Regarding critical care of the burn patient: The first 48 hours

To the Editor:

We read with much interest the recent review by Dr. Latenser on the care of burn patients in the first 48 hrs (1). Although the review was well-written, concise, and informative, we believe two assertions deserve clarification.

First, Dr. Latenser states that the Parkland formula has been renamed the "Consensus formula." This is incorrect. It was first used by the authors of the Advanced Burn Life Support course, in which fluid requirements of burn patients during the first 24 hrs after burn were estimated as 2 to 4 mL/kg per percentage total body surface area burn (2). This represents a compromise between physicians who advocated for the Parkland formula (which estimates 4 mL/kg per percentage burn) and those who advocated for the modified Brooke formula (which estimates 2 mL/kg per percentage burn). Although the Parkland formula is most commonly used in US burn centers, there is no consensus regarding which of the two formulas is superior (3). No prospective, randomized, controlled trial has ever been performed comparing the Parkland formula and the modified Brooke formula. Our group recently performed a retrospective analysis of patients with major thermal injuries from the current combat operations in Iraq and Afghanistan who were resuscitated by either the Parkland formula or the modified Brooke formula (4). Both Parkland formula and modified Brooke formula patients received more fluid than estimated by the formulas. However, the Parkland formula patients received substantially more than the modified Brooke formula patients. Regardless of which formula is used to initiate fluid resuscitation, however, it is more important to recognize the importance of careful fluid titration in the ensuing hours based on a compilation of various end points to successfully resuscitate the patient at the lowest physiologic cost.

Second, Dr. Latenser suggests that colloids do not play any role during the resuscitation of severe burns. Yet, Dr. Saffle, in his recent review, proposed that a strategy that incorporates colloid on select patients may reduce the consequences of "fluid creep" (5). Furthermore, the American Burn Association's practice guidelines for burn shock resuscitation gave it a grade A recommendation based on available data (2).

Clearly, much controversy exists when dealing with burn resuscitation. However, this "concise definitive review" is not quite definitive when it comes to these two issues.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or Department of Defense. The authors have not disclosed any potential conflicts of interest.

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Critical care of the burn patient

To the Editor:

Barbara A. Latenser's article "Critical care of the burn patient: The first 48 hours" (1) asserts that "central catheters should be changed to a new site every 3 days to minimize bloodstream infections." Her recommendation is based on a study by King et al (2) that has serious methodologic limitations, as recognized by the authors. This study does not describe the characteristics of the patients, nor does it consider whether the venous catheter is placed in burned or healthy skin or evaluate relevant outcomes, such as the problems associated with systematic changes, mortality, or lengths of stay. The consensus (3–5) in scientific literature today currently indicates, backed by extensive evidence, that the regular changing of arterial or central venous catheters is an approach that should not be considered a routine part of central line-associated bloodstream infection prevention. Prospective, random, well-designed studies are necessary to establish the advisability of a different prevention strategy for this class of patients.

The author has not disclosed any potential conflicts of interest.

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DOI: 10.1097/CCM.0b013e3181cd0ba4

The author replies:

I greatly appreciate the letters from Drs. Galeiras and Chung et al regarding the article (in the October 2009 issue of *Critical Care Medicine,* 37:2819–2826) entitled "Critical care of the burn patient: The first 48 hrs." Optimal burn resuscita-

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tion remains an emotionally charged issue for many burn care practitioners. Both letters to the editor have reflected on the very essence of resuscitating critically burned patients and on much of the controversy that surrounds our more immediate care of these patients. I agree wholeheartedly with Dr. Galeiras that well-designed studies are necessary to establish class I recommendations for central line management in critically burned patients. Unfortunately, the "current recommendations in the scientific literature" have excluded burn patients in their cohort when recommending line placement and line changes.

Dr. Chung et al are correct that the Parkland Formula has not formally been renamed the Consensus Formula. Dr. Chung and I are in agreement that resuscitation guidelines are just that, and resuscitation should be individualized based on physiologic end points. I tried to stress that point in the article. For those centers not having a resuscitation protocol, I included (and recommended) Dr. Saffle's protocol (1), which recommends colloid for certain patients.

The author has not disclosed any potential conflicts of interest.

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Cardiac function index by transpulmonary thermodilution and left ventricular systolic function

To the Editor:

I read the recent publication by Julien et al (1) with great interest. They concluded that cardiac function index provided by transpulmonary thermodilution was an indicator of left ventricular systolic function. The estimation is confirmed for its efficacy, as noted by Julien et al (1); however, there are some practical problems.

First, the limitation of the approach in cases of isolated right ventricular failure is reported (2). Second, tidal ventilation also significantly affects the result of determination (3). These issues should be kept in mind, and the clarification on these possible inferences is needed.

The author has not disclosed any potential conflicts of interest.

Viroj Wiwanitkit, Wiwanitkit House, Bangkhae, Bangkok, Thailand

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The authors reply:

We thank Dr. Wiwanikit for pointing out two potential limitations of using the Cardiac Function Index (CFI) provided by transpulmonary thermodilution as a marker of left ventricular systolic function. The first limitation is that CFI is underestimated in cases of right ventricular enlargement because the denominator of the CFI ratio takes into account the end-diastolic volume not only of the left ventricle but also of the four cardiac chambers. We agree with this limitation, as we cautiously pointed out in our article (1) and in another study (2). Importantly, we showed that in patients with a right ventricular enlargement, the sensitivity of CFI for detecting a low left ventricular ejection fraction was still good (92%), whereas its specificity was reduced (50%). This indicates the way in which the CFI should be used in clinical practice. The CFI should be considered as a warning variable: when it is low, it means an echocardiography should be performed. In the majority of cases, echocardiography will confirm an impairment of the left ventricular systolic function and it will explore the cardiac abnormality in more detail. In cases in which the low CFI is attributable to a right ventricular enlargement, echocardiography will easily detect it. In other words, low values of CFI should always alert the physician about potential cardiac trouble.

The second limitation pointed out by Dr. Wiwanikit refers to tidal ventilation. In fact, the study of Renner et al (3) did not explore the effects of high tidal volume on CFI such that this point remains to be investigated.

The authors have not disclosed any potential conflicts of interest.

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Mandatory checklists at discharge may have the potential to prevent readmissions

To the Editor:

Recently in *Critical Care Medicine*, Chrusch et al (1) showed that intensive care unit (ICU) readmission or unexpected death after ICU discharge were not only dependent on age, particular diagnoses, Acute Physiology and Chronic Health Evaluation II score, and ICU length of stay but also dependent on ICU discharge at a time of no vacancy (relative risk of 1.56; 95% confidence interval, 1.05–2.31). From this finding the authors conclude that overloading the capacity of an ICU could affect physician decision-making, resulting in premature ICU discharge. In that same issue of *Critical Care Medicine*, Byrnes et al (2) showed that a daily mandatory checklist covering a diverse group of ICU protocols improved physician consideration and practice patterns. Of interest, after initiation of this daily mandatory checklist, a more than two-fold increase was noticed in transferring patients out of the ICU on telemetry (from 16% to 35%) and physical therapy (from 28% to 42%).

Although most patients surviving critical illness no longer require life support interventions after ICU discharge, 4% to 10% of patients are reported to be readmitted to the ICU (3). Patients with unplanned ICU readmission have higher mortality rates and longer length of stay than patients who survive critical illness and stay out of the ICU after transfer (3, 4). One complicating factor is that ICU discharge criteria are often subjective and may not be reproducible. Even within the same ICU these criteria could fluctuate daily, particularly when there is overload of the ICU capacity. Another complicating factor is that the sometimes higher-than-recognized standards of care provided in the ICU may mask high demands of patients at risk for ICU readmission. Finally, hand-over processes at ICU discharge are usually not standardized, leading to frequent information corruption and omission of important details of care delivery once the patient is discharged to the floor service.

Recognition of patients at risk, preferably before transfer, may allow for additional measures to prevent clinical deterioration and eventually ICU readmission, including appropriate hand-over, transfer to a higher acuity step-down or progressive care unit than "the floor," if available; increased supervision on the floor with overlapping rounds by outreach teams, or simply keeping the patient in the ICU until further improvement is observed, even when there is overload of the ICU capacity. A mandatory checklist at ICU discharge may not only prevent premature ICU discharge and readmission but also have the potential to improve and standardize hospital care delivery beyond ICU.

The authors have not disclosed any potential conflicts of interest.

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The authors reply:

In our recent study we showed that intensive care unit (ICU) census pressure measured at the time of each individual patient's discharge is an independent risk factor for unit readmission or unexpected death with an adjusted relative risk of 1.56 (95% confidence interval 1.05, 2.31) (1). Drs. Schultz and Gajic speculate as to whether a checklist at discharge may prevent readmissions. While a formal ICU discharge checklist was not used during our study, there were practices and policies surrounding the decision to transfer a patient out of ICU that were likely protective.

The decision to discharge a patient and the choice of discharge location (regular ward versus step-down) was made by the attending intensivist in consultation with the ICU team of nurses, respiratory therapists, and physiotherapists. The decision would take into consideration patient needs such as monitoring, assistance with pulmonary toilet, and the ability to call for help, as well as the capabilities of a given discharge location. Under normal conditions, patients remained in ICU and were not discharged to a level of care lower than they were deemed to require. By policy, patients were not allowed to physically leave the unit in transfer until an ICU case summary was on the chart and both the attending physician and ward resident accepting the patient were given a verbal sign-over. The mandatory verbal sign-over allowed the ward medical team the opportunity to clarify the treatment plan and to potentially refuse transfer if they felt they could not adequately care for the patient. Post-discharge follow-up was done on the ward at the discretion of the attending intensivist and ICU housestaff. Whether formal outreach teams decrease readmission rates is not certain (2).

Keeping patients in ICU during overcapacity conditions was not an option because of a lack of physical space and additional nursing staff. Overcapacity patients were cared for in either the Emergency Department, Coronary Care Unit or the Post-Anesthesia Recovery Room; locations that not infrequently had their own capacity issues. This inability to keep patients in ICU is what led to triage discharge decisions. That it was only discharge from an overcapacity ICU that led to an increased risk of readmission implies that the policies and practices surrounding transfer decisions under normal conditions are reasonably sound. Whether formalizing the components of the discharge decision process into a checklist would decrease the risk of readmission requires more study. Another important approach for institutions to explore is developing flexible and cost-effective strategies for managing times of overcapacity.

The authors have not disclosed any potential conflicts of interest.

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Heterogeneity in microcirculatory blood flow and heterogeneity in observations

To the Editor:

It is with great interest that we read the article by Dr. Verdant et al (1) regarding the relationship between microcirculatory alterations in the sublingual and gut mucosal region in an animal sepsis model. The authors hypothesize that monitoring microcirculatory alterations in the sublingual region will be representative for other regions of the body (e.g.,

the gut) under conditions of sepsis. In their opinion, previous reports in an animal sepsis model (2) and in human abdominal sepsis (3), which challenged this optimistic view, were hampered by two methodologic errors: a semiquantitative way of red blood cell flow analysis and the potential for increased abdominal pressure.

Let us first focus on the theoretical backgrounds of these arguments. The microvascular flow index semiquantitatively classifies the predominant capillary flow per quadrant in four categories. Because the overall microvascular flow index is an average of at least 12 quadrant scores, data can be expressed as continuous by the rules of statistics. By definition, this way of quantification goes hand-in-hand with some loss of detail. If such loss of detail were to be the true cause of a complete dispersion of flow between two microvascular beds as reported (3), then this would implicate random assessment. However, both intraobserver and interobserver agreement for individual quadrant scores is reported to be excellent, sublingually and in intestinal villi (4). Furthermore, Dubin et al (5) reported a robust relationship between microvascular flow index and measured red blood cell velocity in hemorrhagic shock, again, both in the sublingual and intestinal mucosal region. The second potential bias in previous studies is suggested to be an increase in abdominal pressure. Because intra-abdominal hypertension may only influence intestinal perfusion, one would expect it to cause a systematically lower intestinal microcirculatory flow in comparison to sublingual microcirculatory flow. However, a complete scatter was reported in our study (3), meaning there were also individuals with a normal intestinal microcirculatory blood flow and an almost standstill of sublingual microcirculatory flow. Furthermore, why did this dispersion disappear over time (3)? One would expect intra-abdominal pressure to increase over time. And why did this affect the mucosa and not the serosa (2)?

Whatever arguments may be true, we applaud the efforts of Dr. Verdant et al to test their hypothesis in an animal experiment. Apart from well-known limitations, this type of research provides the opportunity to control parameters of interest. However, this fails to be the case in their experiment. Why was intra-abdominal pressure not increased stepwise to measure its effect on the correlation between the two microvascular beds? And why did the authors simply not provide microvascular flow index? Instead, another semiquantitative parameter of microcirculatory flow is provided (flow or no flow), and multiple measurements per animal (including baseline) in a very small number of pigs (n = 7) were used to calculate the coefficient of correlation, with a considerable risk of overestimation. Taking the available literature into account, including the article by Dr. Verdant et al, the conclusion cannot be drawn that sublingual microcirculation always follows the intestinal microcirculation.

The author has not disclosed any potential conflicts of interest.

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Of course the emperor has no clothes

To the Editor:

We enjoyed reading the editorial by Dr. Leibowitz (1). However, the realization that "the emperor has no clothes" should not come as a surprise because there are three fundamental errors that seem to have escaped everyone's attention. The first is that there are families of ventricular function curves, the second is mathematical coupling, and the third is disparate ventricular function.

Initial studies of the right ventricular ejection fraction (RVEF) pulmonary artery catheter enthusiastically reported stronger correlations of right ventricular end-diastolic volume (RVEDV) with stroke volume and cardiac index than with pulmonary artery occlusion pressure (2). Actually, RVEDV is a calculated, not measured, variable. In large populations, there can be no significant correlation between any estimate of fiber length (either filling pressure or end-diastolic volume) and cardiac index (or work) because patients' hearts operate on different ventricular function curves. Whether they use the Ross and Brawnwald normal, compromised, and failing curves or one of Sarnoff's "family" of ventricular function curves, we should remember that removing the lines joining the plotted points leaves a scattergram. Try drawing all of them on one graph and see for yourself. Living in the real world of patient care as we did back in the day, from the outset none of us should have believed that correlations such as those reported could have been of help in managing patients.

Second, because high correlations were unlikely physiologically, Archie's (3) description of mathematical coupling provided the answer for the "excellent data:" cardiac output and heart rate are included in the calculation of both RVEDV [(cardiac output/heart rate)/RVEF] and stroke volume (cardiac output/heart rate); similarly, cardiac output is included in the calculation of cardiac index (cardiac output/body surface area). The common variables must be factored out. We must use stroke volume index rather than stroke volume to have something left as the dependent variable: (cardiac output/heart rate)/body surface area is plotted on the y-axis and (cardiac output/heart rate/RVEF is plotted on the x-axis, leaving the inverse of body surface area to be plotted against the inverse of RVEF! A study conducted at the University of Miami several years ago showed that, after factoring out the common elements, the "high correlations" were no longer present (4).

The last fundamental error is assuming that the ventricles are operating on similar ventricular function curves so that an assessment of RVEDV is of value in determining left ventricular work. One of the first descriptive studies using the two-lumen pulmonary artery catheter found that filling pressures were different on both sides and did not necessarily move in the same direction during therapy (5).

We suggest that Dr. Leibowitz tell the child in Hans Christian Anderson's tale that the RVEF catheter does not measure

RVEDV and that we do not know what to do with RVEF and RVEDV. As a Lyle Lovett song proclaims, "And that's just a cryin' shame."

The authors have not disclosed any potential conflicts of interest.

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Immortal time bias in critical care

To the Editor:

We are grateful to Dr. Linde-Zwirble (1) for his insightful editorial on our article published in the November 2009 issue of *Critical Care Medicine*, in which we demonstrate the potential impact of immortal time bias in critical care research and demonstrate a simple, yet scientifically sound method of analysis by which to avoid this bias (2). To avoid confusion, however, about our previous study on delirium as a predictor of mortality (3), we write to correct some comments included in the aforementioned editorial. Although we are happy to admit previous errors—and have done so in our recent article on immortal time bias (2) by citing our older work on delirium and ICU costs (4), an analysis likely affected by immortal time bias—we did use appropriate statistical methods to avoid error in our analyses of the relationships between delirium and intensive care unit (ICU) length of stay and mortality (3). This is a point that Dr. Linde-Zwirble seems to have misunderstood. When this original work was undergoing review at *JAMA*, all of the reviewers pointed out the possibility of immortal time bias during their initial reviews, and all recommended reanalysis of our data using a method that addresses immortal time bias (i.e., time-varying Cox regression). The final results, therefore, published in *JAMA* in 2004 (3), were generated using the approach we have now proven valid in the simulation study we report in our recent *Critical Care Medicine* article (2). As a result of the new analysis sparked by the *JAMA* reviewers and eventually used to generate the data that we published, we concluded that delirium was not associated with ICU length of stay—a result in contrast to those of other studies that did not account for immortal time bias—but was associated with hospital length of stay and 6-month mortality. We conducted our simulation study and wrote our recent report on immortal time bias in ICU research to reveal a lesson we learned, one that has helped us avoid publishing biased messages to the ICU community. These experiences have intensified in our research group a spirit of uncompromising scientific rigor. Although the medical community in general prizes simple methodology whenever possible, we contend that oversimplification of the research process can profoundly restrict progress in health care. Thus, we are in great agreement with Dr. Linde-Zwirble's assertion that simple is often "too simple," especially when conducting observational critical care research.

The authors have not disclosed any potential conflicts of interest.

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Transcranial Doppler ultrasound in therapeutic hypothermia for cardiac arrest survivors

To the Editor:

The article of Seder and Van der Kloo (1) in the July 2009 supplement of *Critical Care Medicine* outlines neuromonitoring options during therapeutic hypothermia, with a single reference to transcranial Doppler ultrasonography (TCD) as noninvasive measurement of intracranial pressure. However, some other important confirmed utilities of TCD are thereby overlooked, including early prognosis after recovery of cardiac arrest (2).

Goal-directed hemodynamic optimization combined with therapeutic hypothermia could improve outcome of comatose cardiac arrest survivors. Systemic hemodynamics monitoring is achieved with several portable noninvasive techniques. By contrast, accurate measurements of cerebral blood flow, until recently, have been restricted to complex techniques, such as single-photon emission computed tomography or positron emission tomography, which can generally be undertaken only in research laboratories. However, there is strong evidence that changes of the mean blood flow velocities registered by TCD in the main arteries of the circle of Willis faithfully reflect changes of the cerebral blood flow in patients undergoing cardiopulmonary resuscitation and after return of spontaneous circulation (3).

By using TCD, in the middle cerebral arteries, five combinations of mean blood flow velocities measured in cm/sec and pulsatility index calculated as the ratio of the difference from systolic to diastolic velocities by the mean blood flow veloci-

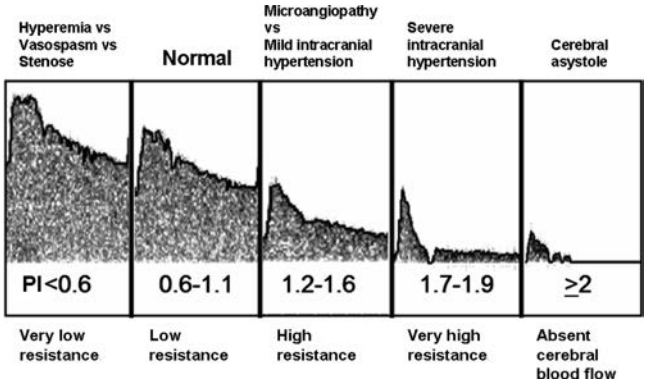

Figure 1. Transcranial Doppler spectra after recovery from cardiac arrest. *PI*, pulsatility index. From Álvarez Fernández JA, Pérez Quintero R: Use of transcranial Doppler ultrasound in the management of post-cardiac arrest syndrome. *Resuscitation* 2009; 80:1321–1322.

ties could be identified. These represent five different possibilities in cerebral hemodynamics after initial recovery of a cardiac arrest (Fig. 1) (2).

In patients who remain comatose at least 20 mins after recovery from a cardiac arrest, predominant TCD pattern includes low mean blood flow velocities and high pulsatility index as a result of a failure in reperfusion, despite adequate cerebral blood flow, probably caused by the presence of microthrombosis and vasospasm initiated during cardiac arrest, a macroscopic cerebral hyperemic reperfusion caused by the increase of the cerebral perfusion pressure, and the deterioration of the cerebral autoregulation (4). If no complications were presented, then normal values must be reached after 72 hrs, and the persistence of this hypodynamic pattern is a reliable indicator of poor neurologic prognosis because of intrinsic permanent injury in the microcirculation or because of the presence of severe myocardial dysfunction. The early or delayed presence of a diffuse hyperdynamic TCD pattern (high mean blood flow velocities and low pulsatility index) in the middle cerebral arteries should be vigorously treated because it is associated conclusively with evolution to severe intracranial hypertension, cerebral asystole, and brain death, and its appearance on the rewarming process should lead to immediate return to moderate hypothermia (4, 5).

A good prognosis should be expected with a normodynamic TCD pattern after return of spontaneous circulation (4). However, in these patients cerebrovascular reactivity must be assessed to find anomalies. The presence of focal hypodynamic TCD patterns that may predict the occurrence of stroke, and focal hyperdynamic spectra that may reflect a vasospasm related to subarachnoid hemorrhage or complicating a thrombolytic therapy.

Cerebral hemodynamics complications and patients with severely disabling or fatal outcome could be identified early, within the first 24 hrs after recovery of a cardiac arrest, by using serial TCD examinations. This approach has an additional advantage because TCD does not interfere with hypothermia therapy or sedative support.

The authors have not disclosed any potential conflicts of interest.

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The authors reply:

We thank Drs. Alvarez-Fernandez and Perez-Quintero for their informative discussion of the utility of transcranial Doppler ultrasound in cardiac arrest survivors during and after therapeutic hypothermia. Although transcranial Doppler ultrasound is typically limited to intermittent measurements and therefore does not meet the usual criterion (of being continuously measured) to be considered a neuromonitoring tool, it does provide a wealth of information regarding the presence or absence of intact cerebral autoregulation (1). Its use in screening for intracranial hypertension might identify patients in whom invasive intracranial pressure monitoring is appropriate.

Based on a series of carefully performed animal models (2–4), Dr. Safar and his research group believed that blood pressure augmentation was powerfully neuroprotective in the period immediately after resuscitation, serving to treat the vasospasm and microvascular thrombosis described by Drs. Alvarez-Fernandez and Perez-Quintero (5). If such a protocol were tested in humans, then transcranial Doppler ultrasound might prove a reasonable means of evaluating and titrating blood flow augmentation.

Although transcranial Doppler ultrasound is somewhat cumbersome, operator-dependent, and too specialized to perform routinely on the population of cardiac arrest survivors, it is noninvasive. The identification of a low-flow, high-resistance pattern on transcranial Doppler ultrasound begs treatment, but further research will be required to determine the proper therapy. We hope that investigators will target this subpopulation of cardiac arrest survivors for further study.

The authors have not disclosed any potential conflicts of interest.

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Cholinesterase inhibitors and delirium after cardiac surgery

To the Editor:

We have read with interest the article of Gamberini et al (1) concerning the use of rivastigmine, a cholinesterase inhibitor, in cardiac surgery. The authors showed, in a double-blind, randomized, placebo-controlled trial, that prophylactic administration of rivastigmine failed to prevent postoperative delirium in elderly patients undergoing cardiac surgery with cardiopulmonary bypass. The effectiveness of cholinesterase inhibitors in the treatment of delirium after cardiac surgery was not addressed by the authors.

We have previously reported two cases of delirium after cardiac surgery, successfully treated with physostigmine, an intravenous cholinesterase inhibitor (2). A 56-yr-old man and a 71-yr-old woman underwent coronary artery bypass graft surgery under cardiopulmonary bypass. Both patients presented postoperatively with severe agitation, disorientation, and cognitive disorders not responding to sedative drugs. After ruling out neurologic, hemodynamic, and metabolic disorders, a central anticholinergic syndrome was suspected. Physostigmine 0.04 mg/kg intravenously was effective in treating delirium in both cases and patients left the cardiac surgery unit with no neurologic disorders. Other authors have also reported the use of cholinesterase inhibitors to treat delirium related to postoperative central anticholinergic syndrome (3, 4).

We agree with Gamberini et al that delirium in elderly patients after cardiac surgery is an important clinical problem. Although the prophylactic use of cholinesterase inhibitors may not be effective in preventing postoperative delirium, these drugs should be considered as one of the pharmacologic options to treat this complication.

The authors have not disclosed any potential conflicts of interest.

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Drug-induced cortisol deficiency as a cause of intensive care unit weakness

To the Editor:

Discussions in the October 2009 supplement to *Critical Care Medicine* were informative and well-documented. However, they would have been more complete had they included consideration of the possibility that both concurrent cortisol deficiency and previous corticosteroid therapy are risk factors for intensive care unit-associated weakness (ICUAW) and for its contribution to delayed extubation of ventilator-maintained patients.

Muscular weakness is a prominent symptom of cortisol deficiency and its absolute or relative deficiency is present in many critically ill patients, most of whom had received multiple medications that individually inhibit cortisol formation. These medications include opioids (1), benzodiazepines (2, 3), propofol (4), etomidate (2), and several less frequently prescribed medications. Corticosteroid therapy also inhibits cortisol formation for varying intervals after its discontinuation.

We recently reviewed a few of the many studies documenting rapid opioid-induced inhibition of cortisol formation while reporting lower cortisol levels in opioid-naïve ICU patients who had received opioids within the 24 hrs preceding analysis (1). Several of the many studies (2) documenting a similar inhibition by benzodiazepines, and in studies by others (3), were referenced while highlighting contributions by opioids and benzodiazepines to etomidate-associated cortisol deficiency. Similarly, propofol profoundly impairs cortisol formation, with cortisol levels decreasing by 50% during 100 mins of propofol anesthesia preceding elective surgical intervention (4).

A large percentage of ventilator-maintained patients manifest ICUAW, the presence of which is associated with much more prolonged weaning times. Large percentages of ventilator-maintained patients are also cortisol-deficient (5), with their weakness suggesting a major contribution by this deficiency to ICUAW. Cortisol-deficient ventilator-maintained patients often respond dramatically to cortisol replacement (50 mg Solu-Cortef every 6 hrs) with improved strength and accelerated weaning (5), suggesting that this replacement also contributes to effective therapy for their ICUAW.

Kay et al (3) reported serial cortisol and adrenocorticotropic hormone levels in a series of 14 patients receiving three weekly injections of epidural triamcinolone. Subjects were randomized to receive either no premedication or 0.07 mg per kg of midazolam intravenously. One week after the first injection, and before their second, those who had received midazolam demonstrated 40% to 60% suppression of both cortisol and adrenocorticotropic hormone in comparison with the levels in patients receiving triamcinolone without premedication. This pattern persisted for adrenocorticotropic hormone through their 2-wk period of three epidural injections, at which time cortisol levels were equally and severely suppressed in both groups. Four weeks after the third injection, adrenocorticotropic hormone and cortisol levels remained 30% suppressed in those who had received midazolam. Their observations confirm the cortisol-depleting influence of the benzodiazepines and suggest that corticosteroid therapy in ICU patients may contribute to prolongation of drug-induced cortisol depression, thereby contributing to whatever portion of ICUAW is the result of associated adrenal insufficiency. Our observations suggest that cortisol deficiency should be considered in the differential diagnosis of ICUAW and

that measurement of cortisol levels with replacement therapy may be appropriate in those with adrenal insufficiency.

The author has not disclosed any potential conflicts of interest.

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The authors reply:

The letter to the editor by Dr. Daniell (1) questions whether there is an association between adrenal insufficiency (lack of cortisol) and intensive care-acquired weakness (ICAW) and questions our omission of this ICAW detail from the October Supplement of *Critical Care Medicine* (2).

There is little disagreement that chronic cortisol deficiency is associated with weakness and that acute adrenal insufficiency may also arise in the critically ill and may well be exacerbated or even mediated by drugs that are administered during their care. Leaving aside the considerable debate over the measurement and definition of acute adrenal insufficiency, we believe the basic tenant of the letter to the editor that acute adrenal insufficiency is firmly and causally associated with ICAW is unproven. An association between the extent of weakness and prolonged weaning does not imply that ICAW is the only factor that prolongs weaning, and we emphasized that all of the factors that contributed to prolonged weaning could also contribute to weakness, given the effects of disuse on muscle function. The study by Huang and Lin (3) suggesting shorter weaning in which patients with relatively short-stays with stress test-defined acute adrenal insufficiency were randomized to placebo or supraphysiological cortisol replacement therapy does not demonstrate an effect on ICAW *per se*, and these authors admit they do not have a mechanistic explanation for their observation. We would agree with this cautious interpretation of their findings because there could be cardiovascular, pulmonary, or psychological changes independent of a direct effect on ICAW. We hope future exploration of the mechanisms associated with short-term ICAW may expose a plausible physiologic link with adrenal insufficiency, but this is as yet unproven. The points made by Dr. Daniell also suggest that future descriptive studies determining the association between steroids, sedative, neuromuscular blocking, and analgesic agents and ICUAW should stratify patients for adrenal function, if a reasonable determination of normal and abnormal adrenal function in the context of critical illness can be agreed on.

We thank the author for raising this interesting hypothesis but believe it is in need of firm physiologic proof, which is an issue in research focus that we firmly support. This author was generous to commend the Supplement and as the Coeditors we must acknowledge the fine work of our contributing authors. We request their indulgence in our responding to the comments by Dr. Daniell in the absence of their input.

The authors have not disclosed any potential conflicts of interest.

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Organ dysfunction in patients with cancer admitted to the intensive care unit

To the Editor:

We read with great interest the article by Soares et al (1) published in the January 2010 issue of *Critical Care Medicine*. They conducted a multicenter study with the aim of evaluating the characteristics and outcomes of 717 patients with cancer requiring intensive care. The intensive care unit (ICU) and hospital mortality rates were 21% and 30%, respectively, and were higher in patients admitted because of medical complications, followed by emergency surgical and scheduled surgical patients. In their study, the mortality was mostly dependent on the severity of organ failures, performance status, and need for mechanical ventilation.

For the past two decades, the nature of cancer treatment has changed dramatically with the introduction of new and intensified treatment protocols and improved supportive care. Part of this improvement is probably ascribable to better selection of cancer patients for ICU admission. The main prognostic factors in critically ill cancer patients admitted to the ICU are the degree of dysfunction and the number of organ failure at ICU admission (2–4). We described the utility of the Sequential Organ Failure Assessment (SOFA) score in assessing the severity of organ dysfunction in patients with cancer before admission to the ICU (4). In our study, when the SOFA score before admission or on the day of admission to ICU was >7, predicted mortality was 68.1% and the area under the receiver-operating characteristic curve was 0.87 (sensitivity, 0.82; specificity, 0.79). The cardiovascular and renal dysfunction was associated with the highest contribution to the outcome. Our results suggested that the course of organ dysfunction over first days of life-sustaining treatment before admission to ICU seems to be of critical value to predict outcome. Consequently, the organ failure over the first hours or days of full life-support treatment could be a simple and objective tool for oncologist and intensivists group to identify patients who should be admitted earlier to ICU. The ICU admission should help to prevent, detect, or treat organ dysfunction. However, hematologists and oncologists also provide supportive care in the wards.

Cancer patients are at greater risk for severe sepsis than the general population, probably related to immunosuppression caused by the malignancy itself or its treatment. According to a multicenter study involving 606,176 cancer hospitalizations, the incidence of severe sepsis was nearly four times higher in cancer versus non-cancer patients (5). Soares et al (1) reported sepsis as one of the main reasons for ICU admission (107/15%), but they do not mention the prognosis of patients with severe sepsis and septic shock.

The SOFA score is based on the assessment of the degree of dysfunction of six vital organ systems: respiratory, cardiovascular, central nervous system, coagulation, liver, and renal (6). The authors may provide the values for each clinical and laboratory parameter included in the SOFA score in this group of patients. Finally, is there any reason to exclude patients with a stay <24 hrs?

The authors have not disclosed any potential conflicts of interest.

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The authors reply:

We read with interest the comments of Dr. Ñamendys-Silva and Dr. Herrera-Gómez (1). Their observations regarding the impact of organ dysfunctions on the outcomes of patients with cancer requiring admission to intensive care units (ICU) are in agreement with recent literature (2, 3). Lamia et al (2) demonstrated that baseline scores on the first day of ICU admission and subsequent changes in organ dysfunction scores seem to perform similarly in predicting survival for these patients. However, we believe that the decision to provide or forgo life-sustaining therapies should not be based solely on these parameters. The outcomes of critically ill patients with cancer are dependent not only on the nature and severity of acute physiologic derangements and organ dysfunctions but also on additional variables such as the performance status and burden of comorbidities (4).

We did not include specific information on patients with sepsis in our article (5). As mentioned, because of the relevance of this severe and frequent complication to critically ill patients with cancer, we believe that it deserves to be addressed in a separate and deep analysis. However, we can confirm that in the present study, ICU and hospital survival in the 194 patients admitted with severe sepsis/septic shock were 42% and 55%, respectively. We have decided not to include patients with <24 hrs of ICU admission in our study, because it is usually considered to be tricky to evaluate the appropriateness of providing intensive care for these patients.

Finally, the decision to admit a patient with cancer to the ICU is multifaceted and, besides outcome-related aspects, the perspective of being able to receive optimally aggressive radical surgical resections, chemotherapy, and radiation therapy regimens after ICU admission and patient's and family's wishes and preferences should also be taken in consideration. Of note in all these clinical decisions, close collaboration among intensivists and oncohematologists is essential, because several specific issues must be appraised in details.

Dr. Soares is supported in part by individual research grant from CNPq. Dr. Salluh has not disclosed any potential conflicts of interest.

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Nonexcitable muscle membrane predicts intensive care unit-acquired paresis in mechanically ventilated, sedated patients

To the Editor:

We read with great interest the work by Weber-Carstens et al (1) recently published in *Critical Care Medicine*. The elucidation of a simplified diagnostic/monitoring tool that can be utilized in the early identification of patients likely to have intensive care unit (ICU)-acquired paresis develop is assuming an ever-increasing importance as we try to improve the functional outcome of our patients. The validation of interventions targeting an improved functional outcome, such as the recently described early exercise with bedside cycle ergometry by Burtin et al (2), may in the future rely on such tools to identify the group of ICU patients who may benefit the most.

In their study, Weber-Carstens et al evaluated a range of electrophysiological measurements and their ability to predict the development of clinically significant weakness on patient awakening. This included direct muscle stimulation for the first time in this role. Their results included sensitivities and specificities of 83.3% and 88.8% for direct muscle stimulation of the anterior tibial muscle, 92% and 44.4% for compound muscle action potential of the peroneal nerve, and 48% and 93% for pathologic spontaneous activity on electromyography of the anterior tibial muscle, respectively.

Whereas direct muscle stimulation certainly appears the most accurate of these tools, it is a technically more demanding and time-consuming measurement. It is thus the least clinically practical of these assessment tools.

Latronico et al (3) have evaluated the compound muscle action potential after peroneal nerve stimulation to the electrophysiological diagnosis of ICU-acquired paresis. They found that the specificity of this technique varied with the chosen threshold reduction in compound muscle action potential used, although without reducing its high sensitivity. The threshold reduction in compound muscle action potential used in the work by Weber-Carstens et al is not clear from their article. Because peroneal nerve compound muscle action potential is the more practical of the simplified diagnostic/monitoring tools, it would be valuable to know the threshold reduction that was used to ensure the correct interpretation of the results.

The authors have not disclosed any potential conflicts of interest.

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The authors reply:

We appreciate the comments of Drs. Appleton and Kinsella (1), and completely agree that a simplified diagnostic/monitoring tool that can be utilized in the early identification of patients likely to have intensive care unit-acquired paresis provide the opportunity to identify patients who may benefit from therapies such as early physical exercise.

In this context in our study (2), evaluation of muscle membrane activity through direct muscle stimulation offers two advantages. First, of all electrophysiological parameters it was the one with the best sensitivity (83.3%) and specificity (88.8%) in predicting intensive care unit-acquired paresis. Second, in agreement with Drs. Appleton and Kinsella, it appears to be the most accurate of the electrophysiological tools and offers the opportunity to differentiate critical illness myopathy from critical illness polyneuropathy at a very early stage of disease. This may have impact on development of future therapies.

We do not agree with Drs. Appleton and Kinsella that direct muscle stimulation is the least clinically practical tool for assessing neuromuscular pathology. In fact, it is easy to learn and does not require additional electrophysiological equipment. We recommend concentric needle electrodes for recording and surface electrodes for stimulation.

Others (3) have evaluated the compound muscle action potential after peroneal nerve stimulation to identify neuromuscular abnormalities during early critical illness and improved its low specificity when compound muscle action potentials after peroneal nerve stimulation were measured below two standard deviations of the lower limit of normality. For us, this seems to be a more complicated procedure; furthermore, the related levels of paresis are not reported in this study.

In our study, we considered patients as having abnormal muscle membrane excitability consistent with the electrophysiological diagnosis of a primary myopathy if amplitude of compound muscle action potential after direct muscle stimulation decreased <3 mV according to published data (4). In our opinion, this measure is simpler and is supported by a documented close relationship to a clinical apparent paresis (MRC <4) at compound muscle action potential after direct muscle stimulation <3 mV in receiver-operator curve analysis.

The authors have not disclosed any potential conflicts of interest.

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Is hypotension a real predictive outcome factor after cardiac arrest? A response to significance of arterial hypotension after resuscitation from cardiac arrest

To the Editor:

With great interest we read the article by Trzeciak et al (1) in which the authors emphasized that hypotension registered within 24 hrs in the intensive care unit (ICU) after cardiac arrest (CA) is associated with a higher in-hospital mortality and predicted the functional status of survivors.

The authors exposed that in-hospital mortality after return of spontaneous circulation was high despite early recognition and intervention of cardiac arrest situations. Mortality rates in the ICU of patients who, after return of spontaneous

circulation, received aggressive therapy remained high in the hypotension present group. These data suggest that the mortality of these patients depended on other factors, mainly on the management before the admission to the ICU.

There are several major influencing factors that make the results of this study difficult to consider. It is known that the initial rhythm of patients influences the outcome of advanced life support, but there was no information about initial rhythm in this study. Furthermore, the initial rhythm after cardiac arrest, the number of shocks used, and the length of resuscitation also had effects on return of spontaneous circulation, survival, and myocardium injury as strong predictors of survival (2). Efficiency of resuscitation and/or advanced life support probably was higher among the staff of emergency department because absence of hypotension after treatment in the emergency department was significantly lower. It is also complicated to draw a conclusion at present because of the quality of cardiopulmonary resuscitation and because the algorithm of advanced life support changed at the end of 2005.

The authors also summarized that the outcome of in-hospital CA depended on several conditions (age, gender, cardiovascular comorbidity, site of origin before ICU admission, therapy after return of spontaneous circulation), but it is suggested that the early recognition of cardiac arrest, the initial rhythm of CA, and the quality of advanced life support also might be influential in the outcome of return of spontaneous circulation in this study.

We hope the overview of large registries of CA will take into consideration every step of the process (from the first recognition of CA to the treatment of the postcardiac arrest syndrome) to increase the chance of survival of patients with CA in the future.

The authors have not disclosed any potential conflicts of interest.

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The authors reply:

We thank Dr. Nagy et al for their interest in our work. We agree that peri-arrest factors such as initial cardiac rhythm (i.e., shockable vs. nonshockable) and quality of cardiopulmonary resuscitation are known to be major determinants of outcome for cardiac arrest victims. More recently, however, factors during the period of critical illness that follows return of spontaneous circulation have also been associated with improved outcome (e.g., lower body temperature through a therapeutic hypothermia strategy) (1–4). The interplay of these peri-arrest and post-arrest factors in determining the final outcome for patients resuscitated from cardiac arrest is likely complex and at present remains incompletely understood.

In our registry study of 8736 adult patients resuscitated from cardiac arrest and admitted to an intensive care unit (ICU), we found that nearly half (47%) manifested early post-return of spontaneous circulation arterial hypotension, defined as a systolic blood pressure <90 mm Hg within 1 hr of arrival to the ICU. Nearly two-thirds (65%) of the subjects with exposure to hypotension died in the hospital compared to 37% of subjects without hypotension, and hypotension exposure was an independent predictor of in-hospital death on multivariable analysis (odds ratio, 2.7; 95% confidence interval, 2.5–3.0). We also found that early exposure to hypotension was associated with significantly worse functional outcomes among survivors with hospital discharge.

As we acknowledged in the limitations, this registry study utilized a critical care database that was "ICU-centric," and thus peri-arrest factors before ICU arrival such as initial cardiac rhythm and cardiopulmonary resuscitation quality could not be included in the multivariable analysis. However, we submit that the determinants of survival at the time of the cardiac arrest event and during cardiopulmonary resuscitation have already been studied extensively and are well-established, whereas the factors associated with survival after return of spontaneous circulation (particularly after arrival to the ICU) are poorly understood. Therefore, registry studies of post-return of spontaneous circulation factors from an ICU-based perspective can yield unique and valuable information.

The interaction (and perhaps effect modification) between factors in these two separate and distinct phases of resuscitation, i.e., the cardiac arrest event and the postcardiac arrest syndrome, represents an important knowledge gap for resuscitation science. As one step to begin to address this knowledge gap, we recommend that future iterations of the Utstein guidelines for reporting cardiac arrest research include more detailed information on postresuscitation hemodynamic indices (including arterial pressure measurements at fixed time points) after return of spontaneous circulation and through the early hours of ICU care.

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PIRO score for community-acquired pneumonia: A new prediction rule for assessment of severity in intensive care unit patients with community-acquired pneumonia

To the Editor:

With respect to the contribution of Dr. Rello et al (1), we acknowledge the efficacy of their methodology approaching such an extensive and complex topic. Dr. Rello et al proposed a severity assessment score developed using variables selected from the current literature as the more significant in community-acquired pneumonia prognosis, or because they were considered to be of clinical importance by experts, I suppose. The community-acquired pneumonia PIRO (predisposition, insult, response, and organ dysfunction) score concept was prospectively measured on patient admission and compared to Acute Physiology and Chronic Health Evaluation II and American Thoracic Society/Infectious Diseases Society of America scores. The problem with this score is that the ultimate aim of a PIRO system is to assess eligibility for different treatments and not just to predict mortality rate for community-acquired pneumonia (2). There are already several good prognostic scores, such as Acute Physiology and Chronic Health Evaluation II, Acute Physiology and Chronic Health Evaluation III, Simplified Acute Physiology Score III, and others.

Facing the same challenge, Rubulotta et al (3) have defined a composite PIRO score for severe septic patients. The scores of Dr. Rello and Dr. Rubulotta are ultimately composite scores (1, 2), which are consistent but still not the ideal staging system for septic patients. We ask the authors whether, according to them, the composite score gives more information than the other scoring systems. Why is the correlation between scores in Figure 6 so good? Do they agree that, in theory, each variable belonging to the four groups (P, I, R, and O) needs to provide an independent component to the final combination? The issue is that the $P_0I_0R_0O_0$ patient might be part of a different population when compared to a $P_0I_1R_0O_0$ patient. In the ideal scoring system, probably, each letter should be integrated, assessing treatment for the patients with increasing value of P for the same I, R, and O, or with increasing R values but still the same P, I, and O, and with increasing O with the same P, I, and R. The next step could be to define which level or degree of sepsis is more likely to cause death, e.g., $P_1I_1R_1O_1$ corresponds to a low risk of death, $P_2I_2R_2O_2$ corresponds to a mild risk of death, and $P_3I_3R_3O_3$ corresponds to a high risk of death. Another possible analysis would be to understand which variables can be modified and which cannot, or even which PIRO combination is more likely to occur in a given country. Furthermore, we ask Dr. Rello et al if they believe they could have tested treatments given the fact that this is a prospective study and the others were retrospective.

The current article focuses on a selected group of patients and particularly those with community-acquired pneumonia. Nevertheless, the elements reported in this score reflect those presented by other authors (3, 4). Data collected from the Simplified Acute Physiology Score III databasesuggest that P at intensive care unit admission strongly correlates with mortality rate (50% of total predictive value). Age (64–70 yrs) is a leading component in the Simplified Acute Physiology Score III study, as it has been stressed both by Dr. Rello et al and by Dr. Rubulotta et al. Therefore, we ask to Dr. Rello et al if they believe that some variables could be common or similar in designing PIRO models (1, 3, 4).

In conclusion, we acknowledge the effort by Dr. Rello et al. We encourage these authors to continue their research in two main directions: 1) aiming at identifying a complex/combined score instead of a composite score; and 2) using the common or similar variables listed in all PIRO models to develop a common staging score for all patients with community-acquired pneumonia as well as severe sepsis and septic shock.

Dr. Ramsay has consulted with Edwards Lifesciences. Dr. Williams is employed with Eli Lilly, has received stock ownership from Eli Lilly, and has received stock options from Eli Lilly. Dr. Rubulotta has not disclosed any potential conflicts of interest.

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The authors reply:

We read with interest Rubulotta's comments regarding our paper "PIRO score for community-acquired pneumonia: A new prediction rule for assessment of severity in intensive care unit patients with community-acquired pneumonia" (1). We thank for her kind comments and for the opportunity to reply.

First of all, as we state in the methods section of our article, the variables used in the new score were selected from the current literature as being more significant in community-acquired pneumonia (CAP) prognosis or because they were considered with clinical importance. Our objectives were to develop an assessment tool to enable the stratification of critically ill patients with CAP into mortality risk groups to compare the performance of the PIRO (predisposition, insult, response, and organ dysfunction) score with the Acute Physiology and Chronic Health Evaluation II score and 2007 American Thoracic Society/Infectious Disease Society of America criteria (2) as a prognostic index in intensive care unit patients admitted with CAP and to evaluate prediction of PIRO score for healthcare resources use. We agree with Rubulotta that several scores are available to predict mortality in intensive care unit patients. However, we consider that disease-specific customized tools such as the CAP-PIRO score could be useful in risk stratification for specific populations, because many relevant prognostic factors in CAP are missed in general severity assessment tools (3). We agree that some variables will be common to different PIRO models designed in different settings, but we do consider that there are relevant

specific risk factors frequently overlooked in general models. Nonetheless, in our cohort of patients with CAP, our disease-specific PIRO score outperformed a general severity assessment tool (Acute Physiology and Chronic Health Evaluation II) and a specific risk stratification tool (American Thoracic Society/Infectious Disease Society of America major criteria presence). We disagree that correlation between score is good in Figure 6 because discrimination ability of the CAP-PIRO score was clearly superior. In addition, the CAP-PIRO score allowed a stratification of patients in four different risk levels defined as low, mild, high, and very high risk for mortality. Whether such approach might be used to test different treatments as suggested by Rubulotta requires further prospective investigation. The use of clinical scores as a criterion for patient enrollment into clinical trials or as the basis for individual treatment decisions is still controversial (4).

We applaud Rubulotta's effort to develop another approach to the PIRO system considering each domain separately (5). Certainly, the impact of the presence of risk factors into each different domain (P, I, R, and O) on outcome is different as suggested by Rubulotta's paper. We agree this was the first suggested approach when the system was first described. However, we choose to design a composite score system to improve adherence as a result of the simplicity. It is based on easily available variables, all with known impact in CAP mortality, and allows easy risk stratification of patients in different levels of severity with progressive rates of mortality. Complex models might have improved predictive ability; however, adherence could be lower as a result of difficulties to apply it in clinical practice.

Finally, we also encourage Rubulotta et al to continue their research on the PIRO system and severity assessment of critically ill patients. Further studies, in our opinion, should focus on using the PIRO system as a tool for enrollment in clinical trials and identification of patients more likely to benefit from new therapeutic agents.

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Immortal time bias in critical care research

To the Editor:

We read the article by Dr. Shintani et al (1) about immortal time bias and the use of time-varying covariates. Delirium was chosen as an example of a time-varying exposure with an association with outcomes of critically ill patients. In their analysis, they modeled delirium as a time-varying binary exposure by considering that delirium was absent until its onset and then was considered present until an outcome occurred or the case was censored. However, in reality, delirium may subside after a few days because of its natural course or because of treatment. Furthermore, repeated episodes of delirium may occur. Although duration and relapse of delirium may influence its association with outcome, they were not considered in the statistical analysis used in the article.

The article highlights important aspects of analysis considering time-varying exposure, which are frequently neglected in critical care research. The time-varying Kaplan-Meier curves are rarely used 25 yrs after they were introduced by Simon and Makuch (2). Dr. Shintani et al used R version 2.6.0 for constructing the curves, which is capable and sophisticated software but may not be suitable for its use by nonstatisticians. However, other types of statistic software used by clinicians may not provide time-varying Kaplan-Meier curves. Therefore, it would be valuable to learn from the authors which of the commonly used statistic programs offer this type of analysis. The actual computational procedure used in a program like STATA would probably further spread the use of the method.

The authors have not disclosed any potential conflicts of interest.

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Epinephrine in pediatric septic shock: Does the algorithm speak what the recommendations say?

To the Editor:

In their 2007 update "Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine," Brierley et al provided algorithm for stepwise hemodynamic support of infants and children with septic shock. It needs a few clarifications. The algorithm does not properly reflect the very same recommendations with which it is published. In this algorithm, authors have endorsed central dopamine as a first-line drug for reversal of cold shock. Central epinephrine has been

mentioned as the next-line drug if cold shock is resistant to dopamine (1). In our opinion, epinephrine should be the first-line drug, and the algorithm should stress that it is appropriate to use it as an inotrope by peripheral route initially. Time is of essence in managing septic shock and much of the valuable time will be missed if a dopamine "trial" is attempted after achieving central venous access.

There are a few points we raise in support of our opinion. First, the majority of pediatric patients with fluid-refractory septic shock have low cardiac output state with high systemic vascular resistance (2). Both dopamine and adrenalin have been used in the low cardiac output state. However, epinephrine is a more potent inotropic agent and can decrease systemic vascular resistance in low-dose infusions (3, 6). Second, there is age-specific insensitivity to dopamine (4). Third, epinephrine is cheap and easily available even in primary health care settings of most developing countries. It is on the World Health Organization Model List of Essential Medicines for Children (5). Dopamine is an immunosuppressant and it increases pulmonary shunt fraction. Based on results of trials across European intensive care units, a recent review (6) emphasized that dopamine use might actually increase mortality associated with shock states.

Notably, American Heart Association/Pediatric Advanced Life Support guidelines permit initial usage of epinephrine by peripheral intravenous or intraosseous route for cardiopulmonary resuscitation or postcardiopulmonary resuscitation shock. Furthermore, the 2007 update itself now recommends use of inotropes through peripheral route until central venous access is established by skilled personnel (1).

There is a concern that epinephrine may impair splanchnic circulation and may induce lactic acidosis. However, this may not necessarily be a surrogate to poor patient outcome. In fact, no significant difference in mortality or efficacy has been found when epinephrine was compared to other catecholamines in septic shock in adults. A recent review (6) on vasoactive drugs noted the case against adrenaline as a first-line agent in sepsis has been further weakened by recent studies in adults. Placing epinephrine as a first-line drug through peripheral or central venous access in appropriately fluid-resuscitated septic shock patients with cold shock will effectively address the low cardiac output state, which is the most common scenario associated with mortality in pediatric septic shock (2). This will have a direct (positive) impact on survival of pediatric patients with septic shock.

The authors have not disclosed any potential conflicts of interest.

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The author replies:

I completely agree with the summation by Jain and Bansal (1). If I were to choose one drug to use as an inotrope, it would definitely be epinephrine for the reasons eloquently described in the doctor's Letter to the Editor concerning our article (2). Epinephrine can be administered centrally, peripherally, subcutaneously, intramuscularly, intratracheally, and as an aerosol, making it the perfect choice. Nevertheless, there is no firm evidence showing that that it is harmful to use the lesser drugs dopamine or dobutamine as first choices if one quickly adds epinephrine if unsuccessful in attaining hemodynamic goals. The guidelines stress goal-directed time-sensitive therapy more so than drug-directed therapy. Epinephrine should be more effective than dopamine or dobutamine in reaching these goals in a time-sensitive manner.

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