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Clinical and laboratory observations

Randomized, controlled trial of antibiotic therapy for *Escherichia coli* O157:H7 enteritis

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We undertook a prospective, controlled study to evaluate the effect of trimethoprim-sulfamethoxazole in children with proven *Escherichia coli* O157:H7 enteritis on the duration of symptoms, on fecal excretion of pathogen, and on the risk of progression to hemolytic-uremic syndrome. There was no statistically significant effect of treatment on progression of symptoms, fecal pathogen excretion, or the incidence of HUS (2/22 vs 4/25; $p = 0.67$). Our results suggest that a multicentric trial using rapid diagnostic methods to permit early randomization should be carried out. (J Pediatr 1992;121:299-303)

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The role of antibiotic therapy in *Escherichia coli* O157:H7 hemorrhagic colitis has not been defined. In vitro studies have shown that adding trimethoprim-sulfamethoxazole[1] or polymixin B[2] to culture of *E. coli* O157:H7 resulted in increased detection of verotoxin, which has been implicated in the pathogenesis of hemolytic-uremic syndrome. Clinical studies have for the most part failed to show any benefit from antibiotic therapy for hemorrhagic colitis, and some authors have even raised the concern that treatment may precipitate the development of HUS.[3] On the other hand, Cimolai et al.[4] found that appropriate antibiotic therapy lowered the risk that HUS would develop. The retrospective nature of these clinical studies does not allow definitive conclusions to be drawn, because the most severely ill patients were probably treated more often than those with milder cases, resulting in an allocation bias. Consequently, we carried out a prospective, randomized trial of antibiotic treatment with TMP-SMX in children with *E. coli* O157:H7 enteritis. The purpose of the study was to evaluate the effect of treatment of children with *E. coli* O157:H7 enteritis on the risk of HUS, on the clinical course of symptoms, and on the duration of pathogen excretion in the stools.

METHODS

Sainte-Justine Hospital is a tertiary care pediatric hospital in Montreal. From June 1, 1989, to June 1, 1990, all patients seen in the emergency department or hospitalized for a diarrheal syndrome and whose stool specimen contained *E. coli* O157:H7 were eligible for recruitment in this trial. Subjects were excluded from the study if HUS had already developed by the time culture results were available, if the subject could not be enrolled within 24 hours of obtaining culture results, or if the subject had a history of allergy to sulfonamide drugs. Subjects were excluded after randomization if the Laboratoire de Santé Publique du Québec (Provincial Public Health Laboratory) failed to confirm the presence of *E. coli* O157:H7. Patients who failed to provide sufficient clinical data were excluded.

HUS	Hemolytic-uremic syndrome
TMP-SMX	Trimethoprim-sulfamethoxazole

Questionnaires. As soon as a case of *E. coli* O157:H7 infection was identified, parents were contacted by telephone, or were met directly if the child was hospitalized. On the day of randomization, one of us (F.P.) completed a standardized questionnaire with the parents. He obtained information on previous symptoms and prior utilization of antidiarrheal agents. For all patients, daily clinical assessment was carried out by nurses during the hospitalization, or by the parents at home for 14 days after randomization. Assessment included the recording of fever, number of vomiting episodes and bowel movements, presence of gross blood in the stools, and presence of abdominal pain (graded as none, present without incapacity, or present with incapacity).

Stool specimens. Serial stool specimens were obtained by rectal swab in a transport medium (Amies Clear, NCS Diagnostics Inc., Mississauga, Ontario, Canada) on day 1, day 2, and every other day after randomization for a total of 10 days, either by nursing personnel if the patient was hospitalized or by the parents if the child was not hospitalized. Parents were taught how to perform the technique by a nurse and had to bring the samples within 48 hours.

Therapy. Patients were randomly selected, according to a computer-generated list of random numbers, to receive either a standard dose of TMP-SMX (4/20 mg/kg per dose) twice daily for 5 days or to receive no treatment. No placebo was available; neither patients nor the treating physicians were unaware of the treatment.

Outcomes. (1) Gastrointestinal symptoms assessed after randomization included vomiting, abdominal pain, bloody stool, and diarrhea (>5 stools per day); duration of fever (>38.5° C) was also assessed. (2) Stool excretion was evaluated by the duration of bacterial excretion of *E. coli* O157:H7 in each subject's stool after randomization. (3) HUS was defined as the presence of anemia with a hemoglobin value at less than the 3rd percentile for age, the presence of thrombocytopenia (platelet count $<100 \times 10^9$/L), the presence of schistocytes on blood smear, and acute renal failure (with a creatinine value greater than the 90th percentile for age). Signs and symptoms of HUS were explained to parents at entry into the study, and they were instructed to consult our center if any of these developed. During hospitalization, clinical surveillance for HUS was done by the treating physician. After patient discharge and for those who were not hospitalized, telephone surveillance was conducted weekly for 1 month.

At the end of the study, medical records of all cases of *E. coli* O157:H7 infection and records of all cases of HUS that occurred during the study period were reviewed and compared to determine whether HUS had developed among patients who were not recruited in the trial.

Laboratory methods. Stools were examined routinely for the various enteric pathogens according to standard techniques.[5] Sorbitol-negative colonies grown on MacConkey-sorbitol agar were subcultured onto blood agar and screened for *E. coli* O157:H7 by slide agglutination (Difco Laboratories, Inc., Detroit, Mich.). Colonies agglutinating with the antiserum were confirmed as *E. coli* by standard biochemical reactions. All strains were sent to the public health laboratory for serologic confirmation. Antibiotic susceptibility was tested by agar dilution using the Steers replicator.

Table. Characteristics of patients before randomization

	Treated (n = 22)		Not treated (n = 25)	
General: mean ± SD (range)				
Age (mo)	58.9 ± 46.5	(3-166)	68.7 ± 56.2	(4-213)
No. of days to first stool with *E. coli*	5.2 ± 5.6	(1-27)	4.3 ± 3.0	(1-13)
Day of randomization	7.4 ± 5.0	(2-27)	7.2 ± 2.7	(3-14)
Duration of symptoms: No. of days (range)				
Bloody stool	3.0	(0-5)	1.8	(0-8)
Abdominal pain	5.1	(0-12)	4.3	(0-12)
Fever (>38.5)	0.6	(0-6)	0.7	(0-2)
Vomiting	0.85	(0-4)	1.08	(0-4)
Diarrhea (>5/day)	4.95	(2-12)	4.1	(0-6)
Management: n (%)				
Hospitalized	16	(70)	16	(64)
Antidiarrheal agent	2	(9)	5	(20)

Significance: p = not significant for all values.

Statistics. Our results are expressed as mean ± SD. A two-sample t test was used for continuous data. The Mann-Whitney U test was used for numeric discrete variables. The chi-square test or the Fisher Exact Test was used for categoric data. Survival analysis by the actuarial method was used to compare the duration of bacterial stool excretion between groups and statistical significance was assessed by the log-rank test. All calculated p values are two tailed. A p value less than 0.05 was considered significant.

Ethics. The study was approved by the ethics committee of Sainte-Justine Hospital. Written informed consent was obtained for all patients.

RESULTS

From June 1, 1989, to June 1, 1990, a total of 96 cases of enteritis caused by *E. coli* O157:H7 were detected. Forty-seven patients entered the randomized protocol in which 22 were treated and 25 were not. No patients were lost to follow-up. Forty-nine patients failed to be included in the study (no confirmation by the public health laboratory: 1 patient; insufficient clinical data: 1; refusal to participate: 23; failure to contact subjects in time: 24). The mean age of patients not included in the study was 71.5 ± 60.0 months, and that of our study population was 64.1 ± 51.6 months (p = NS). Among all patients included in the study, diarrhea occurred in 100% (47/47), bloody stools in 97.8% (45/46), abdominal pain in 90.7% (39/43), vomiting in 54.4% (25/46), and fever in 27% (10/37).

All strains of *E. coli* O157:H7 were susceptible to TMP-SMX. As shown in the Table, patients were comparable before randomization.

Course of symptoms after randomization. There was no difference between the two groups regarding the duration of follow-up (treated vs nontreated, mean days [range]: 13.4 (5 to 30) vs 12.8 [0 to 24]), bloody stools (0.63 [0 to 4] vs 0.63 [0 to 5]), diarrhea (0.53 [0 to 5] vs 0.91 [0 to 5]), abdominal pain (1.78 [0 to 8] vs 2.05 [0 to 10]), vomiting (0.72 (0 to 9) vs 0.26 [0 to 3]) or fever (0.05 [0 to 1] vs 0.12 [0 to 2]).

Pathogen excretion after randomization. All patients submitted the stool specimens specified in the protocol except for three who were excluded from the analysis. On the day of randomization, 80% of patients in both groups were still excreting the pathogen in the stools. Duration of excretion of the microorganisms did not differ between groups (p = NS) (Figure). Sixty-six percent excreted between 1 and 2 weeks and 24% excreted for less than 1 week after onset of symptoms. Five patients (9%), equally distributed within the groups, still had positive culture results more than 2 weeks after the onset of symptoms.

Occurrence of hemolytic-uremic syndrome. Overall, HUS developed in six patients. Two (8%) were in the treated group and four (16%) in the control group (relative risk = 0.57, 95% confidence interval = 0.09 to 3.46; p = 0.67). Three were male and three, female. Mean age was 60.2 ± 51.9 months (range 15 to 156). The mean interval between onset of symptoms of enteritis and diagnosis of HUS was 7.5 days (range 2 to 13 days). HUS developed in 2 of the 49 patients who failed to be recruited. This proportion was not statistically different from that observed in the study population.

DISCUSSION

To our knowledge, this is the first randomized, controlled study assessing the effect of antibiotic therapy in patients with *E. coli* O157:H7 enteritis. Despite our efforts, we could

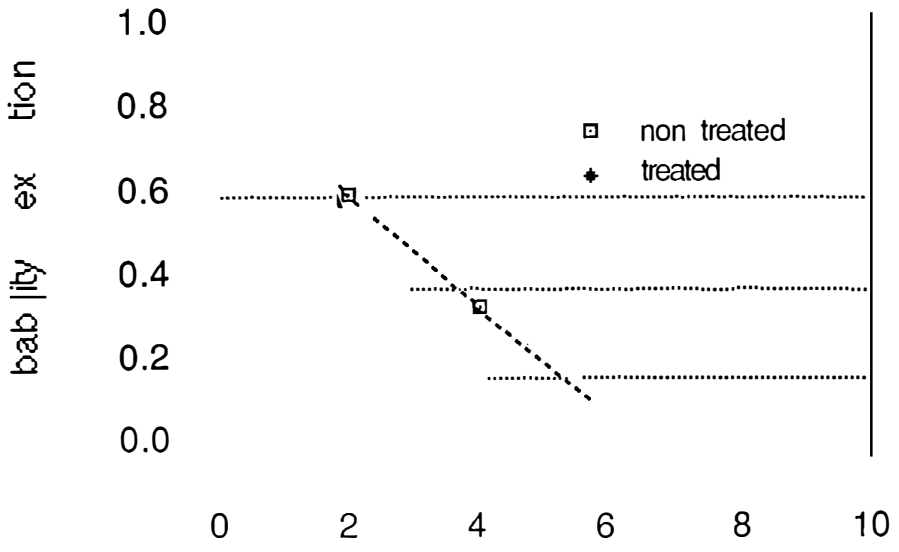

Figure. Survival analysis for bacterial excretion of *E. coli* O157:H7 in the stools for treated and control groups after randomization (p = NS). *Day 0* represents the day of randomization.

not obtain a satisfactory placebo. Most of the study endpoints (duration of bacterial excretion and occurrence of HUS) were defined with objective criteria; a detection bias seemed unlikely, and a blind study design appeared a less important issue.

Antibiotic therapy did not improve the clinical course of *E. coli* O157:H7 enteritis; the main reason may be that the day of randomization in most patients was rather late in the course of illness. This was attributable to the time interval between onset of symptoms and consultation, and to the minimum 48 hours' delay in obtaining the preliminary report of the stool cultures. Total duration of disease in our patients was comparable to that found in previous reports,[4-6] suggesting that lack of clinical benefit from antibiotic therapy was not due to the selection of a population with milder disease. It remains possible that the earlier initiation of treatment could be of clinical benefit, as shown in *Campylobacter* enteritis.[7]

Antibiotic therapy did not shorten the duration of pathogen excretion. The limitations of our study in this regard are twofold. First, there exists no enrichment procedure permitting detection of small amounts of *E. coli* O157:H7 in the stools; therefore a longer excretion period at a low level may have been missed. Second, as previously stated, antibiotic therapy was started relatively late.

Although our small sample size limited the power of the study to detect differences in results between treatment groups, there was no evidence of an increased risk of HUS in our treated patients, and in fact there were fewer cases of HUS among those who received TMP-SMX. The two groups were comparable with regard to both duration and severity of illness before randomization. Groups were also comparable for the three known risk factors of HUS: age,[8,9] prolonged pathogen excretion,[9] and use of antimotility agents.[9] Among patients who failed to be included in the trial, the chart review showed no significant difference in mean age or in frequency of occurrence of HUS; therefore there was no evidence of selection bias among our population.

We conclude that antibiotic therapy for *E. coli* O157:H7 enteritis showed no benefit of treatment in duration of symptoms, in duration of bacterial stool excretion, or in the occurrence of HUS. Current use of antibiotic therapy is probably not indicated. Because this trial has not shown an increased risk of HUS, it appears appropriate to set up a multicenter randomized trial of early antibiotic therapy, using new rapid detection methods,[10] to establish the role of early therapy in the management of this illness.

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Use of ciprofloxacin in an infant with ventriculitis

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Ciprofloxacin was used successfully in a neonate with ventriculitis caused by a multiply resistant strain of *Enterobacter cloacae*. Limited pharmacokinetic data indicated that adequate concentrations of drug could be attained in cerebrospinal fluid. (J PEDIATR 1992;121:303-5)

Despite potential adverse effects,[1-3] ciprofloxacin has been used to treat infants and young children with life-threatening infections caused by resistant bacteria.[4-6] However, there is a lack of data concerning the pharmacokinetics of ciprofloxacin in pediatric patients and uncertainty with respect to the levels of the drug that can be achieved. We recently used ciprofloxacin to treat an infant with polymicrobial ventriculitis. The presence of a ventricular drain in this patient enabled us to measure multiple serum and simultaneous cerebrospinal fluid drug levels and to calculate serum pharmacokinetic data, as well as data on penetration of the drug into CSF.

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CASE REPORT

The patient was a 10-month-old girl with multiple medical problems associated with extreme prematurity. She had severe bronchopulmonary dysplasia, had both a tracheostomy and a gastrostomy tube in place, and had undergone numerous courses of broad-spectrum antibiotic therapy for pneumonia, tracheitis, and septicemia. A central venous catheter had been placed for administration of nutrition and medication. Bilateral grade IV intraventricular hemorrhages necessitated placement of a ventriculoperito-

CSF Cerebrospinal fluid

neal shunt, which had required multiple revisions. Ten days after a shunt revision the patient had fever, pallor, irritability, and abdominal distention. Aspiration of CSF from the ventriculoperitoneal shunt yielded thick, dark green material that contained 1030 leukocytes/mm^3 (30% polymorphonuclear cells and 70% mononuclear cells) and 50 erythrocytes/mm^3; the protein content was 304

Table. Ciprofloxacin concentrations in CSF

Dose No.	Dosage (mg/12 hr)	Time from end of infusion (hr:min)	Concentrations		
			Serum (mg/L)	CSF (mg/L)	CSF/serum (%)
6	150	0:15	11.6	1.4	12.1
8	150	0:40	9.5	1.4	14.7
		11:01	0.8	1.4	175.0
24	112.5	1:01	5.0	1.2	24.0
		5:15	2.3	1.5	65.2

mg/dl, and there was no detectable glucose. A radiologic contrast study demonstrated that the distal end of the shunt was in the lumen of the colon. Intravenous treatment with ceftriaxone and tobramycin was begun. Initial culture specimens of material from the shunt yielded *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Escherichia coli*, *Enterobacter cloacae*, and *Candida albicans*.

The ventricular end of the shunt was externalized, and the abdominal portion was withdrawn. Antibiotic therapy was changed to ceftazidime and amikacin, to which all of the isolated organisms were initially susceptible. Fluconazole was added, and all subsequent fungal cultures of blood and CSF specimens remained sterile. Renal function remained normal (serum creatinine level: 0.5 mg/dl) throughout the course of therapy. Follow-up CSF culture specimens obtained while the patient was receiving ceftazidime and amikacin revealed that most of the initial organisms had been eradicated but that a multiply resistant strain of *E. cloacae*, susceptible only to imipenem, amikacin, and ciprofloxacin, had emerged. Therapy with imipenem was begun and ceftazidime use was discontinued. Analysis of ventricular CSF after 7 days of treatment revealed 308 leukocytes/mm^3 (42% polymorphonuclear cells and 58% mononuclear cells) and 83 erythrocytes/mm^3, a glucose concentration of 16 mg/dl, and a protein concentration of 720 mg/dl. Culture of CSF specimens yielded a pure growth of *E. cloacae* susceptible only to ciprofloxacin and amikacin (minimum inhibitory concentrations were 0.25 μg/ml and 2 μg/ml, respectively). Cultures of blood specimens from the central venous line and peripheral veins had no growth. Administration of ciprofloxacin was initiated after discussion with the child's parents about the potential risks and benefits.

Ciprofloxacin, 35 mg/kg per 24 hours, was administered intravenously every 12 hours via the central venous line. Because of the patient's small size and the relatively large volume required for infusion, each dose of the drug was administered during a 2-hour period. Imipenem and amikacin were continued. The presence of an external CSF drain permitted frequent sampling of CSF without further invasive procedures.

Ciprofloxacin therapy was continued for 21 days. The external drain was removed and replaced with a new internal shunt on the seventh day of treatment. Cultures of CSF specimens obtained 5, 12, and 35 days after initiation of ciprofloxacin therapy remained sterile.

METHODS

Pharmacokinetics. Drug levels in serum and CSF were measured by high-pressure liquid chromatography (model 6000A, with fluorescence detector model 420; Waters Associates, Inc., Milford, Mass.) with the method described by Morton et al.[7] No ciprofloxacin was detected in CSF or serum samples obtained before initiation of therapy.

The serum level of ciprofloxacin before the fifth dose was 0.9 μg/ml. A postinfusion level in serum drawn 15 minutes after the end of infusion of the sixth dose was 11.6 μg/ml. A simultaneously obtained CSF level was 1.4 μg/ml. The dosage was then decreased to 25 mg/kg per 24 hours.

Elimination half-life was estimated from serum concentrations measured before and after the eighth and twenty-fourth doses. The elimination half-life calculation was based on the assumption of the log-linear first-order kinetic model.[8] Elimination half-lives for the eighth and twenty-fourth doses were calculated at 2.89 hours and 3.79 hours, respectively. Concentrations of ciprofloxacin in CSF were also measured during administration of the sixth, eighth, and twenty-fourth doses. The results are shown in the Table.

DISCUSSION

Fluoroquinolone antibiotics inhibit DNA gyrase.[9] Because of their unique mechanism of action, fluoroquinolones are valuable agents in the treatment of life-threatening polymicrobial infections in which resistance to other antibiotics has developed. As an antibiotic class the fluoroquinolones have moderate penetration into CSF,[10] and ciprofloxacin has been successfully used to treat ventriculitis in adults.[11] The concentration of ciprofloxacin in CSF in adults with meningitis has been reported to be as high as 40% of serum levels 60 minutes after the end of infusion,[12] whereas, in the absence of meningeal inflammation, CSF peak levels averaged 8% of serum levels.[13]

Case reports of successful ciprofloxacin treatment in infants and children with meningitis[4, 5] have usually not included measurements of CSF concentration of the drug. However, Bannon et al.[6] reported a mean CSF concentra-

tion of 64% of the corresponding postdose serum levels, a percentage based on two measurements of CSF in an infant with meningitis; the time of CSF sampling in relation to drug infusion was not specified. The high ciprofloxacin penetration reported by Bannon et al. may have been due to differences in drug penetration across the neonatal blood-brain barrier compared with that in adults, or may have resulted from the timing of specimen collection.

In our patient the estimated half-lives of 2.89 hours after the eighth dose and 3.79 hours after the twenty-fourth dose were similar to the half-life of 3 to 4 hours reported in adults.[9, 10] The increase in half-life from the eighth to the twenty-fourth dose may represent an accumulation phenomenon, although we are cautious about this conclusion because our half-life calculations are based on only two points. Alternatively, the observed differences may be the result of variation in drug administration and sampling.

The CSF level of ciprofloxacin remained nearly constant at each sampling interval in our patient, even 5 and 11 hours after drug infusion. Thus ciprofloxacin levels remained at least fourfold greater than the minimum inhibitory concentration of ciprofloxacin to the *E. cloacae* isolate. These levels were consistent with eradication of the organism.

Our experience with this patient suggests that CSF levels of ciprofloxacin adequate for treatment of ventriculitis may be attained in infants. Although ciprofloxacin must still be used cautiously because of the potential for adverse effects, this antibiotic may be a valuable agent in the treatment of some infants who have central nervous system infections with bacteria resistant to other antibiotics.

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