Influence of Ceftriaxone on Emergence of Clostridium difficile

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Clostridium difficile is a recognized cause of antibiotic-associated diarrhea and an important nosocomial pathogen. Its role in etiology of pseudomembranous colitis is well known. Several antibiotics, including the broad-spectrum cephalosporins, appear to predispose C. difficile-associated diarrhea more often than others (3). C. difficile has been demonstrated in stools of patients after a single dose of ceftriaxone (1) but the risk of acquiring C. difficile after long-term therapy with ceftriaxone is unknown. Lyme borreliosis is a multiorgan disease caused by Borrelia burgdorferi (13). Ceftriaxone has been recommended as the drug of choice for patients with second- and third-stage Lyme borreliosis (2). Since the duration of therapy is, on average, 14 days, we tried to establish the relative risk of acquiring C. difficile after long-term therapy with ceftriaxone in patients lacking other risk factors for acquisition of C. difficile.

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Patients receiving ceftriaxone for treatment of Lyme borreliosis from June to September 1990 were enrolled in the study. Data on preexistent diseases, hospitalizations, and antibiotic therapy in the preceding 6 months, as well as data on bowel habits and concurrent medications, were collected before the beginning of treatment.

Stool samples for isolation of C. difficile were collected before the beginning of treatment and on days 7, 14, and 45 after the institution of therapy. Blood samples for complete leukocyte and erythrocyte counts and for determination of liver enzymes were taken at the same time.

On days 7, 14, and 45 after the beginning of treatment each patient was questioned as to the presence of diarrhea, abdominal cramps, temperature, nausea, vomiting, and rash occurring during or after the treatment. Diarrhea was defined as three or more liquid stools in a day (18).

Stool samples were inoculated on taurocholate-fructose-cyclodextrin-cefoxitin (CCFA) medium (5, 16, 17). The morphologically typical colonies were Gram stained. The colonies that yielded gram-positive and gram-variable bacilli were further purified on egg yolk agar. The quality of CCFA medium was tested by using the reference strains C. difficile B1 (kindly provided by S. P. Borrelli) and VPI 10463 (kindly provided by I. Florin). Quantitation of the number of C. difficile colonies isolated from stools was not done.

The feces were suspended in phosphate buffer and filtrated. Cytotoxicity of the filtrate was tested on Vero cells. The final dilution was 10⁻³. The results were obtained after a 24-h incubation period.

For the final identification, the strains of C. difficile were cultured on PYG medium (7). The volatile fatty acid profile was determined by gas chromatography. The strains with a typical fatty acid profile (7), as determined by comparison with profiles of reference strains C. difficile B1 and VPI 10463, were further tested as to the production of cytotoxin. C. difficile was cultured anaerobically in brain heart infusion for 4 days, and the culture filtrate was tested on Vero cells. The results were obtained after a 24-h incubation. The titer of cytotoxin was defined as the reciprocal value of the solution with 50% of cells changed. Positive samples were confirmed by neutralization with commercial anti-Clostridium sordellii serum (Wellcome).

A total of 89 patients, 71 adults (27 males and 44 females; age range, 18 to 71 years) and 9 children (5 males and 4 females; age range, 5 to 14 years), were treated with ceftriaxone in the period of the study. Two patients withdrew from treatment because of serious allergic reactions. An additional seven patients were excluded from the study because only one or two of their stool samples were available. Stool samples from days zero, 7, and 14 were available from 80 patients, while the fourth sample, from day 45 after the beginning of therapy, was available from only 49 patients.

Of the children, all but one were hospitalized for the total duration of treatment. Twenty-six adults were treated in the hospital, four adults were treated solely as outpatients, and the other adults were hospitalized for some period of time and then treated as outpatients. The mean duration of hospitalization for these adult patients was 8.2 ± 4.9 days, with a mean duration of outpatient treatment being 6.0 ± 5.3 days.

Thirty-two patients (40.0%) had diarrhea during the treatment, 15 (18.7%) reported nausea, and 7 (8.7%) reported a minor change in bowel habits. Several transient laboratory abnormalities were observed: raised liver enzymes in 11 (13.8%), leukopenia in 5 (6.3%), eosinophilia in 7 (8.8%), and thrombocytopenia in 2 patients (2.5%). Fifteen patients (18.7%) were hospitalized in the previous 6 months. In the same period, 23 patients (28.7%) received some kind of antibiotic therapy. None of the patients had a concurrent malignant condition or immunosuppressive therapy.

None of the patients was positive for C. difficile before the beginning of the therapy. C. difficile was isolated from stools of five patients (6.3%). On day 7 of the therapy C. difficile was isolated from a stool sample of 1 out of 80 patients (1.3%), on day 14 it was isolated from a stool sample of 1 out...
of 80 patients (1.3%) and on day 45 it was isolated from stool samples of 3 out of 49 patients (6.1%). Four of the strains of C. difficile produced cytotoxin, although none of the fecal filtrates was positive.

Only 2 (6.3%) out of 32 patients who reported diarrhea during or after the therapy were positive for C. difficile. Diarrhea occurring during the therapy in no case warranted interruption of therapy or endoscopic examination. None of the patients developed frank clinical signs or symptoms of colitis (fever, leukocytosis, abdominal cramping, or pain).

Although the carriage rate of C. difficile in normal healthy population is reported to be approximately 3% (6, 15, 16), none of our 80 patients was positive for C. difficile before the beginning of treatment. The isolation rate of 6.3% in our patients treated with ceftriaxone for 14 days was significantly lower (P < 0.0005) than that from a study by Privitera et al. (12), who found C. difficile in stools of 25% patients receiving ceftriaxone as a single dose for perioperative prophylaxis. The rate of isolation was also lower than expected according to our own experience. In another study in our department, we isolated C. difficile from 16 out of 61 patients (26.2%).

In our opinion, there exist several reasons for this lower isolation rate. The patients enrolled in the present study were essentially healthy without malignant disease or other states causing immunosuppression. None of them had any immunosuppressive medications, surgery, or a prolonged stay in intensive care, all of which are risk factors that predispose C. difficile infection (9, 10, 14). Diarrhea seems to be quite common complaint after ceftriaxone therapy, and these findings are similar to those of other investigators (11). However, only 2 of the 32 patients with diarrhea were positive for C. difficile. We also believe that our patients were quite self-conscious about their bowel habits and tended to report even minor disturbances.

Even though the children in our study were hospitalized for longer periods than the adults, none of them acquired C. difficile. The reason for this could be the strict hygienic practices observed on our pediatric wards. Nosocomial spread is known to be influenced by the practices of personnel on the ward (4).

It is interesting that the highest isolation rate was obtained 1 month after the end of the treatment. This findings confirm the possibility of acquiring C. difficile for some time after the therapy has been completed (8). The significance of this finding remains to be elucidated.

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