90 day mortality
  - Secondary – ARF

RESULTS:
- No difference in mortality
- RRT used more frequently in HES group (7.0 versus 5.8%, p = 0.04)
- HES associated with more adverse events (5.3 versus 2.8%, p< 0.001)

CONCLUSIONS:
- No difference in 90-day mortality between HES (130/0.4) and saline group.
- More patients who received resuscitation with HES were treated with RRT.

Myburgh; NEJM V367 2012

Albumin Replacement in Patients with Severe Sepsis or Septic Shock (ALBIOS)

Caironi et al; NEJM V370 2014
from day 1 to day 28 (or ICU discharge if earlier)

- **Albumin**
  - Plasmatic level of Albumin
    - $\geq 30 \text{ g/L}$
    - $< 30 \text{ g/L}$
      - $\geq 25 \text{ g/L}$
        - No infusion of Albumin
      - $< 25 \text{ g/L}$
        - Infusion of Albumin: 200 ml at 20% in 3* hrs
        - Infusion of Albumin: 300 ml at 20% in 3* hrs

*N.B.: if not available, please refer to the last value available of plasmatic level of albumin*

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**Overall population**  
*(1810 pts)*

- **Albumin**
- **Crystalloids**

Log-rank $P=0.39$

90-day mortality: 41.1% vs. 43.6%  
($P=0.29$)
Conclusions

In patients with sepsis albumin infusion compared to crystalloids alone provided hemodynamic advantages, and more favorable fluid balance without survival benefits.

In patients with septic shock, as recognized at entry, hemodynamic fluid balance advantages were greater than in general population and, in addition, these patients survived significantly more at 90 days.
Crystalloid versus Colloid

- No survival benefit of colloid over crystalloid in majority of severe sepsis.

- Small 90 day survival benefit in septic shock defined by SOFA score 3 or 4 – w.r.t. albumin (post-hoc analysis)

- Hetastarch increases need for RRT and may increase mortality.

Which is a superior target? LA vs ScvO2

→ Essentially no difference in targeting ScvO2 versus LA

Jones et al; JAMA v303 2010
**Question # 5:** When comparing trials testing protocol driven resuscitation (EGDT) against usual care which trials had similar mortality in the EGDT group?

- A) Rivers and ProMISE
- B) ProCESS and Rivers
- C) ARISE and Rivers
- D) ARISE and ProMISE
- E) A and D

**Question # 6:** When comparing trials testing protocol driven resuscitation (EGDT) against usual care which trial had the highest usual care mortality?

- A) ProCESS
- B) ARISE
- C) Rivers
- D) ProMISE
Protocol-based sepsis care

- **Rivers et al**
  - EGDT
- **ProCESS**
  - Treatment group: Similar to River’s; ScvO2 > 70 %, transfuse for HCT > 30%, no A-line
  - Protocolized Standard Care*: Structured treatment based on SBP and physician judgement of fluid status (no CVP, ScvO2, Hb > 7, A-line)
  - Usual care: Treatment based on physicians’ / sites’ practices
  - Conclusions: Protocol-driven resuscitation of patients diagnosed with septic shock did not improve outcomes
- **ARISE**
  - Treatment group: Similar to River’s; Continuous ScvO2, A-line
  - Usual Care: No ScvO2 during first 6 hours
  - Conclusion: Protocol driven care does not offer survival advantage over usual care.
- **ProMISe**
  - Treatment group: Continuous ScvO2 monitoring,
  - Usual Care
  - Conclusions: Techniques in standard resuscitation have evolved since Rivers. Protocol driven management and continuous ScvO2 monitoring did not improve outcomes.
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</tr>
</thead>
<tbody>
<tr>
<td># per group</td>
<td>130, 130</td>
<td>445, 448, 458</td>
<td>792, 796</td>
<td>625, 626</td>
</tr>
<tr>
<td>Standard Rx Mortality</td>
<td>46.5%</td>
<td>18.9%</td>
<td>18.8%</td>
<td>29.2%</td>
</tr>
<tr>
<td>EGDT mortality</td>
<td>30.5%</td>
<td>21.0%</td>
<td>18.6%</td>
<td>29.5%</td>
</tr>
<tr>
<td>APACHE II</td>
<td>20.4</td>
<td>20.7</td>
<td>15.8</td>
<td>18.0</td>
</tr>
<tr>
<td>ScvO2 %</td>
<td>48.5 + / - 11.2</td>
<td>71 + / - 13</td>
<td>72.7 + / - 10.5</td>
<td>70 + / - 12</td>
</tr>
<tr>
<td>ScvO2 &gt; 70 %</td>
<td>3, 3</td>
<td>222, 224, 229</td>
<td>346, 348</td>
<td>312, 313</td>
</tr>
<tr>
<td>Time to Abx*</td>
<td>92.4% in 6 hrs</td>
<td>75% in 72 mins</td>
<td>Median 91 mins</td>
<td>100% in 2.5 hrs</td>
</tr>
<tr>
<td>Volume before randomization</td>
<td>20 – 30 mL / Kg</td>
<td>&gt; 29 mL / kg</td>
<td>&gt; 20 mL / kg</td>
<td>&gt; 1.95 L in 2.5 hrs</td>
</tr>
</tbody>
</table>

Do we “scrap” protocol driven resuscitation?

- Was there clinical equipoise?
  - Was usual care really non-EGDT or are clinicians just using EGDT without ScvO2?
- ScvO2, lactic acid and CVP not perfect as end points or goals but better then no end point or goal
- Mortality has dropped in septic shock because of **early** . . .
  - Recognition
  - Fluids
  - Anti-biotics
  - Defined end-points (ScvO2, U.O., CVP, lactate etc . . .)
  \(\rightarrow\) All essential parts of initial sepsis care bundle

\(\rightarrow\) We are studying a slightly different syndrome than Rivers
- Need to improve / modernize protocols to meet needs of current era of sepsis care
QUESTIONS?

• Thank you.