

ALTERNATIVE VIEWPOINTS

Error Rates Among Clinical Pharmacists in Calculating the APACHE II Score: A Commentary

Richard S. Slavik, B.Sc.Pharm., Pharm.D., ACPR, FCSHP, and
Sean K. Gorman, B.Sc.Pharm., Pharm.D., ACPR

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We read with interest the study by Dr. Greenwood and her colleagues¹ reporting error rates in Acute Physiology and Chronic Health Evaluation (APACHE II) scores by pharmacists, however we would like to highlight several issues that merit consideration. First, the best available evidence supports incorporating APACHE II scoring as one component of a decision model to identify severe sepsis or septic shock patients at high-risk of mortality, and thus who may get the highest absolute benefit from receiving activated protein C (APC).^{2,3} This may promote the most effective, safe, and cost-effective administration of APC. Secondly, serious methodological limitations threaten the internal and external validity of this paper. Thirdly, we identified undisclosed potential, perceived, or actual conflicts of interest (COI) involving authors of this paper, which may threaten this paper's integrity and raises appropriate questions as to the true motivation behind the submission of this article.

APC was approved for use in adult patients with severe sepsis or septic shock after the results of the PROWESS trial were published.² Based on a pre-specified analysis of a large number of patients in PROWESS, the mortality

benefit was restricted to a subgroup of patients at high-risk of death as defined by an APACHE II score ≥ 25 within 24 hours of APC administration.³ There was no differential mortality effect based on number of dysfunctional organs.³ A follow-up study mandated by the FDA prospectively enrolled patients at a lower risk of mortality with APACHE II scores < 25 , single organ failure, or those deemed to be at low risk of death based on the enrolling physician's clinical judgement.⁴ This study was stopped prematurely due to a futility analysis, confirming that the benefits of APC in patients at a low-risk of mortality do not outweigh the harms and costs of therapy, and supports the need to identify patients at high-risk of mortality who may benefit from administration of APC. Therefore, the current best available evidence supports incorporating APACHE II scores into a decision model to identify patients at high-risk of death from severe sepsis or septic shock and who may receive benefit from APC. Because data on the real-world effectiveness and safety of APC has suggested higher mortality and bleeding rates than in published clinical trials, the European Medicines Agency (EMA) has persuaded Eli Lilly to perform a trial to prospectively identify high risk severe sepsis and septic shock patients and confirm whether APC confers an acceptable benefit, risk, and cost-effectiveness profile in this population.⁵⁻⁷ This trial will hopefully provide clinicians with a responsive, reliable, and validated method to identify patients at high-risk of death who may be candidates for APC.

The paper by Dr. Greenwood and her

From the Pharmacy Department of the Interior Health Authority, Kelowna, BC, Canada (Dr. Slavik), the Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada (Drs. Slavik and Gorman) and the CSU Pharmaceutical Sciences of Vancouver General Hospital, Vancouver, BC, Canada (Dr. Gorman).

Address reprint requests to Sean K. Gorman, Pharm.D., CSU Pharmaceutical Sciences, Vancouver General Hospital, 855 West 12th Ave, Vancouver, BC, V5Z 1M9, Canada; e-mail: sean.gorman@vch.ca.

colleagues has serious methodological limitations that threaten its scientific validity and relevance to the care of these patients. Only one-third of the study sample is representative of ICU clinical pharmacists who would have experience in APACHE II scoring and collaborative decision-making related to the prescribing of this agent. The study did not specify a primary endpoint, anticipated effect size, or perform a sample size calculation for inferential statistical analysis. The primary endpoint appeared to be an “error rate” defined as the composite of the number of incorrect calculations or decisions regarding therapy divided by the total number of results for the clinical scenarios. This endpoint is not statistically appropriate or clinically relevant. All clinical scales and scoring tools are associated with some degree of inter-rater variability. Therefore, defining a score derived by study subjects as an “error” if it did not exactly match the value of the adjudicated standard score is not appropriate or valid. The more appropriate clinically relevant question to ask would be if the inter-rater variability in APACHE II scores adjudicated from cases involving ICU pharmacists is associated with statistically higher inter-rater variability than an adjudicated sample from the PROWESS trial. Furthermore, the trial was not powered to test the hypothesis that “Experience in ICU did not appear to significantly affect score derivation error rates...,” and the recommendation, “The uncertainty in APACHE II score derivation justifies including experienced clinician assessment of mortality risk in the decision support process” is flawed because clinician experience has not been conclusively shown to be a more accurate predictor of mortality risk, and expert opinion is amongst the lowest levels of evidence.^{8,9}

There have been several conflict of interest (COI) controversies relating to Eli Lilly, their employees and consultants, the Society of Critical Care Medicine, and the Surviving Sepsis Campaign Clinical Practice Guidelines (CPGs), regarding external influence and undisclosed potential, perceived, or actual COI.^{10, 11} The literature suggests that CPGs are often subject to external influence and bias because they are not independent from the funding body, or they do not identify the role of sponsors in the development and reporting of guidelines.¹² Furthermore, there is considerable interaction between the authors of CPGs and the pharmaceutical industry; failure to develop,

adhere to, and disclose potential, perceived, and actual conflict of interest relationships threatens the external validity and integrity of guidelines.¹³ In our review, we found that two papers challenging the appropriateness and accuracy of incorporating APACHE II scores into decision aids for the administration of APC were co-authored by employees of Eli Lilly.^{1, 14} In fact, the manufacturer’s senior scientific communication associate was co-author of one study.¹⁴ Unfortunately, no potential, perceived, or actual COI or competing interests were declared in the most recent study.¹ Therefore, we fear that the impetus for this publication may not have been to improve prescribing of APC, but to market an uptake in the utilization of number of organ failures as a “simpler” criterion for identifying patients at high-risk of mortality, to ultimately increase prescribing and sales of APC. Until there is evidence to support a superior method of identifying severe sepsis or septic shock patients at high-risk of death who may receive the most benefit from the administration of APC, we feel that incorporating APACHE II scores, time from onset of organ failure, and contraindications from the PROWESS trial into a decision model to guide the administration of APC is supported by the best available evidence.

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Authors' Reply

We are grateful to the editors for allowing us to reply to the communication to which Slavik and Gorman have applied their names and reputations. While entitled “Alternative Viewpoint” we doubt that there is really much disagreement about the importance of correctly prescribing drotrecogin alfa (activated) as recommended in the package insert. The clinical importance of accurately calculating an acuity score to prescribe a medication with serious side effects is a straight forward principal with clear implications for patient safety. In addition, the desirability of knowing whether or not one has prescribed in accordance with the recommendations of the package insert and is afforded the requisite protections is also easily understood. Since APACHE II scoring was not designed as a real time clinical decision tool it makes sense to determine how effectively practicing clinicians can be trained to accurately determine these scores. To accomplish this aim a gold standard, correct, or “adjudicated” score is established and deviations are measured against this standard by statistical comparison of rates using dichotomous inferential statistical methods. In light of the concerns of the correspondents we have confirmed the appropriateness of our methods with a second set of statistical consultants. We chose to use cases that had previously been shown to generate high error rates among trained individuals and had adjudicated scores that we were able to validate. We clearly acknowledged the source of these cases in our manuscript. We did not report inter-observer correlation coefficients because while this analysis speaks to reliability and tells us how well participants agree it does not tell us about

accuracy (i.e., whether individual observers are correct or incorrect in their scoring). While we agree that more sophisticated inferential statistical methods are powerful, neither we nor our statistical consultants believe that they would further help a reasonable person to fairly conclude that the rates of correct derivation that we observed are below those that one would desire.

We are also grateful for the opportunity to openly discuss our potential conflicts of interest because being asked to do so in such a manner provides us with an opportunity to comment on the unprofessional and non-collegial tone of some of the discussions of the optimal use of drotrecogin alfa (activated). The editor has confirmed that at the time of publication we were in full compliance with the requirements of the journal with regard to disclosure and elected in accordance with the policies of the journal not to use valuable page space to include the following details. First, the study was funded in its entirety without financial support from Eli Lilly and Co. Secondly, none of the authors own any Eli Lilly Co. stock or have any other ownership interests in the company. While the correspondents correctly point out that Dr. Levy was an employee of Eli Lilly Co., he had left the company and divested any ownership interest by the time of his participation in this study. Thirdly, none of the authors have other funding from the company; have been paid honoraria, received travel, or even small objects bearing advertising logos. In addition, none of the authors are part of the Surviving Sepsis Campaign or have served on professional society panels charged with crafting guidelines involving drotrecogin alfa (activated). Dr. Lilly has no known blood relation to the founding family of the company.

We believe that resorting to ad hominem arguments and accusations of ethical impropriety are not helpful for accomplishing our shared goals of fighting diseases and saving lives which is best fostered by professional and respectful interactions among investigators and clinicians. These ineffective, malevolent, unprofessional, and destructive forms of adversarial debate have become all too common in discussions of the optimal use of drotrecogin alfa (activated) and are simply unacceptable. Our patients deserve better.

Since the study was not performed for financial gain, we are delighted to have the opportunity to

clarify why the study was undertaken. Like the correspondents, we strongly support the delivery of drotrecogin alfa (activated) according to recommendations on the package insert. Indeed, we have published an electronic methodology for accomplishing this aim.¹ We were surprised by the findings of Booth et al² that individuals trained to calculate APACHE II scores in the setting of clinical trials had high error rates. As pointed out in the original manuscript, we trained both our ICU and non-ICU pharmacists in the derivation of APACHE II scores and APACHE II scores are commonly derived by our non-ICU pharmacists also dispense drotrecogin alfa (activated). We thought that the rates of error for our trained pharmacists would be substantially lower than those observed in the Booth study.² When we found high error rates, we revised our training schedule and added additional oversight to the process to better derive these scores. We decided to publish our results because being aware that conventional training methods may not achieve levels of effectiveness for calculating these scores makes

others aware that accurately deriving these scores can be problematic for active clinicians and having redundancies in the process such as experienced provider review can intercept errors. Finally, we accept the author's point that expert clinical opinion is among the lowest forms of evidence, but respectfully point out that it is among the most effective methods for insuring patient safety.

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Bonnie Greenwood, Pharm.D.
Paul M. Szumita, Pharm.D.
Howard Levy, M.D.
Craig M. Lilly, M.D.