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Reply to Cao et al.

To the Editor—We thank Cao et al. for their response [1] to our recent article [2] on the alternative treatment of secondary bacterial pneumonia after influenza. We agree that interleukin (IL)–10 is an important cytokine in the response to many infections. One poorly understood aspect of severe lung infections is the contribution made by the host inflammatory response to disease and death. In preclinical models, the inflammatory response is needed to control bacterial infections [3], but too much inflammation leads to lung damage and increased mortality [4]. An emerging concept in the study of severe infections is that a balance between anti- and proinflammatory activity is necessary for the resolution of infection and survival [5]. In our preclinical model of secondary pneumococcal pneumonia after influenza, an exaggerated and dysfunctional cytokine response occurs and contributes to mortality [6, 7]. Treatment of these infections with cell wall–active antibiotics eliminates the infecting organisms, but the inflammatory burst that occurs after lysis of the bacteria can be fatal to the host [2, 8]. An ideal treatment regimen would eliminate bacterial pathogens while limiting inflammatory damage to the host, such that both morbidity and mortality would be reduced [9].

Indeed, in earlier studies using our mouse model, IL-10 levels were found to be strikingly elevated in mice with severe pneumonia [6]. In our recent study [2], IL-10 levels were similarly elevated (mean ± SD, 11,304 ± 2037 pg/mL; n = 5 mice) in the lungs of control mice infected with influenza virus followed 7 days later by Streptococcus pneumoniae. However, IL-10 levels did not change after treatment with either ampicillin (mean ± SD, 11,200 ± 1417 pg/mL; n = 8 mice) or clindamycin (mean ± SD, 11,643 ± 1497 pg/mL; n = 8 mice), as has been demonstrated for other proinflammatory cytokines and chemokines [2]. Therefore, although IL-10 may be important in the pathogenesis of severe lung infections, including those caused by bacterial superinfections after influenza, it is unlikely to be responsible for the difficulties inherent in the effective treatment of this disease.

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References

Spontaneous Viral Clearance, Viral Load, and Genotype Distribution of Hepatitis C Virus (HCV) in European HIV-Infected Patients with Anti-HCV Antibodies

To the Editor—Soriano et al. [1] reported that hepatitis C virus (HCV) viremia was less common in HIV–infected patients with anti-HCV antibodies who were also positive for serum hepatitis B surface antigen. The increased probability of HCV clearance in patients with HBV–HCV coinfection was attributed by the authors to a viral interference phenomenon. We find it quite surprising that hepatitis delta virus (HDV) markers have not been reported in this study. In a nationwide survey performed in Spain, triple coinfection with hepatitis B virus (HBV), HCV, and HDV was demonstrated in ~70% of HIV-infected patients with coinfection due to multiple hepatitis viruses [2]. In addition, a number of studies from elsewhere in Europe have reported that, in HIV-infected patients with HBV, HCV, and HDV coinfection, HDV is the dominant virus that suppresses both HBV and HCV replication [3–5]. The authors should discuss whether the inhibition of HCV replication seen in their study was caused by HBV itself and/or by a possible undetected chronic infection with HDV. The current standard of care is to evaluate...
HDV markers in HIV-infected patients with chronic HBV infection [6].

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Reply to Pascual Pareja et al.

To the Editor—We appreciate the comments made by Pascual Pareja et al. [1]. At the time at which the EuroSIDA hepatitis C virological substudy was conducted, no data regarding hepatitis delta virus (HDV) superinfection were available. Since then, HDV antibodies have been examined retrospectively in stored samples obtained from hepatitis B surface antigen (HBsAg)–positive patients.

In the EuroSIDA study [2], in which 1940 HIV-infected individuals who had results positive for hepatitis C virus (HCV) antibodies were examined, detectable HCV viremia and, therefore, chronic hepatitis C were demonstrated in 1496 (77%) of the patients. Overall, 136 (7%) of these HCV antibody–positive patients with HIV infection had serum samples that were positive for HBsAg; the prevalence of HBsAg was lower among patients with HCV viremia than among aviremic patients (5.2% vs. 13.3%; P < .001). We acknowledged that the well-known viral interaction between HBV and HCV was the main explanation for this finding [3].

The prevalence of HDV antibodies among HBsAg-positive patients in the EuroSIDA study was relatively low (~13%). The percentage of HIV-infected patients in the EuroSIDA study who had both serum HBsAg and HCV antibodies who also had HBsAg antibodies was 45 (34%) of 136. This is clearly lower than the ~70% prevalence of HDV antibodies that the authors claim to have found among patients with HIV infection who had markers for HBV and HCV infection in a survey conducted among patients with HIV infection in Spain during 2002 [4]. Differences in study populations could explain discordant rates of HDV superinfection, although the prevalence of HDV antibodies among HIV-infected individuals with markers for both HBV and HCV infection at Hospital Carlos III, a referral HIV clinic located in Madrid, Spain, is 44%, which is a rate that is more in agreement with the EuroSIDA study data.

Finally, the proportion of HCV–antibody positive, HIV-infected individuals with test results positive for HBsAg in the EuroSIDA study who experienced spontaneous HCV clearance did not differ significantly from the proportion who experienced spontaneous HCV clearance in the subset of patients with and without HDV antibodies. Of 28 HBsAg-positive patients without HDV antibodies, 24 (86%) experienced HCV clearance, compared with 23 (100%) of those who had HDV antibodies (P = .12, by Fisher’s exact test). Although the limited size of the comparison groups precluded drawing more-definitive conclusions, the results support the view that viral interference between hepatitis viruses exists and that suppression of HCV replication may result from coinfection with either HBV or HDV.

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