

# Worksheet for Using an Article About Therapy or Prevention

Journal Club Eastern Virginia Medical School

Presenter: Olive Lamm, MD

Date: 8/31/09

CITATION: Rivers, Emanuel, et al. "Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock." *N Engl J Med.* 345:19. 2001. 1368-1377.

|  |   |
|--|---|
| I. WHAT IS BEING STUDIED?  |   |
| 1. Study Objective   | To evaluate the efficacy of early goal directed therapy before admission to the ICU and its impact on mortality and multi-system failure  |
| 2. Study Design  | Prospective randomized partially blinded controlled trial   |
| 3. Inclusion Criteria  | Meeting SIRS criteria; SBP < 90 after fluid challenge of 20-30 cc/kg over 30 mins; lactate level > 4  |
| 4. Exclusion Criteria  | Age < 18 yo; preg; acute CVA; ACS; acute pulm edema; status asthmaticus; cardiac dysrhythmias; contraindications to central venous catheterization; active GI hemorrhage; seizure; drug OD; burn injury; trauma; requirement for immediate surgery; cancer undergoing chemo; immunosuppression (s/p organ transplantation or systemic dz); DNR status; advanced directives restricting any part of protocol   |
| 5. Interventions Compared (for at least 6hr)<br><br>Early goal directed therapy in the ED<br>vs<br>Standard therapy and early admission to the ICU | <u>Early goal directed therapy protocol:</u> 500 cc fluid bolus q 30 min to keep CVP 8-12; for MAP < 60 vasopressors added to maintain MAP > 65; for MAP > 90 vasodilators added for MAP ≤ 90; for CVSO <sub>2</sub> < 70% PRBCs were transfused to keep hct ≥ 30% and if CVSO <sub>2</sub> continues to be < 70% despite this then Dobutamine at 2.5 µg/kg/min was added and increased by same q 30 min (max of 20 µg/kg/min) to keep CVSO <sub>2</sub> > 70%; if hemodynamic optimization goals still could not be met, |

|   |   |
|---|---|
|   | <p>mechanical vent and sedatives given to decrease O2 consumption</p> <p><u>Standard therapy group:</u> clinician discretion to keep CVP <math>\geq</math> 8-12, MAP <math>\geq</math> 65, UO <math>\geq</math> 0.5 cc/kg/hr as outlined by a protocol for hemodynamic support published by the Task Force of the American College of Critical Care Medicine in 1999.</p> |
| <p>6. Outcomes Evaluated</p> <p>Temp, HR, UO, BP, CVP measured continuous for first 6 hrs and then q 12 hrs for 72hrs</p> | <p><u>Primary outcome:</u> In-hospital mortality</p> <p><u>Secondary outcomes:</u> APACHE II, SAPS II, MODS scores with higher numbers indicating more severe organ dysfunction; resuscitation end points; coagulation related variables; consumption of health care resources</p>  |
| <p><b>II. Are the results of the study valid?</b></p>   |   |
| <p>1. Was the assignment of patients randomized?</p>  | <p>Yes, randomized assignments were made by computer in blocks of eight</p>   |
| <p>2. Were all patients who entered the trial properly accounted for and attributed at its conclusions?</p>               | <p>Yes – 288 pts were evaluated but only 263 were enrolled. Out of 263, 27 did not complete the 6hr initial period (14 from STD and 13 from EGD) with reasons included in the article.</p>  |
| <p>3. Was follow-up complete?</p>   | <p>Yes, even the 27 patients that did complete the initial 6 hrs of therapy were followed though not included in the final results. The 27 patients were equally divided between the intervention and control groups.</p>   |
| <p>4. Were patients, health workers and study personnel “blind” to treatment?</p>   | <p>Partially – initial clinicians were not blinded and investigators influenced care in the beginning, however, the health care professionals who assumed care of pt in the ICU were blinded to which group the patient belonged.</p>   |
| <p>5. Were study groups similar at the start of the trial?</p>  | <p>Yes, as described and portrayed in Table 1 of the article. Intervention group may have been slightly sicker with more HIV &amp; CHF. In addition, the intervention group received less Abx in the first 6 hours</p>  |

|  |   |
|--|---|
| 6. Aside from the experimental intervention, were the groups treated equally                         | Hard to say. Patients were treated @ physician's discretion once in the ICU. All patients however were admitted to the same ICU so practice variations may be less likely between treating physicians   |
| <b>III. What were the results?</b>   |   |
| 1. How large was the treatment effect? (difference between treatment and control group). (ARR) (NNT) | <p><u>Absolute Risk Reduction</u>: the decrease in a specific risk in a population from a particular treatment (<math>P_A</math>) vs a control (<math>P_B</math>)</p> <p><u>Equation</u>: <math>ARR = P_B - P_A</math></p> <p>In hospital mortality: STD – 46.5% and EGDT – 30.5 %</p> <p><math>ARR = .47 - .31 = .16</math><br/> <math>ARR = 16\%</math> in this case presentation</p> <p><u>Number Needed to Treat</u>: the number of patients that need to be treated to have one positive outcome</p> <p><u>Equation</u>: <math>NNT = 1/ARR</math></p> <p>In this case: <math>ARR = .16</math><br/> <math>NNT = 1/.16 = 6.25</math><br/> NNT in this case is ~ 6 patients</p> |
| 2. What was the estimated treatment effect at a 95% confidence interval?                             | <p><u>Primary Outcome of In-Hospital Mortality</u>:<br/> STD – 59 (46.5 %)<br/> EGDT – 38 (30.5%)<br/> P value 0.009</p> <p>See table below for secondary outcome measures</p>  |
| IV. Will the results help me in caring for my patients? (applicable?)                                | Yes – shows that early goal directed therapy in the ED reduces in hospital mortality and morbidity  |
| 1. Were all clinically important outcomes considered?  | Yes – deaths, organ dysfunction, health care cost, length of stay in the hospital all seem relevant and important   |
| 2. Are treatment outcomes worth the potential harms?   | Yes, with “potential harm” being health care resource consumption. Patients receiving STD stayed longer in the hospital than EGDT (18.4 vs 14.6 with $p=0.04$ )   |

Additional Comments:

Patients in the EGDT received more fluids, transfusions, inotropic support during the initial 6 hrs of treatment. During the 7-72 hrs afterwards, the STD group received more fluids, transfusions, vassopressors, mechanical ventilation, and pulm art catherization. Overall fluid and inotropic administration was similar from 0-72 hrs.

| <b>FOR THE INITIAL 6 HOURS OF THERAPY</b> |                  |                     |  |
|---|------------------|---------------------|--|
| Variable Measured                         | Standard Therapy | Early Goal Directed | Comments   |
| HR  | Similar          | Similar             |  |
| CVP                                       | Similar          | Similar             |  |
| MAP                                       | Lower            | Higher              | Both met goal of MAP > 65                        |
| CVSO2                                     | Met by 60%       | Met by 86%          | STD group had lower CVSO2                        |
| Lactate                                   | Similar          | Similar             |  |
| Base Deficit                              | Higher           | Lower               |  |
| Arterial pH                               | Similar          | Similar             |  |
| <b>FOR THE PERIOD FROM 7 TO 72 HRS</b>    |                  |                     |  |
| APACHE II                                 | Higher           | Lower               | Higher scores signifies greater end organ damage |
| SAPS II                                   | Higher           | Lower               |  |
| MODS                                      | Higher           | Lower               |  |
| Hct                                       | Lower            | Higher              |  |
| PT  | Higher           | Lower               |  |
| PTT                                       | Similar          | Similar             |  |
| Fibrinogin                                | Similar          | Similar             |  |
| Fibrin split products                     | Higher           | Lower               |  |
| DDimer                                    | Higher           | Lower               |  |
| Platelets                                 | Similar          | Similar             |  |