

**End-of-life care and organ procurement for transplantation: Palliation or euthanasia?**

**To the Editor:**

Sprung et al. (1) highlighted a sensitive area in the everyday practice of critical care medicine. How can we differentiate between two distinct end-of-life (EOL) practices, palliation (the relief of pain and suffering) or euthanasia (the deliberate intent to shorten the dying process and hasten death), when common medications such as opiates and sedatives are given to intensive care unit patients undergoing withdrawal of life-support therapy? Sprung et al. provided certain pertinent findings: 1) terminal extubation and discontinuation of mechanical positive-pressure ventilation could unexpectedly lengthen the time to death; 2) increasing the doses of opiates and benzodiazepines proportionally shortened the time to death in euthanasia; 3) physicians' true intentions determined whether the EOL practice was palliation or euthanasia because of inevitable overlapping of the doses of medications given and time to death in both practices; and 4) physicians' true intentions can be difficult to ascertain because intentions are subjective and private, therefore only self-reporting, or an analysis of extreme physician actions can be determinant. From the legal perspective, physician actions in assisted death are judged by the intent and proximate causation of death.

Federal regulations, state laws, and health regulatory agencies compliance rules were introduced with the intent to increase the procurement of transplantable organs at the EOL, i.e., donation after cardiac death (DCD) in the United States (2). In DCD, organ procurement is a time-sensitive intervention at the EOL. Cardiorespiratory arrest must ensue after the withdrawal of mechanical ventilation and hemodynamic support within a short time range (30–120 mins) to procure transplantable organs. If cardiorespiratory arrest does not ensue within the desired timeframe, it can lead to abandonment of procurement. We have previously expressed

concerns about euthanasia practice in DCD for the recovery of transplantable organs at the EOL (3). The inaccuracy of predicting the time to death can be overcome by the use of large doses of opiates and sedatives to shorten the warm ischemia interval and to fulfill the necessary criteria to begin the procurement process in a timely manner (4). In addition to these medications, we have expressed concerns about: 1) medications and interventions required for organ preservation before procurement, and 2) expediting the moment when surgical procurement can begin, both of which also shorten the dying process in organ donors (2).

The findings of Sprung et al. heighten those concerns about EOL practice, especially when organ procurement in DCD has exponentially grown over the past 3 years in the United States (5). It may be argued that Sprung et al. reporting on European EOL practice may not be applicable in the United States. Nevertheless, when procurement of transplantable organs is the explicit (or implicit) intent at the EOL, it is impossible to dispel the perception that opiates and sedatives are given to hasten death upon the withdrawal of life-support therapy. Indeed, in a U.S. survey, healthcare professionals and providers expressed their perception of euthanasia, and moral distress about current DCD practice at the EOL (6). To alter the negative perceptions and attitudes about DCD, the transplant community has launched intense educational (or ideological) campaigns to improve the acceptability of DCD among healthcare professionals and providers (7).

Respect for spirituality and religious beliefs are significant domains in EOL care. Nevertheless, the DCD proponents and transplant community have avoided confronting major religions about the realities of organ procurement (8), and the need for physician assisted death, if organ donation is to be a continuum of EOL care in society (9). In support of broad societal rejection of physician assisted death, Sprung et al. reported on a large European survey that most of the intensive care unit physicians, and patients' families from all major religious affiliations strongly opposed active shortening of the dying process or euthanasia at the EOL (10). Physicians' actions that run contrary to patients and their families' strongly held religious or personal be-

liefs that are performed without the patients', or surrogates' knowledge, or discussion represent serious violations of trust and integrity of medical practice.

The authors have not disclosed any potential conflicts of interest.

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## The crystal ball in end-of-life care

### To the Editor:

With interest we have read the latest analysis of the End-of-Life Practices in European Intensive Care Units study (1). The authors conclude that there is a gray area in end-of-life care between palliative care and intended shortening of the dying process (SDP). We have serious concerns:

First, the authors define "euthanasia" as hastening death. This is not a correct use of the term. It should only and strictly be used for deliberate termination of life at the patient's request by deadly injection (most often a sedative, barbiturate, and a muscle relaxant) after which death immediately ensues (2). The reported long time to death of many SDP patients clearly shows that this was not the case. Euthanasia and giving opioids and/or benzodiazepines in doses that do not directly result in death should be distinguished from each other. Using them synonymously causes confusion and does not make the discussion any clearer.

Second, that a physician has the intention to hasten death does not necessarily mean that death is in fact caused by the administered drugs. In 72 patients, the reporting physicians considered that the doses of these agents definitely led to the patient's death. As the authors cite, doses of these agents and their actions are often the same in normal palliative care. Looking at Table 1 in the article, doses of morphine and/or diazepam are often in normal palliative ranges. Still, this is reported as active SDP causing death. In 2003, the authors themselves stated that opiates "would seem to be most likely the cause of death if the patient dies within 1 min of the injection" (3). That the administered doses are not in deadly ranges is reflected by the timeframe from the administration of the drugs until death, which often exceeded several hours. In our opinion, it is "crystal ball medicine" to speculate that death is caused in these patients. Within which time period should these patients have died, when no opioids/sedatives were given? No one knows. This study provides no reliable evidence

for the statement that the dying process is shortened.

Third, showing that larger doses for SDP correlated with a quicker death does not provide evidence that these agents hasten death. This might simply mean that higher doses are required for more severe symptom relief of sicker patients who naturally die faster. Information on symptoms such as pain and distress, medication tolerance, and severity of disease is lacking.

Fourth, is there evidence that opioids/sedatives shorten life? Morphine can actually delay death by decreasing work of breathing (4). When oxygen demand is decreased, lower levels of oxygen delivery are tolerated before fatal dysfunction of the organism occurs (5,6). So, instead of hastening death, it is also plausible that it prolongs life. These patients could in fact have lived longer because of opioids and sedatives; instead their dying process was actively shortened, and time to death after withdrawal of intensive care unit treatment would be shorter without opioids and/or sedatives.

The authors have not disclosed any potential conflicts of interest.

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## Troublesome terminology for a tough truth

### To the Editor:

We would like to congratulate Dr. Sprung and coworkers with their efforts to shed light on end-of-life issues as withholding or withdrawing treatment, and relief of suffering in the intensive care unit (1, 2).

In our view, however, the terminology used in their article "Relieving suffering or intentionally hastening death: Where do you draw the line?" (1) tends to increase the confusion about what is really happening during the end-of-life phase in the intensive care unit. The word "euthanasia" in our opinion is not useful, as it has a different meaning in different parts of the world (3).

As stated in the introduction, "active euthanasia is controversial, and only legal in The Netherlands and Belgium (on the patient's direct request)."

There are two problems introduced here. First of all, Dutch law does not use the word euthanasia, as it uses "termination of life on request"; it also does not define "active" as opposed to "passive" ([http://www.justitie.nl/images/wettekst\\_tcm34-2589.pdf](http://www.justitie.nl/images/wettekst_tcm34-2589.pdf)).

The use of adjectives as "active" and "passive" only leads to increased misunderstanding. Active euthanasia is often used for or understood as physician-assisted (or mediated) suicide, but also (mis)used for the act of terminating life without consent of the patient. Passive euthanasia is not only understood as "letting die" by withdrawal of treatment, but is also used as a synonym for palliative (terminal) sedation.

Second, termination of life, as defined under Dutch and Belgium law requires a sustained request to die by a competent patient, it is extremely rare in the intensive care unit.

Another argument against using the term euthanasia in international literature on end-of-life issues is that the word euthanasia is too emotionally charged. Euthanasia is associated with the Nazi regime, where it was used to name the termination of life considered by another to be not worth living (4).

Therefore, the introduction of the term "active shortening of the dying process", seems a good step; it however has its own drawbacks. As it is defined to be "distinct from legal and ethically accept-

able practices, such as withholding and withdrawing treatment” it may easily lead to the same confusion as the term euthanasia. Furthermore, in the present study, end-of-life actions termed shortening of the dying process were not distinguishable from actions aimed at relieving suffering during the dying process. As the authors conclude, the terms used are more associated with the intent of the doctors prescribing medications, than with the actual therapeutic actions (1). Part of the 94 patients (of a total of 4,248 patients) who were classified as shortening of the dying process might in fact have been good palliative care, as also suggested in the accompanying editorial (5).

We propose that the debate on end-of-life issues uses simple terms that describe exactly what actions take place (e.g., withdrawal of treatment, continuation of care, relief of pain and suffering, allowing to die), and not hint at either “intent” or “result.” The use of terms as (active) euthanasia or shortening of the dying process does not help to draw the line between ethical and unethical; these terms merely obfuscate this line.

The authors have not disclosed any potential conflicts of interest.

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## The gray area between palliative care and active shortening of the dying process

### In reply:

Dr. Verheijde and colleagues noted that our findings heighten concerns about end-of-life practices in the particular situation of donation after cardiac death. Indeed, there is a major risk of confusing intent when the procurement of transplantable organs is the aim at the end-of-life as it is impossible to dispel the perception that opiates and sedatives are given to hasten death upon the withdrawal of life support. Under the pressure of the transplant team, the physician in charge of the patient might experience a great conflict of interest. We agree that the “gray area” between palliative care and active shortening of the dying process (SDP) in end-of-life care has important moral and ethical implications for the practice of intensive care medicine especially when the timing of the procurement of transplantable organs is dependent on the doctor’s end-of-life practice. Therefore, we suggest that decision makers in each country promulgate explicit, precise, and detailed rules for donation after cardiac death to provide safeguards for patients and physicians. The end does not always justify the means. The question of donation after cardiac death, however, was never an issue during the Ethicus study that was performed before such donations occurred. We also agree that physicians should respect their patients’ and families’ religious and personal beliefs when they act.

Dr. Kompanje and colleagues, and Drs. Kuiper and Gerritsen take issue with our use of the term euthanasia. First, we did not define euthanasia. In fact, the physicians who completed the Ethicus questionnaires were never confronted with the word euthanasia, but were explicitly asked about active SDP to describe their actions. As noted in the original Ethicus report (1), the term *SDP* was coined instead of *active euthanasia* because Dutch investigators insisted that the term active euthanasia could not include most intensive care unit patients who could not request the action. Several other terms were considered but SDP was accepted by all investigators as it describes the intent and the action that occurs. Figure 2 is a conceptual illustration to help clarify the spectrum of actions and intentions when palliative care

or euthanasia occurs. The illustration shows that euthanasia occurs when there is intent to explicitly hasten death, and the action is one with adequate doses of a drug to definitely hasten death. Other non-Dutch authors have used definitions for euthanasia similar to this as “purposely terminating the life of a patient” (2) or “performs an act with the specific intent of causing or hastening a patient’s death” (3) without mentioning the patient’s request or immediate death (2, 3). It is not just the amount of medication that is significant but the intent of the physician. Although there are problems with the terms active euthanasia and SDP, and they are not uniformly accepted, other terms will not be more helpful, will not adequately describe an act that terminates the life of a human being, will also generate debate, and will also not draw the line between ethical and unethical behavior.

Dr. Kompanje and colleagues disagree with our statement that the study provides evidence that the dying process was shortened. We stated that “medications given concomitantly with withdrawal of therapy may instead of shortening the time to death actually sometimes delay an inevitable death (4, 5).” Despite this fact, we in our article and others (6) have presented objective data demonstrating that when hastening death is explicitly intended, larger doses of opiates and benzodiazepines given, do in fact lead to a quicker death. Therefore, the dying process was shortened. Despite not having information on symptoms, medication tolerance, or disease severity, and many patients not dying immediately, when doctors state that their intent was to actively shorten the dying process and inject 200 mg of morphine sulfate, 100 mg of diazepam, and/or 1 or 2 g of thiopental in an intravenous bolus, and the patient dies within minutes, no crystal ball is required to know the cause of death. Although some cases of SDP may have been good palliative care as suggested by Drs. Koogler and Hoehn (7) and Drs. Kuiper and Gerritsen, many patients received overdoses of medications that were clearly more than just palliative care. Of the 66 SDP patients with available medication dose data, 39 received intravenous boluses of at least 50 mg of morphine sulfate, 50 mg of diazepam, and/or 1 g of thiopental, and 26 received intravenous boluses of at least 100 mg of morphine sulfate, 100 mg of diazepam, and/or 1 g of thiopental.

We understand the attempt of Dr. Koogler to reclassify SDP patients to palliative care. Unfortunately, the reality is that in some situations, doctors intentionally terminate the life of patients. This reality seems shocking to some considering the comments we received. The reasons that led to SDP were not evaluated. It may be that waiting for the inevitable death of patients is just unbearable for families and caregivers. Whether active SDP for the comfort of families or caregivers can still be called good palliative care is questionable.

The key point of our article that does not seem to be an issue for Dr. Kompanje and colleagues, Drs. Koogler and Hoehn, and others is that there is a “gray area” between palliative care and active SDP in end-of-life care.

The authors have not disclosed any potential conflicts of interest.

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## Relieving suffering or hastening death: A misrepresentation

### To the Editor:

Sprung et al. (1) set out to ask a vital question in an extensive survey, but sadly they have misinterpreted their results, and misrepresented palliative care as a consequence.

First, the authors state it is “well known” that relief medications can shorten life, and “exceedingly difficult” to separate relief measures from life shortening measures. Both statements are incorrect. There is increasing evidence on the safety of opioids and sedatives, even in critical care situations in terminal patients having ventilation withdrawn (2). Median opioid and sedative requirements are now well established in palliative care, and there is a stark contrast between the palliative practice of giving small, repeated doses titrated to each individual to avoid serious adverse effects, and the use of high doses (often as intravenous boluses) given to opioid- or benzodiazepine-naïve patients.

Second, there are two fundamental flaws in their methodology. Expressing analgesic doses as morphine equivalents ignores the wide variance in individual patient equivalences. More importantly, relying on physicians to classify their actions is unreliable, especially retrospectively (3). The details of the questionnaire are missing, and Sprung et al. need to demonstrate that no leading questions were used. A perception that a patient’s life was shortened is not proof that this happened.

Third, if some of the clinicians chose morphine with the intention of shortening life this is at odds with the experience in the Netherlands where euthanasia is legal, but opioids are the least common euthanasia agent because of their unreliability in shortening life (4).

Fourth, the median dose of morphine used was 15 to 20 times higher than the median dose required to treat cancer pain, and the median dose of diazepam used was seven to eight times higher than the equivalent doses of midazolam used to manage agitation in palliative care (5, 6). It is well recognized in palliative care that high doses of both the drugs can lead to paradoxical agitation, and the doses demonstrated in this survey are alien to palliative care (5, 6). In addition, the claim of a clear relationship between morphine dose and time to death is not supported by

the data presented, and contradicts several studies in similar patients (2).

Finally, despite such high doses being used, it is surprising that in only 1.7% of cases did physicians believe the drugs had definitely shortened life. But even the authors question this interpretation when they admit that “confusion among physicians causes them to misclassify or misrepresent their own actions.” The authors were also surprised that the time to death was similar in both life-shortened and non-life-shortened patients, and that extubated patients lived longer than nonextubated patients. However, they fail to offer the most obvious explanation—that these drugs did not hasten death. Without clear evidence of life shortening, the authors’ interpretation is without foundation.

There is nothing in this article’s data that supports the authors’ belief that there is an overlap between euthanasia and palliative care.

The authors have not disclosed any potential conflicts of interest.

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## Palliative care approach can provide safeguards for end-of-life care in the intensive care unit

We read with interest the article by Dr. Sprung et al. (1) in which they highlight some of the key issues in providing symptom control for dying critical care patients. They identified a small number of cases in which patients were given large doses of opioids and benzodiazepines with the express purpose of shortening the dying process. This correlated with a quicker death for these patients. They also found that in some cases where shortening the dying process was intended by the physician, the mean doses were similar to those used for symptom relief in earlier studies, with no difference in the time to death when compared with patients who only underwent treatment withdrawal.

These findings underline first the lack of confidence felt by some intensive care unit (ICU) clinicians in managing patients in the dying phase, leading to deliberate steps being taken to hasten death, and second, the mistaken belief held by some that the administration of appropriate doses of medications for symptom control will shorten the dying process. A third implication of this study is that a cohort of patients may be receiving inadequate symptom control so as not to risk hastening death.

The need for clear guidelines and protocols to provide direction, and support for ICU clinicians in end-of-life care has been previously reported (2). Protocols have been developed, but only from a critical care perspective, looking at the process of treatment withdrawal and advice around symptom control (2, 3). An action research project in the United Kingdom has taken a widely accepted palliative care document, and developed it for use in the ICU—the Liverpool Care Pathway for the Dying Patient is a multiprofessional integrated care pathway, incorporating evidence-based practice, which provides a template of care (4). Although originally developed for the care of cancer patients in the acute hospital, it has since been amended for the care of patients in other care settings, regardless of diagnosis. The ICU version corresponds with many of the quality measures seen as indicative of excellent palliative care in the ICU (5).

Sprung et al. discussed an important safeguard for those involved in end-of-life care in the ICU as being the proper doc-

umentation of the use of potentially life-shortening measures, such as the administration of drugs for symptom control. The Liverpool Care Pathway for the Dying Patient replaces all other documentation in this phase of care, becoming the legal record of care given. It allows health care professionals to record “variances” against the symptom control goals, and then record the steps taken to remedy the situation, including drugs given, and incorporates guidelines covering drug dosages and escalation regimes. The advantages of using a framework such as the Liverpool Care Pathway for the Dying Patient are:

- Clinicians can feel confident that they are practicing within an agreed standard of care,
- Clarity around the distinction between acceptable doses of medication for patient comfort and inappropriately high doses, which are equivalent to euthanasia,
- The assurance that all ICU patients receive adequate care and symptom control at the end-of-life.

The authors have not disclosed any potential conflicts of interest.

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## The authors reply:

We thank the authors of the letters. In our article (1), we specifically stated that absolute doses of medications may not be indicative of euthanasia or active shortening of the dying process (SDP) as prior exposure, tolerance, and duration of medications are important. We also noted that medications given concomitantly with withdrawal of therapy may actually sometimes delay an inevitable death instead of shortening the time to death. We recognize that many variables that may influence medication use and survival were not evaluated. Although it is clear that many doctors do not use adequate doses of medication to relieve pain and suffering, it is also clear from our data that some doctors sometimes give much larger doses of medications than needed for relief of pain or suffering to actively shorten the dying process.

We disagree with Drs. Chapman and Ellershaw who stated that deliberate steps by physicians to hasten death imply their lack of confidence in managing dying patients. Some doctors may simply have a different approach. In addition, although a cohort of patients may be receiving inadequate symptom control so as not to hasten death, we do not believe this conclusion can be made from our results. We certainly agree that such protocols as they describe are important.

We believe Drs. Regnard and Finlay missed the point of our study and make incorrect statements. Patients cared for in palliative units are very different from intensive care unit patients and this may have led to some confusion. During the study, doctors prospectively determined whether there was SDP as defined in the methods. The results indicate that larger doses of medication used for SDP did correlate with a quicker death. In addition, we clearly demonstrated that without the knowledge of the doctor's intent it is exceeding difficult to differentiate relief measures from life-shortening actions. Finally, our results showed that 77% and not 1.7% of doctors thought that the medications used for SDP definitely led to the patients' deaths.

Although this issue is extremely controversial and disagreements may occur, we believe everyone can agree with our conclusion that “physicians should administer drugs in sufficient amounts to relieve pain and suffering because the importance of palliative care cannot be over-

emphasized, but the drugs should not be intended to directly cause death.”

The authors have not disclosed any potential conflicts of interest.

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### Relieving suffering or intentionally hastening death: Drawing the line in function of the patient

#### To the Editor:

The End-of-Life Practices in European Intensive Care Units study group performed excellent work in documenting attitudes toward end-of-life practices worldwide in an overwhelming number of patients, and have thus indeed provided interesting data for an ethical debate (1).

The findings confirm previous observations and the general perception that even when the intention for shortening the dying process exists, the medication used in most of the cases is only a continuation of the existing medication but at higher doses. The study illustrates that increasing doses of opiates and benzodiazepines is associated with a shorter time to death, but this was not shorter than in patients in whom withdrawal was performed. It is reported that physicians consider the fact that using higher doses of benzodiazepines and opiates has a double effect, and is not synonymous for euthanasia. The Dutch guidelines for palliative sedation underline that increasing the dose of morphine is contraindicated as a tool for life shortening (2). Although morphine may induce drowsiness it seldom induces sedation. Additionally, overdoses of morphine may induce serious side effects such as delirium and myoclonus.

We fully agree with the plea issued in this article that there is a need for more

transparency at which proper safeguards for end-of-life medical care can be developed and maintained.

However, we would like to add the following consideration. Healthcare providers are all trained to save lives and to do anything that is possible to cure the patient. At a given point a cure is no longer possible and good care remains the only option left. Therefore, alleviating symptoms and improving the quality of “life or dying” remain the ethical obligation. In these end-of-life situations, it is important to introduce the knowledge of palliative care to achieve a dignified death without useless prolongation of suffering. Therefore, the education and training in palliative care for all caregivers in the intensive care unit must be obligatory and should be a part of the basic curriculum. The multidisciplinary approach of this holistic care must be part of a good clinical care in intensive care units.

The authors have not disclosed any potential conflicts of interest.

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### Relieving pain and suffering does not hasten death

Sprung et al. have recently published an article in this journal with the “objective to demonstrate that there is no clear-cut distinction between treatments administered to relieve pain and suffering, and those intended to shorten the dying process” (1).

Sprung et al. used empirical data to show that increasing dosages of opiates and benzodiazepines were associated with a shorter time to death. In their analysis, however, they do not correct for characteristics that are known to be related both

to patient survival and medication use (type and dosage) such as, diagnosis and age of the patient, and previous history of opioid and benzodiazepine use. A causal relationship between medication dosage and time to death cannot be demonstrated without correcting for such factors. Therefore, the conclusion that is written in the editorial accompanying this article: “this study shows that larger doses of opioids and benzodiazepines led to shorter times before death” is debatable (2). In fact, there have been studies that specifically studied the effect of opioids and benzodiazepines at the end-of-life, which have shown that life is not shortened by these medications if they are titrated against pain and symptoms, not even when these medications are given in large or increasing dosages (3–7). These studies argue that, the worry should not be that death is hastened by medication to relieve pain and symptoms, but that physicians do not give enough medication to relieve pain and symptoms because of an unfounded fear to hasten the end-of-life of the patient.

Although these studies were not performed in the intensive care unit, they support the results of smaller studies that were performed in the intensive care unit that were referred to by Sprung et al. and in the editorial.

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## Surviving sepsis in developing countries

### To the Editor:

We note with interest the updated 2008 Surviving Sepsis guidelines, which summarize the evidence for the acute management of severe sepsis (1). We wish to highlight the widespread problem of severe sepsis in regions where there are significant resource constraints.

Most of the world's population lives outside the developed world, but the epidemiology of severe sepsis in these developing regions is largely unknown. Limited available evidence suggests that outcomes are catastrophic. In a large teaching hospital in Pakistan, mortality from severe sepsis was recently reported as 80% (2). Even in middle-income countries, outcomes may be equally poor. In a study from a tertiary center in Turkey, the mortality from sepsis associated with at least one organ dysfunction was 92% (3). In a clinical trial of patients with severe sepsis due to melioidosis in a provincial center in Thailand, the mortality was 90% (4).

We emphasize the need for sepsis bundles that use cheap and cost-effective interventions that may be readily implemented in low- and middle-income countries. Many principles advocated by the Surviving Sepsis guidelines, such as early fluid resuscitation and hemodynamic management, timely and appropriate antibiotic administration, and source control, may be adaptable for use in under-resourced environments. However, interventions with debated benefits even in developed countries, such as activated protein C, low-dose corticosteroids, and intensive insulin therapy, are unlikely to improve outcomes in the absence of more elementary supportive measures. Furthermore, for many countries, development of critical care services entails competition for scarce resources. Ideally, therefore, effective and low-cost management approaches can be integrated into existing healthcare systems.

Research is required to develop and evaluate creative and cost-effective alternatives to current sepsis therapies that are applicable to resource-constrained countries. Some examples that could be

tested in these settings include noninvasive hemodynamic monitoring and noninvasive ventilation devices. Education of healthcare workers should focus on the recognition and management of sepsis as a syndrome, tailored as much as possible to the epidemiology of local infectious diseases. Population-focused strategies that emphasize prevention of infection are critical. Epidemiologic, clinical, and microbiological studies are also required to define the burden and determine the etiology of severe sepsis outside developed countries.

Sepsis is a common presentation of many infectious diseases and is understudied in developing regions, the very areas where it may be most deadly. We submit that research and education on sepsis in resource-constrained environments are of paramount importance to reduce the lethal burden of this syndrome globally.

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### The authors reply:

We believe that Cheng et al. make very good points concerning the applicability of some of the Surviving Sepsis Campaign (SSC) Guidelines in low and middle income countries (LMICs).

The total set of indicators of the sepsis bundles that are currently being used as part of the international Surviving Sepsis Campaign performance improvement program are primarily targeted at hospitals that, although not tertiary academic centers, are better resourced than those in LMICs. Even in well-resourced countries achieving hospital-wide process change that elevates the practice standard to a level that achieves all 11 goals (indicators) in a patient with severe sepsis (less in a patient without sepsis-induced tissue perfusion) is an arduous task. We agree that the critical first 6 hrs of management of severe sepsis and in particular sepsis-induced tissue hypoperfusion is best served by concentration on timely and appropriate antibiotic administration, early fluid resuscitation/hemodynamic management, and source control, all of which are likely adaptable for use in under-resourced environments. These aspects of the SSC guidelines form part of current World Health Organization recommendations for the clinical management of sepsis from human avian influenza (1), the development of which included consideration of the needs and resources of LMICs.

Each hospital should view the recommendations and bundles as best practice and then attempt to do whatever the resources allow. The important thing is to decide what can be done, educate to do it, and score performance. The current grading system may assist in goal selection. We are aware that in some countries with fewer resources, early goal-directed therapy, for example, is being performed with intermittent venous blood gas measurements or central venous pressure measurement alone. But as to intermittent measurement of central venous blood gases as opposed to continuous monitoring, this is also true for some North American and European SSC performance improvement sites where it is not done out of necessity but by choice.

Finally, we would encourage those capable of creating alternative sepsis bundles (based on the guidelines) that could be field tested in poorly resourced environments to do so. There is currently considerable interest on funding improved health in LMICs that should facilitate research and education in sepsis management in these environments. The SSC guidelines target patients who develop severe sepsis, but we do not yet have the scientific knowledge to provide precise guidance on the identification of these patients, clearly an essential first step for adequate treatment. In LMICs, targeting resources toward the prevention of sepsis may be more important than treatment of the developed syndrome. Perhaps it is time for a Preventing Sepsis Campaign.

The authors have not disclosed any potential conflicts of interest.

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Surviving Sepsis Campaign Guidelines 2008: Revisiting vasopressor recommendations

### To the Editor:

We congratulate Dr. Dellinger and colleagues (1) on the updated Surviving Sepsis Campaign guidelines and wish to

comment on their recommendations and suggestions regarding vasopressors. First, in view of the fact that only two prospective studies that included a total of 38 patients have addressed the critical arterial blood pressure limit (2, 3), we feel that the recommendation to maintain a mean arterial blood pressure of  $\geq 65$  mm Hg is not based on sufficient scientific grounds. Since mean arterial blood pressure was only one of several therapeutic goals in the Early Goal Directed Therapy study, its influence on mortality cannot be reliably determined (4). The study by Varpula et al. (5), although highly interesting, was not adjusted for disease severity and bears the significant risk of overestimating the critical blood pressure limit. Second, despite the widespread use of dopamine, there is little scientific evidence to support the recommendation that dopamine (or norepinephrine) should be the first-choice vasopressor agent to correct hypotension in septic shock. In contrast, several studies showed that dopamine is less potent than norepinephrine and carries an unpredictable risk of adverse side effects (6). Third, although limited, current evidence suggests that epinephrine is equally effective as norepinephrine for the therapy of septic shock (7) and does not report any benefit of using epinephrine as an alternative to norepinephrine or dopamine in poorly responsive shock states. More clinical studies indicate that the addition of arginine vasopressin (AVP) improves hemodynamic function and probably survival in some patients (8). Fourth, accordingly, it is wrong to state that an effect equivalent to norepinephrine alone can be anticipated from the addition of AVP to norepinephrine. Because of its nonadrenergic properties, the idea of a supplementary AVP infusion is to limit high, potentially toxic catecholamine dosages without exerting their adverse effects. Fifth, the suggestion not to administer  $>0.03$ – $0.04$  IU/min of AVP, although adopted in the protocol of a recent multicenter trial, is based only on the retrospective finding in one study that higher dosages were associated with a decrease in cardiac index and that five patients who had refractory shock and developed cardiac arrest received AVP at  $>0.04$  IU/min (9). In contrast, a recent study suggested that in advanced shock states, AVP at  $0.067$  IU/min was more effective to restore cardiovascular stability than  $0.033$  IU/min (10).

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### The authors reply:

We thank Drs. Dunser and Hasibeder for their comments about vasopressor therapy in the Surviving Sepsis Guidelines (1).

We will address the points raised by Drs. Dunser and Hasibeder one by one:

1. We agree that the recommendation to maintain a mean arterial pressure of at least 65 mm Hg is somewhat arbitrary and that the need for vasopressor support should be individualized, but we wanted to provide the practitioner with simple recommendations for initial resuscitation. Furthermore, the goal used in the early goal-directed therapy study was derived from the consensus recommendation (2, 3).
2. We agree that dopamine is a less potent vasoconstrictor than norepinephrine, but it may increase blood flow more effectively. There is no prospective randomized evidence to suggest that norepinephrine administration is associated with better outcomes than dopamine. However, a recent observational study did demonstrate an association between dopamine administration and mortality in shock (4). Dopaminergic stimulation may decrease prolactin production, but may also improve blood flow distribution and facilitate the resorption of lung edema (5).
3. We agree there is no good indication for epinephrine as a first-line agent in septic shock.
4. The benefits of vasopressin administration have not been proven (5) and doses higher than 0.03–0.04 IU/min may be harmful (6).

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## New recommendations for the use of corticosteroids in sepsis: Not so fast!

### To the Editor:

The recent Surviving Sepsis Campaign guidelines include a revised recommendation for the use of corticosteroids in patients with severe sepsis (1). On the basis of a recently published randomized controlled trial (2), a weak recommendation was included in the revised guidelines (1). Corticosteroids have been in and out of the clinical scenario for the treatment of sepsis for the last 20 yrs, but their benefits remain uncertain. In this sense, the Corticus study was designed to answer the most imperative questions (2). However, there are significant limitations of this study, including its relatively small sample size with limited power to appropriately evaluate important outcomes, which precludes generalization of the results. Furthermore, these results conflict with those of the French multicenter trial (3). These discrepant results may be explained by differences in the timing of drug administration as well as in patient characteristics. Patients from the French study were apparently more severely ill: They had higher Simplified Acute Physiology Score II, received higher doses of vasopressors, and had higher mortality rates. In addition, there were significant differences in the sites of infection, with an unexpectedly high frequency of abdominal infections

(48% vs. 16%) and a relatively low frequency of pneumonia in the Corticus study (34% vs. 44%) (2, 3). Recently, the infusion of hydrocortisone was shown to improve mortality in patients with severe community-acquired pneumonia (4). Moreover, in a *post hoc* analysis of the French study, steroid therapy was associated with improved survival in patients with sepsis and acute respiratory distress syndrome (60% of them with pneumonia), especially in nonresponders, but not in patients without a diagnosis of acute respiratory distress syndrome (5). Regarding the inclusion criteria, the study by Annane et al. (3) included only patients with very early (<8 hrs) refractory septic shock, whereas patients in the Corticus study were treated later (up to 72 hrs) (2). Timing of drug infusion and disease severity have been associated with different responses to therapeutic interventions in sepsis (1). Also, there is recent evidence of a clinical benefit of steroid administration in patients with documented impairment of the adrenal function (3). Nevertheless, the Corticus study concluded that the corticotropin stimulation test must not be used to guide the decision to offer steroids (2). Random cortisol concentrations are also used for the diagnosis of adrenal insufficiency in highly stressed patients, such as those with severe sepsis. Taking into consideration the patients in the interventional arm, baseline cortisol levels of nonresponders were much lower in the study by Annane et al. than in the Corticus study ( $18 \pm 12 \mu\text{g/dL}$  vs.  $30 \pm 20 \mu\text{g/dL}$ , respectively) but similar in responders ( $30 \pm 16 \mu\text{g/dL}$  vs.  $29 \pm 19 \mu\text{g/dL}$ , respectively) (2, 3). Finally, contrasting with the previous results, higher rates of adverse events, such as hyperglycemia and nosocomial infection, were present in those treated with hydrocortisone in the Corticus study (2, 3). Unfortunately, flaws in patient selection and drug protocol in an underpowered study mean that a new clinical trial is necessary before corticosteroids can be routinely recommended or, alternatively, abandoned in the treatment of severe sepsis.

The authors have not disclosed any potential conflicts of interest.

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### The authors reply:

We thank Drs. Salluh and Soares for their thoughtful comments. We note that they provide an elegant summary of new data that are somewhat discrepant with prior work both with relation to the strength of evidence that steroids reduce mortality in severe sepsis and septic shock, and with the potential role of tests of the adrenal axis to guide therapy. We viewed these discrepancies as widening the uncertainty around the role of steroids in severe sepsis, and this increased uncertainty is reflected in the revised guidelines. We do, however, disagree with them as to quality of the design of the Corticosteroid Therapy of Septic Shock trial.

The revised guidelines used a new grading system which allowed recommendations to be graded for strength, either 1 (strong) or 2 (weak). Because the two largest trials published on effect of treatment of septic shock with steroids had different findings, any recommendation could only be a grade 2. One reason for the different findings could be that the two study populations were different, and we considered separate recommendations for each population. However, such an approach was considered confusing and too complex, given the uncertainty of the evidence. The final statement reflected the only area upon which there was broad agreement: that we would suggest steroids “only” for the subset

of patients for whom there was potential benefit. Limitations in application of both trials’ results to support a precise target population for steroid use led to a quality of evidence of C.

The authors have not disclosed any potential conflicts of interest.

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### Surviving Sepsis Campaign: Guideline Clarification

#### Dear Editor:

We read with great interest the recent update of the Surviving Sepsis Campaign’s guidelines for the management of severe sepsis and septic shock (1). The concerted effort necessary for the compilation of a comprehensive guideline of that scale are immense. Therefore, we applaud the authors for their achievement.

Regarding the choice of vasopressor, we would like to ask the authors to clarify the appraisal of the underlying evidence, as we cannot follow how the evidence stated leads to the guidelines’ recommendation of dopamine and norepinephrine as first choice vasopressors. Current evidence, although critically discussed (2), does not suggest any relevant differences to epinephrine as an alternative choice (3).

The authors applied the much acclaimed Grading of Recommendations Assessment, Development, and Evaluation system (4) suggesting that a systematic review of the literature would have to

be performed before any grading of evidence could take place. Therefore, we would be extremely grateful if the authors could provide the reader with the search strategy and search results related to vasopressor use in sepsis.

Again, we would like to thank the members of the Surviving Sepsis Campaign for their great effort and would support the notion that further high quality guidelines are needed to increase their clinical use. This, together with the current guideline of the Surviving Sepsis Campaign, would further underline the achievements of guideline development of recent years (5).

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### The authors reply:

We appreciate the kind and supportive comments from Seeling and colleagues. These authors write to seek clarifications related to the Surviving Sepsis Campaign guidelines recommendation for first-line vasopressor in septic shock (1).

Concerning the search technique used for delineating literature for use in the evidence-based medicine approach, the search items were clinical trials: vasopressor and sepsis, vasopressor and severe sepsis, vasopressor and septic shock, hypotension and sepsis, hypotension and severe sepsis, hypotension and septic shock, blood pressure and sepsis, blood

pressure and severe sepsis, and blood pressure and septic shock.

The strong (grade 1) recommendation for either dopamine or norepinephrine as the first-line drugs to support blood pressure in the presence of sepsis-induced hypotension is based on the logic of using a combined inotrope/vasopressor, because persistent hypotension after adequate fluid resuscitation is due to some combination of vasodilatation and decreased contractility. Although a beta-agonist will increase heart rate and myocardial oxygen consumption, a pure vasopressor would decrease cardiac index that would decrease macrocirculatory flow. In terms of specific choice, we judged the quality of evidence as *C* on the basis of indirectness of evidence (substitute endpoints in most of the studies), and lack of precision of estimates in the study quoted by Seeling (relative risk for mortality 0.86, 95% confidence interval 0.65–1.14). Despite low overall quality of evidence, we decided on a strong rather than weak recommendation because (a) when looking at the three inotrope/vasopressors available for use, there is human data that raise concern about a decrease in splanchnic blood flow in septic shock with epinephrine compared with norepinephrine and dopamine (2); and (b) as to the alternative of a pure

vasopressor there is human data showing that a pure vasopressor administered in septic shock decreases survival (3). The Annane trial used a protocol driven by cardiac output and blood pressure measurement and demonstrated no difference when comparing epinephrine vs. norepinephrine plus dobutamine (4). However, the outcome was better in the norepinephrine plus dobutamine group and the study could have been underpowered. We do believe that epinephrine should be the first alternative agent in septic shock unresponsive to dopamine and/or norepinephrine.

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