We continue to have difficulty interpreting the finding of a single band with a molecular weight of 29,000 on Western blotting. However, this band was found repeatedly with the use of both rabbit anti-yersinia antiserum and monoclonal antibodies against the O-polysaccharide chain of yersinia lipopolysaccharide. We think that this band is a final degradation product of yersinia lipopolysaccharide, because remarkable degradation occurred in one hour (as shown in Fig. 3 of our article). So far, the patients' own serum samples have not been used to study the antigenic material in synovial-fluid cells.

KAISA GRANFORS, PH.D.
SIRPA JALKANEN, M.D.
AULI TOIVANEN, M.D.
SF-20520 Turku, Finland University of Turku

NOSOCOMIAL *CLOSTRIDIUM DIFFICILE* INFECTIONS

To the Editor: The report by McFarland et al. (Jan. 26 issue)* contributes new information about the acquisition of *Clostridium difficile* by hospitalized patients. A number of points were omitted from the results that, if available, would be useful in interpreting their data.

First, the fact that the late-acquisition group differed significantly from the early-acquisition group in terms of the severity of illness might lead one to propose some protective mechanism whereby severe illness prevents or delays colonization by *C. difficile*. Logically, one would expect more severely ill patients to receive more intense care and therefore be at greater risk for exposure to the organism. I wonder if differences in the length of stay could account for this finding, since the more severely ill patients could be expected to have longer stays, with a greater chance of infection after two weeks; those with shorter stays must acquire the organism more quickly or not at all. If the data were evaluated in terms of the risk of infection per day of potential exposure, the finding of delayed acquisition among the severely ill might be better understood.

A second question is raised by the authors' definition of *C. difficile*–associated diarrhea as "diarrhea not attributable to any other cause (infectious, medication related, or mechanical), which occurred at the same time as a positive culture." Certainly, this definition should be used when one is seeking a treatable cause of diarrhea. In attempting to interpret the data presented, however, it would be useful to know more about the methods used to exclude other causes. Routine stool culture is insensitive to many common causes of diarrhea (such as *Campylobacter jejuni*, toxicogenic *Escherichia coli*, and viral agents). What, specifically, was excluded? I would also like to inquire about the incidence of diarrhea among the 316 patients whose cultures were negative for *C. difficile*. How many of them had diarrhea for which a cause could not be found? This background rate would be useful in an evaluation of the excess morbidity attributable to *C. difficile* among the population studied.

The authors provide useful information about how *C. difficile* is acquired and how its acquisition might be blocked; additional information is necessary to estimate the value of mounting such an effort. (The authors themselves do not recommend that all measures be taken to prevent the disease; for example, they advise against treating asymptomatic carriers.) I have no intention of forgoing hand washing, but before taking on the expense of other types of prophylactic environmental surveillance and disinfection, I would like to know what improvement in morbidity I can expect. The study undertaken by McFarland et al. may provide these data, but they were not included in their report. To their call for intervention studies to define the effectiveness of preventive measures, I would add a solicitation for studies of cost–benefit analysis. I am fully aware of the potentially serious nature of *C. difficile*–related disease, but in this study, even the most extreme prophylactic measures would not have decreased the incidence of colitis (since none occurred).

JAMES J. CIMINO, M.D.
New York, NY 10032 Columbia–Presbyterian Medical Center

*McFarland LV, Mulligan ME, Kwok RYY, Stamm WE. Nosocomial acquisition of *Clostridium difficile* infection. N Engl J Med 1989; 320:204-10.

The above letter was referred to the authors of the article in question, who offer the following reply:

To the Editor: As Dr. Cimino surmises, the severity of illness and the length of stay were highly correlated in our data set, as they are in most analyses of hospital-acquired infections. We doubt that there is a protective mechanism whereby severe illness prevents or delays colonization by *C. difficile*. Rather, we suspect that the higher proportion of patients with severe illness in the late-onset group reflects their longer hospitalization and the associated increased cumulative risk of exposure to antimicrobial agents, other medications, and procedures that enhance the likelihood of colonization by *C. difficile*.

Regarding the definition of *C. difficile*–associated diarrhea, all patients with diarrhea had stool specimens cultured for common bacterial enteropathogens, specifically salmonella, shigella, *C. jejuni*, and *Yersinia enterocolitica*, and an examination of stool samples for parasitic infections. We did not evaluate our patients for toxicogenic *E. coli* or for viral agents. Patients in whom the onset of diarrhea was temporally associated with enteral alimentation or medications known to be common causes of diarrhea were excluded. Among the 316 patients whose cultures were negative for *C. difficile*, 63 had diarrhea attributed to the following causes: medications (26), substance-abuse withdrawal (15), malabsorption (7), other enteric pathogens (6), nasogastric-tube feedings (4), inflammatory bowel disease (3), and radiation therapy (2); the cause was unknown in 32.

We agree with Dr. Cimino that studies evaluating the prevention of *C. difficile* transmission and disease within hospitals should also assess the cost benefit of such measures. Other than providing the relative distribution of cases of diarrhea or colitis and of patients who became colonized with *C. difficile* during hospitalization, our data do not allow us to address this issue. Of interest was the fact that none of the 83 patients with incident nosocomial *C. difficile* in our study had colitis, whereas 4 of the 29 patients with nonincident nosocomial or community-acquired *C. difficile* had colitis. Thus, a lengthy follow-up may be required to assess the true effect of the nosocomial acquisition of *C. difficile*, since the onset of disease may often occur after the patient has been sent home.

LYNNE MCFARLAND, PH.D.
WALTER E. STAMM, M.D.
Seattle, WA 98195 University of Washington

MUCORMYCOSIS AMONG PATIENTS ON DIALYSIS

To the Editor: Mucormycosis has recently been reported as an infectious complication in patients on dialysis who do not have diabetes mellitus. As of January 1, 1989, a total of 24 cases had been reported among such patients,[1-6] and we are aware of other, unpublished but documented, cases. At the time of recognition of the illness that later proved to be mucormycosis, at least 21 of the 24 patients were receiving deferoxamine for the treatment of either aluminum overload (18 patients) or iron overload (3). Table 1 shows certain salient features of the 24 reported cases.

The status of iron stores in the patients was highly variable, with evidence of iron overload in 6 and no evidence in 12; the iron status of 3 patients was not reported. When cultured, the causative fungus invariably belonged to the rhizopus genus. Dissemination of the infection was reported in 12 cases, accounting for a fulminant course, and the infection was fatal in 21 of the 24 patients. In the

Table 1. Clinical and Biochemical Features of 24 Patients Undergoing Regular Dialysis Who Had Mucormycosis.

	LENGTH OF THERAPY*	SERUM FERRITIN	HEMATOCRIT	SERUM BICARBONATE
	mo	*ng/ml*	*%*	*meq/liter*
Mean	8	1700	31	21
Range	1–18	23–11,000	20–37	14–26

*Twenty-one patients were treated with deferoxamine.

reports of this disorder in patients on dialysis, this infection was often associated with the use of deferoxamine. The prevalence of mucormycosis in patients on dialysis who are not receiving deferoxamine is unknown, however, and the pathogenesis of this infection in such patients remains uncertain. With the increasing use of deferoxamine in patients on dialysis, there is an urgent need to identify the factor or factors that predispose patients on dialysis to this infection. Therefore, an international registry of cases of mucormycosis developing during long-term dialysis has been established in the hope of identifying the risk factors responsible.

JOHAN R. BOELAERT, M.D.
B-8000 Brugge, Belgium Algemeen Ziekenhuis Sint Jan

ANDREW Z. FENVES, M.D.
Dallas, TX 75246 Baylor University Medical Center

JACK W. COBURN, M.D.
Los Angeles, CA 90073 West Los Angeles VA Medical Center

1. Boelaert JR, Van Roost GF, Vergauwe PL, Verbanck JJ, de Vroey C, Segaert MF. The role of desferrioxamine in dialysis-associated mucormycosis: report of three cases and review of the literature. Clin Nephrol 1988; 29:261-6.
2. Windus DW, Stokes TJ, Julian BA, Fenves AZ. Fatal rhizopus infections in hemodialysis patients receiving deferoxamine. Ann Intern Med 1987; 107: 678-80.
3. Segal R, Zoller KA, Sherrard DJ, et al. Mucormycosis: a life-threatening complication of deferoxamine therapy in long-term dialysis patients. Kidney Int 1988; 33:248. abstract.
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6. Morris DJ, Altus P. Rhinocerebral mucormycosis in an anephric patient. South Med J 1988; 81:400-3.

OMEPRAZOLE VERSUS RANITIDINE FOR GASTRIC ULCER

To the Editor: The double-blind study of Walan et al. (Jan. 12 issue)[1] comparing the effectiveness of ranitidine (150 mg) twice a day with omeprazole (20 or 40 mg) once a day in the treatment of gastric ulcer contains a damaging design flaw. Although patients who missed more than 25 percent of their medication were excluded from the analysis, patients who missed less than 25 percent were included and considered equivalent. In the ranitidine group, however, a missed dose automatically resulted in missing active drug treatment and compromised therapy for that day. In the omeprazole group, a missed dose may have been a placebo, which would have had no adverse effect on omeprazole's therapeutic efficacy.

Thus, although similar rates of noncompliance in the treatment groups were reported, the effect of noncompliance was much greater among patients taking ranitidine. This led to more days of inadequate therapy and a lower healing rate among the ranitidine group and may well be the explanation for omeprazole's small superiority (89 percent and 96 percent healed at eight weeks vs. 85 percent with ranitidine).

The choice of twice-daily treatment with ranitidine is surprising, since several studies have shown equivalent efficacy of a regimen of 300 mg per day in the treatment of gastric ulcer.[2-4] A comparison of such a regimen would have been more logical and would have eliminated a "noncompliance bias."

ROBERT E. SCHOEN, M.D.
New York Hospital–
New York, NY 10021 Cornell Medical Center

NANCY BERNSTEIN, M.P.H.
New York, NY 10010 Hunter School of Health Sciences

1. Walan A, Bader J-P, Classen M, et al. Effect of omeprazole and ranitidine on ulcer healing and relapse rates in patients with benign gastric ulcer. N Engl J Med 1989; 320:69-75.
2. Ryan FP, Jorde R, Ehsanullah RS, Summers K, Wood JR. A single night time dose of ranitidine in the acute treatment of gastric ulcer: a European multicentre trial. Gut 1986; 27:784-8.
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4. Farley A, Levesque D, Pare P, et al. A comparative trial of ranitidine 300 mg at night with ranitidine 150 mg twice daily in the treatment of duodenal and gastric ulcer. Am J Gastroenterol 1985; 80:665-8.

To the Editor: When a combination of H_1 and H_2 blockers is used to help control hives, the dosage of ranitidine, when that drug is used, is often 300 mg twice a day. Although it was not included in the protocol of Walan et al., this higher dose should perhaps have been considered.

GEORGE GOLDMAN, M.D.
Cambridge, MA 02138 Mount Auburn Hospital

To the Editor: Walan et al. report that benign gastric ulcers healed more rapidly in patients treated with omeprazole (20 mg or 40 mg per day) and that post-treatment relapse rates were lower among such patients than among those treated with ranitidine (150 mg twice a day).

Seventy-two percent of the patients in this study had gastric ulcers, and 28 percent had prepyloric ulcers. Unfortunately, both groups were combined for the statistical analyses, and it is impossible to determine from the data presented whether either dose of omeprazole was superior to ranitidine in the treatment of the more common gastric ulcers. Prepyloric ulcers are pathophysiologically and therapeutically more like duodenal ulcers than gastric ulcers. It therefore seems possible that the differences in overall healing rates are attributable to more rapid ulcer healing with omeprazole in patients with prepyloric ulcers rather than to increased healing of gastric ulcers. Furthermore, in this study the prepyloric ulcers were smaller than the gastric ulcers, so that controlling for initial ulcer size (which overall had a significantly greater effect on healing than did treatment) would bias statistical analysis in favor of improved healing in patients with prepyloric ulcers.

The figure for the recurrence of ulcer after treatment with either omeprazole or ranitidine is misleading, since it fails to compare relapse rates from a common base line (i.e., 100 percent healing). Table 1 shows the estimates of three-month and six-month recurrence rates (values taken from the life-table graph shown in Fig. 1 of Walan et al.) among the patients whose ulcers had healed. In contrast to statements in their article, these results indicate that the rate of relapse of symptomatic gastric ulcer was actually lower among patients treated with ranitidine.

Table 1. Three-Month and Six-Month Rates of Recurrence of Ulcers after Treatment with Omeprazole or Ranitidine.

	OMEPRAZOLE		RANITIDINE, 300 mg
	20 mg	40 mg	
	percent		
3 mo	26	25	22
6 mo	35	35	30

Greenford, Middlesex UB6 0HE, England JOHN R. WOOD, M.B., PH.D.
Glaxo Group Research Limited

The above letters were referred to the authors of the article in question, who offer the following reply:

To the Editor: Dr. Schoen and Ms. Bernstein argue that the effect of noncompliance on healing rates was greater among patients taking ranitidine. As we stated in our paper, a double-placebo technique was used. This means that two 20-mg capsules of omeprazole were given each morning in the group receiving 40 mg per day, whereas in the group receiving 20 mg, one active 20-mg capsule and