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In Reply:

We thank Dr. Baldo for his interest in reading our article "Evaluation of a New Routine Diagnostic Test for Immunoglobulin E (IgE) Sensitization to Neuromuscular Blocking Agents."[1] Dr. Baldo is a pioneer in the study of immunologic mechanisms of the sensitization to neuromuscular blocking agents. His group has been the first in demonstrating the presence of IgE reacting against drugs containing quaternary and tertiary ammonium in patients sensitized against muscle relaxants, using quaternary and tertiary chemical compounds coupled to epoxy-Sepharose.[2,3] We confirmed these results 3 yr after their previous observation, using the same procedure.[4,5] We disagree with Dr. Baldo's comment "the French NMBD [neuromuscular blocking drug]-anaphylaxis literature for many years attributes the introduction of a choline solid phase support for the detection of NMBD-reactive IgE antibodies to research results published in the early 1990s," and we did cite eight of Dr. Baldo's publications. We invite him to read our recent review on this topic, which clearly chronicles his contribution in the field.[6]

In our experience, the use of the epoxy-Sepharose solid phase was problematic for diagnostic use, and this led us to subsequently improve a quaternary ammonium Sepharose-radioimmunoassay, which shared superiority in several aspects[7]: the epoxy-Sepharose procedure provided a much lower coupling efficiency of the chemical compound than the quaternary ammonium Sepharose reactive phase, with consequences in the sensitivity of the assay; and the epoxy-Sepharose procedure introduced an aliphatic hydrophobic chain between the Sepharose gel and the coupled drug, which could produce a nonspecific binding of hydrophobic IgE.[8] In contrast, the choline is directly coupled to Sepharose by an ether bond, with a high coupling efficiency and no addition of any aliphatic chain, in the quaternary ammonium Sepharose assay. These differences may explain that the quaternary ammonium Sepharose-radioimmunoassay produces higher sensitivity and specificity than the epoxy-Sepharose method, in our experience.[7] We would also like to point out that the radioimmunoassay with aminophenylphosphorylcholine was as efficient as the quaternary ammonium Sepharose-radioimmunoassay, in our hands.[9] Finally, the diagnostic value of the choline solid phases used in France[7,9] has been carefully evaluated and used in many clinical studies; these studies explain that they have been recommended by the European Network of Drug Allergy and the French Society for Anaesthesia and Intensive Care.[10]

The concept of using a morphine solid phase to bind neuromuscular blocking agent (NMBA)-specific IgE is not new[11] and was used in Dr. Baldo's laboratory for years.[12] However, this homemade assay was not available outside Australia. In contrast, the assay that we evaluated is the first commercial test using morphine as a sensitive marker to detect NMBA-specific IgE and is available to any specialized laboratory worldwide. This is why the word "new" was associated with "routine" in the title of our article. The morphine-based assay may have some limitations for its predictive value.[1] For example, Florvaag *et al.* demonstrated a high prevalence of IgE antibodies against morphine in Norwegians, probably in relation to the high consumption of pholcodine-containing syrups in this country.[13]

Dr. Baldo found questionable the name used to designate the assay we tested (quaternary ammonium, morphine), according to the nature of the ammonium ions responsible for NMBA allergy. The topic of our article was the clinical evaluation of a diagnostic test measuring sensitization to NMBA, and we have not discussed in any great detail the allergenic epitopes involved in NMBA allergy. We agree with Dr. Baldo that quaternary as well as tertiary ammonium ions are recognized by IgE from NMBA-allergic patients. This implicates that the positive charge on the nitrogen is essential for IgE antibody recognition, not primarily whether the nitrogen is quaternary or tertiary. The terminologic use of quaternary ammonium ions in NMBA allergy probably has its origin from the fact that all NMBAs contain at least one quaternary ammonium ion. We agree that the current terminology was not stringent. However, the proposed use of "substituted ammonium ions" as a generic term is less specific, because it also includes secondary and primary ammonium ions. The most prudent use of terminology when referring to NMBA epitopes should be "quaternary and tertiary ammonium ions." Finally, the commercial test for IgE antibodies against NMBA described in our article is actually not marketed as a quaternary ammonium test but as "c260 morphine," thus reflecting the actual antigen on the solid phase.

We appreciate that ultimately Dr. Baldo does agree with our conclusion that this commercial test for NMBA sensitization is a useful diagnostic tool.

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Erythrocyte Transfusion: A Fair Balance

To the Editor:

We read with interest Glance *et al.*'s paper and the related editorial.[1,2] Several retrospective studies have already reported an association between perioperative blood transfusion and altered outcome.[3–8] What is new in the Glance *et al.* study is that a similar negative association may exist in preoperative anemic patients having received only one or two units of packed erythrocytes (PRBCs) during the surgical procedure. However, we believe the results of this study should be interpreted with caution for several reasons.

First, as Carson *et al.*[9] wrote, observational studies are subject to uncontrolled confounding. In fact, patients who receive blood transfusions are probably more severely ill than those who do not receive them, and patients who are more severely ill have more adverse clinical outcomes (death, infection, *etc.*) than less ill patients. Thus, no matter how refined the adjustment is for differences in illness burden, it is never possible to ensure a complete adjustment for differences between patients receiving and not receiving blood transfusion.

Second, the transfusion trigger that was used in the study population was not specified. Was it a hemoglobin-based transfusion trigger or based on objective indices of oxygen delivery deficiency?[10–12] PRBC transfusions are administered to increase oxygen transport and restore tissue oxygenation when oxygen demand exceeds supply.[13] The oxygen extraction ratio reflects the adequacy of the cardiorespiratory response of the patient to anemia. Some authors have explored the utility of oxygen extraction ratio for guiding erythrocyte transfusion.[14,15] Erythrocyte transfusions can also be based on signs and symptoms of impaired global oxygenation with the use of lactate or mixed venous oxygen saturation. The mixed venous oxygen saturation or its surrogate, the central venous oxygen saturation, integrates the relationship between whole-body oxygen uptake and oxygen transport and has been proposed by Vallet *et al.* as a simple physiologic transfusion trigger.[16]

Third, the indication for transfusion was not specified in the study. The reason why some anemic patients were transfused with one or two units while other "similar" anemic patients were not was not explained. Reasons could include several factors such as the importance of blood loss, the hemodynamic stability of the patients, and their underlying pathologies that could by themselves influence the postoperative outcome. To minimize the confounding effect of surgical blood loss on patient outcome, the authors have excluded patients who received four or more PRBC units; however, this effort does not completely eliminate the effect of blood loss on the indication for transfusion. They also attempted to take into account the underlying pathologies of their patients but could not evaluate the effect of these pathologies on the transfusion trigger used by the clinician taking care of the patient.

Fourth, another important point that has not been specified is the etiology of anemia in the patient population. Different etiologies may differentially affect the postoperative outcome. Indeed, Kulier *et al.* showed that anemic patients have an increased risk of postoperative adverse events, but the extent of preexisting comorbidities substantially affects perioperative anemia tolerance. They recommended that the assessment of blood transfusions should take into account not only the preoperative hemoglobin concentration but also the extent of concomitant risk factors.[17]

This letter was sent to the author of the above-referenced article. The author felt that a reply was not necessary.—James C. Eisenach, M.D., Editor-in-Chief.