Early Goal Directed Therapy in Sepsis and Septic Shock: Controversies and New Trials

Anand Kumar, MD
Section of Critical Care Medicine
Section of Infectious Diseases
University of Manitoba, Winnipeg Manitoba
Physiologic Oxygen Supply Dependency

Oxygen Consumption

Lactic Acidosis

Critical Delivery Threshold

Oxygen Delivery
Pathologic Oxygen Supply Dependency

Supply Dependent Oxygen Consumption: Physiologic vs. Pathologic

- O$_2$ Consumption ($\text{VO}_2$)
- O$_2$ Extraction Ratio
- Serum Lactate

O$_2$ Delivery (DO$_2$)
Median Cardiac Index in the Treatment and Control Groups

Median Oxygen Delivery in the Treatment and Control Groups

# Elevation of Systemic Oxygen Delivery in Critically Ill Patients

## Outcome Data

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control Group (n=50)</th>
<th>Treatment Group (n=50)</th>
<th>Not Randomized (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Days in unit - median (range)</strong></td>
<td>10 (1 - 64)</td>
<td>10 (1 - 48)</td>
<td>10 (1 - 29)</td>
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<tr>
<td><strong>Ventilation</strong></td>
<td></td>
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<tr>
<td><strong>No. of days - median (range)</strong></td>
<td>8 (0 - 54)</td>
<td>8 (0 - 41)</td>
<td>2 (0 - 26)</td>
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<tr>
<td><strong>No. of patients</strong></td>
<td>44</td>
<td>46</td>
<td>7</td>
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<tr>
<td><strong>Days in hospital - median (range)</strong></td>
<td>23.5 (1 - 244)</td>
<td>19 (1 - 244)</td>
<td>20 (11 - 102)</td>
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<tr>
<td><strong>Mortality - %</strong></td>
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<tr>
<td><strong>In intensive care unit</strong></td>
<td>30</td>
<td>50</td>
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<tr>
<td><strong>In hospital</strong></td>
<td>34</td>
<td>54</td>
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<tr>
<td><strong>Predicted risk of death - median % (range)</strong></td>
<td>34 (3 - 91)</td>
<td>34 (3 - 85)</td>
<td>6 (3 - 32)</td>
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<tr>
<td><strong>Cause of death - no. of patients</strong></td>
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<tr>
<td>Intractable hypotension</td>
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<tr>
<td>Cardiac event</td>
<td>2</td>
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<tr>
<td>Multiple organ failure</td>
<td>9</td>
<td>17</td>
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</table>

Patients Treated with EGT Received More Fluids, RBCs and Dobutamine

The Importance of Early Goal Directed Therapy for Septic Shock

- Early goal-directed therapy* in patients with severe sepsis produced
  - 42% ↓ in relative risk of in-hospital and 28-day mortality (P=0.009, P=0.01)
  - 33% ↓ in relative risk of death at 60 days (P=0.03)
- NNT to prevent 1 event (death) = 6-8

*Aggressive resuscitation begun in emergency department.
Studies Using EGDT and/or Bundled Care to Treat Sepsis

The Challenge (Intermountain Health Care) – Compliance > 80%
The Challenge (Intermountain Health Care–Mortality < 10%)

Mortality Rate
Sepsis Patients - ER to ICU Transfers Only
System

<table>
<thead>
<tr>
<th>Year</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q1</th>
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Studies of Severe Sepsis Bundles Survival

Author/Yr
Rivers ‘01
Trzeciak '06
Kortgen '06
Shapiro '06
Micek '06
Nguyen '07
Jones '07
El Solh ‘08

Overall Odds Ratio of Survival (95% CI)

0.01 0.1 1 10 100
Favors Control Favors Bundle

p < 0.0001

Heterogeneity $I^2 = 0\%, p = 0.97$

Studies of Severe Sepsis Bundles (what changes?): Hours to Antibiotics

Author/Yr
Rivers ‘01
Trzeciak ’06
Kortgen ’06
Shapiro ’06
Micek ’06
Nguyen ’07
Jones ’07
El Solh ‘08

Heterogeneity
$\text{i}^2 = 0\%, \ p = 0.89$

Weighted Mean Difference (± 95% CI)

Favors Control
Favors Bundle

$p < 0.0001$
Studies of Severe Sepsis Bundles Resuscitation Components (what changes?)

Author / Year
- Rivers '01
- Trzeciak '06
- Kortgen '06
- Shapiro '06
- Micek '06
- Nguyen '07
- Jones '07
- El Solh '08

Crystalloid Usage (L)

Vasopressor Usage

Inotropes

RBC

Severe Sepsis Bundle Studies Summary

- Antibiotics given significantly earlier and more appropriately in all studies
- No consistent change in use of fluids, pressors, PRBCs, steroids, or rhAPC
- Small increase in inotropes
Delay of Antimicrobial Therapy Increases Mortality in Septic Shock

Kumar et al. Crit Care Med 2006

Time (h) from hypotension onset

Kumar et al. Crit Care Med 2006
## Benefit of Early versus Late Antibiotics

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>Miner</td>
<td>2001</td>
<td>171</td>
<td>Meningitis</td>
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<tr>
<td>Larche</td>
<td>2002</td>
<td>88</td>
<td>Bact/pneumonia*</td>
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<td>Houck</td>
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<td>13,771</td>
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<td>Proulx</td>
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<td>Meehan</td>
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<td>Gacouin</td>
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<td>Iregui</td>
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<td>VAP</td>
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<td>Lodis</td>
<td>2003</td>
<td>167</td>
<td>S. aureus</td>
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<tr>
<td>Kang</td>
<td>2003</td>
<td>123</td>
<td>P. aeruginosa</td>
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</table>

* Patients with cancer

**Odds Ratio of Survival (95% CI)**

<table>
<thead>
<tr>
<th>Harm</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01</td>
<td>100</td>
</tr>
<tr>
<td>0.1</td>
<td>10</td>
</tr>
</tbody>
</table>

Legend:
- Red line segments represent the odds ratio of survival for each study.
Time to Antimicrobials in Rivers
NEJM 2001

Distribution of Antimicrobial Delays
Clinical Trial of the Optimal Endpoint of Early Sepsis Resuscitation (LactATES)

- Bioequivalence study of serum lactate vs central venous saturation catheter (standard therapy)
- Open label multi-center RCT, n=300
- Septic shock with lactate >4 mmol/L
- Among patients with septic shock who were treated to normalize central venous and mean arterial pressure, additional management to normalize lactate clearance compared with management to normalize ScvO2 did not result in significantly different in-hospital mortality.

Jones et al, JAMA 2010
Australasian Resuscitation In Sepsis Evaluation Randomised Controlled Trial (ARISE)

- Standard therapy vs EGT for severe sepsis
- Multi-center (ANZICS) RCT, n=1600
- 90 day all cause mortality
- EGDT involves treatment with intravenous fluids, and medications to support the blood pressure and heart following a protocol. A special catheter is inserted to monitor central blood oxygen levels and the standard treatments are given according to the blood oxygen level reading. EGDT is given for 6 hours, then the patient receives standard care.
- Estimated completion Dec 2013
Promise (England)

- Multi-center RCT in England, n=1260
- 1047 entered to date
- 90 day all cause mortality
- EGDT involves treatment with intravenous fluids, and medications to support the blood pressure and heart following a protocol. A special catheter is inserted to monitor central blood oxygen levels and the standard treatments are given according to the blood oxygen level reading. EGDT is given for 6 hours, then the patient receives standard care.
- Scheduled completion spring 2014
Protocolized Care for Early Septic Shock (ProCESS)

- Standard therapy vs protocolized care vs EGT for septic shock over first 6 hrs; then standard therapy
- 5 year NIH-funded multi-center RCT, n=1500
- Hospital mortality (discharge or 60 days)
- EGT subjects will have a CVC inserted for continuous monitoring of their CVP and Scv02. Early structured treatment will be provided based on subjects' CVP, MAP and Scv02.
- Protocolized care: Routine equipment will be used to monitor subjects BP and oxygen levels. Early structured treatment is based on the subjects' systolic blood pressure and the study doctors' judgment of fluid status and perfusion status.
- Estimated completion: August 2013 (ie done)
Conclusions

• Early goal-directed therapy improves survival in sepsis and septic shock
• The critical components of EGT (resuscitation vs antimicrobials) that improve outcome is uncertain
• It is not clear that a central venous oximetric catheter to follow central venous saturation is necessary
• Ongoing studies may shed light on some of these issues