Clinical Practice Guideline:
Does Early Goal Directed Therapy Decrease Mortality in Patients with Septic Shock? (2/14/10)

Reviewed and approved by the AAEM Clinical Practice Committee.

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1. Define the Issue and State the Question

    A. Topic Area: Sepsis

    B. General Issue: Early goal directed therapy

    C. Specific Question: Does early goal directed therapy decrease mortality in patients with septic shock?

    D. Executive Summary:

Answer: Yes. Though adoption of EGDT has been slow and multiple barriers exist, it appears that EGDT improves mortality in adult patients with septic shock. Further study is needed, however, to quantify the exact effect size of each individual component and the protocol in its entirety. It is important to highlight that, with the distinct exception of the original trial, the remaining references are Grade C or below thus limiting the level of recommendation which can be assigned to this body of evidence. (Level of Recommendation: Class B2)

Nine articles were identified and reviewed including one randomized controlled trial, six prospective observation trials and two retrospective studies.[1-9]   The original trial by Rivers et al in which the authors reported a 28-day mortality absolute risk reduction of 15.9% (P = 0.01) remains the only randomized controlled trial in support EGDT.[7]. Common criticisms of the study, however, include difficulty with its delivery in a busy ED, a high

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mortality rate in the control group and the single center nature of the design.[10-12]

The largest report to date evaluating the EGDT protocol by Nguyen et al prospectively enrolled 330 patients over a two-year period after beginning a sepsis bundle protocol based upon the Surviving Sepsis Campaign (SSC) recommendations.[13] The in-hospital mortality in patients completing EGDT at 6 hours was 25.8 vs. 38.8% in those patients whom did not complete the protocol (p = 0.03). In another large multi-center trial utilizing a before-after design, Ferrer et al reported the effect of a sepsis educational program based on the SSC recommendations in 23 Spanish ICUs.[2] In multivariate analysis the interventional cohort (after) had decreased hospital mortality (OR, 0.81; 95% CI, 0.67 – 0.98; p = 0.03). El-Sohl et al reported a prospective observational study of 87 consecutive elderly patients after implementation of a sepsis protocol. They reported a 16% ARR in 28-day mortality (95% CI, 2%-31%). A retrospective cohort study by Kortgen et al evaluated a similar protocol for patients in septic shock. They reported 28-day mortality for the entire protocol was 53% for the control group and 27% for the treatment group (p < 0.05). Finally, in a before and after study, Micek et al reported a 28-day mortality ARR of 18.3% (p=0.04) following the implementation of a standardized order set for septic shock of which EGDT was a significant component. With respect to mortality, the three final studies did not demonstrate significant benefit, though none were powered for this outcome.[3, 8, 9] Collectively, they demonstrated feasibility of the protocol delivery and improvement of quality of care indicators such as antibiotic delivery.

The lack of a corroborative RCT and the potential implementation barrier notwitchstanding, the available evidence suggests of the efficacy the EGDT protocol in patients with septic shock. Furthermore, the protocol makes physiologic sense as it addresses all of the components of oxygen delivery such as preload (central venous pressure), afterload (mean arterial pressure), arterial oxygen content (hemoglobin) and contractility (ScvO2).

2. Search
- Define separate strategy for each database / search process used in this review.
- Attach additional search strategies for other database / search process in this review.

SEARCH _1_

A. Keywords used in search: sepsis OR severe sepsis OR septic shock OR infection OR sepsis syndrome AND early goal directed therapy OR goal directed therapy

B. Database Searched / Process Performed (Ovid, BIOMEDNET, PubMed, Cochrane, EMBASE, Textbook / Article Reference Review, etc):

Ovid

C. Dates searched: From 1966 To 2009 with # of references 109

D. Limits applied

limit Human

limit Adult

limit English

E. Final Search Result with # of references 31

SEARCH 2

A. Keywords used in search: sepsis OR severe sepsis OR septic shock OR infection OR sepsis syndrome AND early goal directed therapy OR goal directed therapy

B. Database Searched / Process Performed (Ovid, BIOMEDNET, Pubmed, Cochrane, EMBASE, Textbook / Article Reference Review, etc):

_____Ovid_____

C. Dates searched: From 1966 To 2008 with # of references 111

D. Limits applied

limit Human

limit Adult

limit English

E. Final Search Result with # of references 32

SEARCH 3

A. Keywords used in search: sepsis OR severe sepsis OR septic shock OR infection OR sepsis syndrome AND early goal directed therapy OR goal directed therapy OR resuscitation

B. Database Searched / Process Performed (Ovid, BIOMEDNET, Pubmed, Cochrane, EMBASE, Textbook / Article Reference Review, etc):

Ovid

C. Dates searched: From 1990 To 2008 with # of references 112

D. Limits applied

limit Human

limit Adult

limit English

E. Final Search Result with # of references 32

Additional Search Documentation

SEARCH __

A. Keywords used in search: _____

_____

B. Database Searched / Process Performed (Ovid, BIOMEDNET, Pubmed, Cochrane, EMBASE, Textbook / Article Reference Review, etc):

_____

C. Dates searched: From _____ To _____ with # of references_____

D. Limits applied

limit _____ with # of references_____

limit _____ with # of references_____

limit _____ with # of references_____

E. Final Search Result with # of references_____

SEARCH __

A. Keywords used in search: _____

_____

B. Database Searched / Process Performed (Ovid, BIOMEDNET, Pubmed, Cochrane, EMBASE, Textbook / Article Reference Review, etc):

_____

C. Dates searched: From _____ To _____ with # of references_____

D. Limits applied

limit _____ with # of references_____

limit _____ with # of references_____

limit _____ with # of references_____

E. Final Search Result with # of references_____

3. Final Evidence Database – Grade of Evidence Review
- For each reference from step 2, assign a grade of evidence using reference focus, design and methodology.
- Attach list of final evidence database with assigned grade of evidence

Grade A	Randomized clinical trials or meta-analyses (multiple clinical trials) or randomized clinical trials (smaller trials),directly addressing the review issue
Grade B	Randomized clinical trials or meta-analyses (multiple clinical trials) or randomized clinical trials (smaller trials), indirectly addressing the review issue
Grade C	Prospective, controlled, non-randomized, cohort studies
Grade D	Retrospective, non-randomized, cohort or case-control studies
Grade E	Case series, animal / model scientific investigations, theoretical analyses, or case reports
Grade F	Rational conjecture, extrapolations, unreferenced opinion in literature, or common practice

4. Final Evidence Database – Quality Ranking
- Critically assess each reference with regards design and methodology.
- Design Consideration – of the reference under review, consider the focus, model structure, presence of controls, etc.
- Methodology Consideration -- of the reference under review, consider the methodology.
- Attach list of final evidence database with assigned quality of evidence

Ranking	Design Consideration Present	Methodology Consideration Present	Both Considerations Present
Outstanding	Appropriate	Appropriate	Yes, both present
Good	Appropriate	Appropriate	No, either present
Adequate	Adequate with Possible Bias	Adequate	No, either present
Poor	Limited or Biased	Limited	No, either present
Unsatisfactory	Questionable / None	Questionable / None	No, either present

5. Assign the Reference Support of the Question[1-9]

- Separate the references into 3 categories: supportive, neutral, opposed.
- Construct 3 tables assigning the references to the appropriate location using both Grade of Evidence and Quality of Evidence.
- Use lead author name, journal abbreviation, and year of publication as reference.

Supportive Evidence

Quality / Grade	A	B	C	D	E	F
Outstanding	• Rivers,NEJM, 2001					
Good			• Nguyen,CCM,2007; • Ferrer, JAMA 2008			
Adequate			• Micek, CCM, 2006; • El Sohl, J Am Ger Soc, 2008	• Kortgen, CCM, 2006		
Poor						
Unsatisfactory						

Neutral Evidence

Quality / Grade	A	B	C	D	E	F
Outstanding						
Good			• Jones,Chest, 2007; • Shapiro,CCM, 2006			
Adequate				• Trzeciak,Chest, 2006		
Poor						
Unsatisfactory						

Opposing Evidence

Quality / Grade	A	B	C	D	E	F
Outstanding						
Good						
Adequate						
Poor						
Unsatisfactory						

6. Recommendation
- Answer the clinical question, if possible.
- Assign a level of recommendation.
- Make a recommendation.

A. Recommendation: The delivery of early goal directed therapy significantly improves mortality for patients in septic shock.

B. Level of recommendation: B2

Level of Recommendation	Criteria for Level of Recommendation	Mandatory Evidence
Class A recommended with outstanding evidence	• Acceptable • Safe • Useful • Established / definitive	• Level A / B grade • Outstanding quality • Robust • All positive
Class B acceptable & appropriate with good evidence	• Acceptable • Safe • Useful • Not yet definitive	• Level A / B grade lacking • Adequate to Good quality • Most evidence positive • No evidence of harm
Class B 1	• Standard approach	• Higher grades of evidence • Consistently positive
Class B 2	• Optional or alternative approach	• Lower grades of evidence • Generally, but not consistently, positive
Class C not acceptable or not appropriate	• Unacceptable • Unsafe • Not useful	• No positive evidence • Evidence of harm
Class Indeterminate Unknown	• Minimal to no evidence	• Minimal to no evidence

7. List all conflicts of interest:
   No Conflicts of Interest

8. Discussion

- Discuss the clinical question -- Address the issue
- Make a recommendation -- Succinctly discuss the rationale and evidence supporting the recommendation.

Introduction

Worldwide, the disease prevalence and mortality of patients with severe sepsis and septic shock has significant impact.[14, 15] In the U.S. alone, sepsis claims approximately 210,000 lives of an estimated 750,000 reported cases annually and its incidence is rising.[14, 16] Half of these patients are admitted to an intensive care unit (ICU) where sepsis remains the leading cause of death.[14, 17] Annually, sepsis costs approximately $16.7 and $10.5 billion in the U.S. and in Europe respectively (USD). The majority of these patients initially present to an emergency department (ED) and often have lengths of stay greater than 4 hours while receiving resuscitation and waiting for an inpatient bed.[15, 18]

Improving patient outcomes in sepsis is linked to early identification and early intervention; as such ED management has become an integral component in the success of sepsis protocol implemetation.[7, 19] Management of severe sepsis and septic shock has evolved in the last several years and has included a number of important trials involving early goal directed therapy (EGDT), steroid administration and activated protein C.[7, 13, 20-24] Sepsis guidelines are available highlighting evidence based recommendations for patients with severe sepsis and septic shock, however, full adoption of the ED-specific recommendations has been limited due to multiple barriers. [10, 13, 25] The objective of this guideline to provide evidence based recommendation for the use of early goal directed therapy to decrease mortality in patients with septic shock.

Clinical Question:

Does early goal directed therapy decrease mortality in patients with septic shock?

Answer: Yes. Though adoption of EGDT has been slow and multiple barriers exist, it appears that EGDT improves mortality in adult patients with septic shock. Further study is needed, however, to quantify the exact effect size of each individual component and the protocol in its entirety. It is important to highlight that, with the distinct exception of the original trial, the remaining references are Grade C or below thus limiting the level of recommendation which can be assigned to this body of evidence. (Level of Recommendation: Class B2)

Methods

A comprehensive MEDLINE search was performed from January 1950 through August 2009. The primary search included the following keywords: sepsis, severe sepsis, septic shock, septic syndrome, early goal directed therapy and goal directed therapy. Results were limited to studies involving all adult (19 plus years), human subjects written in the English language. The additional publication-type limits were set to include randomized controlled trials, all clinical trials, controlled clinical trial, meta-analysis and multicenter

trial. This search strategy yielded 32 unique relevant articles. Only prospective, original research trials which utilized *all* of the principles and endpoints of EGDT as defined by the original trial by Rivers et al were included and formulated into this recommendation.[7] These results were supplemented by manual review of key journals, bibliographies and relevant source material to collect all identifiable evidence available to provide the final list of potential papers applicable to this recommendation. Nine articles were ultimately identified and reviewed including one randomized controlled trial, six prospective observation trials (including before-after designs and trials with historical controls) and two retrospective studies.[1-9]

Two members of the sepsis sub-committee then reviewed all identified abstracts meeting pre-specified criteria to arrive at a final list of references, which are included in the subsequent recommendations. The final list of references were graded and ranked based upon study design and quality. Each was further assigned a level of support for the specific clinical

Author, Year	Study Design # Subjects	Author reported mortality benefit	Grade	Quality	Reference Support
Rivers et al,	Randomized controlled trial	In-hospital mortality:	A	Outstanding	Supporting

question: supporting, neutral or opposing. Finally, the strength of the recommendation was determined based upon the volume and quality of the selected literature (Table 1).

Critics of the original protocol have highlighted the absence of corroborating evidence, the single center nature of the study and the lack of data to support any individual component of the trial.[10-12, 25, 26] It is important to distinguish between *true* early goal directed therapy which is strictly adherent to a set progression of endpoints and good "protocolized" care in which a set protocol is followed encompassing various endpoints. The former is a well-defined and methodic intervention while the later focuses on detailed attention to the patient coupled with reasonable resuscitation goals, which may or may not overlap with the endpoints dictated for EGDT. Evidence regarding individual components of the EGDT protocol has been graded in previous recommendations.[13, 27] The objective of this recommendation was to provide evidence for the protocol in its entirety.

Nine studies were identified that specifically evaluated the EGDT protocol solely or as a component of a larger sepsis intervention.[1-9] No studies reproduced the randomized controlled design of the original trial. The designs utilized quasi-experimental methods including prospective observational, before and after or prospective observational with historical controls. There were several studies which evaluated various sepsis protocols but were distinctly different from the original protocol such that they could not be considered early goal directed therapy.[28-34] Studies were excluded unless they specifically mentioned they followed EGDT or listed each specific EGDT endpoint as study targets in the methods.

The original trial by Rivers et al in which the authors reported a 28-day mortality absolute risk reduction of 15.9% (P = 0.01) remains the only randomized controlled trial in support EGDT.[7] Two-hundred sixty-three patients diagnosed with sepsis whom had either an elevated lactate (> 4.0 mmol/L) or a systolic blood pressure < 90 mmHg (despite at least 20 to 30 cc / kg or crystalloid infusion) were randomized to receive either standard therapy or early goal directed therapy; all patients received both arterial and central venous catheterization as well as central venous oximetry (ScvO2) monitoring. Patients receiving standard therapy were managed at the treating physicians' discretion in

accordance with a protocol, which included central venous pressure, urine output and mean arterial pressure as hemodynamic targets. Patients receiving EGDT received a six hour protocol with a set progression of endpoints based on central venous pressure (CVP), mean arterial pressure (MAP) and ScvO2 monitoring. Baseline characteristics were the same in both groups. The authors reported a 28-day mortality absolute risk reduction of 15.9% (P = 0.01). Fewer patients in the treatment group received mechanical ventilation (p = 0.02), vasopressor therapy (p = 0.02) and pulmonary artery catheterization (p = 0.01). Common criticisms of the study, however, include difficulty with its delivery in a busy ED, a high mortality rate in the control group and the single center nature of the design.[10-12]

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The largest report to date evaluating the EGDT protocol by Nguyen et al prospectively enrolled 330 patients over a two-year period after beginning a "sepsis bundle protocol" (including EGDT, antibiotics, assessment for steroids, monitor lactate clearance). They reported an improved guideline adherence (zero to 51.2%) following the implementation of their sepsis protocol. Patients whom had completed the bundle had lower lactate levels and higher ScvO2 levels versus patients who had not, suggesting that patients completing the bundle had less severe disease at baseline. For patients completing the bundle, in-hospital mortality improved even after controlling for these baseline imbalances between the groups (odds ratio [OR], 0.36; 95% confidence interval [CI], 0.16-0.78; p = 0.01). A significant advantage of this article was that the authors were able to tease out the specific effect of the individual bundle elements including the completion of EGDT at 6 hours. In multivariate logistic regression, completing EGDT at 6 hours improved mortality (OR, 0.36; 95% CI, 0.17 – 0.79; p = 0.01). The in-hospital mortality in patients completing EGDT at 6 hours was 25.8 vs. 38.8% in those patients whom did not complete the protocol (p = 0.03).

A more recent large multi-center trial utilizing a before-after design reported the effect of a sepsis educational program in Spain.[2] This study which focused on the completion of the sepsis protocol based on the Surviving Sepsis Campaign recommendations in 23 ICUs showed a 4.3% reduction of in-hospital mortality (p = 0.04) and improved compliance with published guidelines.[13] Hospital and 28-day mortality were both significantly decreased, but ICU and hospital lengths of stay remained unchanged. Completion of the sepsis protocol was shown to improve time to antibiotic administration, volume of fluid infusion and assessment of resuscitation endpoints (central venous pressure, lactate and ScvO2). Overall, in multivariate analysis the interventional cohort (after) had decreased hospital mortality (OR, 0.81; 95% CI, 0.67 – 0.98; p = 0.03). It is difficult to interpret its weight in favor of EGDT, though, as ScvO2 was measured only in 11.4% of the patients post-intervention compared to 6.4% pre-intervention. A measurement of ScvO2 is a staple of EGDT yet it is absent in the vast majority of patients in this trial.

Three smaller publications contributed additional supporting evidence in the quasi-experimental form. El-Sohl et al reported a prospective observational study of 87 consecutive elderly patients after implementation of a sepsis protocol. They reported a

16% ARR in 28-day mortality (95% CI -31% - -2%). Kortgen et al published a retrospective cohort study evaluating a "standard operating procedure" (SOP) for patients in septic shock which included EGDT, activated protein C, tight glucose control, lung-protective ventilator strategies and steroids. The reported 28-day mortality for the entire protocol was 53% for the control group and 27% for the group receiving the SOP (p < 0.05). Finally, in a before and after study, Micek et al reported a 28-day mortality ARR of 18.3% (p=0.04) following the implementation of a standardized order set for septic shock of which EGDT was a significant component.

With respect to mortality, the three final studies did not demonstrate significant benefit, though none were powered for this outcome. Shapiro et al published a prospective study following the implementation of their institutional sepsis protocol. Though there was no demonstrable mortality benefit, patient quality of care indicators such as fluid administration and antibiotic administration were significantly improved in the post-intervention period. In a small study of 22 patients, Trzeciak et al demonstrated the feasibility of achieving the endpoints of EGDT in the ED by achieving all end points of resuscitation in 20 of 22 cases following implementation of EGDT. The authors reported a non-significant in-hospital mortality improvement compared to historical controls (18.2% vs. 43.8%; p = 0.09). Jones et al reported on 79 pre-intervention and 77 post-intervention patients following the implementation of a sepsis resuscitation initiative. The authors demonstrated improved delivery of antibiotics and administration of corticosteroids. Mortality between the groups and total hospital length of stay was unchanged and a significantly higher number of patients in the "after" group received mechanical ventilation (9% vs 35%; p < 0.001).

Ideally, the trial should be replicated in its original form to affirm efficacy and further refine the effect size. The lack of a corroborative RCT and the potential implementation barriers notwithstanding, overall the available evidence supports the use of the EGDT protocol in patients with septic shock. Furthermore, the protocol makes physiologic sense as it addresses all of the components of oxygen delivery such as preload (central venous pressure), afterload (mean arterial pressure), arterial oxygen content (hemoglobin) and contractility (ScvO2).

References

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