SELECTED ARTICLES

Goal-directed therapy in the emergency department of patients with severe sepsis and septic shock

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Clinical question
Does goal directed therapy in the emergency department (ED) improve outcomes in patients with severe sepsis and septic shock?

Article chosen
Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345(19):1368-77.

Objective
To determine whether early goal-directed therapy (EGDT) before admission to the intensive care unit reduces the incidence of multiorgan dysfunction, mortality and the utilization of health care resources in patients with severe sepsis or septic shock.

Background
The systemic inflammatory response syndrome (SIRS) often progresses to severe sepsis and septic shock. Global tissue hypoxia, as a result of an imbalance between oxygen delivery and oxygen demand, is a key development in the continuum leading to multiorgan dysfunction syndrome and death. Focusing on hemodynamic monitoring and maintenance of vital signs, central venous pressure (CVP), and urine output neither detects nor specifically corrects persistent global tissue hypoxia. Goal-directed therapy involves adjustments in preload, afterload and contractility in attempt to balance oxygen delivery with oxygen demand. Many of the previous studies on goal-directed therapy and hemodynamic manipulation in order to improve tissue oxygen delivery enrolled patients with diverse causes of disease and did so at a later time after admission.

Population studied
All adult patients who presented to the ED of an 850-bed academic tertiary care centre between March 1997 and March 2000 who met criteria for sepsis syndrome, severe sepsis or septic shock were assessed for enrollment. Patients were eligible for inclusion if they fulfilled 2 of 4 SIRS criteria and had a systolic blood pressure less than 90 mm Hg after crystalloid fluid resuscitation or a blood lactate concentration greater than 4 mmol/L. Exclusion criteria included age under 18 years, pregnancy, acute cerebrovascular event, acute coronary syndrome, acute pulmonary edema, status asthmaticus, primary cardiac dysrhythmias, active gastrointestinal bleed, seizure, drug overdose, burns, trauma, need for immediate surgery, active cancer, immunosuppression, DNR status, or advance directives precluding implementation of the study protocol.

Study design
Eligible patients were randomized to standard therapy or EGDT. Standard therapy was based on clinician's discretion, using a predefined hemodynamic support protocol maintaining central venous pressure between 8 to 12 mm Hg, mean arterial pressure (MAP) above 65 mm Hg, and urine output at least 0.5 mL/kg/h, with admission to an intensive care unit as soon as possible. EGDT included the same hemodynamic goals plus maintenance of central venous oxygen saturation [S_{O_2}] > 70% in the ED for at least 6 hours prior to transfer of care. Specific measures to optimize O_2 saturation included red cell transfusion to achieve a hematocrit of 30% or more, and titrating dobutamine infusions after hemodynamic optimization to achieve a central venous S_{O_2} > 70%. If still unsuccessful, sedation and mechanical ventilation were invoked. All patients had central venous S_{O_2} monitoring, but this information was only available to the care providers in the EGDT group. The critical care clinicians, who assumed care of all patients, were blinded to study assignment, and no further experimental interventions were made after transfer out of the ED.

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Outcomes measured

The primary end point was in hospital mortality. Secondary end points included organ dysfunction scores, treatments administered and health care resource utilization. Patients were followed for 60 days or until death.

Results

There were 288 patients identified and 263 enrolled — 130 in the EGDT group and 133 in the standard therapy group. Of these, 236 completed the initial 6-hour study period. Reasons for not completing the initial 6-hour ED treatment period were evenly distributed between groups, and all 263 patients were included in the intention-to-treat analysis. There were no significant differences between groups at baseline. In-hospital mortality occurred in 38 (30.5%) EGDT patients and in 59 (46.5%) standard therapy patients ($p = 0.009$). Although both groups followed the same hemodynamic objectives and intervention guidelines, the EGDT group had significantly better CVP, MAP, central venous SO_2, lactate and base deficit levels, as well as better APACHE II scores, to 6 hours. With the exception of CVP, these benefits persisted to 72 hours (Table 1).

During the initial 6 hours, patients assigned to EGDT received more crystalloid, more transfusions, and more inotropic support ($p < 0.001$ for each) than those assigned to standard therapy. This trend was reversed during the period from 7 to 72 hours post admission. Of the patients who survived to hospital discharge, those in the standard therapy group had significantly longer hospital stays ([18.4 ± 15.0] vs. [14.6 ± 14.5] days, $p = 0.04$).

Conclusion

The authors conclude that, although delivered for only a brief period of hospitalization, early goal directed therapy to restore a balance between oxygen delivery and demand has significant short- and long-term benefits for ED patients with severe sepsis and septic shock.

Commentary

Across urban North America, EDs are overcrowded, and admitted patients experience ever-increasing delays waiting for inpatient beds. This is particularly true for critically ill patients, who cannot be managed on medical wards when critical care units are full.

This well designed randomized clinical trial suggests that early interventions to improve the balance between

Table 1. Critical hemodynamic variables for early goal-directed therapy (EGDT) vs. standard therapy groups

Variable Rx Group	Baseline (T = 0 hours)	Hours after initiation of therapy 0–6	 6	 7–72
CVP (mm Hg)				
Standard Rx	6.1 ± 7.7	10.5 ± 6.8	11.8 ± 6.8	11.6 ± 6.1
EGDT	5.3 ± 9.3	11.7 ± 5.1	13.8 ± 4.4	11.9 ± 5.6
p value	0.57	0.22	0.007	0.68
MAP (mmHg)				
Standard Rx	76 ± 24	81 ± 16	81 ± 18	80 ± 15
EGDT	74 ± 27	88 ± 16	95 ± 19	87 ± 15
p value	0.60	<0.001	<0.001	<0.001
Central venous SO_2 (%)				
Standard Rx	49.2 ± 13.3	65.4 ± 14.2	66.0 ± 15.5	65.3 ± 11.4
EGDT	48.6 ± 11.2	71.6 ± 10.2	77.3 ± 10.0	70.4 ± 10.7
p value	0.49	<0.001	<0.001	<0.001
Lactate (mmol/L)				
Standard Rx	6.9 ± 4.5	5.9 ± 4.2	4.9 ± 4.7	3.9 ± 4.4
EGDT	7.7 ± 4.7	5.5 ± 4.2	4.3 ± 4.2	3.0 ± 4.4
p value	0.17	0.62	0.01	0.02
Base deficit (mmol/L)				
Standard Rx	8.9 ± 7.5	8.6 ± 6.0	8.0 ± 6.4	5.1 ± 6.7
EGDT	8.9 ± 8.1	6.7 ± 5.6	4.7 ± 5.8	2.0 ± 6.6
p value	0.81	0.006	<0.001	<0.001
APACHE II score				
Standard Rx	20.4 ± 7.4	–	17.6 ± 6.2	15.9 ± 6.4
EGDT	21.4 ± 6.9	–	16.0 ± 6.9	13.0 ± 6.3
p value	0.08		<0.001	<0.001

CVP = central venous pressure; MAP = mean arterial pressure; SO_2 = oxygen saturation

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oxygen delivery and oxygen demand may impede the progression to multiorgan dysfunction and death. These results contrast with previous studies that used goal-directed hemodynamic therapy to raise the cardiac index and achieve supranormal oxygenation.[1,2] The explanation for this may lie in the timing of patient enrollment and initiation of therapy. Previous studies enrolled patients later in their disease course, after admission to the intensive care unit (ICU) and, given the pathophysiology involved, there is reason to believe that early aggressive therapy should be beneficial.

Progression from SIRS to sepsis to severe sepsis to multiorgan dysfunction syndrome and, ultimately, to death, occurs as a result of tissue hypoxia and inflammatory mediator release.[3] The initial insult causes endothelial activation and an inflammatory cascade that disrupts the homeostatic balance between coagulation, vascular permeability and vascular tone. In this study, EGDT was associated with lower lactate levels and base deficits, suggesting improved tissue oxygen availability. Perhaps early intervention, prior to amplification of the inflammatory cascade, is a key to maximizing benefit.

Early ED interventions have improved mortality, morbidity and hospital lengths of stay related to other inflammatory processes, such as asthma,[4,5] community-acquired pneumonia[6] and meningitis.[7] This study involves more advanced invasive monitoring and supportive measures to maintain homeostasis, but the principle is familiar and attractive: Treat early and treat aggressively to prevent progression to an irreversible state.

The absolute risk reduction for in-hospital death was 16%, corresponding to a number needed to treat of 6.25. The investigators also measured important surrogate markers such as MAP, central venous S_{O_2}, base deficit, lactate levels, coagulation variables and APACHE II scores using technology and techniques appropriate for any tertiary care ED. While further studies are required to validate these findings, consideration should be given to initiating goal-directed therapy, using invasive monitoring, as early as possible in patients who present with severe sepsis — especially where transfer to the ICU does not occur immediately.

References

1. Gattinoni L, Brazzi L, Pelosi P, Latini R, Tognoni G, Pesenti A, et al. A trial of goal-oriented hemodynamic therapy in critically ill patients. N Engl J Med 1995;333:1025-32.

2. Hayes MA, Timmins AC, Yau E, Palazzo M, Hinds CJ, Watson D. Elevation of systemic oxygen delivery in the treatment of critically ill patients. N Engl J Med 1994;330:1717-22.

3. American College of Chest Physicians / Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992;20:864-74.

4. Rowe BH, Spooner C, Ducharme FM, Bretzlaff JA, Bota GW. Emergency department treatment of acute asthma with systemic corticosteroids [Cochrane review]. In: Cochrane Database of Systematic Reviews, 2001.

5. Edmonds ML, Camargo CA Jr, Pollack CV Jr, Rowe BH. Early use of inhaled corticosteroids in emergency department treatment of acute asthma [Cochrane review]. In: Cochrane Database of Systematic Reviews, 2001.

6. Battleman DS, Callahan M, Thaler HT. Rapid antibiotic delivery and appropriate antibiotic selection reduce length of hospital stay of patients with community-acquired pneumonia: link between quality of care and resource utilization. Arch Intern Med 2002;162:682-8.

7. Aronin SI, Peduzzi P, Quagliarello VJ. Community-acquired bacterial meningitis: risk stratification for adverse clinical outcome and effect of antibiotic timing. Ann Intern Med 1998;129:862-9.

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