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CASE REPORT

Encephalopathy, disseminated intravascular coagulation, and hemolytic–uremic syndrome after infection with enterohemorrhagic *Escherichia coli* O111

Sadaya Matano · Katsuhisa Inamura · Michio Konishi · Toshiya Okumura · Hiroshi Kawai · Toshiyuki Okamura · Yoshiko Takata · Keiko Yamada · Misato Obata · Hajime Nagata · Yoshiko Muramoto · Tatsuho Sugimoto

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Abstract An outbreak of enterohemorrhagic *Escherichia coli* (EHEC) occurred in Toyama and other prefectures in Japan during 2011. Some patients, including adults, showed complications such as encephalopathy, disseminated intravascular coagulation, and hemolytic–uremic syndrome, and the disease course was extremely aggressive. This report describes the clinical features of four patients infected with *Escherichia coli* (*E. coli*) O111 who developed very severe to fatal complications. The initial symptoms in all patients included abdominal pain, diarrhea, and bloody stools, and neurological abnormalities started to appear from 1 to 3 days after admission. Vomiting and pyrexia developed in three patients. Leukocyte counts, lactate dehydrogenase (LDH), and fibrin/fibrinogen degradation products were elevated, and thrombocytopenia was evident. Extremely elevated LDH and severe thrombocytopenia were characteristic at the time encephalopathy became apparent. All patients received oral fosfomycin, intravenous antibiotics, and anticoagulant therapy, three received gamma globulin, plasma exchange, and blood transfusion, and two received steroids and dialysis. Three patients required mechanical ventilation, and two adult patients died. *E. coli* O111 positive for Shiga toxin 2 was detected in stool culture in two patients, and serological tests for *E. coli* O111 were positive in the other two patients. In conclusion, EHEC O111 can cause severe illness in children and adults, and the prognosis becomes poorer as the severity of complications increases. Close monitoring including platelet counts and LDH are useful. Once these clinical parameters change, intensive treatment should be provided to prevent the development of severe complications.

Keywords Shiga toxin-producing *Escherichia coli* · Outbreak · Thrombocytopenia · Acute abdomen · Lactate dehydrogenase

S. Matano (✉) · Y. Muramoto
Infection Control Unit, Tonami General Hospital, Tonami, Toyama 939-1395, Japan
e-mail: eievui7@p1.tst.ne.jp

K. Inamura · H. Kawai · T. Okamura · Y. Takata · T. Sugimoto
Department of Gastroenterology, Tonami General Hospital, Tonami, Toyama 939-1395, Japan

M. Konishi · K. Yamada · M. Obata
Department of Pediatrics, Tonami General Hospital, Tonami, Toyama 939-1395, Japan

T. Okumura
Department of Nephrology, Tonami General Hospital, Tonami, Toyama 939-1395, Japan

H. Nagata
Department of Clinical Laboratory, Tonami General Hospital, Tonami, Toyama 939-1395, Japan

Introduction

Infection with enterohemorrhagic *Escherichia coli* (EHEC) causes many severe illnesses, including hemolytic–uremic syndrome (HUS), disseminated intravascular coagulation (DIC), and encephalopathy. The key virulence factors associated with complications are Shiga toxins (Stx), Stx-1 and Stx-2. The most prevalent serotype is EHEC O157, but other serotypes can also cause these complications. About 2,000 EHEC infections in Japan were reported during 2010. Most infections were caused by O157 (69%), followed by O26 (17.0%) and O111 (1.8%) [1]. Several EHEC O111 outbreaks have occurred in Japan [2–6]. Tanaka et al. described 22 children who developed acute

enteritis associated with EHEC O111. Five (22.7%) were hospitalized, and 1 (0.5%), who developed HUS, died [2]. Kishimoto [3] detected EHEC O111 in 40 patients, among whom only 4 (10%) attended a hospital and none was admitted. Outbreaks of EHEC O111 infection in other countries have also been reported [7–9]. Piercefield et al. [8] described an EHEC O111 outbreak in Oklahoma in which HUS or neurological abnormalities developed in some infected patients. Gerber et al. [9] described 394 pediatric patients with HUS, some of whom had EHEC O111 infection. These findings indicate that EHEC O111 infection can cause severe illness.

An outbreak of EHEC occurred in Toyama and other prefectures in Japan between late April and early May 2011. The Toyama Prefectural Department of Health announced on June 10 that 163 persons were infected within the prefecture, and 81 of them had symptoms of EHEC infection. Both EHEC O111 and EHEC O157 were identified in these patients. Details of this outbreak required a considerable amount of time to collect because of the number of patients involved. The courses of some patients were extremely aggressive, and some were fatal. Because EHEC O111 outbreaks may occur again at any time, we describe four patients with EHEC O111 infection who developed complications of encephalopathy, DIC, and HUS to clarify the clinical characteristics of EHEC infection.

Case reports

Case 1 (Fig. 1). A 14-year-old Japanese boy had been in good health until mid-April 2011 when symptoms of vomiting, diarrhea, and bloody stools developed. He had consumed raw meat 2 days before the symptoms developed. He presented to our hospital, where he received oral fosfomycin (FOM). He was admitted 1 day after receiving medication because of persistent symptoms. Proteinuria and hematuria were evident, hematological findings revealed obvious leukocytosis, and lactate dehydrogenase (LDH) and C-reactive protein (CRP) were mildly elevated. Administration of oral FOM was continued. Somnolence and convulsions started 1 day after admission. At this point he had mild anemia, severe thrombocytopenia, and extremely elevated creatinine, LDH, and fibrin/fibrinogen degradation products (FDP). Cranial computed tomography (CT) revealed an area of low density, mainly at the basal ganglia, and brain edema. He was treated with intravenous antibiotics, low molecular weight heparin, dexamethasone, and an anticonvulsant, and with plasma exchange, dialysis, and mechanical ventilation. He became comatose, and renal failure persisted despite these strategies. A serological test detected antibodies against *Escherichia coli* (*E. coli*) O111, although stool cultures were negative for this pathogen. As of the time of writing, the patient remains hospitalized and is still receiving treatment.

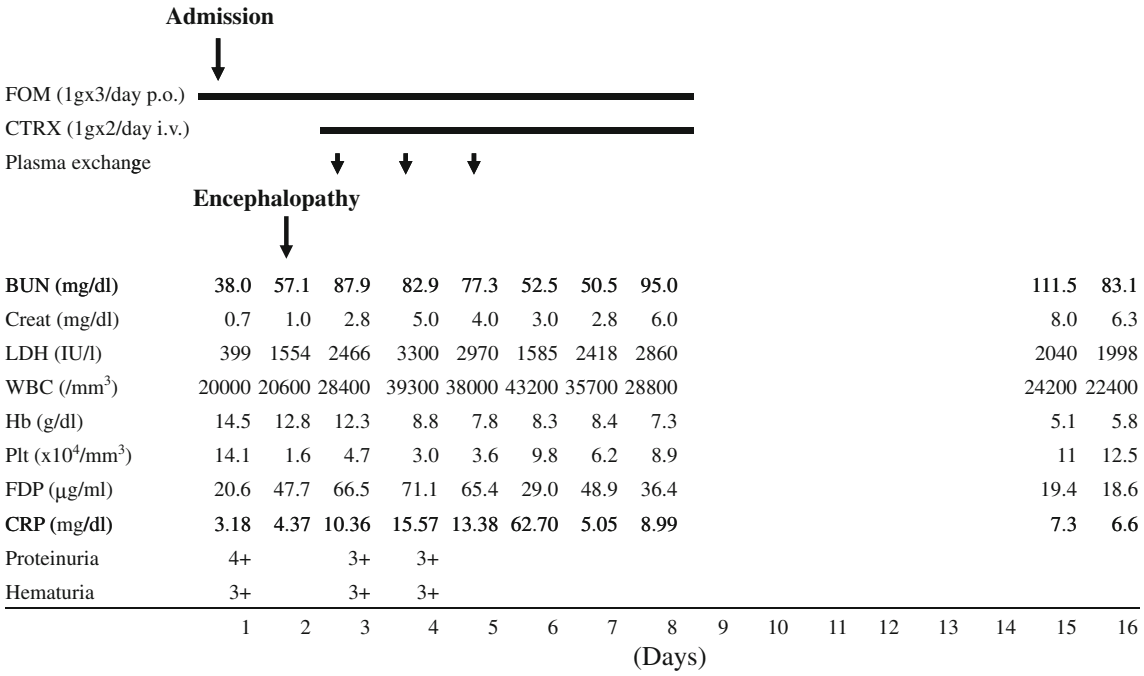


Fig. 1 Clinical course: 14-year-old boy. *FOM*, fosfomycin; *p.o.*, per os; *CTRX*, ceftriaxone; *i.v.*, intravenous; *BUN*, blood urea nitrogen; *Creat*, creatinine; *LDH*, lactate dehydrogenase; *WBC*, white blood cell count; *Hb*, hemoglobin; *FDP*, fibrin/fibrinogen degradation products; *CRP*, C-reactive protein

Case 2 (Fig. 2). A 43-year-old Japanese woman had been in good health until mid-April 2011, when symptoms of abdominal pain, diarrhea, and bloody stools developed. She had consumed raw meat 3 days earlier. Mild leukocytosis, anemia, elevated CRP, and proteinuria were found. She was admitted to our hospital, and oral FOM was administered. She became somnolent and rapidly progressed to coma 2 days later. Hematological findings revealed obvious leukocytosis and severe thrombocytopenia, and biochemical findings revealed extremely elevated LDH, FDP, and creatinine. Cranial CT revealed an area of low density, mainly at the basal ganglia, and brain edema. She was treated with intravenous antibiotics, plasma exchange, dialysis, gamma globulin, gabexate mesilate, mechanical ventilation, and dexamethasone. Neurological abnormalities and renal failure progressed despite these treatments, and she died 7 days after admission. Serological tests confirmed antibodies against *E. coli* O111, although stool cultures were negative for this pathogen.

Case 3 (Fig. 3). A 63-year-old Japanese man had been healthy until mid-April 2011, when abdominal pain, diarrhea, and bloody stools developed. He had consumed raw meat 3 days earlier. He was immediately admitted to our hospital upon presentation with obvious leukocytosis, mildly elevated CRP, proteinuria, and hematuria. Oral FOM was administered. However, he became lethargic 3 days after admission. At that time, leukocyte counts and LDH were extremely elevated, creatinine was mildly elevated, and he had severe thrombocytopenia. Cranial CT demonstrated no abnormalities. He received intravenous antibiotics, gabexate mesilate, fresh frozen plasma, and platelet transfusion. The neurological abnormalities and renal failure gradually improved. *E. coli* O111 was detected in stool cultures, and was found to be positive for Stx-2 by polymerase chain reaction (PCR). The patient was discharged and no longer requires treatment.

Case 4 (Fig. 4). A 70-year-old Japanese woman had been previously administered prednisolone to treat myositis. Abdominal pain, diarrhea, and bloody stools developed during mid-April 2011. She had consumed raw meat 3 days earlier. She was immediately admitted to our hospital upon presentation with proteinuria and mildly elevated leukocyte counts, LDH, and CRP values. Oral FOM was administered. Convulsions appeared 3 days later. At that time she had obvious leukocytosis, extremely high LDH and creatinine levels, and severe thrombocytopenia. Cranial CT revealed an area of low density, mainly at the basal ganglia, and brain edema. She was treated with intravenous antibiotics, gamma globulin, nafamostat mesilate, and an anticonvulsant, as well as plasma exchange and mechanical ventilation. The neurological abnormalities and renal failure did not improve, and she died 6 days after admission. *E. coli* O111 was detected in stool cultures and was found to be positive for Stx-2 by PCR.

We described four patients with *E. coli* O111 infection and severe complications. Diagnosis was confirmed by bacterial examinations in two patients, in whom PCR detected Stx-2, and by serological tests in the other two. The clinical features of these patients are shown in Table 1. All four patients had eaten raw meat at the implicated restaurant and started to develop symptoms after an incubation period of 2–3 days. All patients developed gastrointestinal and neurological symptoms including seizure. All patients underwent cranial CT, and an area of low density mainly at the basal ganglia and brain edema was identified in three patients. These patients also developed pyrexia

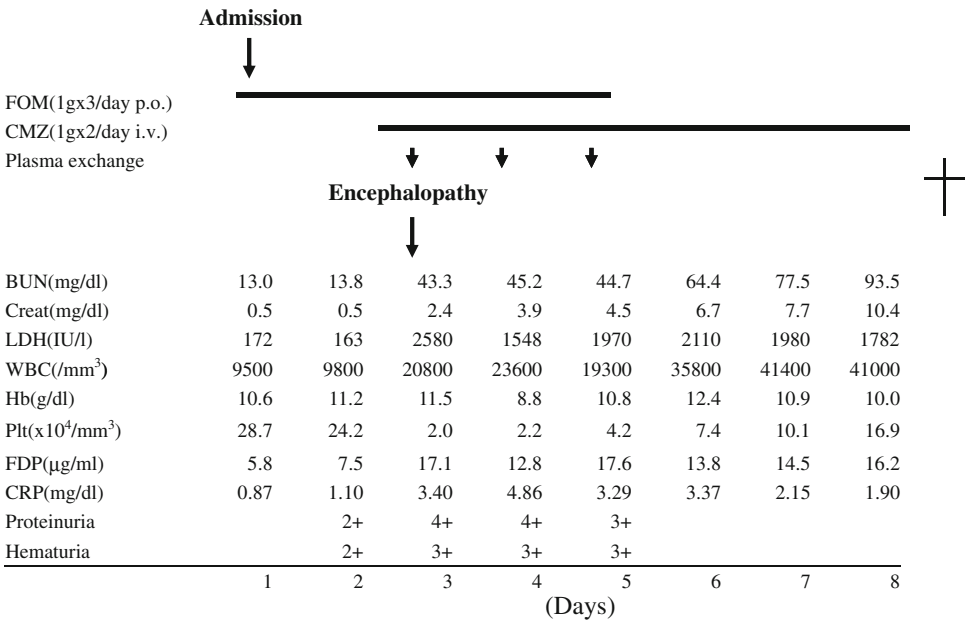
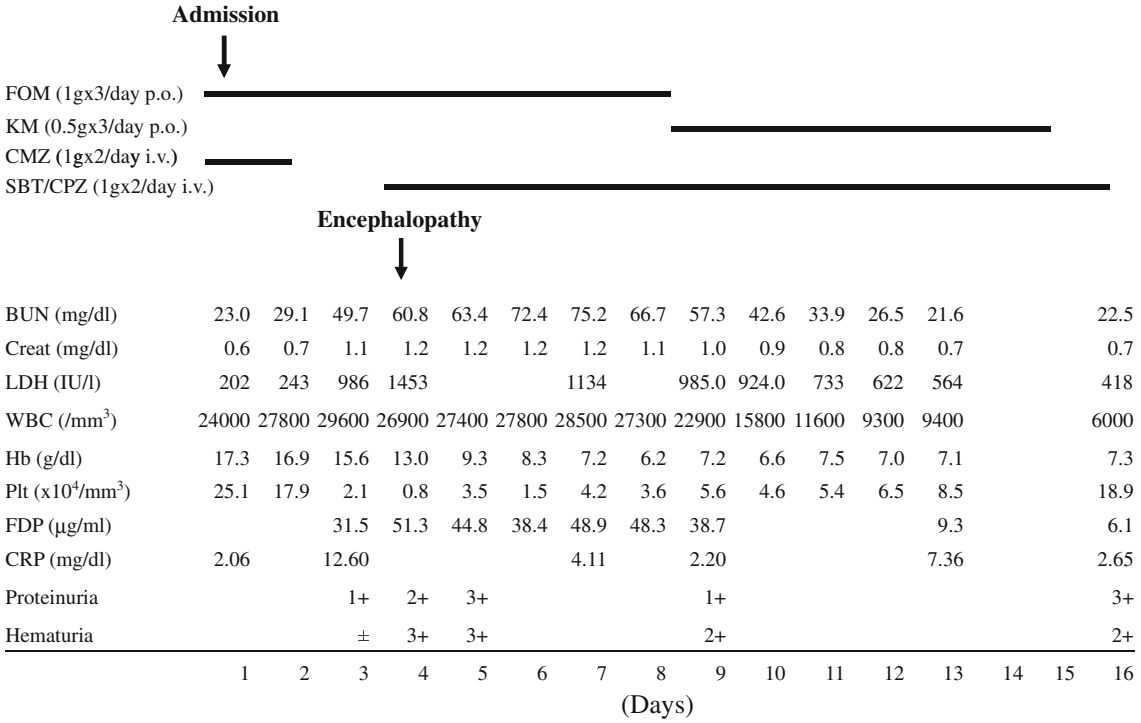


Fig. 2 Clinical course: 43-year-old woman. *CMZ*, cefmetazole

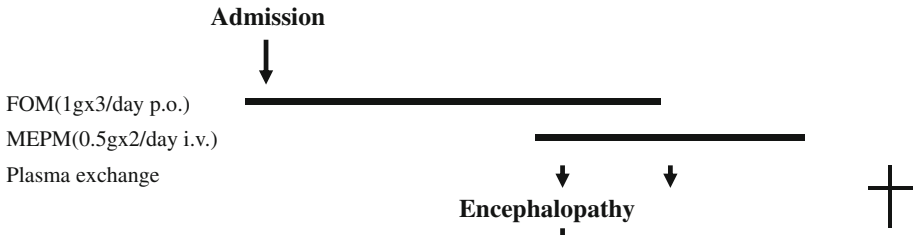


BUN (mg/dl)	23.0	29.1	49.7	60.8	63.4	72.4	75.2	66.7	57.3	42.6	33.9	26.5	21.6			22.5
Creat (mg/dl)	0.6	0.7	1.1	1.2	1.2	1.2	1.2	1.1	1.0	0.9	0.8	0.8	0.7			0.7
LDH (IU/l)	202	243	986	1453			1134		985.0	924.0	733	622	564			418
WBC (/mm^3)	24000	27800	29600	26900	27400	27800	28500	27300	22900	15800	11600	9300	9400			6000
Hb (g/dl)	17.3	16.9	15.6	13.0	9.3	8.3	7.2	6.2	7.2	6.6	7.5	7.0	7.1			7.3
Plt (x10^4/mm^3)	25.1	17.9	2.1	0.8	3.5	1.5	4.2	3.6	5.6	4.6	5.4	6.5	8.5			18.9
FDP (μg/ml)			31.5	51.3	44.8	38.4	48.9	48.3	38.7				9.3			6.1
CRP (mg/dl)	2.06		12.60				4.11		2.20				7.36			2.65
Proteinuria			1+	2+	3+				1+							3+
Hematuria			±	3+	3+				2+							2+
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16

(Days)

Fig. 3 Clinical course: 63-year-old man. *KM*, kanamycin; *SBT/CPZ*, sulbactam/cefoperazone

Fig. 4 Clinical course: 70-year-old woman. *MEPM*, meropenem



BUN(mg/dl)	25.0	34.0	52.8	67.4	80.0	100.6	109.5
Creat(mg/dl)	0.9	1.5	2.1	3.0	4.8	6.9	7.9
LDH(IU/l)	272	335	467	1074	917	1413	
WBC(/mm^3)	12500	17900	22100	20200	18400	21400	20600
Hb(g/dl)	15.1	15.8	15.2	15.4	13.7	10.6	9.8
Plt(x10^4/mm^3)	27.8	23.1	12.1	3.2	2.2	8.7	9.8
FDP(μg/ml)			27.1	21.9	15.9	29.7	
CRP(mg/dl)	3.24	17.17	20.03	19.09	23.60	28.67	
Proteinuria	1+	-	3+	4+			
Hematuria	-	±	3+	3+			
	1	2	3	4	5	6	7

(Days)

after admission. All patients initially received oral FOM, followed by intravenous antibiotics with anticoagulant therapy after the neurological abnormalities appeared. Three received gamma globulin, plasma exchange, blood transfusion, and mechanical ventilation, and two received dexamethasone and dialysis. Only case 3 was discharged, and case 1 remains hospitalized and under treatment. Cases 2 and 4 died at 7 and 6 days after admission, respectively.

The results of the hematological tests are summarized in Table 2. Upon admission, leukocyte counts were >20,000/

Table 1 Clinical features, treatment, and prognosis of patients infected with *Escherichia coli* O111

Patient no.	Age (years)	Sex (M/F)	Incubation period (days)	Symptoms			Therapy								Outcome
				Gastrointestinal	Neurological	Fever (>38°C)	Antibiotics		Anticoagulants	Transfusion	Others	Dialysis	Plasma exchange	Mechanical ventilation	
							Oral	Intravenous							
1	14	M	2	Abdominal pain, bloody stool, diarrhea, vomiting	Seizure, coma	Yes	FOM	CTRX	Low molecular weight heparin	RBC	DEX, gamma globulin	Yes	Yes	Yes	Alive
2	43	F	3	Abdominal pain, bloody stool, diarrhea, vomiting	Coma	Yes	FOM	CMZ	Gabexate mesilate	RBC, platelets	DEX, gamma globulin	Yes	Yes	Yes	Dead
3	63	M	3	Abdominal pain, bloody stool, diarrhea	Lethargy	No	FOM, KM	CMZ, SBT/CPZ	Gabexate mesilate	RBC, platelets, FFP		No	No	No	Alive
4	70	F	3	Abdominal pain, bloody stool, diarrhea, vomiting	Seizure, coma	Yes	FOM	MEPM	Nafamostat mesilate		Gamma globulin	No	Yes	Yes	Dead

FOM fosfomycin, *KM* kanamycin, *CTRX* ceftriaxone, *CMZ* cefmetazole, *SBT/CPZ* sulbactam/cefoperazone, *MEPM* meropenem, *DEX* dexamethasone, *RBC* red blood cells, *FFP* fresh frozen plasma

Table 2 Hematological findings of patients infected with *Escherichia coli* O111

Patient no.	WBC (/mm^3)		Hb (g/dl)		Platelets ($\times 10^4$/mm^3)		LDH (IU/l)		Creatinine (mg/dl)		FDP (μg/ml)		CRP (mg/dl)	
	Admission	Maximum	Admission	Minimum	Admission	Minimum	Admission	Maximum	Admission	Maximum	Admission	Maximum	Admission	Maximum
1	20,000	43,200	14.5	5.1	14.1	1.6	399	3,300	0.7	8.0	20.6	71.1	3.18	15.57
2	9,500	41,400	10.6	8.8	28.7	2.0	172	2,580	0.5	10.4	5.8	17.6	0.87	4.86
3	24,000	29,600	17.3	6.2	25.1	0.8	202	1,453	0.6	1.2	31.5	51.3	2.06	12.60
4	12,500	21,400	15.1	9.8	27.8	2.2	272	1,413	0.9	7.9	27.1	29.7	3.24	28.67

WBC white blood cell count, *Hb* hemoglobin, *LDH* lactate dehydrogenase, *FDP* fibrin/fibrinogen degradation products, *CRP* C-reactive protein

mm^3 in two patients, and the leukocyte counts of all patients eventually increased to >20,000/mm^3. Anemia was initially identified in one patient. Hemoglobin in all patients decreased to <10 g/dl during the clinical course. Although thrombocytopenia could not be identified upon admission, the platelet counts of all patients decreased to <22,000/mm^3. LDH value was initially elevated in two patients, and that of all patients also clearly increased over time. Serum creatinine levels appeared essentially normal upon admission but became elevated thereafter. FDP values upon admission were elevated in three patients but later increased in all patients. CRP values upon admission were mildly elevated in all patients but reached 10 mg/dl during the course of the disease in three patients. The transition of platelet counts and LDH occurred within 3 days. In addition, LDH values were >1,000 IU/l and platelet counts were <22,000/mm^3 when the neurological abnormalities occurred.

Discussion

Many severe illnesses, including HUS, DIC, and encephalopathy, are caused by EHEC. Gerber et al. described 394 children in Germany and Austria who developed HUS and found that HUS was associated with EHEC infection in 83% of patients. The most frequent serotype was O157, but O111 was detected in 6 patients [9]. Brooks et al. described non-O157 EHEC infections including 21 patients with HUS in the United States. About half the patients with HUS were infected with EHEC O111 [10]. Piercefield et al. described an EHEC O111 outbreak in the United States in which 16.7% of patients had confirmed or probable EHEC O111 infection complicated with HUS, and 26.4% of hospitalized patients developed neurological abnormalities. Elevated leukocyte counts and creatinine values upon admission and vomiting before admission were associated with subsequent HUS [8]. Outbreaks of EHEC O111 in Japan have been reported [2–6], but the infection was fatal in only one pediatric patient [2]. To our knowledge, this is the first report of Japanese adults infected with EHEC O111 who developed a lethal clinical course.

All the patients described herein were considered to be in good health, except for one who had previously been prescribed steroid. One patient had vomited before admission, none had fever, all had normal serum creatinine values, and two had leukocyte counts >20,000/mm^3. In contrast to other reports [8, 11], neither the clinical data nor the symptoms upon admission could predict the likelihood of subsequent HUS or encephalopathy developing during this outbreak. The incubation period for the reported patients was within 3 days, and this short period might have been associated with subsequent HUS and encephalopathy. We also consider that platelet counts and LDH are useful markers as these data rapidly and noticeably changed after admission; LDH increased to 1,000 IU/l and the platelet count decreased to <22,000/mm^3 when encephalopathy occurred. This is a preliminary report, and details of this outbreak are now under investigation. The usefulness of these laboratory data should be reevaluated in a future study. Cranial CT findings were abnormal in three of our four patients. Two of three patients who showed abnormal cranial CT findings died, and one remains hospitalized and under treatment. Cranial CT findings were similar to those of acute necrotizing encephalopathy in children [12]. We agree with other investigators that cerebral involvement is associated with poor prognosis [9, 11]. The present study found that all detectable EHEC O111 was positive for Stx-2, which is closely associated with an increased risk of HUS [10, 11]. These findings suggest that close monitoring including LDH and platelet counts is important, especially for patients with Stx-2-producing EHEC. Intensive treatment is indicated as soon as the platelet count decreases or LDH increases to prevent subsequent complications.

With respect to treatment, the Ministry of Health, Labour and Welfare recommended in 1997 that EHEC infections should be treated with oral antibiotics. All four of our patients developed severe complications despite the administration of oral FOM, in contrast to the good course of many other patients infected with EHEC O111 during this outbreak who were treated with oral FOM. We consider that, although effective, oral FOM cannot always prevent severe complications in patients infected with EHEC O111. The Japanese Society for Pediatric Nephrology proposed guidelines for treating HUS caused by EHEC infection in 2000. These guidelines recommend supportive therapy including infusion, dialysis, blood transfusion, and treatment for encephalopathy and DIC, whereas plasma exchange, gamma globulin, and antibiotics are controversial strategies. Others have also reviewed treatment for EHEC infection [11]. The present study could not define an optimal treatment strategy with which to prevent HUS or encephalopathy. We consider that current treatment strategies are ineffective once severe complications have developed. Therefore, intensive therapy such as plasma exchange, gamma globulin, intravenous antibiotics, continuous hemodiafiltration, and polymyxin-B immobilized fiber therapy, pulse steroid treatment, and recombinant thrombomodulin should be started before complications arise.

In conclusion, EHEC O111 infection can become complicated with HUS, DIC, and encephalopathy. Intensive treatment offers little benefit after these complications become evident. We propose that treatment should start under conditions of thrombocytopenia or rapidly increasing LDH values, especially for patients infected with Stx-2-positive EHEC.

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