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World Health Organization Responds to Concerns about Surgical Site Infection Prevention Recommendations

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To the editor:

We read with great interest the editorial by Hedenstierna et al.[1] on the recent World Health Organization (WHO) guidelines for the prevention of surgical site infections (SSIs). Some of the issues raised have been already addressed in Lancet Infectious Diseases in response to previous comments.[2,3]

It is important to note that guidelines developed by WHO are not based simply on meta-analyses, as suggested by Hedenstierna et al. Rather, WHO uses the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to rate the quality of a body of evidence and to produce information that is used by guideline panels to formulate recommendations. This includes carefully considering the balance of benefits and harms and aspects related to patient values and preferences, resource implications, feasibility, and acceptability.[4] The guideline panels are composed of international experts from several countries and with different professional and cultural backgrounds.[5] Through this process, the issues raised by Hedenstierna et al. were examined, and the panel consensus deemed it appropriate to formulate a recommendation for this intervention.

Hedenstierna et al. argue that the administration of an 80% fraction of inspired oxygen (Fio_2) in surgical patients does not lead to a reduced risk of SSIs. Our meta-analysis of all available randomized controlled studies at that time (n = 15) indicated that 80% Fio_2 may reduce SSI incidence.[6] However, there was substantial clinical and statistical heterogeneity in the studies, and the 95% CI included no effect (odds ratio [OR] 0.84; 95% CI, 0.66 to 1.06). Upon detailed review, the guideline panel reasoned that an important portion of the heterogeneity was related to differences in the patient population characteristics and delivery of the intervention. Subsequently, subgroup and metaregression analyses were done to investigate the sources of the heterogeneity. These analyses showed robust evidence for a reduction of SSIs in patients under general anesthesia with endotracheal intubation receiving 80% Fio_2, and the panel decided that this intervention should be recommended for this group (OR: 0.72; 95% CI, 0.55 to 0.94). We emphasize that the recommendation is not only based on this subgroup, it is strictly limited to it. There is no generalization of this recommendation to other patients, unlike the recently published recommendations by the American College of Surgeons and Surgical Infection Society, who recommend it for all patients undergoing general anesthesia.[7] Of note, the WHO recommendation for this group of patients was recently echoed in the Centers for Disease Control and Prevention guideline for the prevention of SSIs.[8]

Hedenstierna et al. are concerned about the lack of “solid and large trials.” We agree that such trials would have made the panel’s task easier, but in their absence, the panel had to make recommendations based on the best available evidence from smaller trials. The combined sample size from these trials exceeded the optimal information size by a large margin, and there was thus no serious imprecision.[9] Of note, the largest trial included more than 2,000 patients and showed a

statistically significant reduction in SSIs.[10] Hedenstierna et al. suggest that if we had excluded this study, which used 70% nitrous oxide (N_2O) in place of oxygen in the control group, the effect would no longer be statistically significant. Excluding this trial post hoc would be inappropriate because it met all the inclusion criteria of the systematic review. To address the concerns raised, we conducted a subgroup analysis of trials without the use of N_2O. The estimate from these trials was in line with the overall effect (OR 0.74; 95% CI, 0.58 to 0.95), and there was no evidence for modification of the effect of 80% Fio_2 dependent on whether or not patients received N_2O. The results from all other trials were compatible with a reduction in SSIs, except for one small outlying trial.[11] There was little evidence that results differed between trials at higher and lower risk of bias, and risk of bias was generally low.

The study by Kurz et al.[12] was not included because it was published outside the predetermined time period of our review. We included this study in a post facto analysis, and we found little effect on the estimates: OR 0.75 (95% CI, 0.59 to 0.96) including the Kurz et al. study versus OR 0.72 (95% CI, 0.55 to 0.94) when excluding it.

The editorialists also expressed concern about potential harms of hyperoxia. However, the literature cited in support of these concerns is based on evidence from settings that differ from the routine clinical settings our recommendations relate to, for example, intensive care units or an animal model.[1] In the review of studies used for our analysis, which included more than 5,000 patients, no evidence of excess pulmonary dysfunction (atelectasis, pneumonia) was found in the groups of patients treated with 80% Fio_2. Furthermore, the WHO guidelines state that patients with chronic lung disease were excluded from most trials, and therefore our recommendation does not apply to these patients.

Finally, Hedenstierna et al. used unfortunate language suggesting that we advocated for in-hospital production of oxygen, which would be a gross misrepresentation of the WHO guidelines. The guidelines highlight that the production or procurement of oxygen is an additional cost for the healthcare facility or patient in resource-limited settings. We did not suggest, nor intend to suggest, that oxygen local production should be given priority in low-income countries. Several panel members from low- and middle-income countries contributed to formulating the text and were confident that the guidelines adequately informed decision-makers in resource-limited settings.

Competing interests

The authors declare no competing interests.

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