

40 months. Even though no cases of hyperplasia were identified, only 101 of the 150 participants (67%) underwent endometrial biopsy at the end of the treatment. Even a few cases of hyperplasia in the women who did not undergo biopsy would alter the findings. Although there are distinct advantages of levonorgestrel-containing IUDs, including contraception in perimenopausal women and consistent delivery of progestin for up to 5 years, the lack of robust data on safety and the

fact that the use of IUDs requires a procedure for placement and for removal limit their role in postmenopausal hormone therapy.

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## Management of Sepsis

**TO THE EDITOR:** The review by Russell (Oct. 19 issue)<sup>1</sup> recommends the protocol used by Rivers et al.<sup>2</sup> and adopted in the Surviving Sepsis Campaign guidelines<sup>3</sup> for the initial resuscitation in severe sepsis. Although others<sup>4</sup> have warned against the use of this protocol, this warning did not receive the attention we think it deserves. Estimates of intravascular volume based on any given level of filling pressure do not reliably predict the response to fluid administration. In addition, patients with sepsis have characteristically high central venous oxygen saturation because of decreased oxygen extraction. The initial mean central venous oxygen saturation of 50% in the study by Rivers et al. and the high mortality rate raise the possibility that these patients arrived at the hospital in a state of late, untreated, hypovolemic sepsis.<sup>5,6</sup> This may be due in part to reduced access to health care and in part to the cost of care.<sup>5</sup> We believe that the hemodynamic component of these guidelines cannot, at this time, be applied to all patients with sepsis, particularly those in whom sepsis develops while they are in the hospital. Both physiologically and clinically this protocol may be wrong for many patients with sepsis.

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Dr. Perel reports serving on the advisory board of Pulsion Medical Systems, Germany.

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**TO THE EDITOR:** Two points in the article by Russell warrant further discussion. First, in the discussion of early, goal-directed therapy, the author recommends maintaining a central venous pressure of 8 to 12 mm Hg. Surviving Sepsis Campaign guidelines recommend the same central venous pressure but add that in mechanically ventilated patients a higher target central venous pressure, 12 to 15 mm Hg, is recommended to account for the increased intrathoracic pressure.<sup>1</sup> Second, in the discussion about activated protein C, there is one important observation that Russell does not mention. In the Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis (ADDRESS) trial,<sup>2</sup> post hoc analysis of the subgroup of patients who had undergone recent surgery (within the previous 30 days) indicated that surgical patients with single-organ dysfunction who received activated protein C had a higher 28-day mortality than the placebo group (20.7% vs. 14.1%,  $P=0.03$ ). This particular finding triggered a retrospective analysis of the same

subgroup in the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study, and a similar effect was noted.<sup>3</sup> This outcome clearly argues against the use of activated protein C in this subgroup of patients.

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**TO THE EDITOR:** I wish that Russell's review had included a more comprehensive discussion of the role of recombinant human activated protein C. His coverage of the ADDRESS trial results excludes the disturbing data on the subgroups of patients with multiple-organ failure and those with an Acute Physiology and Chronic Health Evaluation (APACHE II) score greater than 24 (approved uses): no treatment benefit was shown, and the 28-day mortality rate was even higher with activated protein C than with placebo.<sup>1-3</sup> In contrast, favorable data on high-risk subgroups in the PROWESS trial are highlighted. The high overall rate of serious bleeding reported in the Extended Evaluation of Recombinant Human Activated Protein C (ENHANCE) trial also deserved comment, in my estimation.<sup>1</sup>

Russell suggests that activated protein C may be useful in the emergency care of patients with sepsis, yet doubts regarding any role for activated protein C have been expressed. Additional concerns have arisen from the PROWESS trial: important differences between study groups in the severity of disease at baseline, especially in higher-risk subgroups<sup>2,3</sup>; inadequate blinding; differences in the rates of do-not-resuscitate orders; the lack of reduced mortality rates at 28 days among patients without severe, long-term illness; disappointing data on discharging patients to home<sup>4</sup>; and the distinct possibility that meeting the

criteria for stopping the trial early occurred by chance.<sup>3</sup>

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**TO THE EDITOR:** The review by Russell states that our randomized, controlled trials investigating the effect of intensive versus conventional insulin therapy in patients in the surgical intensive care unit (ICU) (1548 patients) and the medical ICU (1200 patients) did not include patients with sepsis.<sup>1,2</sup> However, among the mixed medical and surgical populations in these randomized, controlled trials, 950 patients could be identified as having sepsis at the time of admission to the ICU.<sup>3,4</sup> We report here the effect of intensive insulin therapy in the patients with sepsis as compared with the effect in 1798 other patients (Table 1).

Despite a higher incidence of hypoglycemia among patients with sepsis than among those without sepsis (intensive insulin therapy, 20% vs. 7%;  $P < 0.001$ ; conventional insulin therapy, 3% vs. 1%;  $P = 0.02$ ), the effect of intensive insulin therapy on the outcome for patients with sepsis was similar to the effect on the outcome for other patients. This post hoc analysis lacked the statistical power to prove that the observed 4% absolute reduction in mortality was significant in an intention-to-treat analysis (this would require 2200 patients per group). However, the 8% absolute reduction in mortality and the 21% reduction in critical illness polyneuropathy among patients with sepsis and long stays in the ICU who were treated with intensive insulin therapy were significant, and the analysis did not reveal harm to

Characteristic	Patients with Sepsis (N=950)†			Other Patients (N=1798)			P Value for Patients with Sepsis vs. Other Patients
	Conventional Insulin Therapy (N=471)	Intensive Insulin Therapy (N=479)	P Value	Conventional Insulin Therapy (N=917)	Intensive Insulin Therapy (N=881)	P Value	
<b>Baseline characteristics</b>							
Age — yr	61±16	62±15	0.30	64±14	64±14	0.80	0.001
Body-mass index‡	25±5	25±5	0.40	26±5	26±5	0.40	<0.001
Male sex — no. (%)	295 (63)	335 (70)	0.02	644 (70)	565 (64)	0.006	0.60
Medical ICU — no. (%)	307 (65)	307 (64)	0.70	298 (32)	288 (33)	0.90	<0.001
APACHE II score	20±10	20±10	0.80	13±8	13±8	0.20	<0.001
Ventilated — no. (%)	434 (92)	431 (90)	0.30	752 (82)	721 (82)	0.90	<0.001
History of diabetes — no. (%)			0.08			0.90	<0.001
No diabetes	414 (88)	400 (84)		774 (84)	753 (85)		
Insulin-treated diabetes	27 (6)	54 (11)		57 (6)	50 (6)		
Diabetes treated with diet, oral anti-diabetic drugs, or both	30 (6)	25 (5)		86 (9)	78 (9)		
Cancer — no. (%)	139 (30)	142 (30)	0.90	108 (12)	114 (13)	0.50	<0.001
Blood glucose level at admission — mg/dl	161±70	163±73	0.60	147±55	141±49	0.009	<0.001
ICU stay ≥3 days — no. (%)	324 (69)	345 (72)	0.30	378 (41)	342 (39)	0.30	<0.001
<b>Insulin therapy</b>							
Blood glucose level — mg/dl	150±30	106±26	<0.001	152±33	104±22	<0.001	0.40
Mean blood glucose strata — no. (%)§			<0.001			<0.001	0.40
<110 mg/dl	24 (5)	330 (69)		63 (7)	605 (69)		
110–150 mg/dl	225 (48)	127 (27)		414 (45)	247 (28)		
>150 mg/dl	219 (46)	18 (4)		437 (48)	23 (3)		
Daily insulin dose — IU/day			<0.001			<0.001	<0.001
Median	6	66		0	55		
Interquartile range	0–35	45–95		0–16	35–78		
Lowest blood glucose level — mg/dl	92±29	56±21	<0.001	102±27	66±19	<0.001	<0.001
Patients with hypoglycemia (blood glucose level, ≤40 mg/dl at any time) — no. (%)	14 (3)	94 (20)	<0.001	11 (1)	60 (7)	<0.001	<0.001
<b>Outcome measures</b>							
Kidney injury — no. (%)	49 (10)	34 (7)	0.07	58 (6)	27 (3)	0.001	<0.001
In ICU ≥3 days — no./total no. (%)	45/324 (14)	32/345 (9)	0.06	56/378 (15)	24/342 (7)	0.001	
In ICU <3 days — no./total no. (%)	4/147 (3)	2/134 (1)	0.50	2/539 (<1)	3/539 (<1)	0.70	
Critical illness polyneuropathy — no. (%)¶	114/214 (53)	69/216 (32)	<0.001	102/222 (46)	58/173 (34)	0.01	0.60
Death in the ICU — no. (%)	128 (27)	112 (23)	0.17	97 (11)	67 (8)	0.03	<0.001
In ICU ≥3 days — no./total no. (%)	110/324 (34)	91/345 (26)	0.03	85/378 (22)	58/342 (17)	0.06	
In ICU <3 days — no./total no. (%)	18/147 (12)	21/134 (16)	0.40	12/539 (2)	9/539 (2)	0.50	

**Table 1. (Continued.)**

Characteristic	Patients with Sepsis (N=950) <sup>†</sup>			Other Patients (N=1798)			P Value for Patients with Sepsis vs. Other Patients
	Conventional Insulin Therapy (N=471)	Intensive Insulin Therapy (N=479)	P Value	Conventional Insulin Therapy (N=917)	Intensive Insulin Therapy (N=881)	P Value	
Death in the hospital — no. (%)	172 (37)	160 (33)	0.30	155 (17)	117 (13)	0.03	<0.001
Odds ratio (95% CI)		0.87 (0.67–1.13)	0.30		0.75 (0.58–0.97)	0.03	
Odds ratio corrected for hypoglycemia (95% CI)		0.72 (0.54–0.95)	0.02		0.63 (0.48–0.82)	<0.001	
Odds ratio for patients with hypoglycemia (95% CI)	2.8 (1.8–4.2)		<0.001 <sup>  </sup>	6.5 (3.9–10.8)		<0.001 <sup>  </sup>	
In ICU ≥3 days — no./total no. (%)	142/324 (44)	124/345 (36)	0.03	124/378 (33)	83/342 (24)	0.01	
Odds ratio (95% CI)		0.72 (0.52–0.98)	0.03		0.66 (0.47–0.91)	0.01	
Odds ratio corrected for hypoglycemia (95% CI)		0.57 (0.41–0.79)	<0.001		0.52 (0.37–0.74)	<0.001	
Odds ratio for patients with hypoglycemia (95% CI)	2.9 (1.8–4.6)		<0.001 <sup>  </sup>	4.4 (2.5–8.0)		<0.001 <sup>  </sup>	
In ICU <3 days — no./total no. (%)	30/147 (20)	36/134 (27)	0.20	31/539 (6)	34/539 (6)	0.70	
Odds ratio (95% CI)		1.4 (0.82–2.49)	0.20		1.1 (0.67–1.82)	0.70	
Odds ratio corrected for hypoglycemia (95% CI)		1.4 (0.80–2.46)	0.20		1.0 (0.63–1.76)	0.80	
Odds ratio for patients with hypoglycemia (95% CI)	1.3 (0.4–4.5)		0.70 <sup>  </sup>	3.6 (1.0–13.3)		0.05 <sup>  </sup>	

\* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. APACHE denotes Acute Physiology and Chronic Health Evaluation, and CI confidence interval.

<sup>†</sup> Sepsis was defined according to modified Bone criteria<sup>4</sup> as suspected or documented infection on the day of admission to the ICU and fulfillment of at least two of the three criteria for the system inflammatory response syndrome for which data were available (i.e., receiving ventilatory support, white-cell count ≤4000 or ≥12,000 per cubic millimeter, and body temperature ≤36°C or ≥38°C). Patients who had had cardiac surgery or trauma were excluded for this definition.

<sup>‡</sup> The body-mass index is the weight in kilograms divided by the square of the height in meters.

<sup>§</sup> Among the patients with sepsis, data on blood glucose levels were not available for three patients receiving conventional insulin therapy and four patients receiving intensive insulin therapy. For other patients, such data were not available for three patients receiving conventional insulin therapy and six patients receiving intensive insulin therapy.

<sup>¶</sup> Critical illness polyneuropathy was diagnosed with the use of electromyography by an investigator who was unaware of the patients' treatment status. Data are for patients who were screened (i.e., those who were in the ICU ≥7 days).

<sup>||</sup> The P value is for the comparison of patients who had hypoglycemia with those who did not.

patients treated with intensive insulin therapy for less than 3 days.

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**THE AUTHOR REPLIES:** Perel and Segal suggest that filling pressures do not reliably predict the response to fluid. Central venous oxygen saturation was very low in the study by Rivers et al.<sup>1</sup>;

thus, they studied late, untreated hypovolemic sepsis. Relationships among central venous oxygen saturation, intravascular volume, fluid therapy, and outcomes are complex. The study by Rivers et al. is the only adequately powered trial of early, goal-directed therapy; unfortunately, there are no similar trials regarding inpatients with sepsis. Although other investigators have found higher initial central venous oxygen saturation in patients with sepsis in the emergency setting<sup>2</sup> than did Rivers et al., additional studies are needed to describe the range of baseline values for central venous oxygen saturation in such patients.

Khurana and Vinayek suggest that ventilated patients require higher central venous pressure because of increased intrathoracic pressure; I agree. The study by Rivers et al.<sup>1</sup> suggests that the response of the central venous pressure (and central venous oxygen saturation) to fluid challenge may be helpful in assessing fluid resuscitation. I agree that surgical patients who have single-organ dysfunction are at increased risk for death when they are treated with activated protein C and therefore should not receive this treatment.

Mackenzie and Bartelink note that there was “no treatment benefit . . . and the 28-day mortality rate was even higher with activated protein C than with placebo” in a subgroup of high-risk patients in the ADDRESS study.<sup>3</sup> The APACHE II high-risk subgroup of the ADDRESS trial was small (324 patients), and the power was only 0.63 (to refute the mortality results in the PROWESS trial in high-risk patients absolutely); thus, it is difficult to determine statistically whether the subgroup result in the ADDRESS trial is a true negative result. The bleeding rates in the ENHANCE trial are difficult to assess because there was no concurrent control group; however, I would re-emphasize the need for careful assessment and monitoring of patients treated with activated protein C. Mackenzie and Bartelink raise concerns regarding the PROWESS trial (my responses are in parentheses), such as baseline characteristics (overall, they were balanced; also see Ely et al.<sup>4</sup>), inadequate blinding (difficult to assess without

data about outcomes), do-not-resuscitate rates (difficult to compare with other studies, since do-not-resuscitate orders are underreported), chronic illness (post hoc subgroup analysis with inadequate power), disappointing rates of discharge to home (overall discharge rate was significantly higher [ $P=0.03$ ]<sup>5</sup> with activated protein C, especially in the high-risk APACHE II subgroup), and early stopping by chance (the overall  $P$  value of 0.005 suggests a 5 in 1000 chance of a false positive result).

I thank Van Cromphaut and colleagues for reporting on subgroups of patients with sepsis from their trials of intensive insulin therapy.<sup>6,7</sup> They argue that intensive insulin therapy decreased mortality among patients with sepsis who had a long stay in the ICU ( $\geq 3$  days). This post hoc subgroup analysis is hypothesis generating and indicates the need for a trial that examines the association between the duration of the ICU stay and intensive insulin therapy in patients with sepsis.

Before the publication of my article, I informed the *Journal* that I had received grant support from Eli Lilly, Chiron, and Glaxo. This information was inadvertently omitted from the article.

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