Iron Overload as a Mechanism for the Lowered Survival in AIDS Patients Receiving Dapsone–Iron Protoxalate for Secondary Prophylaxis of Pneumocystis carinii Pneumonia

To the Editor—Salmon-Cérón et al. [1] found lower survival in AIDS patients receiving dapsone compared with those receiving aerosolized pentamidine for secondary prophylaxis of Pneumocystis carinii pneumonia. Their study is of great interest because in their trial, the dapsone compound used contained 200 mg of iron protoxalate per tablet, which at the least confounds the interpretation of the data and at most may have been responsible in large part for the lowered survival rates.

In their discussion, Salmon-Cérón et al. [1] concentrate on dapsone toxicity as a mechanism for the lower survival in the dapsone arm of the trial, while minimizing the possible effects of iron overload. However, it should be noted that Bozette et al. [2], who used a dose of dapsone that was twice as great (50 mg, twice a day) but in a form free of iron, found no decreased survival in a three-arm randomized primary prophylaxis trial involving more patients observed over a longer time. In that trial, dapsone, aerosolized pentamidine, and trimethoprim-sulfamethoxazole were of similar effectiveness. It might be argued that the patients in the secondary prophylaxis trial of Salmon-Cérón et al. [1] were more immunosuppressed than those in the primary prophylaxis trial of Bozette et al. [2], yet in patients with <100 CD4 lymphocytes/µL, Bozette et al. still did not find lesser survival with dapsone treatment [2].

It should also be noted that the effects of iron overload are not simply limited to “rare cases of listeriosis,” as Salmon-Cérón et al. state in their discussion [1]. Infections caused by Yersinia species, Vibrio vulnificus, and Salmonella species, in addition to Listeria monocytogenes, have been clinically recognized in patients with iron overload, and these and other organisms (including Mycobacterium avium, Pasteurella multocida, and Legionella pneumophila) demonstrate increased virulence in experimental models using iron-stressed animals (reviewed in [3–5]).

Finally, in the penultimate paragraph of their discussion, Salmon-Cérón et al. [1] mistakenly state that dapsone–iron protoxalate inhibits the growth of P. carinii, citing data from my laboratory [6]. I have shown that iron chelators (e.g., deferoxamine) inhibit the growth of P. carinii in cell culture and effectively treat experimental P. carinii pneumonia in animals [6, 7]. However, I have never tested dapsone–iron protoxalate.

In conclusion, it is quite possible that the lowered survival in the dapsone arm of the trial of Salmon-Cérón et al. [1] was in large part due to the concurrent administration of iron protoxalate. Absorption of a significant fraction of the extra 30 mg per day of elemental iron may have occurred despite chronic inflammation, because the gastrointestinal mucosal block to absorption of excess iron is easily overcome and because many patients will have increased absorption of excess iron in the presence of other substances, such as ascobic acid, ethanol, or tobacco [3, 4, 8]. As an increased iron burden appears to be characteristic of progressive human immunodeficiency virus infection and in view of the fascinating data of Salmon-Cérón et al. [1], further research on the modulation of iron intake and metabolism is merited [8].

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The Changing Epidemiology of Pneumococcal Bacteremia in Human Immunodeficiency Virus Infection

To the Editor—The high incidence of pneumococcal disease in human immunodeficiency virus (HIV)-infected patients has been well documented [1-3]. There is a 7-fold increased risk of pneumococcal pneumonia [2] and an increase in the frequency of recurrent pneumococcal infection in HIV-infected patients [4, 5]. The incidence of pneumococcal bacteremia in AIDS patients has been 1%/year in studies in San Francisco [3] and New Jersey [4] compared with 0.07%/year in the non-HIV-infected population. A significantly elevated incidence of pneumococcal bacteremia has also been noted in HIV-infected patients not meeting the current Centers for Disease Control and Prevention (CDC) criteria for AIDS [3, 4]. The serotypes involved and clinical course have been similar in both HIV-infected and uninfected patients, with the only notable difference being a lower mortality rate in HIV-infected patients [1, 6].

Because of this increased incidence of pneumococcal disease, the pneumococcal vaccine has been recommended as an early intervention in HIV patients [7]. Although there is often a poor response to vaccine administered late in the course of HIV infection [8], Weiss et al. [9] published that recent seroconvertors generate a ‘normal’ humoral response to all vaccine components except serotype 8.

The US Navy has screened all active-duty members for HIV infection every 1-3 years since an initial required screening in 1985-1986. Routine pneumococcal vaccination of all newly diagnosed HIV-infected subjects began at our institution in 1989. Since 1990, trimethoprim-sulfamethoxazole (TMP-SMZ) has been the first option for primary Pneumocystis carinii pneumonia (PCP) prophylaxis in all patients with CD4 cell counts <250/μL. About 700 HIV-infected patients use our hospital and HIV clinic for their routine care; 30% have AIDS by the revised CDC criteria.

We performed a retrospective review of pneumococcal bacteremia in HIV disease at our institution by reviewing the hospital blood culture logs from July 1989 until October 1994 (64 months) to identify all cases of pneumococcal bacteremia. One hundred seventy-eight cases were seen at this hospital during that time. This list of 178 patients was cross-referenced to patients followed in the HIV clinic, and 8 cases of pneumococcal bacteremia were identified in 7 HIV-infected patients. Four patients had bacteremia in 1990, 2 in 1991, and 1 in 1993. All 7 patients met the current AIDS definition at the time of pneumococcal bacteremia. The annual incidence of pneumococcal bacteremia in AIDS patients over the last 5 years at this hospital (0.90%) was similar to that found in previous studies [3, 4] but has dropped markedly over