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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In Reply:

We thank Dr. Solomkin *et al*. for their Letter to the Editor regarding our critical editorial on perioperative hyperoxia and surgical site infection (SSI).[1] A Letter was expected and desirable to settle issues where we are at variance. We will therefore make fully clear that we are not arguing against the statistical tools that have been used to calculate the meta-analyses that serve as the basis for the World Health Organization (WHO) recommendations for perioperative hyperoxia. We are also pleased to read that the WHO panel considers their primary analysis of perioperative hyperoxia to prevent SSI statistically insignificant and with high heterogeneity.

What we were concerned with, and still are, is how this can form the basis for a strong recommendation with moderate quality of evidence.[2] Our concerns are based on two major points:

1. Quality of evidence from randomized clinical trials starts according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach as "high-quality evidence" on the scale: high-, moderate-, low-, very low-quality evidence.[3,4] However, it may be downgraded for several reasons within the domains of (1) study limitations, (2) indirectness of evidence, (3) inconsistency of results, (4) imprecision of results, and (5) publication bias. The WHO recommendation for SSIs is "moderate-quality evidence" (that is, downgraded one level due to inconsistency),[2] but this is in contrast to the current Cochrane review, [5] which interprets evidence from almost the same trials as "low quality of evidence" (that is, downgraded two levels due to risk of bias and imprecision).[5]

Available evidence from trials investigating perioperative hyperoxia for SSI comes from trials of which approximately two thirds are at high or unclear risk of bias,[2,5] and quality of evidence should therefore be downgraded one level for overall risk of bias.[5] Imprecision of results is also an issue, because the CI is wide (*e.g.*, from a 44% relative risk reduction to a 6% relative risk increase for SSI in the primary WHO analysis).[2] Another limitation is the inconsistency of results, because the high overall heterogeneity is not eliminated in the subgroup of patients undergoing general anesthesia with endotracheal intubation (I^2 = 44%, P = 0.05), although the reasons for undertaking the *post hoc* subgroup analyses is stated to be identification of reasons for heterogeneity. In addition, we cannot see the scientific basis as to why the WHO panel "reasoned that an important portion of the heterogeneity was related to differences in the patient population characteristics and delivery of the intervention."

Higgins and Green[4] strongly advise against performing numerous *post hoc* subgroup analyses, because "it is usually possible to find an apparent, but false, explanation for heterogeneity by considering lots of different characteristics." We are still not able to understand the biologic difference between administering oxygen through a face mask or through an endotracheal tube. Although we acknowledge

that the quality assessment is a unique consideration for each meta-analyst group, the factors above convince us that we currently have "low quality of evidence."

2. Strength of recommendations can be classified as strong or weak, and strong recommendations should be given "when the desirable effects of an intervention clearly outweigh the undesirable effects. . . . On the other hand, when the trade-offs are less certain—either because of low quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced—weak recommendations become mandatory."[3,4]

Some of the available evidence for undesirable effects of perioperative hyperoxia were described in our editorial, and the support for the recommendations would have been even weaker today with new studies coming out that do not agree with the recommendations. The PeRioperative OXygen fraction – effect on surgical site Infection and pulmonary complications after abdominal surgery (PROXI) trial found higher long-term incidence of myocardial infarction[7] and shorter cancer-free survival[8] in the 80% oxygen group, which of course are hypothesis-generating findings. A registry study in almost 74,000 noncardiothoracic surgeries found that high intraoperative oxygen concentrations were associated in a dose-dependent manner with major postoperative respiratory complications and with 30-day mortality.[9] Thus, hyperoxia can be harmful, and we are not convinced of a positive trade-off between desirable and undesirable effects of hyperoxia. We would therefore support a weak recommendation for effect on SSI in intubated patients. Another prospective study, larger than any previous one, shows so far no benefit of perioperative hyperoxia for SSI (written personal communication with Andrea Kurz, M.D., Department of Outcomes Research, Cleveland Clinic, Cleveland, Ohio, June 2017).

In addition to the studies during anesthesia, there are many studies documenting that providing hyperoxic gas to a normoxic patient may rather worsen than improve the conditions and outcome. A recent study on myocardial infarction concluded that routine use of supplemental oxygen to patients without hypoxemia did not improve outcome, and 1-yr mortality was similar between hyperoxic and normoxic groups.[10] An editorial to the paper made it even more clear: "supplemental oxygen offers no benefit in patients with acute myocardial infarction who had normal oxygen saturation."[11] Similar conclusions have been drawn regarding hyperoxic gas to normoxic stroke patients[12] and in a review on post cardiac arrest, traumatic brain injury, and sepsis.[13] These studies can be added to the list already mentioned in our critical editorial. Admittedly, all these studies relate to patients with severe disease who were normoxic. The anesthetized patient is also normoxic unless specific complications have occurred.

We have misinterpreted in-hospital production of oxygen and apologize for the unfortunate language. However, in summary, additional studies do not support the WHO recommendation, and we would categorize the effect of hyperoxia to prevent SSI in patients under general anesthesia with endotracheal intubation to merit, at the most, a weak recommendation based upon low-quality evidence. We insist on claiming that high arterial oxygen concentrations are scarcely useful and can be harmful when given to patients with or without preexisting lung disease.

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Competing Interests

The authors declare no competing interests.

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Preoperative Prediction of Chronic Postsurgical Pain after Thoracotomy: Need for Adequately Sized Population-based Samples

To the Editor:

The article by Bayman *et al.*,[1] evaluating predictors of chronic pain 6 months after thoracic surgery, provides important evidence of the high incidence and severity of chronic postsurgical pain (CPSP) after both thoracotomy and video-assisted thoracic surgery. However, we are surprised the authors found that none of the preoperative factors studied (demographics, psychosocial variables, pain, or quantitative sensory testing) were associated with the emergence of CPSP in this setting, unlike other postsurgical settings.

In a prospective multicenter cohort study published in this journal in 2015,[2] we enrolled 503 patients scheduled for thoracotomy (part of a mixed surgical cohort of 2,929) and confirmed CPSP by physical examination at 4 months. We found an incidence of CPSP at 6 months that was similar to the rate of 33% reported by Bayman *et al.*,[1] and we were able to build a preoperative risk model that identified more than 73% of the CPSP cases. Risk was based on six preoperative variables: (1) surgical procedure, (2) age, (3) physical health (Short Form Health Survey-12), (4) mental health (Short Form Health Survey-12), (5) preoperative pain in the surgical field, and (6) preoperative pain in another area. Moderate or intense postoperative pain at 24 h did not substantially improve the model's predictive value (unpublished analysis).

Earlier, Althaus *et al.*[3] were also able to model preoperative risk for CPSP at 6 months using data from 150 patients who underwent different types of surgery, including thoracic surgery. Their model identified four preoperative predictors: (1) capacity overload, (2) preoperative pain in the operating field, (3) other chronic preoperative pain, and (4) comorbid stress symptoms. In contrast to our findings, their data yielded one postoperative predictor: acute postsurgical pain, although that predictor improved the performance of the model only slightly.

Considering the results of these two studies, we emphasize the importance of the limitation that Bayman *et al.*[1] mention in their discussion: "the small sample size...and the large number of associations tested." Their cohort, drawn from two hospitals, included only 107 patients at 3 days and 99 evaluable cases at 6 months, ultimately yielding 27 cases of CPSP at 6 months. Current analysis on the appropriate planning of a frequentist approach for this type of study recommends that there be a minimum of 10 events per variable to avoid overfitting of the model and to support confidence in a predictive model's reliability.[4,5] We know that a Bayesian approach may offer advantages over the conventional frequency-based methods, especially in small samples with many predictors, but we still think that the statistical power in small studies like this one[1] will be insufficient to address the main research question. Therefore, we stress the need for larger prospective observational studies to confirm the prevalence of CPSP in settings like thoracic surgery by thoracotomy and video-assisted thoracic surgery. We need such studies so that we can better understand the preoperative factors that may be modifiable.[6] Furthermore, when planning larger prospective observational studies, it is also useful to have information from population-based studies of events after surgery on which to base power analyses.

Competing Interests

The authors declare no competing interests.

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