

The *Critical Point*

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Sepsis Overview

This issue primarily will focus on sepsis and it's management



Page 1-3

Heparin and Platelets

The complicated association seen with heparin administration and thrombocytopenia made easier courtesy of TriHealth's Anticoagulation Task Force.

Page 3

Early Goal Directed Therapy

The backbone of early resuscitation of severely septic patients is outlined

Page 4

Sedation in the ICU

The Society of Critical Care Medicine guidelines for sedation of the ICU patients are highlighted.

Page 5

Xigris and Severe Sepsis

Better understanding of components of the "sepsis cascade" has lead to the development of more specific therapy.

Page 5

References and Recommended Reading List

Articles referenced in the topics discussed are provided in abstract form.

Page 6

The ICU & Evidence Based Medicine

The 21st century catch phrase has become "evidence based medicine." While not to imply evidence was never used before, it is technically defined as "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients." It integrates individual clinical expertise with the best available systematic research and judgement acquired through clinical experience and clinical practice.

Historically, the ICU has been rugged turf for EBM. Controlled clinical trials are not often practical or feasible and as the standard level of care improves, it is increasingly difficult to document significant impact on outcome from a new intervention. Moreover, the heterogeneity of the population does not easily lend itself to matched controls and diseases may behave very differently at different stages.

The Surviving Sepsis Campaign (much of which is featured in this issue) reflects the current best strategies to impact sepsis mortality. Incorporating these principles into a standardized protocol may offer an opportunity to reduce what is still unacceptably high mortality.

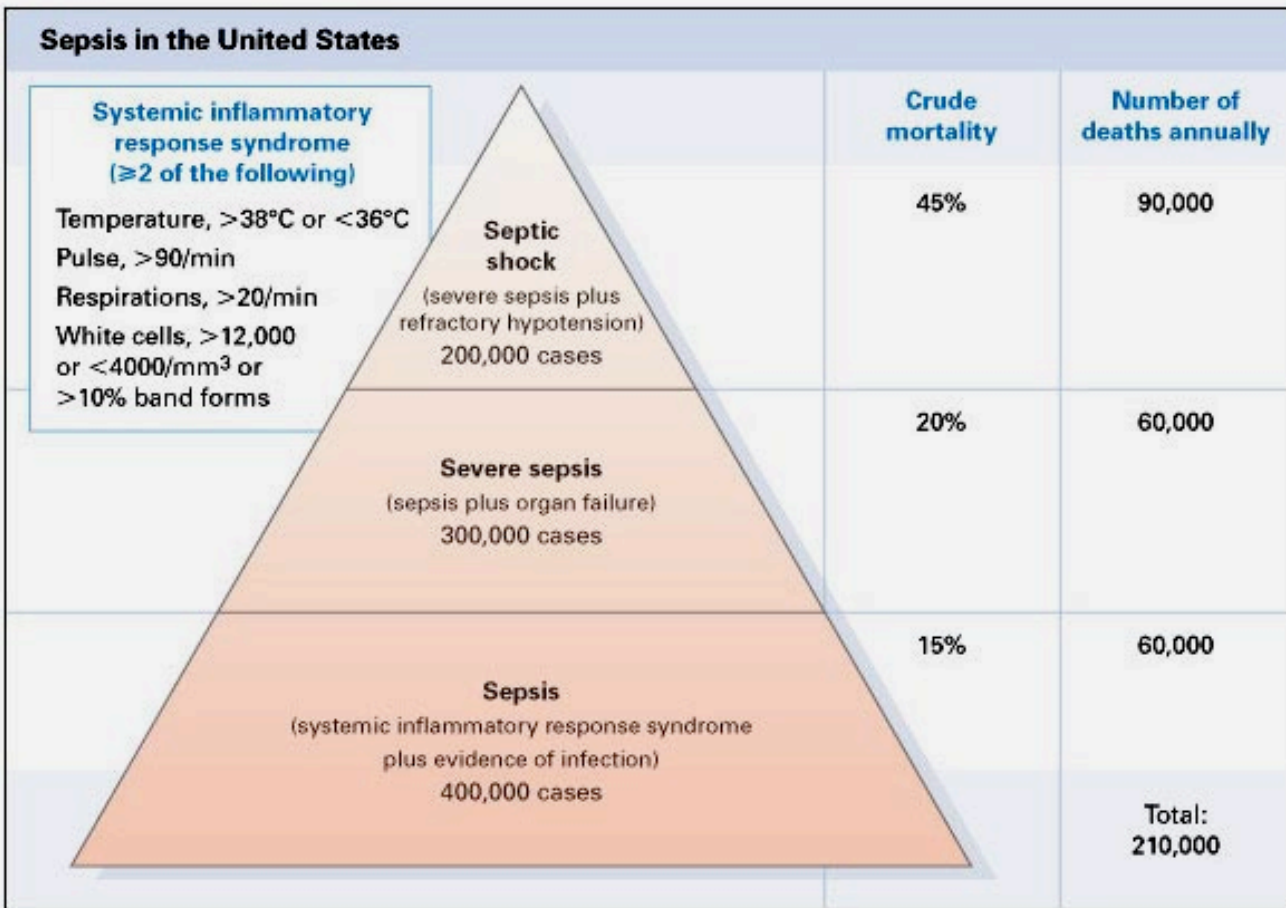
Sepsis: An Overview

Broadly interpreted, sepsis represents the clinical syndrome defined by the presence of infection and a systemic inflammatory response. The true incidence in the U.S. is not clearly known but it has been estimated that more than 750,000 Americans develop severe sepsis every year. This most likely is a conservative estimate given that severe sepsis is more often coded as a complication rather than as a primary diagnosis making it vastly underreported. With both the incidence and the mortality being increased among the elderly, it is estimated that the graying of American will double the number of cases in the next fifty years. Without even waiting 5 decades, it is sobering to note that today more Americans die in one year from sepsis than from breast cancer, lung cancer and stroke combined.

Spanning a gamut ranging from a perturbation of common vital signs to organ dysfunction to refractory hypotension, the figure on the following page depicts the spectrum of sepsis in the U.S.

It is recognized that infection involves invasion by a microbial entity (bacteria in 90% of cases of sepsis) and a host response. While the latter may at times be beneficial, in the majority of ICU patients it is this response that is the cause of the advanced disease. Within the past couple decades, it has become clear that microbes and their products lead to the release of bioactive mediators prompting secondary cascades which then release literally hundreds of different molecules.

In short, a microbial toxin or clinical insult stimulates endothelial cells to release proinflammatory cytokines and other mediators of the immune system (including tumor necrosis factor, various interleukins, interferon- γ , and platelet activating factor). These cytokines directly trigger coagulation. The proinflammatory cytokines also trigger anti-inflammatory cytokines which normally downregulate this response. In patients susceptible to sepsis, there is a failure to regulate the early response to these mediators thus allowing them to initiate the process of tissue injury and diffuse capillary damage. It is at this point that the overwhelming unchecked inflammatory response begins to interfere with normal tissue function and leads to organ dysfunction and ultimately failure.



In spite of this expanding knowledge there has yet to be much available directly targeting these pathways or mediators. Xigris (activated protein C) is the notable exception and is discussed in an accompanying article. Attempts at neutralizing endotoxin with monoclonal antibodies have not yet proved successful nor have strategies to inactivate mediators such as anti-TNF therapy. Additionally, as was seen in the PROWESS trial, the ability to impact mortality may only be applicable at certain stages of disease. In this study, it was actually the sicker patients (as defined by the APACHE II score) who were significantly impacted. To further complicate matters, there is the counterintuitive but important concept that, since these mediators are actually a part of the host response, they may have some beneficial effects which would best not be entirely negated.

Where then does that leave us in 2005?

In spite of the explosion of knowledge on the basic science front and the paucity of new options on the pharmacologic front, all is not lost. Applying previously sound principles coupled with some “less sexy” therapies which have been shown to reduce mortality in severe sepsis still provides the opportunity to make a difference. It is important to think of these as a “bundle” rather than individually. In the absence of combining these strategies into a standardized protocol, management may be haphazard, random and suboptimal.

It was with this in mind that a committee of 11 international agencies from the fields of critical care medicine and infectious disease convened (in the absence of industry input or sponsorship) to review the available evidence and issue a series

of recommendations which formed the basis of what became known as the Surviving Sepsis Campaign guidelines published in March 2004 (Crit Care Med 2004; 32:858-73).

Grade A recommendations (supported by at least 2 large randomized trials with clear cut results) included:

- Against high dose steroids (see page 3))
- Deep vein thrombosis prophylaxis
- Stress ulcer prophylaxis
- Use of spontaneous breathing trials

Grade B recommendations (supported by 1 large randomized trial with clear cut results) included:

- Against antithrombin for severe sepsis
- Against renal dose dopamine

(Continued on page 4)

HIT Decision Tree Available

Nancy Wuestefeld, PharmD

Heparin-associated thrombocytopenia (HAT or HIT type I) is a transient non-immune-mediated interaction between heparin and platelets. Up to 20% of patients exposed to a heparin preparation may develop HAT within 4 days of exposure. Asymptomatic, mild thrombocytopenia results and is reversible despite continued heparin therapy.

Heparin-induced thrombocytopenia (HIT type II), a severe immunologic drug reaction affects up to 5% of patients exposed to heparin. Typically presenting four or more days after initiation of heparin (usually between 5-10 days), HIT can occur within 12 hours of re-exposure to heparin if the previous exposure was relatively recent (within the past 100 days). As an immunologic reaction, it can develop with any heparin exposure including heparin flushes, heparin-coated catheters, SQ or IV heparin and LMWHs. Patients treated with heparin who acquire HIT constitute a cohort with substantially increased thrombotic risk (arterial or venous). Limb ischemia, MI, DVT/PE, and stroke may be seen.

The diagnosis of HIT includes clinical observations and an otherwise unexplained platelet count fall to $<150 \times 10^3/\text{mm}$ or a drop of 50% from baseline (even if the platelet count nadir remains "normal"). The diagnosis can be confirmed by functional assays including the platelet aggregation test and an ELISA test to detect antibodies to heparin-platelet factor 4 complex. If both tests are positive, the positive predictive value is 100%. If both tests are negative, the negative predictive value is 100%.

The treatment of HIT is to first remove all forms of heparin and then to initiate a non-heparin anticoagulant. Direct-thrombin inhibitor (DTIs) such as argatroban and lepirudin can be used for initial parenteral anticoagulation until oral warfarin has achieved therapeutic anticoagulation and the platelet count has fully recovered. A DTI order set has been developed to aid in the dosing and monitoring of these agents. It is available in all GSH critical care areas. The Trihealth Anticoagulation Taskforce has developed a HIT decision tree that is available on SourceNet under 'clinical order sets'. The decision tree helps guide diagnosis and treatment strategies for patients with HIT.

Steroids in Sepsis.... Back from the Dead?

Bellbottom pants, the Volkswagen Beetle and the Cincinnati Bengals: in, out and back in again. Add corticosteroids for sepsis to that list.

What doesn't work at high doses may still have life saving clinical efficacy at lower doses. Witness the now standard of care of using low dose beta blockers in severe cardiomyopathy, a therapy which would have landed one in some pretty hot water in morning report just 10 or so years ago.

In the mid 1980's, high dose corticosteroids were in vogue for treating septic shock on the premise they may obliterate the inflammatory response. Two large controlled trials near the end of that decade put an end to the practice by showing no benefits and a trend toward increased mortality. However, it is known that corticosteroids can regulate the synthesis and function of catecholamines and their receptors which are otherwise altered by proinflammatory cytokines. Downregulation of catecholamine receptors also occurs from prolonged exogenous catecholamine use. Recognition that corticosteroids may reverse this process led to a number of clinical trials revisiting the issue using lower doses and for longer periods than used in the 1980 trials.

A number of small prospective randomized placebo controlled trials were conducted which showed that lower dose corticosteroids could hasten independence from vasopressors and had a higher rate of shock reversal as well as trends towards earlier reversal of organ dysfunction and improved survival. This was followed by the largest and most widely cited study to date in which Annane and colleagues conducted a multicenter randomized trial of 300 patients with vasopressor dependent septic shock treated with hydrocortisone and fludricortisone for 7 days. All patients also received an ACTH stimulation test prior to steroid administration.

The results demonstrated significantly improved survival in nonresponders to the ACTH test (i.e. those with $<10 \text{ mg/dL}$ increase from random cortisol level and considered to have "relative adrenal insufficiency"). No comparable benefit was seen in those with adrenal insufficiency who did respond to the ACTH stimulation test. It may be that, rather than targeting inflammation, steroid administration is merely correcting an acquired deficiency. Currently an international multicenter study (CORTICUS) is underway to better address mortality, organ system failure reversal and duration of hospitalization.

The trials conducted to date have not reported problems with superinfection or higher incidences of complications as had been seen in earlier high dose steroid trials. At present, the use of moderate dose corticosteroids for refractory septic shock (ongoing pressor requirement in spite of intravascular volume restoration) in patients who are nonresponders to an ACTH stimulation test has been given a Grade C guideline recommendation. Furthermore, it is not recommended that one wait for the results of the ACTH stimulation test before instituting corticosteroids.

An Editorial Note

I appreciate the feedback and encouragement received in response to the first issue of The Critical Point. The subscription list is slowly growing but can hopefully be expanded. I will be exploring ways to get the back issues made available on the Web in the future. In the meantime, feel free to continue to notify me with feedback, e-mail addresses of new subscribers or suggestions for topics. Also, the format will lend itself to letters to the editor, op-ed pieces, guest columns, etc. It would certainly make for a more entertaining read to gain a diversity of opinions.

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Sepsis Guidelines (cont)

- Early Goal Directed Therapy (below)
- RBC transfusion for Hgb < 7 gm/dL
- Renal replacement therapy
- Low tidal volumes in ARDS (6ml/kg)
- Protocols to guide sedation
- Xigris for APACHE II score \geq 25

Grade C recommendations (supported by small randomized trials with uncertain results) included:

- 7 day course of replacement steroids
 - Fluid resuscitation
 - Permissive hypercapnia ventilation
- Grade D recommendations (nonrandomized contemporaneous controls) include:
- Control blood glucose <150 mg/dL
 - Initiate empiric anti-infective therapy
 - Obtain blood cultures

Grade E recommendations (nonrandomized historic controls, case series, uncontrolled studies, expert opinion) include:

- Enteral nutrition
- Steroids before ACTH test results back
- IV antibiotics within 1 hour
- Prone positioning in ARDS
- Replacing vascular access devices
- Dobutamine as the first line inotrope
- Use of PEEP

Early Goal Directed Therapy

In 2001, Emanuel Rivers published a landmark article detailing a simplified approach to the hemodynamic management of severely septic patients basing the principles of care on the concept of global tissue hypoxia. As an E.R. physician, he recognized that 50% of sepsis cases present through the E.D. where waiting times can be lengthy. Even from a medical floor, time to transfer septic patients can be as long as an hour and an additional several hours may pass before hemodynamic optimization occurs. The implications are significant as studies have shown that the development of severe sepsis/shock in the ICU has a 24% mortality vs a 70% mortality managed outside the ICU.

Cardiovascular insufficiency and global tissue hypoxia are comorbid variables in the pathogenesis of sepsis. Hypovolemia, vasodilation, myocardial suppression and increasing metabolic demands result from inflammatory mediators. The progression from severe sepsis to shock with the attendant increase in mortality can occur subtly and over hours. Moreover, global tissue hypoxia can exist with relatively normal vital signs. These factors lead to a need for

more sensitive measures of defining problems than have generally been used in initial evaluation and management.

A central venous catheter can access the central circulation and provide central venous oxygen saturations (SvO₂) as acceptable surrogates for mixed venous saturations and, when reduced, define an imbalance between O₂ delivery and consumption. Central venous pressure also can help establish a patient's intravascular volume status. Measurement of serum lactate level is a noninvasive screen for global tissue hypoxemia and, when elevated, corroborates a "supply dependent" state. With these measurements, candidates for further hemodynamic augmentation or optimization can be recognized.

The hypothesis of the study was that early goal directed therapy which could be initiated in the E.D. could decrease morbidity and mortality as well as health care resource consumption. Patients with suspected infection with SIRS, lactates >4 and SBP <90 after a fluid challenge were randomized to the protocol. A central line was placed and fluids administered to achieve a CVP of 8-12 mm Hg and vasoactive drugs given as needed to attain a mean arterial pressure of >65 mm Hg. The SvO₂ was assessed and if less than 70 mm Hg, trans-

fusions were initiated to achieve a Hgb of 10 gm/dL. In those whom the Hgb met that goal, dobutamine was titrated up to achieve an SvO₂ of 70% while maintaining a heart rate of <100bpm.

The two study groups were evenly matched for age and gender. The receiving ICU team was blinded to the randomization protocol and the intervention during the 6 hrs the study patients were kept under management of the research team in the E.D. (control patients were transferred to the ICU as soon as a bed was available)

While both groups ultimately received similar volumes of fluid and met CVP and MAP goals, 40% of the control group failed to meet the SvO₂ of 70% vs 5% of the study group. Study patients in-hospital mortality was 16% less vs controls (P=0.009) and remained significant at 28 and 60 days.

From this study, the panel of the Surviving Sepsis Campaign concluded that the early assessment of global tissue hypoxia with the use of SvO₂ and lactate monitoring coupled with interventions to maximize suboptimal hemodynamics can have a benefit over "usual" care of volume resuscitation, vasopressors and blood pressure/urine volume measurements and clinical signs of perfusion alone.

Daily Interruption of Continuous Sedation

The American College of Critical Care Medicine (ACCM) and the Society of Critical Care Medicine (SCCM) published guidelines in 2002 regarding sedation titration of the critically ill patient. The following is a Grade A recommendation: "Titration of the sedative dose to a defined endpoint is recommended with systematic tapering of the dose or daily interruption with re-titration to minimize prolonged sedative effects".

This information led to a policy change in the GSH critical care units. Effective April 2005, all patients on a sedative infusion of propofol or a benzodiazepine (excluding these indications: alcohol withdrawal, paralytics, or pressure control ventilation) will have a daily awakening. The infusions are turned off at midnight and the patient is allowed to awaken. If the patient awakens and becomes agitated, the drip will be restarted and titrated to a predefined goal sedation score. If the patient awakens and is not agitated, the drip will remain off. Daily awakenings have been shown to decrease complications of oversedation including prolonged ventilation time, ventilation-associated pneumonia, and prolonged length of stay.

Other key recommendations from these guidelines include: 1) A therapeutic plan and goal of analgesia should be established for each patient and communicated to all caregivers to ensure consistent analgesic therapy. 2) Sedation of agitated critically ill patients should be started only after providing adequate analgesia and treating reversible physiological causes. 3) A sedation goal or endpoint should be established and regularly redefined for each patient. 4) Regular assessment and response to therapy should be systematically documented. 5) The use of sedation guidelines, an algorithm, or a protocol is recommended.

Crit Care Med 2002;30;1 pp. 119-141



A Novel Antisepsis Therapy Has Moved From Bench to Bedside

Nancy Wuestefeld, PharmD

Even with advances in supportive strategies, antimicrobial agents and a better understanding of the physiology of sepsis, mortality rates have continued to be unacceptably high. After two decades of failed sepsis therapies, the FDA approved drotrecogin alpha (Xigris) in 2001 as the first medication indicated for the reduction of mortality in adults with severe sepsis (sepsis associated with acute organ dysfunction) who have a high risk of death. Results from the PROWESS study showed that Xigris reduced the relative risk of death from sepsis with associated acute organ dysfunction by 19.4%. The mortality rates were 24.7% among Xigris treated subjects versus 30.8% among subjects treated with placebo. Subset analysis among patients with APACHE II scores of 25 or greater revealed an even greater difference in absolute mortality (Xigris 31% vs placebo 44%) with a relative risk reduction of 29%. The just published post-marketing ADDRESS trial in patients with a low risk of death (APACHE II <25) due to severe sepsis showed no difference in mortality compared to placebo. Currently Xigris is indicated in high-risk patients only.

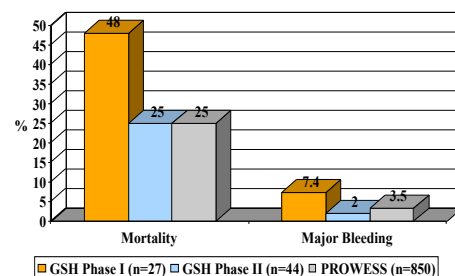
Xigris is a recombinant version of naturally occurring activated protein C that modulates the inflammatory, procoagulant and fibrinolytic host response to infection. In the PROWESS trial, the incidence of serious bleeding was higher in the Xigris group compared to that of placebo (3.5% vs 2% p=0.06). Serious bleeding occurred primarily in patients with an identifiable predisposition to bleeding (GI ulceration, aPPT >120s, INR>3, persistent platelet count <30,000/cm, or traumatic injury to a blood vessel or highly vascular organ).

Xigris is contraindicated in patients in which bleeding could be associated with a high risk of death or significant morbidity including anyone with active internal bleeding, recent hemorrhagic stroke or intracranial surgery, head trauma, epidural catheter or intracranial neoplasm, or cerebral herniation.

The acquisition cost to treat a 70kg patient at 24 mcg/kg/hr for the recommended 96 hour infusion is \$7,000. Because of the cost implications as well as the increased bleeding risk, GSH, like most other ICUs across the country, developed in-house guidelines for use. Patients must meet inclusion and exclusion criteria and be admitted to the ICU with APACHE II scores of at least 25.

Xigris Outcomes at GSH

(Phase I: 2001-03; Phase II: 2003-05)



Seventy-one critically ill patients at GSH have received drotrecogin alpha over the past 4 years. The figure above shows the mortality and bleeding associated with its use. GSH Phase I represents data from the first 27 patients treated and GSH Phase II represents the subsequent 44 patients' data. Phase I mortality and bleeding percentages near double that of phase II. The reduction in mortality in Phase II represents a greater familiarity in the use of the drug as well as an increased recognition to initiate earlier treatment. The reduction in bleeding complications probably represents a comfort level with lower platelet counts as well as treatment with platelet transfusions for counts less than 30,000/uL.

The use of goal-directed therapy through a sepsis protocol which has recently been developed may further refine the need for Xigris in the future.

References and Further Reading

Efficacy and Safety of Recombinant Human Activated Protein C for Severe Sepsis

Gordon R. Bernard, M.D., Jean-Louis Vincent, M.D., Ph.D., Pierre-Francois Laterre, M.D., Steven P. LaRosa, M.D., Jean-Francois Dhainaut, M.D., Ph.D., Angel Lopez-Rodriguez, M.D., Jay S. Steingrub, M.D., Gary E. Garber, M.D., Jeffrey D. Helterbrand, Ph.D., E. Wesley Ely, M.D., M.P.H., Charles J. Fisher, M.D., for The Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) Study Group *N Engl J Med* 2001;344:699-709

Background Drotrecogin alfa (activated), or recombinant human activated protein C, has antithrombotic, antiinflammatory, and profibrinolytic properties. In a previous study, drotrecogin alfa activated produced dose-dependent reductions in the levels of markers of coagulation and inflammation in patients with severe sepsis. In this phase 3 trial, we assessed whether treatment with drotrecogin alfa activated reduced the rate of death from any cause among patients with severe sepsis.

Methods We conducted a randomized, double-blind, placebo-controlled, multicenter trial. Patients with systemic inflammation and organ failure due to acute infection were enrolled and assigned to receive an intravenous infusion of either placebo or drotrecogin alfa activated (24 μ g per kilogram of body weight per hour) for a total duration of 96 hours. The prospectively defined primary end point was death from any cause and was assessed 28 days after the start of the infusion. Patients were monitored for adverse events; changes in vital signs, laboratory variables, and the results of microbiologic cultures; and the development of neutralizing antibodies against activated protein C.

Results A total of 1690 randomized patients were treated (840 in the placebo group and 850 in the drotrecogin alfa activated group). The mortality rate was 30.8 percent in the placebo group and 24.7 percent in the drotrecogin alfa activated group. On the basis of the prospectively defined primary analysis, treatment with drotrecogin alfa activated was associated with a reduction in the relative risk of death of 19.4 percent (95 percent confidence interval, 6.6 to 30.5) and an absolute reduction in the risk of death of 6.1 percent ($P=0.005$). The incidence of serious bleeding was higher in the drotrecogin alfa activated group than in the placebo group (3.5 percent vs. 2.0 percent, $P=0.06$).

Conclusions Treatment with drotrecogin alfa activated significantly reduces mortality in patients with severe sepsis and may be associated with an increased risk of bleeding.

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., Michael Tomlanovich, M.D., for the Early Goal-Directed Therapy Collaborative Group *N Engl J Med* 2001;345:1368-1377

Background Goal-directed therapy has been used for severe sepsis and septic shock in the intensive care unit. This approach involves adjustments of cardiac preload, afterload, and contractility to balance oxygen delivery with oxygen demand. The purpose of this study was to evaluate the efficacy of early goal-directed therapy before admission to the intensive care unit.

Methods We randomly assigned patients who arrived at an urban emergency department with severe sepsis or septic shock to receive either six hours of early

goal-directed therapy or standard therapy (as a control) before admission to the intensive care unit. Clinicians who subsequently assumed the care of the patients were blinded to the treatment assignment. In-hospital mortality (the primary efficacy outcome), end points with respect to resuscitation, and Acute Physiology and Chronic Health Evaluation (APACHE II) scores were obtained serially for 72 hours and compared between the study groups.

Results Of the 263 enrolled patients, 130 were randomly assigned to early goal-directed therapy and 133 to standard therapy; there were no significant differences between the groups with respect to base-line characteristics. In-hospital mortality was 30.5 percent in the group assigned to early goal-directed therapy, as compared with 46.5 percent in the group assigned to standard therapy ($P=0.009$). During the interval from 7 to 72 hours, the patients assigned to early goal-directed therapy had a significantly higher mean (\pm SD) central venous oxygen saturation (70.4 ± 10.7 percent vs. 65.3 ± 11.4 percent), a lower lactate concentration (3.0 ± 4.4 vs. 3.9 ± 4.4 mmol per liter), a lower base deficit (2.0 ± 6.6 vs. 5.1 ± 6.7 mmol per liter), and a higher pH (7.40 ± 0.12 vs. 7.36 ± 0.12) than the patients assigned to standard therapy ($P<0.02$ for all comparisons). During the same period, mean APACHE II scores were significantly lower, indicating less severe organ dysfunction, in the patients assigned to early goal-directed therapy than in those assigned to standard therapy (13.0 ± 6.3 vs. 15.9 ± 6.4 , $P<0.001$).

Conclusions Early goal-directed therapy provides significant benefits with respect to outcome in patients with severe sepsis and septic shock.

Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock.

Dellinger, R. Phillip MD; Carlet, Jean M. MD; Masur, Henry MD; Gerlach, Herwig MD, PhD; Calandra, Thierry MD; Cohen, Jonathan MD; Gea-Banacloche, Juan MD, PhD; Keh, Didier MD; Marshall, John C. MD; Parker, Margaret M. MD; Ramsay, Graham MD; Zimmerman, Janice L. MD; Vincent, Jean-Louis MD, PhD; Levy, Mitchell M. MD; for the Surviving Sepsis Campaign Management Guidelines Committee *Crit Care Med.* 32(3):858-873, March 2004.

Objective: In 2003, critical care and infectious disease experts representing 11 international organizations developed management guidelines for severe sepsis and septic shock 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 outcome 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: We used a modified Delphi methodology 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 were provided to contrast adult and pediatric management.

Results: Key recommendations, listed by category and not by hierarchy, include early goal-directed resuscitation of the septic patient during the first 6 hrs after recognition; appropriate diagnostic studies to ascertain causative organisms before starting antibiotics; early administration of broad-spectrum antibiotic therapy; reassessment of antibiotic therapy with microbiology and clinical data to narrow coverage, when appropriate; a usual 7-10 days of antibiotic therapy

guided by clinical response; source control with attention to the method that balances risks and benefits; equivalence of crystalloid and colloid resuscitation; aggressive fluid challenge to restore mean circulating filling pressure; vasopressor preference for norepinephrine and dopamine; cautious use of vasopressin pending further studies; avoiding low-dose dopamine administration for renal protection; consideration of dobutamine inotropic therapy in some clinical situations; avoidance of supranormal oxygen delivery as a goal of therapy; stress-dose steroid therapy for septic shock; use of recombinant activated protein C in patients with severe sepsis and high risk for death; with resolution of tissue hypoperfusion and in the absence of coronary artery disease or acute hemorrhage, targeting a hemoglobin of 7-9 g/dL; appropriate use of fresh frozen plasma and platelets; a low tidal volume and limitation of inspiratory plateau pressure strategy for acute lung injury and acute respiratory distress syndrome; application of a minimal amount of positive end-expiratory pressure in acute lung injury/acute respiratory distress syndrome; a semirecumbent bed position unless contraindicated; protocols for weaning and sedation/analgesia, using either intermittent bolus sedation or continuous infusion sedation with daily interruptions/lightening; avoidance of neuromuscular blockers, if at all possible; maintenance of blood glucose <150 mg/dL after initial stabilization; equivalence of continuous veno-veno hemofiltration and intermittent hemodialysis; lack of utility of bicarbonate use for pH \geq 7.15; use of deep vein thrombosis/stress ulcer prophylaxis; and consideration of limitation of support where appropriate. Pediatric considerations included a more likely need for intubation due to low functional residual capacity; more difficult intravenous access; fluid resuscitation based on weight with 40-60 mL/kg or higher needed; decreased cardiac output and increased systemic vascular resistance as the most common hemodynamic profile; greater use of physical examination therapeutic end points; unsettled issue of high-dose steroids for therapy of septic shock; and greater risk of hypoglycemia with aggressive glucose control.

Conclusion: Evidence-based recommendations can be made regarding many aspects of the acute management of sepsis and septic shock that are hoped to translate into improved outcomes for the critically ill patient. The impact of these guidelines will be formally tested and guidelines updated annually and even more rapidly as some important new knowledge becomes available.

Daily Interruption of Sedative Infusions in Critically Ill Patients Undergoing Mechanical Ventilation

John P. Kress, M.D., Anne S. Pohlman, R.N., Michael F. O'Connor, M.D., and Jesse B. Hall, M.D. *N Engl J Med* 2000;342:1471-1477.

Background Continuous infusions of sedative drugs in the intensive care unit may prolong the duration of mechanical ventilation, prolong the length of stay in the intensive care unit and the hospital, impede efforts to perform daily neurologic examinations, and increase the need for tests to assess alterations in mental status. Whether regular interruption of such infusions might accelerate recovery is not known.

Methods We conducted a randomized, controlled trial involving 128 adult patients who were receiving mechanical ventilation and continuous infusions of sedative drugs in a medical intensive care unit. In the intervention group, the sedative infusions were interrupted until the patients were awake, on a daily basis; in the control group, the infusions were interrupted only at the discretion of the clinicians in the intensive care unit.

Results The median duration of mechanical ventilation was 4.9 days in the intervention group, as compared with 7.3 days in the control group ($P=0.004$), and the median length of stay in the intensive care unit was 6.4 days as compared with 9.9 days, respectively ($P=0.02$). Six of the patients in the intervention group (9 percent) underwent diagnostic testing to assess changes in mental status, as

compared with 16 of the patients in the control group (27 percent, $P=0.02$). Complications (e.g., removal of the endotracheal tube by the patient) occurred in three of the patients in the intervention group (4 percent) and four of the patients in the control group (7 percent, $P=0.88$).

Conclusions In patients who are receiving mechanical ventilation, daily interruption of sedative-drug infusions decreases the duration of mechanical ventilation and the length of stay in the intensive care unit.

Effect of Treatment With Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patients With Septic Shock

Djillali Annane, MD, PhD; Véronique Sébille, PhD; Claire Charpentier, MD; Pierre-Edouard Bollaert, MD, PhD; Bruno François, MD; Jean-Michel Korach, MD; Gilles Capellier, MD, PhD; Yves Cohen, MD, PhD; Elie Azoulay, MD; Gilles Troché, MD; Philippe Chaumet-Riffaut, MD; Eric Bellissant, MD, PhD *JAMA*. 2002;288:862-871.

Context Septic shock may be associated with relative adrenal insufficiency. Thus, a replacement therapy of low doses of corticosteroids has been proposed to treat septic shock.

Objective To assess whether low doses of corticosteroids improve 28-day survival in patients with septic shock and relative adrenal insufficiency.

Design and Setting Placebo-controlled, randomized, double-blind, parallel-group trial performed in 19 intensive care units in France from October 9, 1995, to February 23, 1999.

Patients Three hundred adult patients who fulfilled usual criteria for septic shock were enrolled after undergoing a short corticotropin test.

Intervention Patients were randomly assigned to receive either hydrocortisone (50-mg intravenous bolus every 6 hours) and fludrocortisone (50- μ g tablet once daily) ($n = 151$) or matching placebos ($n = 149$) for 7 days.

Main Outcome Measure Twenty-eight-day survival distribution in patients with relative adrenal insufficiency (nonresponders to the corticotropin test).

Results One patient from the corticosteroid group was excluded from analyses because of consent withdrawal. There were 229 nonresponders to the corticotropin test (placebo, 115; corticosteroids, 114) and 70 responders to the corticotropin test (placebo, 34; corticosteroids, 36). In nonresponders, there were 73 deaths (63%) in the placebo group and 60 deaths (53%) in the corticosteroid group (hazard ratio, 0.67; 95% confidence interval, 0.47-0.95; $P = .02$). Vasopressor therapy was withdrawn within 28 days in 46 patients (40%) in the placebo group and in 65 patients (57%) in the corticosteroid group (hazard ratio, 1.91; 95% confidence interval, 1.29-2.84; $P = .001$). There was no significant difference between groups in responders. Adverse events rates were similar in the 2 groups.

Conclusion In our trial, a 7-day treatment with low doses of hydrocortisone and fludrocortisone significantly reduced the risk of death in patients with septic shock and relative adrenal insufficiency without increasing adverse events.

Heparin-induced thrombocytopenia: recognition, treatment, and prevention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy.

Warkentin TE; Greinacher A *Chest* 2004 Sep;126(3 Suppl):311S-337S.

This chapter about the recognition, treatment, and prevention of heparin-induced thrombocytopenia (HIT) is part of the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence Based Guidelines. Grade 1 recommendations are strong and indicate that the benefits do, or do not, outweigh risks, burden, and costs. Grade 2 suggests that individual patients' values may lead to different choices (for a full understanding of the grading, see Guyatt et al, *CHEST* 2004; 126:179S-187S). Among the key recommendations in this chapter are the following: For patients in whom the risk of HIT is considered to be > 0.1%, we recommend platelet count monitoring (Grade 1C). For patients who are receiving therapeutic-dose unfractionated heparin (UFH), we suggest at least every-other-day platelet count monitoring until day 14, or until UFH is stopped, whichever occurs first (Grade 2C). For patients who are receiving postoperative antithrombotic prophylaxis with UFH (HIT risk > 1%), we suggest at least every-other-day platelet count monitoring between postoperative days 4 to 14 (or until UFH is stopped, whichever occurs first) [Grade 2C]. For medicalobstetric patients who are receiving prophylactic-dose UFH, postoperative patients receiving prophylactic-dose low molecular weight heparin (LMWH), postoperative patients receiving intravascular catheter UFH "flushes," or medicalobstetrical patients receiving LMWH after first receiving UFH (risk, 0.1 to 1%), we suggest platelet count monitoring every 2 days or 3 days from day 4 to day 14, or until heparin is stopped, whichever occurs first (Grade 2C). For medicalobstetrical patients who are only receiving LMWH, or medical patients who are receiving only intravascular catheter UFH flushes (risk < 0.1%), we suggest clinicians do not use routine platelet count monitoring (Grade 2C). For patients with strongly suspected (or confirmed) HIT, whether or not complicated by thrombosis, we recommend use of an alternative anticoagulant, such as lepirudin (Grade 1C+), argatroban (Grade 1C), bivalirudin (Grade 2C), or danaparoid (Grade 1B). For patients with strongly suspected (or confirmed) HIT, we recommend routine ultrasonography of the lower-limb veins for investigation of deep venous thrombosis (Grade 1C); against the use of vitamin K antagonist (VKA) [coumarin] therapy until after the platelet count has substantially recovered; that the VKA antagonist be administered only during overlapping alternative anticoagulation (minimum 5-day overlap); and begun with low, maintenance doses (all Grade 2C). For patients receiving VKAs at the time of diagnosis of HIT, we recommend use of vitamin K (Grade 2C) [corrected] For patients with a history of HIT who are HIT antibody negative and require cardiac surgery, we recommend use of UFH (Grade 1C).

Drotrecogin Alfa (Activated) for Adults with Severe Sepsis and a Low Risk of Death

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Background In November 2001, the Food and Drug Administration (FDA) approved drotrecogin alfa (activated) (DrotAA) for adults who had severe sepsis and a high risk of death. The FDA required a study to evaluate the efficacy of DrotAA for adults who had severe sepsis and a low risk of death.

Methods We randomly assigned adult patients with severe sepsis and a low risk of death (defined by an Acute Physiology and Chronic Health Evaluation [APACHE II] score <25 or single-organ failure) to receive an intravenous infusion of placebo or DrotAA (24 µg per kilogram of body weight per hour) for 96 hours in a double-blind, placebo-controlled, multicenter trial. The prospectively defined primary end point was death from any cause and was assessed 28 days after the start of the infusion. In-hospital mortality within 90 days after the start of the infusion was measured, and safety information was collected.

Results Enrollment in the trial was terminated early because of a low likelihood of meeting the prospectively defined objective of demonstrating a significant reduction in the 28-day mortality rate with the use of DrotAA. The study enrolled 2640 patients and collected data on 2613 (1297 in the placebo group and 1316 in the DrotAA group) at the 28-day follow-up. There were no statistically significant differences between the placebo group and the DrotAA group in 28-day mortality (17.0 percent in the placebo group vs. 18.5 percent in the DrotAA group; $P=0.34$; relative risk, 1.08; 95 percent confidence interval, 0.92 to 1.28) or in in-hospital mortality (20.5 percent vs. 20.6 percent; $P=0.98$; relative risk, 1.00; 95 percent confidence interval, 0.86 to 1.16). The rate of serious bleeding was greater in the DrotAA group than in the placebo group during both the infusion (2.4 percent vs. 1.2 percent, $P=0.02$) and the 28-day study period (3.9 percent vs. 2.2 percent, $P=0.01$).

Conclusions The absence of a beneficial treatment effect, coupled with an increased incidence of serious bleeding complications, indicates that DrotAA should not be used in patients with severe sepsis who are at low risk for death, such as those with single-organ failure or an APACHE II score less than 25.