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Letter to the Editor

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Dear Editor,

Collier et al¹ reported a spectacular reduction in the mortality of acutely injured patients by the administration of vitamins C and E and selenium. However, they compared a patient group that was routinely administered antioxidants with a historical control group that was not administered antioxidants; such comparisons have a high risk of bias. There may be substantial differences between the groups other than age, gender, and the probability of survival. In fact, the striking effect of adjusting for the 3 variables on the estimates suggests that there may be other great differences between the study groups.

Nevertheless, the interpretation of study findings depends not only on the study design but also on the consistency with other information on the topic. A number of animal studies have found that vitamins C and E protect against infections,² which indicates that the physiological effect of these antioxidants is not restricted to preventing overt deficiency. A recent Cochrane review found 3 controlled trials that investigated whether vitamin C prevents pneumonia and 2 that investigated whether it might help in curing pneumonia, and each of these trials found benefit of vitamin C supplementation.³ The randomized, placebo-controlled, double-blind trial by Hunt et al⁴ with elderly patients hospitalized because of lower respiratory infections is particularly interesting in this context.

Hunt et al⁴ found that 200 mg of vitamin C per day significantly reduced the total respiratory score in the most severely ill patients, but the vitamin had no effect on the less ill patients. Furthermore, there were 6 deaths during the trial—all among the most severely ill patients. Five of the deaths occurred in the placebo group and 1 in the vitamin C group. This variation in the role of vitamin C, based on disease severity, is similar to the findings of Collier et al,¹ who also observed that the benefit of antioxidants was restricted to participants with the poorest prognosis. Thus, it seems that further studies should stratify patients on the basis of the severity of the disease or should focus on the most severely ill patients.

Collier et al¹ used a mixture of 3 antioxidants, but there may be substantial differences between them, and

sometimes the effects can even be harmful. In studies with animals and humans, vitamin E has harmed the immune system and increased the severity of infections.^{2,5} In a large trial, 50 mg of vitamin E per day transiently increased the risk of tuberculosis in middle-aged males who had high dietary vitamin C intake.⁶ Thus, it would seem important to analyze the effect of antioxidants using a factorial design to find out whether there are positive or negative interactions between them, instead of just testing an arbitrary antioxidant mixture.

Finally, it seems that Collier and colleagues' calculation of the number needed to treat (NNT) is incorrect. The NNT is the inverse of the risk difference (RD) between the compared groups. Their crude data give RD = 2.34% (8.46%-6.11%), which gives NNT = 42.7 (1/0.0234). Furthermore, if we assume that their adjusted odds ratio is a valid estimate of the risk ratio, we can calculate that the adjusted mortality rate of the antioxidant cohort would be 2.70% (0.32 × 8.46%). With this approach we get NNT = 17.4; that is, 17 patients need to be treated to prevent 1 death. These NNT values are magnitudes lower than the NNT = 1710 calculated by Collier et al. Evidently, these low NNT values emphasize the importance of further research on the effects of antioxidants on critically ill patients.

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