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#### **Case Report**

# *Escherichia coli* spontaneous community-acquired meningitis in adults: A case report and literature review

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#### ABSTRACT

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Keywords: Escherichia coli Gram-negatiive meningitis Spontaneous community-acquired Gram-negative bacillary meningitis occurring post-trauma and following neurosurgical procedures has been described widely. However, reports of spontaneous cases are sparse, particularly community-acquired cases. Spontaneous community-acquired *Escherichia coli* meningitis is a rare (although increasingly seen) and specific entity that is poorly reported in the literature. A review of the literature identified only 43 cases of community-acquired *E. coli* meningitis reported between 1946 and 2016. This article describes two new cases of spontaneous community-acquired *E. coli* meningitis encountered in Marseille, France, and presents the results of a literature review on spontaneous community-acquired *E. coli* meningitis.

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#### Introduction

Gram-negative bacilli (GNB) are an uncommon cause of community-acquired meningitis in adults, ranging from 0.7% in the Netherlands (van de Beek et al., 2004) to 3.6% in the USA (Pomar et al., 2013) and 7% in Spain (Pomar et al., 2013). It is reported that 36–50% of cases of GNB meningitis occur after neurosurgical procedures (Berk and McCabe, 1980; Huang et al., 2001). Neurosurgery, head trauma within the past month, a neurosurgical device, and cerebrospinal fluid (CSF) leak represent portals of entry in 75% of nosocomial cases (Durand et al., 1993). Spontaneous, non-traumatic GNB meningitis is usually community-acquired and occurs in patients with identified risk factors. Spontaneous community-acquired GNB meningitis represents 8.7% of all spontaneous community-acquired meningitis, with an annual incidence of two cases per 100 000 adults. *Escherichia coli* represents 41.9% of these cases (Pomar et al., 2013).

This article describes two cases of spontaneous communityacquired *E. coli* meningitis diagnosed at the authors' institution and provides a review of other cases reported in the literature. The objective was to identify risk factors and to collect demographic, microbiological, and therapeutic data in order to prevent death and optimize the management of these patients.

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#### Case reports

#### Case 1

A 67-year-old woman who had previously been in good health was admitted to the emergency department with fever and altered consciousness. Two days after admission, she presented an episode of sporadic vomiting, symptoms of a urinary tract infection, and non-specific diffuse abdominal pain. She had no history of medical, surgical, or cranial trauma and was not receiving any daily treatment. Upon admission, the patient presented a fever (39 °C), blood pressure of 147/66 mmHg, a heart rate of 94 beats per minute, and capillary glycemia of 1.16 g/l. Her Glasgow Coma Scale (GCS) score was 9, with respective scores of 5, 2, and 2 for motor, eye, and verbal responses. She showed no localized motor or sensory deficits, but was agitated and neck stiffness was noted. She reported impaired hearing in her right ear. The clinical examination was otherwise normal.

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A rapid urine test was positive for leukocytes and nitrites, although a subsequent urine test culture was sterile. Blood cultures were also sterile. A lumbar puncture showed 900 elements/mm<sup>3</sup>, including 90% neutrophils, hypoglycorrhachia less than 0.1 mmol/l, and an elevated protein level in the CSF at 4.36 g/l. Cultures of CSF grew *E. coli* expressing low levels of AmpC beta-lactamase. Computed tomography (CT) of the brain, chest, abdomen, and pelvis showed no deep infection or evidence of neoplasia.

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Initial antimicrobial therapy included 75 mg/kg/day of ceftriaxone, 75 mg/kg/day of amoxicillin, and 15 mg/kg/day of acyclovir (probabilistic). Antimicrobial therapy was then adapted to CSF sample findings with ceftriaxone given at a meningeal dose of 2 g twice a day for 21 days. The patient did not receive corticosteroid treatment. The patient's evolution was favorable, with partial regression of her neurological symptoms; biological inflammatory parameters and lumbar puncture test results returned to normal. Acoustic tests and referral to a specialist for consultation revealed a right transmission hearing impairment due to chronic otitis with no CT scan abnormality. A slight and fluctuating anosognosia was noted 2 months after the end of antimicrobial therapy.

#### Case 2

A 34-year-old man presenting with coma due to status epilepticus was transferred to Timone University Hospital. The patient's medical history included chronic alcoholism in an attempt to withdraw from baclofen, as well as sciatica which was being treated with corticosteroids. He was found unconscious at home the day before admission. His vital signs showed a normal blood pressure at 120/80 mmHg, tachycardia at 150 beats per minute, altered GCS at 7, and anisocoria. His temperature (36.5 °C) and capillary glycemia (1.15 g/l) were normal. Seizures ceased after a 10-mg intravenous injection of diazepam. As the patient continued to display neurological failure, he was sedated, intubated, and transferred immediately to the local hospital. Blood analysis revealed bicytopenia with platelets at  $10 \times 10^9$ /l, leukopenia at  $2 \times 10^9$ /l, and neutropenia at  $0.2 \times 10^9$ /l. Atypical lymphocytes were found in the blood analysis. An inflammatory syndrome was noted with elevated C-reactive protein (CRP) at 330 mg/l. The prothrombin ratio (PR) was preserved at 98%, while cholestatic cytolysis with elevated bilirubin was noted. Lactate was elevated at 3.92 mmol/l. The status epilepticus was treated and the patient was sedated before being transferred on the same day to Timone University Hospital.

Upon admission, the patient showed signs of septic shock with a high fever  $(39.5 \,^{\circ}C)$  associated with a low blood pressure. His neurological evaluation was unchanged. His serum was negative for ethanol, and he was treated for hypokalemia (potassium at 2.2 mmol/l). The hematological analysis indicated probable disseminated intravascular coagulation (DIC) with a fall in PR to 61% and thrombocytopenia at  $4 \times 10^9$ /l. Serology for HIV, hepatitis B virus, and hepatitis C virus was negative; furthermore, the patient had been vaccinated against hepatitis B. A lumbar puncture showed turbid CSF, hypoglycorrhachia less than 0.1 g/l with normal glycemia, an elevated CSF protein level at 3 g/l, and 144 elements/mm<sup>3</sup> including 90% neutrophils. Direct Gram-staining of the CSF showed Gram-negative bacilli. A CT of the brain, chest, abdomen, and pelvis was normal.

Antimicrobial therapy was initiated with meningeal doses of amoxicillin, ceftriaxone, and acyclovir (probabilistic). The patient's condition deteriorated rapidly, with gingival bleeding and areactive mydriasis, followed by brain death on the day of admission to the hospital. Post-mortem CSF cultures revealed an *E. coli* producer of low-level penicillinase with resistance to trimethoprim–sulfamethoxazole. The same bacterium was encountered on blood culture and urinalysis.

#### Discussion

A search of PubMed, ResearchGate, and Google Scholar was performed, and data were collected for analysis. Keywords included *Escherichia coli*; coli bacillus; community-acquired meningitis; adults; and spontaneous. A total of 43 cases of spontaneous community-acquired *E. coli* meningitis reported between 1946 and 2016 were identified; in addition to the two new cases described above (Table 1).

Eight articles were excluded from this study due to a lack of information on the type of meningitis (nosocomial and/or post-traumatic versus spontaneous community-acquired), or the presence of exclusion criteria indicating hospital-acquired or post-traumatic meningitis. Articles concerning children were also excluded, as *E. coli* meningitis is more common in this population. The excluded studies are listed in Table 2.

Data from the literature review cases and the two new reported cases were combined (n = 45). The mean age of the subjects was 56 years; the patient's age was unknown in 16% of cases. The female to male sex ratio was 1.4, showing a slight predominance of female cases (20 female and 14 male); the sex was unknown in 24% of cases.

Table 1

Reported cases of spontaneous community-acquired Escherichia coli meningitis in a literature review-1946 to 2016.

Year	Reference	Number of cases
2016	Ishida K, et al. Clin Case Rep 2016;4:323–6 (Ishida et al., 2016)	1
2015	Kohlmann R, et al. BMC Infect Dis 2015;15:567 (Ishida et al., 2016)	1
2013	Kangath RV, et al. BMJ Case Rep 2013;2013 (Kangath and Midturi, 2013)	1
2013	Pomar V, et al. BMC Infect Dis 2013;13:451 (Pomar et al., 2013)	1
2012	Weyrich P, et al. Ann Clin Microbiol Antimicrob 2012;11:4 (Weyrich et al., 2012)	1
2009	Cabellos C, et al. Medicine (Baltimore) 2009;88:115-9 (Cabellos et al., 2009)	6
2008	Cabellos C, et al. Clin Microbiol Infect 2008;14:35-40 (Cabellos et al., 2008)	5
2008	Briongos-Figuero LS, et al. Rev Clin Esp 2008;208:262	1
2008	Miletic D, et al. Orthopedics 2008;31:182 (Miletic et al., 2008)	1
2007	Samson D, et al. Ann Fr Anesth Reanim 2007;26:88–90 (Samson et al., 2007)	1
2007	Ashish A, et al. Crit Care Shock 2007;10:148–50 (Sule and Tai, 2007)	1
2005	Chang KH, et al. J Formos Med Assoc 2006;105:756-9 (Chang et al., 2006)	1
2005	Yang TM, et al. Jpn J Infect Dis 2005;58:168–70 (Yang et al., 2005)	4
2004	Van de Beek D, et al. N Engl J Med 2004;351:1849–59 (van de Beek et al., 2004)	4
2002	Hovette P, et al. Press Med 2002;22:1021-3 (Hovette et al., 2002)	1
2000	Mofredj A, et al. Scand J Infect Dis 2000;32:699–700 (Mofredj et al., 2000)	1
1998	Almirante B. Clin Infect Dis 1998;27:176–80 (Almirante et al., 1998)	1
1986	Smallman L, et al. J Clin Pathol 1986;39:366–70 (Smallman et al., 1986)	2
1985	Christopher GW, et al. Arch Intern Med 1985;145:1908 (Christopher, 1985)	1
1978	Crane LR, et al. Medicine (Baltimore) 1978;57:197–209 (Crane and Lerner, 1978)	4
1965	Kunin C, et al. Arch Intern Med 1965;115:652–8 (Kunin et al., 1965)	2
1965	Manesis J, et al. Arch Neurol 1965;13:214-6 (Manesis and Stanosheck, 1965)	1
1946	Crawley FE, et al. Lancet 1946;247:461-2 (Crawley, 1946)	1

#### Table 2

Escherichia coli meningitis cases excluded from the study because of their nosocomial or post-traumatic character, or the absence of details about the type of meningitis.

Year	Reference	Number of cases
2015	Teckie G, et al. Int J Infect Dis 2015;30:38–40 (Teckie and Karstaedt, 2015)	9
2014	Okike IO, et al. Clin Infect Dis 2014;59:e150–7 (Okike et al., 2014)	353
2013	Pomar V, et al. BMC Infect Dis 2013;13:451 (Pomar et al., 2013)	15
2010	Laguna-Del Estal P, et al. Rev Neurol 2010;50:458–62 (Laguna-del Estal et al., 2010)	3
2006	Bouadma L, et al. Clin Microbiol Infect 2006;12:287–90 (Bouadma et al., 2006)	23
2005	Seydi M, et al. Med Mal Infect 2005;35:344-8 (Seydi et al., 2005)	10
1997	Pauwels A, et al. J Hepatol 1997;27:830-4 (Pauwels et al., 1997)	9
1983	Gilmore RL, et al. South Med J 1983;76:1202-3 (Gilmore et al., 1983)	1

Risk factors are reported in Table 3. In order of frequency, the risk factors identified were chronic alcoholism and cirrhosis (each accounting for 20% of cases), diabetes mellitus (16% of cases), disseminated strongyloidiasis (6% of cases), and HIV, chronic obstructive pulmonary disease, and chronic organ insufficiency (each accounting for 4% of cases). Hemochromatosis, myelodysplasia, hemophagocytic lymphohistiocytosis, urinary tract instrumentation, B lymphoma, long-term glucocorticoid therapy, Marfan syndrome, and human T-lymphotropic virus type 1 seropositivity were also reported as risk factors, each representing 1% of cases in this study. Risk factors were unknown for 11 patients (24%), while 9% of cases were previously healthy. Concerning the two newly reported cases, one displayed chronic alcoholism as a risk factor, but the second patient, who was previously healthy, displayed no risk factors. Finally, the cause of infection was unknown in 40% of cases. When identified, portals of entry were bacteremia (31%). urinary tract infection (24%), pneumonia (9%), septic arthritis

#### Table 3

Risk factors and suspected causes of spontaneous community-acquired Escherichia coli meningitis.

<i>N</i> = 45	n	%		
Risk factors				
Chronic alcoholism	9	20		
Cirrhosis	9	20		
Diabetes mellitus	7	16		
Disseminated strongyloidiasis	3	7		
COPD	2	4		
HIV	2	4		
Chronic organ insufficiency	2	4		
Hemochromatosis	1	2		
Myelodysplasia	1	2		
Hemophagocytic lymphohistiocytosis	1	2		
Urinary tract instrumentation	1	2		
B lymphoma	1	2		
Long-term corticosteroids	1	2		
HTLV1	1	2		
Healthy	4	9		
Others <sup>a</sup>				
Unknown	11	24		
Suspected cause				
Bacteremia	13	30		
Urinary tract infection	10	23		
Pneumonia	4	9		
Peritonitis	1	2		
Septic arthritis	1	2		
Unknown	1	41		

COPD, chronic obstructive pulmonary disease; HTLV1, human T-lymphotropic virus type 1.

<sup>a</sup> Others: chronic organ failure (n=6), hemophagocytic lymphohistiocytosis (n=1), hemochromatosis (n=1), chronic obstructive pulmonary disease (n=1), myelodysplasia (n=1), human T-lymphotropic virus 1 (n=1).

(including one case of *E. coli* spondylodiscitis) (4%), and primary peritonitis (2%).

Microbiology, treatment, and outcome data are presented in Table 4. When available, microbiological data revealed a majority of wild-type *E. coli* (20% of cases). *E. coli* was a producer of penicillinase in 9% of cases and was rarely quinolone- or trimethoprim–sulfamethoxazole-resistant (2% each). A notable and significant rate of *E. coli* producing extended-spectrum beta-lactamases (ESBLs) was encountered: 7% of community-acquired cases. Bacterial sensitivity was not reported for 60% of cases. One of the newly reported cases exhibited a high resistance profile, with an *E. coli* producing penicillinase and with resistance to trimethoprim–sulfamethoxazole. The other case displayed a wild-type *E. coli*.

#### Table 4

Microbiology treatment, and outcome of patients diagnosed with spontaneous community-acquired *Escherichia coli* meningitis.

N=45	n	%
Microbiology		
Wild-type	9	20
Penicillinase-producer	4	9
Fluoroquinolone-resistant	1	2
Trimethoprim-sulfamethoxazole-resistant	1	2
ESBL	3	7
Unknown	27	60
Treatment		
Ceftriaxone	10	22
Gentamicin	6	13
Penicillin G	4	9
Amoxicillin	4	9
Ampicillin	5	11
Chloramphenicol	2	4
Cefotaxime	2	4
Meropenem	3	7
Amikacin	1	2
Moxalactam	1	2
Ceftazidime	1	2
Cephalothin	1	2
Vancomycin	1	2
Ciprofloxacin	1	2
Sulfathiazole	1	2
Unknown	12	27
Duration of treatment		
Days	15.81 (1-21.25)	
Unknown	31	69
Outcome		
Death	21	47 (25-100)
Favorable	15	33
Unknown	9	20

ESBL, extended-spectrum beta-lactamase.

Microbiology = resistance profile of the *E.coli* strains, N = number of the cases, and % = percentage; Treatment = antibiotics used for the treatment, N = number of cases, % = percentage.

Concerning antimicrobial agents, the most widely used drugs were ceftriaxone (22%), gentamicin (13%), ampicillin (11%), penicillin G (9%), amoxicillin (9%), and meropenem (7%). Most courses of treatment included either beta-lactams or penicillins, and more rarely amikacin, moxalactam, sulfathiazole, and chloramphenicol. Treatment was not provided for 12 patients. The average duration of therapy was 15.81 days (range 1–21.25 days), but this duration was unknown in 68% of cases. Both of the newly reported cases received meningeal doses of cephalosporin, for a course of 21 days in the case of the first patient.

With regard to the outcome, the mortality rate was high at 47% (range 25–100%); this included one death from status epilepticus and DIC on day 1 after admission. This rate is similar to the rates reported in previous studies, in which mortality has ranged from 50% to 90%, reaching 86% when associated with disseminated strongyloidiasis, or 100% in cirrhotic patients (Berk and McCabe, 1980; Lu et al., 1998; Cherubin et al., 1981; Kohlmann et al., 2015).

The hypothesis that concomitant bacteremia or a coma may worsen the prognosis is strengthened by the case of the second patient reported here, who died after being admitted with an initial coma. This study focused on a binary outcome (death or survival), but neurological sequelae should also be taken into consideration. Such sequelae occur in 30% to 50% of cases (Kohlmann et al., 2015). This is supported by the first of the two new cases reported here; the patient manifested persistent slight anosognosia at 2 months after the end of antimicrobial therapy.

This study has some limitations. The first regards the important lack of data in the literature, with data missing in 16% to 63% of cases. As summarized in Table 2, 423 cases were excluded due to a lack of precise information. The conclusions of this review are drawn from a small sample of cases; thus, a larger group of patients would be required to confirm the results. Finally, some cases were reported as long ago as 1946, when microbiological identification and antimicrobial sensitivity testing were not as reliable as they are now, which may have introduced potential errors. The same concern is raised regarding the antimicrobial agents, for which recommendations have changed. For instance, chloramphenicol and sulfathiazole are no longer recommended as first-line treatment for *E. coli* meningitis.

In conclusion, spontaneous community-acquired E. coli meningitis in adults, although described as a rare entity, is likely to be underestimated and not as infrequent as reported in most articles. New underlying conditions have been described as risk factors, in addition to chronic alcoholism, cirrhosis, diabetes mellitus, HIV seropositive status, chronic obstructive pulmonary disease, and chronic organ insufficiency. These include urinary and digestive tract disorders, among them Marfan syndrome, large meningocele in contact with the bowels, disseminated strongyloidiasis, urinary tract infection, and pyelonephritis. Although the majority of cases were caused by wild-type E. coli, the emergence of statistically relevant community-acquired ESBL-producing E. coli meningitis is concerning. Finally, the prognosis is determined by the diagnosis and the timeliness of antimicrobial drug administration. The presence of coma, bacteremia, or disseminated strongyloidiasis worsens the prognosis.

Prospective studies with large cohorts and properly collected demographic, clinical, microbiological, and therapeutic information are required to confirm these results.

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#### Conflict of interest

None.

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