Early Goal Directed Therapy for Sepsis

Derek C. Angus, MD, MPH, FRCP

The CRISMA Laboratory
Critical Care Medicine
School of Medicine
University of Pittsburgh
Today's Goals

- Review EGDT
  - Review the argument for EGDT
  - Assess whether further study is necessary
  - Consider design challenges for evaluation of EGDT
  - Review proposed studies

- Use EGDT as a case study for the evaluation of complex interventions

Severe sepsis

- 1995
  - 750,000 cases per year
  - 34% hospital mortality
  - Angus et al Crit Care Med 2001

- 2004
  - 571,000 cases of suspected severe sepsis in US EDs
  - Wang et al Crit Care Med 2007

- Cases
- Incidence/1,000 Population

Age/Years

- Number of cases
- Incidence rate
**Initial management**

Surviving Sepsis Guidelines (GRADE system)  
Dellinger et al CCM 2008

- Blood cultures before antibiotic therapy (1C)
- Prompt imaging studies to confirm potential source (1C)
- Broad-spectrum antibiotics within 1 hr of shock (1B)
- Source control (1C)
- Stress-dose steroids if BP poorly responsive (2C)
- Early goal directed therapy (EGDT) (1C)
  - Fluid challenge to restore mean circulating filling pressure (1C)
  - Norepinephrine or dopamine to maintain MBP > 65 mm Hg (1C)
  - Inotrope therapy if cardiac output low despite resuscitation (1C)

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**Early Goal-Directed Therapy**

Supplemental oxygen & endotracheal intubation and mechanical ventilation  
SIRS + Infection + (SBP < 90 mmHg after bolus OR LA > 4 mmol/L)  
Central venous and arterial catheterization  
Sedation and/or paralysis (if intubated)

- CVP: $< 8$ mm Hg  
- MAP: $< 65$ mm Hg  
- $> 90$ mm Hg  
- $\geq 65$ and $\leq 90$ mm Hg  
- ScvO$_2$: $< 70\%$  
- $\geq 70\%$

Transfusion of red cells to hematocrit $\geq 30\%$

Crystalloid

Colloid

Vasoactive agents

Inotropic agents

Goals achieved

Hospital admission
Rationale for EGDT

- Systemic hypoperfusion (global tissue hypoxia) is a cardinal, yet often cryptic, feature of severe sepsis and septic shock

- In sepsis, global tissue hypoxia results from
  - Inflammatory cascade leading to cardiovascular insufficiency
  - Increased metabolic demands
  - Decreased oxygen delivery
    - Hypovolemia, vasodilation, myocardial depression
  - Increased oxygen extraction
  - Mitochondria defects and/or cytopathic hypoxia

- EGDT may provide early recognition and resolution of global tissue hypoxia

Identifying Global Tissue Hypoxia

- SvO₂ reflects balance between oxygen delivery and oxygen demand

- ScvO₂ correlates with SvO₂ in shock states
  - ScvO₂ > SvO₂ by 5-7%
  - Difference diminishes at lower saturations (<50%)

- ScvO₂ feasible in the ED

- Combination of ScvO₂ and lactate allows for recognition of global tissue hypoxia
EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

EMANUEL RIVERS, M.D., M.P.H., BRYANT NGUYEN, M.D., SUZANNE HAVSTAD, M.A., JULIE RESSLER, B.S., ALEXANDRIA MUZZIN, B.S., BERNHARD KNOBLICH, M.D., EDWARD PETERSON, PH.D., AND MICHAEL TOMLANOVIČ, M.D., FOR THE EARLY GOAL-DIRECTED THERAPY COLLABORATIVE GROUP*

✿ Single center study
   ● N=263

✿ Protocolized EGDT vs. usual care

✿ 16% absolute mortality reduction
   ● 30% vs. 46%

EGDT in the First Six Hours

Control: 3.5L IV fluids
EGDT: 5.0L IV fluids

But…, no differences by 72 hours
Rivers concerns

- Why is control arm mortality so high?
- What ‘is’ the intervention, exactly?
  - The suite of physiology-based instructions and therapies?
  - Is Manny Rivers just a really good doctor?
- Is the catheter necessary?
- Are the blood and inotropes necessary?
- Given FACTT, is so much fluid really that valuable?
- Why is this study positive when others were negative?
  - After all, is ‘early’ really ‘early’?

Control Group Mortality in Rivers et al much higher than comparables

![Graph showing the relationship between APACHE II Score and 28-day Mortality. The graph has a linear trend line with an R² value of 0.95. The control group mortality in Rivers et al. 2001 is significantly higher compared to comparables.]
Blood

- PRBC used in 2/3 of EGDT subjects in first 6h
  - Three-fold increase over the control arm

- Long ago abandoned as primary fluid resuscitation
  - Risk of blood borne Infection
  - Transfusion reactions
  - TRALI

- No benefit to transfusion beyond a threshold of 7 g/dL

- PRBC (especially older units)
  - Deficient in 2,3-DPG
  - Relatively noncompliant
  - Can decrease the delivery of O2 to tissues
  Marik and Sibbald *JAMA* 1993;269:3024-3029

Dobutamine

Table 5. Hospital Mortality and Length of Stay

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lactate Clearance Group (n = 150)</th>
<th>ScvO2 Group (n = 150)</th>
<th>Proportion Difference (95% Confidence Interval)</th>
<th>P Value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality, No. (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>25 (17)</td>
<td>34 (23)</td>
<td>6 (~3 to 15)</td>
<td>.10</td>
</tr>
<tr>
<td>Intent to treat</td>
<td>25 (17)</td>
<td>33 (22)</td>
<td>5 (~3 to 14)</td>
<td>.11</td>
</tr>
<tr>
<td>Length of stay, mean (SD), d</td>
<td>ICU</td>
<td>5.9 (9.48)</td>
<td>5.6 (7.36)</td>
<td>.75</td>
</tr>
<tr>
<td></td>
<td>Hospital</td>
<td>11.4 (10.89)</td>
<td>12.1 (11.68)</td>
<td>.60</td>
</tr>
<tr>
<td>Hospital complications</td>
<td>Ventilator-free days, mean (SD)</td>
<td>9.3 (10.31)</td>
<td>9.9 (11.09)</td>
<td>.67</td>
</tr>
<tr>
<td></td>
<td>Multiple organ failure, No. (%)</td>
<td>37 (25)</td>
<td>33 (22)</td>
<td>.68</td>
</tr>
<tr>
<td></td>
<td>Care withdrawn, No. (%)</td>
<td>14 (9)</td>
<td>23 (15)</td>
<td>.15</td>
</tr>
</tbody>
</table>

Abbreviations: ICU, intensive care unit; ScvO2, central venous oxygen saturation.

<sup>a</sup>Primary study end point.

<sup>b</sup>Continuous data are compared using an unpaired t test; categorical variables, using the χ² test.

International View

Early goal-directed therapy: An evidence-based review

Andrew Rhodes, MD; E. David Bennett, MD

Objective: In 2003, critical care and infectious disease experts representing 11 international organizations developed management guidelines for early goal-directed therapy that would be of practical use for the bedside clinician, under the auspices of the Surviving Sepsis Campaign, an international effort to increase awareness and improve outcomes in severe sepsis.

Design: The process included a modified Delphi method, a consensus conference, several subsequent smaller meetings of subgroups and key individuals, teleconferences, and electronic-based discussion among subgroups and among the entire committee.

Methods: The modified Delphi methodology used for grading recommendations built on a 2001 publication sponsored by the International Sepsis Forum. We undertook a systematic review of the literature graded along five levels to create recommendation grades from A to E, with A being the highest grade. Pediatric considerations to contrast adult and pediatric management are in the article by Parker et al. on p. S591.

Conclusion: During the first 6 hrs of resuscitation of sepsis-induced hypoperfusion, specific levels of central venous pressure, mean arterial pressure, urine output, central venous (or mixed venous) oxygen saturation should be targeted. When central venous oxygen saturation remains low, despite achieving central venous pressure and mean arterial pressure targets, packed red blood cell transfusions should be considered. Increasing cardiac index to an arbitrarily predefined elevated level is not recommended (Chest 2004; 125(Suppl.):S448–S460).
Post-Rivers

- Endorsement in Surviving Sepsis Campaign
  - CCM 2004
  - CCM 2008

- Several single center reports of benefit
  - ‘Before-and-after’ designs

- But, adoption slow overall
  - Logistical burden to initiate change
  - Knowledge transfer
  - Skepticism
    - Huang et al CCM 2007
    - Cardblom et al CCM 2008

- Pilot studies
  - 3 centers
  - Mortality rate 20-25%
  - Transfusion rate ~10%

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New Therapy for Sepsis Infections Raises Hope but Many Questions
By THOMAS M. BURTON
August 14, 2008; Page A1

Seven years ago, doctors got some hopeful news about sepsis, a fast-moving bloodstream infection that kills four million people a year world-wide. A study said an aggressive new therapy cut the death rate by a third. Two medical groups endorsed the new therapy, and scores of U.S. hospitals have adopted it. But now some doctors are questioning the rigor of the research behind it, which was done at a single hospital. Adding to the concerns: That hospital held patents on a medical device critical to the therapy. And one of the groups that later endorsed the treatment had financial backing from the maker of the device.
Response to specific case: 68yo male with presumed pneumonia and hypotension

Treatment of low Hb / ScvO2

Do nothing else. Transfuse PRBCs for Hb > 10 g/dl. Increase norepinephrine and assess CO. Add inotropes, if no need to assess CO. Place CO monitor and Rx as indicated. Do nothing else. Clinical examination and act as indicated.

Reade et al Emerg Med J 2010
Treatment of persistent low ScvO2

Compliance

Only one of 1348 complied with all aspects of EDGT
**EGDT in Spain**

- ‘Before and after study’
  - Surviving Sepsis Resuscitation ‘bundle’
- N=58 hospitals, >2,500 patients

- **Compliance**
  - Before: 5%
  - After: 9%
  - 1y later: 5%

Ferrer et al JAMA 2008

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**ProCESS**

- **Protocolized Care of Early Septic Shock**

- **NIH-funded program-project (P50)**
  - Subproject #1: Clinical efficacy
  - Subproject #2: Mechanism of action
  - Subproject #3: Cost, cost-effectiveness, and logistics

- **Primary questions**
  - Is team-based protocolized resuscitation with timed instructions superior to ‘usual’ care?
  - If so, does the addition of scvO2 monitoring with titration of blood and inotropes to optimize scvO2 further improve survival?
Clinical efficacy

- **Primary endpoint**
  - 60-day mortality

- **Secondary endpoints**
  - Long-term survival (minimum 1 year)
  - Organ failure
  - Process of care

- **Powered to find 6-7% mortality reduction**
  - Allows control mortality to range between 46% and 20%

- **N=650 per arm x 3 arms**
  - ‘Usual care’
  - Sepsis team delivering protocolized standard of care
  - Sepsis team delivering the Rivers EGDT protocol

- **20 large University teaching hospitals**
  - 1 patient per site per week
  - Two year enrollment

Considerations

- **3 vs. 2 arms**
  - Incremental benefits of the Rivers protocol

- **Randomizing by patient, not site**
  - Risk by patient is contamination
    - Reduces treatment benefit
    - Counteract with sample size
  - Risk by site is uneven baseline variables
    - Potential fatal flaw

- **Using a sepsis team**
  - Standardized identification, training, and QA of team
    - Can be ED or ICU based
    - Easier to describe, reproduce, and disseminate
  - Minimize drift between usual care and intervention arms
Mechanism of action

- ‘Why’ might EGDT work?
  - Four likely pathways
    - Inflammation
    - Ischemia
    - Ischemia/reperfusion
    - Coagulation
  - Leading to organ dysfunction, and then death

Approach

- Measure serum biomarkers (0, 6, 24 and 72h)
  - Each of the 4 pathways
  - Organ dysfunction
- Compare
  - Effect of interventions vs. control on biomarkers (causal)
  - Relationship between biomarkers and outcome (association)

Costs and cost-effectiveness

- Quality assurance
- Costing
- Formal cost-effectiveness analysis
Sites

- University of Alabama, Birmingham, AL
- Brigham-Women’s Hospital, Boston, MA
- Maricopa Medical Center, Phoenix, AZ
- LA County/USC, Los Angeles, CA
- UC Davis, Davis, CA
- Norwalk Hospital, Norwalk, CT
- George Washington University, Washington DC
- Tampa General Hospital, Tampa, FL
- Methodist Hospital, Indiana, IN
- Massachusetts General Hospital, Boston, MA
- North Shore University Hospital, Manhasset, NY
- Duke University Medical Center, Durham, NC
- University of North Carolina, Chapel Hill, NC
- Metrohealth/Case Western, Cleveland, OH
- State University, Buffalo, NY
- Temple University, Philadelphia, PA
- Yale, New Haven, CT
- University of Utah, Salt Lake City, UT
- LDS Hospital, Salt Lake City, UT
- University of Pittsburgh, Pittsburgh, PA

ProCESS Update

- Expanding to 40 sites under additional NIH funding
- Obama ARRA
- 530 patients enrolled thus far
Generalizability

- Measure of effect dependent on control arm
- Therefore, differences in current usual care between regions and countries will threaten generalizability
- We know there are differences in usual care
- Must conduct ‘ProCESS’ in different countries
  - But, unlike PROTECT or NICE-SUGAR, multiple studies
    - Stand-alone
    - Be combined post-hoc, based on pre-hoc plan

ARISE

- 2-arm trial
- EGDT vs. usual care
- Single primary aim: all-cause 90 day mortality
- N~1300 (650 per arm)
- 20-40 centers
- Enrolled 100 patients to date
- Both ARISE and ProCESS are enrolling at near-identical rates per site
  - Common intervention
  - Common procedures
ProMISE

- 2-arm trial
- Two aims:
  - Clinical effectiveness
  - Cost-effectiveness
- EGDT vs. usual care
- N~1300 (650 per arm)
- 50 centers
- Just funded - in site set-up mode

Plans to understand generalizability

- 3 national studies
  - ProCESS (funded, US NIH)
  - ARISE RCT (ANZICS CTG, funded by Australian MRC)
  - ProMISE (ICNARC/ICS, funded by UK MRC)
- Prospectively-defined, patient-level meta-analysis
  - PRISM
    - Reade et al Intensive Care Med 2010
- Oversight and coordination
  - Common Rivers intervention arm
  - Standardized training and implementation
  - Common entry criteria
  - Common data collection variables
- Advantages
  - Each study informs locally of likely benefit
  - Power to find overall smaller but still clinically useful effects
  - Power to explore subgroups of patients
Conclusion

- EGDT can potentially revolutionize initial sepsis management
- But, current evidence only represents proof of concept
- Intervention is incredibly complex
- Background context is a dominating factor
  - Very different from ‘placebo’
  - Precludes traditional ‘multinational’ approach
- Attempt multiple national clinical trials
  - Coordinated aspects to facilitate prospective meta-analysis

And, we’ll know the answer ...

- Probably 2012