The Clinical Characteristics and Therapeutic Outcomes of *Escherichia Coli* Meningitis in Adults

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Abstract

Background: To examine the clinical characteristics and therapeutic outcome of *Escherichia (E.)* coli adult bacterial meningitis (ABM).

Methods: The demographic data, clinical and laboratory features and therapeutic outcome of 25 *E. coli* ABM patients were examined retrospectively. The clinical features of the reported *E. coli* ABM cases were also included for analysis.

Results: The 25 *E. coli* ABM patients included 12 women and 13 men, aged 33-78 years (mean= 59.9). Of these 25 patients, 13 had a postneurosurgical state as the underlying condition. As to the underlying medical conditions, diabetes mellitus was the most common, found in 9 of the 25 cases. Of the clinical manifestation, severe neurologic manifestations including altered consciousness (19), hydrocephalus (10), seizure (7) acute/subacute cerebral infarct (5), brain abscess (2), subdural empyema (1) and spinal abscess (1) were found, and the other clinical features included fever (21), septic shock (8), bacteremia (6) and hyponatremia (3). With treatment, the mortality rate was ≥ 44.0% and the presence of septic shock was a significant prognostic factor. With literature review, 29 community-acquired and 12 postneurosurgical *E. coli* ABM cases were enrolled, and severe neurologic manifestation and high mortality rate were also found.

Conclusions: This preliminary overview of *E. coli* ABM revealed the underlying conditions, severe neurologic manifestation and high mortality rate. Further large-scale, prospective study is needed for a better delineation of this specific infectious syndrome of adult *E. coli* meningitis.

Keywords:

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BACKGROUND

Escherichia (E.) coli is a Gram-negative, facultative anaerobic, rod-shaped, coliform bacterium of the genus Escherichia and it is commonly found in the lower intestine of warm-blooded organisms [(1)]. *E. coli* is an

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important implicated pathogen of bacterial meningitis in pediatric patients, and especially in neonates (0-3 days old in preterm neonates and 11-15 days old in term neonates) [2,3-5], but it is uncommon as a pathogen of adult bacterial meningitis (ABM) [6-8]. In neonatal meningitis, including *E. coli* meningitis, low birth weight and born by cesarean section are important preceding conditions, and their clinical presentations include fever, seizure, poor feeding and irritability [3-5]. In 2005, we reported a brief analysis of *E. coli* ABM [7]. In recent years, except the one reported by Bichon et al. [9] who described two spontaneous community-acquired *E. coli* ABM cases and made a literature review, there is no other study which examines this specific infectious syndrome solely. Therefore, we analyzed the clinical characteristics, laboratory data and therapeutic outcome of 25 adult patients with *E. coli* ABM, and we also made a literature review in order to have a better delineation of the clinical features of this specific infectious syndrome.

METHODS

We retrospectively reviewed the clinical characteristics, laboratory data and therapeutic outcomes of adult patients (≥18 years) with culture-proven *E. coli* meningitis admitted to Chang Gung Memorial Hospital (CGMH) – Kaohsiung over a study period of 29 years (January 1989 to December 2017). CGMH-Kaohsiung is a 2686 bed teaching hospital providing both primary and tertiary care, and is also the largest medical center in southern Taiwan. During the study period, a total of 572 patients with ABM were identified, and among them, 514 belonged to monomicrobial infection, while the other 58, mixed infection. A total of 35 ABM patients with *E. coli* infection were found, and 25 of them belonged to monomicrobial infection while the other 10 mixed infection. In this study, the clinical and laboratory features and therapeutic outcome of the 25 *E. coli* ABM patients were included for analysis. This study was approved by the hospital Ethics Committee (IRB No: 201900553B0).

In this study, the criteria of bacterial meningitis diagnosis followed our previous study [6]. A definite diagnosis of *E. coli* meningitis were: (1) a positive cerebrospinal fluid (CSF) culture for *E. coli*; (2) clinical features of meningitis including fever, altered consciousness, seizures, acute hydrocephalus and signs of meningeal irritation; and (3) purulent CSF features, with at least one of the follows: pleocytosis with leukocyte count > 0.25 x 10^9/ L and predominant polymorphonuclear cells, lactate concentration > 3.5 mmol/L, glucose ratio (CSF glucose / serum glucose) < 0.4 or CSF glucose level < 2.5 mmol/L if no simultaneous blood glucose level was determined [9]. Those without a positive culture result were not included in this study.

In this study, the procedures for *E. coli* identification were as follows: The CSF was inoculated on 5% sheep blood agar, EMB and Chocolate agar. Bacterial typing was performed for all positive cultures. The suspected colonies were confirmed primarily Gram-negative rods. The pure colonies subjected for conventional biochemical test using Triple Sugar fermentation reaction, Citrate utilization test, Urease test, Indole test and Voges-Proskauer test before June 2013. From June 2013, freshly grown bacterial isolates were selected and smeared onto the target plate for analysis by MALDI-TOF MS. Identification of microbes were performed using the MALDI BioTyper 3.0, software for microbial identification (Bruker Daltonik GmbH, Bremen, Germany). One of the limitations of MALDI – TOF MS is its current inability of discrimination of the pathogenic *E.coli* from Shigella spp.[10-12]. Shigella spp. and *E. coli* are closely related, and cannot be distinguished using MALDI BioTyper 3.0, software databases. The supplemental rapid indole test was performed when *E. coli* was identified by MALDI – TOF MS. *E.coli* was comforted by means to positive indole test. While the indole tests were negative, organisms were inoculated onto the BD Phoenix system for the identification [13]. The antimicrobial susceptibility tests were processed by Kirby-Bauer Disk Diffusion Susceptibility Test Protocol from January 1989 to July 2008 [14] and the BD Phoenix system from August 2008 [13].

In this study, the patients who developed meningitis related to head trauma with skull fractures or neurosurgical procedures were classified as having ‘‘postneurosurgical” meningitis. In addition, the patients who demonstrated no clear distinctive disease characteristics and who had not undergone any invasive procedures were classified as having ‘‘spontaneous” meningitis [6]. A ‘‘nosocomial” infection was defined as a positive bacterial infection not present when the patient was admitted to hospital,

Table 1. The clinical characteristics and therapeutic outcomes of the 25 adults with Escherichia coli meningitis

No.	Basic profiles (Marriage status; occupation; religion)	Age (years) / Sex	Antibiotics or managements	Underlying disease	Infection pattern	Clinical manifestation	Bacteremia	mRS
1.	Married; unknown; Daoism	57 / F	Aq-penicillin G	Diabetes mellitus, old cerebral infarct	Spontaneous	Fever, altered consciousness, seizure, septic shock, brain abscess	Yes	6
2.	Married; housewife; Buddhism	60 / F	Olfloxacin	Diabetes mellitus	Spontaneous	Fever	Yes	Unknown
3.	Married; nil; Daoism	66 / M	Ceftazidime	Diabetes mellitus, old cerebral infarct, alcoholism	Spontaneous	Fever, altered consciousness, seizure, septic shock	Yes	Unknown
4.	Married; service industry; Daoism	45 / F	Aq-penicillin G	Diabetes mellitus, traumatic head injury	Post-NS	Fever, altered consciousness, septic shock	Yes	6
5.	Married; housewife; Buddhism	72 / F	None	Spontaneous ICH s/p removal of hematoma	Post-NS	Fever, altered consciousness	No	5
6.	Married; nil; Buddhism	67 / F	Imipenem	SAH and hydrocephalus s/p ventriculostomy	Post-NS	Fever, altered consciousness, seizure, septic shock, SIADH	Yes	6
7.	Married; worker; nil	66 / M	Aq-peniclilin G	Spontaneous ICH s/p removal of hematoma	Post-NS	Altered consciousness, septic shock, hydrocephalus	No	6
8.	Single; worker; nil	53 / M	None	Traumatic head injury	Post-NS	Fever, altered consciousness, septic shock, hydrocephalus	No	6
9.	Married; service industry; Daoism	55 / M	Ceftriaxone	Myelodysplastic syndrome	Spontaneous	Headache	No	2
10.	Married; worker; nil	48 / M	Revision of VP shunt + Ceftazidime	Traumatic head injury, spontaneous ICH and hydrocephalus s/p VP shunt	Post-NS	Fever	No	0
11.	Married; worker; Buddhism	58 / M	Ceftriaxone	Diabetes mellitus, traumatic head injury	Post-NS	Fever, altered consciousness	No	5
12.	Divorced; worker; nil	48 / M	Meropenem	Traumatic head injury, brain tumor	Post-NS	Fever, altered consciousness	No	5
13.	Married; nil; Buddhism	70 / F	Ceftriaxone	Diabetes mellitus	Spontaneous	Fever, altered consciousness, hydrocephalus	No	5
14.	Married; nil; nil	57 / M	Ceftazidime	Spontaneous ICH s/p VP shunt	Post-NS	Fever, altered consciousness, seizure, hydrocephalus	No	6

Table 1. The clinical characteristics and therapeutic outcomes of the 25 adults with Escherichia coli meningitis (Continue)

No.	Basic profiles (Marriage status; occupation; religion)	Age (years) / Sex	Antibiotics or managements	Underlying disease	Infection pattern	Clinical manifestation	Bacteremia	mRS
15.	Married; nil; Daoism	71 / F	Ceftriaxone	Diabetes mellitus, HIVD s/p laminectomy	Post-NS	Fever, altered consciousness, seizure, subdural empyema, spinal abscess	No	3
16.	Married; housewife; Buddhism	62 / F	Ceftriaxone	Diabetes mellitus, spontaneous ICH	Spontaneous	None	No	6
17.	Married; worker; nil	59 / M	Cefepime	Diabetes mellitus, traumatic head injury with ICH and SAH	Post-NS	Fever, altered consciousness, hydrocephalus, brain abscess	No	5
18.	Single; cleaner; Daoism	33 / M	Ceftriaxone	Spontaneous ICH, substance abuser, multiple sclerosis	Spontaneous	Acute / subacute cerebral infarct	No	3
19.	Married; nil; Daoism	52 / M	Cefepime	None	Spontaneous	Fever, altered consciousness, acute / subacute cerebral infarct	No	0
20.	Widow; nil; Daoism	78 / F	Ceftriaxone	Non-Hodgkin's lymphoma	Spontaneous	Fever, altered consciousness	No	6
21.	Widow; worker retired; Buddhism	71 / F	Ertapenem à Cefepime	Liver cirrhosis, lumbar spondylosis s/p laminectomy	Post-NS	Fever, altered consciousness, acute / subacute cerebral infarct, seizure, hydrocephalus	No	6
22.	Married; farmer retired, Daoism	74 / M	Meropenem	Liver cirrhosis	Spontaneous	Fever, altered consciousness, seizure, septic shock, hydrocephalus, hyponatremia	Yes	5
23.	Married; housewife; Buddhism	62 / F	Meropenem	Liver cirrhosis, lumbar spondylosis s/p laminectomy	Post-NS	Fever, hydrocephalus, acute / subacute cerebral infarct, hyponatremia	No	1
24.	Married; housewife; Buddhism	61 / F	Ceftriaxone	None	Spontaneous	Fever, altered consciousness, septic shock, hydrocephalus	No	6
25.	Married; service industry; Christian	50 / M	Ceftazidime	Nasopharyngeal carcinoma	Spontaneous	Fever, altered consciousness, hydrocephalus, acute / subacute cerebral infarct, hyponatremia	No	6

NO: number; M: male; F: female; MRS: modified Rankin scale; post-NS: post neurosurgical; s/p: status post; ICH: intracerebral hemorrhage; SAH: subarachnoid hemorrhage; SIADH: Syndrome of inappropriate antidiuretic hormone secretion; VP shunt: ventriculo-peritoneal shunt; HIVD: herniated intervertebral disc

Table 2. The results of the antibiotic susceptibility tests of the 16 isolated Escherichia coli strains (2000-2018)

Antibiotics	Susceptible N (%)	Resistant N (%)	Intermediate N (%)	Not tested N (%)
Ampicillin	4 (25.00)	10 (62.50)	2 (12.50)	0 (0.00)
Ceftazidime	14 (87.50)	1 (6.25)	1 (6.25)	0 (0.00)
Ceftriaxone	12 (75.00)	2 (12.50)	2 (12.50)	0 (0.00)
Cefepime	11 (68.75)	1 (6.25)	0 (0.00)	4 (25.00)
Meropenem	16 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
Ciprofloxacin	8 (50.00)	3 (18.75)	0 (0.00)	5 (31.25)

N: number

clinical evidence of an infection no sooner than 48 h after admission, or clinical evidence of meningitis within a short period of time (usually < 1 month after discharge from the hospital where the patient had received an invasive procedure, especially a neurosurgical procedure). Otherwise, the patients were considered to have a ‘‘community-acquired” infection.

In this study time period, the antibiotics used for the treatment of ABM was as follows: Intravenous administration of 3rd- or 4th-generation cephalosporins (ceftriaxone, ceftazidime, cefepime) combined with vancomycin was the initial empiric antibiotics used for the treatment. Further antibiotics were adjusted according to the results of susceptibility tests. For the analysis of therapeutic outcome, the patients were divided into survivor and non-survivor groups, and we analyzed their prognostic factors using Fisher’s exact test for the underlying diseases and clinical manifestations, and the Mann-Whitney test for CSF profile, scores of Glasgow coma scale and age. The modified Rankin scale (mRS) was used for prognostic analysis and those with a mRS score 0-2 was considered to have a good therapeutic outcome and those with a score ≥3, a poor therapeutic outcome.

For a better delineation of the clinical features of *E. coli* ABM, we also made a literature review on the adults with *E. coli* meningitis. For this purpose, a search of PubMed was performed, and the clinical features of the reported *E. coli* ABM cases were collected for analysis. The keywords used for PubMed searching were bacterial meningitis, *Escherichia coli* and adult. The reported cases were excluded from this study if there was a lack of information on the demographic data and if they were not in English. Articles concerning children were also excluded from this study.

RESULTS

The 25 patients with *E. coli* ABM were 12 women and 13 men, aged 33-78 years (mean=59.9, median=61), and their clinical and laboratory features and therapeutic outcomes are listed in the Table 1. Partial clinical data loss was noted in Cases 2 and 3. Of the 25 *E. coli* ABM patients, 13 had a postneurosurgical state as the underlying condition, while the other 12, spontaneous infection. The postneurosurgical states of the 13 patients included traumatic head injury (THI) (6), spontaneous intracerebral hemorrhage (ICH) s/p removal of hematoma (2), spontaneous ICH s/p ventriculoperitoneal (VP) shunt (2), subarachnoid hemorrhage (SAH) and hydrocephalus s/p ventriculostomy (1), traumatic ICH and SAH (1), lumbar spondylosis s/p laminectomy (2) and herniated intervertebral disc s/p laminectomy (1). Other underlying conditions of the 25 *E. coli* ABM patients were diabetes mellitus (DM) (9), liver cirrhosis (3), old cereal infarct (2), alcoholism (1), spontaneous ICH (1), myelodysplastic syndrome (1), multiple sclerosis (1), brain tumor (1), non-Hodgkin’s lymphoma (1) and nasopharyngeal carcinoma (1). As to the clinical presentations, fever was the most common, found in 21 patients, and the others were altered consciousness (19), hydrocephalus (10), septic shock (8), seizure (7), acute/subacute cerebral infarct (ASCI) (5), hyponatremia (3), brain abscess (2), subdural empyema (1), and spinal abscess (1). Positive blood culture of *E. coli* was noted in 6 of the 25 enrolled *E. coli* ABM patients.

The CSF profiles of the 25 enrolled ABM patients were as follows: white blood cell counts: 0.002 to 25.280 109/L (mean=5.105), glucose level: 0.167 to 13.043 mmol/L (mean=3.143); total protein level: 0.04 to 8.00 g/L (mean=3.69) and lactate level: 0.44 to 24.86 mmol/L (mean=11.81). The data of antibiotic susceptibility test of the *E. coli* strains isolated from the clinical specimens of Cases 1-9, *i.e.* before the year 2000, were lost, therefore, only the data of Cases 10-25 were available. The antibiotic susceptibility test results (Table 2) revealed that the susceptibility rates to ampicillin, ciprofloxacin, cefepime, ceftriaxone, ceftazidime and meropenem were 25.0% (4/16), > 50% (8/16), > 68.75% (11/16), 75.0% (12/16), 87.5% (14/16) and 100% (16/16), respectively. Despite management, 11 of the 25 patients with *E. coli* meningitis died (Table 1), the overall mortality was ≥44.0% (11/25). Statistical analysis of the clinical manifestations, laboratory data, and underlying conditions between the survivors and non-survivors revealed that presence of septic shock ($p = 0.032$) was a significant prognostic factor (Table 3). Table 4 shows comparisons of the clinical features between the adult patients with *E. coli* and non-*E. coli* bacterial meningitis. The results showed that age, initial Glasgow coma scale, septic shock, ischemic infarct and hyperglycemic crisis were potential factors. However, after logistic regression analysis, only the presence of cerebral infarct was significant.

In a literature review, a total of 41 reported *E. coli* ABM cases (29 community-acquired infection and 12 postneurosurgical infection) were identified [9,15-34]. Of the reported 29 community-acquired adult *E. coli* meningitis patients, liver cirrhosis, and alcoholism were the most common underlying conditions. Of these 41 reported cases, 22 died during the therapeutic course.

DISCUSSION

Bacterial meningitis has a predilection of frequent epidemiologic change [35], and this change may influence the therapeutic strategies including the choice of empiric antibiotics which may have prognostic significance [36,37]. The frequent changes of ABM epidemiologic trend have been depicted in our serial studies of ABM in Taiwan [6,38,39], in which we have shown the change of the relative frequencies of the implicated pathogens and a gradual increase of patients with a postneurosurgical state as the underlying condition. In this 29-year study time period, *E. coli* infection accounted for 5.1% (25/489) of the ABM patients with monomicrobial infection, and its infection was found in 17.2% (10/58) of the patients with mixed infection. Previously, *Klebsiella pneumoniae* was the most common implicated pathogen of spontaneous, community-acquired ABM in Taiwan [39], but because the case number of ABM patients with postneurosurgical infection has outnumbered those with spontaneous infection, staphylococcal infection has become the most frequent one [6]. Nevertheless, the incidences of *E. coli* infection in monomicrobial ABM did not change much, accounting for 2.1%-5.0% of the implicated pathogens [6,38].

In the current study, 52.0% (13/25) of the *E. coli* ABM patients had a postneurosurgical state as the underlying condition, and the other 12 *E. coli* ABM patients with spontaneous infections had underlying medical condition as the preceding event (Table 1). This high incidence of underlying medical condition as the preceding event is also noted in the reported community-acquired *E. coli* ABM cases in which 69.0% (20/29) of the cases had underlying medical condition as the preceding event. The presence of DM was the most common underlying medical condition of our 25 enrolled *E. coli* ABM patients, accounting for 36.0% (9/25) of them. DM is a serious medical disease causing heavy burden of medical care system [39] and more than 10% of the adults in Taiwan are diabetic [40]. Therefore, in Taiwan, DM is one of the important underlying medical conditions of ABM, and this specific group of ABM patients have their own epidemiologic trend with a high incidence of *Klebsiella pneumoniae* as the implicated pathogen for spontaneous community-acquired infection especially in those with a concomitant liver disease such as cirrhosis [6,41,42]. Nevertheless, the relationship between the high incidence of DM and the *E. coli* ABM patients shown in the current study deserves further observation.

Severe neurologic manifestations including altered consciousness, hydrocephalus, seizure and ASCI were noted in 67.9% (19/25), 40.0% (10/25), 28.0% (7/25) and 20.0% (5/25) of our *E. coli* ABM patients, respectively. In the meanwhile, fever and septic shock were found in 84.0% (21/25) and 32.0% (8/25) of them, respectively. From the reported cases, high incidence of altered

consciousness as one of the clinical manifestations was also noted in the reported *E. coli* ABM cases.

As shown in Table 4, the clinical manifestations of the adult patients with *E. coli* and non-*E. coli* meningitis were quite similar; however, the patients with *E. coli* meningitis had a significantly higher incidence of cerebral infarct. Because of the limited number of cases, further large-scale studies of adult *E. coli* meningitis are needed to verify this finding.

Despite the severity of clinical manifestations found in our 25 and other reported *E. coli* ABM patients, these manifestations were not unique and can be found in the ABM caused by other bacterial pathogen infection [6]. Therefore, the diagnosis of *E. coli* infection related ABM can only be confirmed by positive culture result and/or by positive multiplex PCR assay [6].

Antimicrobial non-susceptible *E. coli* strains including the strains which are non-susceptible to carbapenem are known to be increasing in Taiwan [43]. In the current study (Table 2), all 16 isolated *E. coli* strains were susceptible to meropenem, and nonsusceptible strains to 3rd and 4th generation cephalosporins were noted. In clinical practice of ABM management [6,37], ceftriaxone and ceftazidime are the suggested empirical antibiotics, but so far, meropenem is not a suggested one and it is usually used in the situation in which resistant strains to the 3rd or 4th generation cephalosporins are identified. As shown in Table 3, 12.5% (2/16) and 25.0% of the isolated *E. coli* strains were not susceptible to ceftazidime and ceftriaxone, respectively. Therefore, there is usually a time lag in using the appropriate empiric antibiotic in the initial therapy of ABM which is an important factor which may influence the therapeutic outcome [38,41,42]. Presently, it is highly suggested to start empiric treatment within one hour of arrival in all suspected meningitis cases, and choice of antibiotics needs to be differentiated according to the different patient groups and local resistance rates of frequently implicated bacterial pathogens to the commonly used antibiotics for ABM treatment [31]. Therefore, the consensus of choosing appropriate empiric antibiotic in treating ABM including *E. coli* ABM needs further evaluation.

With treatment, 11 of the 25 *E. coli* ABM patients expired, and this figure of mortality rate 44.0% (11/25) was higher than that of the overall ABM (25.5%) [6]. In current study, the presence of septic shock was an important prognostic factor for the *E. coli* ABM patients (Table 3), and 57.1% (8/14) of the survivors (Table 1) had a poor therapeutic outcome. Although other severe neurologic manifestations such as altered consciousness, hydrocephalus, seizure and ASCI are also known as important prognostic factors of ABM [38], they were of no prognostic significance in the current study.

CONCLUSIONS

In Taiwan, *E. coli* infections accounted for 5.1% of the monomicrobial ABM, and 52.0% of the *E. coli* ABM patients have postneurosurgical condition as the preceding event. Besides postneurosurgical condition, DM is another important underlying condition, accounting for 36.0% of the *E. coli* ABM patients. Severe neurologic manifestations including altered consciousness, hydrocephalus, seizure and ASCI are found in the patients with *E. coli* ABM. The mortality rate of *E. coli* ABM is high (44.0%) and the presence of septic shock is a significant prognostic factor. The other survivors of *E. coli* ABM had severe neurologic deficits. This high mortality and morbidity are also noted in the reported *E. coli* ABM cases. This study offers an overview of the *E. coli* ABM; but because of the limited case number and because of the partial data loss in some of the enrolled *E. coli* ABM cases, further large scale prospective study is needed for a better delineation of the clinical characteristics of this specific infectious syndrome of adults.

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Available of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical approval

This retrospective study was approved by the Kaohsiung Chang Gung Memorial Hospital Ethics

Committee (IRB No: 201900553B0)

Consent for publication

Not applicable

Competing interests

The authors have declared they have no interest.

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