gram-negative bacillary BSI [6]. Of 8 patients in the study with clinically significant BSIs, 88% had femoral and 62% had upper-body VRE colonization. The temporal relationship between VRE skin colonization and infection was not determined in the study, and complete molecular typing information was not available; however, the study results suggest that catheter-related VRE BSI could result from skin colonization by the organism followed by catheter hub colonization, similar to the pathogenesis of coagulase-negative staphylococcal BSIs. Of 46 patients with VRE BSIs in our study, 40 (87%) had a central venous catheter in place when infection developed. Colonization of sites other than the gastrointestinal tract may be important in the development of VRE BSI.

The Medical Center at the University of California, San Francisco has shown a marked decline in oral vancomycin use from 1988 to 1994 [1], as have others [3]. However, deducing risk factors for VRE acquisition using the ecologic data concerning intravenous and oral vancomycin use [1] is problematic. Exposure on an individual level may be similar, unrelated, or even opposite to trends in vancomycin use on an institutional level. The absolute number of grams of an antimicrobial used in a medical center may bear little relationship to the risk of VRE colonization or infection for an individual patient. Use of vancomycin and other antimicrobials in oncology and intensive care units hospitalizing severely ill patients at greatest risk of acquiring VRE may be more important. In addition, a "case" of VRE was not defined by Luber et al. Did these 3 patients have gastrointestinal colonization or clinical infection? If cases were only colonized, then many other cases may not have been detected if surveillance culturing was not routinely done. Last, colonization with VRE on admission does not rule out previous nosocomial acquisition, as gastrointestinal colonization may be prolonged [7]. There may be multiple risk factors for VRE acquisition; however, it is not possible to conclude that oral vancomycin exposure is a risk factor for VRE colonization or infection on the basis of the apparently low prevalence of VRE in one institution that has decreased usage of oral vancomycin.

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Folinic Acid Supplements to Pyrimethamine-Sulfadiazine for *Toxoplasma* Encephalitis Are Associated with Better Outcome

To the Editor—Safrin et al. [1] described an increased risk of therapeutic failure and death associated with the use of folinic acid in conjunction with trimethoprim-sulfamethoxazole for treatment of *Pneumocystis carinii* pneumonia (PCP) [1]. Folinic acid has also been largely used to treat *Toxoplasma* encephalitis (TE) in AIDS patients to reduce the hemotoxicity frequently associated with high doses of sulfadiazine-pyrimethamine [2, 3].

To determine whether folinic acid influences the outcome of treatment of acute TE, we retrospectively reviewed the charts of all patients with TE registered in the Swiss Human Immunodeficiency Virus Cohort Study from three centers (Geneva, Lausanne, and Zurich) from July 1992 to December 1994. We identified 130 cases of TE. Folinic acid had been given to 118 patients (91%). Six patients died within 30 days of initiation of TE therapy because of TE progression. Four of 12 patients who did not receive folinic acid died compared with 2 (<2%) of 118 who received folinic acid (relative risk [RR] of death associated with the absence of folinic acid, 19.7; 95% confidence interval [CI], 4.0–96.5; $P < .001$). Complete response to therapy was significantly associated with prescription of folinic acid (80 of 118 patients vs. 3 of 12; RR of complete response with folinic acid, 2.7; CI, 1.0–7.1; $P = .008$). A change to less effective therapies and dose reduction because of hemotoxicity was less frequent in the group receiving folinic acid (8 [7%] of 118 vs. 5 [42%] of 12; RR, 6.1; CI, 2.4–15.8; $P = .002$). Of the 4 patients who died and had not received folinic acid supplements, none was receiving sulfadiazine-pyrimethamine at time of death. Two switched drugs because of hemotoxicity (to atovaquone and azithromycin) and 2 because

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of allergic skin reactions (to clindamycin-pyrimethamine). One of the 2 patients who died and had received folinic acid switched to clindamycin-pyrimethamine because of an allergic skin reaction. All patients who had complete response to therapy were receiving sulfadiazine-pyrimethamine (65 patients) or clindamycin-pyrimethamine (18 patients).

In our retrospective study, in contrast with the results for PCP [1], we found that folinic acid supplements were associated with a better outcome (i.e., less mortality and higher proportions of complete responses). This may be due to decreased hematologic toxicity and, in turn, less need for dose reductions or changes to less effective therapies. Folinic acid does not interfere with the antitoxoplasmic effect of pyrimethamine or sulfadiazine because of the absence of a membrane transport system for exogenous folinic acid in *Toxoplasma gondii* [4]. In experimental murine toxoplasmosis, survival increased when folinic acid was given with pyrimethamine because of protection from the toxic effects of pyrimethamine without interference with the action of the drug against *T. gondii* [5, 6]. In the absence of a well-conducted prospective trial, we continue to recommend the use of folinic acid as an adjuvant to pyrimethamine-sulfadiazine during treatment of acute TE.

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