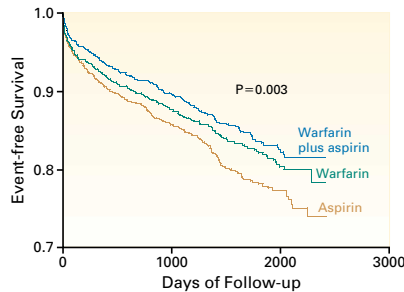




This Week in the Journal

September 26, 2002

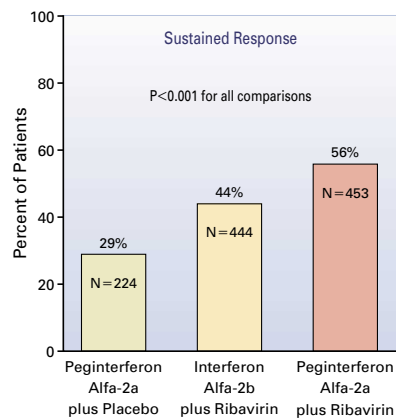


Warfarin, Aspirin, or Both after Myocardial Infarction

Antithrombotic therapy is routinely prescribed after myocardial infarction. This study compared the effect of warfarin, aspirin, or the combination of both medications on a composite end point of death, nonfatal reinfarction, or thromboembolic stroke. Both warfarin regimens were superior to the aspirin regimen. The combined-therapy regimen was somewhat more favorable than the warfarin-alone regimen but not significantly so.

Aspirin is the most commonly used antithrombotic drug after myocardial infarction, but this study suggests that warfarin or warfarin plus aspirin may be more effective in reducing coronary events. However, the risk of bleeding episodes was higher with the warfarin regimens, a fact that must be considered in clinical decision making.

see page 969 (editorial, page 1019)



Peginterferon Alfa-2a plus Ribavirin for Chronic Hepatitis C

Interferon-based therapies combined with ribavirin are effective for chronic hepatitis C, but many patients do not have a response and side effects are common. Pegylated interferons are more efficacious than standard interferons. In this large trial, peginterferon alfa-2a plus ribavirin resulted in a higher rate of sustained virologic response (56 percent) than interferon alfa-2b plus ribavirin (44 percent) and peginterferon alfa-2a alone (29 percent). Side effects occurred less often with peginterferon alfa-2a plus ribavirin than with interferon alfa-2b plus ribavirin.

Peginterferon alfa-2a plus ribavirin appears to be better treatment than interferon alfa-2b plus ribavirin for chronic hepatitis C, because the regimen containing pegylated interferon is more effective with fewer side effects.

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PERSPECTIVE

Treating Sepsis

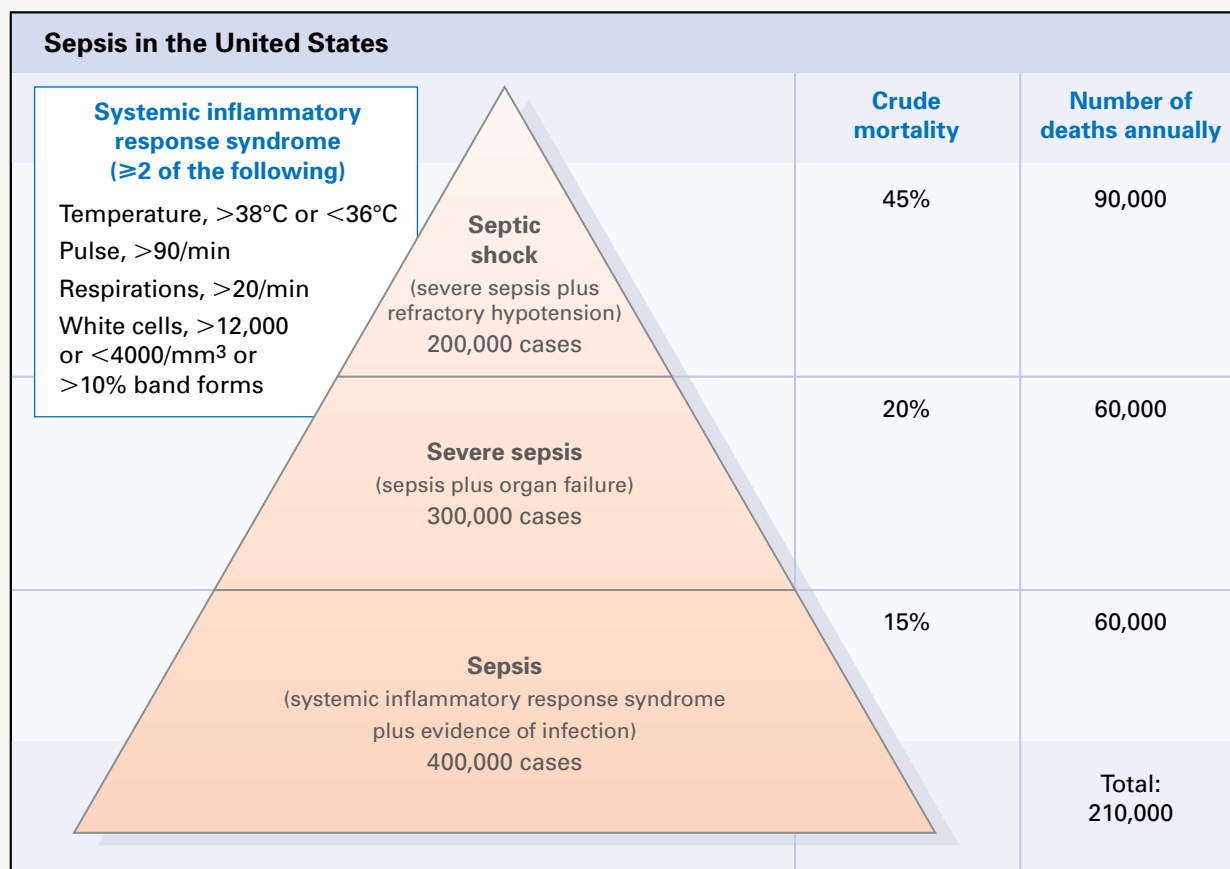
Sepsis, a leading cause of death in the United States, is now viewed physiologically as a proinflammatory and procoagulant response to invading pathogens. There are three recognized stages in the hierarchy of the inflammatory response, with progressively increased risk of end-organ failure and death: sepsis, severe sepsis, and septic shock. Patients with infection plus two or more elements of the systemic inflammatory response syndrome meet the criteria for sepsis; those who also have end-organ failure are considered to have severe

sepsis; and those who also have refractory hypotension are considered to be in septic shock (see Figure). Because the crude mortality from all stages of sepsis translates to approximately 210,000 deaths annually, any adjunctive therapy that led to improved outcomes would be welcomed.

Clearly, the early use of appropriate antibiotics can reduce mortality from sepsis. Thus, the skill of the clinician can be measured by the effectiveness of empirical therapy that targets both the species and the antibiotic sensitivity of likely pathogens. For patients who are in septic shock, there are some data suggesting that the early use of vasopressors, bolus intravenous fluids, and physiologic doses of hydrocortisone favorably influences mortality. However, the holy grail that has

eluded investigators for two decades is a novel therapy targeting the biologic triggers of sepsis.

Recently, it has been recognized that important responses to sepsis occur on endovascular surfaces. Microorganisms stimulate macrophages to elaborate a variety of provocative cytokines, which, in turn, target proteins located on small vessels and thereby alter the normally antiinflammatory and anticoagulant ecology by causing inflammation and clotting. A key vascular protein orchestrating many of the normal regulatory functions is activated protein C. However, in severe sepsis and septic shock, levels of activated protein C are often reduced, with coincident procoagulation, failure of normal fibrinolysis, leaky capillaries, and other correlates of inflammation.



“Functional variants of the NPT2a gene provide genetic evidence that a defect in renal phosphate reabsorption may contribute to these two common disorders.”

Nephrolithiasis and Osteoporosis with Hypophosphatemia Caused by Mutations in the Type 2a Sodium–Phosphate Cotransporter

Familial aggregation occurs among persons with renal calcium stones or bone demineralization, suggesting a genetic propensity toward these disorders. In this study of 14 patients with stones and 6 with bone demineralization, all of whom also had hypophosphatemia and decreased renal phosphate reabsorption, 2 patients were found to have unique mutations in the type 2a sodium–phosphate cotransporter.

Considering additional phenotypic features in persons with common clinical conditions can aid in selecting candidate genes in which mutations may explain the clinical abnormalities.

see page 983 (editorial, page 1022)

In March 2001, Bernard and colleagues presented data in the *Journal* from their pivotal study, showing a reduction in 28-day mortality among patients with severe sepsis and septic shock who received recombinant human activated protein C. The death rate was 30.8 percent among controls and 24.7 percent in the group receiving activated protein C ($P=0.005$). Subsequently, 10 members of an advisory panel of the Food and Drug Administration (FDA) voted for approval of the drug and 10 voted against it, but drotrecogin was licensed in November 2001.

Controversy surrounds both the study and the FDA approval. In the latter half of the study, the sponsor (Eli Lilly) not only modified the eligibility criteria but also used a different cell line for the production of human recombinant activated protein C. In terms of outcomes, the absolute difference in mortality — 6.1 percent — seemed small to some, and there was an increased risk of serious bleeding (an absolute difference of 1.4 percent) associated with activated protein C therapy. Subsequently, the FDA performed a post hoc analysis of the data and found that activated protein C benefited primarily the most seriously ill patients — those with scores of 25 or more on the Acute Physiology and Chronic Health Evaluation (APACHE II).

The FDA’s analysis became the basis of an unprecedented indication for a drug: a score calculated on the basis of current physiological markers and chronic health status has never before been a criterion for approved treatment. Furthermore, the cost of activated protein C is approximately \$7,000 per course — a substantial investment at a time of budget constraints in critical care units.

In this issue of the *Journal*, three articles and a letter to the editor frame the issues of the debate over the value of activated protein C. In a Sounding Board article (see pages 1030–1034), Siegel, from the Center for Biologics Evaluation and Research, argues that the changes in eligibility criteria created inconsistencies over time only in the lower-risk population (patients with APACHE II scores of 24 or less). Concluding that the amended protocol did not account for the subsequently improved study outcomes, he defends the FDA approval. In another Sounding Board article (see pages 1027–1030), Warren and colleagues (all of whom were consultants to the FDA’s Anti-Infective Drugs Advisory Committee) argue that the results of post hoc analyses require confirmation in a new study. They conclude that the existing data fail to support the use of activated protein C as the standard of care. Manns and col-

leagues (see pages 993–1000), who created mathematical models of the economic value of activated protein C, estimate that the cost of a life-year gained with the use of the drug would be about \$28,000. However, in patients with an APACHE II score of less than 25, the cost could exceed \$500,000 per life-year gained.

In a letter to the editor (see pages 1035–1036), Ely and colleagues, authors of the original study, provide some updated information: almost 2800 patients have received activated protein C, with a crude mortality of 25 to 26 percent — the same figure observed in the treated group in the pivotal study. Furthermore, of the 13 patients with intracranial hemorrhage (0.5 percent), 9 had meningitis, marked thrombocytopenia (a platelet count of less than 30,000 per cubic millimeter), or both. From these four pieces, those of us who are reviewing the arguments surrounding the current debate on the value of activated protein C will gain insights that may guide us in answering the key clinical question: Which patients with severe sepsis or septic shock should receive recombinant human activated protein C?

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“The use of activated protein C in patients with severe sepsis, greater severity of illness, and a reasonable life expectancy if they survive the episode of sepsis is associated with a cost-effectiveness ratio similar to those for other accepted medical therapies.”

Special Article: An Economic Evaluation of Activated Protein C Treatment for Severe Sepsis

Recombinant human activated protein C has been shown to reduce mortality among patients with severe sepsis. Given the high cost of activated protein C (\$6,800 per therapeutic course) and the high incidence of severe sepsis, the economic implications of widespread use of activated protein C are important. In this cost-effectiveness analysis, the authors report that activated protein C is associated with a cost of about \$28,000 per year of life gained and \$47,000 per quality-adjusted year of life gained. However, treatment of patients with an APACHE II score of 24 or less is associated with a cost of \$575,000 per year of life gained.

When used in patients with severe sepsis and greater severity of illness (an APACHE II score of 25 or more), activated protein C is associated with favorable cost-effectiveness ratios. It is not clear that treatment of patients with an APACHE II score of 24 or less is economically justifiable.

see page 993 (Perspective, page 966)

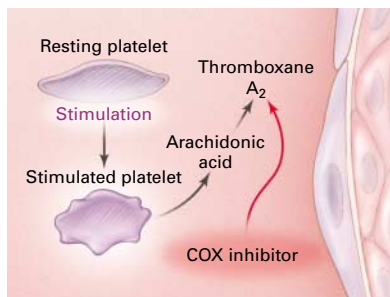


Clinical Practice: Raynaud's Phenomenon

A 37-year-old woman reports that her fingers turn blue when they are exposed to the cold and that she has fatigue, arthralgias, and a history of small, painful digital ulcers. How should she be evaluated and treated?

This article reviews the evaluation and treatment of patients with Raynaud's phenomenon.

see page 1001



Clinical Implications of Basic Research: COX Inhibitors and Thromboregulation

Prostacyclin inhibits platelets and dilates blood vessels, whereas thromboxane A_2 activates platelets and constricts vessels. In mice lacking receptors for prostacyclin, intimal injury provokes a severe reaction within the artery, whereas in mice lacking thromboxane A_2 receptors the response is subdued. These findings are relevant to clinical concerns that cyclooxygenase-2 inhibitors, which specifically impair the formation of prostacyclin, may increase susceptibility to cardiovascular events. Aspirin, which inhibits both prostacyclin and thromboxane A_2 , protects against arterial thrombosis.

see page 1025