Jpn. J. Infect. Dis., 58, 168-170, 2005

Short Communication

Clinical Characteristics of Adult *Escherichia coli* Meningitis

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(Received December 13, 2004. Accepted February 2, 2005)

SUMMARY: The clinical characteristics and therapeutic outcomes of adult meningitis due to *Escherichia coli* alone have not been examined adequately. In this study, we analyzed the clinical and laboratory data of 15 adult patients with monomicrobial *E. coli* meningitis. The 15 patients, collected over a period of 18 years (January 1986 - December 2003), included 7 men and 8 women, aged 45 - 77 years. They accounted for 5% (15/306) of our cases of adult bacterial meningitis with single pathogen infection. This study also revealed that a post-neurosurgical state is the most important factor predisposing adult patients to develop *E. coli* meningitis. In this study, all of the tested *E. coli* strains showed susceptibility to imipenem and/or meropenem, however, *E. coli* strains that are not susceptible to third-generation cephalosporin have emerged since 2001. As to the therapeutic results of these 15 cases, all 4 patients without appropriate antibiotic treatment died and the other 11 patients with appropriate antibiotic treatment showed a mortality rate of 27%. The emergence of third-generation cephalosporin non-susceptible *E. coli* strains in adult bacterial meningitis, as shown in this study, has created a therapeutic challenge in choosing initial empirical antibiotics for treating adult patients with post-neurosurgical meningitis. Our results emphasize that the timely use of appropriate antibiotics is essential for the management of this potentially fatal central nervous system infection. However, it should be noted that the number of cases examined in this study is too small to reach a therapeutic conclusion regarding adult *E. coli* meningitis, and further large-scale studies will be needed for this purpose.

Escherichia coli is a common pathogen of pediatric bacterial meningitis (1), but it is uncommon as a pathogen of adult bacterial meningitis (ABM) (2-4). In Taiwan, the most common Gram-negative pathogens of ABM are *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* (3,4); nonetheless, ABM caused by *E. coli* infection has been increasing (5). Although there have been several reports on ABM generally (2-4), the clinical characteristics of ABM due to *E. coli* infection have rarely been examined. In this study, we retrospectively reviewed the medical records and the microbiological records of cerebrospinal fluid (CSF) analysis of patients with ABM admitted to the Chang Gung Memorial Hospital-Kaohsiung over a period of 18 years (January 1986 - December 2003). All data were taken from preexisting standardized forms. During the study period, 329 cases of culture-proven ABM were identified. We analyzed the 15 of these 329 cases that had monomicrobial *E. coli* infection. The criteria for a definite diagnosis of adult *E. coli* meningitis included a positive CSF culture of *E. coli* in patients with clinical presentations of acute bacterial meningitis, including fever, consciousness disturbance, signs of meningeal irritation and/or seizures, and at least one of the following purulent inflammation features of CSF: i) a leukocyte count > 0.25×10^9/L with predominant polymorphonuclear cells; ii) a CSF lactate concentration > 3.5 mmol/L; iii) a glucose ratio (CSF glucose/serum glucose) < 0.4 or CSF glucose concentration < 2.5 mmol/L if no simultaneous blood glucose was determined.

The *E. coli* strains cultured from the CSF specimens of the 15 cases were examined. Antibiotic susceptibility was tested using the Kirby-Bauer disc diffusion method (BBL, Mueller-Hinton II agars; Becton Dickinson Microbiology Systems, Cockeysville, Md., USA). The GNS methodology of the Vitek System (VITEK®, bioMerieux Vitek, Hazelwood, Mo., USA), an established automated method of obtaining MIC data, was also used to further determine antimicrobial susceptibility. For this study, only the antibiotics (ceftazidime, ceftriaxone, cefepime, imipenem, and meropenem) used commonly in the treatment of ABM were collected. The basic clinical data of the 15 cases are listed in chronological order from 1986 to 2003 in Table 1. Diabetes mellitus (DM) and post-neurosurgical states were the common underlying conditions. The interval between the neurosurgical procedure and the onset of meningitis in the post-neurosurgical group was between 19 and 61 days (mean = 30 days). Fever and altered consciousness were the most common manifestations. The initial CSF data of the 15 studied cases were as follows: glucose 0.22 - 7.00 mmol/L (median 2.48 mmol/L), total protein 0.46 - 8 g/L (median 3.34 g/L), lactate 2.43 - 24.64 mmol/L (median 10.92 mmol/L), and white blood cell (WBC) count 0.01 - 18×10^9/L (median 3.68×10^9/L). Blood cultures were performed for all of the patients, and were positive in eight cases. A positive urine culture was also found in one patient. A positive wound culture was found in six patients who were in a post-neurosurgical state. Peripheral leukocytosis was found in 11 cases and leukopenia in just one.

The results of the antibiotic susceptibility test of the 15 *E. coli* strains are listed in Table 1. *E. coli* strains that were resistant or non-susceptible to third-generation cephalosporin emerged in 2001 (Patient 10), but they still retained their susceptibility to both cefepime and carbapenem. The antibiotics used in the treatment of these 15 patients are listed in

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Table 1. Basic clinical and laboratory data of the 15 adult patients with *E. coli* meningitis

Patient	Sex/ Age(yr)	Antibiotics treatment		Infectious pattern	Underlying disease	Clinical manifestation	Result of antibiotic susceptibility test of *E. coli* strains				
		dosage, length of treatment	duration (days)				Ceftazidim	Ceftriaxone	Cefepime	Imipenem	Meropenem
1	F/57	Penicillin G 24 × 10^5 u/day, IV; Chloramphenicol 4g/day, IV	8*	Community-acquired	DM, stroke	Altered consciousness, fever, septic shock, seizure, BA, HHNK	S	S	–	S	–
2	F/62	Moxalactam 6g/day, IV	28	Community-acquired	DM	Fever	S	S	–	S	–
3	M/66	Ceftazidime 8g/day, IV	20	Community-acquired	DM, alcoholism, stroke	Altered consciousness, fever, septic shock, seizure	S	S	–	S	–
4	F/45	Penicillin G 24 × 10^5 u/day, IV; Chloramphenicol 4g/day, IV	2*	Nosocomial	DM, HI s/p craniotomy	Altered consciousness, fever, septic shock, HHNK	S	S	–	S	–
5	F/72	Cefuroxime 6 g/day, IV	12	Nosocomial	ICH s/p craniotomy	Altered consciousness, fever	S	S	–	S	–
6	F/67	Imipenem/cilastatin 1 g/day, IV	14*	Nosocomial	SAH s/p craniotomy	Altered consciousness, fever, septic shock, seizure, SIADH	S	S	–	S	–
7	M/66	Penicillin G 24 × 10^5 u/day,IV; Chloramphenicol 4g/day, IV	2*	Nosocomial	ICH s/p craniotomy	Altered consciousness, fever, septic shock, hydrocephalus	S	S	–	S	–
8	M/53	Oxacillin 6 g/day, IV	5*	Nosocomial	HI s/p ventriculostomy	Altered consciousness, fever, septic shock, hydrocephalus, seizure	S	S	–	S	–
9	M/55	Penicillin G 24 × 10^5 u/day, IV; Ceftriaxone 4g/day, IV	29	Community-acquired	MDS	Headache	S	S	–	S	–
10	M/48	Rocephin 4 g/day, IV	12	Community-acquired	Subdural effusion s/p subdural-peritoneal shunt	Fever, headache, dizziness	I	R	S	S	S
11	F/58	Meropenem 2 g/day, IV	60	Nosocomial	DM, HI s/p ventriculostomy and V-P shunt	Altered conscious, fever	S	S	S	S	S
12	M/57	Meropenem 1 g/day, IV	4*	Community-acquired	Hypertension, ICH s/p V-P shunt, chronic renal failure with hemodialysis	Fever, altered consciousness, sepsis, septic shock	R	R	S	S	S
13	M/60	Cefepime 6 g/day, IV	21	Nosocomial	DM, hypertension, heart disease s/p pacemaker, HI s/p ventriculostomy	Fever, hydrocephalus	S	S	S	S	S
14	F/71	Rocephin 2 g/day, IV	27	Nosocomial	DM, hypertension, lumbar spondylosis s/p instrumentation	Altered consciousness, fever, seizure, HHNK, paraspinal abscess	S	S	S	S	S
15	F/77	Rocephin 2 g/day, IV	6*	Nosocomial	COPD pneumonia, DM, hypertension, acute respiratory failure	Altered consciousness, fever, sepsis, septic shock	S	I	S	S	S

M, male; F, female; yr, years old; *, mortality; DM, diabetes mellitus; HI, head injury; s/p, status post; V-P, ventriculo-peritoneal shunt; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; MDS, myelodysplastic syndrome; BA, brain abscess; HHNK, hyperosmolar hyperglycemic nonketotic coma; SIADH, syndrome of inappropriate antidiuretic hormone.

MIC breakpoints (NCCLS guidelines): ceftazidim (S: ≦ 8 mg/L, I: 16 mg/L, R: ≧ 32 mg/L); ceftriaxone (S: ≦ 8 mg/L, I: 16-32 mg/L, R: ≧ 64 mg/L); cefepime (S: ≦ 8 mg/L, I: 16 mg/L, R: ≧ 32 mg/L); imipenem (S: ≦ 4 mg/L, I: 8 mg/L, R: ≧ 16 mg/L); meropenem (S: ≦ 4 mg/L, I: 8 mg/L, R: ≧ 16 mg/L); − , not done.

Nosocomial meningitis was defined as a positive bacterial infection not present when the patient was admitted to the hospital, or clinical evidence of infection no sooner than 7 days after admission. Otherwise, the patient was considered to have “community-acquired meningitis”. Meningitis related to head trauma as a result of skull fractures, neurosurgical procedure, or any cause of skull defects was classified as “post-neurosurgical meningitis”. Otherwise, patients who demonstrated no clearly distinctive disease characteristics and who had not undergone invasive procedures were classified as “spontaneous meningitis”.

Table 1. Appropriate antibiotic therapy (the administration of one or more antimicrobial agents shown to be effective against *E. coli* and capable of passing through the blood-brain barrier in adequate amounts) was given to 11 patients (Patients 2, 3, 5, 6, 9 - 15). The four patients (Patients 1, 4, 7, 8) who did not receive appropriate antibiotic therapy died in a fulminant and rapid clinical course. However, final culture results were not available before their death. Aside from appropriate antibiotic therapy, a revision of a V-P shunt was performed in two cases (Patients 11, 12). The other three patients (Patients 7, 8, 13) with hydrocephalus did not undergo V-P shunt insertion, and they all subsequently died. The therapeutic results for these 15 adult *E. coli* meningitis patients showed that eight patients (Patients 2, 3, 5, 9 - 11, 13, 14) survived and seven patients (Patients 1, 4, 6 - 8, 12, 15) died. Of the eight who survived, seven (Patients 2, 3, 9-11, 13, 14) resumed normal lives and one (Patient 5) was in a vegetative state.

This study revealed that *E. coli* meningitis accounted for 5.0% (15/306) of our cases of ABM with single pathogen infection. Both DM and post-neurosurgical states are known risk factors for the development of bacterial meningitis due to an impairment of the host defense (6,7). But as this study has shown, a post-neurosurgical state has become the most important facter for the development of adult *E. coli* meningitis in recent years, and most of our adult patients contracted this infection nosocomially. In Taiwan, *E. coli* is a common pathogen of both urinary tract infection and bacteremia (8-11). Resistance of *E. coli* to certain broad-spectrum antibiotics is higher and more acute in Taiwan than in most Western countries (8-11). In recent years, the emergence of extended-spectrum beta-lactamase-producing *E. coli* strains has become a therapeutic problem, and this emergence is associated with the use of extended-spectrum cephalosporin (8-11). In this study, although no *E. coli* strains tested showed resistance to either imipenem or meropenem, *E. coli* strains that are resistant or non-susceptible to third-generation cephalosporin have emerged since 2001. As the antibiogram (Table 1) shows, these third-generation cephalosporin non-susceptible and resistant *E. coli* strains were still susceptible to cefepime, an antimicrobial agent that has recently been used in the management of ABM. The emergence of third-generation cephalosporin-resistant *E. coli* strains, as shown in this study, may creat a therapeutic challenge in choosing empiric antibiotics for the treatment of adult patients with post-neurosurgical meningitis. If further large scale studies can confirm the increase of third-generation cephalosporin non-susceptible *E. coli* strain-related adult *E. coli* meningitis, the use of one of the carbapenems as one of the initial empiric antibiotics in the treatment of adult patients with post-neurosurgical meningitis should be considered. In this study, the mortality rate was 100% in those four patients who did not receive appropriate antibiotic treatment. Appropriate antibiotic treatment with or without shunt revision was the management strategy used for the other 11 patients, and 73% (8/11) survived. The overall mortality of these 15 adult patients with *E. coli* meningitis was 47% (7/15). This mortality rate was higher than that of our ABM patients overall (4); however, the underlying neurosurgical conditions of this specific group of patients may have been one of the factors contributing to this high mortality rate. However, it should be noted that the number of cases examined in this study is too small to make a therapeutic conclusion regarding adult *E. coli* meningitis, and therefore, further large-scale studies will be needed.

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