Letters to the Editor

Re: Hypothermia reduces resistance to surgical wound infections

To the Editor,—

A recent study by Barone et al.¹ (The American Surgeon, 65:356–359, April 1999) criticizes our study of surgical wound infections that was published in the New England Journal of Medicine in 1996.² Their paper includes a number of curious assertions. For example, the authors wrongly conclude that we included the preoperative period in our calculations of hospital duration. In fact, only the postoperative days were considered. (The duration was long, but this is typical in Europe where financial pressures remain less intense than in the United States.) The authors’ criticism of this point seems strange because their own results show a 16 per cent prolongation in hospitalization, which is exactly what we reported. The fact that our result was statistically significant whereas theirs was not quite significant simply indicates that the study of Barone et al.¹ was under-powered (i.e., a type II statistical error).

Barone et al.¹ also express concern because our hypothermic patients were given more allogenic blood than those kept normothermic. This is a natural consequence of the coagulopathy induced by hypothermia² and would be expected in any randomized trial. However, our report specifies that all of the blood in our study was leukocyte depleted; it is well established that this procedure eliminates the correlation between transfusion and infection.⁴ Furthermore, multivariate regression indicated that transfusion requirement did not independently contribute to the incidence of wound infections. It is, thus, unlikely that observed temperature-dependent differences in the incidence of infection resulted from transfusion-mediated immune suppression.

Barone et al.¹ further criticize our study because smoking was more common among our patients than theirs. However, we fail to understand how this would influence our conclusions because the prevalence of smoking did not differ in the hypothermic and normothermic groups. They then comment that “the obvious solution is to repeat the study excluding smoker because smoking may be a factor in contributing to poor wound healing.” A more practical approach might be multivariate analysis to eliminate the contribution of smoking to the incidence of infection. This is the approach we used, and a nonlinear, mixed-effects model is reported in our paper. The results clearly indicate that hypothermia is an independent predictor of infection.

The methodology of Barone et al.¹ also deserves attention, especially given the well-known limitations of uncontrolled, retrospective studies. A key issue is temperature monitoring. Distal esophageal temperature is an excellent indicator of core temperature. However, values can be wrong by several °C when the probe is positioned in its usual proximal position for optimal monitoring of breath sounds.⁹,¹⁰ It is unlikely that the probes in these retrospectively studied patients were properly positioned. Core temperatures during recovery were measured “using a tympanic membrane sensor.” This presumably was an infrared aural canal sensor rather than a thermocouple carefully positioned on the tympanic membrane. This is a critical issue because numerous studies indicate that infrared aural canal monitors are remarkably inaccurate.¹¹,¹²

A more serious concern is the authors’ arbitrary decision to exclude readmissions they believe unrelated to surgery. On what basis was this decision made? Were patients excluded by an independent investigator blinded to core temperature? In this case, we need to at least consider the possibility that the responsible surgeons might be somewhat biased in their determinations of which complications were related to surgery. To the extent that the authors believe that their groups are otherwise comparable, a firm rule of statistical analysis is to consider all outcomes re-
lated to the factor of interest. Without this ill-advised post hoc exclusion, their data show that readmission was significantly increased by hypothermia. Barone et al. make a similar error in concluding that the significance of delayed solid-food intake in our study was unclear because “the decision to start feeding was not standardized.” (If it had been standardized, the results would have been identical in each group.) The major point of randomized, blinded trials is precisely to identify such important outcomes especially when, as in our case, it was a prospectively defined factor of interest.

There also appears to be a number of numerical errors in the study of Barone et al. For example, they define hypothermia as a “temperature less than 95.5°F (34.3°C)” at any time during or after surgery (page 357, paragraph 1). However, the 95.5°C is actually 35.3°C, which presumably explains why the average “lowest recorded temperature” in the hypothermic patients exceeds the stated hypothermic criteria (Table 1). The authors specify that their overall infection rate was 6 per cent (Page 357, paragraph 5). However, the incidence reported in Table 4 and in the Discussion section is 12 per cent, which is typical in these patients.

Table 4 also indicates that postoperative length of stay did not differ significantly, with a P value of 0.258. However, the text on page 358, paragraph 4, states that the P value is nearly statistically significant at 0.058. It is difficult to interpret the reported data because the manuscript violates a basic statistical rule in failing to indicate whether variance is reported as standard errors or standard deviations. Assuming the latter though, the P value of 0.258 is incorrect. These are simply examples of obvious inconsistencies within the authors’ manuscript; one wonders what other careless errors may have contributed to their conclusions.

We also fail to understand why the authors cited and discuss a small retrospective study by Frank et al. (page 359, paragraph 4). The same group subsequently published a large prospective, randomized, and blinded trial that was published to considerable acclaim in the Journal of the American Medical Association. Similarly, the authors cite a study showing that hypothermia slightly impairs enzymatic aspects of clotting. However, they fail to mention the far more important effect of hypothermia on platelet function, an effect mediated by reduced release of thromboxane A2. The authors then curiously conclude that “the impact of this information on patient outcome has yet to be studied.” Although this article was cited in our study of wound infection, the authors seem unaware that we published a prospective randomized trial in Lancet in 1996 showing that even mild hypothermia increases blood loss and allogeneic transfusion requirements. Numerous subsequent studies have confirmed this finding.

In summary, we do not accept the assertion of Barone et al. that their retrospective uncontrolled analysis invalidates the results of our multicenter, prospective, randomized, and blinded trial.

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REFERENCES


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Authors' response:
We are happy to respond to Drs. Sessler, Kurz, and Lenhardt, but are disappointed that such distinguished academicians have attempted to defend their work with the degree of condescension and number of gratuitous insults expressed in their letter. We will address their comments in order.

Although Sessler et al. state that their hospital length of stay included only the postoperative period, they consistently used the terms “number of days of hospitalization” or “duration of hospitalization” in both the Methods and Results sections of their paper.1 It is unclear how the reader would have been expected to infer that they meant only postoperative length of stay.

The fact that more patients in the hypothermia group in their paper received blood has implications beyond the putative immunosuppressive effects of the transfusions. More blood transfusions might indicate that the cases were more difficult and, thus, more prone to infection. The number of patients receiving transfusions in their series seems to be quite high and not typical of colorectal surgery practice in the United States.2 Many more of their patients received transfusions than did ours, a difference that is statistically significant. The comparison of the use of blood in both series is illustrated in Table 1. In addition, the hypothermic patients in the Kurz1 paper received an average of twice as much blood as the normothermic patients, a statistically significant difference. Although it is possible that the hypothermia resulted in more blood loss, it is also possible that the hypothemic patients in their series were sicker or required more technically resections.

We accept their comment on the issue of smoking. As far as the difference in temperature monitoring techniques, we feel that any errors induced in our paper would at least have been consistent over the entire patient population. The 49 hypothermic patients still would have been colder than the normothermic patients.

We have no idea what Sessler and colleagues are referring to when they question our supposed exclusion of patient readmissions. Our Table 6 explicitly identifies all readmissions, which were broken down into those related or unrelated to surgery in an effort to more fairly describe the patient groups. If all readmissions are considered, the Table 6 clearly shows that the normothermic patients had a significantly higher rate of readmission.

The comment about the typographical errors in our paper is valid. However, such errors can be found in the writings of even the most scholarly individuals. For example, the original letter of Sessler et al. contained six typographical or grammatical errors. Some of their errors are as follows: subject and verb disagreements ("... results clearly indicates..." and "... esophageal temperatures is..."), absence of an apostrophe ("authors" on page 4, first line of the second full paragraph); redundant words "Table 4 four" on page 5; use of the word “later” when they meant “latter.” None of our typographical errors alter the results or conclusions of our paper.

They criticize our statistical analysis of the postoperative length of stay of our patients. We would like to

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<th>Table 1. Number of Patients Transfused/Total Number of Patients (%)</th>
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*χ², patients in series of Kurz et al. versus Barone et al.
point out an important fact. The data were not normally distributed, as we are certain was the case with Kurz's data. Because there are usually very few early discharges, length of stay nearly always results in a Poisson distribution. (see Fig. 1) A $t$ test is inappropriate. The correct test of comparison of groups in this instance is the Mann-Whitney rank sum test, which is what we used. The correct $P$ value was 0.258. Furthermore, length of stay is a very soft end point that may be affected by factors not directly related to a patient's condition, such as ability or willingness of the patient or family to care for the patient at home and availability of transitional care beds (skilled nursing facility, rehabilitation, or other facility).

We never stated that the paper of Kurz et al. was "invalid." We simply stated that we did not see an increased infection rate in our hypothermic patients. We wonder if Sessler and his group are so defensive because of the response to their paper. Four letters critical of their paper were published in the New England Journal of Medicine.\textsuperscript{1-4} Sessler and Kurz responded to these criticisms and brought to light more information about their paper. Regarding a question about the actual temperatures of patients with and without infection in their paper,\textsuperscript{5} they responded that the mean temperature of those with infection was $35 \pm 1\,^{\circ}\mathrm{C}$ versus $35.8 \pm 1.1\,^{\circ}\mathrm{C}$ in those without.\textsuperscript{7} This raises the issue of whether a $0.8\,^{\circ}$ mean difference in core temperature, while statistically significant, is really clinically significant? Also, because the standard deviations overlap, the true significance of this temperature difference is hard to assess. For example, if a patient had a temperature of $35.4\,^{\circ}\mathrm{C}$, would he be more or less prone to infection? In addition, Sessler and Kurz stated that their wound infection rate might have been higher because their "... university-based population had a substantial degree of underlying disease." It is interesting to note that patient comorbidities were not mentioned in the actual paper of Kurz et al. Perhaps their infected patients simply had more comorbidities.

We would also point out that their multicenter trial, which took place over a 21-month period, included 155 patients from one center, 30 patients from another center, and 15 patients from yet another. Why were so few patients from the other two hospitals (less than one per month in one center) enrolled? Could this have confounded their results? And, as noted in the editorial comments of Mortensen and Garrard,\textsuperscript{6} the number of wound infections at each center was not stated.

We stand by our results and leave the resolution of these issues to the discerning reader. We agree with Mortensen and Garrard\textsuperscript{6} that more studies on the subject are necessary.

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