Pulmonary coagulopathy as a new target in therapeutic studies of acute lung injury or pneumonia

To the Editor:

We read with great interest the recent article by Dr. Schultz and colleagues and wish to congratulate them for their literature review (1). In the last part of their article, the authors underline that anticoagulant therapy in acute lung injury (ALI) or pneumonia might be either beneficial, by attenuating the destructive effects of the inflammatory response, or harmful, by attenuating the host response. We wish to add further support to their statement.

Indeed, due to sequential changes in the alveolar coagulation/fibrinolysis balance, the inhibition of coagulation activation may have beneficial or negative effects according to the pathologic stage. During the earliest phase of ALI, a fibrin deposition can be observed on the epithelial as well as the endothelial side of the alveolar-capillary barrier, reflecting the activation of the coagulation pathways (2). During the first 72 hrs of human acute respiratory distress syndrome, the procoagulant activity is maximal and fibrinolytic activity is decreased; then, from the 4th to the 15th day, fibrinolysis inhibition persists, whereas the procoagulant activity is moderately increased (3, 4).

In such a situation, the inhibition of fibrin formation appears to be an attractive therapeutic approach. However, an early inhibition might also impede the natural process of alveolar "sealing." Indeed, we previously documented that the early inhibition of coagulation could be deleterious. In an experimental model of Pseudomonas aeruginosa pneumonia in the rat, the inhibition of thrombin formation by antithrombin increased vascular pulmonary permeability and increased lung damage (5). More recently, we observed that intravenous administration of recombinant activated protein C in the early stage of P. aeruginosa-induced lung injury in rats tends to increase lung edema with a loss of the inflammatory response compartmentalization (6). Taken together, these studies indicate that inhibition of thrombin formation may have deleterious effects in the early stage of pneumonia, and they suggest a beneficial role of the intra-alveolar coagulation activation limiting the extension of the pneumonic process and permeability disorders.

On the contrary, in the later stage of ALI, the presence of alveolar fibrin deposits (through prolonged coagulation activation and decreased fibrinolysis) triggers and prolongs fibroblast proliferation and fibrosis. Inhibition of thrombin formation and/or enhancement of secondary fibrinolysis could then reduce alveolar damage and limit lung fibrosis (7). Our experimental studies have several limitations affecting extrapolation of the results to clinical situations. We used a model of ALI in the rats at the very early phase of the injury, and patients are usually seen at a later phase. However, our findings underline the crucial importance of the timing in studies of agents modulating intra-alveolar coagulation. The chronology of coagulation disorders should be considered for the design of future clinical studies.

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Different pathogens at different time points in pneumonia: Do potential anticoagulant therapies need to be time—and species—tailored?

The authors reply:

We thank Dr. Robriquet et al. for their thoughtful comments on our review. Indeed, we underlined that anticoagulant therapy in pneumonia might be either beneficial by attenuating the destructive effects of the inflammatory response or harmful by attenuating the immune response. Early inhibition might impede the natural process of alveolar "sealing": In a rat model of Pseudomonas aeruginosa pneumonia, inhibition of thrombin formation by antithrombin increased vascular pulmonary permeability and lung damage (1). Similarly, administration of recombinant human activated protein C (rhAPC) in the early stage of P. aeruginosa-induced lung injury in rats tended to increase lung edema with loss of the inflammatory response compartmentalization (2). These studies, in fact, suggest a beneficial role of the intra-alveolar coagulation activation.

However, we must be cautious in the interpretation of these results. First, as already mentioned, the rat model of acute lung injury used in these two studies focused on the very early phase of lung injury, and patients are usually seen at a later phase. Also important to note is the fact that data on respiratory pathogens other than P. aeruginosa are presently lacking. Pathogens behave differently with regard to the induction of pulmonary inflammation (3) and thus may have different effects on alveolar fibrin turnover. Furthermore, patients with pneumonia are usually treated with antibiotics, which was not the case in the models referred to in the letter. Finally, and of utmost importance, one secondary anal-
ysis of PROWESS showed survival benefit in community-acquired pneumonia patients with severe sepsis (4). This finding fits very well with results from several other pathophysiologic studies: a) inflammatory pulmonary conditions, including pneumonia, are associated with local activation of coagulation and suppression of fibrinolysis resulting in fibrin deposition in the bronchoalveolar spaces (5–7); and b) intravenous administration of rhAPC exerts an anticoagulant effect in the human lung challenged with lipopolysaccharide (8).

Based on the analysis by Laterre et al. (4) as well as on the suggestion that the positive effect of rhAPC may partially be the result of local (i.e., pulmonary) anticoagulant activity, it seems correct to state that rhAPC should become part of the standard of care for treating patients with pneumonia who fulfill the criteria in the PROWESS study. Whether this also applies to patients with pneumonia without sepsis has to be determined. This issue is being addressed in at least two clinical studies in which the chronology of coagulation disorders is being studied, as is the extent to which different pathogens may cause alveolar coagulopathy. Dr. Michael Matthy at the University of California, San Francisco, is carrying out a double-blind, randomized phase II NIH-sponsored clinical trial of rhAPC for the treatment of acute lung injury (part of an Acute Lung Injury SCCOR grant); Dr. Schultz at the University of Amsterdam, Amsterdam, the Netherlands, and Dr. Groeneveld at the Free University, Amsterdam, the Netherlands, are carrying out a double-blind randomized phase II clinical trial of rhAPC for the treatment of inflammatory lung injury.

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Empiric application of clinical trials to standard of care in the intensive care unit: The unexpected harm to patient care?

To the Editor:

It took almost 4 yrs since the original publication and its follow-up (1, 2) recommending intensive insulin therapy to target blood glucose <110 mg/dL in the intensive care unit to reach the opposite conclusion, that it was not only ineffective to reduce mortality but could have resulted in unintended death of patients who had otherwise low severity of illness and were expected to survive (27% vs. 19%; relative increase of risk for death, 42%; p = .045) (3). Based on the original publication, many professional organizations prematurely mandated intensive insulin therapy as the standard of care for all intensive care patients across the United States, and in certain instances authors of the original work were advisors to formulate the practice guidelines (4). The serious efforts to disseminate that practice indiscriminately, without robust scientific evidence, culminated in preventable loss of life. It is impossible to determine the actual number of deaths attributed to intensive insulin therapy across the United States over the past 4 yrs. Many of the deceased patients might have been expected to die because of the critical illness, or insulin was not considered as the culprit for death in the absence of hypoglycemic events. Even if a causal relationship between unexpected death and intensive insulin therapy was suspected, reporting the adverse outcome to the Food and Drug Administration would not have been mandated because of its labeled use. The futile or harmful effects linked to intensive insulin therapy on clinical outcome in acute critical illness had been reported from several studies in the literature (5–9).

In fact, Van den Berge et al. (10) reported in the follow-up publication that daily insulin dose was an independent risk factor for intensive care unit death in multivariate analysis. Survival benefit of glycemic control may be explained by early resolution of stressors and iatrogenic interventions for the underlying illness influencing glucose metabolism.

The most vulnerable hospitalized patients are those in the intensive care unit: They cannot provide informed consent to every detail of their treatment or care, and they trust their health care professionals to “do no harm.” Persistent pressure to introduce results of clinical trials into practice without robust validation raises some serious questions: Who should bear the responsibility for empirical implementation of clinical trials into intensive care practice that culminate in adverse outcome? Who should be accountable for flawed evaluation or interpretation of clinical trials and scientific evidence; the authors who conducted the original research, the editorial board that validated the scientific merit of the work, the professional organizations that endorsed the practice guidelines, or the physicians who applied the practice guidelines at the bedside? Although these questions are open for debate, they must be answered so that unintended harm does not escalate into the public domain and bring scientific integrity and trust in intensive care research under scrutiny.

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Evidence-based medicine, or how to apply results of clinical trials to patient care

The authors reply:

Dr. Rady writes that intensive insulin therapy causes harm that would have culminated in preventable loss of life. He also claims that this was shown by our recent trials on intensive insulin therapy in the intensive care unit (ICU) (1, 2). This is, of course, an unprecedented blunt misinterpretation. Dr. Rady also calls for robust evidence before disseminating results of clinical trials into clinical practice, one concern that we do share with him. Hence, we advise Dr. Rady, as any other clinician, to carefully read the publications and then apply the basic principles of evidence-based medicine.

Until the results of our first study on intensive insulin therapy became available (2), tolerating hyperglycemia during critical illness was common practice in the ICU. Hyperglycemia was considered to be beneficial in acute stress, and thus it was recommended not to be treated. However, there was no evidence to support this clinical practice. More and more reports of an association between the severity of hyperglycemia and adverse outcome of critical illness subsequently came available. This, together with strong data from research on diabetic complications (3) and our observation that lack of insulin effect is associated with adverse outcome of prolonged critical illness (4), fueled the rationale for our study on the effect of maintaining insulin-titrated euglycemia during critical illness. A hypothesis was formulated and a first randomized trial was conducted, the normal first step in evidence-based medicine. Our study showed that maintenance of normoglycemia with insulin during critical illness saved lives and prevented morbidity in the surgical ICU. Clearly, the results of this study could not be extrapolated to other disease states such as medical critical illness. As this is another basic principle in evidence-based medicine, we performed a second randomized trial, this time in the medical ICU of our tertiary referral academic center (1). The study showed significant mortality and morbidity benefit in the predetermined target population of long-stay ICU patients (2). Indeed, our previous surgical study (2) had shown that ≥3 days of intensive insulin therapy, started on ICU admission, are needed to reduce hospital mortality rate. Thus, it was scientifically and ethically correct to statistically power our medical study for mortality effect among those treated ≥3 days (1). As hypothesized, a significant 10% absolute mortality reduction was observed in this target population, along with 5% lower mortality in the intention-to-treat group, numbers remarkably similar to the surgical study. Further analysis revealed that mortality in the intention-to-treat group was, in fact, significantly reduced (odds ratio, 0.77; 95% confidence interval, 0.60–0.99; p = 0.04) when correcting for preexisting cancer, end-stage organ failure, and severity of illness upon medical ICU admission.

Morbidity was significantly reduced in all medical and surgical ICU patients (1, 2). Patients, families, health care providers, and insurers all recognize the benefits of reduced mechanical ventilation time and shorter ICU and hospital stays (4 days less in the intention-to-treat and 10 days less in the target group on intensive insulin). Furthermore, these morbidity endpoints have been the goal of earlier important studies on ICU outcome (5).

Numerically, however, more deaths occurred among medical (1), not surgical (2), patients on intensive insulin for <3 days. Not only was this difference not statistically significant, it was also entirely attributable to selection bias. Surprisingly, Dr. Rady concludes from these data (1, 2) that intensive insulin therapy would be harmful to patients in the ICU. This conclusion clearly is not based on the available data. In contrast, there is more robust evidence for tight glycemic control than ever has been for tolerating hyperglycemia (1, 2, 6).

Clinical trials are crucial for evidence-based patient care. Physicians have the obligation to read reports of trials in full and interpret the data correctly. Professional organizations have the obligation to review the available data in order to reach consensus among experts in the field. This consensus then becomes the basis for guidelines in medicine. While we are awaiting results of further studies, to accurately determine who will benefit most from intensive insulin therapy and what is the best blood glucose target for different patient populations, current evidence is in favor of tight blood glucose control in the ICU. There is no place for fanatical nihilism on this important topic.

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Closed-format intensive care: Time to act now

To the Editor:

In the March 2006 issue of Critical Care Medicine, Dr. Arabi and colleagues again confirm earlier reports showing that time of admission (day, night, or weekend) does not affect outcome in a closed-format intensive care unit (ICU) with on-site 24-hr intensivist coverage (1, 2). These findings are in concordance with the nice review of Dr. Sinuff et al. in the same issue, noting that ICU physicians discriminate more accurately between survivors and nonsurvivors than do scoring systems (3). These articles add to the growing body of evidence favoring better outcomes in closed-format ICUs. Consequently, a recommendation about the level of ICUs and corresponding staff (intensivists and qualified nurses) has been published in the Netherlands (4). Level 3 ICUs must have qualified intensivists exclusively available for the ICU around the clock, and a formation of four ICU nurses/24 hrs per ventilated patient. Level 2 ICUs must have qualified intensivists exclusively for the ICU at daytime and available at nighttime. Level 1 ICUs must have a qualified intensivist present at daytime and available for consultation at nighttime. This classification has important implications for the category of patients for whom different levels of ICUs are allowed to provide care.

Implementing changes in the ICU, even on the basis of sound evidence, still appears to be difficult (5). In our opinion, on-site 24-hr intensivist coverage is a major tool for quality improvement in the ICU and will save many lives. It might be wise to first accomplish this, instead of participating in the next multicenter trial. It is time to act now.

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The authors reply:

As stated by Dr. Durbin, the President of the Society of Critical Care Medicine (SCCM), "having an intensivist is undoubtedly the most effective intervention to improve survival of the critically ill that has been devised in the past 30 years," and about "30% to 50% fewer patients would die if an intensivist rounded daily on all critically ill patients" (1). Studies have shown that the presence of an intensivist led to earlier recognition of developing problems and thus earlier treatment (2).

Therefore, in an area like the intensive care unit (ICU), where outcome is directly affected by the prompt institution of proper therapy, it is intuitive that having an on-site qualified intensivist improves outcome.

Our study, performed in a tertiary care ICU with high acuity of illness, suggests that having 24-hr/day on-site intensivists is a potentially improved model of ICU coverage. We agree with Dr. Ligtengberg and colleagues that tertiary care ICUs should adopt an on-site qualified intensivist coverage model (3). We also strongly support their call to consider this recommendation as an issue of high priority. As the Society of Critical Care Medicine, along with several other professional organizations, has marked the month of May as National Critical Care Awareness and Recognition Month (4), we call upon the society to consider this model in its campaign as an initiative for patient safety and quality improvement.

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