Correspondence

Cytomegalovirus Load in Bronchoalveolar Lavage Fluid: A Clue to the Diagnosis of Cytomegalovirus Pneumonia?

To the Editor—We read with interest the article by Westall et al. [1], recently published in the *Journal of Infectious Diseases,* addressing the issue of human cytomegalovirus (HCMV) load in lung transplant recipients (LTRs) with or without HCMV pneumonia. Although these authors add a substantial amount of data to the few published studies that include histopathological documentation of HCMV pneumonia [2, 3], we feel that some clarifications are necessary.

As shown by Westall et al., the contribution of qualitative polymerase chain reaction, be it on bronchoalveolar lavage (BAL) or plasma samples, to the diagnosis of HCMV pneumonia is limited by the less-than-perfect specificity of positive results for the presence of pneumonia in this patient population. In addition, the reported series included 2 patients with plasma samples that were negative at the time of pneumonia, suggesting that a negative plasma sample cannot be used to exclude HCMV pneumonia. This is consistent with our own unpublished observations. We are interested to know whether the quantitation of HCMV load in respiratory samples can provide more information as to the presence of HCMV pneumonia. However, the way Westall et al. arrived at their HCMV load threshold of 46,000 copies/mL is unclear. We concur that "intuitively, higher virus loads are more likely to be associated with more-severe HCMV disease in LTRs" (p. 1081) and that a threshold above which the likelihood of HCMV pneumonia is high might possibly be defined. This threshold should be set somewhere between the HCMV loads found in patients with and without HCMV pneumonia—for example, "a virus load 2 SD above the mean virus load of all those LTRs without histological evidence of HCMV infection" (p. 1081). However, as stated by the authors in the subsection entitled "HCMV DNAemia in BAL and plasma samples: histologically proven HCMV infection," the mean HCMV load in the BAL samples *from those LTRs in whom HCMV pneumonia was not detected histologically* (and not, as written by the authors, "from those LTRs in whom HCMV DNA was not detected" [p. 1079], an apparent typographical error) was 5873 ± 1543 copies/mL, which should point to a threshold of ~9000 copies/mL. This is substantially different from the 46,000 copies/mL computed by the authors. Setting a threshold of 46,000 copies/mL appears, therefore, to be both inconsistent with the proposed method (i.e., different from the choice of an HCMV load 2 SD above the mean) and illogical (i.e., higher than the HCMV load of 19,460 ± 4917 copies/mL observed in patients with proven HCMV pneumonia). Perhaps a convenient way to clarify this point would be to explicitly demonstrate, in Westall et al.'s figure 3, which thresholds correspond to the different points of the receiver operating characteristic curve, since the best threshold appears obvious on the basis of the curve shape.

Clarifying these points is important, since other authors have presented evidence similar to that of Westall et al.—namely, evidence that a substantial overlap does exist in the BAL HCMV loads in patients with and without HCMV pneumonia [2–4]. Whether this diagnostic problem could be resolved by expressing the relationship between HCMV load and the probability of HCMV pneumonia as a sigmoid curve for HCMV load varying from 10,000 to 30,000 copies/mL rather than as a dichotomous relationship, as shown by Riise et al. [3], or by estimating HCMV load in the epithelial lining fluid (as computed using urea dilution) with a cutoff of ~10,000 copies/mL, similarly to Zedtwitz-Liebenstein et al. [4], is yet unclear to us. We hope this letter will provide Westall et al. with an opportunity to clarify these points in their interesting article.

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Reply to Meylan and Zanetti

To the Editor—We thank Meylan and Zanetti [1] for their positive review of our article [2] and are encouraged to see that