

Correspondence



Recombinant Human Activated Protein C for Severe Sepsis

To the Editor: Bernard and coworkers (March 8 issue)¹ conclude that recombinant human activated protein C (drotrecogin alfa [activated]) is efficacious in patients with sepsis. The placebo and treatment groups appeared to be closely matched, with one important exception: the interval between the diagnosis of sepsis and the administration of appropriate antibiotic therapy. The authors state only that appropriate antibiotic therapy was started within 48 hours of the diagnosis of severe sepsis.

It is axiomatic that the more severe the sepsis, the more important the requirement for prompt administration of appropriate antibiotic therapy. In a study of gram-negative bacterial sepsis in mice, we demonstrated that each hour that appropriate antibiotic therapy was delayed resulted in progressive increases in mortality.² After a delay of three to eight hours, depending on the bacterial species, mortality by day 4 was no longer reducible. Windows of antibiotic effectiveness can also close so rapidly during severe sepsis in humans that even prompt initiation of antibiotic therapy may not reduce mortality significantly.³ We agree that difficulty determining the time of onset of sepsis is a major impediment to progress in clinical trials, whereas animal models do not pose this problem.⁴ Nevertheless, because each hour of delay in initiating appropriate antibiotic therapy in patients with severe sepsis may affect the outcome, the greatest possible precision must be used in showing that this factor is similar in the study groups before any differences in outcome are attributed to other antiseptic treatments. In a previous trial in-

volving sepsis, the investigators applied this principle, performing a statistical analysis to compare the study groups.⁵

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To the Editor: Bernard et al. report the efficacy and safety of recombinant human activated protein C for the treatment of severe sepsis. The authors state, "reductions in the relative risk of death were observed regardless of whether the patients had a deficiency of protein C at base line." They also state that "measurements of protein C are not necessary to identify which patients would benefit from treatment with drotrecogin alfa activated." The results of a stratified analysis, presented in Table 4 of their article, indicate that in the group of patients who did not have a deficiency of protein C at base line, the reduction in the risk of death with the use of drotrecogin alfa activated was not statistically significant.

The incidence of serious bleeding was higher in the group

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assigned to drotrecogin alfa activated than in the placebo group (3.5 percent vs. 2.0 percent). Serious bleeding occurred primarily in patients with an identifiable predisposition to bleeding. It would be interesting to know whether the authors stratified the risk of bleeding in relation to the presence or absence of protein C deficiency at base line as well. This type of analysis might be valuable because it would allow a more complete risk-benefit analysis for this subgroup of patients.

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To the Editor: Bernard et al. conclude that drotrecogin alfa activated significantly reduced mortality in patients with severe sepsis. However, the randomization scheme evidently failed, and the authors did not adjust for this in their analyses. Nor did they or the editorialist¹ discuss possible selection bias. Table 1 of their article does not give P values, but it shows that the patients in the placebo group were more fragile and ill than those in the group assigned to drotrecogin alfa activated. Of the nine categories of prior preexisting conditions listed, eight were more prevalent in the placebo group than in the treatment group; the difference was significant for congestive cardiomyopathy (P=0.038) and it approached significance for chronic obstructive pulmonary disease and cancer (P=0.065 and P=0.062, respectively). More patients in the placebo group underwent mechanical ventilation (P=0.039), and more patients in this group were in shock and needed vasopressors (P=0.066). A remarkable error is the enrollment of one patient in the treatment group who did not meet the inclusion criterion of a dysfunctional organ system.

There is an additional reason to doubt the validity of the trial. All base-line data on coagulation and inflammation were missing more often in the placebo group than in the treatment group (Table 3), and the difference in plasma D-dimer levels was significant (P=0.028). Did the patients in the placebo group initially receive less attention, care, or both? Taken together, these discrepancies between the study groups may account for the observed difference in survival after 28 days. A 6.1 percent absolute reduction in mortality from severe sepsis with the use of a single drug would be a striking achievement, even if this reduction occurred in a highly selected group of patients. However, we are not convinced that the use of drotrecogin alfa activated really represents such a breakthrough.

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To the Editor: Bernard et al. state, “In the United States, approximately 750,000 cases of sepsis occur each year, at

least 225,000 of which are fatal.” If septicemia were responsible for this number of deaths, it would be the third leading cause of death in the United States, after diseases of the heart and cancers, and would account for 9.72 percent of all reported deaths in 1997.

The *Statistical Abstract of the United States*, 2000 edition, provides data on deaths and death rates according to selected causes. In Table 126, septicemia is reported to have been the cause of 23,600 deaths in 1998, with a crude death rate of 8.7 per 100,000 population.¹

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1. U.S. Census Bureau. Statistical abstract of the United States: 2000 edition. (Accessed June 29, 2001, at <http://www.census.gov/prod/www/statistical-abstract-us.html>.)

The authors reply:

To the Editor: Greisman and colleagues are concerned about the interval between the onset of sepsis and the administration of appropriate antibiotic therapy.^{1,2} According to the judgment of a blinded clinical-evaluation committee, 89.3 percent of the patients in the drotrecogin alfa activated group and 89.1 percent of those in the placebo group received appropriate antibiotics within 24 hours of the onset of severe sepsis.

Kapur et al. ask about treatment effects in the patients who did not have a deficiency of protein C. In this subgroup of 195 patients, the relative reduction in the risk of death associated with the administration of drotrecogin alfa activated was 41.7 percent (P=0.06). Two of 90 patients who received drotrecogin alfa activated (2.2 percent) had a serious bleeding event — an event rate similar to that in the overall study population.

Ott and Verbrugh suggest that a maldistribution of patients with certain prior or preexisting conditions may have confounded the analysis. However, the misuse of significance testing to determine potentially relevant imbalances in baseline characteristics is well documented.³ A more appropriate approach is to use analyses of mortality from all causes at 28 days, stratified according to clinically relevant covariates selected a priori, as we did in our trial; the results are shown in Table 4 of our article. For the covariates discussed by Ott and Verbrugh, the adjusted relative reduction in the risk of death was as follows: congestive cardiomyopathy, 18.9 percent (P=0.008); chronic obstructive pulmonary disease, 19.5 percent (P=0.007); cancer, 19.8 percent (P=0.006); mechanical ventilation, 18.5 percent (P=0.009); shock, 19.8 percent (P=0.006); and use of vasopressors, 18.7 percent (P=0.008). Thus, formal adjustment of these covariates produced results similar to those for the overall trial (relative reduction in the risk of death, 19.4 percent; P=0.005).

Ott and Verbrugh also suggest that less attention, care, or both might have been given to patients in the placebo group in whom base-line measurements of coagulation and inflammation were not obtained. Actually, in both study groups, these measurements were obtained in more than 90 percent of patients, indicating that a very committed group of investigators participated in this double-blind, multinational study.

O'Connor asks about the data we cited on the incidence of severe sepsis and mortality attributable to it. We acknowledge that there is a dearth of reliable statistics on this question. For our report, we relied on recent work by Angus et al., whom we believe have performed the most robust exploration of this question to date.⁴ They report that death associated with severe sepsis occurs as often as death associated with acute myocardial infarction, just as O'Connor suggests. In any case, there is little doubt that severe sepsis is a huge threat to public health. Furthermore, considering the striking age-related incidence and mortality rates, the burden of severe sepsis will probably become an even larger problem as our population ages.

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Renal-Artery Stenosis

To the Editor: In their review article on renal-artery stenosis (Feb. 8 issue),¹ Safian and Textor indicate that the results of surgery and interventional radiology are better for hypertension associated with fibromuscular hyperplasia than for atherosclerotic renal-artery stenosis.

The explanation for this may lie in the finding by my colleagues and me^{2,3} that fibromuscular hyperplasia may not cause renal-artery stenosis and that the saccular dilatations reshape the pulse wave to a flat sine wave, without diminishing the perfusion of the kidney.

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To the Editor: I read the review article on renal-artery stenosis by Safian and Textor with great expectations, since the

topic is of intense familial interest. The article was in the Medical Progress section of the *Journal*, so I probably shouldn't have been surprised that a review of a topic that a few years ago would have been at least subtitled "Goldblatt hypertension"¹ made not a single reference to Harry Goldblatt's pioneering work² on the subject.

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The authors reply:

To the Editor: We appreciate Dr. Reich's comments, which offer insight into the mechanism of hypertension associated with fibromuscular disease of the renal artery. However, personal observations with intravascular ultrasonography indicate that multiple weblike defects are often present in patients with fibromuscular dysplasia, contributing to clinically significant stenoses that are frequently inapparent on angiography. Thus, renal ischemia may lead to renovascular hypertension in such patients. These weblike structures can be easily disrupted by balloon inflations, a fact that may partially explain the value of angioplasty in hypertensive patients with fibromuscular dysplasia.

Dr. Goldblatt accurately describes the pioneering work of Harry Goldblatt and his contributions to the understanding of renin-dependent hypertension. In truth, our failure to mention Harry Goldblatt's work in our review has more to do with space limitations than our failure to recognize his enormous contributions.

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Genetic Variation in Alcohol Dehydrogenase and Myocardial Infarction

To the Editor: Hines et al. (Feb. 22 issue)¹ report that a polymorphism of the gene encoding alcohol dehydrogenase (*ADH*) — namely, the slow-oxidizing allele of the *ADH3* gene — in male patients who consumed moderate amounts of alcohol significantly reduced the risk of myocardial infarction. However, alcohol elimination occurs by oxidation to acetaldehyde and acetate by way of both alcohol dehydrogenase and aldehyde dehydrogenase (which is encoded by *ALDH*). The genes for these enzymes are polymorphic at

the *ADH2*, *ADH3*, and *ALDH2* loci in humans,² and the degrees of polymorphism are different in different racial and ethnic groups.

Polymorphisms of the *ADH* and *ALDH* genes have been well studied in the Chinese population, in which the incidence of myocardial infarction is among the lowest in the world (as shown in the Monitoring Trends and Determinants in Cardiovascular Disease project of the World Health Organization).³ The fast-oxidizing *ADH2*2* and *ADH3*1* alleles, which encode the β_2 and γ_1 subunits of alcohol dehydrogenase, predominate in the Chinese population.⁴ Approximately 50 percent of Chinese persons lack the aldehyde dehydrogenase type 2 activity that is encoded by the dominant *ALDH2* allele, *ALDH2*2*, and that is associated with the "flushing response."⁵ This facial flushing and other symptoms have been thought to be a genetic deterrent to heavy drinking and alcoholism.

It is the combination of *ADH* and *ALDH* polymorphisms that determines the true rate of ethanol metabolism. Persons possessing the *ADH2*2* and *ADH3*1* alleles generate acetaldehyde more rapidly after alcohol consumption than persons with other alleles. Deficiency of aldehyde dehydrogenase type 2 would slow the elimination of acetaldehyde, thus slowing the overall metabolism of alcohol. The combination of such genetic polymorphisms in the *ADH* and *ALDH* genes may offer insight into the basis of genetic predisposition to myocardial infarction, especially in the Chinese population.

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The authors reply:

To the Editor: We agree that both alcohol dehydrogenase and aldehyde dehydrogenase predominantly determine the rate of ethanol metabolism. Our study involved a white population, in which variant alleles at the *ADH2* and *ALDH2* loci are uncommon (occurring in less than 10 percent of the population).¹ Thus, it is unlikely that polymorphisms at these loci would substantially contribute to variations in metabolic capacity in white persons. Furthermore, it would take a study population considerably larger than ours to provide adequate power to investigate the role of these less common polymorphisms. Allele frequencies often depend on the race or ethnicity of the population, an indication of the impor-

tance of investigating the role of genetic variation among different groups. It would be of interest to investigate the role of *ADH2* and *ALDH2* polymorphisms and predisposition to myocardial infarction in Asian populations. However, the flushing response due to acetaldehyde toxicity may influence the drinking habits of persons with certain genotypes. Thus, it may be difficult to tease apart the effect of the capacity for ethanol metabolism, according to *ADH* and *ALDH* genotypes, on the risk of myocardial infarction independently of the effect of these genotypes on the amount of alcohol consumed, which would also influence the risk of myocardial infarction.

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Appendectomy and Protection against Ulcerative Colitis

To the Editor: Like prior case-control studies, a follow-up study from Sweden (March 15 issue)¹ reported that appendectomy is associated with a low risk of subsequent ulcerative colitis. These findings have led to speculation about causality, suggestions that appendectomy might be therapeutic, and even proposals that appendectomy be performed prophylactically in first-degree relatives of patients.² These are not trivial conclusions. However, the literature on this subject is fraught with methodologic problems,³ some of which are also present in the study by Andersson et al.¹

Andersson et al. excluded 294 patients with ulcerative colitis that occurred at or before or within one year after the appendectomy, as compared with 192 of the controls — a difference of 102. That there was an excess number of case patients with ulcerative colitis who were excluded most likely occurred because patients with ulcerative colitis, whether established or incipient, can have symptoms so suggestive of appendicitis that surgery is indicated. It is not surprising that when outcomes among subjects with the exposure variable under evaluation, in this case appendectomy, are excluded from the study, a protective effect for that exposure is found in the remaining subjects.

Notably, the excess of 102 almost exactly matches the difference in the number of cases of ulcerative colitis reported during follow-up (304 among the case patients and 410 among the controls; a difference of 106), leaving the total number of cases of ulcerative colitis virtually identical in the two groups (598 and 602, respectively). Hence, the finding by Andersson et al. of an inverse association of appendectomy with the risk of ulcerative colitis can be accounted for by their exclusion policies. In a cohort study that addressed the same issue, we found no association between ulcerative colitis and appendectomy in 154,434 Danish patients who had undergone appendectomy.³ In our view, there is also no ef-

fect of appendectomy on the risk of ulcerative colitis in the data analyzed by Andersson et al.

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To the Editor: The study by Andersson et al. strengthens the evidence that appendectomy is associated with a low risk of subsequent ulcerative colitis. Some aspects of the study, however, deserve comment. First, the mean age at the diagnosis of ulcerative colitis seems older (33.7 years) than the one usually reported in Scandinavian countries. Indeed, the first peak in the incidence of ulcerative colitis occurs between the ages of 20 and 25 years in Western countries.¹ Another report stated that the median age at diagnosis is 12.2 years in Sweden.² Could the authors have missed a significant number of patients?

A second concern is the lack of data on smoking status. Along with appendectomy, smoking has been repeatedly reported to confer protection against ulcerative colitis.³ Thus, it may be an important confounding factor. A significant association between acute appendicitis and smoking in adults and passive smoking in children has been reported.⁴

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To the Editor: Andersson and coworkers suggest that appendectomy protects against ulcerative colitis, but only if it is performed before the age of 20 years. The alternative hypothesis — namely, that ulcerative colitis protects against appendicitis — is also attractive. Ulcerative colitis involves the mucosal lining of the bowel, and appendiceal lesions are common, especially in patients with less extensive colonic disease.¹ Destruction of the mucosal lining of the appendix in patients with ulcerative colitis could cause fibrosis and

obliteration of the appendix, reducing the risk of subsequent obstructive appendicitis. Pathological changes, including fibrosis, were found in more than half of appendices in patients undergoing colectomy for ulcerative colitis.²

If ulcerative colitis protects against appendicitis by inducing fibrosis within the appendiceal lumen, it would explain why the apparent protection of appendectomy against ulcerative colitis in the study by Andersson et al. was limited to younger patients. In the general population, the frequency of appendiceal fibrosis increases with age and might be similar to that in patients with ulcerative colitis.

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The authors reply:

To the Editor: The hypothesis that ulcerative colitis protects against appendicitis, suggested by Lowenfels and Maisonneuve, has been proposed by others who did not consider the temporal relation between appendectomy and ulcerative colitis. This interpretation of our results is not valid, since we selected patients whose appendectomy preceded their diagnosis of ulcerative colitis. In fact, the larger number of case patients with a diagnosis of ulcerative colitis before or at the time of appendectomy than of controls suggests that ulcerative colitis is a risk factor for appendicitis and appendectomy. This is also consistent with the findings of appendiceal inflammation in patients who underwent colectomy for distal ulcerative colitis.¹

In response to the comments of Frisch and Biggar, we think it is correct to exclude patients in whom the study outcome has occurred before or at the time of the exposure. Similarly, in order to exclude patients who had undiagnosed ulcerative colitis at the time of the appendectomy, we also chose to start the follow-up one year after the operation.

We have reviewed our results and found one error in Table 1. Thirty-nine of the 74 case patients who were identified as having received a diagnosis of ulcerative colitis within the first year after the appendectomy had actually already been given the diagnosis at the time of the operation. The correct number of exclusions because of a diagnosis of ulcerative colitis before or at the time of appendectomy is therefore 259 case patients (instead of 220) and 168 controls.

We recalculated our results, starting the follow-up immediately after the appendectomy and including the 35 case patients and 24 controls who had been given a diagnosis of ulcerative colitis within one year after the operation. We found little change. The incidence-rate ratio of ulcerative colitis among the patients who underwent appendectomy for appendicitis as compared with the controls was 0.77 (95 percent confidence interval, 0.65 to 0.90); after appendectomy

for mesenteric lymphadenitis it was 0.56 (95 percent confidence interval, 0.32 to 0.94); and after appendectomy for nonspecific abdominal pain it was 1.34 (95 percent confidence interval, 0.79 to 2.30). For the patients who underwent surgery for appendicitis before the age of 20 years it was 0.45 (95 percent confidence interval, 0.33 to 0.61), and for patients who underwent surgery at or after the age of 20 years it was 1.00 (95 percent confidence interval, 0.81 to 1.22).

Frossard et al. comment on the age at diagnosis of ulcerative colitis, which is older in our study than in other studies of ulcerative colitis. Since we included only patients who had received a diagnosis of ulcerative colitis more than one year after the appendectomy, the mean age at the start of follow-up was 23.1 years. In addition, had information regarding whether or not the subjects smoked been available, we believe it would have marginally affected our results. This has been the result in previous studies in which an adjustment for smoking status was made.²⁻⁵

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Myocarditis and Cardiomyopathy Associated with Clozapine Use in the United States

To the Editor: We summarize cases of myocarditis and cardiomyopathy reported to the Food and Drug Administration (FDA) in patients treated with the atypical antipsychotic medication clozapine. Because it carries risks of agranulocytosis and seizures, clozapine is indicated for patients with severe schizophrenia who have no response to or who cannot tolerate standard antipsychotic agents. Between the U.S. approval of clozapine in September 1989 and December 2, 1999, the FDA received reports of 28 cases of myocarditis, including 18 deaths, and 41 cases of cardiomyopathy, including 10 deaths, that were temporally associated with the use of clozapine and that met at least one of the criteria described in Table 1.^{1,2} Thirteen of the 18 deaths from myocarditis were confirmed at autopsy.

As compared with patients who died of myocarditis, those who survived tended to have been treated for a shorter time (median, 2 weeks vs. 4 weeks) and to have taken a lower daily dose (median, 225 mg vs. 450 mg); the lower medi-

TABLE 1. CARDIOMYOPATHY AND MYOCARDITIS ASSOCIATED WITH THE USE OF CLOZAPINE IN THE UNITED STATES.

VARIABLE	CARDIOMYOPATHY	MYOCARDITIS
Total no. of cases reported	41	28
No. of confirmed cases*	22	17
Age — yr		
Range	20–59	25–66
Median	34	36
Sex — no.		
Male	32	15
Female	9	13
Duration of therapy		
Range	2 wk–7 yr	2 wk–7 yr
Median	9 mo	3 wk
Deaths — no. (%)	10 (24)	18 (64)

*Confirmed cases of cardiomyopathy met the following criteria: signs or symptoms of heart failure plus characteristic electrocardiographic changes, positive echocardiographic findings, or both. Confirmed cases of myocarditis met the following criteria: sudden, unexpected onset of heart failure plus either definitive histologic findings at autopsy (in 13 cases) or improvement on withdrawal of the drug, with a positive reaction on rechallenge (in 4 cases).

an dose may reflect a shorter duration of treatment, since the dose is titrated early in its administration. In contrast, among patients with cardiomyopathy, the median dose (450 mg and 400 mg) and the duration of therapy (8 months and 10 months) were similar in those who survived and those who died.

Data provided by the U.S. Clozaril National Registry indicated that through December 1999 a total of 189,405 persons had been exposed to clozapine. Assuming that all patients had taken clozapine for at least one month and including only the 5 cases with autopsy-confirmed myocarditis during the first month of therapy, we estimated that the incidence of fatal myocarditis in the first month of therapy was 321 per million person-years of observation. This greatly exceeds the background rate of 4 per million per year.³ Although the risk of fatal myocarditis is greatest in the first month of treatment with clozapine, it is not limited to this period, and patients may be at increased risk as long as they are taking the drug.

Although clozapine therapy continues to have a role in severe schizophrenia that cannot be managed effectively with other medications, physicians should be aware of the associations between the use of clozapine and these cardiac complications. Having a high index of clinical suspicion in the case of patients with cardiac symptoms may prevent life-threatening disease.

(The views expressed are those of the authors and do not necessarily represent those of, nor imply endorsement from, the FDA or the U.S. government.)

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Pamidronate for Bone Pain from Osteolytic Lesions in Langerhans'-Cell Histiocytosis

To the Editor: A 23-year-old woman with Langerhans'-cell histiocytosis presented with severe pain in the right iliac crest and right shoulder of three months' duration. The patient had undergone excision and radiation of a skeletal lesion of the left hip at the age of 10; diabetes insipidus had developed when she was 15; and she had been treated with mercaptopurine and prednisone at the age of 19. Skeletal-survey radiographs showed osteolytic lesions in the frontal bone of the skull and the right femoral head. Sustained-release morphine sulfate (60 mg twice daily) was prescribed, and the patient had partial relief of the pain.

The presence of osteolytic lesions and severe bone pain prompted a trial of pamidronate. Immediately after the intravenous administration of the first dose of 90 mg, the patient's pain decreased from a level of 9 to a level of 6, as assessed on a 10-point visual-analogue scale. Treatment was continued on a monthly schedule, and after four infusions, the patient had resolution of pain to a level of 2 on the visual-analogue scale. The sustained-release morphine sulfate was gradually discontinued. Currently, the patient is free of bone pain and has stable osteolytic lesions while receiving pamidronate on a monthly schedule. She has now started chemotherapy with a combination of mercaptopurine, pred-

nisone, and vinblastine because of Langerhans'-cell histiocytosis involving the gastrointestinal tract.

Pamidronate, a second-generation amino bisphosphonate, is a potent inhibitor of osteoclastic bone resorption.¹ Experience with this medication in patients with multiple myeloma and those with metastatic breast cancer has shown it to be effective in reducing the extent of osteolytic lesions and the incidence of vertebral and long-bone fractures.²⁻⁴ In addition, it has been associated with relief of the pain associated with bone metastases and improvement in the quality of life in 50 percent of treated patients.⁵

In view of the remarkable relief of pain in our patient, we suggest a trial of pamidronate therapy for bone pain in patients with osteolytic lesions due to Langerhans'-cell histiocytosis.

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