associated with refractory hypotension and excessive activation of nuclear factor (NF)-κB; these features are rapidly reversed with stress doses of hydrocortisone.5,7,8

Sepsis is frequently associated with stress-induced hyperglycemia. A combination of several factors including insulin resistance, the presence of excessive counter regulatory hormones such as glucagon, growth hormone, catecholamines, glucocorticoids (sometimes), and cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor-α combined with exogenous administration of catecholamines, dextrose, and nutritional support are responsible for this metabolic syndrome.9 Hyperglycemia has been demonstrated to have potent proinflammatory effects.10 Glucose induces an increase in NF-κB, a fall in cytosolic IκB, and an increase in IκB kinase.11,12 Glucose also has been shown to exert prothrombotic effects and to increase oxidative stress by causing lipid peroxidation.13,14 Besides controlling hyperglycemia, insulin has immune-modulatory and anti-inflammatory properties similar to glucocorticoids. Insulin has been shown to suppress NF-κB, the expression of intercellular adhesion molecule-1, the chemokine, monocyte chemotactic protein-1, tissue factor, and plasminogen activator inhibitor-1.15-17 Tight blood glucose control with insulin is therefore likely to have important immunomodulating effects in patients with severe sepsis.

An overwhelming body of evidence has demonstrated that sepsis is characterized by a systemic microvascular injury.1 Activity of the coagulation cascade with impaired fibrinolysis results in widespread microvascular thrombosis.2 This microvascular injury has been pathogenetically implicated in the progressive organ failure that occurs in patients with severe sepsis. Decreased levels of activated protein C are believed to play an important role in propagating the microvascular injury in sepsis. This concept is supported by data from the PROWESS study (Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis Study Group),3 which demonstrated that drotrecogin alfa (activated) significantly deceased the 28-day mortality in patients with severe sepsis if administered late in the course of their disease.

The therapeutic value of these biological agents in sepsis is complementary; the use of one does not preclude the use of the others. Stress doses of hydrocortisone are indicated in all vasopressor-dependant patients with septic shock who have a stress (random) cortisol level of < 25 μg/dL. An insulin infusion is indicated in all critically ill septic patients with stress hyperglycemia. Similarly, drotrecogin alfa (activated) should be administered to all patients with severe sepsis in whom a contraindication to the drug does not exist. Timing, however, is critical. It likely that these agents will have minimal impact on the outcome of patients with severe sepsis if administered late in the course of their disease.

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REFERENCES


10. Dandona P, Aljada A, Rangaswamy A, et al. The potential therapeutic role of insulin in acute myocardial infarction in patients admitted to intensive care and in those with unspec-
ified hyperglycemia. Diabetes Care 2003; 26:516–519


12. Yorek MA, Dunlap JA. Effect of increased concentration of D-glucose or L-fucose on monocyte adhesion to endothelial cell monolayers and activation of nuclear factor-κB. Metabolism 2002; 51:225–234


Reporting of Predictive Logistic Models Should Be Based on Evidence-Based Guidelines

To the Editor:

Moss et al (March 2003)3 reviewed the deficiencies in reporting multivariable logistic regression analysis in the pulmonary and critical care medicine literature. They also suggested some potential guidelines to improve this reporting in both descriptive and predictive modeling. We would like to make some further suggestions, with emphasis on predictive models.

Recently, guidelines have been developed to adequately report randomized controlled trials (Consolidated Standards of Report-
ing Trials), meta-analyses of randomized controlled trials (Quality of Reporting of Meta-analyses), and diagnostic research studies (Standards for Reporting of Diagnostic Accuracy). These guidelines were based on empirical evidence on factors affecting the reader’s understanding, validity, reliability, and generalizability of the findings. Even though predictive research studies are common in the literature, published guidelines are not sufficiently supported by such empirical evidence.

Adequate reporting of predictive research should be based on elements that reflect how valid and precise the analyses were done. In predictive studies, overfitting is the key problem, which is related to several aspects of the modeling process. We suggest to report the number of candidate variables in addition to the variables in the final logistic model. The risk of overfitting after extensive modeling using many variables is high, especially in small data sets, and this unfortunately cannot be remedied by standard stepwise selection techniques. Also, a description of the choices underlying coding of variables and, in particular, selection of variables are of paramount importance. The number of outcome events must also be reported additionally to the number of total observations, because further overfitting is likely if the number of events per candidate variable is low, eg, < 10. Attempts of internal validation (eg, cross-validation or bootstrapping) can also reduce overfitting, using statistical “shrinkage” of coefficients. Further, predictive performance (calibration and discrimination) and internal/external validation should be described.

We further suggest to avoid the reporting of some technicalities. The report of coefficients, SEs, and p values are not important, since the relevant information can be obtained from the odds ratios and their 95% confidence intervals of the final model variables. Moreover, we would not stress the report of collinearity in a predictive model, because we are primarily interested in the predictive performance of the whole model, but not in the regression coefficients of individual variables. If two variables are strongly correlated, no additional predictive information comes available once one is included in a predictive model. Even though we agree that collinearity is important in descriptive modeling, its report does not improve the judgement of the reader.

Predictive modeling using logistic regression analyses is becoming more important in the medical literature. Although Moss et al made an important contribution by noting where some deficiencies in reporting are, evidence-based recommendations for a proper reporting are still lacking and are urgently needed.

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References

To the Editor:

Dr. Hernandez and colleagues recommend additional considerations when reporting multivariable logistic regression analyses for predictive models. In our review of the pulmonary and critical care literature, only 6% of articles used multivariable logistic regression modeling in a predictive manner. Therefore, we focused our suggested requirements for the proper reporting of descriptive models that identify the effect of an individual variable on a specific outcome while adjusting for differences in other factors. In regard to predictive modeling techniques, we agree that reporting collinearity is less important. Like Hernandez and colleagues, we would encourage those interested in a more complete understanding of methodological standards for predictive modeling strategies to read the articles by Laupacis and colleagues in JAMA, and Wasson and colleagues in the New England Journal of Medicine.

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COPD and Hepatitis C

To the Editor:

Kanazawa et al (February 2003) reported an accelerated decline of lung function in COPD patients with concomitant hepatitis C infection. They have suggested that the airway disease may be related to the underlying chronic inflammatory disorder.

