Drotrecogin Alfa (Activated) Administration: Too Many Subgroups

To the Editor:

It is always very dangerous to look at many subgroups in a trial, even a positive one. Although those decisions were logical, it is precisely what both the Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products have done when licensing activated protein C (Xigris) only in the most severe patients. Acute Physiology and Chronic Health Evaluation II score >25 and multiple organ failures were used, respectively, by the Food and Drug Administration and European Agency for the Evaluation of Medicinal Products to select the most appropriate patients for the drug usage. The recent paper from Dr. Ely and colleagues (1) provides important information on those different subgroups but also raises many unsolved issues.

The first main problem is that there is a poor consistency in the results of the different groups selected with the different markers of "low severity" analyzed in the paper. For example, the effect of the drug is striking in the first interleukin-6 quartile (lowest levels) and far lower in the three upper quartiles (no effect at all in the second one), although interleukin-6 levels should be correlated, at least in part, with severity.

Similarly, the effect of the drug is surprisingly more important in the first Sequential Organ Failure Assessment quartile than in the three other ones.

The multivariate logistic regression performed in the placebo group allowed the authors to calculate a predicted risk of mortality, and it represents the most innovative piece of information of this paper. Unfortunately, the effect of the drug is not correlated with this mortality risk index. In particular, there is no effect at all in the 317 patients with a risk of mortality between 20% and 30% (in contrast with what is mentioned in the summary), and obviously the difference between placebo and treated patients appears, as mentioned in the discussion section, only above a predicted mortality rate of 30% (753 patients).

The second concern is that there is no relationship between the effect of the drug and the importance of protein C deficiency. On the contrary, the effect of the drug is more evident in the group without protein C deficiency, even if the confidence interval crosses one, in this small group of 196 patients.

Finally, and even more important, no data are provided on the comparability of the placebo and treated arms in patients with an Acute Physiology and Chronic Health Evaluation II >25 and with more than one organ system failure.

Small and insignificant imbalances in the incidence of preexistent diseases (but apparent for every of those, except hypertension) were already worrisome in the pivotal paper from Bernard et al. (2). Due to the absence of any global score assessing the "past" of the patient (like McCabe or ASA), which have been shown to be independent prognostic factors (3), it was not possible to compare the two groups in this respect other than looking at imbalances in each of those underlying diseases.

The striking difference in mortality rate induced by the drug in patients with an Acute Physiology and Chronic Health Evaluation score >25 could very well be due to more pronounced imbalances between the two arms in this subgroup, in particular concerning age and underlying diseases. This happened in the past for other compounds (4, 5). It is surprising that both North American and European agencies agreed to license the drug without asking for this information.

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The authors reply:

First, we would like to thank Dr. Carlet for his comments regarding the important and innovative aspects of our report. We most wholeheartedly agree that it is potentially dangerous to consider too many subgroups, because one may be tempted to draw erroneous conclusions regarding the meaning of their results. Nevertheless, regulatory agencies and many practicing clinicians routinely require/request an array of subgroup data, which fueled the need for us to plan publication of such analyses on data derived from our study of activated protein C. The investigators designed the PROWESS study to answer the question: "Is 28-day all-cause mortality reduced by activated protein C?" The answer is clearly yes. As we emphasize in our article (1), there are numerous important limitations to overanalyzing smaller and underpowered subgroups of patients within the overall trial. Therefore, subgroup analyses, if they must be done, should be viewed as hypothesis generating for future studies (see Refs. 3–9 in our article) (1).

When one considers the number (i.e., ~80) of subgroups that were prospectively defined, one of the main conclusions would have to be that there was actually remarkable consistency across subgroups—well beyond what would be predicted from a statistical perspective. In all circumstances except one (interleukin-6 lowest quartile), the confidence limits of the subgroups overlapped the point estimate of the overall trial, which was the *a priori* definition of consistency. Dr. Carlet points out a few intriguing findings, however, and we will certainly discuss those now. When examining results by "predicted risk of death," as indicated either by Acute Physiology and Chronic Health Evaluation (APACHE) II quartiles or by using the multivariable model derived from placebo patients and

published in the subgroup manuscript (1) (which "fit" better than APACHE II for these data, but which we do not propose using for individual patients), there does appear to be a treatment interaction with more absolute risk reduction in the highest risk subgroups (e.g., third and fourth APACHE II quartile or those with two or more dysfunctional organs). Indeed, the subgroup of multiple organ dysfunction patients is described in an article in *Intensive Care Medicine* (4). These findings have led to an ongoing randomized trial of drotrecogin alfa (activated) in patients with severe sepsis at low risk of death (powered to include >10,000 patients). In contrast, however, were the findings that some of the largest point estimates in mortality reduction were observed in subgroups such as the lowest interleukin-6 quartile, normal protein C concentration, normal prothrombin time, lowest total Sequential Organ Failure Assessment quartile, and "no mechanical ventilation at baseline." Although each of these favorably affected subgroups traditionally would indicate lower severity of illness, these intriguing findings should not confuse the main trial results outlined previously. To be clear, if one had to choose the patient likely to benefit the most from drotrecogin alfa (activated), data would support treating patients who are in shock or on a ventilator due to sepsis (or any two dysfunctional organ combinations), as long as the team plans to continue with aggressive care and the patient can safely receive an anticoagulant.

Dr. Carlet's question regarding the observed treatment effect in patients with normal protein C concentrations is explained as follows: Protein C concentrations were assessed only at baseline, and because the normal range of protein C is quite large, patients with "normal" protein C concentrations could have actually sustained a relatively large decrease in their baseline protein C concentration and still have remained in the normal range.

As Dr. Carlet indicates, a major problem with subgroup analyses is that of potential imbalances in baseline characteristics within a subgroup strata. This additional limitation of subgroup analyses makes it all the more important to remember that the unadjusted *p* value in PROWESS was .005 and the *p* value adjusted for APACHE II scores, age, and protein C concentrations was also .005 (2). To address the question of baseline disease imbalances in congestive cardiomyopathy, chronic obstructive pulmonary disease, cancer, mechanical ventilation, and use of vasopressors, we provided the adjusted relative reduction in the risk of death for these covariates in our response to letters in the *New England Journal of Medicine* (3). All of these analyses indicated efficacy after adjusting for those imbalances. Last, using chronic health points of APACHE II, a statistically significant interaction between treatment and chronic health points was observed ($p = .03$), with a larger treatment effect observed in patients with underlying comorbidities compared with patients without comorbidities.

Finally, the Food and Drug Administration and the European Agency for Evaluation of Medicinal Products are well aware of the dangers of subgroup analyses. By approving drotrecogin alfa (activated) in specified subgroups of patients, they focused the use of the drug in the populations with the most favorable benefit-risk profile. In a letter to the Anti-Infective Drugs Advisory Committee of the Food and Drug Administration, Dr. Jay Seigel of the Food and Drug Administration expressed the following regarding PROWESS: "Indeed, this trial, stopped early with a p-value of 0.005, has one of the most powerful findings of mortality benefit amongst drug development trials" (5).

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Insulin Dose or Glycemic Control for the Critically Ill?

To the Editor:

In their recent seminal article, Dr. Van den Berghe and colleagues (1) showed that the use of intensive insulin therapy to maintain blood glucose between 80 and 110 mg/dL dramatically reduces mortality and morbidity rates in surgical critically ill patients. They were, however, unable to differentiate between the direct effect of insulin and that of normoglycemia. To answer this question, Dr. Van den Berghe and colleagues (2) further analyzed their data, coming to the conclusion that the lowering of blood glucose, rather than the actual amount of insulin given, was the most important determinant of reduced mortality rate. In fact, in a multivariable logistic regression model, both the insulin daily dose and the mean blood glucose concentration were independent positive predictors of the risk of death.

We argue that such a result was expected and does not support the authors' conclusion. The goal of any multivariable analysis is to statistically adjust the estimated effect of each variable in the model for all other variables included (3). Applying this concept to the logistic regression model developed by Dr. Van den Berghe and colleagues, the higher the insulin requirement, at a parity of blood glucose concentration, the higher the risk of death. Similarly, the higher the blood glucose concentration, at a parity of insulin dosage, the higher the risk of death. Both conclusions simply relate to the well-known relationship between insulin resistance and increased mortality rate (4).

We shouldn't forget that insulin has many metabolic functions other than regulation of glucose, and the available biological evidence supports a primary role for insulin in promoting anabolism in critically ill patients (5).

Due to the intrinsic characteristics of their study protocol, Dr. Van den Berghe and colleagues cannot analyze the separate impact of normoglycemia and the

amount of insulin infused on mortality and morbidity rates. To do this, an *ad hoc* trial should be planned.

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The author replies:

Dr. Bertolini and colleagues do not agree with the conclusion of our article "Outcome benefit of intensive insulin therapy in the critically ill: Insulin dose versus glycemic control" (1). In this *post hoc* analysis of our earlier large-scale, randomized, controlled trial on the effects of intensive insulin therapy (2), we addressed the question of the differential impact on outcome of insulin dose vs. that of metabolic control. This is a crucial question, because if it were merely the additional amount of insulin given that was important rather than the lowering of the blood glucose concentration, the intervention could be much simplified. Indeed, administering a fixed amount of insulin and glucose, allowing elevated blood glucose concentrations, is much easier. This method would be comparable to the glucose-insulin-potassium (GIK) strategy (3) that has been applied to stimulate myocardial metabolism of glucose instead of fatty acids when oxygen supply is compromised.

We addressed this key question by reexamining the results of our intervention study (2). We performed a multivariate logistic regression analysis, correcting the effect of intensive insulin therapy for all preexisting univariate determinants of mortality and adding the mean daily insulin dose to the model as well as the mean concentration of blood glucose achieved. Both the latter variables appeared as independent positive risk factors for mortality. Dr. Bertolini and colleagues argue that this merely reflects the link between insulin resistance and severity of illness. In an observational study, this would be correct, but in an intervention study like ours, the data do indicate that the additional amount of insulin administered per se cannot possibly explain the reduced mortality rate achieved with the intervention, as in that case, insulin dose would have appeared as a negative risk factor. Instead, the data point toward effects of intensive insulin therapy, glycemic control, or other effects monitored by the changes in blood glucose concentration, rather than the insulin amount per se, as the statistical explanation of the improved outcome. Other effects occurring concomitantly with glycemic control include improvement of the dyslipidemia (D Mesotten, J Swinnen, F Vanderhoydonc, et al., unpublished data, 2003), prevention of excessive inflammation (4), and theoretically, although at this time still under investigation, amelioration of hypercoagulation, deficient fibrinolysis, and impaired endothelial function. The relevance for clinical practice of this statistical finding is the importance of titrating insulin infusion to its most important metabolic effect in the clinical setting, which is glucose control, rather than just administering a fixed amount of insulin in combination with glucose.

Dr. Bertolini and colleagues further believe that the improved outcome with intensive insulin therapy is entirely explained by insulin-induced anabolism. Although this may have been one of the mechanisms involved, our trial did not provide the evidence for such a conclusion, as markers of anabolism were not studied. Furthermore, we recently showed that gene expression of phosphoenolpyruvate carboxykinase in the liver, the key enzyme controlling hepatic glyconeogenesis from amino acids provided by skeletal muscle breakdown, was completely unaffected by intensive insulin therapy, indicating that an anticatabolic effect of insulin was not playing a major role (5).

The *ad hoc* trial that Dr. Bertolini and colleagues refer to as a way to define how much of the benefit can be attributed to the insulin dose and how much to the glycemic control would be one in which the effects of a "glycemic clamp" are compared with those of an "insulin clamp." We are convinced that Dr. Bertolini and colleagues appreciate the difficulty of performing such a study with mortality as an end point in the clinical setting. Instead, this aspect could be more easily addressed in an animal model of prolonged critical illness (6).

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Evidence-Based Medicine

To the Editor:

The editorial "Evidence-based medicine: What do you do when there's no evidence?" (1) neatly summarized one of the difficulties facing practitioners who wish to apply evidence-based medicine principles to patient care. Recourse to the evidence to resolve clinical questions is estimated to occur up to five times for each

inpatient (2), but only 2% of the publications are of direct clinical use (3), so it is unsurprising that often a search of the literature does not solve the clinical dilemma. It is has been stated that only 82% of primary interventions have the support of an evidence base (4).

When evidence is found of sufficient quality, interpretation and application to individual patients of data obtained by epidemiologic methods are in themselves an art, particularly in the more esoteric clinical scenario.

Two further limitations of evidence-based medicine have been identified (5), which are not discussed in the editorial. First, the practice of evidence-based medicine is a time- (and resource-) consuming process that restricts its implementation by busy clinicians. Second, there is no evidence to suggest that using evidence-based medicine improves patient outcomes.

The current emphasis on proof to support clinical decision making is laudable, but the "art" of medicine is a long way from being substituted by science: There will always be a role for the clinician to marry patient expectations with the evidence as it exists.

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The author replies:

Well said.

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Open Versus Closed Units: Chaos Versus a Well-Oiled Machine

To the Editor:

Dr. Cassell and colleagues (1) should be applauded for their phenomenally insightful ethnographic study comparing various intensive care unit (ICU) administrative models. Although the focus of their study was on end-of-life issues, their report embraces the core values of the open vs. closed administrative model and how these models affect the delivery and quality of health care. An ethnographic research approach allows one to describe the fundamental distinctions between these ICU models in a way not achievable using "validated quantitative measuring instruments."

Dr. Cassell and colleagues (1) ask, "How generalizable are the findings produced by this research?" As an intensivist who has practiced (and studied) critical care medicine in many different ICUs with different administrative structures on both sides of the great divide (Atlantic Ocean), (2) I am confident in my assertion that their findings typically describe the core differences in structure and function as well as the social, political, and economic values between a truly closed ICU, a "semiopen" ICU, and an open ICU. In addition, their report highlights the differences between the delivery of health care in a country with a healthcare system devoted to the provision of high-quality health care to all its citizens rather than one driven by market forces (3).

Dr. Cassell and colleagues (1) note that in the closed New Zealand ICU, "all (the intensivists) spent most of their working time in the unit." What a novel concept! In U.S. academic centers, unless you have "extramural funding" and a "lab" where you spend most of your time, you are considered a second class academician. Furthermore, in the world of private practice critical care, it is not uncommon for the patient's primary attending to spend $<$20 mins per day in the ICU, whereas most of his or her time is spent in his or her "office," which may be miles (or kilometers) from the hospital.

It is abundantly clear that the organizational structure of an ICU has an enormous impact on the quality of care delivered and patient outcome (4, 5). Open units are those in which admission of patients to the ICU is uncontrolled and management of the patients is at the discretion of each attending physician. Admissions are based on a first-come, first-served basis. Because the attending of record frequently does not have the time or skills to provide "comprehensive critical care," he or she "portions off" the patients' care to a number of organ-specific subspecialists (the "SODs" or single organ doctors). This frequently results in conflicting treatment strategies. Furthermore, both accountability and responsibility are also portioned off, with no physician assuming ultimate responsibility for patients' care. Such a system is highly cost inefficient and not conducive to achieving optimal patient care. The role of the intensivist in an open unit is to attempt to achieve a balance between all the consultants involved in the care of the critically ill patient and to attempt to prevent the patient from "falling through the cracks" due to the fractionated care.

Closed units are those in which the intensivist screens all admissions and discharges and assumes full responsibility for all aspects of the patients' care. The closed ICU is a highly structured and controlled environment and (usually) functions like a well-oiled machine. Intensivists are available 24 hrs a day to provide care at the bedside. Ideally, the patients' primary care physician/surgeon and subspecialists remain closely involved in the patients' care and interact collaboratively with the *critical care team*. Numerous studies have demonstrated an improvement in the quality of care and patient outcome when open units are "closed" (4, 5).

According to many of our esteemed colleagues, the concept of a closed (surgical) ICU is "unacceptable and should be repugned with vigor" (6). Furthermore, many believe that "unless you have had your hands in the patient's belly (or chest)," you cannot possibly have the necessary knowledge, skills, and insights required to manage critically ill and injured patients. Clearly, the "tall poppies need to be cut down."

In critical care, it is the intensive attention at the bedside by both doctors and nurses working together in a compassionate and caring environment that will achieve the best outcome for our patients. This can only be achieved by dedicated intensivists (who have no competing obligations) and critical care nurses who have undergone specialized clinical training to provide them with the necessary knowledge, skills, and attitudes

required to achieve the best outcome for the critically ill.

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The authors reply:

We thank Dr. Marik for his laudatory comments on our recent ethnographic study (1). We agree that there are many aspects of a closed administrative model that appear to facilitate the clinical care of critically ill patients, including perhaps their care at the end of life.

However, we remain somewhat unsure of the extent to which confounding cultural differences between U.S. and New Zealand society determine end-of-life care practices in our study. These profound differences include different views of the roles of individuals and institutions in our societies, substantially different per capita funding on health care, and mechanisms by which this funding is distributed, including to physicians. We hope that some of the different practices that can arise from these differing perspectives (e.g., see Reference 2) may lead to "transferable technologies" in end-of-life care, and we are planning to explore these in the near future.

Both societies have a considerable shortage of intensivists compared with the number of intensive care units, and in the United States this undoubtedly also mitigates against the sea-change that a wholesale transformation from "open" to "closed" intensivist-staffed ICUs would require.

Finally, we appreciate the need for improvements in end-of-life care in critically ill patients and agree that these improvements will occur only after appropriate research and strong advocacy. However, we believe that improvements in this and other aspects of critical care might occur more rapidly in the United States if the crucible of debate is fired to a moderate temperature that encourages accommodation and innovation rather than white-hot evaporation of the debaters' views.

We agree with Dr. Marik that intensive care unit patients are ideally "managed by dedicated intensivists, be they of surgical or medical background, who have undergone specialized multidisciplinary training to provide them with the necessary knowledge, skills, and attitudes required to achieve the best outcomes for critically ill and injured patients" (3), but we gently caution against the reaction and conservatism that can arise when potentially polarizing views (3, 4) are hotly expressed.

Joan Cassell, the lead author of our report (1), has recently completed a much more extensive study of these important issues and has written a monograph that is presently under review for publication.

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