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Comment on "Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008" by Dellinger et al.

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Sir: We read with interest the recent revision of the Surviving Sepsis Campaign (SSC) guidelines by Dellinger et al. [1]. The use of the GRADE system to classify the strength of the recommendations has certainly improved the guidelines. However, we regret that not all guidelines were adjusted according to the current literature.

First of all, the absence of a recommendation regarding selective digestive tract decontamination (SDD) is striking. The guidelines group was evenly split, with equal numbers weakly in favor and against recommending the use of SDD. This is remarkable, since SDD is one of the best ever evaluated therapies in intensive care medicine, with more than 50 randomized controlled trials and 10 meta-analyses showing that SDD reduces pneumonia by 65% and mortality by 22% [2].

The authors gave several reasons why they chose not to recommend SDD in their guidelines. They argue that no studies regarding SDD specifically focused on septic patients. However, several other guidelines based on general ICU populations (i.e., stress ulcer prophylaxis, deep vein thrombosis prophylaxis, glucose control and bicarbonate therapy) received strong recommendations.

Furthermore, the authors state that studies comparing SDD with non-antimicrobial interventions, such as ventilator bundles, are needed. Are they seriously suggesting that until these studies have been performed a therapy with proven high efficiency should be withheld from patients with severe sepsis? It seems that no scientific arguments, no study whatsoever could change the apparently biased authors.

The main argument against the use of SDD is the persistent concern regarding emergence of antimicrobial resistance in critically ill patients. Antimicrobial resistance was not a clinical problem in 10 SDD studies monitoring resistance for 2–9 years [3–11]. SDD even seemed to reduce the resistance of aerobic Gram-negative bacilli, the target microorganisms of SDD [12, 13], possibly because the addition of enteral to parenteral antimicrobials prevents spontaneous mutation of target bacteria and eradicates mutants. In their "rationale" the authors are especially concerned about emergence of resistant Gram-positive infections. The SDD prophylaxis is not active against vancomycin-resistant enterococci (VRE) and methicillin-resistant *S. aureus* (MRSA) and may promote gut overgrowth of these intrinsically resistant bacteria. Therefore, in ICUs with endemic MRSA enteral vancomycin is required as a component of SDD. VRE did not emerge in any of the studies using enteral vancomycin, and there is no evidence that SDD promotes infection due to Gram-positive bacteria [14–19]. On the contrary, the continued use of only systemic antibiotics may lead to a further rise in drug-resistant Gram-positive bacteria. We propose, therefore, that the authors of the SSC guidelines use the available literature instead of their bias.

Secondly, the strong recommendation in favor of the use of stress ulcer prophylaxis is not, in our view, in line with currently available evidence. This recommendation is, like that in the guidelines of 2004, still mainly based on ancient studies performed in the 1980s [20–23], a meta-analysis from 1991 [24], and a large trial in 1998 [25] without a control arm. However, the most recent meta-analysis [26] shows no reduction of clinical important bleeding – but is somehow completely ignored. Whether the results of these older trials are applicable nowadays is questionable, since the incidence of stress ulcer-related bleeding has significantly decreased over recent decades due to improved ICU treatment [27, 28]. This definitely affects the balance between the benefit of prevention of gastro-intestinal bleeding and the increased risk of ventilator-associated pneumonia due to higher stomach pH [29]. Several recent trials show comparable rates of bleeding and endoscopic evidence of stress-related injury between treatment and placebo groups [30–33]. These results are pathophysiologically plausible, since stress ulcers are caused not by increased secretion of gastric acid, but by splanchnic hypoperfusion. Unfortunately, many recent trials only compare H2 blockers with proton pump inhibitors, without a placebo group. Altogether, according to the most recent meta-analysis and the more recent trials, a strong recommendation not to use stress ulcer prophylaxis would be more appropriate.

Thirdly, we disagree with the strength of the recommendation to reduce blood glucose levels in patients with severe sepsis. On the current evidence, this should be at most a weak recommendation. The beneficial effect of intensive insulin therapy has been demonstrated only in surgical patients, not in septic patients [34–36]. The benefit versus

harm balance of intensive insulin therapy may be quite different for patients with severe sepsis than for the investigated surgical patients. It is not unreasonable to assume that septic patients may be more at risk for hypoglycemia, because sepsis may be associated with a deficiency of counterregulatory hormones. In the study of medical patients by van den Berghe [36], as well as the VISEP study [35] and the Glucontrol study [34], the risk of hypoglycemia was substantially increased, and hypoglycemia was an independent risk factor for mortality. None of these studies followed up the patients with hypoglycemia for neurocognitive impairment. Furthermore, the target glucose level of <150 mg/dl recommended in the guidelines is based solely on expert opinion and is not supported by data from any trial. Therefore, the beneficial effect, the harmlessness, and the target glucose level of intensive insulin therapy remain to be demonstrated in septic patients.

In conclusion, the revised SSC guidelines have certainly been improved by the use of the GRADE system to classify the strength of the recommendations. However, a strong recommendation in favor of the use of SDD should have been implemented. The strong recommendations in favor of stress ulcer prophylaxis and glucose control are not in line with current evidence.

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