Correspondence

Is Mannose-Binding Lectin Deficiency Associated with Infection due to Gram-Positive Bacteria?

To the Editor—We read with great interest the article by Eisen et al. [1], in which the authors report an ambitious multivariable analysis of several articles on the impact of mannose-binding lectin (MBL) deficiency on the outcome of severe bacterial infection and sepsis. Although genetic polymorphisms in the genes encoding different molecules of the innate immune system have been associated with increased mortality in patients with severe sepsis and septic shock [2–4], examination of the association of MBL deficiency with death among patients in the intensive care unit has yielded conflicting results [5, 6]. In fact, in the study by Eisen et al. [1], only a trend toward an increased risk of death among MBL-deficient patients in the intensive care unit was observed, which could be attributable to the high heterogeneity of the patients included in these studies. Similar conflicting results are observed when the relationship between a microorganism or a group of microorganisms and MBL deficiency is analyzed. Although some studies have found an association between infection due to gram-positive bacteria and MBL deficiency [6], other studies have observed a link between infection due to gram-negative bacteria and MBL deficiency [7]. With regard to this question, in the study by Eisen et al. [1], an increased risk of death was observed for patients with low serum levels of MBL and pneumococcal infection. It is worth mentioning that most of the articles that have focused on this topic have not been able to establish an association between the incidence or outcome of Streptococcus pneumoniae infection and the existence of MBL deficiency. In fact, in vitro studies have demonstrated that S. pneumoniae has a low binding capacity to MBL [8]. Additionally, the level of expression of the capsule of S. pneumoniae, which has a negative impact on MBL binding, may vary during different phases of the infection [9]. Finally, minor differences in the sugar-array composition of the membranes of S. pneumoniae, which is responsible for the different serotypes of the bacteria, may account for additional differences in the ability of S. pneumoniae to bind to MBL.

In the same study by Eisen et al. [1], no significant association was found between MBL deficiency and death due to Staphylococcus aureus infection, probably because of the small number of patients with this condition who were included in the analysis. In vitro studies have demonstrated that S. aureus binds to MBL with high affinity [8]; therefore, MBL deficiency should be related to high mortality. In the 2007 European Society of Clinical Microbiology and Infectious Diseases conference, we addressed this issue by analyzing the MBL2 genotypes of 49 white patients with S. aureus bacteremia [10]. The study was conducted with the approval of the hospital Ethics Committee, and informed consent was obtained from the patients. No significant differences were observed with regard to the frequencies for low-expression MBL2 genotypes (LXA/O and O/O) between a group of healthy control individuals and the patients with S. aureus bacteremia. In our study, death was not related to low-expression MBL2 genotypes. We did not analyze the effect of the serotypes of S. aureus on the clinical outcomes of the patients. The analysis of all the serotypes together could be masking the influence of different serotypes on MBL binding. In conclusion, to properly evaluate the role of MBL in different infectious settings, it is fundamental to focus not only on the host (i.e., the level of MBL) but also on bacterial characteristics, particularly the binding capacity of MBL to different strains or serotypes.

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Reply to Smithson et al.

To the Editor—Mannose-binding lectin (MBL) deficiency has been associated with a predisposition to numerous infectious diseases, and our recent data indicate that patients with pneumococcal infection who have MBL levels <0.5 μg/mL are more likely to die [1]. The data included in our recent meta-analysis excluded the initial study that showed a strong association between MBL2 variant allele homozygosity and invasive pneumococcal infection [2], because these patients’ MBL blood levels were not measured. If these patients could have been included, the association we ascertained between MBL deficiency and death in pneumococcal infection would very likely have been even stronger than our finding of an OR of 5.62 (95% CI, 1.27–24.92). In their letter, Smithson et al. [3] indicate that conclusions regarding the significance of MBL deficiency need to be viewed in the context of in vitro data that describe the binding of this protein to bacterial cells and the consequent deposition of complement. The earliest data relating to *Streptococcus pneumoniae* demonstrated binding of the bacteria to MBL [4], but more-recent data indicate that encapsulation of pneumococci abrogates binding [5]. One crucial aspect of the contribution of MBL to the killing of pneumococci that has not been studied to date is the contribution of neutrophils. Until these data are available, it is premature to ignore the strong association between MBL deficiency and poor outcomes of pneumococcal infection.

It is important to examine the possible association between *Staphylococcus aureus* sepsis and MBL deficiency, because of the in vitro observations of MBL binding to *S. aureus* and the resulting increased phagocytosis [6]. The only published data on *S. aureus* sepsis come from our 2 studies [1, 7] and are summarized in the recent meta-analysis. On the basis of 49 patients with staphylococcal sepsis, no clear association with MBL deficiency was demonstrated. If we assume that the magnitude of effect of MBL deficiency is the same in staphylococcal and pneumococcal sepsis, a minimum sample size of 60 would be required for an appropriately powered study. The study of the relationship between MBL deficiency and staphylococcal sepsis is certainly a priority in this field of research.

The central theme of the biology of MBL is its pleiotropy. This pattern-recognition molecule binds to pathogen-associated molecular patterns from an extraordinarily broad range of organisms. The numerous documented associations of MBL with diverse infections [8] support this broad range of action, but proof of a critical role in the prevention or amelioration of infectious diseases morbidity relies on human clinical trials.

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Laboratory-Acquired *Clostridium difficile* Polymerase Chain Reaction Ribotype 027: A New Risk for Laboratory Workers?

To the Editor—*Clostridium difficile* is not recognized as a pathogen that presents a risk of acquisition in the laboratory, and no particular safety precautions are recommended for working with this microorganism [1]. We report 2 cases of laboratory acquisition of *C. difficile* infection.